12ª. ESCOLA LATINO-AMERICANA DE VERÃO EM EPILEPSIA
12ª. ESCUELA LATINO-AMERICANA DE VERANO EN EPILEPSIA
12th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 15 – 23 DE FEVEREIRO DE 2018
Centro de Convenções Santa Mônica

COORDENAÇÃO GERAL
Prof. Dr. Esper A. Cavalheiro

COMISSÃO LATINO AMERICANA DA DA INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE)
Prof. Dr. Roberto Caraballo

ACADEMIA LATINO AMERICANA DE EPILEPSIA DA INTERNATIONAL LEAGUE AGAINST EPILEPSY
Prof. Dr. Alejandro Scaramelli

PRESIDENTE DA LIGA BRASILEIRA DE EPILEPSIA (LBE)
Profa. Dra. Maria Luisa Manreza

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Prof. Dr. Samuel Wiebe

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Esper A. Cavalheiro - UNIFESP
Fernando Cendes - UNICAMP
Fulvio Alexandre Scorza - UNIFESP
Jaime Carrizosa - Universidade de Antioquia

O DESPERTAR DA HIPEREXCITABILIDADE NEURONAL

A 12ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) é uma atividade educacional 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 ILAE tornaram-se uma referência como experiência didática. Como professores e alunos permanecem em contato próximo por cerca de 10 dias consecutivos, este tipo de Escola tem facilitado a integração entre pesquisadores básicos, clínicos, cirurgiões na área de epilepsia e alunos permitindo uma melhor compreensão das novas descobertas para o benefício das pessoas com epilepsia. A 12ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) realizada em Cabuçu, Serra da Cantareira, São Paulo entre 15 e 23 de fevereiro de 2018 aborda o tema O Despertar da Hiperexcitabilidade Neuronal em sua segunda década de atividades em prol da epileptologia latino-americana.

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

A COMISSÃO ORGANIZADORA

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12th. Latin-American Summer School on Epilepsy (LASSE IX)
15 – 23 February 2018 – São Paulo, Brazil

PROGRAM

/ /

Esper Cavalheiro (Brazil)

WELCOME AND INTRODUCTION TO LASSE

Rodrigo Quian Quiroga (UK)

KEYNOTE LECTURE: CODING AND DECODING IN NEURAL NETWORKS

Christophe Bernard (France)

EXCITABILITY IN THE SNC

Alfonso Represa (France)

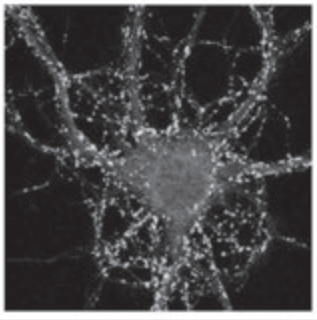
INHIBITION IN THE SNC

Inhibition in the SNC

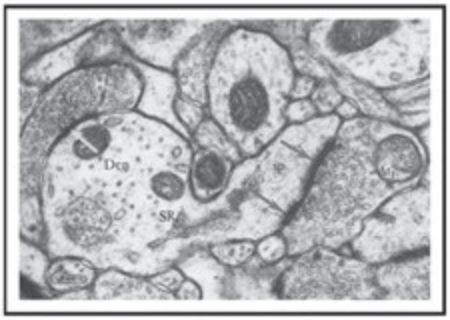
Alfonso Represa MD, PhD
INMED, INSERM U901, Luminy (Marseille)

Inmed | Inserm | Aix-Marseille université

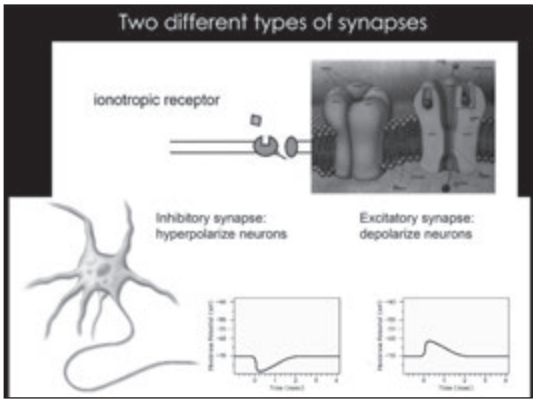
On average each neuron is in direct contact with one thousand neurons



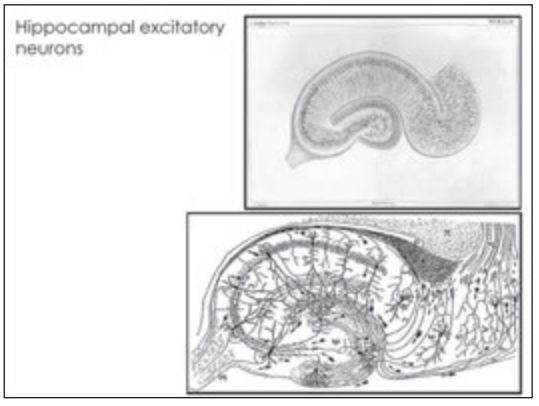
Two different types of synapses



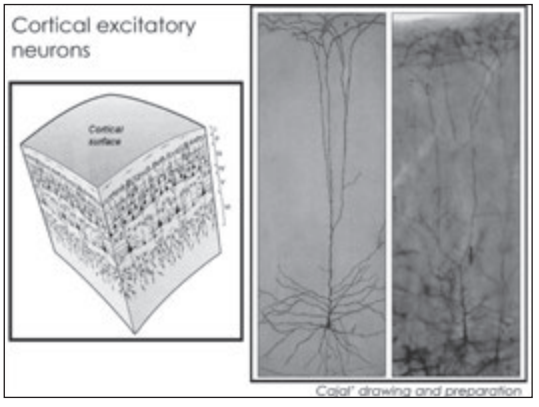
Two different types of synapses



Hippocampal excitatory neurons

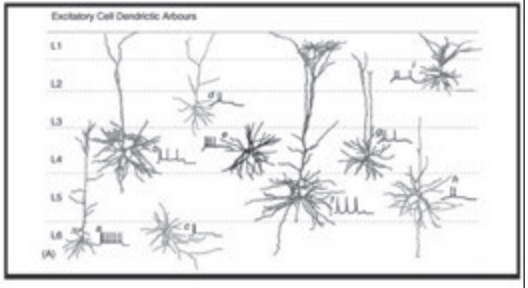


Cortical excitatory neurons



Cajal' drawing and preparation

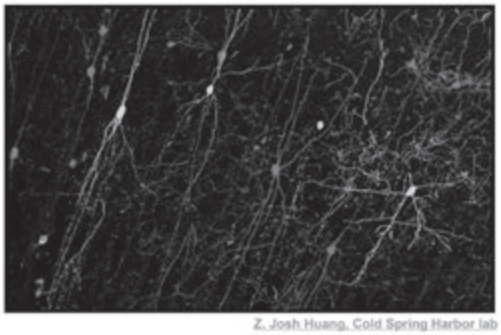
Diversity of excitatory neurons accors cortical layers: dendritic shape and firing rate



Banister et al 2005

Diversity of excitatory neurons accors cortical layers:
axonal projection

Cortical inhibitory neurons



Z. Josh Huang, Cold Spring Harbor lab

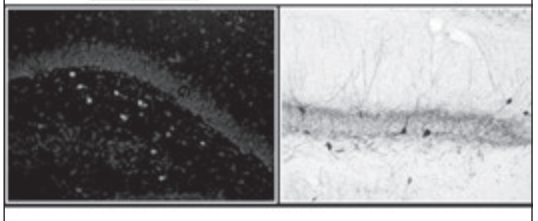
Classification of interneurons based on:

- Location of the cell body
- Dendritic and axonal branching patterns
- Afferent and efferent connection types
- Types of peptides and/or receptors expressed
- Intrinsic membrane properties
- Temporal distribution of firing (in vivo)

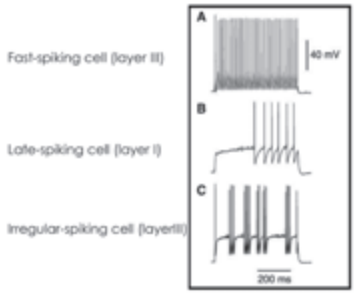
Interneurons diversity:
cell body distribution & molecular markers

Somatostatin
mRNA/CV

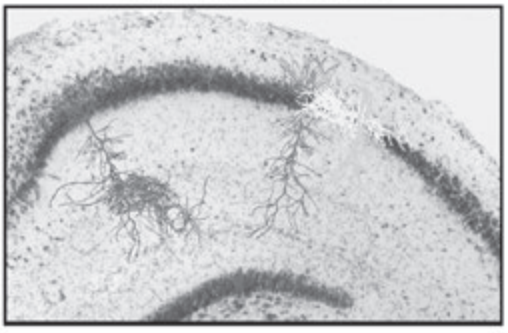
Parvalbumin
IHC



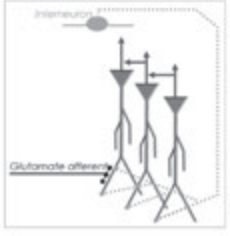
Interneurons diversity:
Patterns of action potential firing in response to a current step, recorded in interneurons in cortical slices

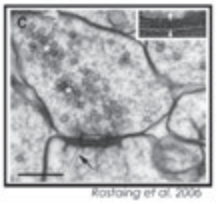


Interneurons diversity:
Distribution of axonal branches



Efferent inputs determine different inhibition types:
Dendritic innervation

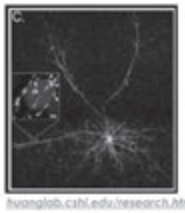




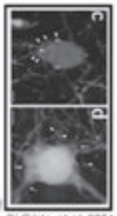
Rostaing et al. 2006

Dendritic inhibition limits excitatory afferent inputs and regulates input plasticity

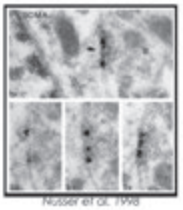
Efferent inputs determine different inhibition types:
Perisomatic innervation



huanglab.cshl.edu/research.html



Di Cristo et al. 2004



Nusser et al. 1998

Perisomatic inhibition mitigates the strength of neuron output . It appears to be critical in synchronizing the activity of ensembles of pyramidal cells

"Basket" hippocampal neuron

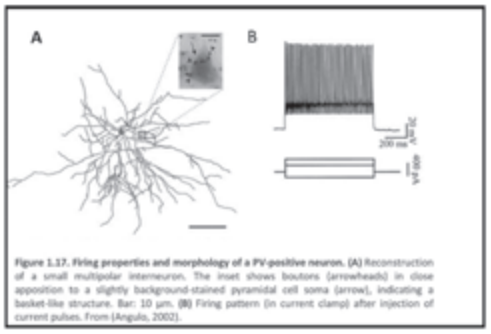
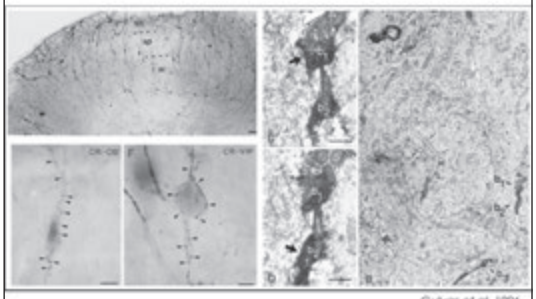


Figure 1.17. Firing properties and morphology of a PV-positive neuron. (A) Reconstruction of a small multipolar interneuron. The inset shows boutons (arrowheads) in close apposition to a slightly background-stained pyramidal cell soma (arrow), indicating a basket-like structure. Bar: 10 µm. **(B)** Firing pattern (in current clamp) after injection of current pulses. From (Angulo, 2002).

Interneurons innervating interneurons



Gulyas et al. 1996

Afferent inputs determine different inhibition types

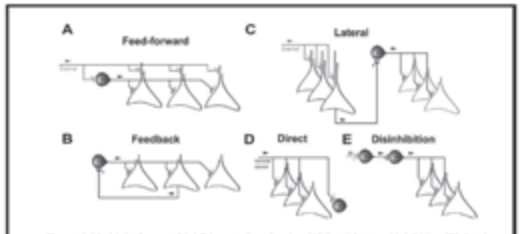
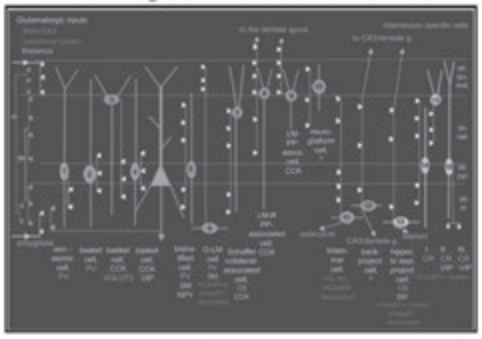


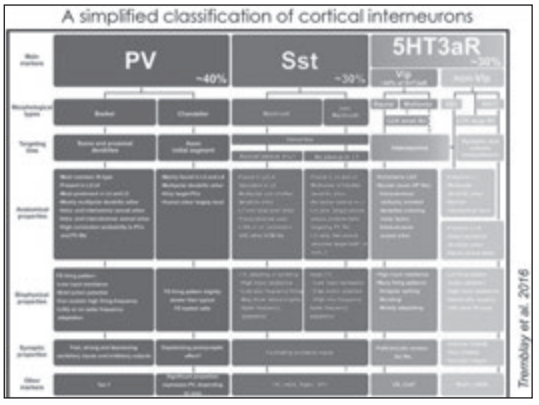
Figure 1.16. Main forms of inhibitory microcircuits. (A) Feed-forward inhibition **(B)** Feed-back inhibition. **(C)** Lateral inhibition. **(D)** Direct inhibition. **(E)** Disinhibition. Interneurons are in red, afferent excitatory inputs from an external source in green and local principal neurons in black. Modified from (Roux and Buzsáki, 2015).

For an integrated classification of interneurons

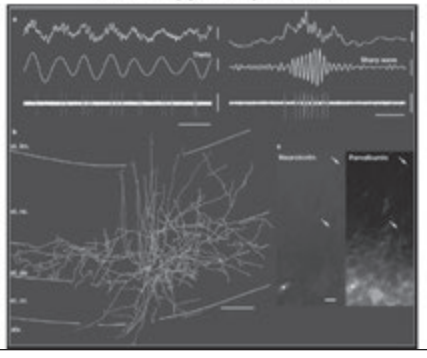


Somogyi and Klausberger, J. Physiol 2005

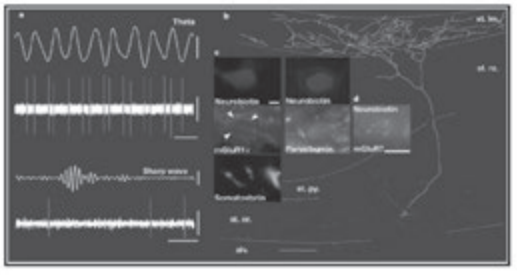
A simplified classification of cortical interneurons



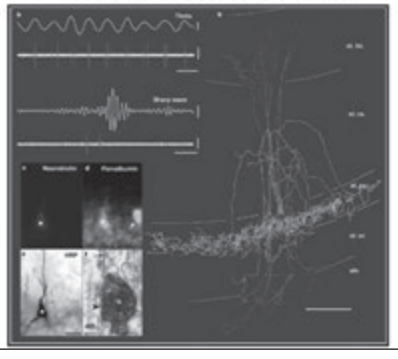
Contribution of interneurons to network rhythms:
"Basket" hippocampal neuron



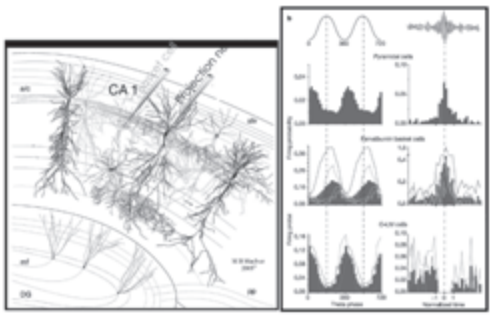
Contribution of interneurons to network rhythms:
O-LM hippocampal neuron



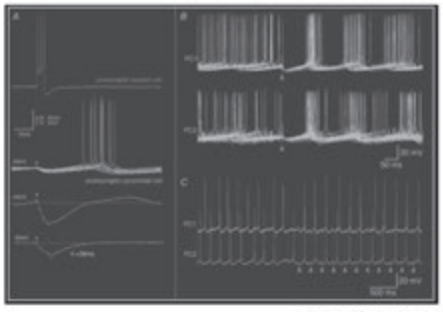
Contribution of interneurons to network rhythms:
Axo-axonic hippocampal neuron



Involvment of interneurons on oscillatory cortical activities



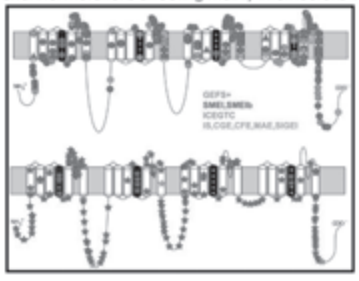
Hippocampal basket cells phase and synchronize pyramidal cell firing



Somogyi & Klausberger 2005

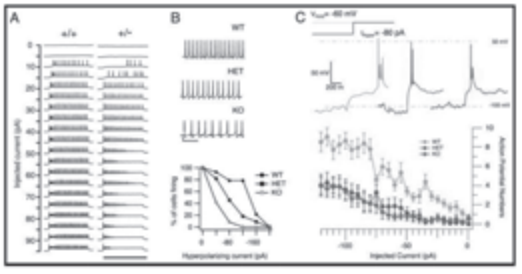
Interneuronopathies: the example of Dravet syndrome

Nav1.1 channel mutations affecting mainly interneurons function



William A. Catterall 2012

Interneuons from NaV1.1 KO mice
Dysplay a significant reduction of firing properties



William A. Catterall 2012

Interneuons from NaV1.1 KO mice
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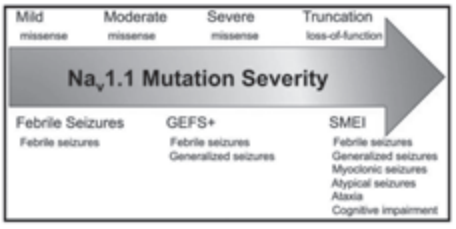


William A. Catterall 2012

Only 10% of neurons are interneurons: so why bother?

- Principal neurons are covered with synapses from interneurons
- Interneuron innervates up to 1000 pyramidal cells
- Interneurons play a major role on regulating interactions between principal cells
- Interneurons are key players on network operations
- Variability on their connectivity enables them to carry multiple different tasks
- Interneuronopathies are cause of epilepsy (Dravet syndrome) and other neurological conditions

Silvia Kochen (Argentina)

ELECTRICAL STIMULATION DURING STEREOELECTROENCEPHALOGRAPHY IN CANDIDATES TO SURGERY EPILEPSY

MEETING THE TUTORS

Alfonso Represa (France)

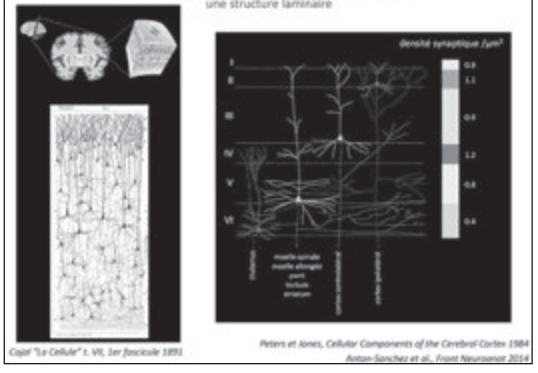
NEURODEVELOPMENT OF THE NEOCORTEX

Neurodevelopment of the neocortex

Alfonso Represa, MD, PhD
Institut de Neurobiologie de la Méditerranée
INMED, Campus de Luminy, Marseille (France)

Inmed Inserm Aix-Marseille université

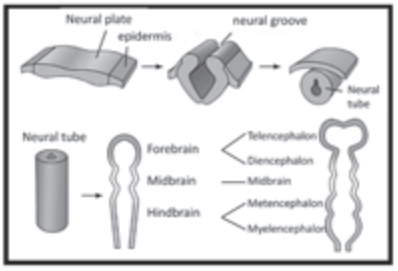
Le néocortex (isocortex) des mammifères :
une structure laminaire

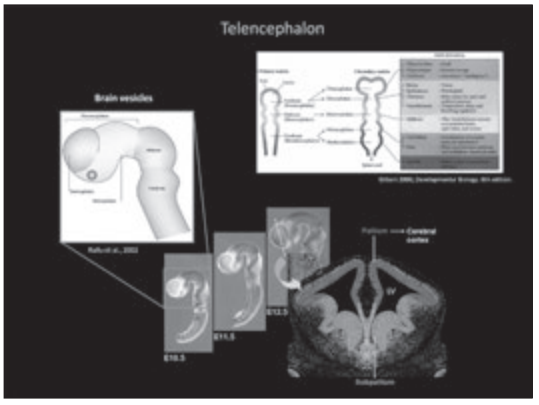


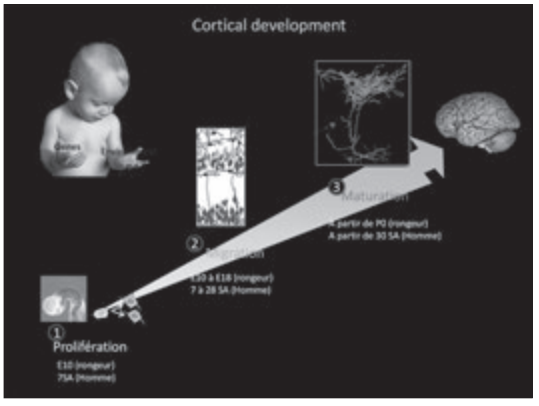
Cajal "Le Cellule" t. VII, 1er fascicule 1891

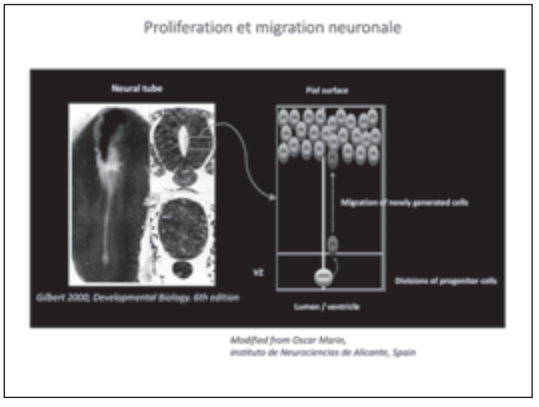
Peters et Jones, Cellular Components of the Cerebral Cortex 1984
Anton-Sanchez et al., Front Neuroanat 2014

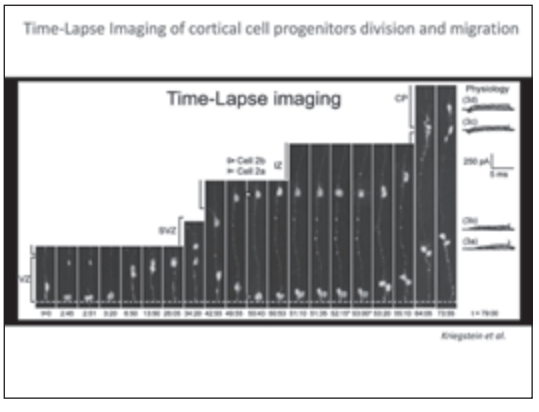
Early events of mammalian nervous system development



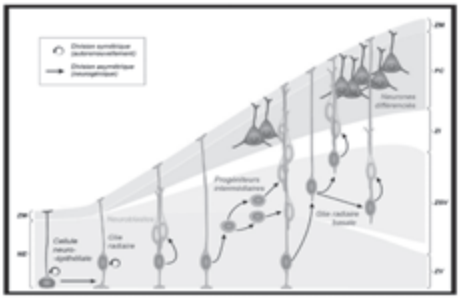

Telencephalon
Brain vesicles
E10.5
E11.5
E12.5
Cerebral cortex


Cortical development
3 Maturation
A partir de P0 (rongeur)
A partir de 30 SA (Homme)
2
E10 à E18 (rongeur)
7 à 28 SA (Homme)
1
Prolifération
E10 (rongeur)
7SA (Homme)

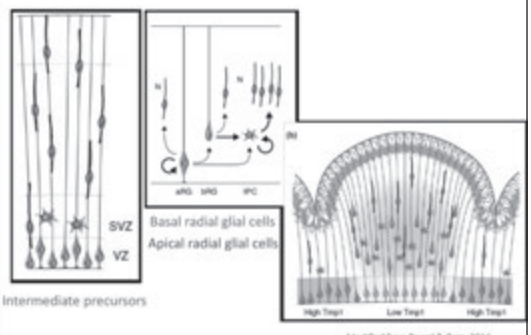

Proliferation et migration neuronale
Neural tube
Piel surface
Migration of newly generated cells
VZ
Divisions of progenitor cells
Lumen / ventricle
Gilbert 2000, Developmental Biology. 6th edition
Modified from Oscar Marin,
Instituto de Neurociencias de Alicante, Spain


Time-Lapse Imaging of cortical cell progenitors division and migration
Time-Lapse imaging
CP
Physiology
250 pA
5 ms
SVZ
VZ
Kriegstein et al.

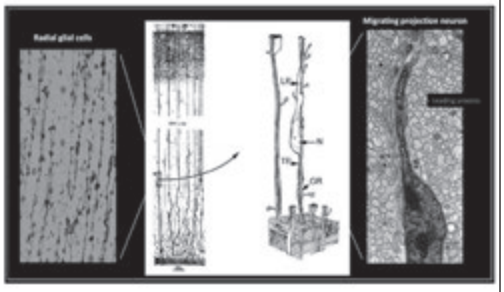
Cortical progenitors: radial glial cells and intermediate progenitors



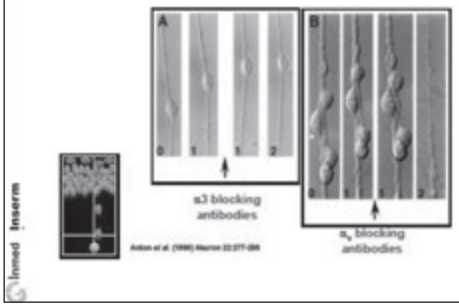
Radial glial cells and intermediate precursors



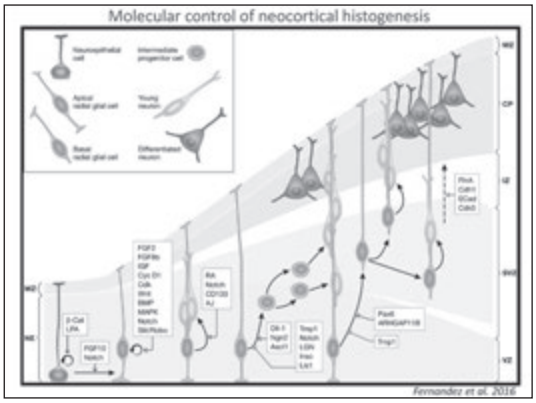
Cortical projection neurons migrate along radial glial fibers



Cortical projection neurons migrate along radial glial fibers

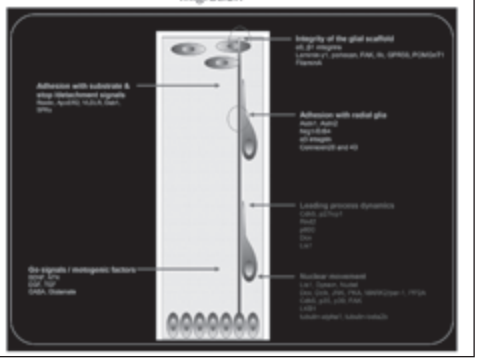


Molecular control of neocortical histogenesis

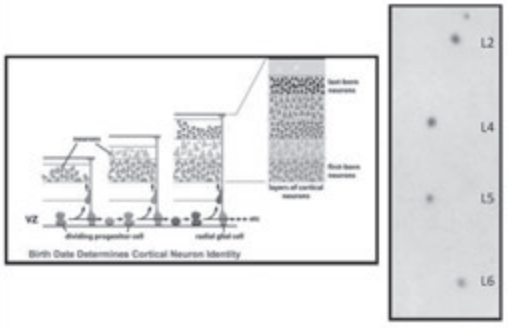


Fernandez et al. 2016

Cell-autonomous and cell-to-cell signaling events controlling radial migration



Cortical projection neurons migrate in an 'inside-to-outside' fashion to form columns and layers



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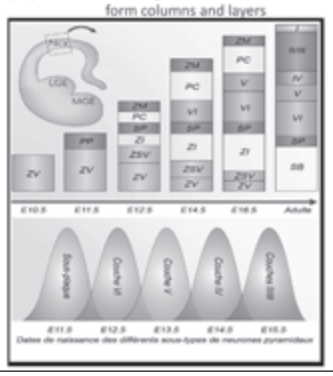
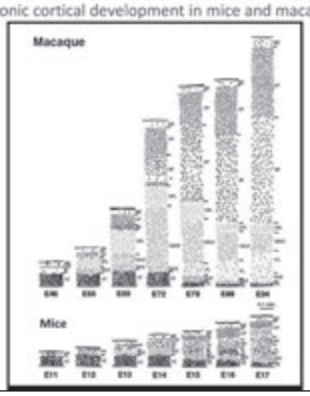
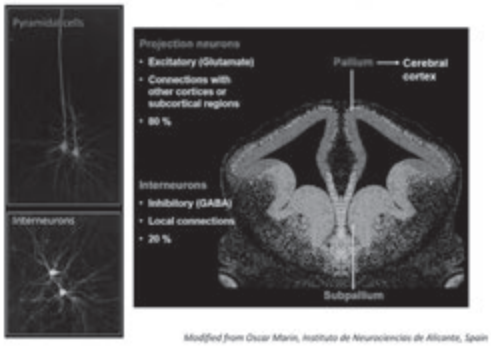


Embryonic cortical development in mice and macaque



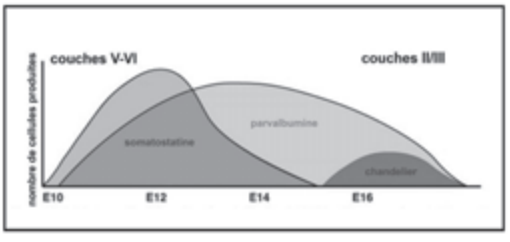
Smart et al. 2002

Interneurons are generated in the subpallium



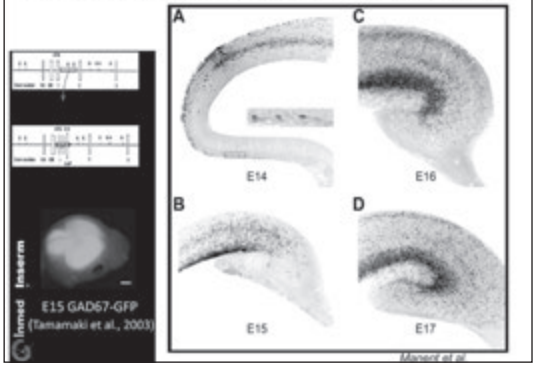
Modified from Oscar Marin, Instituto de Neurociencias de Alicante, Spain

Temporal sequency of interneuron subtype generation



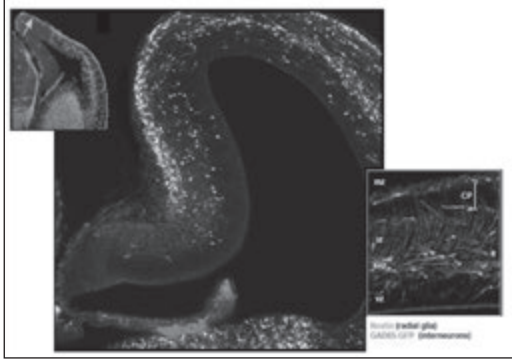
Bandler et al 2016

Interneurons migrate tangentially to reach their cortical destination

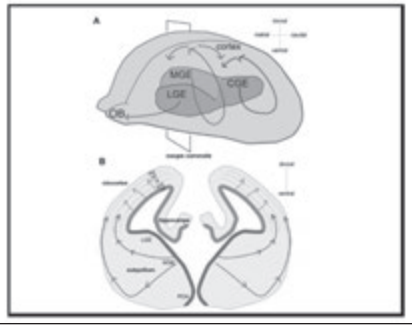


Manent et al.

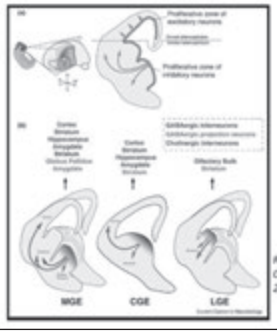
Interneurons migrate tangentially to reach their cortical destination



Migratory routes of cortical GABAergic neurons

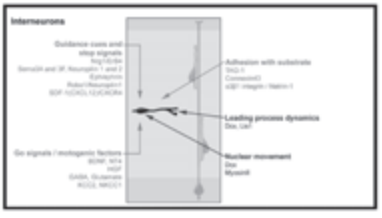


Ganglionic eminence produces GABAergic interneurons and projection neurons.

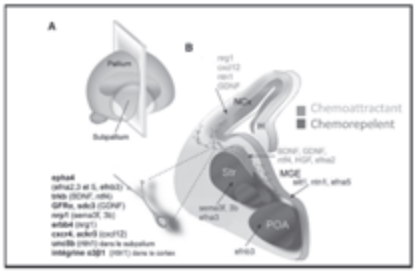


RC Bondiec, C Mayer, G Fishell; Current Opinion in Neurobiology 2017

Cell-autonomous and cell-to-cell signaling events controlling tangential migration

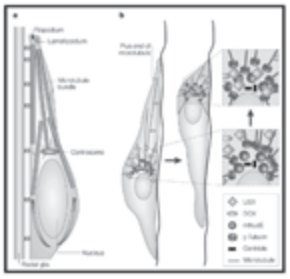


Diffusible molecules involved in the regulation of tangential migration



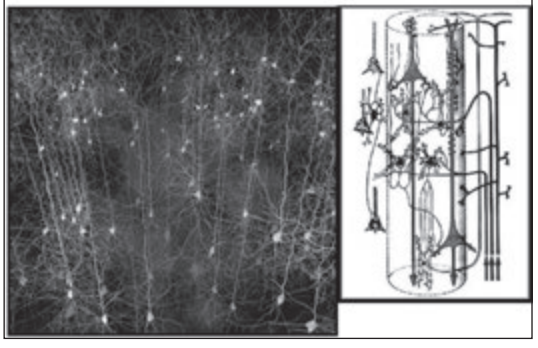
O Marin 2013

Microtubule-based nuclear translocation in neuronal migration

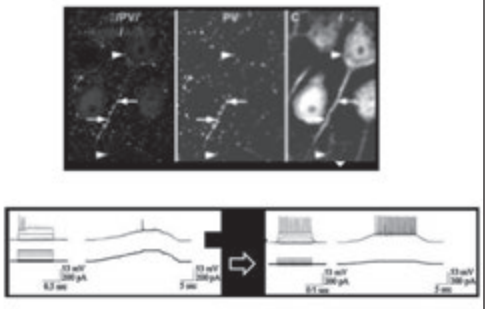


1) Microtubules extension in the leading process (DCX + MAPs)
2) Lis1 recruitment at the centrosome and microtubules shortening (= pulling forces)

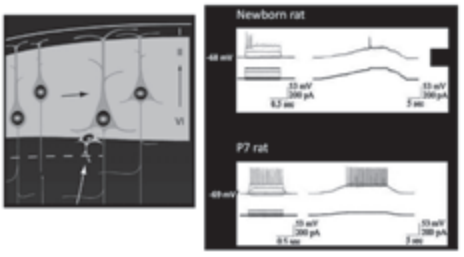
Cortical Neuronal Networks



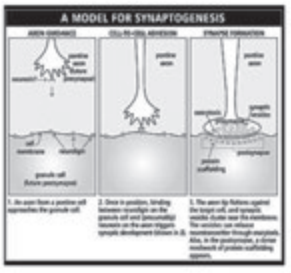
Neuronal maturation: axon maturation and genesis of action potentials



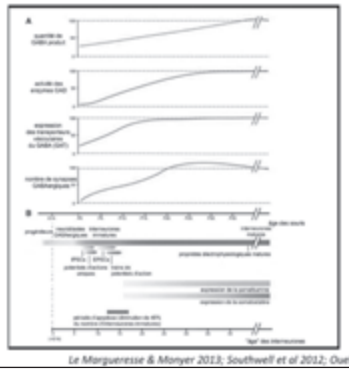
Neuronal maturation: genesis of action potentials



Neuronal maturation: Synaptogenesis and network activity maturation

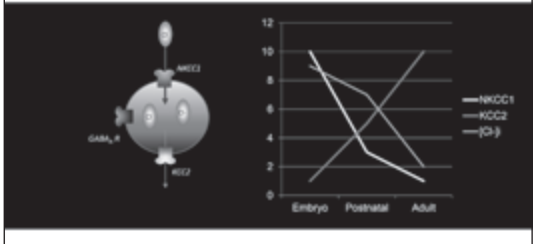


Postnatal development of GABA interneurons in mice



Le Magueresse & Monyer 2013; Southwell et al 2012; Ouellet &Villers-Sidani

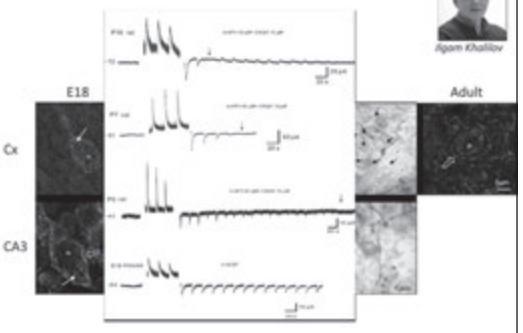
$[Cl^-]_i$ in developing brain



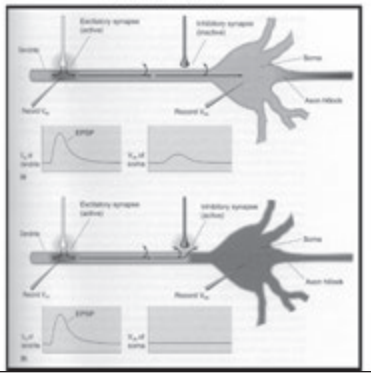
Tyzio et al., 2006 Science; 2007 Epilepsia; 2008 Eur. J. Neurosci.
Valeeva et al., 2010 Front. Cell. Neurosci.

KCC2 and Dynamic Regulation of choride

Ilgam Khalilov



Shunt inhibition

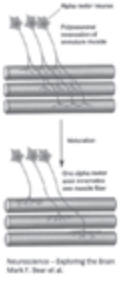


Activity-dependent pruning of synapses

Initially in development axons connect more targets and targets are contacted by more axons

Activity-dependent remodeling depending on degree of correlation in spiking patterns:
Pruning of exuberant axon collaterals that show uncorrelated activity to develop precise connectivity

Examples
NMJ, Corpus callosum, pyramidal tract, climbing fiber input to cerebellar Purkinje cells, ocular dominance columns in visual cortex



Neuroscience – Exploring the Brain
Mark F. Bear et al.

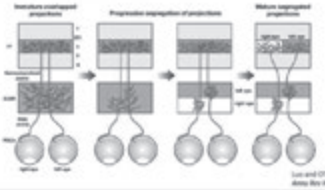
Activity-dependent pruning of synapses – Critical periods

Retinogeniculate and geniculocortical projections of the visual system

Input to target cell is reduced from binocular to monocular by Hebbian mechanism (NMDARs):

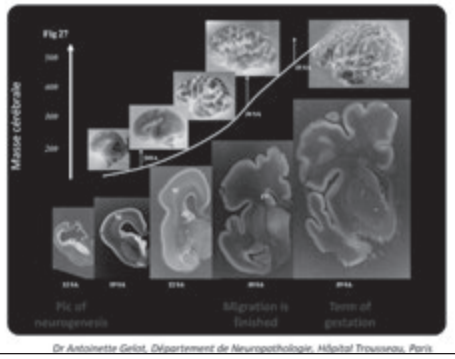
Correlated activity – strengthening the synapse
Uncorrelated activity – synapse weakening and elimination } Fire together – Wire together

Monocular deprivation experiments, Hubel and Wiesel



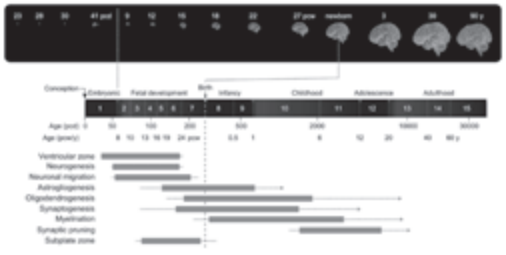
Timeline of neurodevelopmental processes in human and rodents

Neocortical histogenesis in humans: Fetal cortical development



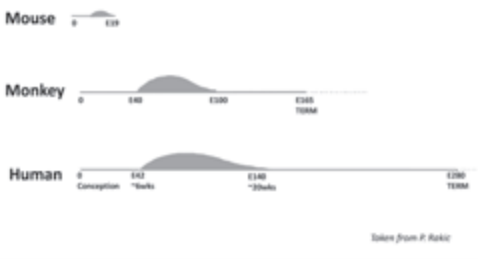
Dr Antoinette Gelot, Département de Neuropathologie, Hôpital Trousseau, Paris

L'histogenèse néocorticale :
développement et maturation corticale chez l'humain



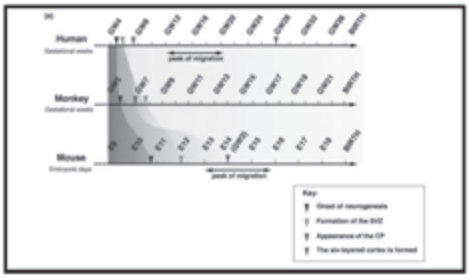
Silbereis et al., Neuron 2016

Species differences in the length of neocortical neurogenesis

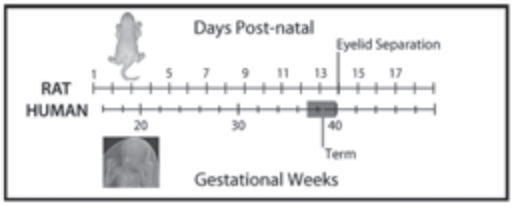


Taken from P. Rakic

Relative timelines of conserved cortical development hallmarks in human, primate and mouse



Species differences in the time of eyelid separation



Christophe Bernard (France)

HYPEREXCITABILITY IN THE NEOCORTEX

Marina Bentivoglio (Italy)

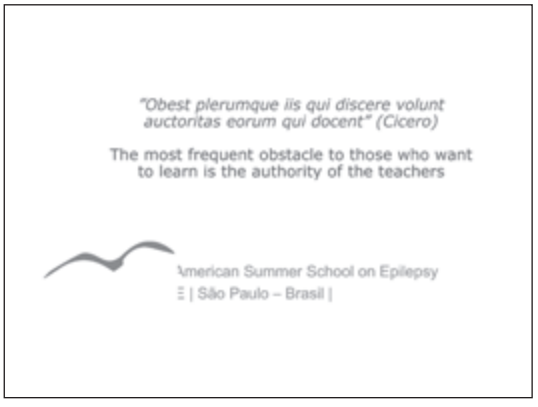
PRINCIPLES OF THALAMIC ORGANIZATION

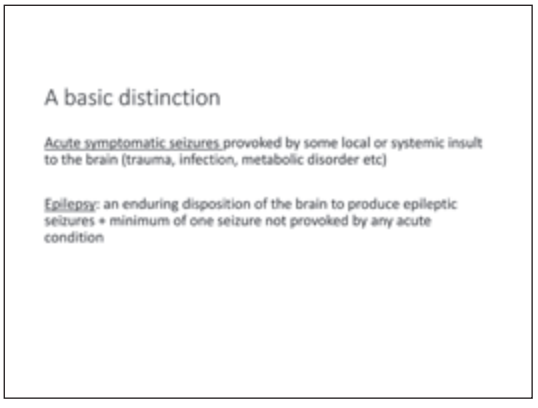
Marina Bentivoglio (Italy)

THE EXCITABLE THALAMUS AND EPILEPSY

Peter Wolf (Denmark)

DO SPONTANEOUS SEIZURES EXIST?





ILAE practical definition of epilepsy (Fisher et al 2014)

Epilepsy is a disease of the brain defined by any of the following conditions

- 1. At least two unprovoked (or reflex) seizures occurring >24 h apart
- 2.One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- 3. Diagnosis of an epilepsy syndrome

Consequence

- Once epilepsy is established, seizures are considered to occur as autonomous symptoms of the condition.
- For patients, their spontaneous and unpredictable recurrence is considered one of their most distressing aspects: loss of control

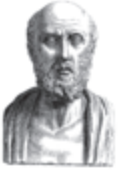
Fritz Dreifuss (1926 – 1997)

"Maybe unprovoked seizures do not exist at all. We may only not yet have discovered all the provocative mechanisms."

Hippocrates (460 – ca 370 BC) On the Sacred Disease

Treatment of epilepsy:

- "Avoid what is favourable to the disease and apply what counteracts it".
- Understanding of seizures as resulting from an interplay of provocative and inhibitory factors



Can you provide examples of factors?

Definitions

- Facilitation = non-specific mechanisms that temporarily increase the seizure risk (alcohol, sleep deprival, menstruation)
- Precipitation (reflex seizures) = direct induction of a seizure (within seconds to minutes) by sensory or cognitive stimulation. The stimuli are specific for syndrome, seizure types, sometimes individual patients.

Seizure provocation

A clinical perspective (500 refractory patients)

The Importance of Seizure-Inducing Factors in the Control of Refractory Forms of Epilepsy

Robert B. Aird

Department of Neurology, School of Medicine, University of California, San Francisco, California

Aird RB (1983)

Seizure-inducing factors and their dynamic balance

TABLE 1. *Seizure-inducing factors and their dynamic balance*

Excitatory	Factors	Inhibitory (normal)
Relaxation, drowsing, light and REM sleep, and arousal[a]	Wake-sleep cycle (level of consciousness)	Normal rest, vigilance, and activity
Fatigue[a] and sleep deprivation	Physical activity	Avoidance of excesses
Prolonged and intense emotional stress	Emotional balance	Good adjustment to environment
Sensory (photic, etc.), drugs and their withdrawal effects	CNS stimulation	Avoidance of excesses
Abnormal (menses, pregnancy, other)	Cyclic hormone balance	Normal
Hydration	Water balance	Normal or slight dehydration
Alkalosis (HV)	Acid-base balance	Modified ketogenic diet, avoidance of HV, etc.
Hypoxia (HV), hyperbaric states	Oxygenation	Normal
Fever	Temperature	Normal
Hypoglycemia, hyperalcemia, etc.[a]	Metabolic balance	Normal
Renal and hepatic failure, ischuptyxis, porphyria, etc.	Toxic states	Normal

Aird RB
Classification of factors

TABLE 3. *Seizure-inducing factors: criteria of classification*

1. Indeterminate
   Obscured by severity of seizures
   Not reported and factors suggested by EEG but not confirmed by observation
2. Minor
   Reported and/or suggested by EEG, but found to be of minor importance, and seizure control was by drugs alone
3. Important
   Regulation of confirmed factors was of definite therapeutic value, as determined by a reduction of seizure incidence of 30% or more, but still not crucial
4. Crucial
   Regulation of confirmed factors crucial to complete control of seizures

TABLE 4. *Therapeutic use of seizure-inducing factors in 500 patients with refractory seizures*

Group	Number	Incidence
1. Indeterminate	57	11.4%
2. Minor	229	45.8%
3. Important	128	25.6%
4. Crucial	86	17.2%

Aird RB
Therapeutic impact

First seizures in life (30 consecutive adults)

Non-medical treatment of first epileptic seizures in adolescence and adulthood

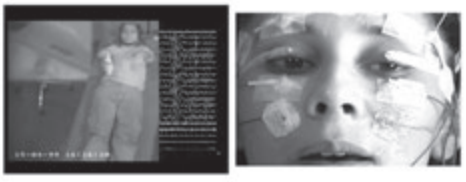
PETER WOLF

Table 2: Precipitating factors

Disturbance of sleep–waking cycle	16
Extraordinary stress	6
Intermittent lights	4
Television	3
Increased alcohol intake	3
Hunger, hypoglycemia	2
Fever	2
Migraine	1
Runstroke	1
Specific movement	1
None	1

Juvenile myoclonic epilepsy

Photosensitivity and Eye closure sensitivity



Orofacial reflex myocloni and praxis induction

Reading-induced PORMs and praxis induction by writing to dictation

Patient with Juvenile Myoclonic Epilepsy

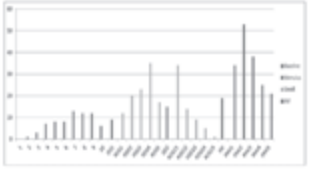
Temporal lobe epilepsy

Temporal lobe epilepsy and smells

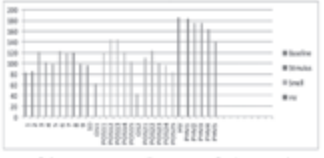
1. Olfactory auras (5.5 – 11 %)
2. Aromatherapy (Betts) and seizure arrest by olfactory stimulus (Efron)
   1. What can inhibit a seizure can also provoke it (exogenous modulation of seizure activity)
3. Rare case reports of seizure provocation by olfactory stimuli
4. Targeted study of modulation of EEG spike activity by olfactory stimuli reveals increase in 30 % and decrease in 15 % of TLE patients (and opposite relations in idiopathic generalized epilepsies). Only half the patients unaffected. One TLE patient had a seizure following stimulation. *(Lunardi et al 2016)*

Conclusion: the solitary published cases are the tip of an iceberg

Patient with TLE, low spontaneous spike density
Delayed spike increase following OSs
Typical hyperventilation response



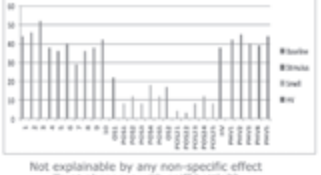
Patient with IGE, high spontaneous spike density. Increase with hyperventilation, over some minutes returning to baseline (typical reaction to HV)
During both periods of olfactory stimulation (OS) reduction of spikes, immediate return to baseline



Columns represent spike count per 3 minute epochs

Presumably non-specific effect of increased attention during OS

IGE patient with rather high spontaneous spike density and no hyperventilation reaction.
An inhibitory response develops during both OSs and increases after their termination .



Not explainable by any non-specific effect
Treat absences with sniff bottle??

Visceral stimuli?

"Clinical observations indicate that the degree of autonomic nervous system (ANS) activity may be important in providing an appropriate milieu for the occurrence of seizures. For instance, highly emotionally charged situations increase sympathetic activity, which may be associated with increased seizure activity in some patients. Whether the ANS plays any more specific and direct role in the precipitation of seizures is unknown." *(Wannamaker HB, Epilepsia 1985; 26 Suppl 1, S31)*

Practically no research.

Conclusions on TLE

- Spontanuous seizures more likely than in JME
- But: many of the recognized factors are less obvious and may be more easily overlooked.
- Emotional, sexual, visceral triggers very little explored.
- "Maybe we just have not yet discovered all the precipitating mechanisms" (Dreifuss)

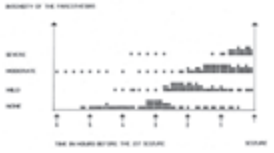
Neocortical epilepsies: spontaneous?

- Frontal:
- Central:
- Parietal:
- Occipital:

Somatosensory: touch

"Epilepsies with exogenous modulation"

- EpExMo: a very peculiar finding is that the same stimuli which in reflex epilepsies can provoke seizures, at other instances even in the same subjects can prevent or stop seizure activity



Inhibition in reflex epilepsy?

- Guaranha MSB et al: Provocative and inhibitory effects of a video-EEG neuropsychological protocol in JME. Epilepsia 2009

Patients with unprovoked spikes (n = 31)	
Only provocation	3 (10%)
Only inhibition	17 (55%)
Provocation and inhibition	11 (35%)

Inhibition by non-specific arousal?

76 patients with JME without or with unprovoked spikes. Investigation of praxis induction and PORM with neuropsychological protocol

Caveat

Definitions of Matsuoka et al, Mayer et al, Guaranha et al:

- provocation: > 2x increase of average spike frequency
- inhibition: > 2x decrease of average spike frequency during task as compared to baseline

Spike count per 5 min in 50 min baseline of a JME patient

Investigation of 60 pts with JME

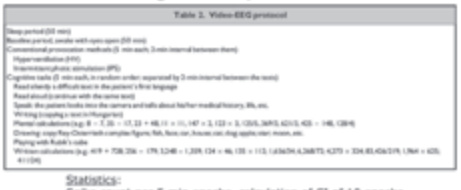


Table 1. Video-EEG protocol

Statistics:
Spike count per 5 min epochs, calculation of CI of 10 epochs
Provocation = count in 5 min test > 95% CI
Inhibition = count in 5 min test < 95% CI

Results (60 pts)

Provocation of ED

Hyperventilation 13

Intermittent lights 6

Cognitive tasks 11

Inhibition

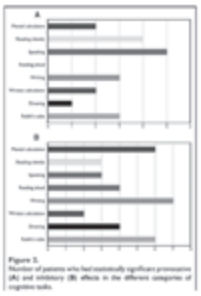
Hyperventilation 1

Intermittent lights 2

Cognitive tasks 11

SHOULD COGNITIVE STIMULATION BECOME PART OF STANDARD EEG?

UNDER INVESTIGATION



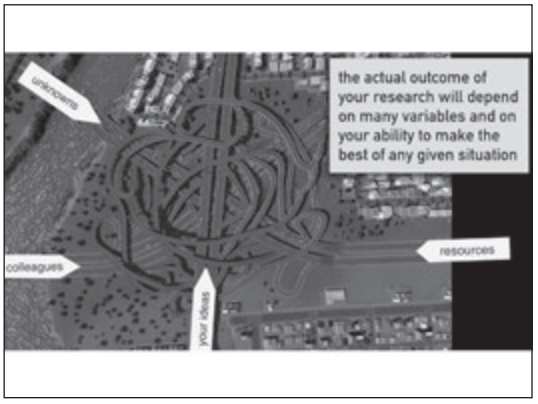
Conclusion

- Truly spontaneous seizures may exist, but only in some conditions
- Not in others, like JME
- Spontaneaus seizures are rare
- Not all facilitating and precipitating mechanisms discovered
- Especially endogenous provocation little investigated and probably underrecognized
- Where there is provocation there is inhibition: epilepsies modifiable by exogenous and enogenous stimuli
- Knowledge could be used more for prevention and counteraction

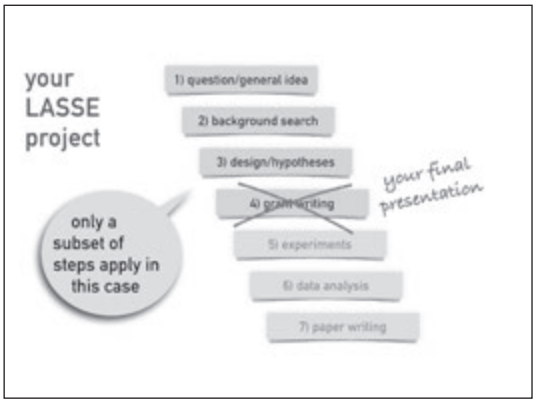
Giuseppe Bertini (Italy)

THE DESIGN OF A RESEARCH PROJECT

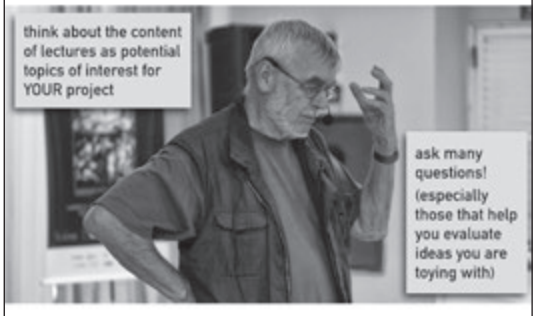

usually, it's neither extreme. more like...
A COMPLEX WEB OF POSSIBILITIES


unknowns
the actual outcome of your research will depend on many variables and on your ability to make the best of any given situation
resources
colleagues
your ideas


1) question/general idea
2) background search
3) design/hypotheses
4) grant writing
5) experiments
6) data analysis
7) paper writing
what does a typical research project look like?
here's a simplified outline


your LASSE project
1) question/general idea
2) background search
3) design/hypotheses
4) grant writing
5) experiments
6) data analysis
7) paper writing
your final presentation
only a subset of steps apply in this case

1. QUESTION, GENERAL IDEA



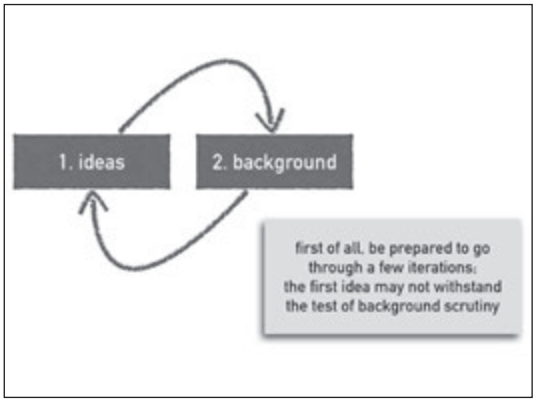

use every opportunity to get insight from your tutor, but do not delegate choices and responsibilities to them


INTERACT


group work is obviously crucial for a good outcome


but be also prepared to do your own "homework"
you should bring your own contribution to the group (independent of background and specific expertise)

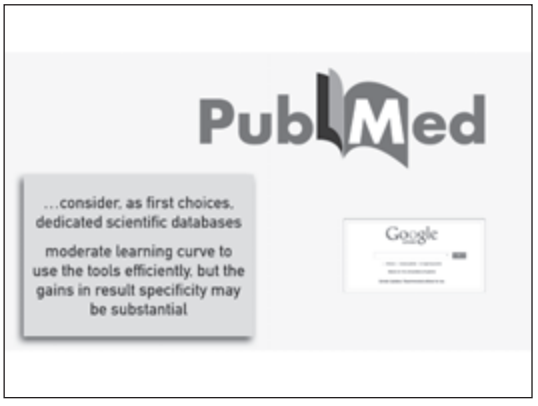
2. BACKGROUND SEARCH



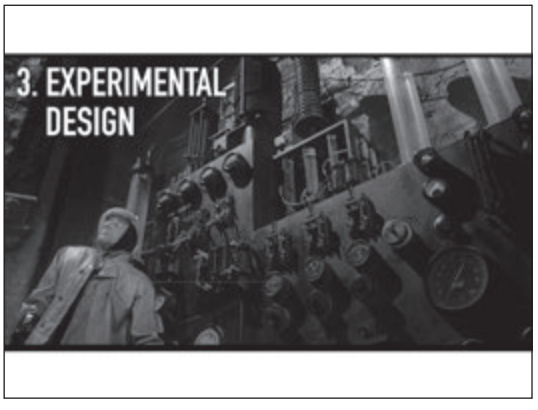
STAND ON THE SHOULDERS OF GIANTS

Read your literature!


searching relevant papers is in itself a skill to be developed
while Google is nowadays "second nature"…
Google
PubMed


PubMed
…consider, as first choices, dedicated scientific databases
moderate learning curve to use the tools efficiently, but the gains in result specificity may be substantial
Google

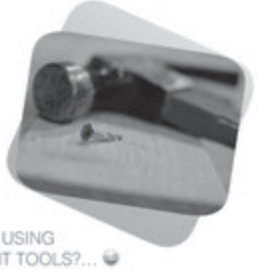

search for "smith[au] 2014[dp]" instead
limit search to review papers
try out advanced searches!
keep an eye on the actual query


3. EXPERIMENTAL DESIGN

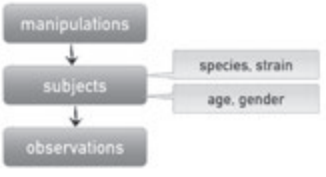
time to design your study…

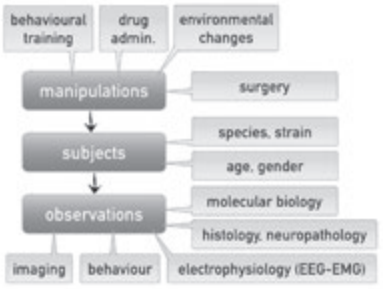
choosing an experimental approach…

too many flavors, too little time!



