9ª. ESCOLA LATINO-AMERICANA DE VERÃO EM EPILEPSIA
9ª. ESCUELA LATINO-AMERICANA DE VERANO EN EPILEPSIA
9th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 22 DE FEVEREIRO A 3 DE MARÇO DE 2015
Centro de Convenções Santa Mônica

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“ EPILEPSIA: COMPLICAÇÕES E COMORBIDADES”

A 9ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) é uma atividade da International League Against Epilepsy (ILAE) e da Academia Latino-Americana de Epilepsia (ALADE) com o apoio da Liga Brasileira de Epilepsia (LBE).

Com início em 2002, as “Escolas de verão em epilepsia”, organizadas pela International League Against Epilepsy (ILAE) têm se tornado uma referência como experiência didática. Como professores e alunos permanecem em contato bastante próximo por quase duas semanas consecutivas, esse tipo de Escola tem facilitado a integração entre pesquisadores e alunos permitindo uma melhor compreensão das novas descobertas para o benefício das pessoas com epilepsia. A nona edição “Escola Latino-Americana de Verão em Epilepsia (LASSE)” realizada em Guarulhos entre 22 de fevereiro e 03 de março de 2015 aborda o tema complicações e comorbidades em epilepsia.

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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"EPILEPSY: Complications and comorbidities"
22 February - 3 March 2015 – São Paulo, Brazil

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/ /

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WELCOME AND INTRODUCTION TO LASSE

Alicia Bogacz (Uruguay)

ILAE NEW OPERATIONAL DEFINITION OF EPILEPSY: WHAT ARE THE CONSEQUENCES?

NUEVA DEFINICIÓN OPERACIONAL DE EPILEPSIA

Dra. Alicia Bogacz
Sección Epilepsia
Instituto de Neurología
LASSE 2015


ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

DEFINICIÓN CONCEPTUAL

- 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.
- 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)

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. • Se ajusta a la manera de pensar de la mayoría de los epileptólogos. • Puede ser usada para propósitos específicos.	• Puede crear confusión entre los pacientes de si tienen o no epilepsia. • No es claro su efecto sobre los estudios epidemiológicos. • 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 contusión, 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), este 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%
- 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.

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 de tiempo 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).

RESOLUCION 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.

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).

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 epileptogenicidad 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 etiológias específicas

Peter Wolf (Denmark)

FOCAL AND GENERALIZED ICTOGENESIS

EPILEPSIHOSPITALET FILADELFIA

The concepts of generalized and focal ictogenesis

Peter Wolf, Denmark

9th LASSE, Guarulhos
February 22 - March 3, 2015

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The historical concepts

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

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Focal seizures

At Queen Square, London, Jackson together with the neurosurgeon Victor Horsley (1857-1916) identified anatomical sites of epileptogenic lesions. June 22, 1886, first operation on semiology alone.

Horsley in his report coined the term "focal" for this kind of seizures

June 22, 1886 birthdate of semiological significance of the clinical presentation, of term focal, and of epilepsy surgery.

New nosological understanding ⇒ therapeutic consequence

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"Generalized"

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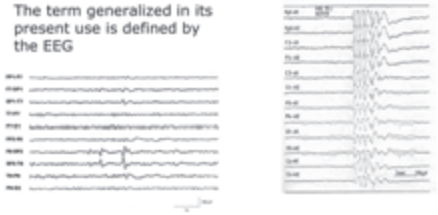
- The term generalized in its present use is defined by the EEG



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Concepts of ictogenesis: 1970 Classification

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- 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 concept of generalized epilepsy

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

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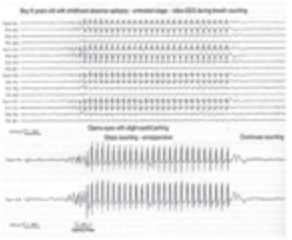
Generalised SW discharges typically are symmetric, synchronous and widespread -

but typically also have a frontal accentuation, especially at onset



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

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

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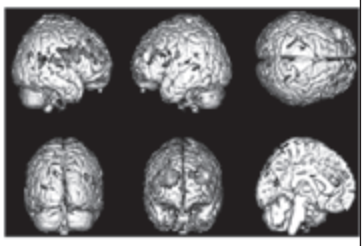
JME:
Global ⇑ of FMZ binding ($GABA_A$ receptors), especially in dorso-lateral pre-frontal cortex -

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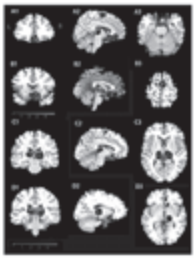
Cao et al (2013): meta-analysis of 7 studies of JME with voxel-based morphometry:

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



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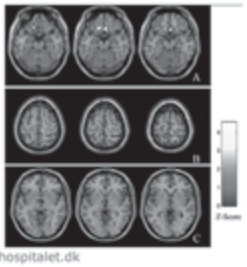
Voxel-based morphometry: JME, absence epilepsy, healthy controls: *Betting et al NeuroImage 2006; 32:498-502*

- 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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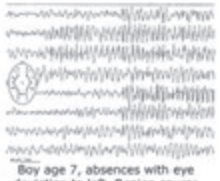
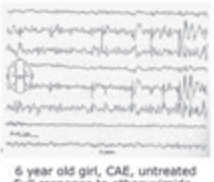


Boy age 7, absences with eye deviation to left. Benign course.



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

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Absence seizures: Individual patterns revealed by EEG-fMRI

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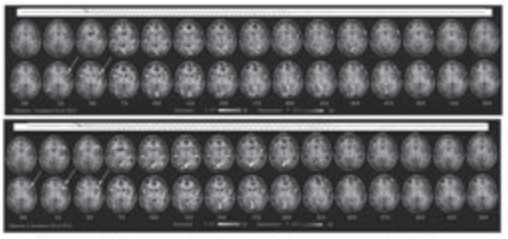

Sliding window analysis of 2 absences in the same patient

From: Moeller F et al. Epilepsia 2010

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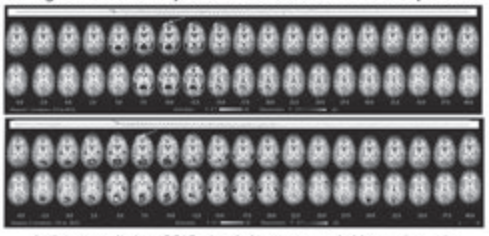
Sliding window analysis of 2 absences in other patient



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

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

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

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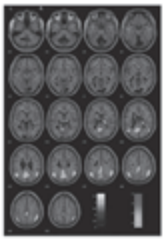
Benuzzi F et al, Epilepsia 2012; 53: 622-630: Changes of BOLD signal before and during absences: 15 Pat

<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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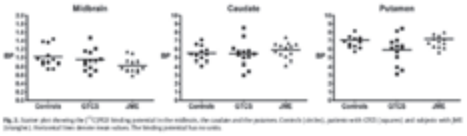
Ciumas C et al. The dopamine system in idiopathic generalized epilepsies: Identification of syndrome-related changes. NeuroImage 2010; 51: 606-15



Binding potential of dopamin transporter marking ligand [^{11}C]PE21 reduced in midbrain with JME, in Putamen with GTCS

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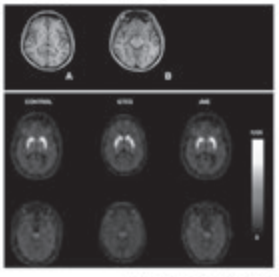
Ciumas et al, Dopamin marker PET



A: GTCS
B: JME

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Dopamin PET: Fallyprid
Reduction of receptor availability in putamen

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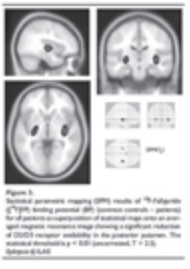
FULL-LENGTH ORIGINAL RESEARCH

Alteration of dopamine D2/D3 receptor binding in patients with juvenile myoclonic epilepsy



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Regional Reductions in Serotonin 1A Receptor Binding in Juvenile Myoclonic Epilepsy

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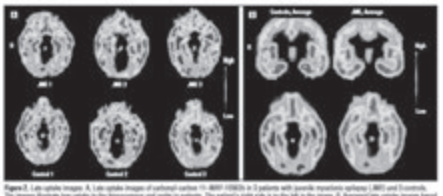
Arch Neurol 2005;62:946-950

PET with serotonin receptor antagonist carbonyl-carbon 11-WAY-100635: reduced binding potential in dorsolateral prefrontal cortex, raphe nuclei and hippocampus



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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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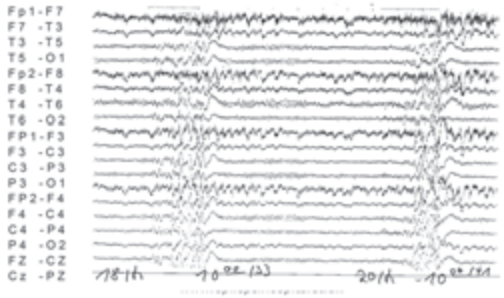

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DOI: 10.1093/brain/awg109 *Brain* (2003), **126**, 1164–1172

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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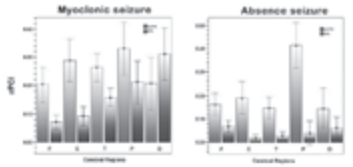
rPCI = relative phase clustering index



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

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Parra et al 2003

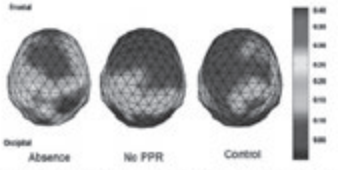

Fig. 7 Spatial distribution of the rPCI changes per magnetic sensor over the helmet. (*Left plot*) average of the mean rPCI from four trials followed by PPR at 20 Hz stimulation, compared with two trials not followed by PPR in the same subject (*middle plot*), and the average of four trials in an age- and sex-matched control (*right plot*).

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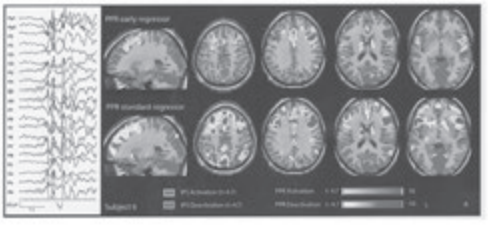
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2 years. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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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."

Thalamus, FS + absence: fMRI

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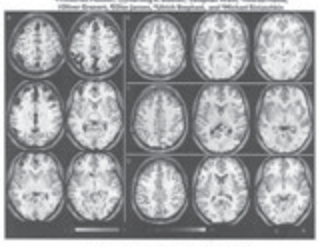
BRIEF COMMUNICATION

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



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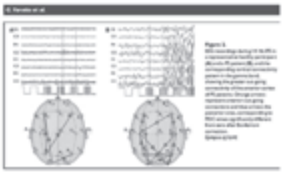
FULL-LENGTH ORIGINAL RESEARCH

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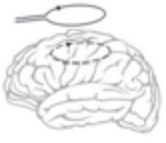
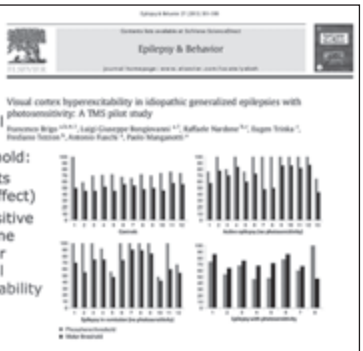
Transcranial magnetic stimulation (TMS): visual cortex and motor cortex

- 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.



Visual cortex

- 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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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,[4] Mark R. Symms,[1,3] Pamela Thompson,[1,3] Veena Kumari,[5] John S. Duncan,[1,3] Dieter Janz,[6] Mark P. Richardson[5] and Matthias J. Koepp[1,3]

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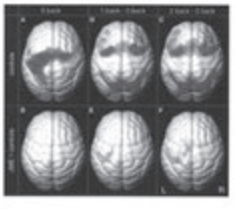
"Working memory paradigm": a spot appears in random sequence in one of 4 fields: where is it now? where was it last time? where the time before?

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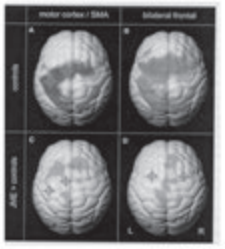
Vollmar et al. Motor system hyperconnectivity in JME: a cognitive fMRI study. Brain 2011; 134:1710-1719



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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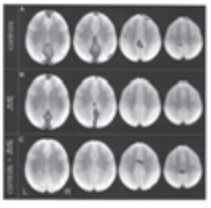
Concomitant deactivion of default mode network (frontopolar and præcuneus)

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, *Ferruccio Panzica, ¶Peter Wolf, and **Giuseppe Capovilla

*Department of Neurophysiology, IRCCS Foundation Neurological Institute "Carlo Besta," Milano, Italy; †Department of Neurological, Neuropsychological, Morphological and Movement 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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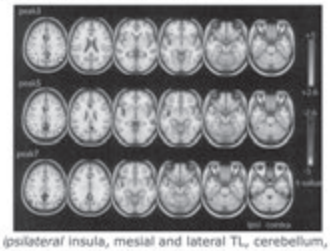

Activation: *ipsilateral* insula, mesial and lateral TL, cerebellum, *bilateral* mid-cingulate gyrus
Deactivation: *bilat.* inferior parietal lobules, posterior cingulate gyrus, precuneus, *contralat.* post. temp. cortex *Fahoum et al Epilepsia 2012*

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14 pts with frontal lobe epilepsy

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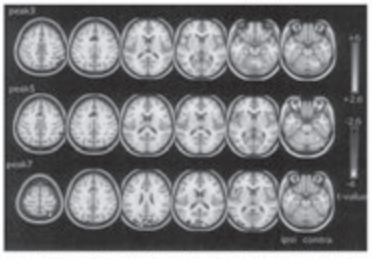

Activation: *bilateral* cingulate gyrus, *ipsilat* frontal operculum,medial thalamus, internal capsule, *contralat* cerebellum
Deactivation: *bilateral* cuneus, *contralat* inf and sup parietal lobules

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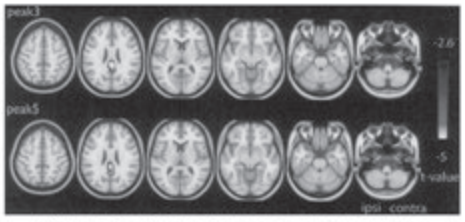
20 pts with posterior cortical epilepsies



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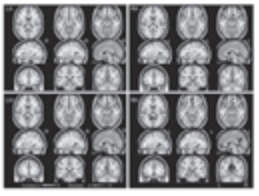
- For RA and RH, functional connectivity is significantly decreased in the brain areas of the DMN, the ventromesial limbic prefrontal regions, and the contralateral mesial temporal structures;
- For LA and LH, a significant decreased connectivity is present in DMN and contralateral hippocampus. Additional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

BRAIN

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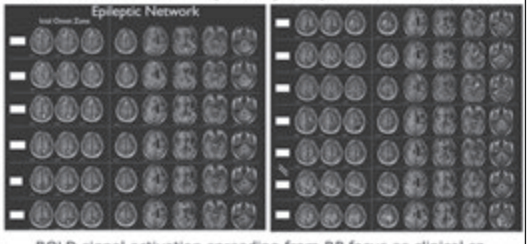
Ictal: Donaire et al (2009) sequential fMRI,rPLsz



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

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

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)

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

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

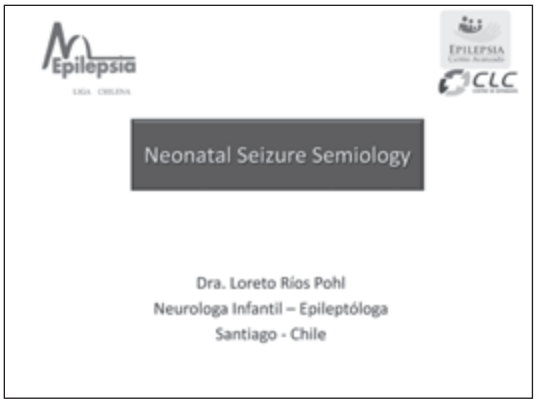
System epilepsies

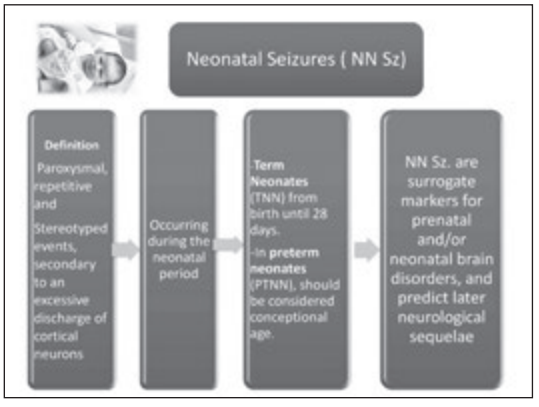
- Possible trigger zones variable within network
- Involvement of distributed bilateral (symmetric or asymmetric) selective cortical-subcortical networks
- Using pre-existent , syndrome-specific physiological systems

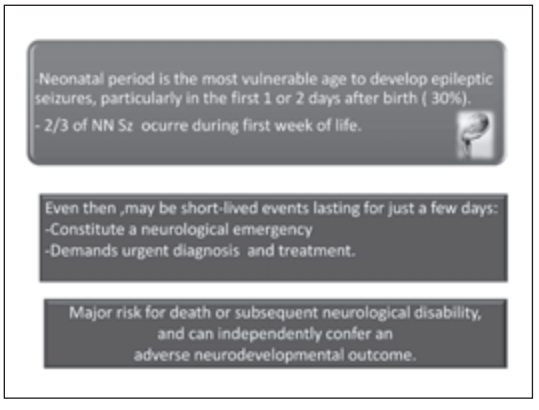
www.epilepsihospitalet.dk

Loreto Rios (Chile)

SEIZURES DURING THE NEONATAL PERIOD







Epidemiology

- Prevalence 1,5%
- Incidence: 1,8 a 3,5/1000 RNV
- In PTNN incidence increases to 57-132 per 1000 births.(LBW <1500gr)

Etiology

Hypoxic-ischemic encephalopathy
- 40-60%

Intracranial hemorrhage and Stroke
- 7-18%

Malformations of cortical development
- 5-9%

Transient Metabolic causes
- 1-4%
  - Hipoglicemia
  - Hypocalcemia/hypomagnesaemia
  - Hypernatraemia/hyponatraemia

Central Nervous System Infections
- 3%

Inborn errors of metabolism
- 1%
- Disturbances in Neurotransmitter metabolism
  - Non Ketotic Hyperglycinaemia
  - Fyridoxine –dependent Epilepsy
- Disorders of energy production
- Biosythetic defects: Brain malformation and dysfunction

Etiology Neonatal Seizures

Neonatal epilepsy Syndromes

-Benign Idiopathic Neonatal Convulsions (fifth day fits)
-Benign familiar neonatal seizures (20q13-3 /8q24)
-Early Myoclonic Encephalopathy
-Early Infantil epileptic Encephalopathy "Ohtahara Syndrome"

Miscellaneous causes

- Drug Deprivation
- Inadvertent administration of local anesthetics during childbirth

Semiology

Usually are difficult to recognize and diagnose:

-Most of them can be clinically subtle, inconspicuous and difficult to recognize from the normal behaviors.

-There is no recognizable post-ictal state.

-Generalized tonic–clonic seizures (GTCSs) are exceptional.

These difficulties frequently induce on untrained eyes, overdiagnosis or a delay in it.

Near 25% of infants experience several seizure types and that the same seizure may manifest with subtle, clonic, myoclonic, autonomic or other symtoms.

Frecquent Electroclinical dissociation

Persistence of EEG alterations with no clinical association.

Duration of neonatal seizures

They are usually brief (10 s to 1-2 min)

Longer seizures and status epilepticus develop faster at this age, but...

... is not as severe as in older ages.

Status Neonatal

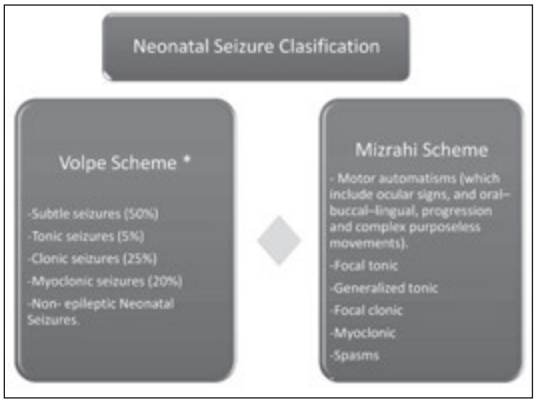
More frequent 1-3,5 /1000

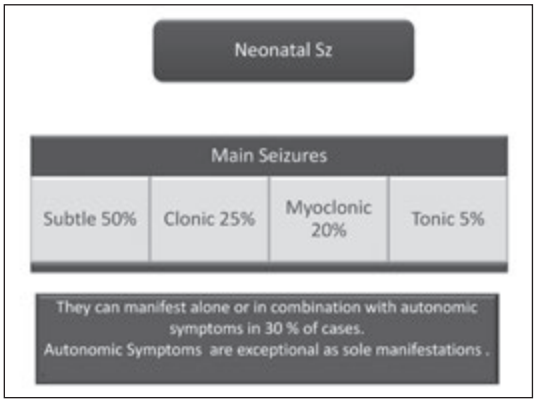
Different clinical and phenomenological characteristics.

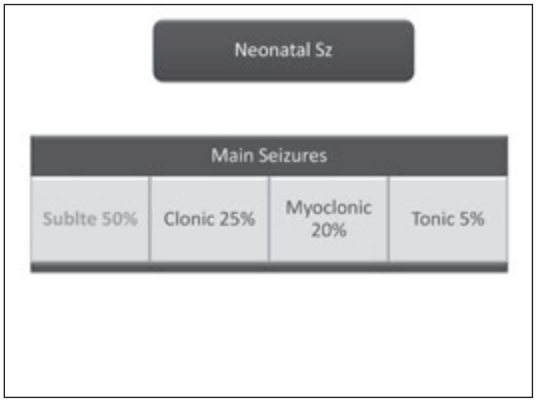
Difficult the diagnosis.

50% of ictal activity during EEG register.

Silverstein Ann Neurology 62 2007


Neonatal Seizure Clasification
Volpe Scheme *
-Subtle seizures (50%)
-Tonic seizures (5%)
-Clonic seizures (25%)
-Myoclonic seizures (20%)
-Non- epileptic Neonatal Seizures.
Mizrahi Scheme
- Motor automatisms (which include ocular signs, and oral–buccal–lingual, progression and complex purposeless movements).
-Focal tonic
-Generalized tonic
-Focal clonic
-Myoclonic
-Spasms


Neonatal Sz
Main Seizures
Subtle 50%
Clonic 25%
Myoclonic 20%
Tonic 5%
They can manifest alone or in combination with autonomic symptoms in 30 % of cases.
Autonomic Symptoms are exceptional as sole manifestations .


Neonatal Sz
Main Seizures
Sublte 50%
Clonic 25%
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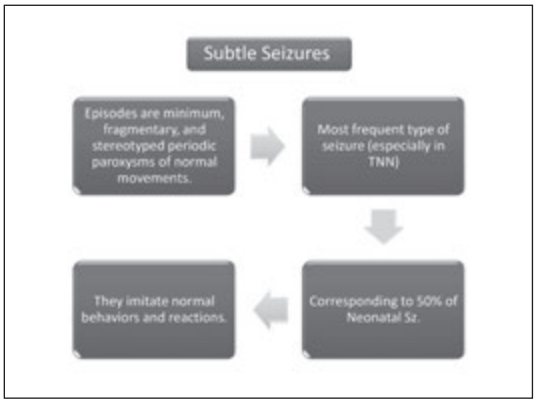

Subtle Seizures
Episodes are minimum, fragmentary, and stereotyped periodic paroxysms of normal movements.
Most frequent type of seizure (especially in TNN)
Corresponding to 50% of Neonatal Sz.
They imitate normal behaviors and reactions.

Subtle Seizures

Clinical Manifestations:

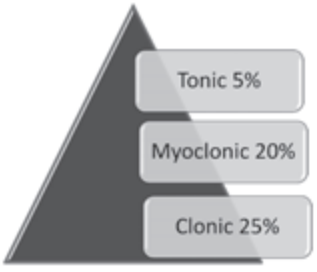
- **Ocular movements:**
  - Random and roving eye movements to sustained conjugate tonic deviation with or without jerking.
  - Eyelid blinking or fluttering.
  - Eyes rolling up, eye opening, fixation of a gaze or nystagmus may occur alone or with other ictal manifestations
- **Oral–buccal–lingual movements** (sucking, chewing, smacking and tongue protrusions)
- **Progression movements** (rowing, swimming, pedalling, cycling, thrashing or struggling movements)
- **Complex purposeless movements** (sudden arousal with episodic limb hyperactivity and crying)

Subtle Seizures

Associated with diffuse CNS injury:	• Structural malformations • Hypoxic-ischemic encephalopathy
Differential diagnosis:	• Normal Neonatal Reflexes and behaviors. • Brainstem Apneas

EEG: Poor Correlation EEG except tonic deviation of the eyes

Motor Seizures



Neonatal Sz

Main Seizures			
Subtle 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

Clonic Seizures

- Most frequent Semiology in TNN
- Easy diagnosis
- Always with EEG correlation
- Slow rhythmic movements (1 a 4 Hz).
- Suggest structural focal lesion

Clonic Seizures can be:

- Multifocal (Several segments, not Jacksonian migratory pattern)
- Focal (Face, Neck, Trunk or body extremities)

Etiology

-Structural (malformations, cortical dysplasias) - Focal lesion -Hypoxic-ischemic (EHI)	**Metabolic Alterations:** -Transient (hypoglycemia, hypocalcemia) -Persistent (EME)

Differential Diagnosis:

- Neonatal tremor

Differential Diagnosis:

Neonatal tremor / jitteriness

- Occurring in up 2/3 of NN in the first 3 days of life.
- Most frequently in sleepy or active infant
- Tremor are stimulus sensitive.
- Diminish with passive flexion of the extremity.
- Frequently is of higher frequency and less amplitude.
- Normal EEG.

Etiology :

- Inmadurity of spinal inhibitory interneurons casuing an excessive muscle stretch reflex.
- Elevated levesl of circulatin catecholamines account for the tremor.

It can be:

- Symptomatic: metabolic, HIE.(clue is the persistence)
- Benign: "if the child is held supine and allowed to suck, the jitteriness should resolve.

Neonatal Sz

Main Seizures			
Subtle 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

Myoclonic Seizures

Semiology

- Sudden movements in flexor muscles of the extremities.
- Uncommon in the NN.
- Usually during sleep.

3 types

- Focal: flexor muscles of an upper limb .
- Multifocal: abrupt asynchronous contractions of different parts of the body.
- Generalized: bilateral myoclonus of upper limbs and sometimes lower limbs also.

They differ from clonic Sz. Because of the rapid flexor movement component (fast phase) and frequency (more than three beats per second).

Myoclonic Seizures

Etiology:

Always must think in EME
(Early Myoclonic Encefalophathy)

EEG with Abnormal Pattern:

- Burst- Suppression

Early Myoclonic Encephalopathy: EME

« Neonatal myoclonic encephalopathy »
Aicardi and Goutieres, 1978

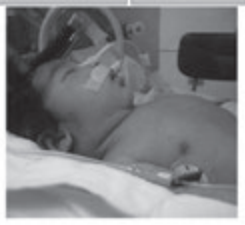
-Massive myoclonic sz, erratic myoclonia, focal seizures.
-Onset before D28.
-Abnormal neurological exam.
-Suppression Bursts EEG pattern.
-Refractory Seizures.

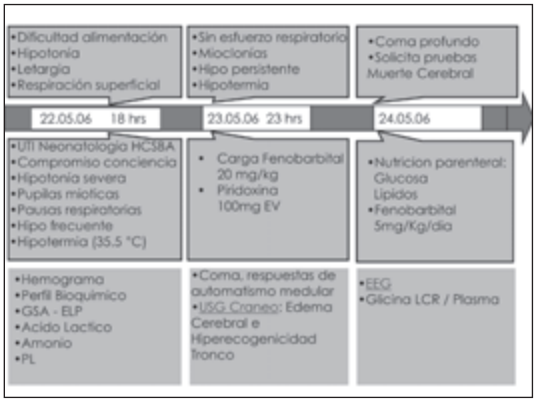
The metabolic study must be comprehensive:
-Nonketotic hyperglycinemia.
-Organic acidemias (d-glyceric, propionic, methylmalonic).
- Molybdenum cofactor deficiency.
-Pyridoxine deficiency, biotin deficiency.
Some with specific treatment that substantially changed the prognosis

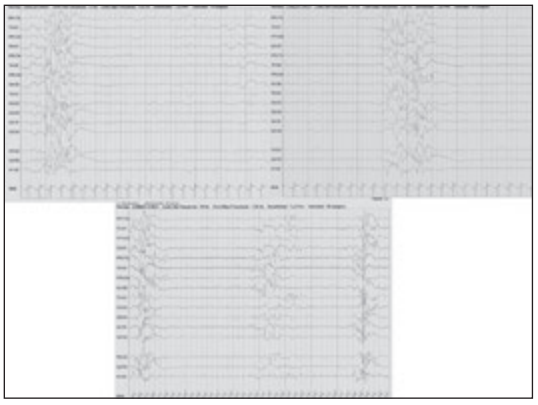
---

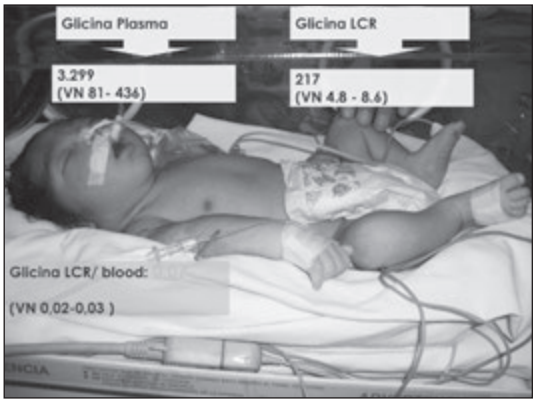
- First child.
- Young, healthy parents.
- Non consanguineous.
- Monitored pregnancy.
- Without pathologies.
- Frequent hiccups.

- J .R.C
- RNT AEG 40 sem
- Regular Birth









Differential Diagnosis:

- Neonatal benign myoclonus
- Benign myoclonus during sleep.

Differential Diagnosis:

- Benign myoclonus during sleep.

•They are brief limb movement, a jerk, caused by a muscle contraction.
•They occur only in sleep.
•Is the most common condition misdiagnoses for epilepsy.
•It tends to ocurr in term helthy NN, is bilateral and repetitive, and may involve all limbs but not faces.
•It can last for up an hour (Dd: Status epilepticus).
•EEG normal.

Neonatal Sz

Main Seizures			
Subtle 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

Tonic Seizures:

- Sustained posture of trunk and/or extremities, associated or not with tonic oculo-cefalic deviation.

Tonic Seizures

Focal:			Generalized:		
Slow and maintained asymmetric changes of posture	Cyanosis and apnea is frequent associated	Good Clinical-EEG correlation	Most frequent presentation	Tonic extention of upper an lower extremeties	EEG pattern: Burst Suppresion

Tonic Seizures

Etiology:

- Severe CNS involvement
- Ohtahara Syndrome.

Early Infantile Encephalopathy with Epilepsy: EIEE Ohtahara et al 1976

-Epileptic Spasms, tonic spasms, focal seizures.

-Onset from D1, up to 2 or 3 months.

-Abnormal neurological examination.

-Burst –Suppression EEG pattern.

-Abnormal findings on Neuro radiology: Malformations are often found.

-No familiar history.

Differential Diagnosis:

- Decerebrate postures/decortication
- Stiff-baby syndrome

Differential Diagnosis:

- Stiff-baby syndrome / Hyperplexia

•Rare disorder seen in NN, characterized by generalized muscle rigity, excessive startle or NE tonic spasm.
•They can developed a severe apnea with a secondary hypoxic seizure or even SIDS.
•It can elicit with nose tapping and some time with bath.
•Autosomal dominant condition with mutation of presynaptic glycine receptor, gene GLRA1 (Cr. 5q33-35).
•Clonazepam is the first choice treatment.
•It gets resolved by 3 years of age.

Non-epileptic neonatal seizures

They look like subtle, tonic or Myoclonic Sz. but are not associated with ictal EEG discharges.

Exaggerated reflex behaviours 'brain-stem release phenomena'.

Correlate with diffuse abnormal brain processes (HIE) and a poor short-term outcome.

EEG evidende a severe cortical deppresion.

NN Seizure Physiopathology

- During NN period exist an enhaced excitability of the brain.

- This hyper –excitability permit robust activity-dependent synaptic formation , plasticity an remodeling.

How is this enhaced excitability?

Decrease efficacy of inhititory neurotransmission

GABA A exitatory

Other mechanism of Hyperexcitability

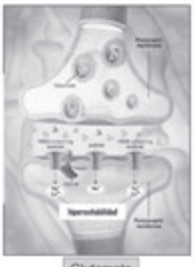
Ion Channel configuration favors depolarization

Hyperexcitability by neuropeptides

Enhanced potential for inflamatory response

"Normal" Function of GABA and Glutamato

GABA
Hiperpolariza
Inhibe



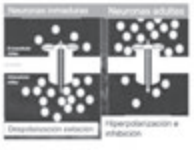
Glutamato
Depolariza

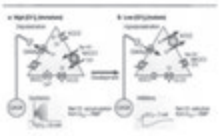
Physiopathology

Initally the GABA synapses are excitatory.

Glutamatergic exitability appears before GABAergic inhibition.

Glutamatergic overexpression: subtype NMDA and AMPA.





Lawrence. Semin Pediatr Neurol 17:2010
Ben-Ari. Epileptic Disord 2006;8 (2):

Ben-Ari, 2002

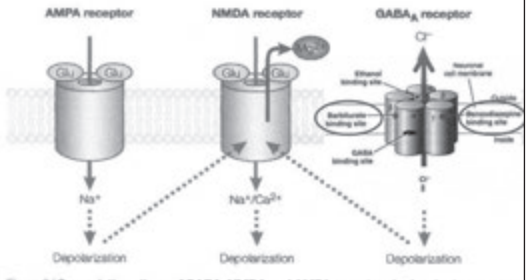
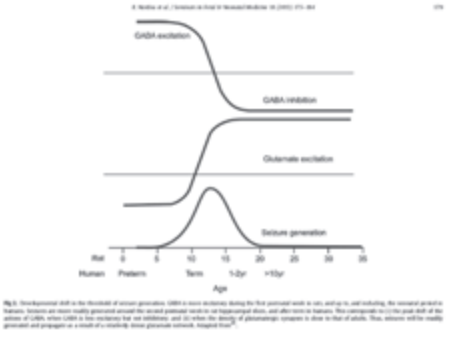
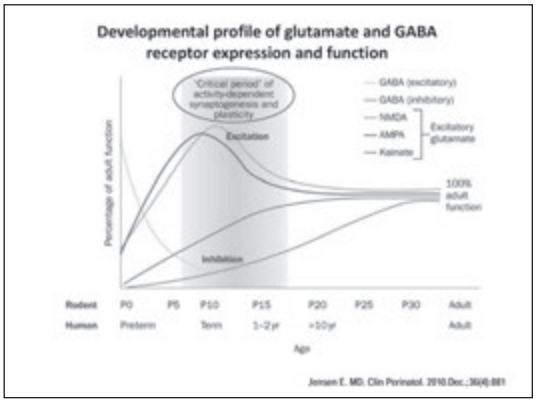
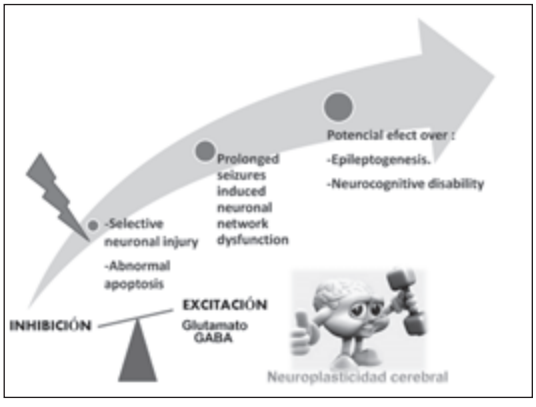
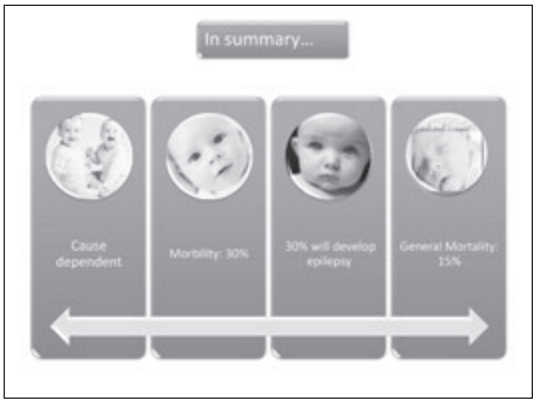


Figure 3 | **Synergistic actions of GABA, NMDA and AMPA receptors in developing neurons.**


GABA excitation
GABA inhibition
Glutamate excitation
Seizure generation
Rat
Human
Preterm
Term
1-2yr
>10yr
Age


Developmental profile of glutamate and GABA receptor expression and function
"Critical period" of activity-dependent synaptogenesis and plasticity
Excitation
Inhibition
GABA (excitatory)
GABA (inhibitory)
NMDA
AMPA
Kainate
Excitatory glutamate
100% adult function
Percentage of adult function
Rodent P0 P5 P10 P15 P20 P25 P30 Adult
Human Preterm Term 1–2 yr >10 yr Adult
Age
Jensen E. MD. Clin Perinatol. 2010.Dec.;37(4):861


Potencial efect over :
-Epileptogenesis.
-Neurocognitive disability
Prolonged seizures induced neuronal network dysfunction
-Selective neuronal injury
-Abnormal apoptosis
INHIBICIÓN
EXCITACIÓN
Glutamato
GABA
Neuroplasticidad cerebral


In summary...
Cause dependent
Mortality: 30%
30% will develop epilepsy
General Mortality: 15%


Gracias, Thank you, Obrigado!!

VERA TERRA (BRAZIL)

SEIZURES DURING CHILDHOOD

SEIZURES IN CHILDHOOD

Vera Cristina Terra

Epicentro – Centro Integral de Diagnóstico e Tratamento das Epilepsias
Curitiba - PR

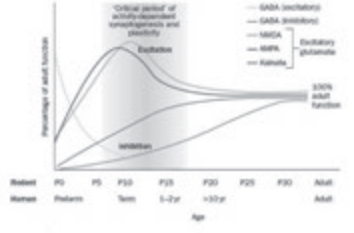
SEIZURES IN CHILDHOOD

Clinical Semiology

- Semiologic descriptions based on clinical history has a number of limitations.
- A review of videos demonstrates that the accuracy of the description of seizures by patients or family members is 45% for seizures and 70% for non seizures. (Deacon et al., 2003).
- Seizures with altered consciousness may arise from any lobe in focal or generalized epilepsy.

SEIZURES IN CHILDHOOD

Normal brain development



SEIZURES IN CHILDHOOD

Epilepsy and epileptogenesis

Development of synaptic processes.
Myelination
Dendritic branching.
Morphology of dendritic spines
Development of synapses
Neurotransmitters

↓

Changes in seizure semiology with age

Vera Cristina Terra

SEIZURES IN CHILDHOOD

Epilepsy and epileptogenesis

The same etiology can cause different clinical symptoms...

↓

Intrinsic epileptogenicity of lesions
Ex: MTS, MCD

SEIZURES IN CHILDHOOD

TABLE 1. Value of Positive and Negative Motor Signs in Lateralizing Seizure Onset to the Right or the Left Hemisphere

Sign	Hemisphere of Seizure Onset	Observed Rate	Positive Predictive Value*
Positive motor signs			
Early ictal tonic head turn	Ipsilateral	30%	
Late convulsive forced head turn	Contralateral	23%–38%	
Late (pre)ictal forced head turn	Ipsilateral		
Eye deviation	Contralateral	Rarely solitary	High if occipital
Focal clonic	Contralateral	36%	>90%
Asymmetric clonic ending	Ipsilateral	78% of secondary generalized seizures	83%
Dystonic limb	Contralateral	67%	93%
Tonic limb	Contralateral	13%	83%
Complex postures			
"Figure 4" sign	Contralateral to extended limb	70% of seizures generalizing from temporal lobe; 51% of extratemporal	89%
Negative motor signs			
Todd paresis	Contralateral	5% of complex partial seizure patients 13% of partial seizure patients	100% 80%–100%

*The positive predictive value is the number of true positives divided by the sum of true positives and false positives.

(So, 2006)

SEIZURES IN CHILDHOOD

TABLE 2. Importance of Automatisms, Autonomic Signs, and Peri-ictal Speech Signs in Hemispheric Lateralization or Lobar Localization of Partial Seizure

Characteristic	Location*
Automatisms	
Contralateral limb automatism	Ipsilateral to seizure focus; 95%–99%
Contralateral eye blinks	Ipsilateral to focus; 85%–99%
Postictal cough	80% of temporal lobe seizure patients; 5% of nondominant or frontal lobe seizure patients
Postictal nose wiping	70% of temporal and 10% of frontal lobe seizures; 80%–90%
Bipedal automatisms	50% of frontal and 10% of temporal lobe seizure patients
Ictal spitting or drinking	Rare, but high association with right temporal seizures
Automatisms with preserved responsiveness	Nondominant (usually right) temporal, or extratemporal or other side
Gelastic seizures	Hypothalamic, sometimes rostral temporal or frontal cingulate origin
Autonomic signs	
Ictus emeticus	Rare, but usually right temporal
Ictal urinary urge	Rare (2%), but localizes to right temporal
Piloerection (gooseb umps)	Mostly left temporal
Peri-ictal speech	
Ictal speech arrest	Seen in 75% of temporal lobe seizure patients, but only 15%–20% for dominant hemisphere focus
Ictal speech preservation	Seen in only 15%, but 89% of 15% for non-dominant hemisphere focus in temporal lobe seizure patients
Postictal dysphasia	90% dominant hemisphere involvement

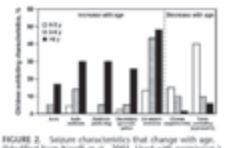


FIGURE 2. Seizure characteristics that change with age. (Modified from Nordli et al., 2001. Used with permission.)

(So, 2006)

SEIZURES IN CHILDHOOD

In Children...

SEIZURES IN CHILDHOOD

Natural hystory of epilepsy

- Recurrence of a single seizure in 2 years :

32%: idiophatic epilepsies.

57%: symptomatic epilepsies. *(Berg & Shinnar, 1991)*

- Risk factors after the onset of epilepsy

Number of seizures.

Seizures in the first 6 months.

Response first AED.

SEIZURES IN CHILDHOOD

Semiology

- **Neonatal period:** Cardiovascular changes, cycling, hypomotor crises.
- **Until 6 mo:** Rare focal seizures, epileptic spasms still occur, awakenings.
- **2 years:** symmetric tonic posture as a manifestation of focal seizures. Action of subcortical structures and the brain stem?
- Seizures with less exuberant motor components.

SEIZURES IN CHILDHOOD

Semiology

3-6 years

- Tonic, clonic, myoclonic, atonic.
- Epileptic spasms.
- Hypermotor seizures.
- Oroalimentar and simple gestural automatisms.
- Forced unilateral blink.

SEIZURES IN CHILDHOOD

Semiology

After 7 years

- More complex automations.
- Less frequent tonic seizures.
- Dystonic posturing.
- Increased incidence of generalized tonic-clonic seizures.

SEIZURES IN CHILDHOOD

Ictal Semiology

Epilepsia, 42(9):1212–1218, 2001
Blackwell Science, Inc.
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ILAE Commission Report

Glossary of Descriptive Terminology for Ictal Semiology: Report of the ILAE Task Force on Classification and Terminology

Warren T. Blume—Chair, Hans O. Lüders, Eli Mizrahi, Carlo Tassinari, Walter van Emde Boas, and Jerome Engel, Jr., Ex-officio

SEIZURES IN CHILDHOOD

II TERMS DESCRIBING EPILEPTIC SEIZURE SEMIOLOGY

1.0 MOTOR
1.1 ELEMENTARY MOTOR
1.1.1 TONIC
1.1.1.1 EPILEPTIC SPASM
1.1.1.2 POSTURAL
1.1.1.2.1 VERSIVE
1.1.1.2.2 DYSTONIC
1.1.2 MYOCLONIC
1.1.2.1 NEGATIVE MYOCLONIC
1.1.2.2 CLONIC
1.1.2.2.1 JACKSONIAN MARCH
1.1.3 TONIC-CLONIC
1.1.3.1 GENERALIZED TONIC-CLONIC SEIZURE
1.1.4 ATONIC
1.1.5 ASTATIC
1.1.6 SYNCHRONOUS
1.2 AUTOMATISM
1.2.1 OROALIMENTARY
1.2.2 MIMETIC
1.2.3 MANUAL OR PEDAL
1.2.4 GESTURAL
1.2.5 HYPERKINETIC
1.2.6 HYPOKINETIC
1.2.7 DYSPHASIC
1.2.8 DYSPRAXIC
1.2.9 GELASTIC
1.2.10 DACRYSTIC
1.2.11 VOCAL
1.2.12 VERBAL
1.2.13 SPONTANEOUS
1.2.14 INTERACTIVE
2.0 SOMATOSENSORY OR SOMATOSENSORY
2.1 AURA
2.2 SENSORY
2.2.1 ELEMENTARY
2.2.1.1 SOMATOSENSORY
2.2.1.2 VISUAL
2.2.1.3 AUDITORY
2.2.1.4 OLFACTORY
2.2.1.5 GUSTATORY
2.2.1.6 EPIGASTRIC
2.2.1.7 CEPHALIC
2.2.1.8 AUTONOMIC
2.2.2 EXPERIENTIAL
2.2.2.1 AFFECTIVE
2.2.2.2 MNEMONIC
2.2.2.3 HALLUCINATORY
2.2.2.4 ILLUSORY
2.3 DYSCOGNITIVE
3.0 AUTONOMIC EVENTS
3.1 AUTONOMIC AURA
3.2 AUTONOMIC SEIZURE
4.0 SOMATOTOPIC MODIFIERS
4.1 LATERALITY
4.1.1 UNILATERAL
4.1.1.1 HEMI-
4.1.2 GENERALIZED (syn. "bilateral")
4.1.2.1 ASYMMETRICAL
4.1.2.2 SYMMETRICAL
4.2 BODY PART
4.3 CENTRICITY
4.3.1 AXIAL

SEIZURES IN CHILDHOOD

1.1.1.1 EPILEPTIC SPASM (Formerly Infantile Spasm)

Noun: A sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not so sustained as a tonic seizure (i.e., ~1 s). Limited forms may occur: grimacing, head nodding. Epileptic spasms frequently occur in clusters.

SEIZURES IN CHILDHOOD

Epileptic spasm

SEIZURES IN CHILDHOOD

1.1.1.2 POSTURAL

Adoption of a posture that may be bilaterally symmetric or asymmetric (as in a "fencing posture").

SEIZURES IN CHILDHOOD

Tonic symmetric

SEIZURES IN CHILDHOOD

Tonic asymmetric

SEIZURES IN CHILDHOOD

1.1.2 MYOCLONIC (adjective); MYOCLONUS (noun)
Sudden, brief (<100 ms) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).

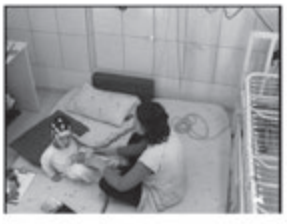
1.1.2.1 NEGATIVE MYOCLONIC
Interruption of tonic muscular activity for <500 ms without evidence of preceding myoclonia.

SEIZURES IN CHILDHOOD

1.1.5 ASTATIC
Loss of erect posture that results from an atonic, myoclonic, or tonic mechanism. Synonym: drop attack.

SEIZURES IN CHILDHOOD

Myoclonic Astatic Epilepsy



SEIZURES IN CHILDHOOD

Drop	Astatic	Tonic
Duration of drop	Straight, directed to the buttocks. Depend on the center of gravity	Propulsive
Post-ictal confusion	Absente	Depends on seizure length, confusion and automatism may occur
Manifestation in supine position	Up ocular version	Trunk flexion and abduction of the upper limbs
Ictal EEG	Spike-wave complex; atenuation of background activity	Recrutant rhythm
Related syndrome	MAE	LGS

SEIZURES IN CHILDHOOD

1.1.2.2.1 JACKSONIAN MARCH
Noun: Traditional term indicating spread of clonic movements through contiguous body parts unilaterally.

1.1.3 TONIC–CLONIC
A sequence consisting of a tonic followed by a clonic phase. Variants such as clonic–tonic–clonic may be seen.

1.1.3.1 GENERALIZED TONIC–CLONIC SEIZURE (syn. bilateral tonic–clonic seizure) (Formerly "Grand Mal" Seizure)
Noun: Bilateral symmetric tonic contraction and then bilateral clonic contractions of somatic muscles, usually associated with autonomic phenomena.

SEIZURES IN CHILDHOOD

Jacksonian March

SEIZURES IN CHILDHOOD

Tonic-clonic seizure

SEIZURES IN CHILDHOOD

1.2 AUTOMATISM
Noun: A more or less coordinated, repetitive, motor activity usually occurring when cognition is impaired and for which the subject is usually amnesic afterward. This often resembles a voluntary movement and may consist of an inappropriate continuation of ongoing preictal motor activity.
The following adjectives are usually employed to modify "automatism."

SEIZURES IN CHILDHOOD

Focal epilepsies undoubtedly or probably symptomatic

Limbic epilepsy:

- Medial Temporal lobe epilepsy with hippocampal sclerosis.
- Medial Temporal lobe epilepsy defined by specific etiologies.

SEIZURES IN CHILDHOOD

Focal epilepsies undoubtedly or probably symptomatic

Neocortical epilepsy

Frontal lobe

Temporal lobe

Parietal lobe

The occipital lobe

Focal epilepsies with specific forms of precipitation

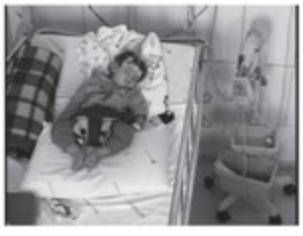
SEIZURES IN CHILDHOOD

1.2.5 HYPERKINETIC

1. Involves predominantly proximal limb or axial muscles producing irregular sequential ballistic movements, such as pedaling, pelvic thrusting, thrashing, rocking movements.
2. Increase in rate of ongoing movements or inappropriately rapid performance of a movement.

SEIZURES IN CHILDHOOD

Hyperkinetic



SEIZURES IN CHILDHOOD

1.2.6 HYPOKINETIC
A decrease in amplitude and/or rate or arrest of ongoing motor activity.

SEIZURES IN CHILDHOOD

Hypokinetic

SEIZURES IN CHILDHOOD

1.2.12 VERBAL
Single or repetitive utterances consisting of words, phrases, or brief sentences.

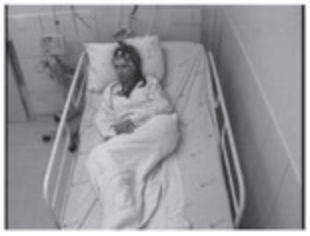
1.2.13 SPONTANEOUS
Stereotyped, involve only self, virtually independent of environmental influences.

SEIZURES IN CHILDHOOD

FRONTAL LOBE EPILEPSY

SEIZURES IN CHILDHOOD

TEMPORAL LOBE EPILEPSY

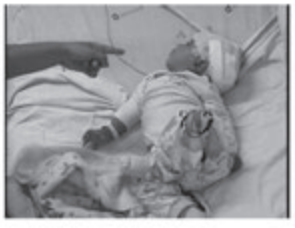


SEIZURES IN CHILDHOOD

TEMPORAL LOBE EPILEPSY

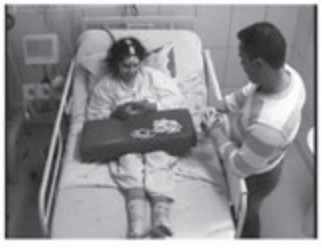
SEIZURES IN CHILDHOOD

PARIETAL LOBE EPILEPSY



SEIZURES IN CHILDHOOD

OCCIPITAL LOBE EPILEPSY



SEIZURES IN CHILDHOOD

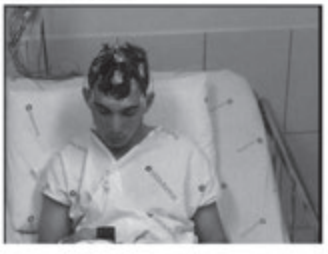
OCCIPITAL LOBE EPILEPSY

SEIZURES IN CHILDHOOD

1.2.9 GELASTIC
Bursts of laughter or giggling, usually without an appropriate affective tone.

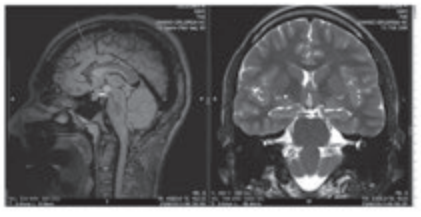
SEIZURES IN CHILDHOOD

HYPOTHALAMIC HAMARTOMA



SEIZURES IN CHILDHOOD

HYPOTHALAMIC HAMARTOMA



SEIZURES IN CHILDHOOD

5.1.3.2 REFLEX

Objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by activity of the patient. Afferent stimuli can be *elementary* [i.e., unstructured (light flashes, startle, a monotone)] or *elaborate* [i.e., structured, (a symphony)]. Activity may be elementary [e.g., motor (a movement)], or elaborate [e.g., cognitive function (reading, chess playing)], or both (reading aloud).

SEIZURES IN CHILDHOOD

Reflex seizure

SEIZURES IN CHILDHOOD

ABSENCE SEIZURES

Lapses of awareness, sometimes with staring. They begin and end abruptly, lasting only a few seconds, occur more in children and can be so brief that they sometimes are not detected for months.

Simple absence seizures: the person usually just stares into space for less than 10 seconds.

Complex absence seizures: the person will make some kind of movement in addition to staring into space. Movements may include blinking, chewing, or hand gestures. A complex absence seizure can last up to 20 seconds.

Atypical absence seizures: The person will stare (as they would in any absence seizure) but often is somewhat responsive. These seizures usually last 5 to 30 seconds (commonly more than 10), with a gradual beginning and ending.

http://www.epilepsy.com/learn/types-seizures/absence-seizures

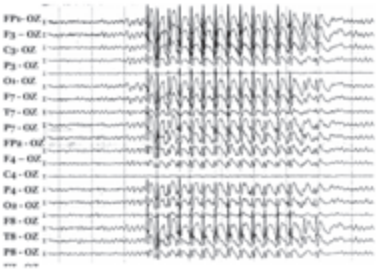
SEIZURES IN CHILDHOOD

Childhood absence epilepsy

- 2-8 years, 6-7 years peak.
- Very frequent absence seizures may be present.
- Female.
- Genetic predisposition.
- EEG: regular 3 Hz SWC.
- TC seizures in adolescence.

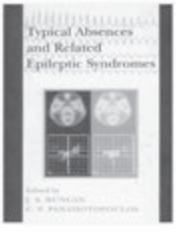
SEIZURES IN CHILDHOOD

Childhood Absence



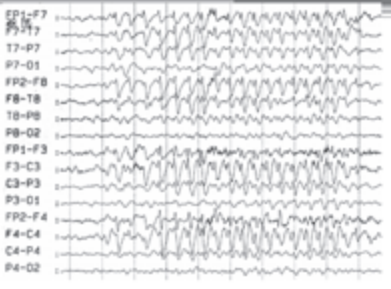
SEIZURES IN CHILDHOOD

Panayiotopoulos et al., 1989



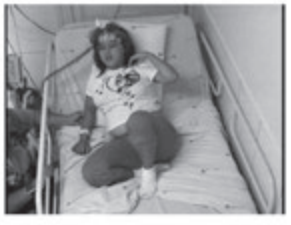
- All absence epilepsies are similar?

SEIZURES IN CHILDHOOD



SEIZURES IN CHILDHOOD

Atypical Absence



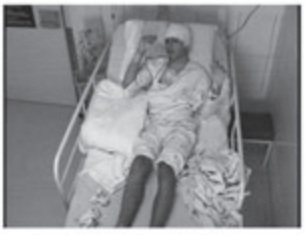
SEIZURES IN CHILDHOOD

6.1 STATUS EPILEPTICUS

A seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients *or* recurrent seizures without interictal resumption of baseline central nervous system function.

SEIZURES IN CHILDHOOD

CONTINUOUS PARTIAL EPILEPSY



SEIZURES IN CHILDHOOD

Focal Genetic Epilepsies

- BCE – rolandic form.
- Occipital early onset epilepsy – Panayiotopoulos.
- Occipital late onset epilepsy – Gastaut.
- Atypical benign epilepsy.

SEIZURES IN CHILDHOOD

Focal Genetic Epilepsies

- Affect 22% of children with non-febrile seizures.
- Children clinically normal / normal image.
- Favorable outcome: considering seizure frequency and cognitive aspects.

SEIZURES IN CHILDHOOD

Focal Genetic Epilepsies

- Prognosis – Self-limited epilepsy with centrotemporal spikes:
  - 10-20% with frequent seizures.
  - 1% evolve to more severe forms of epilepsy.

SEIZURES IN CHILDHOOD

Benign Childhood Epilepsy

- Prognosis – Panayiotopoulos Syndrome
  - 25% with frequent seizures.
  - 10% with seizures lasting longer.
  - Atypical evolution in < 3%.

SEIZURES IN CHILDHOOD

Focal Idiopathic Epilepsies

- Prognosis – Self-limited epilepsy with occipital spikes (Gastaut):
  - 40 - 50% with rare CPS or TC seizures.
  - Atypical evolution is rare.

SEIZURES IN CHILDHOOD

SHORT COMMUNICATION

Oxcarbazepine and atypical evolution of benign idiopathic focal epilepsy of childhood

S. Grosso, M. Balestri, R. M. Di Bartolo, L. Cortini, G. Vatti, P. Curatolo and P. Balestri

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

SEIZURES IN CHILDHOOD

Lennox-Gastaut Syndrome

- from 1 to 8 years.
- Family history in 3-27% of cases.
- Generalized seizures and focal.
- Idiopathic x Symptomatic.
- Mental retardation.
- History of West syndrome: 30 to 40%.
- Treatment.

SEIZURES IN CHILDHOOD

Lennox-Gastaut Syndrome

Prognosis

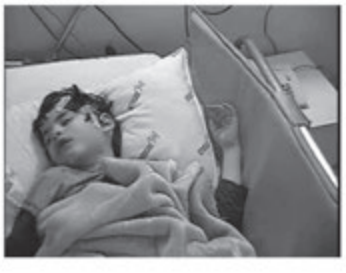
- Rare total seizure control.
- Dependence on family care.
- Daily seizures.
- Earlier onset related to more severe mental retardation.
- Status epilepticus badly aggravates the evolution.

SEIZURES IN CHILDHOOD

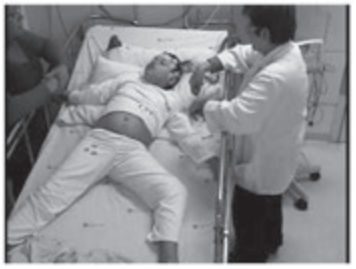
Lennox-Gastaut Syndrome

SEIZURES IN CHILDHOOD

Lennox-Gastaut Syndrome



SEIZURES IN CHILDHOOD



SEIZURES IN CHILDHOOD

NATURAL HYSTORY OF EPILEPSY

- **Mortality:**

Higher risk in the first 5 years of diagnosis and after 10 years of diagnosis.

Number of seizures in the first 6 months.

Response to AEDs.

SEIZURES IN CHILDHOOD

NATURAL HYSTORY OF EPILEPSY

- **Mortality – causes:**

Not related: tumors outside CNS, cardiac ischemia, pneumonia, etc..

Related to background disease: *cerebral tumors, cérebro-vascular diseases*, encephalitis, brain abscesses, metabolic diseases.

SEIZURES IN CHILDHOOD

NATURAL HYSTORY OF EPILEPSY

- **Mortality – causes:**

Related to epilepsy: suicide, adverse effects of AEDs, AED idiossincratic reactions, related seizures *per se*, (trauma, burns, drowning), status epilepticus, asphyxia, aspiration pneumonia after a seizure, *SUDEP*.

SEIZURES IN CHILDHOOD

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

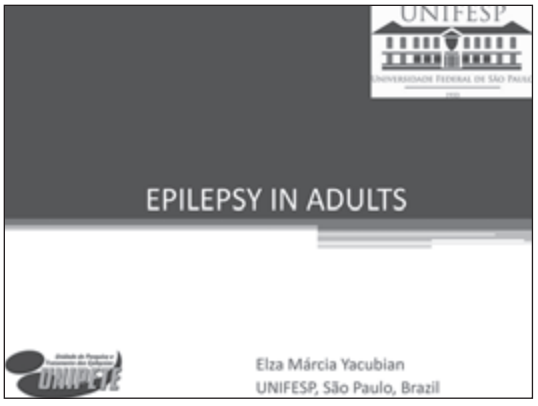
K. van Rijckevorsel; Seizure (2006) 15, 227–234

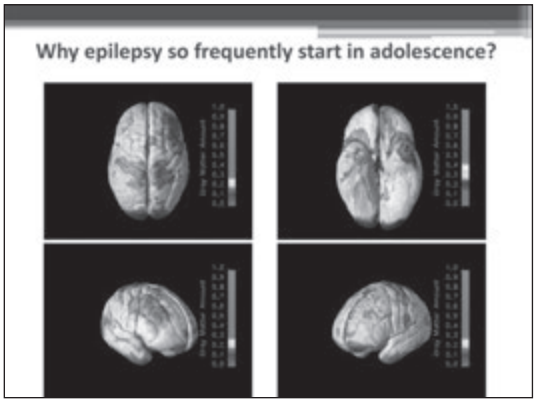
SEIZURES IN CHILDHOOD

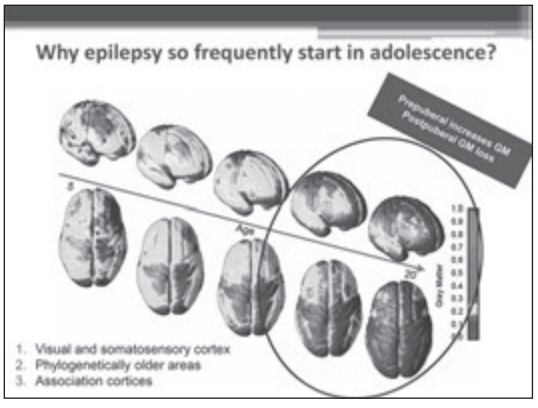
THANK YOU

Elza Marcia Yacubian (Brazil)

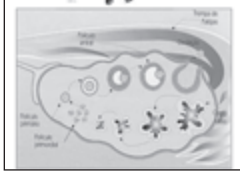
SEIZURES IN ADULTS







Epileptogenesis in adolescence



- The secretion of neuroinhybitory steroid progesterone only begins when menstrual cycles become ovulatory, one or two years after menarche
- The neuroexcitatory steroids (estrogens) are present 4-6 six years before the progesterone and can promote excitatory synaptogenesis and epilepsy development

Epileptogenesis in adolescence

- In males it is believed that different levels of testosterone metabolites in the brain are able to act as an anticonvulsant (such as 3-α-androstanediol) or pro-convulsant (such as estradiol)

Epilepsy syndromes with adolescence onset

Idiopathic generalized epilepsies with variable phenotypes	Juvenile myoclonic epilepsy
	Juvenile absence epilepsy
	Epilepsy with generalized tonic-clonic seizures on awakening
Photosensitive epilepsies	
Reading epilepsy	
Mesial temporal sclerosis with hippocampal sclerosis	
Progressive myoclonic epilepsies	

Epilepsy syndromes with adolescence onset

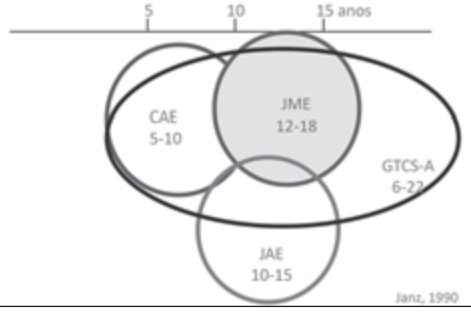
Idiopathic generalized epilepsies with variable phenotypes	Juvenile myoclonic epilepsy
	Juvenile absence epilepsy
	Epilepsy with generalized tonic-clonic seizures on awakening
Photosensitive epilepsies	
Reading epilepsy	
Mesial temporal sclerosis with hippocampal sclerosis	
Progressive myoclonic epilepsies	

Idiopathic generalized epilepsies with variable phenotypes

Idiopathic generalized epilepsies with variable phenotypes

1. Which are the differences between these syndromes?
2. What do they have in common?

Age of onset and overlap of IGE syndromes of childhood and adolescence



What do they have in common?

- The combination, in different proportions, of three types of crises: absences, myoclonic and tonic-clonic seizures;
- The timing of seizures related to: awakening, early morning and relaxing in the late afternoon or early evening;
- Precipitating factors of seizures:
  - Sleep deprivation
  - Excessive use of alcohol
  - Stress
  - Menstruation

1. JUVENILE MYOCLONIC EPILEPSY

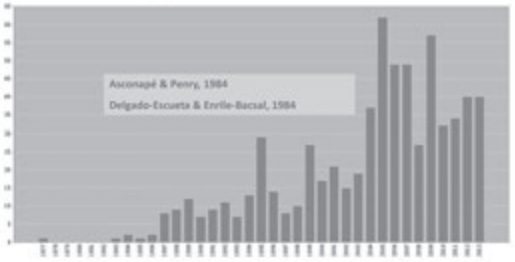
HERPIN-RABOT-JANZ SYNDROME

Herpin, 1867

Rabot, 1899

Janz and Christian, 1957

JME- 670 publications since 1977



Number of publications since 1977 with JME in the title- bibliographic basis Web of Science

Commission on Classification ILAE, 1985

Why Juvenile Myoclonic Epilepsy?

- 10% of all epilepsies; idiopathic (genetic) generalized epilepsy;
- Three seizure types: myoclonic jerks 100%; GTCS 80% and absences 30%;
- Age-dependent photosensitivity: 8-90%;
- Chronosensitivity: upon awakening, mainly in the morning;
- Pharmacosensitivity and pharmacodependence- a lifelong disease?
- 20% pseudo-refractory and 20% refractory to treatment.

✓The general concept among neurologists is that JME is a benign syndrome and seizures are easily controlled with low doses of sodium valproate

JME: What is it really? Nolot Trenité et al., Epilepsy Behav 2013; 28(Suppl 1)

Precipitant factors in JME

Dieter Janz

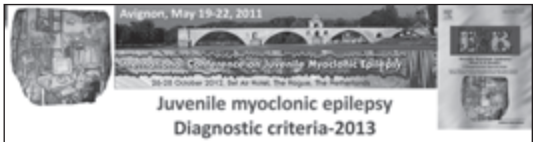
- Unprovoked jerks caused by 'nervousness';
- Medical interview will show that alcohol intake and sleep deprivation are likely precipitant factors; abstinence from alcohol and regular and sufficient sleep will be recommended;
- Such recommendations may, even in the absence of accurate diagnosis, lead to cure.

Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-86

Precipitant factors in JME

- General precipitant factors: sleep deprivation, stress, photic stimulation, among others;
- Endogenous precipitant factors: activation of higher cognitive functions (praxis, language) could precipitate seizures in JME, which would be the most sensitive syndrome to this form of activation.

Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-86
Castells & Mendilaharsu. Acta Neurol Latinoamer 1958; 4:23-48
Delgado-Escueta & Enrile-Bacsal. Neurology 1984; 34:285-94
Asconapé & Penry. Epilepsia 1984; 25:108-14
Inoue et al. In: Wolf P, ed. Epileptic seizures and syndromes, 1994: 81-91
Panayiotopoulos et al. Epilepsia 1994; 35:285-96
Murthy et al. Seizure 1998; 7: 43-7
Inoue & Kubota. In: Schmitz B, Sander T, eds. JME: the Janz syndrome, 2000: 73-81
Wolf & Inoue T. In: Schmitz B, Sander T, eds. JME: the Janz syndrome, 2000: 55-9



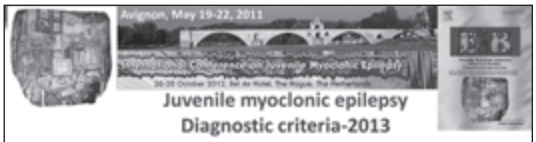
Juvenile myoclonic epilepsy Diagnostic criteria-2013

- **Class I** criteria:
  1. Myoclonic jerks without loss of consciousness repeatedly occurring on awakening, i.e., within 2h after awakening;
  2. EEG (routine, sleep, or sleep deprivation) shows normal background and ictal generalized polyspike-waves with concomitant myoclonic jerks;
  3. Normal intelligence;
  4. Age at onset between 10 and 25 years.

Video

The hallmark of JME

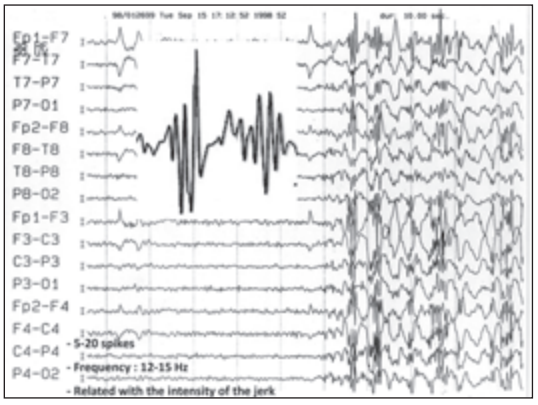
JME: What is it really? Nolet Tremiè et al., Epilepsy Behav 2013; 28(Suppl 1)

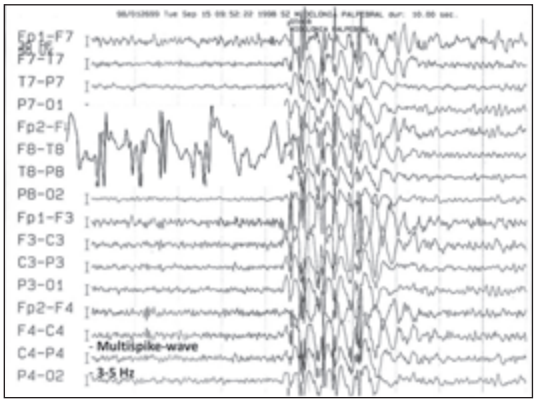


Juvenile myoclonic epilepsy Diagnostic criteria-2013

- **Class II** criteria:
  1. Myoclonic jerks *predominantly* occurring on awakening;
  2. Myoclonic jerks facilitated by sleep deprivation and stress and provoked by *visual stimuli* and *praxis* or GTCSs preceded by myoclonic jerks;
  3. EEG shows normal background *and at least once* interictal generalized spike or polyspike-waves with *some asymmetry* allowed ,with or without myoclonic jerks;
  4. No *mental retardation* or *deterioration*;
  5. Age at onset between *6 and 25 years*.

JME: What is it really? Nolet Tremiè et al., Epilepsy Behav 2013; 28(Suppl 1)



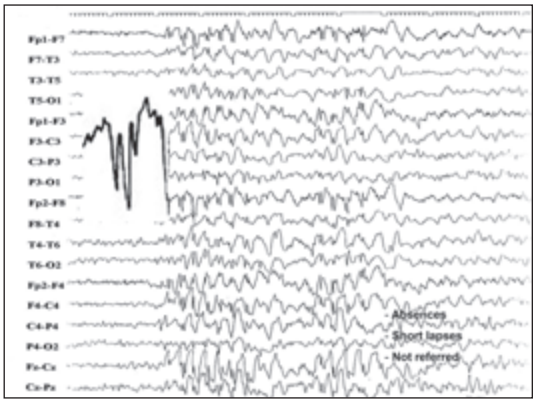


Clonic-tonic-clonic seizures- 80% of the cases

Video

Absences- 30% of the cases

Video



Video-EEG protocol

- Patients are admitted to the Video-EEG Unit in the evening;
- Sleep deprivation (4 hours of sleep);
- Baseline recording, awake, for 30 minutes;
- Eyes-opening and closure for 5 minutes;
- Language tasks: Reading in Portuguese (10 min silently+10 min aloud); Reading in English (10 min silently+10 min aloud); Speaking for 5 min;
- Praxis tasks: Writing for 5 min; Written calculation: 15 x 67 x 23 x 48; Drawing: a house, a family and a clock; Spatial construction (Puzzles 10 min each);
- Mental calculation: 18 – 7, 23 + 46, 11 x 11, 125 ÷ 5;
- Intermittent photic stimulation for 5 min (1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 33, 50 and returning); photosensitivity range;
- Hyperventilation for 5 min and sleep;
- Discharges Indexes.

After Wolf & Meyer

UNIFESP

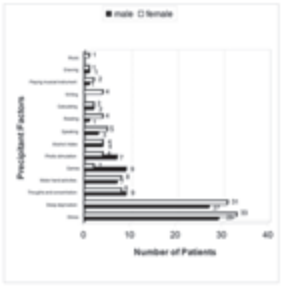
Phenotypic characterization

Self-perception of factors that precipitate or inhibit seizures in juvenile myoclonic epilepsy

- 75 Brazilian patients
- 39 women; 36 men
- 92% identified at least one precipitant factor

Can you avoid seizures?
- 77% unable to avoid the occurrence of seizures
- 22% keeping calm

Self-perception of precipitant factors



- Stress: 62 (83%)
- Lack of sleep: 58 (77%)
- Concentration: 17 (23%)
- Praxis: 15 (20%)
- Photic stimulation: 11 (15%)
- Alcohol intake: 8 (11%)
- Speaking in public: 8 (11%)
- Reading: 5 (6%)

- Premenstrual phase: 33% (3rd place in women)

Juvenile Myoclonic Epilepsy Fundamental questions-2015

- Is it really lifelong? May some patients have their AEDs withdrawn? Who are they?
- Which factors could influence AEDs response and prognosis?
- Phenotypic variations:
  - Photosensitivity?
  - Praxis and language induction?
  - Psychiatric profile?
- Neuroimaging findings?
- Genetic characteristics?

JME: What is it really? Note Trenité et al., Epilepsy Behav 2013; 28(Suppl 1)

PHOTOSENSITIVITY: 30%
EYE-CLOSURE SENSITIVITY: 20%

Video

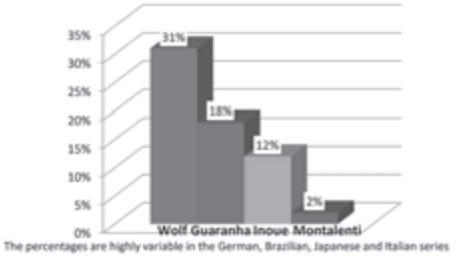
PRAXIS INDUCTION

Video

PERIORAL MYOCLONI

Video

Precipitant factors in JME
Praxis induction



The percentages are highly variable in the German, Brazilian, Japanese and Italian series

Wolf P, Mayer T. Petersfield: Wrightson Biomedical; 2000. p. 34-9.
Guaranha et al. Epilepsia 2009;50:2446-55.
Inoue et al. In: Wolf P, ed. Epileptic seizures and syndromes, 1994: 81-91.
Montalenti et al. J Neurol Sci 2001; 184:65-70.

Precipitant factors in JME
Perioral myoclonia

Ethnic? Linguistic??

Wolf P, Mayer T. Petersfield: Wrightson Biomedical; 2000. p. 34-9.
Guaranha et al. Epilepsia 2009;50:2446-55.
Inoue et al. In: Wolf P, ed. Epileptic seizures and syndromes, 1994: 81-91

Treatment of JME

- Matsuoka et al. (1992): 68% seizure control (n=32). Aggravating factors: focal EEG discharges and NPA;
- Inoue et al. (1994): complete seizure control 31% praxis-induction (n=16) x 69% non-provoked group (N=71);
- Inoue & Kubota (2000): seizure control > 3y: dropped from 69% (only general PF) (n= 77) to 56% in photosensitive (n=32) x 48% in praxis-sensitive patients (n=25);
- Sousa et al. (2005): 4 cases persistance of perioral myoclonia and praxis induction.

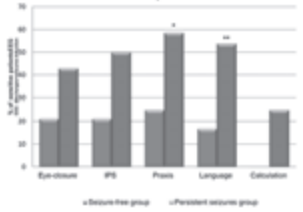
Matsuoka et al. Jpn J Psychiatr Neurol 1992; 46 (2): 293-6
Inoue et al. In: Wolf P, ed. Epileptic seizures and syndromes, 1994: 81-91
Inoue & Kubota. In: Schmitz & Sander. JME: the Janz syndrome, 2000: 73-81.
Sousa et al. Epileptic Dis 2005; 7(2): 123-27

Prognosis of juvenile myoclonic epilepsy is related to endophenotypes

Mirian S.B. Guaranha*, Gerardo M. de Araújo Filho, Kátia Lin, Laura M.F.F. Guilhoto, Luis Otávio S.F. Caboclo, Elza Márcia T. Yacubian

Mirian Guaranha

65 JME patients followed for at least 3 years



Prognosis for patients with reflex traits expressed as EEG discharges and/or seizures induction.
*$p = 0.04$; **$p = 0.026$.

Photosensitivity was only marginally related to the persistence of seizures (50% vs. 21.1% in patients without seizures, $p = 0.064$).

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Psychiatric characterization

Juvenile myoclonic epilepsy 'Personality traits'

Dieter Janz e Walter Christian
1957

"... contrary to 'typical epileptic behaviour', their (JME patients) mental behaviour is very often characterized by unsteadiness, lack of discipline, hedonism and indifference towards their disease... they promise more than they can deliver... Their behaviour often has (negative) effects on their therapy. They will declare that they adhere to all prescriptions, but in fact they forget to attend control visits and to take their medication regularly... Their mood changes rapidly and frequently... They are easy to encourage and to discourage, they are gullible and unreliable..."

Based on clinical observations

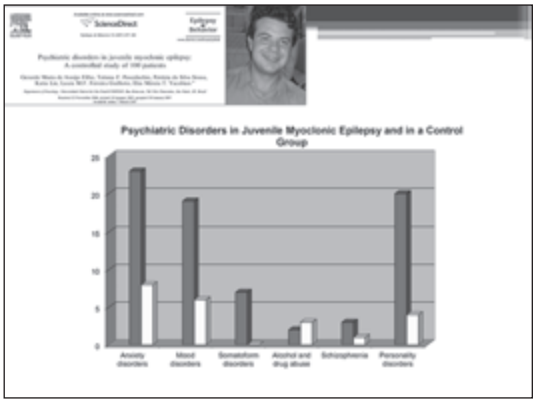
Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-86

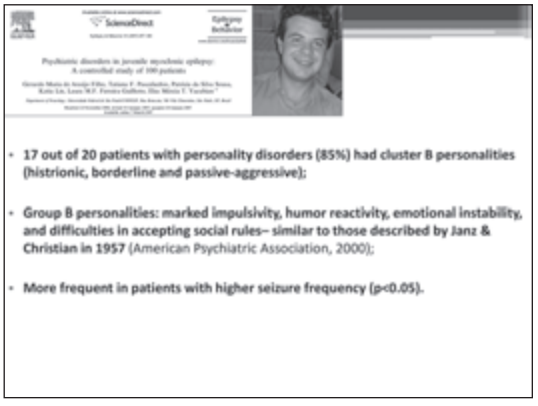
Psychiatric influence on prognosis- DSM-IV

Data from 155 JME patients from Marseille and Nice

58.3% had psychiatric problems	Only 19% had psychiatric problems
Difficult to treat patients	Good response to adequate AED

Genton et al. Epilepsia 1999;40(Suppl 2):S2-12.





- **17 out of 20 patients with personality disorders (85%) had cluster B personalities (histrionic, borderline and passive-aggressive);**
- **Group B personalities: marked impulsivity, humor reactivity, emotional instability, and difficulties in accepting social rules– similar to those described by Janz & Christian in 1957** (American Psychiatric Association, 2000);
- **More frequent in patients with higher seizure frequency ($p<0.05$).**

Psychotherapy

UNIFESP

- Psychotherapy may lead to seizure freedom even in pharmaco- and counseling- resistant patients

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2. JUVENILE ABSENCE EPILEPSY

2. Juvenile absence epilepsy

- Onset 7-16 years (peak 10-12);
- Absences: less important impairment of consciousness;
- 9-10/day – spanioleptic absences;
- Absences are the predominant type of seizures, although most patients experience myoclonia and rare tonic-clonic seizures;
- This type of epilepsy does not present remission, although absences improve with age as to degree of impairment of consciousness, duration and frequency.

Panayiotopoulos et al., 1989

Video

ABSENCE IN JUVENILE ABSENCE EPILEPSY

Longer duration (16,3±7,1s in juvenile absence epilepsy, childhood absence 12,4±2,1s in the epilepsy and 6,6±4,2 in juvenile myoclonic epilepsy)

Panayiotopoulos CP, Obeid T, Waheed G. Ann Neurol 1989;25(4):391-7.

3. EPILEPSY WITH GENERALIZED TONIC-CLONIC SEIZURES ON AWAKENING

Epilepsy with generalized tonic-clonic seizures on awakening (tonic-clonic seizures only?)

- Generalized tonic-clonic seizures on awakening;
- For some this name should be restricted to the pure form of generalized tonic-clonic seizures that occur 1-2 hours after awakening;
- The awakening independent of time of day, there is a second peak in the relaxation period at the end of the day (> 90% of the time);
- Sleep deprivation, fatigue and over-consumption of alcohol.

Janz, 1994; ILAE Commission, 1989; Wolf & Goosses, 1986; Engel 2001

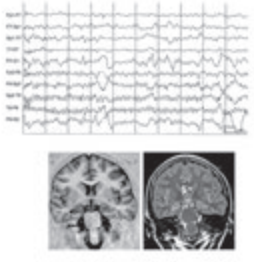
Epilepsy with generalized tonic-clonic seizures on awakening (tonic-clonic seizures only?)

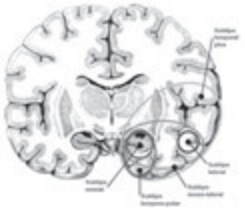
- Seizure frequency is low. Six seizures (?). <6 oligoepilepsies;
- With this definition, this syndrome is extremely rare;
- More benign than JME: less frequent seizures, less sensitivity to these precipitating factors;
- Photosensitivity is common (13% of cases) and response to therapy is satisfactory.

Janz, 1994; ILAE Commission, 1989; Wolf & Goosses, 1986; Engel 2001

MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

SUBTYPES OF TEMPORAL LOBE EPILEPSY



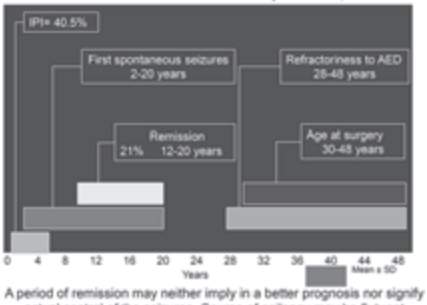


MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

- Hippocampal epilepsy (mesiobasal limbic or rhinencephalic or psychomotor epilepsy)
- Comprises 70-80% of all temporal lobe epilepsies;
- Most common epilepsy type in adults;
- Initial precipitant injury in 50% of the cases- febrile seizures;
- Better surgical outcomes; 80% of patients are currently operated without invasive monitoring.

Commission on Classification ILAE, 1981; French et al., 1983

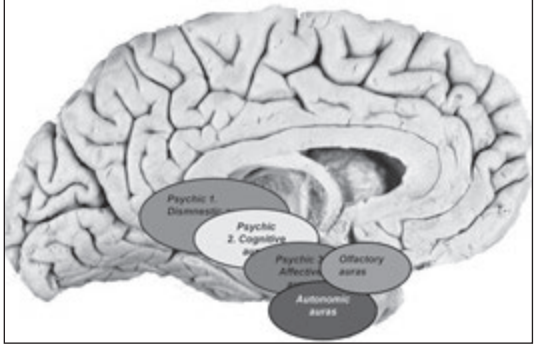
Course of epilepsy related to mesial temporal sclerosis in 180 patients
Miyashira et al., 2004



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

ELECTROCLINICAL CHARACTERISTICS

SEMIOLOGY OF COMPLEX PARTIAL SEIZURES (DISCOGNITIVE) - AURAS



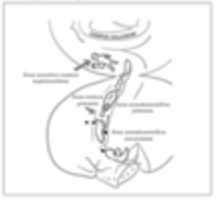
Video

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.

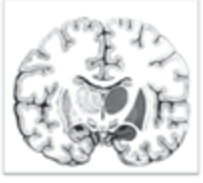
• Somatosensory auras (18) and visual auras (27): Engel II, III and IV



THE MEANING OF DYSTONIC POSTURE IN TLE-HS

Video

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

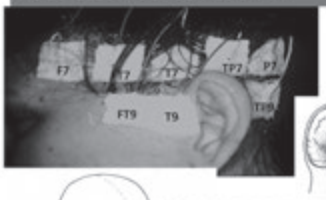
CPC – CTCG

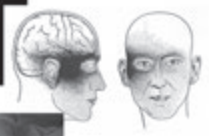
• Indicative of poor surgical prognosis?

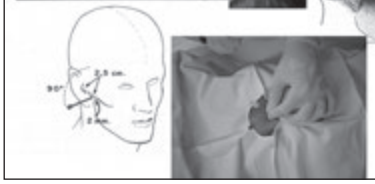
Not in our series (161 cases) 2 and 5 years after surgery

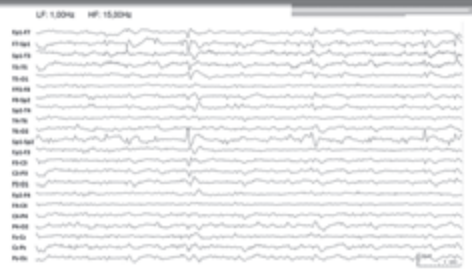
Dal-Cól *et al.*, 2008; Bossi *et al.*, 1980; Janszky *et al.*, 2005; Uchida et al., 2013

VIDEO-ELECTROENCEFALOGRAM

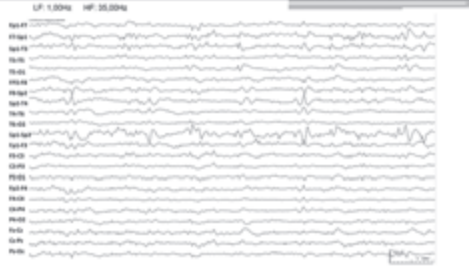






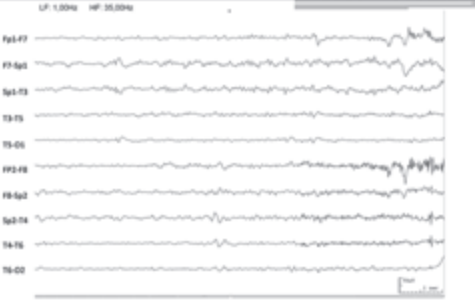


EPILEPTIFORM DISCHARGES LEFT TEMPORAL LOBE

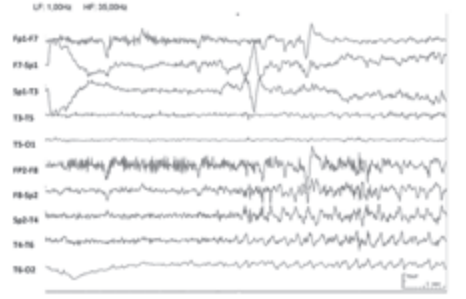


EPILEPTIFORM DISCHARGES RIGHT TEMPORAL LOBE

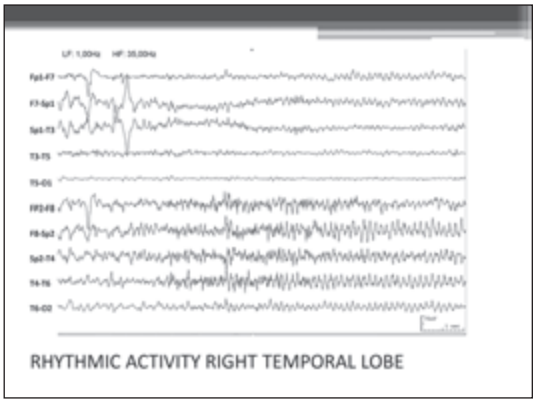
65% of cases bilateral epileptiform discharges



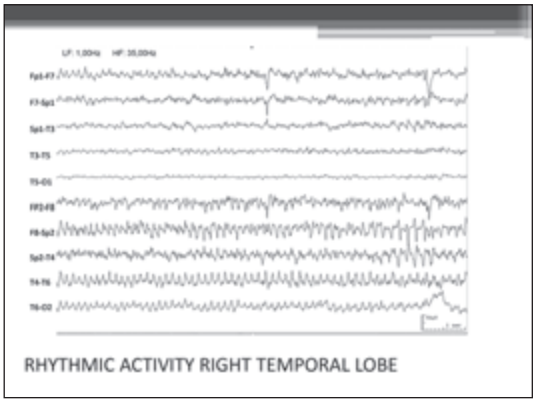
ICTAL ONSET RIGHT TEMPORAL LOBE



RHYTHMIC ACTIVITY RIGHT TEMPORAL LOBE



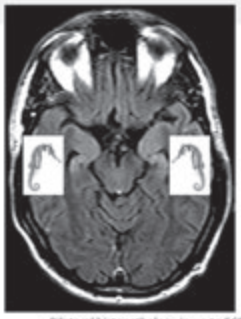
RHYTHMIC ACTIVITY RIGHT TEMPORAL LOBE

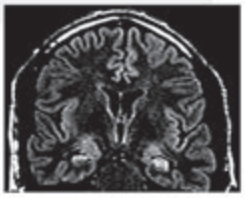


RHYTHMIC ACTIVITY RIGHT TEMPORAL LOBE

IMAGING CHARACTERISTICS

CLASSICAL HIPPOCAMPAL SCLEROSIS

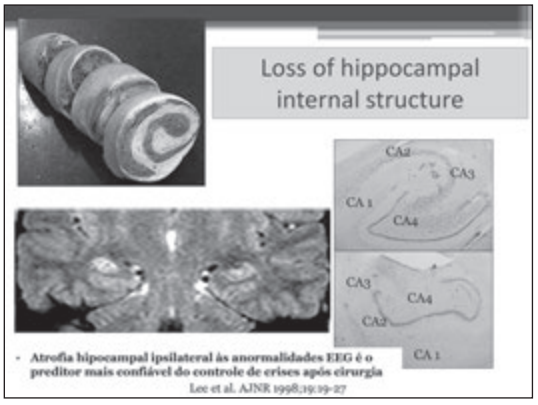


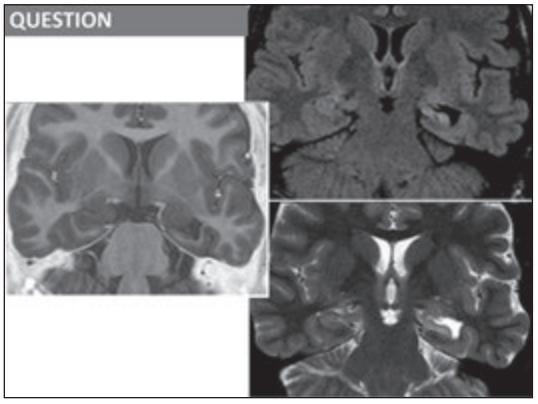


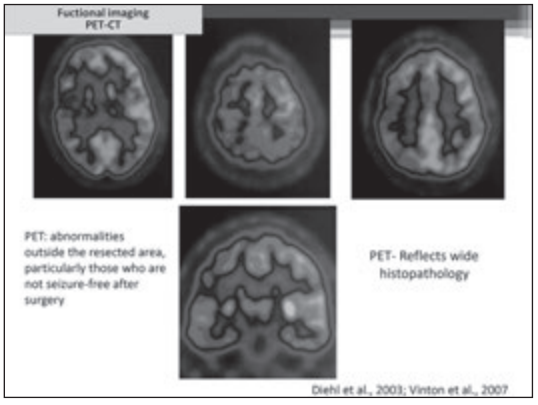
- Hippocampal atrophy
- Loss of internal structure
- T1 hyposignal
- T2 hypersignal

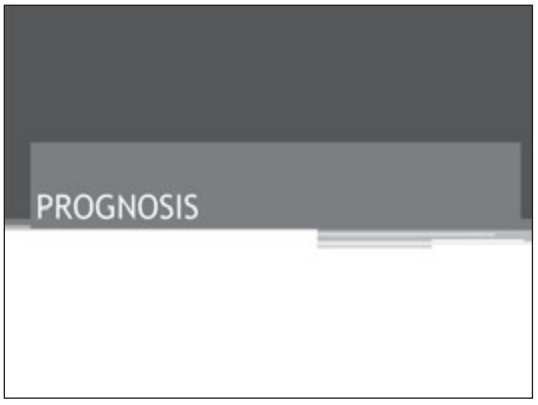
Bilateral histopathology in up to 56%, although often asymmetric

Meencke et al., 1996; Margerison & Corsellis, 1966; Quigg et al., 1997


Loss of hippocampal internal structure
CA2
CA3
CA 1
CA4
CA3
CA4
CA2
CA 1
- Atrofia hipocampal ipsilateral às anormalidades EEG é o preditor mais confiável do controle de crises após cirurgia
Lee et al. AJNR 1998;19:19-27

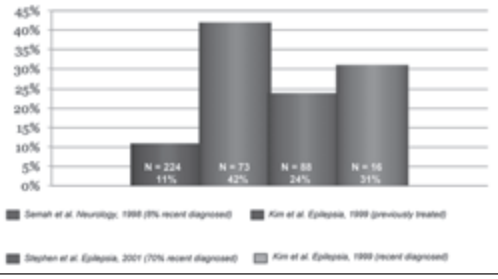

QUESTION


Fuctional imaging
PET-CT
PET: abnormalities outside the resected area, particularly those who are not seizure-free after surgery
PET- Reflects wide histopathology
Diehl et al., 2003; Vinton et al., 2007


PROGNOSIS

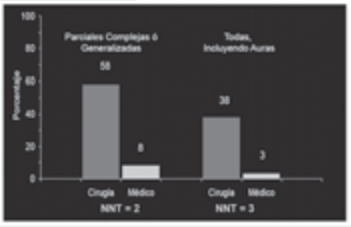
HIPPOCAMPAL SCLEROSIS

Percentage of patients who get control of seizures with AED




The New England Journal of Medicine

SURGICAL TREATMENT



NUMBER OF PATIENTS SEIZURE FREE AFTER 12 MONTHS

[1] Schmidt et al. Epilepsia 2004;45:179-186

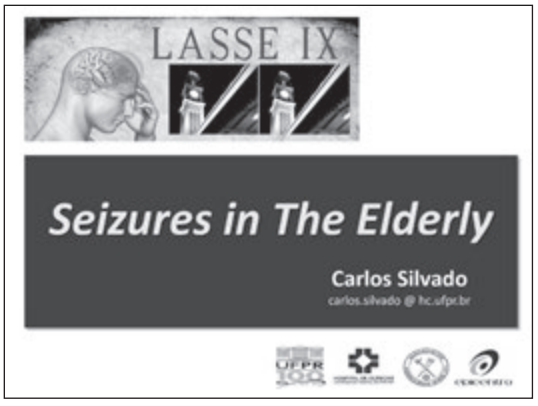
CONCLUSIONS

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

Thank you very much!

Carlos Silvado (Brazil)

SEIZURES IN THE ELDERLY



The Elderly

"The ageing process is of course a biological reality which has its own dynamic, largely beyond human control.

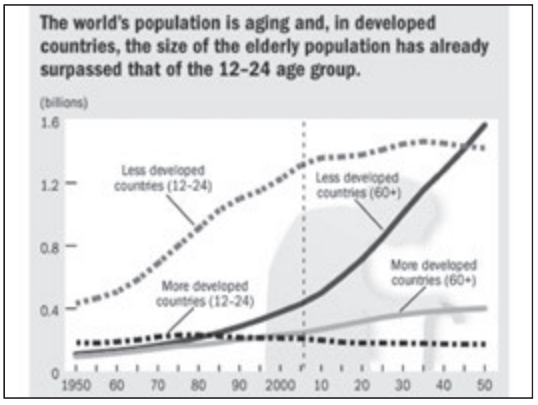
The age of 60 or 65, roughly equivalent to retirement ages in most developed countries, is said to be the beginning of old age..."

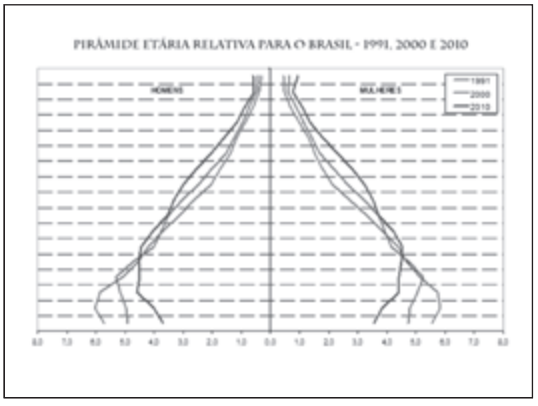
www.who.int/healthinfo/survey/ageingdefnolder/en/index.html

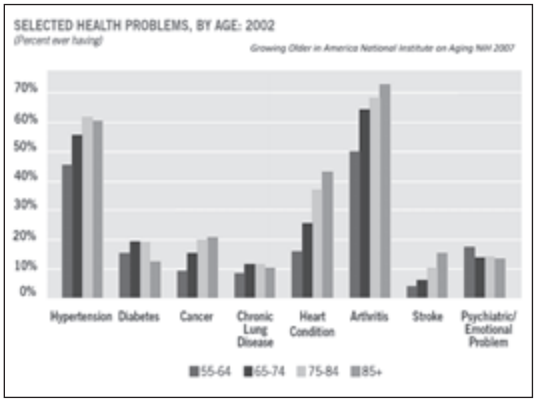
It has been suggested that the first person to live up to 150 years may have already been born.

Brit, 100, is world's oldest marathon runner

What define one person must be the functional, cognitive and clinical condition, not the years of age.


The world's population is aging and, in developed countries, the size of the elderly population has already surpassed that of the 12–24 age group.
(billions)
1.6
1.2
0.8
0.4
0
Less developed countries (12–24)
Less developed countries (60+)
More developed countries (60+)
More developed countries (12–24)
1950 60 70 80 90 2000 10 20 30 40 50


PIRÂMIDE ETÁRIA RELATIVA PARA O BRASIL - 1991, 2000 E 2010


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


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

The Aged Brain: Normal Aging

- Gray matter volume in aging brains can decrease due to cell shrinkage or compaction, not necessarily cell loss.
- Largely retained cell number during aging has prompted reevaluation of long-standing hypotheses of age-related cell loss as causal for age-related impairments in brain functioning.
- Age-related functional declines may reflect, in part, neuronal dysfunction (e.g., receptor or synapse loss, signal transduction deficits) instead of neuronal death.

Long et al. - J Gerontol 1999

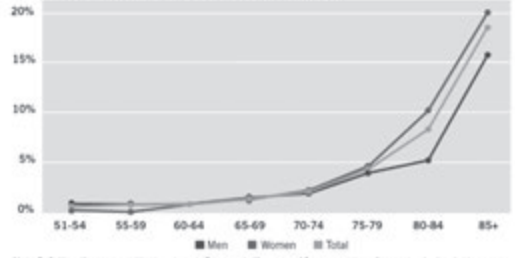
Normal Aging and Brain Physiology

Intracellular recordings of aged rats hippocampal neurons indicate that most biophysical properties do not change with age, including:

- membrane time constant
- resting membrane potential
- input resistance
- EPSP rise time and half width amplitude and duration of Na+- and Ca2+-mediated AP

Rosenzweig & Barnes - Prog Neurobiol 2003

FIG. 1-4
SEVERE COGNITIVE LIMITATION, BY AGE AND GENDER: 1998



Note: Definition of severe cognitive impairment: Errors on half or more of 9 very easy items from a standard geriatric screen for mental status for self-respondents, IQCODE score of 3.9 or higher on Jorm proxy assessment.

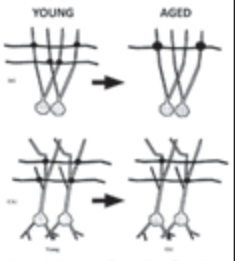
Source: HRS 1998.

The neurobiology of aging

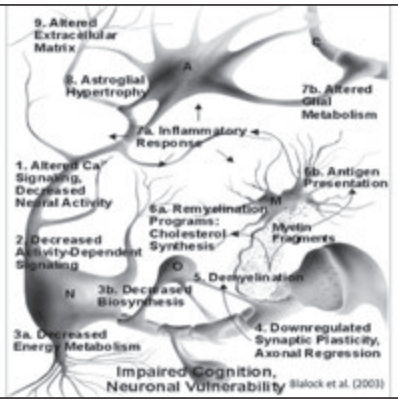
K.M. Kelly[a,*], N.L. Nadon[b], J.H. Morrison[c], O. Thibault[d], C.A. Barnes[e], E.M. Blalock[d]

Epilepsy Research 685 (2006) 55–520

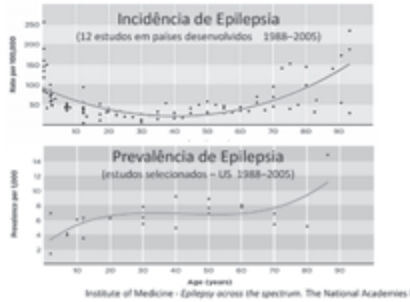
Apical and basal dendrites from monkey pre-frontal cortex



Schematic diagram of granule cells in the hippocampus of rats

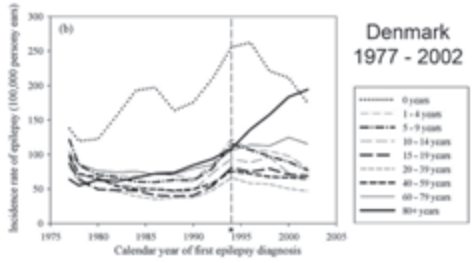


Epilepsia Através das Idades



Institute of Medicine - *Epilepsy across the spectrum*. The National Academies Press 2012

Incidence of Epilepsy in Elderly



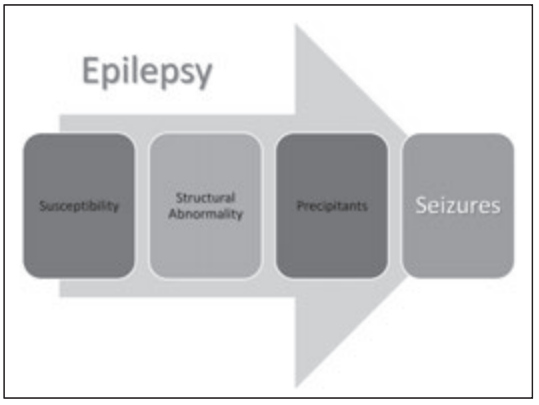
Christensen J et al. – Epilepsy Res. 2007

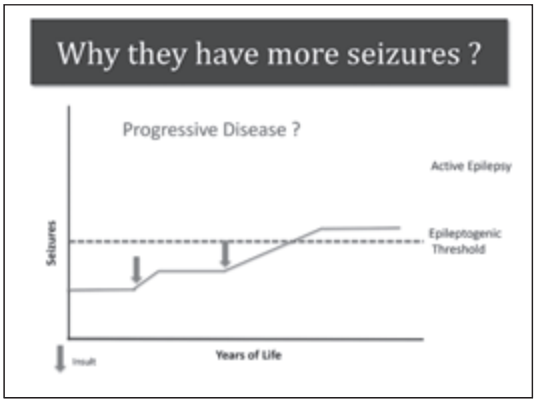
Incidence of Epilepsy in Elderly

Campinas and São Jose do Rio Preto:

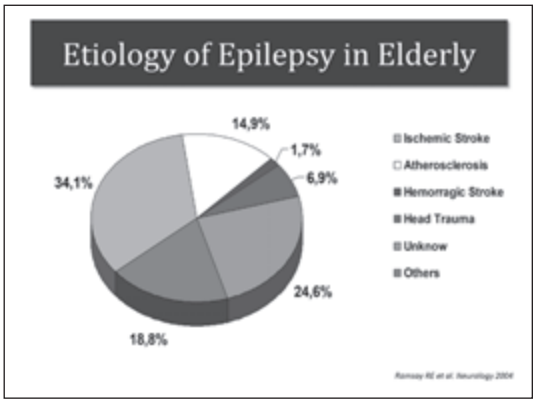
- 96300 people of all age
  - prevalence of active epilepsy = 5.4/1,000
  - "Treatment Gap" = 38%
- 60 years or more
  - prevalence of active epilepsy = 8,5 / 1,000
  - "Treatment Gap" = 51%

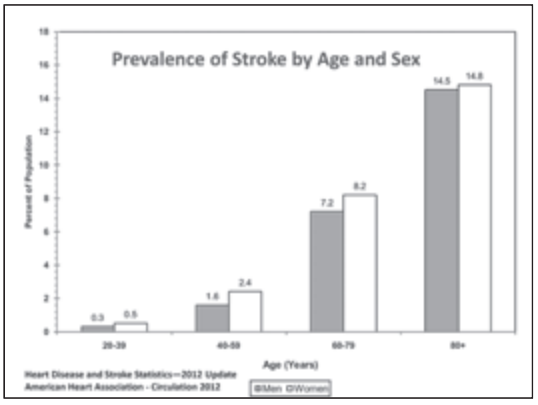
Noronha AL et al. – Epilepsia 2007


Epilepsy
Susceptibility
Structural Abnormality
Precipitants
Seizures


Why they have more seizures ?
Progressive Disease ?
Active Epilepsy
Epileptogenic Threshold
Seizures
Years of Life
Insult


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


Etiology of Epilepsy in Elderly
14,9%
1,7%
6,9%
34,1%
24,6%
18,8%
Ischemic Stroke
Atherosclerosis
Hemorragic Stroke
Head Trauma
Unknow
Others



Poststroke Epilepsy in the Elderly

- ~15% of stroke survivors will have an unprovoked seizure within 5 years after stroke.
- Risk of developing epilepsy remains significantly elevated for at least 20 years after stroke.
- More frequent with hemorrhagic infarcts than with ischemic infarcts.
- Typically associated with large cortical infarcts
- Watershed infarcts most likely to provoke acute seizures.
- Both early and initial late seizures are associated with an increased risk of epilepsy (recurrent unprovoked seizures

Kelly K – AES Meeting 2010

Post Stroke Epilepsia

Epilepsy Prevalence for Medicare beneficiaries, 2005:
10 states with the highest epilepsy prevalence in and not in the "Stroke Belt".

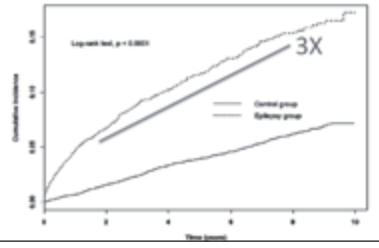
Pisu M et al. Epilepsia 2012

Stroke Belt
States among the 10 with the highest epilepsy prevalence and in the Stroke Belt
States among the 10 with the highest epilepsy prevalence not in the Stroke Belt

Increase Risk for Stroke in Epilepsy Patients

3812 newly diagnosed with epilepsy x 15,248 nonepilepsy matched according to sex, age, and index year
(Taiwan National Health Insurance claims data 2000-2008)

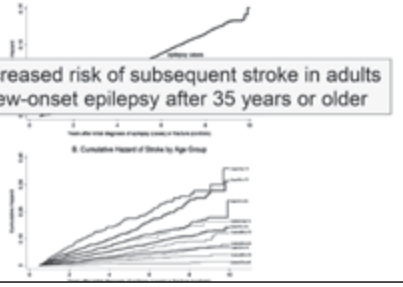
Chang C et a. Seizure 23 (2014) 377–381



Stroke after adult-onset epilepsy

South Carolina hospital discharge and emergency department (ED) data (2000 to 2011) - 21,035 cases with epilepsy and 16,638 controls

Wannamaker B et al. Epilepsy & Behavior 43 (2015) 93–99

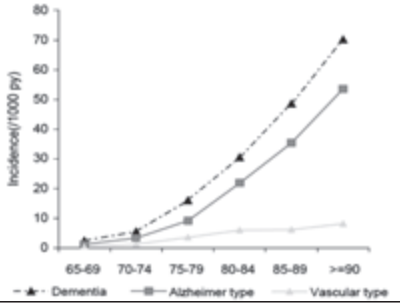


60% increased risk of subsequent stroke in adults with new-onset epilepsy after 35 years or older

EURODEM

(European Community Concerted Action Epidemiology an Prevention of Dementia)

Borr C et al. Eur Neuropsychopharmacol 2005

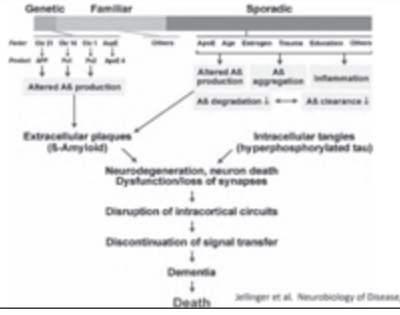


Seizures in Alzheimer's Disease

- 1.5% of patients with AD developed seizures during a mean of 3.7 years follow-up.
- Most were generalized convulsions and nonrecurrent
- Younger age was associated with higher risk
- No association between seizures and either estimated disease duration or cognitive or functional performance.
- Unprovoked seizures are uncommon in AD but occur more frequently than in the general population

Scarmeas et al. - Arch Neurol 2009

Physiopathology of AD



Jellinger et al. Neurobiology of Disease, 2007

Epilepsia and Dementia

What is the relationship ?

- Elderly has a increased risk of seizures and co-morbilities who could cause it
- Seizures do not occur in most of cases of Alzheimer
- Generalized epilepsy do not cause progressive cognitive deficit, only temporal epilepsy with mesial temporal sclerosis

Two not related concomitant diseases ?

Table 1. Human AD gene mutations leading to elevated Aβ and epilepsy

Noebels J. Epilepsia 2011

Gene	Mutation	Phenotype	Reference
APP	Val1717gly	Seizures	Rossor et al. (1993)
APP	Thr714Ala	Seizures	Lindquist et al. (2008)
APP	Duplication	Seizures	Cabrejo et al. (2006)
APP	Trisomy 21	Seizures	Menendez (2005)
Presenilin 1	M139V	Seizures	Fox et al. (1997)
Presenilin 1	IS169L	Seizures	Takao et al. (2001)
Presenilin 1	L420R	Seizures	Shrimpton et al. (2007)
Presenilin 1	E280A	Seizures	Velez-Pardo et al. (2004)
Presenilin 1	Multiple	Seizures	Larner (2010)
Presenilin 2	M239V	Seizures	Marcon et al. (2004)
Presenilin 2	N141L	Seizures	Jayadev et al. (2010)

Epilepsia and Dementia

What is the relationship ?

- Seizures are more frequent in AD, mostly in early AD
- Animals models of AD have a high incidence of epilepsy associated to mutations of APP/Aβ pathway

Two presentations of the same disease ?

Future Neurol. 2012 March 1; 7(2): 177–192. doi:10.2217/fnl.12.8.

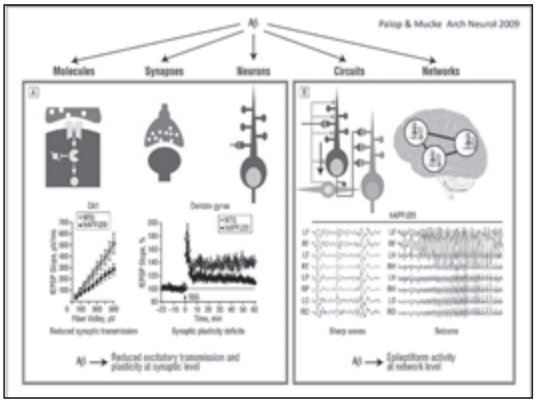
Alzheimer's disease and epilepsy: insight from animal models

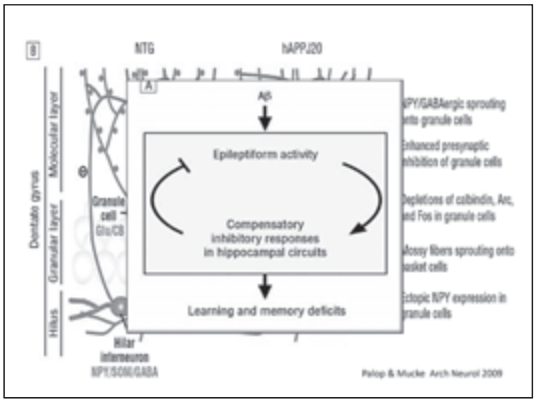
Helen E Scharfman

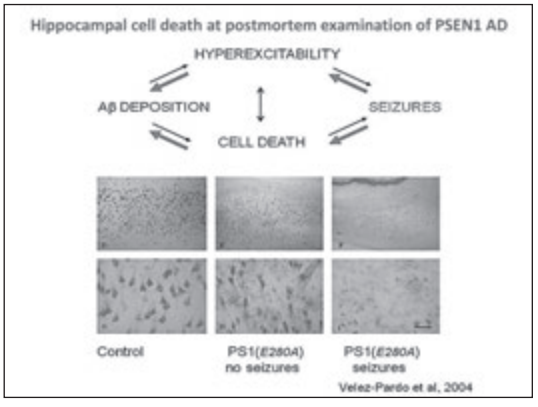
confluence of hyperexcitability,
compensatory hyperinhibitory,
excitotoxicity and abnormal networks

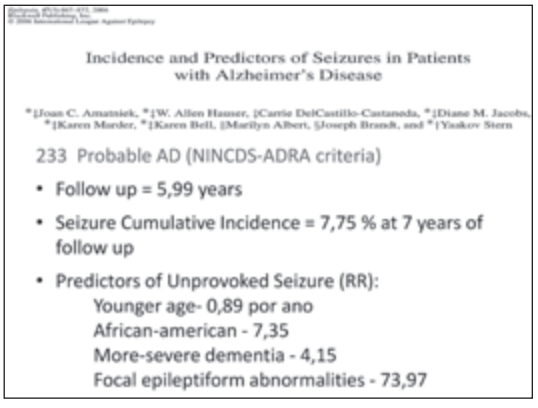
Alzheimer's Disease and Neuronal Network Activity

Marc Gleichmann · Mark P. Mattson









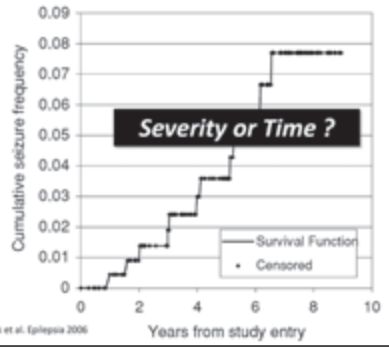
Incidence and Predictors of Seizures in Patients with Alzheimer's Disease

*‡Joan C. Amatniek, *‡W. Allen Hauser, ‡Carrie DelCastillo-Castaneda, *‡Diane M. Jacobs, *‡Karen Marder, *‡Karen Bell, §Marilyn Albert, §Joseph Brandt, and *†Yaakov Stern

233 Probable AD (NINCDS-ADRA criteria)

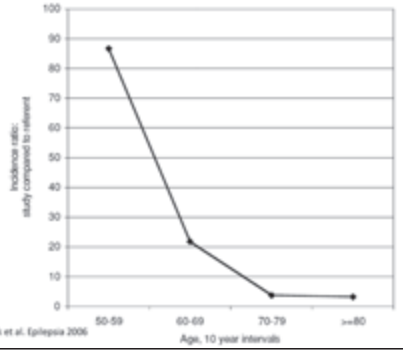
- Follow up = 5,99 years
- Seizure Cumulative Incidence = 7,75 % at 7 years of follow up
- Predictors of Unprovoked Seizure (RR):
  - Younger age- 0,89 por ano
  - African-american - 7,35
  - More-severe dementia - 4,15
  - Focal epileptiform abnormalities - 73,97

Cumulative incidence of seizures in Alzheimer disease



Amantniek et al. Epilepsia 2006

Incidence ratio by age: observed compared with expected



Amantniek et al. Epilepsia 2006

A β + Seizures

Basic research in epilepsy and aging

Ilo E. Leppik[a,*], Kevin M. Kelly[b], Leyla deToledo-Morrell[c], Peter R. Patrylo[d], Robert J. DeLorenzo[e,1], Gary W. Mathern[f], H. Steve White[g]

Epilepsy Research 685 (2006) 521–537

Geriatric epilepsy: Research and clinical directions for the future☆

Erik D. Roberson[a,b], Omotola A. Hope[c], Roy C. Martin[a,*], Dieter Schmidt[d,**]

Epilepsy & Behavior 22 (2011) 103–111

International Review of Neurobiology

Volume 81, Pages 1-343 (2007)

The Neurobiology of Epilepsy and Aging

Edited by R. Eugene Ramsay, James C. Cloyd, Kevin M. Kelly, Ilo E. Leppik and Emilio Perucca

Animal Models of Geriatric Epilepsy

Lauren J. Murphree[a,1], Lynn M. Rundhaugen[b], Kevin M. Kelly[b]

Animal Models in Gerontology Research

Nancy L. Nadon

Cooperative Study VA # 428

128 epileptic patients

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

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

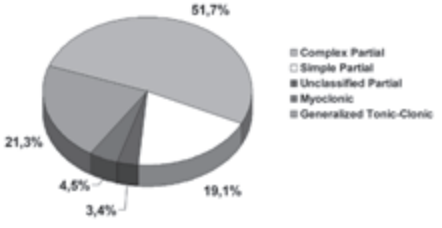
Epilepsy in Elderly

Why the diagnosis is difficult ?

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

Epilepsy in Elderly

Types of Epileptic Seizures



Key questions for elderly patients and witnesses when assessing a suspected epileptic seizure

Ask the patient	Ask the witness
What were you doing at the time?	What was the patient doing at the time?
Did you get any warning?	Did you notice or did the patient complain of anything before the event happened?
Did you "black out"? If so, for how long?	Did they lose consciousness, have altered responsiveness, or seem unaware of your presence? If so, for how long did this last?
What happened afterwards?	Were they still or did they jerk, twitch, or move?
Do you take any medications and have any been changed recently?	What happened after the event?
Was there a witness?	Did anyone try to take the pulse?

Adapted from "Epilepsy in later life—a good practice guide",* with permission from Epilepsy Scotland.

Table 1: Key questions for elderly patients and witnesses when assessing a suspected epileptic seizure

Brodie M et al. Lancet Neurol 2009

Epileptic Seizures in the Elderly

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

First seizure in the older patient: Clinical features and prognosis

Nicholas Lawn*, Andrew Kelly, John Dunne, Judy Lee, Andrew Wesseldine Epilepsy Research (2013) 107, 109—114

Hospital-based first seizure service (2000-2011)

	Age ≥65 ys	Age 16-64 ys
Number of cases	139 (13,8%)	869 (86,2%)
Cumulative probability of seizure recurrence		
One Year	53%	48
Two Years	60%	54%
Five Years	75%	61%
Mean days to seizure recurrence (median)	362	273
Injury with initial / second seizure (%)	14 / 4	26 / 15 *

* P = 0,304

VEEG in Elderly

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

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

McBride et al. - Epilepsia 2002

Non Epileptic Seizure in Elderly

Late onset psychogenic nonepileptic attacks

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

Duncan R et al – Neurology 2006

EEG patterns compatible with nonconvulsive status epilepticus are common in elderly patients with delirium: a prospective study with continuous EEG monitoring

Epilepsy & Behavior 36 (2014) 18–21

Gilles Naeije [a,*], Chantal Depondt [a], Claire Meeus [a], Kestsh Korpak [b], Thierry Pepersack [b], Benjamin Legros [a]

Patients over 65 years old presenting with delirium in the emergency room were prospectively included and underwent either routine 20-minute EEG or cEEG within 24 h after admission

	24 hs EEG	20 min EEG
Number of Cases	32	32
Age (years)	83	81
History of epilepsy	1	4 *
Epileptiform Activities (%)	44 %	22%
Non Convulsive Status Epilepticus	28%	6%
GPED	16%	6%
3-Hz Spike Wave	3%	
PLEDS	3%	
BIPLEDS	3	
Interictal Discharges	16%	16%

Epilepsy in Elderly

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

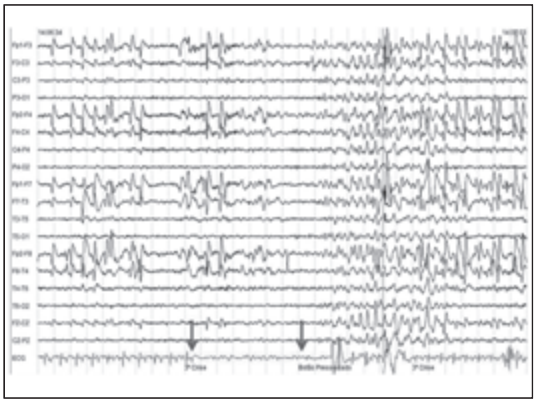
Epilepsy in Elderly

Elderly Normal EEG

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

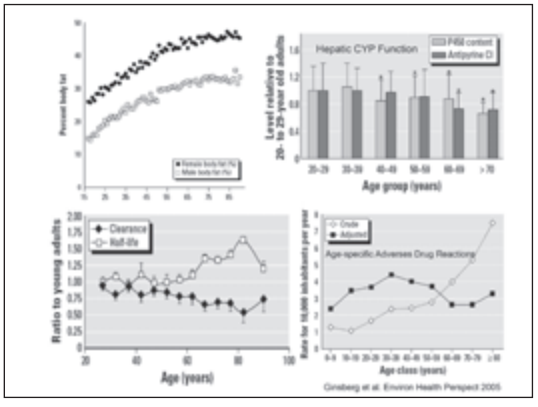
CF, 78 anos, fem

6 months of seizures instead CBZ and PHT



Epilepsy in the Elderly

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



Ginsberg et al. Environ Health Perspect 2005

Metabolização DAEs em Idosos

Antiepiléptico	% Médio de Redução do Clearence Oral	Eliminação Hepática (%)	Eliminação Renal (%)
Valproato	40	> 95	
Fenobarbital	22	75	25
Fenitoina	20-30	> 90	
Carbamazepina	25-40	> 90	
Lamotrigina	37	90	
Topiramato	20	30-50	50-70
Oxcarbazepina	25-35	45	45
Gabapentina	30-50		100
Vigabatrina	30-50		100
Levetiracetam	20-40		> 90

Adaptado de Perucca et al. 2006 e French & Gidal Epilepsia 2000; 41(suppl 8):S30-36

Outcomes by Age at Starting Treatment in Newly Diagnosed Epilepsy

90 newly diagnosed epilepsy
64% seizure free for at least 12 months on modest doses 1st prescribed AED

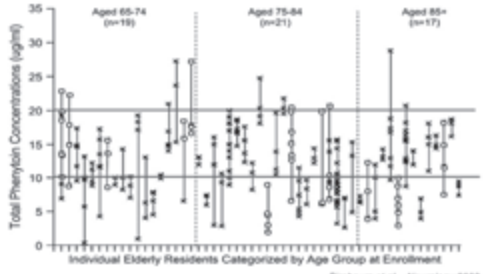
Patients	Age (ys)	N	Remission (%)	Relapse (%)	Uncontrolled (%)
Adolescent	< 20	170	65	12	23
Adult	20-64	520	53	4	43
Elderly	> 64	90	85*	1	14

* Remission rates in elderly patients versus adolescents and adults $p < 0.001$

☆

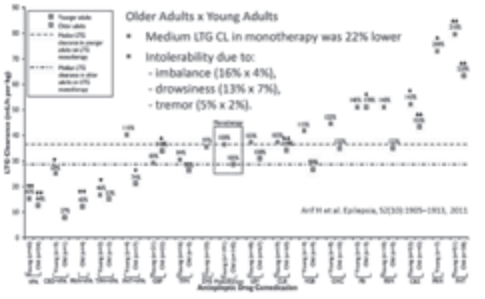
Brodie & Stephen - Int Rev Neurobiol 2007

Phenytoin in Elderly



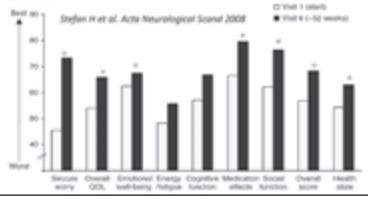
Birnbaum et al. - Neurology 2003

Lamotrigine in the Elderly



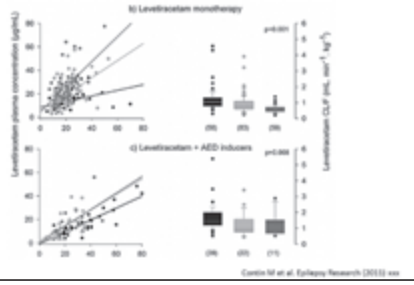
Topiramate in Elderly

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



Levetiracetam in Elderly

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

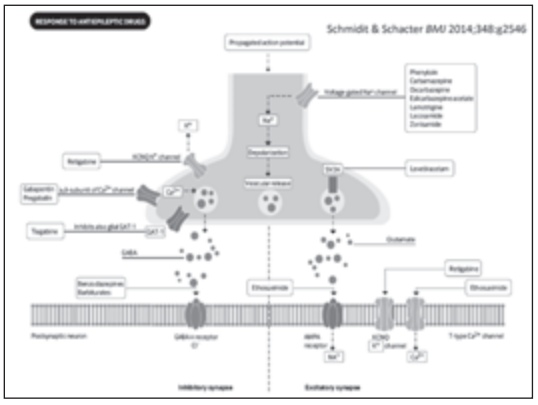


Epilepsy in Elderly

Reason to Choice the AED

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

Global Health Condition



Qual DAE Escolher ?

18-center, randomized, double-blind, double dummy, parallel study of 593 elderly subjects with newly diagnosed seizures
GBP 1,500 mg/day, LTG 150 mg/day, CBZ 600 mg/day
VA Cooperative Study 428 Group

Rowan et al., Neurology 2005

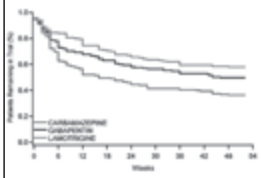


Figure 2. Percentage of patients remaining in the trial over time (52 weeks).

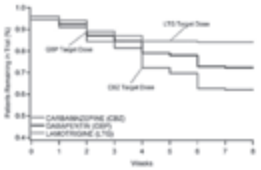


Figure 3. Percentage of patients remaining in the trial over time (6-week titration time).

Epilepsy in Elderly

Response to first antiepileptic drug in elderly people with newly diagnosed epilepsy

AED	*n*	Seizure-free	Uncontrolled	Not tolerated
Carbamazepine	39	26 (67%)	8	5
Lamotrigine	35	22 (63%)	7	6
Sodium valproate	23	15 (65%)	6	2
Oxcarbazepine	13	7 (54%)	5	1
Phenytoin	6	3 (50%)	3	0
Gabapentin	1	1 (100%)	0	0
Total	117	74 (63%)	29	14

Stephen L et al. Epilepsy Behav 2006

Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease

Epilepsy & Behavior 17 (2010) 461–466

Eduardo Cumbo *, Leonarda D. Ligori

Prospective, randomized, three-arm parallel-group, case–control study of 95 patients

	LEV (*n* = 38)		PB (*n* = 28)		LTG (*n* = 29)	
	n	%	*n*	%	*n*	%
Seizure-freedom	11	28.95	8	28.57	7	24.13
50–99% reduction	16	42.05	10	35.71	10	34.48
Total responders	27	71.08	18	64.28	17	58.62
Increased seizures	0	0	0	0	0	0

	ADAS-Cog score (SD)			Difference (12 months/baseline)
	Baseline	6 months	12 months	
LEV	58.29 (2.750)	58.29 (2.750)	58.06 (2.578)	−0.23/0.690
PB	56.48 (3.666)	56.65 (3.668)	56.65 (3.868)	+0.174/0.491 ↓
LTG	56.52 (3.664)	56.64 (3.740)	57.20 (3.547)	+0.680/0.627 ↓
Controls	57 .02 (3.089)	54.03 (3.086)	53.10 (3.128)	−3.92/1.816

What is the best AED ?

Evidences, Clinical Trials and Day-to-Day Available - Brazil 2015

1st → Lamotrigine or Gabapentine or Carbamazepine

2nd → Valproate or Oxcarbazepine or Topiramate

3rd → Phenytoin or Phenobarbital

Lacosamide ?

Epilepsy in the Elderly

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

Outcomes by Age at Starting Treatment in Newly Diagnosed Epilepsy

90 newly diagnosed epilepsy
64% seizure free for at least 12 months on modest doses 1st prescribed AED

Patients	Age (ys)	N	Remission (%)	Relapse (%)	Uncontrolled (%)
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Elderly	> 64	90	85*	1	14

* Remission rates in elderly patients versus adolescents and adults $p < 0.001$

☆

Brodie & Stephen - Int Rev Neurobiol 2007

Don´t forget ...

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

No more seizures. What to do ?

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

Epilepsy Surgery in Elderly

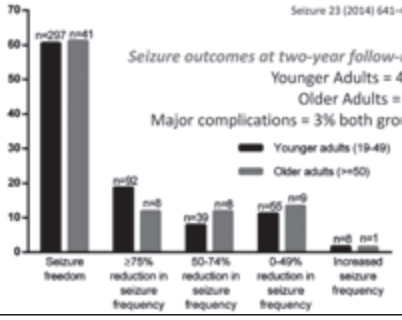
Medically Refractary Epilepsy

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

Outcomes after resective epilepsy surgery in patients over 50 years of age in Sweden 1990–2009 – A prospective longitudinal study

Fatima Bialek [a], Bertil Rydenhag [a], Roland Flink [b], Kristina Malmgren [a,*]

Seizure 23 (2014) 641–645



Seizure outcomes at two-year follow-up

Younger Adults = 491

Older Adults = 67

Major complications = 3% both group

Case 1

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

Jose, 76 years old

Possible Epileptic Seizure

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

Jose, 76 years old

Possible Epileptic Seizure

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

Case 2

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

Beatriz, 82 years old

Symptomatic Localized Epilepsy

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

Beatriz, 82 years old

Symptomatic Localized Epilepsy

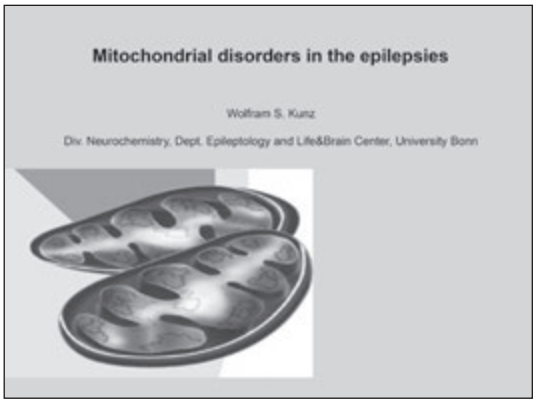
- What I did ?
  - Started valproate 250 → 500 mg/day in 30 days
  - Reduced phenytoin. Stopped it in 30 days
  - Vitamin D 400 IU daily

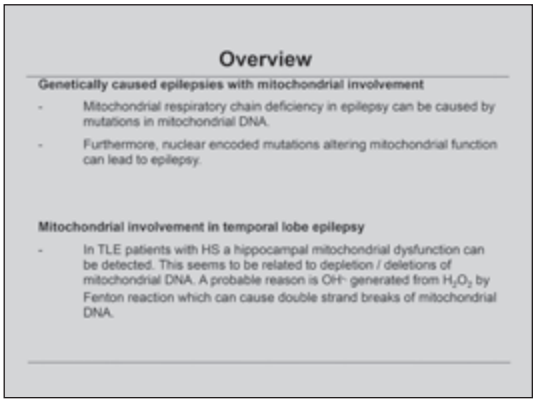
Alon Friedman (Canada/Israel)

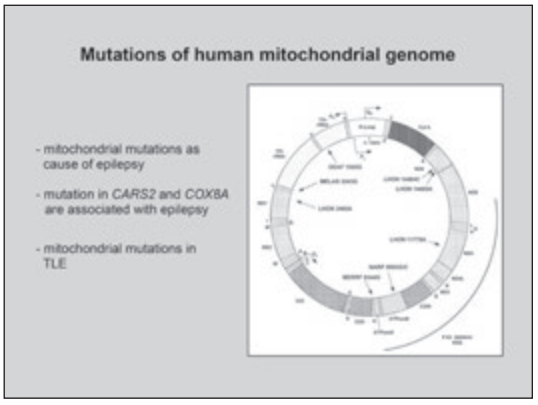
ROLE OF INFLAMMATION IN EPILEPTOGENESIS

Wolfram Kunz (Germany)

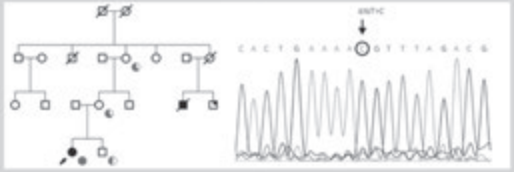
MITOCHONDRIAL DISORDERS IN THE EPILEPSIES



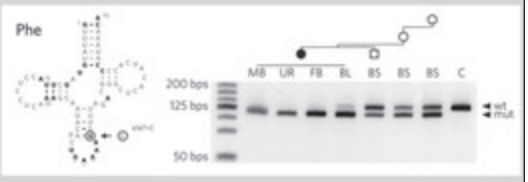




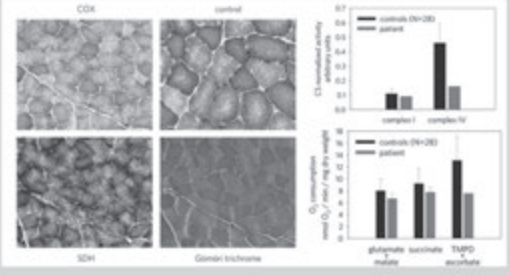
Homoplasmic $tRNA_{Phe}$ mutation in a child with epilepsy



$tRNA_{Phe}$ mutation detection by RFLP



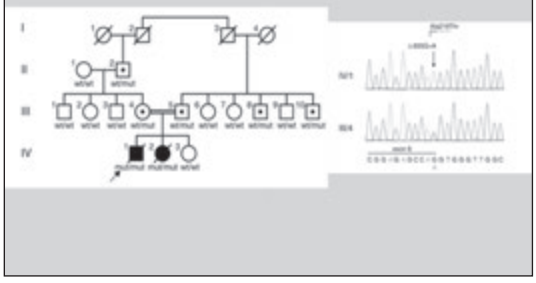
Muscle histology and biochemistry



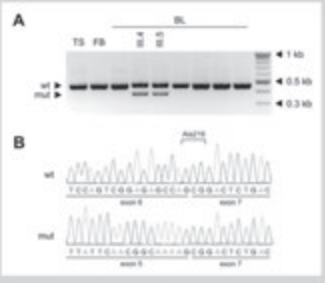
Epilepsy-associated mutations of human mitochondrial genome

- Rare multisystemic disorders.
- Mitochondrial mutations occur either sporadic or are maternal inherited.
- Muscle biopsy frequently without evidence for mitochondrial disease.

Identification of a novel c.655G>A *CARS2* splice site mutation in a family resembling MERRF syndrome

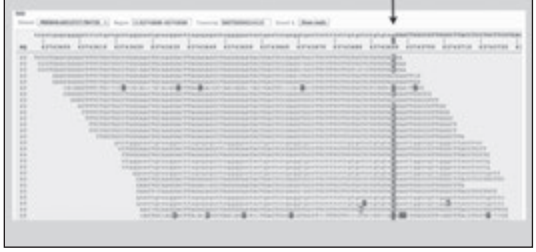


Skipping of exon 6 of *CARS2* due to a splice site mutation in a family resembling MERRF syndrome

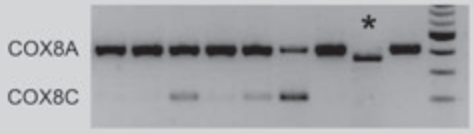


Localization of amino acids belonging to exon 6 of *CARS2*

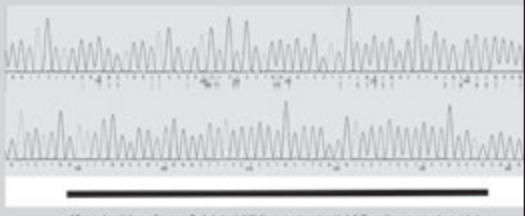
Identification of a novel homozygous c.115-1G>C *COX8A* splice site mutation in a Turkish individual with severe mitochondrial disease and seizures



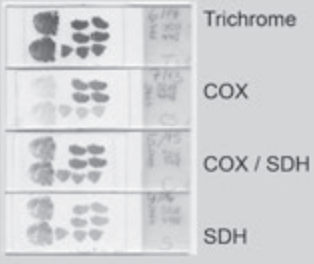
mRNA alterations by the homozygous c.115-1G>C *COX8A* splice site mutation in a Turkish individual with severe mitochondrial disease and seizures



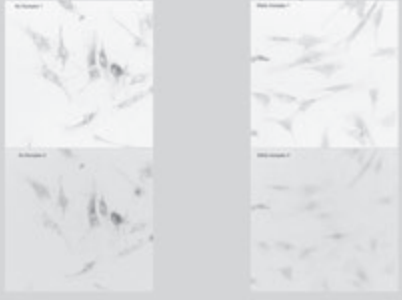
mRNA alteration by the c.115-1G>C *COX8A* splice site mutation in an individual with severe mitochondrial disease



The c.115-1G>C *COX8A* splice site mutation in an individual with severe mitochondrial disease causes a muscular COX deficiency similarly to *SURF1* c.845_846delCT



The c.115-1G>C *COX8A* splice site mutation in an individual with severe mitochondrial disease causes COX deficiency due to impaired COX assembly



Relevance of mitochondrial impairment in epilepsy

Summary I

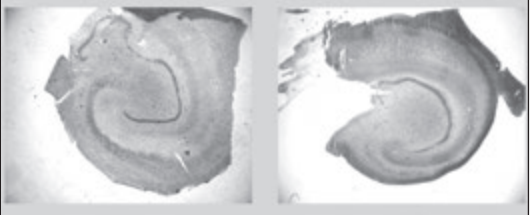
In many genetic syndromes with mitochondrial involvement caused by mutations in mitochondrial and nuclear genes epilepsy is detected.

The phenotype of these patients includes frequently multisystemic involvement.

Most frequently these patients present with severely progressive and difficult to treat myoclonic epilepsy.

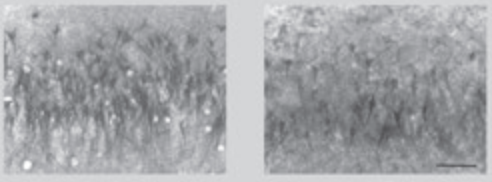
Classical forms of diagnostics might fail and novel genetic techniques like whole exome sequencing should be applied.

Hippocampus sclerosis in epilepsy (Nissl staining)



lesion HS

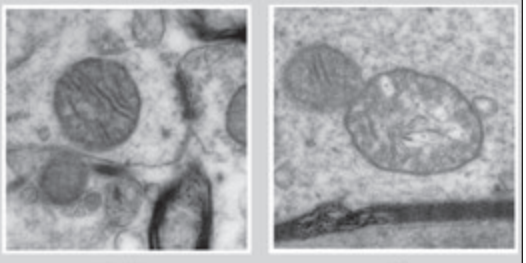
COX / SDH double staining of CA3 neurons in human epileptic hippocampus



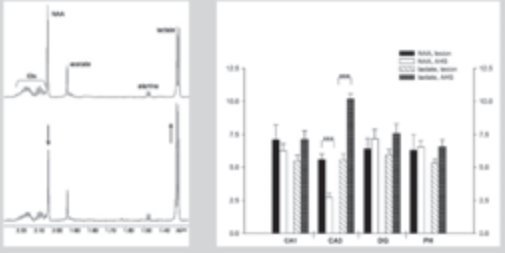
lesion HS

COX / SDH double staining of hilar neurons of human epileptic hippocampus

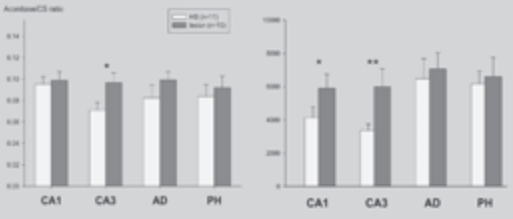
Electron microscopy in CA3



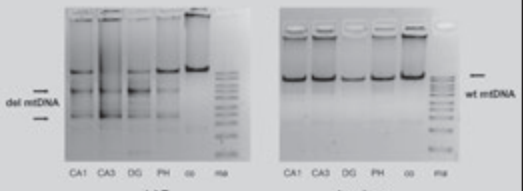
Hippocampal NAA distribution in TLE



Decreased aconitase activity and mtDNA depletion in HS



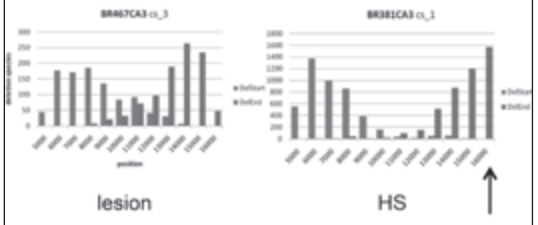
Clonally expanded mtDNA deletions in HS



HS
f, 34 years

lesion
m, 32 years

mtDNA deletion breakpoint spectra in TLE determined by mtDNA deep sequencing



lesion HS

mtDNA deletion breakpoints depend on mechanism of deletion formation

Standard mtDNA deletional spectra depend on the distribution of imperfect direct repeats in mtDNA.

ROS generate random double strand breaks. DSBR causes frequent recombination with the free end of 7S DNA and generates 16070-type deletions.

Presence of the prominent 7.4 kb mtDNA deletion in HS and lesion samples

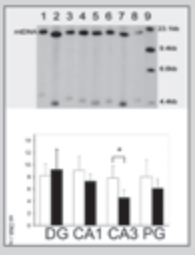
Detection of the 8649 : 16084 7.4 kb deletion in CA3 subfield by multiplex PCR:

63 HS samples : 38 positive and 25 negative

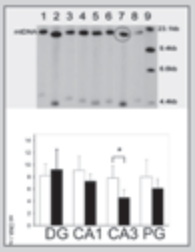
21 lesion samples: 1 positive and 20 negative *

* Different with p = 0.002 (two tailed Fisher's exact test)

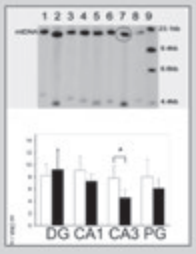
Mitochondrial DNA depletion in an epilepsy model

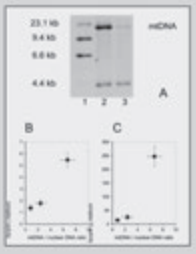


Mitochondrial DNA depletion in an epilepsy model



Mitochondrial DNA depletion in an epilepsy model

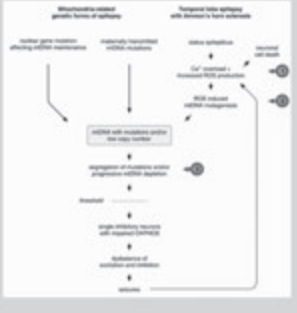




mtDNA mutagenesis by ROS

Mitochondrially produced ROS can attack mtDNA,
but also externally produced H_2O_2 by microglial cells might be relevant

Postulated mitochondrial involvement in epilepsy



Is TLE caused by mutations of mitochondrial genome ?

- Sporadic point mutations of mtDNA and nuclear mutation affecting mitochondrial function can cause epilepsy.
- In human TLE with HS specific clonal deletions and local depletion of mtDNA are detectable.
- → Underlines the possible causal role of mtDNA mutations also for TLE with HS.

Hypothesis linking mitochondrial dysfunction and epilepsy

Relevance of ROS for mitochondrial dysfunction in TLE

Summary II

Evidence for ROS involvement in TLE:

- mtDNA depletion, mtDNA deletions and aconitase deficiency are frequently observed in TLE with HS and other neurodegenerative diseases.
- Specific 3' breakpoints at np 16070 in epilepsy point to mtDNA double strand breaks as molecular cause. Deletional spectra are a molecular trace.

Consequences:

- Impaired mitochondrial function in mitochondria-rich inhibitory interneurons can affect network inhibition which might lead to seizures.

Our Team

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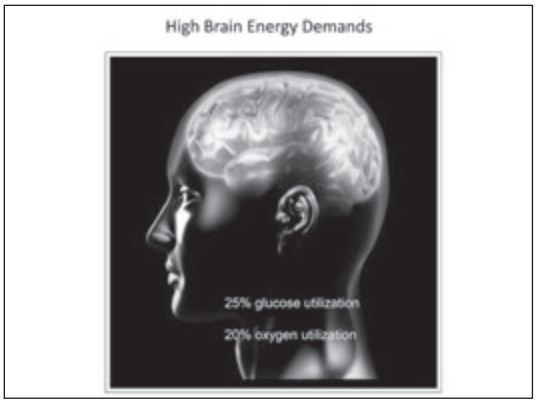
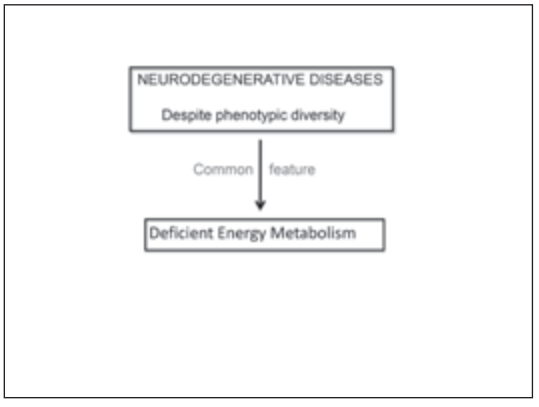
Rudolf Wiesner (Köln)

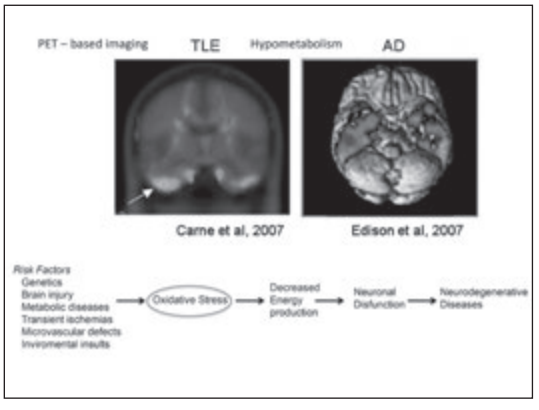
life ⁞ brain

YURI ZILBERTER (FRANCE)

CAUSAL LINK BETWEEN ENERGY DEFICIENCY, OXIDATIVE STRESS AND NEURONAL HYPERACTIVITY

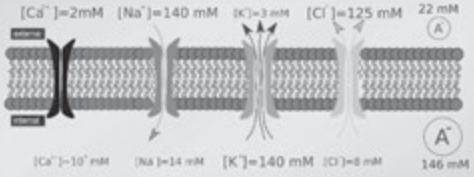






Transmembrane ionic channels

determinants of membrane ionic permeability and membrane resting potential, V_m

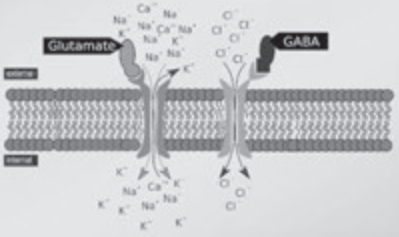


$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_{ex} + P_{Na}[Na^+]_{ex} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{ex}}$$

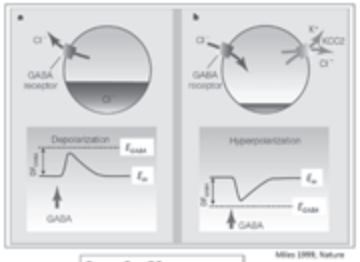
$V_m \sim -80$ mV

$P_K : P_{Na} : P_{Cl} = 1 : 0{,}04 : 0{,}4$

Glutamate and GABA are the main excitatory and inhibitory neurotransmitters



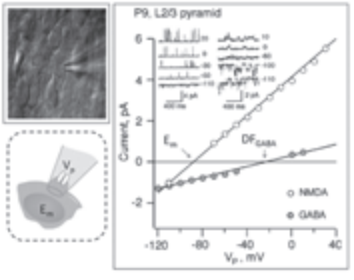
Resting potential (E_m) and GABA-mediated current reversal potentia (E_{GABA})

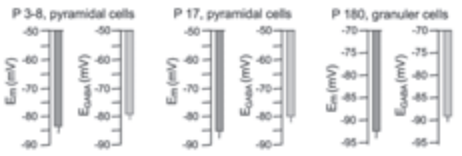


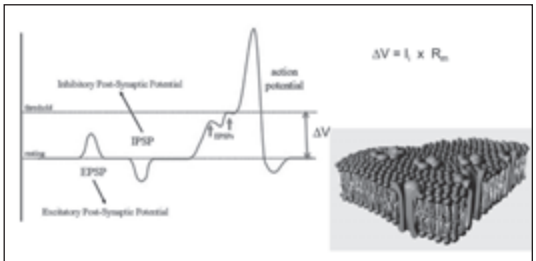
$E_{GABA} = E_m - DF_{GABA}$

NMDA channels GABA channels

Resting potential (E_m) and GABA-induced current reversal potential (E_{GABA})

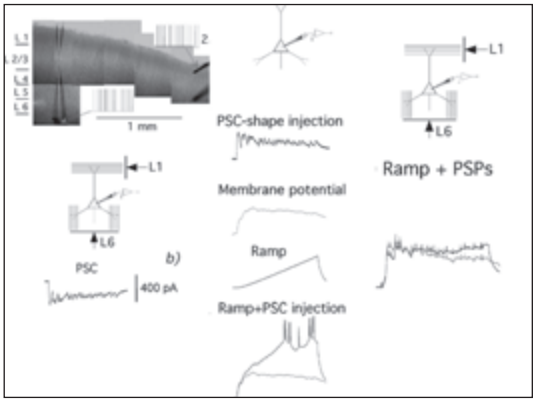


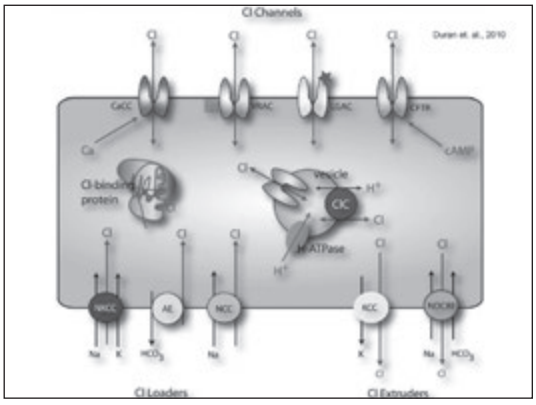


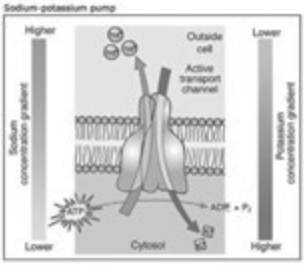


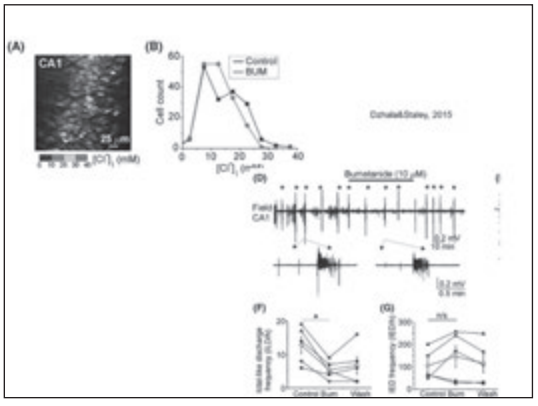
Reversal potential for glutamate receptors is close to 0 mV.
That is why they have large driving force ($DF_{Glut} = E_m$) for current generation.

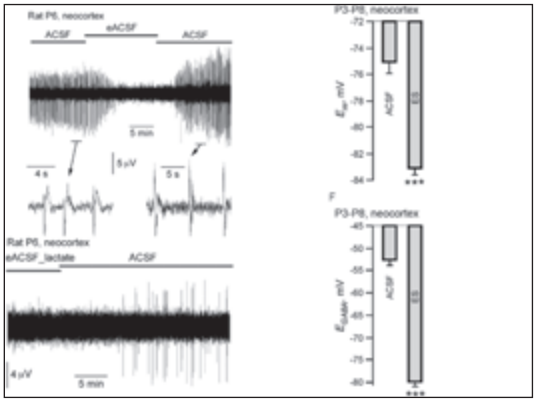
Reversal potential for GABA receptors is close to E_m and DF_{GABA} is close to 0 mV.

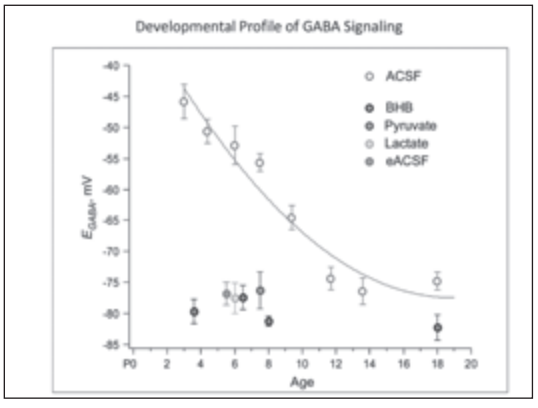




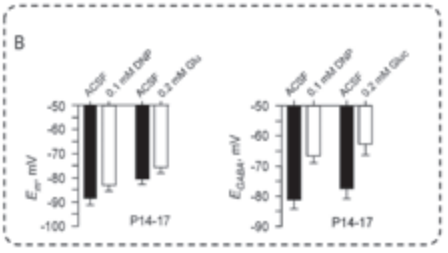

Sodium-potassium pump
Higher
Lower
Outside cell
Active transport channel
Sodium concentration gradient
Potassium concentration gradient
ATP
ADP + Pi
Cytosol
Lower
Higher

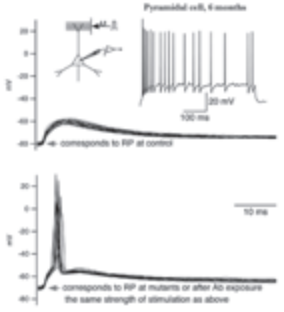

(A)
CA1
25 μm
(B)
Control
BUM
Cell count
Ochalek&Staley, 2015
Bumetanide (10 μM)
Field
CA1
0.2 mV
10 min
0.2 mV
0.5 min
(F)
(G)
Control
Bum
Wash

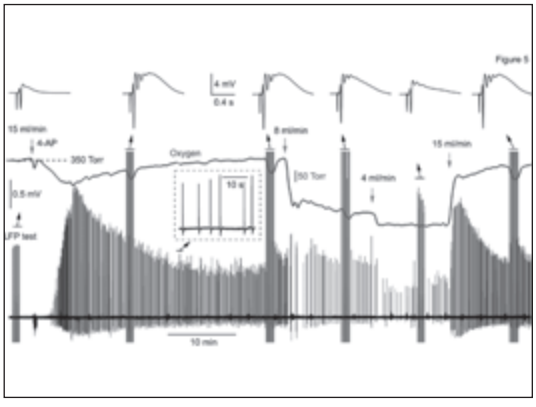

Rat P6, neocortex
ACSF
eACSF
ACSF
5 min
4 s
5 μV
5 s
Rat P6, neocortex
eACSF_lactate
ACSF
4 μV
5 min
P3-P8, neocortex
ACSF
ES
***
P3-P8, neocortex
ACSF
ES
***


Developmental Profile of GABA Signaling
ACSF
BHB
Pyruvate
Lactate
eACSF
Age

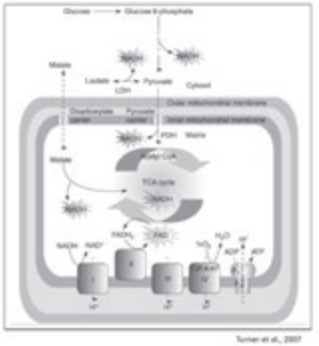
E_{in}, E_{GABA} and energy supply - P14-P17





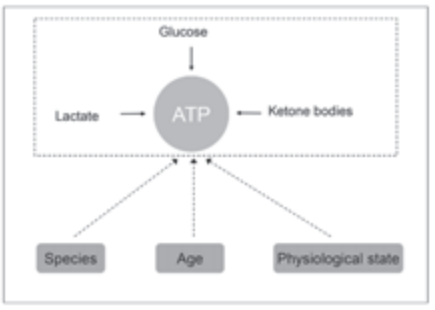


NADH in Energy Metabolism

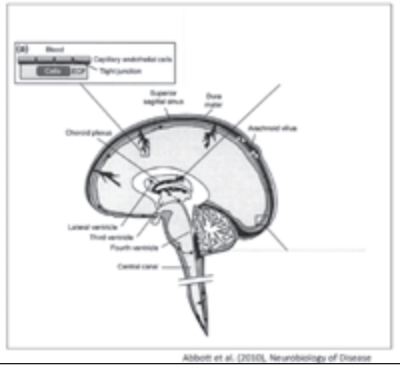


Turner et al., 2007

Major sources of Energy - General



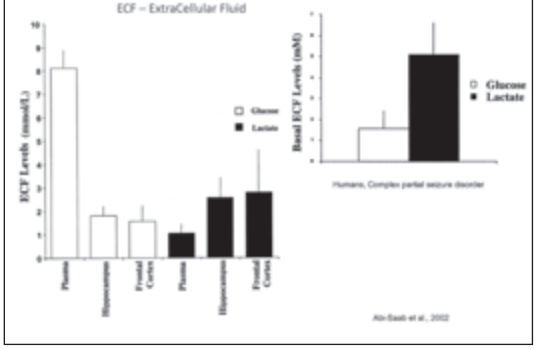
Blood-brain Barriers



Abbott et al. (2010), Neurobiology of Disease

Concentrations of glucose and lactate in brain tissue

ECF – ExtraCellular Fluid



Humans, Complex partial seizure disorder

Abi-Saab et al., 2002

A short history of ACSF

THEORY AND PRACTICE OF PARENTERAL FLUID ADMINISTRATION

Artificial "Spinal Fluid"

ALEXIS F. HARTMANN, M.D.
ST. LOUIS

Eighty-Fifth Annual Session of the American Medical Association, Cleveland, June 15, 1934.

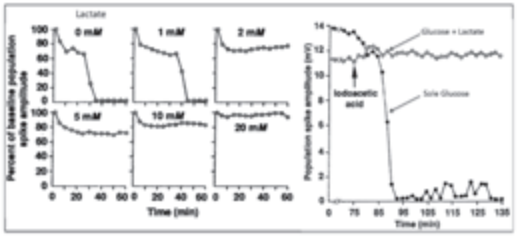
CLINICAL USES OF AN ARTIFICIAL CEREBROSPINAL FLUID

R. C. LEWIS, M.D., AND K. A. C. ELLIOTT, PH.D.
Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute, Montreal, Canada

(Received for publication October 11, 1948)

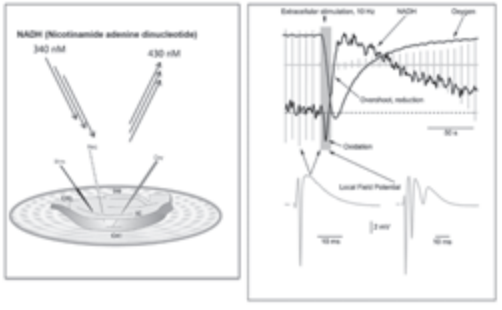
J Neurosurg. 1950 May;7(3):256-60.

Lactate can substitute glucose in hippocampal slices

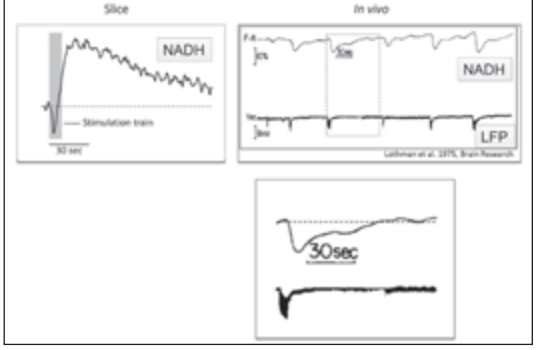


Schurr et al. (1988), Science

Measurements of energy metabolism parameters during neuronal activity

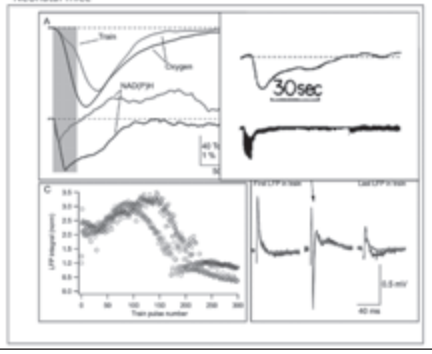


NAD(P)H response to evoked neuronal activity *in vitro* and *in vivo*

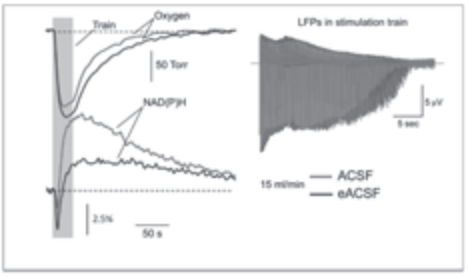


Lothman et al. 1975, Brain Research

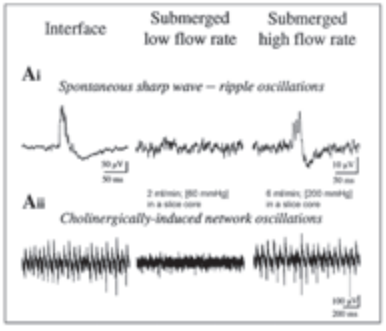
Lactate in ACSF is more efficient than glucose



Supplementary energy substrates enhance oxidative metabolism

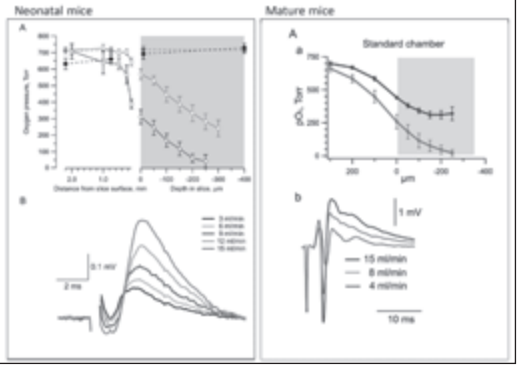


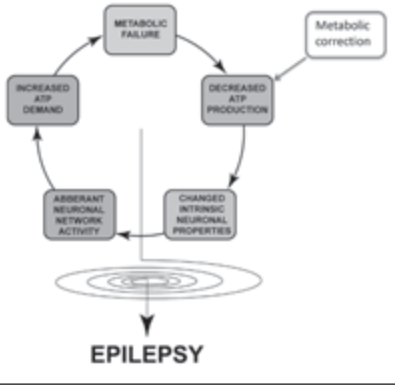
Occurrence of physiological-like oscillation in slices depends on oxygen supply

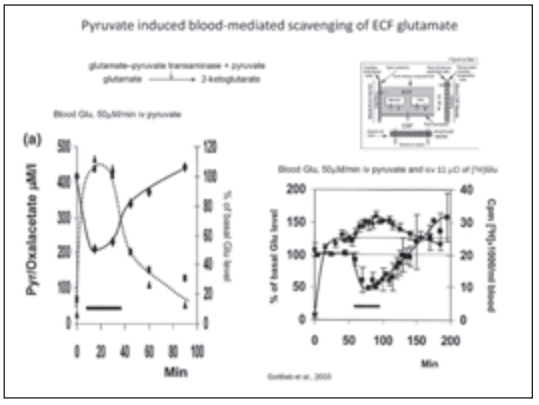


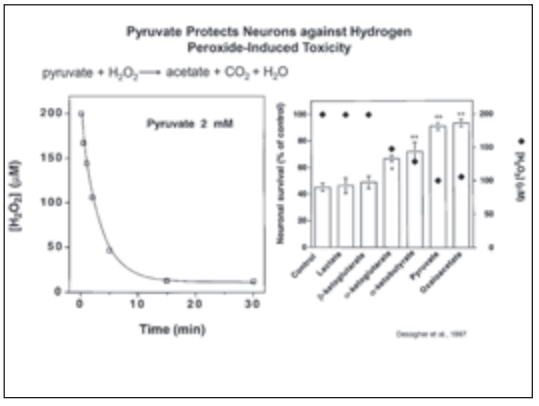
Hajos et al. (2009), EJN

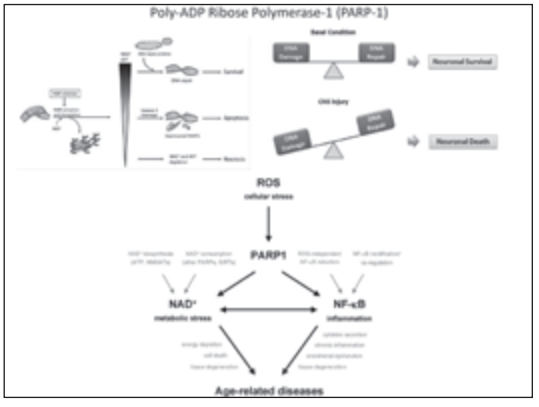
Oxygen distribution in a slice

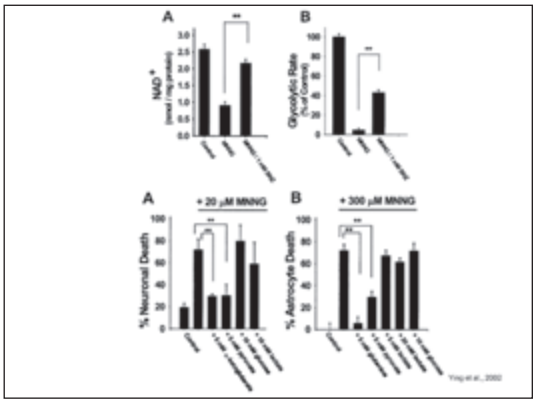


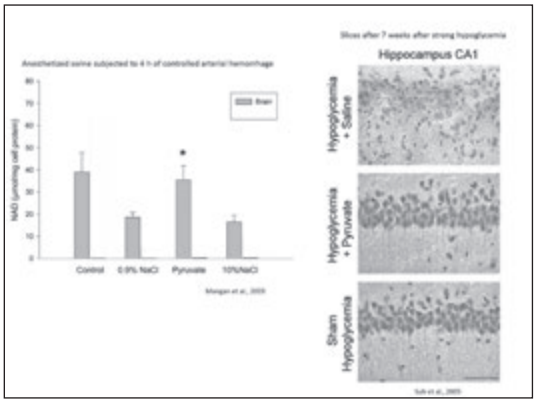


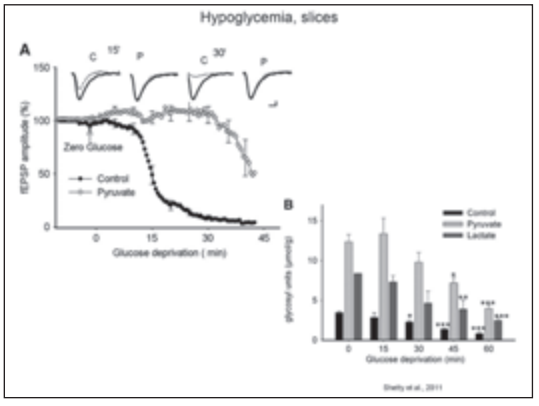

Pyruvate induced blood-mediated scavenging of ECF glutamate
glutamate-pyruvate transaminase + pyruvate
glutamate → 2-ketoglutarate
Blood Glu, 50μM/min iv pyruvate
(a)
Pyr/Oxaloacetate μM/l
% of basal Glu level
Min
Blood Glu, 50μM/min iv pyruvate and iov 11 μCi of [14C]Glu
% of basal Glu level
Cpm [14C]Glutamate/ml basal
Min
Gottlieb et al., 2003

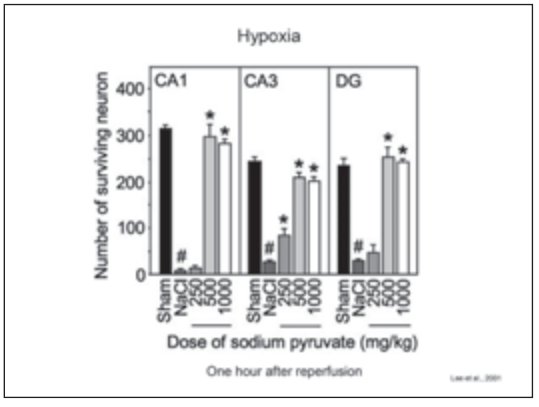

Pyruvate Protects Neurons against Hydrogen Peroxide-Induced Toxicity
pyruvate + H2O2 → acetate + CO2 + H2O
Pyruvate 2 mM
[H2O2] (μM)
Time (min)
Neuronal survival (% of control)
Control
Lactate
β-ketoglutarate
α-ketoglutarate
α-ketobutyrate
Pyruvate
Oxaloacetate
Desagher et al., 1997

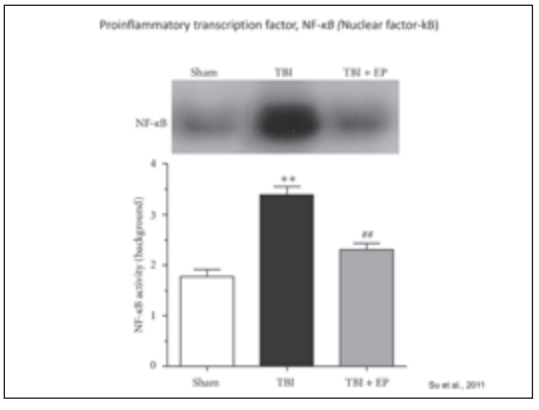

Poly-ADP Ribose Polymerase-1 (PARP-1)
Basal Condition
DNA Damage
DNA Repair
Neuronal Survival
Cell Injury
DNA Damage
DNA Repair
Neuronal Death
ROS
cellular stress
PARP1
NAD+
metabolic stress
NF-κB
inflammation
Age-related diseases

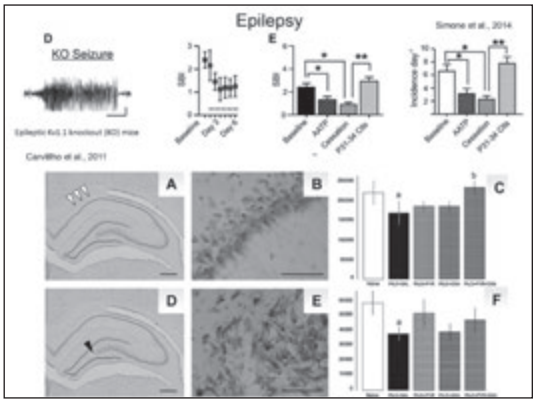

A
B
NAD+ level / mg protein
Glycolytic Rate (%of Control)
A
+ 20 μM MNNG
B
+ 300 μM MNNG
% Neuronal Death
% Astrocyte Death
Ying et al., 2002


Hippocampus CA1
Hypoglycemia + Saline
Hypoglycemia + Pyruvate
Sham Hypoglycemia
Control
0.9% NaCl
Pyruvate
10%NaCl


Hypoglycemia, slices
Zero Glucose
Control
Pyruvate
Glucose deprivation (min)
Lactate
Glucose deprivation (min)

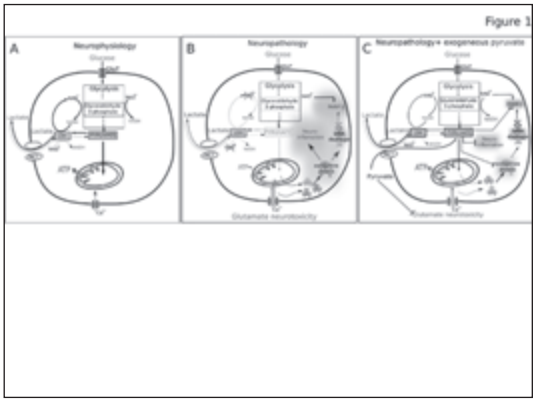

Hypoxia
CA1
CA3
DG
Number of surviving neuron
Sham
NaCl
250
500
1000
Dose of sodium pyruvate (mg/kg)
One hour after reperfusion


Proinflammatory transcription factor, NF-κB (Nuclear factor-kB)
Sham
TBI
TBI + EP
NF-κB
Sham
TBI
TBI + EP

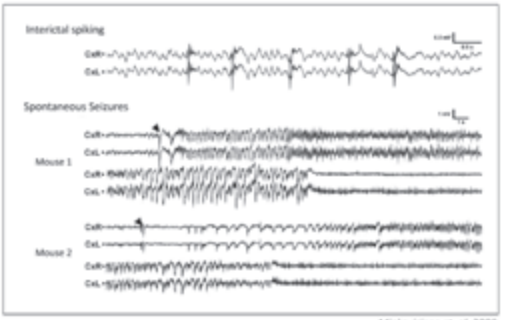


Unique neuroprotective properties of **Pyruvate**

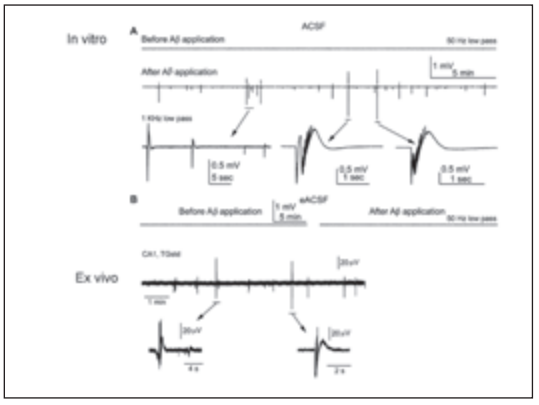
1. Pyruvate is the most efficient energy substrate.
2. Pyruvate reduces the blood glutamate level, facilitating the excessive glutamate efflux from the brain thus reducing the glutamate-induced neurotoxicity.
3. Pyruvate is efficient antioxidant.
4. Pyruvate abates hyperactivation of PARP-1 and thus prevents depletion of NAD^+, inhibition of glycolysis and insufficient ATP generation.
5. Pyruvate is a potent anti-inflammatory agent.
6. Pyruvate boosts accumulation of astrocytic glycogen thus increasing neuronal tolerance to ischemia and hypoglycemia.
7. Presumably due to the properties above, **pyruvate is a powerful antiepileptic agent**.