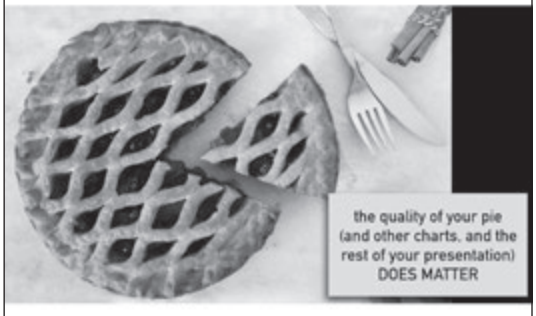
ARE YOU USING THE RIGHT TOOLS?…





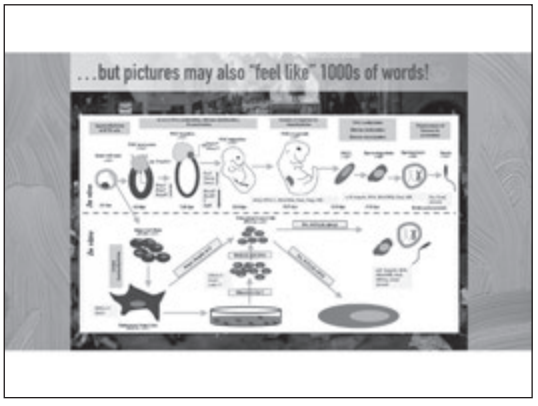
4. RESEARCH PROPOSAL

i.e. your LASSE presentation



a picture worth a thousand words


...but pictures may also "feel like" 1000s of words!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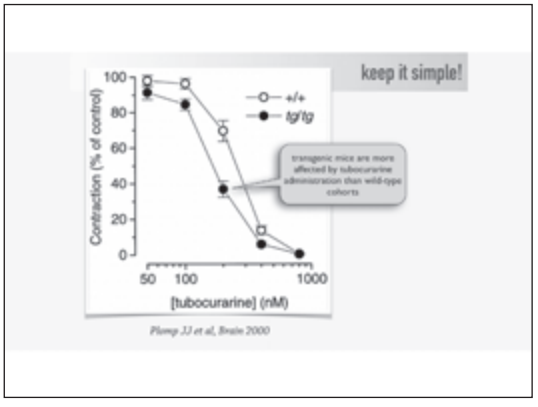

keep it simple!
Contraction (% of control)
100
80
60
40
20
0
+/+
tg/tg
transgenic mice are more affected by tubocurarine administration than wild-type cohorts
50
100
1000
[tubocurarine] (nM)
Plomp JJ et al, Brain 2000


GOOD LUCK!

Marina Bentivoglio (Italy)

GOOD PRACTICES IN PREPARING A RESEARCH PROJECT AND WRITING AND PUBLISHING SCIENTIFIC PAPERS

Peter Wolf (Denmark)

ICTOGENESIS IN FOCAL AND GENERALIZED SEIZURES

Ictogenesis of focal and generalized seizures

Peter Wolf, Dianalund & Florianópolis

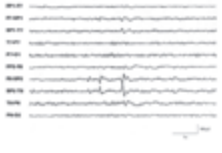
.atin-American Summer School on Epilepsy
IE | São Paulo – Brasil | February 15 – 23, 2018

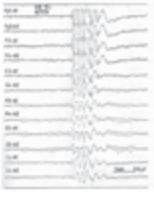
Definitions

- Epileptogenesis: the processes that establish epilepsy in a previously normal brain
- Ictogenesis: the processes that generate individual seizures in an epileptic brain

"Generalized"

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





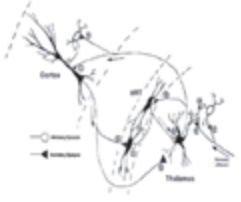
Concepts of ictogenesis: 1970 Classification

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

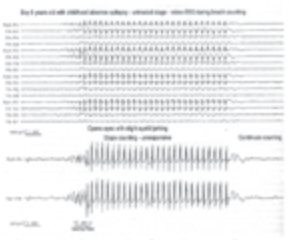
The common view of generalized epilepsy

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

Thalamo-cortical hypothesis of generalized ictogenesis (Gloor 1969)



Generalised SW discharges typically are symmetric, synchronous and widespread - but typically also have a frontal accentuation, especially at onset

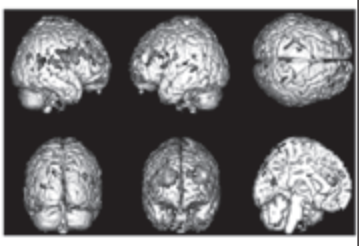


Prototypical example of an absence, from Loiseau et al. *Childhood Absence Epilepsy*. In: Roger et al, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2002

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

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

but also PO

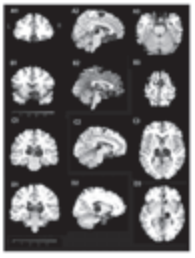


Koepp MJ & Duncan JS. PET in IGE: Imaging beyond structure. In: Juvenile myoclonic epilepsy: The Janz syndrome. Schmitz B, Sander T (Eds). Wrightson, London, 2000: 91-99.

Morphological findings

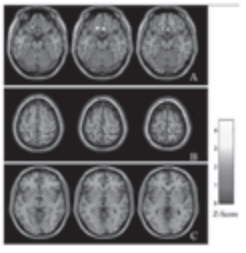
Cao et al (2013): meta-analysis of 7 studies of JME with voxel-based morphometry:

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

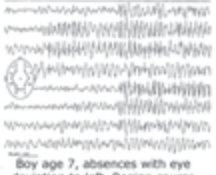


Voxel-based morphometry: JME, absence epilepsy, healthy controls: *Betting et al NeuroImage 2006; 32:498-502*

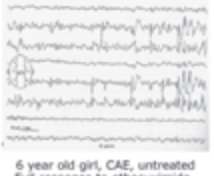
- A: JME pts vs ctrls: fronto-basal increased GMD
- B: AE pts vs ctrls: fronto-dorsal – parietal > GMD
- C: all patients with absences (JME + AE) vs ctrls: GMD increased in anterior thalamus



"pseudofocal" discharge in absence epilepsy

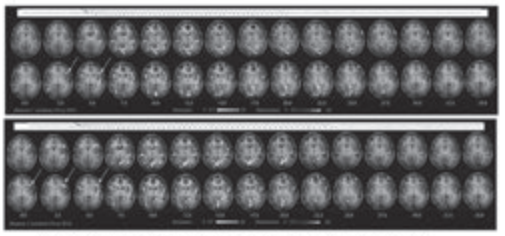


Boy age 7, absences with eye deviation to left. Benign course.



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

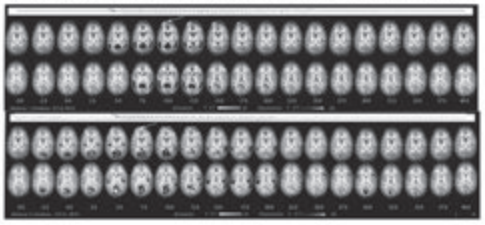
Absence seizures: Individual patterns revealed by EEG-fMRI



Sliding window analysis of 2 absences in the same patient

From: Moeller F et al. Epilepsia 2010

Sliding window analysis of 2 absences in one 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

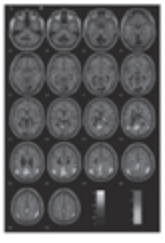
Moeller et al Absence seizures: individual patterns revealed by EEG-fMRI. *Epilepsia* 2010

- 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)

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)



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
- Temporal lobe little involved
- Triggered off from variable cortical loci (intraindividually consistent?)
- Precuneus the leading structure
- Pathological deactivation of the DMN explains absence?

Are "generalized" szs really focal szs?

- Single or multiple local cortical triggers seem often to have a role in the generation of "generalized" SWs and seizures
- What happens at these loci is not known at present
- Concordant with consistent local onset of SW in EEG?
- Difficult to merge findings of fMRI and MEG
- The signature of absences / GSW is the bilateral distributed syndrome-specific ictogenic circuit
- This does not exist in focal epilepsies
- To avoid misunderstandings, a clear distinction should be made between "local" and "focal"

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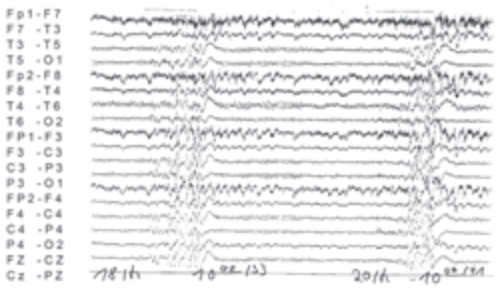
*good research topic

Reflex epileptic mechanisms: another type of local input into ictogenesis

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

Reflex epileptic mechanisms offer unique insight into natural ictogenesis

TV-induced seizures: photoparoxysmal EEG response



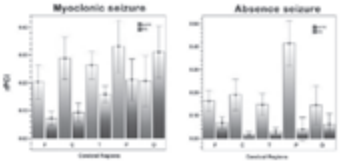
DOI: 10.1093/brain/awg109 Brain (2003), 126, 1164–1172

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".

rPCI = relative phase clustering index

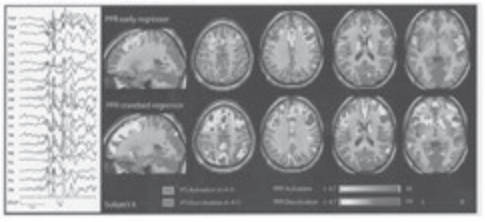


Red: stimulation with photoparoxysmal response (PPR)
Blue: stimulation without PPR

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)

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



Conclusions

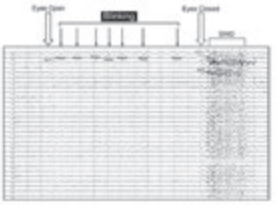
- "In contrast to spontaneous GSW, these results suggest that PPR (photoparoxysmal response) is a cortical phenomenon with an involvement of the parietal and frontal cortices."
- Photosensitivity reflects upregulation of occipito-frontal and occipito-parietal pathways: Basic mechanism of JME (90% of pts)?

Eye closure sensitivity

- SW within 2 (-3) sec after eye closure (= immediate, qualitative)
- mostly occipital dominant
- often overlapping, but not identical with photosensitivity
- found in about 15 - 20% of JME
- related to absences with eyelid myocloni (seizure type) or eyelid myclonus with absence (syndrome): short reflex loop
- Visual factor? Dark and lit environment!

Eye closure sensitivity:

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

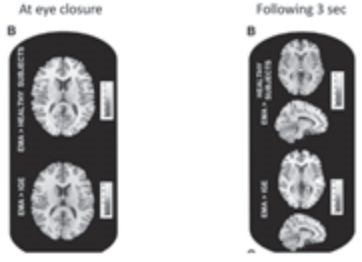


Video: ECS in JME patient

Eye closure sensitivity

- 20 subjects with ECS
- Different syndromes
- Only with slow eye closure (supplementary motor area)
- Not with automatic or nociceptive blinks (brain stem)
- Myocloni and SW discharge can dissociate in both directions

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



Praxis induction

- 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
- Focal myocloni in a "generalized" epilepsy?!

Focal seizures in a generalized epilepsy

Patient with orofacial reflex myocloni and praxis induction

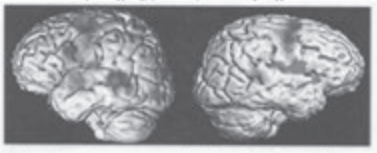
Reading-induced PORMs and praxis induction by writing to dictation

Patient with Juvenile Myoclonic Epilepsy

Orofacial reflex myocloni: JME, Reading Epilepsy

FULL-LENGTH ORIGINAL RESEARCH

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



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

Focal features in generalized epilepsy

Q: How is it possible that focal seizures occur in a generalized epilepsy?

A: Because generalized epilepsy is a misconcept from the beginning

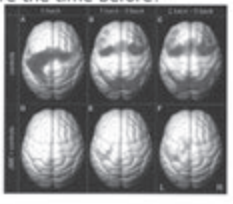
Cortical connectivity in JME

BRAIN

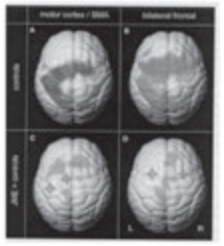
Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study

"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



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:

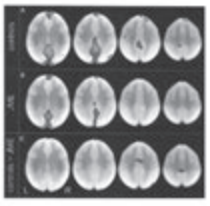
A+B: motor connectivity and working memory network in healthy controls

C+D: increased connectivity in JME patients

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".

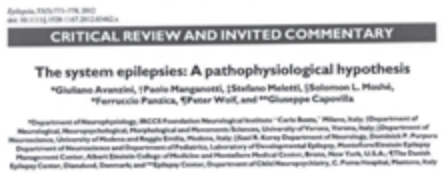


Conclusion

- Pathological activity in a functional anatomical system normally serving physiological function (complex visuo-motor coordination)
- = the probable basis for praxis induction
- seizures occur in a local reflex loop in the system's periphery producing focal motor seizures in a "generalized" epilepsy

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 +?)



CRITICAL REVIEW AND INVITED COMMENTARY

The system epilepsies: A pathophysiological hypothesis

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*

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

Concepts of ictogenesis: 1970

- Partial szs: "Activation of an anatomical and/or functional system of neurons limited to a part of a single hemisphere; in which the inconsistently present electrographic seizure patterns are restricted, at least at their onset, to one region of the scalp (the area corresponding to the cortical representation of the system involved); and in which the initial neuronal discharge usually originates in a narrowly limited or even quite diffuse cortical (the most accessible and vulnerable) part of such a system."

Concepts of ictogenesis: 1981

Partial (focal, local) seizures

"Partial seizures are those in which, in general, the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to part of one cerebral hemisphere."

"There is considerable evidence that simple partial seizures usually have unilateral hemispheric involvement and only rarely have bilateral hemispheric involvement; complex partial seizures, however, frequently have bilateral hemispheric involvement."

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.

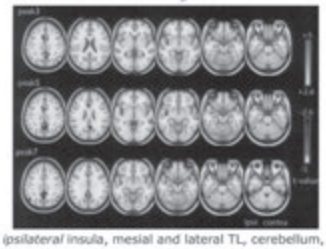
Focal ictogenesis: investigation methods

- 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

Focal ictogenic networks

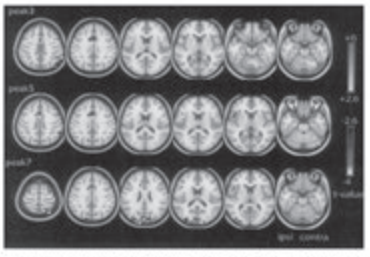
- The networks around focal epileptic lesions are quite widespread
- It is not yet quite clear to what extent they represent excitation and to what extent, inhibition
- Inhibition contributes to synchronisation and is, thus, an important factor of ictogenesis

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



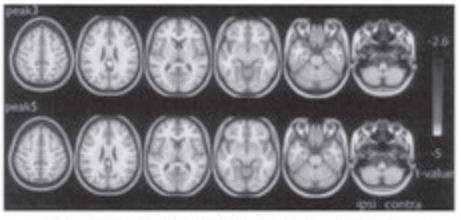
Activation: *ipsilateral* insula, mesial and lateral TL, cerebellum, *bilateral* mid-cingulate gyrus
Deactivation: *bilat.* inferior parietal lobules, posterior cingulate gyrus, precuneus, *contralat.* post. temp. cortex *Fahoum et al Epilepsia 2012*

14 pts with frontal lobe epilepsy



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

20 pts with posterior cortical epilepsies



Bilateral deactivation clusters in posterior cingulate cortex and precuneus

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?

Musicogenic seizures

- Temporal lobe epilepsies of varying etologies
- Only very small subgroup within this frequent syndrome
- Many patients have above average musical abilities
- Hypothesis: ictogenesis in enriched functional anatomical network serving acquired musical abilities: network established by learning
- Similarity to system epilepsies

Reflex seizures in focal epilepsies

- Touch-induced
- Movement-induced (kinesthetic proprioception)
- Startle
- Hot water
- Musicogenic
- Eating
- Tooth-brushing
- Miscellaneous (smells, voices, writing etc)

Touch and movement – induced szs

- Seizure types: focal sensorimotor
- Typically lesional epilepsies (FCD, Rasmussen etc)
- Anatomical relation of trigger stimuli to lesion
- Ictogenic mechanisms not fully elucidated but probably related to abnormal neuronal circuitry in and around lesion favouring hypersynchrony by loss of complexity
- Probably not characteristic for all focal epilepsies

Focal ictogenesis in idiopathic LREs

- Rolandic childhood epilepsy: components
- There is no lesion or constant epileptic focus
- Age-dependence: functional instability of immature systems in the developing brain (Avanzini et al 2012)
- Seizures arise in the arm and face field of the motor cortex and can be generated in alternate sides
- 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
- Somatosensory system (contralateral spikes evoked by tapping or electrical stimulation, Manganotti et al 1998)

Focal ictogenesis in Rolandic childhood ep.

- Presumably again involvement of a pre-existing physiological cortico-thalamic circuit serving sleep-generating mechanisms.
- Interaction with an instable cortex in a vulnerable phase of development.
- Ends spontaneously at maturation of the motor system responsible for challenging fine-tuned movements.
- Different from lesional focal ictogenesis.

Conclusion

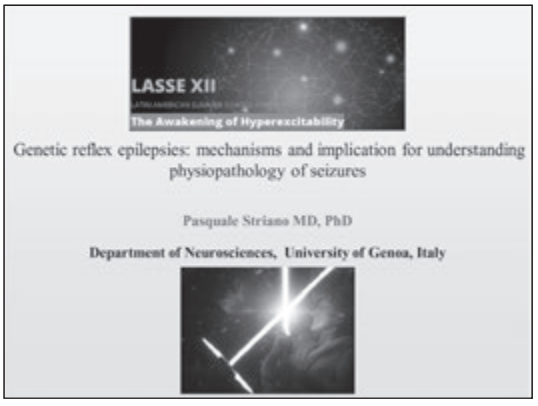
Ictogenesis of focal seizures in Rolandic epilepsy totally different from symptomatic focal epilepsies

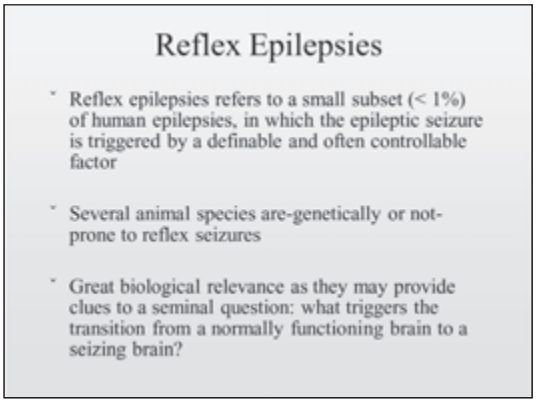
Uses physiological functional anatomical networks

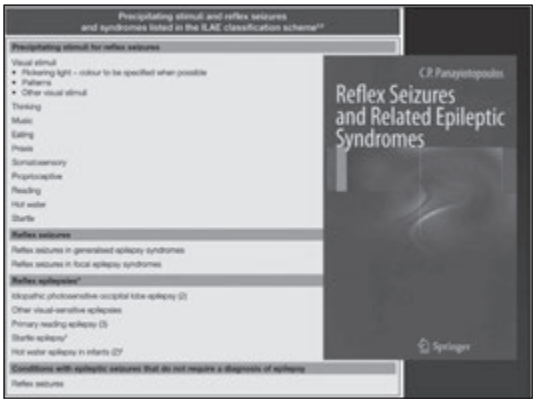
Idiopathic LREs are "system epilepsies" (Avanzini et al 2012)

Pasquale Striano (Italy)

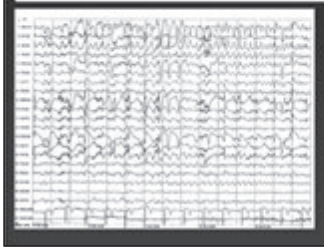
GENETIC REFLEX EPILEPSIES: MECHANISMS AND IMPLICATION FOR UNDERSTANDING PHYSIOPATHOLOGY OF SEIZURES

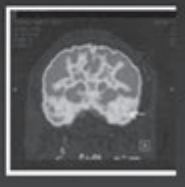


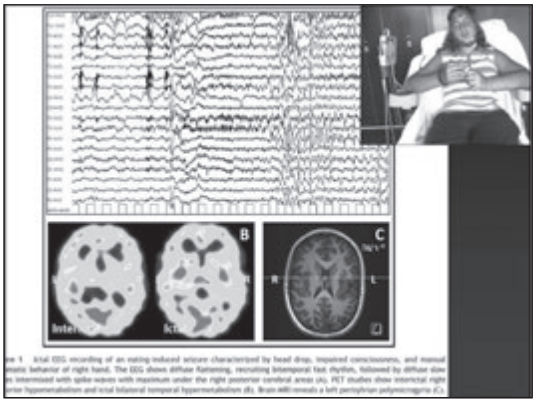




Eating Epilepsy is Associated With Initial Precipitating Events and Therapy Resistance

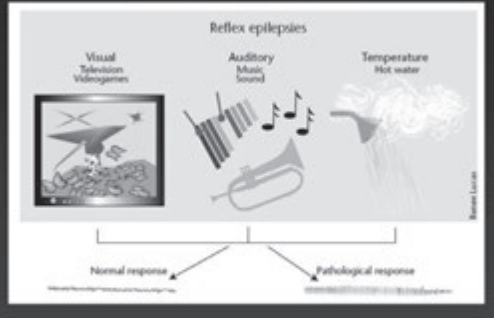






Reflex Epilepsies: the impact of genetics

1. Do reflex epilepsies have a genetic etiology ?
2. Have progresses in the genetics of reflex epilepsies been made?
3. Which strategies can we adopt to study the genetics of reflex epilepsies ?



Data on Animal Models (1)

- In 1960, Crawford selected the Fayoumi chicken line with photosensitive epilepsy
- Fayoumi chicken was long considered an excellent model of reflex photosensitive epilepsy
- 30 years later, it was demonstrated that also high-amplitude sounds may induce seizures in Fayoumi chicken

Data on Animal Models (2)

- The *Papio papio baboon* (Senegal) is the best animal model of photosensitivity

- Up of 60% of the animals are photosensitive
- In this model of reflex epilepsy, ILS induces myoclonus (eyelids and then entire the body)

Family data on Humans

- There is ample evidence for genetic transmission of PPR (Stephani, 2004; Verrotti, 2005)
- The expression of PPR phenotype is influenced by several factors: age, gender, ethnicity, ormonal factors, etc.....

Candidate gene analysis of the succinic semialdehyde dehydrogenase gene (*ALDH5A1*) in patients with idiopathic generalized epilepsy and photosensitivity

Susanne Lorenz[a,b], Armin Heils[d], Kirsten P. Taylor[a,b], Anne Gehrmann[a,b], Hiltrud Muhle[c], Meike Gresch[c], Tim Becker[d], Ulrike Tauer[c], Ulrich Stephani[c], Thomas Sander[a,b,*]

Neuroscience Letters 397 (2006) 256–259

Association of *BRD2* polymorphisms with photoparoxysmal response

Susanne Lorenz[a,b], Kirsten P. Taylor[a], Anne Gehrmann[a], Tim Becker[c], Hiltrud Muhle[d], Meike Gresch[d], Ulrike Tauer[d], Thomas Sander[a,b,*], Ulrich Stephani[d]

Neuroscience Letters 400 (2006) 155–159

Am. J. Hum. Genet. 73:261–270, 2003

BRD2 (RING3) Is a Probable Major Susceptibility Gene for Common Juvenile Myoclonic Epilepsy

Deb K. Pal,[1,2,*] Oleg V. Evgrafov,[2,*] Paula Tabares,[2] Fengli Zhang,[2] Martina Durner,[1] and David A. Greenberg[1,2,3,4]

[1]Division of Statistical Genetics, Department of Biostatistics, Mailman School of Public Health, [2]Department of Psychiatry, and [3]Columbia Genome Center, Columbia University, and [4]Clinical and Genetic Epidemiology Unit, New York State Psychiatric Institute, New York

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Seizure

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

Short communication

Bromodomain-Containing Protein 2 gene in photosensitive epilepsy[☆]

Ebru Nur Yavuz[a], Ozkan Ozdemir[b], Suzin Catal[b], Nerses Bebek[a,b], Ugur Ozbek[b], Betul Baykan[a,b,*]

Methods: Fifty-four PSE patients with normal findings on neurological examination and neuro-imaging studies were included. All had a clear photoparoxysmal response in the EEG as reported by 2 experienced EEG interpreters. We investigated the BRD2 gene by denaturing high performance liquid chromatography followed by direct DNA sequencing.

Results: We failed to detect any mutations of the BRD2 gene. However, several single-nucleotide polymorphisms (SNPs) were observed in the gene; three of them were novel SNPs. The comparison of the patients showing these SNP changes with the remaining patients suggested a link between carrier status and prognosis.

Conclusion: Our study did not confirm the presence of the genetic variants previously found to link the BRD2 gene to the idiopathic form of photosensitive epilepsy. SNP changes of the BRD2 gene may be clinically relevant but these findings need to be verified by larger studies.

Reflex Epilepsies

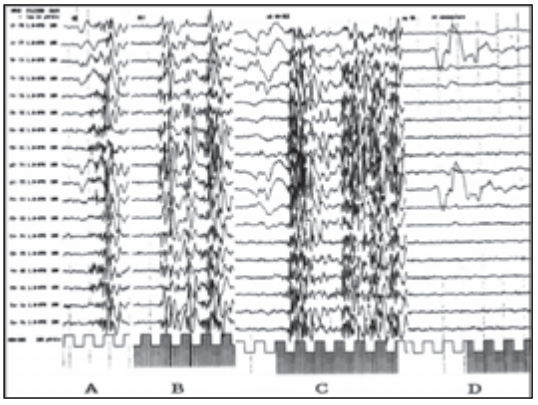
Relationships with other epilepsies

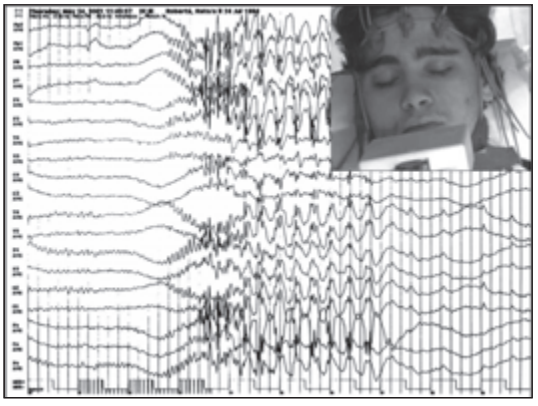
TABLE 1. *Photosensitivity in epilepsy*

Pure photosensitive epilepsy (40%)
Seizures only with flickering light source or visual pattern
Epilepsies with photosensitivity (60%)
Seizures with flickering light source or visual pattern and spontaneous, including
Early-onset absence epilepsy
Childhood absence epilepsy
Myoclonic epilepsy in infancy/childhood
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Eyelid myoclonia and absences (Jeavons syndrome)
Epilepsy with generalized tonic–clonic seizures on awakening
Other myoclonic epilepsies/syndromes[a]
Focal epilepsies
Progressive myoclonic epilepsies

[a]Epilepsy with myoclonic absences, severe myoclonic epilepsy in infancy, facial myoclonias with absences, myoclonic astatic epilepsy.

Epilepsia, Vol. 46, Suppl. 9, 2005


A
B
C
D



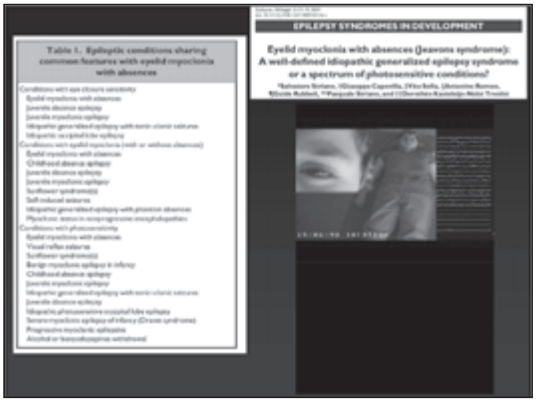


Table 1. Epileptic conditions sharing common features with eyelid myoclonia with absences
EPILEPSY SYNDROMES IN DEVELOPMENT
Eyelid myoclonia with absences (Jeavons syndrome): A well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions?

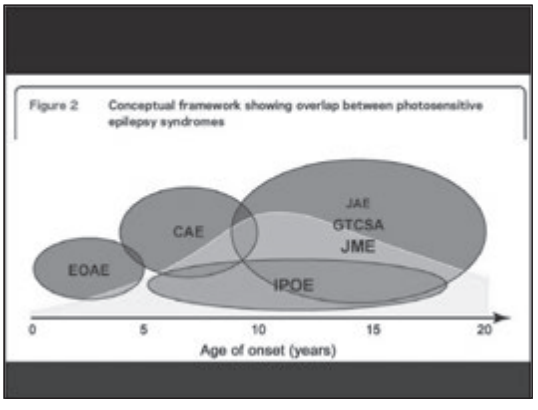


Figure 2 Conceptual framework showing overlap between photosensitive epilepsy syndromes
JAE
GTCSA
JME
CAE
EOAE
IPOE
0
5
10
15
20
Age of onset (years)

Genetic Dissection of Photosensitivity and Its Relation to Idiopathic Generalized Epilepsy

Ulrike Tauer, MD,[1] Susanne Lorenz,[1,2] Kirsten P. Lemke,[1,2] Armin Heils, MD,[1] Hiltrud Muhle, MD,[1] Heike Grosch,[1] Bernd A. Neubauer, MD,[1] Stephan Wilde, MD,[1] Gabrielle Rudolf, PhD,[3] Mourad Mantheiren,[3] Konstantin Strauch, PhD,[4] Peter Nürnberg, PhD,[5] Bettina Schmitz, MD,[1] Ulrich Stephani, MD,[1] and Thomas Sander, MD[1,2]

Table 1. Clinical Characterization of the Family Samples

Family Sample[a]	Family (N)	Individual (N)	PPR	PPR Only	PSE	IGE	GSW Only	IPE	SS	FC
PPR/All	60	295	166	67	19	72	8	7	5	4
PPR	19	98	57	35	15	—	—	6	2	2
PPR/IGE	25	121	68	8	—	63	6	—	3[b]	1[b]

[a]PPR/All = entire family sample; PPR = PPR-multiplex families without IGE; PPR/IGE = PPR-multiplex families with IGE.
[b]One patient displayed PPR but had no IGE or unprovoked GSW.

IGE = idiopathic generalized epilepsy; IPE = idiopathic partial epilepsy; SS = unprovoked single generalized tonic-clonic seizure; FC = febrile convulsions; PSE = photosensitive epilepsy; GSW = unprovoked generalized spike-wave electroencephalogram discharges; PPR = photoparoxysmal response.

PPR trait: PPR type I µ IV IGE trait: IGEs + GSW discharges

Table 2. NPL and MOD Score Results

Family Sample[a]	N	Trait Definition	Chromosome	Position (cM)	NPL	p	Position (cM)	MOD Score	Penetrance[b] $f_{+/+}$	$f_{+/-}$	$f_{-/-}$	Allele Frequency	T_{max}[c]
PPR/All	60	PPR	11	29.1	2.55	0.0018	27.0	2.25	0.80	0.80	0.01	0.45	0.00018
PPR	19	PPR	06	53.2	2.01	0.0048	50.7	1.38	0.80	0.80	0.07	0.21	0.00086
PPR/IGE	25	PPR	11	65.2	3.06	0.0013	65.2	3.01	0.80	0.01	0.15	0.28	0.00015
PPR/IGE	25	PPR + IGE	11	65.2	2.54	0.0039	65.8	2.62	0.01	0.01	0.01	0.06	0.00003
PPR/IGE	25	IGE	11	71.6	3.18	0.0007	68.3	4.83	0.01	0.01	0.01	0.02	—[d]

[a]PPR/All = entire family sample; PPR = 10 PPR-multiplex families without IGE; PPR/IGE = 25 PPR-multiplex families with IGE/GSW.
[b]Penetrances of the diozic gene genotypes; + = wild-type allele; m = mutant allele.
[c]Empirical type I error rate.
[d]None of 100,000 replicates simulated under the assumption of no linkage provided a MOD score that exceeded the observed MOD score of 4.83.

NPL = nonparametric linkage; PPR = photoparoxysmal response; IGE = idiopathic generalized epilepsy.

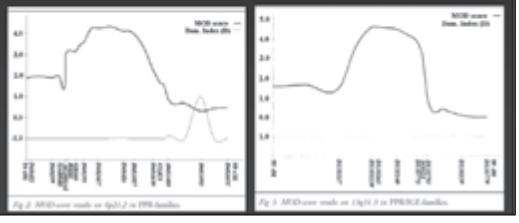


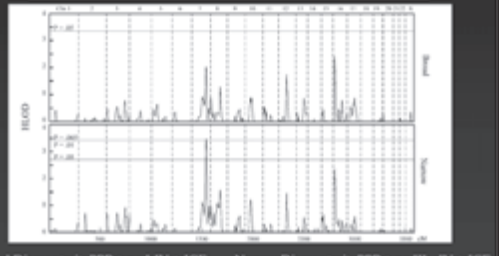
Fig 2. MOD-score results on 6p21.3 in PPR-families.

Fig 3. MOD-score results on 11q14.3 in PPR/IGE-families.

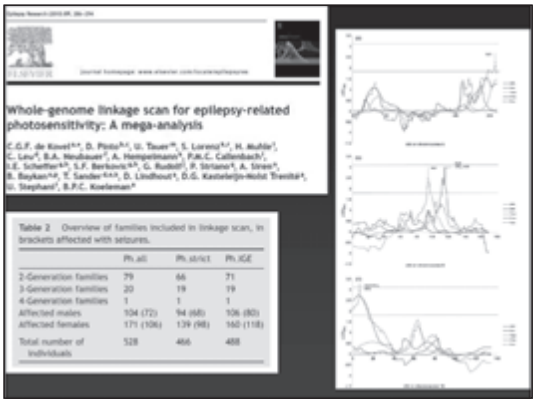
Genome-wide linkage scan of epilepsy-related photoparoxysmal electroencephalographic response: evidence for linkage on chromosomes 7q32 and 16p13

Human Molecular Genetics, 2005, Vol. 14, No. 1

Dalila Pinto[1,4], Birgit Weeland[1], Gerrit-Jan de Haan[2], Gabrielle Rudolf[3], Berta Martins da Silva[3], Edouard Hirsch[3], Dick Lindhout[1], Dorothée G.A. Kasteleijn-Nolst Trenité[1,*] and Bobby P.C. Koeleman[1]



Broad Disease trait: PPR type I-IV + IGE Narrow Disease trait: PPR type III - IV + IGE

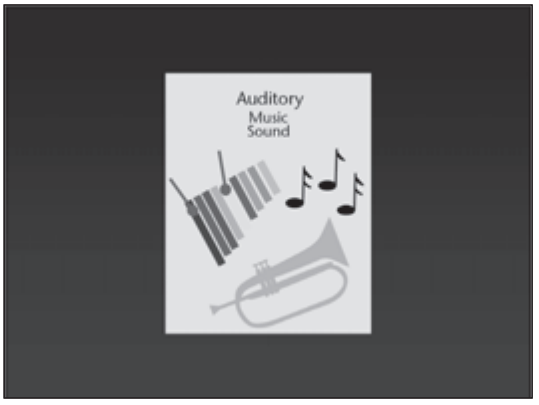


Whole-genome linkage scan for epilepsy-related photosensitivity: A mega-analysis

C.G.F. de Kovel[1,*], D. Pinto[1,4], U. Tauer[1], S. Lorenz[1,2], H. Muhle[1], C. Leu[2], B.A. Neubauer[1], A. Hempelmann[1], P.W.C. Callenbach[1], J.E. Scheffer[4,5], S.F. Berkovic[4,5], G. Rudolf[3], P. Striano[6], A. Strian[6], B. Baykan[7,8], T. Sander[1,2,5], D. Lindhout[1], D.G. Kasteleijn-Nolst Trenité[1], U. Stephani[1], B.P.C. Koeleman[1]

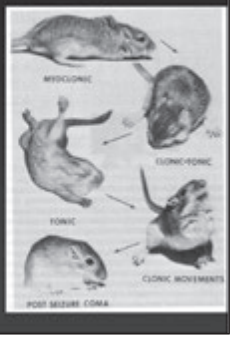
Table 2 Overview of families included in linkage scan. In brackets affected with seizures.

	Ph.all	Ph.strict	Ph.IGE
2-Generation families	79	66	71
3-Generation families	20	19	19
4-Generation families	1	1	1
Affected males	104 (72)	94 (68)	106 (80)
Affected females	171 (106)	139 (98)	160 (118)
Total number of individuals	528	466	488



Animal Models

- Audiogenic seizures (mouse, rat, chicken, rabbit)
- DBA/2 line mouse suffers from violent, generalized, often fatal, seizures if exposed to intense auditory stimulus (90-120 dB)
- Wistar rat is a genetically-prone model of AS but also spontaneous seizures (pharmacological model of human generalized epilepsies)



Animal Models

- Audiogenic seizures in DBA/2 mice and Wistar rats are caused by mutation in MASS1

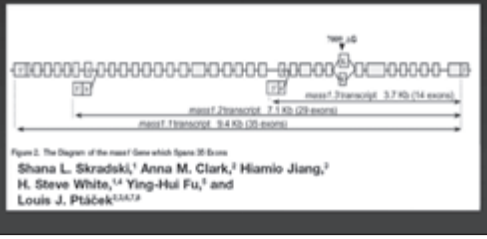
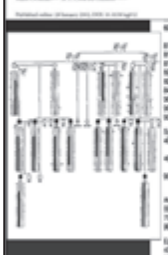


Figure 2. The Diagram of the mass1 Gene which Spans 35 Exons

Shana L. Skradski,[1] Anna M. Clark,[2] Hiamio Jiang,[2] H. Steve White,[1,4] Ying-Hui Fu,[5] and Louis J. Ptáček[2,3,6,7,8]

Mutations in *LGI1* cause autosomal-dominant partial epilepsy with auditory features



Ottman et al., 1995

MUTATION UPDATE

LGI1 Mutations in Autosomal Dominant and Sporadic Lateral Temporal Epilepsy

Variable age of onset (4-40 years, average ~20)

Simple Partial Seizures

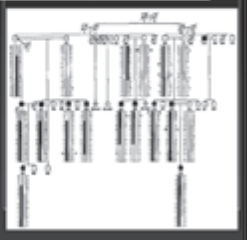
Auditory aura (Visual symptoms, aphasia)

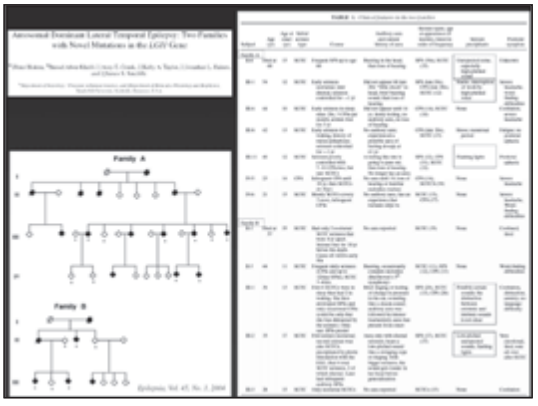
Secondarily Generalized Tonic-Clonic Seizures

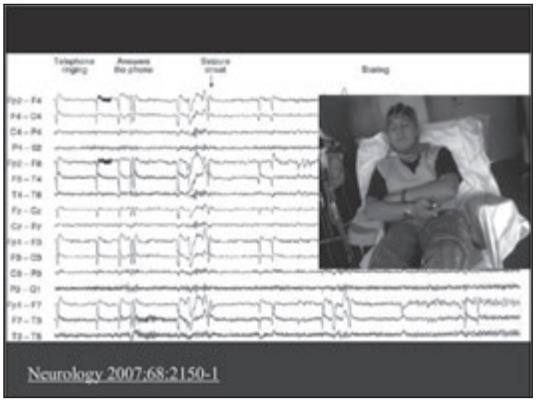
Seizures commonly responsive to therapy

Normal interictal EEG or mild temporal abnormalities

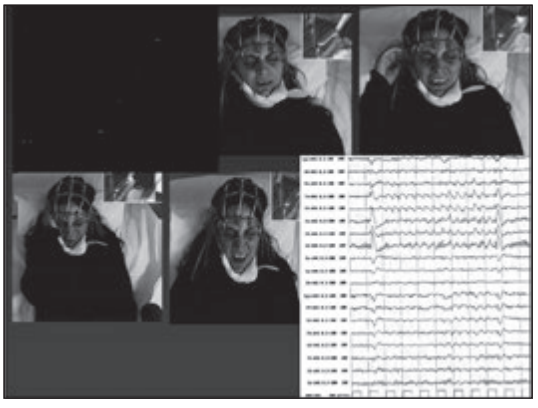
Absence of psychomotor delay or brain lesions



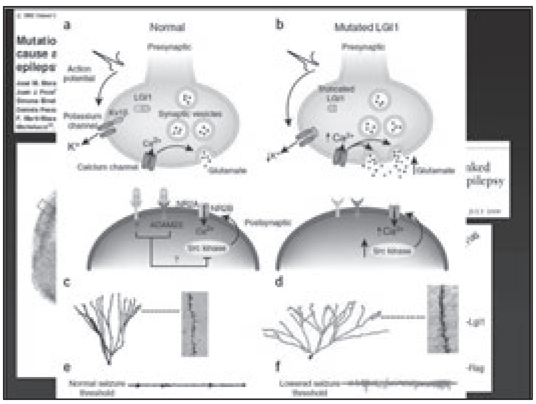


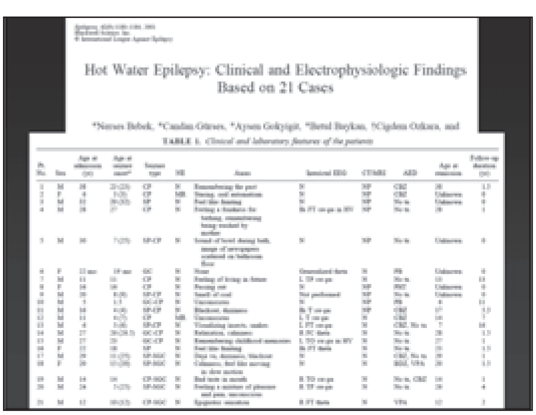


Neurology 2007;68:2150-1



Symptom type	Frequency (%)	Description
Auditory	64	Elementary and unformed sounds (whistle, buzzing, ringing, humming etc.) (84%); complex sounds (structured voices, specific songs or music) (10%); sudden hearing loss or attenuation/distorted perception of sounds and voices (6%)
Aphasia	17	Loss of speech comprehension and difficulty in speaking
Visual	17	Unformed images (flashes, lights, colors, simple figures)
Psychic	16	Déjà vu; depersonalization; fear; pleasure; dreamy state
Autonomic	12	Nausea; flushing; palpitation; epigastric symptoms
Vertiginous	9	Dizziness; vertigo
Other	13	Olfactory; focal motor seizures; staring





Severe myoclonic epilepsy of infancy

Clinical features

- Onset at 1 y with febrile or afebrile seizures
- Myoclonic jerks
- Intractable epilepsy
- Psychomotor delay within 2 years from the onset of the seizures
- No history of acquired brain injury
- Normal cognitive and motor development before seizure onset

Genetic features

- Usually Sporadic
- Increased incidence of febrile seizures and Epilepsy in relatives of probands

De Novo Mutations in the Sodium-Channel Gene *SCN1A* Cause Severe Myoclonic Epilepsy of Infancy

Lieve Claes, Jurgen Del-Favero, Berten Ceulemans, Lieven Lagae, Christine Van Broeckhoven, and Peter De Jonghe

Spectrum of *SCN1A* mutations in severe myoclonic epilepsy of infancy

Table: Genotype-phenotype correlations

Clinical characteristics	No mutation, n = [illegible]	Mutation present, n = [illegible]	Fisher exact test, p	Point mutations, n = [illegible]	Protein deletion, n = [illegible]	Fisher exact test, p
General information						
Sex ratio (M/F)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Familial FS [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Familial epilepsy [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Type of the first seizure						
Afebrile seizures	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Febrile seizures	[illegible]	[illegible]		[illegible]	[illegible]	
Type of seizures						
Clonic generalized	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Unilateral motor	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Complex partial	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Absence	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Status epilepticus	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Febrile susceptibility [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Other neurologic symptoms						
Clinical photosensitivity	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ataxia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Psychomotor delay						
M	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
MO	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
S	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

p Values are calculated using the Fisher exact test. The p values indicated with * are corrected for multiple comparison according to Bonferroni correction for multiple testing.

Family data on Humans

- Family history of HWE is found in 7-15% of Indian patients (Satishchandra, 1988)
- Monozygotic and dizygotic twins with HWE have been reported as well as some families from India with high association of febrile seizures

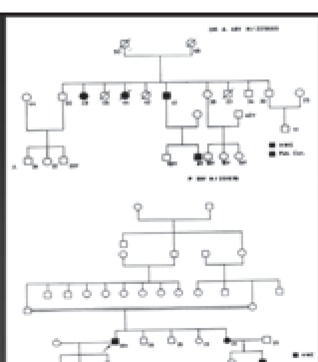


FIG. 4. A and B. Pedigrees of families with hot water epilepsy. Note the coexistence of hot water epilepsy and febrile convulsions.

Reflex Epilepsies

Hot-Water Epilepsy

A case of hot water epilepsy in the monozygotic cotwin.

Bish N, Kartha J, Kanna K.

Correlates of hot water epilepsy in rural south India: a descriptive study.

Gururaj G, Satishchandra P.

Department of Epidemiology National Institute of Mental Health and Neuro Sciences, Bangalore, India.

Seizures precipitated by the stimulus of hot water known as 'hot water epilepsy' (HWE) have been commonly reported from South India. The present report outlines certain descriptive epidemiological aspects of 76 cases from two rural satellite clinics of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India. Geographical clustering was observed in one of the centres. HWE was common in the age group of 20–30 years with a male to female ratio of 2.6:1. The frequency of seizure occurrence was more than 1–4 attacks/month in 89% of cases. Past history of febrile convulsions and family history of HWE was noticed in 21 and 18% of our cases, respectively. The conversion of reflex to nonreflex epilepsy occurred in 30.6% of cases. Population-based epidemiological studies are essential for further understanding of HWE for developing strategies towards prevention and control.

Familial autosomal dominant reflex epilepsy triggered by hot water maps to 4q24-q28

X-linked focal epilepsy with reflex bathing seizures: Characterization of a distinct epileptic syndrome

---

D. K. Nguyen et al.

Figure 2.

Periictal findings for PLM. (V4). (A) Ictal rhythmic theta activity over the right centrotemporal region spreading to the right hemisphere with incremental amplitude and decremental frequency during a seizure triggered by rubbing the face with a wet towel (filters used: high-frequency filter, 15 Hz, low-frequency filter, 1 Hz). (B) Right temporolimbic activation on ictal SPECT.

Epilepsia © ILAE

Reflex Bathing Seizures

Figure 3.

Back home messages

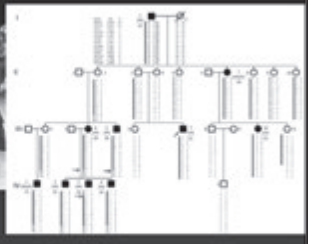
Genetics of Reflex Epilepsies

Reflex Epilepsies

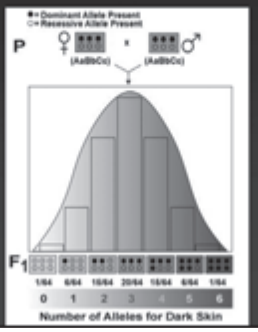
Conclusions

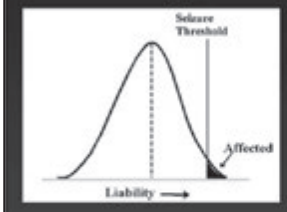
Reflex epilepsies are a subgroup of epileptic disorders showing most of the features that make genetic research difficult in human epilepsy:

- Clinical heterogeneity
- Heterogenous etiology
- Genetic heterogeneity
- Complex mode of inheritance
- Possible gene-environment interactions

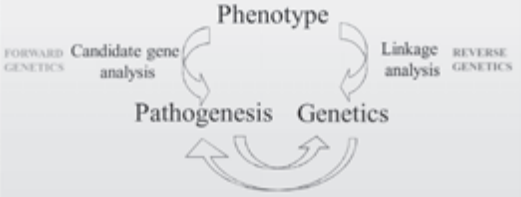


Complex Continuous traits
(Dark Skin)

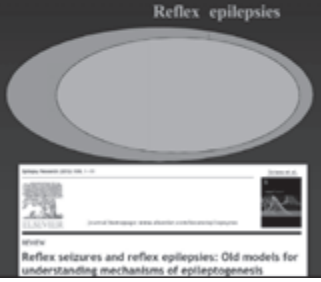


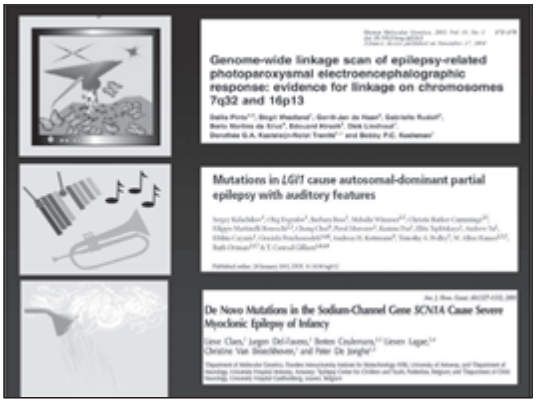


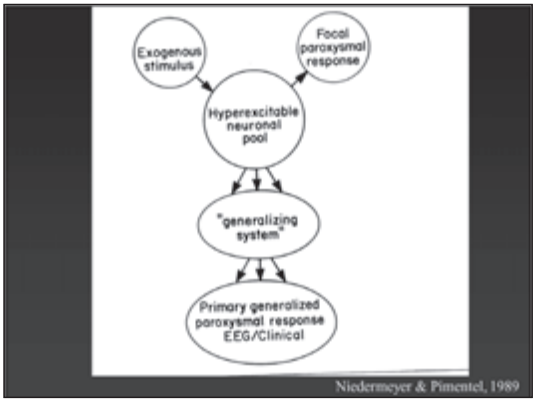
Reflex Epilepsies

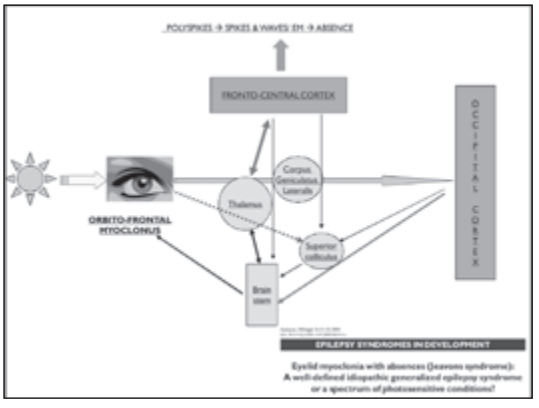


Biological relevance of Reflex Epilepsies




Genome-wide linkage scan of epilepsy-related photoparoxysmal electroencephalographic response: evidence for linkage on chromosomes 7q32 and 16p13
Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features
De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy


Exogenous stimulus
Focal paroxysmal response
Hyperexcitable neuronal pool
"generalizing system"
Primary generalized paroxysmal response EEG/Clinical
Niedermeyer & Pimentel, 1989


POLYSPIKES → SPIKES & WAVES: EM → ABSENCE
FRONTO-CENTRAL CORTEX
OCCIPITAL CORTEX
Corpus Geniculatus Lateralis
Thalamus
Superior colliculus
Brain stem
ORBITO-FRONTAL MYOCLONUS
EPILEPSY SYNDROMES IN DEVELOPMENT
Eyelid myoclonia with absences (Jeavons syndrome): A well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions?

doi:10.1093/brain/awh446 *Brain* (2005), **128**, 700–710

REVIEW ARTICLE

Cortical triggers in generalized reflex seizures and epilepsies

Edoardo Ferlazzo,[1,5] Benjamin G. Zifkin,[4] Eva Andermann[1,2] and Frederick Andermann[1,3,4]

Table 1 *Regions and systems activated by stimuli triggering generalized reflex seizures*

Generalized reflex seizures	Typical effective stimulus	Regions or systems subserving the trigger
Sensitivity to visual stimuli		
(i) Photosensitivity	Environmental flicker, screen content	Occipital cortex
(ii) Pattern sensitivity	Striped patterns, screen content	Occipital cortex
Sensitivity to other sensory stimuli	Sudden touch or noise	Sensorimotor cortex (?)
Sensitivity to non-verbal cognitive stimuli		
(i) Thinking induction	Mental arithmetic, Brooks letter task, action-programming	Non-dominant parietal lobe or biparietal networks for non-verbal visuo-spatial thought
(ii) Praxis induction	Block design	Non-dominant parietal lobe or biparietal networks for non-verbal visuo-spatial thought, and rolandic areas
Sensitivity to verbal cognitive stimuli	Reading, talking, writing	Both hemispheres predominantly dominant fronto-temporal lobes

Ferlazzo et al, 2005

Reflex Epilepsies

Pathogenesis

Photosensitive Epilepsy
- Abnormal processing of visual informations in the visual cortex

Reading Epilepsy
- Abnormalities in the visual system
- Central language and cognitive mechanisms
- Proprioceptive inputs from the peripheral muscles (jaw, larynx and eyes)

Hot-Water Epilepsy
- Aberrant thermoregulatory system

Movement-induced Epilepsy
- Central mechanisms related to the elaboration of movement
- Proprioceptive impulses from suddenly activated muscle groups

Alfonso Represa (France)

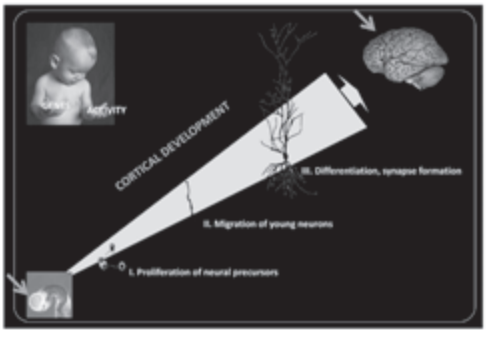
MOLECULAR MECHANISMS THAT UNDERLIE CORTICAL NETWORK DEVELOPMENT AND FUNCTION IN HEALTH AND DISEASE

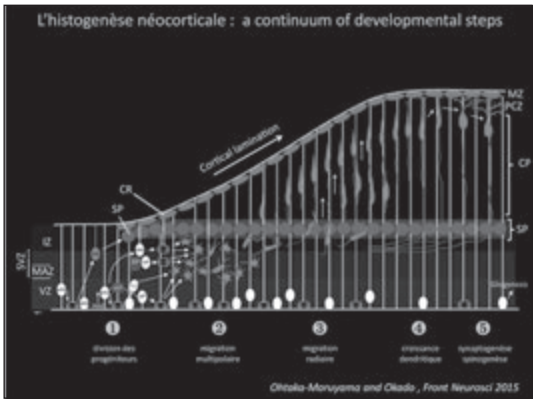
Molecular mechanisms that underlie cortical network development and function in health and disease

Alfonso Represa, MD, PhD
INMED, Marseille (France)

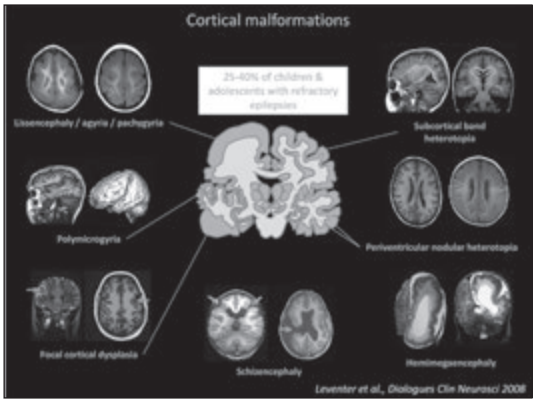
Inmed | Inserm | Aix Marseille université

Main stages in cortical development





Cortical malformations



Neuronal migration disorders: clinical manifestations

- **Epilepsy**
- **developmental delay**
- **mental retardation**
- Locomotor manifestations
- failure to grow and thrive
- difficulties with feeding
- smaller than normal head
- Behavior alterations (autism)
- Language disorders

- **Account for 30-40 pharmaco-resistant epilepsies in children**
- **More than 25 syndromes resulting from abnormal neuronal migration have been described.**
- Autism, schizophrenia, dyslexia can be related to neuronal migration defects

Questions:

1. Link between cause and phenotype: understanding the pathophysiology of cortical development disorders

2. Link between the developmental alteration and the epileptic condition

Questions:

1. Link between cause and phenotype: understanding the pathophysiology of cortical development disorders

   Physiopathological mechanisms depend on the
   a) The developmental period concerned
   b) Genetic or Environmental causes
   c) The cell type affected

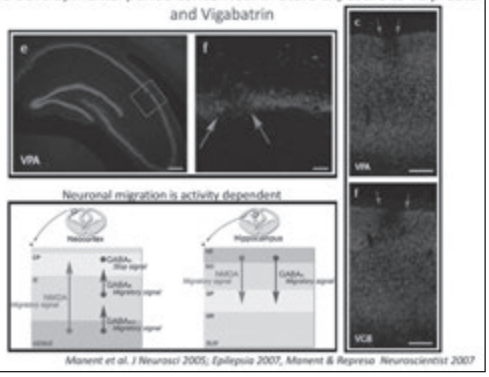
Environmental factors and conditions which can potentially influence the developing brain

- Therapeutic drugs
- Retinoic acid
- Anti-thyroid drugs
- Oestroprogrestative drugs
- Testosterone and derivatives
- Anti-mitotic drugs
- Lithium and psychotropic drugs
- Benzodiazepines
- Neuroreceptors acting drugs
- Recreational drugs
- Tobacco
- Caffeine
- Ethanol
- Cocaine
- Heroin
- L.S.D.
- Marijuana
- Physical and chemical agents
- Dioxins
- Heavy metals
- Organic solvents
- Ionizing radiations
- Head trauma
- Repeated head shaking
- Maternal factors and conditions
- Sexual hormones

- Catecholamines
- Thyroid hormones
- Diabetes
- Non treated phenylketonuria
- Coagulopathies
- Peptides (vasoactive intestinal peptide)
- Hormones from placenta and decidua
- Hypoxic-ischemic conditions
- Chorioamniotitis
- Hyperthermia
- Infectious agents (human pathogens)
- Herpes simplex virus I and II
- Varicella zoster
- Human cytomegalovirus
- Benign lymphocytic choriomeningitis virus
- Rubella virus
- Parvovirus B19
- Coxsackie viurus (B group)
- Pestivirus
- HIV
- Influenza virus
- BK and JC viruses
- Toxoplasma gondii
- Listeria monocytogenes
- Treponema pallidum (syphilis)

Gressens et al, 2003

a) The developmental period concerned: in utero exposure to Valproate and Vigabatrin



Manent et al. J Neurosci 2005; Epilepsia 2007, Manent & Represa Neuroscientist 2007

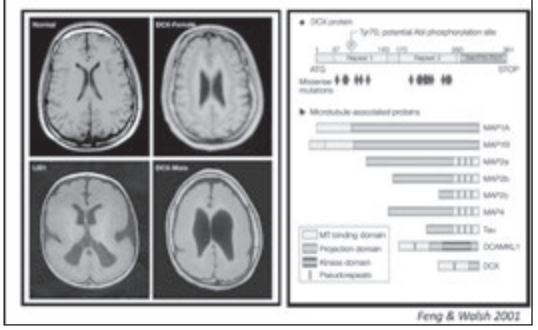
a) The developmental period concerned: postnatal exposure to sevoflurane

em construção, in construction, en construccion, em construção, in construction, en construccion

b) The genetic or environmental cause: diversity of genes and functions

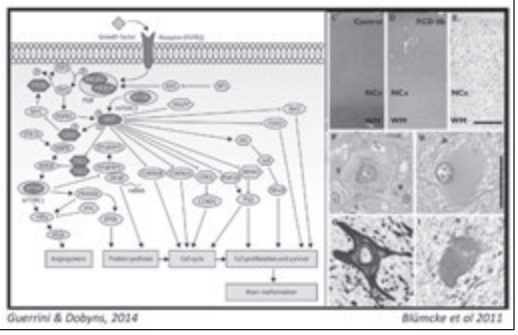
Genes involved			Type of malformation
TSC1	*PIK3CA*	*DEPDC5*	Abnormal proliferation/differentiation (Tuberosclerosis, Megalencephaly and FCDs)
TSC2	*PIK3R2*	*EZH2*	
AKT3	*MTOR*	*NPRL3*	
ARX	*DCX*	*TUBA1A*	Abnormal migration : lissencephaly, Pachiryria, Subcortical band heteroropia
YWHAE	*TUBG1*	*TUBG1*	
DYNC1H1	*RELN*	*TUBB2*	
LIS1	*ACTG1*	*VLDLR*	
ACTB	*KIF2A*	*CDK5*	
KIF5C			
FLNA	*ERMARD*	*FAT4*	Abnormal migration : Periventricular Heterotopia
FMR1	*DCNS1*	*LRP2*	
ARGEF2			
FCMD	*FKRP*	*LARGE*	Cobblestone, Syndrome Walker-Warburg, Syndrome Muscle-eye-brain
GPR56	*SNAP29*	*B3GALNT2*	
POMGnT1	*POMT1*	*POMT2*	
B3GNT1	*GTDC2*	*ISPD*	
TMEM5	*LAMB1*		
SRPX2	*TRB2*	*TUBA1A*	Abnormal cortical organization/Gyration, polymicrogyria
GPR56	*DYNC1H1*	*TUBB2B*	
KIAA1279	*PAX6*	*TUBB3*	
NSDHL	*EOMES*	*TUBB5*	
SNAP29	*COL18A1*	*PIK3R2*	

b) The genetic or environmental cause: microtubule associated proteins and lissencephaly (Tubulinopathy)



Feng & Walsh 2001

b) The genetic or environmental cause: MTOR and Focal cortical dysplasia



Guerrini & Dobyns, 2014 Blümcke et al 2011

A developmental and genetic classification for malformations of cortical development (see Barkovich et al, Brain 2012)

(I) MALFORMATIONS SECONDARY TO ABNORMAL NEURONAL AND GLIAL PROLIFERATION OR APOPTOSIS

- (A) SEVERE CONGENITAL MICROCEPHALY (MIC), pre-migrational reduced proliferation or excess apoptosis
- (B) MEGALENCEPHALY (MEG) including both congenital and early postnatal
- (C) CORTICAL DYSGENESIS WITH ABNORMAL CELL PROLIFERATION BUT WITHOUT NEOPLASIA
- (D) CORTICAL DYSPLASIAS WITH ABNORMAL CELL PROLIFERATION AND NEOPLASIA

(II) MALFORMATIONS DUE TO ABNORMAL NEURONAL MIGRATION

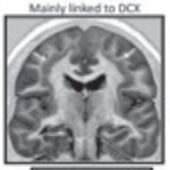
- (A) MALFORMATIONS WITH NEUROEPENDYMAL ABNORMALITIES: PERIVENTRICULAR HETEROTOPIA
- (B) MALFORMATIONS DUE TO GENERALIZED ABNORMAL TRANSMANTLE MIGRATION (radial and non-radial)
- (C) (C) MALFORMATIONS PRESUMABLY DUE TO LOCALIZED ABNORMAL LATE RADIAL OR TANGENTIAL TRANSMANTLE MIGRATION

(III) MALFORMATIONS DUE TO ABNORMAL POSTMIGRATIONAL DEVELOPMENT

- (A) MALFORMATIONS WITH PMG OR CORTICAL MALFORMATIONS RESEMBLING PMG.
- (B) CORTICAL DYSGENESIS SECONDARY TO INBORN ERRORS OF METABOLISM
- (C) FOCAL CORTICAL DYSPLASIAS (WITHOUT DYSMORPHIC NEURONS) DUE TO LATE DEVELOPMENTAL DISTURBANCES
- (D) POSTMIGRATIONAL DEVELOPMENTAL MICROCEPHALY

c) The cell type affected: gray matter heterotopia

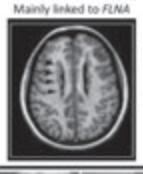
Double cortex (SBH)
Mainly linked to DCX



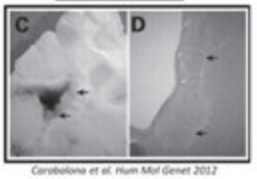
JB Manent

Gleeson et al., 1998.