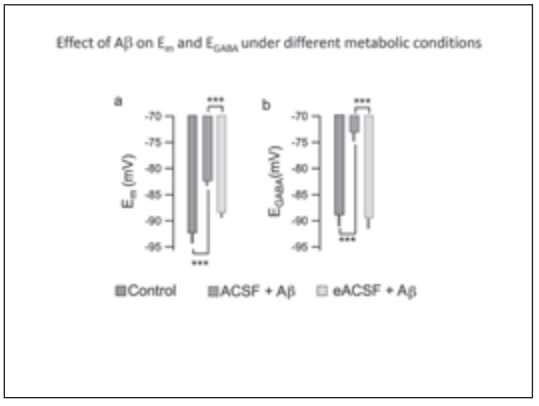


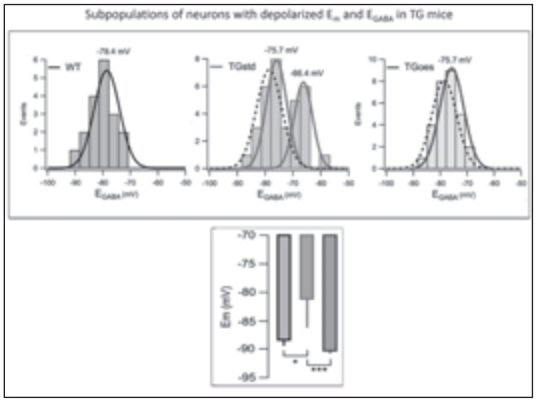
Epileptiform activity in mouse AD model (APPswe/PS1dE9)

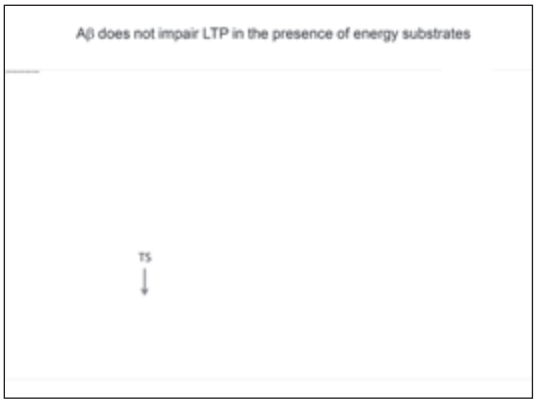


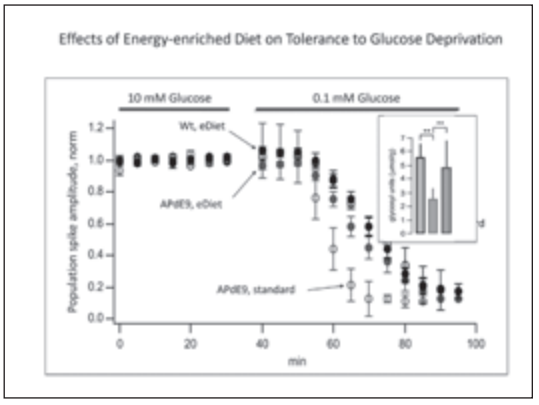
Minkeviciene et. al. 2009

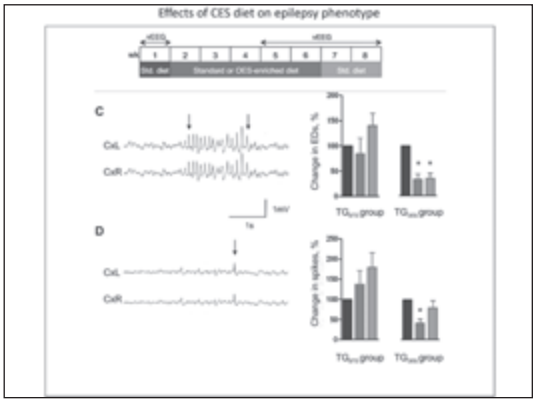

In vitro
A
ACSF
Before Aβ application
After Aβ application
B
eACSF
Before Aβ application
After Aβ application
Ex vivo

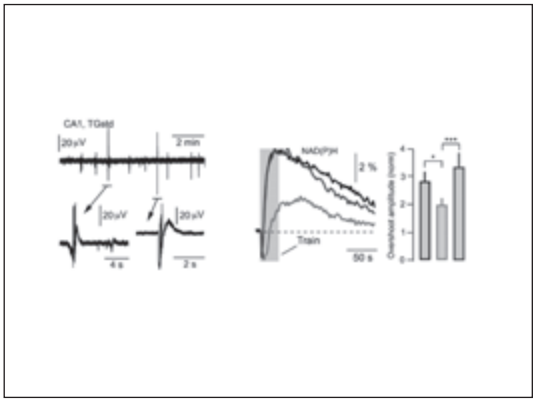

Effect of Aβ on E_m and E_{GABA} under different metabolic conditions
a
b
E_m (mV)
E_{GABA}(mV)
Control
ACSF + Aβ
eACSF + Aβ

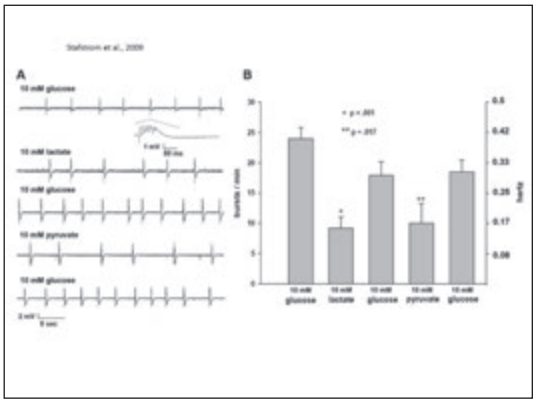

Subpopulations of neurons with depolarized E_m and E_{GABA} in TG mice
WT
TGstd
TGoes
Em (mV)


Aβ does not impair LTP in the presence of energy substrates
TS


Effects of Energy-enriched Diet on Tolerance to Glucose Deprivation
10 mM Glucose
0.1 mM Glucose
Wt, eDiet
APdE9, eDiet
APdE9, standard
Population spike amplitude, norm
min


Effects of CES diet on epilepsy phenotype
Std. diet
Standard or CES-enriched diet
Std. diet
C
CxL
CxR
Change in EDs, %
D
CxL
CxR
Change in spikes, %


CA1, TGdd
20 µV
2 min
20 µV
20 µV
4 s
2 s
NAD(P)H
2 %
Train
50 s
Overshoot amplitude (norm)


Stafstrom et al., 2009
A
10 mM glucose
10 mM lactate
10 mM glucose
10 mM pyruvate
10 mM glucose
B
10 mM glucose
10 mM lactate
10 mM glucose
10 mM pyruvate
10 mM glucose

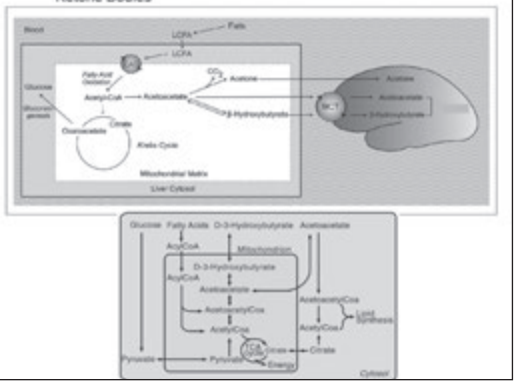
Seizure suppression via glycolysis inhibition with 2-deoxy-D-glucose (2DG)

Epilepsia, **49**(Suppl. 8):97–100, 2008

Interpretation: The glycolytic inhibitor 2DG exerts acute anticonvulsant and chronic antiepileptic actions

Because 2-DG competitively blocks glucose metabolism, 2-DG induces a c rise in alternative substrates, primarily keton

Ketone Bodies



Mechanisms of Ketogenic Diet

The KD is a high-fat, low carbohydrate diet that has been utilized as a treatment for epilepsy for over 80 years.

Bough & Rho, 2007

Two hallmark features of KD treatment are the rise in ketone body production by the liver and a reduction in blood glucose levels. Stafstrom & Rho, 2012

Glucose

In humans: Mild hypoglycemia in infants, small decrease in blood glucose in adults.

Glucose levels are lower on average in ketogenic diet treated ***individuals but remain within normal limits*** despite a decreased intake of carbohydrates.
Review Maalouf et al., 2009

In rodents: In most studies – no change in plasma glucose.
Cerebral glucose in rodents: either no change or increase

Cortical ATP in adult rats

6.6% increase (DeVivo et al., 1978); 18% increase (Nakazava et al., 1983)

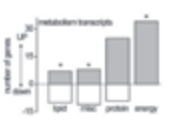
No change (Al-Mudallal *et al.* 1996; Bough *et al.* 2006; Nylen *et al.* 2009)

Nothing is more important to a cell than maintaining a constant supply and concentration of ATP. The rate of oxidation of cellular fuels is regulated with such sensitivity and precision that fluctuates only slightly in most tissues, even during extreme variations in energy demand. ATP is formed only as fast as it is used in energy-requiring cellular activities (Lehninger, 2005).

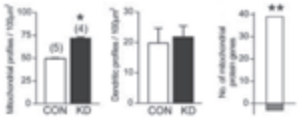
Statements of decreased brain glucose or increased ATP levels during the KD are not substantiated experimentally

104 metabolism – related genes were changed after KD

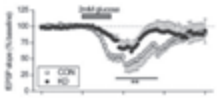
Bough et al., 2006



Mitochondrial biogenesis in the hippocampus of rats on KD



Synaptic transmission is more resistant to hypoglycemia in rats on KD



KD activates a genetic program that leads to mitochondrial biogenesis, which results in enhanced energy stores. This results in enhanced ability of neurons to manage metabolic challenges

KD Side Effects

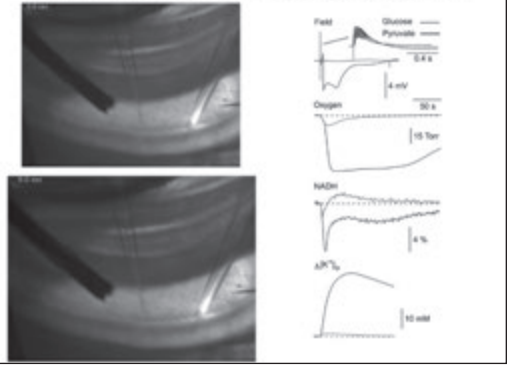
Side effects do occur with diet therapies, as these treatments are neither alternative nor designed to be healthy (Review Kossoff & Hartman, 2012).

General: Inadequate nutrition, Poor compliance, Poor palatability

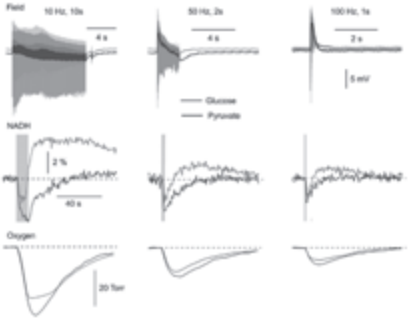
In children: delay of growth and development in children, depression, asthenia, metabolic syndrome, and others.

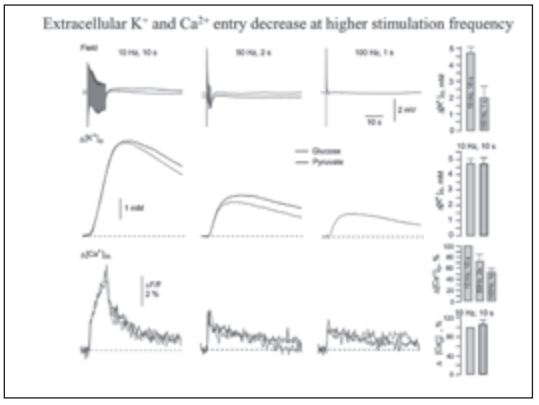
In adults: the short-term adverse effects profile being gastro-intestinal (30%), and the long-term effects being cardiovascular complications, hypercholesterolemia, mineral deficiencies, acidosis, constipation (Reviews: Levy et al., 2011; Payne et al., 2011; Kossoff & Hartman, 2012).

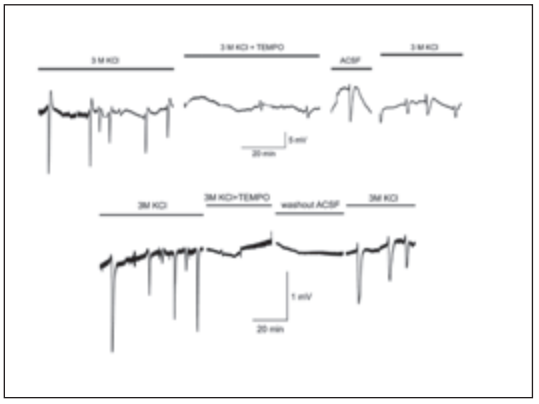
Metabolic Collapse in pyruvate at high frequency stimulation

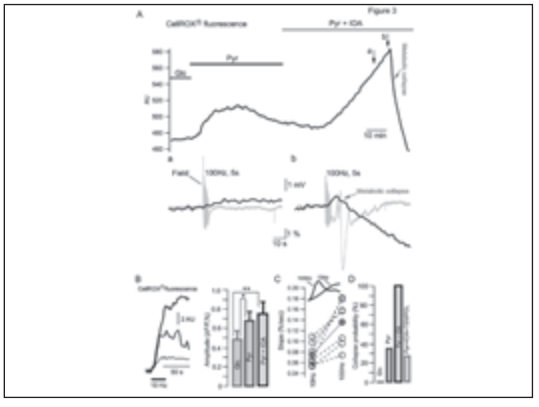


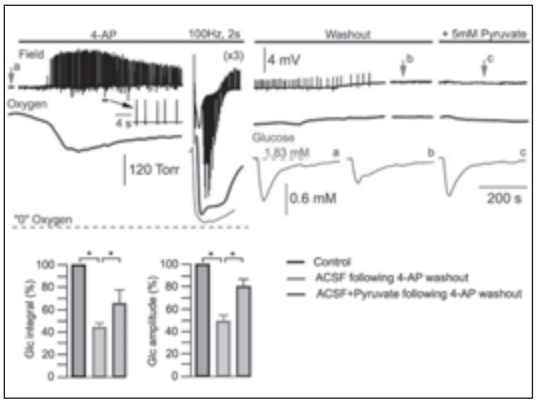
Energy consumption decreases at higher stimulation frequency

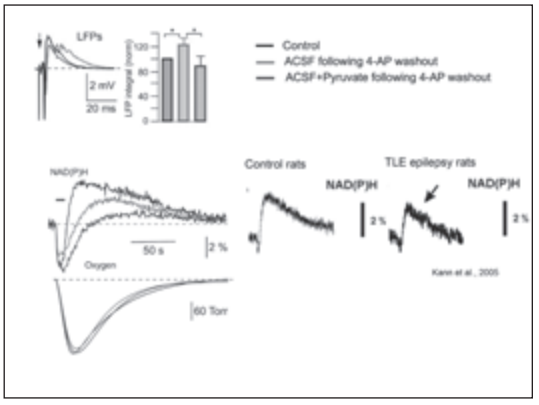


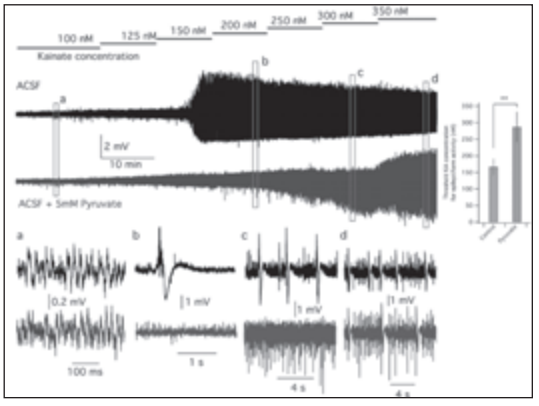

Extracellular K+ and Ca2+ entry decrease at higher stimulation frequency
Field
10 Hz, 10 s
50 Hz, 2 s
100 Hz, 1 s
2 mV
10 s
Glucose
Pyruvate
1 mM
10 Hz, 10 s
50 Hz, 2 s
100 Hz, 1 s
10 Hz, 10 s

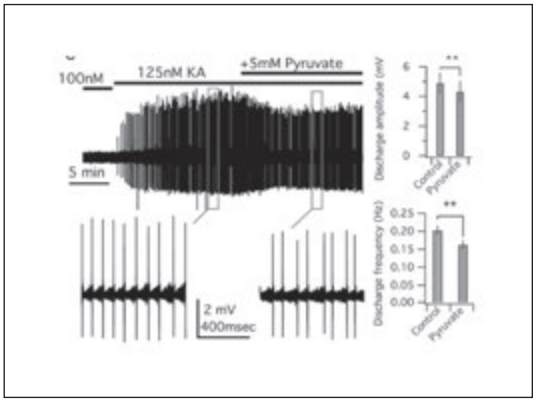

3 M KCl
3 M KCl + TEMPO
ACSF
3 M KCl
5 mV
20 min
3M KCl
3M KCl+TEMPO
washout ACSF
3M KCl
1 mV
20 min

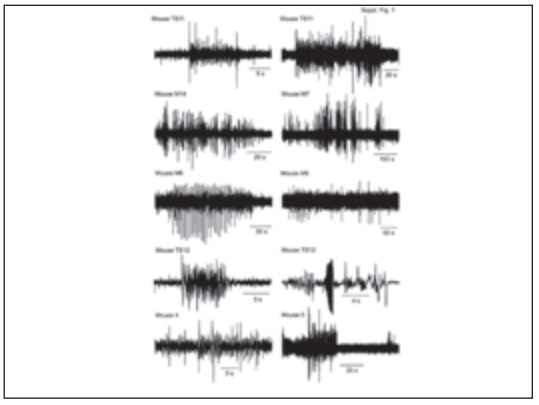

A
Figure 3
Pyr
Pyr + IOA
42 min
Field
100Hz, 5s
1 mV
100Hz, 5s
2 s
B
C
D
Pyr

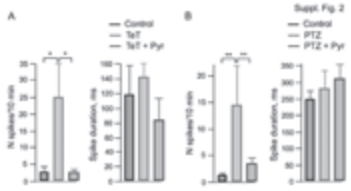

4-AP
100Hz, 2s
Washout
+ 5mM Pyruvate
Field
(x3)
4 mV
Oxygen
4 s
120 Torr
"0" Oxygen
Glucose
1.83 mM
0.6 mM
200 s
Glc integral (%)
Glc amplitude (%)
Control
ACSF following 4-AP washout
ACSF+Pyruvate following 4-AP washout


LFPs
2 mV
20 ms
LFP integral (mV/s)
Control
ACSF following 4-AP washout
ACSF+Pyruvate following 4-AP washout
NAD(P)H
50 s
2 %
Oxygen
60 Torr
Control rats
TLE epilepsy rats
NAD(P)H
NAD(P)H
2 %
2 %
Kann et al., 2005


100 nM
125 nM
150 nM
200 nM
250 nM
300 nM
350 nM
Kainate concentration
ACSF
a
b
c
d
2 mV
10 min
ACSF + 5mM Pyruvate
0.2 mV
1 mV
100 ms
1 s
4 s


100nM
125nM KA
+5mM Pyruvate
5 min
2 mV
400msec
Discharge amplitude (mV)
Discharge frequency (Hz)
Control
Pyruvate
**




A
B
Suppl. Fig. 2
Control
TeT
TeT + Pyr
PTZ
PTZ + Pyr
N spikes/10 min
Spike duration, ms

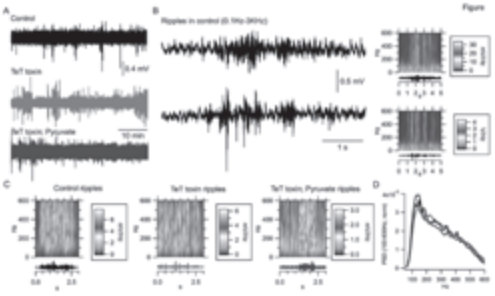
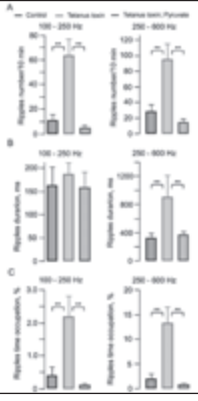


Figure
A
Control
TeT toxin
TeT toxin, Pyruvate
B
Ripples in control (0.1Hz-3KHz)
C
Control ripples
TeT toxin ripples
TeT toxin, Pyruvate ripples
D


A
Control
Tetanus toxin
Tetanus toxin, Pyruvate
100 - 250 Hz
250 - 600 Hz
Ripples number/10 min
B
Ripples duration, ms
C
Ripples time occupation, %

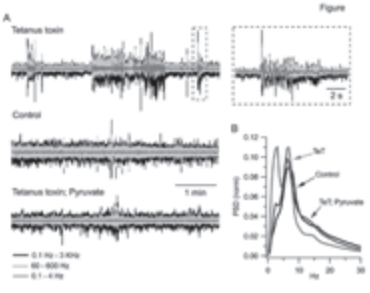


Figure
A
Tetanus toxin
2 s
Control
1 min
Tetanus toxin, Pyruvate
0.1 Hz - 3 KHz
80 - 600 Hz
0.1 - 4 Hz
B
TeT
Control
TeT, Pyruvate
PSD (norm)
Hz

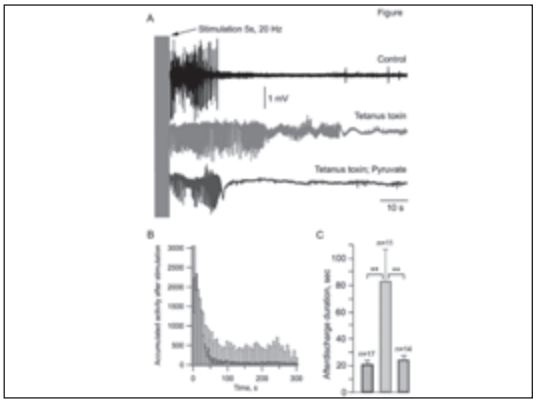
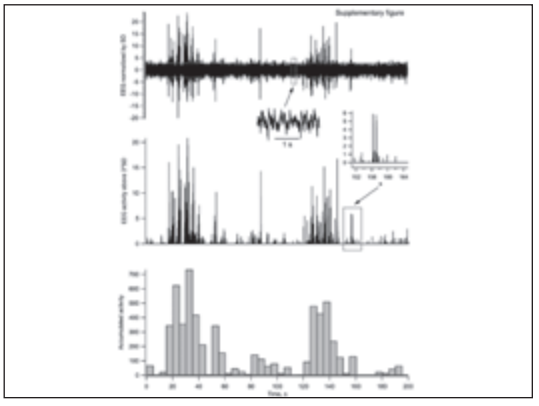
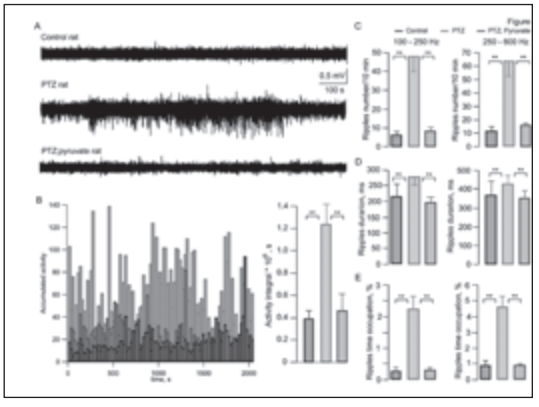


Figure
A
Stimulation 5s, 20 Hz
Control
1 mV
Tetanus toxin
Tetanus toxin; Pyruvate
10 s
B
C
Time, s
n=17
n=11
n=14


Supplementary figure
1 s
Time, s

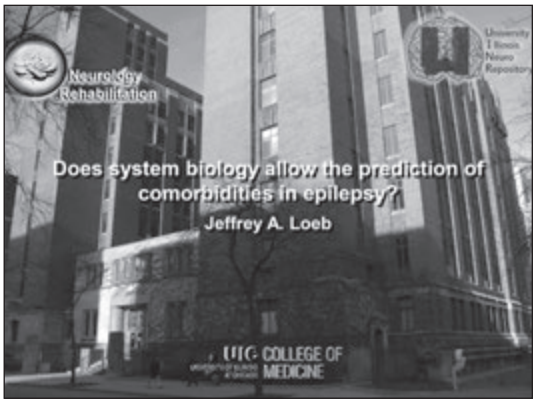

A
Control rat
PTZ rat
PTZ,pyruvate rat
0.5 mV
100 s
B
Time, s
C
Control
PTZ
PTZ, Pyruvate
100 – 250 Hz
250 – 600 Hz
D

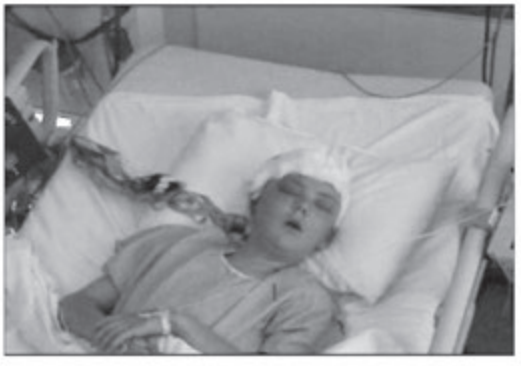
Uwe Heineman (Germany)

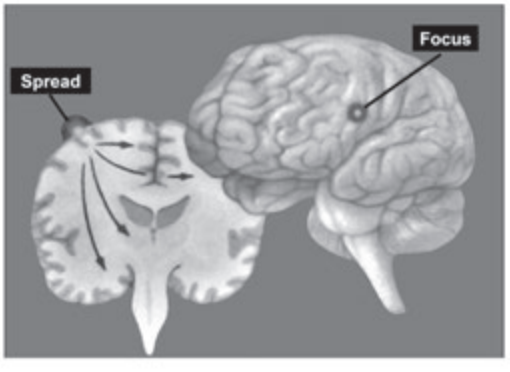
EXPERIMENTAL STATUS EPILEPTICUS

Jeffrey Loeb (USA)

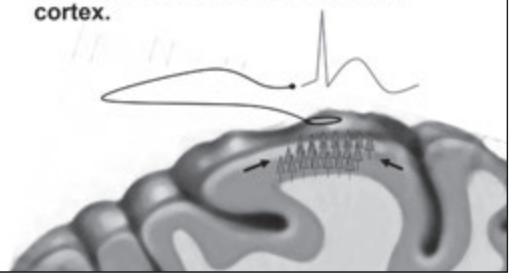
DOES SYSTEM BIOLOGY ALLOW THE PREDICTION OF COMORBIDITIES IN EPILEPSY?

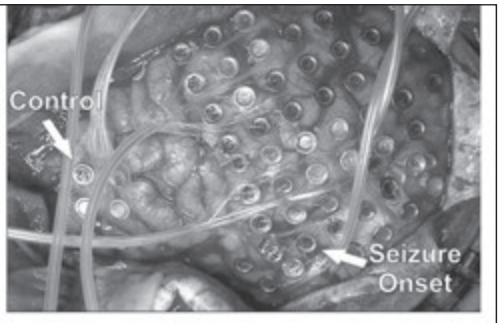






Seizure: Clinical manifestations of excessive, hypersynchronous abnormal activity of neurons in the cerebral cortex.





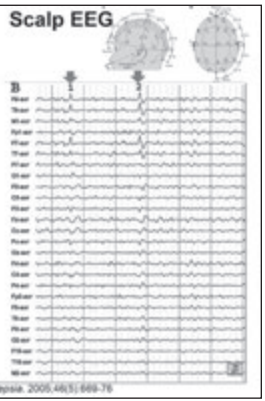
The Spike on EEG:
"Tip of the Iceberg"

Surface area of cortex required to detect a spike on scalp EEG?

< 6 cm² Undetectable
> 10cm² Detected 90% of the time

Tao JX, Ray A, Hawes-Ebersole S, Ebersole. *JS. Epilepsia.* 2005;46(5):669-76

Scalp EEG

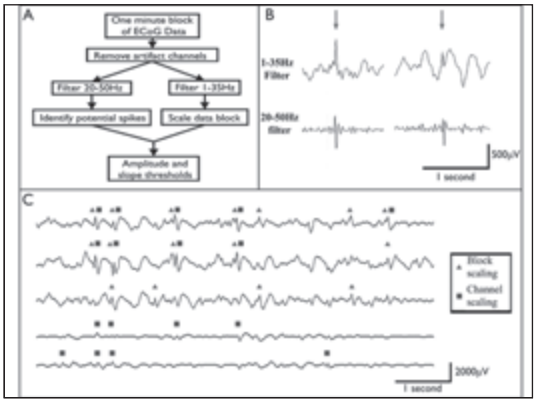


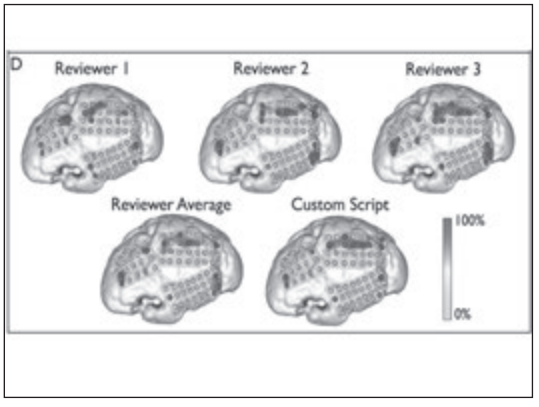
Tao JX, Ray A, Hawes-Ebersole S, Ebersole. *JS. Epilepsia.* 2005;46(5):669-76

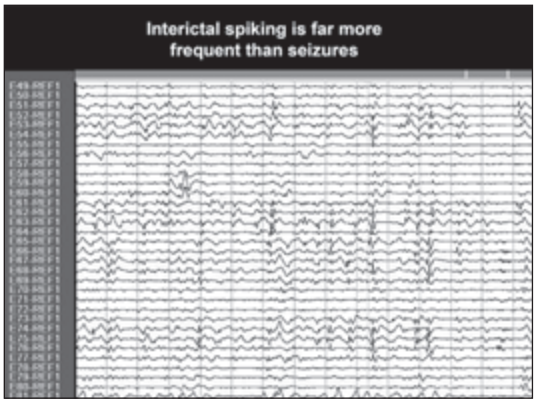
What is a spike? - EEGers have trouble agreeing…

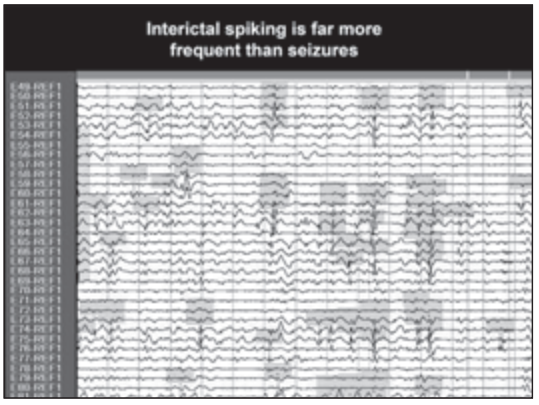
	Total number of detections			Percent of spikes marked by:	
	Reviewer 1	Reviewer 2	Reviewer 3	>=2 Reviewers	All 3 Reviewers
Patient 1	1159	7	7161	12.7%	0.0%
Patient 2	1425	371	757	30.9%	4.3%
Patient 3	1410	326	351	26.5%	4.9%
Patient 4	4500	750	6530	17.8%	0.5%
Patient 5	6534	9481	11935	39.2%	0.7%
Patient 6	1112	378	1985	18.1%	1.3%
Patient 7	3178	1508	4990	35.7%	5.9%
Patient 8	177	36	77	16.0%	2.9%
Patient 9	2485	1382	3576	32.3%	7.4%
Patient 10	722	0	2440	8.1%	-
Mean	24702	14239	39802	23.7%	3.1%

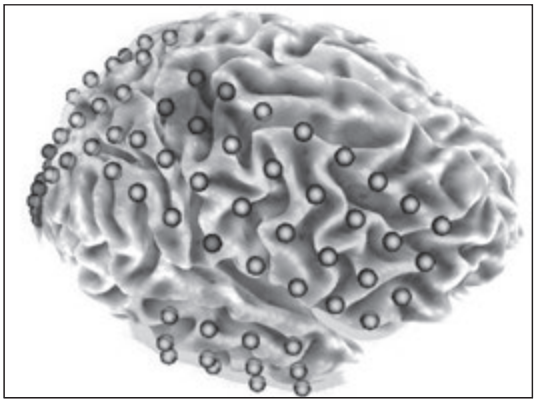
Barkmeier, DT, Shah AK, Flanagan D, Atkinson MD, Agarwal R, Fuerst DR, Jaffari-Khouzani K Loeb JA. (2012). High inter-reviewer variability of spike detection on intracranial EEG addressed by an automated multi-channel algorithm. Clin Neurophysiol 123(6): 1088-1095.



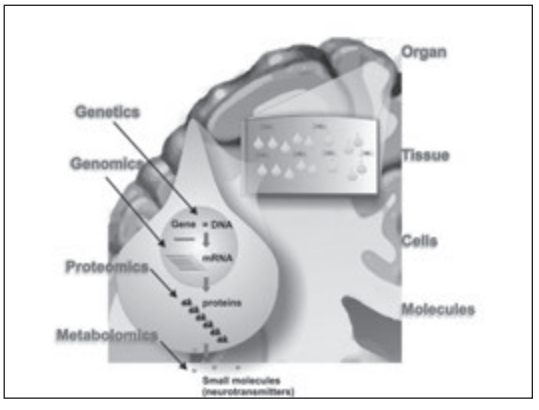


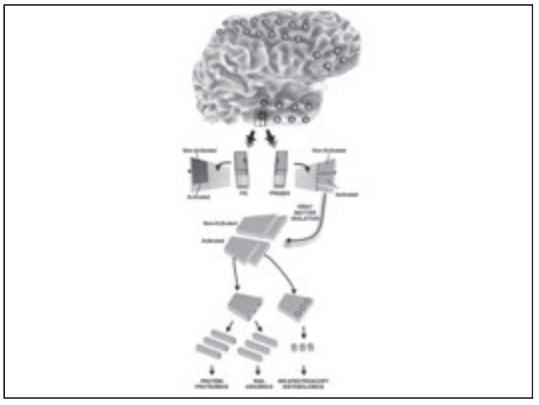


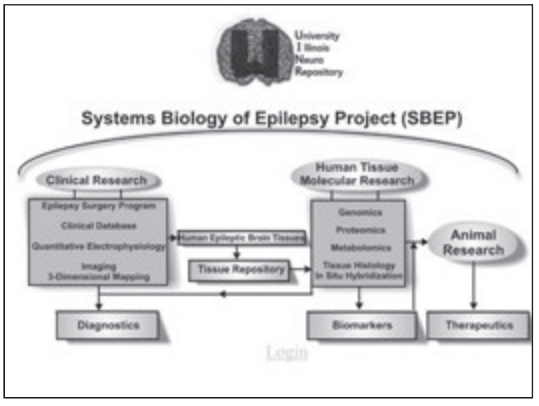

Interictal spiking is far more
frequent than seizures




Wayne State University Systems Biology of Epilepsy Project
Systems Biology - "The ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools."


Organ
Genetics
Genomics
Tissue
Gene = DNA
mRNA
Cells
Proteomics
proteins
Molecules
Metabolomics
Small molecules
(neurotransmitters)




University
Illinois
Neuro
Repository
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Human Tissue
Molecular Research
Epilepsy Surgery Program
Clinical Database
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Metabolomics
Tissue Histology
In Situ Hybridization
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Research
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Biomarkers
Therapeutics
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Welcome to SBEP
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Electrophysiology and Grid Information
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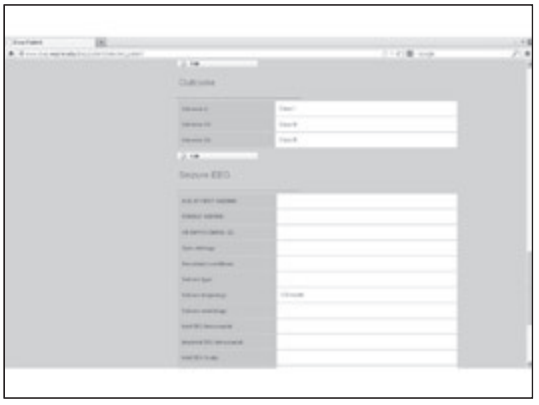
Search Results


Wayne State Systems Biology of Epilepsy Project
Patient Clinical Information


Medication
Neuroimaging

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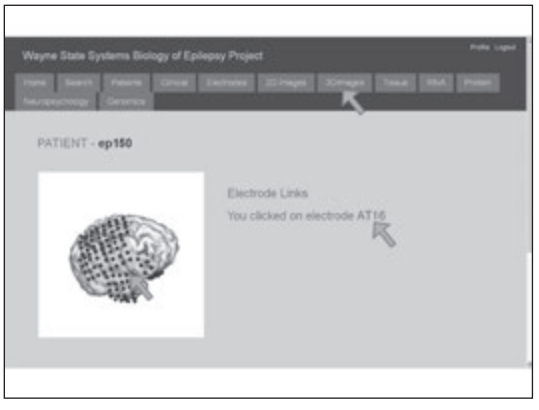
Search Patients
Neuropsychology Categories
Intellectual
Academic
Language


Search Electrodes
Electrode List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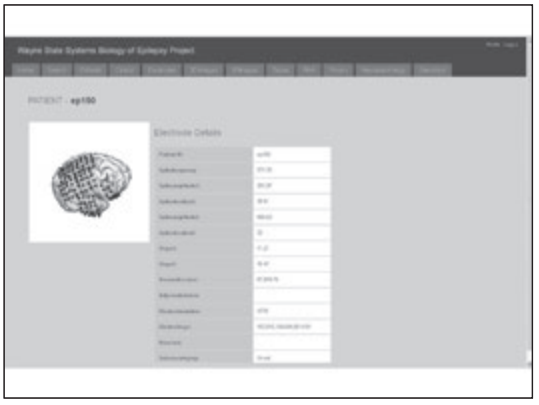
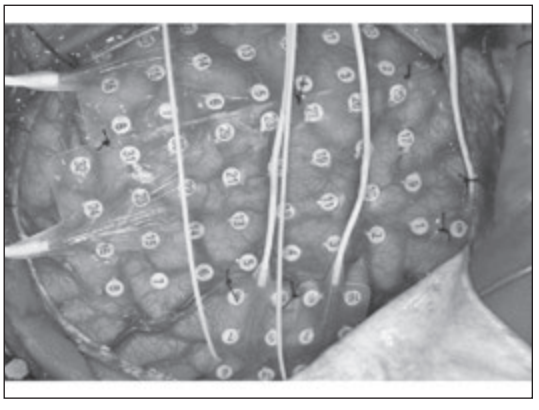
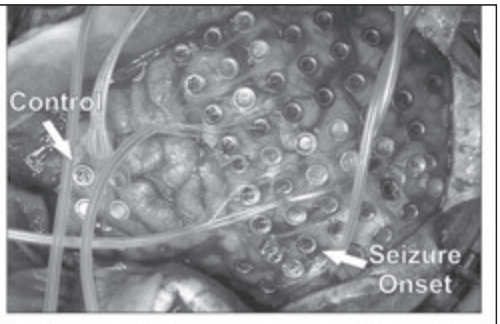
3D Images
Tissue
MMA
Protein
Neuropsychology
Generics
PATIENT - ep150
Electrode Links
You clicked on electrode AT16

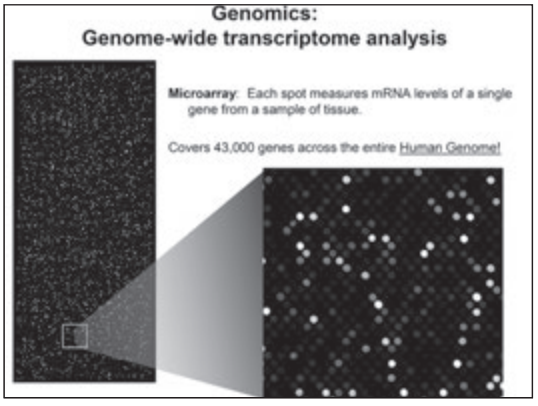

Wayne State Systems Biology of Epilepsy Project
PATIENT - ep150
Electrode Details

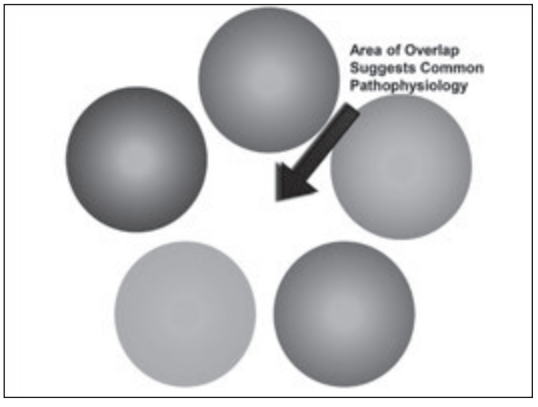

Wayne State Systems Biology of Epilepsy Project
Tissue List

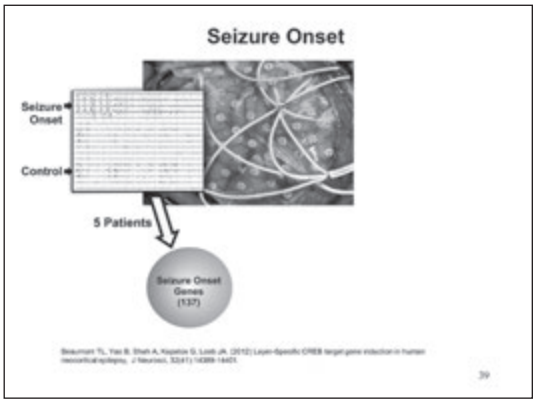

Wayne State Systems Biology of Epilepsy Project
Images List




Control
Seizure
Onset

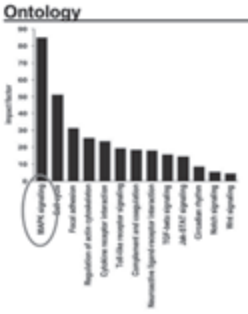

Genomics:
Genome-wide transcriptome analysis
Microarray: Each spot measures mRNA levels of a single gene from a sample of tissue.
Covers 43,000 genes across the entire Human Genome!


Area of Overlap
Suggests Common
Pathophysiology


Seizure Onset
Seizure
Onset
Control
5 Patients
Seizure Onset
Genes
(137)

Common Pathway Activation in Human Seizure Onset Neocortex

Ontology | **Model**



Epileptic Activity
↓
MAPK

Common Pathway Activation in Human Seizure Onset Neocortex

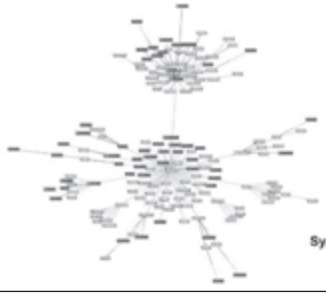
Promoter Analysis | **Model**

~40% CREB-dependent transcription

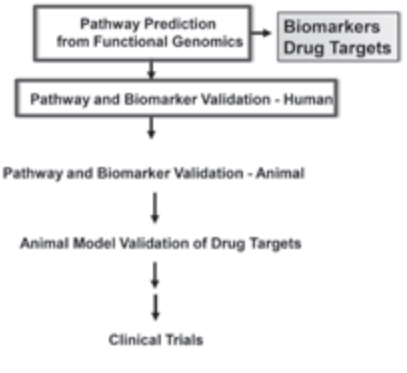
Epileptic Activity
↓
MAPK
↓
CREB activation

Common Pathway Activation in Human Seizure Onset Neocortex

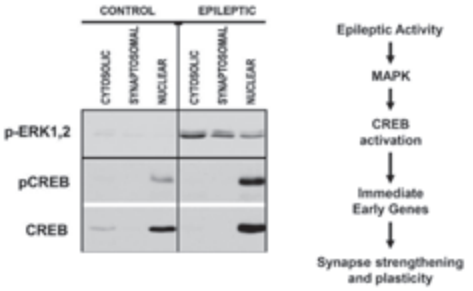
Pathway Analysis | **Model**



Epileptic Activity
↓
MAPK
↓
CREB activation
↓
Immediate Early Genes
↓
Synapse strengthening and plasticity

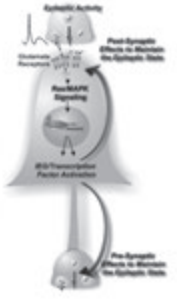


How to Validate a Drug Target? Go back to the tissue…



Epileptic Activity
↓
MAPK
↓
CREB activation
↓
Immediate Early Genes
↓
Synapse strengthening and plasticity

Evidence for *Common Pathways* in human neocortical epilepsy

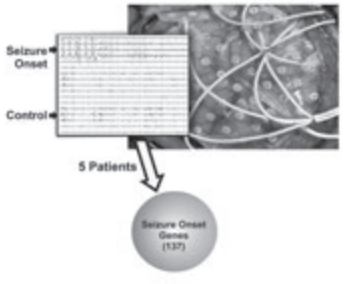


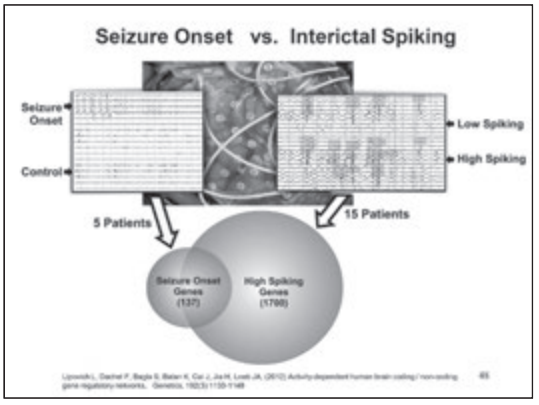
Focus on Interictal Spiking Rather than Seizures

High Spiking vs. Control

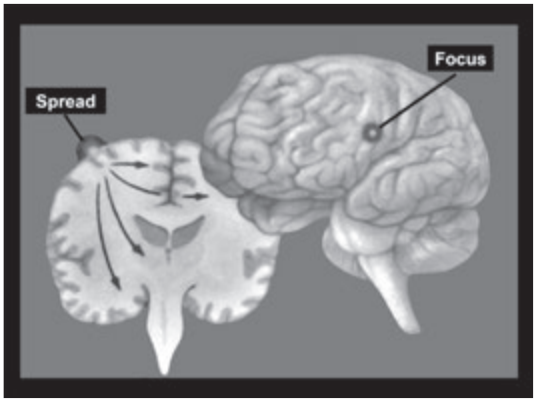
Patient No.	Age/Sex	Spike Frequency (High:Low)	Patient Diagnosis
1	15/F	6:0	Polymicrogyria
2	10/F	116:1	Diffuse gliosis, acute inflammation but normal laminar pattern
3	33/M	576:157	Normal temporal lobe
4	11/F	5:0	Heterotopia
5	7/F	425:0	Mild gliosis.
6	27/M	27:2	White matter gliosis
7	1/M	85:0	Mild gliosis
8	3/F	141:66	White matter gliosis, superficial heterotopia
9	3/F	212:56	Mild gliosis
10	7/F	215:25	Cortical dysplasia
11	6/F	124:26	Mild gliosis
12	8/M	172:3	Mild gliosis
13	56/F	299:51	Hippocampal sclerosis
14	16/M	176:44	Diffuse gliosis
15	11/F	66:2	Cortical dysplasia

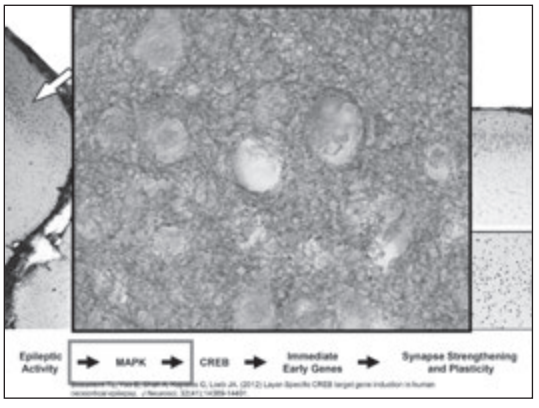
Seizure Onset vs. Interictal Spiking

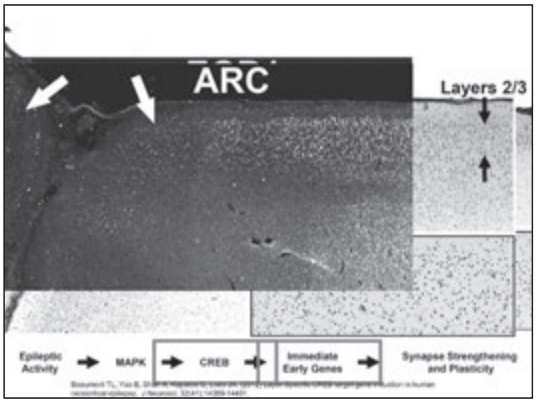




What does epilepsy look like?



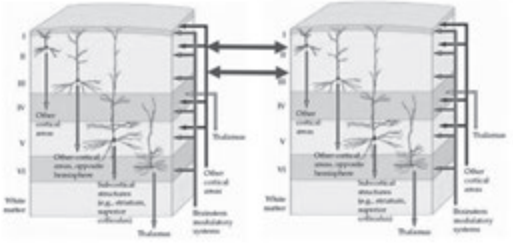


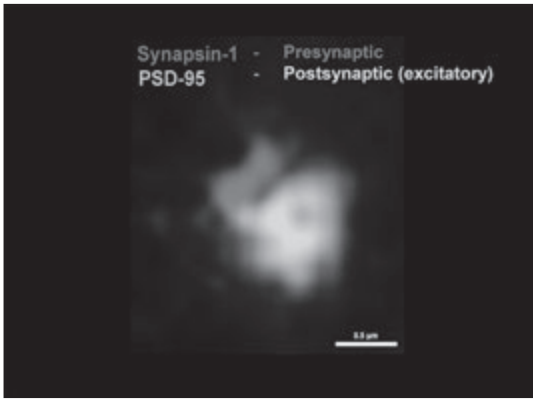


Why Layer 2/3 Neurons?

Intralaminar cortico-cortical connections

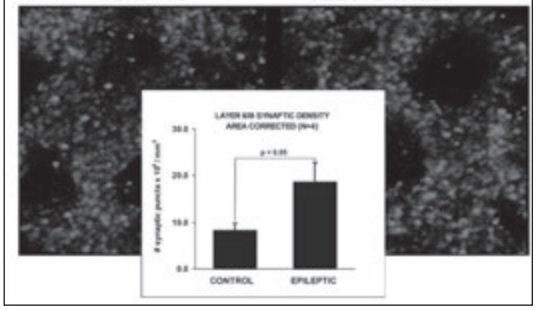
Lateral excitation





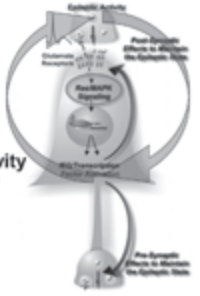
Presynaptic density: Layers 2/3

Synapsin-1 CONTROL SEIZURE ONSET



Feedback Hypothesis:

Ongoing interictal epileptic activity drives pathways that produce *SYNAPTIC* changes that maintain hypersynchrony.



SYSTEMS BIOLOGY OF HUMAN EPILEPSY

Comorbidities in Systems Biology

Linking Systems Biology to Genetic Disorders

Multivariate Interactome Links Co-Morbidities

Animal Model and Co-Morbidities

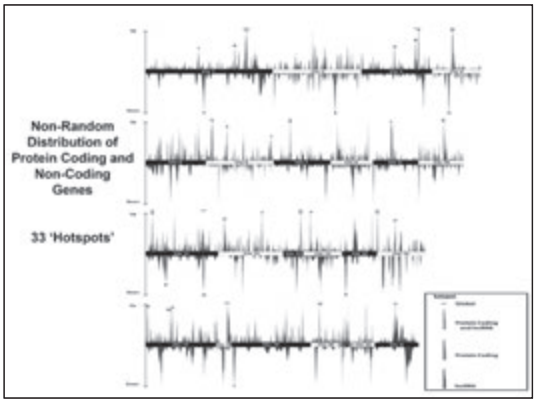
Epigenetics of Human Brain Activity…

or

This is what your brain DNA looks like on seizures…

Dachet F, Ahmad S, Loeb HE, Loeb JA (2014) Non-random clustering of activity-dependent human brain transcription, ?.(in preparation).

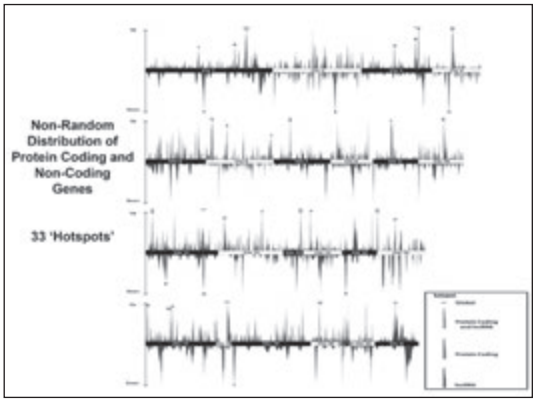
Patient	Microarray (C/Coding, Non/Coding)	Age (years)	Sex	Spike frequency		Diagnosis
				Low	High	
ep102	C_N	15	F	0	0	Polymicrogyria
ep132	C_N	10	F	1	116	Diffuse gliosis, acute inflammation, normal laminar pattern
ep139	C	17	F	42	44	Mild gliosis
ep140	C	11	F	0	5	Heterotopia
ep146	C	7	F	5	425	Mild gliosis
ep150	C_N	16	M	107	576	Normal temporal lobe
ep156	C	1	M	0	85	Mild gliosis
ep159	C_N	27	M	2	27	White matter gliosis
ep164	C_N	3	F	66	182	White matter gliosis, superficial heterotopia
ep165	C_N	3	F	56	212	Mild gliosis
ep167	C_N	7	F	21	215	Cortical dysplasia
ep168	C_N	6	F	26	124	Mild gliosis
ep169	C	8	M	3	172	Mild gliosis
ep178	C	1	M	2	80	Gliosis, Cortical dysplasia
ep179	C	23	M	69	137	Mild gliosis
ep180	C	36	F	51	299	Hippocampal sclerosis
ep188	C	16	M	44	176	Diffuse gliosis
ep189	C	11	F	2	66	Cortical dysplasia
ep192	C	7	M	7	7	Gliosis
ep196	C	2	M	8	76	Mild gliosis



Many hotspots are highly evolved

Makes us unique as humans?

LABEL	Type of HARs Overlapping	Neanderthal Sweep _ Green2010	Primate Sweep_Akey_2009_GenomeRes_	UltraConserved
A	1 HAR		Sweep25;Sweep24	uc.36
B			Sweep37	
C			Sweep47;Sweep46;Sweep44;Sweep42	
D	2 HARs	NSS130		
E	2 HARs			
F		NSS137		
G	1 HAR			
H		NSS145	Sweep206;Sweep207	
I	2 HARs		Sweep289;Sweep290;Sweep291	uc.188
L			Sweep425	
M	3 HARs	NSS41	Sweep505	
P			Sweep575; Sweep576	
R	1 HAR			uc.395
U	3 HARs			
2	4 HARs		Sweep107	
7		NSS45	Sweep524	
8	9 HARs			uc.385;uc.382
9	5 HARs			
11	**4 HARs**			



Hotspots contain known genetic disease mutations associated with seizures and developmental comorbidities

Cluster	Gene/Symbol	OMIM Disease related to seizures
A	RBM15 / DBT / GPSM2	Spinal muscular atrophy, autosomal recessive, Miller-Dieker lissencephaly syndrome, type 1 / Amyotrophic lateral sclerosis 25
C	CRB1 / ASPM / F13B / CFHR1	Leber congenital amaurosis 8 / Microcephaly 5, primary, autosomal recessive / Factor XIII B deficiency / Hemolytic uremic syndrome, atypical, susceptibility to
I	DYNRP1	Hermansky-Pudlak syndrome 7
L	AHW	3-methylglutaconic aciduria, type I
M	CEP57 / MED17 / MRE11A / ATM / AGAT1 / TYR	Mosaic variegated aneuploidy syndrome 2 / Microcephaly, postnatal progressive, with seizures and brain atrophy / Ataxia-telangiectasia-like disorder / Ataxia-telangiectasia / Alpha-methylacetoacetic aciduria / Waardenburg syndrome
N	PEX5 / EMG1 / AZM	Peroxisome biogenesis disorder 2A (Zellweger) / Bowen-Conradi syndrome / Acrocephalosyndactyly, Noack type
R	CLN3	Spinal muscular atrophy, myopathy, and
T	NDUFS7 / GAMT	Leigh syndrome / Cerebral creatine deficiency syndrome 2
U	GPC3 / HPRT1 / PHF6	Simpson-Golabi-Behmel syndrome, type 1 / Lesch-Nyhan syndrome / Borjeson-Forssman-Lehmann syndrome
2	AGPS / CEBIG / PRKRA	Rhizomelic chondrodysplasia punctata, type 3 / Retinitis pigmentosa 24 / Dystonia 16
4	LIPA	Wolman disease
7	TMEM5 / GNS	Muscular dystrophy-dystroglycanopathy, type A2 / Mucopolysaccharidosis type IIID
8	BUB1B	Mosaic variegated aneuploidy syndrome
11	TNFRSF11A / PIGN / CCRE1 / RAX	Osteogenesis, autosomal recessive 7 / Multiple congenital anomalies-hypotonia-seizures syndrome 1 / Hennekam lymphangiectasia-lymphedema syndrome / Microphthalmia, isolated 3

SYSTEMS BIOLOGY OF HUMAN EPILEPSY

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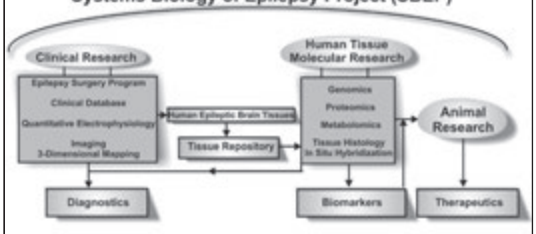
Multivariate Interactome Links Co-Morbidities

Animal Model and Co-Morbidities

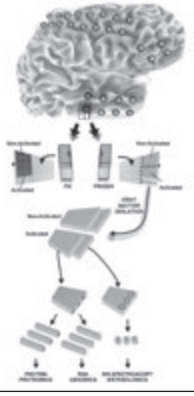
SYSTEMS BIOLOGY OF HUMAN EPILEPSY

Multivariate Interactome

Systems Biology of Epilepsy Project (SBEP)



Dachet F and Loeb JA



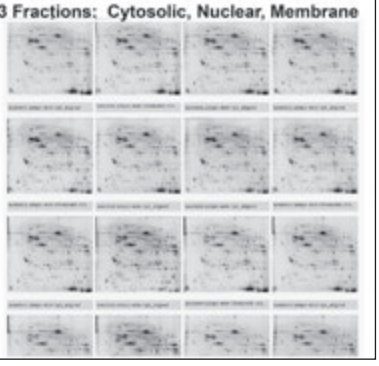
Proteomics

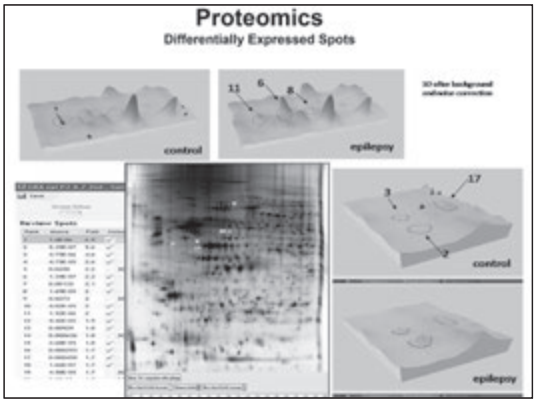
3 Fractions: Cytosolic, Nuclear, Membrane

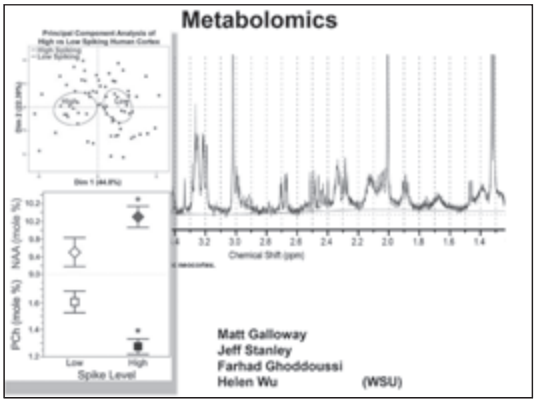
Cy2 – Internal Standard

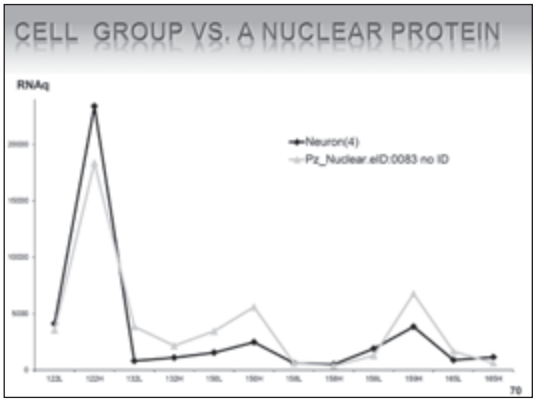
Cy3/Cy5 dye swap between High & Low spike frequency

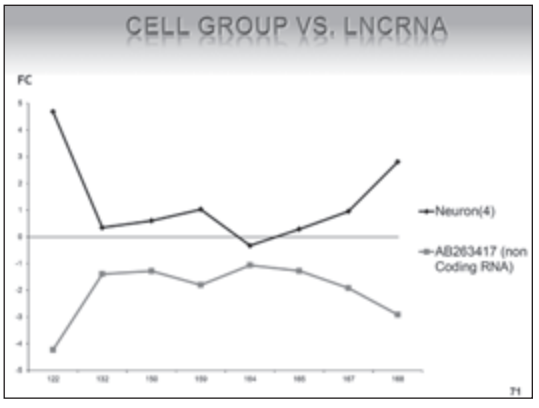
Gal Aviram
Ed Dratz
MSU
(Montana/Chemistry)

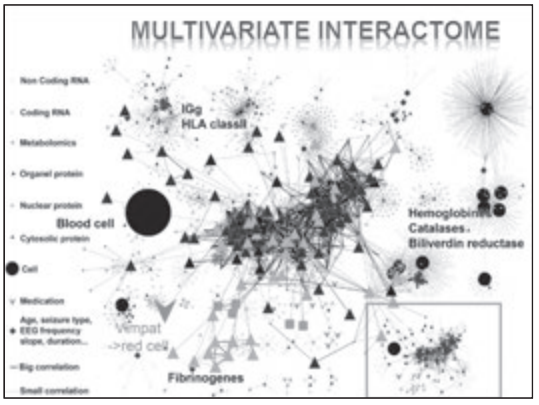


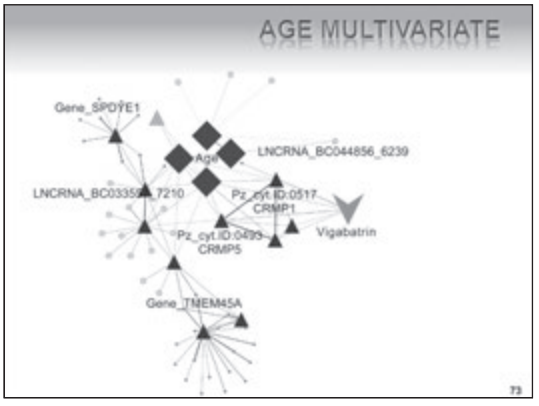

Proteomics
Differentially Expressed Spots
control
epilepsy
11
6
8
17
3
control
epilepsy

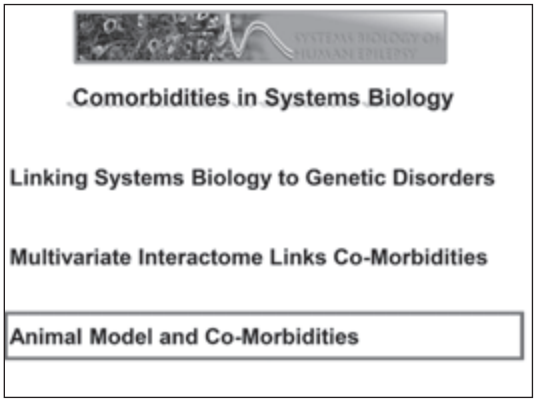

Metabolomics
Principal Component Analysis of
High vs Low Spiking Human Cortex
High Spiking
Low Spiking
Dim 1 (44.8%)
Chemical Shift (ppm)
NAA (mole %)
PCh (mole %)
Low
High
Spike Level
Matt Galloway
Jeff Stanley
Farhad Ghoddoussi
Helen Wu
(WSU)


CELL GROUP VS. A NUCLEAR PROTEIN
RNAq
Neuron(4)
Pz_Nuclear.eID:0083 no ID
70


CELL GROUP VS. LNCRNA
FC
Neuron(4)
AB263417 (non Coding RNA)
71


MULTIVARIATE INTERACTOME
Non Coding RNA
Coding RNA
Metabolomics
Organel protein
Nuclear protein
Blood cell
Cytosolic protein
Cell
Medication
Age, seizure type, EEG frequency slope, duration...
Big correlation
Small correlation
IGg
HLA classII
Hemoglobins
Catalases.
Biliverdin reductase
Vimpat
->red cell
Fibrinogenes


AGE MULTIVARIATE
Gene_SPDYE1
Age
LNCRNA_BC044856_6239
LNCRNA_BC033581_7210
Pz_cyt.ID:0517
CRMP1
Pz_cyt.ID:0439
CRMP5
Vigabatrin
Gene_TMEM45A
73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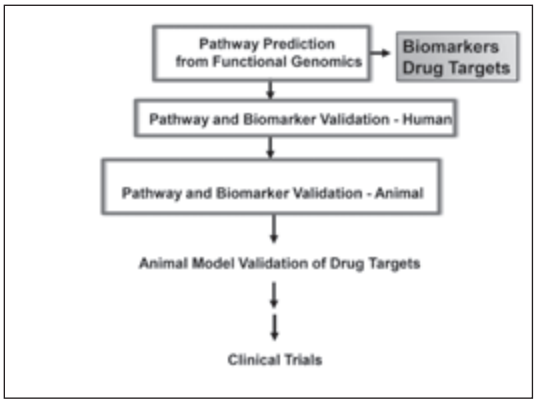
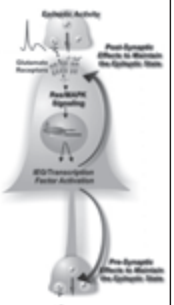

Pathway Prediction from Functional Genomics
Biomarkers Drug Targets
Pathway and Biomarker Validation - Human
Pathway and Biomarker Validation - Animal
Animal Model Validation of Drug Targets
Clinical Trials

Need An Animal Model of Human Neocortical Epilepsy



Goals:

- Electrically Similar
- Same Molecular 'Fingerprint'
- Development of Targeted Therapeutics

Berkmeier DT., Senador D, Leclercq K, Pai D, Hua J, Boulos NN, Kaminski RM, Loeb JA. (2012) Electrical, Molecular and Behavioral Consequences of the Interictal Epileptic State in the Rat. Neurobiol Disease, 47(1):93-101.

Tetanus Toxin Somatosensory Cortex Interictal Spiking Model

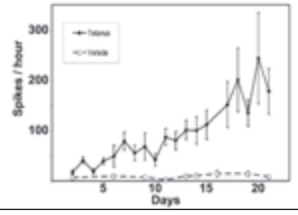
Setup

Record

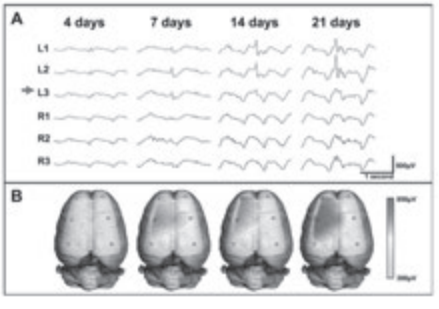
Divide tissue

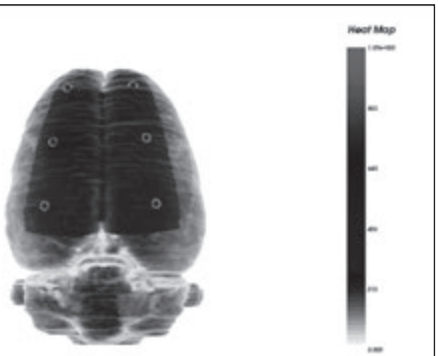
Focal interictal spiking

Chronic and progressive

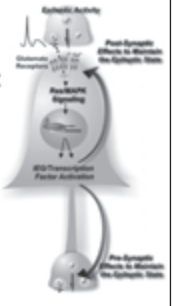


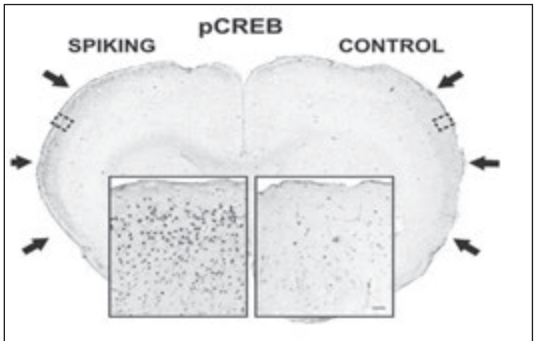
Spread of interictal spike field



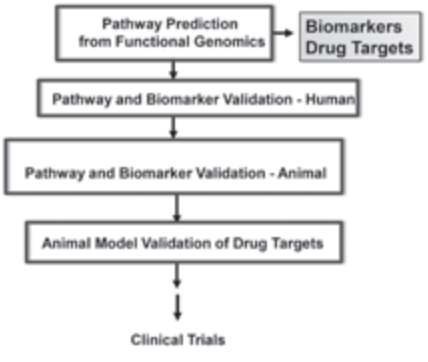


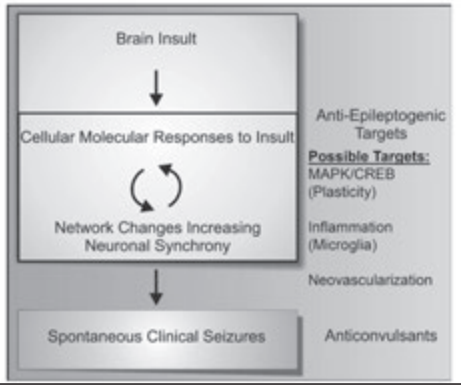
Is interictal spiking sufficient to replicate the molecular/ cellular changes in human epilepsy?

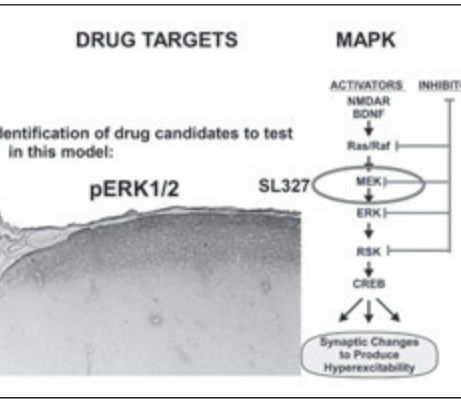


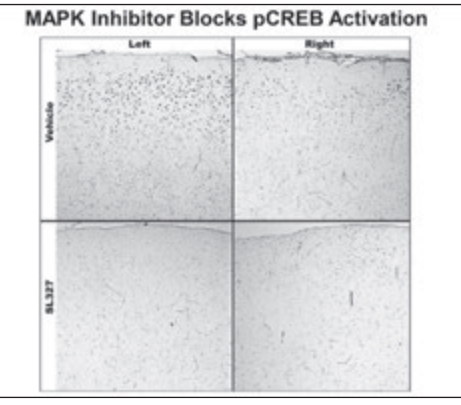


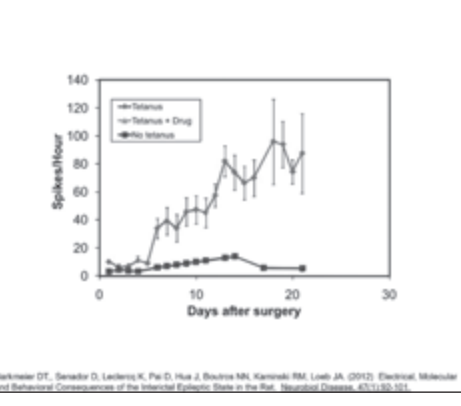
CREB is phosphorylated on spiking side in layers 2/3



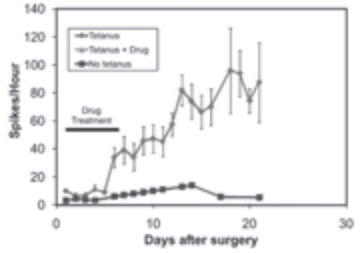








Barkmeier DT., Senador D, Leclercq K, Pai D, Hua J, Boutros NN, Kaminski RM, Loeb JA. (2012) Electrical, Molecular and Behavioral Consequences of the Interictal Epileptic State in the Rat. Neurobiol Disease. 47(1):93-101.



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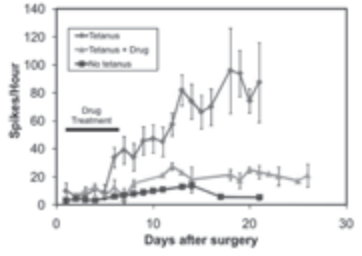
MAPK Inhibitor Blocks the Development of Epileptic Spiking (Interictal)



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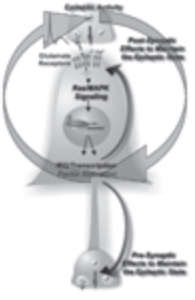
MAP Kinase inhibition blocks the development of interictal spiking

"Morning after pill"



The Interictal Epileptic State and Behavior

1. Improved behavior in epileptic children with reduced interictal spiking.
2. Many patients psychiatric disorders have interictal spiking with or without seizures (ADHD).

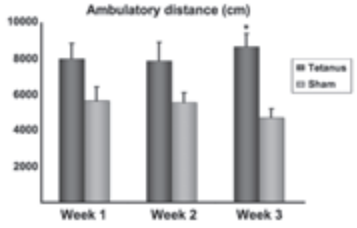
Barkmeier DT., Senador D, Leclercq K, Pai D, Hua J, Boutros NN, Kaminski RM, Loeb JA. (2012) Electrical, Molecular and Behavioral Consequences of the Interictal Epileptic State in the Rat. Neurobiol Disease. 47(1):92-101.

Open field activity

Does interictal spiking alter behavior?

Spiking rats are 'hyperactive'

Interictal spiking rats move more than sham-operated controls (n=4+4)



Focal Interictal Spikes:

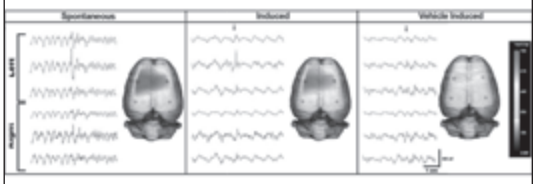
No Associated Clinical Symptoms

Associated Clinical Symptoms - 1

Associated Clinical Symptoms - 2

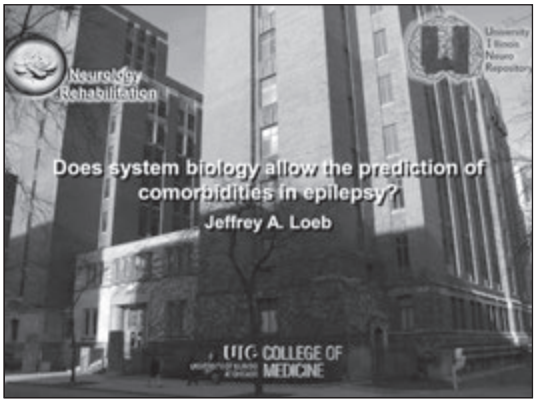
Inducible with Audiogenic Stimulus

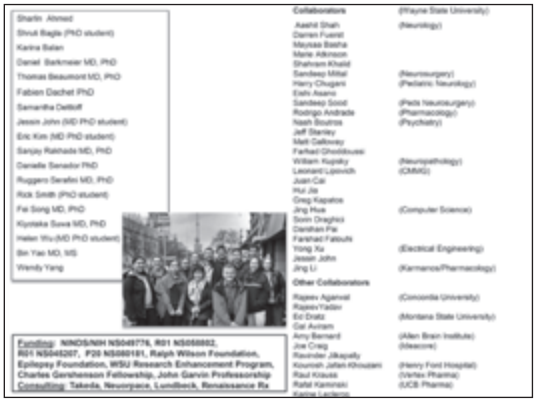
Environmentally-Induced
Spikes have a Similar Field as Spontaneous Interictal Spikes



The Interictal Epileptic State and Behavior

- Interictal spiking modulates behavior in animals.
- First demonstration that the environment (auditory stimulus) induces interictal spiking.
- Raises questions as to whether drugs that could block or prevent interictal spiking could be useful for psychiatric symptoms in brain injured patients with and without epilepsy.





Merab Kokaia (USA)

NEONEUROGENESIS AND ITS ROLE IN EPILEPTOGENESIS AND COMORBIDITIES

Eugene Trinka (Austria)

ANTIEPILEPTOGENESIS IN HUMANS – TIME TO TRANSLATE?

Alon Friedman (Canada/Israel)

PRO-CONVULSANT PLASTICITY

Uwe Heneman(Germany) & Yuri Zilberter (France)

UNCOUPLING BETWEEN NEURONAL AND METABOLIC ACTIVITIES

João Pereira Leite (Brazil)

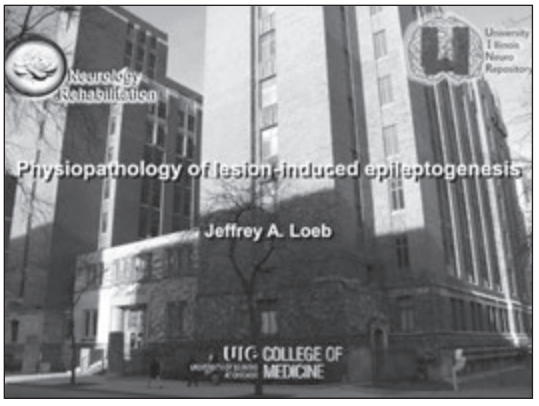
CHANGES IN THALAMO-CORTICAL PATHWAYS MAY UNDERLIE PSYCHIATRIC COMORBIDITIES IN EPILEPSY

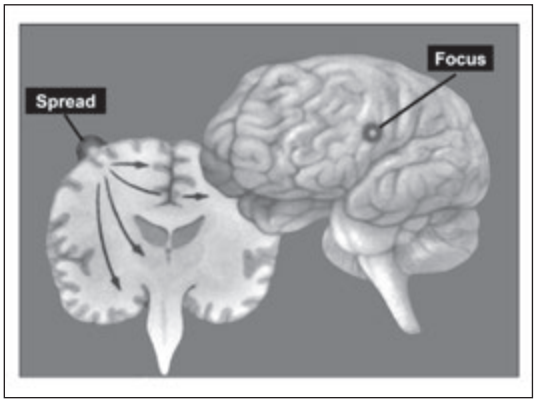
Alon Friedman (Canada/Israel)

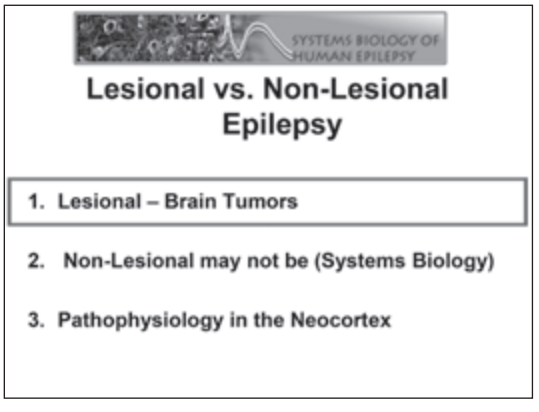
NEUROVASCULAR INTERACTIONS IN EPILEPTOGENESIS

Jeffrey Loeb (USA)

PHYSIOPATHOLOGY OF LESION-INDUCED EPILEPTOGENESIS

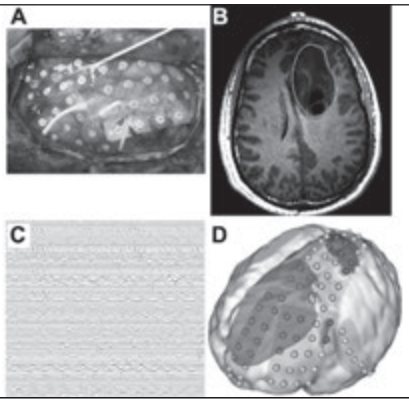






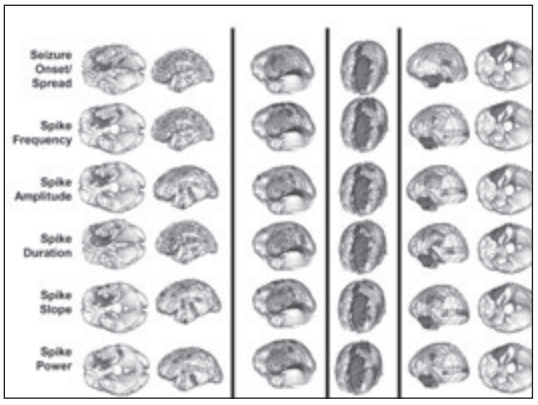
What about brain tumors?

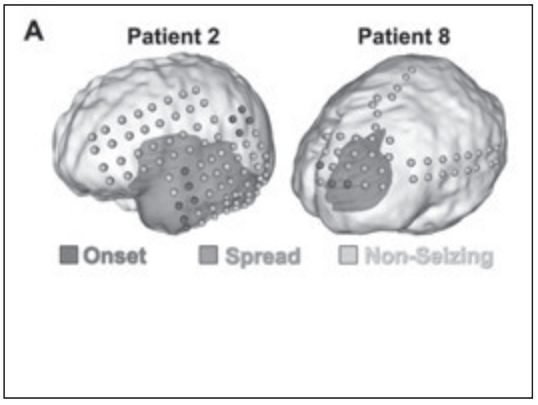
Dan Barkmeier, MD, PhD
Aashit Shah, MD
Sandeep Mittal, MD

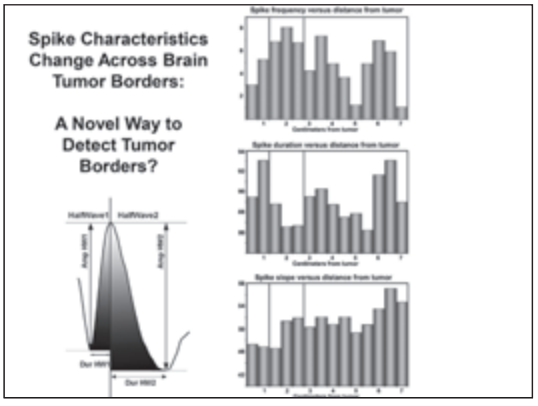


Brain Tumor Patients with Long-Term Grid Recordings

Patient	Tumor Type	Age	Sex	Infiltrating	Acad/Extra-axial	Tumor outcome
1	Oligodendroglioma with astrocytic component - Grade 2	34	M	Y	A	No recurrence
2	Oligoastrocytoma - Grade 3	45	M	Y	A	Recurrence - Died
3	Oligodendroglioma infiltrating	23	M	Y	A	No recurrence
4	Ganglioglioma	22	M	Y	A	No recurrence
5	DNET	47	F	N	A	No recurrence
6	Mixed high grade tumor: Oligoastrocytoma - Grade 3	42	F	Y	A	Recurrence - Died
7	Anaplastic mixed glioma - Grade 3	26	F	Y	A	No recurrence
8	Oligoastrocytoma - Grades 2 and 3 mixed	44	M	Y	A	No recurrence
9	Dermoid cyst	28	F	N	E	No recurrence
10	Epidermoid	50	M	N	E	No recurrence
11	Meningioma (transitional type)	40	F	N	E	No recurrence







What about brain tumors?

1. Systems biology to study epilepsy in the context of brain tumors.
2. Seizures and Spikes are often outside the tumor resection margin.
3. Does the placement of long-term grids improve seizure outcome?
4. Does the placement of long-term grids improve brain tumor outcome?

Lesional vs. Non-Lesional Epilepsy

1. Lesional – Brain Tumors
2. Non-Lesional may not be (Systems Biology)
3. Pathophysiology in the Neocortex

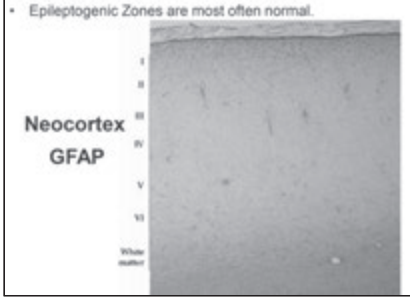
SYSTEMS BIOLOGY OF HUMAN EPILEPSY

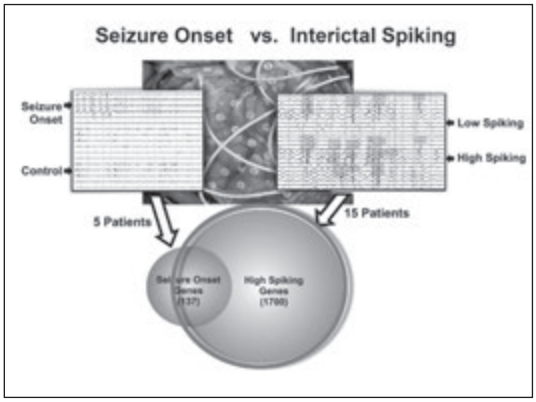
Is Non-Lesional Epilepsy truly Non-Lesional?

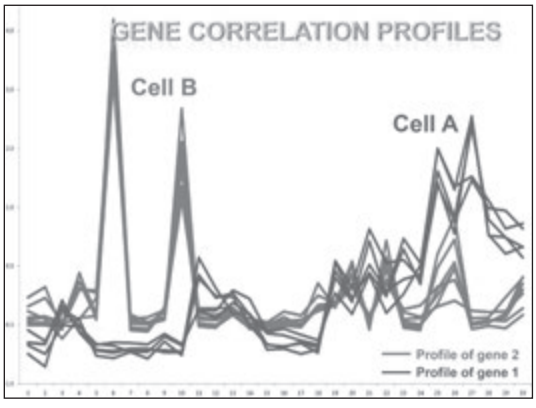
'Cellular Interactome'

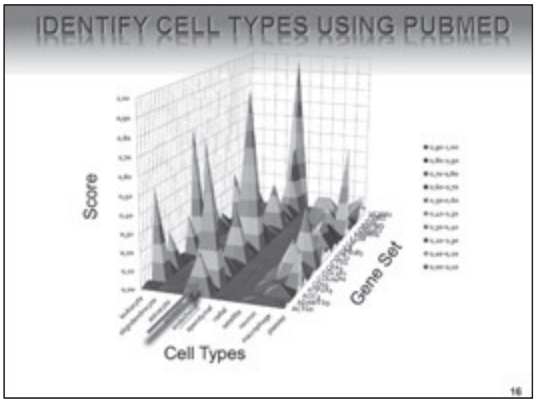
Dachet F, Bagla S, Keren-Aviram G, Morton A, Balan K, Saadat L, Valyi-Nagy T, Kupsky W, Song F, Dratz E, Loeb JA (2015) Predicting novel histopathological microlesions in human epileptic brain through transcriptional clustering. Brain.

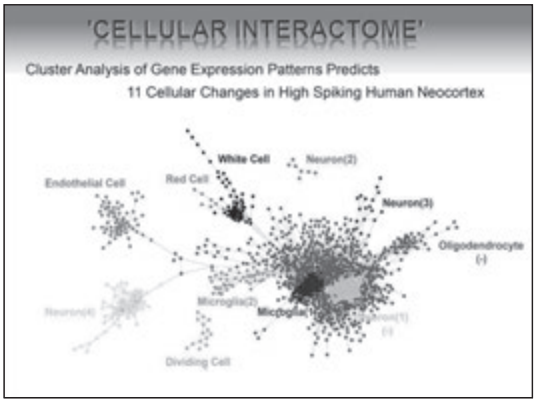
- Many Lesions Associated with Neocortical Epilepsy
- Epileptogenic Zones are most often normal.

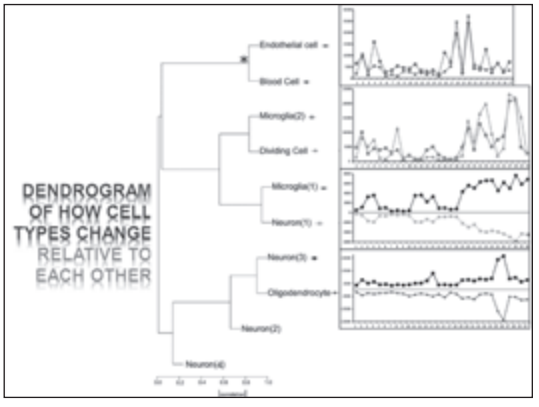


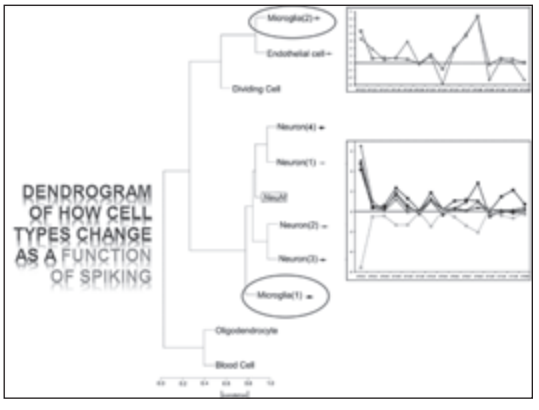


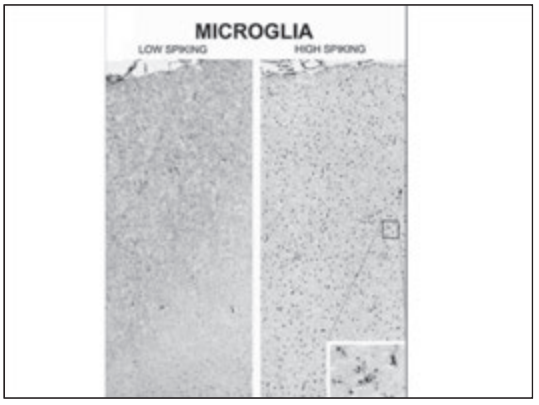


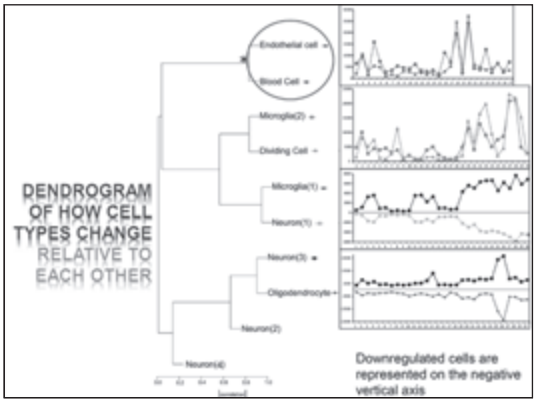

IDENTIFY CELL TYPES USING PUBMED
Score
Gene Set
Cell Types
16

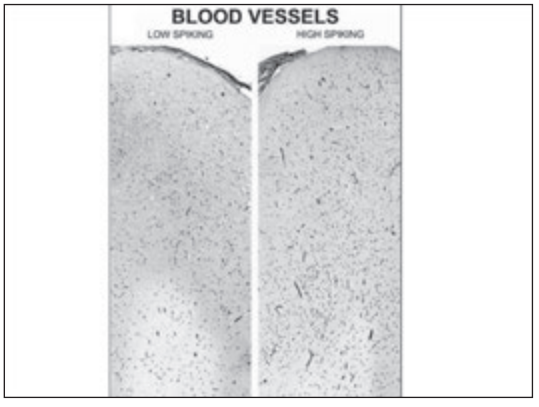

'CELLULAR INTERACTOME'
Cluster Analysis of Gene Expression Patterns Predicts
11 Cellular Changes in High Spiking Human Neocortex
White Cell
Neuron(2)
Endothelial Cell
Red Cell
Neuron(3)
Oligodendrocyte
(-)
Microglia(2)
Dividing Cell

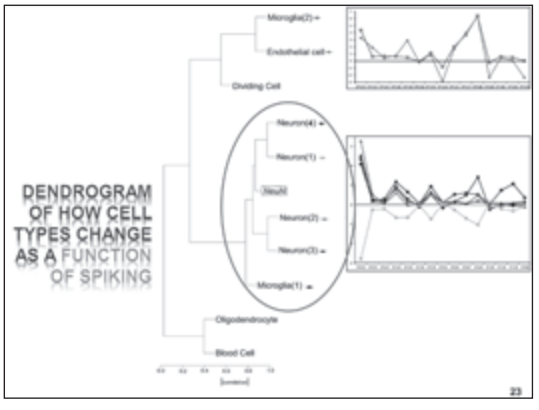

DENDROGRAM
OF HOW CELL
TYPES CHANGE
RELATIVE TO
EACH OTHER
Endothelial cell
Blood Cell
Microglia(2)
Dividing Cell
Microglia(1)
Neuron(1)
Neuron(3)
Oligodendrocyte
Neuron(2)
Neuron(4)


DENDROGRAM
OF HOW CELL
TYPES CHANGE
AS A FUNCTION
OF SPIKING
Microglia(2)
Endothelial cell
Dividing Cell
Neuron(4)
Neuron(1)
Neuron(2)
Neuron(3)
Microglia(1)
Oligodendrocyte
Blood Cell

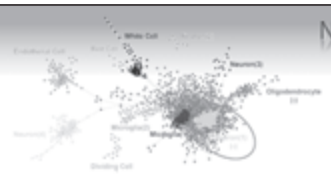

MICROGLIA
LOW SPIKING
HIGH SPIKING


DENDROGRAM OF HOW CELL TYPES CHANGE RELATIVE TO EACH OTHER
Endothelial cell
Blood Cell
Microglia(2)
Dividing Cell
Microglia(1)
Neuron(1)
Neuron(3)
Oligodendrocyte
Neuron(2)
Neuron(4)
Downregulated cells are represented on the negative vertical axis


BLOOD VESSELS
LOW SPIKING
HIGH SPIKING


DENDROGRAM OF HOW CELL TYPES CHANGE AS A FUNCTION OF SPIKING
Microglia(2)
Endothelial cell
Dividing Cell
Neuron(4)
Neuron(1)
Neuron(2)
Neuron(3)
Microglia(1)
Oligodendrocyte
Blood Cell
23

NEURON (1)



- Cluster of 280 genes downregulated
- The layer IV gene ***RorB*** is part of this cluster
- The NeuN gene is part of this cluster
- Predicts a decrease in layer IV NeuN neurons in high spiking brain

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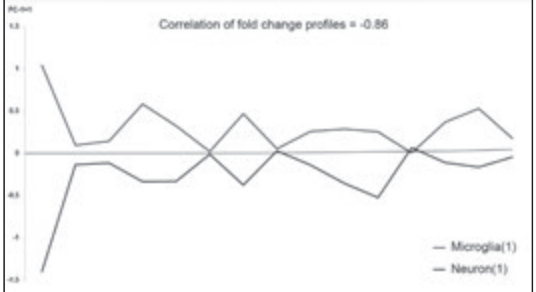
INVERSE RELATIONSHIP BETWEEN NEURON (1) AND MICROGLIA (1)



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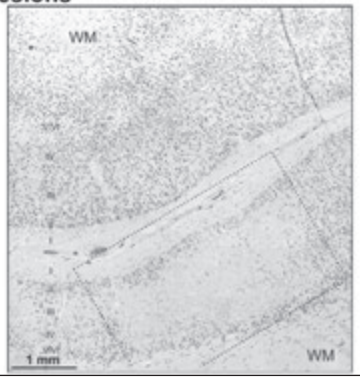
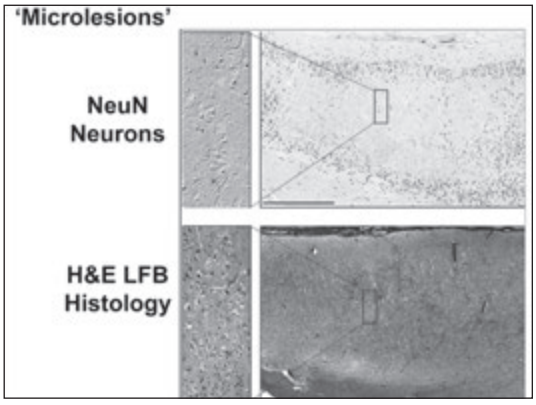
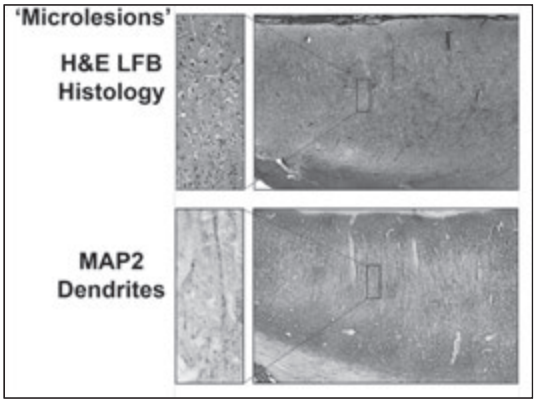
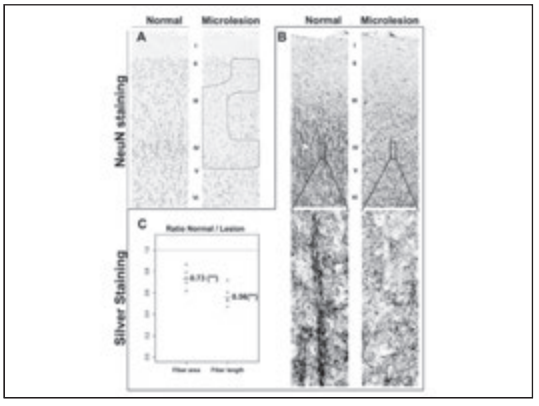
'Microlesions'

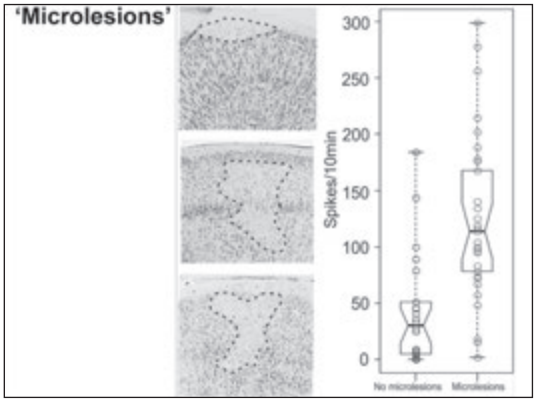


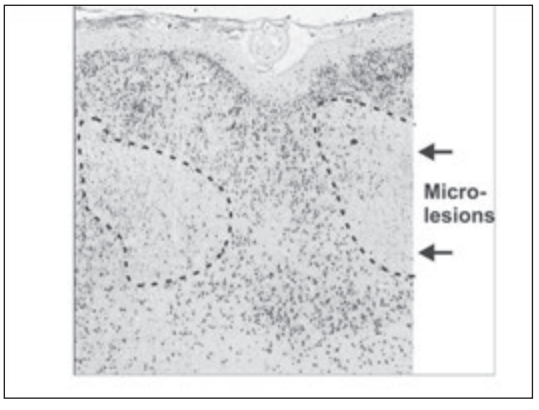
'Microlesions'




'Microlesions'
H&E LFB
Histology
MAP2
Dendrites

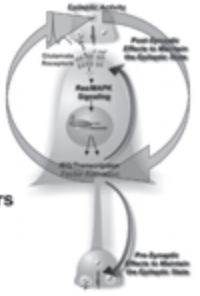

Normal
Microlesion
Normal
Microlesion
A
B
NeuN staining
C
Ratio Normal / Lesion
Silver Staining


'Microlesions'
300
250
200
150
100
50
0
Spikes/10min
No microlesions
Microlesions


Micro-
lesions

Activation of MAPK-CREB in superficial layers linked to ongoing interictal spiking

Highly associated with 'microlesions' in deeper layers



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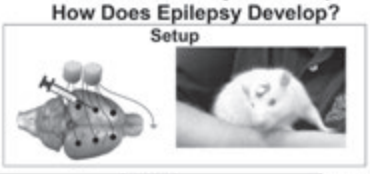
Lesional vs. Non-Lesional Epilepsy

1. Lesional – Brain Tumors
2. Non-Lesional may not be (Systems Biology)
3. Pathophysiology in the Neocortex

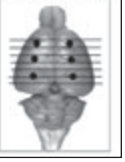
Tetanus Toxin Somatosensory Cortex Spiking Model How Does Epilepsy Develop?

Setup



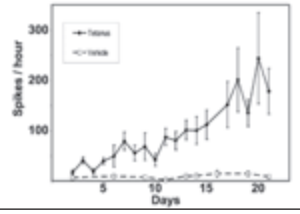
Record

Divide tissue

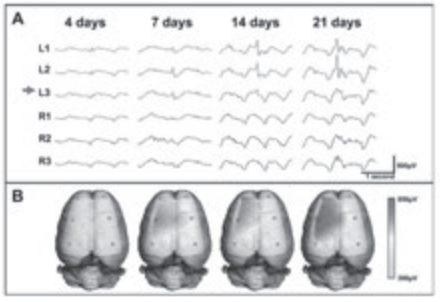


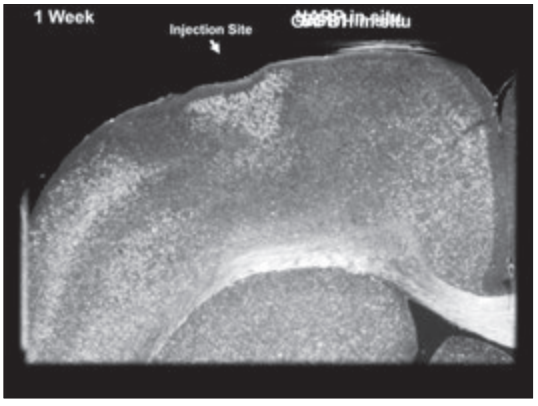
Focal interictal spiking

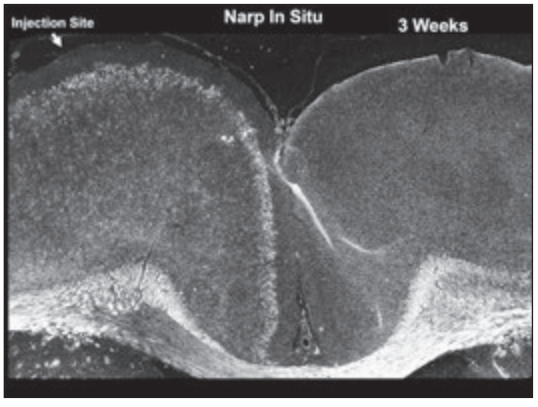
Chronic and progressive

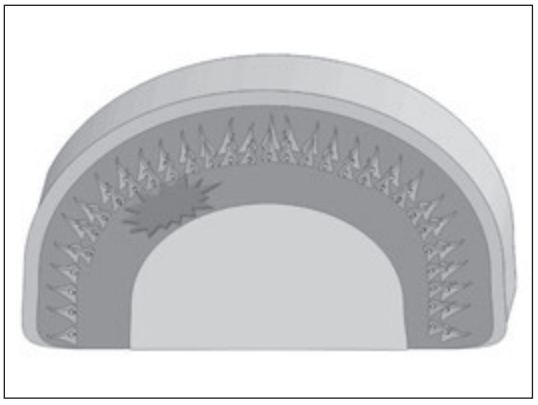


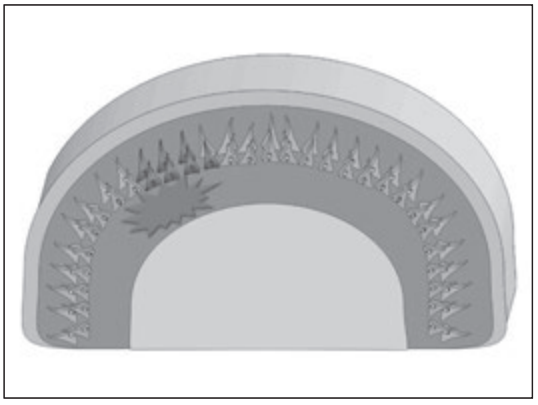
'Lateral' Spread of Interictal Spike Field

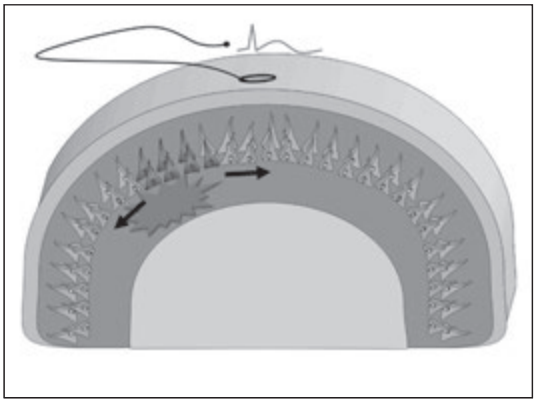


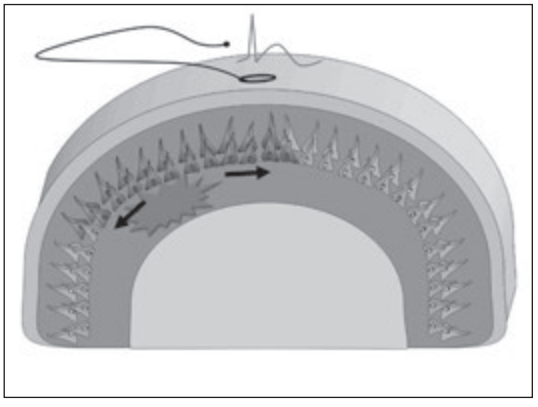


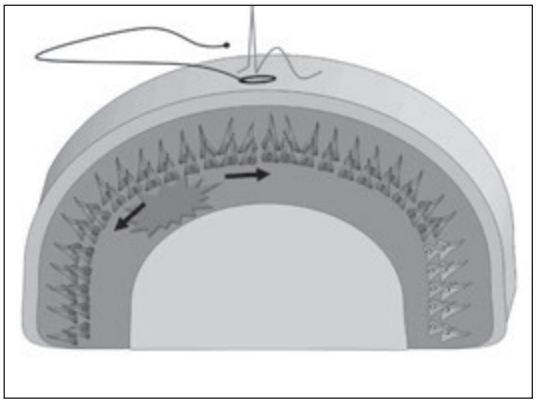


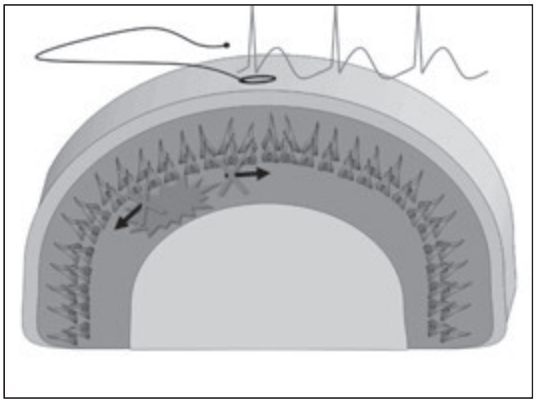




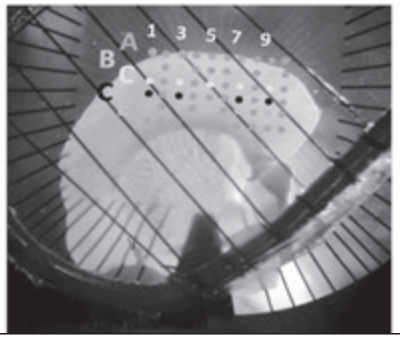




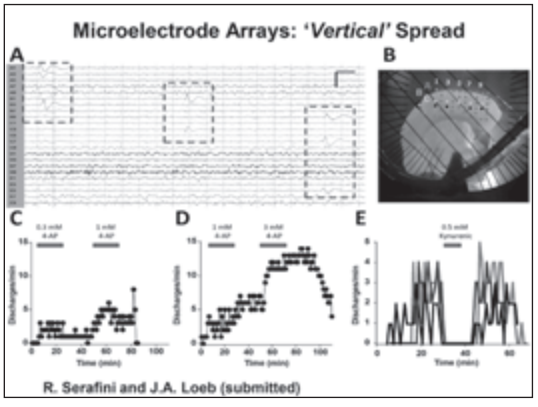




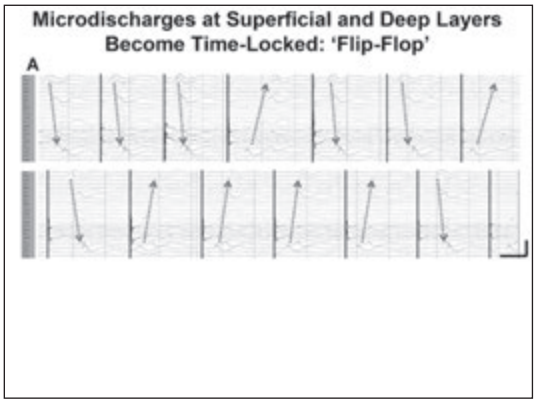
Microelectrode Arrays: '*Vertical*' Spread



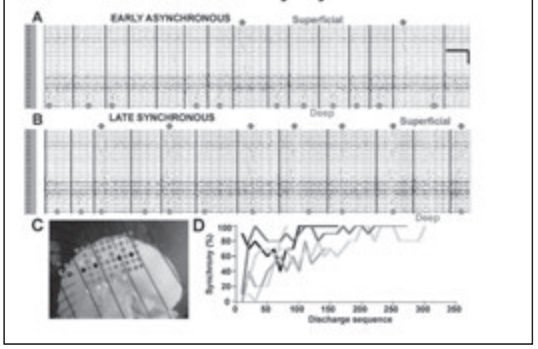
Microelectrode Arrays: '*Vertical*' Spread



Microdischarges at Superficial and Deep Layers Become Time-Locked: 'Flip-Flop'

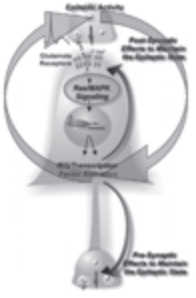


Microdischarges at Superficial and Deep Layers Become '*Vertically*' Synchronous

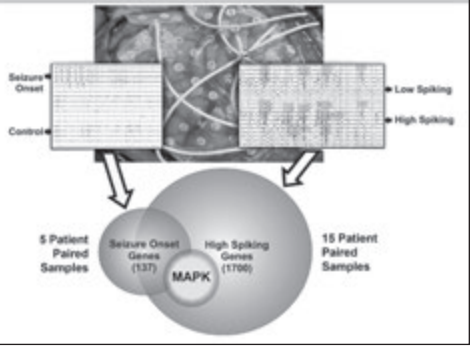


Ongoing interictal epileptic activity drives pathways that produce *SYNAPTIC* changes that maintain hypersynchrony and spreads both *laterally* and *vertically*.

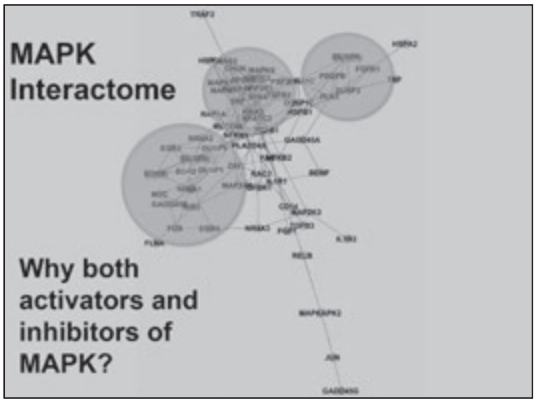
Is there anything that stops the lateral spead?

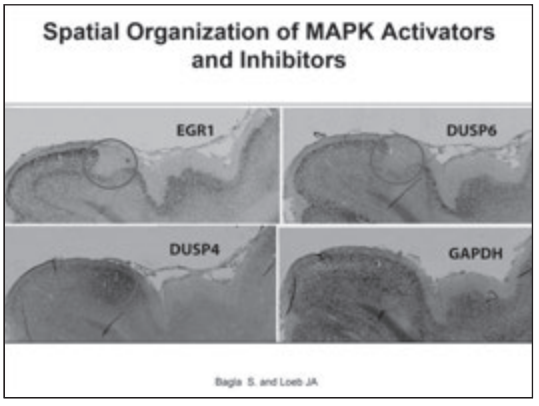


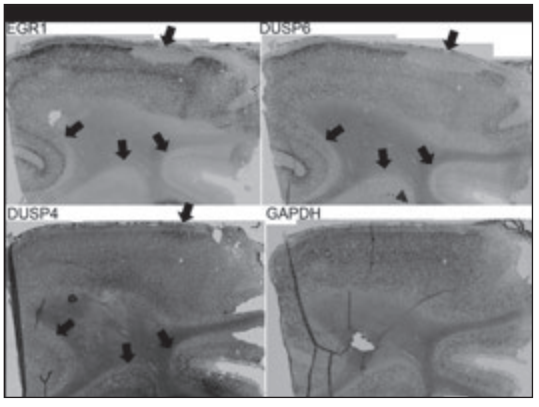
MAPK Pathway is linked to Interictal Activity, not to Seizures

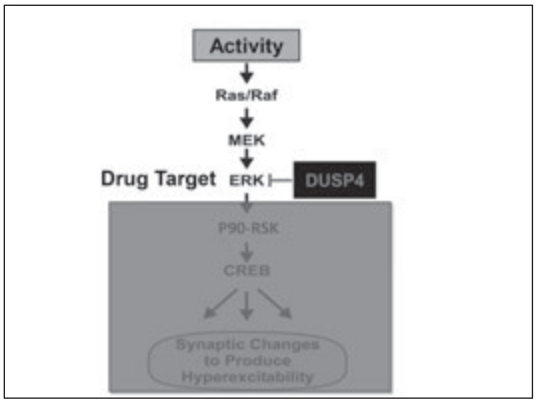


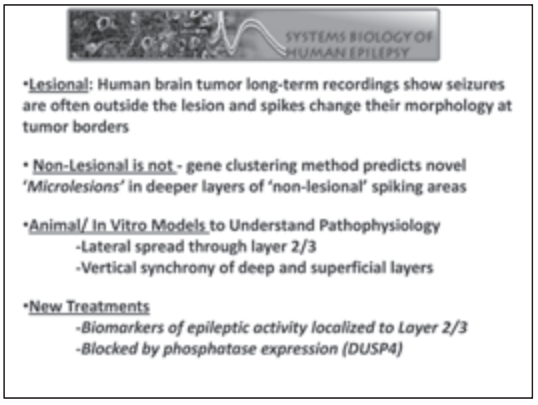
MAPK Interactome

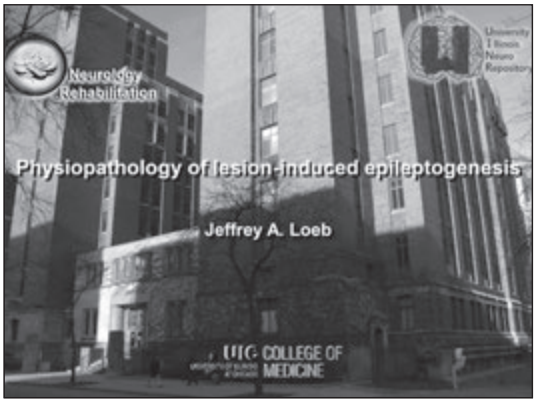

MAPK
Interactome
Why both
activators and
inhibitors of
MAPK?

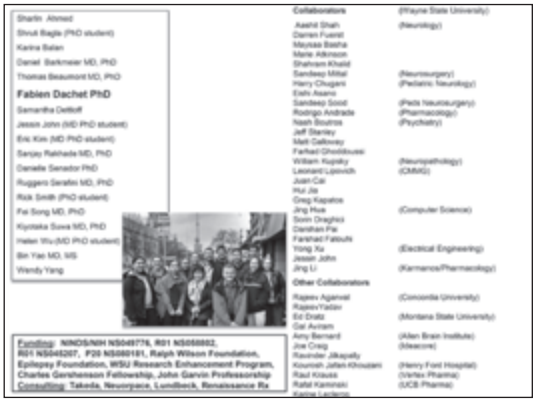

Spatial Organization of MAPK Activators
and Inhibitors
EGR1
DUSP6
DUSP4
GAPDH
Bagla S. and Loeb JA


EGR1
DUSP6
DUSP4
GAPDH


Activity
Ras/Raf
MEK
Drug Target
ERK
DUSP4
P90-RSK
CREB
Synaptic Changes
to Produce
Hyperexcitability


SYSTEMS BIOLOGY OF HUMAN EPILEPSY
•Lesional: Human brain tumor long-term recordings show seizures are often outside the lesion and spikes change their morphology at tumor borders
• Non-Lesional is not - gene clustering method predicts novel '*Microlesions*' in deeper layers of 'non-lesional' spiking areas
•Animal/ In Vitro Models to Understand Pathophysiology
-Lateral spread through layer 2/3
-Vertical synchrony of deep and superficial layers
•New Treatments
-*Biomarkers of epileptic activity localized to Layer 2/3*
-*Blocked by phosphatase expression (DUSP4)*


Neurology Rehabilitation
University Illinois Neuro Repository
Physiopathology of lesion-induced epileptogenesis
Jeffrey A. Loeb
UIC COLLEGE OF MEDICINE


Fabien Dachet PhD
Collaborators
Other Collaborators
Funding: NINDS/NIH NS045776, R01 NS050892, R01 NS045207, P20 NS080181, Ralph Wilson Foundation, Epilepsy Foundation, WSU Research Enhancement Program, Charles Gershenson Fellowship, John Garvin Professorship
Consulting: Takeda, Neuropace, Lundbeck, Renaissance Rx

Uwe Heineman (Germany)

MODELS OF REFRACTORY EPILEPSY

Merab Kokaia (USA)

TEACHING INHIBITORY INTERNEURONS TO DO THEIR JOB

Giuseppe Bertini (Italy)

HOW TO DESIGN A TRANSLATIONAL RESEARCH?

Antonio Lucio Teixeira (Brazil)

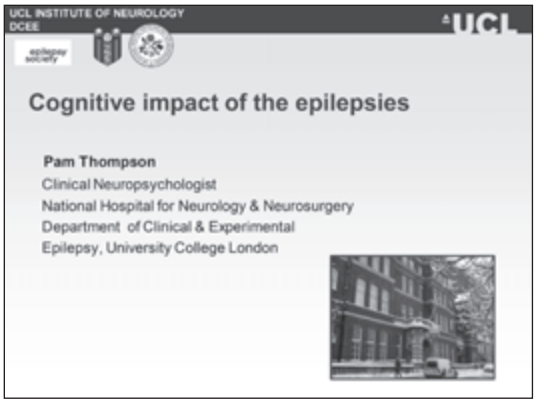
MOOD DISORDERS IN EPILEPSY: EPIDEMIOLOGY, CLINICAL DIAGNOSIS AND BIOMARKERS

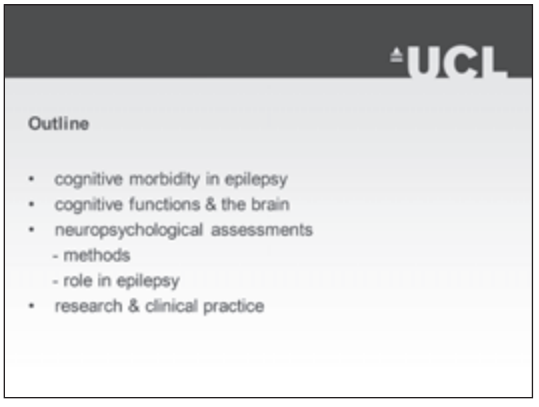
Andres Kanner (USA)

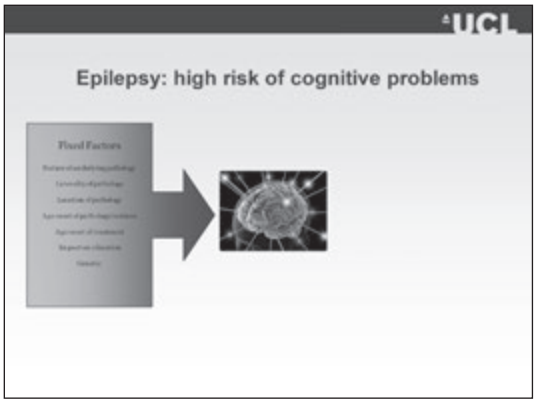
WHO? WHY? WHEN? WHAT SHOULD BE THE ROLE OF THE NEUROLOGIST IN THE EVALUATION AND MANAGEMENT OF COMMON PSYCHIATRIC COMORBIDITIES IN PATIENTS WITH EPILEPSY?

PAMELA THOMPSON (ENGLAND)

COGNITIVE IMPACT IN THE EPILEPSIES

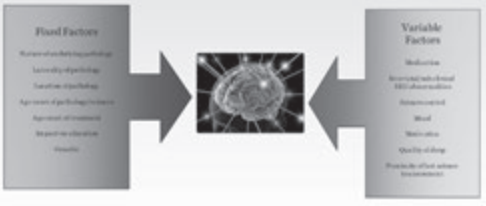






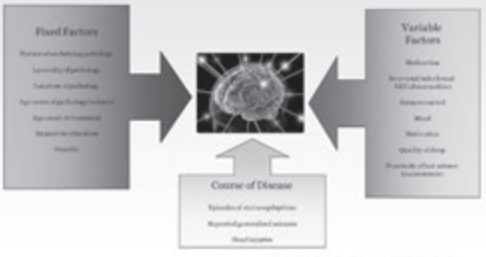
UCL

Epilepsy: high risk of cognitive problems



UCL

Epilepsy: high risk of cognitive problems



Adapted from Baxendale & Thompson 2010

UCL

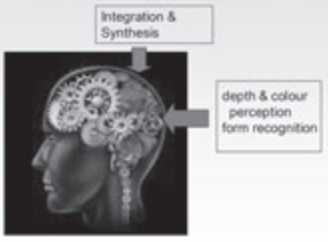
Left Hemisphere
Language
talking
understanding
reading/ writing

Right Hemisphere
Visual/spatial
reasoning
integration
identification

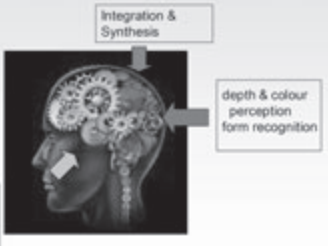
UCL

depth & colour
perception
form recognition

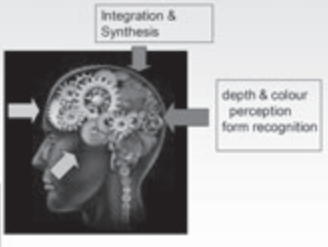
UCL



UCL



UCL



UCL

Neuropsychological Assessment

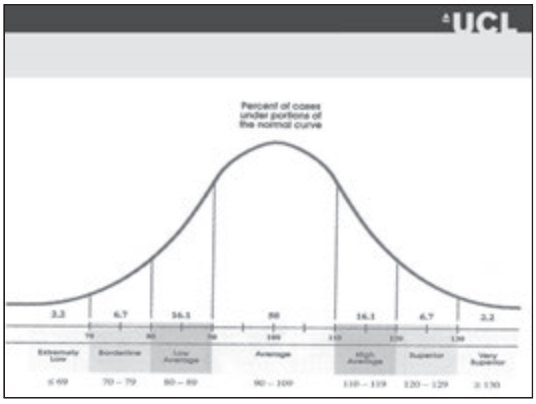
- systematic measurement: standardised tests
- compare to normative data
- assess change over time
- domains

  verbal abilities, visuo-spatial abilities, memory, language & executive functions

WAIS IV (2010)

- Four index scores representing major components of intelligence:
- Verbal Comprehension Index (VCI)
- Perceptual Reasoning Index (PRI)
- Working Memory Index (WMI)
- Processing Speed Index (PSI)

- Two broad scores used to summarize general intellectual abilities:
- Full Scale IQ (FSIQ)
- General Ability Index (GAI)



Verbal Comprehension Index

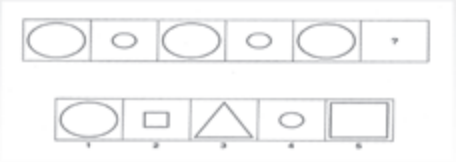
- Similarities
  - horse & tiger
  - sadness & happiness
- Vocabulary
  - chair
  - confide
- Information
  - What do we use a thermometer for?
  - What is the circumference of the earth at the equator?

Perceptual Reasoning Index (PRI)

- Block Design
- Matrix Reasoning
- Visual puzzles

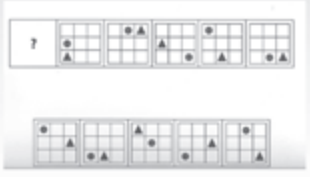
UCL

Matrix Reasoning



UCL

Matrix Reasoning



UCL

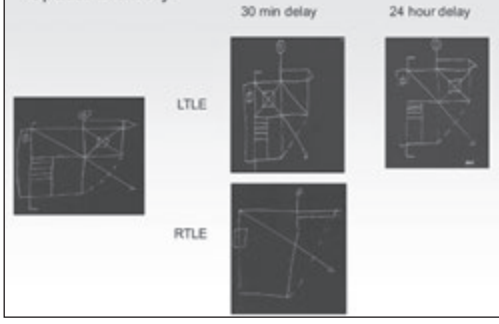
Memory

Verbal:
- Story Recall
- List Learning
- Word Recognition

Visuo-spatial:
- Figure Recall
- Design Learning
- Face/Scene Recognition

UCL

Spatial Memory



UCL

Naming



UCL

Executive functions

Trail Making A

UCL

Executive functions

Trail Making B

UCL

Executive functions

The Stroop Test

RED BLUE GREEN RED BLUE ..

BLUE GREEN RED BLUE RED BLUE GREEN

UCL

Memory Questionnaire

Memory Failures Questionnaire (MFQ): 19 questions

- How frequently do you?

  Forget where you have put something.....
  Forget peoples names....
  Find that a word is on the tip of the tongue
  Forget events that happen to you..
  Forget you were told something....
  Forget to take your medication

- frequency rating < 6 months to > once a day
- severity rating 0= no nuisance – 3 = severe nuisance

UCL

Dysexecutive Questionnaire DEX

20 questions: self-rating & observer versions

- I act without thinking, doing the first thing that comes to mind
- I have difficulty thinking ahead or planning for the future
- I lose my temper at the slightest thing
- I am easily distracted

severity rating: 0= never – 5 very often

UCL

Neuropsychological assessment: role

- ↑ risk of cognitive deficits: early identification important
  school & work performance
  social functioning & self-esteem
- may contribute to diagnosis
  localisation related epilepsies v generalised epilepsies
- prognosis
  is there evidence for a progressive condition?
- impact of treatment
  drugs and surgery

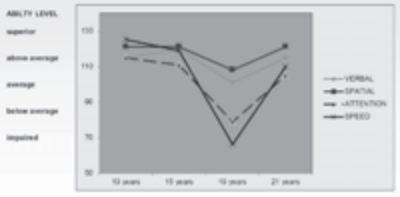
UCL

KR: focal epilepsy

- age of onset = 11 years
  EEG: right hemisphere inter-ictal EEG abnormalities
  MRI: normal
- seizure history
  11-15 years: well controlled
  15-16 years: up to 2/week → medication changes
  18 years: 1/month
- academic performance
  16 years doing well = 9 excellent grades; GCSEs (7@ A*)
  18 years failed Advanced levels (E & F grades)

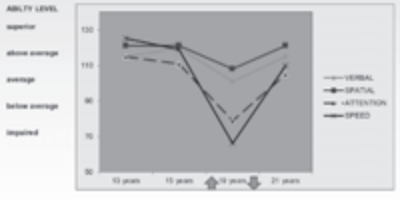
UCL

KR:Performance levels on the WAIS-IV



UCL

KR:Performance levels on the WAIS-IV



TOPIRAMATE

UCL

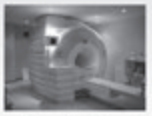
Research evidence: Topiramate

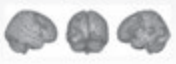
- Thompson et al 2000
  cognitive deficits going on TPM
  reduced working memory; mental slowing
- Kockelmann et al 2003
  cognitive gains coming off TPM
- Loring et al 2011
  TPM dose related deficits in healthy controls

UCL

Topiramate: mechanisms

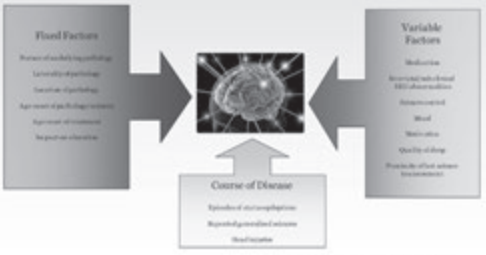
Yasuda et al 2013
fMRI studies
Verbal fluency paradigm
- X-sectional TPM+ /TPM-
- 2 patients on/off
- healthy controls single dose





UCL

Epilepsy: high risk of cognitive problems



Adapted from Baxendale & Thompson 2010

UCL

Persisting deficits

- temporal lobes
  - most epileptogenic region
  - brain structures most involved with memory
  - memory the *signature* cognitive impairment
- frontal lobes
  - impaired flexibility
  - poor planning
  - reduced working memory capacity
  - difficulties focusing & maintaining attention

UCL

Executive skills weakness

Juvenile Myoclonic Epilepsy (JME)
most common idiopathic epilepsy syndrome

EM 24 yrs

- was well controlled on LTG
- 18 years :A levels: History, Music, Art A & B grades
- then moved to University
- poor grades exams & assignments
- re-sitting 3rd year
- increase in seizures

UCL

Executive skills deficits: EM; JME

Cognitive domain	centile	Ability level
word knowledge	95th	Superior
verbal reasoning	99th	Very Superior
spatial reasoning	99th	Very Superior
visual analysis	99th	Very Superior
naming	95th	Superior
verbal memory	79th	High Average
visual memory	99th	Very Superior

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Executive skills deficits: EM; JME

executive skills	centile
working memory	18th
Stroop (interference)	10 th
Cognitive switching	10 th
Verbal response suppression	< 5 th

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Research: Cognitive function in JME

- "immature', 'impulsive', 'disinibited'
- impaired frontal lobe functions
  Zamarian et al 2013
  Wandschneider et al 2012
- MRI studies: thalamo-fronto-cortical abnormalities
  O'Muircheartaigh et al 2012
  Vollmar et al 2012

UCL

Research: Cognitive function in JME

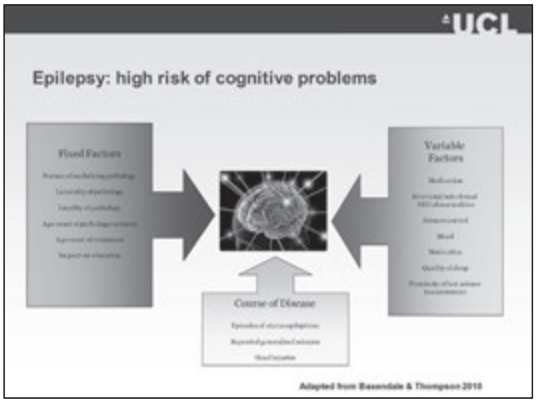
Wandschnieder et al 2013
- 22 JME : 11 controls
- IOWA Gambling task:
  ↑ gains with ↑ risks
  ↓ gains with ↓ risks

Impaired IGT in JME with ongoing seizures
WM abnormalities in the Default Mode Network

UCL

Persisting deficits

EM
- executive function weaknesses
- due to frontal network abnormalities in JME
- deficits ↑ prominent due to
  - ↓ external prompting @ university
  - ↑ reliance on self-directed learning
  - ↑ demands living away from family home
- findings & implications discussed with EM


UCL
Epilepsy: high risk of cognitive problems
Fixed Factors
Variable Factors
Course of Disease
Adapted from Baxendale & Thompson 2010

Marco Mula (England)

NEW ANTICONVULSANT DRUGS AND PSYCHIATRIC COMORBIDITIES

Antiepileptic drugs and behaviour

Marco Mula MD PhD
St George's University Hospital
London

Outline

- Positive effects of AEDs
- Negative effects of AEDs
- AEDs and behaviour: a class effect?

Indications of AEDs

- Epileptic seizures
- Neuropathic pain
- Migraine
- Movement disorders (i.e. essential tremor)
- Bipolar disorder (i.e. acute mania, maintenance treatment)
- Anxiety disorders (i.e. GAD)
- Potential use: impulse control, addiction, withdrawal, somatic complaints

Psychiatric Effects of AEDs

- CNS effects of AEDs not restricted to modulation of cortical excitability
- May modify systems that regulate mood and behaviour
- Antiepileptic and Psychotropic effects not independent and some AEDs used for depression, panic disorder, agitation, social phobia and anxiety
- Seizure control may have effect on mental state
- In any individual, any AED may have psychiatric effects and may often go unrecognized

Edwards et al. Epilepsy & Behavior 2001;2(1):28-36
Schmitz. Textbook of Epilepsy 2008
Pencle et al. Am J Psychiatry. 2003;160(3):533-40.
Feltner et al. J Clin Psychopharmacol. 2003;23(3):240-9

Positive and Negative psychotropic properties of AEDs

	POSITIVE	NEGATIVE
Barbiturates	Anxiolytic, hypnotic	Depression, irritability, ADHD-like
Carbamazepine Oxcarbazepine Eslicarbazepine	Mood stabilizer, anti-manic	Irritability
Ethosuximide	?	Psychosis (Forced normalisation)
Felbamate	Antidepressant?	Depression, anxiety, irritability
Gabapentin	Anti-anxiety (panic, social phobia)	Behavioural problems in children/ID
Lacosamide	?	-
Lamotrigine	Antidepressant, mood stabilizer	Insomnia, agitation, problems in ID/children
Levetiracetam	?	Aggression, emotional lability
Perampanel	?	Depression/Aggression
Phenytoin	Anti-manic	Encephalopathy
Pregabalin	Anti-anxiety (GAD)	-
Retigabine	?	Depression
Tiagabine	?	Depression/irritability
Topiramate	Binge eating disorder	Depression, psychosis, word finding difficulties
Valproate	Mood stabilizer (Acute mania)	Encephalopathy
Vigabatrin	?	Depression, aggression, psychosis,
Zonisamide	?	Depression, psychosis

AGENTS MAY NOT BE LICENCED FOR THESE INDICATIONS IN YOUR COUNTRY
Please consult your local prescribing information

Mula. Clinical Medicine Insights: Therapeutics 2013:2 285–289

AEDs in Bipolar Disorder

		CBZ	GBP	LTG	OXC	VPA
American Psychiatric Association (APA) Hirschfeld et al. 2002	Acute mania/mixed mania	☑	☒	☒	☑	☑
	Acute bipolar depression	☒	☒	☑	☒	☒
	Acute rapid cycling	☒	☒	☑	☒	☑
	Maintenance	☑	☒	☑	☑	☑
British Association of Psychopharmacology (BAP) Goodwin et al. 2003	Acute mania/mixed mania	☑	☒	☒	☒	☑
	Acute bipolar depression	☒	☒	☑	☒	☑
	Rapid cycling	☒	☒	☑	☒	☑
	Maintenance	☑	☒	☑	☑	☑

AGENTS MAY NOT BE LICENCED FOR THESE INDICATIONS IN YOUR COUNTRY
Please consult your local prescribing information

Hirschfeld et al. Am J Psychiatry 2002;159(Suppl 4):1-50
Goodwin GM. Recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 2003;17(2):149-173

EXPERT REVIEWS

Investigating psychotropic properties of antiepileptic drugs

Marco Mula MD PhD

- What can we learn from classic pharmacology of AEDs?
- Is the KNOWN mechanism of action relevant when investigating psychotropic properties of AEDs?

Development of AEDs

Rationale	Drugs
Theoretical assumption	Bromides, Barbiturates
Animal models	Phenytoin, Carbamazepine, Valproate, Ethosuximides
Molecular targets	Vigabatrin, Tiagabine, Gabapentin, Lamotrigine, Zonisamide, Felbamate, Zonisamide, Lacosamide etc

Animal models and AEDs

- Pentylenetetrazole, kainic acid
  - (Myoclonic/Absence seizures)
- Maximal electroshock
  - (Generalized tonic-clonic seizures)
- Amygdala kindling -> acute mania?
  - (Complex partial seizures)

Classical animal models - I

Compounds	(Mice, i.p., ED_{50} mg/kg)		
	MES GTCS	PTZ Absence	KA Absence
Lamotrigine	7.5	>40.0	>40.0
Topiramate	33.0	>800	>500
Phenytoin	6.5	>50	>50
Carbamazepine	9.9	>50	>50
Valproate	287	209	209
Ethosuximide	>1000	130	130

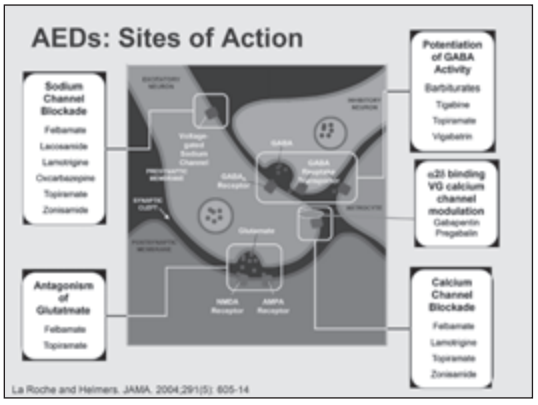
Rogawski 2006

Classical animal models-II

Compounds	Amygdala Kindling	Efficacy in acute mania
Lamotrigine	++	-
Topiramate	+/-	-
Phenytoin	+/-	+/-
Carbamazepine	+/-	+/-
Valproate	+	+
Ethosuximide	-	-
Gabapentin	+/-	-

Rogawski 2006; Mula 2013

AEDs: Sites of Action



La Roche and Helmers. JAMA. 2004;291(5): 605-14

GABAergic AEDs

I-II mechanism

- **BDZ**
- FLB
- **TGB**
- TPM
- **VGB**
- VPA

Still controversial

- OXC
- LEV
- GBP

The Role of Anticonvulsant Drugs in Anxiety Disorders
A Critical Review of the Evidence

GABAergic AEDs in anxiety

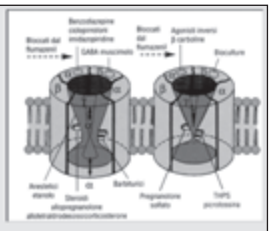
TIAGABINE

- 2 open studies:
  - 1 **GAD** = 40 pts (Rosenthal 2003)
  - 1 **panic disorder** = 23 pts (Sheehan et al. 2007)
- 3 controlled studies:
  - **GAD** (Pollack et al. 2008) No evidence for primary endpoints

VIAGABATRIN

- 1 open study in PTSD = 5 pts (MacLeod 1996)
- No controlled studies

GABA-A



- Tonic inhibition (delta)
- Phasic inhibition (gamma)
- Sedative hypnotic (alpha 1 –5)
- Anxiolytic (alpha 2)

Anticonvulsants as Anxiolytics, Part 2

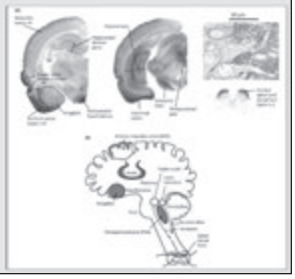
Pregabalin and Gabapentin as α2δ Ligands at Voltage-Gated Calcium Channels

Stephen M. Stahl, M.D., Ph.D.

J Clin Psychiatry 2004;65(4):460-461

Voltage-gated Ca channel blockers

- CBZ (L)
- FLB (L)
- **GBP** (N, P/Q)
- LTG (N, P/Q, R)
- OXCBZ (N, P)
- **PGB** (N, P/Q)
- **ZNM** (N, P, T)



REVIEW ARTICLE

The Role of Anticonvulsant Drugs in Anxiety Disorders
A Critical Review of the Evidence

Drug	PD	OCD	PTSD	SA	GAD
Carbamazepine	II?	III	III		
Gabapentin	II?	IV	IV	II	
Lamotrigine		IV	II		
Levetiracetam	III		III	III	
Oxcarbazepine	IV	IV	IV		
Phenytoin			IV		
Pregabalin				II	I
Tiagabine			III		I?
Topiramate		III	III	III	
Valproate	III	IV	III	III	
Vigabatrin	IV		IV		

Psychiatric Adverse Effects of AEDs in Epilepsy

Direct (drug-related)

- Mechanism of action of the drug
- Drug toxicity
- Drug withdrawal

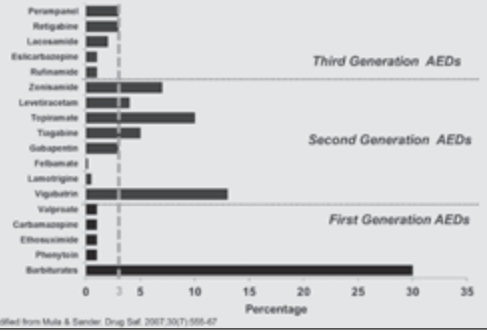
Indirect (epilepsy-related

- "Forced normalization"
- "Release phenomenon"
- Postictal and periictal psychoses
- Severity of the epilepsy
- Limbic system abnormalities

Past psychiatric history and family psychiatric history

Mula & Sander. Drug Saf. 2007;30(7):555-67
Mula & Monaco. Epileptic Disord. 2009;11(1):1-9.

Mood problems with AEDs



Modified from Mula & Sander. Drug Saf. 2007;30(7):555-67

Mechanisms for AED-related psychiatric problems

- GABA enhancement
- Polytherapy
- Folate deficiency
- Forced normalization phenomenon
- Past psychiatric history
- Hippocampal sclerosis (febrile seizures?)

Mula & Sander. Drug Saf. 2007;30(7):555-67

GABA and Depression Outside Epilepsy

- BDZ and depression
  - During therapy[1]
  - Withdrawal[2]
- GABA and depression[3]

1. Trimble & George 2010
2. Olajide and Lader. Psychol Med. 1984;14(4):937-43.
3. Petty et al. Biol Psychiatry. 1995 Nov 1;38(9):578-91.

GABA and Depression in Epilepsy

- Barbiturates
  - *Robertson et al. Neurology 1982*
- Vigabatrin
  - *Levinson and Devinsky Neurology. 1999 22;53(7):1503-11*
- Tiagabine
  - *Trimble et al. Seizure. 2000;9(4):249-54.*
- Topiramate
  - *Mula et al. Epilepsia. 2003;44(12):1573-7.*

Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults

R. Martin, PhD, R. Kuzniecky, MD, S. Ho, MD, FRACP, H. Hetherington, PhD, J. Pan, MD, K. Sinclair, BS, F. Gilliam, MD and E. Faught, MD

NEUROLOGY 1999;52(2):321-7

Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults

R. Kuzniecky, MD; S. Ho, MD, FRACP; J. Pan, MD, PhD; R. Martin, PhD; F. Gilliam, MD; E. Faught, MD; and H. Hetherington, PhD

NEUROLOGY 2002;58:368–372

Polytherapy

- Interactions
  - GABA potentiation
  - Modifications in drug kinetics
- Drug-resistant epileptic syndromes

Reynolds and Shorvon. Epilepsia. 1981;22(1):1-10.

Folate Deficiency

- Depression most common mental disturbance
- Folate levels often low on treatment with barbiturates and phenytoin
- Little or no effect on other AEDs

Sander and Patsalos. Epilepsy Res. 1992;13(1):89-92.
Shorvon et al. Br Med J. 1980;281(6247):1036-8.
Reynolds Clin Haematol. 1976;5(3):661-96.

The Forced Normalization Phenomenon

"Forced Normalization is the phenomenon characterised by the fact that, with the occurrence of the psychotic states, the EEG becomes more normal or entirely normal as compared with previous and subsequent EEG findings"

Landolt H. Some clinical EEG correlations in epileptic psychoses (twilight states). EEG Clin Neurophysiol 1953; 5:121

Psychopathology of Forced Normalization

Paranoid hallucinatory psychosis	19
Prepsychotic dysphoria	9
Hysterical episode	5
Hypochondriacal episode	3
Depressive episode	2
Dysphoric episode	2
Manic episode	2
Twilight state	1
Depersonalization	1

Wolf. P. Folia Psychiatr Neurol Jpn 1984; 38: 167-82.

The Past Psychiatric History

Drugs appear to be driving the underlying constitutional liability of the patients, the direction in which they are driven being given by the past psychiatric profile

Trimble et al. Seizure. 2000;9(4):249-54.

Psychiatric History May predict Psychiatric and Cognitive AEs on Topiramate

- 596 consecutive patients aged ≥16 years who started topiramate for epilepsy
  - 54% women, mean age 36 years
  - Most started as add-on therapy
- Prospective follow-up at 6 months or time of discontinuation
- Past psychiatric history in 27%
  - Depression 19%, anxiety disorder 6%, personality disorder 6%, ADHD 1%, psychotic disorder 1%

Predictors of psychiatric AEs	Predictors of cognitive AEs
Topiramate dose P=0.05	Psychiatric history P=0.01
History of anxiety disorder P=0.06	Depression history P=0.001

Kanner et al. Epilepsy & Behavior. 2003;4(5):548-552.

Hippocampal Sclerosis and Depression

Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis

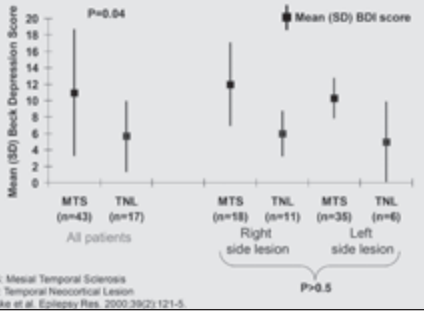
Ansgar Quiske *, Christoph Helmstaedter, Silke Lux, Christian E. Elger

University Hospital of Epileptology, Sigmund-Freud-Straße 25, 53105 Bonn, Germany

Received 29 August 1999; accepted 16 November 1999

Epilepsy Research 39 (2000) 121–125

Depression Increased in Hippocampal Sclerosis: Beck Depression Inventory Score



MTS: Mesial Temporal Sclerosis
NTL: Temporal Neocortical Lesion
Quiske et al. Epilepsy Res. 2000;39(2):121-5.

Epilepsia, 50(5):1072–1076, 2009
doi: 10.1111/j.1528-1167.2008.01799.x

FULL-LENGTH ORIGINAL RESEARCH

The role of titration schedule of topiramate for the development of depression in patients with epilepsy

*Marco Mula, †Dale C. Hesdorffer, ‡Michael Trimble, and §Josemir W. Sander

Model 1: Occurrence of Depression During Therapy with Topiramate - Independent Effect of Rapid Titration

Factor	Depressed n = 44	Not depressed n = 379	Odds Ratio†	95% CI
Rapid TPM titration + febrile seizures (FS)				
Rapid TPM titration	59%	22%	4.8	2.5–9.3
History of FS	41%	19%	2.8	1.4–5.6
Rapid TPM titration + Hx of depression				
Rapid TPM titration	59%	22%	5.1	2.6–9.9
History of depression	30%	10%	4.1	1.9–9.0
Rapid TPM titration + hippocampal sclerosis				
Rapid TPM titration	59%	22%	4.7	2.5–9.1
Hippocampal sclerosis	20%	16%	1.6	0.7–3.4

Model 1 examined the independent effect of rapid TPM titration schedule on the development of depression after separate adjustment for febrile seizures, history of depression, and hippocampal sclerosis

† OR adjusted

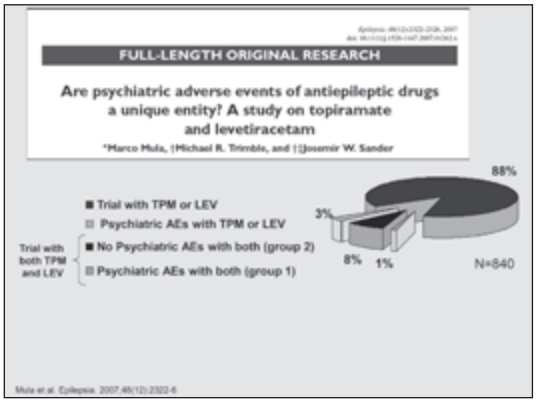
Mula et al. Epilepsia. 2009;50(5):1072-6.

Model 2: Effect of Co-occurrence of Depression with Other Histories During Rapid Topiramate Titration

Factor	Depressed n = 44	Not depressed n = 379	Odds Ratio	95% CI
Rapid TPM titration + febrile seizures				
Rapid TPM titration only	36%	17%	5.9	2.5–13.5
History of FS only	18%	14%	3.7	1.4–9.9
Both	23%	5%	12.7	4.7–34.4
Rapid TPM titration + Hx of depression				
Rapid TPM titration only	41%	21%	4.7	2.2–10.0
History of depression only	11%	8%	3.5	1.2–10.6
Both	18%	2%	23.3	7.3–74.1
Rapid TPM titration + hippocampal sclerosis				
Rapid TPM titration only	41%	17%	4.9	2.3–10.4
HS only	9%	11%	1.7	0.5–5.6)
Both	18%	5%	7.6	2.8–20.4

Model 2: Effect of the co-occurrence of rapid titration in combination with either a history of febrile seizures, previous history of depression, or presence of hippocampal sclerosis for the development of depression during therapy with topiramate

Mula et al. Epilepsia. 2009;50(5):1072-6.



Mula et al. Epilepsia. 2007;48(12):2322-6

Characteristics of Patients Who Did and Did Not Experience Psychiatric AEs on TPM + LEV

	Psychiatric AEs with TPM + LEV (n=9)	No Psychiatric AEs with TPM + LEV (n=71)
Gender, male	5	37
Age, mean (SD) years	40.2 (9.6)	35.5 (10.0)
Age at onset of epilepsy, mean (SD) years	10.1 (8.1)	11.8 (7.3)
Duration of epilepsy, mean (SD) years	30.1 (5.6)	23.5 (9.6)
Epilepsy syndrome CP/IG/SP/Others	2/1/6/0	25/10/35/1
Family history of epilepsy	1	11
History of febrile convulsions	5*	11
Learning disabilities	1	11
Psychiatric history	6**	17
Family psychiatric history	2***	0

*P<0.05, **P<0.01, ***P=0.001

Mula et al. Epilepsia. 2007;48(12):2322-6

Genetic biomarkers

- LEV and aggressive behaviour
  - Polymorphism in dopamine receptor D2-associated ANKK1 TAQ-1A (Halmstaedter et al. 2013)
- Other targets? (SV2A?)

Nature Medicine 5, 888 - 894 (1999)

Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits

Kang Chen, Tallie Z. Baram, Ivan Soltesz

AEDs and behaviour: a class effect?

- No class effect in psychiatric disorders
- Class effect in epilepsy!
- Underlying neurological disorder major determinant

Use of AEDs in pts with comorbidities

	Other indications	Potential benefits	Alert
PB		Anxiolytic, hypnotic	Major depression, ADHD
CBZ OXC ESL	Bipolar disorder (A), pain	Addiction, withdrawal syndrome, dyscontrol	ADHD
ETX	None	NK	None (?Psychosis)
FLB	None	NK	Major depression, anxiety disorders
GBP	Pain	Anxiety disorders	ADHD
LCM	None	NK	None
LTG	Bipolar disorder (M)		?Anxiety disorders, ?ADHD
LEV	None	NK	Anxiety disorders, dyscontrol
PRP	None	NK	NK
PHT	None	Mania	Major depression
PGB	GAD, Pain		NK
TGB	None	NK	Major depression
TPM	Migraine	Binge eating disorder	Major depression
VPA	Bipolar disorder (A)	?Anxiety disorders	None
VGB	None	NK	Major depression, psychosis
ZNM	None		Major depression, psychosis

AGENTS MAY NOT BE LICENCED FOR THESE INDICATIONS IN YOUR COUNTRY

Mula. Clinical Medicine Insights: Therapeutics 2010:2 265–280

Effects of AEDs on behavior
Take home message

- Screen mental state before starting any AEDs
  - Usually no complains unless specifically assessed
  - Consider any relevant comorbidity (Medical, Cognition, Psy)
  - Identify high risk endophenotypes (Fam Hx, Past Hx, FS or SE)
  - Any mood disorder -> red flag!
- With any AED start low and go slow
  - Lowest doses needed to control epilepsy
  - Avoid barbiturates and GABAergics if possible
  - Minimize polytherapy

Jaime Carrizosa (Colombia)

EPILEPSY AND DEVELOPMENTAL DISORDERS

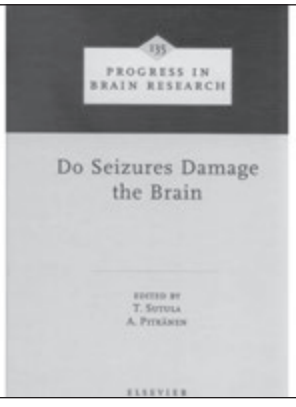
Gregory Holmes (USA)

INTERICTAL EPILEPTIC ACTIVITY AND ITS IMPACT ON COGNITION AND NEUROPLASTICITY IN CHILDHOOD

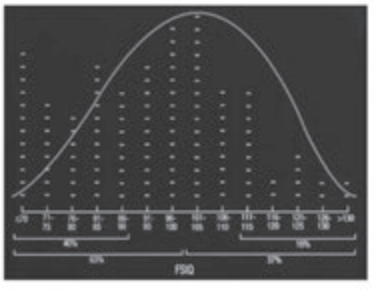
Interictal Epileptic Activity and Its Impact on Cognition and Neuroplasticity in Childhood

Gregory L. Holmes
Department of Neurological Sciences
University of Vermont College of Medicine
Burlington, Vermont

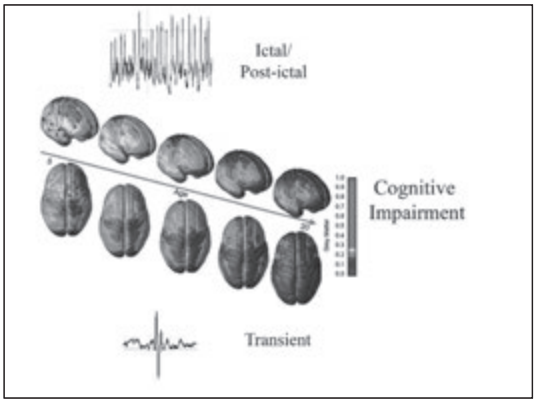
The UNIVERSITY of VERMONT

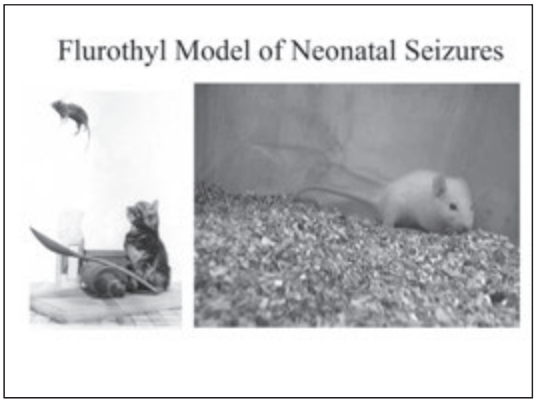


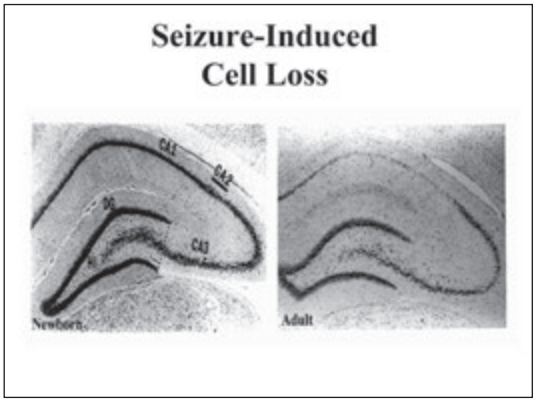
Full-Scale Intelligence Quotient (FSIQ) Score of Patients with Epilepsy and Controls

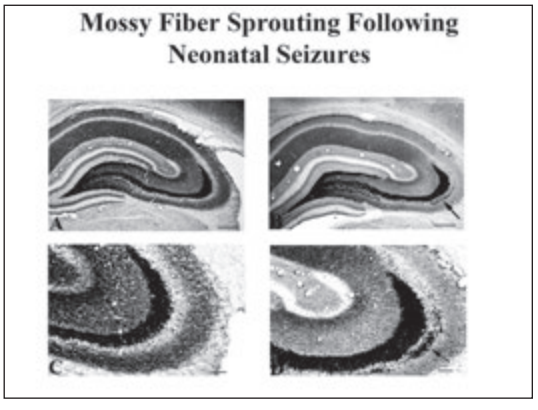


Farwell et al. 1985

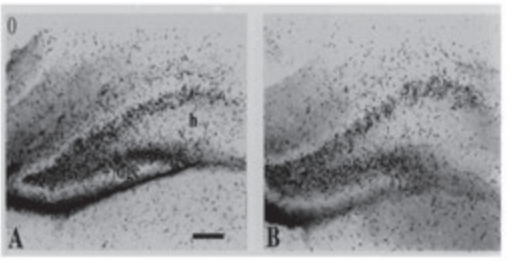

Ictal/
Post-ictal
Cognitive
Impairment
Transient


Flurothyl Model of Neonatal Seizures


Seizure-Induced
Cell Loss
CA1
CA2
DG
CA3
Newborn
Adult

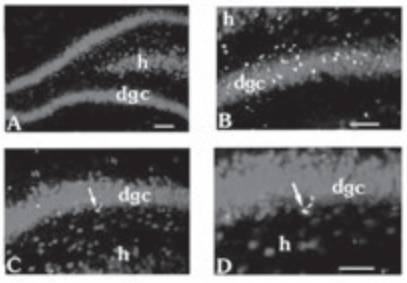

Mossy Fiber Sprouting Following
Neonatal Seizures
A
C

Reduced Neurogenesis Following Neonatal Seizures

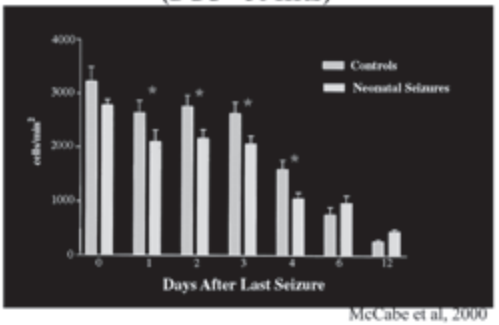


McCabe et al. 2000

NeuN-BrdU Double Labeling

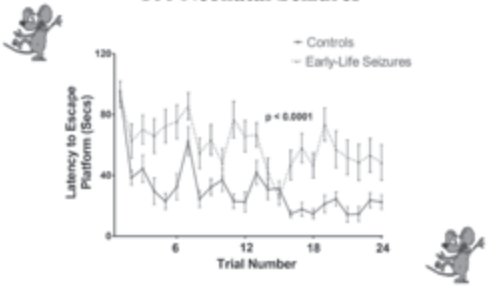


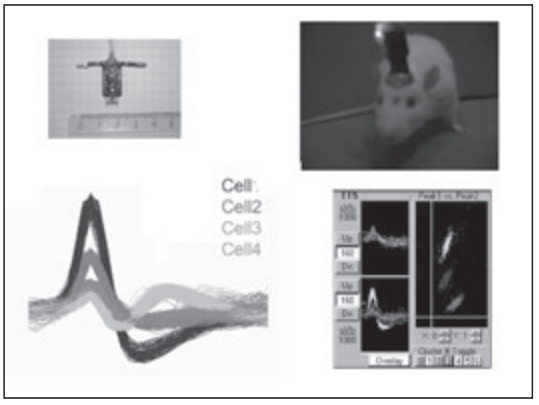
BrdU–LABELED CELLS (DGC – 36 HRS)

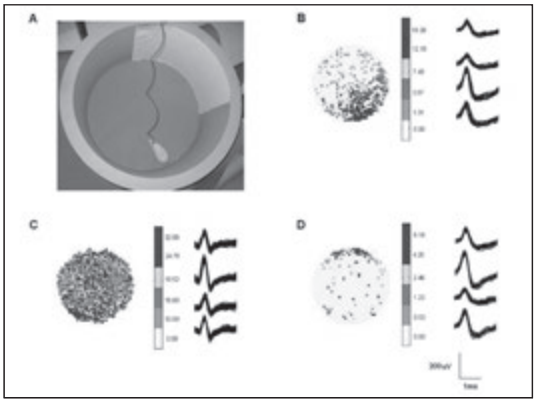


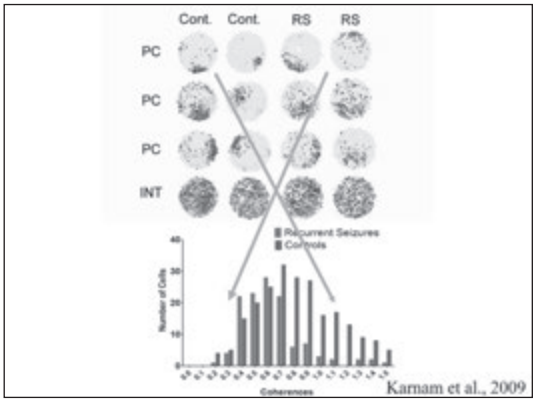
McCabe et al, 2000

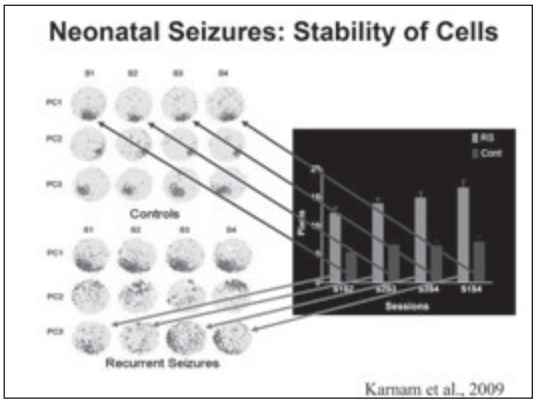
Time to Escape Platform Following 100 Neonatal Seizures




Cell:
Cell2
Cell3
Cell4


A
B
C
D

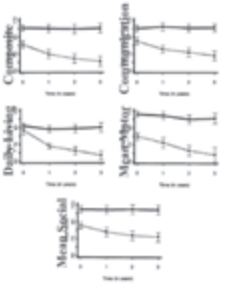

Cont.
Cont.
RS
RS
PC
PC
PC
INT
Recurrent Seizures
Controls
Number of Cells
Coherences
Karnam et al., 2009


Neonatal Seizures: Stability of Cells
Controls
Recurrent Seizures
RS
Cont
Sessions
Karnam et al., 2009

Longitudinal Adaptive Behavior in Children with New Onset Epilepsy

- Prospective study of 613 children with newly diagnosed epilepsy.
- Vineland below average at baseline.
- Declines occurred in children with epileptic encephalopathies and symptomatic etiology.
- There was an independent effect of intractable seizures from etiology.

Berg et al, 2004



Age of Epilepsy, Pharmacoresistance, and Cognition

Table 2 Multiple linear regression results for the primary analytic sample*

	Full scale IQ	Processing speed	Verbal comprehension	Perceptual organization	Freedom from distractability
Positive imaging or examination results	−10.16 (4.15)	−9.56 (3.80)	−7.66 (3.70)	−9.16 (4.05)	−9.02 (3.82)
p Value	0.02	0.01	0.04	0.02	0.02
Age at onset	−0.47 (0.72)	0.09 (0.66)	−0.73 (0.64)	0.14 (0.70)	−0.25 (0.66)
p Value	0.51	0.89	0.26	0.82	0.71
Pharmacoresistance	−26.22 (6.96)	−18.83 (6.39)	−20.12 (6.22)	−22.04 (6.81)	−17.91 (6.42)
p Value	0.0002	0.004	0.001	0.001	0.006
Age × pharmacoresistance	4.74 (1.62)	2.89 (1.46)	3.68 (1.43)	4.69 (1.56)	2.14 (1.47)
p Value	0.003	0.05	0.01	0.003	0.15

*N = 198. Data are effect estimates (SE) for predicting cognitive scores 9 years after initial diagnosis as a function of positive imaging or examination findings, age at onset, pharmacoresistance, and the interaction between pharmacoresistance and age.

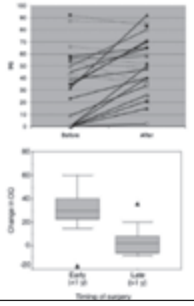
Berg et al., 2012

Pharmacoresistant

Developmental Outcome After Epilepsy Surgery in Infancy

- Study of 50 infants undergoing epilepsy surgery.
- After surgery, seizure frequency and developmental quotient improved.
- Patients who were operated on at younger age and with epileptic spasms showed the largest increase in development after surgery.

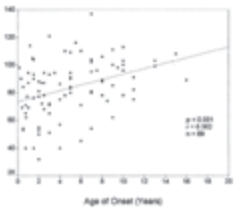
Loddenkemper et al., 2007



Early Age of Seizure Onset and IQ

- Intellectual function assessed in 100 patients with intractable epilepsy (age 2-20 years) due to focal lesions.
- Younger age of onset associated with lower IQ.
- Authors concluded that early age of intractable epilepsy is risk factor for mental retardation, especially if the seizures occur daily.

Vasconcellos et al., 2001



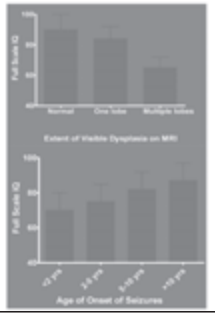
Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury

	Severe Seizures N = 11	Mild/Moderate Seizures N = 14	No Seizures N = 52	P*
WPPSI-R FSIQ mean (95% CI)				
-Unadjusted	64.7 (52.6 – 76.9)	83.1 (72.4 – 93.9)	100.2 (94.6 – 105.8)	<0.0001
-Adjusted**	67.2 (54.6 – 79.8)	82.7 (72.7 – 92.7)	96.9 (90.7 – 103.1)	0.001

Glass, 2009

Early Seizure Onset and Dysplasia Independently Disrupt Cognition

- 57 children with histopathologically verified dysplasia.
- Poor cognitive outcomes associated with early age of onset of epilepsy and wide-spread dysplastic involvement.
- Each factor contributed independently to cognitive dysfunction.