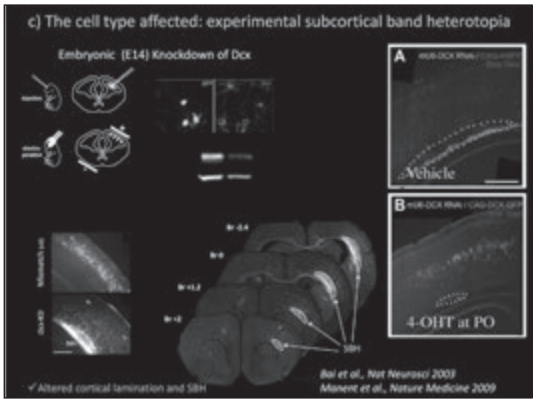
Periventricular nodular heterotopia (PNH)
Mainly linked to *FLNA*

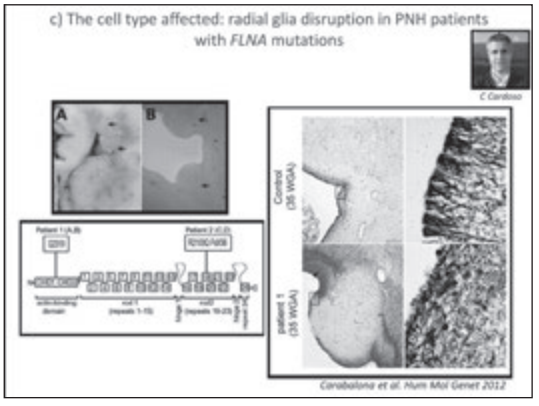


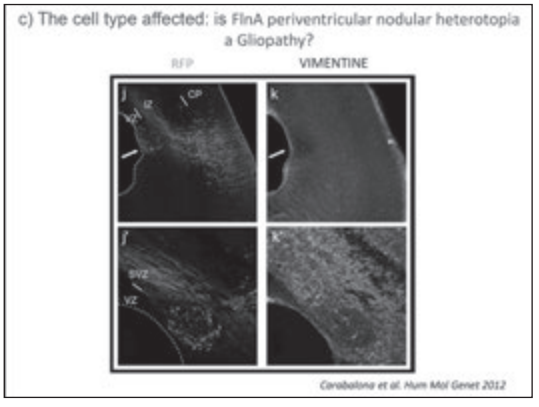
C Cardoso

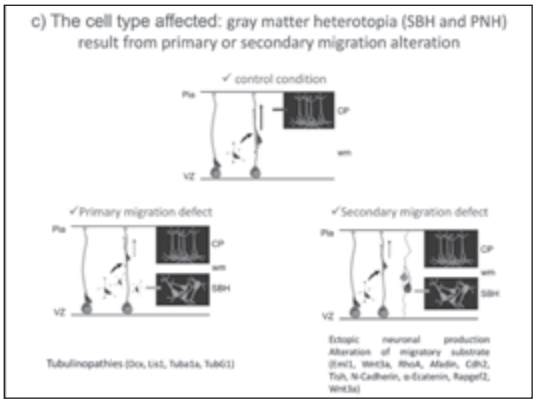


Carabalona et al. Hum Mol Genet 2012


c) The cell type affected: experimental subcortical band heterotopia
Embryonic (E14) Knockdown of Dcx
A
Vehicle
B
4-OHT at PO
SBH
✓Altered cortical lamination and SBH
Bai et al., Nat Neurosci 2003
Manent et al., Nature Medicine 2009


c) The cell type affected: radial glia disruption in PNH patients with FLNA mutations
C Cardoso
A
B
Control (35 WGA)
Patient 1 (35 WGA)
Carabalona et al. Hum Mol Genet 2012

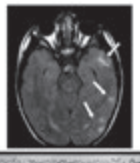

c) The cell type affected: is FlnA periventricular nodular heterotopia a Gliopathy?
RFP
VIMENTINE
CP
iz
SVZ
VZ
Carabalona et al. Hum Mol Genet 2012

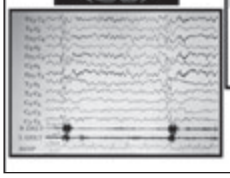

c) The cell type affected: gray matter heterotopia (SBH and PNH) result from primary or secondary migration alteration
✓ control condition
Pia
CP
wm
VZ
✓Primary migration defect
SBH
Tubulinopathies (Dcx, Lis1, Tuba1a, TubG1)
✓Secondary migration defect
Ectopic neuronal production
Alteration of migratory substrate
(Eml1, Wnt3a, RhoA, Afadin, Cdh2, Tish, N-Cadherin, α-Ecatenin, Rapgef2, Wnt3a)

Questions:

2. Link between the developmental alteration and the epileptic condition
   - Cell autonomous changes
   - Network changes

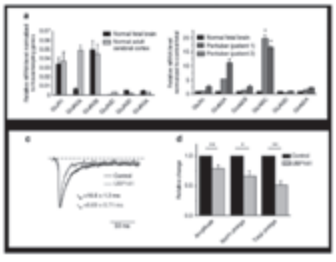
Cell autonomous changes: exploring human postsurgical samples and animal models for Tuberous Sclerosis and FCDs

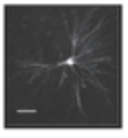




Recordings from postoperational human brain tissue from TSC patient

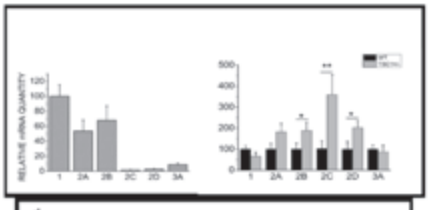
N Bumashev

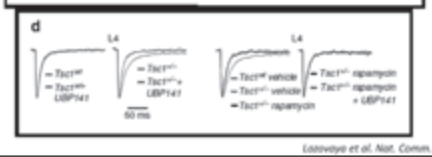




Lozovaya et al. Nat. Comm. 2014

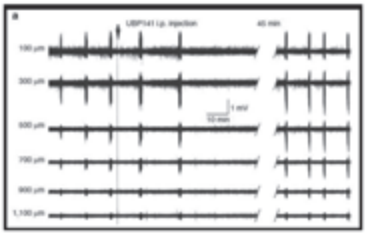
Relative expression of NMDAR subunits in wild type and *Tsc1* $^{+/-}$ mice





Lozovaya et al. Nat. Comm. 2014

Acute antiepileptic effects of NR2C/D antagonists and dapamycin in a mouse model of TSC



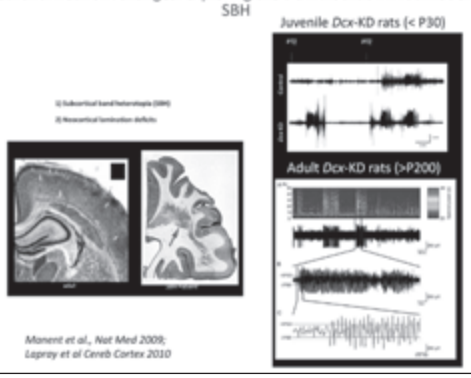
Lozovaya et al. Nat. Comm. 2014

Cell autonomous changes and TSC: conclusion

Tsc1 or TSC2 mutations induces cell intrinsic epileptogenic changes

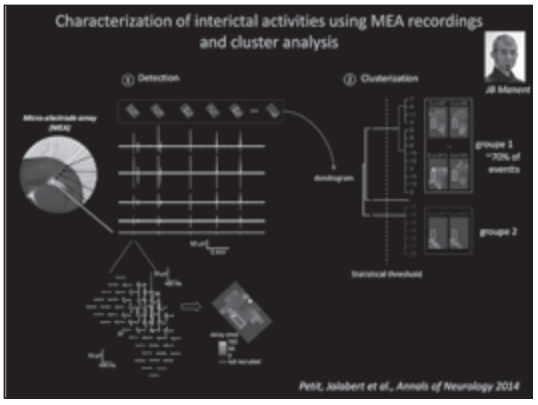
- Selective up-regulation of the NMDA receptors mediated component (NR2C/D) in neurons from TSC and FCD patients (a new therapeutic target)

Neuronal network changes: exploring the Dcx Knockdown rat model of SBH



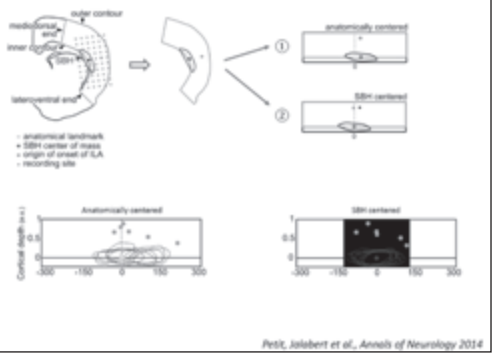
Manent et al., Nat Med 2009;
Lapray et al Cereb Cortex 2010

Characterization of interictal activities using MEA recordings and cluster analysis



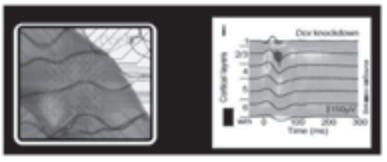
Petit, Jolabert et al., Annals of Neurology 2014

Origin of interictal activity



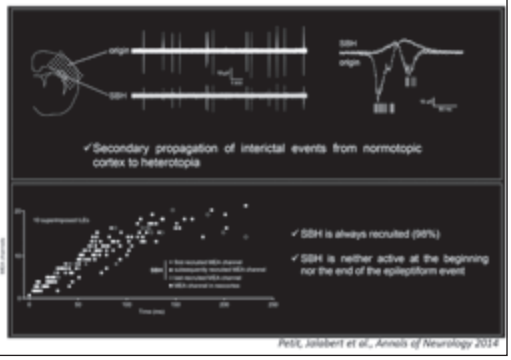
Petit, Jalabert et al., Annals of Neurology 2014

The epileptogenic focus on the cortical slices of DCX-KD rats is out of the heterotopia



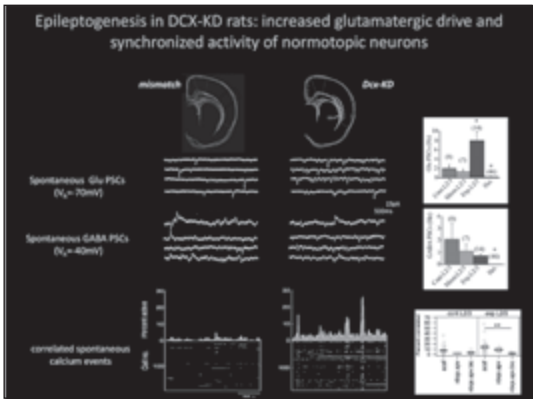
Petit, Jalabert et al., Annals of Neurology 2014

Propagation of interictal events in the cortex of DCX-KD rats

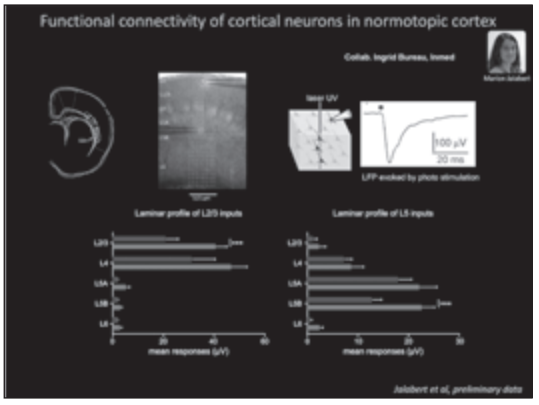


Petit, Jalabert et al., Annals of Neurology 2014

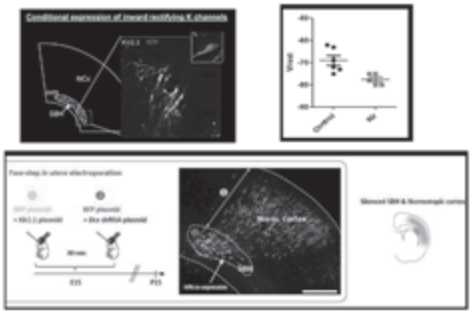
Epileptogenesis in DCX-KD rats: increased glutamatergic drive and synchronized activity of normotopic neurons



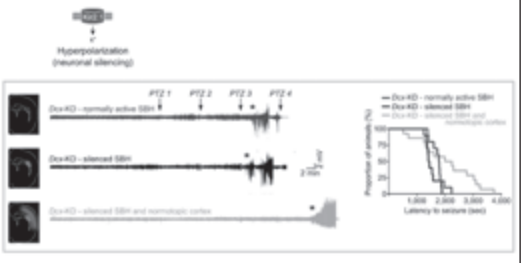
Functional connectivity of cortical neurons in normotopic cortex



In vivo manipulation of neuronal activity in Dcx-KD rats and seizure outcome



Supression of neuronal network excitability

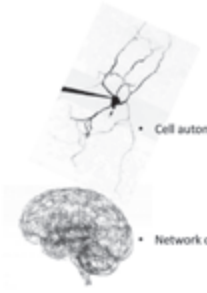


Pont, Jalabert et al., Annals of Neurology 2014

DCX epileptogenesis: conclusion

- ✓ Synaptogenesis and neuronal circuitry altered, within the heterotopic band (synaptic deficit), but also over the heterotopic band (hyperexcitability, impaired connectivity)
- ✓ Network alterations/excitability leads to the emergence of seizures and might contribute to the cognitive deficits described in patients
- ✓ Network excitability might be corrected by inducing the expression of Kir channels: a new therapeutic option

Understanding the pathophysiology of epilepsy in MCDs



- Cell autonomous : intrinsic and synaptic properties of affected cells

- Network dependent: structural and/or functional remodeling

Peter Wolf (Denmark), Rūta Mameniškienė (Lithuania), Katia Lin (Brazil) - team 1

CASE-ORIENTED STUDY 1

GROUP WORK WITH TUTORS - TEAM 2

Peter Wolf (Denmark), Rūta Mameniškienė (Lithuania), Katia Lin (Brazil) – team 2

CASE-ORIENTED STUDY 1

GROUP WORK WITH TUTORS – TEAM 1

Alicia Bogacz

OPERATIONAL DEFINITION OF EPILEPSY

DEFINICIÓN DE EPILEPSIA

Dra. Alicia Bogacz
Sección Epilepsia Instituto de Neurología
LASSE 2018

DEFINICIÓN CONCEPTUAL

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

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

DEFINICIÓN CONCEPTUAL

- Epilepsia se define como una condición neurológica crónica caracterizada por crisis epilépticas recurrentes.
(Hausser W.A.y col,1991) (Blume W.T. y col,2001)

- Epilepsia es un desorden cerebral caracterizado por la predisposición persistente a generar crisis epilépticas y por las consecuencias neurobiológicas, cognitivas, psicológicas y sociales de esta condición.
(Fisher, R y col., 2005)

ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

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)

¿ENFERMEDAD o DESORDEN?

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

CRISIS PROVOCADAS versus CRISIS NO PROVOCADAS

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

RIESGO DE RECURRENCIA

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

CRISIS ÚNICA más LESIÓN o EEG PATOLÓGICO

- No llenan los requisitos de la definición de manera definitiva.
- Los estudios disponibles muestran diferentes resultados:

- Shinar, 1990: 56%
- Dutch Epilepsy Study, 1998: 71%
- Lawn, 2015: 76%

- No hay datos de cómo se combinan o suman los riesgos por lo que hay que decidir en cada caso individual.
- El riesgo de recurrencia está en relación al tiempo transcurrido, cuanto mayor el tiempo desde la crisis menor el riesgo (Lawn,2015).

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.

SPECIAL ARTICLE

Evidence-based guideline: Management of an unprovoked first seizure in adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Se debe informar a los pacientes que presentaron una primera crisis no provocada:

- El riesgo de recurrencia es alto durante los primeros dos años luego de la crisis.
- Este riesgo se incrementa si se asocia con: una lesión cerebral previa, un EEG con alteraciones epileptiformes, una imagen cerebral anormal y crisis nocturnas.
- El inicio precoz del tratamiento reduce el riesgo de crisis en los primeros 2 años, pero no mejora la calidad de vida y en el largo plazo no mejora el pronóstico en relación a la libertad de crisis.
- El riesgo de efectos adversos con el tratamiento de FAE está en un rango entre 7% a 31% y en general son leves y reversibles.

CRISIS SEPARADAS EN EL TIEMPO

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

RESOLUCIÓN DE LA EPILEPSIA

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

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

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

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 %. En un seguimiento más de 10 años (hasta 21 años) el 61% estaba libre de crisis (Berg,AT, 2016).

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".

CONCLUSIONES

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

Elza Márcia Yacubian (Brazil)

THE NEW CLASSIFICATION OF EPILEPTIC SEIZURES

A CLASSIFICAÇÃO OPERACIONAL DAS CRISES EPILÉPTICAS E EPILEPSIA

Elza Márcia Yacubian
Unidade de Pesquisa e Tratamento
das Epilepsias
Hospital São Paulo
UNIFESP

CLASSIFICAÇÃO- IMPLICAÇÕES
Por que classificar?

- O tipo de crise pode sugerir um tratamento particular;
- O tipo de crise tem implicações prognósticas;
- O tipo de crise é dependente do processo patológico subjacente;
- O tipo de crise implica em restrições na vida diária, como por exemplo, direção de veículos.

Classificação- Intenções

Robert Fisher Chair

- Desenvolver uma classificação das crises inteiramente nova, baseada na anatomia, redes neurais ou patofisiologia;
- Ainda não há conhecimento científico suficiente para permitir isto;
- Atualização dos sistemas existentes, uma classificação observacional- **classificação operacional**.

Classificação- O lema

Robert Fisher
Chair

Tudo deve ser feito tão simples quanto possível; mas não mais simples.

- Quando eu uso uma palavra - disse Humpty Dumpty num tom de desprezo - ela significa exatamente aquilo que eu quero que signifique ... nem mais nem menos.

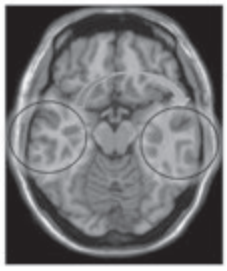
Crises parciais simples ?
Crises parciais complexas?

Operational Classification of Seizure Types by the International League Against Epilepsy

Participants: Robert S. Fisher[1], J. Helen Cross[2], Jacqueline A. French[3], Norimichi Higurashi[4], Edward Hirsch[5], Fleur E. Jansen[6], Lieven Lagae[7], Solomon L. Moshé[8], Jukka Peltola[9], Elaine Roulet Perez[10], Ingrid E. Scheffer[11], Sameer M. Zuberi[12]

2017

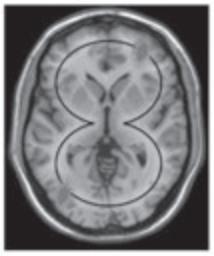
Crises focais- 2017



- Crises epilépticas focais são aquelas que se originam em redes neuronais limitadas a um hemisfério cerebral, as quais podem ser restritas ou distribuídas de forma mais ampla;

Berg et al. Epilepsia 2010;51(4):676-85

Crises generalizadas



- Crises epilépticas generalizadas são aquelas que se originam em algum ponto de uma rede neuronal e rapidamente envolvem e se distribuem em redes neuronais bilaterais.

Berg et al. Epilepsia 2010;51(4):676-85

Classificação- Dois documentos

ILAE POSITION PAPER

Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology

ILAE COMMISSION REPORT

Instruction manual for the ILAE 2017 operational classification of seizure types




Márcia Morita Lécio Figueira Elza Márcia Yacubian Mirian Fabiola Mendes

LBE

COMISSÃO DE CONSENSO DA LBE

Os cinco tipos de envolvimento de consciência

CONTROVERSY IN EPILEPSY

CINCO TIPOS DE ALTERAÇÕES DA CONSCIÊNCIA

1. Auras: **ilusões e alucinações;**
2. Crises discognitivas: **alterações funções cognitivas superiores com consciência intacta: Exemplo: crise afásica;**
3. Delirium ictal epiléptico **(status não convulsivo)- pensamento confuso, comprometimento atenção, olhos abertos, alucinações e ilusões vívidas; amnésia completa do evento;**
4. Crises dialépticas **(verbo gr. *dialepein* = *epilepein*= parar, interromper)- arresponsividade a estímulos externos, amnésia completa do evento;**
5. Coma ou estupor epiléptico.

Epilepsia 2014;55(8):1140-4.

vídeo

vídeo

PERDA (OU COMPROMETIMENTO) DA CONSCIÊNCIA

Dois tipos de crises com comprometimento de consciência

O público entende bem quando se diz que uma pessoa tem comprometimento de consciência durante uma crise parcial complexa?

Determinação retrospectiva da consciência

Dificuldades crises parciais complexas ou com comprometimento da consciência

Um classificador não treinado pode considerar que, para mostrar **comprometimento da consciência durante uma crise** uma pessoa precisaria estar no solo, imóvel, não perceptiva e não responsiva ('desmaiada').

Classificação
Dificuldades: definir consciência

Robert Fisher
Chair

Consciência é um fenômeno complexo que engloba componentes subjetivos **e** objetivos

Consciousness
Os quatro componentes da Consciência

Robert Fisher
Chair

Consciousness: a state of mind with both subjective and objective aspects, comprising a sense of self as a unique entity, awareness, responsiveness and memory.

Consciência: um estado da mente com aspectos objetivos e subjetivos, que compreende um sentido do eu como uma entidade única. Quatro componentes: percepção de si próprio e do meio, responsividade e memória.

TERMO SUBSTITUTO
Awareness
Percepção

Robert Fisher
Chair

Awareness: knowledge of self and environment.
Perceptividade: conhecimento do eu e do meio ao redor.

Focal aware seizure
Crise focal perceptiva

Awareness: an aspect of consciousness pertaining to knowledge of self and environment.

Perceptividade: um aspecto da consciência que permite o conhecimento de si próprio e do meio ambiente.

Focal Seizure with Impaired Awareness
Crise Focal Disperceptiva

Impaired awareness: impaired or lost awareness is a feature of focal impaired awareness seizures, previously called complex partial seizures. Impaired awareness is also seen in other seizure types.

Disperceptiva: comprometimento ou perda da perceptividade é uma característica das crises focais disperceptivas, previamente denominadas crises parciais complexas. Comprometimento da percepção é também visto em outros tipos de crises.

Por que disperceptiva?

- *Dis*= prefixo latino que significa afastamento, separação, ruptura
- Dispersão: dis + pergere= continuar = ruptura da continuidade
- Disperceptiva: ruptura, dissolução da percepção

ACRÔNIMOS

Robert Fisher
Chair

FAS- Focal aware seizure

International League Against Epilepsy

FIAS- Focal impaired awareness seizure

CFP- Crise focal perceptiva

LBE

COMISSÃO DE CONSENSO DA LBE

CFD- Crise focal disperceptiva

Cognitive
Cognitiva

Cognitive: pertaining to thinking and higher cortical functions, such as language, spatial perception, memory, praxis. The previous term for similar usage was psychic.
Cognitiva: pertencente ao pensamento e funções corticais superiores, como linguagem, percepção espacial, memória, praxia. O termo prévio indicado para uso similar era psíquica.

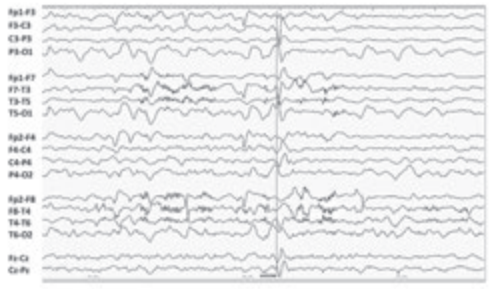

Classificação dos Tipos de Crises da ILAE 2017 [1]
Robert Fisher
Chair
Esquema simplificado
1. Início focal
2. Início generalizado
3. Início desconhecido
Perceptivas
AWARE
Disperceptivas
IMPAIRED AWARENESS
Início motor
Início não motor
Focal evoluindo para tônico-clônica bilateral
Motoras
Tônico-clônicas
Outras motoras
Não motoras (ausências)
Motoras
Tônico-clônicas
Outras motoras
Não motoras
parada comportamental
4. Não classificadas [2]
[1] Definições, outros tipos de crises e descritores estão listados no artigo e no glossário de termos
[2] Por informação inadequada ou impossibilidade de inserir nas outras categorias


Classificação dos Tipos de Crises da ILAE 2017 [1]
Esquema expandido
Robert Fisher
Chair
1. Início focal
2. Início generalizado
3. Início desconhecido
Perceptivas
Disperceptivas
Início motor
automatismos
atônicas[2]
clônicas
espasmos epilépticos[2]
hipercinéticas
mioclônicas
tônicas
Início não motor
autonômicas
parada comportamental
cognitivas
emocionais
sensoriais
Motoras
tônico-clônicas
clônicas
tônicas
mioclônicas
mioclono-tônico-clônicas
mioclono-atônicas
atônicas
espasmos epilépticos[2]
Não motoras (ausências)
típicas
atípicas
mioclônicas
mioclonias palpebrais
Motoras
tônico-clônicas
espasmos epilépticos
Não motoras
parada comportamental
4. Não classificadas [3]
Focal evoluindo para tônico-clônica bilateral
[1]Definições, outros tipos de crises e descritores são listados no artigo e glossário de termos
[2] Estas podem ser focais ou generalizadas, com ou sem alteração da perceptividade
[3] Por informação inadequada ou impossibilidade de inserir nas outras categorias

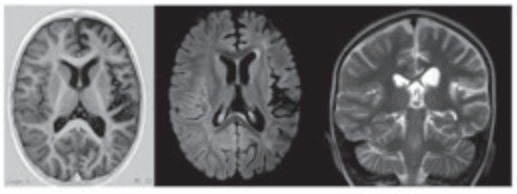

Classificação dos tipos de crises ILAE 2017
Início focal
Perceptivas
Disperceptivas
Início generalizado
Motor
Início desconhecido
Motor
Início motor
1. automatismos
2. atônicas
3. clônicas
4. espasmos epilépticos
5. hipercinéticas
6. mioclônicas
7. tônicas
Início não motor
1. autonômicas
2. parada comportamental
3. cognitivas
4. emocionais
5. sensoriais
1. tônico-clônicas
2. clônicas
3. tônicas
4. mioclônicas
5. mioclono-tônico-clônicas
6. mioclono-atônicas
7. atônicas
8. espasmos epilépticos
Não motor (ausências)
1. típicas
2. atípicas
3. mioclônicas
4. mioclonias palpebrais
1. tônico-clônicas
2. espasmos epilépticos
Não motor
1. parada comportamental
Focal evoluindo para tônico-clônica bilateral
Não classificadas


Criança de 3 anos 8 meses
Início das crises aos 3 anos
vídeo
Permite o uso de exames complementares para a Classificação do tipo de crise

Classificação dos Tipos de Crises da ILAE 2017



Encefalite de Rasmussen
Hemisfério esquerdo



Classificação dos tipos de crises ILAE 2017

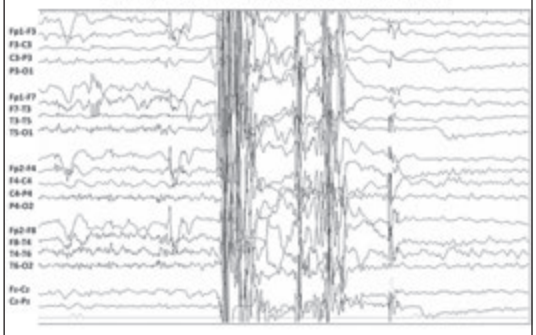
Início focal		Início generalizado	Início desconhecido
Perceptiva	Disperceptiva	Motor	Motor
Início motor 1. automatismos 2. atônicas 3. clônicas 4. espasmos epilépticos 5. hipercinéticas 6. mioclônicas 7. tônicas **Início não motor** 1. autonômicas 2. parada comportamental 3. cognitivas 4. emocionais 5. sensoriais		1. tônico-clônicas 2. clônicas 3. tônicas 4. mioclônicas 5. mioclono-tônico-clônicas 6. mioclono-atônicas 7. atônicas 8. espasmos epilépticos **Não motor (ausências)** 1. típicas 2. atípicas 3. mioclônicas 4. mioclonias palpebrais	1. tônico-clônicas 2. espasmos epilépticos **Não motor** 1. parada comportamental
Focal evoluindo para tônico-clônica bilateral			**Não classificadas**

Criança de 3 anos 8 meses
Início das crises aos 3 anos

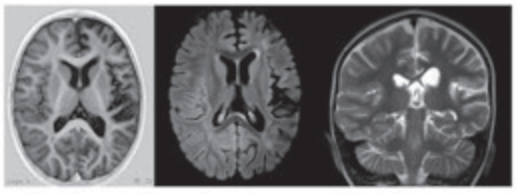
vídeo

Permite o uso de exames complementares para a Classificação do tipo de crise

Classificação dos Tipos de Crises da ILAE 2017



Encefalite de Rasmussen
Hemisfério esquerdo



Classificação dos tipos de crises ILAE 2017

Início focal		Início generalizado	Início desconhecido
Perceptiva	Disperceptiva	Motor	Motor
Início motor 1. automatismos 2. atônicas 3. clônicas 4. espasmos epilépticos 5. hipercinéticas 6. mioclônicas 7. tônicas **Início não motor** 1. autonômicas 2. parada comportamental 3. cognitivas 4. emocionais 5. sensoriais		1. tônico-clônicas 2. clônicas 3. tônicas 4. mioclônicas 5. mioclono-tônico-clônicas 6. mioclono-atônicas 7. atônicas 8. espasmos epilépticos **Não motor (ausências)** 1. típicas 2. atípicas 3. mioclônicas 4. mioclonias palpebrais	1. tônico-clônicas 2. espasmos epilépticos **Não motor** 1. parada comportamental
Focal evoluindo para tônico-clônica bilateral			**Não classificadas**

Regras para classificar

- Ao classificar crises, ao decidir se as crises têm início focal ou generalizado, o médico deve usar o intervalo de confiança de 80%;
- Se a percepção é comprometida **em qualquer ponto durante uma crise focal**, ela será classificada como crise focal disperceptiva;
- O primeiro sinal ou sintoma proeminente de uma crise focal deve ser usado para a classificação, com exceção da parada comportamental transitória. Uma crise focal somente será considerada uma **crise de parada comportamental** se este sintoma for a característica mais proeminente de toda a crise;
- Clínicos são encorajados a acrescentar a descrição de outros sinais e sintomas;
- É possível usar exames complementares para a classificação;
- Crises podem ser não classificadas por informação inadequada ou incapacidade de inseri-la em outras categorias.

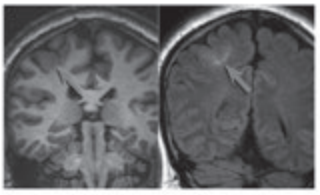
Exemplos

1. Uma mulher desperta e encontra seu marido tendo uma crise na cama. O início não é testemunhado, mas ela é capaz de descrever um enrijecimento global seguido por abalos bilaterais. Seu EEG e RM são normais.

1. Uma mulher desperta e encontra seu marido tendo uma crise na cama. O início não é testemunhado, mas ela é capaz de descrever um enrijecimento global seguido por abalos bilaterais. Seu EEG e RM são normais.

1. Esta crise é classificada como de **início desconhecido tônico-clônica**. Não há informação suplementar para determinar se o início foi focal ou generalizado. Na Classificação de 1981, esta crise seria inclassificável.

2. Num cenário alternativo do caso #1, o EEG mostra um alentecimento claro parietal direito. A RM mostra uma área displásica parietal direita.



2. Num cenário alternativo do caso #1, o EEG mostra um alentecimento claro parietal direito. A RM mostra uma área displásica parietal direita.

2. Nesta circunstância, a crise pode ser classificada **como focal evoluindo para tônico-clônica bilateral**, a despeito do seu início não ter sido testemunhado, porque foi identificada uma etiologia focal. Na Classificação de 1981, esta crise seria classificada como de início parcial, secundariamente generalizada.

3. Um homem de 20 anos relata que suas crises têm início com uma sensação de parestesia no braço direito. Esta sensação progride para abalos rítmicos do braço direito que duram 30 segundos. Ele mantém a perceptividade e a memória do evento.

vídeo nos slides

3. Um homem de 20 anos relata que suas crises têm início com uma sensação de parestesia no braço direito. Esta sensação progride para abalos rítmicos do braço direito que duram 30 segundos. Ele mantém a perceptividade e a memória do evento.

3. Este é um evento com manifestações sequenciais.

Como descrever manifestações sequenciais?

- Esta é uma crise *focal (início não motor) sensitiva*. Descrições adicionais são úteis, daí a descrição como *crise focal sensitiva* com manifestações somatosensitivas progredindo para atividade clônica do braço direito;
- Se os eventos motores e sensitivos forem separados ou o clínico considere que seja, duas crises separadas (bifocal ou multifocal), cada componente deveria ser classificado como uma crise separada;
- Na classificação de 1981 ela seria classificada como uma *crise parcial simples sensitivomotora*. Uma vantagem da classificação de 2017 é a especificação do início sensitivo, o que acarreta importância clínica.

4. Uma mulher de 25 anos descreve crises que se iniciam com 30 segundos de uma sensação intensa de que 'está tocando uma música familiar'. Ela pode ouvir as pessoas falando, mas depois ela não pode determinar o que eles estão dizendo. Após um episódio, ela está discretamente confusa, e precisa 'se reorientar'.

4. Uma mulher de 25 anos descreve crises que se iniciam com 30 segundos de uma sensação intensa de que 'está tocando uma música familiar'. Ela pode ouvir as pessoas falando, mas depois ela não pode determinar o que eles estão dizendo. Após um episódio, ela está discretamente confusa, e precisa 'se reorientar'.

4. As crises seriam classificadas como **crises focais disperceptivas**. Embora a paciente fosse capaz de interagir com seu meio, ela não pode interpretá-lo e fica discretamente confusa. Segundo a regra, se a percepção é comprometida **em qualquer ponto durante uma crise focal**, ela será classificada como **crise focal disperceptiva.**

5. Um homem de 22 anos tem crises durante as quais permanece completamente perceptivo, com os 'pelos de meus braços muito eriçados' e se sente ruborizado.

5. Um homem de 22 anos tem crises durante as quais permanece completamente perceptivo, com os 'pelos de meus braços muito eriçados' e se sente ruborizado.

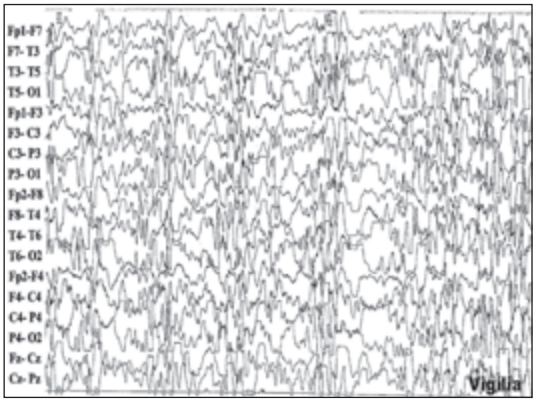
Classificação dos tipos de crises ILAE 2017

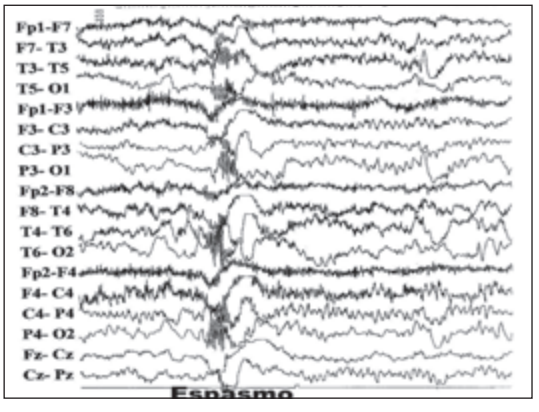
Início focal		Início generalizado	Início desconhecido
Perceptivo	Disperceptivo	Motor	Motor
Início motor automatismos atônicas clônicas espasmos epilépticos hipercinéticas mioclônicas tônicas		tônico-clônicas clônicas tônicas mioclônicas mioclono-tônico-clônicas mioclono-atônicas atônicas espasmos epilépticos	tônico-clônicas espasmos epilépticos **Não motor** parada comportamental
Início não motor autonômicas parada comportamental cognitivas emocionais sensoriais		**Não motor (ausências)** típicas atípicas mioclônicas mioclonias palpebrais	
Focal evoluindo para tônico-clônica bilateral			**Não classificadas**

5. São classificadas como **crises focais perceptivas não motoras autonômicas**, ou, mais sucintamente, crises focais perceptivas autonômicas. A classificação de 1981 as chamaria de crises parciais simples autonômicas.

6. Uma menina de 14 meses tem flexão de ambos os braços com flexão da cabeça durante 2 segundos. Estas crises ocorrem em grupos. O EEG mostra hipsarritmia com descargas bilaterais.

vídeo





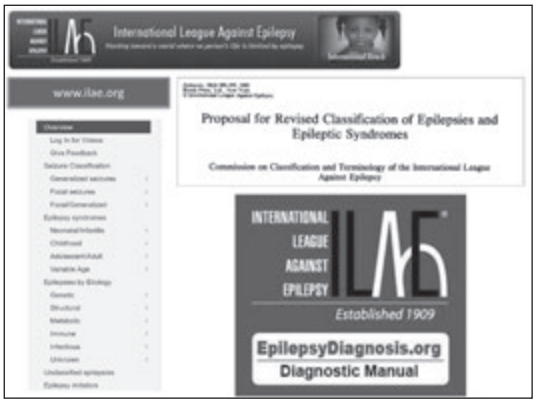
6. Uma menina de 14 meses tem flexão de ambos os braços com flexão da cabeça durante 2 segundos. Estas crises ocorrem em grupos. O EEG mostra hipsarritmia com descargas bilaterais.

6. Pela informação auxiliar, o tipo de crise deve ser considerado como **espasmos epilépticos generalizados**. A Classificação prévia os denominaria espasmos infantis, sem a informação adicionais.

7. Um homem de 75 anos relata uma sensação interna de tremor no corpo. Não há outras informações disponíveis.

7. Um homem de 75 anos relata uma sensação interna de tremor no corpo. Não há outras informações disponíveis.

7. Este é um evento não classificado e pode ou não ser uma crise epiléptica.



The new ILAE seizure classification: 63 seizure types?

Beniczky et al. Epilepsia 2017;58(7):1300-1

Table 1. List of seizure types according to the new ILAE seizure classification

Three-step classification			Name of seizure type	Code
Focal onset	Aware	Motor onset—not further specified	Focal aware motor onset seizure	1.A.01
		Myoclonic	Focal aware myoclonic seizure	1.A.02
		Clonic	Focal aware clonic seizure	1.A.03
		Tonic	Focal aware tonic seizure	1.A.04
		Atonic	Focal aware atonic seizure	1.A.05
		Autonomic	Focal aware autonomic seizure	1.A.06
		Hyperkinetic	Focal aware hyperkinetic seizure	1.A.07
		Nonmotor onset—not further specified	Focal aware nonmotor onset seizure	1.A.08
		Behavior arrest	Focal aware behavior arrest seizure	1.A.09
		Sensory	Focal aware sensory seizure	1.A.10
		Emotional	Focal aware emotional seizure	1.A.11
		Cognitive	Focal aware cognitive seizure	1.A.12
		Autonomic	Focal aware autonomic seizure	1.A.13
		Onset not further specified	Focal aware seizure	1.A.14
	Impaired awareness	Motor onset—not further specified	Focal impaired awareness motor onset seizure	1.B.01
		Myoclonic	Focal impaired awareness myoclonic seizure	1.B.02
		Clonic	Focal impaired awareness clonic seizure	1.B.03
		Tonic	Focal impaired awareness tonic seizure	1.B.04
		Atonic	Focal impaired awareness atonic seizure	1.B.05
		Automatisms	Focal impaired awareness automatism seizure	1.B.06
		Hyperkinetic	Focal impaired awareness hyperkinetic seizure	1.B.07
		Nonmotor onset—not further specified	Focal impaired awareness nonmotor onset seizure	1.B.08
		Behavior arrest	Focal impaired awareness behavior arrest seizure	1.B.09
		Sensory	Focal impaired awareness sensory seizure	1.B.10
		Emotional	Focal impaired awareness emotional seizure	1.B.11
		Cognitive	Focal impaired awareness cognitive seizure	1.B.12
		Autonomic	Focal impaired awareness autonomic seizure	1.B.13
		Onset not further specified	Focal impaired awareness seizure	1.B.14

Continued

Table 1. Continued.

Three-step classification			Name of seizure type	Code
	Awareness not known or not specified	Motor onset—not further specified	Focal motor seizure	1.C.01
		Myoclonic	Focal myoclonic seizure	1.C.02
		Clonic	Focal clonic seizure	1.C.03
		Epileptic spasms	Focal epileptic spasm	1.C.04
		Tonic	Focal tonic seizure	1.C.05
		Atonic	Focal atonic seizure	1.C.06
		Automatisms	Focal automatismo seizure	1.C.07
		Hyperkinetic	Focal hyperkinetic seizure	1.C.08
		Nonmotor onset—not further specified	Focal nonmotor seizure	1.C.09
		Behavior arrest	Focal behavior arrest seizure	1.C.10
		Sensory	Focal sensory seizure	1.C.11
		Emotional	Focal emotional seizure	1.C.12
		Cognitive	Focal cognitive seizure	1.C.13
		Autonomic	Focal autonomic seizure	1.C.14
		Onset not further specified	Focal seizure	1.C.15
	Focal to bilateral tonic–clonic		Focal to bilateral tonic–clonic seizure	1.D.01
Generalized Onset	Motor	Onset not further specified	Generalized motor seizure	2.A.01
		Myoclonic	Generalized myoclonic seizure	2.A.02
		Myoclonic–atonic	Myoclonic–atonic seizure	2.A.04
		Myoclonic–tonic–clonic	Myoclonic–tonic–clonic seizure	2.A.04
		Clonic	Generalized clonic seizure	2.A.05
		Epileptic spasm	Generalized epileptic spasm	2.A.06
		Tonic	Generalized tonic seizure	2.A.07
		Atonic	Generalized atonic seizure	2.A.08
		Tonic–clonic	Generalized tonic–clonic seizure	2.A.09
	Absence	Typical	Typical absence seizure	2.B.01
		Atypical	Atypical absence seizure	2.B.02
		Myoclonic absence	Myoclonic absence seizure	2.B.03
		Eyelid myoclonia	Eyelid myoclonia with absence/without absence	2.B.04
Unknown onset	Motor	Tonic–clonic	Tonic–clonic seizure of unknown onset	3.A.01
		Epileptic spasm	Epileptic spasm with unknown onset	3.A.02
		Motor—not further specified	Motor seizure with unknown onset	3.A.03
	Nonmotor	Behavior arrest	Behavioral arrest with unknown onset	3.B.01
		Nonmotor—not further specified	Nonmotor seizure with unknown onset	3.B.02
	Unknown		Unclassified seizure	3.C.01

Response to the numbering of seizure types

Fisher et al. Epilepsia 2017;58(7):1301

- Não temos objeções para a elaboração de uma lista com códigos para uso da Classificação por grupos especializados.

Márcia Morita Lécio Figueira Elza Márcia Yacubian Mirian Fabiola Mendes

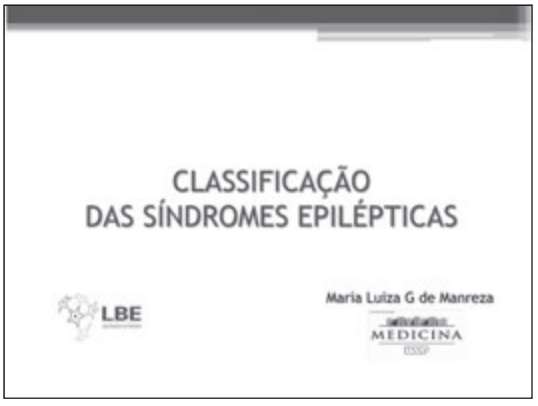
LBE

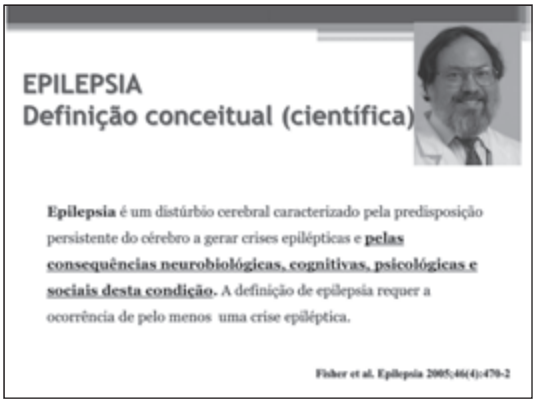
COMISSÃO DE CONSENSO DA LBE

Muito obrigada!

Maria Luiza Manreza

THE NEW CLASSIFICATION OF EPILEPSIES





EPILEPSIA
Definição operacional (prática)

- ✓ Epilepsia é uma **doença do cérebro** caracterizada por uma das seguintes condições:
- Pelo menos duas crises não provocadas (ou duas crises reflexas) ocorrendo em um intervalo superior a 24 horas;
- **Uma crise não provocada** (ou uma crise reflexa) e chance de uma nova crise estimada em pelo menos 60%;
- Diagnóstico de uma síndrome epiléptica

Fisher et al. Epilepsia 2014;55(4):475-82

WWW.ILAE.org.br **PowerPoint Presentation on the 2017 Classification of the Epilepsies**

2017;58: 512

AGENDA

- ✓ Importância do tema
- ✓ 10 PASSO – Diagnóstico da crise epiléptica
- ✓ 20 PASSO – Diagnóstico da síndrome
  - Epilepsias generalizadas idiopáticas
  - Epilepsias focais auto-limitadas
- ✓ 30 PASSO - Etiologias

CLASSIFICAÇÃO DAS EPILEPSIAS
Propósito: Diagnóstico

Linguagem transparente: usa palavras que significam o que dizem

CLASSIFICAÇÃO DAS EPILEPSIAS
FINALIDADES

- ✓ Finalidade principal: diagnóstico dos pacientes
- a pesquisa em epilepsia
- o desenvolvimento de terapias antiepilépticas
- comunicação em todo o mundo

- ✓ Origem -> documento apresentado para comentários do público em 2013

PROPÓSITOS DA CLASSIFICAÇÃO

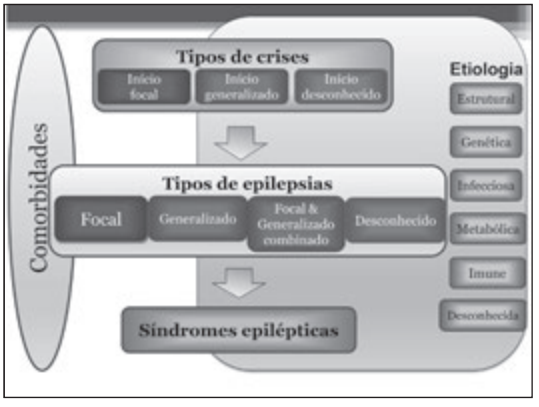
- ✓ Compreender o **tipo de crise** do paciente bem como os outros tipos de crises mais propensos a ocorrer nesse indivíduo, os potenciais desencadeantes para suas crises, e muitas vezes, o prognóstico
- ✓ Informar os riscos de comorbidades, como dificuldades de aprendizagem, deficiência intelectual, características psiquiátricas, tais como distúrbio do espectro do autismo e o risco de mortalidade, incluindo SUDEP

ESQUEMA PARA CLASSIFICAÇÃO DAS EPILEPSIAS

- ✓ Três níveis, para permitir a classificação das epilepsias em ambientes clínicos diferentes

1- Tipo de crise, *de acordo com a nova* classificação da ILAE de 2017
2- Tipo epilepsia
3- Síndrome epiléptica, onde um diagnóstico sindrômico específico pode ser feito.

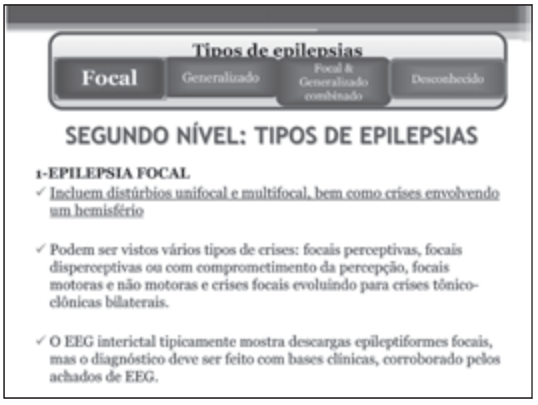
- ✓ **Etiologia** ao longo de cada etapa, dividida em seis subgrupos, selecionados por suas potenciais consequências terapêuticas
- ✓ **Comorbidades**



ESQUEMA PARA CLASSIFICAÇÃO DAS EPILEPSIAS

PRIMEIRO NÍVEL
TIPOS DE CRISES

1- Diagnóstico do tipo de crise epiléptica de acordo com a atual classificação de crises epilépticas



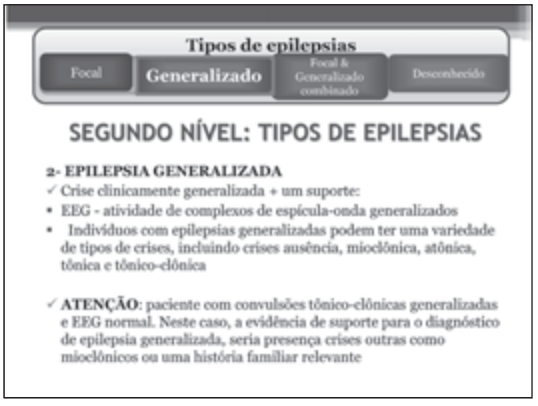
SEGUNDO NÍVEL: TIPOS DE EPILEPSIAS

1-EPILEPSIA FOCAL

✓ Incluem distúrbios unifocal e multifocal, bem como crises envolvendo um hemisfério

✓ Podem ser vistos vários tipos de crises: focais perceptivas, focais disperceptivas ou com comprometimento da percepção, focais motoras e não motoras e crises focais evoluindo para crises tônico-clônicas bilaterais.

✓ O EEG interictal tipicamente mostra descargas epileptiformes focais, mas o diagnóstico deve ser feito com bases clínicas, corroborado pelos achados de EEG.



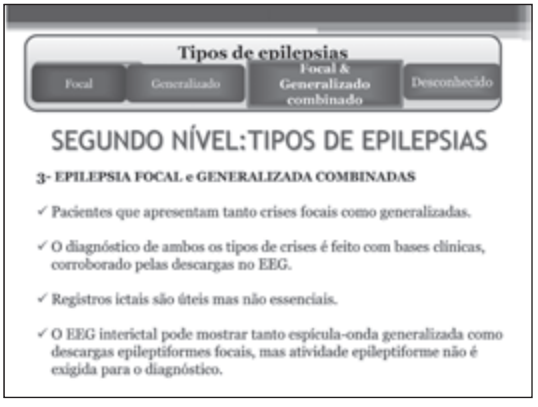
SEGUNDO NÍVEL: TIPOS DE EPILEPSIAS

2- EPILEPSIA GENERALIZADA

✓ Crise clinicamente generalizada + um suporte:

- EEG - atividade de complexos de espícula-onda generalizados
- Indivíduos com epilepsias generalizadas podem ter uma variedade de tipos de crises, incluindo crises ausência, mioclônica, atônica, tônica e tônico-clônica

✓ **ATENÇÃO**: paciente com convulsões tônico-clônicas generalizadas e EEG normal. Neste caso, a evidência de suporte para o diagnóstico de epilepsia generalizada, seria presença crises outras como mioclônicos ou uma história familiar relevante



SEGUNDO NÍVEL:TIPOS DE EPILEPSIAS

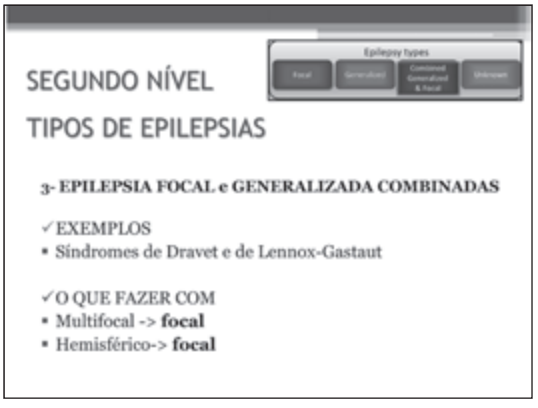
3- EPILEPSIA FOCAL e GENERALIZADA COMBINADAS

✓ Pacientes que apresentam tanto crises focais como generalizadas.

✓ O diagnóstico de ambos os tipos de crises é feito com bases clínicas, corroborado pelas descargas no EEG.

✓ Registros ictais são úteis mas não essenciais.

✓ O EEG interictal pode mostrar tanto espícula-onda generalizada como descargas epileptiformes focais, mas atividade epileptiforme não é exigida para o diagnóstico.



SEGUNDO NÍVEL

TIPOS DE EPILEPSIAS

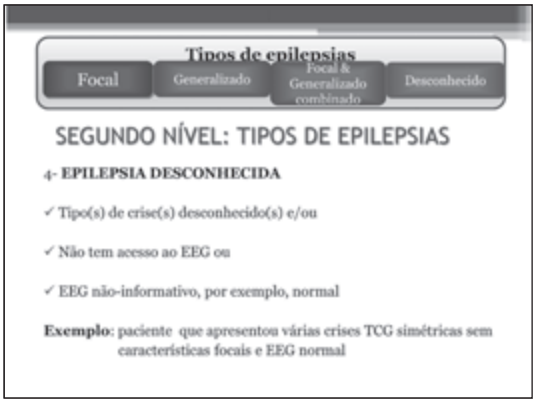
3- EPILEPSIA FOCAL e GENERALIZADA COMBINADAS

✓EXEMPLOS

- Síndromes de Dravet e de Lennox-Gastaut

✓O QUE FAZER COM

- Multifocal -> **focal**
- Hemisférico-> **focal**



SEGUNDO NÍVEL: TIPOS DE EPILEPSIAS

4- **EPILEPSIA DESCONHECIDA**

✓ Tipo(s) de crise(s) desconhecido(s) e/ou

✓ Não tem acesso ao EEG ou

✓ EEG não-informativo, por exemplo, normal

Exemplo: paciente que apresentou várias crises TCG simétricas sem características focais e EEG normal

SEGUNDO NÍVEL

TIPOS DE EPILEPSIAS

EPILEPSIAS EM QUE O DIAGNÓSTICO FICA NESTE NÍVEL

Epilepsias nas quais não é possível fazer diagnóstico de uma síndrome ou de uma etiologia

✓ Muitos exemplos
- Epilepsia do lobo temporal
- Crises tônico-clônicas generalizadas em uma criança de 5 anos com espículas generalizadas no EEG
- Paciente com crises focais disperceptivas e crises de ausência
- Paciente apenas com crises tônica-clônica: focal ou generalizada

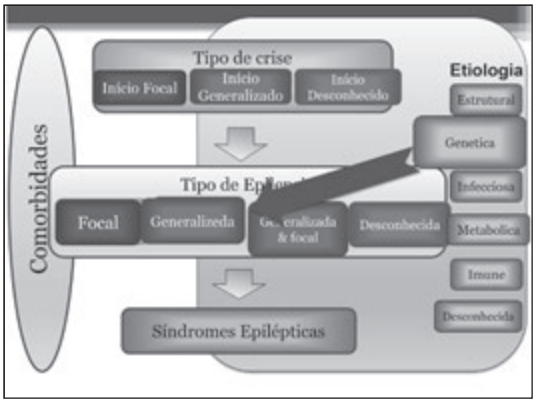
TERCEIRO NÍVEL

Síndromes epilépticas

✓ Conjunto de características como:
- tipos de crises, características do EEG e de imagem que tendem a ocorrer em conjunto
- idade, como idade de início e remissão (quando aplicável)
- fatores desencadeadores de crises
- variação durante o dia, prognóstico por vezes
- comorbidades, como disfunção intelectual e psiquiátrica

✓ Embora o EEG a imagem possam por vezes terem implicações etiológicas, prognósticas e de tratamento associadas .....