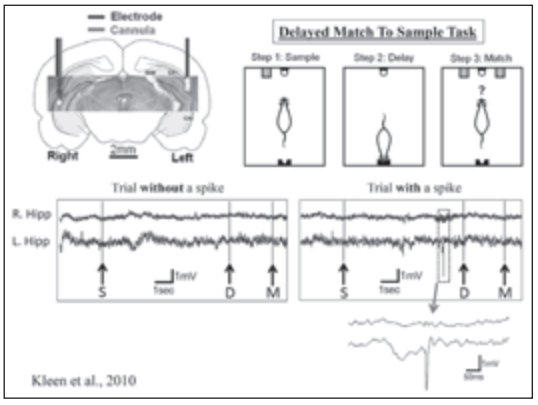


Korman, et al., 2013

Interictal Spikes (IIS)

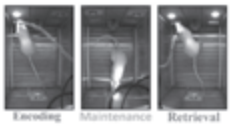
Rat

Human

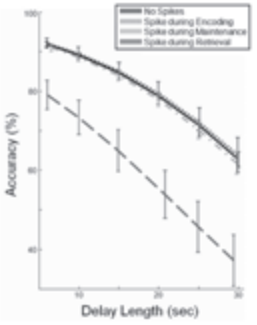


Kleen et al., 2010

Hippocampal function specificity - *Phases of memory processing*



- Retrieval disrupted by hippocampal spikes
- Encoding and Maintenance not affected



Cognitive testing for transient impact of EEG abnormalities

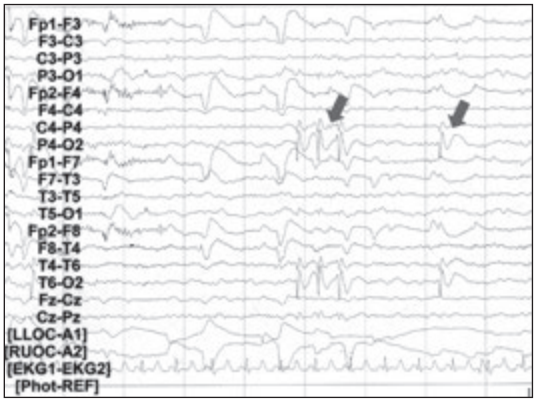
Perform trials of a cognitive task
+
Record EEG simultaneously

Note timing of transient epileptiform EEG abnormalities

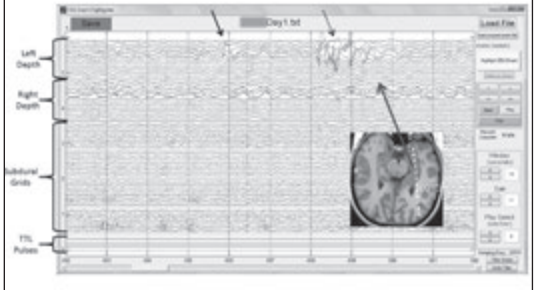
- Generalized spike-wave
- Interictal spikes

If one occurs <u>during a trial</u>

→ disrupts accuracy <u>in that trial</u>



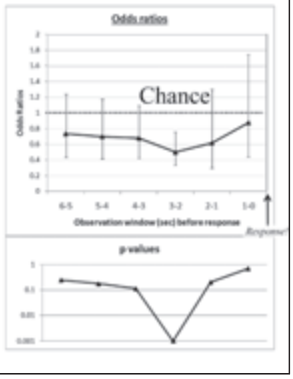
Transitory Cognitive Impairment in TLE



Sternberg Task of Working Memory

Predictability of an error following a spike during retrieval

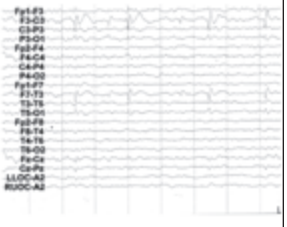
Spikes 2-3 seconds before response were highly predictive of a subsequent error.



Kleen et al., 2013

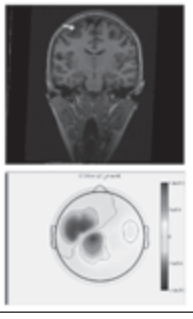
IIS in BECTS

- Vast majority of studies have found that children with BECTS have a variety of cognitive impairments.
- Some but not all authors find lateralized deficits.
- Some of the variability in function may be explained by fluctuations in IIS frequency and cognitive performance (Ewen, 2011).

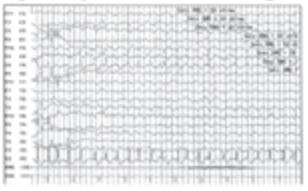


IIS in BECTS: Transitory Cognitive Impairment (TCI)

- Transitory cognitive impairment has been studied during IIS in 33 children with BECTS using EEG and computerized testing in a visual discrimination between words and pseudowords (Fonseca, 2007).
- A small percentage of children (15.4%) made a significantly greater proportion of errors during IIS than during IIS-free periods. The IIS were inhibited by the task, likely due to increased alertness, in 20 of the 33 children.



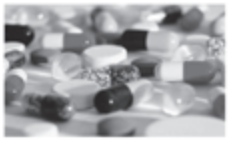
Frequency of IIS and Cognition



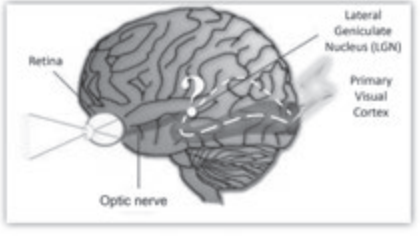
- In a study of IIS in 182 children with a variety of epilepsy syndromes Ebus et al. (2012) calculated IIS index using a 24 hr ambulatory EEG and compared findings to neuropsychological tests.
- Patients with diurnal IIS in ≥10% of the EEG record showed impaired central information processing speed, short-term verbal memory and visual-motor integration.
- This effect was seen independently from other EEG-related and epilepsy-related characteristics including syndrome.

Treatment of IIS in BECTS

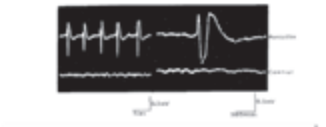
- In a DBPC crossover study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or vice versa (Pressler, 2005).
  - Global rating of behavior significantly improved only in patients who showed a significant reduction in either frequency or duration of discharges during active treatment.
- In a small study using sulthiame to treat the IIS in BECTS, it was found that children had a significant deterioration in their reading ability, despite a reduction in IIS frequency (Wirrell et al., 2008).

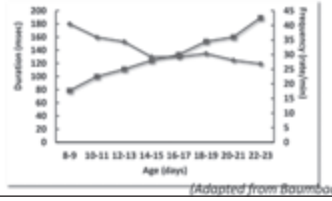


What are the Downstream Effects of Interictal Spikes?

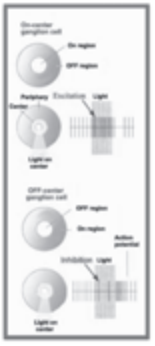


Penicillin-Induced Interictal Discharges Recorded in Striate Cortex of Rabbits





(Adapted from Baumbach et al 1981)



Percentage of Cells in Each Receptive Field Category Sampled in LGN of Normal Rabbits and Rabbits with Cortical Epileptiform Focus

	Adolescent		Adult	
	Focus	Control	Focus	Control
No. cells	100	79	41	191
Non-responsive	18	1	0	0
Indefinite	13	2	2	0
Concentric	29	59	56	68
Uniform	12	16	34	21
Motion	12	20	7	8
Directional	6	1	0	3

Adapted from Baumbach et al 1981

Interictal Spikes During Development: The Model

P18-19
Electrode/cannula implantation

20G cannula with 2 EEG leads on either side

Implanted into the prelimbic region of the right PFC

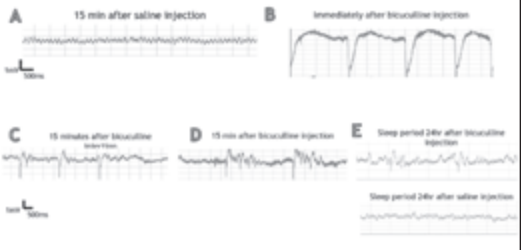
P21-26
Intra-cerebral injections

4 injections per day
0.5µL per injection at a rate of 0.2µL/min

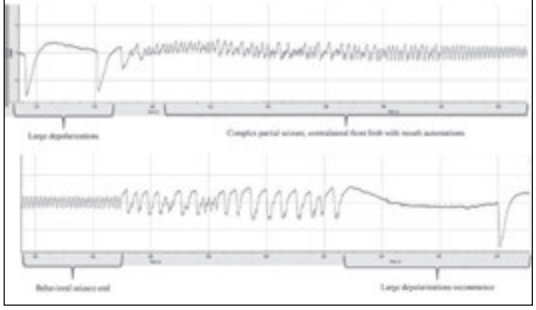
175µM Bicuculline Methiodine in sterile PBS
Sterile PBS controls

P45-60
Excitatory short-term plasticity assessed

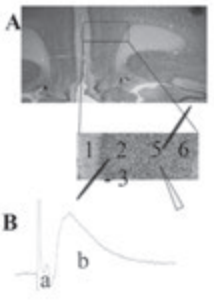
Model Phenotype



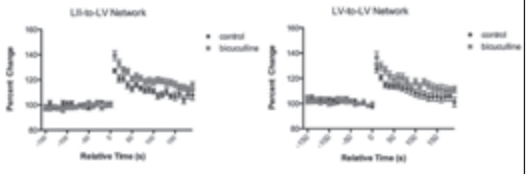
Bicuculline-Induced Seizures



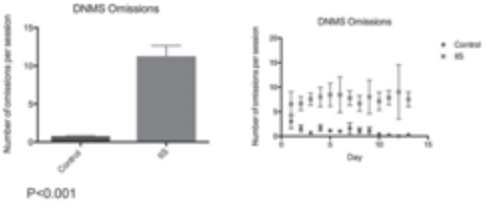
Two networks in the prefrontal cortex



Unilateral Bicuculline Injection alters Post-Tetanic Potentiation

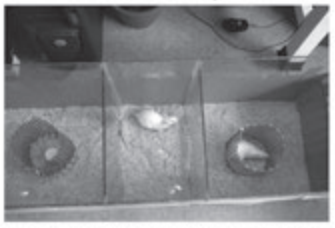


Selective alterations in attention after early life IIS



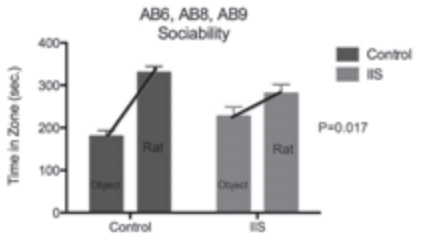
P<0.001

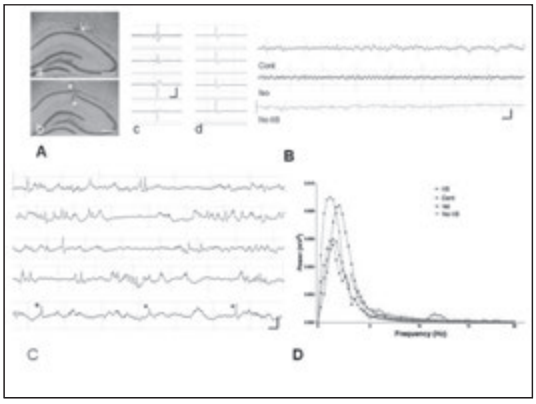
Effect of Developmental IIS on Cognition: Sociability



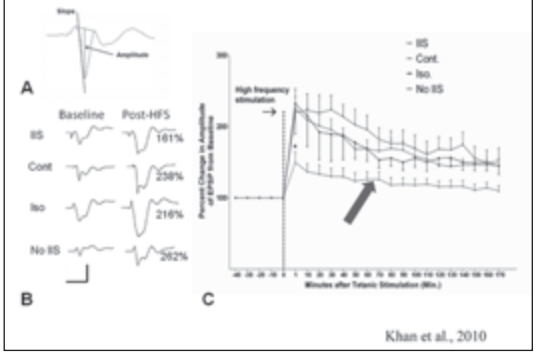
- "The skill, tendency or property of being *sociable* or social, of interacting well with others"
- Wild-type rodents will spend significantly more time with a novel animal than with a novel object when given the choice
- Genetic mouse models of autism show deficits in sociability as measured with the three chamber sociability task

Sociability is altered after early life epileptiform activity



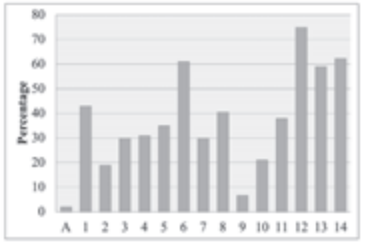


Interictal Spikes During Early Life Impairs LTP



Khan et al., 2010

Interictal Spikes in ASD/PDD

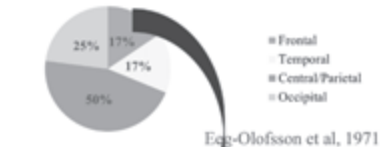


A = normal population
1. Hashimoto et al., 2001
2. Rossi et al., 1995
3. Akshoomoff et al., 2007
4. Baird et al., 2006
5. Canitano et al., 2005.
6. Chez et al., 2006.
7. Gabis et al., 2005.
8. Giannotti et al., 2008
9. Giovanardi et al. 2000
10. Hara et al., 2007
11. Hrdlicka et al. 2004
12. Hughes and Melyn, 2005
13. Kim et al. 2006
14. Parmeggiani et al. 2007

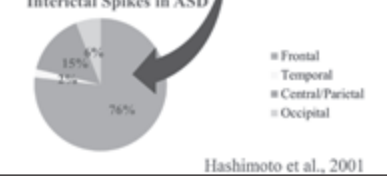
Spence and Schneider, 2009

Types of Epileptiform Discharges in ASD

Hashimoto et al., 2001



Ege-Olofsson et al, 1971



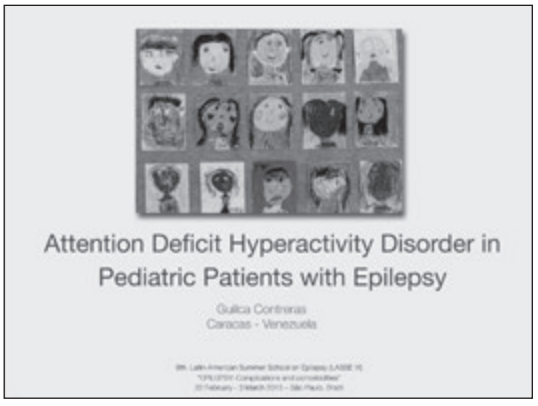
Hashimoto et al., 2001

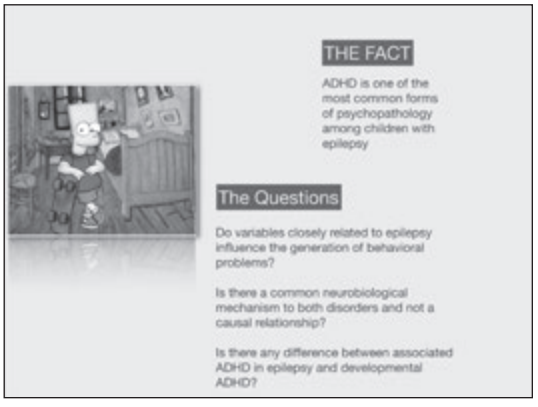
IIS: The Chicken vs the Egg

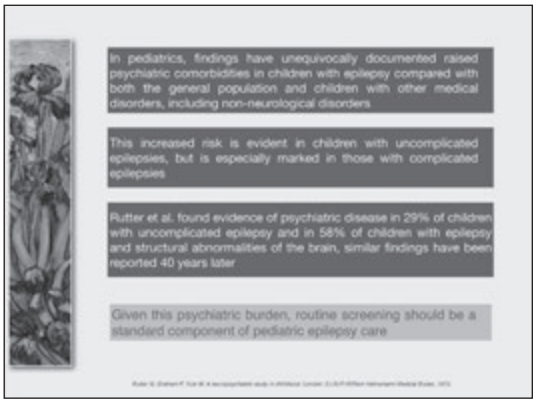
- Epilepsy is a disturbance of brain function and epileptiform discharges are reflective of a dysfunctional brain.
- Epileptiform discharges, regardless of their cause, contribute to or cause cognitive impairment.

Guilca Contreras (Venezuela)

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PEDIATRIC PATIENTS WITH EPILEPSY







Ounsted (1955) was among the first to call attention to the syndrome of hyperkinetic disorder and its complications in children with epilepsy

Three important investigations determined the rate of ADHD and its subtypes in pediatric epilepsy using contemporary diagnostic criteria that now recognize specific subtypes of the disorder (DSM-IV) (Hesdorffer et al., 2004; Dunn et al., 2003; Sherman et al., 2007)

ADHD affects 3–7% of all children in the general population (Rappley, 2005; Polanczyk et al., 2007)

- 80% combined type
- 10-15% inattentive type
- 5% hyperactive and impulsive type

An increased risk for seizures is a symptom that is often associated with ADHD

ADHD

- Personal and social consequences
- Additional psychiatric comorbidities

What is ADHD

Neurobehavioral disorder marked by:

Inattention

Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities

Often has trouble holding attention on tasks or play activities

Often does not seem to listen when spoken to directly

Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked)

Often has trouble organizing tasks and activities

Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework)

Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)

Is often easily distracted

Is often forgetful in daily activities

DSM IV TR

What is ADHD

Neurobehavioral disorder marked by:

Excessive motor activity

Difficulties controlling impulses

Often fidgets with or taps hands or feet, or squirms in sea

Often leaves seat in situations whe remaining seated is expecte

Often runs about or climbs in situations where i is not appropriate (adolescents or adults may b limited to feeling restless

Often unable to play or tak part in leisure activities quiet

Is often "on the go" acting as if "driven by a motor"

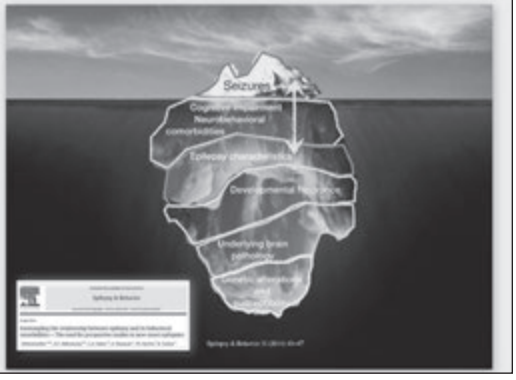
Often talks excessivel

Often blurts out an answer befor a question has been complete

Often has trouble waiting his/her tur

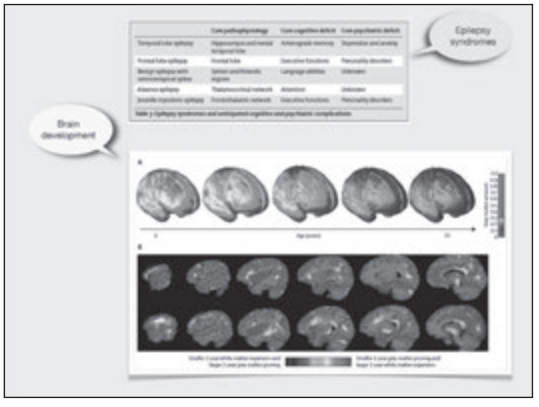
Often interrupts or intrudes on others (e.g., butts into conversations or games)

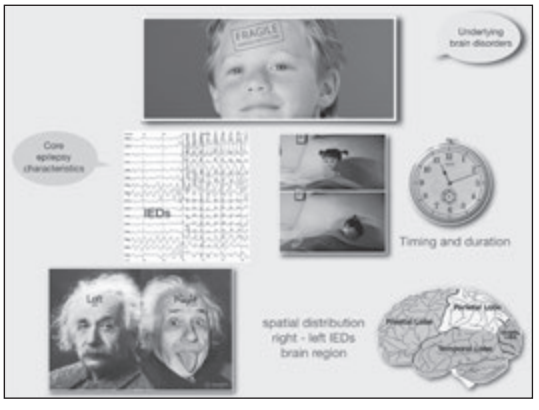
DSM IV TR




Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan
Core epilepsy characteristics
Genotypic, psychological and sociocultural influences
Brain development and aging
Neurobehavioral comorbidities Cognitive Psychiatric Social
Underlying brain disorders
Epilepsy syndromes


Neurobehavioral comorbidities Psychiatric - Cognitive - Social
A National Profile of Childhood Epilepsy and Seizure Disorder


Epilepsy syndromes
Brain development

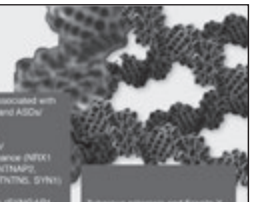

FRAGILE
Underlying brain disorders
Core epilepsy characteristics
IEDs
Timing and duration
Left
Right
spatial distribution right - left IEDs brain region
Parietal Lobe
Occipital Lobe
Temporal Lobe

Core epilepsy characteristics

	Motor and cognitive speed	Memory	Mood	Psychosis
Phenobarbital	(-)	-	-	++
Carbamazepine	(-)	-	a*/++	++
Phenytoin	(-)	-	-/++	- (related to toxicity)
Valproate	(-)	-	a*/++	++
Vigabatrin	++	++	-	-
Oxcarbazepine	++	++	a*/++	++
Gabapentin	++	++	++	++
Lamotrigine	++	++	a*/++	++
Levetiracetam	++	++	-	-
Progabulin	-/++	++	a*/++	++
Topiramate	-/++	-	-	-
Tiagabine	(-)	-	-	-
Zonisamide	-/++	-	-	-

Data from Meda and Khoraza,[1]* unless otherwise stated. --negative effect, ++positive effect, +-no effect. *Data from psychiatry published work.

Epilepsy and ADHD
The genetic link



- ADHD symptoms 12-70%
- ASDs symptoms 15-35%
- In the ASDs population 40-70% of individuals meet full ADHD diagnostic criteria
- Autistic-like communication and social deficits are evident in 28–82% of ADHD children

Candidate genes associated with childhood epilepsy and ASDs/ ADHD comorbidity

- Synaptic formation/ remodeling/maintenance (NRX1 CNTN4, DCLK2, CNTNAP2, TRIM32, ASTN2, CTNTNS, SYN1)
- Neurotransmission (SYNGAP1, GABRG1, CHRNA7)
- DNA methylation/chromatin remodeling (MBD5)

CHRNA7

Tuberous sclerosis and Fragile X syndrome may serve as models for understanding the common pathogenic pathways leading to ASDs and ADHD comorbidities in children with epilepsy

CAE, JAE, JME, GTCS, Rolandic epilepsy

ADHD
Classic autism PDD-NOS
Asperger syndrome
Autistic features

Review article

Epilepsy associated with autism and attention deficit hyperactivity disorder: Is there a genetic link?

The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy

Research participants included children with new/recent onset epilepsy (n = 75) and healthy first-degree cousin controls (n = 62), aged 8–18 years, all attending regular schools. Children with epilepsy were recruited from pediatric neurology clinics at two Midwestern medical centers

Selection criteria included: (1) diagnosis of epilepsy within the past 12 months; (2) chronological age between 8–18 years; (3) no other developmental disabilities (e.g.autism); (4) no other neurological disorder and (5) normal clinical MRI

- Assessment of DSM-IV ADHD: Lifetime-to-date psychiatric status was assessed using the Kiddie-SADS-PL (K-SADS), the semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria
- Medical record review and structured interview by an independent investigator, blinded to the psychiatric information

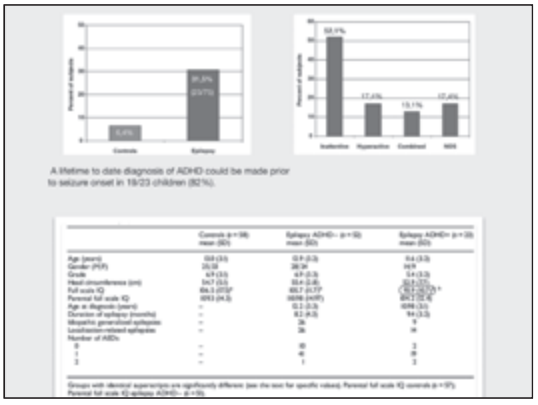
Neuropsychological assessment
Children with epilepsy and controls were administered a comprehensive test battery that included standard clinical measures of intelligence, language, immediate and delayed verbal memory, executive functions and speeded motor/psychomotor processing

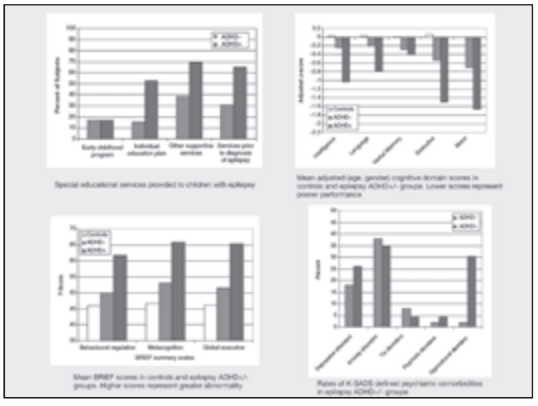
Table 1 Neuropsychological test battery

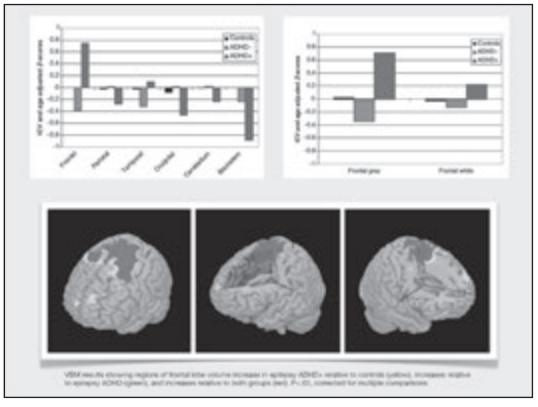
Domain	Ability	Tests
Intelligence	Verbal	Wechsler Abbreviated Scale of Intelligence (verbal IQ)
	Non-verbal	Wechsler Abbreviated Scale of Intelligence (performance IQ)[a]
Language	Confrontation naming	Boston Naming Test[a]
	Expressive naming	Expressive Vocabulary Test[a]
	Receptive language	Peabody Picture Vocabulary Test-III[a]
	Generative naming	Delis–Kaplan Executive Function System (letter fluency)[a]
Memory	Verbal learning	Children's Memory Scale (word list—immediate)[a]
	Verbal memory	Children's Memory Scale (word list—delayed)[a]
Executive function	Problem solving	Delis–Kaplan Executive Function System (card sort—confirmed)[a]
	Response inhibition	Delis–Kaplan Executive Function System (color-word interference test)[a]
	Divided attention	Delis–Kaplan Executive Function System (switching fluency—accuracy)[a]
	Inattentiveness	Conners' Continuous Performance Test-II (omission errors)[a]
	Impulsiveness	Conners' Continuous Performance Test-II (commission errors)[a]
Motor function	Speeded fine motor dexterity	Grooved Pegboard[a]
	Psychomotor speed	Wechsler Intelligence Scale for Children-III (Digit Symbol Test)[a]

[a]Standard scores, [b]Scaled scores, [c]T-scores, [d]Raw scores.

- Parent interview
- Behavior rating inventory of executive function (BRIEF)
- Yale neuropsychoeducational assessment scale (YNPEAS)
- Brain MRI







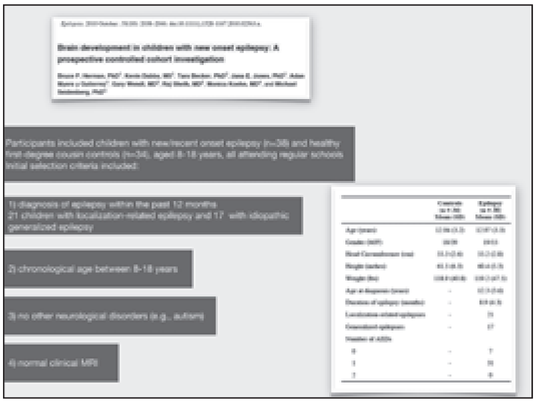
Conclusions

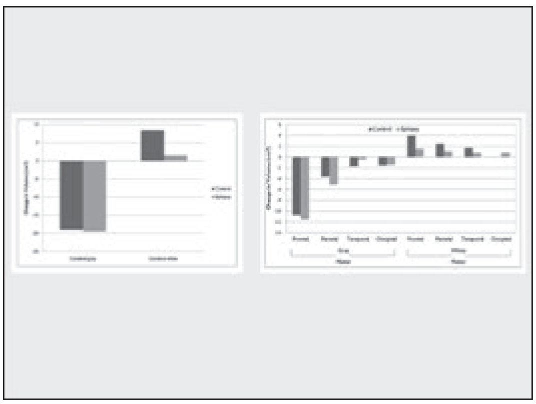
(1) ADHD is a prevalent disorder in children with recent onset epilepsy characterized predominantly by the inattentive variant

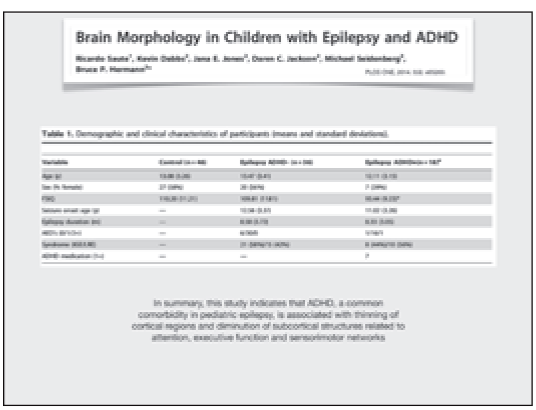
(2) ADHD in children with epilepsy is closely associated with several critical co-occurring problems including academic underachievement requiring provision of school-based educational services, neuropsychological complications and wide ranging problems in day-to-day behaviors dependent upon executive function

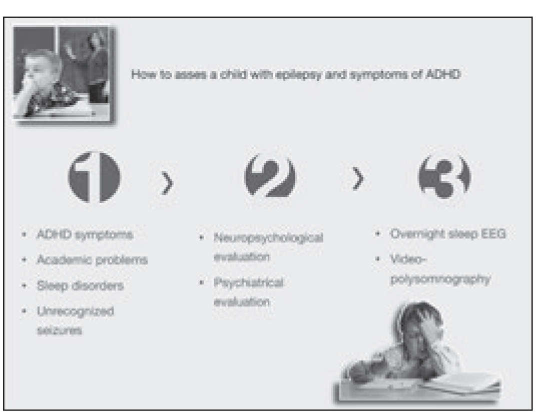
(3) The etiology of ADHD and its complications in epilepsy appear to have origin prior to the diagnosis of epilepsy and even the first recognized seizure in a substantial proportion of children, but without significant associations with traditional clinical epilepsy or demographic characteristics, psychiatric comorbidities (depression/anxiety), or anomalies during pregnancy and delivery

(4) ADHD in pediatric epilepsy is associated with a distributed pattern of neurodevelopmental anomalies in brain structure


Brain development in children with new onset epilepsy: A prospective controlled cohort investigation
Participants included children with new/recent onset epilepsy (n=38) and healthy first-degree cousin controls (n=34), aged 8-18 years, all attending regular schools. Initial selection criteria included:
1) diagnosis of epilepsy within the past 12 months
21 children with localization-related epilepsy and 17 with idiopathic generalized epilepsy
2) chronological age between 8-18 years
3) no other neurological disorders (e.g., autism)
4) normal clinical MRI




Brain Morphology in Children with Epilepsy and ADHD
In summary, this study indicates that ADHD, a common comorbidity in pediatric epilepsy, is associated with thinning of cortical regions and diminution of subcortical structures related to attention, executive function and sensorimotor networks


How to asses a child with epilepsy and symptoms of ADHD
1
ADHD symptoms
Academic problems
Sleep disorders
Unrecognized seizures
2
Neuropsychological evaluation
Psychiatrical evaluation
3
Overnight sleep EEG
Video-polysomnography

CONCLUSIONS

ADHD is a common comorbiditie in pediatric epilepsy

Emerging clinical evidence and experimental evidence suggest the involvement of specific neurobiological mechanisms in the evolution of neurobehavioral deficits in patients with epilepsy

Developmental aspects of both epilepsy and its comorbidities, as well as the frequently reported reciprocal connection between these disorders, both add other dimensions to the already complex problem

CONCLUSIONS

In light of progress in effective seizure management in many patients with epilepsy, the importance of neurobehavioral comorbidities has become acute, as the latter are frequently more detrimental to patient's quality of life compared with seizures

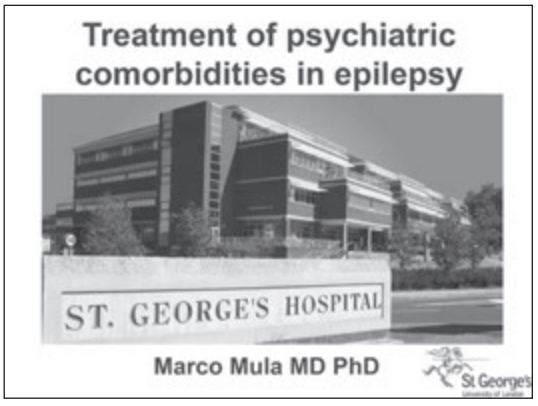
Research efforts should lie in producing an arsenal of evidence-based diagnostic tools and therapeutic interventions which would at minimum mitigate and at maximum prevent or abolish neurobehavioral comorbidities of epilepsy

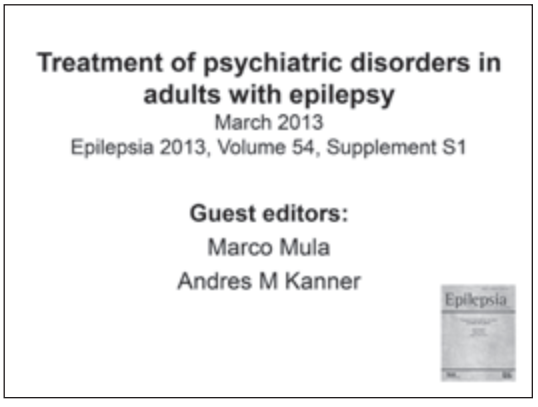
Andres Kanner (USA)

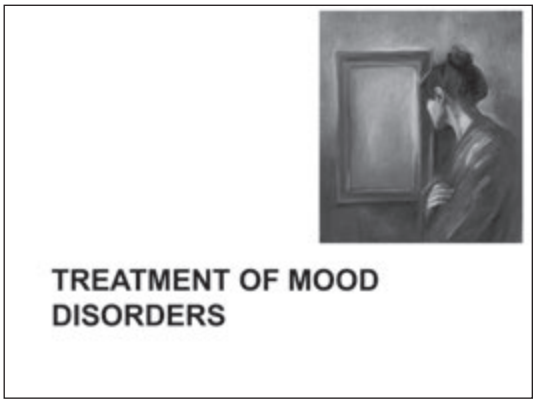
ARE PSYCHIATRIC COMORBIDITIES IN EPILEPSY DIFFERENT FROM PRIMARY PSYCHIATRIC DISORDERS?

Marco Mula (England)

TREATMENT OF PSYCHIATRIC COMORBIDITIES IN EPILEPSY







Challenges in comorbidity

- Mixed and complicated psychiatric syndromes
- Lack of guidelines and literature
- Pharmacologic interactions (both phamacokinetic and pharmacodynamic)
- Management of side effects in special population

Antidepressants as first line agents

- Mood disorders
  - Major depression
  - Dysthymia
  - Double depression
- Anxiety disorders
  - Panic disorder w/wo agoraphobia
  - Post-traumatic stress disorder
  - Generalized anxiety disorder
  - Social anxiety disorder
  - Obsessive compulsive disorder

Epilepsia, 54(Suppl. 1):3–12, 2013
doi: 10.1111/epi.12180

PSYCHIATRIC DISORDERS IN EPILEPSY

The treatment of depressive disorders in epilepsy: What all neurologists should know

Andres M. Kanner

Table 1. Efficacy of SSRIs and SNRIs in primary depression and anxiety disorders

Antidepressant drug	Depression	Panic disorder	Generalized anxiety	Starting dose	Maximal dose
Paroxetine[a]	+	+	+	10	60
Sertraline[a]	+	+		25	200
Fluoxetine[a]	+	+		10	80
Citalopram[a]	+			10	60
Escitalopram[a]	+	+	+	5	30
Fluvoxamine	+	+	+	20	80
Venlafaxine[a]	+	+	+	37.5	300
Duloxetine[a]	+	?	+	30	120

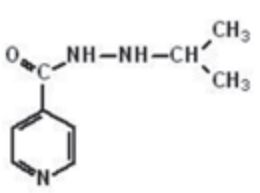
[a]SSRI, [b]SNRI.

Classification of antidepressants

- **Reversible Inhibitors Mono-Amino-Oxidase (RIMAs)**
  - Moclobemide
- **Tricyclic antidepressants (TCAs)**
  - Amitriptyline, Nortriptyline, Clomipramine, Imipramine, Desipramine
- **Selective Serotonin Re-uptake Inhibitors (SSRIs)**
  - Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, Escitalopram
- **Noradrenergic Re-uptake Inhibitors (NARIs)**
  - Reboxetine
- **Dopaminergic Re-uptake Inhibitors (NARIs)**
  - Bupropion
- **Noradrenaline - Serotonin Re-uptake Inhibitors (NSRIs)**
  - Venlafaxine, Duloxetine
- **Noradrenaline and Specific Serotonergic Antidepressant (NaSSA)**
  - Mirtazapine
- **Serotonin Antagonist Re-uptake Inhibitors (SARIs)**
  - Trazodone, Nefazodone
- **Serotonine modulators**
  - Vortioxetine

Mula M. Curr Drug Metab 2008

MAO INHIBITORS



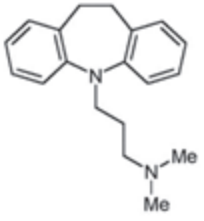
- Non Selective vs. Selective
  - MAO-A → NE, 5-HT
  - MAO-B → DA
- Irreversible vs. Reversible

IPRONIAZIDE - 1951

Muis M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Tricyclic Antidepressants

- The first tricyclic antidepressant discovered was imipramine, which was discovered accidentally in a search for a new antipsychotic in the late 1950s.



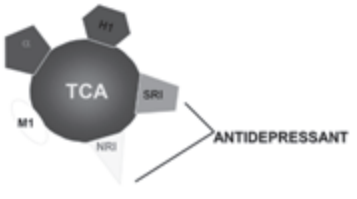
Imipramine (Tofranil)

Tricyclic Antidepressants

- Amytriptiline
- Imipramine
- Desipramine
- Nortriptyline
- Trimipramine
- Protryptyline
- Doxepin

Muis M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Tricyclic Antidepressants



Muis M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Tricyclic Antidepressants

Tertiary amine Secondary amine

$3^o \Rightarrow 2^o$

Muto M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Tricyclic Antidepressants

3°Amines: Imipramine, Amitriptyline

⇓ ⇓ Phase I Metabolism

2°Amines: Desipramine, Nortriptyline

Selectivity 3° Amines -- 5-HT ≥ NE

2° Amines -- NE ≥ 5-HT

Muto M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Receptor blocking in TCA

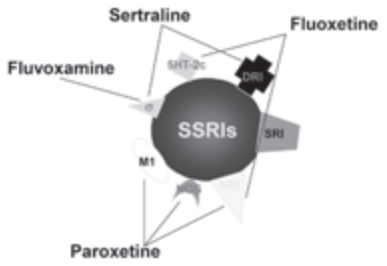
Muto M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Tricyclic Antidepressants

	NE	5HT	Ach	Sed	Comments
amitriptyline (Elavil).....	low	high	high	high	pain, MgrHA
amoxapine (Asendin).....	high	low	mod	low	tetracyclic
clomipramine (Anafranil).	low	high	high	high	tx OCD; SSRI-like
desipramine (Norpramin)	high	low	low	low	activating
doxepin (Sinequan).....	low	low	mod	high	used for insomnia
imipramine (Tofranil).....	low	low	mod	mod	pain; enuresis
maprotiline (Ludiomil).....	high	low	low	mod	tetracyclic
nortriptyline (Pamelor).....	mod	low	mod	mod	chronic pain
protriptyline (Vivactil).....	high	low	mod	low	most activating
trimipramine (Surmontil)..	low	low	high	high	sedative

Muto M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Are SSRIs really selective?



Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

SSRIs

Half-life

- Short (<24 h): paroxetine, fluvoxamine (missed doses can result in uncomfortable symptoms)
- Moderate (24-48 h): sertraline, citalopram, escitalopram
- Long (>48 h): fluoxetine (good for people who may miss doses)

Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

SSRIs Adverse Effects

- Hyponatremia / SIADH
  - Assess if confusion, weakness, malaise, HA
- Bleeding
  - Platelets release 5-HT to initiate aggregation
  - Inhibiting 5-HT uptake in platelets can inhibit platelet aggregation
  - Data shows that SSRIs associated with risk of GI bleed, similar to low dose ibuprofen; concomitant use of SSRIs & NSAIDs or ASA greatly increases risk

Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

SSRIs Adverse Effects

- Extrapyramidal side effects
  - Through 1997, 28 published reports in 48 pts
  - Estimated rate: 1 case per 1,000 pts treated
  - Dystonic rxn, Parkinsonism, akathisia
  - Mechanism unclear
    - Serotoninergic neurons may inhibit DA neurons in the extrapyramidal system
  - Risks: rapid dose escalation, dose changes, concurrent antipsychotics, elderly, women, 1st month of tx

Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

SSRIs Adverse Effects

- Sexual dysfunction
  30 - 70 % SSRIs

  <10-20% Moclobemide,
  Mirtazapine, Bupropion,
  Nefazodone,
  Duloxetine

Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Selective antidepressants

Reboxetine

Citalopram (H-rec)
Escitalopram ?

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Dual action antidepressants

Bupropion

Venlafaxine
Duloxetine

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Specific serotonin antidepressants

Mirtazapine

Trazodone

Nefazodone

Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Antidepressants and QTc interval

- Immediate (trazodone)
- Short-term use (clomipramine, nortriptyline, doxepine)
- Tertiary TCAs (amitriptyline, imipramine) > Secondary TCAs (nortriptyline, desipramine)
- SSRIs? Recent warning!
- No effect for sertraline, paroxetine, bupropion

Goodnick et al. 2002
Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

CYP ISOENZYME	INHIBITORS		INDUCERS
	ANTIDEPRESSANTS	ANTIPSYCHOTICS	
CYP 1A2	Fluvoxamine Fluoxetine Paroxetine Sertraline		St. J W
CYP2C9/10/19	Fluoxetine Sertraline Fluvoxamine	Thioridazine Clozapine	Phenobarbital Carbamazepine
CYP2D6	Fluoxetine Paroxetine Sertraline Bupropion Duloxetine Clomipramine	Thioridazine Haloperidol Clozapine Olanzapine Risperidone	
CYP3A4	Norfluoxetine Nefazodone Fluvoxamine	Chlorpromazine Thioridazine Haloperidol Risperidone	Carbamazepine Barbiturates Phenytoin St. J W

Mula 2008

Negative Dynamic Interactions

- Cardiotoxicity (TCA – Na channel blockers)
- Sedation (VPA, PB)
- Weight gain (TCA, NaSSAs, SARIs – VPA, CBZ)
- Tremor (TCA – VPA, CBZ)
- Serotonin syndrome (SSRIs)
- Extrapyramidal symptoms (SSRIs - VPA)
- Low sodium levels (SSRIs – OXCBZ, CBZ)

Dursun 1993, Gerrard 1991, Mula M. Basic Principles in the Management of Depression in Neurologic Disorders. In: Kanner AM. Depression in Neurologic Disorders: Diagnosis and Management. 2012

Seizures and Antidepressants

- No systematic data
- Most of the studies in psychiatric patients
  - Drug related seizures in non epileptic patients predict risk in patients with epilepsy?
  - Different syndromes are associated with different seizure risk?
- No controlled studies

Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports

Kenneth Alper, Kelly A. Schwartz, Russell L. Kolts, and Arif Khan

BIOL PSYCHIATRY 2007;62:345–354
© 2007 Society of Biological Psychiatry

Drug	N pts	N seizures	%
Bupropion IR	4419	26	0.6
Citalopram	4168	12	0.3
Fluoxetine	6000	12	0.2
Venlafaxine	2181	3	0.1
Bupropion SR	3094	3	0.1
Paroxetine	2963	2	0.07
Nefazodone	2256	1	0.04
Mirtazapine	2796	1	0.04
Escitalopram	715	0	0.0
Duloxetine	2314	0	0.0
Sertraline	2979	0	0.0

Drug	N pts	Seizure rate (%)	Source
Duloxetine	2418	0.2	EMEA
Fluoxetine	10782	0.2	PDR
Fluvoxamine	10401	0.2	PDR, PEM study
Paroxetine		0.1	PDR
Sertraline	4800	0.1-0.2	PDR
Citalopram	1063	0.3	PDR
Escitalopram	5200	0.04	Lundbeck
Bupropion SR	3100	0.1	Dunner et al. 1998
	11735	0.1	PEM study
Bupropion IR	3341	0.4	Johnson et al. 1991
Mirtazapine	2796	0.04	PDR
Reboxetine	-	0.2	PDR
Trazodone	-	0.0	PDR
Venlafaxine	3082	0.3	PDR
Venlafaxine XR	2363	0.0	PDR

Montgomery S. Int J Clin Pract 2005

Seizures and antidepressants

DRUG	DOSE	REPORTED (%)	EXPECTED (%)
Amitriptyline	<200 mg	0.1	0.25
	>200 mg	0.6	(CI 0.20-0.35)
Imipramine	50-600 mg	<0.1-0.9	
Clomipramine	>200 mg	0.5	
Maprotiline	150-200 mg	0.4	
Fluoxetine	20-60 mg	0.2	
Fluvoxamine	<100 mg	0.2	
Sertraline	50-100 mg	<0.1	
Paroxetine	20-60 mg	0.1	
Bupropion	300 mg SR	0.1	
	300-450 mg IR	0.4	
	>450mg IR	>0.6	
Mirtazapine	30 mg	<0.1	

Modified from Mula et al. Expert Opin Pharmacother 2008

ECT and Epilepsy

- The brain seizure, not the method of induction, is the essential element in the efficacy of convulsive therapy (Max Fink 2014).
- Enhancement of seretoninergic and mesocorticolimbic neurotransmission (Baldinger et al. 2014)
- ECT does NOT cause epilepsy (Ray 2013)
- ECT is safe in epilepsy (Lunde et al. 2006)
- ECT is anti-convulsant! (Coffey et al. 1995)
- Potential treatment for refractory status epilepticus? (Lambrecq et al. 2012)

PSYCHOSES AND THOUGHT DISORDERS

Seizure-related psychotic symptoms

- PREICTAL
- ICTAL
- POSTICTAL

PERI-ICTAL

- ALTERNATIVE

PARA-ICTAL

INTER-ICTAL

Ictal Psychoses

- Generalized non-convulsive status (RARE!)
- Focal non-convulsive status
- Continuous form: prolonged twilight or confusional state
- Cyclic form: partial responsiveness
- Temporal type vs. Extra-temporal type: impairment of consciousness, speech disturbances

Trimble 1991; March & Rao 2002; Nadkarni et al. 2007

POST-ICTAL PSYCHOSES

- Nuclear type: lucid interval, typical phenomenology
- Atypical peri-ictal type: no lucid interval, polymorphic presentation
- Excitation, mixed mania (Right-temporal focus)
- Ecstatic moods (Angst-Glücks-Psychose)
- Hallucinations, paranoid delusions, violent episodes, suicide attempts

Oshima et al. 2006; Adachi et al. 2007; Kanemoto et al. 2010

Inter-ictal psychoses of epilepsy

- often subtle
- polymorphic in nature
- paranoid and religious themes
- preserved personality
- warm affect
- significant component of mood change
- better prognosis than schizophrenia

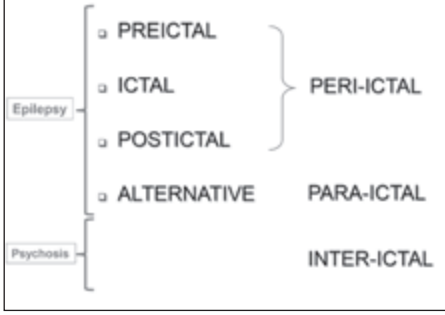
Trimble MR. 1991

Inter-ictal psychoses of epilepsy: risk factors

- Onset of epilepsy in early adolescence
- Interval onset of seizures to onset of psychosis ~ 14 years
- TLE
- Family history of psychosis
- Borderline intellectual functioning

Adachi et al. 2000

Treatment of seizure-related psychotic symptoms



Treatment of Ictal Psychoses

- Adequate seizure control (AEDs or surgical procedures)
- Careful review and verification of diagnosis
- Confirmation by EEG recording
  - Sometimes indistinguishable from other psychoses
  - Surface EEG sometimes normal in frontal focus

Treatment of Post-Ictal Psychoses

- Better antiepileptic drug therapy
- Compliance (educate patient)
- BDZ (e.g. clobazam) for 24-48 hours
- Neuroleptics (small doses for short periods)

Treatment of Alternative Psychoses

- Reduce AED without drug discontinuation
- Compliance (educate doctor)
- Neuroleptics (haloperidol 0.5-10 mg)

Treatment of Inter-ictal psychoses

- Psychiatric setting
- Chronic conditions sometimes high functioning
- Atypical/New antipsychotics

Old generation/Typical Antipsychotics

Tablets	Trade Name	Usual daily dose (mg)	Max. daily dose (mg)
Chlorpromazine	Largactil	75-300	1000
Haloperidol	Haldol	3-15	30
Pimozide	Orap	4-20	20
Trifluoperazine	Stelazine	5-20	
Sulpiride	Dolmatil	200-800	2400

New generation/ Atypical Antipsychotics

Tablets	Trade Name	Usual daily dose (mg)	Max. daily dose (mg)
Amisulpride	Solian	50-800	1200
Aripiprazole	Abilify	10-30	30
Clozapine	Clozaril	200-450	900
Olanzapine	Zyprexa	10-20	20
Quetiapine	Seroquel	300-450	750
Risperidone	Risperdal	4-6	16

Seizures and neuroleptics

- No systematic data
- Most of the studies in psychiatric patients
  - Drug related seizures in non epileptic patients predict risk in patients with epilepsy?
  - Different syndromes are associated with different seizure risk?
- No controlled studies

Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports

Kenneth Alper, Kelly A. Schwartz, Russell L. Kolts, and Arif Khan

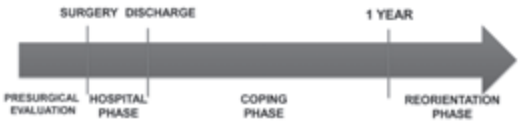
BIOL PSYCHIATRY 2007;62:345–354
© 2007 Society of Biological Psychiatry

Drug	N pts	N seizures	SIR (95%CI)
All antipsychotics	20368	154	2.05 (1.74-2.40)
All excluding clozapine	18626	93	1.35 (1.09-1.66)
Clozapine only	1742	61	9.50 (7.27-12.20)
Olanzapine only	2500	23	2.50 (1.58-3.74)
Quetiapine only	2387	18	2.05 (1.21-3.23)

Postsurgical psychiatric complications

- **Early onset** (immediate after surgery before discharge)
- **Late onset** (within 1 year after surgery)
- **Exacerbation** of a presurgical comorbidity
- **De novo**

Psychiatric schedule for epilepsy surgery



Koch-Stocker et al. 2013

Late onset complications
Depression

Main features

- 10-30%
- Onset after 3 months
- Major depression
- Worsening in presurgical pts (dysphoria in IDD, major depression in dysthymia, suicide)
- Transient course

Principal interventions

- SSRIs (citalopram, sertraline)
- Agomelatine (mild/moderate severity with insomnia)
- SNRIs if SSRIs fail
- 6 months after remission
- Pre-treatment?
- CBT (12-16 weeks)
- IPT

Macrodimitris et al. 2011, Mula 2012, Koch-Stoecker et al. 2013

Late onset complications
Anxiety

Main features

- Up to 40% during the first 3 months
- Onset during the hospitalization phase
- Mixed aetiology (organic and psychoreactive)

Principal interventions

- Acute symptomatic (BDZ)
- Long term (SSRIs) if exacerbation of depression coexists
- Consider burden to normality
- Psychotherapy

Macrodimitris et al. 2011, Koch-Stoecker et al. 2013, Mula 2013

Late onset complications
Mania

Main features

- <2%
- Subtle onset during hospitalization (e.g. excessive gratefulness, joy for new life, closeness with strangers)
- Socially inappropriate behaviors
- Hypomanic symptoms

Principal interventions

- Right temporal resection
- Bitemporal foci
- Low dose atypical antipsychotics for a few days up to 2 weeks
- Undetected BD
- No antidepressants

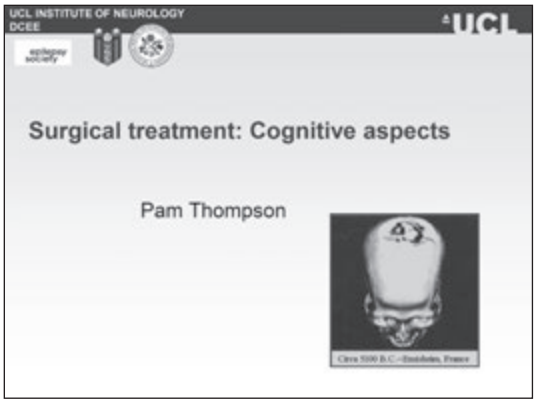
Carran et al 2003, Macrodimitris et al. 2011, Koch-Stoecker et al. 2013

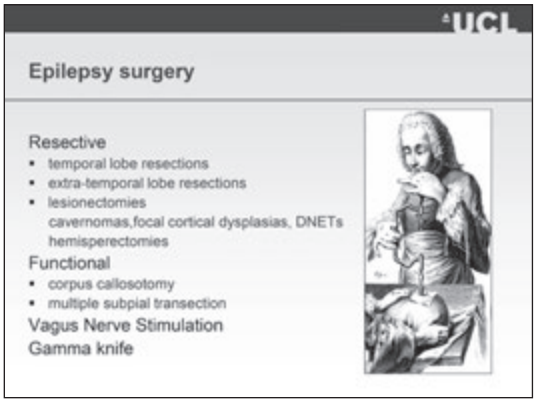
Conclusions
Take home message

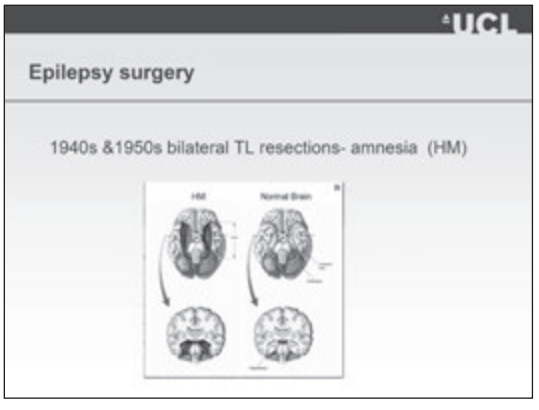
- Different clinical situations requiring different skills and treatment approaches
- Guidelines of treatment outside epilepsy taking into account specific needs (interactions, seizure worsening etc)
- Tailored treatment strategies based on specific phenotypes
- Close collaboration among neurologist/epileptologist – psychiatrist/neuropsychiatrist – psychologist - GP

Pamela Thompson (England)

COGNITIVE ASPECTS FOLLOWING THE SURGICAL TREATMENT OF THE EPILEPSIES







UCL

Henry Gustav Molaison

Born February 26, 1926
Hartford, Connecticut

Died December 2, 2008 (aged 82)
Windsor Locks, Connecticut

This portrait of Henry Gustav Molaison, or H.M., was taken shortly before he underwent the experimental surgery in 1953 that would destroy his ability to form long-term memories.

HM *Suzanne Corkin*

HM - I don't remember things

SC - Do you know what you did yesterday?

HM – No, I don't

SC - How about this morning?

HM - I don't even remember that

SC - Can you tell me what you had for lunch today?

HM - I don't know, to tell you the truth

SC - How long have you had trouble remembering things?

HM - That I don't know myself. I can't tell you, because I don't remember.

SC - Well do you think it has been more than a year that you've had this problem?

HM - I think it's about that, about a year or more, because I believe I had, this is just a thought that I'm having myself, that I possibly have had an operation or something

SC - What do you do to try to remember?

HM - That I don't know, because I don't remember when I try to

---

HM *SC*

SC: Have we met before?

HM: Yes in High School

SC: In High School?

HM: Yes

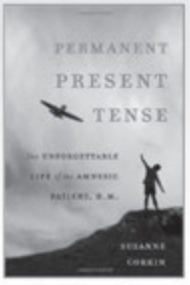
SC: And what year was that, about?

HM: 1945

SC: Have we met any place besides high school

HM: No I don't think so

UCL



UCL

Temporal lobe surgery

Case reports unilateral operations → amnesia

- Dimsdale et al, 1964 **NT**
- Right temporal lobe resection @ 54 years
- pre-surgery: visual good > verbal memory weak
- after surgery: developed amnesia
- surgical specimen – no pathology
- died @ 79 years: autopsy – severe lhs

UCL

Neuropsychological assessment

Integral to pre-surgical assessment

- temporal lobe epilepsy
  - verbal memory deficit — left temporal ↓
    prose passage, lists of words
  - visual memory deficit — right temporal ↓
    visual spatial recall & recognition

UCL

Ana / Silveira / dirigia por uma rodovia / a caminho do casamento de seu primo. / De repente, um lobo / cruzou a pista vindo na direção de seu carro. / Ela tentou desviar / mas acabou caindo em um buraco do asfalto / que estragou / uma das rodas de seu carro / e a fez parar. / Dona Ana, então, pegou o mapa / e resolveu caminhar. / O motorista de um trator a viu e lhe ofereceu uma carona./ Ela aceitou a carona e foi na carroceria do trator, / quase caindo, / sentada em sacos de batata. Com meia hora de atraso, chegou no casamento / coberta de pó / e com os sapatos estragados. / Embora todos tenham ficado felizes ao vê-la, / ela começou a chorar.

UCL

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6 (delay)
church						
horse						
chair						
field						
basket						
tree						
soup						
glass						
pillow						

UCL

Neuropsychological assessment

Integral to pre-surgical assessment

- temporal lobe surgery
  - verbal memory deficit — left temporal ↓
    prose passage, lists of words
  - visual memory deficit — right temporal ↓
    visual spatial recall & recognition

UCL

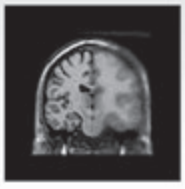
UCL

RHS:Figure Recall

UCL

The intracarotid amobarbital test

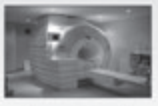
- Juhn Wada 1949
- developed @ the MNI
- screening for amnesic risk
- post-op memory function
- language lateralisation

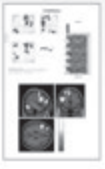


UCL

fMRI paradigms

- non invasive
- more flexible
- less stressful
- outpatient assessment
- routine for language
- under research for memory
- interpretation ?



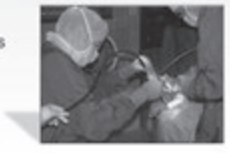


UCL

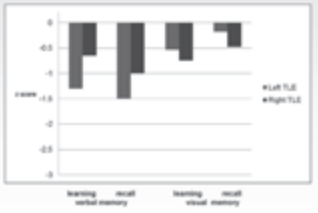
Queen Square: surgical programme

neuropsychological assessments:

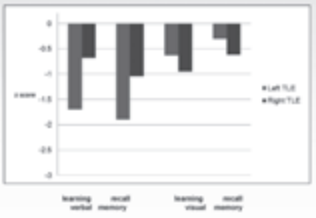
- N= 799 @ 3-6ms; 724 @1 year
- 18- 68 years
- 53% female
- 54% left sided surgeries
- 91% temporal lobe
- 8% frontal lobe



Pre-operative memory test performance



Post-operative memory test performance



Research studies: past

- improving & developing assessment methods
- predicting post-operative cognitive decline


The Role of the Intracarotid Amobarbital Procedure in Predicting Verbal Memory Decline after Temporal Lobe Resection

Post-operative memory decline

Significant predictors
- left sided surgery
- good verbal memory
- older age >40
- additional pathology

not significant
- age of onset; duration
- VIQ
- post-op seizure control

Amytal test findings → little added value

Predicting memory outcome

- follow up > 5 years
- 70 patients
- 53% right TL surgery
- 43 % seizure free
- progressive decline
  - female
  - not seizure free

Developing assessment methods: fMRI memory paradigms

Button-press response:
- Pleasant or unpleasant

- **210 stimuli:**
  1 every 4 secs

- **Recognition test:**
  out of scanner
  60 min delay

Developing assessment methods: fMRI memory paradigms

Words activated left hippocampus

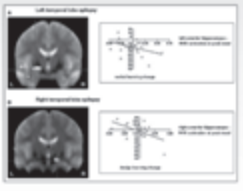
Faces activated right hippocampus

Objects activated both left & right

predicting memory decline

Left temporal lobe epilepsy
↑ LH activation
- **better pre-op verbal memory**
- **↓ verbal memory post-op**

Right temporal lobe epilepsy
↑RH activation
- **better pre-op visual memory**
- **↓ visual memory post-op**



Bonelli et al, 2010

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Current studies

- **fMRI language paradigms**
- psychiatric outcome
- older cohorts
- executive skills pre/post
- memory rehabilitation
- frontal lobe surgery

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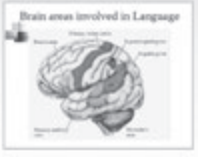
Language fMRI

- language dominance
  right v left
- phonemic fluency
  beginning with 's'
- covert speech
  thought not spoken
- frontal speech networks



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fMRI: Predicting language decline

- temporal lobe speech areas
  - picture naming
  - auditory naming
  - category fluency
- spoken responses

UCL

Picture naming

What is it?

Counting 1,2

Counting 1,2

UCL

fMRI: Predicting language decline

- Naming from description
  What animal barks?
  What insect gives us honey?
- Listen to sentence in reverse
  counting 1,2

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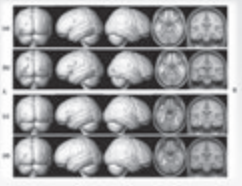
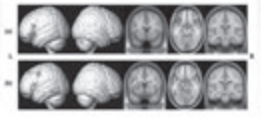
Picture naming



Auditory naming



UCL

Current studies

- fMRI language paradigms
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- older cohorts
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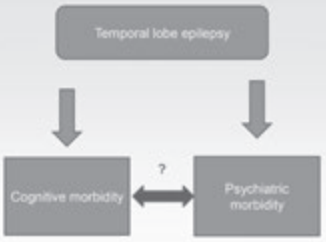
- frontal lobe surgery

UCL

UCL



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Post-surgical psychiatric outcome

- psychiatric symptoms de novo: 5-25%
- pre-existing psychiatric symptoms may worsen
- Cleary et al 2012 ; retrospective study
  N=280; 49% seizure free @ 4 years
  38% psychiatric disorder
  18% de novo disorder
- Pre –op psychiatric history → poorer seizure outcome
  Kanner et al., 2009; Cleary et al.,2012

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Cognition & psychiatric outcome

- TLE ↑ Cognitive deficits & depression
  Hermann et al 1999
  Paridiso et al 2001
  Helmsteadter et al 2004 (LTLE)
- TLE extra-temporal lobe dysfunctioning
  Stretton et al 2012

Hypothesis: Pre-operative executive function deficits (indicators of frontal lobe dysfunctioning) would be associated with poorer post-operative psychiatric outcomes.

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Prospective study

- 87 TLE surgical case
- 49 pre and post –op (25 RTLE; 24 LTLE)
- Assessments: before surgery @3-6m & @12m
- + executive function tests
- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)

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+ Executive Function Measures

- CANTAB Spatial Working Memory Task

- Wisconsin Card Sorting Task (WCST)
- Trail Making Test
- Dysexecutive Questionnaire

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Dysexecutive Questionnaire DEX

20 questions: self-rating & observer versions

- I act without thinking, doing the first thing that comes to mind
- I have difficulty thinking ahead or planning for the future
- I lose my temper at the slightest thing
- I am easily distracted

severity rating: 0= never – 5 very often

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Prospective study: findings

Pre-operative findings
- 1 in 3 pre-op psychiatric history
- 1 in 6 pre-op psychiatric diagnosis
- ↓ WCST scores and ↑ depression

Post-operative findings
- 4 in 5 seizure free @ 12ms
- 1 in 6 de novo psychiatric disorder
- WCST & DEX scores predictors
  ↑ post operative depression & anxiety symptoms

UCL

Current studies

- fMRI language paradigms
- psychiatric outcome
- **older cohorts**
- executive skills pre/post
- memory rehabilitation
- frontal lobe surgery

UCL

Cognitive impact of surgery in older cohorts

- TLE surgery > 50 years increasing
- Bialek et al., 2014 review
  seizure freedom rates = younger groups
- cognitive impact of surgery on an ageing brain?
  ↑ cognitive vulnerability - Girvas et al 2006; Costello et al 2009
  = younger groups – Murphy et al 2010; Patra et al 2014
  ↓ cognitive vulnerability – Chapin et al, 2013

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Cognitive impact of surgery in older cohorts

- N= 55 TLE surgical cases 50 years +
- N= 185;18-30 years; N=220; 31-49 years
- pre & one year cognitive assessments
  verbal learning & recall
  visual learning & recall
  naming
  subjective ratings: 0 = no problems to 3= severe problems

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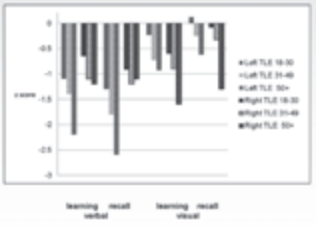
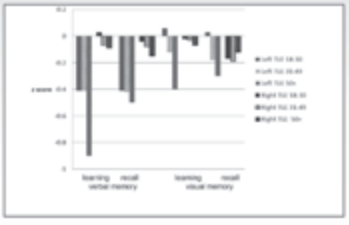
Pre-operative performance x age group



UCL

Post-operative change scores at one year



UCL

Cognitive impact of surgery in older cohorts

- Memory tests
  ↑ memory impairments before surgery
  ↑ verbal memory decline after surgery
- Subjective ratings
  28% 18- 29 years; **30%** 30-49 years; **46%** 50+ years
- Language decline
  9% 18-30 years; **19%** 30-49 years; **30%** 50+ years

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Summary

- pre-surgical neuropsychological assessments
  integral to pre-surgical investigations
  essential for pre-surgical counselling
  cognitive & psychiatric risks are high
- post-surgical assessments
  provide data key for pre-surgical counselling
  enable early identification of problems
- pre & post-surgical assessments
  unique research opportunity
  HM onwards ↑ understanding of brain function

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In collaboration with

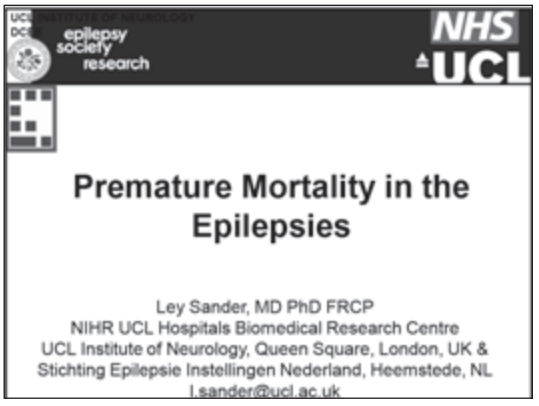
Members of the Department of Clinical & Experimental Epilepsy UCL
past & present
Clinicians at National Hospital for Neurology & Neurosurgery UCLH
past & present
People with epilepsy & their families

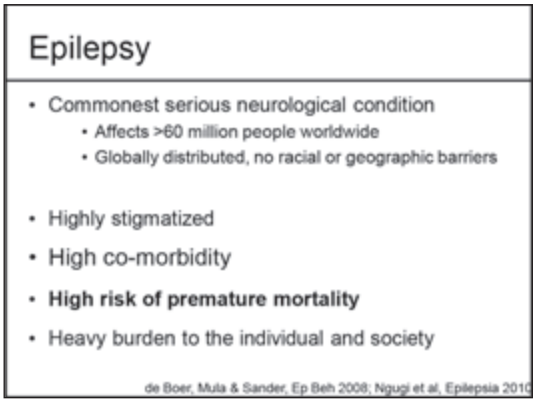
with support from

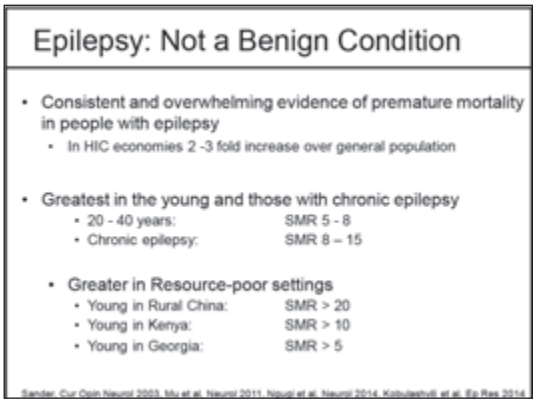
epilepsy society
The Henry Smith Charity
epilepsy action
wellcome trust | Celebrating 75 Extraordinary Years
action medical research for children, for life

LEY SANDER (ENGLAND)

THE RISK OF PREMATURE MORTALITY IN EPILEPSY/EPILEPSY AND SUICIDE







Mortality of Epilepsy

- Methodological problems
  - **Definitions**
    - **What is epilepsy? What type?**
    - **When does it start, when does it cease?**
    - **Attribution ?**
  - **Case ascertainment / selection**
    - **Death certificates**
    - **Clinical - autopsy series and case reports**
    - **Life insurance policy holders**
    - **Cohort studies**
    - **General population**

Mortality of Epilepsy

- Methodological problems
  - Methods of analysis
    - **Proportional mortality ratio (PMR)**
    - **Standardised mortality ratio (SMR)**
    - **Survivorship ratio (SR)**
  - Failure to confirm survival status
  - Death unclassified or unaccounted for

Standardised Mortality Ratio

- Use the age specific mortality rates of the population
- Calculate number of deaths expected in that time period in observed population, if it experienced those age specific mortality rates
- Compare the observed number of deaths with the expected number – a ratio

Incidence: How Many People Develop Epilepsy?

- In the developed world:
  - 40 – 70 /100,000 /year (50 /100,000 /year)
- In resource-poor countries:
  - 80 – 190 /100,000 /year (120 /100,000 /year)

Sander, Cur Op Neurol 2003; Nouri et al, Neurology 2011

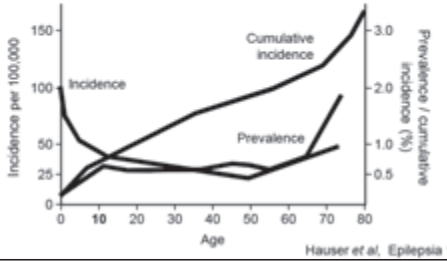
Epilepsy Epidemiological Paradox

- If seizures do not remit without treatment, the number of people who have ever developed epilepsy (incidence) would be similar to the number of people with current epilepsy (prevalence)
  - In developed countries, the difference between rates largely attributed to cessation of seizures induced by AEDs
- Incidence of Epilepsy much higher in resource-poor countries
  - over 70% of people with epilepsy in these settings not treated
- Prevalence, however, similar independent of location
  - 4 - 10/1,000

Sander, Epilepsia 2003; Bell, Neligan & Sander, Epilepsia (in press)

Incidence and Cumulative Incidence of Epilepsy

Age-specific incidence rate, cumulative incidence rate and prevalence rate of epilepsy in Rochester, Minnesota (1983–1974)



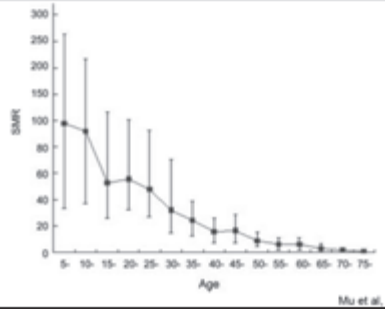
Hauser *et al*, Epilepsia 1983

Difference Between Rates in Resource-poor and Developed Countries

- Methodological problems
  - Unlikely
  - Acute symptomatic seizures ?
- Spontaneous remission ?
  - circumstantial evidence
- Role of mortality ?
  - Strong circumstantial evidence

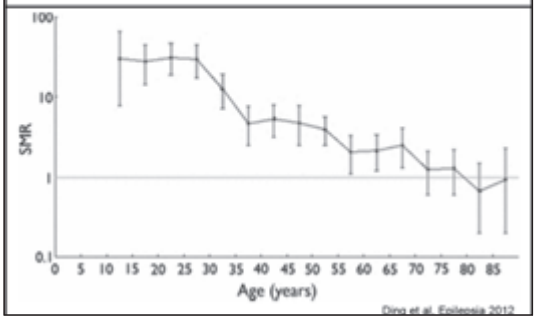
Sander, Cur Opin Neurol,2003

Age-specific SMR of Treated Convulsive Epilepsy in Rural West China



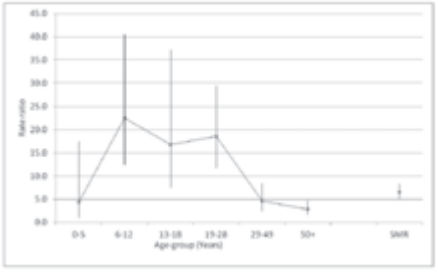
Mu et al, Neurology 2011

Premature Mortality Risk: Long Follow-up of a Cohort in Rural China



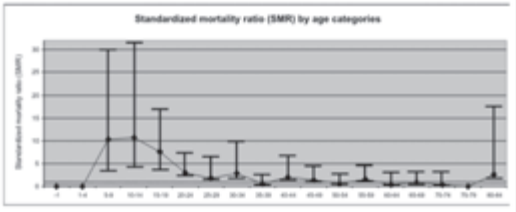
Ding et al. Epilepsia 2012

Age-specific SMR of Treated Convulsive Epilepsy in Rural Kenya



Ngugi et al Neurology 2014

Age-specific SMR of epilepsy in Urban Georgia



Kobulashvili et al. Ep Res 2013

Long Term Mortality in the UK

- 792 people who developed epilepsy over 25 years ago and followed from onset
- Premature mortality persistently ▲ despite most becoming seizure-free
  - 82% of people seizure-free at 25 years
- Mortality 2.6 fold ▲ at 20-25 years from diagnosis
  - SMR significantly ▲ (2.3) in those always seizure free
  - Most deaths due to non-epilepsy related causes
- Role of co-morbidity

Neligan et al. Brain 2011

Cause of Death in Epilepsy

- Unrelated to epilepsy
  - Co-morbidity
- Related to underlying disease causing epilepsy
  - SMR ↑ for CNS tumours, cerebrovascular disease, CNS infections, inherited disorders
- Related to epilepsy
  - Treatment
  - Condition

Death Related to Underlying Disease

- Particularly in the first few years following diagnosis (newly diagnosed epilepsy)
  - SMRs significantly raised in early years after diagnosis
  - Suicide, SUDEP, accidents rare in this setting

➢Largely attributed to condition causing epilepsy
- Stroke, neoplasm, CNS infection, degenerative condition

- Increase mortality in terminal remission
  - Role of co-morbidity ?

Loiseau et al. Epilepsia 1999;

UCL

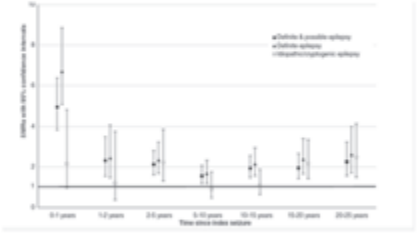
• Mortality in the early years

- NGPSE (n = 792)
  - Highest in first year
  - Consistently significantly increased
  - "Trend largely result of early death from underlying disease such as strokes & tumours: SMR highest in remote and acute symptomatic cases because of the underlying lesion, with majority of these deaths occurring in the first 2 years"

Cockerell et al, Lancet 1994

UCL

• SMRs in people with epilepsy



Neligan et al, Brain 2011

UCL

• Mortality in the early years

- Dutch study of newly diagnosed epilepsy (N = 1355)
- SMR significantly ↑ until 35 years FU
  - 0-1 years, SMR 16
  - 2-4 years, SMR 7.0
  - 5-9 years, SMR 6.9
  - 10-14 years, SMR 3.9
  - In first 2 years of follow-up…*conditions*…possibly accountable for acute symptomatic epilepsy, responsible for 19% of death
  - After the first 2 years, underlying causes responsible for 15% of mortality

Shackleton et al. JNNP 1999

Mortality of Chronic Epilepsy

- Death more likely to be epilepsy-related
  - Suicide
  - Seizure-related deaths
    - Status epilepticus
    - Accidents (including drowning)
    - SUDEP

Death in epilepsy: accidents

- People with epilepsy likely to have accidents
- >30% had at least 1 seizure-related injury in previous 12 months
  - Predicted by type, frequency and severity of seizures
- In a Swedish study death from injury 5 times higher than expected
- Almost 20 fold increase in risk of drowning

Bell et al. Neurology 2008

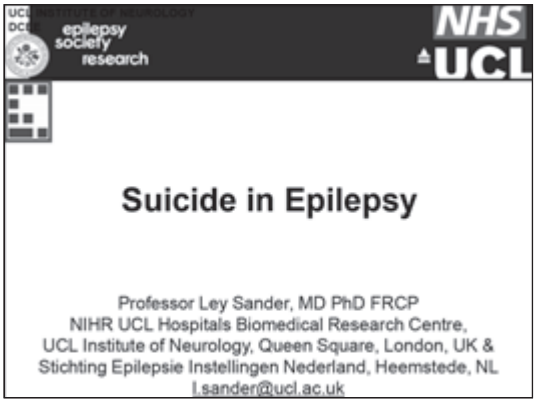
SUDEP

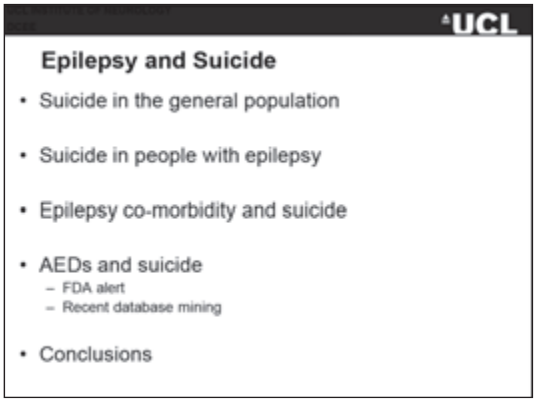
- Most frequent cause of death directly related to epilepsy, and most often in chronic epilepsy
- Most important risk factors related to poorly controlled seizures, suggesting is a seizure-related event
- Cardiac arrhythmia, respiratory dysfunction, dysregulation of systemic or cerebral circulation and seizure-induced hormonal and metabolic changes suggested as potential pathomechanisms
- Most probably triggered by the peri-ictal concurrence of a number of predisposing and precipitating factors

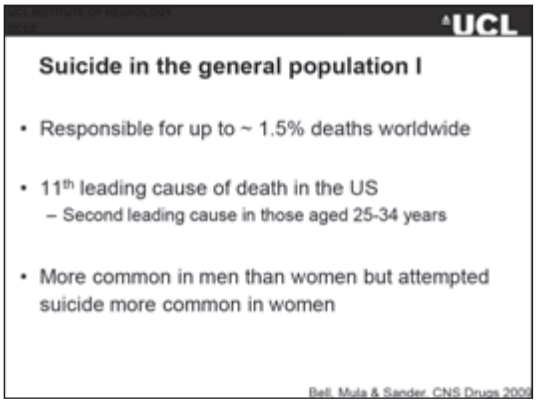
Surges et al. Nat. Rev Neurol 2009

Premature Mortality: Conclusions

- Consisting evidence of premature mortality
- Responsible for good part of societal burden
- Plays a role in "good prognosis"
  - The epidemiological paradox!
  - Underplayed, under recognised & under recorded
- Causes of epilepsy as causes of death in early epilepsy most probably true but poorly described or studied
- More studies required to understand fully drivers of staggering high premature mortality
- Role of co-morbidities







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Suicide in the general population II

- 90% of people who commit suicide have ≥1 psychiatric disorder at the time
- SMRs for suicide increased in people with:
  - Major depression SMR 20.3
  - Bipolar disorder SMR 15.0
  - Anxiety disorders SMR 10.0
  - Schizophrenia SMR 8.5

Harris & Barraclough. Br J Psychiat 1997

UCL

Suicide in the general population III

- Previous attempt ↑ risk of completed suicide
- Suicidal ideation seems to be a risk factor for later suicide

Harris & Barraclough. Br J Psychiat 1997

UCL

Do people with epilepsy commit suicide?

- 1940s – prevailing opinion: 'rarely commit suicide'
  - But 'it does occur… rather frequently'
- 1997 meta-analysis – SMR for suicide in people with epilepsy 5.1

Prudhomme. J Nerv Mental Dis 1941; Harris & Barraclough. Br J Psychiat 1997

UCL

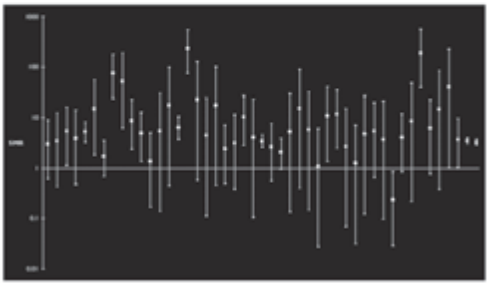
Do people with epilepsy commit suicide?

- Most recent meta-analysis
  - 76 cohorts of people with epilepsy
  - 190 observed deaths by suicide vs. 58.4 'expected'
- SMR for suicide in people with epilepsy 3.3
  - ↑ in many groups of people with epilepsy
  - Higher in people with TLE and following epilepsy surgery

Bell et al. Epilepsia 2009

UCL

Death in epilepsy: suicide



Bell et al. Epilepsia 2009

UCL

Death in epilepsy: suicide

Bell et al. Epilepsia 2009

UCL

Risk factors for suicide in people with epilepsy

- 1980 – due to social disadvantages?
- Large case-control study
  - 5 registries from Denmark
  - 17 year period
  - Up to 20 live controls for each person who committed suicide
  - 21,169 committed suicide
    - 492 had epilepsy

Christensen et al. Lancet Neurol 2007

UCL

Large case control study II

- Overall rate ratio 3.17 for people with epilepsy
- Excluding people with psychiatric disease
  - RR for people with epilepsy 1.99 (P<0.0001)
- In people with psychiatric disease
  - RR for people with epilepsy 1.21 (P=0.009)
- Risk of suicide ↓ with time from diagnosis
- Risk of suicide ↓ with ↑ age

Christensen et al. Lancet Neurol 2007

UCL

Suicide in people with epilepsy

- Risk factors:
  - Psychiatric disease
  - Use of antipsychotic drugs
  - Early onset of epilepsy
- But
  - Strong association between epilepsy and psychiatric disease
  - Psychiatric illness strong risk factor for suicide in the general population

Nilsson et al Epilepsia 2002; Christensen et al Lancet Neurol 2007

UCL

Suicide in people with epilepsy

- Risk factors for suicide may be different for people with epilepsy
  - Borderline personality disorder and psychosis more associated with suicide in people with epilepsy
  - Suicide may be associated with ictal or interictal episodic manifestations
    - Post-ictal Psychosis

Bell, Mula & Sander CNS Drugs 2009

UCL

Epidemiology - Depression

Risk of seizure in depression

- OR = 6.0 (95% CI = 1.56 to 22) for unprovoked seizure in major depression

Rates of depression in epilepsy

Community-based studies: 9% to 22%

Hospital-based studies: 27% to 60%

DEPRESSION ⟷ EPILEPSY

CI, confidence interval; OR, odds ratio

Hesdorffer et al. Ann Neurol 2000; Hesdorffer Neurology 2007

UCL

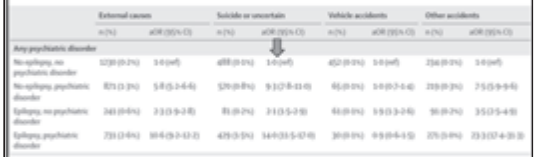
Suicide attempt, depression & seizures

- People with new onset seizures
  - Each case matched with 2 controls
- Cases 1.7-fold more likely to have history of major depression
- Cases 5.1-fold more likely to have history of suicide attempt
- Major depression & suicide independent risk factors
  - Different underlying mechanisms?

Hesdorffer et al. Ann Neurol 2006

Comorbidity in Premature Mortality

- Premature mortality in epilepsy and the role of psychiatric comorbidity
  - Swedish Study covering the whole population (n=69,995)



Fazel et al, Lancet 2013

UCL

Anti-epileptic drugs

- In high-income countries, most people with epilepsy take AEDs
- AEDs also prescribed for many other conditions
  - Probably the majority of prescriptions for newer AEDs are for conditions other than epilepsy

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FDA meta-analysis I

- In 2005 the FDA requested data from placebo-controlled trials of AEDs
- Performed a meta-analysis of suicidal behaviour and ideation
- Used previously defined criteria

FDA advisory 2008

UCL

FDA meta-analysis II

- 2008 analysis published:
  - 199 studies
  - 11 different AEDs
  - Indications epilepsy, psychiatry, 'others'
  - >27,000 people took AEDs, >16,000 took placebo

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FDA meta-analysis III

- 4 suicides – all in people taking AEDs
- 30 suicide attempts in people taking AEDs
  - (>27,000 population)
- 8 suicide attempts in people taking placebo
  - (>16,000 population)
- OR for suicidal behaviour or ideation 1.8

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FDA meta-analysis IV

- 1/4 of people involved in trials for epilepsy
- >1/4 in trials for psychiatric conditions
- Almost 1/2 for 'other' indications
  - Pain
  - Insomnia
  - Migraine
  - Neuropathy
  - Tremor

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FDA meta-analysis V

- Odds ratios for suicidality:
  - Epilepsy indications: OR 3.53 (CI 1.3, 12.1)
  - Psychiatric indications: OR 1.5 (CI 0.95, 2.5)
  - 'Other' indications: OR 1.87 (CI 0.8, 4.8)
- Used spontaneously reported events
  - Risk of reporting bias

Hersodorffer et al Epilepsia 2009

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FDA meta-analysis VI - problems

- In trials for epilepsy
  - In 81%, AED polytherapy
  - Probably intractable epilepsy
  - No information about seizure control
    - Forced normalisation?
- Suicide in people with epilepsy not a new phenomenon
  - Not related to new AEDs
  - FDA meta-analysis was predominantly new AEDs

Bell, Mula & Sander CNS Drugs 2009

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FDA meta-analysis VII - problems

- Only 33% studies used in the analysis
- Short duration (mean 89 days)
- No information on suicidality before entry
- No account taken of post-ictal depression or suicidal ideation

Hersodorffer et al Epilepsia 2009

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FDA meta-analysis VIII - problems

- Different classes of AEDs grouped together
  - Different mechanisms of action
- Only significantly ↑ ORs for LTG and TPM
  - Both already mentioned suicidality in inserts
- Risk of stopping AEDs usually greater than risk of continuing
  - Status Epilepticus
  - SUDEP ?

Hersodorffer et al Epilepsia 2009; Mula & Sander Neurology 2010

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Subsequent studies I:

- VA database with new prescription for monotherapy AED
  - 7,445 for epilepsy
  - 104,651 not for epilepsy
- 64 people with suicidal ideation or behaviour
  - Up to 12 controls for each
- Strongest predictor of suicidality was previous affective disorder

Van Cott et al. BMC Med 2010

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Subsequent studies II:

- Danish national registries
- 6780 suicides
  - 365 people on monotherapy AED at time of suicide
- Crossover design – each case had a previous period used as control
- AED initiation increased risk – OR 1.84
  - Risk increased for CNZ, SVP, LTG and PB

Olesen et al Pharmacoepidemiol Drug Saf. 2010

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Subsequent studies III:

- US medical and pharmacy claims database
- Incident AED use in people with no recent suicidal behaviour, cancer or HIV
- Compared with topiramate
  - ↑ risk suicidal behaviour or violent death in people taking GBT, LTG, OXB, TGB or SVP
  - Median FU 60 days
  - Most did not have epilepsy
  - Significant comorbidities

Patorno et al JAMA 2010

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Subsequent studies IV:

- UK GP data (THIN)
  - Excluded people with suicide attempt
- In people with epilepsy or bipolar disease:
  - AEDs did not ↑ risk of suicide-related events
- In people with depression:
  - AEDs →↑ risk of suicide-related events
- In people without epilepsy, bipolar or depression:
  - AEDs →↑ risk of suicide-related events

Arana et al NEJM 2010

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Subsequent studies V:

- UK GP data (GPRD)
  - Nested case-control study, outcome self-harm or suicidal behaviour
- People with epilepsy treated with AEDs
- Divided AEDs into 4 groups
  - Barbiturates
  - Conventional AEDs
  - Newer AEDs with low depression potential
  - Newer AEDs with high depression potential
- Only newer AEDs with high depression potential increased risk

Andersohn et al Neurology 2010

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AED and Suicide - Summary

- Inconsistent findings from different databases
  - Controlling for prior suicide attempt – important!
  - Confounding by indication
  - Knowledge of past history influences follow-up
- Prospective, randomised, double-blind controlled trial needed
  - Relevant variables systematically gathered
  - Separate trials for different conditions
  - Logistically possible ?

Hersodorffer Epilepsy Currents 201

UCL

Epilepsy and Suicide - Conclusions

- Increase suicide risk in epilepsy, at least 3-fold over general population
  - Differing risk in different patient sub-groups
- Epilepsy has high psychiatric co-morbidity
  - Part of the risk related to this ?
- Bi-directional risk ?
- Findings on AEDs inconsistent

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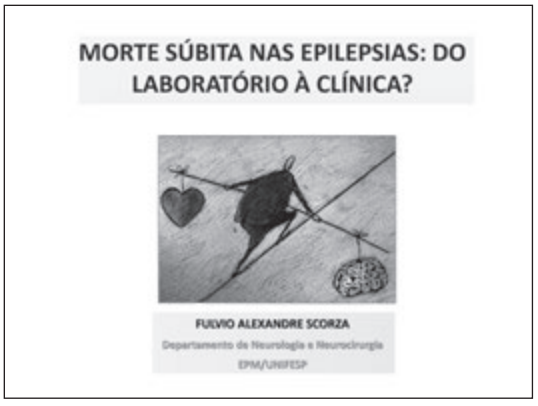
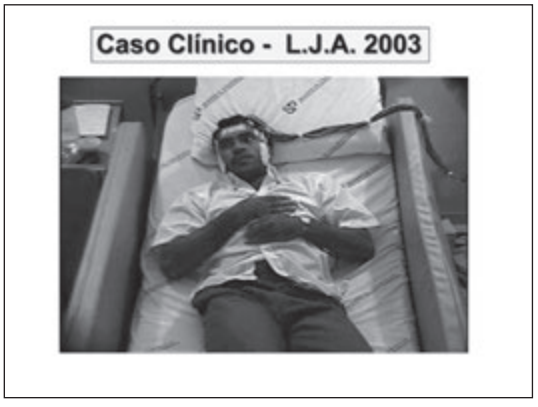
Epilepsy and Suicide – Conclusions II

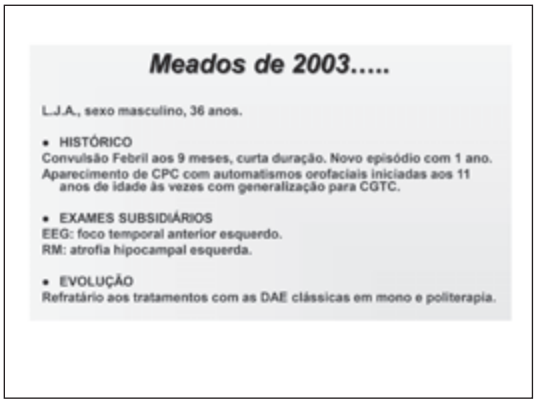
- Vital that all treating people with epilepsy identify those at risk of suicide and preventative measures taken
  - Screen mental state; usually no complaints about mood or behaviour unless specifically assessed
- Important that risk factors, prognosis, and CoD in epilepsy are fully understood, to reduce avoidable morbidity and mortality
- In the interim, adequate seizure control and taking precautions to avoid more deaths

Fúlvio Scorza (Brazil)

PREVENTION OF SUDDEN UNEXPECTED DEATH IN EPILEPSY: GOLD RUSH BY A WINDING ROAD





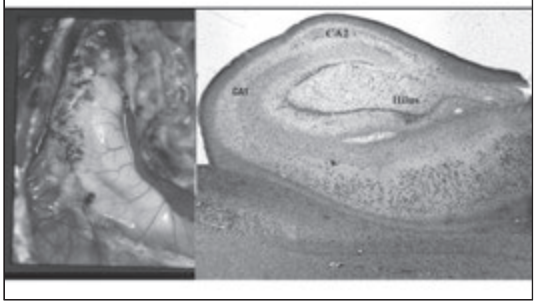


EPILEPSIA DO LOBO TEMPORAL

* 40% de todos os casos de epilepsias *(Thom et al, 2010; Duncon et al., 2006).*

* Alta refratariedade ao tratamento farmacológico
(Thom et al, 2010; Duncon et al., 2006)

ANATOMIA HIPOCAMPAL



Meados de 2003.....

L.J.A., sexo masculino, 36 anos.

- HISTÓRICO

Convulsão Febril aos 9 meses, curta duração. Novo episódio com 1 ano.
Aparecimento de CPC com automatismos orofaciais iniciadas aos 11 anos de idade às vezes com generalização para CGTC.

- EXAMES SUBSIDIÁRIOS

EEG: foco temporal anterior esquerdo.
RM: atrofia hipocampal esquerda.

- EVOLUÇÃO

Refratário aos tratamentos com as DAE clássicas em mono e politerapia.

MORTE SÚBITA DURANTE O SONO

MORTE SÚBITA NAS EPILEPSIAS (SUDEP)


CRITICAL REVIEW AND INVITED COMMENTARY

Unifying the definitions of sudden unexpected death in epilepsy

- Falta de achados de necropsia
- Casos raramente testemunhados de SUDEP

↓

DIFICULDADE DEFINIÇÕES

O óbito deve ocorrer de maneira não traumática, sem afogamento, pode ter ou não relatos de crise, excetuando-se *status epilepticus*, e os exames realizados após a morte não podem revelar causas anatômicas ou toxicológicas

(Nashef et al., 2012; Nashef & Ryvlin, 2009; Nashef, 1995).

DADOS EPIDEMIOLÓGICOS


Epilepsy & Behavior

Review Article

Sudden unexpected death in epilepsy

Estudos Populacionais: 1/1000 pessoas-ano

Atendimento Terciário (Especializado): 2-5/1000 pessoas-ano

Candidatos para Cirurgia: 6-9/1000 pessoas-ano

Adultos com epilepsia/População geral: 24 vezes mais chances de morrer subitamente.


FULL-LENGTH ORIGINAL RESEARCH

Combined analysis of risk factors for SUDEP

Não controle das crises epilépticas, **idade, início precoce das epilepsias, tempo de duração das epilepsias, tipos de crises epilépticas, regime de drogas antiepilépticas adotado, crises noturnas, gênero masculino .**

CRIANÇAS COM EPILEPSIA ...


Sudden unexplained death in children with epilepsy

Elizabeth J. Donner, MD, Charles R. Smith, MD, and O. Carter Snead III, MD

Lancet 2002; **359:** 1801–06.

Death in children with epilepsy: a population-based study

Carol S Camfield, Peter R Camfield, Paul J Veugelers

Journal of Paediatrics and Child Health

REVIEW ARTICLE

Sudden unexpected death in epilepsy in children

Original article

Mortality and causes of death in children referred to a tertiary epilepsy center

SUDEP (8 SUDEP cases per 10,000 patient years)

Conclusions: This study confirms that SUDEP must not be disregarded in the pediatric age group. The vast majority of SUDEP cases in this study displays numerous risk factors similar to those described in adult epilepsy patients. Including SUDEP, only 30% of the mortality was directly seizure related.

Epilepsy & Behavior

Editorial

Clarice Lispector: The voice of the writer inspired me to talk about sudden unexpected death in epilepsy

"Nosso coração bate setenta vezes por minuto. Sete é o ritmo do homem. A cura da ferida mais profunda ocorre em sete dias, se o agente causador não estiver por perto."

PEDIATRIC EPILEPSY SURGERY AND SUDDEN UNEXPECTED DEATH IN EPILEPSY: THE CONTRIBUTION OF A BRAZILIAN EPILEPSY SURGERY PROGRAM

Vera C.Terra; Roberta M. Cysneiros; Regina F. Fernandes; Kylvia D. Pinto; Lauro Wichert-Ana; Américo C. Sakamoto; Hélio R. Machado; Ricardo M. Arida; Esper A. Cavalheiro; Fulvio A. Scorza *

* ***Cohort*** - crianças com epilepsia - zero a 18 anos (2000-2009)

* **Crianças avaliadas**: n= 1054

* **SUDEP**: 12 casos (11.3/1000)

* **Características**: idade (7 anos), refratariedade, CTCG, politerapia

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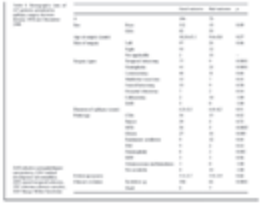
Pediatric epilepsy surgery and sudden unexpected death epilepsy: the contribution of a Brazilian epilepsy surgery program



Small people, big reasons: The need to focus on sudden unexpected death in children with epilepsy

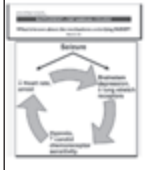
Fulvio A. Scorza Vera C. Terra Américo C. Sakamoto Ricardo M. Arida

Ônibus escolar - Nova Delhi

Ônibus escolar - Japão

MORTE SÚBITA NAS EPILEPSIAS (SUDEP)

CAUSAS



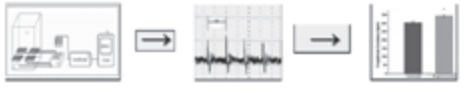
Atividade respiratória central **pode ser suprimida diretamente pela crise ou indiretamente pela hipóxia provocada pela parada cardíaca durante a crise.**

MECANISMO PATOFISIOLÓGICO

SUDDEN UNEXPECTED DEATH IN EPILEPSY: FROM ANIMALS TO HUMANS

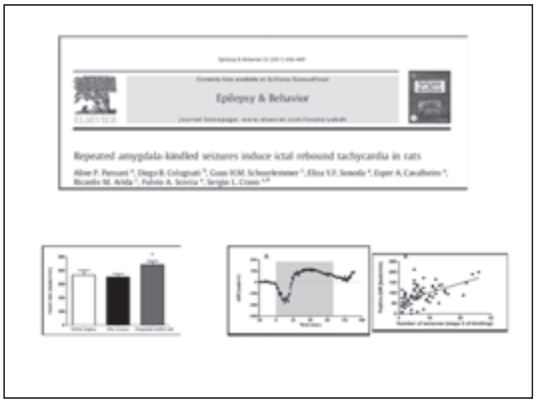
Fulvio A. Scorza* and Josemir W. Sander

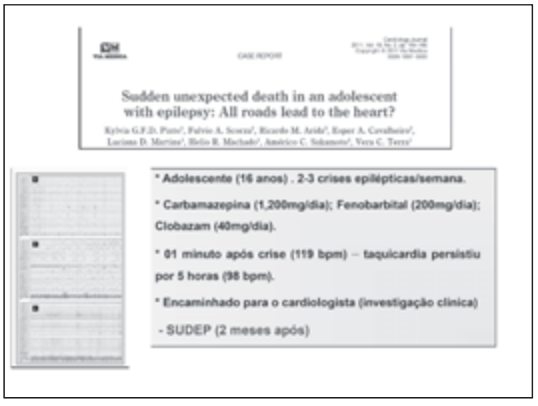
" The epilepsy academic community should make efforts to learn *from animal models*, as they could potentially help *elucidate common putative mechanisms for the SUDEP phenomenon and may facilitate the deployment of preventative measures.* Basic scientists can bring new insights into mechanisms which may or may not prove to be relevant to SUDEP in people with epilepsy, but either way, we will make important progress."



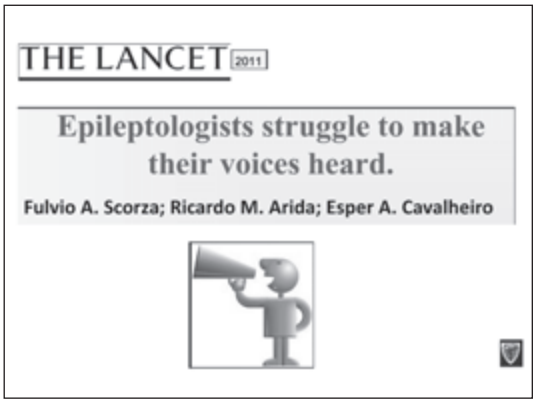
CONCLUSÃO

Sob a influência do SNC, o coração pode apresentar alterações funcionais que aumentam a probabilidade de SUDEP


Epilepsy & Behavior
Repeated amygdala-kindled seizures induce ictal rebound tachycardia in rats


Sudden unexpected death in an adolescent with epilepsy: All roads lead to the heart?
* Adolescente (16 anos) . 2-3 crises epilépticas/semana.
* Carbamazepina (1,200mg/dia); Fenobarbital (200mg/dia); Clobazam (40mg/dia).
* 01 minuto após crise (119 bpm) – taquicardia persistiu por 5 horas (98 bpm).
* Encaminhado para o cardiologista (investigação clínica)
- SUDEP (2 meses após)


MORTE SÚBITA NAS EPILEPSIAS (SUDEP)
MEDIDAS PREVENTIVAS


THE LANCET 2011
Epileptologists struggle to make their voices heard.
Fulvio A. Scorza; Ricardo M. Arida; Esper A. Cavalheiro

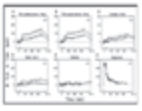
ÔMEGA-3: EPILEPSIAS E SUDEP

ELSEVIER

ejp

Anticonvulsant effect of polyunsaturated fatty acids in rats, using the cortical stimulation model

Robert A. Vreugdenhil [a,*], Martin Vreugdenhil [a], Jing X. Kang [a], Alexander Leaf [a]



Modelo da Estimulação Cortical

↓

Ômega-3

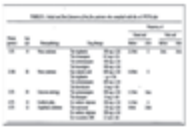
↓

Aumenta o Limiar para Atividade Convulsiva

Brief Communication

Diet Enriched with Omega-3 Fatty Acids Alleviates Convulsion Symptoms in Epilepsy Patients

*Simon Schlanger, †Meir Shinitzky, and †Daniel Yam



5g Ômega-3 → café da manhã → 6 meses

↓

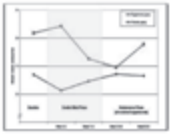
< Freqüência de crises epilépticas

ELSEVIER

Epilepsy & Behavior

Omega-3 fatty acid supplementation in patients with chronic epilepsy: A randomized trial [☆]

Alan W.C. Yuen [a,b], Josemir W. Sander [a,b,*], Dominique Fluegel [a,b], Philip N. Patsalos [a,b], Gail S. Bell [a,b], Tony Johnson [a], Matthias J. Koepp [a,b]



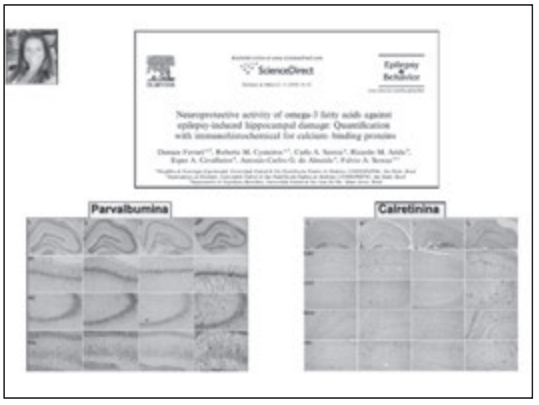
ÔMEGA- 3 → 12 semanas

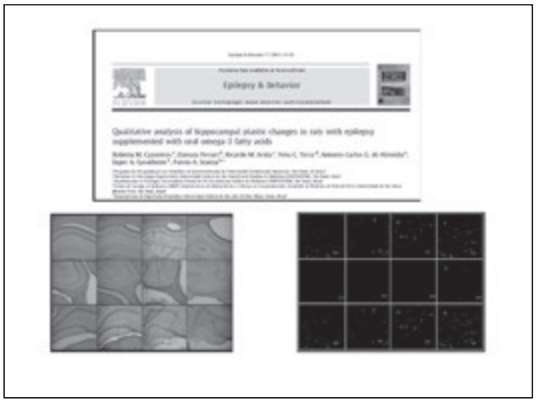
↓

1as 6 semanas → < *freqüência de crises*

↓

SEM Alteração Concentração Plasmática AED


Parvalbumina
Calretinina




CORAÇÃO – INFLAMAÇÃO - SUDEP


Arteriosclerosis, Thrombosis, and Vascular Biology
Circulation Research
Commentaries on Cutting Edge Science
You Can't Run From Inflammation

REVIEW

Marine omega-3 fatty acids and coronary heart disease

Philip C. Calder* and Parveen Yaqoob**

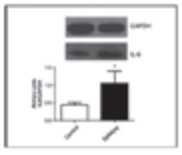
Review

Dietary Fat and Heart Failure: Moving From Lipotoxicity to Lipoprotection

2012

INTERLEUKIN-6 BARES A DARK SIDE IN SUDDEN UNEXPECTED DEATH IN EPILEPSY

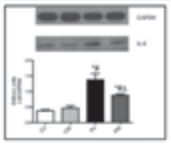
Mariana B. Nejm; André A. Haidar; Aparecida E. Hirata; Ricardo M. Arida; Maria da Graça Naffah-Mazacoratti; Esper A. Cavalheiro; Roberta M. Cysneiros; Fulvio A. Scorza

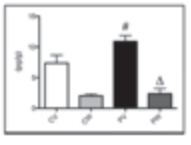


2014, *in press*

REDUCED INFLAMMATION OF HEART MEDIATED BY SUPPLEMENTATION WITH OMEGA 3 AND SUDDEN UNEXPECTED DEATH IN EPILEPSY

Mariana B. Nejm; André A. Haidar; Aparecida E. Hirata; Ricardo M. Arida; Maria da Graça Naffah-Mazacoratti; Esper A. Cavalheiro; Roberta M. Cysneiros; Fulvio A. Scorza *



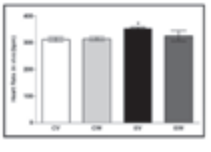


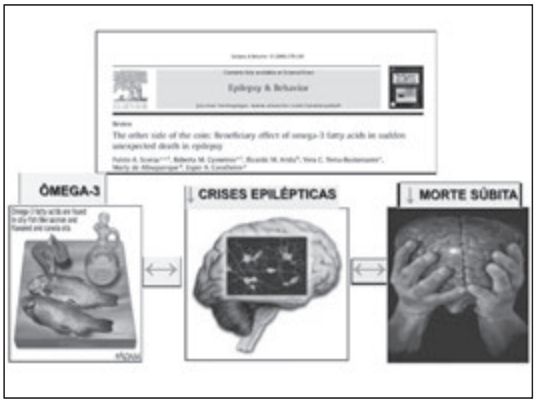
Epilepsy & Behavior

Brief Communication

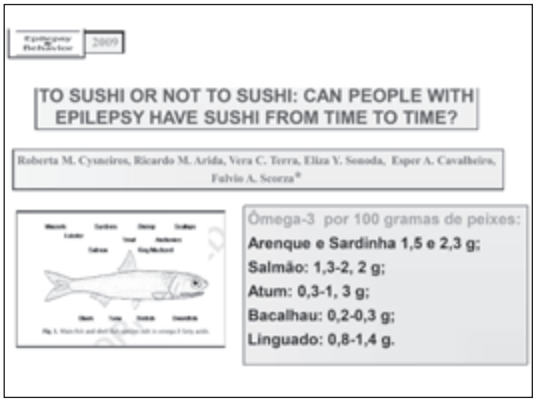
Omega-3 fatty acid supplementation reduces resting heart rate of rats with epilepsy

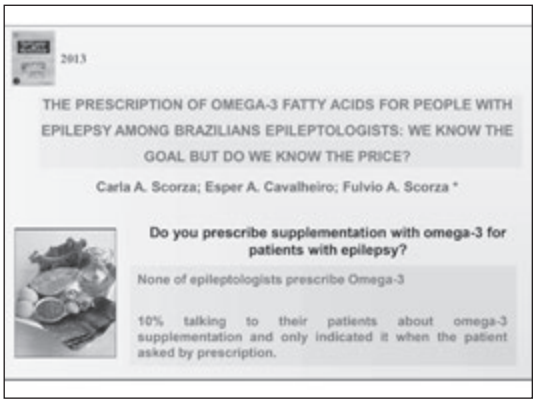
Márcio D. Lopes *, Diego B. Colugnati *, Annibio C. Lopes *, Carla A. Scorza *, Esper A. Cavalheiro *, Roberta M. Cysneiros *, Fulvio A. Scorza *,*




Epilepsy & Behavior
ÔMEGA-3
CRISES EPILÉPTICAS
MORTE SÚBITA


ÔMEGA-3 : O QUE DEVEMOS INGERIR?


2009
TO SUSHI OR NOT TO SUSHI: CAN PEOPLE WITH EPILEPSY HAVE SUSHI FROM TIME TO TIME?
Roberta M. Cysneiros, Ricardo M. Arida, Vera C. Terra, Eliza Y. Sousda, Esper A. Cavalheiro, Fulvio A. Scorza*
Ômega-3 por 100 gramas de peixes:
Arenque e Sardinha 1,5 e 2,3 g;
Salmão: 1,3-2, 2 g;
Atum: 0,3-1, 3 g;
Bacalhau: 0,2-0,3 g;
Linguado: 0,8-1,4 g.

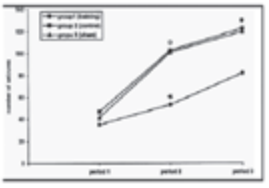

2013
THE PRESCRIPTION OF OMEGA-3 FATTY ACIDS FOR PEOPLE WITH EPILEPSY AMONG BRAZILIANS EPILEPTOLOGISTS: WE KNOW THE GOAL BUT DO WE KNOW THE PRICE?
Carla A. Scorza; Esper A. Cavalheiro; Fulvio A. Scorza *
Do you prescribe supplementation with omega-3 for patients with epilepsy?
None of epileptologists prescribe Omega-3
10% talking to their patients about omega-3 supplementation and only indicated it when the patient asked by prescription.

ATIVIDADE FÍSICA: EPILEPSIA E SUDEP

Epilepsy Research, 1999

Effect of physical exercise on seizure occurrence in a model of temporal lobe epilepsy in rats

Ricardo Mario Arida, Fabio Alexandre Scorza, Neide Ferreira dos Santos, Clovisde Araujo Peres, Esper Abrão Cavalheiro *



Physical training reverts hippocampal electrophysiological changes in rats submitted to the pilocarpine model of epilepsy

Ricardo Mario Arida*,1, Emilio Rafael Garrido Sanabria², Andre Cesar da Silva², Leonardo Coutinho Faria², Fabio Alexandre Scorza²,³, Esper Abrão Cavalheiro²

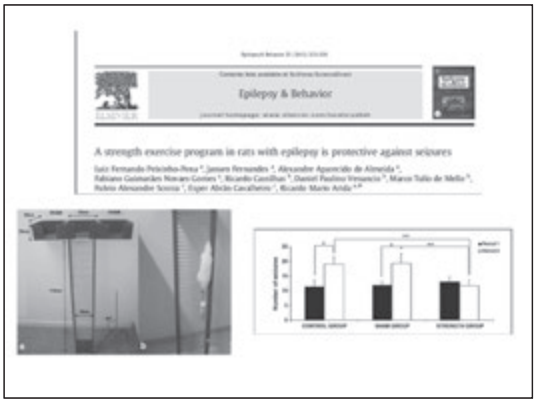
Physiology & Behavior, 2003

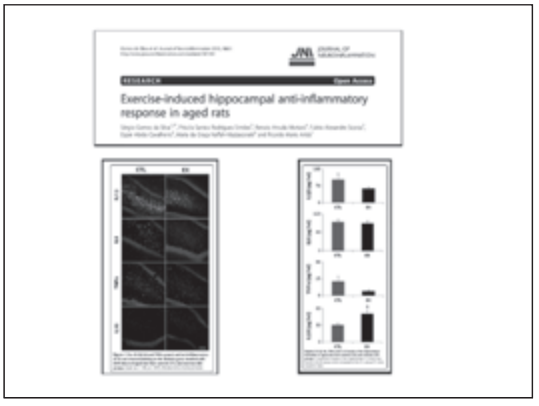
Evaluation of physical exercise habits in Brazilian patients with epilepsy

Ricardo Mario Arida,*,1 Fabio Alexandre Scorza,*,§ Marly de Albuquerque,* Roberta Monterazzo Cysneiros,* Ricardo Jaco de Oliveira,* and Esper Abrão Cavalheiro*

Table 1
Leisure time activities (n = 100)

Activity	Participation
Cultural activities (cinema, theatre, etc.)	23
Social contact with friends	47
Sports activities	31
Walking	46
Night life (dancing, bars, etc.)	19
Shopping	47
Driving	19
No answer	0


Epilepsy & Behavior
A strength exercise program in rats with epilepsy is protective against seizures


RESEARCH
Open Access
Exercise-induced hippocampal anti-inflammatory response in aged rats


JUDO: IPPON SCORED AGAINST EPILEPSY
Ricardo M. Arida; Douglas E. Vieira; Esper A. Cavalheiro; Fulvio A. Scorza*


Neuroscience and Biobehavioral Reviews
Is physical activity beneficial for recovery in temporal lobe epilepsy? Evidences from animal studies
NOVEL THERAPEUTIC TARGETS AND APPROACHES
Favorable effects of physical activity for recovery in temporal lobe epilepsy

Mini-review

Physical activity in sudden unexpected death in epilepsy: much more than a simple sport

Ricardo M. ARIDA, Carla A. SCORZA, Bety SCHMIDT, Marly de ALBUQUERQUE, Espen A. CAVALHEIRO, Fulvio A. SCORZA

Clinical and experimental data: physical activity can decrease seizure frequency, as well as lead to improved cardiovascular health in patients with epilepsy

FAPESP CNPq CAPES

AGRADECIMENTOS

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Escola Paulista de Medicina

Vital Brasil
O elo de sua vida.

Liga Brasileira de Epilepsia

Colaboradores Nacionais

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Profa. Dra. Iscia Lopes-Cendes (UNICAMP)
Profa. Dra. Vera C. Terra (UFPR)
Prof . Dr. Antonio-Carlos Guimarães de Almeida (UFSJ)
Profa. Dra. Roberta M. Cysneiros (Machenzie)
Profa. Dra. Maria da Graça Naffah-Mazzacoratti (EPM/UNIFESP)
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Dra. Elisa Y.F. Sousda (EPM/UNIFESP)
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Prof. Dr. John R. Hughes (University of Illinois Medical Center, USA)
Profa. Dra. Claudia Stillberger (Krankenanstalt Rudolfstiftung, Austria)
Prof. Dr. Josef Finsterer (Krankenanstalt Rudolfstiftung, Austria)

Samuel Wiebe (Canada)

SUDEP: IMPACT OF EPILEPSY SURGERY AND PREVENTATIVE MEASURES

Mario Fales (Italy)

SUFFERING AND PAIN IN THE ANCIENT NEAR-EAST

KIMFORD MEADOR (USA)

PREGNANCY AND EPILEPSY

Epilepsy and Pregnancy

Kimford Meador, MD

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Financial Disclosures

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•NIH/NINDS 3 U01 NS038455-13S1. Meador (Multi-PI). "Metabolomic Indicators of Risk in the MONEAD Cohort."

•PCORI 527. Loring (PI) "Cognitive AED Outcomes in Pediatric Localization Related Epilepsy (COPE)." Role: Co-PI.

•NIH/NINDS R01NS088748-01. Drane (PI). "Dissecting the Cognitive Roles of Hippocampus and Other Temporal Lobe Structures." Role: Co-I.

•NIH 1 R01 NS076665-01A1. Marino (PI) "Characterizing and Predicting Drug Effects on Cognition." Role: Consultant.

Consultant (Note direct no personal income):

•**Epilepsy Consortium (funds paid to my university)*** for Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Upsher Smith Laboratories, UCB Pharma and Vivus Pharmaceuticals .

Other: Clinical income: EEG procedures and patient care*

***Items with asterisk involve income > $10,000 for recent years.**

Historical Background

- 1850s – 1st AED discovered
- 1956 – 18 USA states with sterilization for people with epilepsy
- 1960s – 1st reports of malformations & AEDs
- 1980 – last US state law repealed forbidding people with epilepsy to marry
- 1980s – 1st AED specific defect: Spina bifida & Valproate
- 1980s – Animal studies suggests AEDs could have behavioral teratogenesis
- 2000s – Human studies show differential AED risks for both anatomical & behavioral teratogenesis

Beyond Seizure Control: Key Issues That Affect Women Taking AEDs

- Menstrual cycle abnormalities
- Bone health
- Sexual dysfunction
- Reproductivity & Family planning
- Pregnancy and Fetal Outcomes
  - Seizures & AED blood level changes
  - OB & Neonatal complications
  - Depression
  - Anatomical & Behavioral Teratogenesis
  - Breastfeeding

Childbearing in Women with Epilepsy: Clinical Dilemma

- Drugs generally contraindicated in pregnancy.
- Most women with epilepsy are unable to stop using AEDs due to risks of seizures.
  - Injury, Death, Miscarriage, Developmental delay, & Loss of job or driving
- As a group, both somatic & functional neurodevelopment are reduced.
- Majority of the children are normal.

Which antiepileptic drug does not affect hormonal contraceptives and is not affected by them?

A. Carbamazepine
B. Lamotrigine
C. Oxcarbazepine
D. Topiramate
E. Valproate

Which antiepileptic drug does not affect hormonal contraceptives and is not affected by them?

A. Carbamazepine
B. Lamotrigine
C. Oxcarbazepine
D. Topiramate
E. Valproate

AEDs & Hormonal Contraceptive Agents

Lower hormone levels
- Carbamazepine
- Clobazam
- Felbamate
- Oxcarbazepine (>1200mg)
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide
- Topiramate (>200mg)

No significant effects
- Clonazepam
- Ethosuximide
- Ezogabine
- Gabapentin
- Lacosamide
- **Lamotrigine***
- Levetiracetam
- Pregabalin
- Tiagabine
- **Valproate****
- Vigabatrin
- Zonisamide

* Estradiol lowers lamotrigine level
** Valproate can interact with other drugs but not OCPs

AED-induced Hemorrhagic Disease

- Bleeding in first 24 hours of life
- Deficiency in Vit K clotting factors
- EIAEDs: CBZ, PB, PHT, PRM
- Incidence = 10%
- Mortality = 30%
- Mother: Vit K 10mg PO daily last month?
- Child: Vit K 1mg IM at birth

EIAEDs = enzyme inducing AEDs; CBZ = carbamazepine; PB = phenobarbital; PHT = phenytoin; PRM = primidone

ABLs Changes in Pregnancy

- **"Reasoned" Noncompliance**
- **Malabsorption**
- **Change in Volume of Distribution**
- **Increased AED Elimination**
- **Increase in mean peak clearance***
  - **191 % Lamotrigine**
  - **207 % Levetiracetam**
  - **12 % Carbamazepine**
- **Highly variable across individual women & across repeat pregnancies**

*Reisinger et al, Epilepsy Behav 2013

A 17 year old girl suffers a convulsion. She has had myoclonic jerks some mornings. Her EEG shows generalized spike wave discharges. Which antiepileptic drug would you recommend?

A. Carbamazepine
B. Lamotrigine
C. Levetiracetam
D. Topiramate
E. Valproate

A 17 year old girl suffers a convulsion. She has had myoclonic jerks some mornings. Her EEG shows generalized spike wave discharges. Which antiepileptic drug would you recommend?

A. Carbamazepine
B. Lamotrigine
C. Levetiracetam
D. Topiramate
E. Valproate

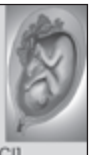
Congenital Malformations

AED Pregnancy Registry
1-888-233-2334

- **General Population = 2 - 3%**
- **Infants of Mothers with Epilepsy = 4 - 8% (Range = 1.25 - 18.6%)**

Major Malformations: Heart Defects, Orofacial Clefts, Skeletal, Urological & Neural Tube Defects (Valproate = 1.5%, Carbamazepine = 0.5%)

Meta-analysis: pregnancy outcomes in women with epilepsy



Treatment	Malformations		
	t (*n*)	%	[95% CI]
Women without epilepsy	9 (108,084)	3.27	[1.37, 5.17]
AED Monotherapy			
Carbamazepine	24 (4,411)	4.62	[3.48, 5.76]
Lamotrigine	5 (1,337)	2.91	[2.00, 3.82]
Phenobarbital	14 (945)	4.91	[3.22, 6.59]
Phenytoin	16 (1,198)	7.36	[3.60, 11.11]
Valproate	19 (2,097)	**10.73**	**[8.16, 13.29]**

t = number of treatment arms

Meador KJ, et al.
Epilepsy Research 2008;81(1):1-13.

Danish Medical Birth Registry 1996 - 2009

	# women	# MCM (%)	OR (95% CIs)
Unexposed	836,263	19,911 (**2.4%**)	1.0
Newer AEDs	1532	49 (**3.2%**)	1.35 (1.02-1.80)
Lamotrigine	1019	38 (**3.7%**)	1.59 (1.15-2.20)
Oxcarbazepine	393	11 (**2.8%**)	1.18 (0.65-2.15)
Topiramate	108	5 (**4.6%**)	1.99 (0.81-4.88)
Gabapentin	59	1 (**1.7%**)	0.71 (0.10-5.10)
Levetiracetam	58	0	Not estimated

Molgaard-Neilson & Hviid, JAMA 2011;305:1996-2002

MCM=major congenital malformations; OR=odd ratio; CIs=confidence intervals

Other AEDs

- **Levetiracetam**[1] 671 pregnancies
  - MCM in 2/304 monotherapy (**0.70%; CIs 0.9 : 7.7**)
  - mean daily dose = 1670mg (250-5000)
- **Topiramate**[2-3] >600 pregnancies
  - MCMs in monotherapy (**4 – 5%**)
  - **Oral Cleft = 1.4%** vs. 0.38-0.55% other AEDs[3]
- **Inadequate Data or Most Other AEDs**

1. Mawhinney et al. Neurology 2013;80;1-6. **2.** Hunt et al. Neurology 2008;71;272-276; Hernández-Díaz et al., Neurology 2012; Holmes et al., Birth Defects Res A Clin Mol Teratol 2012. **3.** FDA warning March 4, 2011. MCM = major congenital malformations; CIs = 95% Confidence Intervals

N. Am. AED Pregnancy Registry

	#	% MCM (CIs)	RR
Unexposed	442	1.1 (0.4-2.6)	reference
Lamotrigine	1562	2.0 (1.4-2.8)	1.8
Carbamazepine	1033	3.0 (2.1-4.2)	2.7
Levetiracetam	450	2.4 (1.2-4.3)	2.2
Phenytoin	416	2.9 (1.5-5.0)	2.6
Topiramate	359	4.2 (2.4-6.8)	3.8
Valproate	323	9.3 (6.4-13.0)	9.0
Phenobarbital	199	5.5 (2.8-9.7)	5.1
Oxcarbazepine	182	2.2 (0.6-5.5)	2.0

MCM=major congenital malformations; CIs=confidence intervals; RR=rel risk

Hernández-Díaz et al, Neurology 2012;78:1692–1699

EURAP: Dose Dependent Effects on MCMs

Antiepileptic Drug	N	% Seizure Free	% Malformations
Cabamazepine			
<400 mg/d	148	64%	**3.4%**
400 to <1000 mg/d	1047	67%	**5.3%** *
≥1000 mg/d	207	62%	**8.7%** *
Lamotrigine			
<300 mg/d	836	67%	**2.0%**
≥300 mg/d	444	68%	**4.5%** *
Phenobarbital			
<150 mg/d	166	71%	**5.4%** *
≥150 mg/d	51	69%	**13.7%** *
Valproate			
<700 mg/d	431	71%	**5.6%** *
700 to <1500 mg/d	480	66%	**10.4%** *
≥1500 mg/d	99	61%	**24.2%** *

Tomson et al., Lancet Neurol 2011;10: 609-17 * More MCMs than LTG<300mg/d

EUROCAT

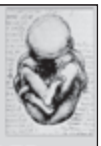
European Surveillance of Congenital Anomalies

- **Case-control study**
  98,075 cases with malformations among 3.8 million births in Europe
  19 registries in 14 countries from 1995 – 2005

	Odds Ratio	(95% CIs)
• **Valproate**		
Spina bifida	12.7	(7.7 – 20.7)
Atrial septal defect	2.5	(1.4 – 4.4)
Cleft palate	5.2	(2.8 – 9.9)
Hypospadius	4.8	(2.9 – 8.1)
Polydactyly	2.2	(1.0 – 4.5)
Craniosynostosis	6.8	(1.8 – 18.8)
• **Carbamazepine**		
Spina bifida	2.6	(1.2 – 5.3)

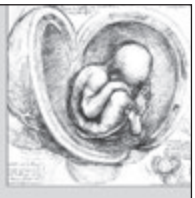
Jentnik et al, NEJM 2010;362:2185-93 & BMJ 2010;341:c6582

Conclusions: Anatomical Teratogenesis



- Valproate poses special risk (9.3%)
- Possible dose dependent risks for all AEDs
- Spina Bifida:
  - Valproate = 12.7 X, Carbamazepine = 2.6 X
- Phenobarb (5.5%), Topiramate (4.2%)
- Risks of most AEDs and specific polytherapy combination are uncertain
- North American AED Pregnancy Registry
  - 1-888-233-2334

In Utero AEDs & Behavioral Neurodevelopment in Animals



- **Phenobarb reduces brain weight & impairs behavior in mice.**
- **Phenytoin impairs coordination & learning in rats.**
- **Phenytoin can cause hyperactivity in monkeys.**
- **Neurobehavioral effects also found for valproate.**

Vorhees CV. Environ Health Perspect. 1994;102 Suppl 2:145-53. Review.

Neurodevelopment in Children of Women with Epilepsy

- **Maternal seizure type**
- **# of seizures during pregnancy**
- **IQ & education of parents**
- **AEDs & other drugs**
- **Other environmental factors**

Cognitive Effects of In Utero AEDs

- **Phenobarbital:** 2 retrospective Danish cohorts **without** maternal IQ (n=114 PB total): PB vs. general population: -7 VIQ[1]
- **Phenytoin:** Two studies **without** maternal IQ (n=87 PHT): PHT vs. controls: -8 IQ[2,3]
  Prospective Canadian cohort (n=34 PHT, 36 CBZ): PHT vs. controls: -10 IQ when compared without control for maternal IQ. (PHT **not** different when analyses using maternal IQ; also **no** effect for CBZ)[4]
- Carbamazepine: Prospective Finnish cohort **without** maternal IQ): VPA vs. CBZ: -12 VIQ[5] (n=13 VPA MonoTx). No difference for CBZ vs. unexposed[3]

1. Reinisch et al. *JAMA* 1995;274:1518-1525. 2. Vanderloop et al. Neurotox Terat 1992;14:196-92. 3. Wide et al. Acta Paediatr 2002;409-14. 4. Scolnik et al, JAMA 1994;271:767-70. 5. Gaily E, et al. *Neurology.* 2004;62:28-32.

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

Meador et al. NEJM 2009;360:1597-605
Mean IQs (95% CIs difference from VPA) adjusted for maternal IQ, age, AED dose, gestational age & folate.

Fetal valproate exposure associated with lower IQ.

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Mean IQ	**98**	**101**	**99**	**92**
Difference	**6**	**9**	**7**	
(CIs)	(0.6:12.0)	(3.1:14.6)	(0.2:14.0)	

Funded by NIH/NINDS #2RO1 NS 38455 and #1 R01050659

Fetal Exposure to Valproate Associated with Lower IQ at Age 6

Mean IQs (95% Difference CIs from VPA)
adjusted for maternal IQ, AED dose, gestational age & folate:

	CBZ	LTG	PHT	VPA
Mean IQ	**105 ***	**108 ***	**108 ***	**97**
Difference	**7**	**10**	**10**	
DCIs	(3:12)	(6:15)	(5:16)	
# Children	93	100	56	62

* Significantly better than VPA.
CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

Meador et al. Lancet Neurology 2013: 12(3):244-52.

Verbal & Non-verbal Index Scores

	CBZ	LTG	PHT	VPA
Verbal	**104 ***	**105 ***	**106 ***	**97**
CIs	100:108	102:110	96:107	87:98
Non-verbal	**104 T**	**108 ***	**106 T**	**101**
CIs	100:108	102:110	96:107	87:98
Difference	-0.74	**-2.82****	0.89	**-4.37****

* Signficantly better than VPA
T Trend for better than VPA
** Verbal significantly less than Non-verbal
CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

Meador et al. Lancet Neurology 2013: 12(3):244-52.

Handedness

Group	Dextral	Non-dextral
WISC	173 (93%)	14 (7%)
CBZ	54 (93%)	4 (7%)
LTG	**59 (83%)***	**12 (17%)**
PHT	34 (89%)	4 (11%)
VPA	**38 (79%) ***	**10 (21%)**

* Differ significantly from the WISC normative sample.
CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

Meador et al. Lancet Neurology 2013: 12(3):244-52.

General Memory Index (GMI), NEPSY Exec Index, & BRIEF (Parent Index) Results

	CBZ	LTG	PHT	VPA
GMI	**104 ***	**106 ***	**101 ***	**92**
CIs	100:108	102:110	96:107	87:98
Exec Index	**105**	**107 ***	**103**	**101**
CIs	103:108	104:109	100:106	98:104
BRIEF	**101**	**100**	**100**	**105**
CIs	98:104	97:103	95:104	101:108

* Signficantly better than VPA.

CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

Meador et al. Lancet Neurology 2013: 12(3):244-52.

Dose Dependent Effects: Partial Correlations

	CBZ	LTG	PHT	VPA
IQ	-.08	.19	-.11	**-.56***
Verbal Index	-.03	.12	.06	**-.40***
Non-verbal Index	-.17	.10	-.17	**-.42***
GMI	-.06	.05	-.20	**-.30***
Nepsy Exec Index	-.05	.03	-.10	**-.42***
BRIEF**	-.20	.15	.31	**.35***

****Lower BRIEF scores better** * **Significant correlations**

CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

Meador et al. Lancet Neurology 2013: 12(3):244-52.

Valproate Dose Effects

- **NEAD** Significant for birth defects & multiple cognitive measures
  - 24.2% ≥ 900 mg/day vs. 9.1% < 900 mg/day
- **North America** Not significant
  - 1033 mg/day (±434) with malformations vs. 983 mg/day (±431) without
- **Australia** Significant
  - 34.5% malformations > 1400 mg/day vs. 5.5% at ≤ 1400 mg/day
- **Finland** Significant
  - 23.8% for doses >1500mg/day vs. 9.5% for doses ≤1500mg/day
- **UK** Not significant
  - 9.1% >1000 mg/day, 6.1% 600-1000 mg/day, 4.1% <600 mg/day
- **UK Liverpool** Significant
  - Reduce VIQ 15 points > 1500mg/d, 9.9 at 801-1500mg/d, 2.2 ≤ 800mg/d
- **Finland** Significant
  - Reduce VIQ 20 points > 1500mg/d, 16.6 at 800-1500mg/d, 4.2 < 800mg/d
- **Sweden and GSK data** Not analyzed for dose effect of VPA

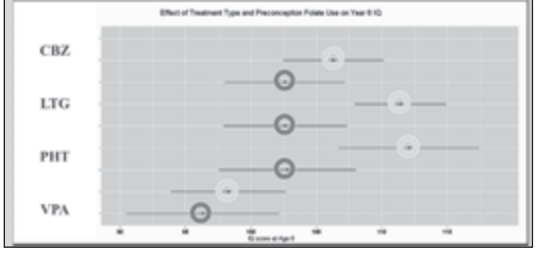
Child IQ & Periconceptional Folate

F=11.4, p<.0009. Adjusted Mean IQs (95% CIs):

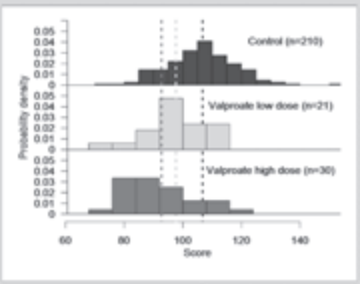
Folate = 108 (106, 111) No Folate = 102 (98, 104)

Meador et al. Lancet Neurology 2013: 12(3):244-52.

= Folate
= No Folate



Distribution of IQ scores: Controls & Low/High Valproate Groups



Baker et al, Neurology 2015;84(4):382-90

Fetal Valporate & Autism

- **Early cases & small series for valproate and autism.**
  - Christianson, et al, Dev Med Child Neurol. **1994**:361–9.; Williams & Hersh. Dev Med Child Neurol. **1997**:632–4; Williams, et al. Dev Med Child Neurol. **2001**;43:202–6.; Rasalam et al, Dev Med Child Neurol. **2005**;47(8):551–5.
- **Norway population based study (1996-2006): Christensen et al, JAMA. 2013;309(16):1696-1703.**
  - 655,615 children born (ASD = 5437; autism = 2067)
  - 508 children exposed to valproate
  - **ASD = 4.42%** (95% CI, 2.59%-7.46%) **(adj HR = 2.9)**
  - **Autism 2.50%** (95% CI, 1.30%-4.81%) **(adj HR = 5.2)**
- **Some other studies with showing behavioral deficits.**
  - Vinten et al, Epilepsy Behav. **2009**;14(1):197–201; Cohen et al, Epilepsy Behav. **2013**;29(2):308–15.

ASD = autism spectrum disorder

Fetal Levetiracetam: 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 Ctrls
L=sig less than LEV

Shallcross et al, Neurology 2014

Conclusions: Behavioral Teratogenesis

- Present studies suggest that valproate poses a special risk for behavioral as well as anatomical teratogenesis.
- Reasons for individual variability are unclear.
- Risks for many AEDs and polytherapies are uncertain.

Possible Mechanisms of AED Effects on Fetal Development

- Neuronal Suppression
- Folate Related Mechanisms
- Ischemia & Hypoxia
- Reactive Intermediates
  - ❖ Free Radicals
  - ❖ Arene Oxides (epoxides)
- Neuronal Apotosis
  - — NMDA antagonist & GABA agonist
  - — Antagonism of neutropins & signal proteins
- Neuronal Migration Disorders

AEDs and Apoptosis in Developing Brain

- Widespread neural apoptosis in rats aged 3-30 days
  - – Present for **clonazepam, diazepam, phenobarb, phenytoin, valproate, & vigabatrin**[1,2]
  - – Absent for **carbamazepine, lamotrigine, levetiracetam, & topiramate monotherapy**[3-8]
- Reduced expression of neutrophins & extracellular signal proteins[2]
- Effects can be prevented by β-estradiol[2]

1. Bittigau et al. Proc Natl Acad Sci U S A. 2002. 2. Bittigau et al. Ann N Y Acad Sci. 2003. Glier et al. Exp Neurology. 2004. 4. Manthey et al. Exp Neurol 2005. 5. Kim et al. JPET 2007. 6. Katz et al, JPEG 2007. 7. Forcelli et al, JPEG 2012. 8. Forcelli et al, Ann Neurol 2012.

Conclusions: Mechanisms

- **Mechanisms and reasons for individual variance are unknown.**
- **Neonates may also be at risk given the common use of benzodiazepines and phenobarbital in neonates.**

A woman on antiepileptic drug has just become pregnant and ask if she can breastfeed after delivery. Which of the following would you advise?

A. Advise that she can breastfeed if she desires.
B. Advise that she should not breastfeed.
C. Advice depends on the antiepileptic drug.
D. Unsure.

A woman on antiepileptic drug has just become pregnant and ask if she can breastfeed after delivery. Which of the following would you advise?

A. Advise that she can breastfeed if she desires.
B. Advise that she should not breastfeed.
C. Advice depends on the antiepileptic drug.
D. Unsure.

Known Positive Effects of Breastfeeding

- Beneficial for the infant and mother.
- Child: reduced risk of severe lower respiratory tract infections, atopic dermatitis, asthma, acute otitis media, non-specific gastroenteritis, obesity, type 1 and 2 diabetes, leukemia, SIDS, enterocolitis, and possibly cognition.
- Mother: reduced risk for type 2 diabetes, breast cancer, ovarian cancer, and maternal postpartum depression.

Ip S, et al. Breastfeed Med 2009;4 Suppl 1:S17-30.

Cognitive Effects of Breastfeeding

- **General Population: Positive Cognitive Effects.**
  - Bernard JY, et al. J Pediatr 2013;163(1):36-42.
  - Belfort MB, et al. JAMA Pediatr 2013;167(9):836-844.
  - Julvez J, et al. Dev Med Child Neurol 2014;56(2):148-56.
- **Controversy Remains.**
  - Walfisch A, et al. BMJ Open 2013 Aug 23;3(8):e003259.
- **Age 3 Outcomes in Children Breastfed on AEDs.**
  No adverse effects found.
  - Meador KJ, et al. Neurology 2010;75(22):1954-60.
  - Veiby G, et al. JAMA Neurol 2013;70(11):1367-1374.

Effects of Breastfeeding when on AEDs

- Mean adjusted* IQ scores at age 6 yrs (95% confidence intervals) across all AEDs:

Breastfed	**108 (105:111)**
Non-breastfed	**104 (101:106)**
Mean Difference	**4 (0:8), p=.045**

- 181 children, 43% breastfed, mean duration of 7.2 mos.
- * Adjusted for other significant factors in the model (i.e., maternal IQ, AED group, AED dose, periconceptional folate, and breastfeeding) plus the propensity score.

Meador et al, JAMA Pediatr 2014
(pub online: doi:10.1001/jamapediatrics.2014.118)

Clinical Implications

- Most children born to WWE are normal.
- WWE of childbearing potential should be taking folate.
- WWE should receive informed consent outlining risks **PRIOR** to conception.
- Valproate is a poor 1st choice AED for most WWE of childbearing potential. If used, dose as low as possible.
- Breastfeeding on AEDs appears safe.
- Risks for many AEDs uncertain.

WWE=Women with epilepsy

Epilepsy Pregnancy Websites

- **Patients**
  - EF General info for women:
  - http://www.epilepsyfoundation.org/living/women/index.cfm
  - EF Pregnancy info:
  - http://www.epilepsyfoundation.org/living/women/pregnancy/weipregnancy.cfm
  - Epilepsy Therapy Project:
  - http://www.epilepsy.com/info/women_pregnancy
  - North American Antiepileptic Drug Pregnancy Registry
  - http://www.aedpregnancyregistry.org/ 1-888-233-2334
- **Health Care Providers**
  - Epilepsy Therapy Project Professional page:
  - http://professionals.epilepsy.com/page/women_guide.html
  - EFA pregnancy info for providers:
  - http://www.epilepsyfoundation.org/about/professionals/
  - EURAP Pregnancy Registry
  - http://www.eurapinternational.org/

Further research needed to:

- Delineate cognitive effects of fetal & neonatal exposure for other AEDs.
- Establish relations based on AED blood levels.
- Determine AEDs effects on cerebral lateralization.
- Confirm effects of periconceptional folate.
- Determine risks for maternal outcomes.
- Determine reasons for individual variability.
- Explore underlying mechanisms.

MONEAD Study

Maternal Outcomes & Neurodevelopmental Effects of Antiepileptic Drugs

http://www.neadstudy.com

Funded by NIH/NINDS #2U01-NS038455-11A1

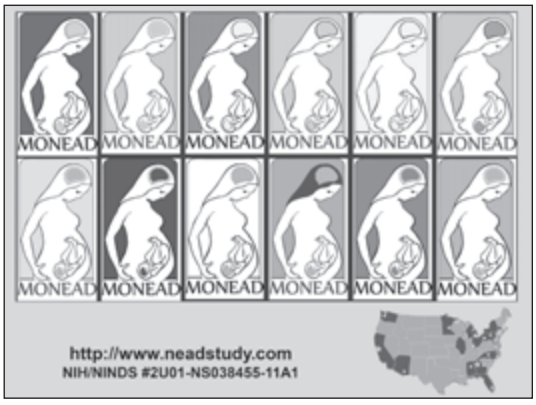
20 sites

MONEAD Study

- MATERNAL OUTCOMES:
  Risks in WWE during pregnancy
  - **Seizures**
  - **OB Complications**
  - **Depression** (pregnancy & postpartum)
- OUTCOMES in CHILDREN of WWE:
  - **Neurodevelopment** Cognitive & behavioral
  - **Neonatal Outcomes**
  - **Breastfeeding** Effects if WWE taking AED.
- Pharmacokinetics: Relation of AED exposure & outcomes
- Groups expanded: WWE on new AEDs, polytherapy, and no AED, and also 2 control groups (nWWE & HP)

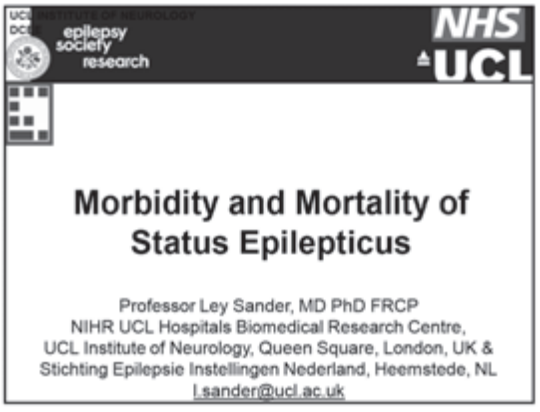
AEDs=Antiepileptic Drugs; WWE=Women with Epilepsy; p=pregnant; n=non-pregnant; HP=healthy pregnant

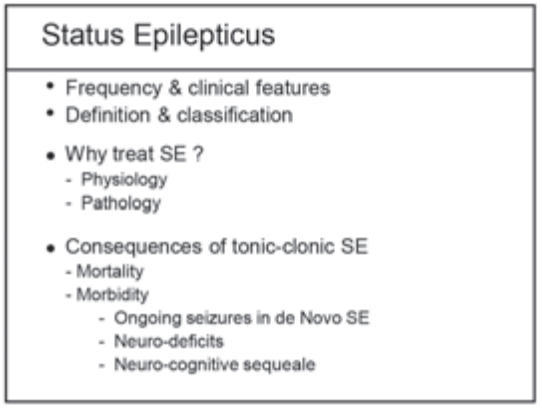
My Epilepsy Story
www.myepilepsystory.org/

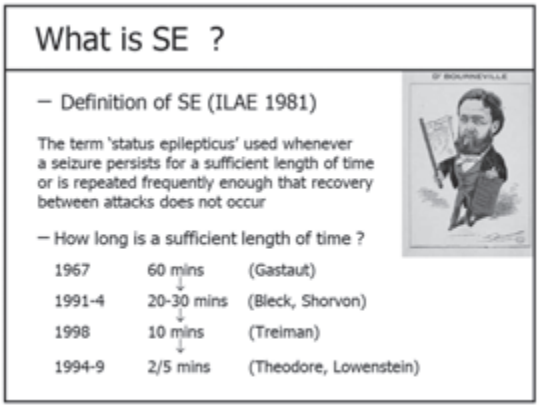


LEY SANDERS (ENGLAND)

MORTALITY AND MORBIDITY ASSOCIATED TO STATUS EPILEPTICUS/EPILEPSY AND HEADACHES







SE Classification: a Simplistic Approach!

- **Status epilepticus confined to the neonatal period:**
  - Neonatal SE
  - Status epilepticus in neonatal syndromes
- **Status epilepticus confined to infancy and childhood:**
  - Infantile spasm (West Syndrome)
  - Febrile SE
  - SE in the myoclonic syndrome
  - SE in benign partial syndromes
  - Electrical SE during slow wave sleep (ESES)
  - Syndrome of acquired epileptic aphasia

SE Classification: a Simplistic Approach!

- **Status epilepticus in childhood and adult life:**
  - Tonic clonic SE
  - Absence SE
  - Epilepsia partialis continua (EPC)
  - Myoclonic SE in coma
  - Simple partial SE
  - Other specific forms of nonconvulsive SE
  - Complex partial SE
  - Boundary syndromes
- **Status epilepticus confined to adult life:**
  - De Novo absence SE of late onset

Tonic-clonic Status Epilepticus

- > 65% de novo, without prior history of epilepsy
  - Associated to acute cerebral event
    - Vascular, trauma, infection or acute metabolic/drug-induced cause
- In pre-existing epilepsy, often precipitated
  - Drug reduction/withdrawal
  - Intercurrent illness
  - Metabolic disturbance
  - Progressive disease
- SE in 5% of adults & 10-25% of children with epilepsy

Six Population-based Studies of Status Epilepticus

	Richmond VA, US	Rochester MN, US	French speaking Switzerland	Hessen, Germany	Bologna, Italy	London UK
Population	202,774	1,090,055	1,735,420	743,285	336,876	805,230
Number of cases	166	199	172	150	44	176 (first-ever cases)
Incidence of SE (per 100,000 per year)	41 (raw) 61 (adjusted)	18.3 (adjusted)	9.9 (raw) 10.3 (adjusted)	15.0	13.1	12.5-14 (adjusted; 1st-ever SE episode)
F:M	1:1.2	1:1.9	1:1.7	1:1.9	1:0.74	1:1.12
History of epilepsy	42%	44%	32.8%	33%	39%	7%*
Exclusion	<1 mn	-	Post anoxic	<18 yr	<20yr	NCSE >15 yrs
Case ascertain-ment	Prospective hospital record	Record linkage system	Prospective hospital record	Prospective hospital record review	Prospective active surveillance	Prospective active surveillance

Tonic-clonic Status Epilepticus

- Incidence approximately 10-41/100,000/year ?
- 0.1% of all A&E visits
  - Rates higher:
    - in children
    - learning disability
    - structural cerebral pathology
    - frontal pathology

At Risk Groups

Who Is at Risk for Seizure Emergencies?

Patient History	Unstable AED Levels	Situational Triggers
• Acute repetitive seizures • Early-onset epilepsy • Developmental disabilities • Neurologic illnesses or injuries • Frequent seizure emergencies • Pediatric seizure syndromes and encephalopathies • 42% have history of epilepsy • 5% of patients with refractory epilepsy have repeat prolonged seizures or SE	• Treatment noncompliance – Missed doses – Irregular physician visits • Changes to chronic AED therapy – Drug-drug interaction/enzyme induction – Variations in generic drug formulations may affect blood levels	• Illness • Hormonal changes • Travel • Stress or anxiety • Disruption of sleep patterns • Fatigue

Tonic-clonic SE – Progressive Changes

- **Premonitory stage**
  - Increasing serial seizures/myoclonus and EEG correlates
- **Biphasic pattern of physiological change**
  - Phase of compensation
  - Phase of decompensation
  - Reflected in progressive clinical and EEG changes
  - Switch from compensated → decompensated state = 60-120 minutes in convulsive SE (an approximation, dependant on site, nature, severity of the SE)
- **Window of opportunity for treatment**
  - Risk of cerebral damage increases with time after 60-120 mins – 'time is brain'
  - Treatment failure increases with time

Tonic-clonic SE – Phase of Decompensation

- **Cerebral changes**
  - Failure of central auto-regulation, thus cerebral blood flow becomes dependent on systemic blood pressure
  - Hypoxia
  - Hypoglycaemia
  - Falling lactate concentrations
  - Falling energy state
  - Rising intracranial pressure and cerebral oedema
- **Other medical complications**

Tonic-clonic SE – Phase of Decompensation

- **Systemic changes**
  - Metabolic and respiratory acidosis
  - Hypoglycaemia and other metabolic changes
  - Hepatic and renal dysfunction
  - Consumptive coagulopathy/DIC/multi-organ failure
  - Rhabdomyolysis
  - Hypoxia
  - Falling blood pressure
  - Falling cardiac output
  - Respiratory and cardiac impairment
  - Cardiac arrhythmia
  - Hyperpyrexia

Duration of SE: Major Determinant of Outcome

- The longer SE continues the more difficult it is to control and outcome worse
- Early and effective treatment essential
- The more severe the SE, the greater the risk of subsequent morbidity and mortality
- SE always a medical emergency

Duration & Outcome of Status Epilepticus

	Country	Number of cases	Duration (for poor outcome)/r	Study design
Towne et al. (1994)	USA	N = 253	>1 h: 32% mortality	Retrospective all aged > 16 years
			<1 h: 2.7% mortality OR 17.9	
Eriksson and Koivikko (1997)	Finland	N = 65	>2 h [illegible] mortality	Retrospective paediatric study
			< 1 h 31.7% mortality P < 0.025	
Sagduyu et al. (1998)	Turkey	N = 66	>1 h: [illegible] mortality	Retrospective all ages (range 6–77 years)
			<1 h: 3% mortality OR 2.41 P < 0.003	
Gulati et al. (2005)	India	N = 30	>45 min 100% mortality	Retrospective paediatric study
			<45 min 9.5% mortality P < 0.001	
Drislane et al. (2009)	USA	N = 119	>10 h: OR 4.3 (95% CI 1.21, 15.3) P = 0.0242	Retrospective adult population (range 24–[illegible] years)
			>24 h OR 1.8 (95% CI 0.74, 4.36) P = 0.19 (NS)	

EEG Patterns

- EEG important tool for diagnosis & management but role in predicting outcome less clear
- Controversy over presence of periodic epileptiform discharges (PEDs) or periodic lateralised epileptiform discharges (PLEDs) as marker of poor outcome
- Association not strong: PLEDs and PEDs more likely in certain aetiologies with poor prognosis (acute anoxic cerebral damage)

Neligan & Shorvon, 2011

Mortality of GCSE

Table 1. Summary of 7 Population-Based Studies of SE

Variable	Richmond, Virginia[1]	Rochester, Minnesota[2]	French-Speaking Switzerland[3]	Hessen, Germany[4]	California[5]	Bologna, Italy[6]	London, United Kingdom[7]
Study years	1989–1991	1965–1984	1997–1998	1997–1998	1991–1998	1998–2000	2002–2004
Population, denominator, No.	202 774	1 098 093	1 735 420	140 285	NA	336 676	609 230
Cases, No.	166	199	172	150	19 691	44	226 total, 176
Case fatality, %	22	19	7.6	9.3	10.7	39	3

- SE aetiology primary determinant of mortality and morbidity with age also important prognosis determinant
- In population studies, mortality lowest in sole paediatric study (N London – 3%) & when cases of SE secondary to anoxia/ hypoxia excluded (Swiss Study – 7.5%)

Neligan & Shorvon 2010

Mortality of GCSE

Mortality Associated with Prolonged Seizures and Status Epilepticus

DURATION	STAGE	%	INTERVENTIONS	SETTING	MORTALITY
0-2 min	Seizure	100%	Supportive measures	Community	<1%
>2 min	Prolonged	10%	Benzodiazepine	Com/Amb/ER	<5%
>30 min	SE	5-7%	1st line: Benzodiazepine 2nd line: Fosphenytoin/Phenytoin 3rd line: Phenobarbital/Valproate/ Levetiracetam	ER	10-20%
2 hours	RSE	1-2%	Continuous Infusion therapy Midazolam/Propofol/Pentobarbital	ICU	40%
>48 hours	NRSE	<1%	Alternative Continuous Infusion Therapy Novel Therapeutic Options	ICU	>50%

Neligan & Shorvon 2011

Mortality of GCSE

Table 4. Approximate Frequency and Mortality of SE of Different Etiologies[a]

	Proportion of Cases of SE, %	Associated Acute Mortality in Patients With SE, %
Drug reduction/withdrawal, poor compliance, or low AED levels	10-20	0-10
Cerebrovascular disease	10-40	20-60
Metabolic disorders	5-15	10-35
Acute CNS infections[b]	0-10	0-30
Anoxia	5-10	60-100
Alcohol abuse	5-15	0-10
Head trauma	0-10	0-25
Drug overdose/toxicity	0-10	10-25
Brain tumors	0-10	0-20
Cryptogenic/idiopathic	5-15	5-20

Neligan & Shorvon, 2010

Risk of Seizures post-de Novo SE

- De Novo SE in 40-65% with no prior history of epilepsy
- Risk of developing seizures long-term significantly higher when SE duration prolonged (refractory SE)

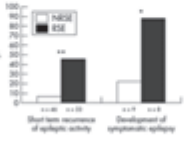


Figure 2 Short term recurrence of epileptic activity in the first 24 hours after seizure termination and development of post status epilepticus symptomatic epilepsy. Data are presented as the rate of episodes in each subgroup (non-refractory status epilepticus [NRSE] and refractory status epilepticus [RSE]) with the particular feature. Short term recurrence of epileptic activity and development of symptomatic epilepsy were seen significantly more often after RSE. *p<0.05; **p<0.001.

Holtkamp et al., 2005

Risk of Morbidity post SE

- Morbidity risk highest in RSE
- Prospective study over 2 years, 29/128 episodes of SE were RSE

Table 3. Outcome in patients with incident refractory and nonrefractory SE

	Refractory	Nonrefractory	p-value	Test
Returned to baseline (episodes)	6/29 (20.7%)	62/99 (62.6%)	**<0.001**	χ^2
Death (patients)	11/28 (39.3%)	10/90 (11.1%)	**0.001**	χ^2
Hospitalization time (days) (surviving patients) (median, range)	20 (2–260)	11 (1–160)	**0.005**	U
Rehabilitation need (surviving patients)	14/17 (82.4%)	28/80 (35.0%)	**0.001**	Fisher's

Novy et al., 2010

Global audit of treatment of refractory status epilepticus

Multinational database: intensivists and neurologists from around the world are invited to collect informations about cases of refractory and super-refractory status epilepticus

www.status-epilepticus.net

SE: Conclusions

- Duration, aetiology and age major determinant of outcome
- Earliest treatment initiation better outcomes
- Outcome and mortality in children and adults varies with best outcomes in young children and worst in the elderly
- Reason largely related to different underlying aetiologies at different ages
  - not clear whether age is a factor independent of aetiology

UCL INSTITUTE OF NEUROLOGY

epilepsy society research

NHS UCL

Headache, Migraine & Epilepsy

Professor Ley Sander, MD PhD FRCP
NIHR UCL Hospitals Biomedical Research Centre,
UCL Institute of Neurology, Queen Square, London, UK &
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Second Epilepsy Mantra

- Epilepsy and what else?
  - High Prevalence of Co-morbidity
    - ➢Psychiatric
      - ➢Higher risk of depression, anxiety, personality disorders, psychosis
    - ➢Somatic
      - – Higher risk of vascular disorders (CVA, MI, PVD, LVH hypercholesterolaemia), migraine, GI (IBS, Crohn's, bleeding), hypertension, systemic auto immune diseases, dementia, cancer, obstructive sleep apnoea, injuries and fractures

Gaitatzis et al. Epilepsia 2012; Devinsky et al., Epilepsy Curr 2013; Ong et al. JAMA Neurol 2014

Epilepsy & Headaches

- Epilepsy and what else?
  - – Headache & migraine often linked to epilepsy
  - – Migraine & epilepsy are probably genetically determined disorders in which an imbalance between excitatory & inhibitory factors results in spells of altered brain function & autonomic symptoms
  - – Convincing evidence of association or similarities between migraine & epilepsy from epidemiologic, genetic & pathophysiologic studies

Gaitatzis et al. Epilepsia 2012; Bauer et al. Curr Pain Headache Rep 2013

Epilepsy & Headaches

- What comes first?
  - Epilepsy co-morbid with migraine
  - Migraine co-morbid with epilepsy
  - – Does it matter? Probably bi-directional
- And these?
  - – Migraine-triggered seizure
  - – Hemicrania epileptica
  - – Post-ictal headache
    - Confounders ?

Gaitatzis et al. Epilepsia 2012; Bauer et al. Curr Pain Headache Rep 2013

Epilepsy & Headaches

- Co-occurrence of headache / migraine with epilepsy contradictory
- Partly caused by classification issues of headache & migraine in various studies
-
- Headache is a subjective complaint, migraine has classification criteria but often "migraine", "headache" or "migrainous headache" used interchangeably obscuring results & confusing interpretation

Gaitatzis et al. Epilepsia 2012; Bauer et al. Curr Pain Headache Rep 2013

Epilepsy & Headaches

- Headache & migraine often self-reported or assessed with limited questionnaires without validation by direct interview
- Diagnostic criteria not clearly applied
- Diagnosis of migraine can be wrong or be missed

Bauer et al. Curr Pain Headache Rep 2013

Migraine & Epilepsy: a meta-analysis

Aims:

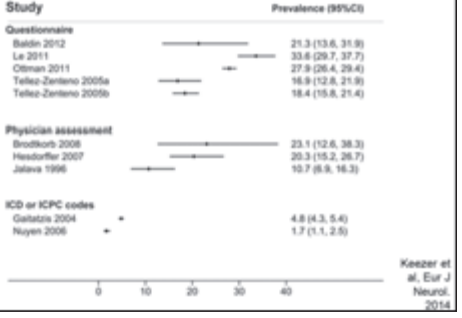
- To examine:
  - The relative lifetime prevalence of **migraine** in **people with epilepsy** (PWE)
  - The relative lifetime prevalence of **epilepsy** in **people with migraine** (PWM)
- Population-based cohorts

Keezer et al. Eur J Neurol. 2014

Migraine & Epilepsy: a Meta-analysis: Search Strategy

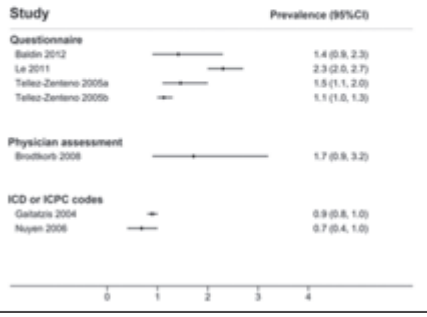
Keezer et al, Eur J Neurol. 2014

Lifetime Prevalence of Migraine in PWE



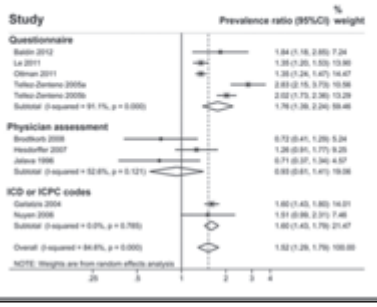
Keezer et al, Eur J Neurol. 2014

Lifetime prevalence of Epilepsy in PWM



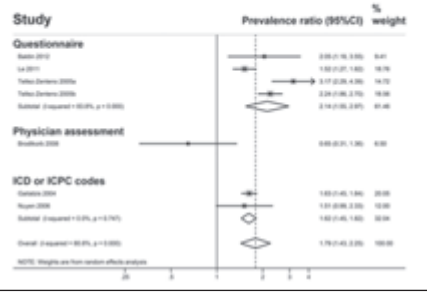
Keezer et al, Eur J Neurol. 2014

Prevalence Ratio of Migraine in PWE



Keezer et al, Eur J Neurol. 2014

Prevalence Ratio of Epilepsy in PWM



Keezer et al, Eur J Neurol. 2014

Strengths & Limitations

- Population-based studies => generalisability

Sources of potential bias:

- Case ascertainment (non-validated tools)
- Insufficient correction for confounding factors
- Possible publication bias (asymmetric funnel plots)

Keezer et al, Eur J Neurol. 2014

International Classification of Headache Disorders

Criteria	Migraine-triggered seizure	Hemicrania epileptica	Post-ictal headache
A	Migraine fulfilling criteria for migraine + aura	Headache lasting seconds to minutes, with features of migraine, fulfilling criteria C and D	Headache with features of tension-type headache or, in a patient with migraine, of migraine headache and fulfilling criteria C and D
B	A seizure fulfilling diagnostic criteria for 1 type of epileptic attack occurs during or within 1 hour after a migraine aura	The patient is having a partial epileptic seizure	The patient has had a partial or generalised epileptic seizure
C		Headache develops synchronously with the seizure and is ipsilateral to the ictal discharge	Headache develops within 3 hours following the seizure
D		Headache resolves immediately after the seizure	Headache resolves within 72 hours after the seizure

ICHD-II, 2004

Migraine-triggered seizures

- Also known as 'migralepsy'!
- Seizure triggered by a migraine aura fulfilling the ICHD-II criteria
- Should occur during or within 1 hour after migraine aura & fulfill diagnostic criteria of ILAE seizure
- Extremely rare & may have been confounded with occipital seizures

Hemicrania Epileptica

- Headache with migraine features lasts seconds to minutes with person also having signs of a partial seizure
- The headache develops synchronously with the seizure ipsilateral to ictal discharges resolving immediately after seizure

Diagnosing Migralepsy (and Hemicrania Epileptica!!)

- Ictal EEG essential !
- In most cases of migralepsy EEGs unavailable so uncertain as whether migraine aura triggered seizure or if part of the seizure
- When clear descriptions of attacks and EEG available almost half of cases were epileptic seizures & not of migralepsy
- Only a handful cases fulfil criteria for migralepsy (or hemicrania epileptica!)

Ictal Epileptic Headache

- Headache only manifestation of an epileptic seizure (separate entity?)
- Proposed criteria: headache associated to clearcut EEG discharges (either ipsi- or contralateral)
- Diagnosis requires EEG abnormalities present with headache resolving on IV AED
- Incidence difficult to estimate as EEG not routinely done on headache without other complaints
- Only few cases reported

Occipital Lobe Seizures Mimicking Migraine Aura

- OLS can resemble a migraine aura as main symptoms visual hallucinations, illusions & reduced vision
- May also present with oculomotor symptoms as repetitive movements or eye deviation
- Visual symptoms of OLS can be confused with a migraine aura

Occipital Lobe Seizures Mimicking Migraine Aura

- Epileptic visual hallucinations onset usually within seconds & typically last a few minutes
- Migraine aura hallucinations develop slower over minutes & typically last over 15 minutes
- Epileptic visual hallucinations usually coloured and circular and in migraine uncoloured & linear
- To complicate matter more than 50% of OLS have concomitant migraine-like post-ictal headache!!!

Peri-Ictal Headache (Pre-ictal, Ictal, Post-ictal)

- Common in epilepsy (particularly pre-ictal and post-ictal) but often underdiagnosed & often underplayed by physicians & patients
  - Need to ask !
- Pathophysiology not well understood
  - Patchy response to analgesics
- May have migraine characteristics but by definition not migraine as in ICHD-II migraine not attributable to another disorder (in case of an underlying disorder termed "symptomatic migraine")

Peri-Ictal Headache (Pre-ictal, Ictal, Post-ictal)

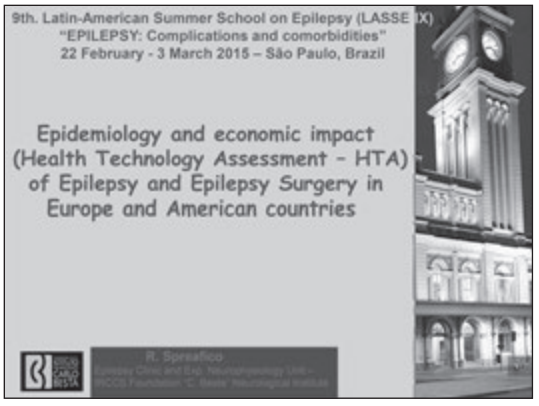
- Pre-ictal headache starts within 24 hours before seizure & may last until seizure onset regardless of headache duration
- Ictal headache very rare but can only be diagnosed if person with intact consciousness during the seizure
- Post-ictal headache start up to after 3 hours after seizure but usually present when person regains consciousness & may last up to 72 hours
  - Most commonly seen in:
    - AED polytherapy
    - early age of onset
    - convulsions

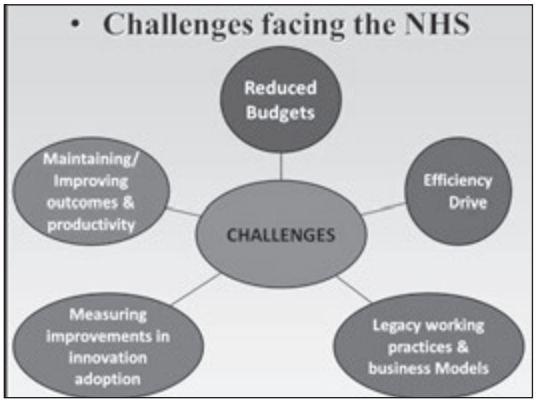
Conclusion

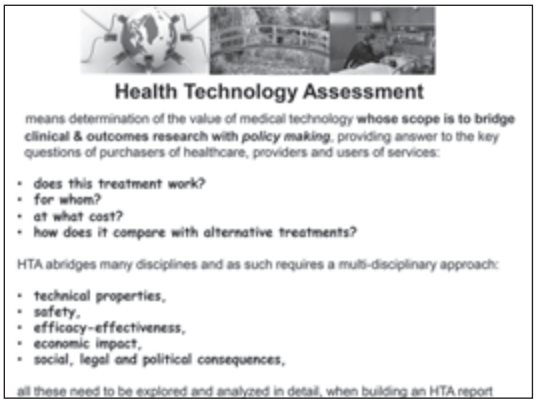
- Common co-morbidities
  - Need to ask explicitly ask if peri-ictal headache present
- Epilepsy & migraine have bidirectional association
  - ✓ Genetic susceptibility
  - ✓ Pathophysiological mechanisms
    - CSD
    - Cortical excitability
- Part of a functional sprectrum ?
- Classification in which headache & epilepsy co-occur during attacks challenging

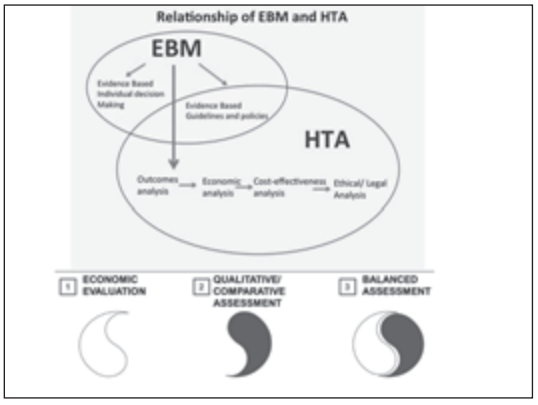
Roberto Spreafico (Italy)

HEALTH TECHNOLOGY ASSESSMENT REPORT ON THE PRESURGICAL EVALUATION AND SURGICAL TREATMENT OF DRUG-RESISTANT EPILEPSY

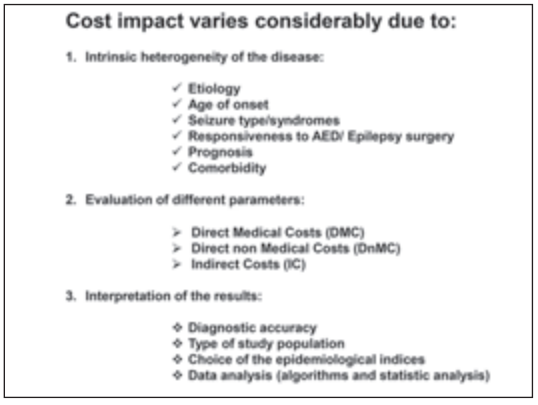







Relationship of EBM and HTA
EBM
Evidence Based Individual decision Making
Evidence Based Guidelines and policies
HTA
Outcomes analysis
Economic analysis
Cost-effectiveness analysis
Ethical/ Legal Analysis
1 ECONOMIC EVALUATION
2 QUALITATIVE/ COMPARATIVE ASSESSMENT
3 BALANCED ASSESSMENT


FULL-LENGTH ORIGINAL RESEARCH
Estimating the cost of epilepsy in Europe:
A review with economic modeling
*Maura Pugliatti, †Ettore Beghi, ‡Lars Forsgren,
Comparison of costs among European countries are difficult due to
Monetary differences (in the UK and, before 2000, also for other countries)
Different clinical practice
Different healthcare systems
Moreover


Cost impact varies considerably due to:
1. Intrinsic heterogeneity of the disease:
✓ Etiology
✓ Age of onset
✓ Seizure type/syndromes
✓ Responsiveness to AED/ Epilepsy surgery
✓ Prognosis
✓ Comorbidity
2. Evaluation of different parameters:
➢ Direct Medical Costs (DMC)
➢ Direct non Medical Costs (DnMC)
➢ Indirect Costs (IC)
3. Interpretation of the results:
❖ Diagnostic accuracy
❖ Type of study population
❖ Choice of the epidemiological indices
❖ Data analysis (algorithms and statistic analysis)


Direct and Indirect Health care Costs
Two main types of costs are associated with health care :
Direct costs : are those that result from outpatient and inpatient health services (including surgery), laboratory and radiological tests, drug therapy, supplies and equipment
Indirect costs: are the costs of those resources for which no direct payment is made, but for which there is an opportunity cost or foregone benefit. Guidelines for economic evaluation studies in health care recommend the inclusion of indirect costs in any such study. which have been defined as "resources forgone as a result of a health condition," fall into various categories:
• Value of lost work. Days missed from work are a cost to both employees and employers (in work not completed).
• Insurance. Employers pay higher life insurance premiums
• Wages. with lower wages and lower household income.
Indirect costs are harder to identify and measure than direct costs.

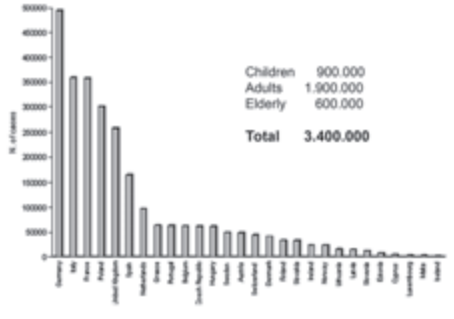
Studies on Cost of illness in Europe

Country	Cost Categories			Population	€ cost/pat. (2004)			Ref
	DMC	DnMC	IC		SF	DR	Not spec.	
FR, Germ UK	+	+	+	300 adults	674	1.876		Van Hout et al. 1997
UK	+			786 all ages	281	2.650		Jacoby et al. 1998
Italy	+			189 Ped.			1.635	Guerini et al. 2001
Italy	+			525 all ages	412	2.198		Tetto et al 2002
Netherland	+	+	+	116 adults			3.732 4.721	Kotsopulos et al. 2003
Italy	+			1.942 all ages	519	2.027		Beghi et al.2004

Price inflated to 2004 and converted in € and adjusted for Purchasing Power Parity (PPP)
(**DMC**= direct medical costs; **DnMC**= direct non medical costs; **IC**= indirect costs;
DR =drug resistant; **SF**= seizure free)

Modified from Pugliatti et al. Epilepsia 2007

Number of prevalent cases of Epilepsy in Europe



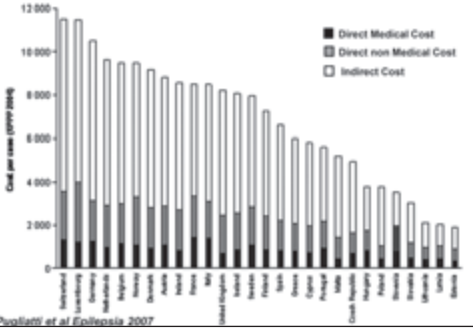
Children 900.000
Adults 1.900.000
Elderly 600.000

Total 3.400.000

Modified from Pugliatti et al. Epilepsia 2007

Cost per case in epilepsy in Europe (2004)

The total cost per case differed significantly across Europe, ranging from €2,000 to €11,500.