✓**ATENÇÃO**: uma síndrome não tem uma correlação um-para-um com um diagnóstico etiológico e tem o próposito de orientar



Síndromes epilépticas

TERCEIRO NÍVEL

- ✓ Algumas síndromes epilépticas não são reconhecidas pela ILAE
- ✓Algumas síndromes epilépticas são reconhecidas ILAE
- ✓www. epilepsydiagnosis.- uma relação das epilepsias e das etilogias mas podem orientar a conduta

https://www.epilepsydiagnosis.org

ETIOLOGIA DA EPILEPSIA ANTIGAS E NOVA CLASSIFICAÇÃO

1989	2010	2017
IDIOPÁTICA (etiologia presumidamente genética)	GENÉTICA (conhecida ou presumida)	GENÉTICA ESTRUTURAL METABÓLICA INFECCIOSA IMUNE DESCONHECIDA
SINTOMÁTICA (alteração do SNC conhecida ou presumida)	ESTRUTURAL/METABÓLICA (distúrbios subjacentes distintos)	
CRIPTOGÊNICA (presumidamente sintomática)	DESCONHECIDA (outras que não as à cima)	

ETIOLOGIAS

Scheffer et al., 2014

ETIOLOGIA ESTRUTURAL

Estrutural

- ✓ Anormalidade estrutural que tem risco estar associada com a epilepsia e é visível na neuroimagem
- ✓ Podem ser
  - Adquiridas: AVC, trauma e infecção
  - Genéticas: malformações do desenvolvimento
- ✓ Lesão estrutural sutil -> estudos de RM apropriados usando protocolos específicos de epilepsia.

ETIOLOGIA ESTRUTURAL

Estrutural

- ✓ Associações bem reconhecidas dentro das epilepsias com uma etiologia estrutural.
  - crises mesiais do lobo temporal com esclerose do hipocampo.
  - crises gelásticas com hamartoma hipotalâmico
  - síndrome de Rasmussen com: hemiconvulsão-hemiplegia-epilepsia
- ✓ O reconhecimento dessas associações é importante para assegurar que o exame foi cuidadoso e possibilidade de cirurgia

Genética

ETIOLOGIA GENÉTICA

- ✓ Epilepsia genética é a que resulta diretamente de uma mutação genética conhecida ou presumida em que as crises são um sintoma central da doença
- ✓ Na maioria o gene não é conhecido:
- história familiar de uma doença autossômica dominante com gene definido ou não
- etiologia genética sugerida por pesquisa clínica em populações com a mesma síndrome, como EAJ OU EMJ
- Existe uma base molecular

Genética

ETIOLOGIA GENÉTICA

GENÉTICO NÃO SIGNIFICA HEREDITÁRIO

- ✓ Um número crescente de mutações de novo está sendo identificado tanto em epilepsia leves como graves
- ✓ Pacientes podem ser mosaico para uma mutação
- ✓ Uma etiologia genética não exclui uma contribuição ambiental

Infecciosa

ETIOLOGIA INFECCIOSA

- ✓ É a etiologia mais comum em todo o mundo
- ✓ Resulta diretamente de uma infecção conhecida em que crises são o sintoma central da doença.
- ✓ Não confundir com crises sintomáticas agudas
- ✓ Uma etiologia infecciosa tem implicações terapêuticas específicas
- ✓ Esta etiologia por vezes tem um correlato estrutural

- Exemplos comuns em regiões específicas do mundo incluem neurocisticercose, tuberculose, HIV, malária cerebral, panencefalite esclerosante subaguda, toxoplasmose cerebral e infecções congênitas como o vírus Zika e citomegalovírus. Estas infecções, por vezes, têm um correlato estrutural

Metabólica

ETIOLOGIA METABÓLICA

- ✓ A epilepsia é o resultado direto de um distúrbio metabólico conhecido ou presumido no qual o sintoma central do distúrbio são as crises epilépticas
- ✓ Alguns são distúrbios metabólicos bem definidos com alterações em todo organismo como a porfiria, aminioacidopatias, piridoxina
- ✓ Alguns tem etiologia genética outros são adquiridos
- ✓ O diagnóstico é importante porque têm implicações terapêuticas

Imune

ETIOLOGIA IMUNE

- ✓A epilepsia resulta de um distúrbio imune no qual o sintoma central do distúrbio são as crises epilépticas
- ✓Ocorrem tanto em adultos com em crianças
- ✓Pode ser diagnosticada quando há evidência de uma inflamação imuno-mediada no SNC
- ✓Tem implicações terapêuticas como as imunoterapias

TERMINOLOGIA ANTIGA E NOVA

LBE

TERMO ANTIGO
EPILEPSIAS GENERALIZADAS IDIOPÁTICAS

EPILEPSIAS GENERALIZADAS IDIOPÁTICAS

- ✓ DISCUSSÃO
- **"Idiopático"** = nenhuma etiologia conhecida ou suspeita além da predisposição hereditária -> impreciso

mas...

- **Genética ≠ "herdado"**
- Importância de mutações de novo em epilepsias "leves e graves"
- Problema crítico do estigma em algumas partes do mundo

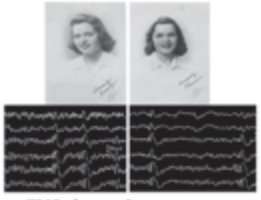
- ✓ EPILEPSIAS IDIOPÁTICAS GENERALIZADAS ou
- ✓EPILEPSIAS GENERALIZADAS GENÉTICAS (EGGs), poderia ser usado nos casos em que existem evidências de que se trata de etiologia genética: pesquisa em gêmeos, etc

A epilepsia é hereditária?

- ✓ Depende do tipo de epilepsia
- ✓ A maioria dos pacientes com epilepsia não tem uma forma hereditária
- ✓ A epilepsia familiar ocorre em cerca de 5% de todos os pacientes (câncer, 5 a 30%; hipertensão, 50%; diabetes mellitus 50%)
- ✓ A epilepsia familiar geralmente tem prognóstico favorável (responde aos FAE, é autolimitada, comorbidades, etc)
- ✓ A etiologia genética é identificada em uma pequena fração de pacientes particularmente em encefalopatias epilépticas de início recente
- ✓ A mutação de um gene não necessariamente resulta em uma forma hereditária de encefalopatia epiléptica

Genético ≠ Teste Genético

- ✓ Normalmente, a mutação não é conhecida
- ✓ O acesso ao teste genético molecular não é necessário
- ✓ Diagnosticado na pesquisa clínica, por ex.: gêmeos, família, etc



EMJ gêmeos; Lennox 1941

EAI gêmeos; Lennox 1950

AUTO-LIMITADA e/ou FARMACORRESPONSIVA

- ✓ Substituem o termo benigno na caracterização de determinadas epilepsias
- Epilepsia não deve ser considerada benigna pois pode estar associado efeitos cognitivos transitórios ou duradouros bem como consequências psicossociais significativas

mas, por outro lado

- As crises podem ser controladas com ou mesmo sem medicação

AUTO-LIMITADA e/ou FARMACORRESPONSIVA

- ✓ **Início na infância**
- Epilepsia autolimitada com descargas centrotemporais (Epilepsia Rolândica)
- Epilepsias autolimitadas occipitais da infância, com a forma de início precoce descrita por Panayiotopoulos e a forma tardia de Gastaut

- ✓ **Início na adolescência e na vida adulta**
- Epilepsias auto-limitadas do lobo frontal, do lobo temporal e do lobo parietal

EPILEPSIAS NÃO RESPONSIVAS

✓Substituem termos como:

- Epilepsias catastróficas
- Epilepsias malignas

NOVAS DEFINIÇÕES

LBE

ENCEFALOPATIA EPILÉPTICA

✓ **Encefalopatia epiléptica ->** a atividade epileptiforme por si contribui para o comprometimento cognitivo e comportamental à cima e além do esperado pela patologia subjacente

- pode piorar com o passar do tempo
- a melhora da atividade epileptiforme pode melhorar o consequente distúrbio do desenvolvimento
- pode ser aplicável a epilepsias em todas as idades
- deve ser utilizado mais amplamente do que apenas para as epilepsias graves com início na infância.
- Exemplos: POCS, síndromes de West e de Lennox-Gastaut

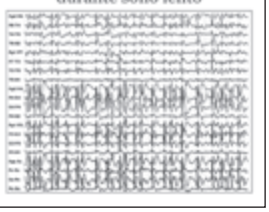
Berg AT et al. Epilepsia. 2010;51(4):676
Scheffer IE et al. Epilepsia. 2017

ENCEFALOPATIA EPILÉPTICA

A atividade epiléptica pode contribuir para o comprometimento cognitivo e comportamental maior e além daquele que seria esperado pela patologia subjacente e que pode piorar ao longo do tempo

Berg et al. Epilepsia 2010;51(4):676-85

Ponta-onda contínua durante sono lento



ENCEFALOPATIA EPILÉPTICA E/OU DO DESENVOLVIMENTO

- ✓ Para muitas encefalopatias, existe um componente de desenvolvimento independente da encefalopatia epiléptica
- ✓ O atraso no desenvolvimento pode preceder o início da crise
- ✓ Co-morbidades? Ex. Paralisia cerebral, distúrbio do espectro autista, deficiência intelectual
- ✓ Resultados pobres, mesmo que as crises epilépticas parem, por exemplo: KCNQ2, encefalopatias STXBP1

ENCEFALOPATIA DO DESENVOLVIMENTO

✓ **Encefalopatias do desenvolvimento ->** doenças que têm consequências diretas sobre o desenvolvimento independente e por vezes além do efeito da atividade epiléptica frequente. Pode haver:

- atraso de desenvolvimento pré-existente, complicado por parada ou mesmo involução após o início das crises ou com crises prolongadas
- alteração desenvolvimento no contexto de um desenvolvimento normal, com a desaceleração surgindo antes mesmo da presença de atividade epiléptica frequente no EEG como na síndrome de Dravet

Scheffer IE et al. Epilepsia. 2017 |

ENCEFALOPATIA DO DESENVOLVIMENTO E EPILÉTPICA

✓ **Encefalopatia do desenvolvimento e epiléptica** -> epilepsias em que nitidamente ocorre a associação das encefalopatias epiléptica e do desenvolvimento

Scheffer IE et al. Epilepsia. 2017

VELHOS TERMOS 'EPILEPSIAS GENERALIZADAS SINTOMÁTICAS'

- Usado para dois diferentes grupos de patologias

RESUMO

1. Simplificado o quadro
2. Etiologia – considerada em todos os estágios
3. Define Encefalopatias de desenvolvimento e / ou epilépticas
4. Novos termos: Auto-limitado, farmacorresistente
5. Epilepsias genéticas generalizadas
   - Epilepsias generalizadas idiopáticas = CAE, JAE, JME, GTCA
6. Epilepsias generalizadas sintomáticas utilizadas para ambos

-> Encefalopatias de desenvolvimento e epilépticas

-> Encefalopatia com epilepsia (estática)

DÚVIDAS ????

www.epilepsia.org.br

Nova Classificação da ILAE 2017 e slides

Drs Elza Márcia Yacubian, Lécio Figueira, Marcia Morita e Mirian Fabíola SG Mendes

Patricia Braga (Brazil)

APPLYING THE NEW CLASSIFICATIONS

Guilca Contreras (Venezuela)

VNS IN THE TREATMENT OF CHILDHOOD EPILEPSIES (GROUP 1)

Estimulación del Nervio Vago en el tratamiento de las epilepsias en edad pediátrica

Epilepsy: Awakening of hyperexcitability
12th Latin American Summer School on Epilepsy - LASSE XII
Guilca Contreras

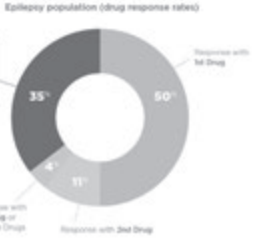
Epilepsia Fármacoresistente

Definición de la ILAE

- Epilepsia Fármacoresistente se define como la falla a un adecuado y sostenido control de crisis luego del ensayo de dos FAEs apropiadamente seleccionados, tolerados y dosificados (ya sea en monoterapia o combinados).

1. Kwan P, et al. Epilepsia 2009; doi: 10.1111/j.1528-1167.2009.02091.x
2. Mohanraj R and Brodie MJ. Eur J Neurol. 2006;13:277-282.

Epilepsia Farmacoresistente



Kwan P, Brodie MJ. N Engl J Med. 2000;342:314-319
Mohanraj R et al. European Journal of Neurology. 2006; 13:277-282
Brodie MJ. Epilepsia. 2013; 54:11-6

Estudios de epilepsia fármacoresistente

William R Gowers
1845-1915

- **1881: 36% resistente a los bromuros[1]**
- **1971: 33-38% resistentes[2]**
- **2005: 38% resistente[3]**

1Gowers, 1881; 2Coastworth, 1971, 3Mohanraj & Brodie, 2005

Biomarcadores de EFR

- Marcadores clínicos
  - Crisis frecuentes previo al inicio del tatamiento[1]
  - Respuesta al primer FAE y falla luego de 3 FAEs[1]
  - Etiología sintomática o criptogénica vs idiopática[1]
  - Edad temprana de inicio de las crisis[2]
  - Crisis tónicas y focales simples[2]
- EEG[2]
  - Actividad de base anormal con enlentecimiento difuso
  - Actividad epileptiforme focal
- Imagenológicos (PET, MRI, CT)[3,4]

The tendency of the disease is toward self-perpetuation; each attack facilitates occurrence of another by causing instability of the nerve elements

[1]Mohanraj R and Brodie MJ. Eur J Neurol. 2006;13:277-282.
[2]Ko TS and Holmes GL. Clin Neurophysiol. 1999;110:1243-1251.
[3]Duque S, et al. Arch Neurol. 2000;57:1331-1336.
[4]Haseloh RK, et al. Epilepsia. 2000;41(7):843-849.

Dimensiones de la EFR

Kwan P and Brodie MJ. Seizure. 2002;11:70

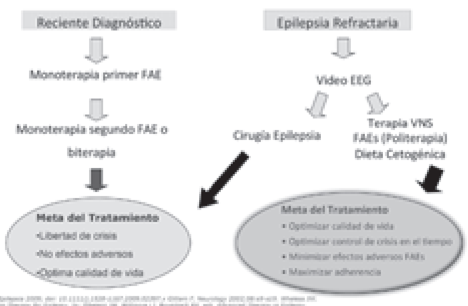
Evaluación del paciente con EFR

- Dos ensayos con FAEs, solos o en combinación sin éxito;
- ✓ Identificación de pacientes con epilepsia "Pseudorefractaria"
  - Falta de adherencia al tratamiento
  - Crisis disparadas por estilos de vida irregular
  - Consumo de drogas y alcohol
- Video-EEG
  - Identificación de eventos no epilépticos: 20 - 30% de los pacientes
  - Establecer el diagnóstico del síndrome epiléptico: generalizado o focal (básico para la selección del FAE)
  - Determinar si es candidato para cirugía

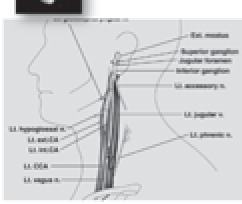
Tratamientos de la epilepsia

Tratamiento	Edad	Indicación	Eficacia	Efectos secundarios
FAEs	Niños Adultos	Tipos de crisis	64% libre de crisis [1]	Varian según el FAE
Dieta Cetogénica	Niños especialmente	Todo tipo de crisis	54% tienen >50% reduccion de crisis (a los 3 meses)[2]	Trastornos de los lípidos, cetoacidosis
Cirugía de epilepsia	Niños Adultos	Epilepsia refractaria	85% libre de crisis(TLE)[3]	Efectos cognitivos y relacionados con la cirugía
Terapia VNS	>12 años	ER Crisis focales (FOA)	43% tienen >50% reduccion de crisis a los 3 años[4]	Disfonía, faringitis, tos y disnea

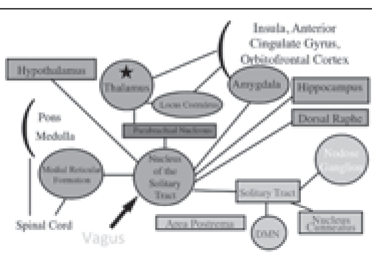
Objetivos del tratamiento



Nervio Vago



- Nervio vago izquierdo
  80% fibras aferentes mayormente amielínicas
  20% fibras eferentes, la mayoría parasimpáticas amielínicas viscerales y fibras mielínicas para las cuerdas vocales
- Nervio vago derecho
  tiene más potencial para efectos cardiacos en modelos animales



- El nervio vago izquierdo hace sinapsis bilateralmente con el NTS en la medula
- El NTS envía proyecciones a núcleos en el tallo cerebral (**locus coeruleus** y **rafe magno**), que modulan la serotonina y noerepinefrina en todo el cerebro
- El NTS tiene extensas proyecciones con el sistema límbico, formación reticular y estructuras cerebrales autonómicas

Mecanismo de acción del ENV

- **La acción del ENV está soportada por investigación en:**
  - **Anatomía del Cerebro Humano**
  - **Modelos animales de epilepsia**
  - **Electroencefalograma (EEG)**
  - **LCR**
  - **Imagenología funcional cerebral**

12

Estudios en Modelos Animales 1984–2001

Animal	Modelo	Resultados de ENV
Rata Gato Perro Mono	Pentilentetrazol Bicuculina/PTZ Estricnina/PTZ 3-MPA/PTZ Cobalto Tópico Penicilina tópica Gel Alumina Electroshock máximo	Crisis terminadas con la aplicación del ENV Crisis menos frecuentes y de menor duración al aplicar series de ENV Mayor efecto después de meses de usar el ENV Curva Dosis-Respuesta Previene estadio IV de kindling

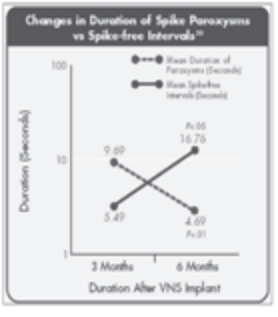
Núcleo del Locus Coeruleus y EV

- ENV demostró un efecto anticonvulsivante en ratas en el modelo de electroshock máximo
- Lesiones químicas agudas y crónicas en el locus coeruleus (LC)
- Después de lesionar el LC, ENV perdió su efecto protector o atenuante de las crisis
- Conclusiones:
  - LC está involucrado en el efecto anticonvulsivante del ENV
  - Efecto del ENV puede requerir la liberación de norepinefrina, un neuromodulador que tiene efecto anticonvulsivante

Efecto del ENV en el EEG de humanos

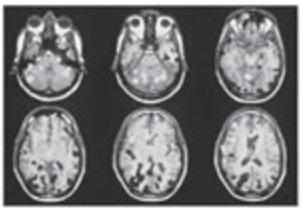
- **Cambios progresivos en el EEG**
- **Reducción de brotes de actividad epileptiforme seguido de períodos progresivos de intervalos libres de puntas**
- **Niños y adultos**

n=21 (4 - 31ª)



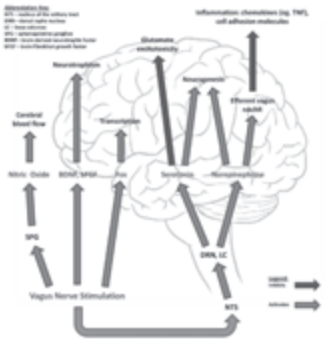
EV modula flujo sanguíneo cerebral

- Cambios bilaterales significativos en flujo cerebral son observados al utilizar la ENV[1]
- Incremento en el flujo sanguíneo en el tálamo tiene una correlación significativa con el control de crisis a largo plazo (P<0.001)[2]

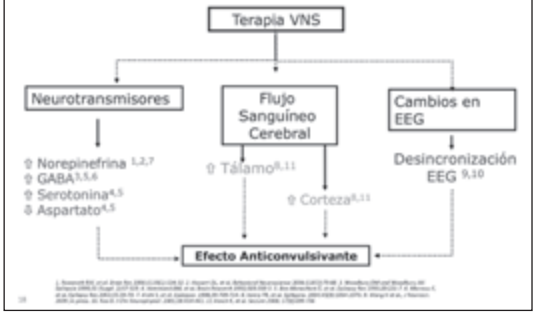


La EV es un tratamiento a través del cual la estimulación periférica del X nervio craneal es utilizada para tratar una enfermedad que está completamente relacionada con eventos fisiopatológicos que ocurren dentro del cerebro[3].

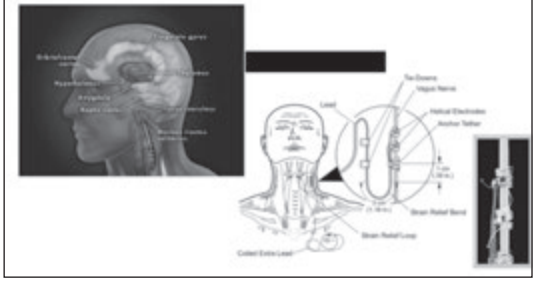
La EV ha demostrado que modula la liberación de una variedad de factores que regulan importantes mecanismos fisiopatológicos, como el flujo sanguíneo cerebral, neurotrofism, neurogenesis, excitotoxicidad, e inflamación[3].



Terapia VNS: Mecanismos de Acción

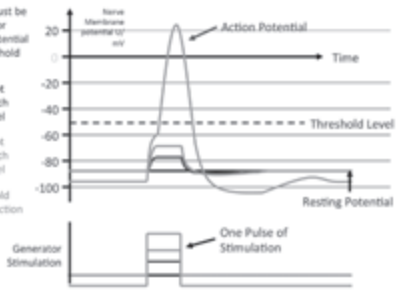


VNS



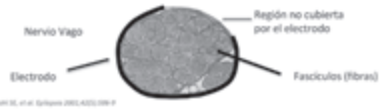
Potencial de acción: objetivo de la estimulación

- Stimulation must be high enough for membrane potential to reach Threshold Level
- Stimulation not enough to reach Threshold Level
- Stimulation not enough to reach Threshold Level
- When Threshold Level is met, Action Potential is initiated

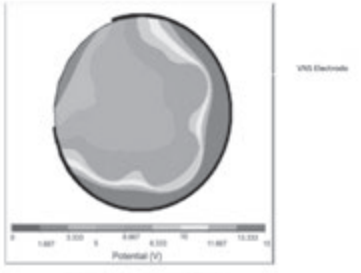


La respuesta a la estimulación puede variar entre los pacientes[1]

- El Primer Paso del Dosing debe ser encontrar la corriente mínima necesaria para generar el potencial de acción que lleve el estímulo hasta el Cerebro
- Tomando en cuenta la anatomía, sabemos que:
  - ✓ La posición de los fascículos y fibras del Nervio Vago son determinantes
  - ✓ Estos fascículos, necesarios para la estimulación, varían entre los pacientes
  - ✓ Dependiendo del tamaño del nervio, el electrodo puede o no cubrir la circunferencia total del mismo
  - ✓ Si las fibras necesarias para la activación están en una zona no cubierta por el electrodo es posible que se necesite corriente adicional

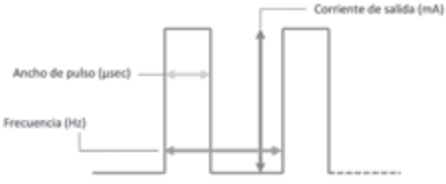


Modelo computacional de activación del nervio



Terapia VNS: parámetros de estimulación

(Aplicable para el modo normal, modo imán y modo de autoestim)



Corriente de salida: Candtidad de corriente eléctrica que se entrega en cada pulso de estimulación.

Ancho de pulso: Duración de cada pulso de estimulación.

Frecuencia: Número de pulsos por segundo.

Programar el VNS

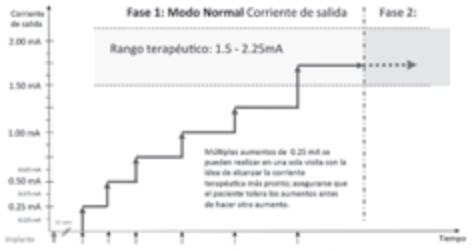
- Programar y ajustar la terapia VNS se realiza utilizando un computador manual y un mango programador [1]
- Luego de un ascenso progresivo de la corriente de salida, los parámetros típicos son:

Parameters	Units	Range	Typical
Output current	Milliamps (mA)	0 – 3.5	1 – 2
Signal frequency	Hertz (Hz)	1 – 30	20 – 30
Pulse width	Microseconds (μsec)	130 – 1000	250 – 500
Signal ON time	Seconds (sec)	7 – 60	30
Signal OFF time	Minutes (min)	0.2 – 180	5

© Cyberonics, Houston, TX. Cyberonics, Inc.

Terapia VNS- Fase 1

Ascenso de la corriente del modo normal



- Aumentar la corriente de salida del modo normal para alcanzar el rango terapéutico tan rápido como sea posible y tolerado.
- Visitas más frecuentes (1-2 sem) se sugieren en la fase 1.

25 *VNS Therapy Dosing Guideline. Houston, TX: Cyberonics, Inc.*

VNS
Fase 2

El ciclo de trabajo refleja el porcentaje de tiempo durante el cual ocurre estimulación.

Fase 2: Ciclo de trabajo

ON TIME (seconds) \ OFF TIME (minutes)	0.2	0.3	0.5	0.8	1.1	1.8	3	5	10
7	58%	44%	30%	20%	15%	10%	6%	4%	2%
14	69	56	41	29	23	15	9	6	3
21	76	64	49	36	29	19	12	8	4
30	81	71	57	44	35	25	16	10	5
60	89	82	71	59	51	38	27	18	10

Recommended
Not recommended*
Recommended progression for duty cycle
Not available with AutoStim Enabled

Ciclo de trabajo [%] = [tiempo On + 4] / [tiempo On + tiempo Off (seg)] x 100

Modo de estimulación con el magneto

- Mayor control para los pacientes y sus familiares[1,2]
- Estimulación
  - ✓ Puede interrumpir o disminuir la severidad de las crisis[1-3]
  - ✓ Puede mejorar el periodo postictal[2]
- Parar la estimulación

  Se pueden manejar de forma aguda los efectos secundarios[3]

[1]Boon P, et al. J Clin Neurophys. 2001;18:402-407.
[2]Fromes GW, et al. Epilepsia. 2000;41(suppl 7):117.
[3]Schachter SC and Saper CB. Epilepsia. 1998;39:677-686.

VNS
Efectos adversos

- Efectos adversos asociados con la terapia VNS

1. Ocurren solo durante el periodo de estimulación [1,2]
2. Generalmente disminuyen con el tiempo [2]
3. Pueden ser disminuidos o eliminados ajustando los parámetros [2]
4. Pueden ser controlados con el uso del magneto [3]
5. Similar en todas la edades [4,5]

1. Ben-Menachem E, et al. Neurology. 1999;53(6):1362-1367. 2. Ben-Menachem E. J Clin Neurophysiol. 2001;Sep;18(5):415-418. 3. Schachter SC. Neurology. 2000;55(Suppl 4):S17-S20. 4. Alexopoulos AV, et al. Seizure. 2006;15(7):491-503. 5. Ertan G, et al. Neurology. 2000;54:1179-1182.

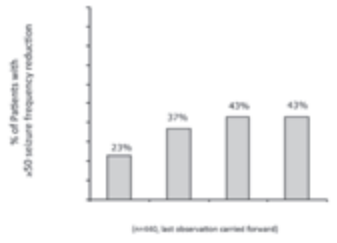
Terapia VNS
Primeros estudios clínicos

- E01 – E05 Evaluaron seguridad, tolerabilidad y eficacia de la terapia VNS
- De 454 pacientes con IDIV, 440 fueron evaluados por largo periodo (3 años)
- Cambios en los FAEs se permitieron en la fase de extensión

Estudio	Diseño	Tipo de Crisis	N	Tiempo
E01/E02	Piloto	Parcial	14	1988-1990
E03	Randomizado, doble ciego, control activo	Parcial	114	1990-1992
E04	Abierto	Todas	124	1991-1995
E05	Randomizado, doble ciego control activo	Parcial	199	1995-1996

Morris GL, et al. Neurology 1999;53:1731-3.

Terapia VNS
Primeros estudios clínicos



Morris GL, et al. Neurology 1999;53:1731-5.

Terapia VNS: Indicaciones

1994
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications.

1994
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications.

1997
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to antiepileptic medications

2010
The Vagus Nerve Stimulation Device VNS System is an electric stimulation device that stimulates the vagus nerves, used as an adjunctive therapy to reduce the frequency of epileptic seizures for drug-resistant refractory epilepsy patients (except for the patients for whom a craniotomy will be effective).

Terapia VNS
Resultados a largo plazo (NYU)

Variable	No. (%) or mean ± SD (range)
Females	220 (50.5%)
Males	216 (59.5%)
Mean age at seizure onset	9.4 years ± 11.5 (birth–59 years)
Mean duration of epilepsy prior to VNS	19.2 years ± 13.0 (8 mos–66 years)
Mean age at VNS insertion	29.0 years ± 16.5 (1.3–76)
Adults (≥18 years)	307 (70.4%)
Children <18 years	129 (29.6%)
Children ≤12 years	86(19.7%)
Median seizure frequency (per week)	4 (0.1–2000)
Mean number of AEDs at baseline	2.7 (0–7)
Mean number of AEDs failed	5.6 (1–19)
Prior failed intracranial epilepsy surgery	127 (29.1%)
Number of seizure types	2.0±1.0 (1–6)
Developmental delay	223 (56.4%)

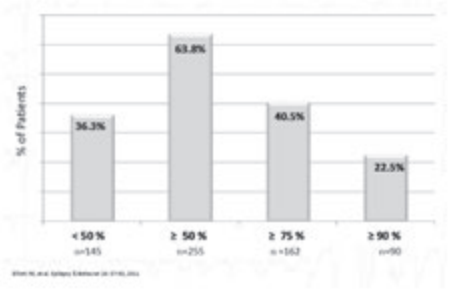
Elliott RE, et al. Epilepsy & Behavior 20: 57-63, 2011.

Datos (436 pacientes) en un solo centro (Elliott RE, et al. 2011).

Epilepsy Etiology	No. Patients	Seizure reduction	P values
		Median	
Neuronal migration disorder	32	41.0%	0.022
Cerebral palsy/static encephalopathy	35	60%	0.09
Lennox-Gastaut syndrome	24	52.1%	0.015
Traumatic brain injury	28	75.0%	0.02
Infection	30	50%	0.025
Tuberous sclerosis complex	12	75.0%	0.003
Tumor/cavernoma/arteriovenous malformation	18	90.2%	0.005
Genetic/metabolic syndrome	15	65.0%	0.002
Hypothalamic hamartoma	5	50.0%	0.04
Unknown	224	60.0%	0.015

Elliott RE, et al. Epilepsy Behav 2011;20(1):57-63.

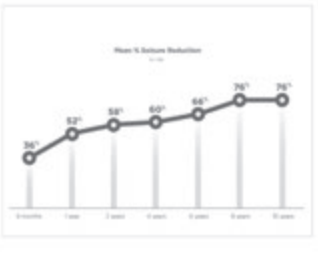
Tasa de Respuesta (NYU, 05 años)



Elliott RE, et al. Epilepsy & Behavior 20: 57-63, 2011.

Resultados a largo plazo (NYU)

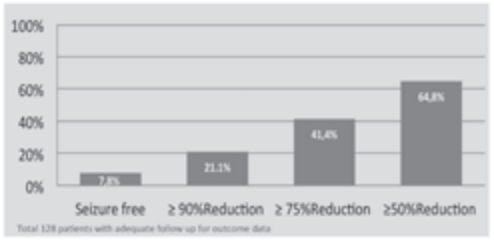
- 2,8 FAEs para el momento
- 6 FAEs fallidos (promedio)
- 20 años con la epilepsia
- 31% Qx previamente



Elliott RE, et al. Epilepsy Behav 2011;20(1):57-63.

Respuesta en pacientes pediátricos (<18 años)

Datos (141 pacientes), un solo centro (Elliott RE, et al. 2011).



Total 128 patients with adequate follow up for outcome data

Elliott RE, et al. J Neurosurg Pediatrics 7: 491-500, 2011

Complicaciones de la terapia VNS

Complication	N (%)	
	Transient or Minor	Permanent or required revision or removal
Neurological	6 (1.4%)	12 (2.8%)
Hoarseness	6 (1.4%)	9 (2.3%)
Dysphagia	—	2 (0.5%)
Unilateral vocal cord paralysis	—	1 (0.2%)
No neurological	8 (1.8%)	11 (2.5%)
Neck/arm pain unrelated to duty cycle	2 (0.5%)	—
Neck pain related to duty cycle	3 (0.7%)	3 (0.7%)
Superficial infection (antibiotics)	2 (0.5%)	-
Deep infection (removal/revision)	—	7 (1.6%)
Seroma/hematoma requiring aspiration	1 (0.2%)	-
Pneumothorax	—	1 (0.2%)

Data (436 pacientes), estudio en un solo centro (Elliott RE, et al. 2011).

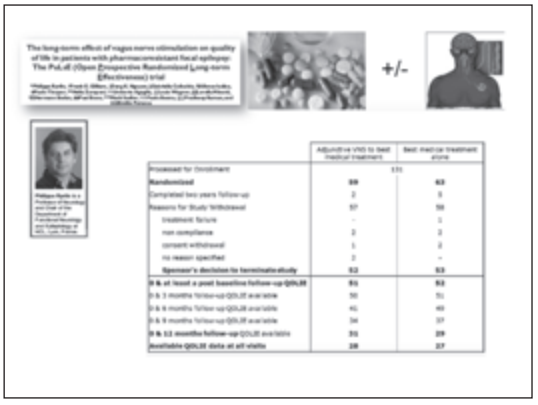
Terapia VNS Respuesta

Labar DR. Seizure. 2009; 13:202-208.
García-Navarrete E et al. Seizure. 2013 Jan; 22(1):9-13.
Chapman Kevin E et al. Journal of Neurology & Neurophysiology. 2013; 4:2.

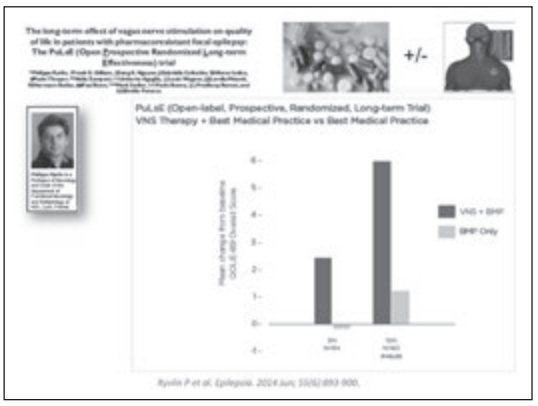
Uso temprano de la terapia VNS

- Terapia VNS temprana: pacientes en los primeros 5 años de su epilepsia
- Grupo control: pacientes tratados luego de los 5 años con epilepsia (promedio 21 años)

Ben-Menachem E et al. Neurology. 2002; 59(Suppl 4):S26-S31.



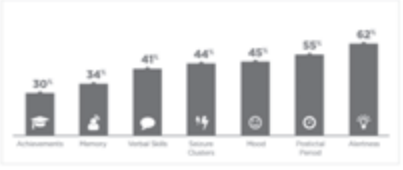
	Adjunctive VNS to best medical treatment	Best medical treatment alone
Processed for Enrolment	131	
Randomized	**69**	**63**
Completed two years follow-up	2	3
Reasons for Study Withdrawal	57	58
treatment failure	-	1
non compliance	2	2
consent withdrawal	1	2
no reason specified	2	-
Sponsor's decision to terminate study	**53**	**53**
0 & at least a post baseline follow-up QOLIE	**51**	**52**
0 & 3 months follow-up QOLIE available	50	51
0 & 6 months follow-up QOLIE available	41	43
0 & 9 months follow-up QOLIE available	34	37
0 & 12 months follow-up QOLIE available	**31**	**29**
Available QOLIE data at all visits	**28**	**27**



Ryvlin P et al. Epilepsia. 2014 Jun; 55(6):893-900.

Otros aspectos relacionados con la EV independientes del control de crisis

La mejoría fue definida cuando el paciente se sentía "mejor"o "mucho mejor"a los 12 meses de terapia (n=2,229)



Quiénes son candidatos para la terapia VNS?

- Pacientes con epilepsia fármacoresistente[1] que **no son candidatos a cirugía**
- Calidad de Vida comprometida:[2,3]
  - Crisis no controladas y efectos secundarios de los FAEs pueden impactar negativamente al paciente desde el punto de vista social, estado de ánimo, vida familiar, trabajo y educación.
- Epilepsias generalizadas, particularmente aquellas con ausencias y crisis atónicas como los síndromes de LG y Doose.
- Pacientes con síndrome de Dravet.
- Pacientes con historia de estado epiléptico recurrente.
- Pacientes en dieta cetogénica.

AG – 9 ã

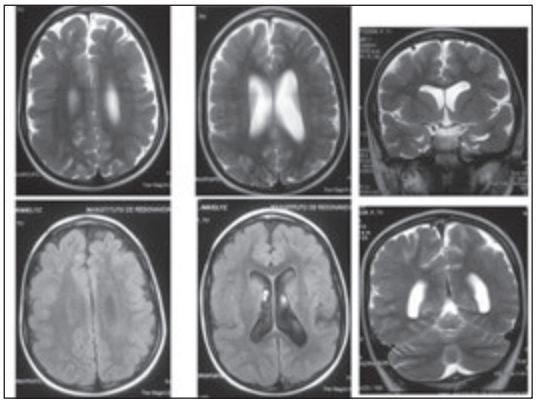
- Historia de crisis desde los 18 meses.
- Primeras crisis caracterizadas por desviación de cabeza y ojos a la izquierda y movimientos rítmicos de la cabeza hacia el mismo lado, sin y con posterior generalización.
- Desde hace tres años presenta episodios dados por disminución del tono cervical con flexión repetitiva del cuello ("siseo") y caída al suelo en ocasiones, parpadeo, salivación, desconexión y supresión transitoria de la actividad para luego retomarla.
- Máximo periodo libre de crisis 15 meses. Actualmente crisis diarias.

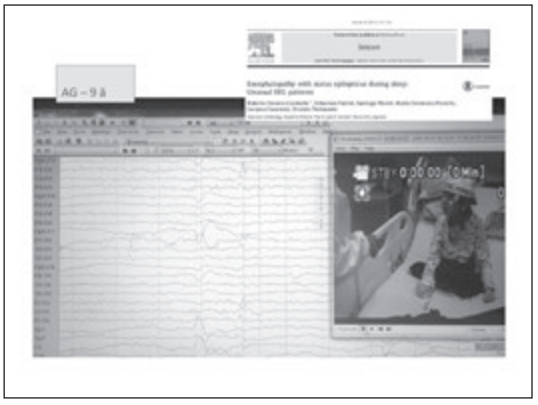
AG – 9 ã

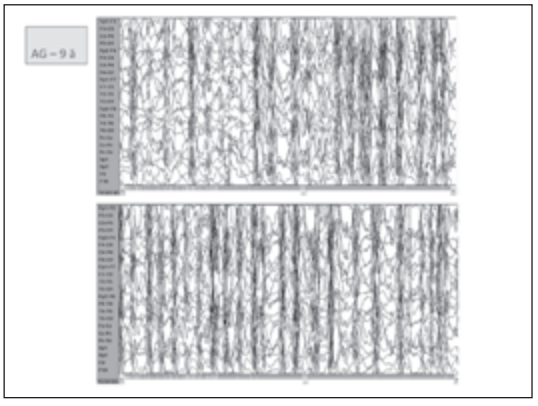
- Obtenida a término por parto inducido. PAN: 2200 gramos.
- Parálisis del VI nervio craneal derecho.
- Triparesia: Hemicuerpo derecho y miembro inferior izquierdo.
- Retraso en la adquisición de los hitos del neurodesarrollo. Discapacidad cognitiva.
- Antecedentes familiares: Abuela materna con epilepsia post traumática.

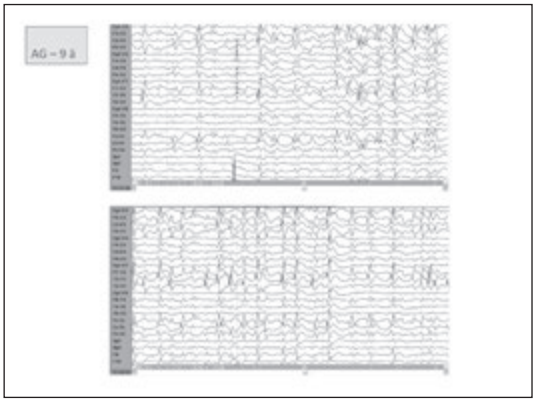
AG – 9 ã

- Ha recibido varios FAEs: LEV, OXC, PHT, VAL, TPM, NTP, CLB, PB. Mejor respuesta con VAL + LEV. Actualmente LEV + CNP.
- Dieta cetogénica desde julio 2013 hasta julio 2016.
- Recibió esteroides e inmunoglobulina.
- En agosto 2015 se implanta ENV, actualmente bajo los siguientes parámetros: corriente de salida: 1.50 mA, ancho de pulso: 250 useg, tiempo "on": 30 seg, tiempo off: 5 min, frecuencia de señal: 30 Hz, iman: corriente de salida: 1,75 mA, tiempo "on": 60 seg, ancho de pulso: 500 useg.




AG – 9 a


AG – 9 a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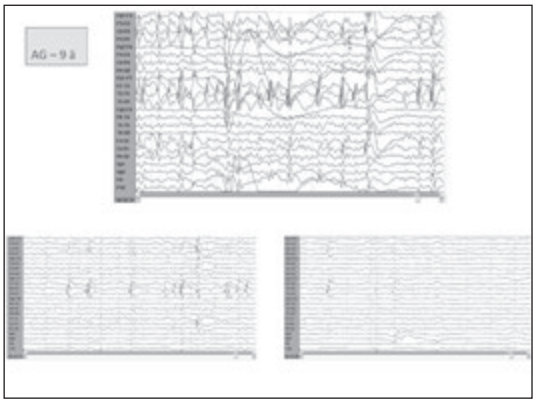
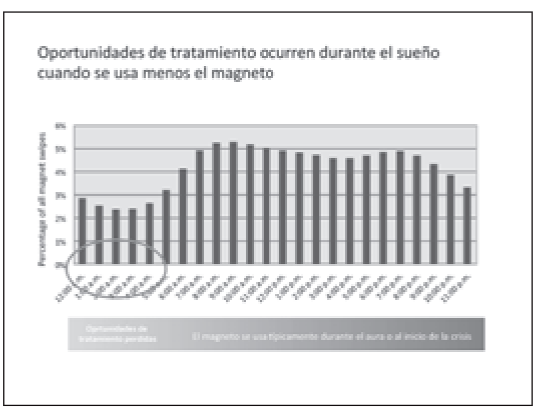
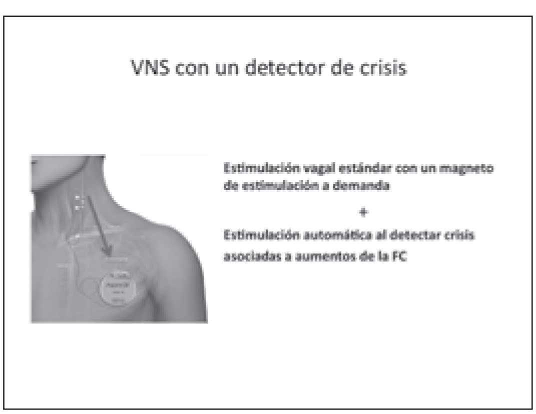

AG – 9 a


Oportunidades perdidas de tratamiento
Crisis durante el sueño
Tiempo insuficiente para aplicar el imán
No aura
Incapacidad de aplicar el imán
Discapacidad motora o cognitiva
Falta de disponibilidad o mal uso del imán


Los pacientes no pueden advertir todas las crisis
Los pacientes fallan en reportar
56%
de todas las crisis
Y más del
86%
de las crisis durante el sueño


Oportunidades de tratamiento ocurren durante el sueño cuando se usa menos el magneto
Oportunidades de tratamiento perdidas
El magneto se usa típicamente durante el aura o al inicio de la crisis

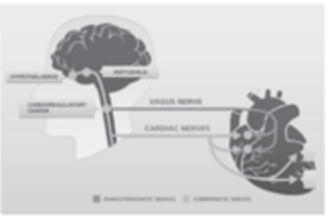

VNS con un detector de crisis
Estimulación vagal estándar con un magneto de estimulación a demanda
+
Estimulación automática al detectar crisis asociadas a aumentos de la FC

Conexión cerebro - corazón

82%

de los pacientes con epilepsia presentan un rápido incremento de la FC asociado con las crisis [1]

Descargas ictales en áreas del cerebro que regulan el sistema nervioso autónomo pueden provocar cambios en



1. Eggleston KS, et al. Seizure 2014;23(7):496-505. 2. Jansen K, et al. Seizure 2010;19(8):455-60.

Definiendo taquicardia ictal

La literatura provee varias definiciones de taquicardia respecto a la magnitud del cambio de la FC

- Más comun: Definición clínica de taquicardia sinusal, e.j., > 100 lpm
- Taquicardia ictal: taquicardia sinusal con el inicio del evento ictal
- También definido en términos del cambio absoluto o relativo de la FC pre ictal, e.j., incremento de 10 o 20 lpm o 20%
- Cuando fue reportado, el cambio promedio fue de 34 lpm por crisis

Eggleston K, Olin B, Fisher R. Ictal Tachycardia: The Head-Heart Connection. Seizure. 2014;23:496–505.

Prevalencia de taquicardia ictal (TIC)

Procentaje de pacientes con TIC

- A través de los estudios de evaluación de crisis clínicas, el porcentaje promedio de pacientes con cambios de la FC fue **82%**

Porcentaje de crisis con TIC

- El porcentaje de crisis focales (con o sin generalización secundaria) asociadas con taquicardia, osciló de **32.9% a 100%,** con un promedio de **71%**
- El porcentaje de crisis generalizadas asociadas con taquicardia, fue de **48% a 100%,** con un promedio de **64%**
- Las mayoría de los estudios reportan incrementos significativos de la FC durante las crisis que tienen origen en el **lóbulo temporal**

Eggleston K, Olin B, Fisher R. Ictal Tachycardia: The Head-Heart Connection. Seizure. 2014;23:496–505.

Temporalidad del cambio

Aparición de la taquicarda en relación al inicio de la crisis

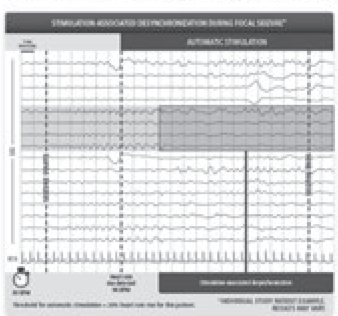
- Incremento en la FC se ha reportado previo al inicio electrográfico (taquicardia pre-ictal) en **23% a 98%** de las crisis
- **La taquicardia ictal** usualmente ocurrió en los **primeros 30 segundos** del inicio de la crisis, con la **FC máxima** alcanzada en la mayoría de las crisis, en los **primeros 60 segundos**
- El momento del cambio puede depender de la región de inicio ictal; cambios más precoces tienden a ocurrir en las crisis del lóbulo temporal en comparación con las de origen extra

Eggleston K, Olin B, Fisher R. Ictal Tachycardia: The Head-Heart Connection. Seizure. 2014;23:496–505.

Autoestimulación: respuesta a los cambios de la FC asociados a las crisis

- Propiedad de un sistema de circuito cerrado que analiza cambios relativos de la FC para detectar y responder a las crisis
  - **Detecta la onda R,** y por tanto, la FC del paciente[1]
  - **Detecta crisis potenciales a través de los cambios de la FC** y una vez detectada, produce una **estimulación automática**[1]
  - **Similar al modo de estimulación con el magneto**, la estimulación automática
    - ✓ Puede abortar o acortar las crisis[2-4]
    - ✓ Puede disminuir la severidad de las crisis[2-4]
    - ✓ Puede mejorar y acortar el periodo postictal[3]

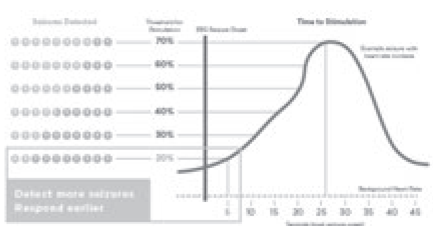
Resultado: interrupción y cese de la crisis



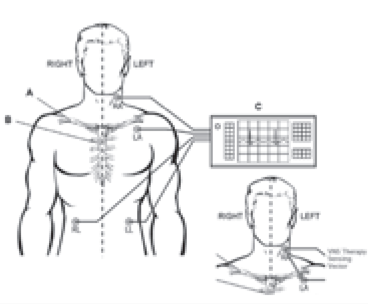
Alrededor del 60% de las crisis tratadas con la estimulación automática terminaron durante el curso de la estimulación

(28/46 crisis tratadas)

Umbral de autoestimulación

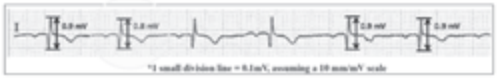


Registro del EKG previo a la cirugía



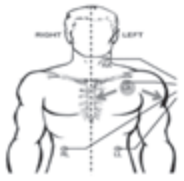
Medición de la Onda R

- Identificar la posición del paciente en la tira de EKG
- Para cada una de las dos posiciones, medir la amplitud punta a punta de mínimo **4** ondas R representativas en la DI del EKG (ver ejemplo)
- Registrar la mínima amplitud para cada posición (no el promedio!)
- La mínima amplitud de la onda R en ambas posiciones debe ser **0.4mV**



Medición de la Onda R

- Si la mínima amplitud de la onda R en todas las posiciones es menor de **0.4mV**, buscar una posición diferente del electrodo **"LA"** del EKG (localización del generador del VNS), y repetir el procedimiento.
- Incrementando el vector RA-LA moviendo el electrodo LA hacia una posición más lateral o medial, puede incrementar la señal del



Ejemplo.....

- Si el promedio de la amplitud de la onda R es de **0.9 mV**, entonces el nivel de ajuste de detección del ritmo cardiaco específico del paciente es

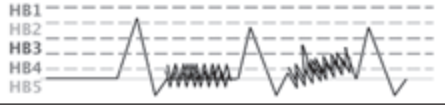
Heartbeat Detection Setting	Median Amplitude (mV) (across different postures)	
	Minimum	Maximum
5	0.40	0.50
4	0.51	0.70
3	0.71	0.85
2	0.86	1.25
1	1.26	-----

Average R-Wave Amplitude: 0.9mV mV

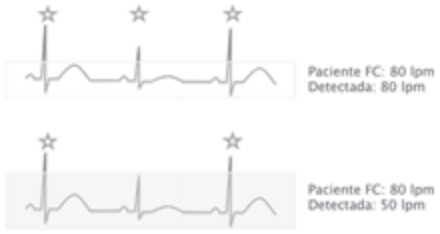
Patient-Specific Heartbeat Detection Setting 2

Ajuste de detección del ritmo cardíaco

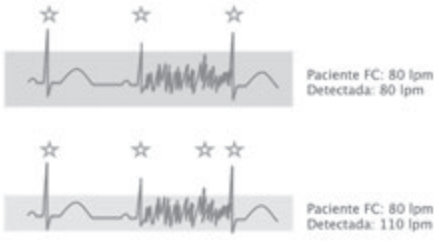
- Debe ser ajustado para afinar los componentes sensores, de tal modo que solo censen los latidos basados en la onda R del EKG
  - 1 = nivel menos sensible
  - 5 = nivel más sensible
- Si la localización de "LA" da para varias posiciones que funcionan, escoger la menor sensibilidad de detección del ritmo cardíaco, y así minimizar el sobre censo y la sobre detección.
- Luego de cada detección de la onda R, ocurre un periodo refractario de 250ms para minimizar la detección de la onda T

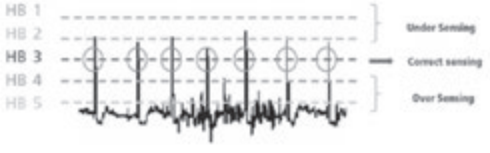


Ejemplos de sub registro



Ejemplos de sobre registro





Umbral para la Auto Estimulación

- AspireSR puede censar la FC y automaticamente produce un estimulación cuando el algoritmo detector de crisis indetifica una crisis potencial.
- El **Umbral de Auto Estimulación** puede ser ajustado para adaptar el sistema a las características individuales del paciente.
- La sensibilidad para la AutoEstim puede ser ajustado seleccionando un valor umbral apropiado que puede estar entre **20% - 70%, donde**:

Ejemplo

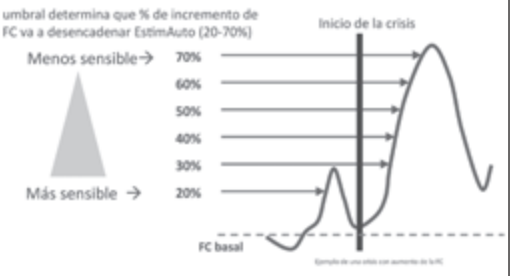
Crisis #	FC Pre-ictal	FC Ictal	Cambio FC	% Increm FC
1	60	93	33	55.00 %
2	60	95	35	58.33 %
3	60	88	28	46.67 %
4	65	105	40	61.54 %

- En este ejemplo el menor % de incremento de la FC es 46.67%.
- Un nivel apropiado del umbral para la EstimAuto podría ser 40%. Ese nivel de umbral podría detectar los cambios de la FC asociados con la mayoría de las crisis.

Umbral para la Autoestimulación
20%
30%
➡ 40%
50%
60%
50%

Umbral para Estimulación Automática (EstimAuto)

El umbral determina que % de incremento de la FC va a desencadenar EstimAuto (20-70%)



AspireSR – Contraindicaciones

- Vagotomía
- Diatermia
- Arritmia cardíaca (Modelo 106)
  - El **Modo de Auto Estimulación** no debe ser usado en pacientes:
    - Con arritmias cardíacas clínicamente significativas
    - En quienes reciben tratamientos que interfieren con las respuestas normales de la FC
      - Dependencia al marcapaso
      - Desfibrilador implantado
      - Tratamiento con beta bloqueantes

SM – 3 ã 6 m

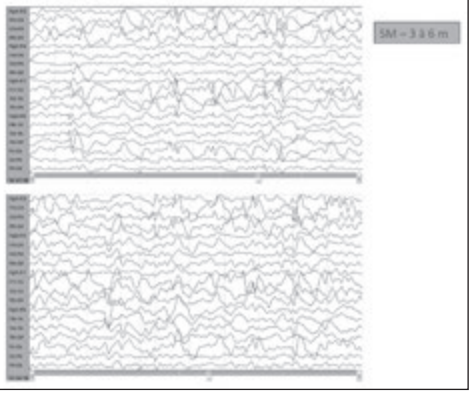
- Historia de crisis desde los 13 meses.
- Primera crisis caracterizada por movimientos clónicos generalizados. Posteriormente, episodios de desconexión con disminución del tono postural y otras con giro del tronco a la izquierda.
- Actualmente describen: 1)Flexión brusca del tronco con Tx frecuentes en la frente; 2)Supresión de la actividad motora + desconexión + salivación; 3)Sacudidas mioclónicas; 4)Crisis tónico clónicas generalizadas.
- Crisis diarias, predominio matutino. Máximo intervalo libre de crisis 10 días.

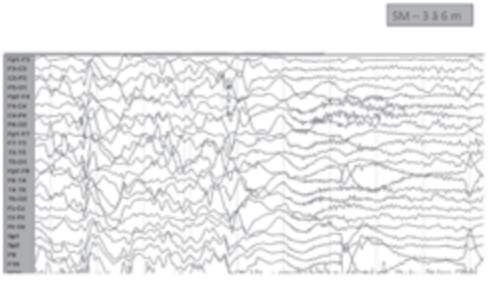
SM – 3 ā 6 m

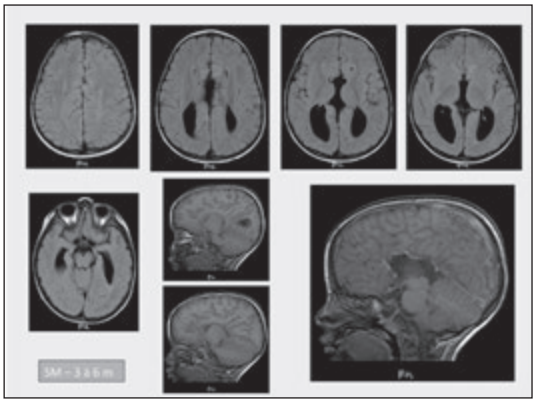
- I gesta. CsUs e HTA desde el cuarto mes. Obtenido a las 36 semanas por cesárea. PAN: 2300 gramos. TAN: 45 cms.
- Ptosis congénita OI.
- Adecuada adquisición de las destrezas motoras. Retraso en el lenguaje y deterioro con las crisis. Asiste al maternal.
- Examen físico: ptosis parcial OI, resto normal.
- Antecedentes familiares (-).

SM – 3 ā 6 m

- Estudio para errores innatos del metabolismo normal.
- EEGs: Asimetría interhemisférica con actividad lenta en HCI. Actividad epileptiforme multifocal de predominio izquierdo.
- VIDEO-EEG: Asimetría interhemisférica. Actividad epileptiforme multifocal de predominio en HCI. Registro de 20 crisis. Sacudida mioclónica seguido de disminución del tono postural en algunas de ellas. Las dos de > duración, sacudidas mioclónicas a nivel de cintura escapular, extensión M.S.Iz, desconexión y salivación. Ictal: Onda lenta seguido de depresión del voltaje y luego actividad rápida. Llama la atención la aparición estereotipada de actividad beta durante el patrón ictal mejor definida en electrodos F4,C4, P4 y O2.

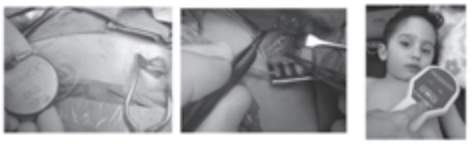






SM – 3 ā 6 m

- Ha recibido diferentes FAEs: PHT, CNP, PB, VAL, TPM. Actualmente OXC + LEV.
- Dieta cetogénica desde mayo hasta agosto 2016.
- El 23/08/16 se implanta VNS modelo 106. Parámetros actuales: Modo normal: 1.50 mA, 500 useg, 30 Hz, 30", 5'. Modo iman: 1.75 mA, 500 useg, 30 Hz, 60". Modo estimulación automática: 1.625 mA, 500 useg, 30 Hz, 60".



Preguntas frecuentes...

- Cuándo debo dejar de incrementar la corriente?
  - Eficacia clínica
  - Tolerabilidad
  - 1.50 - 2. 25 mA
- Cuándo puedo considerar que el paciente No es respondedor?
  - > 18 meses de terapia
  - Haber probado todas las posibilidades (corriente y ciclo)
  - Primero evaluar control de crisis con el dispositivo en OFF
  - Considerar otros beneficios de la terapia VNS
- Son los ciclos rápidos mejores que los estándar?
  - No ha sido investigado en estudios clínicos comparativos
  - Ajustes del ciclo son parte de la estrategia

Guilca Contreras Venezuela

VNS IN THE TREATMENT OF CHILDHOOD EPILEPSIES (GROUP 2)

Jaime Carrizosa (Colombia)

"LA PIEL DEL MEDO" – EPILEPSY IN THE NOVEL BY JAVIER VÁSCONEZ

"LA PIEL DEL MIEDO"

La epilepsia en la novela de Javier Vásconez

JAIME CARRIZOSA MOOG – Universidad de Antioquia
LASSE 2018

Javier Vásconez

Quito, 1944

Estudio en Inglaterra, Italia y Estados Unidos

Estudia Artes Liberales y Filosofía en la Universidad de Navarra y Vincennes

Novelas

- El secreto (1996)
- El viajero de Praga (1996)
- La sombra del apostador (1999)
- El retorno de las moscas (2005)
- Jardín Capelo (2007)
- La piel del miedo (2010)
- La otra muerte del doctor (2012)
- Hoteles del silencio (2016)

Javier Vásconez

"La conservé por mucho tiempo como un secreto... ¿Que más puedo decir? Que *La piel del miedo* es una suerte de *tratado* fantasioso sobre la epilepsia y el miedo, entre otras cosas. Ese miedo que tanto nos paraliza, pero que también nos impulsa a vivir, y a seguir escribiendo... *La piel del miedo*, probablemente sea mi novela más personal..."

Proyecto Patrimonio: Escritores y Poetas en Español Página Chilena al servicio de la Cultura 2017

"... En un reportaje concedido a Mercedes Mafla, el autor confiesa que esta es su novela más autobiográfica y así lo sentimos cuando nos situamos en el tiempo y en el espacio."