M Pugliatti et al Epilepsia 2007

Table 3. Total cost of epilepsy by country (€PPP million, 2004)

	Health care cost	Direct nonmedical cost	Indirect cost	Total cost
Austria	51	88	177	316
Belgium	72	114	240	426
Cyprus	3	5	10	18
Czech Republic	42	60	128	230
Denmark	38	77	159	274
Estonia	2	4	4	11
Finland	28	52	96	176
France	512	678	1,075	2,265
Germany	614	933	2,260	3,808
Greece	50	81	151	282
Hungary	50	56	78	184
Iceland	1	2	4	7
Ireland	19	44	83	146
Italy	495	618	1,196	2,308
Latvia	6	8	8	23
Lithuania	6	9	10	25
Luxembourg	3	7	12	23
Malta	1	2	5	9
Netherlands	96	185	403	684
Norway	25	52	84	161
Poland	128	183	500	811
Portugal	59	77	130	266
Slovakia	16	22	38	75
Slovenia	10	14	12	35
Spain	137	228	452	816
Sweden	52	88	147	287
Switzerland	58	98	214	371
United Kingdom	178	455	876	1,509
Europe	2,953	4,340	8,554	15,546

PPP = purchasing power parity.

The total cost per case differs significantly across Europe
(ranging between € 2.000 and € 11.500)

The estimated cost in Europe (2004)

DMC	€ 2.9 billions (18%)
DnMC	€ 4.2 billions (27%)
IC	€ 8.6 billions (55%)
TOTAL	€ 15.5 billions

(range between € 14 and 17.1 billions)

The estimated average cost of epilepsy per European inhabitant

DMC	€ 6
DnMC	€ 6
IC	€ 18
TOTAL	€ 30

Pugliatti et al Epilepsia 2007

While DMC and DnMC are in general quite easy to estimate, IC are difficult to evaluate and, in general, different parameters are considered

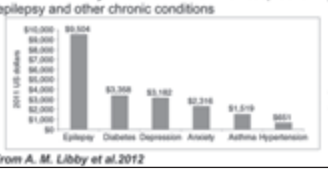
ORIGINAL ARTICLE (*Med Care 2012;50: 928–933*)

Economic Differences in Direct and Indirect Costs Between People With Epilepsy and Without Epilepsy

Anne M. Libby, PhD† Vahram Ghushchyan, PhD*† Robert Brett McQueen, MA* Julia F. Slejko, PhD*‡ Jacqueline L. Bainbridge, PharmD,† and Jonathan D. Campbell, PhD*†*

Indirect Costs: Measures of human capital (education and income) and workplace productivity (employment, missed work).

Education: defined for respondents over 16 years of age: no degree; high school or other degree; or college (bachelor's degree) or higher.
Family Income: categorized as poor or near poor; low or middle income; or high income (as a percentage of the federal poverty level for a family of 4 ($22,050 annually adjusted to 2009 dollars)
Employment :was defined if the person had full-time or part-time paid work with no breaks in employment during the interview year regardless of hours worked)
Missed days of work because of illness or injury: To assess missed days at work respondents reported days (half day or more) of work a respondent missed because of illness or injury.
Lost Productivity: We calculated annual lost productivity for the US population due to epilepsy and other chronic conditions



Estimated annual lost productivity because of epilepsy and other chronic conditions

From A. M. Libby et al.2012

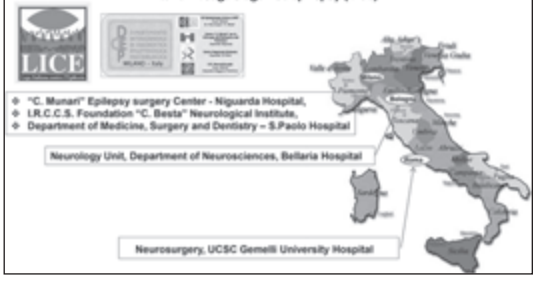
Direct Health Care Costs:	Epilepsy Mean	Epilepsy SE	No Epilepsy Mean	No Epilepsy SE
Utilization category[2]				
Medical provider visits	8.91	0.66	4.90	0.04
Hospital outpatient visits	0.93	0.18	0.47	0.01
Emergency room visits	0.44	0.03	0.18	0.00
Inpatient days	1.57	0.34	0.54	0.01
Prescription medications	27.55	1.30	9.29	0.09
Percent on AEDs	89%	0.02	4%	0.00
Annual number of AED prescriptions (including refills)	10.97	0.45	0.24	0.01
Expenditures ($)[2]				
Total health care expenditures	9073	696	3961	39

Indirect Costs: Human Capital and Productivity	Epilepsy N	Epilepsy %	No Epilepsy N	No Epilepsy %
Human capital[2]				
Highest degree of education				
Under age of 16 y	194	15.42	107,559	23.99
No degree	281	22.56	72,002	14.56
High school or other degree	452	50.83	148,830	43.15
College and higher	90	11.19	52,327	18.30
Family income category				
Poor or near poor	327	24.72	98,100	17.09
Low or middle income	463	44.92	177,739	45.25
High income	256	30.36	107,251	37.67
	N	Mean	SE	N	Mean	SE
Productivity						
Employed full year (%)[2]	266	42%	3.10%	136,914	59%	0.26%
Days of work missed because of illness or injury[2]	256	11.64	3.28	136,577	4.32	0.05
Total annual wage income[3]	687	$17,603	$1907	218,852	$33,880	$276

THE MANAGEMENT OF DRUG-RESISTANT EPILEPSY HTA REPORT

S.Lopatriello, P. Berto, M.P. Canevini, G- Colicchio, G. Rubboli, R. Spreafico, L. Tassi, P. Tinuper

ad hoc task force of the Commission on Epilepsy Surgery of the Italian League against Epilepsy (LICE)



- "C. Munari" Epilepsy surgery Center - Niguarda Hospital,
- I.R.C.C.S. Foundation "C. Besta" Neurological Institute,
- Department of Medicine, Surgery and Dentistry – S.Paolo Hospital

Neurology Unit, Department of Neurosciences, Bellaria Hospital

Neurosurgery, UCSC Gemelli University Hospital

ITALIAN LEAGUE (LICE) 2013

Health Technology Assessment report on the presurgical evaluation and surgical treatment of drug-resistant epilepsy

[a]Carlo Efisio Marras, [b]Maria Paola Canevini, [c]Gabriella Colicchio, [d]Renzo Guerrini, [e,m]Guido Rubboli, [f]Massimo Scerrati, [g]Roberto Spreafico, [g]Laura Tassi, [g]Giorgio Lo Russo, [h]Paolo Tinuper, and on behalf of the Commission on Epilepsy Surgery of the Italian League Against Epilepsy

This report is an analysis from the standpoint of the Hospitals **of the centers participating in the survey of the diagnostic and therapeutic approaches to** patients with drug-resistant epilepsy admitted to epilepsy surgery program

AIMS

- to assess the clinical, organization, financial and economic impact **of managing child, adolescent and adult patients with epilepsy treated pharmacologically but defined as drug-resistant.**
- **to establish** the congruity between costs incurred and NHS reimbursement **in the approach to drug-resistant patients.**

The economic assessment is a key element in the HTA process. The meaning of the term assessment is strongly linked o the idea of the determination of value which in turn is linked to the economic and the clinical, organizational, ethical, individual and collective aspects.
For this reason the assessment needs to be as thorough as possible (hence, not only, but also an economic assessment) that leading experts in the field will acknowledge as essential in an HTA Report.

An HTA is the bridge between science that produces evidence and the decisions that can be taken on the basis of that evidence at different levels of healthcare system provision.
Evidence can touch on safety, efficacy, cost effectiveness and the organizational, social and ethical impact of health technology .

Decision-making occurs on three levels.

- The **macro** level involves policy decisions, i.e. the actions that must be taken by the Health System and/or the Regions on marketing or approval of funding/reimbursement.
- The **meso** level involves decisions by the Regions or individual institutions (Hospitals and Health Trusts) that need to tackle problems concerning the adoption of new drugs in the local Formulary or authorize the purchase of new medical devices.
- The **micro** level involves clinical practice, i.e. the margin of professional autonomy of a physician or ward team with respect to policy and hospital decisions

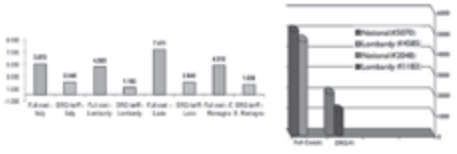
---

From a methodological standpoint, the report is based on **two sources of information**.

1. extensive detailed bibliographic search to collect updated information on current funding of the procedures and relative diagnosis related group (DRG) codes. focused mainly on the following issues:
   - social, ethical impact, and costs of the disease;
   - clinical results, efficacy, and safety of surgery;
   - ethics and quality of life after surgery;
   - economic impact and productivity regained after epilepsy surgery.
2. specific costing search using the microcosting bottom-up technique that constructs the cost of the procedures starting from the basic consumable components and collecting unit prices (provided by the Administrations and Management Control Offices of the participating centers) and composed of three different stages:
   - ✓ non-invasive diagnostic work-up
   - ✓ invasive diagnostic work-up
   - ✓ neurosurgical intervention
   - ✓ postoperative follow-up

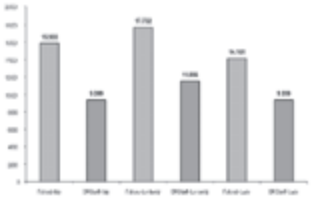
Mean cost of noninvasive presurgical study

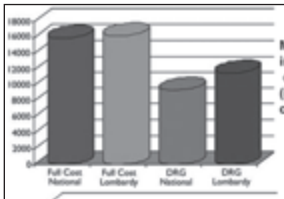
Non-invasive diagnostic stage		Average	MIN	MAX
Instrumental tests		3,985	3,184	5,482
	of which video-EEG*	3,406	2,692	4,698
Hospital stay**		748	560	1,067
Drugs during hospital stay		17	8	27
Staff during hospital stay		664	263	1,135
Other (compressive medication, perfusion)		30	0	97
Total non-invasive diagnostic stage (1st admission)		**5,070**	**3,916**	**7,356**
Total non-invasive diagnostic stage (additional admission)		1,203	0	6,112
Total cost (2nd admission)		**6,273**	**3,916**	**12,223**



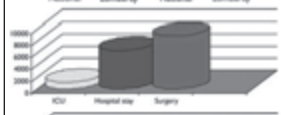
Mean cost of invasive presurgical study

Invasive diagnostic stage	Average	MIN	MAX
Pre-surgical instrumental tests	274	169	380
Hospital stay (excluding the cost of the recording bed)	1,913	1,692	2,134
Drugs during hospital stay	14	6	22
Staff during hospital stay	942	840	1,044
Invasive video-EEG recording	12,757	10,933	14,580
Total invasive diagnostic stage (2nd admission)	**15,900**	**14,098**	**17,762**

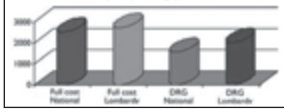




Mean cost of surgery (operating room, intensive care unit, hospital stay) as compared to the DRG002 charge (craniotomy age >17 years, without complications)



Surgery stage. The overall cost (€16,243) differentiated as:
- intensive care unit (ICU; €1,102);
- hospital stay (€6,397)
- surgery (€8,744).



Follow-up costs after 5 years from surgery; full cost and DRG data

Marras et al. Epilepsia 2013 in press

The average funding by the national tariff (DRG) is not remunerative for an average Italian hospital admitting patients for the non-invasive and invasive diagnostic stage.

Cost of surgery is very similar in all three Regions, even when the cost is broken down into different elements. The lack of remuneration of the tariff (DRG 002) is also confirmed for standard surgical intervention in all Regions.

In conclusion

funding of the treatment approach for patients with drug-resistant epilepsy undergoing standard surgery appears insufficient to remunerate the costs incurred by the Hospitals, irrespective of how the approach is implemented by the Regions involved.


Health Technology Assessment
THANK YOU FOR YOUR ATTENTION
Bridging Science and Decisions

Imad Najm (USA)

OUTCOMES OF EPILEPSY SURGERY: SEIZURE, PSYCHIATRIC AND QOL

Marina Bentivoglio (Italy)

MIGRANTS, TRAVELERS AND EPILEPSY IN THE GLOBAL WORLD VILLAGE

KIMFORD MEADOR (USA)

MECHANISMS OF CONSCIOUS AWARENESS

Mechanisms of Conscious Awareness

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Stanford University
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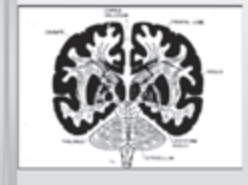
Little "c" "c"onsciousness

Physiology of conscious perception

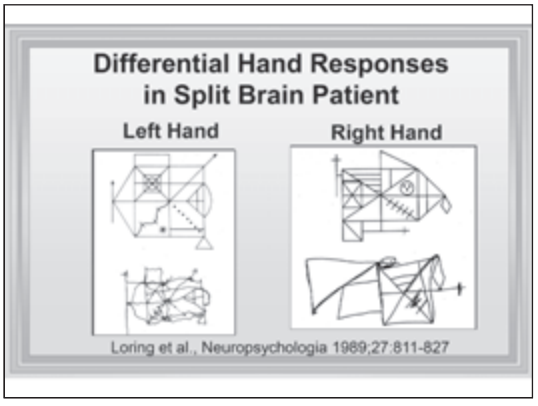
Big "C"

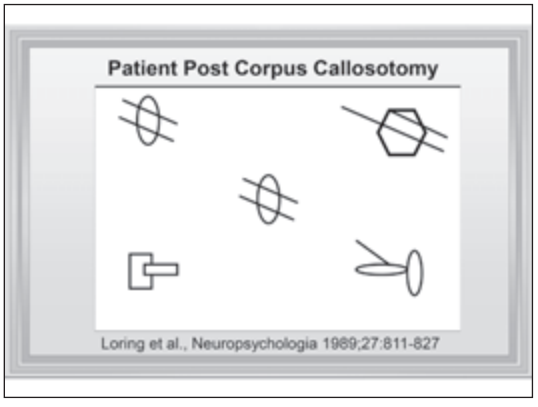
- Left vs Right Brain?
- When?
- Where?
- How?

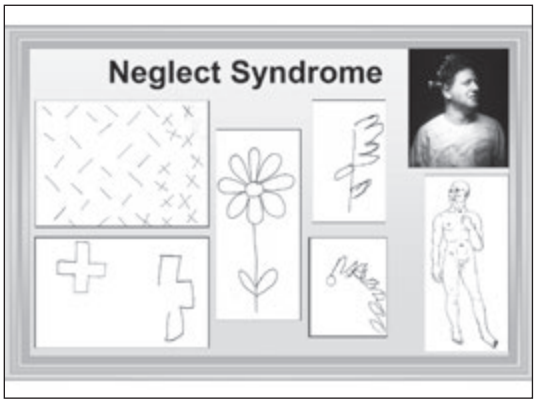
Is the Left Brain Dominant for Consciousness?




Alien Hand
Dr. Strangelove

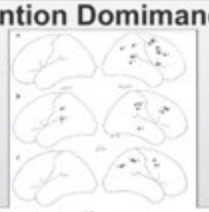

Differential Hand Responses
in Split Brain Patient
Left Hand
Right Hand
Loring et al., Neuropsychologia 1989;27:811-827


Patient Post Corpus Callosotomy
Loring et al., Neuropsychologia 1989;27:811-827


Neglect Syndrome

Right Brain Attention Domimance

PET Study
Tasks:
a = L toe - EC rest
b = R toe - EC rest
c = visual dim - EC rest
Pardo et al,
Nature 1991;349:61-4



fMRI Study
Line bisect task
Ptak & Schnider.
Neuropsychologia
2011;49:3063-70

Bisiach & Luzzitti. Cortex
1978;14(1):129-33.

Meador et, Neurology
1987;37(3):522-6.

Tactile Perceptual Asymmetries

Subjects	N	Left Hand	Right Hand	L/R%
Dextrals		mA (SD)	mA (SD)	
6-73Y/O	**110**	**3.02** (.80)	**3.36** (.94)	**90%**
<20Y/O	22	2.72 (.48)	3.01 (.54)	90%
20-39Y/O	66	2.86 (.61)	3.20 (.64)	89%
40-59Y/O	9	3.17 (.60)	3.36 (.63)	94%
≥60Y/O	13	4.19 (1.16)	4.73 (1.63)	89%
Sinestrals	**16**	**3.38** (.76)	**3.38** (.87)	**100%**

Meador et al, Neurology 1998;51:721-7

Gaze and Tactile Perception

Mean (SD) Thresholds (mA)

Gaze	Left Hand	Right Hand	L/R%
Straight	**3.01** (.56)	**3.46** (.53)	**87%**
Right	**2.99** (.52)	**3.46** (.62)	**86%**
Left	**2.92** (.49)	**3.32** (.57)	**85%**

Gaze to left reduces threshold in both hands 0.07-0.14mA compare to gaze left or straight.

Meador et al, Neurology 1998;51:721-7

When does conscious perception occur?

Throw,

Throw,

Throw,

Throw Now !!!!!!!!!!

Ben Libet

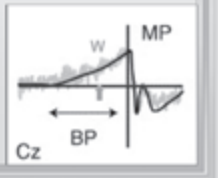
- Demonstration of cortical evoked potentials (SS cortex) to stimuli below perceptual threshold.
- Frontal electrical response (BP) prior to awareness of making a volitional response.
- Utilization Time & referral back in time to 1^0 evoked potential.

1916 - 2007
PubMed 1946 - 2006

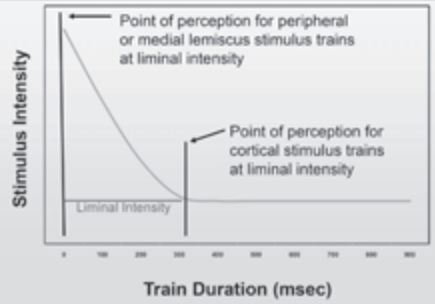
Libet et al, Science. 1967 Dec 22;158(3808):1597-600.
Libet et al, Brain. 1983 Sep;106 (Pt 3):623-42.
Libet et al, Brain. 1979 Mar;102(1):193-224.

Conscious Awareness of Making Volitional Response

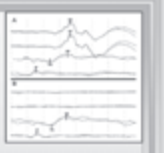
- W = reported time of intenting to act (see orange arrow on EP)
- BP = Bereitschaftspotential or readiness potential (RP)
- W – onset BP = - 200ms
- S = reported time of feeling an electrical pulse
- S - pulse = - 50ms



Libet et al., Brain. 1983;106 (Pt 3):623-42.



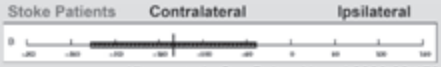
Loss of Somatosensory Evoked Potentials & Perception Timing



Perceptual differences in interstimulus intervals in subjects with & without N20. Perception delayed on average 134ms when N20 absent.

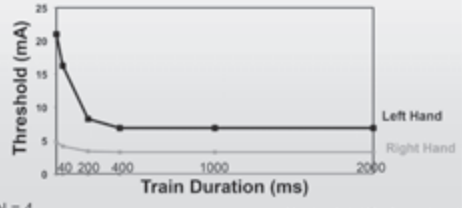
Normals Left Right

Stoke Patients Contralateral Ipsilateral



Kluger et al., Cog Behav Neurol 2009;22:173-9

Train Duration Effects: Right Brain Stroke



N = 4

*Mean duration post infarction = 17 days (7-36)

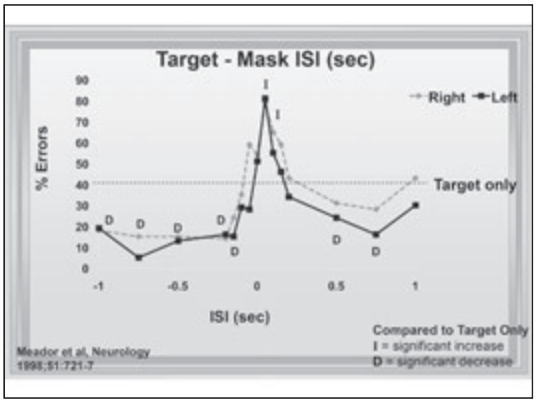
Meador et al, J Clin Neurophysiol 2000;17:406-413

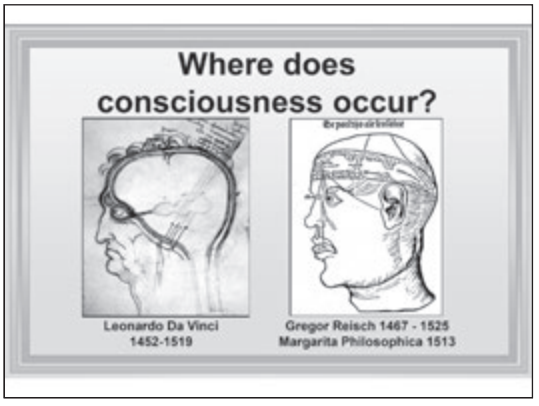
What can the time course of extinction (masking) tell us about when conscious perception occurs?

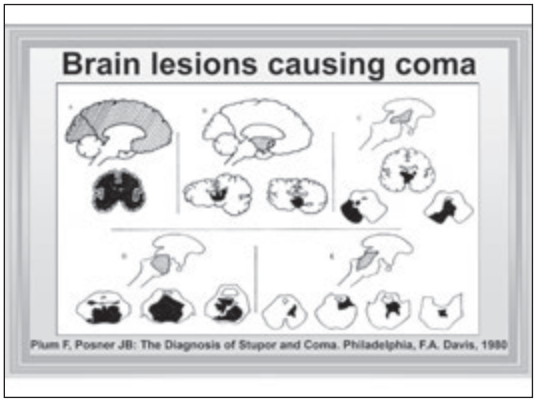
Maximum Masking for Somatosensory Stimuli is at 50-100ms Post Target Stim

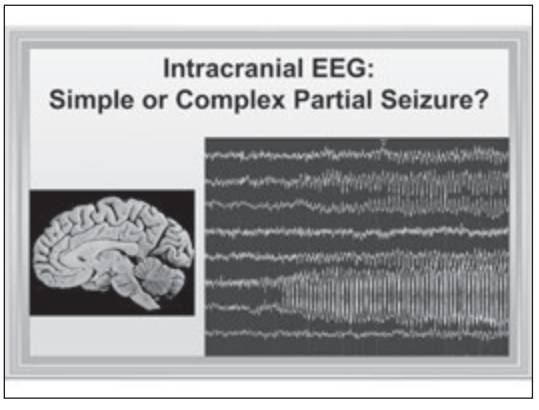
Left hand target = 3.75mA
Right hand mask = 10mA

Meador et al, Neurology 1998;51:721-7


Target - Mask ISI (sec)
% Errors
ISI (sec)
Right
Left
Target only
Compared to Target Only
I = significant increase
D = significant decrease
Meador et al, Neurology
1998;51:721-7

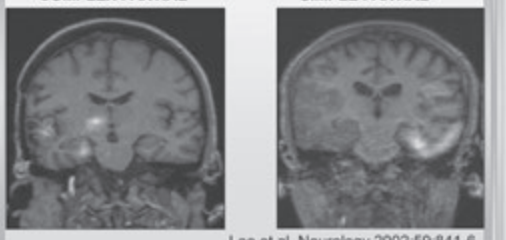

Where does consciousness occur?
Leonardo Da Vinci
1452-1519
Gregor Reisch 1467 - 1525
Margarita Philosophica 1513


Brain lesions causing coma
Plum F, Posner JB: The Diagnosis of Stupor and Coma. Philadelphia, F.A. Davis, 1980


Intracranial EEG:
Simple or Complex Partial Seizure?

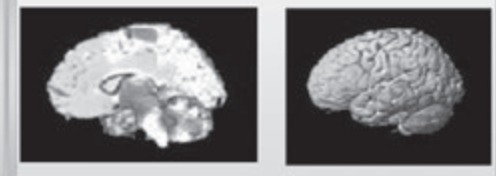
Patients with Partial Seizures

COMPLEX PARTIAL | SIMPLE PARTIAL



Lee et al. Neurology 2002;59:841-6

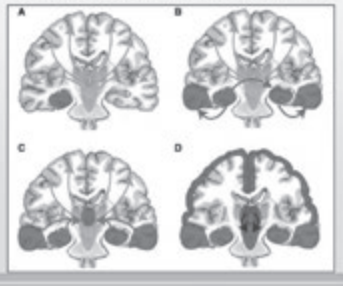
COMPLEX PARTIAL SEIZURES



Blumenfeld et al, Cerebral Cortex 2004;14:892-902

Temporal Lobe Seizures: Consciousness

Englot et al, Brain 2010; 133:3764-3777

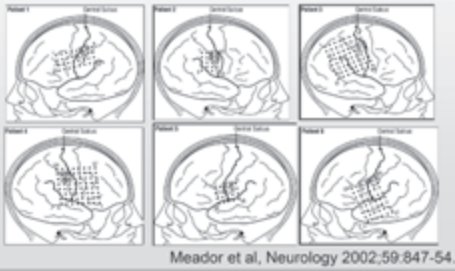


How does consciousness occur?

Does Gamma Activity (>30 Hz) Underlie Conscious Awareness?

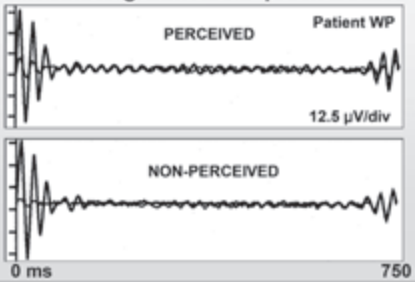
- Crick & Koch (1990) postulated that gamma coherence underlies conscious awareness.
- Ubiquitous in the nervous system.
- Related to attentional mechanisms.
- Greater in awake states but can be seen in sleep and anesthetic states.

Gamma Grid Patients

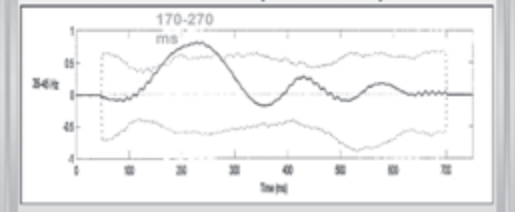


Meador et al, Neurology 2002;59:847-54.

Grand Average Filtered Epochs 35-45 Hz



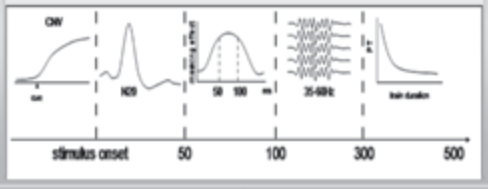
Average Correlation Index for Gamma from 1^0 SS Region for Perceived vs Non-perceived Epochs



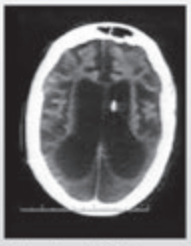
Meador et al, Neurology 2002;59:847-54.

Time Course of Perception

CNV N20 Masking Gamma Train Duration



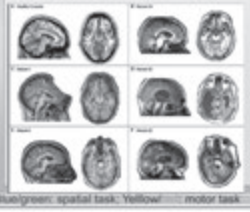
Terri Schiavo 1963-2005



Anoxic Brain Injury from Cardiac Arrest 1990

Brain Response in "Vegetative State"

Monti et al, NEJM 2010;362:579-89
2/7 VS pts: fMRI response to image swing at tennis ball or walk in home.

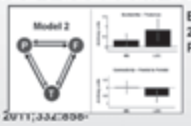


Blue/green: spatial task; Yellow/ : motor task

Cruse et al, Lancet 2011;378:2088-94
3/16 VS pts: EEG response to make fist or wiggle toes.

3/12 controls: no significant EEG change

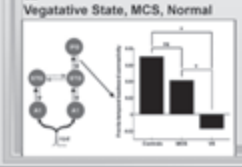
Impaired Feedback Connectivity

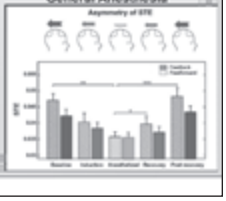


Boly et al., J Neurosci 2012;32(20):7082-90
Propofol Anesthesia

Ku et al., PLoS One 2011;6(10):e25155
Propofol or Sevoflurane
General Anesthesia

Boly et al, Science 2011;332:858-62
Vegatative State, MCS, Normal



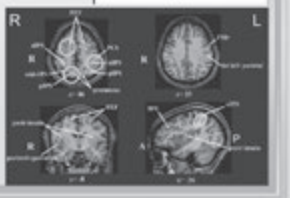


Somatosensory Perception: fMRI

R finger pad stimuli

Strength of inputs to the **Right Posterior Intraparietal Sulcus** from the **Left Post Central Sulcus** & **Right Frontal Eye Field** predicted acuity. 86% of the variance.

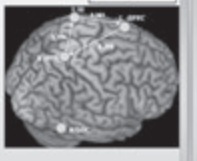
Stilla et al., J Neurosci. 2007;27(41):11091-102.



Somatosensory Perception: EEG

R finger pad stimuli

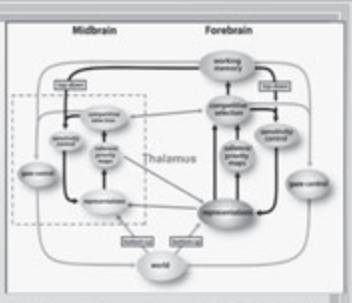
- **Feedforward beta-band network linking all 4 nodes.**
- **Recurrent gamma-band network linking SI, pIPS and dlPFC.**
- **Accuracy of tactile discrimination was significantly correlated with measures of network activity in both bands.**



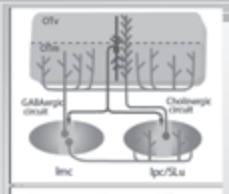
* L primary somatosensory cortex (SI)
* R lateral occipital complex (LOC)
* R posterior intraparietal sulcus (pIPS)
* L dorsolateral prefrontal cortex (dlPFC)

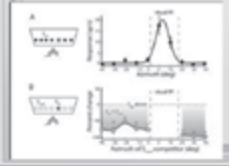
Adhikari et al, NeuroImage 2014;91:300-10.

Midbrain has a critical role in interaction with Forebrain in selective attention & stimulus selection.

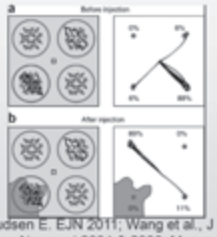


Knudsen E. Eur J Neurosci 2011;33:1961-72.



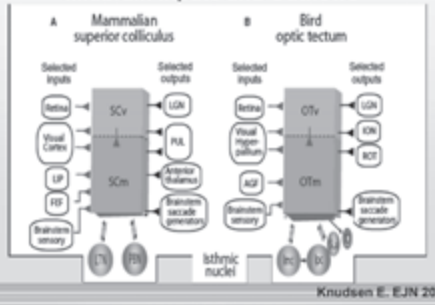


Midbrain & Attention



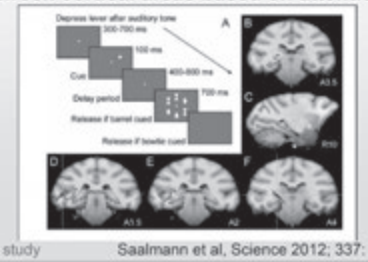
Knudsen E. EJN 2011; Wang et al., J Comp Neurosci 2004 & 2006; Mysore et al. J Neurosci 2010; Lovejoy & Krauzlis Nat Neurosci 2010.

Midbrain Inputs and Outflows



Knudsen E. EJN 2011

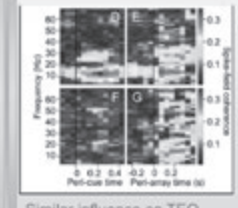
Pulvinar regulates information transmission between cortical areas based on attention



Primate study

Saalmann et al, Science 2012; 337: 753–6

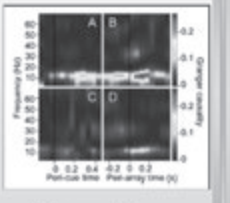
Pulvinar & V4 Synchrony with Attention



Cue in RF

Cue away RF

Granger Causality for Pulvinar to V4



Similar influence on TEO (posterior inferior temporal cortex)

Saalmann et al, Science 2012; 337: 753–6

Somatosensory Perception & Extinction: fMRI Study

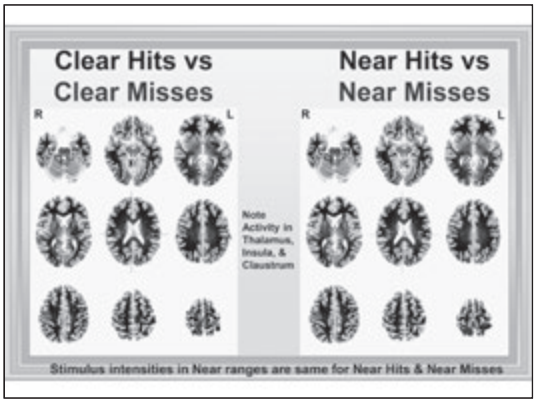
Meador KJ, Pirog-Revill K, Epstein C, Sathian K, Loring DW, Rorden C.
Stanford U, Emory U, Ga Institute of Technology, & U South Carolina

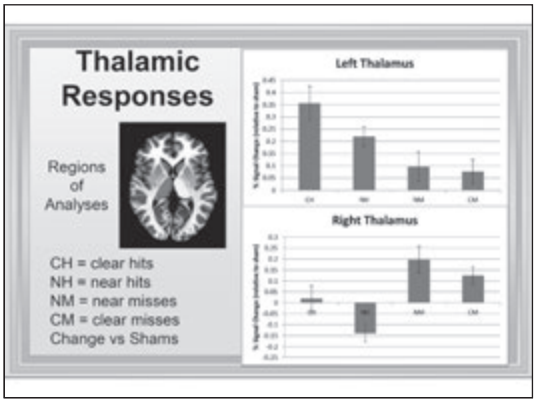
Subjects: n=15 healthy right-handed volunteers

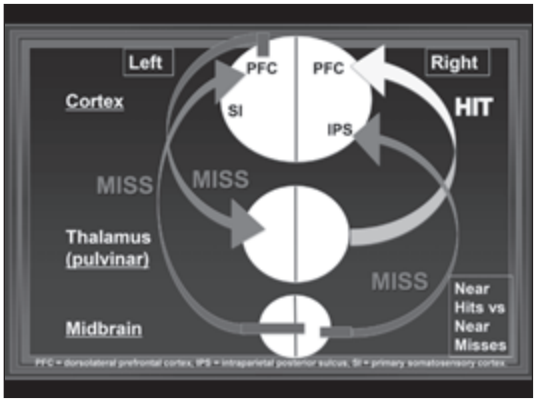
Stimuli: electrical pulse trains to index fingers

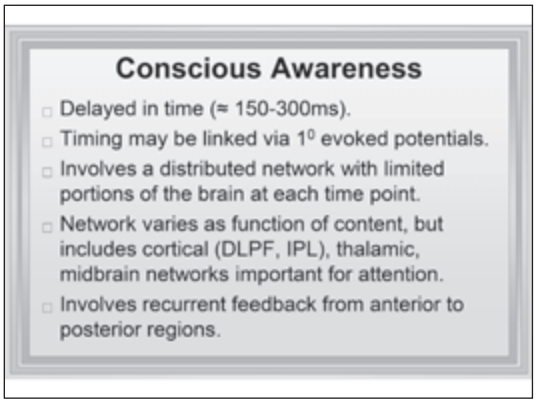
- R hand targets & L hand masks
- 10% sham trials (no target given).
- Trial-by-trial target strength altered.

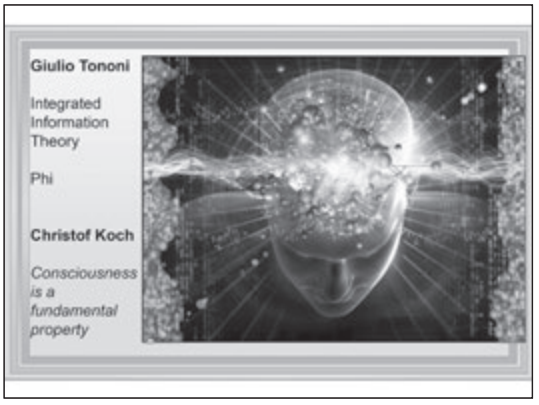
Response: target perceived = R foot pedal
no target perceived = L foot.


Clear Hits vs
Clear Misses
Near Hits vs
Near Misses
R
L
R
L
Note
Activity in
Thalamus,
Insula, &
Claustrum
Stimulus intensities in Near ranges are same for Near Hits & Near Misses


Thalamic
Responses
Regions
of
Analyses
CH = clear hits
NH = near hits
NM = near misses
CM = clear misses
Change vs Shams
Left Thalamus
Right Thalamus

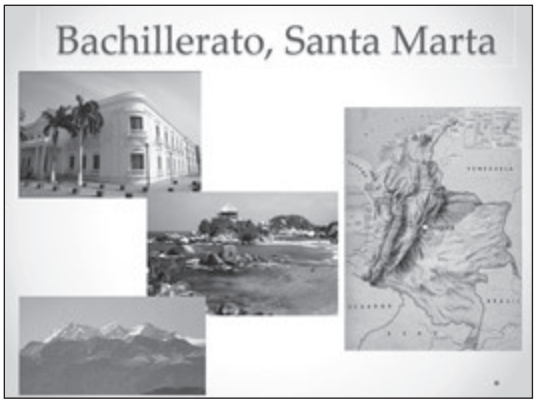

Left
Right
Cortex
PFC
PFC
SI
IPS
HIT
MISS
MISS
Thalamus
(pulvinar)
MISS
Midbrain
Near
Hits vs
Near
Misses
PFC = dorsolateral prefrontal cortex, IPS = intraparietal posterior sulcus, SI = primary somatosensory cortex


Conscious Awareness
Delayed in time (≈ 150-300ms).
Timing may be linked via 1⁰ evoked potentials.
Involves a distributed network with limited portions of the brain at each time point.
Network varies as function of content, but includes cortical (DLPF, IPL), thalamic, midbrain networks important for attention.
Involves recurrent feedback from anterior to posterior regions.


Giulio Tononi
Integrated Information Theory
Phi
Christof Koch
Consciousness is a fundamental property

Jaime Carrizosa (Colombia)

CLEMENCIA TARIFFA: LIGHT ON A CASE OF ABANDONED EPILEPSY



INQUILINATOS EN SANTA MARTA

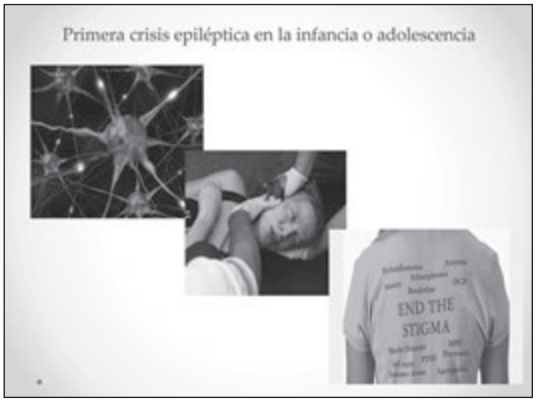
Liceo Celedón

Educador Rafael Guerra Maestre
Liceo del Caribe

15 años bibliotecaria


Inspiradores
PABLO NERUDA
FEDERICO GARCIA LORCA
ANTONIO MACHADO
SOR JUANA INÉS DE LA CRUZ


¿Qué es la poesía para usted?


Primera crisis epiléptica en la infancia o adolescencia
END THE STIGMA


INTRUSA
Me habita otra mujer
Una extraña, una intrusa
Que no alcanzo a entender

Se afirma que la poesía es tarea de muchos pero oficio de pocos…

Lo bello para el poeta es saberse leído por algunos pocos,
y saberse querido por esas líneas que uno ha logrado arrancarle a la poesía.

¿Por qué usted lee poesía?

No sería yo la mujer que soy sin leer poesía.
Un buen libro entre mis manos
me es tan urgente
como un hombre entre mi cuerpo.

RAUL GOMEZ JATTIM

Soy mejor lectora
de poesía que
está en las calles,
de la poesía que
camina con la
gente,
de la poesía que
se desliza con la
sombra de los
alares,
de la poesía que
mueve los arboles
y lanza sus pájaros
al vértigo…

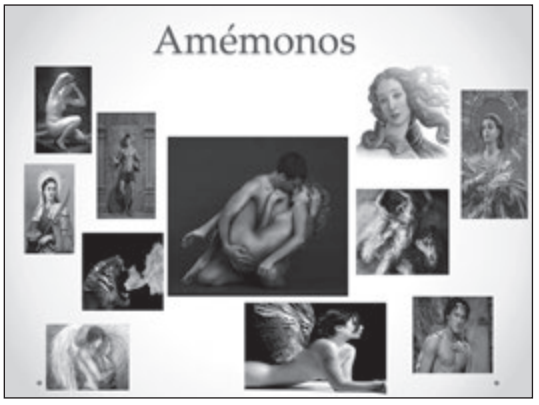
… de la poesía sin
palabras
cuando observo a
mi madre
cosiéndome un
vestido o
preparándome su
mejor plato

…o incluso, algo que
casi no dicen los
poetas,
de la poesía
bronceada en los
músculos de un
hombre
y exacerbada con el
roce de su barba
antes del poema
final de los cuerpos
entrelazados bajo
este cielo caribe

JOSE DE TOGORES

Condición felina

Por mi condición felina
De ser gata peluda
Bajo deliciosamente
a tus pies


Amémonos


Yo no puedo pedir


Llovía


Senos

Juan Carlos Vives Menotti le publica el libro

"El ojo de la noche" (1987)

Bogotá

Fundación Gilberto Alzate Avendaño

Casa de Poesía Silva

La Candelaria

José Gustavo Paba
Casa Caribe Libro Café

No me conoces

Ojos polarizados

CUANDO SOY TIERRA

Ángulo

Llovizna para amar

12 pm

Hernán Vargascarrero

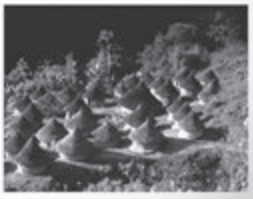
Premio Latinoamericano de Poesía
Koeyu (Caracas)

Premio de Poesía del Instituto de
Cultura del Cesar 1994

Valledupar

Sierra Nevada de Santa Marta



Chantaje

¿Qué sentido tiene para usted escribir poesía?

Yo no se hacer nada desde hace mucho tiempo. Mi madre me hace los vestidos en su máquina negrita, me cocina, me suministra las medicinas todos los días, me cuida.

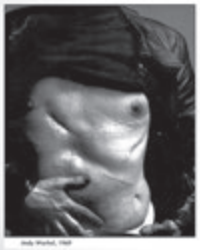
Desde hace muchos años nadie me da un trabajo porque no se hacer trabajo alguno. Lo único que se hacer es escribir poesía…

Y si no pudiera escribir poesía,
mi vida no tendría sentido,
pues no se hacer otra cosa,
ni siquiera me he atrevido a tener un hijo,
porque no sabría como criarlo.
Como puedes ver,
en mi caso,
escribir poesía es salvarme,
es vivir.

CLARIDAD

VACIO

VIGILIA



Cuando Clemencia despertó encontró a su señora madre en el piso, con algo de sangre cerca de su cabeza, y como no pudo "despertarla", pidió la ayuda del casero

A cualquier vecino se le ocurrió decir que la poeta loca había matado a su propia madre con la piedra que reposaba junto a su cabeza y junto al chorro de sangre.

Clemencia seguía detenida, esposada a unas rejas , en el gran patio de la comisaría central.

...realmente en esos momentos la poeta nunca tuvo un manejo de la realidad y nos preguntaba por qué la tenían esposada.

SEÑORAS

PETICIÓN DESHONESTA

CARTA DE LA ANSIEDAD

SUBLEVACIÓN

MALLA

EDUARDO CABALLERO CALDERÓN

CAPULLITO

AZUL

Logramos cuidar a Clemencia durante un año y medio, le alquilamos un mini-apartamento en Mamatoco…

…pues al no verla salir ni entrar, se preocupaba, y en varias ocasiones tuve que ir a recogerla de su cama totalmente convulsionada e inconsciente…

…al no consumir sus medicinas las convulsiones se volvieron frecuentes, tanto en la calle como en su residencia, y a cada caída el rostro de Clemencia se iba llenando de cicatrices…

…motivo por el cual tuvimos que internarla en la clínica mental, pues era eso o la calle. Su familia de tías y primos de Codazzi se negaron a recibirla…

SER

OJOS

MEDIODIA

QUIERO

AHORA

Clemencia murió en la clínica mental de Santa Marta, el 23 se septiembre de 2009; yo me enteré de su muerte a los tres días…

Solo pudo ser sepultada por un grupo muy pequeño de amigos, siete días después de su muerte, gracias a la ayuda del poeta Javier Moscarella, quien desde la alcaldía se encargó de conseguir los gastos del sepelio.

QUE LABIOS

6:40 pm

Les invito a apreciar la obra de Clemencia, mujer que siempre vivió la estética en cada uno de sus versos,

poeta que volvió poesía su tragedia,

mujer que por medio de su canto solo pretendió que la humanidad fuese más solidaria con su angustia, que es lo mismo que decir, más solidaria con todos nosotros.

CLEMENCIA TARIFFA

Roland Coras (Germany)

HIPPOCAMPAL SUBFIELDS AND MEMORY FORMATION: INPUT FROM PATENTS WITH TLE

Pamela Thompson (England)

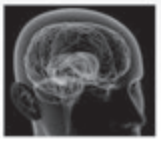
IS MEMORY DISTURBANCE PROGRESSIVE IN TLE WITH HIPPOCAMPAL SCLEROSIS?

UCL INSTITUTE OF NEUROLOGY
DCEE

UCL

Is memory disturbance with hippocampal sclerosis progressive?

Pam Thompson



UCL

Memory decline

- major concern of people with epilepsy
  fear of dementia
- Fisher et al 2000
  large survey ; 46% reported decline
- McCauley et al 2010
  3rd highest Epilepsy Concern Index
- Epilepsy Society helpline:
  1 in 7 calls/annum
- commonest reason for neuropsychological referral

UCL

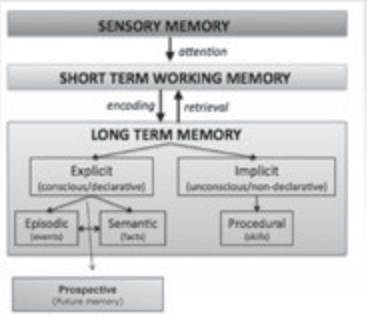
Memory

- is not just about the past
- influences our present
- guides our future
- defines our sense of self
- defines our relationship with others

'It's a poor memory that only works backwards'

The White Queen : Alice through the Looking Glass

UCL



UCL

Memory complaints

- Episodic memory

'I have a good memory for the past and my visual recall of events remains vivid. It's the details from conversations that I forget such as ' Mum can you remind me to..' Mum can you ring Gran back'. This annoys my family & causes me stress ..'

KT 41 yrs LHS

UCL

Memory complaints

- Episodic memory

'autobiographical memory loss'

'Events that happen involving me which stick out in other people's minds I have no recollection of at all much to the surprise of friends because that particular event could only have happened a year ago..... I used to have a very good memory before I developed epilepsy'

FA 38 years RHS

UCL

Hippocampus and memory

- well established association
- Jan 2015 PubMed search
  515 publications
- *Hippocampus* journal
  learning & memory research
- episodic memory
- 'hub' of an autobiographical memory
  network

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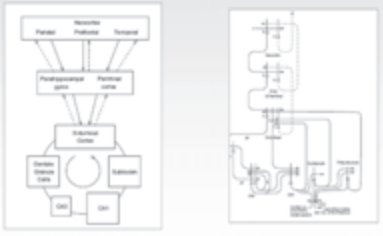
hippocampus networks



From Rolls 2015

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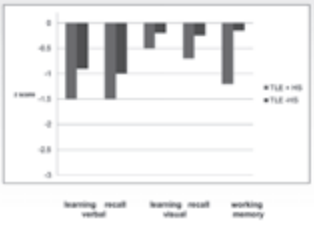
Memory test performance: TLE with HS
TLE without HS

Stretton et al 2014



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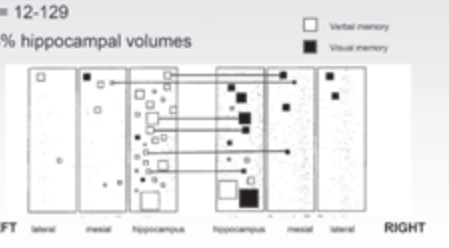
Memory & hippocampal integrity: temporal lobe epilepsy

N = 12-129

88% hippocampal volumes



after Richardson 2011

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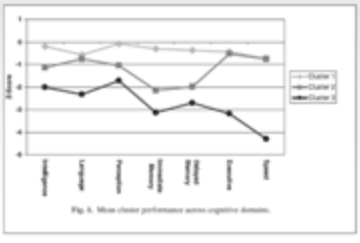
Cognitive phenotypes in temporal lobe epilepsy

Hermann et al, 2007



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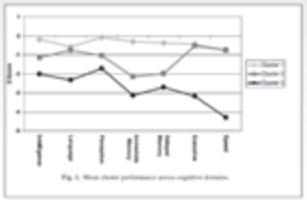
Cognitive phenotypes in temporal lobe epilepsy

Hermann et al, 2007

Cluster 1
cognitively intact
Cluster 2
memory impaired
Cluster 3
memory impaired +

Clusters 2&3
↓ hippocampal volumes
Cluster 3
↓ volumes in temporal, frontal & parietal lobes



UCL

Is memory decline progressive?

Helmstaedter et al,2009

Table 1 Distribution of patients and control subjects over age groups between 6 and 80 years

Age categories	Groups		Total
	Controls	TLE	
6–10	134	28	162
11–15	104	68	172
16–20	83	107	190
21–25	104	139	243
26–30	92	152	244
31–40	94	355	449
41–50	103	208	311
51–60	96	82	180
61–70	136	17	153
71–80	52	0	52
Total	1000	1156	2156

Until the age of 30 years, 5-year increments and in the time after 30 years, 10-year increments were chosen.

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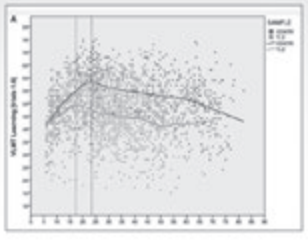
Is memory decline progressive?

Helmstaedter et al,2009



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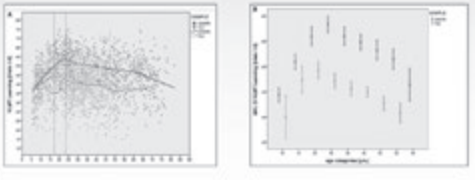
Is memory decline progressive?

Helmstaedter et al,2009



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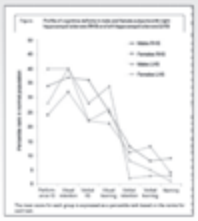
Is memory decline progressive?

Baxendale et al,2009: TLE + HS

- 163 Right HS; 219 Left HS
- age of onset < 18 years
- memory impaired
- no evidence of progression with age



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Cognitive decline: role of seizures

Thompson & Duncan 2005 : retrospective study

- N=132 chronic epilepsy
- 2 cognitive assessments
- > 10 years apart (median = 13 years)
- median age @ time 1 = 31 years; time 2 = 44 years
- 20% hippocampal pathology

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Cognitive decline: role of seizures

TABLE 1. *Demographic and clinical characteristics of the sample*

Gender: male	88 (65%)
Handedness: right	115 (85%)
Source	
Residential care	67 (49%)
Tertiary referrals	69 (51%)
Education (yr; median, range)	11 (9–16)
Age at seizure onset; median, range	8 (1–39)
Duration of epilepsy; median, range	35 (10–64)
Epilepsy type	
Generalized	11 (8%)
Focal	125 (92%)
Annual seizure frequency; median, range	
Complex partial seizures	52 (0–420)
Generalized tonic–clonic	6 (0–240)
Drop attacks (tonic and atonic)	0 (0–300)
History of SE (interval interval)	27 (20%)
History of remission (interval interval)	34 (25%)
Seizure related head injuries (interval interval)	50 (37%)

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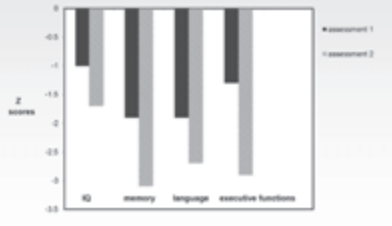
Performance levels expressed as z scores



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Cognitive decline

Associated with:

- age
- episodes of status
- periods of seizure remission >1 year
- seizure frequency (memory & naming)
- no evidence declines greater with HS

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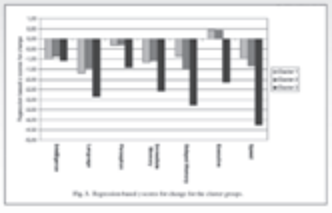
Cognitive decline in temporal lobe epilepsy

Hermann et al, 2007: cognitive change @ 4 years



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Is memory disturbance in hippocampal sclerosis progressive? Case 1

- DD 48 years
- age of onset : 14years
- convulsive seizures: 2/ year
- focal seizures :up to 6/year
- previously worked as a teacher
- MRI scan LHS

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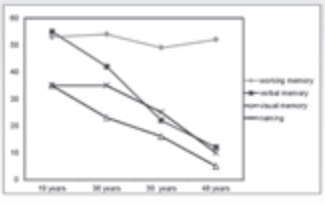
Is memory disturbance in hippocampal sclerosis progressive? Case 1



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Case 2

- AF 53 years
- Age of onset : 18 years
- Seizure control variable
- Various AEDs
- IT consultant
- MRI scan LHS → surgical candidate
- declined surgery @ 41 years

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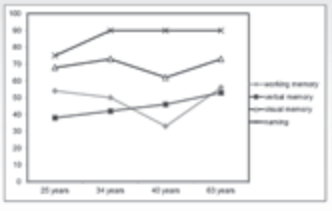
Is memory disturbance in hippocampal sclerosis progressive? Case 2



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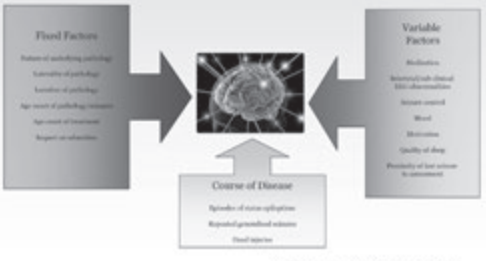
Epilepsy: high risk of cognitive problems



Adapted from Baxendale & Thompson 2010

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Is memory decline inevitable?

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Memory rehabilitation

'In the epileptic here is the fault which results in defective memory, desire is too feeble, there should be regular disciplined mental effort not only daily but hourly, a course duly graded as to time and intensity and alternated with relaxation'

Russell Reynolds 1861

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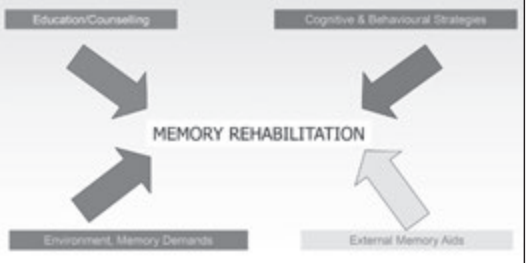
Memory rehabilitation



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Geraldi et al , in preparation
Ribeiro Preto Epilepsy Center

- Participants:
  post left temporal lobe surgery
  good surgical outcomes (Engels I & II)
- Methods:
  N= 9 rehabilitation group; 8 weekly 1 hr sessions
  N=9 control group; no intervention
  cognitive testing @ week 0 and week 8

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Optimizing memory function in TLE?

- Group 1 : traditional approaches
  external memory aids
  diaries, lists, drug wallets
  mobile phone functions/apps

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Cognitive strategies

- Rehearsal
- Visual imagery
- Story method
- Rhymes & songs
- First letter mnemonics
- Peg method
- Method of loci

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Optimizing memory function in TLE?

- Group 2 : Lumosity
  commercial brain training programme $15-20/m
  games : attention, memory, speed, flexibility & reasoning
  see how 'you' compare with others
  see how 'you' improve over time
  training reminders

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Lumosity

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Optimizing memory function groups

	Memory rehab	Lumosity	Both	No intervention
Number	22	18	17	18
Age	44.3 (8.1)	44.2 (8.8)	42.5 (9.8)	42.4 (13.2)
Gender M/F	13/9	11/8	11/6	11/8
IQ	100.8 (15.8)	100.5 (12.4)	100.4 (12.8)	101.8 (12.4)
Epilepsy				
Age of Onset	17.2 (12.4)	16.4 (12.8)	17.9 (15.6)	17.5 (12.8)
Seizure free	5 (23%)	5 (28%)	7 (41%)	8 (42%)

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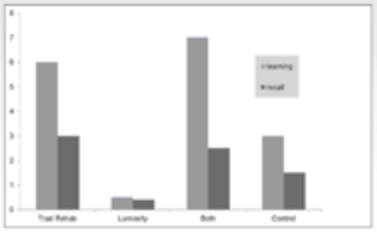
Change in memory scores



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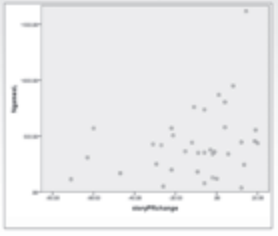
Number of lumosity games & memory change



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Is memory disturbance with hippocampal sclerosis progressive ?

- HS & memory deficits
- ↑ severity ↓ memory
- HS & memory decline?
  - limited evidence
  - selection bias > severer cases
  - longitudinal data lacking
- clinical experience → variable course
- role of interventions?
- more research needed

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In collaboration with

Members of the Department of Clinical & Experimental Epilepsy UCL
past & present
Clinicians at National Hospital for Neurology & Neurosurgery UCLH
past & present
People with epilepsy & their families

with support from

epilepsy society

The Henry Smith Charity

epilepsy action

wellcome trust | Celebrating 75 Extraordinary Years

action medical research for children, for life

Fernando Cendes (Brazil)

IS HIPPOCAMPAL SCLEROSIS PROGRESSIVE? IMAGE FINDINGS

Samuel Wiebe (Canada)

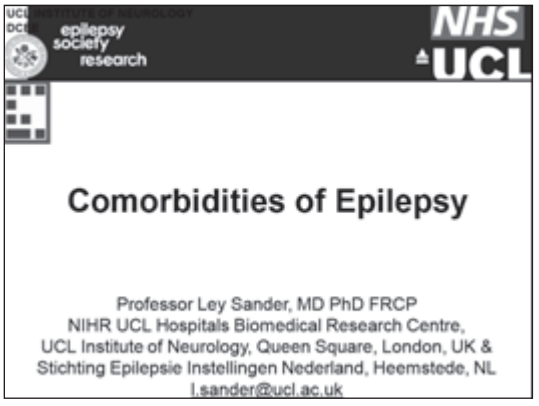
PITFALLS OF IDENTIFYING THE SEIZURE ONSET ZONE IN INTRACRANIAL EEG

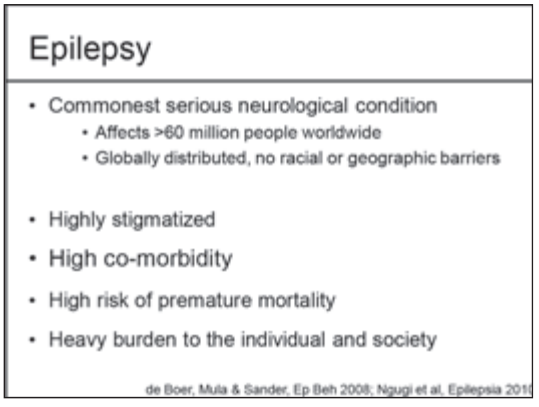
Imad Najm (USA)

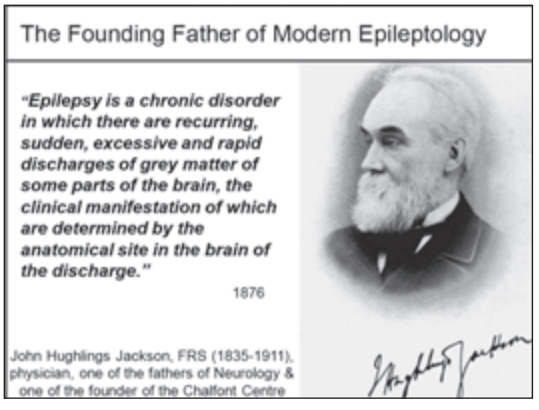
INVASIVE EVALUATIONS IN EPILEPSY: TYPES, COMPLICATIONS AND OUTCOMES

LEY SANDER (ENGLAND)

THE COMORBIDITY OF EPILEPSY AND THE CHANGING FACE OF EPILEPSY







Epilepsy: a Modern Timeline

- Late 1800's: Hughlings-Jackson's work
  - Last paradigm shift!
- Quantum Leaps:
  - 1912: Identification of Pb as an AED
  - 1924 – 1934: EEG use in epilepsy
  - 1950's: "Systematization" of epilepsy surgery
  - Late 1980's: MRI hits epilepsy

What is it?

Epilepsy?

- Just a tendency to have unprovoked seizures
- Result of an underlying problem of the brain, or a system problem
- A symptom-complex not a disease!
- Not like diabetes but more analogous to anaemia
  - Many causes and risk factors
  - Anaemists are history and soon epileptologists will also be!

Current Treatment Paradigm

Currently Available AEDs

Current AED Treatment Paradigm

- Symptomatic
  - Treat seizures & not epilepsy
- Empirical rather than rational!
  - Shoot in the dark & hope it works!
- "Curative", antiepileptogenic or disease-modifying treatment lacking and urgently needed

Kwan & Sander, JNNP 2004

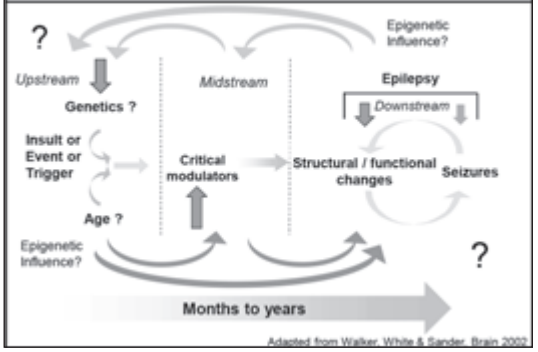
Chance of Remission with AEDs: Decreasing Returns

- About half remit with first AED
- About a third of remainder with second AED
- About 10% of remainder with third AED
- <5% with each drug subsequently

Kwan & Sander, JNNP 2004

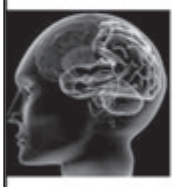
The Epileptogenic Process

Epileptogenic Process: too many Unknowns!



Adapted from Walker, White & Sander, Brain 2002

Cascade of Inflammatory Events in Epilepsy



Vezzani et al., Nature Rev Neurol 2011

The Comorbidity of Epilepsy: Somatic & Psychiatric

First Epilepsy Mantra

- Is it Really Epilepsy, is it? **is it is it is it**
  - Diagnostic accuracy
    - epilepsy can only be diagnosed by taking a history of the index event or by chance observation of a seizure
    - diagnosis is a discretionary judgement dependent on skill and experience, and quality of witness information available
  - 10 - 20% of "chronic" cases referred to tertiary centres do not have epilepsy
  - > 50% of cases suspected or diagnosed in primary care do not have epilepsy

High Prevalence of Co-morbidity

- Co-existence of conditions preceding, co-occurring with, or following diagnosis, related or unrelated to underlying cause
  - Somatic and psychiatric
- Important part of the burden
  - Affects quality of life
  - ⇧ utilization of health service
  - ⇧ financial cost
  - Role in premature mortality
  - Complicates management
- Independent of seizure activity
- What is this telling us ?

Gaitatzis, Sisodiya & Sander Epilepsia 2012, Kadima et al., CDC MMWR 2013

Health-Related Quality of Life

- In Epilepsy adversely affected by:
  - Comorbidity
  - AED adverse effects
  - Seizure frequency & severity
  - Cognitive problems
- In general population affected by:
  - Number of medical conditions (ie, multimorbidity)

Gaitatzis et al. Epilepsia 2012

Increase Utilization of Health Services

- In UK people with epilepsy see their GP more often for:
  - Diabetes
  - Ischemic heart disease
  - Heart failure
  - Hypertension
  - Dementia
  - Stroke
  - Gastro-intestinal bleed
  - Arthritis
- In US people >65 years with new-onset epilepsy (vs. no epilepsy)
  - Five-fold increased life-time risk for admission to hospital
    - Myocardial infarction; gallbladder disease; anemia; angina; alcohol dependence

Gaitatzis et al. Epil Res 2002; Copeland et al. BMC HS Res 2011; Gaitatzis et al. Epilepsia 2012

Seizure-related injuries and seizure frequency (N=3124)

Baker GA et al. Epilepsia, 1997

Increase Utilization of Health Services

- National Comorbidity Survey Replication (US): ≥4 physical comorbidities
  - Epilepsy vs. non-epilepsy population: 41% vs. 15 - 20%
- Comorbidity Survey at Tertiary referral centre (UK):
  - Refractory Epilepsy vs. Non-epilepsy: 53% vs. 15 - 20%*
  - "Community" Epilepsy vs. Non-epilepsy: 32% vs. 15 - 20%*

Kessler et al. Mol Psychiat 2012; Novy et al. 2014

Impacts on Health Costs

- Epilepsy accounts for 1% of total health costs
  - Up to 70% non-epilepsy costs
    - Comorbidity
    - Disability
    - Hospital admissions
- People with epilepsy with comorbidity vs. no comorbidity
    - Four-fold increased rate of hospital admissions
    - 136% higher medical costs

Kotsopoulos et al. Epilepsia 2001; Gaitatzis et al. Ep Res 2002; Lee et al. Ep Behav. 2005; Gaitatzis et al. Epilepsia 2012

Direct and indirect € costs of epilepsy

Example study in Marburg, Germany = 250,000 people

2% of admissions per year due to a fracture or fall

Direct costs	Annual costs	Annual costs per patient
Admissions	1 million	799
Epilepsy Physician costs (family doctor, neurologist)	146,803	113
AED	834,821	642
Diagnostics	39,000	30
Rehabilitation	367,900	283
Other physician costs	152,100	117
Epilepsy-related Comorbidities	479,900	369
Transport costs	2,600	2
Special equipment	10,400	8
Patient fees	55,900	43
Total direct costs	**3.1 million**	**2,406**
Indirects costs (unemployment, sick leave, benefits, etc)	7.7 million	7,738

Strzelczyk A, et al. *Epilepsy Behav* 2012;

Long Term Mortality in those Seizure Free

• 792 people who developed epilepsy over 25 years ago and followed from onset

- Premature mortality persistently ⇧ despite most becoming seizure-free
    - 82% of people seizure-free at 25 years
- Mortality 2.6 fold ⇧ at 20-25 years from diagnosis
    - SMR significantly ⇧ even in those always seizure free
    - Most deaths due to non-epilepsy related causes
    - Role of co-morbidity
- Independent of seizure activity
- What is this telling us ?

Neligan et al. Brain 2011

Mechanisms of Association I

- Spurious
  - Statistically apparent association of unrelated conditions; arise by coincidence or selection bias
- Causal association
  - Same cause for both problems as in perinatal brain insult
- Epilepsy-related (resultant association)
  - Fractures as a result of AED-induced osteoporosis and seizure-related falls
  - Polycystic ovary syndrome associated with SVP or epilepsy effect on LH release

Lipton & Silberstein, Neurol 1994, Gaitatzis et al. Epilepsia 2012

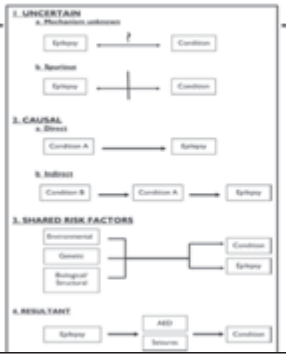
Mechanisms of Association II

- Shared environmental or genetic risk factors
  - Head injury as a common risk factor for both epilepsy & migraine
- Predisposing independent environmental or genetic risk factors
  - Bidirectional relationship: presence of 1 increases risk of another, a brain state that favours both conditions? i.e..

    ▼activity of serotonin, norepinephrine, dopamine, and GABA implicated in epilepsy and depression

Lipton & Silberstein, Neurol 1994, Gaitatzis et al, Epilepsia 2012

Mechanisms of Association



Gaitatzis et al, Epilepsia 2012

Biases and Relations

Gaitatzis et al, Epilepsia 2012

Second Epilepsy Mantra

- Epilepsy and what else?
  - High Prevalence of Co-morbidity
    - ➢Psychiatric
      - ➢Higher risk of depression, anxiety, personality disorders, psychosis
    - ➢Somatic
      - –Higher risk of vascular disorders (CVA, MI, PVD, LVH hypercholesterolaemia), migraine, GI (IBS, Crohn's, bleeding), hypertension, systemic auto immune diseases, dementia, cancer, obstructive sleep apnoea, injuries and fractures

Gaitatzis, Sisodiya & Sander, Epilepsia 2012; Devinsky et al., Epilepsy Curr 2013

Somatic Comorbidity

- Higher risk of vascular disorders (CVA, MI, PVD, LVH hypercholesterolaemia), migraine, hypertension, dementia, cancer, obstructive sleep apnoea, injuries and fractures
  - Diabetes, systemic auto immune diseases
- Epidemiology, 2 major population studies
  - UK General Practice Research Database (GPRD) study
  - Canadian study using nation-wide data from two large national health surveys, the National Population Health Survey and the Community Health Survey

Gaitatzis et al, Epilepsia 2004; Tellez-Zenteno et al; Epilepsia 2005

Somatic Comorbidity I

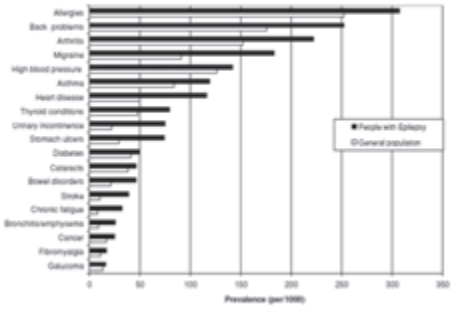
- Infectious, endocrine, neurological, circulatory, respiratory, GI, genito-urinary, dermatological disorders and injuries about 20-60% ▲ in epilepsy
- Brain tumours and meningiomas 55 and 31 times more often in epilepsy
- AD and stroke 7-8 more often in epilepsy
- Migraine in epilepsy higher in men (2.2 vs. 1.6), but usually more frequent in women

Gaitatzis et al, Epilepsia 2004; Tellez-Zenteno et al; Epilepsia 2005

Somatic Comorbidity II

- Urinary incontinence (PR 3.2-4.4), bowel disorders (PR 2.0-3.3), allergies (PR 1.2-1.6) and back problems (1.2-1.4)
- Thyroid conditions, cataracts, asthma, and diabetes higher PRs in one but not both
- Cancer different risk in different populations
  - Increased at severe end of clinical spectrum

Gaitatzis et al, Epilepsia 2004; Tellez-Zenteno et al; Epilepsia 2005; Singh et al, Ep Res 2009



Tellez-Zenteno et al Epilepsy 2005

The Psychiatric Comorbidity of Epilepsy

- May be due to same problem leading to epilepsy and may be compounded by severity and duration of epilepsy
  - may precede, co-occur with or follow diagnosis of epilepsy
- Essential to distinguish between comorbidity versus treatment side effects as they all come together when patient seen

Gaitatzis, Trimble & Sander. Acta Neuro Scand 2004

Psychiatric Disorders in People with Epilepsy

	Epilepsy (Range)	General Population (Range)
Depression	11% – 60%	2% – 4%
Anxiety	19% – 45%	2.5% – 6.5%
Pers. Disorders	18% - 32%	6% - 13%
Psychosis	2% – 8%	0.5% – 0.7%

Kanner 2002

Implications for Current Practice

- Very high prevalence of comorbidity
  - Important part of the burden
  - Major impact on cost
  - Role in premature mortality
- Most clinic assessments about seizure control
  - Complaints may be attributed to AEDs
  - Other conditions may be missed / not reported
  - Physicians usually aim for unifying / single diagnosis
- Epilepsy should increase suspicion that other disorders present
  - High rates of undiagnosed migraine & headaches, pain disorders, sleep problems and celiac disease
  - Other conditions may need treatment→ may help seizure control (ie, OSA, DM1)

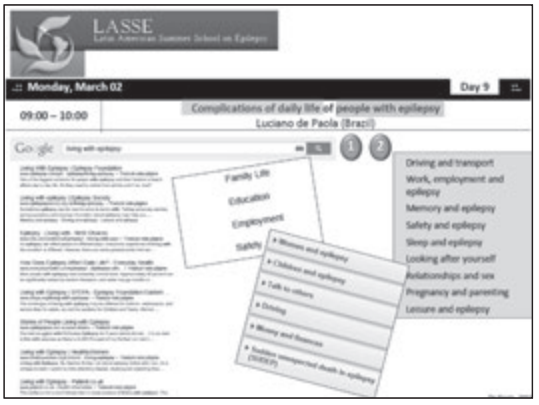
Kessler et al. Mol Psychiat 2012; Novy et al. 2014

Comorbidity of Epilepsy - Conclusions

- Can complicate diagnosis or have adverse prognostic implications
- Should not deter treatment but needs a holistic approach
- Insight into common mechanisms
  - Common genetic predisposition
  - Genetic assessment at earlier stage
- Will have major impact on the future face of epilepsy!

Luciano de Paola (Brazil)

COMPLICATIONS OF DAILY LIFE OF PEOPLE WITH EPILEPSY


LASSE
Latin American Summer School on Epilepsy
Monday, March 02
Day 5
09:00 – 10:00
Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)
Family Life
Education
Employment
Safety
Driving and transport
Work, employment and epilepsy
Memory and epilepsy
Safety and epilepsy
Sleep and epilepsy
Looking after yourself
Relationships and sex
Pregnancy and parenting
Leisure and epilepsy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DRIVING
EDUCATION
RELATIONSHIPS
EMPLOYMENT
SAFETY
LEISURE


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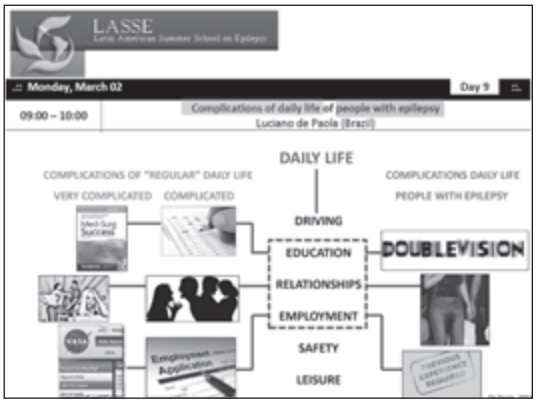
DRIVING
EDUCATION
RELATIONSHIPS
EMPLOYMENT
SAFETY
LEISURE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DAILY LIFE
COMPLICATIONS OF "REGULAR" DAILY LIFE
VERY COMPLICATED
COMPLICATED
COMPLICATIONS DAILY LIFE
PEOPLE WITH EPILEPSY
DRIVING
EDUCATION
RELATIONSHIPS
EMPLOYMENT
SAFETY
LEISURE
DOUBLEVISION

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09:00 – 10:00 — Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

Just about 60-70% of [people] with epilepsy remain seizure-free with very little or no side effects on low to moderate [dose] of well chosen antiepileptic drug. Only this population has little or no limitations on performing daily life activities.

DRIVING
EDUCATION
RELATIONSHIPS
EMPLOYMENT
SAFETY
LEISURE

COMPLICATIONS DAILY LIFE
PEOPLE WITH EPILEPSY
uncontrolled
DOUBLEVISION

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:: Monday, March 02 — Day 5 ::

09:00 – 10:00 — Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

How can they possibly live satisfactory or successfully (even!) with difficult to control seizures? What is it that separates out the ones who can from those who will fail and suffer?

DRIVING
EDUCATION
RELATIONSHIPS
EMPLOYMENT
SAFETY
LEISURE

COMPLICATIONS DAILY LIFE
PEOPLE WITH EPILEPSY
uncontrolled
DOUBLEVISION

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Complications of daily life of people with epilepsy

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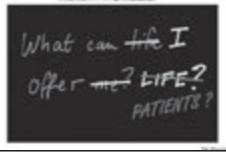
Complications of daily life of people with epilepsy



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Complications of daily life of people with epilepsy

MA, 25 y/o, single, maid

Chief Complain: "got epilepsy"
History: szs started at age 11, "bad feeling & faint". Initial w/u: negative (CT/EEG) still at Peds. Put on phenobarb. Later on CBZ (age 15). Szs are rare (but not off) on 400mg bid, no side effects. Followed once a year.
Remaining personal & family hx: negative

Internal Med (G2) - *his last patient for the day
"same prescription, request labs, to be followed in one year"

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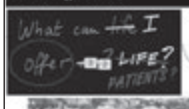

Complications of daily life of people with epilepsy

MA, 25 y/o, single, maid

"Are you working?"
"Are you dating"?
"Do you have friends?"
"Do you exercise?"
"Are you driving?"
"Are you concerned?"
"Do you have any fears?"

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Complications of daily life of people with epilepsy

MA, 25 y/o, single, maid

"Are you working?"
"Are you dating"?
"Do you have friends?"
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Complications of daily life of people with epilepsy

MA, 25 y/o, single, maid

"Are you working?"
"Are you dating"?
"Do you have friends?"
"Do you exercise?"
"Are you driving?"
"Are you concerned?"
"Do you have any fears?"

COMPLIANCE ⇦ EDUCATION ⇨ STIGMA

Q.O.L.

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Complications of daily life of people with epilepsy

MA, 25 y/o, single, maid

Who is responsible for it?

US !!

EDUCATION

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Complications of daily life of people with epilepsy

US !!

Website	Flesch Reading Ease[24]
en.wikipedia.org	39.0
epilepsy.va.gov	42.3
familydoctor.org	48.5
mayoclinic.org	40.9
ninds.nih.gov	33.2
patient.co.uk	47.7
uptodate.com "The Basics"	60.1
uptodate.com "Beyond the Basics"	39.9
Mean	44.0
Standard deviation	8.2

70 = APPROPRIATE (FOR MOST ADULTS)
30-50 = DIFFICULT (UNDERSTAND)

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Complications of daily life of people with epilepsy

DRIVING

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DRIVING & EPILEPSY

:: Monday, March 02 Day 5 ::

Complications of daily life of people with epilepsy

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DRIVING & EPILEPSY

:: Monday, March 02 Day 5 ::

Complications of daily life of people with epilepsy

1st epilepsy related car accident– Thalwitzer, 1906

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DRIVING & EPILEPSY

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Complications of daily life of people with epilepsy

- em March,201 – WHO (192 countries): 2011-2020 Decade for Car Accident Reduction
- 1.3 mi fatalities plus 20-50 mi severe injuries per year
- 90% of the victims: young & developing countries
- National Department of Traffic / USA : 34.000 fatalities (2009)
- CDC (USA), year 2000: 5 mi severely injured (US$ 230 bi)
  - estimate: ~40 mi vehicles / 36 mi licenses / 45.000 fatalities per year
  - 1 vehicle every 6 inhabitants...

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DRIVING & EPILEPSY

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Complications of daily life of people with epilepsy

1. **employment**
2. driving
3. **independence**
4. **social skills & relationships**
5. **"freedom" from AEDs**

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Complications of daily life of people with epilepsy

- not all losses of consciousness are seizures. But around 30% are!
- not all accidents due to medical causes are seizures. But some 20% are!
- not all seizures while driving lead to accidents. But maybe 50% do!
- **drinking** does cause more accidents than seizures!

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Complications of daily life of people with epilepsy

Table 3
Results of the anonymous survey in a reporting state (New Jersey) and a nonreporting state (Arizona).

Question answered	Arizona (n = 97)	New Jersey (n = 62)
Medications affect driving	8%	6%
Counseled by health care provider on seizures and driving law	52%	35%
Crash due to seizure	11%	5%
Drive against medical advice	13%	8%
Driving affected patient-provider evaluation	15%	18%
Patient feels she or he can safely drive	61%	68%

~50%

~60%

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Complications of daily life of people with epilepsy

Socio-demographic and clinical characteristics of Brazilian patients with epilepsy who drive and their association with traffic accidents

~50% drive post dx

~70% during last year!

~59% with active epilepsy!


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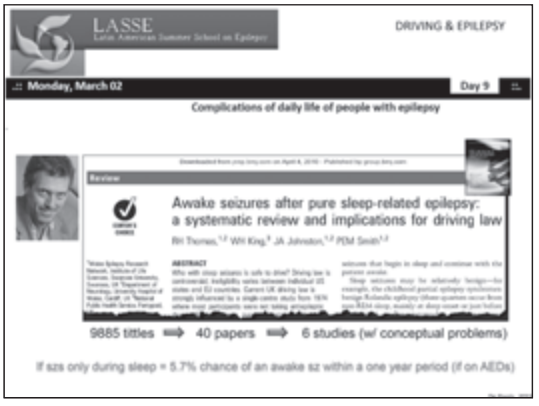
Complications of daily life of people with epilepsy
Generic substitution in the treatment of epilepsy
Case evidence of breakthrough seizures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Day 5
Complications of daily life of people with epilepsy
Review
Awake seizures after pure sleep-related epilepsy: a systematic review and implications for driving law
9885 titles ⇒ 40 papers ⇒ 6 studies (w/ conceptual problems)
If szs only during sleep = 5.7% chance of an awake sz within a one year period (if on AEDs)


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Complications of daily life of people with epilepsy
Diretriz Nacional para Direção de Veículos Automotores por Pessoas com Epilepsia
Resolução 267: O Resgate da Cidadania da Pessoa com Epilepsia


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Day 5
Complications of daily life of people with epilepsy
Epilepsy
RESEARCH PAPER
When is it safe to return to driving following first-ever seizure?

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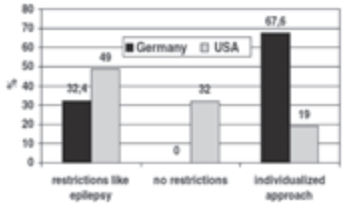
DRIVING & EPILEPSY

:: Monday, March 02 — Day 5 ::

Complications of daily life of people with epilepsy

DRIVING RESTRICTIONS ON PSYCHOGENIC NONEPILEPTIC SEIZURES CASES



Benbadis, 2000
Specht, 2009

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DRIVING & EPILEPSY

:: Monday, March 02 — Day 5 ::

Complications of daily life of people with epilepsy

Conferência SALA 1-CATARATAS

ANÁLISE CRÍTICA DOS ENSAIOS CLÍNICOS PARA TRATAMENTO DE CRISES NÃO EPILÉPTICAS PSICOGÊNICAS

[Palestrante]
WILLIAM CURT LA FRANCE

[Presidente]
LUCIANO DE PAOLA

[Secretária]
LUCIANA PATRIZIA A. DE ANDRADE VALENÇA

"Given the lack of specific protocols , patients diagnosed with PNES should be subjected to the same restrictions applied to patients diagnosed with epilepsy"

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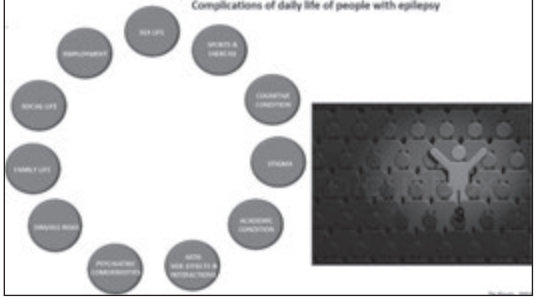
Complications of daily life of people with epilepsy



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Complications of daily life of people with epilepsy

Epilepsy & Behavior

Employment in people with epilepsy from the perspectives of patients, neurologists, and the general population

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Complications of daily life of people with epilepsy

Employment in people with epilepsy from the perspectives of patients, neurologists, and the general population

- 995 patients
- 1042 controls
- 179 neurologists

"where NOT to work?"