DESARROLLO

1) Fenomenología clínica

2) Percepciones del personaje principal sobre la epilepsia

3) Percepciones externas sobre la enfermedad

Fenomenología clínica: crisis

"... Luego del disparo, de repente, el cuarto empezó a dividirse, algo me estaba pasando. Ramón retrocedió hasta la puerta, los objetos se alejaban con una energía descomunal, yo esperaba que pararan las convulsiones, el miedo, porque ya golpeaban como un tambor dislocado dentro de mí. Muy vagamente percibí que alguna vez hubo un mundo real. Recordaba que la puerta se encontraba a la derecha. Podía incluso escaparme por allí, pero el corredor cubierto de un oleaje incontenible en vez de llevarme a la salida me condujo frente a un muro. También podía escuchar, lejanos, los latidos de mi propio corazón, pues yo sabía que era un animal perseguido: vi entonces el horror pintado en los ojos de Adela y de Ramón. Lo más extraño era que yo no estaba en el tiempo, ni siquiera era igual a ellos. A mi entender, había pasado por un desacuerdo con las cosas y las palabras que nombraba a mi alrededor. Experimenté una sensación de inestabilidad y de ruptura acompañada de violentos fogonazos. Como si fuera un testigo impotente de mis propios actos, al que no se le había permitido intervenir o comprometerse con lo que estaba ocurriendo, estallaron algunos relámpagos y sentí una especie de combustión dentro de mi cerebro, al tiempo que una angustia abrazadora avanzaba y me consumía internamente...".

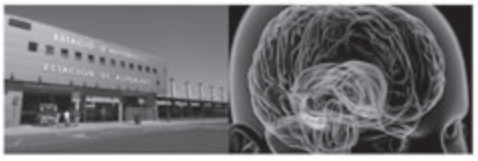
Fenomenología clínica: crisis

" Sin darme tregua, reventaron algunos fogonazos y sentí fuertes palpitaciones en las sienes. Extendí el brazo. Creo que fue lo último que hice, escuché la voz de mi padre en el teléfono..."

Volcán Calbuco - Chile

Fenomenología clínica: Crisis

"Antes de caer doblegado por la epilepsia, vislumbré, sacudido entre los fogonazos del ataque, una calle que conducía a una desolada estación de autobuses, en la que algunos pasajeros esperaban junto a unos edificios de ladrillo..., pese a que tenía la absoluta certeza de que esa estación no se hallaba en la ciudad. "



Estado posictal

"...Cuando desperté tuve un vago recuerdo de lo ocurrido, sin poder identificar el lugar donde me encontraba. Un estremecimiento se agitó en mi pecho... Sentía ansiedad, miedo, un endurecimiento en los brazos y un desgarrón en la corteza cerebral."

"... De pronto caí en un sueño profundo, como si dormir fuera una forma de alejarme de la soledad de la epilepsia..."

Estado posictal

"... Más allá del lugar donde me encontraba confinado, las palabras fueron llegando insuficientes, desarticuladas, impetuosas y en desorden. Sentí alivio y un terror ilimitado. ¿De dónde venían las palabras? Al mirar a mi alrededor tuve la sensación de que nunca había estado allí. Tal vez adivinaba a la mujer delante mis ojos. Volvía a escuchar el impetuoso rumor de la vida antes que las palabras huyeran con la crisis. Me preguntaba dónde me encontraba, porque parecía no haber existido desde hacía mucho tiempo..."

Otros aspectos clínicos

"- Después del almuerzo tengo mucho sueño. Me pasa todo el tiempo. Me quedo dormido en clase.

- Lo podemos remediar. Es por la medicina que tomas. Hay que cambiarla. Pero tienes que dormir bien. Descansar. Evitar beber alcohol."

Pronóstico

"Quizá debas esperar para curarte, aunque esperar sea insoportable. Pasarán años, el nudo se aflojará. No conozco a nadie que después de los cincuenta padezca estas crisis con la misma violencia que en la juventud, pero es posible que nunca te cures."

Eduardo Urbano Merino
Tlazolteotl

Percepciones del personaje principal sobre la epilepsia

Clarividencia

"...Entonces se abrió un abanico de luz que me permitía atisbar sin escrúpulos la mente de los otros."

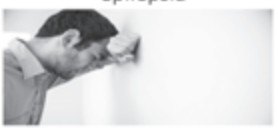
"Imaginaba que podía penetrar en la mente de los demás."

Percepciones del personaje principal sobre la epilepsia

Autocompasión:

"... Mis fantasías y el horror de las convulsiones me hicieron pensar que todo el mundo debía quererme."

Percepciones del personaje principal sobre la epilepsia



Inseguridad:

"... Acosado por un sentimiento de inseguridad, cuyo origen seguramente se debía a las convulsiones, me quedé un instante sin moverme, observando la rapidez con que Ramón se había desnudado para zambullirse en el agua."

Percepciones del personaje principal sobre la epilepsia

Estigma preconcebido:

"... De dónde iba a sacar el valor, dentro de pocas horas, para volver a ser yo mismo en la casa y comportarme como si nada hubiese pasado al día siguiente. Cualquier cosa sería preferible a tener que enfrentarme con los ojos de Ramón Ochoa en el colegio. Pero nadie dio muestras de advertir mi llegada. Quizás eso era lo que más me torturaba, la calma engañosa, la indiferencia que reinaba a mi alrededor... percibí durante el recreo un silencio cargado de presagios y de sutiles murmullos interiores. Todo resultaba tan aterrador como una tormenta a punto de estallar."

Percepciones del personaje principal sobre la epilepsia

Ocultamiento:

"... Podía verme caminando sigiloso por la vida. Supongo que con el propósito de ocultarme de la existencia que me había tocado en suerte vivir o para ocultar bajo un leve misterio la enfermedad que cargaba a mis espaldas."

Percepciones del personaje principal sobre la epilepsia

Rendición:

"... Supongo que aunque el mal reía desaforada, ostentosamente, a mí me atacaba la tristeza. Mi conciencia aún no se había emancipado de la enfermedad. Era su esclavo, debía superar la relación de perplejidad casi servil que mantenía con ella. Hubiera querido sonreír cuando me aquejaban los ataques, limitándome a reconocerla, como si fuera el rostro familiar de mi madre. Friamente, sin apasionamiento, desde lejos, debía aprender a aceptarla con la misma distancia con que se mira una máscara."

Percepciones del personaje principal sobre la epilepsia

Aislamiento:

"... Yo había cumplido diecisiete años y no acudí a la reunión de mi amigo, alegando encontrarme indispuesto."

Percepciones del personaje principal sobre la epilepsia

Doble personalidad/descontrol:

"... - A veces siento que hay otra persona dentro de mí – le dije -. Es como si alguien quisiera decir algo que yo no puedo. Me dan ataques."

Percepciones del personaje principal sobre la epilepsia

Variabilidad fonológica y semántica de las palabras:

"... Había descubierto que una palabra no sonaba igual ni tenía el mismo sentido antes o después de una crisis. En muchos aspectos, la epilepsia desacreditaba las palabras y hasta les quitaba su sentido común en cuanto aparecían escritas en los libros."

Percepciones del personaje principal sobre la epilepsia

Identidad:

"... Si en esos días ya lejanos mantenía un desacuerdo radical con la existencia, debido a los altibajos de mi enfermedad, en la cual me refugiaba como si fuera una fortaleza o una prueba de la crueldad del mundo, ahora, en cambio había empezado a nutrir mis deseos con el tormento insidioso de haber descubierto a Fabiola Duarte."

"... En comparación con el mundo de Rosendo, ¿qué era yo? Una enfermedad."

Percepciones del personaje principal sobre la epilepsia

Confidencialidad/secreto:

"... ¿A quién podía contarle mis temores? ¿A quien decirle que cuando se avecinaba el peligro y estaba a punto de caer abatido por la crisis sentía que se me nublaban los ojos?"

Percepciones del personaje principal sobre la epilepsia

Miedo:

"El miedo me impedía ver el mundo, sin duda doblegado por las convulsiones y los ataques golpeando mi cabeza. Tanto tiempo hundido en el miedo, en el remordimiento, tanto tiempo deseando escaparme de él."

"Aunque lograba dominarlo, el miedo a las convulsiones estaba tan arraigado en mí que corría igual que la sangre por mis venas."

"Pero esa enfermedad, habituada a salir intempestivamente de las sombras, volvería a traerme, como un mensajero puntual, el mismo miedo inconfesable y la familiaridad con el horror."

Percepciones del personaje principal sobre la epilepsia

Astenia/depresión/suicidio::

"...Existe una zona más bien descontrolada, casi letal, en la que lo más oscuro de nosotros aparece súbitamente. En los peores días, cuando me quedaba en cama devastado por las crisis, me asustaban esos instantes en que bordeaba el límite de lo prohibido, en soledad y sin poder recurrir a la voluntad."

"... La habría sacado a bailar si el humillante fantasma de mi enfermedad no me hubiera afectado hasta el punto de mantenerme a la expectativa."

Percepciones externas sobre la enfermedad

Miedo/huida de otros frente a las crisis:

"... O quizá se hallaba en el baño, muerta de miedo, orinando por gotitas mientras sollozaba, en un típico comportamiento de pánico tras haber presenciado uno de mis ataques." "Luego recuerdo su expresión de horror, en tanto se apartaba de la cama y se iba alejando hasta que su silueta se disolvió detrás de la puerta."

Percepciones externas sobre la enfermedad

Revelación:

"... La expresión de Ramón cambió, se puso muy serio cuando le confesé que era epiléptico."

Percepciones externas sobre la enfermedad

Confidencialidad/complicidad:

"... Sin soltarme, juntó mi mano sangrante con la suya y exclamó lanzando la navaja a sus pies: - ¡Ya estamos unidos por la hermandad! ¡Tus secretos son los míos! ¡También tus males serán los míos!"

Percepciones externas sobre la enfermedad

Ambiente hostil con temor:

"... Debo reconocer que nada había cambiado en la ciudad, que seguía envuelta como siempre en su propia desidia, tan lluviosa y encerrada en sí misma, al tiempo que yo me desmoronaba ante los violentos asaltos de la epilepsia."

Percepciones externas sobre la enfermedad

Ambiente hostil con temor:

"... Puedo advertir a mi alrededor síntomas de miedo colectivo, en la ciudad azotada por la lluvia, en los zaguanes donde se refugian los vagabundos, en la sonrisa temblorosa de los niños, en los ojos de las mujeres cuando salen atropelladas de sus trabajos, aunque nunca he descubierto las verdaderas motivaciones ni el origen del miedo."

CONCLUSIÓN

"La piel del miedo" del escritor ecuatoriano Javier Vásconez permite una mirada humana y subjetiva, pero no por ello ficticia, sobre la epilepsia. La real dimensión de la enfermedad trasciende el ámbito y los textos clínicos, escudriñando los aspectos psicológicos y sociales para darle la mirada integral y literaria. El prejuicio y la estigmatización han ocultado la epilepsia, y desnudarla en una de sus facetas más crudas, como lo es el miedo, puede contribuir a entender mejor a nuestros pacientes, sus familias y nuestras sociedades.

Nicola Specchio (Italy)

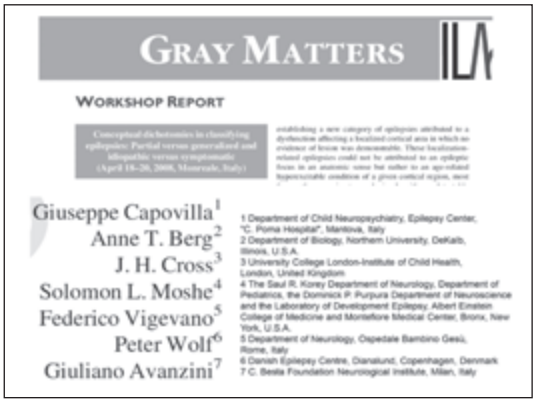
DIFFICULTIES IN THE CLASSIFICATION OF PEDIATRIC EPILEPSIES

GIUSEPPE CAPOVILLA (ITALY)

SYSTEM EPILEPSY


Workshop
"Conceptual dichotomies: idiopathic versus symptomatic and partial versus generalized"

Montreale (Italy) 18th–20th April 2008


GRAY MATTERS

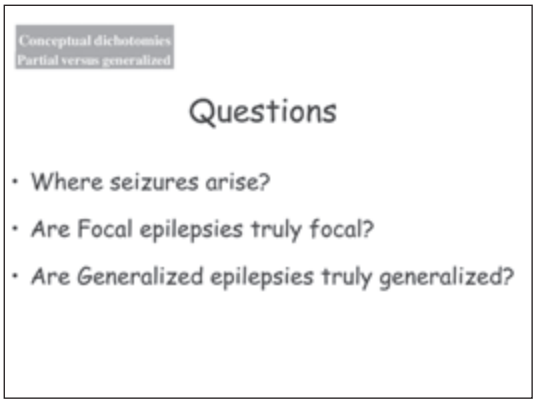
WORKSHOP REPORT

Conceptual dichotomies in classifying epilepsies: Partial versus generalized and idiopathic versus symptomatic (April 18–20, 2008, Montreale, Italy)

establishing a new category of epilepsies attributed to a dysfunction affecting a localized cortical area in which no evidence of lesion was demonstrable. These localization-related epilepsies could not be attributed to an epileptic focus in an anatomic sense but rather to an age-related hyperexcitable condition of a given cortical region, most

Giuseppe Capovilla[1]
Anne T. Berg[2]
J. H. Cross[3]
Solomon L. Moshe[4]
Federico Vigevano[5]
Peter Wolf[6]
Giuliano Avanzini[7]

1 Department of Child Neuropsychiatry, Epilepsy Center, "C. Poma Hospital", Mantova, Italy
2 Department of Biology, Northern University, DeKalb, Illinois, U.S.A.
3 University College London-Institute of Child Health, London, United Kingdom
4 The Saul R. Korey Department of Neurology, Department of Pediatrics, the Dominick P. Purpura Department of Neuroscience and the Laboratory of Development Epilepsy, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, U.S.A.
5 Department of Neurology, Ospedale Bambino Gesù, Rome, Italy
6 Danish Epilepsy Centre, Dianalund, Copenhagen, Denmark
7 C. Besta Foundation Neurological Institute, Milan, Italy


Conceptual dichotomies
Partial versus generalized

Questions

- Where seizures arise?
- Are Focal epilepsies truly focal?
- Are Generalized epilepsies truly generalized?

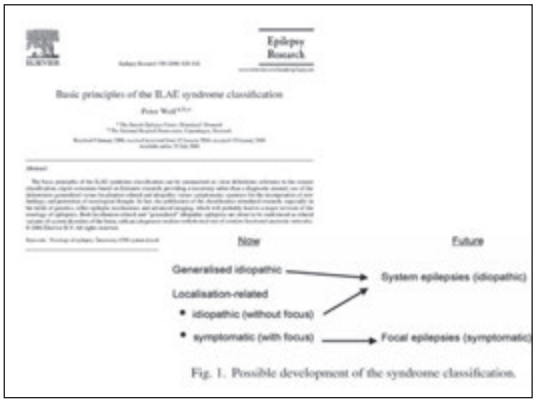
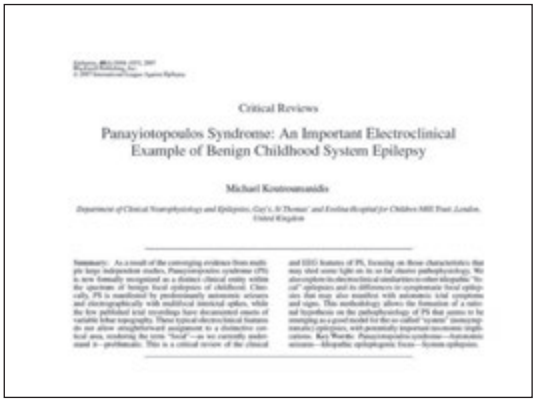


Fig. 1. Possible development of the syndrome classification.


Critical Reviews

Panayiotopoulos Syndrome: An Important Electroclinical Example of Benign Childhood System Epilepsy

Michael Koutroumanidis

Thursday April 22nd

08.30-09.00	Workshop Opening and Welcome Address
Chair:	S. Moshe
09.00-09.30	**System Epilepsy:** origin and evolution of the concept (*G. Avanzini*)
09.30-10.00	The concept of System in mathematics and informatics (*M. Chavez*)
10.00-10.30	The concept of System in the brain (*G. Bertini*)
10.30-11.00	Focal versus System epilepsy (*P. Wolf*)
11.00-11.20	Coffee-break
11.20-11.50	Generalized versus System epilepsy (*A. Arzimanoglou*)
11.50-12.20	How can fMRI support the concept of system epilepsy (*S. Seri*)
12.20-12.50	How can genetic support (or conflict) the concept of System epilepsy? (*F. Zara*)
12.50-13.15	Discussion and synopsis of the 1st Session
13.15-14.30	Light lunch
14.30-17.00	**Some models of System epilepsies:** Rolandic Epilepsies (*P. Mangunetti*), Occipital Epilepsies (*M. Koutroumanidis*), West Syndrome (*G. Capovilla*), CAE (*W. van Emde Boas*), Infantile Seizures (*F. Vigevano*), JME (*P. Wolf*), Reflex Epilepsies (*P. Hirsch*).
17.00-17.30	Coffee-break

Friday April 23rd

09.00-12.00 Working groups

1) The boundaries between local, generalized and system in epilepsy (*G. Capovilla Chair - M. Chavez, W. van Emde Boas, M. Koutroumanidis, C. Ozkara*)

2) Which epilepsies match the concept of system epilepsy (*P. Wolf Chair - A. Arzimanoglou, A. Covanis, N. Fejerman, F. Vigevano*)

3) Which hypothetic changes (and benefits) for the classification (*R. Guerrini Chair - J. Engel, E. Hirsch, S. Moshe, F. Zara*)

4) How the concept of system epilepsy combine with the anatomophysiological concept (*G. Avanzini Chair - G. Bertini, R. Cerebello, P. Mangunetti, S. Seri*)

April 24th

09.00-12.00 How can we propose this new concept?

Chairs: G. Avanzini - S. Moshe

Starting from mathematics and informatic

"A system is a construct or collection of different elements that together produce results not obtainable by the elements alone. The elements, or parts, can include people, hardware, software, facilities, policies, and documents; that is, all things required to produce systems-level results. The results produced by a system can include functions, behavior, system level qualities, properties, characteristics, and performances. The value added by the system as a whole, beyond that contributed independently by the parts, is primarily created by the relationship among the parts; that is, how they are interconnected" (Rechtin, 2000).

There are simple and complex systems (to be distinguished from complicated systems).

Simple systems have a small number of components which act according to well understood law (e.g. the simple pendulum, behavior described using Newton's equations of motion). Examples in neurology could be the pyramidal system; the spinal sensorimotor reflex arc etc.

Complex systems consist of several components interacting among each other in a complex way so that the effects may be only partially predictable. An example of complex system is Internet. Complex systems should not be confused with

Complicated systems. In these, even if they have many components, their interactions are relatively simple and their result highly predictable (Amaral et al, 2004). An example of complicated system is an aircraft which results from a large number of components that are assembled according to a complicated plan to perform a relatively limited number of well defined activities that are in most cases predictable. Unlike complicated systems, emergent properties or functions of a complex system:

1. depend more on the interaction of its components, than on their individual properties
2. do not result from the existence of a central controller (unlike the aircraft, internet is not governed by any central authority), neither from external organizing supervisors
3. postulate the existence of interaction rules that may not be explicitly defined and that are investigated with the assumption that their knowledge would lead to a full understanding of system functioning.

THE CONCEPT OF BRAIN SYSTEM

- A brain system is a set of synaptically interconnected areas whose coordinated physiological activity plays a distinct functional role
- A single brain structure may belong to more than one system: for example, some brainstem structures could be investigated as components of either vigilance control or pain systems; also, some thalamic nuclei can be involved either in relaying sensory inputs to the cortex or in controlling the global level of cortical activity
- Anatomical connections are necessary but not sufficient to define a system, which emerges when the different components actively participate in accomplishing the system's function.

SystE hypothesis

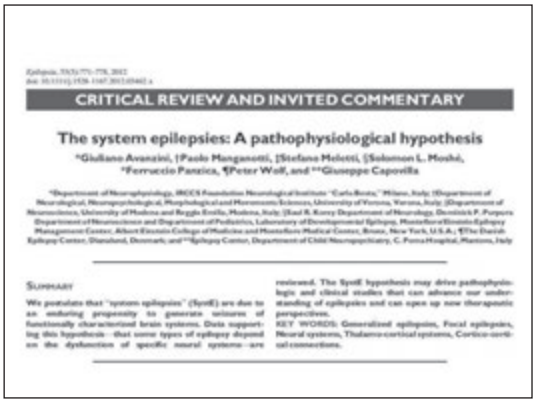
- "The SystE hypothesis postulates that the "enduring propensity to generate seizures" of some epilepsies is due to the specific susceptibility of a system as a whole. The neural system responsible for SystE is revealed by the clinical/EEG semeiology of the seizures, but the concept refers to the persistent susceptibility of the seizure-generating system, which is assumed to exist also in the interictal period"

The concept of System Epilepsy

- **System epilepsy is the result of a simultaneous pathological activation of functionally different anatomical areas of the brain that, as a whole, generates a specific epileptic phenotype**

The concept of System Epilepsy

- So, a dysfunction of a single brain structure cannot be responsible for a complex manifestation as some Epilepsy syndrome are, and the typical electroclinical picture requires the active participation of a pathological system in which different brain areas (the cortex, thalamic nuclei and brainstem) are hyperexcitable and work together. When some of these stations do not work, different electroclinical phenotypes develop"



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

Summary

We postulate that "system epilepsies" (SystE) are due to an enduring propensity to generate seizures of functionally characterized brain systems. Data supporting this hypothesis—that some types of epilepsy depend on the dysfunction of specific neural systems—are reviewed. The SystE hypothesis may drive pathophysiologic and clinical studies that can advance our understanding of epilepsies and can open up new therapeutic perspectives.

KEY WORDS: Generalized epilepsies, Focal epilepsies, Neural systems, Thalamo-cortical systems, Cortico-cortical connections.

CRITICAL REVIEW AND INVITED COMMENTARY

Are the dichotomies generalized versus focal epilepsies and idiopathic versus symptomatic epilepsies still valid in modern epileptology?

Hans O. Lüders, John Turnbull, and Farhad Kaffashi

Summary

In this commentary we discuss the basic concept of an epileptogenicity level, which is variable in different brain regions and is a function of multiple factors including the basic epileptogenicity level, routine environmental or internal stimuli, and various triggering and causative factors. This concept blurs the distinction between focal versus generalized and between idiopathic versus symptomatic epilepsies. We suggest dropping the dichotomy idiopathic versus symptomatic and to instead simply list the different etiologic factors that increase the epileptogenicity level. On the other hand, even if there is a continuum between focal and generalized epilepsies, most epilepsies are either predominantly focal or predominantly generalized. It is useful to maintain this distinction (even if somewhat artificial) because focal epilepsies can be treated with epilepsy surgery, and all focal epilepsies tend to respond to the same type of anticonvulsants. Generalized epilepsies cannot be treated surgically and respond to different anticonvulsants depending on the semiologic type of seizures.

KEY WORDS: Epilepsy classification, Epileptic syndromes, Dichotomies, Epileptogenicity, System epilepsy.

How to test this hypothesis?

- Neuroanatomical knowledge
- Using Neurophysiological studies
- With Studies of EEG-fMRI co-recordings

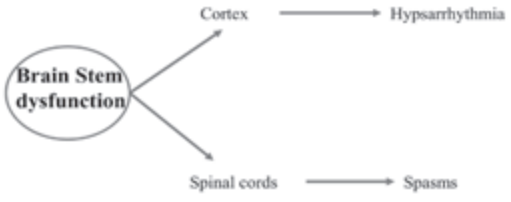
Proposed models

- West Syndrome
- Lennox-Gastaut Syndrome
- CAE
- Janz Syndrome
- Rolandic epilepsy

West syndrome

- Neurophysiological Mechanisms
  - Brainstem theory
  - Cortical theory
- Pathophysiological mechanisms
  - Desynchronization model
  - Hypothalamic-Pituitary Adrenal Axis Dysfunction
  - Immune system dysfunction

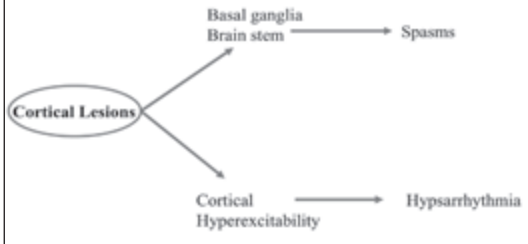
first hypothesis



Brainstem Theory

- Signs of brainstem pathology
  - (Kellaway, 1959; Kamoshita et al.,1970; Tominaga et al., 1986; Frost and Hracovy, 2003 etc)
- Spasms in hydranencephaly (Neville, 1972)

second hypothesis



Cortical theory

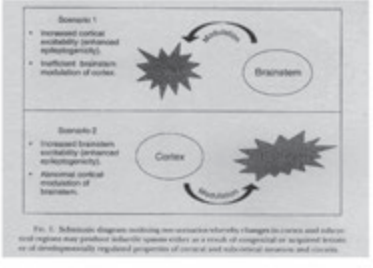
- Signs of cortical pathology in absence of brain stem pathology
  - (Trojaberg and Plum, 1960; Tucker and Solitare,1963; Bignami et al.,1964; Branch and Dyken, 1979)
- PET studies: Chugani hypothesis
  - "the primary dysfunction is a focal or diffuse cortical abnormality that, at a critical maturational stage, triggers (through projection pathways to the brainstem) abnormal activity within the serotonergic raphe nuclei"
- Association with focal seizures

Pathophysiological mechanisms

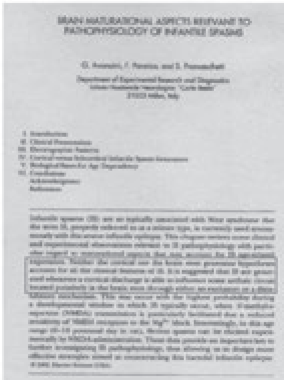
- **HYPOTHALAMIC-PITUITARY-ADRENAL AXIS DYSFUNCTION (Baram hypothesis)**
  - "the basic abnormality is stress related excessive production of corticotropin-releasing hormone (CRH) during early life"
    - reduced CSF levels of ACTH (Nalin et al., 1985; Facchinetti et al.,1985; Baram et al., 1992a, 1995; Nagamitsu et al., 2001;) and cortisol (Baram et al., 1995)

Pathophysiological mechanisms

- **IMMUNE SYSTEM DYSFUNCTION**
  - "Defect of the immune system" (Mandel and Schneider, 1964; Martin, 1964; Hrachovy and Frost., 1989)
    - Antibodies to brain tissue (Mota et al.;1984; Reinskov, 1963),
    - increased numbers of activated B and T cells (Hrachovy et al., 1985).
    - abnormal (HLA) in infantile spasms patients (Howitz and Platz, 1978;
    - Hrachovy et al., 1988a; Suastegui et al., 2001)



From Lado and Moshe, 2002

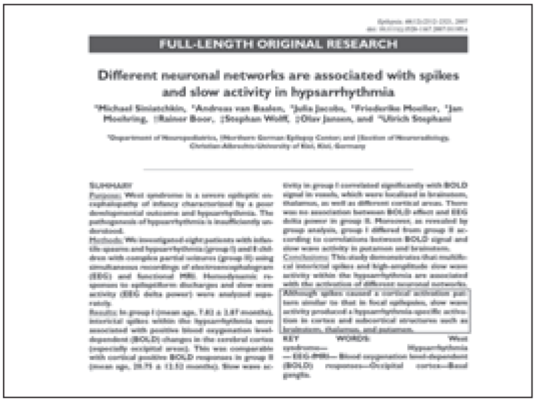

BRAIN MATURATIONAL ASPECTS RELEVANT TO PATHOPHYSIOLOGY OF INFANTILE SPASMS

Frost and Hrachovy, 2005

- "the disturbance of function is crucially dependent on an unbalanced maturational pattern, in which certain brain systems are not able to interact in the normal manner due to their divergent developmental status"

"If the model proposed here is valid, then the search for the basic pathophysiologic substrate of infantile spasms must focus on the identification of brain systems particularly susceptible to disruption by disturbances of the maturational process"

- "then future work should attempt to identify *systems* that are functionally based on two or more closely interacting processes, rather than seeking a single common denominator. The model also provides an explanation for the wide diversity of associated etiologic factors that have been associated with this disorder, because many different pathologic impacts can produce the same functional deficit"



Epilepsia, 48(12):2312–2321, 2007
doi: 10.1111/j.1528-1167.2007.01195.x

FULL-LENGTH ORIGINAL RESEARCH

Different neuronal networks are associated with spikes and slow activity in hypsarrhythmia

*Michael Siniatchkin, *Andreas van Baalen, *Julia Jacobs, *Friederike Moeller, *Jan Moehring, †Rainer Boor, ‡Stephan Wolff, ‡Olav Jansen, and *Ulrich Stephani

*Department of Neuropediatrics, †Northern German Epilepsy Center, and ‡Section of Neuroradiology, Christian-Albrechts-University of Kiel, Kiel, Germany

SUMMARY

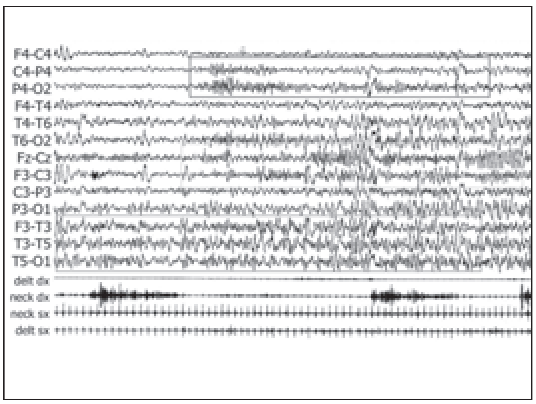
Purpose: West syndrome is a severe epileptic encephalopathy of infancy characterized by a poor developmental outcome and hypsarrhythmia. The pathogenesis of hypsarrhythmia is insufficiently understood.

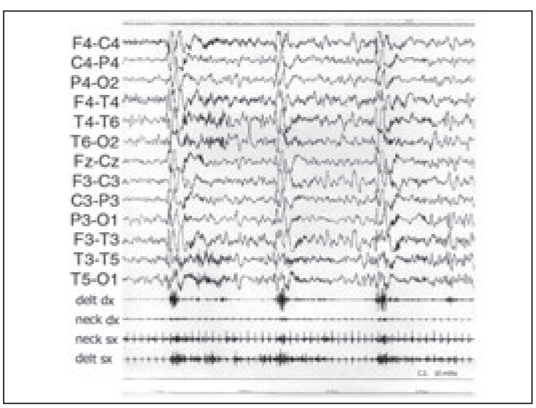
Methods: We investigated eight patients with infantile spasms and hypsarrhythmia (group I) and 8 children with complex partial seizures (group II) using simultaneous recordings of electroencephalogram (EEG) and functional MRI. Hemodynamic responses to epileptiform discharges and slow wave activity (EEG delta power) were analyzed separately.

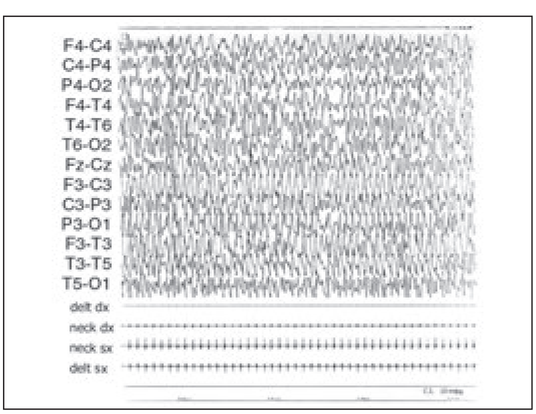
Results: In group I (mean age, 7.82 ± 2.87 months), interictal spikes within the hypsarrhythmia were associated with positive blood oxygenation level-dependent (BOLD) changes in the cerebral cortex (especially occipital areas). This was comparable with cortical positive BOLD responses in group II (mean age, 28.75 ± 13.53 months). Slow wave activity in group I correlated significantly with BOLD signal in voxels, which were localized in brainstem, thalamus, as well as different cortical areas. There was no association between BOLD effect and EEG delta power in group II. Moreover, as revealed by group analysis, group I differed from group II according to correlations between BOLD signal and slow wave activity in putamen and brainstem.

Conclusions: This study demonstrates that multifocal interictal spikes and high-amplitude slow wave activity within the hypsarrhythmia are associated with the activation of different neuronal networks. Although spikes caused a cortical activation pattern similar to that in focal epilepsies, slow wave activity produced a hypsarrhythmia-specific activation in cortex and subcortical structures such as brainstem, thalamus, and putamen.

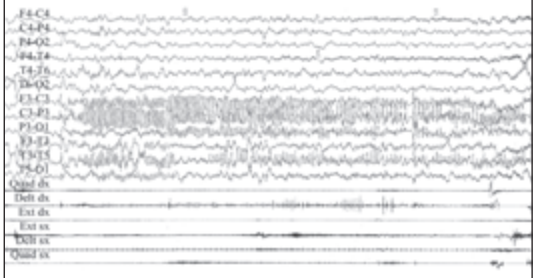
KEY WORDS: West syndrome—Hypsarrhythmia—EEG-fMRI—Blood oxygenation level-dependent (BOLD) responses—Occipital cortex—Basal ganglia.







System epilepsy versus "Systemic" epilepsy



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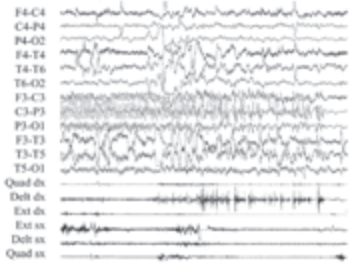

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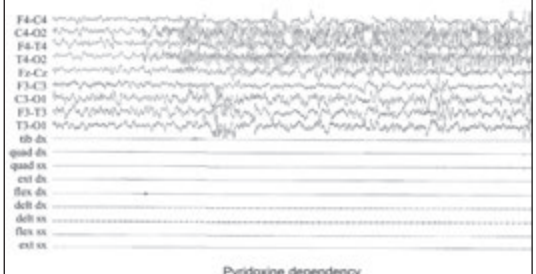
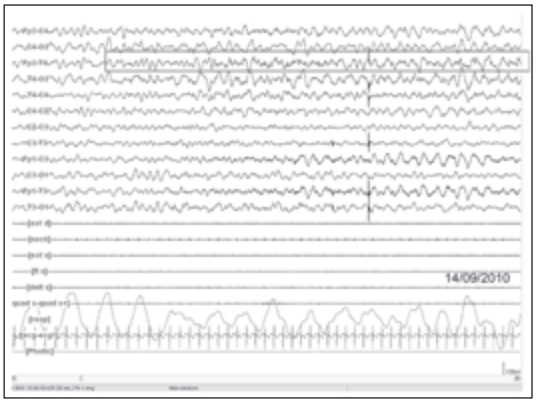


Pyridoxine dependency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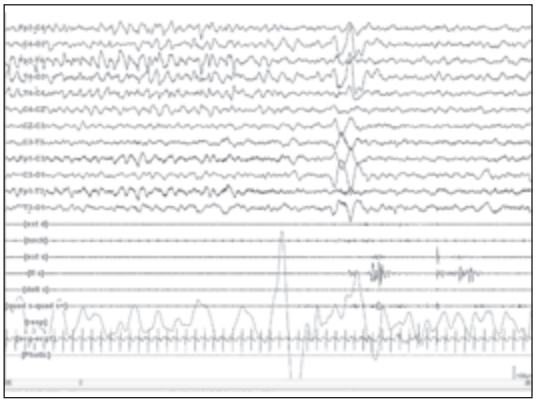

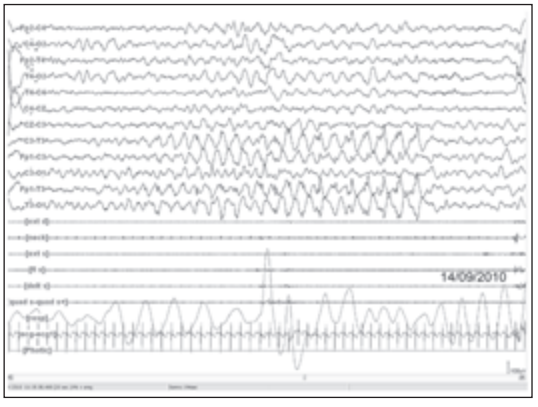
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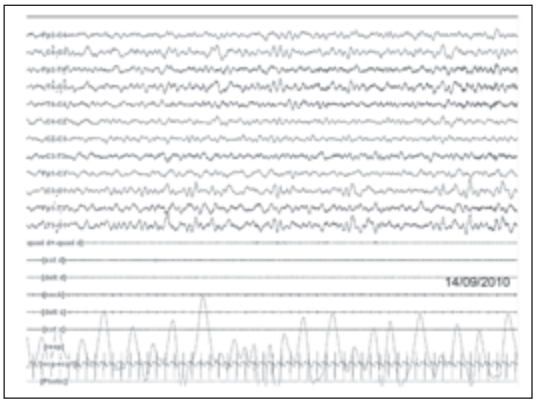
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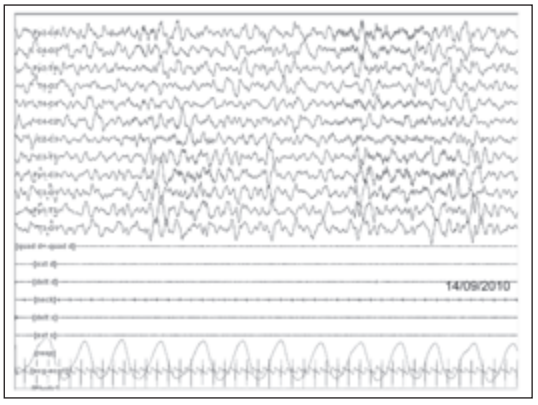
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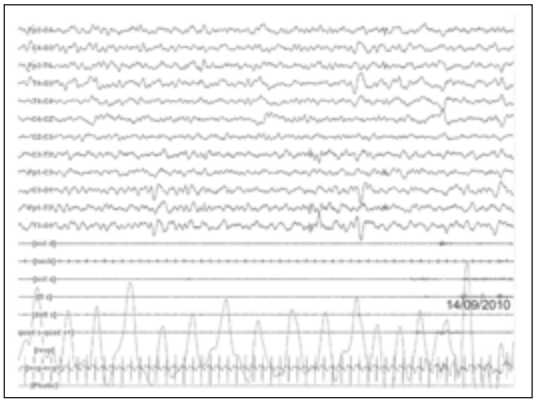
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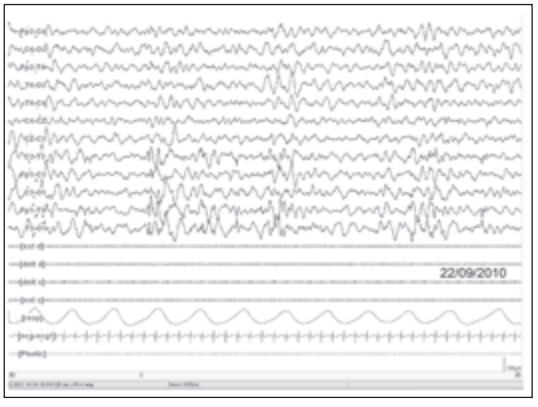
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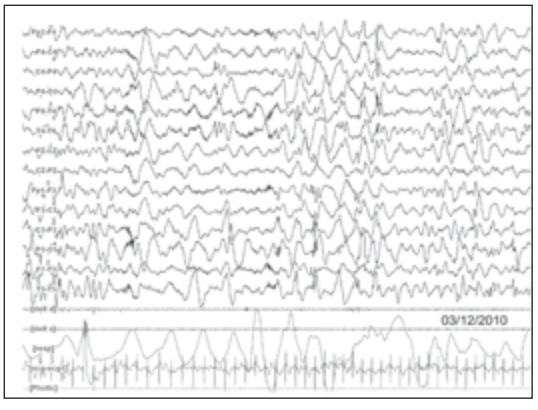
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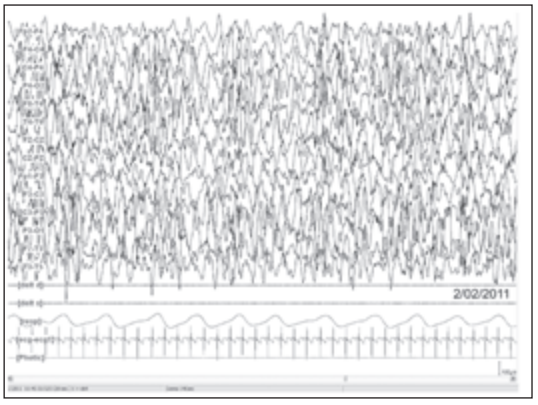


- This case presented with
  - A first period of Focal epilepsy
  - A second period of System epilepsy (West syndrome)

West Syndrome as SystE

- "These findings suggest that the dysfunctioning of a single brain structure cannot be responsible for such a complex manifestation as WS, and that the typical electroclinical picture requires the active participation of a pathological system in which different brain areas (the cortex, thalamic nuclei and brainstem) are hyperexcitable and work together. When some of these stations do not work, different electroclinical phenotypes develops"

Lennox-Gastaut as System Epilepsy

- Very few papers treating neurophysiopathology
  - Blume 2001
  - Beaumanoir 2005
  - Siniatchkin 2012

EPILEPTIC DISORDERS

Pathogenesis of Lennox-Gastaut syndrome: Considerations and hypotheses

Epileptic Disorders, Volume 3, Number 4, 183-96, December 2001, Articles originaux

Summary

Author(s) : Warren T. Blume, University Campus, 339 Windermere Road, London, Ontario, Canada, N6A 5A5.

Summary : No other epilepsy more substantially combines cryptogenicity and intractability than does Lennox-Gastaut Syndrome. Although antecedent neurological conditions have preceded LGS in some patients, others with similar ills fail to develop this syndrome, and precise charting of the pathway between any presumed aetiology and the epilepsy has eluded researchers. Despite these frustrations, LGS has elicited a host of publications over the years, possibly because it combines features of many other epileptic disorders and thereby occupies a crossroads position among them. Lacking a comprehensive experimental model of LGS, this article combines relevant data from several clinical and basic sources in order to formulate a concept of pathogenesis. Data are presented to suggest that the occurrence of factors enhancing excitability during a vulnerable period of cortical and thalamic development may permanently imprint a bilateral, diffuse epileptogenic system upon the mammalian brain.

Keywords : Lennox-Gastaut syndrome, pathogenesis, hypotheses, epilepsy, intractable epilepsy, children

Blume

- **Physiological bases of electrophysiological features**
  - Clinical data
  - Spike-waves and slow spike-waves
  - Cortical events
  - Cortical-thalamic interactions
  - Cortical hyperexcitability
  - Fast rhythmic waves
  - Cortex, thalamus and synchrony

Blume

- Seizures and the immature brain
  - Lower seizure threshold
  - Mechanisms of excitability
  - Epileptic pathways
  - Gap junctions
  - Direction of epileptic discharge propagation

"the occurrence of factors enhancing excitability during a vulnerable period of cortical and thalamic development may permanently imprint a bilateral, diffuse epileptogenic system upon the mammalian brain"

"Thus, enduring synaptic and non-synaptic epileptic systems would form"

Epilepsia, 53(4):766–774, 2012
doi: 10.1111/j.1528-1167.2010.02918.x

FULL-LENGTH ORIGINAL RESEARCH

EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox-Gastaut syndrome

*Michael Siniatchkin, *Diana Coropceanu, *Friederike Moeller, †Rainer Boor, and *†Ulrich Stephani

*Department of Neuropediatrics, Christian-Albrechts-University, Kiel, Germany; and †Northern German Epilepsy Center, Raisdorf, Germany

SUMMARY

Purpose: Even if etiologies of Lennox-Gastaut syndrome (LGS) are diverse, the multiple causes converge into a final common pathway that results in this specific epilepsy phenotype. There is little knowledge, however, about neuronal networks that may be a part of this pathway.

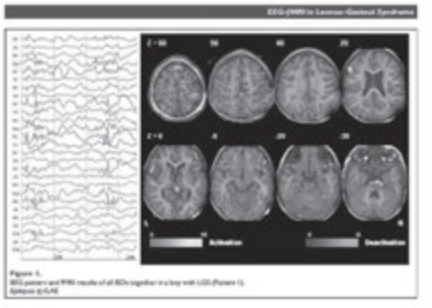
Methods: To investigate these networks, 11 children with LGS and 9 control children with multifocal epileptic activity were investigated using simultaneous recordings of EEG and functional MRI (EEG-fMRI) in a 3 Tesla scanner.

Key Findings: Individual and group analyses revealed significant activation of brainstem and thalamus (especially centromedian and anterior thalamus) associated with epileptiform discharges in patients with LGS. None of the patients with multifocal epileptic activity presented with the same hemodynamic activation pattern.

Significance: Because brainstem activation has been associated with infantile spasms, which often evolve into LGS, and thalamus activation has been observed in patients with primary (idiopathic generalized syndromes) and secondary (focal epilepsies) bilateral synchrony, the described network in LGS may represent the common pathogenetic pathway of these different conditions.

KEY WORDS: Lennox-Gastaut syndrome, EEG-fMRI, Brainstem, Thalamus, Children.

- Activation in the brainstem was the most consistent finding in children with LGS and was observed in 10 patients (91%)
- It seems likely that all SSWs, independently of their localization, were associated with a common neuronal network
- The same is true for positive BOLD signal changes in the thalamus. For all SSWs, activation in the thalamus was observed in eight children with LGS (73%)
- Another consistent finding in patients with LGS was the detection of positive BOLD signal changes in the cerebellum (73%)
- In addition, patients with LGS presented with significant, bilateral activation in various cortical regions
- Note that activation of brainstem, thalamus and, cerebellum was equally significant in both symptomatic and cryptogenic cases of patients with LGS
- In contrast to children with LGS, there were no consistent, positive BOLD signal changes in subcortical structures in children with multifocal partial epilepsy



- Because LGS as a clinical entity can be associated with different etiologies, one may suggest that multiple causes can activate a syndrome-specific neuronal network
- Brainstem nuclei and reticular formation have been discussed as significant parts of this network (Blume, 2001; Hayashi, 2001)

Brainstem

- It seems likely that the brainstem plays a substantial role in mechanisms of tonic axial seizures, an important feature of the LGS.
  - Tonic seizures fail to respond to callosotomy (Rougier et al.,1997)
  - Tonic seizures are less responsive to resection of apparently epileptogenic cortical areas (Bladin, 1985).

"Taking into account results of this study as well as PET and EEG-fMRI studies performed in children with L-G syndrome we argue that brainstem activation (especially in the region of the reticular formation) is a common part of pathogenetic mechanisms in LGS (and West syndrome)"

Thalamus

- A significant role of thalamocortical pathways in LGS was demonstrated previously
  - Centromedian thalamic nucleus stimulation in patients with refractory LGS have been an effective treatment stragegy (Velasco et al., 2006).
  - The anterior thalamus has been frequently and successfully used as a target for deep brain stimulation in patients with multifocal and secondary generalized epileptic activity (Samadani & Baltuch, 2007).

- In Siniatchkin study, positive BOLD signal changes were found in the thalamus, especially in its centromedian and anterior part
- It is not clear, however, whether the thalamus is a primarily or secondarily activated structure

Cortex

- The neurophysiologic basis of SSW in LGS may be similar to that responsible for classic generalized spike wave paroxysms of idiopathic generalized epilepsy, such as primary bilateral synchrony
- or the responsible mechanism may be attributed to the secondary bilateral synchrony resulting from one or more epileptogenic foci

- Evidence for unspecific cortical abnormalities as an origin of SSWs
  - PET studies demonstrated focal or general cortical hypometabolism in cryptogenic and symptomatic cases of LGS (Chugani et al., 1987; Theodore et al.,1987; Ferrie et al., 1996)
  - Their surgical removal gave subsequent clinical improvement of LGS patients (You et al., 2007)

Differently

- the analysis of propagation patterns, so called interhemispheric time difference of SSWs, revealed evidence for primary bilateral synchrony in most patients with LGS
- Moreover, the later part of the bursts appears bilaterally without any sign of propagation that would suggest activation of a central integrating thalamocortical system (Ohtahara et al., 1995)
- Similar positive BOLD signal changes in the thalamus were observed in patients with primary bilateral synchrony who presented with primary generalized epileptiform discharges and bilateral SSWs (Aghakhani et al., 2004, 2006; Hamandi et al., 2006; Moeller et al., 2008a)

- Whether the brainstem nuclei influence thalamic gating and thereby modulate cortical excitability
- or hypersynchronous cortical activity causes activation of the thalamus and interferes with connectivity between the brainstem and mesencephalic structure

remains to be answered in the future

Conclusions

- EE such as LGS (and WS) are a paradigm of System epilepsy for
  - Their electroclinical polymorphisms
  - Evidence of different etiologies
  - Evidence of different altered maturational processes
  - Evidence of involvement of different brain areas
  - Cognitive impairment as a consequence of an enduring pathological activity of a system
  - fMRI data could help to define the "true" LGS

CAE

- Sub-cortical Theory
  - Europe
- Cortical theory
  - Canada

Both are true?

Antalia Workshop

- "the use of the term "focal" to describe the regional onset of SWs can be misleading, as it may create confusion with "true" focal seizures
- the available data support the idea of a trigger zone within a given thalamo-cortical system that has a particular genetically determined epileptogenic susceptibility
- the trigger area becomes a part of the oscillating network during absence seizures
- the oscillations constitute an emerging property of the whole system (as in dynamic, non-linear systems)"

Epilepsia, 53(5):779–789, 2012
doi: 10.1111/j.1528-1167.2012.03421.x

HISTORICAL REVIEW

A brief history on the oscillating roles of thalamus and cortex in absence seizures

*†Massimo Avoli

*Montreal Neurological Institute and Department of Neurology & Neurosurgery, and of Physiology, McGill University, Montreal, Quebec, Canada, and †Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

Summary

This review summarizes the findings obtained over the past 70 years on the fundamental mechanisms underlying generalized spike-wave (SW) discharges associated with absence seizures. Thalamus and cerebral cortex are the brain areas that have attracted most of the attention from both clinical and experimental researchers. However, these studies have often favored either one or the other structure in playing a major role, thus leading to conflicting interpretations. Beginning with Jasper and Penfield's ingénic view of absence seizures as the result of abnormal functions in the so-called centrencephalon, we witness the naissance of a broader concept that considered both thalamus and cortex as equal players in the process of SW discharge generation. Furthermore, we discuss how recent studies have identified fine changes in cortical and thalamic excitability that may account for the expression of absence seizures in naturally occurring genetic rodent models and knockout mice. The end of this fascinating tale is presumably far from being written. However, I can confidently conclude that in the unfolding of this "novel," we have discovered several molecular, cellular, and pharmacologic mechanisms that govern forebrain excitability, and thus consciousness, during the awake state and sleep.

KEY WORDS: Absences, Cerebral cortex, Generalized spike and wave discharges, Thalamus.

Absence Seizures at the Dawn of EEG and the Birth of the "Centrencephalic System"

Berger (1934): "absences are caused by an abrupt withdrawal of tonic inhibitory influences exerted by the thalamus upon the cortex"

The Fabulous 1960s and the "Cortical Invasion"

Back to the Future

Gloor's Corticoreticular Hypothesis and the Feline Generalized Epilepsy Model

The New Millennium and the Comeback of Cortical Networks in SW Discharges

Genetic Rodent Models and the Thalamus Resurgence in the 1980s and 1990s

Back to the Future

1. "generalized SW discharges should be considered as a pathologic phenomenon arising from the malfunction of any of several specific voltage- or ligand-gated mechanism in the thalamocorticothalamic network"...
2. ..."both thalamic and cortical networks are involved in the expression of absence seizures"...
3. ..." fMRI-EEG recordings indicate that brain areas such as the insula or cerebellum are implicated as well in generalized SW discharges"...
4. ..." default mode network involved in monitoring the external world may be deactivated and therefore responsible for the impaired consciousness seen during SW discharges"

FULL-LENGTH ORIGINAL RESEARCH

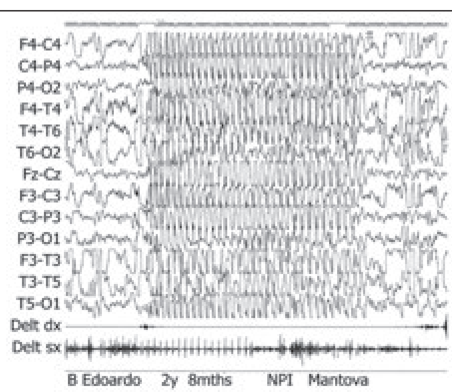
Absence seizures: Individual patterns revealed by EEG-fMRI

Friederike Moeller, Pierre LeVan, Hiltrud Muhle, Ulrich Stephani, Francois Dubeau, Michael Siniatchkin, and Jean Gotman

Thalamus, default mode areas, and caudate nuclei are involved in absence seizures (Salek-Haddadi et al., 2003; Labate et al., 2005; Laufs et al.,2006; Moeller et al., 2008, Meletti, 2011)

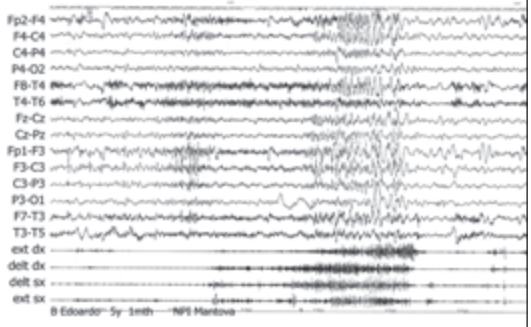
Male, present age 18 yrs 5 mths

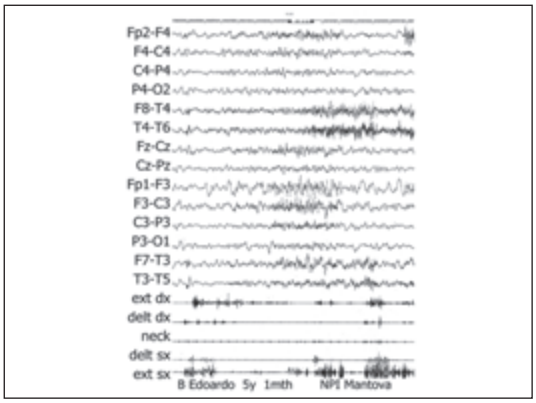
- Positive familiar history for Epilepsy
- Perinatal period uneventful
- Normal psychomotor development
- *At the age of 2 years and 8 months, occurrence of absences with mild myoclonic components*

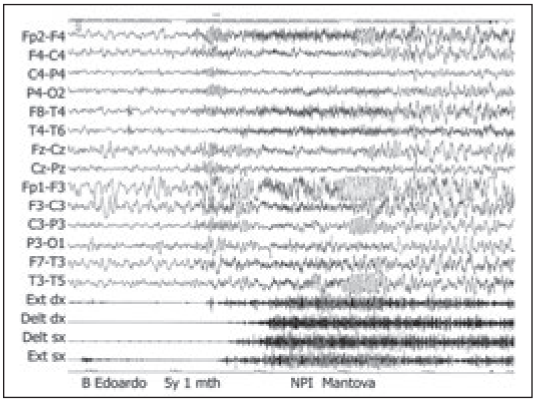


- LTG (2,5 mg/Kg/die) was introduced and complete seizure control was obtained in three months
- After 2 years, at the age of 4.6 years, LTG was gradually withdrawn

- After few months focal seizures occurred, sometimes with secondary generalization, realizing ES



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C4-P4
P4-O2
F8-T4
T4-T6
Fz-Cz
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Fp1-F3
F3-C3
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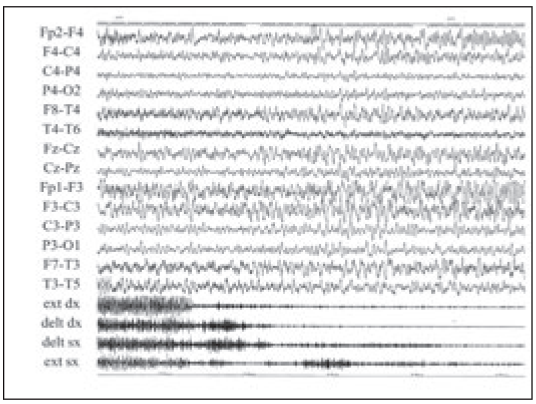
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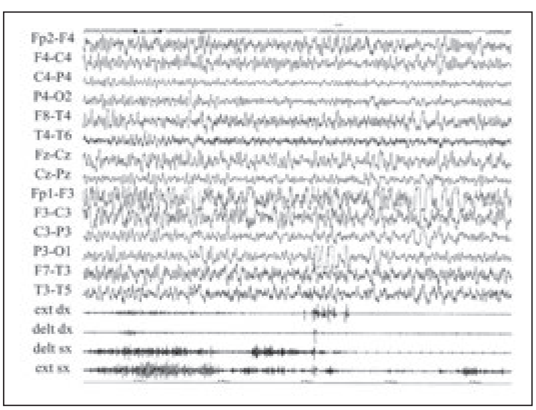
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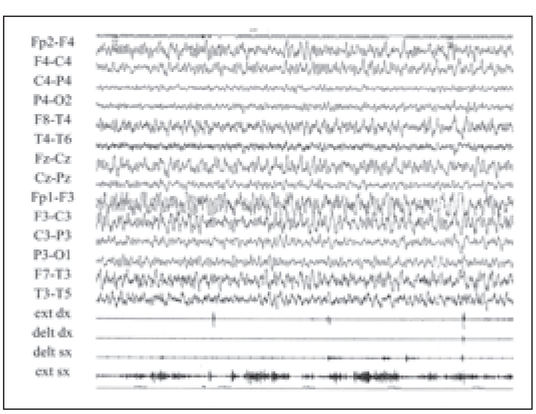
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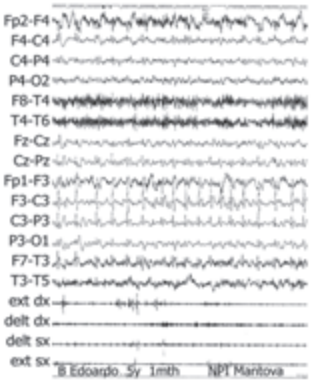
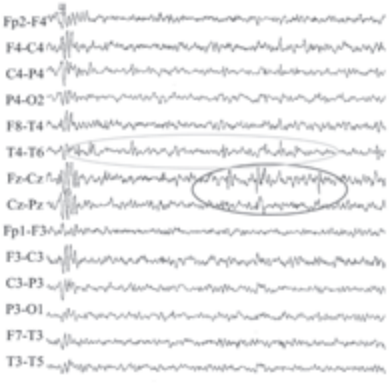
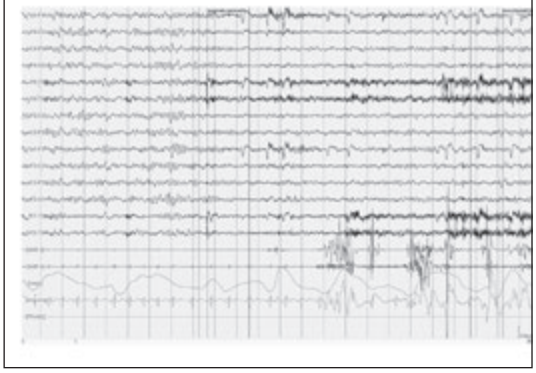


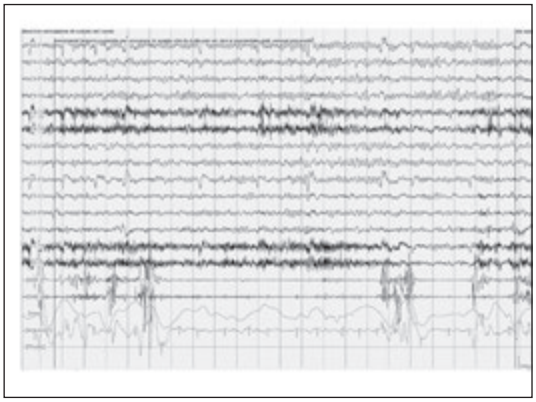


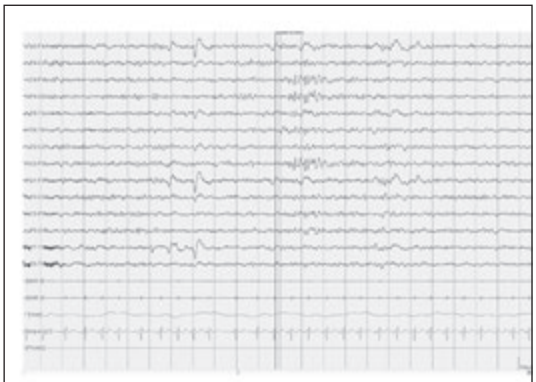
- Normal MRI
- LTG, CLB, CBZ, VPA, TPM
  - Ineffective
- Seizure control with PHT

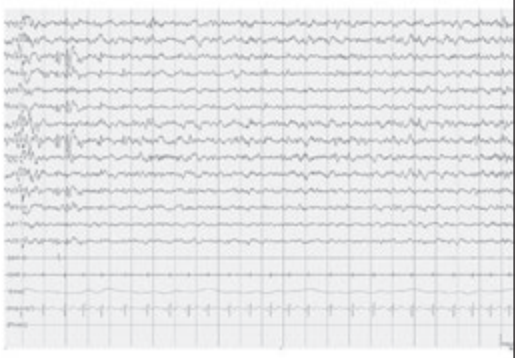
- Persistence of seizure freedom with PHT and CLB
- Normal school performances
- IQ: 128
- At 8 years of age MRI was normal
- EEG normalized at age 8
- CLB was slowly withdrawn

- A third high resolution MRI at the age of 10 years gave normal results
- PHT was gradually reduced
- After 7 months from PHT stop, focal seizures recurred (12 years of age)









- A fourth HR MRI was normal
- OXC (20 mg/Kg/die): complete seizure control
- After 4 years and 5 months no seizures, normal EEG and school performances.

- **This case presented with**
  - **A first period of a system epilepsy (MAE)**
  - **A second and third period of pure focal epilepsies (probably not lesional)**

The difference between
secondary generalization and system epilepsy

- An arson can arise from a single outbreak or be developed from different foci starting to burn simultaneously

The concept of System Epilepsy

- **System epilepsy is the result of a simultaneous pathological activation of functionally different anatomical areas of the brain that, as a whole, generates a specific epileptic phenotype**

System epilepsy

- Doesn't depend on etiology
- Goes beyond dichotomy between focal and generalized

This new concept can be useful

- For therapeutic approach
  - Both medical and surgical
  - With new techniques (DBS etc)
- To provide an interpretive key for pathophysiological mechanisms
- To open new horizons in research
- To spend some time discussing in some wonderful place

Matthias Koepp (UK)

REFLEX SEIZURES, TRAITS, AND EPILEPSIES

Epileptic seizures are believed to be unpredictable and usually arise spontaneously. In a few patients, seizures occur as a "reflex" phenomenon, objectively and consistently evoked and modulated, either precipitated or inhibited, by external afferent stimuli or specific cognitive processes. These stimuli and processes may, or may not lead to seizures with different latencies, making it at times difficult to establish a causal relationship with these reflex traits. Semiology of reflex seizures is either reflective of the network supporting the precipitating stimulus, or stereotypically manifest with myoclonic or absence seizures despite involvement of divers cognitive, motor or sensory systems. Reflex seizures and traits are likely to represent the extremes of a continuum, and understanding their underlying mechanisms could help to explain the transition of "normal" physiological systems to paroxysmal epileptic activity.

To explain the inexplicable, patients commonly experience seizures in response to transient systemic perturbation such as intercurrent illness, emotional stress, sleep loss, or alcohol consumption, which are known to facilitate epileptiform discharges on the electro-encephalogram (EEG). In a few patients, seizures or EEG discharges occur as a "reflex" phenomenon, objectively and consistently evoked and modulated, either precipitated or inhibited, by external afferent stimuli or specific cognitive processes.

Causality is unequivocal if seizures are constantly precipitated by a specific stimulus resulting almost immediately in a seizure. These stimuli relate to specific cortical sensory areas, like flashing lights, or to large-scale brain networks, like reading, result in "reflex-seizures", and are "name-giving", if no spontaneous seizures occur, as in reading, musicogenic or hot-water epilepsy. Such reflex epilepsies are considered to be focal in origin, and often acquired or developmental structural brain abnormalities are detected, typically involving lateral sensori-motor cortex.

More complex stimuli in combination with cognitive processes can increase the probability of a seizure. These stimuli and activities may, or may not lead to seizures with different latencies, making it more difficult to establish a causal relationship. Such reflex traits are predominantly seen in genetic epilepsies with stereotyped seizure semiology of either myoclonic or absence seizures despite rather diverse precipitating stimuli involving various cognitive, motor or sensory systems.

Following a detailed description of reading epilepsy, the prototypic and only reflex epilepsy syndrome listed in the 1989 ILAE syndrome classification, and reflex traits in different genetic epilepsy syndromes, this presentation will compare the concept of system epilepsies with interlinked physiological and epileptic networks to mechanisms of seizure precipitation and inhibition.

Peter Wolf (Denmark), Rūta Mameniškienė (Lithuania), Katia Lin (Brazil) - team 1

CASE-ORIENTED STUDY 2

GROUP WORK WITH TUTORS - TEAM 2

Peter Wolf (Denmark), Rūta Mameniškienė (Lithuania), Katia Lin (Brazil) – team 2

CASE-ORIENTED STUDY 2

GROUP WORK WITH TUTORS – TEAM 1

GIUSEPPE CAPOVILLA (ITALY)

THE CONCEPT OF ENCEPHALOPATHIES

Epileptogenic encephalopathy

G Capovilla, Mantova

Lennox-Gastaut syndrome. Henri Gastaut considered mental retardation as a mandatory symptom of the syndrome and a consequence of the interictal electroencephalographic epileptic activity. The concept that a

EPILEPTIC ENCEPHALOPATHIES

The history of the concept of epileptic encephalopathy

Abstract

neuropsychological deficit could be determined by continuous or subcontinuous interictal electroencephalographic paroxysmal activity was also present in 1957 in the first description of the syndrome by Landau and Kleffner (1957). The concept was further developed by Dulac (2001) in the 1990s, and it was finally included in the proposal of the ILAE classification in 2001 (Engel, 2001), where the term of epileptic encephalopathy was used for conditions in which "the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function." Subsequently, in 2006, Engel writes that "it is important to distinguish between deficits that are due to the cause of the epilepsy, those that are due to pharmacotherapy, and those that are due to the epilepsy itself (EE). Unfortunately, this can be difficult and many EE[s] remain theoretical."

Special Article

Report of the ILAE Classification Core Group

sible. The epilepsy syndromes approved by the General Assembly in 2001, therefore, were evaluated according to the following criteria:

- Epileptic seizure type(s): This includes seizure type(s) that i) must occur in order to diagnose a syndrome, ii) occur but are not necessary for diagnosis, and/or iii) would preclude a diagnosis of this syndrome.
- Age of onset: Is there a distinctive range for age of onset for taxonomic purposes and, if so, how strictly should this range be applied for diagnostic purposes?
- Progressive nature (i.e., epileptic encephalopathy): Evidence that suggests or supports the notion that there is an *epilepsy-dependent* neurodevelopmental or neurodegenerative process involved in the evolution of the syndrome (as opposed to an underlying metabolic, degenerative, or encephalitic process).

Associated interictal signs and symptoms (particularly neurological and neuropsychological status and deficits). It is important to distinguish between deficits that are due to the cause of the epilepsy, those that are due to pharmacotherapy, and those that are due to the epilepsy itself (epileptic encephalopathy). Unfortunately, this can be difficult and many epileptic encephalopathies remain theoretical.

TABLE 2. *Definitions of key terms*

Epileptic seizure type: An ictal event believed to represent a unique pathophysiologic mechanism and anatomic substrate. This is a diagnostic entity with etiologic, therapeutic, and prognostic implications. (new concept)

Epilepsy syndrome: A complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type: thus frontal lobe seizures *per se*, for instance, do not constitute a syndrome. (changed concept)

Epileptic disease: A pathologic condition with a single specific, well-defined etiology. Thus progressive myoclonus epilepsy is a syndrome, but Unverricht–Lundborg is a disease. (new concept)

Epileptic encephalopathy: A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. (new concept)

Benign epilepsy syndrome: A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae. (classified concept)

Reflex epilepsy syndrome: A syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that also are associated with spontaneous seizures are listed as seizure types. Isolated reflex seizures also can occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures. (changed concept)

Focal seizures and syndromes: Replaces the terms partial seizures and localization-related syndromes. (changed terms)

ILAE Commission Report

A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology

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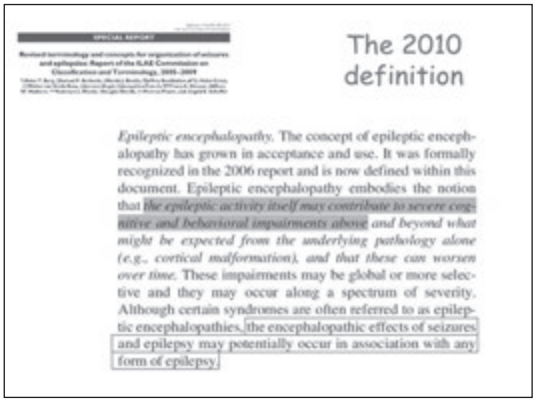
Focal seizures and syndromes: Replaces the terms partial seizures and localization-related syndromes. (changed terms)

Epileptic encephalopathies (in which the epileptiform abnormalities may contribute to progressive dysfunction)	Early myoclonic encephalopathy Ohtahara syndrome West syndrome Dravet syndrome (previously known as severe myoclonic epilepsy in infancy) Myoclonic status in nonprogressive encephalopathies* Lennox–Gastaut syndrome Landau–Kleffner syndrome Epilepsy with continuous spike-waves during slow-wave sleep

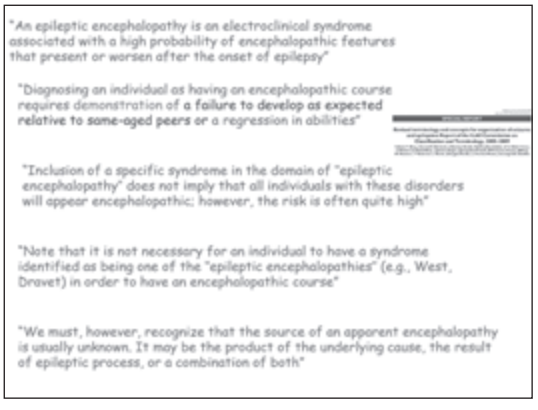


SPECIAL REPORT

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

The 2010 definition

Epileptic encephalopathy. The concept of epileptic encephalopathy has grown in acceptance and use. It was formally recognized in the 2006 report and is now defined within this document. Epileptic encephalopathy embodies the notion that *the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time.* These impairments may be global or more selective and they may occur along a spectrum of severity. Although certain syndromes are often referred to as epileptic encephalopathies, the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy.



"An epileptic encephalopathy is an electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy"

"Diagnosing an individual as having an encephalopathic course requires demonstration of **a failure to develop as expected relative to same-aged peers** or a regression in abilities"

"Inclusion of a specific syndrome in the domain of "epileptic encephalopathy" does not imply that all individuals with these disorders will appear encephalopathic; however, the risk is often quite high"

"Note that it is not necessary for an individual to have a syndrome identified as being one of the "epileptic encephalopathies" (e.g., West, Dravet) in order to have an encephalopathic course"

"We must, however, recognize that the source of an apparent encephalopathy is usually unknown. It may be the product of the underlying cause, the result of epileptic process, or a combination of both"

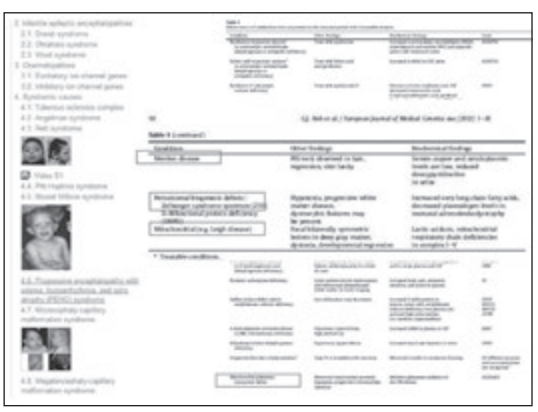
ARTICLE IN PRESS

European Journal of Medical Genetics

Original article

Clinical review of genetic epileptic encephalopathies

Grace J. Noh, Y. Jane Tarver Asher, John M. Graham Jr.*



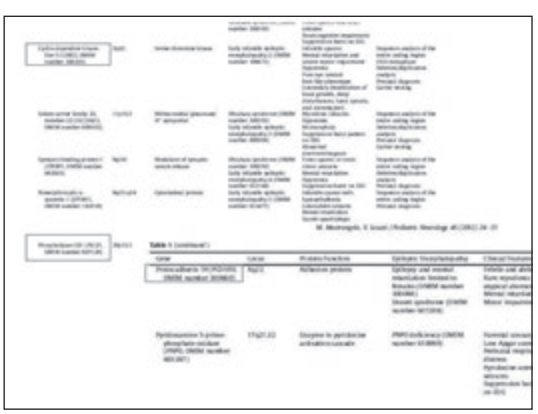



Table 1 – Clinical classification of genetic and metabolic early onset epileptic encephalopathies.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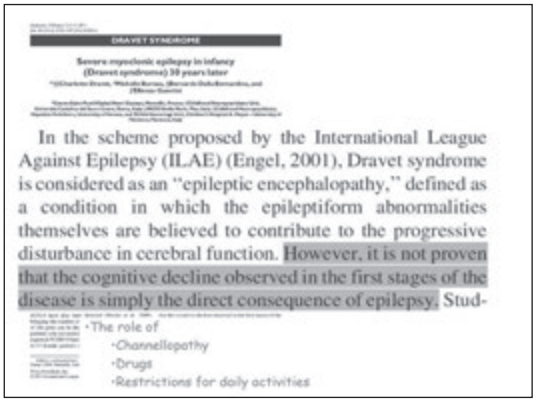
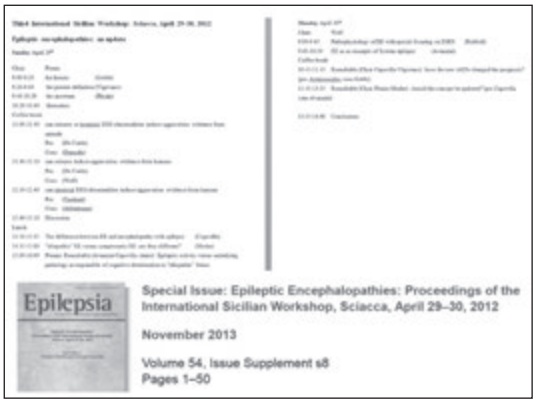

DRAVET SYNDROME
Severe myoclonic epilepsy in infancy
(Dravet syndrome) 30 years later
In the scheme proposed by the International League Against Epilepsy (ILAE) (Engel, 2001), Dravet syndrome is considered as an "epileptic encephalopathy," defined as a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. However, it is not proven that the cognitive decline observed in the first stages of the disease is simply the direct consequence of epilepsy. Stud-
•The role of
•Channellopathy
•Drugs
•Restrictions for daily activities


Epilepsia
Special Issue: Epileptic Encephalopathies: Proceedings of the International Sicilian Workshop, Sciacca, April 29–30, 2012
November 2013
Volume 54, Issue Supplement s8
Pages 1–50

"Although certain syndromes are often referred to as epileptic encephalopathies, the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy"

Cognitive impairment in medicine

Chest. 2010 Jun;137(6):1324-31. doi: 10.1378/chest.09-1979. Epub 2010 Jan 22.

Psychologic distress and maladaptive coping styles in patients with severe vs moderate asthma.

Lavoie KL[1], Bouthillier D, Bacon SL, Lemière C, Martin J, Hamid Q, Ludwig M, Olivenstein R, Ernst P.

⊕ Author information

Abstract

BACKGROUND: Though several biologic factors have been suggested to play a role in the development and persistence of severe asthma, those associated with psychologic factors remain poorly understood. This study assessed levels of psychologic distress and a range of disease-relevant emotional and behavioral coping styles in patients with severe vs moderate asthma.

METHODS: Eighty-four patients (50% women, mean [SD] age 46 years) with severe (n = 42) and moderate (n = 42) asthma were recruited. Severe asthma was defined according to American Thoracic Society criteria. Patients underwent demographic and medical history interviews and pulmonary function and allergy testing. Patients also completed questionnaires measuring asthma symptoms and the Millon Behavioral Medicine Diagnostic Inventory, which assesses psychologic distress and emotional/behavioral coping factors that influence disease progression and treatment.

RESULTS: After adjustment for covariates and applying a correction factor that reduced the significant P level to < .01, patients with severe vs moderate asthma reported experiencing more psychologic distress, including worse cognitive dysfunction ($F = 6.72$, $P < .01$) and marginally worse anxiety-tension ($F = 4.02$, $P < .05$). They also reported worse emotional coping (higher illness apprehension [$F = 9.57$, $P < .01$], pain sensitivity [$F = 10.65$, $P < .01$], future pessimism [$F = 8.53$, $P < .01$], and interventional fragility [$F = 7.18$, $P < .01$]), and marginally worse behavioral coping (more functional deficits [$F = 5.48$, $P < .05$] and problematic compliance [$F = 4.32$, $P < .05$]).

CONCLUSIONS: Patients with severe asthma have more psychologic distress and difficulty coping with their disease, both emotionally and behaviorally, relative to patients with moderate asthma. Future treatment studies should focus on helping patients with severe asthma manage distress and cope more effectively with their illness, which may improve outcomes in these high-risk patients.

NCBI PubMed

In: J Pediatr. 1998 Dec;133(6):782-7.

Hemophilia morbidity, cognitive functioning, and academic achievement.

Usner DW, Donfield SM, Sirois PA, Gomperts ED, Bale JF Jr, Mitchell WG.

Department of Statistics, Oregon State University, Corvallis, Oregon, USA.

Data from the Hemophilia Growth and Development Study (HGDS) were used to evaluate the association between hemophilia morbidity, measured by abnormalities in coordination and gait (CG), and intellectual ability and academic achievement. The CG abnormalities observed in the HGDS participants (n = 333) were primarily due to hemophilia-related morbidity. Although HGDS participants performed within the average range for age on measures of intellectual ability, there were meaningful differences between CG outcomes at baseline and throughout the 4 years of study. Participants without CG abnormalities consistently achieved higher scores than those with CG abnormalities on Reading, Spelling, and Arithmetic subtests of the Wide Range Achievement Test-Revised. Our findings suggest that lowered achievement is related to the functional severity of hemophilia.

PMID: 9842044 [PubMed - indexed for MEDLINE]

Diabetes Care. 1996 Jun;19(6):656-8.

Effect of long-term glycemic control on cognitive function.

Lincoln NB[1], Faleiro RM, Kelly C, Kirk BA, Jeffcoate WJ.

⊕ Author information

Abstract

OBJECTIVE: To investigate the relationship between recurrent hypoglycemia and cognitive impairment in insulin-dependent diabetic patients.

RESEARCH DESIGN AND METHODS: Seventy patients who were diagnosed as diabetic at age 18 years or older, were under 55 years old, and had no condition likely to affect cognitive abilities were recruited from a diabetic register. Patients were interviewed to obtain information on the frequency of major and minor hypoglycemia. Their cognitive abilities were assessed on tests of premorbid intelligence, current intelligence, reaction time, concentration, memory, and information processing.

RESULTS: There was a significant correlation between the apparent decline in intelligence, expressed as the discrepancy between the estimated premorbid and the actual performance intelligence quotient, and the frequency of major hypoglycemic attacks ($r_s = -0.30$; $P < 0.01$). Comparison of patients with and without recurrent hypoglycemia showed few significant differences in cognitive ability.

CONCLUSIONS: Results support previous work that suggests that major hypoglycemic attacks have a significant effect on some aspects of cognitive function, but the clinical importance of this finding remains to be determined.

and memory. Children with a history of severe hypoglycaemia had more neuropsychological impairments, more learning difficulties (as reported by parents), and needed more part-time special education than those in the other groups.

Neurocognitive functioning in children with type-1 diabetes with and without episodes of severe hypoglycaemia

"Epileptogenic" encephalopathy

- "Progressive" conditions with various etiology can give both deterioration (per se) and epilepsy
  - Tumors
    - Hypothalamic Hamartoma
  - Neurodegenerative
    - Alpers disease
  - Metabolic
    - Non Ketotic Hyperglycinemia
  - Inflammatory
    - DESC-FIRES
    - Rasmussen syndrome

"Epileptogenic" encephalopathy

- Deterioration is independent from epilepsy
- Epilepsy can aggravate the clinical picture
- In many cases encephalopathy without epilepsy

Consequences

- According to the concept of EE, you should treat aggressively many of these situation
- Overtreatment can aggravate the neuropsychological picture
- Aggravation of neuropsychological picture can induce further overtreatment

The importance of the messages to the parents

- Don't have prejudices against epilepsy
- Also Napoleon had epilepsy
- If a seizure occurs, keep calm
- But if it doesn't stop use rectal diazepam or oral midazolam
- Because if a seizure is long-lasting, a cerebral damage can occur
- Seizure recurrence can induce a brain damage
- The EEG of your kid is very rich in epileptiform abnormalities
- The epileptiform abnormalities can induce a cerebral dysfunction

Conclusions

- Clarification is needed
- New terms should be used

ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

[1,2,3]Ingrid E. Scheffer, [4]Samuel Berkovic, [5]Giuseppe Capovilla, [6]Mary B. Connolly, [7]Jacqueline French, [8]Laura Guilhoto, [9,10]Edouard Hirsch, [11]Satish Jain, [12]Gary W. Mathern, [13]Solomon L. Moshé, [14]Douglas R. Nordli, [15]Emilio Perucca, [16,17]Torbjörn Tomson, [18]Samuel Wiebe, [19]Yue-Hua Zhang, and [20,21]Samuel F. Zuberi

Epilepsia, **(*):1–10, 2017
doi: 10.1111/epi.13709

NEW TERMINOLOGY AND DEFINITIONS

Developmental and epileptic encephalopathies

The term "epileptic encephalopathy" was redefined in the Berg et al.[3] report as where the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation). Global or selective impairments can worsen over time. These impairments can be seen along a spectrum of severity and across all epilepsies, and can occur at any age.

sion. A key component of the concept is that amelioration of the epileptiform activity may have the potential to improve the developmental consequences of the disorder. This is a critical issue from a clinical perspective and one often mis-

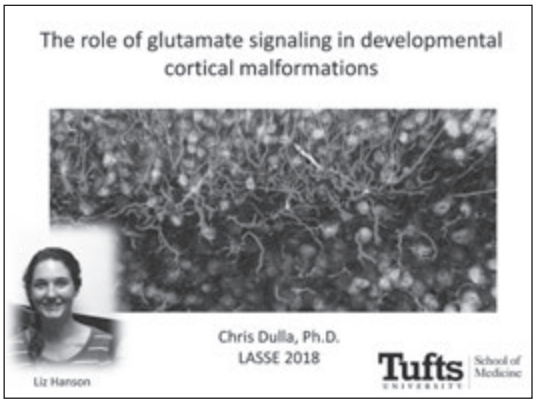
the use of either or both descriptors: developmental encephalopathy where there is just developmental impairment without frequent epileptic activity associated with regression or further slowing of development; epileptic encephalopathy where there is no preexisting developmental delay and the genetic mutation is not thought to cause slowing in its own right, and developmental and epileptic encephalopathy where both factors play a role. Often it may not be possible to disentangle whether the epileptic or developmental component is more important in contributing to a patient's presentation.

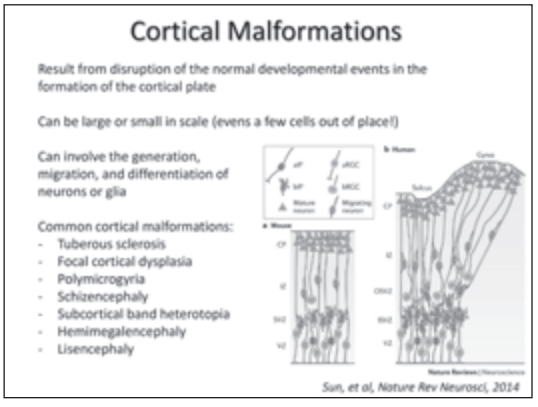
Conclusions

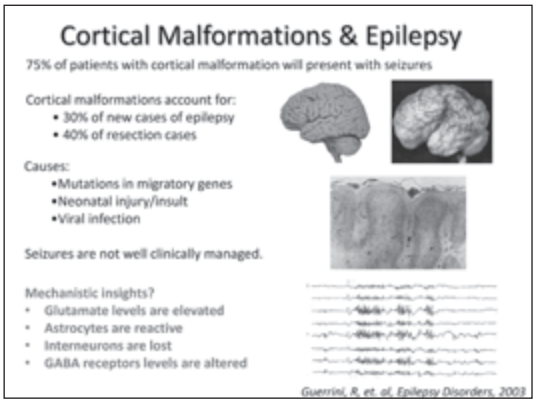
- It is true that some cases of "benign" epilepsy can have cognitive/behavioral problems
- The importance of parental emotional factors has never been studied
- The majority of cases with frequent and long-lasting epileptic seizures, together with a richness of epileptiform abnormalities, do not have cognitive/behavioral problems
- The true Epileptic Encephalopathies are very rare

Chris Dulla (USA)

THE ROLE OF GLUTAMATE SIGNALING IN DEVELOPMENTAL CORTICAL MALFORMATIONS

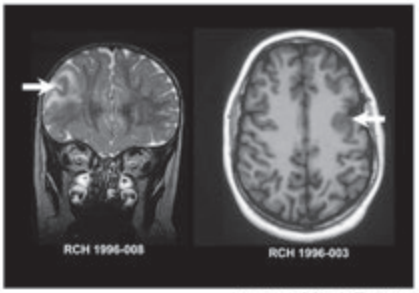






Clinical Syndromes

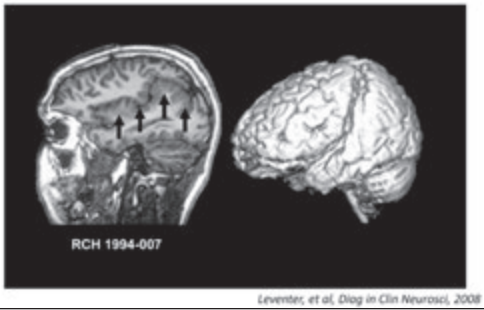
Focal cortical dysplasia



Leventer, et al, Diag in Clin Neurosci, 2008

Clinical Syndromes

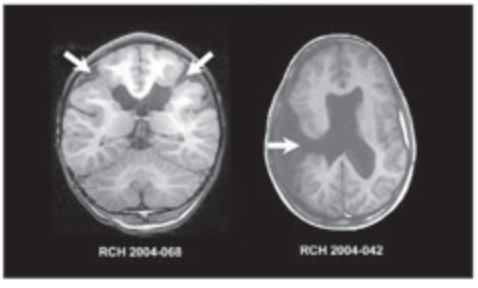
Polymicrogyria



Leventer, et al, Diag in Clin Neurosci, 2008

Clinical Syndromes

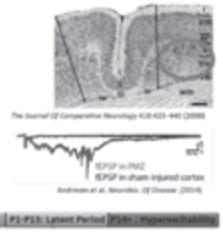
Schizencephaly



Leventer, et al, Diag in Clin Neurosci, 2008

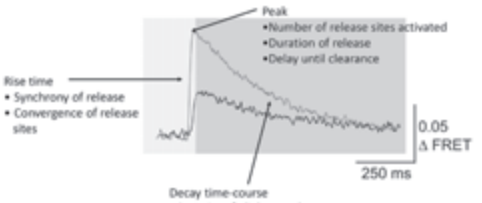
Freeze lesion model of developmental cortical malformations

- **Freeze lesion (FL)**
  - Freezing injury on the surface of the skull at P0 causes formation of a microgyrus
  - Models developmental cortical malformations associated with epileptic foci
  - Paramicrogyral zone (PMZ) becomes hyperexcitable by P14
  - ***Useful model for studying pathological changes during the latent period***



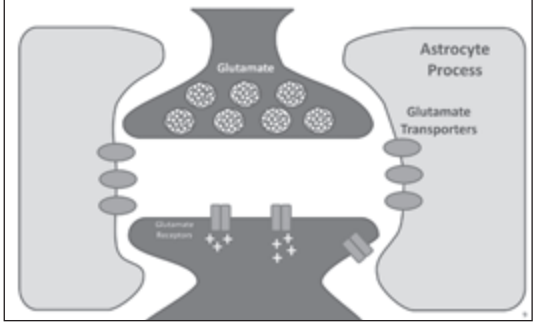
Central Goal: Understand how the temporal and spatial properties of neurotransmission contribute to the function and dysfunction of a neuronal network.

Dissecting the molecular contributors to a neurotransmitter transient

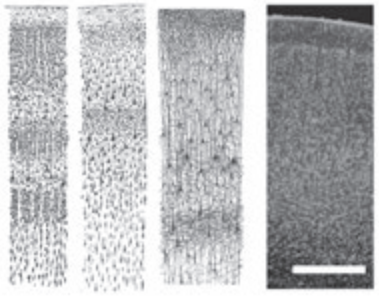


Two main components shape neurotransmitter transients:
•Presynaptic control of neurotransmitter release
•Glial reuptake of released neurotransmitter

Astrocytic glutamate transporters remove glutamate from the extracellular space



The Cerebral Cortex



Glutamate	GABA
Excitatory	Inhibitory
Slow Firing	Fast Firing

Establishing inhibitory networks requires:

- Proliferation of precursor cells
- Differentiation of interneurons
- Interneuron migration to the cortex
- Positioning into the cortical circuit
- Morphological maturation
- Circuit integration

Does dynamic glutamate regulation influence cortical interneuron development?

1. How does **glutamate regulation** change during postnatal cortical development?
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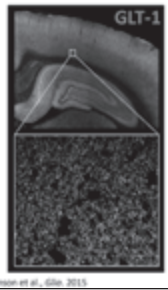
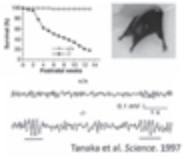
3. Does disruption of tonic glutamate signaling alter the development of **cortical inhibitory networks**?
4. Is disruption of tonic glutamate signaling a **mechanism of epileptogenesis** after neonatal injury?

GLT-1 and GLAST are the primary astrocytic glutamate transporters



Verkhratsky, *Neurochem. Int.*, 2010

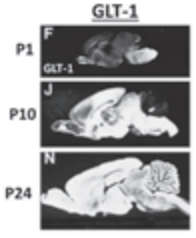


Tanaka et al. *Science*. 1997

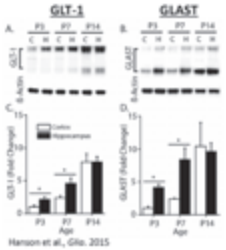
- Keep extracellular glutamate low
- Prevent excitotoxicity
- Maintain synapse specificity of glutamate signaling

Hanson et al., *Glia*. 2015

Glutamate transporter expression increases through development

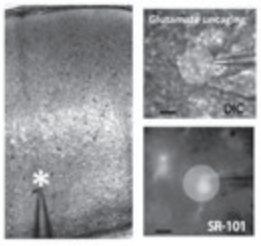


Furuta, et al., *J. Neurosci.*, 1997

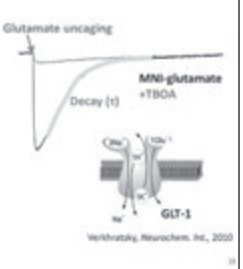


Hanson et al., *Glia*. 2015

Glutamate transporter currents reflect the rate of glutamate clearance

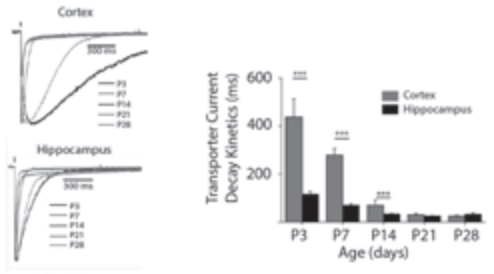


Hanson et al., *Glia*. 2015



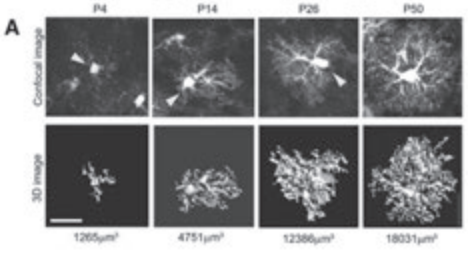
Verkhratsky, *Neurochem. Inc.*, 2010

Glutamate clearance is slow in the neonatal cortex



Hanson et al., Glia. 2015

Astrocyte maturation involves huge changes in morphology

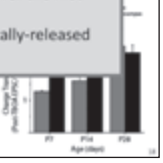


Morel, L., et al., J. Neurosci, 2014

Limited astrocytic glutamate uptake allows unconstrained NMDAR activation

How does glutamate regulation change during postnatal cortical development?

- Glutamate clearance is slow in the neonatal cortex compared to the hippocampus.
- Uptake capacity develops in the cortex over the first three postnatal weeks.
- Astrocytic uptake does not limit synaptically-released glutamate in the neonatal cortex.



Hanson et al., Glia. 2015

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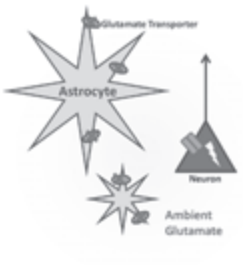
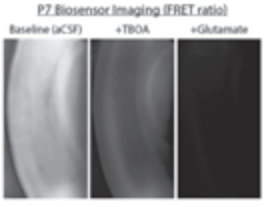
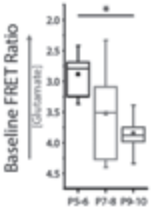
Astrocytic control of ambient glutamate

- **Ambient glutamate** = resting concentration of glutamate in the extracellular space
- Set by a balance of **ongoing release and uptake**
- Reducing uptake…
  - …increases ambient glutamate
  - …and induces NMDAR-mediated tonic currents
- ***Robust astrocytic uptake keeps ambient glutamate low***

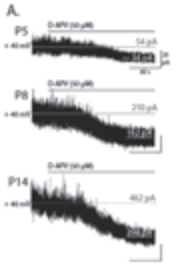


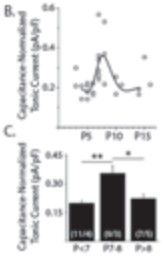
Glutamate biosensor imaging suggests glutamate levels decrease during development



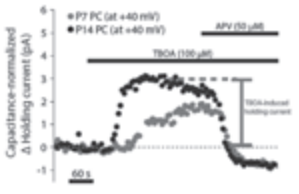


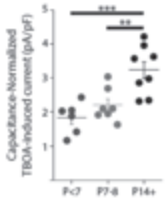
Neurons in neonatal cortex are transiently sensitive to ambient glutamate



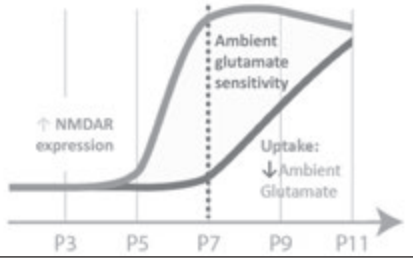


Developmental increases in EAATs constrain ambient glutamate levels

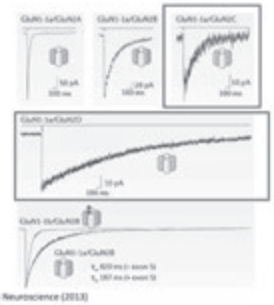




Ambient glutamate sensitivity reflects increasing NMDAR expression and decreasing ambient glutamate



Where does ambient glutamate act?



Paoletti et al., Nature Reviews Neuroscience (2013)

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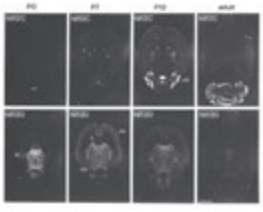
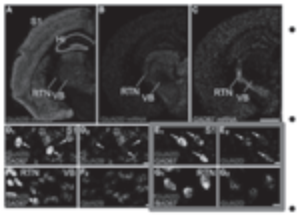


- NR2C/Ds are more highly expressed in young cortex

Monyer et al., Neuron 1994

Where does ambient glutamate act?

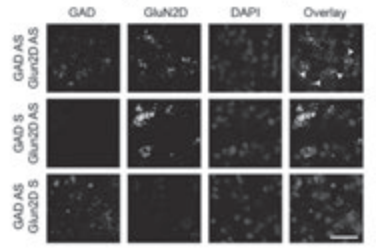


- NR2C/Ds are more highly expressed in young cortex
- Cortical NR2D is expressed mostly in interneurons
- NR2C/Ds have a lower affinity for Mg^{2+}

Yamasaki et al., J. Neurosci. 2014

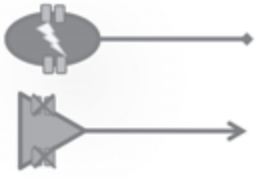
What cell types express Grin2D?

Neonatal GABAergic interneurons express Grin2D



Sharon Swanger – Traynelis Lab

Ambient glutamate preferentially affects GABAergic interneurons



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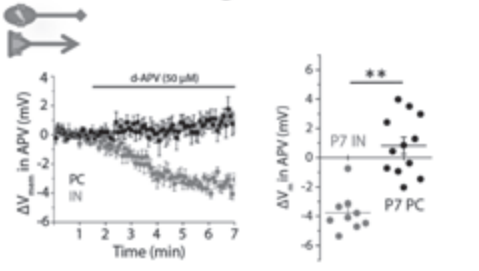

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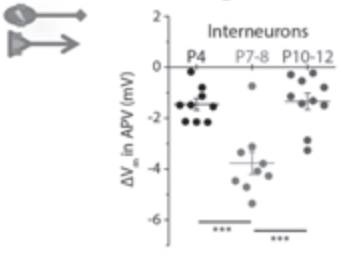

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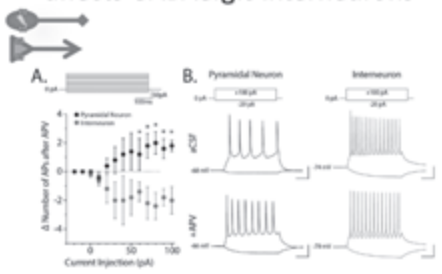
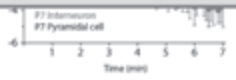


NR2C/D-containing NDMARs mediate the bulk of tonic depolarization

How is ambient glutamate regulated and where does it act in the neonatal cortex?

- Ambient glutamate is elevated in neonatal cortex
- Astrocytic uptake limits ambient glutamate ≥ P7
- Ambient glutamate tonically depolarizes interneurons but not pyramidal cells at P7.
- Tonic depolarization is mediated, in part, by NR2C/D containing NMDA receptors.



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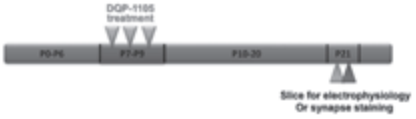
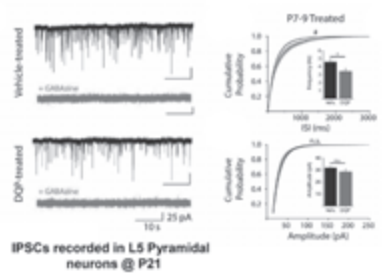
Neonatal blockade of NR2C/D by in vivo DQP treatment



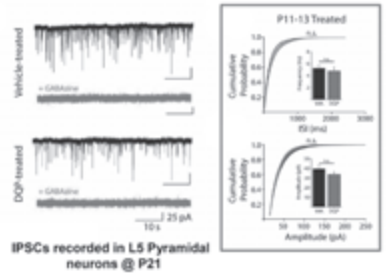
- In vivo treatment with NR2C/D antagonist
- Changes in inhibition in adults
  - mIPSC frequency
  - GABAergic synapse staining
  - Interneuron morphology
  - Network activity

Transient blockade of NR2C/D causes long-term reductions in inhibitory synaptic activity



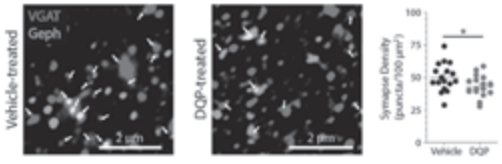
IPSCs recorded in L5 Pyramidal neurons @ P21

Transient blockade of NR2C/D causes long-term reductions in inhibitory synaptic activity

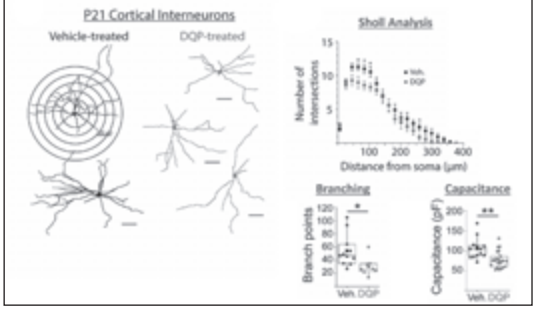


IPSCs recorded in L5 Pyramidal neurons @ P21

Blockade of NR2C/D leads to a reduction in putative inhibitory synapses



Blockade of NR2C/D alters maturation of interneuron morphology



Blockade of NR2C/D leads to network hyperexcitability in mature cortex

Field potential recording

Vehicle-treated

Does disruption of tonic glutamate signaling alter the development of cortical inhibitory networks?

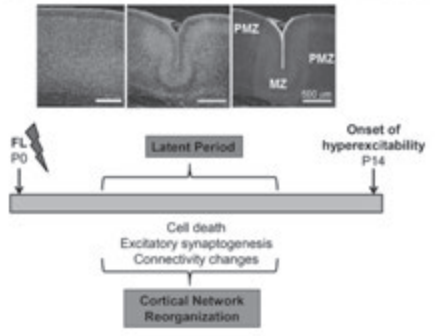
- In vivo blockade of NR2C/D **from P7-P9** causes lasting inhibitory deficits
  - Reduction in mIPSC frequency at P21
  - Reduction in interneuron morphological complexity at P21
  - Increase in network hyperexcitability

Lauren Lau

Does dynamic glutamate regulation influence cortical network development?

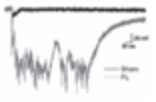
1. How does **glutamate regulation** change during postnatal cortical development?
2. How is **ambient glutamate** regulated and where does it act in the neonatal cortex?
3. Does disruption of **tonic glutamate signaling** alter the development of cortical inhibitory networks?
4. Is disruption of tonic glutamate signaling a **mechanism of epileptogenesis** after neonatal injury?

Freeze lesion model of cortical malformation



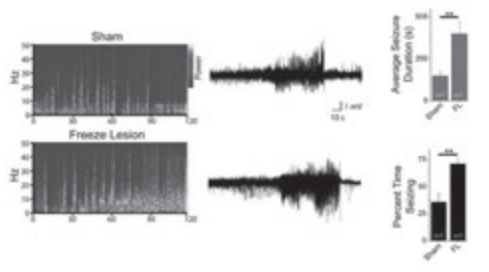
Freeze lesion induces cortical hyperexcitability

Epileptiform fEPSPs



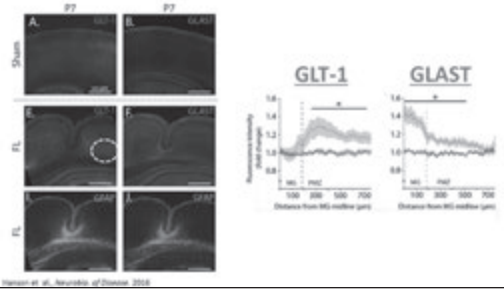
Modified from Andresen, L., Neurobiol. Dis., 2014

Freeze lesion causes in vivo hyperexcitability



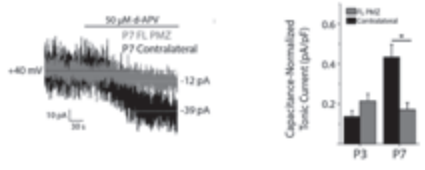
Jamie Maguire
Modified from Andresen, L., Neurobiol. Dis., 2014

Transporter upregulation during the freeze lesion latent period

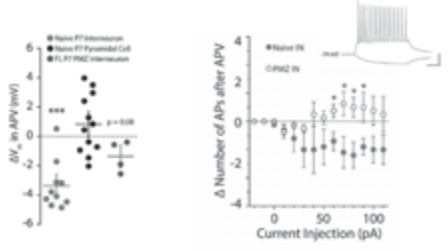


Hanson et. al., Neurobio. of Disease, 2016

Neonatal ambient glutamate levels are decreased by FL



Tonic activation of interneurons is decreased by FL



Astrocyte control of ambient glutamate is increased by FL

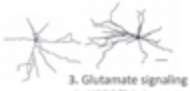
Is disruption of tonic glutamate signaling a mechanism of epileptogenesis after neonatal injury?

- Neurons in PMZ see reduced ambient glutamate during the FL latent period
- Tonic depolarization of interneurons is reduced during FL latent period
- Due to increased interactions with astrocytes and EAAT control?

Conclusions

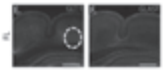
1. Glutamate clearance is slow in the neonatal cortex, when transporter expression is low

2. Elevated ambient glutamate preferentially activates NR2C/D-containing NMDARs on GABAergic interneurons at P7



3. Glutamate signaling via NR2C/D is important for cortical interneuron maturation

4. Does injury induced disruption of ambient glutamate signaling contribute to pathological network reorganization?



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Rūta Mameniškienė (Lithuania)

PRECIPITATION AND INHIBITION OF SEIZURES IN FOCAL EPILEPSIES

Precipitation and inhibition of seizures in focal epilepsies

Rūta Mameniškienė

History

- Reflexly provoked epilepsy was known to the Romans, who caused their newly purchased slaves to gaze at a rotating potter's wheel.
  - If there was any epileptic tendency the slave, after staring at the wheel for a variable interval of time, would fall down in a fit.
- Or they caused their slaves to inhale the fumes of burning jet or horn to determine their seizure threshold.
- If epilepsy was established the purchase money could be reclaimed.

History (2)

- St Augustine gives an early description of a seizure precipitated by sound:
  - 'There was a presbyter named Restitutus, in the parish of the ecclesia Calamensis, who could so abstract himself from sensation that he lay like a corpse, not feeling in the least if pinched and pricked, and sometimes was burnt without any signs of pain, except after he came to himself.
  - That he gave no sign of pain, not from self-restraint, but from insensibility, was proved by this,— that no catching of breath could be detected in him.
  - Yet hom would afterwards say that he had heard a voice as if it were at a distance if any person had spoken very audibly to him.'
- The 17th century physician Taxil described a lame doctor who was seized by an attack every time he heard boys whistle.

Introduction

- A diagnosis of epilepsy requires the occurrence of unprovoked seizures on the background of an enduring disposition to seizures
- "unprovoked" = "unpredictable"
- This view disregards numerous factors influencing the current seizure risk in either direction and acting both as triggers or inhibitors of seizures.

Introduction (2)

- Of these factors, seizure precipitation and inhibition by specific sensory or cognitive stimuli in reflex epilepsies have received particular attention, not the least because of the insight they provide into ictogenic mechanisms in natural human epilepsies but also the interruption of seizure activity at the early stage also can be achieved by nonspecific or by specific focus-targeted sensory or cognitive inputs.

Definitions

Facilitation and precipitation

- Two types of seizure-inducing factors can be distinguished:
  - factors that temporarily increase the risk of having a seizure.
  - triggering stimuli that directly precipitate seizures in certain patients.
- These seizures are called reflex seizures.

Definitions (2)

Prevention and inhibition

- Two types of factors counteracting seizures can be distinguished.
  - A temporary decrease of seizure risk seems mostly to be defined by the absence of facilitating factors.
  - In most patients seizures do not occur during physical acitivity. - physical exercise reduces the risk in the vast majority of patients.

"Of all the immediate causes of epilepsy the most potent are psychical - fright, excitement, anxiety" (Gowers, 1885)

  - Clinical experience suggest that mental activity may in general have similar protective effect - Matsuoka reported an inhibitory effect of neuropsychological activation in 63.9% of 208 patients with paroxysmal discharge in the awake EEG.

Definitions (3)

Focal epilepsies

- Focal seizures originate "within networks limited to one hemisphere"
- Focal seizures occur in focal epilepsies and system epilepsies like JME

Precipitation of focal seizures

- Simple sensory precipitation
- Complex sensory and cognitive precipitation

Simple sensory precipitation

- In focal epilepsies, precipitation by simple sensory stimuli has been described for:
  - vision,
  - touch,
  - movement,
  - caloric
  - olfactory stimuli.
- Simple auditive, and vestibular precipitation are not unequivocally accepted.

Simple sensory precipitation

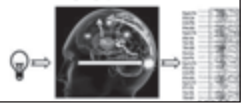
Visual precipitation

- Visually induced reflex seizures are very common in idiopathic system epilepsies like JME and idiopathic localization-related epilepsies, they are extremely rare in focal lesional epilepsies affecting the visual system.
- In some of the idiopathic epilepsies, genetically determined hyperexcitability of the visual cortex with upregulation of the occipito-frontal pathways seems to be a basic mechanism of ictogenesis whereas these features seem usually to be absent in lesional epilepsies.

Simple sensory precipitation

Visual precipitation

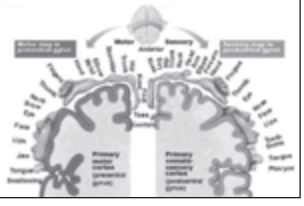
- 11.7% with focal seizures (Wolf & Goosses) among 103 photosensitive adults
  - 2/3 of these presented also generalized clinical and/or EEG features
  - ¼ were in drug withdrawal at the time of the investigation which could be responsible for a temporary photoparoxysmal response.
- Yu et al in a childhood cohort described photosensitivity in 20% of patients with focal seizures.
  - 58% of these, had idiopathic Rolandic childhood epilepsy, i.e. not a focal epilepsy *sensu stricto*,
  - in all cases - only as an EEG trait, without photically induced seizures.



Simple sensory precipitation

Precipitation by movement and touch

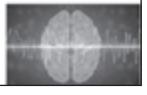
- These two trigger mechanisms seem to be closely related and occur in focal epilepsies of the perirolandic region where they produce focal motor or typically sensorimotor seizures.



Simple sensory precipitation

Precipitation by movement

- Triggering movements are ordinary voluntary movements and specific for the individual case
- The ictogenic mechanisms are not uniform:
  - in some patients cortical movement initiation seems to be crucial
  - in others passive execution of the trigger movement is effective indicating a proprioceptive trigger
- Occasionally, even mere imagination of the stimulus representing a minimal activation of the ictogenic network, or dreaming of the incriminated movement may be sufficient.

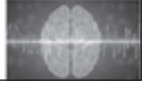


Simple sensory precipitation

Precipitation by movement and touch

- Patients with motor or sensory EPC of any etiology presented such trigger mechanisms in 37%(n=24) of cases:
  - in 12 - active movement
  - in 2 - passive movement
  - in 1 - intention to move
  - in 9 - touch

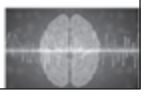
- Inhibition by similar stimuli occurred in 4 (6%)
- in 1, touching a trigger zone could either inhibit the development of sensory EPC or precipitate a tonic seizure, depending on the timing of the stimulus.



Simple sensory precipitation

Precipitation by touch

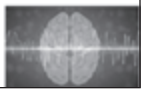
- The quality of the touch is slightly variable.
- In a video-documented case it was a light, single touch lasting for not more than 1-2 sec.
- In the 3 patients reported by Kanemoto et al prolonged rubbing (>10 sec) or repetitive tapping was required
- 4 patients of Sala-Padró et a.l needed to rub the trigger zone between 5 and 20 sec whereas a 5th had facial sensorimotor seizures triggered by contact of the right inner lip with a cold liquid.



Simple sensory precipitation

Precipitation by movement and touch

- Seizures in FCD epilepsies are often generated within the (mainly extratemporal) lesion with its highly abnormal microscopical and functional anatomy where "the failure of neuronal or glial commitment leads to a highly epileptogenic disruption of the local circuit that can also entrain the disruption of anatomically and/or functionally interconnected zones" (Tassi et al, 2001)
- EPC represents an intermediate state between interictal and ictal:
  - continuous seizure activity takes place in a very restricted neuronal pool
  - from here it occasionally spreads to produce an individual focal seizure.



Simple sensory precipitation

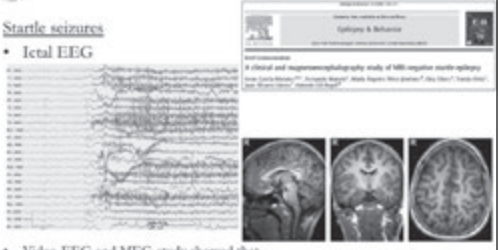
Startle seizures

- Seizures induced by sudden and unexpected sensory stimuli.
- Main triggers:
  - noise
  - somatosensory (touch)
  - visual
- Usually resemble supplementary motor seizures.
- Last <30 s
- Consist of a startle response followed by mostly axial tonic or hemitonic posture, often with autonomic phenomena, can be generalized or lateralized tonic, myoclonic–tonic, tonic–myoclonic seizure.

Simple sensory precipitation

Startle seizures

- Ictal EEG



- Video-EEG and MEG study showed that the cingulate gyrus, along with the supplementary motor area, is also involved in the genesis of startle-induced seizures.

Simple sensory precipitation

Startle seizures

- An exaggerated startle response, possible due to abnormal activity in the nucleus reticularis pontis caudalis, leads to an increase of proprioceptive feedback to the hyperexcitable motor cortex, evoking a seizure.
- Startle-induced seizures can occur cryptogenic or as a reflex in patients with metabolic disturbances or large lesions, possibly due to involvement of the cingulate gyrus and supplementary motor area (SMA).

Simple sensory precipitation

Caloric precipitation. *Infants*:

- Onset - the first year in normal child without a family history.
- Seizures = focal unaware temporal
- iEEG = temporal
- Situation - sat
- No spontane convulsions.
- Ancillary inve
- The trigger effect seems to disappear with age as no seizures were reported beyond 3 yrs of age.
- No drug treatment is needed as long as care is taken to bath the children only in luke-warm water.

This natural course is the main reason to assume a pathogenic role for insufficient thermoregulation as it is physiological for the period in which these patients are at risk.

Simple sensory precipitation

Caloric precipitation *Adults*:

- "head bath": water of > 40-50° C is rapidly poured with a mug over the head.
- Seizures - focal unawaere with automatisms, often with an aura of fear, visual or auditive hallucinations.
- 1/3 (33%) experience an aura of pleasure and are inclined to self-induction of seizures
- Evolution to convulsive seizures is relatively rare (15.7%).
- iEEG: unilateral or bilateral F-T EA
- There are indications that adolescent/adult hot water epilepsy could be a genetic syndrome rather than a mere reflex epileptic trait

Simple sensory precipitation

Olfactory precipitation

- Relations of temporal lobe epilepsy (TLE) to the olfactory system are evident from rather common (5.5 – 11 %) olfactory auras
- Reports on seizure precipitation by smells are scanty.

Simple sensory precipitation

Olfactory precipitation

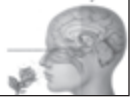
- 55 TLE and 53 IGE
- 3 min ylang-ylang

- In the 15 min post-stimulation period both provocation and inhibition of spike activity were frequently found.
- Provocation:
  - 14% of IGE patients
  - 29% of MTLE patients
- Inhibition:
  - 28% of IGE patients
  - 14% of MTLE patients

Simple sensory precipitation

Olfactory precipitation

- The effect was observed "during or immediately after the exposure".
- In the report of a breakthrough generalized tonic-clonic seizure provoked by essential oils the seizure occurred with a prodrome of fear in the night after an evening exposure but the EEG of the intermediate period is unknown
- There are at present no viable hypotheses on the physiology of these delayed responses which seem to be particular to olfactory stimulation



Simple sensory precipitation

Simple auditive and vestibular precipitation

- Seizures triggered by simple auditive stimuli are well-known in rodents as a genetic trait.
- In humans, however, they are extremely rare, and like with vestibular stimuli the reports are not always convincing.
- Newer and adequately studied cases with video-EEG documentation of both variants seem not to exist.

Complex sensory and cognitive precipitation

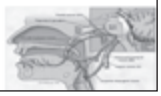
Eating

- Eating-induced seizures are paroxysmal manifestations of epileptic nature, triggered exclusively or mostly by meal.
- Eating epilepsy is one of the rare forms of reflex epilepsy (0.5–1/1.000 of all epileptic patients)
- The most common seizure semiology is focal unaware seizures what often are associated with symptomatic focal epilepsies
- Generalized tonic-clonic seizures, tonic spasms, and status epilepticus have also been reported.

Complex sensory and cognitive precipitation

Eating

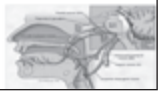
- The fact that seizures can be induced at the beginning of the meal, in the middle of the meal closely after the end or even during "thought about eating" gives an idea about different triggering mechanisms that include:
  - mastication and swallowing
  - oesophageal stimulation
  - gastric distension
  - chemical composition of food
  - the satisfactory feeling associated with eating



Complex sensory and cognitive precipitation

Eating

- Regions of the brain involved in initiating eating-induced szs:
  - The amygdala plays an important role as an integrative centre, particularly in MTLE: hyperexcitability of the temporolimbic area involves susceptibility to gustatory, olfactory, affective, and emotional stimuli.
  - In other patients, the activation of an extralimbic (suprasylvian, perirolandic) focus is also possible.
  - This region have been implicated when the abnormal cortex is in a proprioceptive region and involves other sensory afferents (lingual, buccal, pharyngeal) and is activated by extensive sensory input generated by the complex behaviours involved in eating.
- The origins can originate in frontal operculum or even in the brainstem.



Complex sensory and cognitive precipitation

Tooth brushing

- Seizures start not earlier than after 15 sec and up to 10 min after onset of toothbrushing.
- Rarely, seeing a toothbrush or imagining it may be a sufficient trigger.
- Seizures are typically focal aware motor or sensorimotor, evolution to loss of awareness or generalized convulsions may occur.

Complex sensory and cognitive precipitation

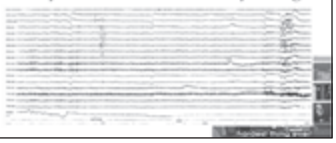
Tooth brushing

- Patients have focal epilepsies of variable etiologies,
  - usually peri-rolandic
  - close to the hand and speech areas
  - without side preference,
  - rarely temporal.
- Three drug-resistant patients were successfully operated, one without a pathology report, one with a cortical dysplasia, and one with a gangliocytoma at the left inferior motor strip (Chan et al; 2016)

Complex sensory and cognitive precipitation

Graphogenic seizures

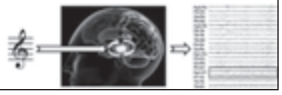
- Seizures induced by writing seem primarily to belong in the realm of system epilepsies where they may occur in the context of praxis induction and of primary reading epilepsy.
- Writing as a solitary trigger of focal seizures is rare.
- A patient (Oshima et al; 2003) had simple motor seizures of the right hand which were always induced within 8-9 sec by writing with his right hand.
- Ictal EEG
- Imaging unrevealing



Complex sensory and cognitive precipitation

Musicogenic seizures

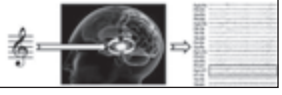
- Most patients do not respond to any type of music but only to a certain style, certain instruments or composers, sometimes even to one particular musical piece.
- Usually the music has an emotional significance.
- The exposure until a seizure occurs is mostly in the range of minutes, rarely only seconds.
- The various components of musical perception (recognition, tone discrimination, emotion etc) can be involved differently.



Complex sensory and cognitive precipitation

Musicogenic seizures

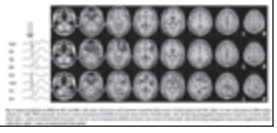
- The relation of musicogenic seizures to TLE is as close as the relation of photosensitivity to JME.
- However, there is the important difference that, whereas photosensitivity in JME is very common and may even express a basic mechanism of ictogenesis in this syndrome, musicogenic seizures in TLE are very rare with not many more than 100 patients described in total, representing a small subgroup in this frequent epilepsy.