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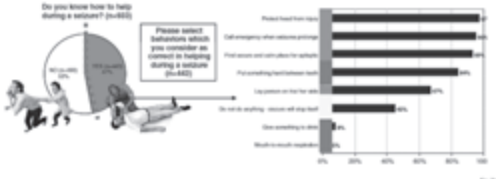
Employment in people with epilepsy from the perspectives of patients, neurologists, and the general population



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:: Monday, March 02 — Day 5 ::

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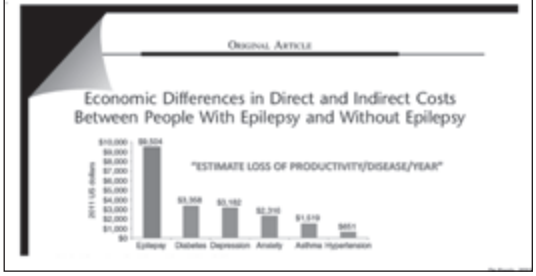
:: Monday, March 02 — Day 5 ::

Complications of daily life of people with epilepsy

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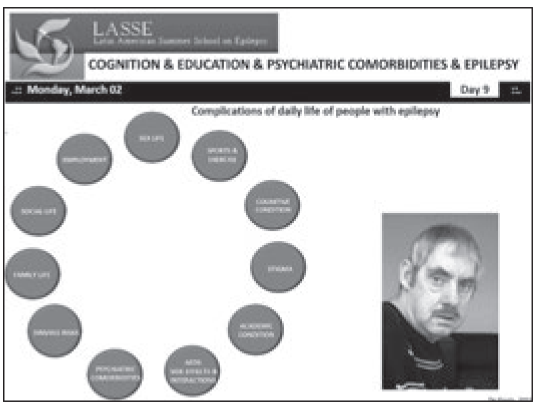
EMPLOYMENT & SOCIAL LIFE & EPILEPSY
Monday, March 02
Day 9
Complications of daily life of people with epilepsy
Epilepsy & Behavior
ELSEVIER
Healthcare utilization and costs in children with stable and uncontrolled epilepsy
Joyce A. Cramer, Zhixiao J. Wang, Eunice Chang, Annette Powers, Ronda Copher, Dasha Cherepanov, Michael S. Broder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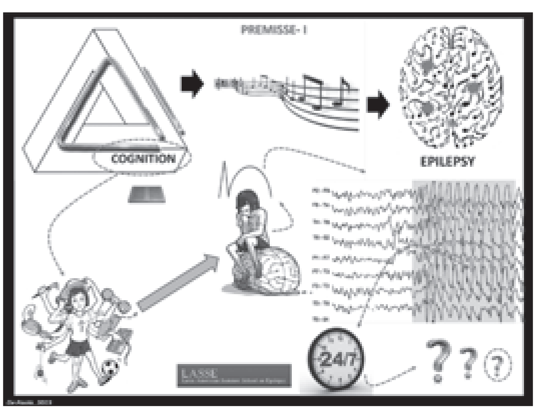
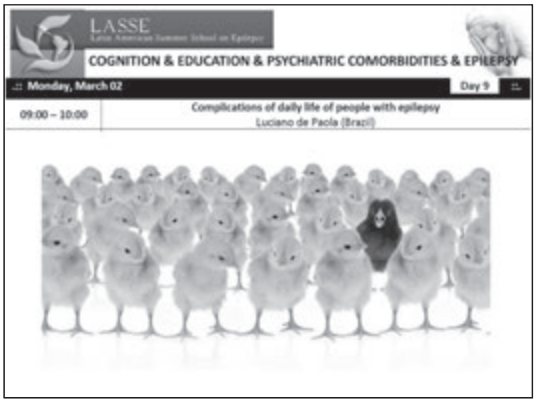
Monday, March 02
Day 9
Complications of daily life of people with epilepsy
SEX LIFE
EMPLOYMENT
SOCIAL LIFE
FAMILY LIFE
STIGMA


PREMISSE- I
COGNITION
EPILEPSY
24/7
LASSE


T1
seizures
T2
cognition
T3
behavior
LASSE


PREMISSE- III
Keighley News
NEWS
Epileptic Lawkholme man attacked in Keighley by gang of five
LASSE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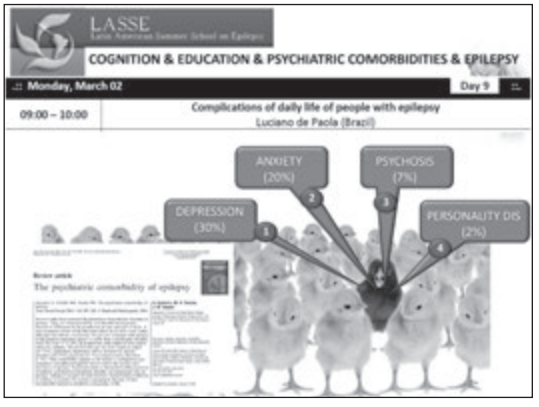
:: Monday, March 02
Day 9
09:00 – 10:00
Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)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09:00 – 10:00
Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)
ANXIETY (20%)
PSYCHOSIS (7%)
DEPRESSION (30%)
PERSONALITY DIS (2%)
The psychiatric comorbidity of epilepsy


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09:00 – 10:00
Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)
Epilepsy & Behavior
Psychiatric comorbidity in patients with pharmacoresistant focal epilepsy and psychiatric outcome after epilepsy surgery
✓ 144 patient evaluations, 84 operated on
✓ 60% psychiatric diagnosis

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:: Monday, March 02 — Day 5 ::

09:00 – 10:00 — Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

Epilepsy & Behavior

Psychiatric comorbidity in patients with pharmacoresistant focal epilepsy and psychiatric outcome after epilepsy surgery

- ✓ 42% affective disorders
- ✓ IDD (interictal dysforic disorder: very common(27%)

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:: Monday, March 02 — Day 5 ::

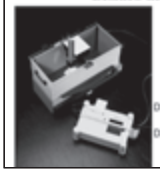
09:00 – 10:00 — Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

BRAIN RESEARCH PROTOCOLS

Protocol

Learned helplessness in the rat: improvements in validity and reliability

Barbara Vollmayr*, Fritz A. Henn



01 – 40 min "sessions", single"inescapable" shocks, 5-15 sec apart

02 – 15 "inescapable" shocks, 60sec "sessions", 24 sec apart

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COGNITION & EDUCATION & PSYCHIATRIC COMORBIDITIES & EPILEPSY

:: Monday, March 02 — Day 5 ::

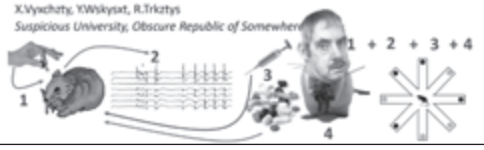
09:00 – 10:00 — Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

PLOS ONE

Where Have I Been? Where Should I Go? Spatial Working Memory If I am a rat with epilepsy, taking a bunch of drugs and feeling like life isn´t worth it living ´til tomorrow!!

X.Vyxchzty, Y.Wskysxt, R.Trkztys

Suspicious University, Obscure Republic of Somewhere



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COGNITION & EDUCATION & PSYCHIATRIC COMORBIDITIES & EPILEPSY

:: Monday, March 02 — Day 5 ::

09:00 – 10:00 — Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

Epilepsy & Behavior

Special Communication

Epilepsy and comorbidities --What are we waiting for?

Miya R. Asato[a,*], Rochelle Caplan[b,†], Bruce P. Hermann[c]

Epilepsy and comorbidities --What are we waiting for?

Miya R. Asato[a,b], Rochelle Caplan[b,c], Bruce P. Hermann[a]

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COGNITION & EDUCATION & PSYCHIATRIC COMORBIDITIES & EPILEPSY

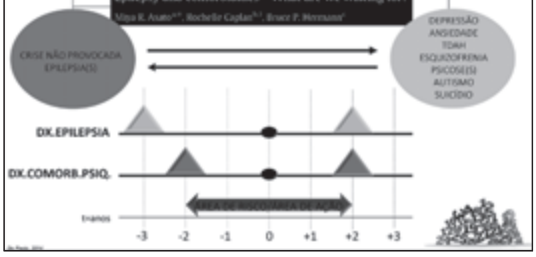
:: Monday, March 02 — Day 9

09:00 – 10:00

Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

Epilepsy and comorbidities --What are we waiting for?

Miya R. Asato[a,b], Rochelle Caplan[b,c], Bruce P. Hermann[a]



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ACCIDENTS & DEATH &EPILEPSY

:: Monday, March 02 — Day 9

Complications of daily life of people with epilepsy

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ACCIDENTS & DEATH &EPILEPSY

:: Monday, March 02 — Day 9

09:00 – 10:00

Complications of daily life of people with epilepsy
Luciano de Paola (Brazil)

Epilepsy & Behavior

Special Communication

Epilepsy across the spectrum: Promoting health and understanding. ☆
A summary of the Institute of Medicine report

Mary Jane England [a], Colleen T. Liverman [b], Andrea M. Schultz [b,*], Lorina M. Strawbridge [b]

" PWE have their lifes shortened by 10 years if the cause is known and by 2 years if the nature of seizures is unknown"

LASSE
Latin American Summer School on Epilepsy

ACCIDENTS & DEATH &EPILEPSY

Accidents in Patients with Epilepsy: Types, Circumstances, and Complications: A European Cohort Study

- 951 children & adults (epilepsy)
- 904 controls)
- prospective
- ~17.000 person-months

- ACCIDENTS

- 199 children & adults (epilepsy)
- 123 controls

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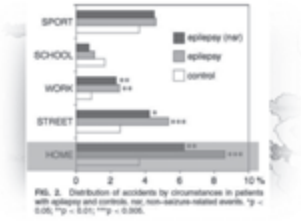

FIG. 2. Distribution of accidents by circumstances in patients with epilepsy and controls. ref, non-seizure-related events. *p < 0.05; **p < 0.01; ***p < 0.005.

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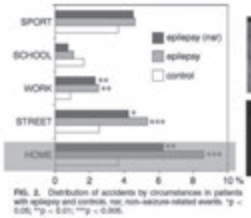

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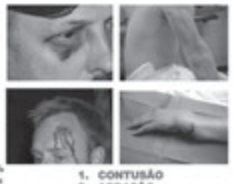

1. CONTUSÃO
2. ABRASÃO
3. FERIDA
4. FRATURA

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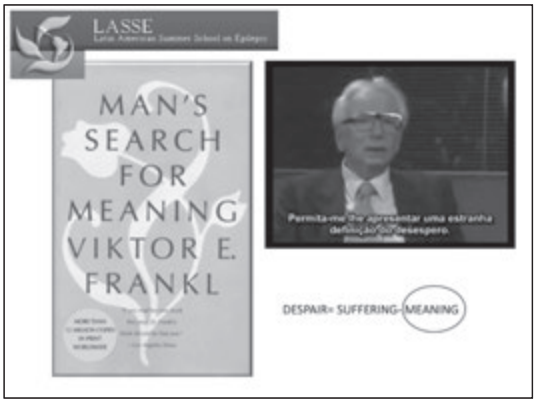
ACCIDENTS & DEATH &EPILEPSY

Seizure

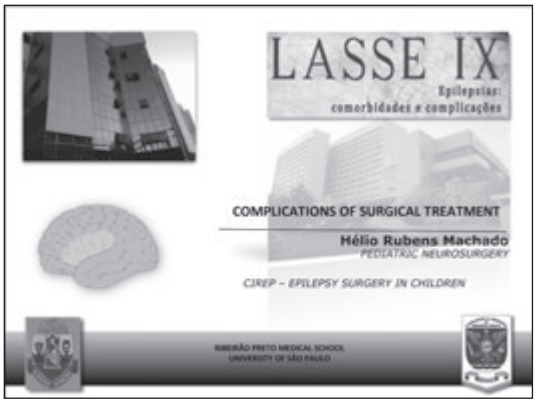
Are we discussing SUDEP?–A retrospective case note analysis


LASSE
MAN'S SEARCH FOR MEANING
VIKTOR E. FRANKL
Permita-me lhe apresentar uma estranha
DESPAIR= SUFFERING-MEANING


LASSE
Permita-me lhe apresentar uma estranha
DESESPERO = SOFRIMENTO - MOTIVO

Helio R. Machado (Brazil)

COMPLICATIONS OF SURGICAL TREATMENT

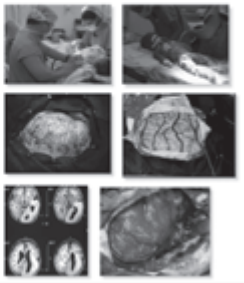


Complexity of pediatric surgery

- Early surgery = major risk

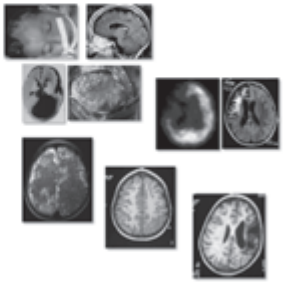
Focal resection	200 – 500 ml
Hemispherectomy	1500 ml
Hemispherotomy	500 ml

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



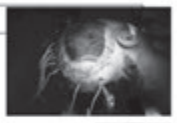
Structural/metabolic epilepsies

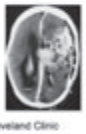
- Sturge Weber syndrome
- Hemimegalencephaly
- Rasmussen encephalitis
- Tuberous Sclerosis complex
- Cortical dysplasia
- Porencephaly



Hemispherotomy

- Risks and reasons for failure
  - Hydrocephalus (22%- Cook et al,04; Lew et al, 13- 23%, risk factor anatomic hemispherectomy or previous surgery)
  - Infection, blood loss, new deficits
  - Mortality (<6%- Di Rocco et al,06)
  - Incomplete disconnection
    - most important cause of failure
    - 17 % (40 pat) persistent sz – 50% sz free (technical failure group) - (Cleveland Clinic series, 2012)
  - Bilateral disease – MCD, Perinatal infarction, Rasmussen

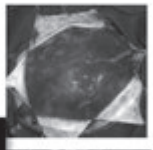


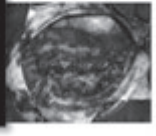


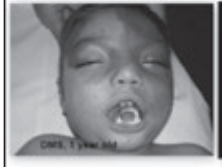
Incomplete disconnection

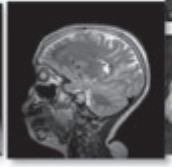
Hemispherotomy

Engel III





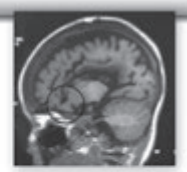


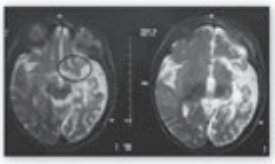


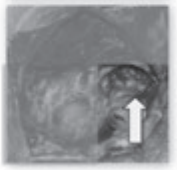
Reoperation

Hemispherotomy

Engel I

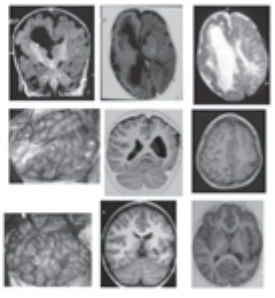




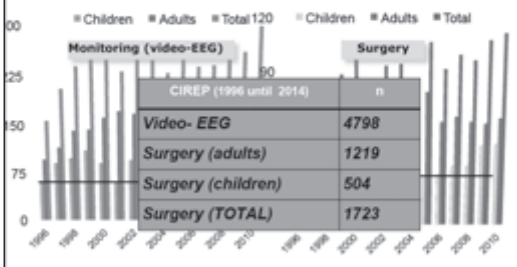


Contralateral MR abnormalities

- LCSL, refractory epilepsy since newborn, surgery at 6 mo and 1y 2 mo age. **ENGEL I**
- LSV, 6y old, sz since 2y, R side hemiparesis, interictal EEG bilateral spikes, video-EEG L hemisphere. **ENGEL I**
- PVSB, 5y old, sz since 2y, daily, refractory, cognitive impairment, R side hemiparesis. **ENGEL I**

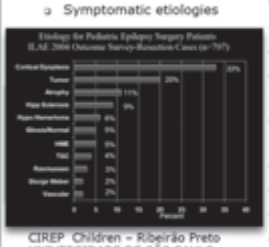


- Presurgical evaluation



CIREP (1996 until 2014)	n
Video- EEG	*4798*
Surgery (adults)	*1219*
Surgery (children)	*504*
Surgery (TOTAL)	*1723*

- Clinical characteristics
  - Symptomatic etiologies



CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

Pathology	
Cortical Dysplasia	152
Gliosis	65
Tumor	63
Mesial temporal sclerosis	57
Rasmussen encephalitis	36
Tuberous sclerosis	21
Porencephaly	20
Difuse atrophy	20
MR normal	9
Sturge-Weber	10
AVM	3

SURGERY

1996 to 2014/ July

Children 485

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

Surgical technique	
Hemispherotomy	118
Temporal Lobectomy	107
Lesionectomy	87
VNS	47
Frontal Lobectomy	30
Posterior(par-occipital) cortex	30
Callosotomy	19
Occipital Lobectomy	15
Multilobar Resection	3
Focal Corticectomy	17
(other)	12
Total	485

Complications of epilepsy surgery in Sweden 1996–2010: a prospective, population-based study

Johan Bjellvi, MD,[1] Roland Flink, MD, PhD,[1] Bertil Rydenhag, MD, PhD,[1] and Kristina Malmgren, MD, PhD[1]

J Neurosurg October 31, 2014

TABLE 1. Complications after 665 surgical procedures

Type of Complication	Major Complications (%)	Minor Complications (%)
Surgical complications		
Infection	1 (<0.1)	16 (2.5)
Hematoma	2 (0.3)	12 (1.8)
DVT/pulmonary embolism	0	5 (0.8)
Hydrocephalus	0	2 (0.3)
CSF leakage	0	4 (0.5)
Brain edema	0	1 (<0.1)
Neurological complications		
Hemichoreoathetosis	12 (1.8)	11 (1.7)
Sensory deficit	1 (<0.1)	2 (0.3)
Hemianopsia	6 (0.1)	1 (<0.1)*
Cranial nerve affects	4 (0.5)	3 (0.5)
Dysphasia	2 (0.3)	9 (1.5)
Other	3 (0.5)†	3
Total	26 (3.9)‡	65 (7.5)§

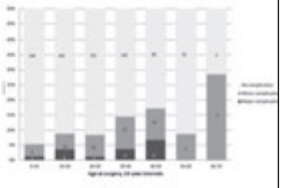


TABLE 3. Complication rates for different surgical procedures in children and adults

Surgical Procedure	No. of Patients	Major Complications (%)	Minor Complications (%)
Pediatric patients			
Temporal lobe resection	122	3 (2.5)	3 (2.5)
Frontal lobe resection	69	3 (4.3)	3 (4.3)
Parietal lobe resection	28	1 (3.6)	1 (10.7)
Occipital lobe resection	15	0	0
Multilobar resection	11	0	1 (9.1)
Hemispherectomy	40	0	3 (7.5)
Callosotomy	24	1 (4.2)	0
Hamartoma disconnection	11	0	1 (9.1)
Multiple subpial transection only	10	0	1 (10)
Stereotactic lesion	1	0	0
Exploration only	1	0	0
Other	1	0	0
Total children	328	8 (2.4)	14 (4.3)
Adult patients			
Temporal lobe resection	401	12 (3.0)	39 (9.7)
Frontal lobe resection	73	1 (1.4)	7 (9.6)
Parietal lobe resection	16	2 (12.5)	2 (12.5)
Occipital lobe resection	17	1 (5.9)	1 (5.9)
Multilobar resection	8	1 (12.5)	1 (12.5)
Hemispherectomy	5	0	1 (20.0)
Callosotomy	7	0	0
Hamartoma disconnection	4	1 (25.0)	0
Multiple subpial transection only	4	0	0
Stereotactic lesion	2	0	0
Exploration only	1	0	0
Other	1	0	0
Total adults	537	18 (3.4)	51 (9.5)

Trends in outcomes, complications, and hospitalization costs for hemispherectomy in the United States for the years 2000–2009

Yimo Lin, Dominic A. Harris, Daniel J. Curry, and Sandi Lam

Epilepsia, 56(1):139–146, 2015
doi: 10.1111/epi.12869

Results: This study identified an estimated total of 552 hospital admissions for hemispherectomy surgery during the years studied in this cohort. The incidence of this procedure increased from 1.2/100,000 admissions in 2000 to 2.2/100,000 in 2009 ($p = 0.05$). Mean age was 6.7 years (range 0–20). There were no significant changes in demographics (age, gender, or race), hospital descriptors (size or type), insurance type, or zip code income quartile. There was a significant increase in total cost, from $42,807 in 2003 to $57,443 in 2009 ($p = 0.015$) (adjusted to 2009 dollars). There were no trends in postoperative complications. In-hospital mortality occurred in five subjects (0.9%). Ventricular shunt placement during hemispherectomy hospitalizations increased over time from 6.7% to 16.5% ($p = 0.056$). Hospitals that performed two or more hemispherectomies yearly had a significantly decreased incidence of in-hospital mortality (odds ratio [OR] 0.08, $p = 0.04$) and an increased incidence of blood transfusion (OR 3.7, $p = 0.01$) compared to hospitals that performed 0–1 procedures a year.

FULL-LENGTH ORIGINAL RESEARCH

Complications of epilepsy surgery: A systematic review of focal surgical resections and invasive EEG monitoring

*Walter J. Hader, †Jose Tellez-Zenteno, *Jenny Metcalfe, ‡Lisbeth Hernandez-Ronquillo, *§Bernard Whiles, ¶Cheri-Ba Kwon, and *§Markella Jette

Summary

Purpose: Underutilization of epilepsy surgery remains a major problem and is in part due to physicians' misconceptions about the risks associated with epilepsy surgery. The purpose of this study was to systematically review the literature on complications of focal epilepsy surgery.

Methods: A literature search was conducted using PubMed and Embase to identify studies examining epilepsy surgery complications. Abstract and full-text review, along with data extraction, was done in duplicate. Minor medical and neurologic complications were defined as those that resolved completely within 3 months of surgery, whereas major complications persisted beyond that time frame. Descriptive statistics were used to report complication proportions.

Key Findings: *Invasive monitoring:* Minor complications were reported in 7.7% of patients, whereas major complications were reported in only 0.6% of patients undergoing invasive monitoring. *Resective surgery:* Minor and major medical complications were reported in 5.1% and 1.8% of patients respectively, most common being cerebrospinal fluid (CSF) leak. Minor neurologic complications occurred in 10.9% of patients and were twice as frequent in children (11.2% vs. 5.5%). Minor visual field defects were most common (13.9%). Major neurologic complications were noted in 4.7% of patients, with the most common being major visual field defects (1.1% overall). Perioperative mortality was uncommon after epilepsy surgery, occurring in only 0.4% of temporal lobe patients (1.3% extratemporal).

Significance: The majority of complications after epilepsy surgery are minor or temporary as they tend to resolve completely. Major permanent neurologic complications remain uncommon. Mortality as a result of epilepsy surgery in the modern era is rare.

KEY WORDS: Surgical risk, Epilepsy, Mortality, Neurologic deficits.

Complications of invasive video-EEG monitoring with subdural grid electrodes

W.M. Blumer, MD, H.H. Morris, MD, E.J. Mosebo, MS, M.T. Kuzniecky, MS, W.E. Hugstrom, MD, M.D. Raj, MD, R.C. Burgess, PhD, D.S. Dinner, MD, N.R. Pokhriyal, DO, J.P. Hahn, MD, P. Kotagal, MD, I. Najm, MD, E. Wyllie, MD, and H.O. Lüders, PhD

NEUROLOGY 2002;58:97-103

Complication	Percentage of patients (%)
Overall	26.3
Infection	12
Meningitis	7
Osteomyelitis	3
Transient deficit	11
Permanent deficit	1.5
Epidural hematoma	2.5
Increased ICP/decreased LOC	2.5
General medical	2

- Review of 198 monitoring sessions over 17 years
- Improvements in grid technology, surgical technique and perioperative care resulted in significant decrease in complications

---

- **Complications related to the surgical procedure in epilepsy surgery in children**
  - Neurological complications
  - General complications
  - Mortality
- Excluded:
  - Reoperations for surgical failures
    - Staged operations
    - Extension of the operation
    - Errors in localization
    - Failure to resect completely a lesion

Neurological complications after epilepsy surgery in children
CIREP - 504 cases

Transient Hemiparesis	
Frontal lobectomy	*2*
Multi-lobar resection	*10*
Posterior quadrantectomy	*2*
Temporal lobectomy	*1*
Callosotomy	*1*
Lesionectomy (motor area)	*6*

Hemianopsia	
Temporal lobectomy	*1*
Lesionectomy	*6*

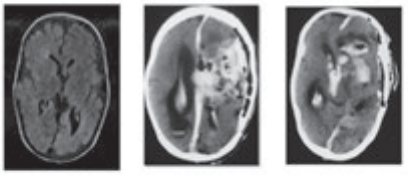
Miscellaneous	
Meningitis	*3*
Sagital sinus laceration	*1*
Epidural hematoma	*1*
Brain hematoma	*1*

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

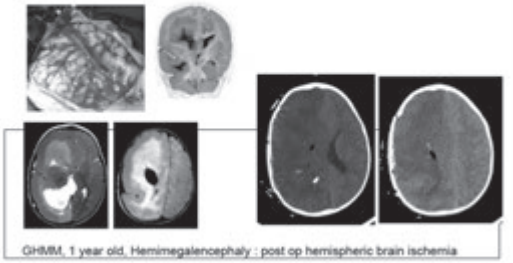
Mortality brain edema/ infarction	
Frontal resection	2
Hemispherotomy	1

Complications of epilepsy surgery - intracranial hematoma after hemispherotomy



SAIR, 1 year old, CD hemispheric, Engel III

Complications of epilepsy surgery - mortality



GHMM, 1 year old, Hemimegalencephaly : post op hemispheric brain ischemia

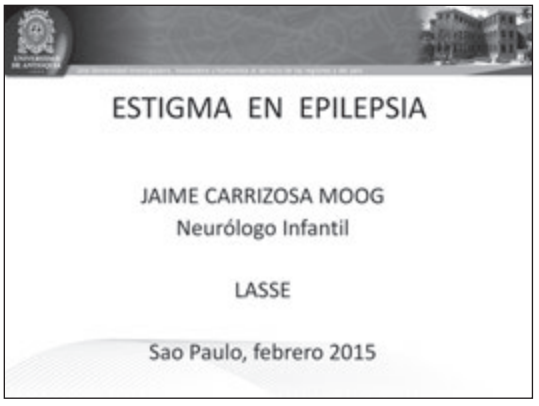
Thank you

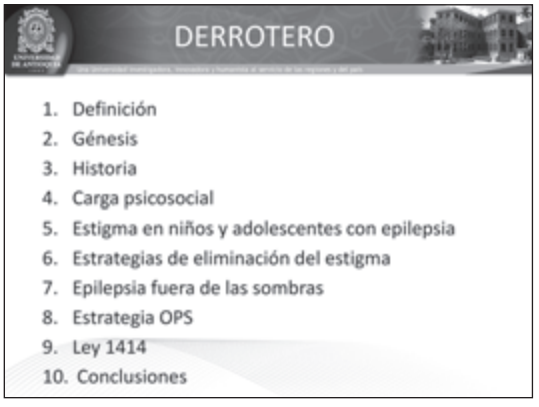
CIREP – CENTER FOR EPILEPSY SURGERY

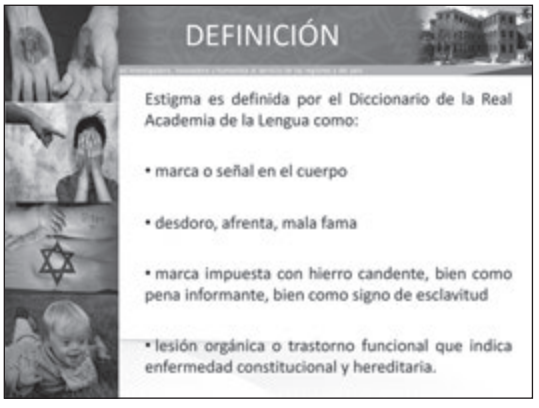
RIBEIRÃO PRETO MEDICAL SCHOOL
UNIVERSITY OF SÃO PAULO

Jaime Carrizosa (Colombia)

STIGMA IN EPILEPSY







DEFINICIÓN

Estigmatizar y desdoro tienen el siguiente significado:

afrentar, ofender, humillar, denostar; poner en aprieto, peligro o lance, capaz de ocasionar vergüenza o deshonra; quitar la fama, honra y estimación a alguien o algo personificado y menoscabo en la reputación, fama o prestigio.

DEFINICIÓN

Lo contrario a estigma sea la estima, que es la consideración y aprecio que se hace de alguien o algo por su calidad y circunstancia.

DEFINICIÓN

En el caso de la epilepsia el estigma se refiere a la magnitud y a la extensión de exclusión social padecidas por las personas con la enfermedad; dicho rechazo se basa en la percepción y el desconocimiento sobre este mal.

Epilepsia 1995; 36(10): 957-959.

DEFINICIÓN

Epilepsy Behaviour 2013; 27: 204 - 205
Epilepsy Behaviour 2002; 3: 521-525
Epilepsy Behaviour 2002; 3:510-520

GÉNESIS DEL ESTIGMA

1. El grupo social establece que algunas diferencias humanas son socialmente relevantes
2. Estas diferencias se asimilan como características negativas
3. Las características negativas promueven el distanciamiento o la separación social
4. Para el afectado ocurre entonces una pérdida de estatus y es sujeto de discriminación
5. El poder político, económico, religioso y social otorgan validez al catalogar una condición específica como estigmatizante

GÉNESIS DEL ESTIGMA

1. Capacidad del fenómeno de ser encubierto
2. Evolución del fenómeno en cuanto se pueda observar por los otros
3. Magnitud de interferencia o perturbación que el fenómeno puede ocasionar en los demás
4. La alteración estética que pudiese generar
5. La etiología del fenómeno como congénito, traumático o intencional
6. El riesgo o peligro que los demás puedan padecer por ese fenómeno

GÉNESIS DEL ESTIGMA

En epilepsia la ausencia de predictibilidad, su visualización en público y la falta de control, da una sensación subjetiva social de imperfección y por lo tanto posible de discriminación.

También se ha de tener en cuenta la capacidad individual de sobrellevar la enfermedad, ya sea ocultándola, revelándola, identificándose con ella o legitimándola para promover luchas legales y sociales.

Lancet Neurol 2005;4:171-178

HISTORIA DEL ESTIGMA EN EPILEPSIA

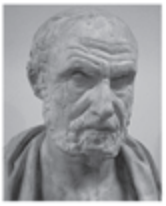
El Código de Hammurabi, hacia 1780 AC, estableció normas de convivencia social, que afectaban directamente a las personas con epilepsia.

Es así como los afectados por este mal no se les permitía ni contraer matrimonio, ni testificar en los estrados judiciales.

También está descrito que el comprador de un esclavo, podía devolverlo con indemnización total, si este presentaba crisis convulsivas en el primer mes después de la adquisición.

Epilepsia 2003;44:512-514.

HISTORIA DEL ESTIGMA EN EPILEPSIA



Hipócrates (400AC) desmitifica la epilepsia, al referir que los brujos, charlatanes, magos y la superstición popular quedaban en entredicho por calificar esta enfermedad como sagrada, aduciendo que los dioses no pueden crear seres impuros y por lo tanto no se les puede culpar de su causalidad.

Él desmitifica este padecimiento al desvirtuar su carácter mágico o divino y la ubica como una enfermedad del cerebro, cuya consistencia se ve afectada por el sol, el frío y los vientos.

Epilepsia 1995;36(1):58-511.

HISTORIA DEL ESTIGMA EN EPILEPSIA

Cultura romana

Así lo describe de forma magistral Margaret George en su libro Memorias de Cleopatra, cuando posterior a una crisis epiléptica padecida por Julio Cesar este le contesta:

"Quieres decir si me hablan los dioses? No. O si lo hacen me conceden tan poco tiempo para oirlos antes de perder el conocimiento, que al despertar no recuerdo nada."

Por cierto se denominan crisis comiciales a los episodios epilépticos, porque cuando Julio Cesar padecia las convulsiones se suspendían las elecciones o los comicios en el senado romano.

George M. Memorias de Cleopatra
1ra ed Barcelona
Libendáplex,S.L.1997(184-185)

HISTORIA DEL ESTIGMA EN EPILEPSIA

El evangelio según San Marcos hace una descripción más detallada de la crisis epiléptica:

"Maestro, aquí te he traído a mi hijo, pues tiene un espíritu que lo ha dejado mudo: dondequiera que se encuentra, el espíritu lo agarra y lo tira al suelo; y echa espuma por la boca, le rechinan los dientes y se queda tieso. He pedido a tus discípulos que le saquen ese espíritu, pero no han podido."

Jesús contestó:

"Gente sin fe! ¿Hasta cuándo tendré que estar con ustedes? ¿Hasta cuándo tendré que soportarlos?

Entonces llevaron al muchacho ante Jesús. Pero cuando el espíritu vio a Jesús, hizo que le diera un ataque al muchacho, el cual cayó al suelo revolcándose y echando espuma por la boca. Jesús le preguntó al padre:

"¿Desde cuándo le sucede esto?"

El padre contestó:

"Desde que era niño. Y muchas veces ese espíritu lo ha arrojado al fuego y al agua, para matarlo. Así que, si puedes hacer algo, ten compasión de nosotros y ayúdanos."

HISTORIA DEL ESTIGMA EN EPILEPSIA

Sandro Botticelli La Transfiguración

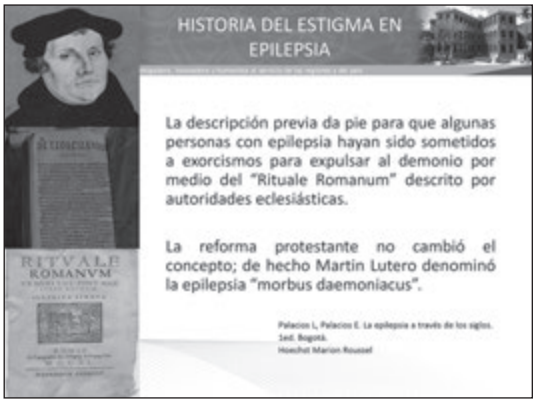
Al ver Jesús que se estaba reuniendo mucha gente, reprendió al espíritu impuro, diciendo:

"Espíritu mudo y sordo, yo te ordeno que salgas de este muchacho y que no vuelvas a entrar en él."

El espíritu gritó, e hizo que le diera otro ataque al muchacho. Luego salió de él, dejándolo como muerto, de modo que muchos decían que, en efecto, estaba muerto. Pero Jesús lo levantó y el muchacho se puso de pie y Jesús les contestó:

"A esta clase de demonios solamente se la puede expulsar por medio de la oración."

El nuevo testamento.
Bogotá: Texto Sociedades Bíblicas Unidas 1994(65)


HISTORIA DEL ESTIGMA EN EPILEPSIA
La descripción previa da pie para que algunas personas con epilepsia hayan sido sometidos a exorcismos para expulsar al demonio por medio del "Rituale Romanum" descrito por autoridades eclesiásticas.
La reforma protestante no cambió el concepto; de hecho Martin Lutero denominó la epilepsia "morbus daemoniacus".
Palacios L, Palacios E. La epilepsia a través de los siglos. 1ed. Bogotá.
Hoechst Marion Roussel


HISTORIA DEL ESTIGMA EN EPILEPSIA
El Talmud advierte a los padres sobre el riesgo que conlleva la infracción de las reglas religiosas sobre las relaciones sexuales, que podrían terminar en un fruto con epilepsia.


HISTORIA DEL ESTIGMA EN EPILEPSIA
AVICENA
En algunas culturas de religión musulmana en el norte y occidente de África, se considera que las personas con epilepsia están poseídas por el *jinn*, que acorde al gran médico islámico Ibn Sina-Avicena (989-1037), son seres gaseosos y transparentes, creados mucho antes de Adán.
En Marruecos los afectados se les denomina *mejnum* o sea afectados por un *jinni* y en Senegal son vistos como bajo la influencia del *djinné*.
Epilepsia 1999;40: 382-386


HISTORIA DEL ESTIGMA EN EPILEPSIA
Los incas también relacionaba la epilepsia con aspectos sobrenaturales o tanatológicos.
Se conocen algunos nombres indígenas de la epilepsia como:
aya huayra que significa viento de la muerte, *huanuy oncuy* y *ovaní keshia* corresponde a enfermedad de la muerte, o *llanquí oncuy* que traduce enfermedad de la tristeza.

HISTORIA DEL ESTIGMA EN EPILEPSIA

Ilustración de Poma de Ayala: esposa de Capac Yupanqui en una crisis epiléptica

No obstante la connotación negativa de los nombres para esta enfermedad, se deduce de algunas crónicas de Molina y Arriaga, que los incas consideraban a las personas afectadas cercanas a fuerzas sobrenaturales.

Describe Arriaga, que cuando los experimentados chamanes observaban padecer a una persona de crisis comiciales, indicaba entonces que los *huancas* o fuerzas intangibles, querían que el sujeto se convirtiera en sacerdote.

HISTORIA DEL ESTIGMA EN EPILEPSIA

Los aztecas tenían dos deidades llamadas *Cihuapiltin* y *Teocihuapiltin*.

La primera fue una niña que murió en su infancia y que cuando ya convertida en diosa, hacia su aparición en determinados días del calendario, afectando a los niños con la epilepsia.

Para evitar dicha maldición, las familias resguardaban a sus hijos en esas fechas.

El segundo dios diseminaba enfermedades crónicas tanto en niños como en adultos y entre ellas la epilepsia.

Epilepsia 2007;48:886-893.

HISTORIA DEL ESTIGMA EN EPILEPSIA

La etnia maya Tzeltal considera la epilepsia como una lesión padecida por el espíritu animal que reside en el hombre, después de una lucha entre los espíritus que sirven el bien y el mal. La enfermedad es percibida como un maleficio.

La tribu Kayamurá en Brasil tiene la creencia de que el ánima de un armadillo cazado por el hombre, es el causante de las convulsiones repetitivas.

En Bolivia, los indígenas Chipayas, denominan la epilepsia *tukuri* y su causa se debe a embrujos que penetran la cabeza por la nariz con el viento. El tukuri se trata con rituales denominados *willoncha*, en las que las infusiones de insectos disecados y de sangre de aves alivia el padecimiento.

Epilepsia 1999;40:1041-1046

HISTORIA DEL ESTIGMA EN EPILEPSIA

Ley para la Prevención de Descendencia con Enfermedades Genéticas, 14 DE Julio de 1933

Esterilización de personas con enfermedades hereditarias:

Retardo mental
Esquizofrenia
Depresión
Epilepsia
Ceguera
Sordera
Alcoholismo
Deformidades físicas

HIGIENE RACIAL
EUGENECIA RACIAL

HISTORIA DEL ESTIGMA EN EPILEPSIA

OPERACIÓN T4

OPERACIÓN EUTANASIA

SOLUCIÓN FINAL

HISTORIA DEL ESTIGMA EN EPILEPSIA

En Estados Unidos les estaba prohibido a las personas con epilepsia contraer matrimonio en 18 estados hasta 1956, y el último estado en abolir esta ley lo hizo solo hasta 1980.

Hasta 1970 era aún legal en el mismo país, negarle el ingreso a las personas con crisis a algunos restaurantes, teatros, centros recreativos y otros espacios públicos.

HISTORIA DEL ESTIGMA EN EPILEPSIA

La Corte Suprema de Estados Unidos afirma en 1987 en la ley sobre discapacidad, que la historia de la epilepsia es un ejemplo fehaciente, de cómo el temor, más que la limitación propia de la enfermedad, es el principal argumento para la discriminación.

Arch Neurol 2002;59:1031-1036

HISTORIA DEL ESTIGMA EN EPILEPSIA

Ley No. 48 de 1920 Sobre Inmigración y Extranjería

Marco Fidel Suarez

ARTÍCULO 7o. No se permite entrar al territorio de la República a los extranjeros que se hallen en algunos de los siguientes casos:

b) A los que sufran de enajenación mental, comprendiendo en ello también la demencia, la manía, la parálisis general, a los alcoholizados crónicos, a los atáxicos, a los epilépticos; a los idiotas; a los cretinos; a los baldados a quienes su lesión impide el trabajo. En el caso de que en algunas familias de inmigrantes, algún miembro de ella estuviere comprendido en la prohibición de este inciso, la respectiva autoridad podrá permitir su entrada siempre que los demás miembros de la familia sean personas sanas y útiles.

Decreto 1060 de 1933

ARTÍCULO 1o. Para que un Cónsul pueda visar el pasaporte de un extranjero, … debe tener a la vista los siguientes documentos: …c) Certificado expedido por un médico de reconocida honorabilidad, en el que conste que el extranjero no padece enfermedades graves, crónicas o contagiosas, o enfermedades mentales, y que no es alcoholizado crónico, atáxico, epiléptico y que no usa drogas heroicas o tóxicas.

Enrique Olaya Herrera

Alfonso López Pumarejo

ESTIGMA Y CARGA PSICOSOCIAL

Los grupos sociales formulan reglas, cuya infracción constituye una desviación o perversión, y al aplicar estas normas a personas con reseñas particulares se les catalogará como intrusos, perturbados o perturbadores.

La "desviación" no es un hecho que la persona haya realizado por su cuenta, sino el resultado de la aplicación de estas normas sociales al "ofensor".

Estas leyes generadoras de estigma fueron y han sido aplicadas para situaciones como escolarización, empleo, matrimonio, conducción, deporte, recreación entre otros.

Epilepsia 2002;43: S26-S30
Epilepsy Behaviour 2005;6:488-503.

ESTIGMA Y CARGA PSICOSOCIAL

Actitudes:

- Familiares: carga moral, vergüenza
- Compañeros: rechazo, sobrenombres
- Personal salud: desconocimiento
- Medios de comunicación: desconocimiento, tergiversación
- Sociedad: religión, cultura, educación

Epilepsy Behaviour 2007;10: 69-76.
Epilepsy Behaviour 2007; 1:71-76.

IMPACTO DE LA EPILEPSIA

FACTORES:

1. SINDROME EPILÉPTICO
2. TRATAMIENTO
3. AMBIENTE PSICOSOCIAL

PERCEPCION DE NIÑOS Y ADOLESCENTES

29 niños de cuarto grado de una escuela de Sao Paulo, refirieron que se trataba de una enfermedad de morderse la lengua, que podía ser mortal, contagiosa, seria y debida a una lesión del cerebro.

Los autores interpretan estos resultados como un prejuicio del "inconsciente colectivo" frente a la epilepsia y consideran necesario realizar proyectos de educación para cambiar esos conceptos.

Epilepsy Behaviour 2005;6:601-603

PERCEPCION DE NIÑOS Y ADOLESCENTES

Una encuesta a 1213 estudiantes de décimo grado

- 98% tenían algún tipo de noción sobre la epilepsia
- 60% la relacionaban con alteraciones mentales
- 63% piensan que es un impedimento para vivir una vida plena
- 41% un obstáculo para llevar un matrimonio
- 57% no tendrían una actividad sexual normales
- 40% afectaría el proceso de aprendizaje
- 45% de los estudiantes perciben que la sociedad discrimina a las personas afectadas.

Epilepsy Behaviour 2006;6:492-497

PERCEPCIÓN DE NIÑOS Y ADOLESCENTES

19441 adolescentes norteamericanos arroja los hallazgos :

- 52% sabían algo sobre epilepsia
- 51% reconocen que no es contagiosa
- menos de un tercio tendrían un noviazgo con una persona con epilepsia
- 40% los consideran individuos peligrosos
- 76% podrían ser sujetos de mofa

Epilepsy Behaviour 2002;3:368-375

PERCEPCIÓN DE ESTUDIANTES

Estudiantes universitarios de Toronto:

- 98% consentirían un matrimonio con una persona afectada
- desconocen la prevalencia de la enfermedad en Canadá
- desconocen que los medicamentos anticonvulsivos pueden ser teratogénicos

Epilepsia 2002;43:652-658

PERCEPCIÓN DE ESTUDIANTES

969 estudiantes secundaria en Nigeria:

- 39,3% causas espirituales
- 64,9% no tendría un amigo con epilepsia
- 69,1% no jugaría con alguien con epilepsia
- 84,2% no se casaría con una persona con epilepsia

Seizure 2013; 22: 299-302

PERCEPCIÓN EN NIÑOS Y ADOLESCENTES CON EPILEPSIA

En una encuesta realizada a 64 adolescentes:

- 60% no ve afectada la relación con amistades, 69% asisten a citas con amigos o a fiestas
- 89% considera tener una vida sexual normal
- 30% se siente afectado por algún tipo de estigma, 53% mantiene su enfermedad en secreto
- 70% nunca habla de su enfermedad en público

Epilepsy Behaviour 2005;7:664-678
Epilepsia 1999;40:1715-1720

PERCEPCIÓN EN NIÑOS Y ADOLESCENTES CON EPILEPSIA

Existe una relación entre baja autoestima y el estigma, más entre los adolescentes entre 12 a 16 años

Mayor posibilidad de estigma:

- severidad de las crisis
- frecuencia de las crisis
- mayor frecuencia de consultas médicas
- mayor duración de la enfermedad
- clase socioeconómica baja
- asistencia a centros de educación especial
- síntomas depresivos
- pobre autoconcepto y actitud negativa.

Una actitud positiva, menor preocupación o ansiedad y las actividades de esparcimiento en familia se relacionan con menor estigma

Epilepsy Behaviour 2003;4:112-117

ESTIGMA EN NIÑOS Y ADOLESCENTES CON EPILEPSIA

Estudio compara 70 adolescentes con epilepsia con un grupo de pares sanos encuentra:

- Mayor frecuencia depresión
- Anhedonia
- Ansiedad social

La falta de conocimiento sobre su enfermedad produce mayores síntomas de depresión y ansiedad social, así como una menor autoestima

Epilepsy Behaviour 2005;6:556-562

ESTIGMA EN NIÑOS Y ADOLESCENTES CON EPILEPSIA

Los niños y adolescentes con epilepsia refractaria pueden verse más afectados por:

- la estigmatización al sentir una fatiga física excesiva como barrera para lograr los objetivos académicos y sociales;
- padecer una angustia emocional e intermitente por lo impredecible de las crisis;
- sufrir de un aislamiento social más intenso por su condición y sobrellevar un aprendizaje interrumpido y fragmentado durante su vida escolar.

Lo anterior obligaría a desarrollar estrategias clínicas y pedagógicas para mitigar esas experiencias negativas

Epilepsy Behaviour 2005;7:664-678

PERCEPCIÓN DE PROFESORES

Investigación realizada a 284 profesores de Tailandia:

- 38% no conocen la enfermedad
- 29,9% la relacionan con trastornos mentales
- 46,6% consideran que no tiene cura o control
- 38% perciben la inteligencia de los enfermos por debajo del promedio normal
- 36,3% no permitirían el matrimonio de uno de sus hijos con una persona afectada

Epilepsia 1999;40:497-501

PERCEPCIÓN DE PROFESORES

En Croacia 216 docentes:
54,2% consideran que la epilepsia se relaciona con alteraciones de conducta
53,2% con un desempeño académico desfavorable

321 profesores griegos:
64% consideran que la epilepsia no causa problemas de comportamiento
y un 67% consideran que pueden ser buenos estudiantes

Tanto maestros croatas como griegos consideran la epilepsia en sus estudiantes como un factor generador de inseguridad y ansiedad en el aula de clase en un 30,6% y 50% respectivamente

Epilepsy Behaviour 2005;6:179-186 / Epilepsy Behaviour 2003;4:142-145

PERCEPCION DE MÉDICOS

Encuesta realizada a 107 médicos generales de Australia:

la existencia de una personalidad epiléptica en un 19%,
la imposibilidad de llevar una vida normal en 32%,
la existencia de discriminación laboral en un 65%,
la necesidad de evitar trabajo físico pesado 28%
la necesidad de evitar trabajo mental extenuantes 19%
que el público general no los entiende 83%
o que el público general les tiene miedo en un 57%

Epilepsia 1994; 35: 1244-1247

PERCEPCION DE MÉDICOS

El estudio realizado en 182 galenos en Tenerife, reporta que existen prejuicio y desconocimiento sobre las capacidades de las personas con epilepsia en cuanto a su comportamiento, habilidad para relacionarse, rendimiento laboral y académico y control emocional

Rev Neurol 2005;40:385-393

PERCEPCION DE MÉDICOS

En Zambia una entrevista realizada a 276 profesionales del área de la salud arroja estos datos sobre el concepto sobre la epilepsia:

20% no permitirían un lazo matrimonial con una persona con esta enfermedad, el 75% consideran que existe rechazo familiar y en un 88,8% comunitario o social de las personas con epilepsia

Epilepsy Behaviour 2007;10:111-119

ESTRATEGIAS DE APOYO

El apoyo familiar incondicional refuerza la confidencialidad y genera seguridad en la persona afectada.

La comunicación intrafamiliar abierta y sincera reafirma los patrones de convivencia saludables para sobrellevar la enfermedad en el diario vivir.

Las familias comprometidas buscan de manera activa y crítica los mejores servicios médicos y sociales; están permanentemente disponibles en el acompañamiento y en la toma de decisiones sociales y de atención en salud.

ESTRATEGIAS DE APOYO

Se hace énfasis en que si se va a revelar su condición, el ambiente debe ser propicio y preparado, para evitar sorpresas y decepciones innecesarias.

Se debe reforzar la convicción de que se poseen habilidades innatas, que su condición física o mental específica no los hace menos personas, y que por lo tanto esta misma no constituye una limitante automática para gozar de todos los beneficios legales y sociales

Lancet Neurol 2005;4:171-178

ESTRATEGIAS DE APOYO

•Los grupos de apoyo refuerzan la seguridad, la autonomía, la autoestima, la confidencialidad y la autoimagen, propiciando un mayor éxito en la vida laboral y social.

•El conocimiento sobre la enfermedad reduce el temor asociado con las crisis comiciales, evita prácticas potencialmente autolesivas y aminora el impacto psicológico de la enfermedad y del tratamiento.

•La educación pública sobre la epilepsia puede disminuir las tendencias de la estigmatización y mejorar por ende la calidad de vida de las personas afectadas.

Epilepsy Behaviour 2002, 3: S2-S2
Epilepsy Behaviour 2002; 3: S21-S25
Seizure 2013, 22: 179-184

Epilepsia fuera de las sombras

ILAE, IBE, OMS:

La epilepsia es el trastorno neurológico crónico más común y serio, que afecta todas las razas, edades, clases sociales y países.

La epilepsia produce una enorme carga física, mental, social, económica y laboral, debido en principio a su desconocimiento, prejuicio y estigmatización.

Este problema es mayor en los países en desarrollo, donde habitan el 85% de las personas con epilepsia y de los que se conoce que cerca de 50 millones no reciben, ni diagnóstico, ni tratamientos acertados ni oportunos.

Epilepsia 2001;42:136-149 / Epilepsy Behaviour 2000;1:S3-S8 / Epilepsia 2001;42:1094-1100

POLÍTICAS PUBLICAS

Declaración de Santiago de Chile para América Latina en el 2000

Se convino como día mundial de la epilepsia el SEGUNDO LUNES de FEBRERO, promoviendo actividades de reflexión y promoción.

International Epilepsy Day

Estrategia y plan de acción sobre la epilepsia OPS- OMS

Programa Ampliado Para Las Américas

Área estratégica 1: Programas y legislación para la atención de las personas con epilepsia y la protección de sus derechos humanos.

Área estratégica 2: Red de servicios de salud para la atención de las personas con epilepsia, con énfasis en la atención primaria de salud y la provisión de fármacos.

Área estratégica 3: Educación y concientización de la población, incluidas las personas con epilepsia y sus familias.

Área estratégica 4: Fortalecimiento de la capacidad para producir, evaluar y utilizar la información sobre la epilepsia

Estrategia y plan de acción sobre la epilepsia OPS- OMS

Objetivo 3.3: Reducir el estigma, la discriminación y la exclusión social que rodea a las personas con epilepsia.

Actividades a nivel regional

3.3.1 Elaborar, a nivel regional, un modelo de trabajo y materiales educativos que puedan ser usados o adaptados por los países para llevar adelante campañas contra el estigma, la discriminación y la exclusión social que rodea a las personas con epilepsia.

Actividades a nivel nacional

3.3.2 Formular y ejecutar una campaña regular y sistemática de lucha contra el estigma y la discriminación de las personas con epilepsia.

LEY 1414 DE NOVIEMBRE DE 2010

"Por la cual se establecen medidas especiales de protección para las personas que padecen epilepsia, se dictan los principios y lineamientos para su atención integral"

Artículo 3°. Prohibición. Se prohíbe a cada persona natural o jurídica, que realice o propicie cualquier acto discriminatorio, en cualquiera de sus formas, que con ocasión a su enfermedad, se presente contra la persona que padezca de epilepsia.

Artículo 4°. Principios se tendrán como principios rectores de la protección integral de las personas que padecen epilepsia:

Igualdad: El Gobierno Nacional, promoverá las condiciones para que la igualdad sea real y efectiva y adoptara medidas en favor de todas las personas que padezcan epilepsia, para que estas gocen de los mismos derechos, libertades y oportunidades sin ninguna discriminación.

LEY 1414 DE NOVIEMBRE DE 2010

Artículo 16. Las personas con epilepsia estarán protegidas de toda forma de explotación y regulación discriminatoria, abusiva o de naturaleza denigrante.

CONCLUSIONES

- Es importante resaltar como las circunstancias ajenas a la mera explicación biológica de una enfermedad, pueden producir una connotación que puede ser más grave que la misma enfermedad.
- Es el caso del estigma en epilepsia, que históricamente por factores culturales, religiosos, antropológicos y sociales, limitan a las personas afectadas en el ejercicio pleno de sus derechos.

CONCLUSIONES

- En la atención de las personas con epilepsia, no solo es necesario el avance en la experticia y tecnología para un diagnóstico acertado, las investigaciones para el desarrollo farmacológico o quirúrgico, sino el combate de los aspectos psicosociales, que limitan además el libre desarrollo de las personas.

- Se han realizado grandes esfuerzos institucionales y gubernamentales para combatir el estigma, pero se requiere de un mayor conocimiento sobre el tema en los profesionales que trabajan con personas con epilepsia; ellos son los que en su trabajo individual van a ayudar a "sacar de la sombra a la persona con epilepsia" y reinsertarla en la sociedad como un ciudadano con plenos derechos y deberes.

CONCLUSIONES

- El proceso de enseñanza aprendizaje de la epilepsia, requiere de un concepto más amplio en su abordaje, liberándose del contexto netamente biológico.

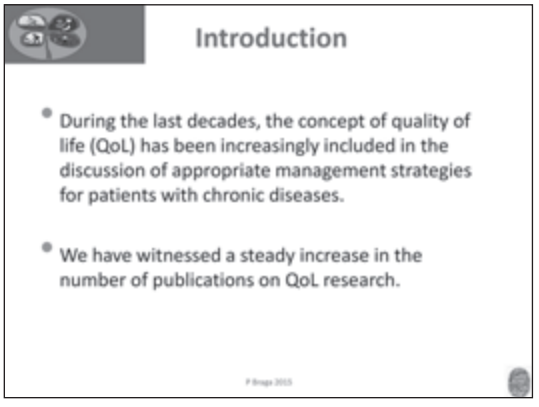
- En nuestro medio es un terreno inexplorado para la investigación interdisciplinaria, pertinente y con posibilidad de impacto social.

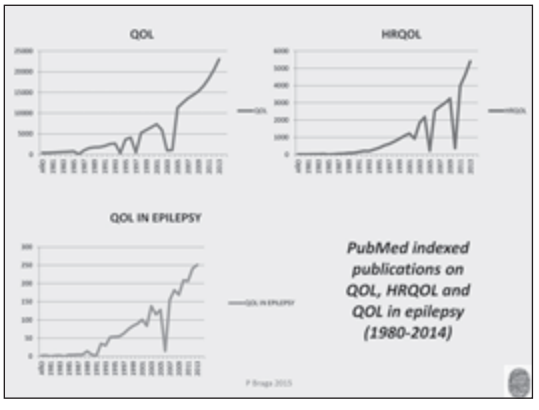
- La conformación de grupos de apoyo y de educación a la comunidad, puede ayudar en la reducción del estigma.

GRACIAS

Patricia Braga (Uruguay)

QUALITY OF LIFE IN EPILEPSY: OUTCOME MEASURE OR TARGET FOR TREATMENT?





QoL research story

1. **Development of quality-of-life instruments**, that had to be valid (measured what they were supposed to) and reproducible (consistent over time in stable patients).
2. Incorporation of **quality of life as an outcome measure** in cancer clinical trials (comparison of treatments where differences in response or survival were modest but toxicities significant).
3. **Evaluation of impact**: at what extent has formal quality-of-life measurement influenced individual patient decision-making or treatment policies?

(Levine, Ganz. 2002)

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What do we understand by QoL?

- QOL is a theoretical construction that evaluates perceptions of the degree of wellbeing, both in different areas (social, mental, physical) and at different levels (personal, community).
- In practice, everyone has an implicit understanding of what it is "quality of life", with significant variation among individuals, including patients, health care providers and researchers.

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QoL: Concepts

- Calman hypothesis (1984): **quality of life measures the difference, or the gap, at a particular period of time between the hopes and expectations of the individual and that individual's present experiences**. (temporal dynamics)
- WHO, 1995: "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment"

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What is known on HRQoL in epilepsy patients?

Development of measurement tools and investigation of QoL determinants in different health related conditions have been the central aspects of most papers, including those focused on epilepsy related QoL.

It has been stated that evaluation of QoL in PWE should explore:

- physical or somatic complaints
- cognitive functioning
- psychological state
- social performance
- economical aspects
- adaptive abilities to cope with seizures and treatment

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Presence, frequency and/or severity of seizures were the expected determinants.

Adverse effects of antiepileptic drugs were also an expected finding.

Results on the role of the type of epilepsy are heterogeneous.

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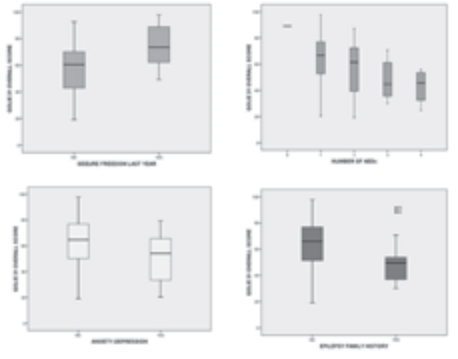

QoL prediction: multiple regression analysis

Resumen del modelo

Independent Variables	R ª	Estadísticos de cambio				
		ΔR²	Cambio en F	gl1	gl2	Sig. del cambio en F
FAMILY HISTORY	,069	,069	5,165	1	92	,025
EPILEPSY DURATION	,113	,044	5,148	1	91	,015
SEIZURE FREE	,231	,118	13,798	1	90	,000
NUMBER OF AEDs	,289	,058	7,309	1	89	,008
ANXIETY-DEPRESSION	,348	,059	7,575	1	88	,007

a. Variables predictoras: (Constante), DURACION EPILEPSIA

b. Variables predictoras: (Constante), DURACION EPILEPSIA, AF EPI FUA NUCLEAR

c. Variables predictoras: (Constante), DURACION EPILEPSIA, AF EPI FUA NUCLEAR, SIN CRISIS ULTIMO ANO

d. Variables predictoras: (Constante), DURACION EPILEPSIA, AF EPI FUA NUCLEAR, SIN CRISIS ULTIMO ANO, NUMERO OAEs

e. Variables predictoras: (Constante), DURACION EPILEPSIA, AF EPI FUA NUCLEAR, SIN CRISIS ULTIMO ANO, NUMERO OAEs, ANSIDEPR

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Anxiety and **depression** clearly

influence self perception of wellbeing,
have relevant impact on QOL in this population,
although the specificity of this finding is debatable.

A significant part of the variation in QOL measures cannot be attributed to the aforementioned factors, so most of its determinants remain unknown.

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Role of comorbidities in QOL in epilepsy

- Somatic and psychiatric comorbidities should be considered while evaluating QOL in PWE.
- Many neurological diseases or conditions underlying the patients' seizures may create cognitive and physical impairments (CNS neoplasm, head injury, stroke, encephalopathy).
- Psychiatric disturbances and psychological profiles may specifically impact on the results of any self-reported test exploring QOL.
- The interpretation of some authors on depression as the most relevant factor affecting QOL in PWE should be considered with caution.

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Taylor RS et al. Predictors of health related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia. 2011 Dec;52(12):2168-80.

- 93 HRQoL studies were included.
- Increases in seizure frequency, seizure severity, level of depression, level of anxiety and presence of comorbidity were strongly associated with reduced HRQoL.
- In the 53 multivariate studies, age, gender, marital status, type of seizure, age at diagnosis, and duration of epilepsy did not appear to be associated with HRQoL
- Predictive influence of educational and employment status, number of antiepileptic drugs (AEDs) and AED side effects was unclear.
- Findings were consistent across individuals whether refractory or seizures controlled or managed by AEDs.

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Refractory epilepsy

61% of the variance in QOLIE-31 scores explained by the final model

Adverse Effects of medication and **depressive symptoms** are far more important determinants of HRQoL than seizures themselves.

When seizure freedom cannot be achieved, addressing depressive comorbidity and reducing the burden of AED toxicity is likely to be far more beneficial than interventions aimed at reducing the frequency of seizures.

Luoni C et al. Epilepsia. 2011 Dec;52(12):2181-91.

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QoL after Epilepsy Surgery

Neurology 1999.

- Positive effect of ATL on patient concerns and HRQOL
- mood, employment, driving ability, and AED use are important postoperative predictors of HRQOL.

Sajobi TT et al. Changes in quality of life after epilepsy surgery: the role of reprioritization response shift. Epilepsia 2014.

The relative importance analysis showed a statistically significant increase over time in the importance of social function, but a significant decrease in the relative importance of seizure worry.

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How do we interpret these results?

Which is the gold standard considered to validate these tools?

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- Lack of a gold standard diagnostic test, inter-individual and transcultural differences, as well as the multiplicity of factors involved in QoL are yet unsolved challenges for researchers on the topic.
- In Latin America, there is some experience with internationally used questionnaires as SF36 or QOLIE 31, which do show similar results worldwide, while some locally developed tools try to capture and identify additional factors and regional specificities.

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Best tool to be determined...

Qual Life Res. 1995 Apr;4(2):115-34.

- The SF-36 Role Physical scale best discriminated among groups differing in disease severity.
- Generic measures, especially measures of social and role functioning and mental health, were best at differentiating groups of patients differing in symptom impact.

Epilepsy Behav. 2013 Dec;29(3):497-503.

- Because of its structure, the WHOQOL-Bref gives clinicians an indication not only of HRQoL but also of Subjective Well-Being, a broader construct.
- A sample of men with epilepsy rated their global QoL as highly as the control group.

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Stigma and QOL

- Recent reports state that PWE continue suffering from both felt and perceived stigma worldwide.
- Higher perceived stigma associated to lower QOL scores.
- It is acknowledged that the very first step towards felt stigma happens during the consultation when the diagnosis of epilepsy is given.
- Medical students and physicians were demonstrated to express almost as much stigmatizing feelings or attitudes as the general population.

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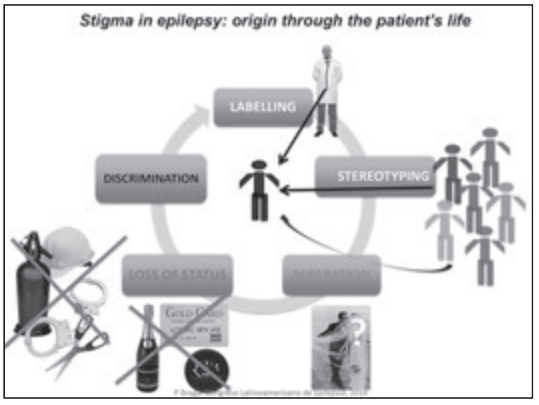
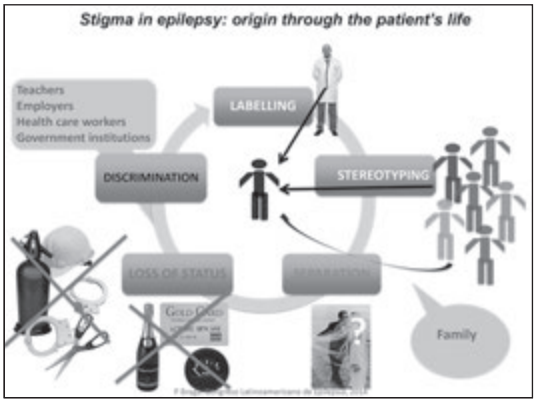
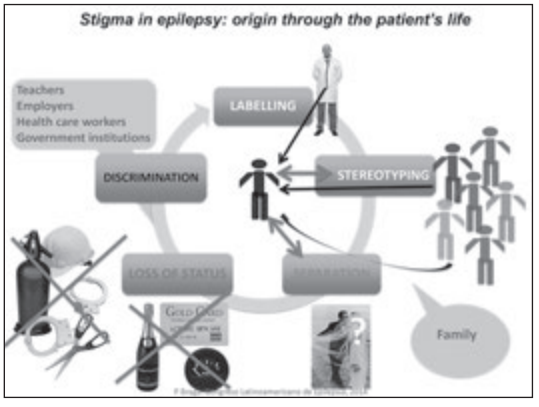

Stigma in epilepsy: origin through the patient's life
LABELLING
STEREOTYPING
DISCRIMINATION
LOSS OF STATUS


Stigma in epilepsy: origin through the patient's life
Teachers
Employers
Health care workers
Government institutions
LABELLING
STEREOTYPING
DISCRIMINATION
LOSS OF STATUS
Family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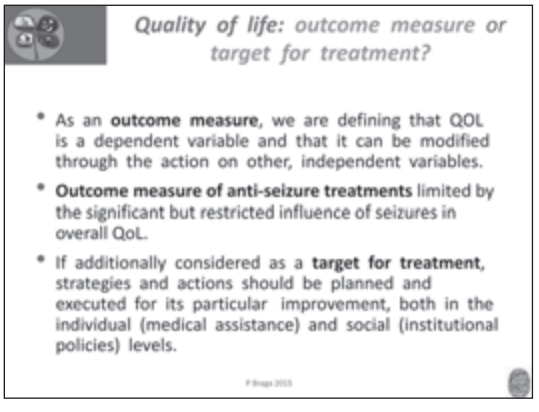
Quality of life: outcome measure or target for treatment?
As an outcome measure, we are defining that QOL is a dependent variable and that it can be modified through the action on other, independent variables.
Outcome measure of anti-seizure treatments limited by the significant but restricted influence of seizures in overall QoL.
If additionally considered as a target for treatment, strategies and actions should be planned and executed for its particular improvement, both in the individual (medical assistance) and social (institutional policies) levels.

- Seizure suppression has always been, and treatment of depression has recently become, clear goals of our treatment in the epilepsy clinic.
- Support, academic and professional orientation and anti-stigma measures may be additional components of our treatment algorithms.
- Anti-stigma campaigns should undoubtedly include physicians, health care workers and providers.

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Anti-Stigma policies
Controversies & Perspectives

- **Teaching patients**
  - **Would you show them videos of their own seizures?**
- **To promote peer-interaction through self-help groups**
  - **Would you attend a self-help group if you had a chronic condition as epilepsy?**
- **Information on academic/professional perspectives**
  - **Timing?**
- **Schooling**
  - **"tolerance" in performance?**
- **Disability benefits vs institutional discrimination**

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HR-QoL measures
Controversies & Perspectives

- It has been suggested that the narrow focus of epilepsy-specific HRQoL questionnaires may give only a partial picture of a patient's quality of life
- In addition, by concentrating on the negative aspects of life with epilepsy, these instruments may distract both the patient and the clinician from what is good about life, denying the patient the benefits of 'positive psychology' and the clinician the opportunity to build the patient's resilience.

Greenway L et al. Epilepsy Behav 2013.

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Strategies with potential impact on QoL

- According to identified determinants of HRQoL in children within the first year postdiagnosis of epilepsy, **psychosocial interventions** to improve child HRQOL outcomes should address:
  - parenting and family stress,
  - fears and concerns,
  - overall coping,
  - anticipatory guidance on managing epilepsy,
  - adherence
  - perceived stigma

  Wu YP et al. Epilepsia 2014.
- **Telemedicine:** A Malaysian controlled study showed that being employed and receiving an additional SMS-based epilepsy education programme emerged as the significant predictors of good HRQoL among PWE.

  Lua PL, Neni WS. Qual Life Res. 2013.

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So...

How does the measurement of quality of life in groups of patients and the administration of a quality-of-life questionnaire to an individual patient ultimately improve care?

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Conclusions

- **In addition to the selection of the best anti-seizure treatment for each patient, remember to explore other QOL determinants that you could help to improve.**
- **Appropriate selection of QOL evaluation tool, according to your goals**
- **Be aware of transcultural differences**
- **Consider patients' perspective**
- **Remember on temporal shifts**

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...improving our focus

Quality of life in epilepsy:

A major goal in the management of epilepsy patients in clinical practice

Uwe Heineman (Germany)

PHARMACORESISTANCE

Pharmacoresistance

Uwe Heinemann
Inst Neurophysiologie
Charité Universitätsmedizin Berlin

Definition of Pharmacoresistance

- Persistance of unacceptable seizures despite reasonable pharmacotherapy
- Trial of monotherapy using two different first line agents plus the addition of a newer antiepileptic drug
- Drugs used to the highest tolerable dosage

Potential Causes of Pharmacoresistance

- Genetics
- Toxic side effects of drugs (Allergy)
- Severity of seizures (Encephalopathies?)
- Tolerance to drug therapy (Periphery, central)
- Open blood brain barrier
- Changes in drug transportation mechanisms
- Alterations in drug targets: cellular vs network

Genetic Factors

- PHT responders and non responders in a rat model

  Cramer (1998) Epilepsia 37:1046-53
- Responders and non responders can exist in human diseases
- Modifier genes act in combination with causative genes Schauwecker (2002) Prog Brain Res 135:139-48
- May play a role in the degree of progression associated with symptomatic epilepsy

  Regesta (1999) Epilepsy Res 34:109-12

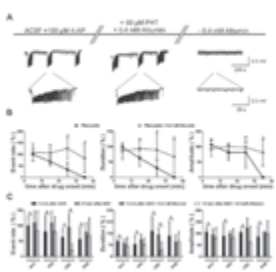
Tolerance to Drug Therapy

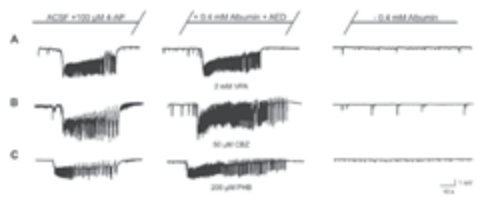
- This may lead to loss of therapeutic efficacy
- Induction of liver enzymes
- Augmented tonic inhibition in CNS structures can lead to reduced sensitivity to GABAergic drugs (homeostatic plasticity)
- General experience with GABAergic drugs: Withdrawal seizures also in non epileptic patients
  eg. Barbiturate and alcohol withdrawal
- Indication of tolerance: Withdrawal seizures

Open blood brain barrier

- Human brain tissue often shows higher tissue drug concentrations than expected from plasma CSF coefficient (Rambeck et al, Sandow et al in prep.)
- Exsudation of plasma proteins
- Many AEDs transported in blood by transporter proteins eg albumine

Open blood brain barrier





Unbound and bound AED levels in Albumin containing solution*

Table 1. Unbound and bound AED levels in albumin-containing solutions

Albumin-containing solution[a]	Detection Method	Total AED, µg/ml	Unbound AED, µg/ml
50 µM PHT	HPLC	13.85	2.1
2 mM VPA	RIA	251.53	202.6
50 µM CBZ	HPLC	13.05	4.63
200 µM PHB	HPLC	48.65	30.65

Unbound AED levels in ACSF containing 0.4 mM albumin and 100 µM 4-AP. Free PHT, VPA, CBZ, and PHB levels were detected by HPLC and radioimmunoassay. Although the free VPA concentration remained almost unchanged, free PHT, CBZ, and PHB concentrations decreased in albumin-containing ACSF compared to albumin-free ACSF.
[a]0.4 mM BSA + 100 µM 4-AP + ACSF.

Salar et al Epilepsia 2014

Immunological Changes

- Associations in literature of focal epilepsies with GAD Ab, GluR3 Ab and anti-GM1 Ab

  Peltola (2002) Neurology 55:46-50
- GluR3 Ab not specific for Rasmussens Syndrome, more prevalent in focal epilepsy

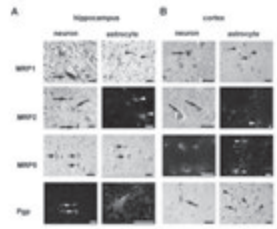
  Wiendl (2001) Neurology 37:1511-4
- Role of immunological factors is uncertain in pathogenesis and mechanisms of pharmacoresistance
- Opening of blood brain barrier may lead to extracellular accumulation of AED transport proteins and thereby to buffering of AEDs

Drug transport inhibitors

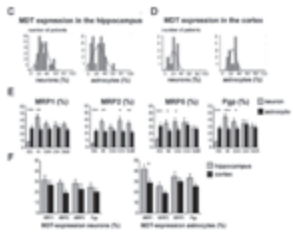
- Inhibitors of P-glycoprotein (PGP)
  - First generation
    - e.g., verapamil, cyclosporin A
      - other effects besides PGP-inhibition
- Inhibitors of multidrug resistance-associated protein (MRP)

  e.g., probenecid (inhibits MRP1 & MRP2), MK-571

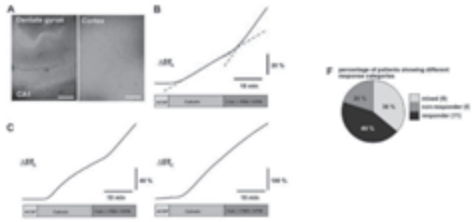
Ectopic expression of drug transporters



Ectopic expression of drug transporters



Efficacy of drug transporters can be determined



Kovacs et al, J Neurosci. Methods, in press

Critique of the Transporter hypothesis

- Unclear which molecules are really transported
- Expression is not identical to function
- Slice from pharmacoresistant patients do not have a blood brain barrier- yet induced seizure like events are pharmacoresitant

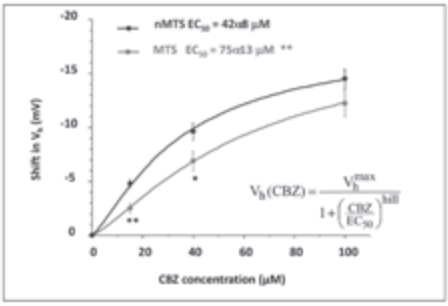
Alterations in Drug Targets

- GABA receptors subunit changes - different subunits mediate tonic and phasic conductances

  Stell (2002) J Neurosci 22:RC223
- Potassium-chloride cotransporter KCC2 - up regulation associated with increased seizures

  Reid (2001) Neurosci lett 308:29-32
- Sodium channel - gain of function mutation in sodium channel gene Scn2a results in seizures may lead to reduced CBZ and PHT sensitivity

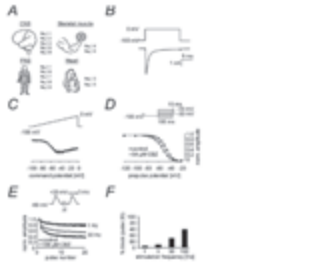
  Kearney(2001) Neuroscience 102:307-17



V_h = ss inactivation of Na^+

Courtesy of W. J. Wadman, Amsterdam

Alterations in drug targets

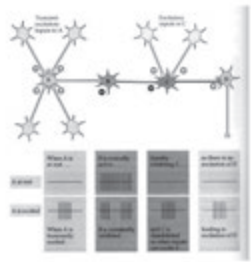


Beck and Remy Brain 2006

Alterations in drug targets

- Subunit change
- Modification by kinases
- Modification by spermines
- Modification by relationship between effects on inhibitory and on principal cells

Changes in connectivity



Function of Inhibitory Micronetworks Is Spared by Na Channel-Acting Anticonvulsant Drugs (Pothman et al J Neurosci, 2014)

- High frequency discharges of interneurones insensitive to CBZ
- Feedforward and feed back inhibition unaltered
- Extends to chronic epileptic tissue
- Verified with voltage sensiticve dye recordings

Animal models

- Models which mimick disease or aspects of disease
- Homologue, Isomorph and predictive
- Homologue: equal cause, equal symptoms, equal therapeutic option ???
- Isomorph: equal symptoms and equal therapy option (status models)
- Predictive: equal therapy option (eg electroconvulsion, low Mg, PTZ etc)

Most epilepsy or seizure models are only predictive and we do not yet take to the full extent the construction of homologous models into account except for many genetic models)

Many of our models represent rare causes of epilepsy

Present models of pharmacoresistance lack validation ie that a drug acting in these models treats pharmacoresistant patients successfully

Current Animal Models of Drug Resistant Epilepsy

- PHT resistant kindled rats
- Picrotoxin kindled animals (Shandra, 1996 Epilepsia)
- NPY -/- mice (short survival)
- Pilocarpine treated rat entorhinal cortex slices
- *in vitro* model of drug resistant status epilepticus incl intact hippocampus
- in vitro models of drug resistent seizures

None of the known models of pharmacoresitance in animals has predictive value

Yet we can learn from these models

and hope that a drug active in such models helps also pharmacoresistant patients

Aquired pharmacoresistance: Limbic status epilepticus

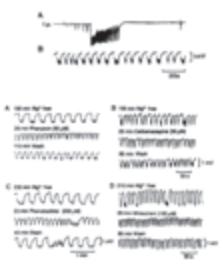
- When not controlled within first hrs often pharmacoresistent
- Leading to cell death
- Leading to secondary epileptogenesis also in man

Patient History

- Female 2nd year medical student
- First seizures end of november
- Visit to neuorlogist: no treatment
- More seizures
- Admission to hospital on chrismas eve with suspicion of encephalitis
- Develops status during night
- Treatment delayed
- Status is pharmacoreistant, progressive edema and eventual disappearance of hippocampus
- Memory loss

Pharmacoresistant status epilepticus

- Inducible by low Mg or 4-AP in acute slices from entorhinal cortex
- Intact hippocampus before P9
- In vitro models of seizure like events are usually pharmacosensitive unless…
- exposure to low Mg or 4-AP for prolonged time or in combination with GABA A receptor antagonists

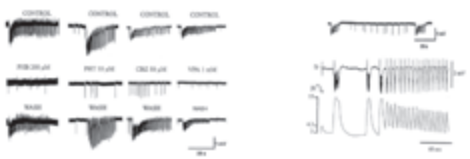


Zhang et al 1993

In vitro models of seizure like events

4-AP induced seizure like events

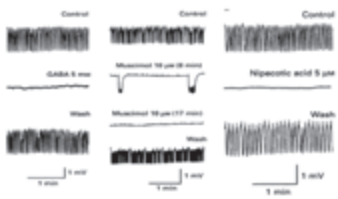
4-AP plus bicuculline



Late recurrent discharges induced by 4-AP plus bicu are pharmacoresistant

Brückner et al 1998

Drug refractory status epilepticus: Dysfunction of GABA-R or GABA release ?

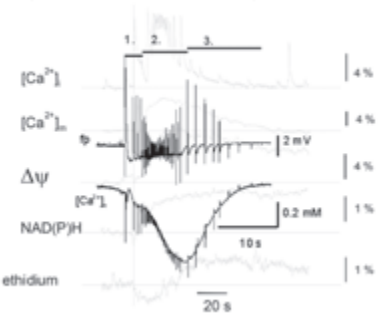


GABA uptake blockers and GABA agonists block late recurrent discharges while non competitive agonists of GABA do not block this activity

Pfeiffer et al 1998

Changes of mitochondrial membrane potential during seizure-like events in hippocampal slice cultures

Changes in mitochondrial parameters during seizure-like events



Kovacs et al Eur J Neuroscience 2001

Changes of mitochondrial membrane potential during seizure-like events in hippocampal slice cultures

Changes in mitochondrial parameters during subsequent seizure-like events

Decline of SLE-associated NADH synthesis

Increase of free radical formation

Decline of SLE-associated $\Delta\Psi$ changes

Comparison of a protonofor (fccp) induced and SLE-associated $\Delta\Psi$ changes

Trnasient to pharmacoresitant staus perhaps prevented by free radical scavengers

Kovacs et al J Neurophysiol 2002

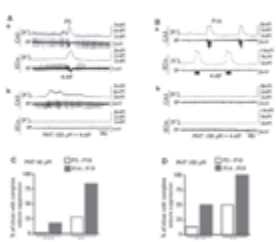
Lessons from status epilepticus studies in slices from healthy rodents

- Recurrent seizure like events result in mitochondrial dysfunction and production of free radicals.
- Alterations in mitochondrial function at time of transition from drug sensitive to refractory state.
- GABA release is impaired.
- Internalization of GABA receptors as well.

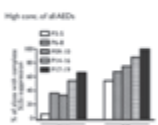
Seizures in babies are frequently pharmacoresistant

- In the intact hippocampal preparation untill P9
- May be related to depolarizing GABA functions and high expression of NKCC1
- Switch in other brain regions later

Pharmacoresistance in young hippocampal tissue

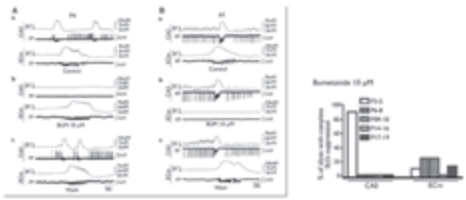


Applies to VPA, CBZ, PB,



Wahab et al Epilepsia 2011

Effects of the NKCC1 blocker bumetanide

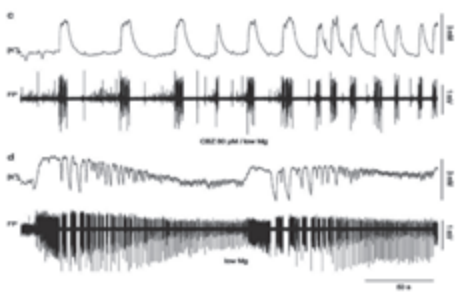


Wahab et al Epilepsia 2011

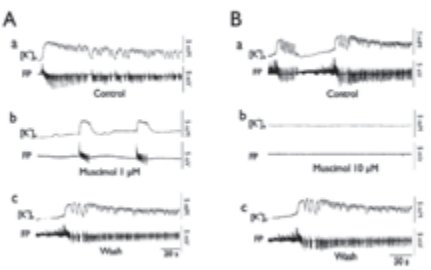
Slice cultures

- Survive for up to 8 weeks
- Mimick some of the reorganisation known from TLE patients
- Have reduced seizure threshold
- Are under some conditions spontaneously active and can present with seizure like events

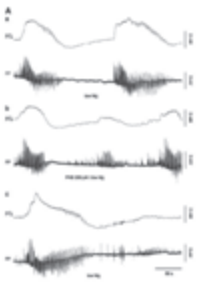
6Organotypic slice cultures share reorganisation with models of TLE: contribution to pharmacoresistance?



6. Not dependent on gross dysfunction of GABA A receptors



Insensitive to CBZ, VPA, PHT but also to midazolam and PHB



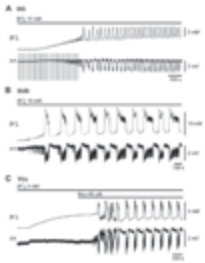
However, stimulus dependent afterdischarges are drug sensitive in the same tissue: Severity of seizures

Albus et al, Brit J Pharm 2007
Wahab et al Epilepsia 2010

Slice cultures

- Slice cultures become pharmacoreistant
- When treated with hypoosmolar solutions and exposed to frequent alcalosis

Induction of seizure like events in slices from patients with pharmacoresistant epilepsy

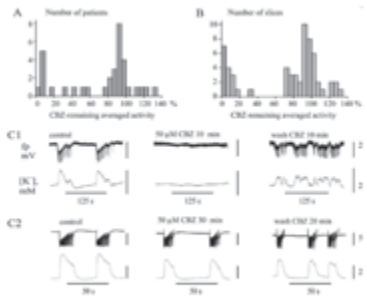


What does not work in human tissue slices GABA antagonists, low Ca, ultra rarely spontaneous seizure like events

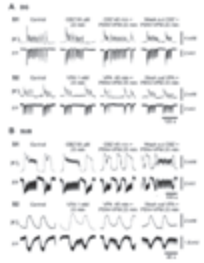
What works sometimes: 4-AP, low Mg

What works frequently: elevation of potassium concentration in combination with xxxx

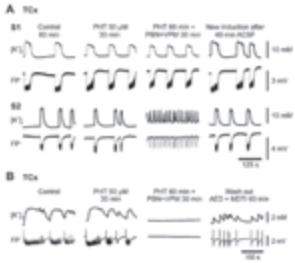
Gabriel et al J Neuroscience 2004, Sandow et al, in prep.



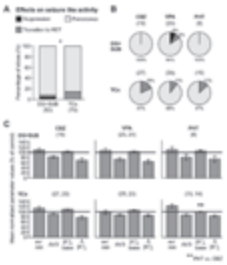
Drug resistance extends to other AEDs



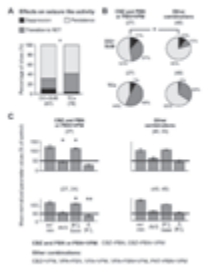
Drug responses can vary from slice to slice from the same patient



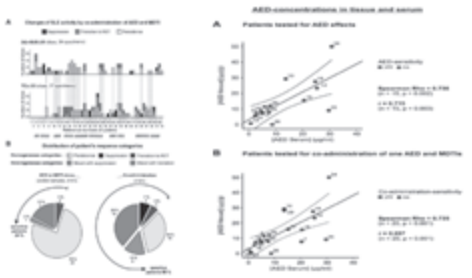
Drug resistance preserved in human slices and extends often into temporal neocortex



Multidrug therapy increases likelihood of seizure supression



Heterogeneity



What we do now

- Three genes seem to be differentially expressed in resistent and pharmacosensitive tissue. New series for confirmation started
- One is Kir 4.1
- Do animals with reduced expressions of astrocytic Kir 4.1 channels present with pharmacoresistance ?
- Test in human tissue with proven drug resistance for effects of new agents

Summary

- There is no simple explanation for drug resistance
- New drugs can now exploit models of pharmacoresistance including human tissue
- Chronic tissue from humans may serve for identifying new mechanisms
- Can be used for pharmacological screening
- May accelerate drug development