Complex sensory and cognitive precipitation

Musicogenic seizures

- Recent studies compared brain activation by ictogenic and non-provocative music using fMRI, EEG source analysis, and multimodal connectivity analysis show that seizure-provoking music activates larger cerebral areas than neutral music.
- In the case investigated by Klamer seizure onset was in the R MTL with spread to the right posterior middle temporal gyrus and thalamus, and further to bilateral mesial frontal regions.
- With neutral music, only signal increase in the primary auditory cortex of the right TL was observed.



Complex sensory and cognitive precipitation

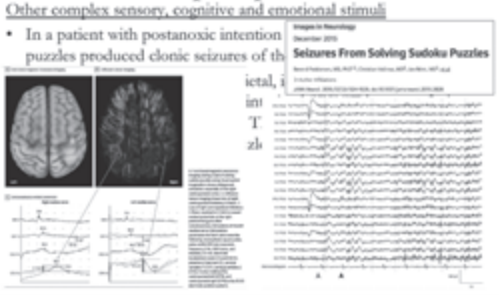
Other complex sensory, cognitive and emotional stimuli

- Of complex sensory triggers only miscellaneous examples have been published:
- A patient with complex partial seizures with temporal and parietal features was sensitive to multiple-digit numbers (e.g. phone numbers, price tags) when she looked at them for several minutes, thought about them or wrote them down.
- One seizure occurred 2 sec after unexpectedly a phone number was announced on television. The cause was a focal cortical dysplasia type 1a which was successfully operated.

Complex sensory and cognitive precipitation

Other complex sensory, cognitive and emotional stimuli

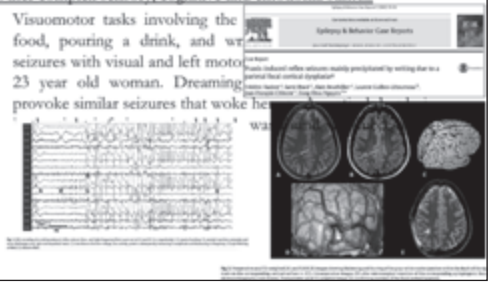
- In a patient with postanoxic intention puzzles produced clonic seizures of th



Complex sensory and cognitive precipitation

Other complex sensory, cognitive and emotional stimuli

- Visuomotor tasks involving the food, pouring a drink, and wr seizures with visual and left moto 23 year old woman. Dreaming provoke similar seizures that woke he



Complex sensory and cognitive precipitation

Orgasm-induced seizures

- Seizures do not occur during orgasm but either immediately afterwards or with minor delay.
- The great majority of patients have RTLE of variable etiology although single examples of left lateralization, frontal lobe epilepsy and idiopathic generalized epilepsy exist.
- It has repeatedly been established that the seizures were dependent not on any sexual stimulation but on the achievement of orgasm, and not caused by hyperventilation.

Prevention and inhibition

- Acute prevention = an attempt to prevent seizure by patient who experiences seizure prodromes.
- Inhibition of seizures an attempt to interrupt seizure after the onset.

Inhibition of focal seizures

- With the exception of absences, generalized seizures seem rarely to be accessible to inhibitory procedures because they are very brief (myoclonic seizures) or begin abruptly, whereas the typically slower and gradual evolution of focal seizures may provide access to inhibitory countermeasures.
- Seizure arrest was a central aspect of epilepsy therapy before the development of modern AEDs, and especially Gowers gave detailed descriptions and advice and understood the importance of an anatomical relation of the stimulus to the seizure onset and spread.
- Both sensory and cognitive methods of arrest have been reported.

Sensory inhibition

Somatosensory

- The proximal ligature for seizure arrest known since the time of Galen and needed to be strong
- A pinch or a prick could occasionally have the same effect.
- Painful cutaneous stimuli seem to be able to arrest incipient focal seizures.
- Whereas to sensory cortex, painful stim
- They also are accompanied by strong arousal which could add a non-specific inhibitory effect.
- Reversely, they seem unlikely triggers because they do not display the necessary anatomical specificity.

Fits triggered by acute pain should be considered syncope until something different is proved.

Proprioceptive inhibition

Movements

- According to Gowers, attacks starting with a general or an epigastric aura "now and then may be stopped by some muscular exertion, as by walking quickly about the room".
- A more targeted intervention, also known since antiquity, is "forcible prevention" of the initial seizure movement by active or passive antagonist movement. This may be done by the patient with the non-convulsing hand or by a helper.

Olfactory and gustatory inhibition

- Jaseja published on oriental folklore where it is advised to let patients in a seizure smell the sole of a shoe to counteract it. He wondered if this could be based on observations of seizure inhibition by smells.
- Gowers in his account of seizure arrest reported that strong gustatory sensations like chewing a piece of ginger and strong olfactory impressions as the application of ammonia to the nostrils or inhalation of nitrite of amyl could sometimes arrest a seizure at the aura stage, especially with olfactory auras.

Olfactory and gustatory inhibition

Cognitive inhibition

- Up to 2/3 of patients with auras at least sometimes try spontaneously to stop their progress to seizures.
- The deliberate action qualifies their strategies as fundamentally cognitive even if sensory or motor stimuli are included.
- Usually they belong to the realms of concentration, relaxation or a combination of both. They may include interaction with other persons.
- Experimentally, inhibition of epileptiform activity by cognitive tasks has primarily been demonstrated in IGE but may to a large extent reflect non-specific arousal.

Therapeutic consequences

- Most patients with focal reflex epilepsies can be treated with the AED commonly used for focal epilepsies, the response primarily depending on etiology, and with surgery as an option for refractory cases.
- However, the existence of precipitating and inhibitory mechanisms may open up for behavioural treatment alternatives

Therapeutic consequences

Stimulus avoidance:

- Strict avoidance of a well-identified trigger is an optimal approach.
- Some triggers in everyday life such as selective pieces of music can be avoided (which, however, few patients seem to do as they often seem to be attracted to the triggering music).
- Others - such as eating - cannot.
- A patient with seizures triggered by Sudoku puzzles became seizure free when he stopped doing Sudokus.

- The applicability of this option will often depend upon individual circumstances. It is always worth considering.

Therapeutic consequences

Epilepsy & Behavior

Review

Self-control of epileptic seizures by nonpharmacological strategies

Therapeutic consequences

Stimulus modification:

- In some cases the triggering stimulus can be modified to become innocuous.
- This applies for hot water epilepsy in infants who can safely be bathed in lukewarm water and need no AEDs.
- Several patients with tooth-brushing seizures noticed that the tooth-brushing needed to be vigourous to produce a seizure, and could modify it.
- Some patients with eating epilepsy have seizures only with bulky meals and can learn to take several small meals instead.

Therapeutic consequences

Stimulus modification:

- Stimulus modification may also refer to timing.
- In a patient with touch-induced focal motor seizures the trigger was only effective when paresthesias reflecting sensory EPC had developed in the trigger zone.
- This development could be prevented when a series of identical stimuli was applied before onset of paraesthesias.

Therapeutic consequences

Acute pharmacological prevention:

- In patients with no spontaneous seizures and where the trigger stimulus is only applied occasionally, acute seizure prevention with a BZD is an effective approach.
- The prototype of this is hot water epilepsy in adolescents and adults where intermittent administration of 5 to 10 mg clobazam (CLB) 60-90 min before bath was fully successful in 85% of the patients without spontaneous seizures.
- In cases with more frequent trigger exposure a short-acting benzodiazepine like midazolam would be preferred.

Therapeutic consequences

Desensitization:

- Forster (1977) devoted his work on reflex epilepsies to a large extent to possibilities of desensitization.
- These included:
  - repetitive presentation to the stimulus altered by unilateral presentation, reduced intensity, or other,
  - threshold alteration (stimulation in postictal refractory period),
  - vigilance inhibition
  - avoidance conditioning.
- The approaches were tailored according to trigger and often highly individualized.
  - Many of the interventions were fundamentally successful but needed constant reinforcement and training which was often not manageable.

Therapeutic consequences

Inhibition

- Most of the patients who spontaneously try to arrest seizures with self-invented methods report that they are at least sometimes successful.
- Others who have regular success are rarely seen by doctors.
- Patients with occasionally positive experiences may profit from professional help in refining their methods.
- The patients' training may involve relaxation techniques, cue-controlled arousal, imagination of the aura with subsequent application of the interruptive stimulus or bio-feedback of the cortical direct current potential. Only few systematic investigations exist.

Therapeutic consequences

Inhibition


Possibilities of non-pharmacological conservative treatment of epilepsy

PETER WOLF* & MATEJA GREGORIC

- 11 (of 25) focal epilepsy:
  - 2 became free of seizures other than isolated auras for >1 year,
  - 2 improved to continue without drugs,
  - 1 achieved full seizure arrest in wakefulness but continued to have GTC seizures during sleep which could not be counteracted and required AED treatment.
  - 2 of these patients had rare seizures related to stressful situations which were approached by lifestyle hygiene and education about coping strategies for stress.
  - 2 others applied maneuvers of arrest focusing on certain thoughts in one, and deliberate initiation of some movement in the other.
  - The fifth patient received treatment unrelated to inhibition.

Treatment consequences

- To conclude, there is at present only limited use of treatments based on counteracting precipition or using inhibition.
- Encouraging reports exist but systematic studies are missing.

Conclusions

- The study of seizure precipitation and inhibition reveals significant differences between focal epilepsies on one side, and generalized and system epilepsies on the other.
- Reflex seizures are well-known in both but seem to have different modes of mechanisms.
- In system epilepsies they primarily relate to the visual system and typically exploit pre-existing physiological functional anatomical networks:
  - in JME, photosensitivity even seems closely related to a basic mechanism of seizure generation.
  - In focal epilepsies, however, they seem related to insufficiently clarified properties of the local epileptogenic tissues with FCD and EPC as possible prototypes.

Conclusions (2)

- The abnormal neuronal structure in FCD may facilitate uninhibited excessive responses.
- EPC reflects an instable local system of ongoing strongly inhibited epileptic oscillations which is easily modifiable by external input.
- Musicogenic epilepsy seems to represent an intermediate type where ictogenesis happens in a pre-existent, acquired functional-anatomic network to which, in the rare cases this happens, the epileptogenic lesion finds access.

Precipitation and inhibition of seizures in focal epilepsies

Rūta Mameniškienė

Thank you

Ačiū

Obrigado!

Matthias Koepp (UK)

IN-VIVO IMAGING OF HYPEREXCITABILITY AND MOLECULAR MECHANISMS IN REFLEX EPILEPSIES

In-vivo imaging of hyperexcitability and molecular mechanisms in reflex epilepsies

Matthias Koepp, MD PhD
UCL Institute of Neurology
London

In-vivo imaging of hyperexcitability in epilepsies

Holy grail of clinical neuroimaging:

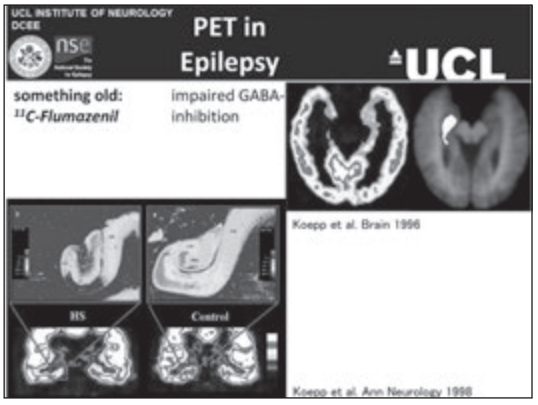
Why PET in epilepsy?

Holy grail of clinical neuroimaging

National Institute of Neurological Disorders and Stroke

2007 NINDS Epilepsy Research Benchmarks

- develop biomarkers to aid discovery of new therapies.
- identify new molecular targets for pharmacotherapy
- develop biomarkers (e.g., genetic, pharmacogenomic, electrophysiologic, imaging, biochemical) to identify patients who are likely to respond to, or develop adverse effects from specific therapies.
- develop higher-throughput cost-effective models for screening drug-herapies for specific types of epilepsy.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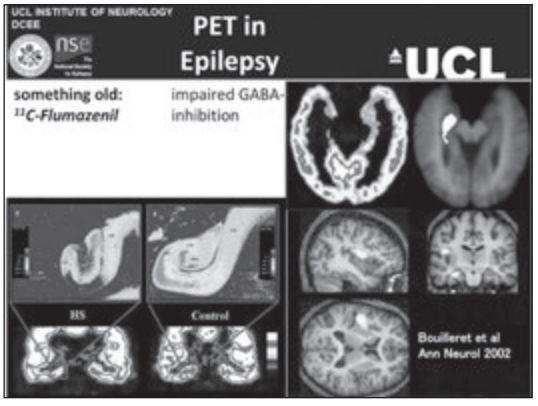
DCEE
PET in Epilepsy
UCL
something old:
11C-Flumazenil
impaired GABA-inhibition
HS
Control
Koepp et al. Brain 1996
Koepp et al. Ann Neurology 1998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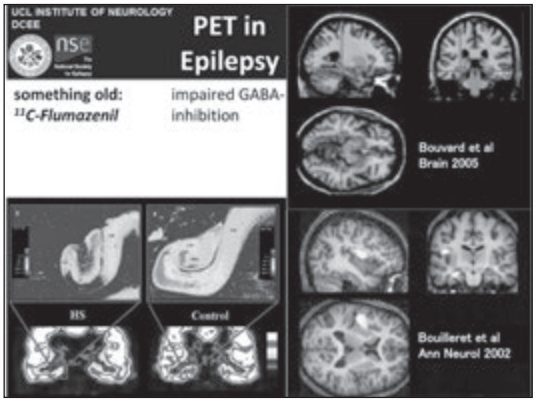
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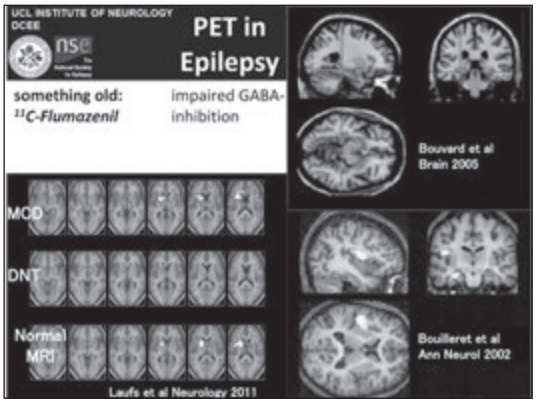
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MCD
DNT
Normal
MRI
Laufs et al Neurology 2011
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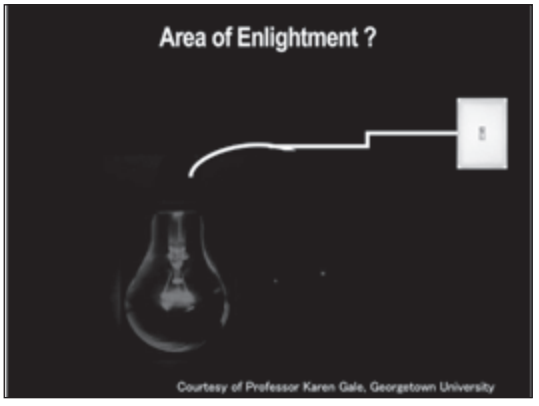
Ann Neurol 2002


Area of Enlightment ?
Courtesy of Professor Karen Gale, Georgetown University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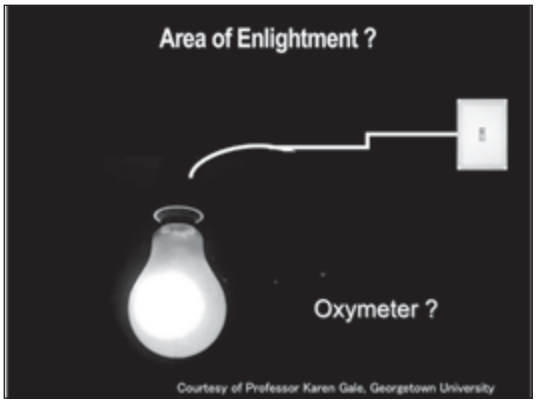
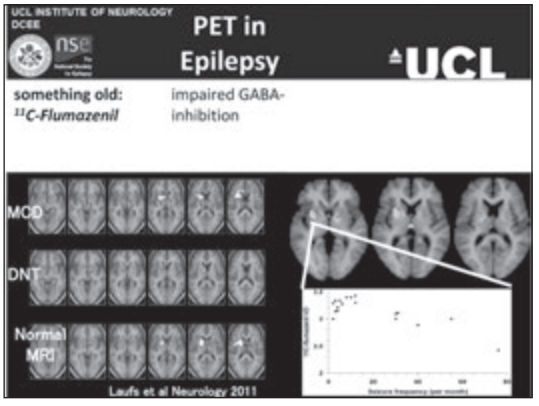

Area of Enlightment ?
Oxymeter ?
Courtesy of Professor Karen Gale, Georgetown University


Focus or spread ?
Courtesy of Professor Karen Gale, Georgetown University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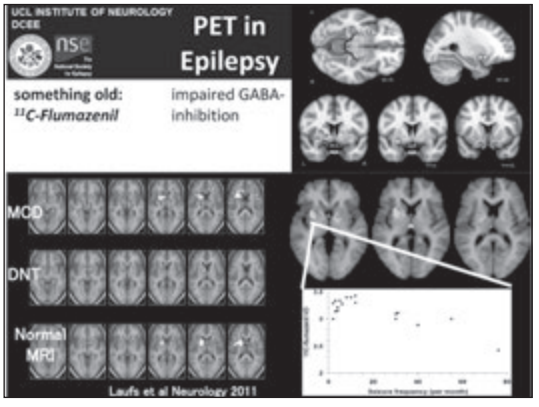
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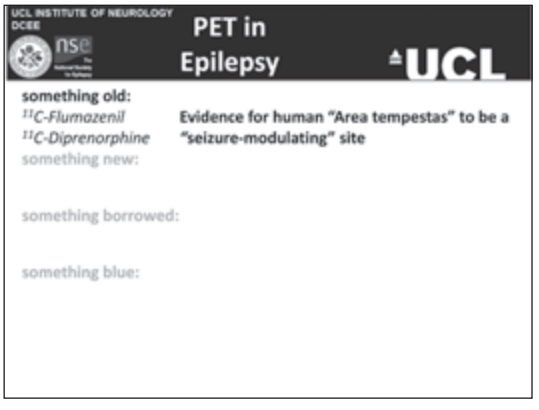
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PET in Epilepsy
UCL
something old:
11C-Flumazenil
11C-Diprenorphine
Evidence for human "Area tempestas" to be a "seizure-modulating" site
something new:
something borrowed:
something blue:

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"Holy Grail" in Epilepsy

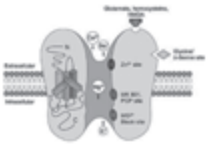
UCL

something old:
^{11}C-Flumazenil
^{11}C-Diprenorphine

Evidence for human "Area tempestas" to be a seizure-modulating site

something new:
^{18}F-GE179

Imaging of NMDA receptors
Guanidine-based NMDA receptor antagonist
binds to intra-channel phencyclidine binding site



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NMDA PET in Epilepsy

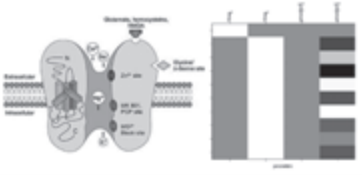
UCL

something old:
^{11}C-Flumazenil
^{11}C-Diprenorphine

Subcortical GABA-binding:
Evidence for human "Area tempestas" to be seizure-modulating site

something new:
^{18}F-GE179

Imaging of NMDA receptors – data analysis
Corrected uptake images
Statistical comparison (SPM8):1patients vs 9controls



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NMDA PET in Epilepsy

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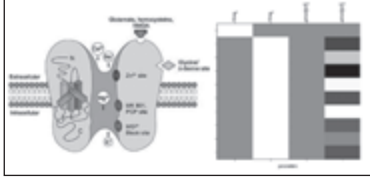

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NMDA PET in Epilepsy

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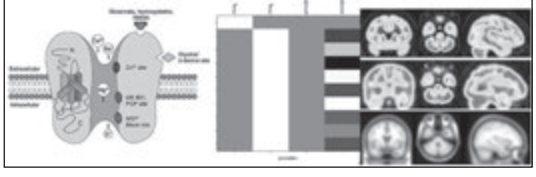
Subcortical GABA-binding:
Evidence for human "Area tempestas" to be seizure-modulating site

something new:
^{18}F-GE179

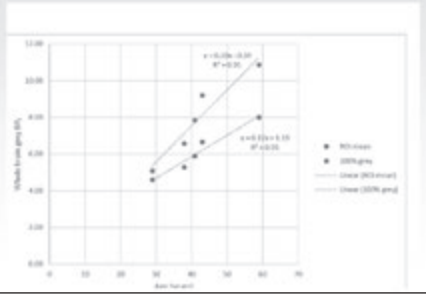
Imaging of NMDA receptors – results:
Significant increase in 4/11 patients



Current studies: ^{18}F-GE-179

UCL

Effect of age



Case for ^{18}F-GE-179

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Focal SUV changes 1 vs. 9/10

- **Increases** (p<0.001 uncorrected) in [^{18}F]GE-179 SUV in:
  - 4/10 controls (1 at cluster level).
  - 6/9 patients (2 movement artefacts due to transmission mismatch).
    - 4/6 MRI-normal patients
    - 3/4 [^{18}F]FDG PET-normal patients
- **Decreases** (p<0.001 uncorrected) in [^{18}F]GE-179 SUV in:
  - 3/10 controls.
  - 5/9 patients
    - 5/6 MRI-normal patients
    - 3/5 [^{18}F]FDG PET-normal patients

Case 1

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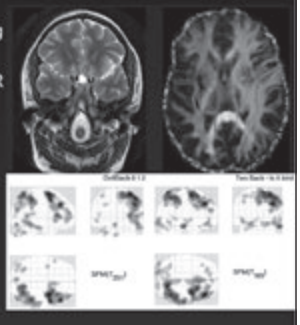
- **Semiology**
  Face twitches, head turning
- **EEG**
  Interictal/ictal: F spikes L>R
- **MRI**
  No abnormality detected.
- **DTI**
  reduced L fronto-temp connectivity
- **fMRI**
  reduced L frontal BOLD response
- **[^{18}F]FDG PET**
  L frontal non-localising



Case 1

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UCL

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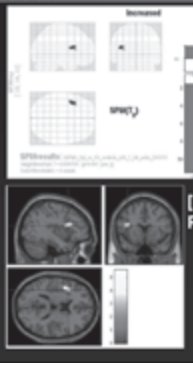

[^{18}F]GE-179 PET
L frontal operculum increase
global VT increase

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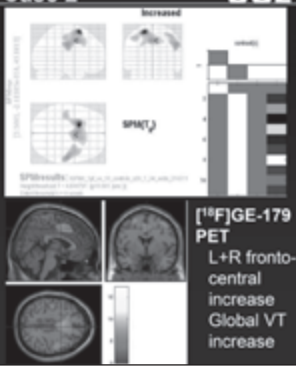
Case 2

UCL

- **Semiology**
  L arm/hand posturing
  +/- moving R hand upwards
- **EEG**
  Interictal: Frontal R>L
  Ictal: Frontal, initially L then R
- **MRI**
  No abnormality detected.
- **[^{18}F]FDG PET**
  Normal



[^{18}F]GE-179 PET
L+R fronto-central increase
Global VT increase

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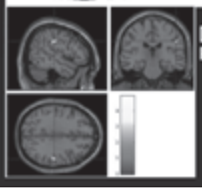
DCEE

Case 2

UCL

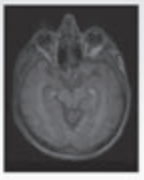
- **Semiology**
  Non-specific auras
  Fidgeting, automatisms
  2° gen.
- **EEG**
  Interictal: R frontal
  Ictal: R fronto-temporal
- **MRI**
- Multiple tubers
- **MEG** – multiple R frontal dipoles
- **Ictal SPECT** – R frontal



[^{18}F]GE-179 PET
R frontal increase
Global V_T increase

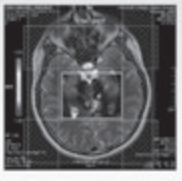
Current studies: ^{18}F-GE179 PET/MRI at UCL

UCL



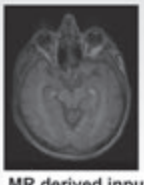
pre- & post-operative scans in TLE:

- 18F-GE179
- ASL
- MRS
- ….



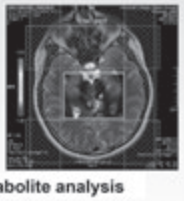
Current studies: ^{18}F-GE179 PET/MRI at UCL

UCL

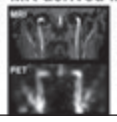


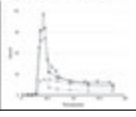
pre- & post-operative scans in TLE:

- 18F-GE179
- ASL
- MRS
- ….

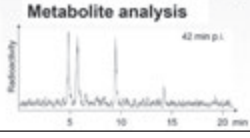


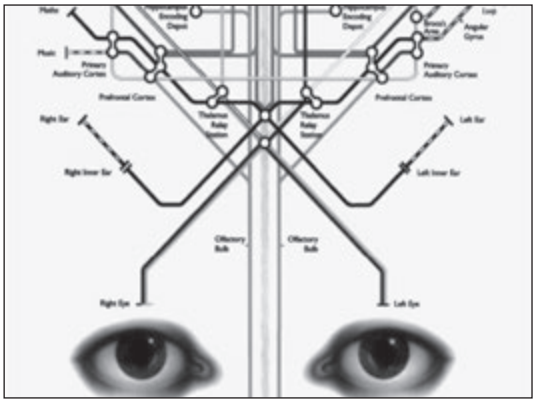
MR derived input function



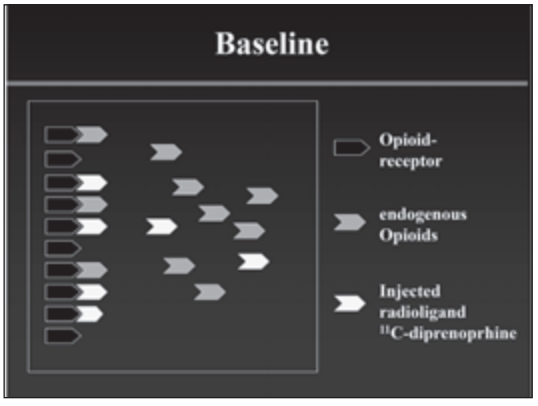


Metabolite analysis

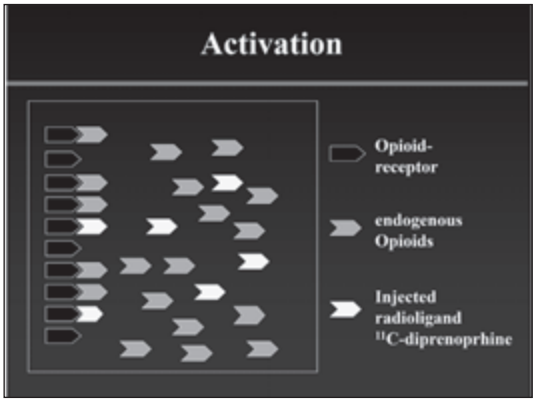




Baseline



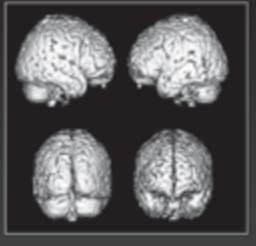
Activation



Endogenous opioid release

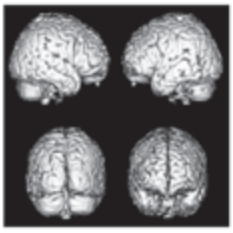
- **Diprenorphine:** non-specific antagonist for opioid receptors
- **Reading Epilepsy (RE):** idiopathic partial epilepsy
- Localised, temporo-parieto-occipital reduction of DPN binding following reading - induced seizures in RE

Lancet 1998;352:952-5



Molecular mechanisms in reflex epilepsies

- Receptor displacement studies



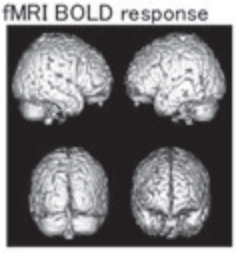
^{11}C-Diprenorphin PET in reading epilepsy:

reduced opioid binding during reading-induced seizures

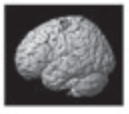
Koepp et al., Lancet 1998

Molecular mechanisms in reflex epilepsies

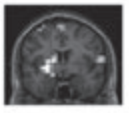
- Receptor displacement studies
- fMRI BOLD response



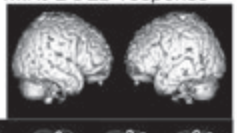
^{11}C-DPN PET



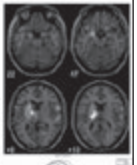
EEG-fMRI



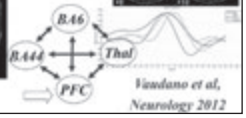
- Receptor displacement studies
- fMRI BOLD response



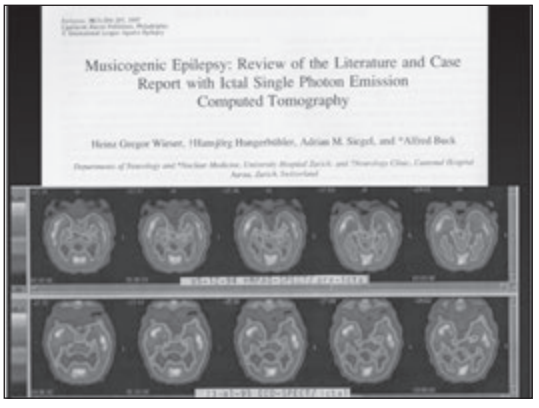
^{11}C-DPN PET



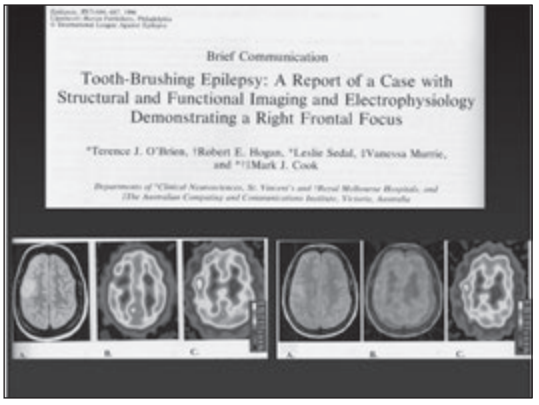
EEG-fMRI



Vaudano et al, Neurology 2012



Musicogenic Epilepsy: Review of the Literature and Case Report with Ictal Single Photon Emission Computed Tomography



Brief Communication

Tooth-Brushing Epilepsy: A Report of a Case with Structural and Functional Imaging and Electrophysiology Demonstrating a Right Frontal Focus

*Terence J. O'Brien, †Robert E. Hogan, *Leslie Sedal, ‡Vanessa Murrie, and *†‡Mark J. Cook

Departments of *Clinical Neurosciences, St. Vincent's and †Royal Melbourne Hospitals, and ‡The Australian Computing and Communications Institute, Victoria, Australia

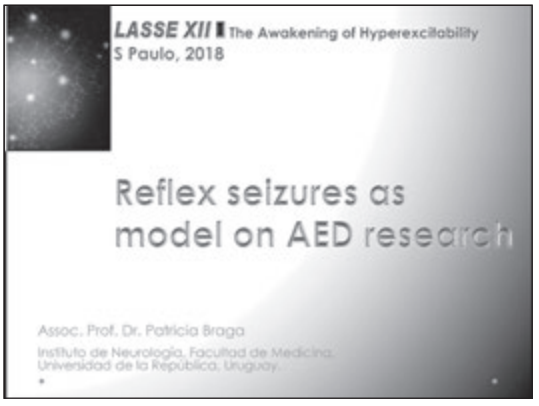
Summary: molecular mechanisms in reading (reflex) epilepsies

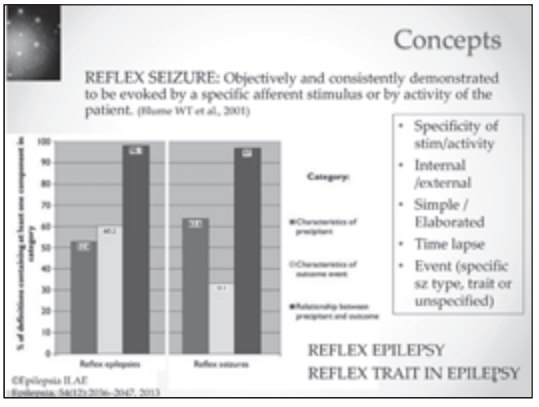
Variable cortical hyperexcitability in bilateral network of areas also involved in language processes:

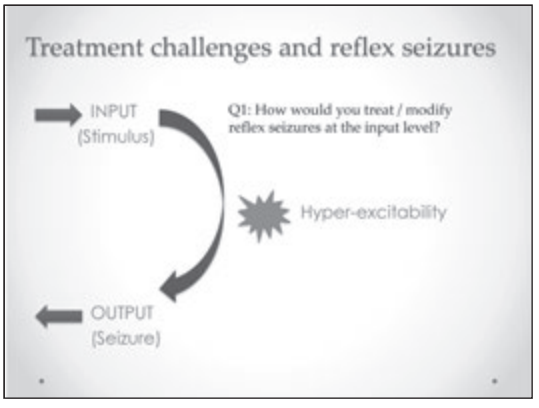
- Multiple areas of ictal endogenous opioid release
- Critical mass functional rather structural
- Variable distribution of epileptic discharges
- Heterogeneity of precipiating mechanisms

Patricia Braga (Uruguay)

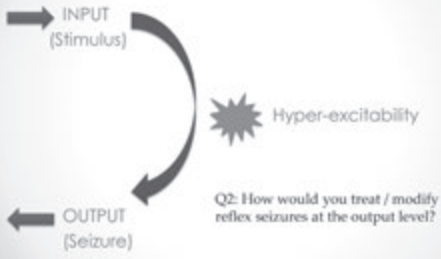
REFLEX SEIZURES AS MODEL ON AEDS RESEARCH





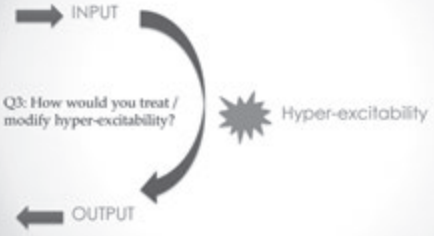


Treatment challenges and reflex epilepsy



Q2: How would you treat / modify reflex seizures at the output level?

Treatment challenges and reflex epilepsy



Q3: How would you treat / modify hyper-excitability?

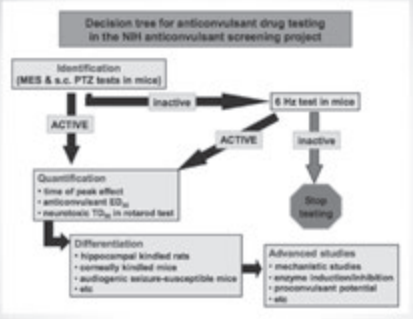
Steps & tools in AED research

- Development
- Toxicity
- PK
- Efficacy (I)
  - Measures
  - Effective dose
- Adverse Events
  - Teratogenesis
- Efficacy (II)
  - Clinical use on sz types, age groups
  - Add-on, monotherapy
- Pharmacovigilance

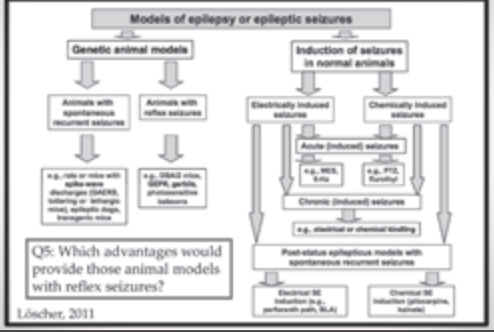
ANIMAL MODELS

HUMAN STUDIES

Q4: Which main limitations do you expect to happen?



Animal models in AED research



Löscher, 2011

Q5: Which advantages would provide those animal models with reflex seizures?

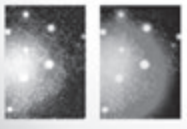
- The possibility to:

1. reproduce seizures in laboratory
2. analyze the characteristics of effective stimulus
3. study the progression of clinical signs
4. study the progression of EEG discharges
5. theoretically easier to translate to human

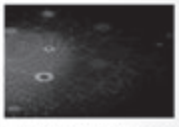
Planning a research study with AEDs in an animal model of reflex seizures

Q6: Which Animal Model?

1. Animal
2. Modality of reflex seizure



Q7: Which drug?



Is there any expected specific relationship drug – type of reflex epilepsy/seizure?

Q8: Outcome measures?

1. Suppression of reflex seizures
2. Increase latency to reflex seizure
3. Severity /Length of seizures
4. Qualitative changes in seizure semiology
5. Other reflex traits, as EEG traits

AED research
in
animal models
with
reflex seizures

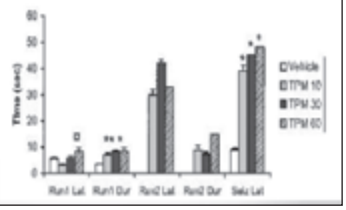
Laboratory Research

Effects of Topiramate in Two Models of Genetically Determined Generalized Epilepsy, the GAERS and the Audiogenic Wistar AS

Marie-Aude Rigoulot, Any Boehrer, and Astrid Nehlig

EFFECTS OF TOPIRAMATE ON WISTAR AS

Fig 3- Effects of increasing doses of TPM on the number of latency times to and duration of wild running episodes and tonic seizures in Wistar AS rats.



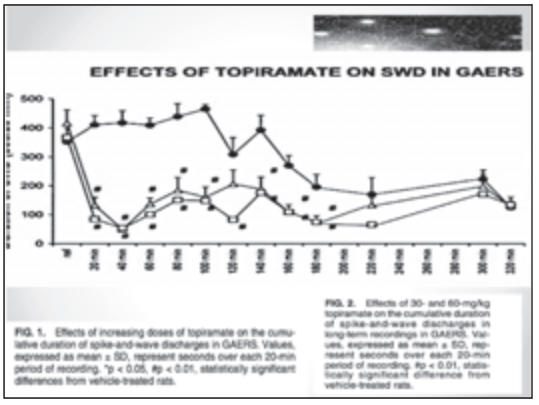


FIG. 1. Effects of increasing doses of topiramate on the cumulative duration of spike-and-wave discharges in GAERS. Values, expressed as mean ± SD, represent seconds over each 20-min period of recording. *p < 0.05, #p < 0.01, statistically significant differences from vehicle-treated rats.

FIG. 2. Effects of 30- and 60-mg/kg topiramate on the cumulative duration of spike-and-wave discharges in long-term recordings in GAERS. Values, expressed as mean ± SD, represent seconds over each 20-min period of recording. #p < 0.01, statistically significant difference from vehicle-treated rats.

FULL-LENGTH ORIGINAL RESEARCH

Effects of carisbamate (RWJ-333369) in two models of genetically determined generalized epilepsy, the GAERS and the audiogenic Wistar AS

Jennifer François, Any Boehrer, and Astrid Nehlig

INSERM U 398 and 666, Strasbourg, France

SUMMARY

Purpose: The antiepileptic effects of carisbamate were assessed in two models of genetic epilepsy, a model of absence seizures, the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) and a model of convulsive seizures, the Wistar Audiogenic Sensitive (AS) rat.

Methods: GAERS were equipped with four cortical electrodes over the frontoparietal cortex and the duration of spike-and-wave discharges (SWD) was recorded for 20–120 min. In Wistar AS, the occurrence of, latency to, and duration of wild running and tonic seizures were recorded.

Results: In GAERS, carisbamate (10, 30, and 60 mg/kg) dose dependently reduced the expression of SWD that totally disappeared at the two highest doses by 40 min after injection. SWD duration returned to control levels by 100 min after the injection of 30 mg/kg carisbamate while SWDs were totally suppressed for 120 min after the injection of 60 mg/kg carisbamate. In Wistar AS, 10 mg/kg carisbamate increased the latency to the first running episode and induced the occurrence of a second running episode in three of eight rats. This episode was not present in untreated rats and was indicative of decreased sensitivity to the stimulus. This dose of carisbamate increased by 327% the latency to the tonic seizure that still occurred in the six of eight rats studied. At 20 and 30 mg/kg, no rats exhibited any wild running or tonic seizure.

Conclusions: The present results support the broad spectrum of antiepileptic activity of carisbamate confirming its efficacy in animal models of primary generalized seizures of both tonic–clonic and of the absence type.

KEY WORDS: Carisbamate, Genetic absence epilepsy, GAERS, Audiogenic seizures.

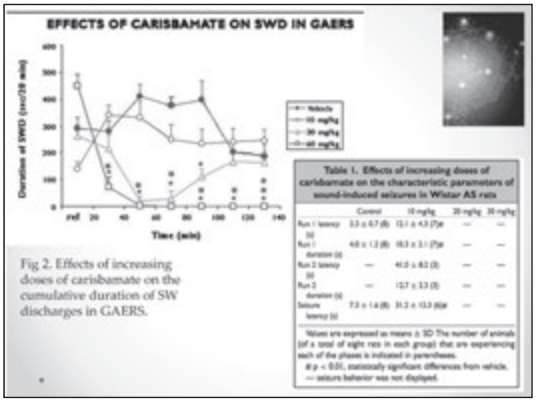
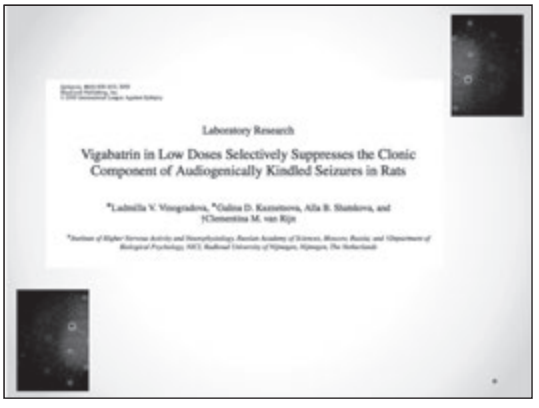


Fig 2. Effects of increasing doses of carisbamate on the cumulative duration of SW discharges in GAERS.

Table 1. Effects of increasing doses of carisbamate on the characteristic parameters of sound-induced seizures in Wistar AS rats

	Control	10 mg/kg	30 mg/kg	30 mg/kg
Run 1 latency (s)	3.3 ± 0.7 (8)	13.1 ± 4.3 (7)#	—	—
Run 1 duration (s)	4.0 ± 1.2 (8)	10.3 ± 2.1 (7)#	—	—
Run 2 latency (s)	—	41.0 ± 8.2 (3)	—	—
Run 2 duration (s)	—	12.7 ± 3.3 (3)	—	—
Seizure latency (s)	7.3 ± 1.6 (8)	31.2 ± 13.3 (6)#	—	—

Values are expressed as means ± SD. The number of animals (of a total of eight rats in each group) that are experiencing each of the phases is indicated in parentheses.
# $p < 0.01$, statistically significant differences from vehicle.
— seizure behavior was not displayed.

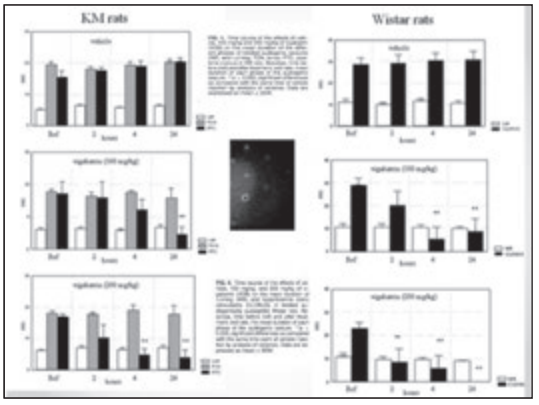


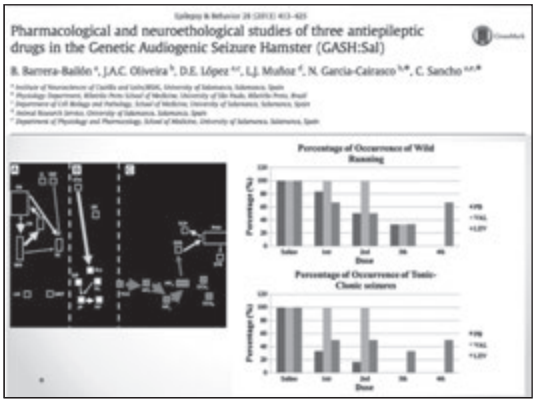
Laboratory Research

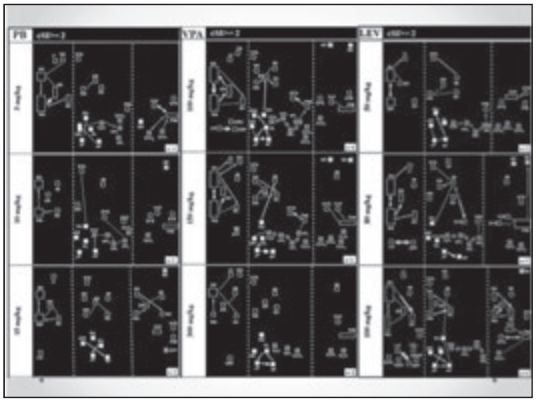
Vigabatrin in Low Doses Selectively Suppresses the Clonic Component of Audiogenically Kindled Seizures in Rats

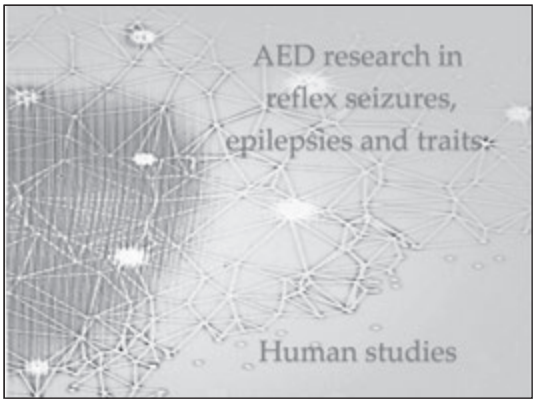
*Ludmilla V. Voiegradova, *Galina D. Kuznetsova, Alla B. Shatskova, and †Clementina M. van Rijn

*Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia; and †Department of Biological Psychology, NICI, Radboud University of Nijmegen, Nijmegen, The Netherlands


KM rats
Wistar rats


Epilepsy & Behavior 28 (2013) 413–425
Pharmacological and neuroethological studies of three antiepileptic drugs in the Genetic Audiogenic Seizure Hamster (GASH:Sal)
B. Barrera-Bailón, J.A.C. Oliveira, D.E. López, L.J. Muñoz, N. García-Cairasco, C. Sancho
Percentage of Occurrence of Wild Running
Percentage of Occurrence of Tonic-Clonic seizures
Dose


PB
VPA
LEV


AED research in reflex seizures, epilepsies and traits:
Human studies

Q9: Which advantages would provide reflex seizures for human AED research?

- The possibility to:

1. easy reproducibility of seizures
2. analyze the characteristics of effective stimulus
3. study the progression of clinical signs
4. study the progression of EEG discharges
5. may shorten the duration of efficacy studies (different outcome measure)

Planning a research study with AEDs in epilepsy patients

1. Condition
   - Symptomatic seizures
   - **Epilepsy**
     - Epilepsy type (focal/generalized)
   - Status epilepticus
2. Drug and Administration
   - One dose
   - **Clinical trial**
   - Long term studies
3. Outcome measure
   - Seizures
     - **Frequency**
     - Type
     - Stopping status
   - EEG
     - IED
     - Specific traits
     - Stopping status

Planning a research study with AEDs in patients with reflex epilepsy / seizures

1. Condition
   - **Modality of stimulus**
   - Specificity of sz type
2. Drug and Administration
   - **One/few doses**
   - Clinical trial
   - Long term studies
3. Outcome measure
   - Seizures
     - Frequency
     - Type
     - Stopping status
     - **Yes /No**
   - EEG
     - IED
     - **Specific traits**
     - Stopping status

Relevant issues to take into account:

- Screening and studying reflex seizures and epilepsies requires a special care in collecting anamnesis.
- This is essential for planning video-EEG and polygraphy, which must be tailored for the single patient;
- The choice of triggers must be planned on the basis of patient's history and knowledge of the literature
- In some cases it could be necessary a long exposure to the trigger, as in musicogenic epilepsy and in other reflexes seizures triggered by higher cortical processes

FULL-LENGTH ORIGINAL RESEARCH

Effects of levetiracetam on EEG abnormalities in juvenile myoclonic epilepsy

*Nicola Specchio, †‡Giovanni Boero, ||Roberto Michelucci, ¶Antonio Gambardella, #Anna Teresa Giallonardo, @Imane Fattouch, #Carlo Di Bonaventura, ‡Alessia de Palo, ‡§Marianna Ladogana, §Paolo Lamberti, *Federico Vigevano, ‡Angela La Neve, and †‡Luigi Maria Specchio

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METHODS

Study design

This was a multicenter, prospective, pragmatic, long-term, open-label treatment study. The clinical trial design has been published elsewhere (Specchio et al., 2008). Briefly, after an 8-week baseline period patients with JME were given levetiracetam at a starting dose of 250 mg twice daily (b.i.d.), which was increased to 500 mg b.i.d. after 2 weeks. They were followed up to 36 months. During this period levetiracetam dose could be increased up to 1,500 mg b.i.d., according to clinician judgement. Visits were scheduled approximately every 3 months.

EEG

At each visit patients underwent an EEG performed using the bipolar and monopolar 10–20 international system. To exclude any confounding factor related to the daytime variation of the paroxysmal activity, as previously reported in patients with JME (Labate et al., 2007) and in patients with ICE (Pinzaldi et al., 2001), the EEGs were performed at least 3 h after awakening. Eleven patients during the study missed one EEG because they did not make the scheduled visit. IPS was performed following international protocols (Kasteleijn-Nolst Trenité et al., 1999).

Table 2. EEG abnormalities and photoparoxysmal response evaluated at baseline and over the study periods

	Baseline (8 weeks)	After level-racetam	p*
EEG abnormalities			
Total sample (n = 48)			
Total	44/48	31/48	<0.0001
Spike-and-waves	36/48	19/48	
Polyspikes-and-waves	7/48	1/48	
Polyspikes	1/48	1/48	
Patients on first monotherapy (n = 10)			
Total	10/10	5/10	
Spike-and-waves	10/10	5/10	
Polyspikes-and-waves	No	No	
Polyspikes	No	No	
Patients on polytherapy (n = 38)			
Total	34/38	26/38	
Spike-and-waves	26/38	14/38	
Polyspikes-and-waves	7/38	1/38	
Polyspikes	1/38	1/38	
Photoparoxysmal response			
Total sample (n = 48)			
Total	17/48	4/48	<0.0001
Patients on first monotherapy (n = 10)			
Total	5/10	2/10	
Patients on polytherapy (n = 38)			
total	12/38	2/38	

*Mc Nemar – chi-square test.

Table 3. Cumulative probability of achieving a 12-month period without days with myoclonia (DWM) in relation to EEG changes and photoparoxysmal response (PPR) after 10 and 20 months of levetiracetam treatment

12-month DWM remission	% of patients with unchanged EEG (n = 21)	% of patients with normalized EEG (n = 23)	p*
10 months	35	69	0.0469
20 months	55	83	
	% of patients with unchanged PPR (n = 9)	% of patients with improved PPR (n = 13)	p*
10 months	49	37	0.864
10 months	78	77	

* Log Rank test.

FULL-LENGTH ORIGINAL RESEARCH

Valproate reduces spontaneous generalized spikes and waves but not photoparoxysmal reactions in patients with idiopathic generalized epilepsies

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SUMMARY

Purpose: Patients with idiopathic generalized epilepsies (IGEs) often present with interictal spike-wave discharges (SWDs) at rest (spontaneous SWDs), during hyperventilation, and in response to photic stimulation (photoparoxysmal response or PPR). Valproic acid (VPA) is a first-line antiepileptic drug for therapy of patients with IGE. Herein we investigated the effect of VPA on all three types of SWDs in children and adolescents with IGE.

Methods: Routine electroencephalography (EEG) during valproic acid monotherapy and up to four times during the first year of the VPA treatment, was analyzed retrospectively. For the analysis of the VPA effect on spontaneous SWDs and SWDs under hyperventilation, the number and duration of SWDs were counted. SWDs under intermittent photic stimulation (IPS) were classified according to the extent of propagation (grading). Response to VPA treatment (not/hyperventilation) was defined as a disappearance of SWDs within the year after VPA introduction.

Key Findings: Eighty-four patients (37 male and 47 female, mean age: 9.8 ± 4.1 years) exhibited spontaneous SWDs or SWDs under hyperventilation. From this sample, 34 patients exhibited the PPR (7 male and 27 female, mean age 10.1 ± 3.9 years). A significant reduction in the number and duration of spontaneous SWDs and SWDs under hyperventilation was observed in the first 4 weeks of treatment ($p < 0.001$, corrected, 87.3% responders). This effect remained stable over the 1 year observation period. Concerning PPR, only 4 (11.9%) of 31 patients were classified as responders. The difference between groups of patients with spontaneous/induced SWDs and PPR according to the number of responders was significant ($p = 0.001$).

Significance: This study provides evidence that the effect of VPA on SWDs differs dependent on the types of SWDs. In the majority of patients, spontaneous SWDs and SWDs induced by hyperventilation disappeared, whereas the PPR mostly remained under VPA treatment. These results point to different pathogenetic mechanisms underlying the spontaneous and the evoked generalized epileptic activity in the IGE.

KEY WORDS: Photoparoxysmal reaction, Idiopathic generalized epilepsy, Valproate therapy, Valproate effect.

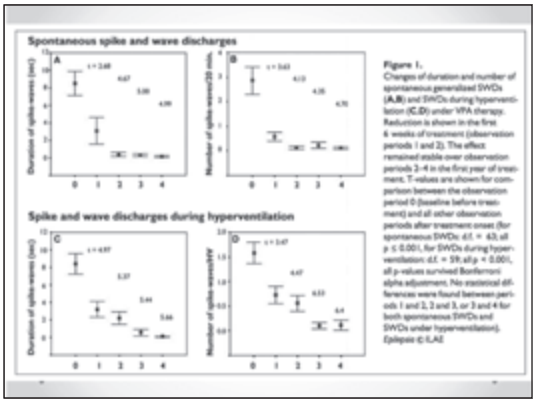
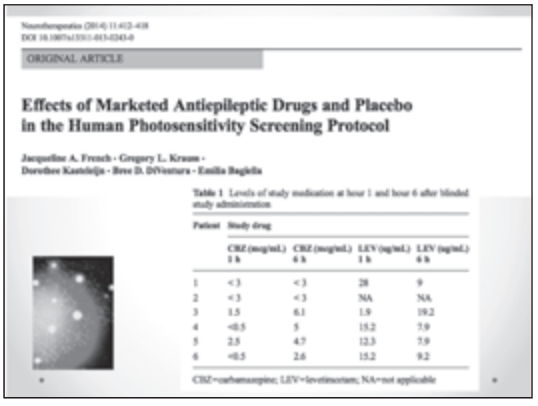


Figure 1.
Changes of duration and number of spontaneous generalized SWDs (**A,B**) and SWDs during hyperventilation (**C,D**) under VPA therapy. Reduction is shown in the first 6 weeks of treatment (observation periods 1 and 2). The effect remained stable over observation periods 3–4 in the first year of treatment. T-values are shown for comparison between the observation period 0 (baseline before treatment) and all other observation periods after treatment onset (for spontaneous SWDs: $df. = 63$; all $p \leq 0.001$, for SWDs during hyperventilation: $df. = 59$; all $p < 0.001$, all p-values survived Bonferroni-alpha adjustment. No statistical differences were found between periods 1 and 2, 2 and 3, or 3 and 4 for both spontaneous SWDs and SWDs under hyperventilation). *Epilepsia* © ILAE



Neurotherapeutics (2014) 11:432–438
DOI 10.1007/s13311-013-0243-0

ORIGINAL ARTICLE

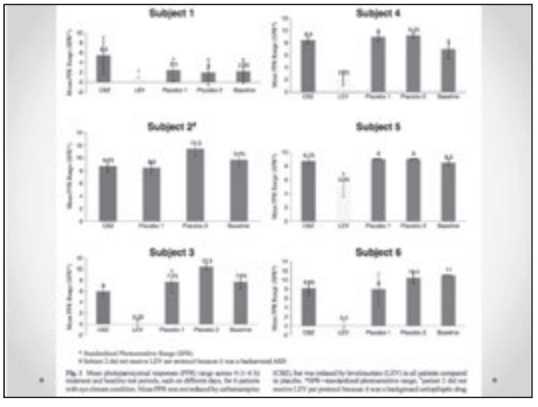
Effects of Marketed Antiepileptic Drugs and Placebo in the Human Photosensitivity Screening Protocol

Jacqueline A. French · Gregory L. Krauss · Dorothee Kasteleijn · Bree D. DiVentura · Emilia Bagiella

Table 1 Levels of study medication at hour 1 and hour 6 after blinded study administration

Patient	Study drug			
	CBZ (mcg/mL) 1 h	CBZ (mcg/mL) 6 h	LEV (ug/mL) 1 h	LEV (ug/mL) 6 h
1	< 3	< 3	28	9
2	< 3	< 3	NA	NA
3	1.5	6.1	1.9	19.2
4	<0.5	5	15.2	7.9
5	2.5	4.7	12.3	7.9
6	<0.5	2.6	15.2	9.2

CBZ=carbamazepine; LEV=levetiracetam; NA=not applicable



Epilepsia, 49(3):420–430, 2008
doi: 10.1111/j.1528-1167.2007.01324.x

FULL-LENGTH ORIGINAL RESEARCH

A pilot trial of levetiracetam in eyelid myoclonia with absences (Jeavons syndrome)

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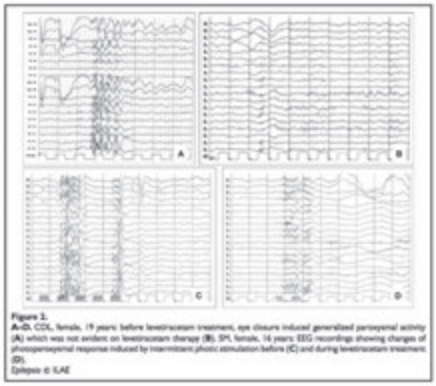


Figure 3.
A–D. CDL, female, 19 years: before levetiracetam treatment, eye closure induced generalized paroxysmal activity (A) which was not evident on levetiracetam therapy (B). SM, female, 14 years: EEG recordings showing changes of photoparoxysmal response induced by intermittent photic stimulation before (C) and during levetiracetam treatment (D).
Epilepsia © ILAE

The efficacy and tolerability of Levetiracetam as an add-on therapy in patients with startle epilepsy

Candan Gürses*, Kadriye Alpay, Farah Diba Çiftçi, Nerses Bebek, Betül Baykan, Ayşen Gökyiğit

Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Millet Caddesi Capa 34390, Istanbul, Turkey

Summary

Purpose: To evaluate the efficacy and tolerability of Levetiracetam as an add-on therapy in patients with startle epilepsy (StEp).
Methods: Ten (7 males and 3 females) were enrolled in the study. LEV was started at 500 mg bid, escalating over 1–2 weeks to maximal doses of 3000 mg daily, based on seizure control and tolerance for 13–28 months.
Results: The onset of startle seizures in patients with StEp varied from birth to 11 years. Six in 10 patients gave good responses to the treatment. There were adverse effects in three patients.
Conclusion: Many AEDs have been used by medically intractable patients with StEp for many years but the results were almost discouraging.

It was observed that 60% of the patients gave good response to LEV. Advanced studies are required to indicate the efficiency of LEV which proved to be effective on animals with audiogenic seizures on reflex epilepsies.

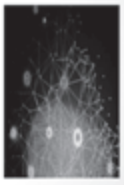
Current and future challenges

Current advances: research studies on AED treatment in animals with reflex seizures

Animal Model?

- Or model animal?
- All reflex sz/epilepsy models are of genetic origin?
- All audiogenic?
- Kindling for reflex seizures

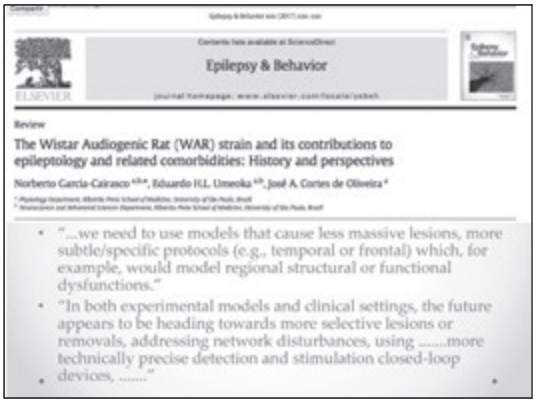
Which drug?



- Specific relationship drug – type of reflex epilepsy/seizure?
- Drug or device?

Outcome measures?

- Neuro-ethology
- Understanding comorbidities and adverse effects from AEDs



Epilepsy & Behavior

Review

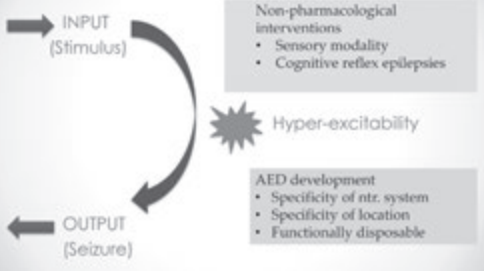
The Wistar Audiogenic Rat (WAR) strain and its contributions to epileptology and related comorbidities: History and perspectives

- "...we need to use models that cause less massive lesions, more subtle/specific protocols (e.g., temporal or frontal) which, for example, would model regional structural or functional dysfunctions."
- "In both experimental models and clinical settings, the future appears to be heading towards more selective lesions or removals, addressing network disturbances, using .....more technically precise detection and stimulation closed-loop devices, ..."

Current challenges: epilepsy treatment from patients with reflex epilepsy / seizures

- Learning from those with identifiable functional networks involved in their seizure precipitation
- Leading to the generation of hypothesis on specific neural networks involved, according to input and output pathways
- Multidisciplinary approach
- Trying to better understand functional networks and neurotransmitters systems
- Adapting pharmacological interventions

Treatment challenges in reflex seizures



Q10: Which do you think are the upcoming challenges in AED research?

a. For reflex epilepsy patients

a. In which studies in reflex epilepsies could help


LASSE XII The Awakening of Hyperexcitability
S Paulo, 2018
Thank you!!

Nicola Specchio (Italy)

VIDEO-SESSION ON SEIZURES SEMIOLOGY

Rodney Scott (USA)

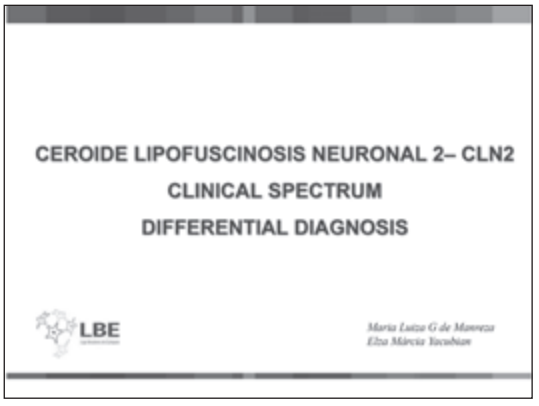
EPILEPSY AND DISORDERS OF SEVERE DEVELOPMENTAL DELAY

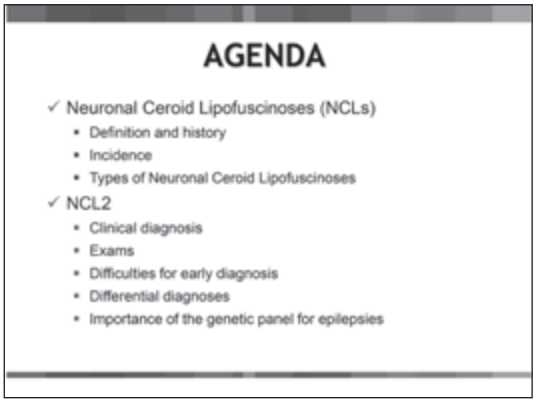
Nicola Specchio (Italy)

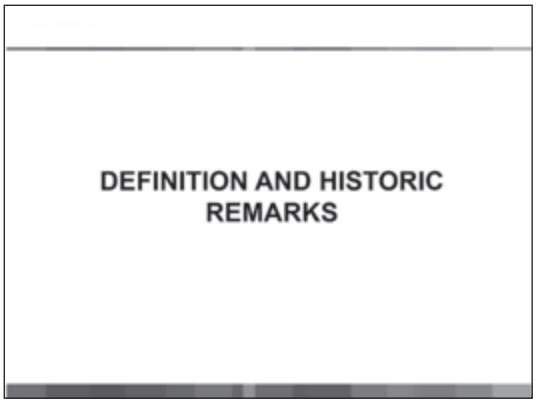
EPILEPTIC ENCEPHALOPATHIES

Maria Luiza Manreza

CEROIDE LIPOFUSCINOSE NEURONAL 2. CLN2. CLINICAL SPECTRUM. DIFFERENTIAL DIAGNOSIS







1. What is Batten's disease?

a. A group of rare inherited, neurodegenerative, lysosomal storage diseases called neuronal ceroid lipofuscinoses - NCLs
b. A focal epilepsy type
c. A sporadic type of ataxia
d. A type of spinal amyotrophy

Frederick Batten in 1894

HISTORY- Batten's disease

- ✓ Dr. Otto Christian Stenge (1826): first clinical description
- ✓ Sachs: 19 century- "family amaurotic idiocy" accumulation of lipids "
- ✓ Frederick Batten (1903): first pathological description
- ✓ Spielmeyer and Vogt (1905): Batten-Spielmeyer-Vogt disease
- ✓Jansky and Bielschowsky: a similar disease with late childhood onset
- ✓ Kufs: adult onset, similar to the others, without vision loss
- ✓ **The field remained unclear until the introduction of the CLN concept by Zeman and Dyken in 1969**

Haltia and Santavuori (1971) described the infantile type with a distinct onset, now called **Classic Infantile neuronal ceroid lipofuscinosis**

Mink JW et al. J Child Neurol 2013;28:1101

HISTORY

A- Otto Christian Stengel
B- Frederick Eustace Batten
C - Walther Spielmeyer
D - Jan Janský
E - Max Bielschowsky
F - Hugo Kufs
G - Matti Haltia
H - Pirkko Santavuori

Nita DA et al. Epileptic Disord 2016;18(S2):73-88.

2. How many types of Batten's disease?

a. 1
b. 3
c. 4
d. 14

Frederick Batten in 1894

INCIDENCE

3. WHICH IS THE INCIDENCE OF BATTEN'S DISEASE?

a. 2-4/100.000 live births
b. 10/100.000 live births
c. 100/100.000 live births
d. 1/1000 live births

Frederick Batten in 1894

FREQUENCE

- ✓ NCL is one of the most common inherited neurodegenerative diseases in childhood
- ✓ Identified in several domestic and laboratory animals
- ✓ Since 1995 -> **13 genes and more than 360 mutations**
- ✓ **Incidence**: depends of the ancestries and geographic area
  - 1:67 000 in Italy and Germany
  - 1:14 000 in Iceland
- ✓ **Prevalence**- is variable- from 1:1.000 000 to 1:100 000 in Scandinavian countries

Hafiba M and Goebel HH. Biochim Biophys Acta. 2013;1832(11):1795-809.

4. WHICH IS THE MOST COMMON TYPE OF BATTEN'S DISEASE?

a. CLN1
b. CLN2
c. CLN3
d. CLN4

Frederick Batten em 1894

FREQUENCY NEURONAL CEROID LIPOFUSCINOSES

- CLN1 NCL- In the Finnish population, the incidence is 1 in 20,000 persons, with a carrier frequency of 1 in 70 persons
- CLN3 NCL - Worldwide, CLN3 NCL is the second most common form of NCL; the incidence is 7 cases per 100.000 live births in Iceland
- CLN2 NCL - The worldwide prevalence is 0.6-0.7 per million inhabitants, with an incidence of 0.46 per 100.000 live births

CLN2- PATHOPHYSIOLOGY

5. WHY SHOULD WE KNOW HOW TO DIAGNOSIS CLN2?

Noah's disease onset at 3 years, already with tremor and speech difficulties

Laine, his sister, had CLN2 diagnosis 5 months after Noah's diagnosis

a. Because of its extraordinary answer to common antibiotics
b. Because it can be controlled with some antibiotics
c. Because it can be improved with ketogenic diet
d. Because it is a deposit disease that has a FDA and EMA approved treatment

6. AT THIS MOMENT, WHICH IS YOUR CONFIDENCE DEGREE IN DIAGNOSING CLN2?

Jan Janský and Max Bielschowsky

a. None
b. Low
c. Satisfactory
d. Very satisfactory

7. Which is late infantile, Bielschowsky-Jansky disease or CLN2?

a. 0,22 to 9/100.000 live births
b. 50/100.000 live births
c. 100/100.000 live births
d. 1000/100.000 live births

Jan Janský and Max Bielschowsky

8. Which is the cause of late infantile, Bielschowsky-Jansky disease or CLN2?

a. Reduction of Tripeptidil-peptidase 1 enzyme (TPP1)
b. Accumulation of poliglicosan
c. Accumulation of mucopolisacarides
d. Accumulation of battenin, the protein codified by chromosome 16

Jan Janský and Max Bielschowsky

NEURONAL CEROID LIPOFUSCINOSIS 2

- CLN2 is a Batten's disease subtype
- Deficiency of enzyme lysosomal TPP1 (**Tripeptidyl-peptidase 1**)
  - Accumulation of ceroid lipofuscin
- The diagnosis of this disease is a challenge
  - Is similar to several other diseases
  - Delay in diagnosis
  - Absence of treatment guidelines
  - Management of the symptoms

Kohlschütter A, Schulz A. Pediatr Endocrinol Rev. 2016;13 Suppl 1:682-8.

PATHOPHYSIOLOGY

Affected gene CLN2

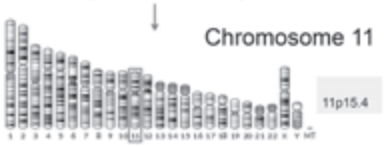
codifies

↓

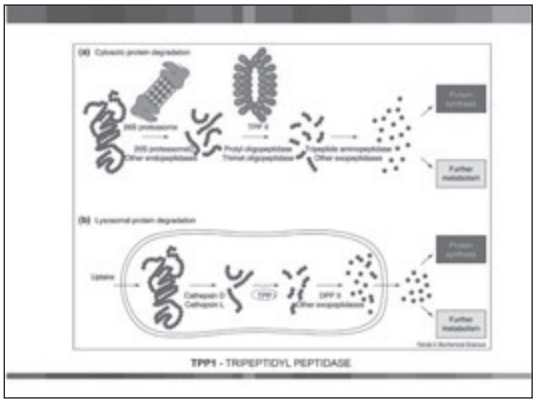
Tripeptidyl-peptidase 1 enzyme

↓

Chromosome 11

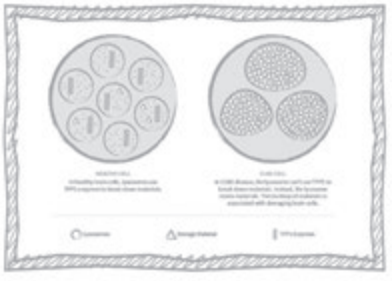


Neverman NJ et al. Biochim Biophys Acta 2015; 6 5925

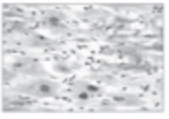


TPP1 - TRIPEPTIDYL PEPTIDASE

LYSOSOMAL STORAGE DISEASE



LIPOFUSCIN



Yellow-brown lipofuscin granules in heart muscle cells

- ✓ Autofluorescent lipopigment of glycoprotein origin
- ✓ Fine pigment, golden brown, resulting from incomplete digestion of damaged blood cells (cellular debris)
- ✓ This pigment serves to detect the cellular life time
- ✓ It is present in cells that do not multiply very much and have a long life, such as myocardial muscles and neurons
- ✓ Usually, the more lipofuscin present, the older the cell
- ✓ Ceroid – that looks like wax

CLINICAL DIAGNOSIS

9. Which of the following is the initial symptom of the disease?

a. Language delay
b. Seizures
c. Ataxia
d. Developmental retardation

Jan Janský e Max Bielschowsky

LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS

- ✓ **Age at onset** – commonly between 2-4 years of age; there are described case with disease onset before 1 year **(Pérez-Poyato et al. J Child Neurol 2013)**
- ✓ **Symptoms**

1 - Speech delay, can be the first symptom
2 – Epilepsy onset 2 – 4 years of age
3 – Psychomotor decline, whose onset follows the epilepsy onset
4 – Neurological signs: ataxia, pyramidal and extrapyramidal signs
5 – Visual deficiency with onset soon after the seizures and can evolve to blindness around 5-6 years of age
6 – Death 6-15 years of age

Carabalio AR et al. Rev Neurol 2005;40(3):135

For some, language loss as the second symptom, after seizures onset

Survey of 18 NCL Experts

Symptom	Brings patient to clinic	First presenting symptom	Pathognomonic symptom
Seizures	11	12	10
Language loss	2	7	8
Developmental delay	4	6	8
Myoclonus	1	5	8
Ataxia	3	2	5
Psychomotor decline	0	3	6
Visual loss	0	1	7
Other	0	1	2
Pyramidal signs	1	0	4

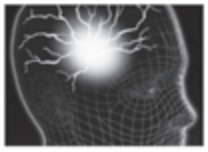
Values are given in number of responses.
De los Reyes E, et al. Ann Neurol;2015. Abstract 88.

Speech delay as first symptom

- Rapid decline in 36 months
  - Mean motor and language decline is 1,9 units/year in a scale of 6
- 83% of 36 patients had significant language delay before other symptoms
- It is important to ask if the patients had CLN2 typical EEG findings

Nickel M et al. Neuropediatrics 2016;47. Abstract FV04-3

10. Which is the most frequent seizure type?



a. Focal seizures
b. Myoclonic seizures
c. Absences
d. Generalized tonic-clonic seizures

LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS
EPILEPSY CHARACTERISTICS

- ✓ Epilepsy is present in all patients
- ✓ Can be preceded by febrile seizures or spontaneous focal seizures
- ✓ Myoclonia is the most characteristic symptom
- ✓ Other seizure types may occur, as generalized tonic-clonic, absences or even focal seizures
- ✓ Seizures are refractory to treatment

LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS
OTHER NEUROLOGICAL SYMPTOMS

- ✓ Ataxia
- ✓ Spasticity
- ✓ Involuntary movements
  - Myoclonia (epileptic and non-epileptic) is a characteristic of CLN2
  - Dystonia and spasticity are also common findings; chorea, atetosis and tremors are also seen. *Status distonicus* and myoclonic status may be life-threatening complications
  - Rarely, parkinsonism, prominent ataxia and chorea are also reported in atypical phenotypes

LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS

Psychomotor involution characteristics

The involution can be described in three phases:

1st phase -> loss of phrases, generally around 3 years of age

2nd phase -> loss of walking and verbal communication

3rd phase-> loss of sitting and use of the hands abilities and of sphincter control. Around 5 years of age patients become wheelchair bound and within months, dysphagic

Pérez-Poyato MS et al. *J Child Neurol* 2013;28(4):470

Clinical presentation CLN2- Summary

- Seizures or language delay
- Language developmental impairment
- Global developmental impairment
- Ataxia, movement disorders

CLN2- Development of symptoms

a. Sleumath R, et al. Curr Mol Med. 2014;14:1093-11; b. Schulz A, et al. Biochim Biophys Acta. 2011;1852:1805-1826; c. Ortiz A, et al. PLoS One. 2013;8:e73138; d. Williams RE, et al. Pediatr Neurol. 2017. [Epub ahead of print].

Noah died in March 2016, weeks before his 12nd. anniversary. Five months after his diagnosis, Laine, today 11, (left) also had CLN2 diagnosis

11. Among the avoidable diagnostic errors, which is the most common?

Jan Janský and Max Bielschowsky

a. Consider seizures as of unknown cause
b. Treat seizures with oxcarbazepine
c. Establish the diagnosis of progressive ataxia
d. Consider language impairment as a physiological language delay

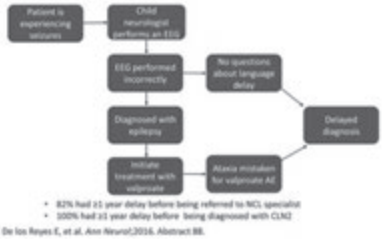
ANCILLARY EXAMS

12. After consider the CLN2 diagnosis, in which disease phase errors occur more often?

Jan Janský and Max Bielschowsky

a. On the EEG request
b. On the neurological examination
c. On the family history characterization
d. On the gestational antecedents

At diagnosis, which is the most frequent error?



- 82% had ≥1 year delay before being referred to NCL specialist
- 100% had ≥1 year delay before being diagnosed with CLN2

De los Reyes E, et al. Ann Neurol;2016. Abstract 88.

13. If I can make a mistake which is the correct form to request the EEG?

a. EEG under sedation
b. Waking and during somnolence and sleep EEG
c. EEG with hyperpnea activation
d. EEG with photic stimulation special characteristics

Diagnosis: EEG

- EEG is the first exam that should be requested
- Background slowing (can be normal in the 1st phase of disease, with generalized epileptiform activities predominating in the posterior areas
- 1-3 Hz photic stimulation
  - It is important to test all the frequencies, not to loose the key EEG characteristics

Fietz M et al. Mol Genet Metab 2016;119:160-7

Photosensitivity is an early marker of neuronal ceroid lipofuscinosis type 2 disease

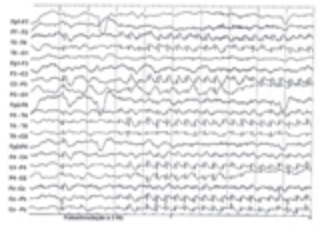
- ✓ N= 14 patients, 2005-2015; age at onset 3 years (2.0-3.8)
- ✓ **SYMPTOMS:**
- Developmental delay or regression, 100% at 3 years of age
- Epilepsy onset (50%) at 3.2 years of age (2.6-3.8). First seizure type:
  - Generalized: myoclonic in 36%, GTC in 29%, atonic in 22%
  - Focal with motor signs in 14%.
- ✓ Independent gait, 100% at 12 months of age
- ✓ **EXAMS**
- EEGs with photoparoxysmal response-> 93%
- First MRI: Cerebellar atrophy in 100%; White matter alteration -79%

Specchio N, et al . Epilepsia. 2017 Jun 20

How to request the EEG?

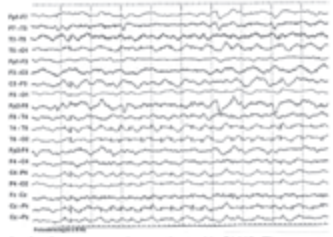
Waking and during somnolence and sleep EEG with photic stimulation emphasizing low flashes frequencies- 0.5/s, 1/s, 2/s and 3/s

Photic stimulation at low frequencies



Flash-per-flash photic response in a patient with CLN2. Giant evoked potentials in the occipital areas, following photic stimulation up to 3 flashes/s. The frequency is identical to that of the stimulation.

Photic stimulation at low frequencies

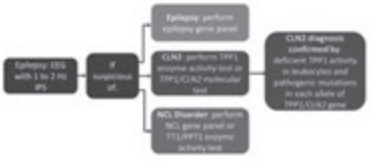


Flash-per-flash photic response in a patient with CLN2. These potentials present reduction in amplitude and are less correlated with the flashes when the frequency of stimulus increases.

14. After the EEG, how should I proceed?

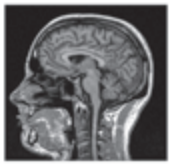
a. Request the dosage of TPP1
b. Request a molecular genetic test
c. Request a brain MRI
d. Request a brain PET

Diagnostic algorithm



Fietz M, et al. *Mol Genet Metab.* 2016;119:160-167.
Giugliani R, et al. *Mol Genet Metab.* 2016;117:S83. Abstract 143.

15. Are there suggestive signs in brain MRI?

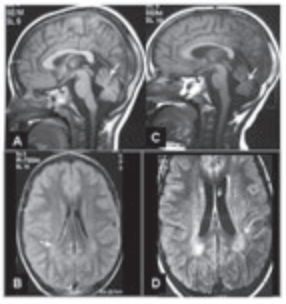


a. Yes, diffuse cortical atrophy
b. Yes, pathognomonic alterations in putamen
c. Yes, pathognomonic alterations in pons
d. No, there are no suggestive findings in image studies

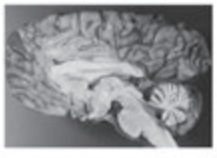
Brain MRI

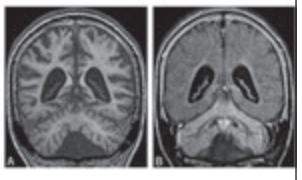
A and C – Grey matter progressive atrophy mainly of infratentorial structures

B and D – Hyperintense signal in periventricular white matter



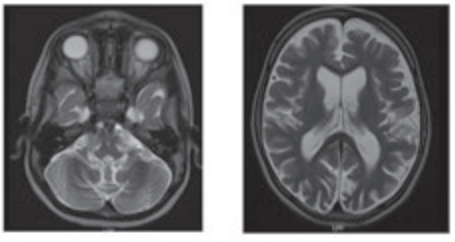
Pérez-Poyato MS et al. J Child Neurol 2012;28:470





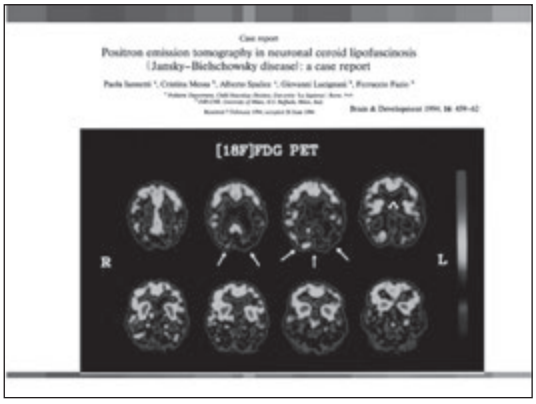
Infantile neuronal ceroid lipofuscinosis. Coronal T1 image (*A*) shows cerebral and cerebellar atrophy. Coronal FLAIR image (*B*) demonstrates diffuse abnormal signal intensity affecting the cortex of both cerebellar hemispheres. Compare the signal intensity of the cerebellar cortex with occipital cortex.

MRI CLN2

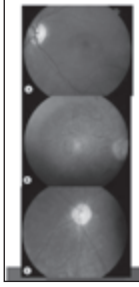


16. Are there other ancillary image studies?

a. Yes, brain PET
b. Yes, cavum XR
c. Yes, abdominal ultrasound
d. No, there are no other exams that could help diagnosing CLN2



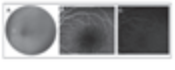
17. The child with CLN2 has visual loss. Is there retina cherry-red spot in CLN2 patients?



a. Yes, and is precocious in the disease course
b. Yes, and occurs late in the disease course
c. No, but there are other retinal alterations
d. The visual loss is due to cortical blindness

LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS

VISUAL DIAGNOSIS



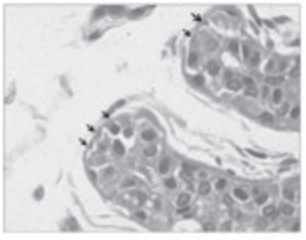
- ✓ Vision loss in CLN2 is secondary to progressive retina degeneration of uncertain pathophysiology
- ✓ CLN2 ophthalmologic manifestations are related to the degree of neurological dysfunction and patient's age and might be useful in the evaluation of new strategic therapeutics
- ✓ Evaluation
  - Visual evoked potential: increase latency
  - Coherence optical tomography: ocular abnormalities
  - Electroretinogram: reduced

Orlin A et al. PLoS One. 2013;8(8):e73126.

18. Of the methods below which would be useful in CLN2 diagnosis?

a. Skin or mucosa hystopathology
b. Electrocardiogram
c. Digestive endoscopy
d. Abdominal ultrasound

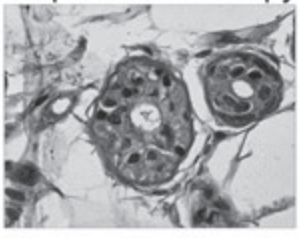
Optical microscopy



H and E, ×400. Section showed two eccrine ducts. Numerous eosinophilic inclusions are seen within the epithelial cell cytoplasm (arrows)

Verma et al. Annals of Indian Academy of Neurology 2013;16(2):282-285

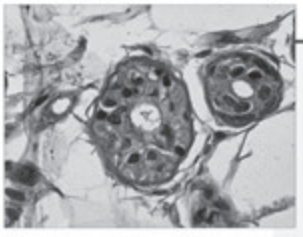
Optical microscopy



Periodic acid Schiff with diastase ×400. Section demonstrated two eccrine ducts in cross section. Arrows revealed rounded intracytoplasmic inclusions within the epithelial cells

Verma et al. Annals of Indian Academy of Neurology 2013;16(2):282-285

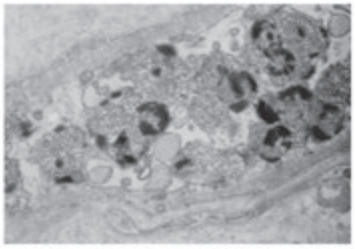
Optical microscopy



Periodic acid Schiff with diastase ×400. Section demonstrated two eccrine ducts in cross section. Arrows revealed rounded intracytoplasmic inclusions within the epithelial cells

Verma et al. Annals of Indian Academy of Neurology 2013;16(2):282-285

Electronic microscopy



Curvilinear inclusions in fibroblasts in one case of CLN2 mutation (ultrathin section stained with uranyl acetate and lead citrate, Â 42 000).

NEURONAL CEROID LIPOFUSCINOSIS TYPE 2

Atypical forms

✓ Atypical phenotypes are rarer, characterized by varied ages at onset and/or varied life expectance, such as:

- JUVENILE TYPE: more benign evolution, extrapyramidal predominance such as chorea, dystonia, parkinsonism
- ADULT TYPE: variant of spinocerebellar ataxia 7 (SCARF7), might no present epilepsy

✓ Some linked phenotypes to the amount of TPP1 deficiency:

1) CLN2, late infantile: "classic or severe" -> TPP1 undetectable

2) Juvenile CLN2, discrete onset or significantly later onset -> medium level of enzyme (10 a 15%)

3) Adult CLN2: ataxia (SCAR7) -> medium residual enzyme

Fietz M et al. Mol Genet Metab. 2016 ;119:160
Kohan R, et al. Biochim Biophys Acta. 2015;1852:2301

GENETICS

19. WHICH IS CLN2 INHERITANCE?

a. Autosomal recessive
b. Autosomal dominant
c. Sex linked
d. It is a *de novo* mutation

FAMILY PLANNING

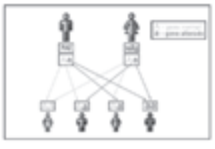
Tracy and Jennifer VanHouten, parents of Noah and Laine, with two other daughters

- Autosomal recessive
- Assess genetic risk for siblings, subsequent pregnancies, first-degree relatives
  - Early diagnosis important for addressing genetic risk for future children

Williams et al. Pediatric Neurol 2017;69:102-112.

DIAGNOSTIC CONCLUSIONS

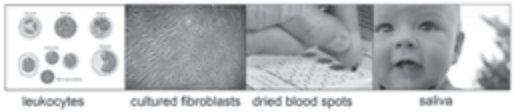
20. NOWADAYS WHICH OF THESE ANCILLARY EXAM IS CONSIDERED MORE DEFINITIVE FOR CLN2 DIAGNOSIS?



a. Molecular genetics
b. Cariotype
c. chromosomal microarray analysis
d.TPP1 assay

DIAGNOSIS- ENZYME ASSAY

- Tripeptidyl peptidase 1 (TTP1) levels can be measured in leukocytes, cultured fibroblasts, dried blood spots, and saliva. Fibroblast TTP1 activity is approximately 17,000 micromoles of amino acids produced per hour per mg of protein. The TTP1 activity in CLN2 is less than **4% of normal**.

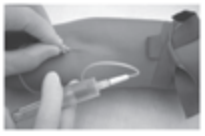


leukocytes cultured fibroblasts dried blood spots saliva

DIAGNOSIS- GENETICS

- DNA testing in peripheral blood lymphocytes may be used, as well as other tissues.

CLN2 gene localizes to chromosome 11p15.5



DIFFERENTIAL DIAGNOSIS

Differential Diagnosis

- Dravet syndrome
- LGS
- Doose syndrome
- Landau-Kleffner syndromes
- Other late infantile CLN
- Ohtahara or West syndrome (infants)
- GLUT1 deficiency
- Benign myoclonic epilepsies
- PMEs
- Channelopathies and metabolic syndromes associated with myoclonic epilepsy

Fietz M et al. Mol Genet Metab 2016;119:160-7

SYMPTOMATIC TREATMENT

21. WHICH OF THESE ANTIEPILEPTIC DRUGS SHOULD BE AVOIDED IN THE TREATMENT OF SEIZURES IN CLN2 PATIENTS SINCE THEY CAN AGRAVATE THEM?

a. Valproate
b. Carbamazepine
c. Levetiracetam
d. Phenobarbital

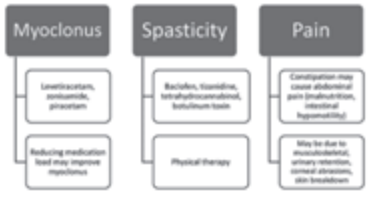
Jan Janský and Max Bielschowsky

Symptomatic treatment: EPILEPSY

- Epilepsy:
  - Valproate, lamotrigine, topiramate, levetiracetam, diazepam, lorazepam
  - Carbamazepine and phenytoin should not used
  - Often refractory
    - Using many medications may reduce QoL
    - AED efficacy variable throughout the disease

Schulz A, et al. *Biochim Biophys Acta*. 2013;1832:1801-1806.

Symptomatic treatment



Schulz A, et al. *Biochim Biophys Acta*. 2013;1832:1801-1806.

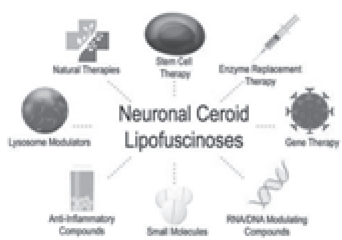
22. WHICH IS THE TREATMENT MODALITY FDA AND EMA APPROVED FOR CLN2 FDA?

a. Cerliponase alfa
b. Stem cells transplantation
c. CLN2 gene silencing
d. Gene therapy

Jan Janský e Max Bielschowsky

FUNCTIONAL TREATMENT

Moving towards effective therapeutic strategies for Neuronal Ceroid Lipofuscinosis



Geraets RD, et al. J Rare Dis. 2016;16;11:40.

NEURONAL CEROID LIPOFUSCINOSIS Therapeutical perspectives

1- ENZYME REPLACEMENT THERAPY – proteina recombinante palmitol tioesterase 1-> directed introduced in the CNS or a modified protein capable to cross the HE barrier for intravenous use

2- GENE THERAPY – functional copy of the defected gene is introduced in a cell through a vetor in such a way the diseased cell can syntetize its own enzyme. Nesta abordagem uma minoria das células no sistema nervoso central são transduzidas

3-Stem cell therapy -> into the CNS

4- TERAPIA COM PEQUENAS MOLÉCULAS que teriam função semelhante à enzima e reduziriam o acúmulo de material de depósito

5- COMBINED THERAPIES

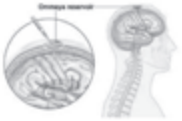
Sands MS. J Child Neurol 2013;28:1151

CLINICAL TRIALS IN NCL- PAST AND PRESENT

Trial ID	NCL Form(s)	Therapeutic Approach	Proposed Mechanism of Action	Preclinical Studies	Trial Phase
[illegible]	INCL	**Anti-inflammatory** Mycophenolate mofetil	Reduction in neuroinflammation and production of autoantibodies	Seehafer 2011 [illegible]	Recruiting
[illegible]	LINCL	**Gene Therapy** AAVrh.10CUhCLN2	Genetically engineer cells to produce non-mutated TPP1	Sondhi 2007 [illegible], Sondhi 2008, Sondhi 2012	Recruiting
[illegible]	LINCL	**Gene Therapy** AAVrh.10CUhCLN2	Genetically engineer cells to produce non-mutated TPP1	Sondhi 2007 [illegible], Sondhi 2008 [illegible], Sondhi 2012 [illegible]	Recruiting
[illegible]	LINCL	**ERT** BMN-190	Source of recombinant functional TPP1 in which diseased cell can uptake and utilize	Vuillemenot 2014 [illegible], Vuillemenot 2014 [illegible]	Active
[illegible]	LINCL	**Gene Therapy** AAV2CUhCLN2	Genetically engineer cells to produce non-mutated TPP1	Sondhi 2005 [illegible], Passini 2006 [illegible]	Active
[illegible]	INCL, LINCL	**Stem Cell** Human CNS Stem cells	Similar to ERT but, human CNS stem cells act as the source of functional PPT1 and TPP1	Tamaki 2009 [illegible]	Complete
[illegible]	INCL	**Small Molecule** Cystagon	Clears lysosome of storage material	Zhang 2001 [illegible]	Complete
[illegible]	INCL, LINCL	**Stem Cell** Human CNS Stem cells	Similar to ERT but, human CNS stem cells act as the source of functional PPT1 and TPP1	Tamaki 2009 [illegible], Selden 2013 [illegible]	Withdrawn

Geraets RD et al. Orphanet J Rare Dis. 2016;11:40

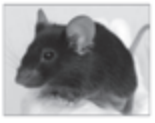
Enzyme replacement therapy Cerliponase alfa



- ✓ FDA and EMA approved
- ✓ Enzyme replacement: human TPP1 (produced through genetic engineer)
- ✓ **Cerliponase alfa intracerebro ventricular** (Ommaya reservoir)
- ✓ Dose: 300 mg fixe dosis
- ✓ Frequency: once each 2 weeks

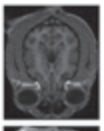
CLN2 MODELS ANIMALS REPRODUCING HUMAN DISEASE

- ✓ **Mice** TPP1-knockout (KO) have tremor, ataxia and neuronal loss
- ✓ **Dachshunds** *TPP1-null* have visual and cognitive deficits, ataxia, tremor, myoclonia and cerebral atrophy
- ✓ Deposit of autofluorescent bodies in the CNS in both models
- ✓ Reduced lifetime: mice, 120 days; dachshunds, 10-11 months

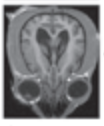


Sleat et al. Neurobiol Dis 2004
Awano et al. Mol Genet Metab 2006

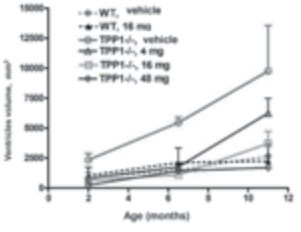
Dachshunds TPP1-null therapy



4 mg TPP1



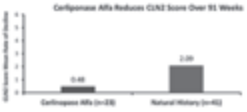
vehicle



✓ MRI showed that treatment with rhTPP1 delayed ventricular enlargement and cortical atrophy

Cedido pela BioMarin

ENZYME REPLACEMENT THERAPY



- Cerliponase alfa
  - Recombinant human TPP1 enzyme
- 300 mg cerliponase alfa every 2 weeks by ICV infusion for 48 weeks
- Nearly all had AEs, though most were grade 1 or 2

Cerliponase alfa was approved by the US Food and Drug Administration in April 2017.
Schulz A, et al. International Conference on Neuronal Ceroid Lipofuscinosis. Abstract O-48. 2016.

Importance
Early diagnosis
CLN2

Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis

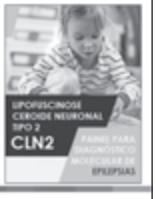
- ✓ Clinical suspicion-> The enzymatic activity of TPP1 should be one of the first tests performed (in conjunction with the palmitoyl-protein thioesterase enzyme activity assay to rule out CLN1 disease).
- ✓ A gene panel for childhood epilepsy research is highly recommended
- ✓ The gold standard for laboratory diagnosis: the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dry blood stains) and the identification of causal mutations in each allele of the TPP1/CLN2 gene.
- ✓ When it is not possible to perform both analyses, either demonstration of a) deficient TPP1 enzyme activity in leukocytes or fibroblasts, or b) detection of two pathogenic mutations in trans is diagnostic for CLN2 disease.

Fietz M et al. Mol Genet Metab 2016;119:160-7

Take home messages

- ✓ NCLs are rare diseases, probably underdiagnosed
- ✓ New therapies: nowadays delay deterioration
- ✓ **Early diagnosis in fundamental**
- ✓ **Epilepsy gene panel**

ADSL, AFG3L2, ALDH5A1, ARSA, ARX, ATM, ATP1A3, BSCL2, C10ORF2, **CDKL5**, CHD2, **CLN3**, CLN5, CLN6, CLN8, DCX, FA2H, FOLR1, GABRG2, GAMT, GATM, GRIN2A, HCN1, KCNA2, KCTD7, LMNB2, MECP2, MEF2C, MFSD8, PCDH19, PLA2G6, **POLG**, **PPT1**, PRDM8, PSAP, ROGDI, RPIA, **SCN1A**, **SCN8A**, SCN9A, SLC2A1, SLC6A1, SPTAN1, STXBP1, **TPP1**, UBE3A, GRIN2B, GABRA1, STX1B, GLB1, SCN2A



OMIKA -> Tel (11) 2385 – 6478
contato@omika.com.br

ACKNOWLEDGMENT

- To Tracy and Jennifer VanHoutan parents of Noah and Laine and creators of Noah Hope for education and development of research aimed at the treatment of CLN2

CONCLUSIONS

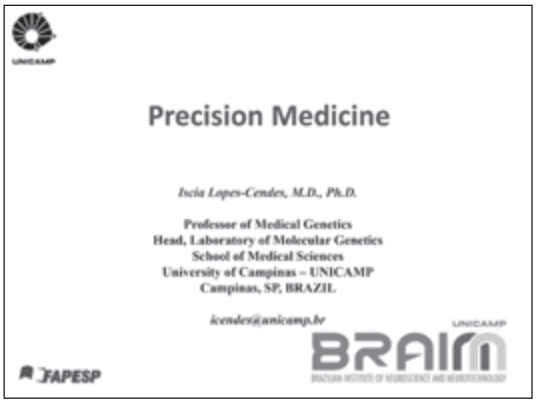
- CLN2 is a rare disease and diagnosis can be challenging
- Marked by seizures and language delay at the beginning
- Rapidly progresses, involving motor, visual, and language abilities
- Palliative care mindset
- Focus not on end of life, but more on QoL
- Investigational therapies are promising

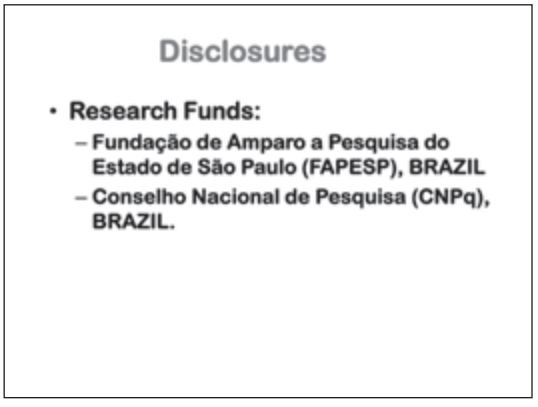
www.epilepsia.org.br
secretaria@epilepsia.org.br

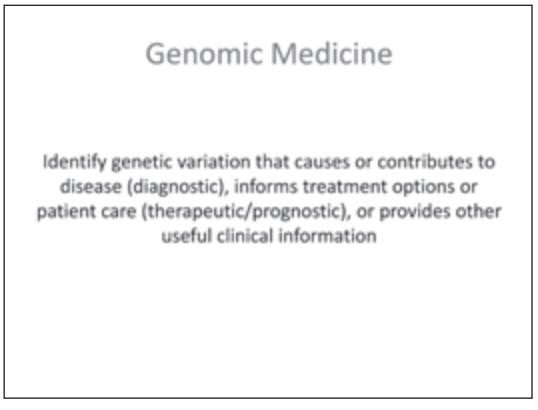
maria.manreza@hc.fm.usp.br
yacublan@terra.com.br

Iscia Cendes (Brazil)

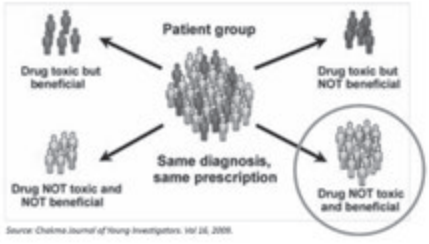
PRECISION MEDICINE: CONCEPT, APPLICATION AND THE BRAZILIAN INITIATIVE







Personalized Medicine



Source: Chakma Journal of Young Investigators. Vol 16, 2009.

Precision Medicine

Current medical practice

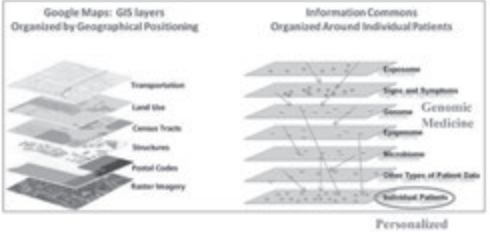
Use vital signs today relative to last visit; assess symptoms; physician uses expert background, experience and judgment to diagnose and prescribe

Precision medicine

Use massive data network that aggregates and analyzes information from huge patient cohorts, healthy populations, experimental organisms – and reaches toward disease mechanisms, and precision diagnosis and treatment for each individual

Modified from:Yamamoto et al. 2014

Precision Medicine



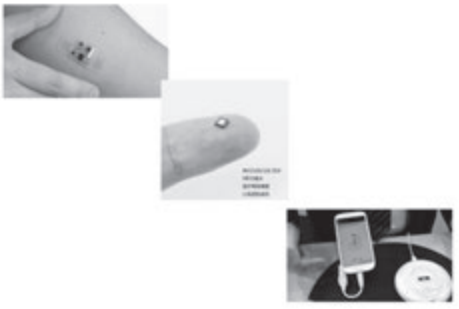
Yamamoto et al. 2014

Precision Medicine

* Diverse data types: *e.g., -omics, imaging (e.g., brain activity, longitudinal MRI), population studies, environmental effects.*
* Digital health: *wearable sensors (biosensors)*
* Data acquisition, aggregation, integration, analysis
* Data storage, security, selective access
* Data sorting and visualization
* **Data sharing**

Modified from:Yamamoto et al. 2014

Biosensors



Google Research Blog

Assisting Pathologists in Detecting Cancer with Deep Learning

Friday, March 03, 2017

Posted by Martin Stumpe, Technical Lead, and Lily Peng, Product Manager

A pathologist's report after reviewing a patient's biological tissue samples is often the gold standard in the diagnosis of many diseases. For cancer in particular, a pathologist's diagnosis has a profound impact on a patient's therapy. The reviewing of pathology slides is a very complex task, requiring years of training to gain the expertise and experience to do well.

To address these issues of limited time and diagnostic variability, we are investigating how deep learning can be applied to digital pathology, by creating an automated detection algorithm that can naturally complement pathologists' workflow. We used images (graciously provided by the Radboud University Medical Center) which have also been used for the 2016 ISBI Camelyon Challenge' to train algorithms that were optimized for localization of breast cancer that has spread (metastasized) to lymph nodes adjacent to the breast.

The results? Standard "off-the-shelf" deep learning approaches like Inception (aka GoogLeNet) worked reasonably well for both tasks, although the tumor probability prediction heatmaps produced were a bit noisy. After additional customization, including training networks to examine the image at different magnifications (much like what a pathologist does), we showed that it was possible to train a model that either matched or exceeded the performance of a pathologist who had unlimited time to examine the slides.

https://research.googleblog.com/2017/03/assisting-pathologists-in-detecting.html

Human genetics becomes GENOMIC (2001-2003)

- J. Craig Venter´s genome
- Sanger technology

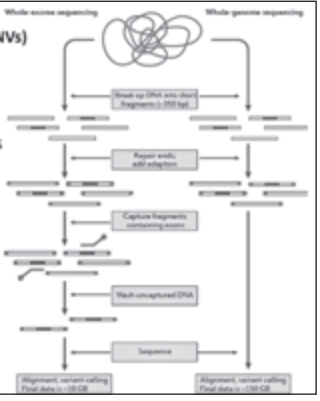
↓

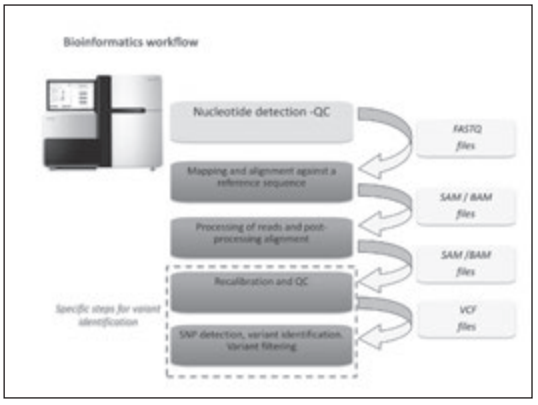
Genomic Medicine

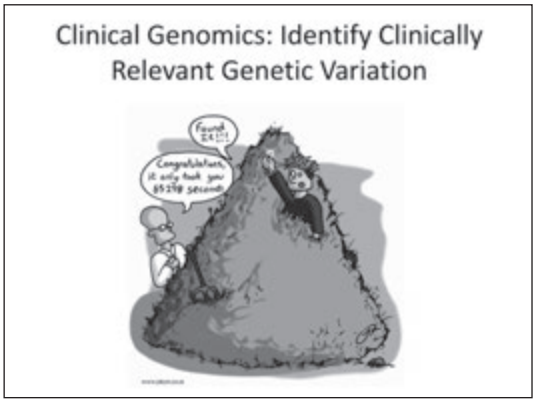
Finding genetic variants (SNVs) causing disease

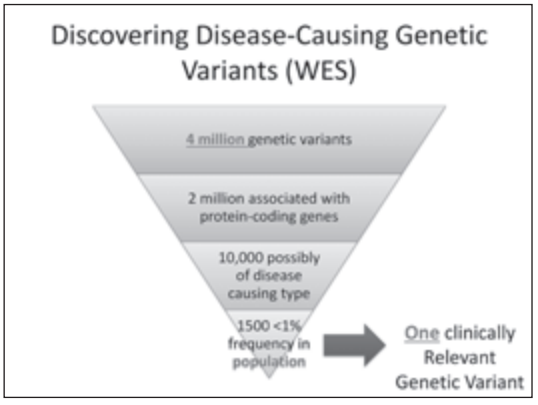
↓

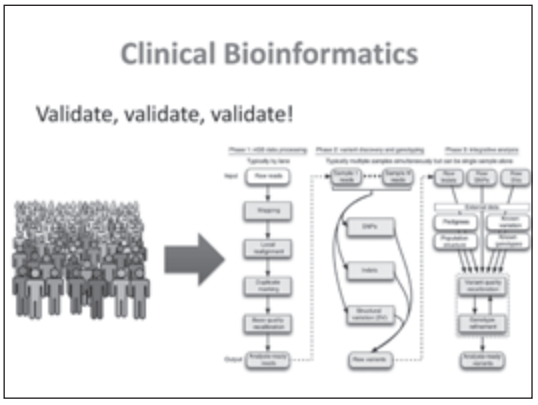
Two genomic strategies Applied to Medicine



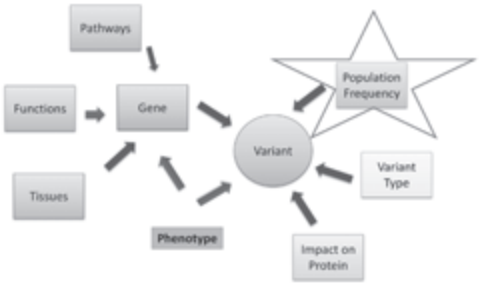

Bioinformatics workflow
Nucleotide detection -QC
FASTQ files
Mapping and alignment against a reference sequence
SAM / BAM files
Processing of reads and post-processing alignment
SAM /BAM files
Recalibration and QC
VCF files
Specific steps for variant identification
SNP detection, variant identification, Variant filtering


Clinical Genomics: Identify Clinically Relevant Genetic Variation
Found it!!!
Congratulations, it only took you 65298 second

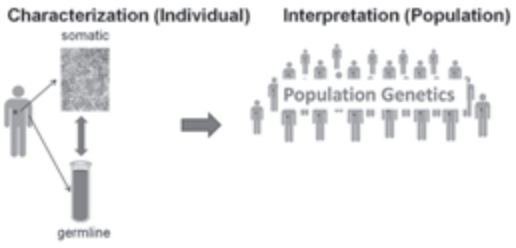

Discovering Disease-Causing Genetic Variants (WES)
4 million genetic variants
2 million associated with protein-coding genes
10,000 possibly of disease causing type
1500 <1% frequency in population
One clinically Relevant Genetic Variant


Clinical Bioinformatics
Validate, validate, validate!

Knowledge Required



Populations are Important



PLOS ONE

RESEARCH ARTICLE

A Prediction Algorithm for Drug Response in Patients with Mesial Temporal Lobe Epilepsy Based on Clinical and Genetic Information

Mariana S. Silva-Alves[1☯], Rodrigo Secolin[1☯], Benilton S. Carvalho[2], Clarissa L. Yasuda[3], Elisabeth Silvestrini[3], Marina K. M. Alvim[3], Renato O. Santos[3], Claudia V. Maurer-Morelli[1], Fernando Cendes[3], Iscia Lopes-Cendes[1]*

1 Department of Medical Genetics, University of Campinas—UNICAMP, and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, São Paulo, Brazil, 2 Department of Statistics, Institute of Mathematics, Statistics and Scientific Computing, University of Campinas—UNICAMP, and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, São Paulo, Brazil, 3 Department of Neurology, University of Campinas—UNICAMP, and the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Campinas, São Paulo, Brazil

☯ These authors contributed equally to this work.
* icendes@unicamp.br

PLOS ONE | DOI:10.1371/journal.pone.0169214 January 4, 2017

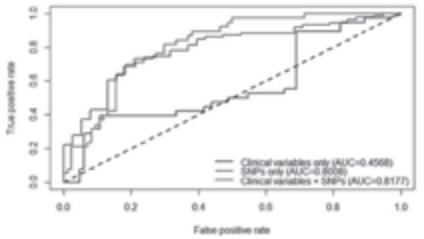


Fig 2. ROC curve showing the true positive rate (sensitivity), in function of false positive rate (1-specificity). The blue line indicates the prediction scenario using only clinical variables (hippocampal sclerosis, age of onset epilepsy, febrile seizures, and gender). The red line indicates the second scenario using the clinical variables plus SNPs. The dark green line indicates the scenario using only SNP genotypes. The area under the curve (AUC) values is showed for the three scenarios. The diagonal dashed line indicates a non-informative prediction (AUC = 0.5).

OPEN ACCESS Freely available online PLoS one

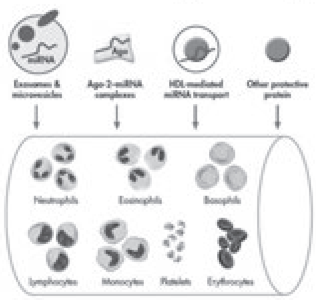
Serum MicroRNAs Are Promising Novel Biomarkers

Shlomit Gilad[1*], Eti Meiri[1*], Yariv Yogev[2], Sima Benjamin[1], Danit Lebanony[1], Noga Yerushalmi[1], Hila Benjamin[1], Michal Kushnir[1], Hila Cholakh[1], Nir Melamed[2], Zvi Bentwich[1+], Moshe Hod[2], Yaron Goren[1], Ayelet Chajut[1+]

September 2008 | Volume 3 | Issue 9 | e3148

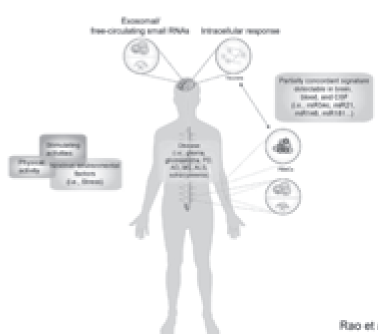
- MicroRNAs are specially enriched in plasma/serum (Chen et al., 2008);
- Blood circulating microRNAs are protected from RNAses by microvesicles, known exosomes (Valadi et al., 2007);
- Damaged tissue tend to liberated specific microRNAS in circulation, which can be used as biomarkers of disease state. (Cortez and Calin, 2009).

microRNA stability in body fluids



Shaffer et al., 2012

Plasma microRNA originate from primary tissue

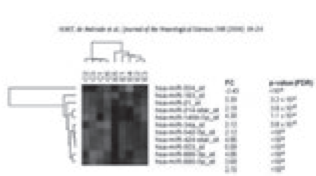


Rao et al, 2013

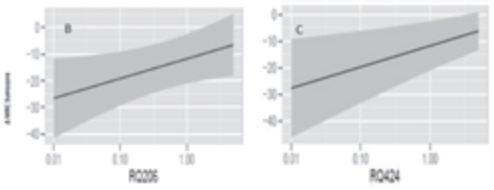
Journal of the Neurological Sciences

MicroRNAs-424 and 206 are potential prognostic markers in spinal onset amyotrophic lateral sclerosis

Helen M.T. de Andrade[a], Milena de Albuquerque[a], Simoni H. Avansini[b], Cristiane de S. Rocha[b], Danyella B. Dogini[b], Anamarli Nucci[a], Benilton Carvalho[b], Iscia Lopes-Cendes[b], Marcondes C. França Jr.[a,*]



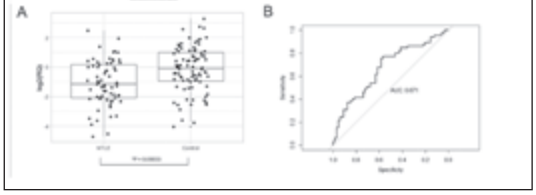
(B/C) Schematic plots showing the predicted variation of MRC sumscores after one year for a hypothetical patient according to the baseline levels of hsa-miR-206 (B) and hsa-miR-424 (C). These plots were obtained assuming that the values of MRC sumscore, disease duration and the expression levels of the other miR at baseline remained stable.



Andrade et al. 2016

PLOS ONE

MicroRNA hsa-miR-134 is a circulating biomarker for mesial temporal lobe epilepsy



FAPESP

BIPMed - Brazilian Initiative on Precision Medicine

BIPMed Brazilian Initiative on PRECISION MEDICINE

www.bipmed.org

Mission

- To help implement precision medicine in Brazil by acting as a catalytic element to foster collaboration among different stake holders (scientist, physicians, health authorities, hospitals, society)

First product: BIPMed genomic database

Technical Committee

- **Benilton de Sá Carvalho** – Assistant Professor – Institute of Mathematics, Statistics and Computer Sciences, University of Campinas (IMECC/UNICAMP)
- **Cristiane Rocha** – Research Associate, Biostatistics and Computation Biology Laboratory (BCB), School of Medical Science, University of Campinas (FCM/UNICAMP) – **PROJECT MANAGER**


BIPMed

Our Products:

- Genomic databases:
  - BIPMed-WES-db: REFERENCE POPULATION
  - BIPMed-Array-db: REFERENCE POPULATION
  - DISEASE SPECIFIC DATABASES
- BIPMed Beacon
- GA4GH R client
- .....

Disease/Phenotype specific projects

- Epilepsy (BRAINN, ILAE-ALADE) - EE
- Stroke (BRAINN, ISGC-Latin aAmerican Initiative)
- Cleft lip and palate (BCFP) – Dr. Vera Lopes
- BRCA – BRCA Challenge (GA4GH, HVP) – Dr. Patricia Prolla and Edenir Palmero
- Pathogenic hemoglobins – Global Globin (HVP) – Monica Melo
- ApoE Challenge (BRAINN, ABN) – Dr. Marcio Balthazar
- Pharmacogenomics (BRAINN, UNIFESP) – Marcelo Briones
- .....

Genomic Databases

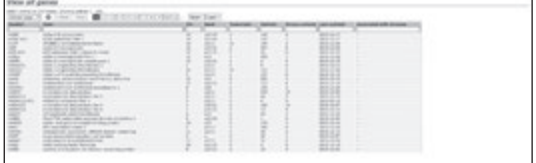
LOVD

- Lieden Open Variation Database
- Web-based gene sequence variation database
- Freely available tool for Gene-centered collection and display of DNA variations.

BIPMed

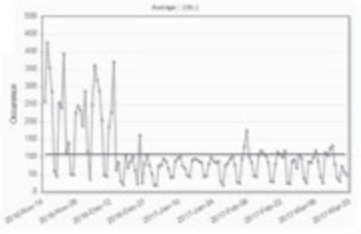
Brazilian Initiative on Precision Medicine

FAPESP

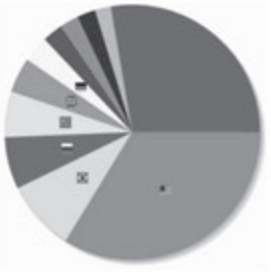


www.bipmed.org

Access Statistics



Countries		
United States	978	33.7 %
Brazil	262	9.0 %
Russian Federation	191	6.5 %
China	169	5.8 %
Great Britain	128	4.4 %
Germany	98	3.3 %
Italy	73	2.5 %
France	72	2.4 %
India	66	2.2 %
Spain	59	2.0 %
Others	803	27.6 %



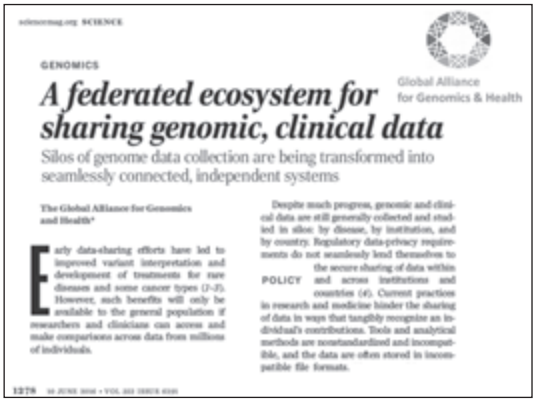
LEVELS OF ACCESS OF GENOMIC INFORMATION DEPOSITED IN THE BIPMED PUBLIC GENOMIC DATABASE

Level 1 or Unrestricted Access: This is the standard access level and it does not require user registration or authentication. Users can access polled statistics, list of variants; frequency. **Users do not have access to individualized data.**

Level 2 or Restricted Access: It requires registration and users can request access to files containing specific datasets. Registered users must sign a *Data Sharing Agreement*, which includes a confidentiality clause. Registered users can request Individual VCF files containing variants information.

Bottleneck Server – a.k.a. IP Throttling

- Beacon slows down requests, if too many come from the same IP. This prevents whole-genome queries for all alleles. This control is done by a "Bottleneck Server";
- Every time someone asks the Beacon one question, the Beacon asks the Bottleneck Server how many questions you already asked in the past and how long ago was the last question;
- If you asked (N+1) questions and waited K seconds between questions N and (N+1), then you will get an answer after (150N-10K) ms;
- If the wait time exceeds 20s, your IP will be blocked for a while and the answers will be much slower after your IP is unblocked.



sciencemag.org SCIENCE

GENOMICS

A federated ecosystem for sharing genomic, clinical data

Global Alliance for Genomics & Health

Silos of genome data collection are being transformed into seamlessly connected, independent systems

The Global Alliance for Genomics and Health*

Early data-sharing efforts have led to improved variant interpretation and development of treatments for rare diseases and some cancer types (1–3). However, such benefits will only be available to the general population if researchers and clinicians can access and make comparisons across data from millions of individuals.

Despite much progress, genomic and clinical data are still generally collected and studied in silos: by disease, by institution, and by country. Regulatory data-privacy requirements do not seamlessly lend themselves to the secure sharing of data within POLICY and across institutions and countries (4). Current practices in research and medicine hinder the sharing of data in ways that tangibly recognize an individual's contributions. Tools and analytical methods are nonstandardized and incompatible, and the data are often stored in incompatible file formats.

1278 10 JUNE 2016 • VOL 352 ISSUE 6291

Mission

Global Alliance for Genomics & Health

To accelerate progress in human health
by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data sharing projects that drive and demonstrate the value of data sharing

↓

Developing documents, products and supporting projects aiming to foster data-sharing

Demonstration Projects – Knowledge Exchanges

Global Alliance for Genomics & Health

The **Beacon Project** is an open web service that tests the willingness of international sites to share genetic data. It is being implemented on the websites of the world's top genomic research organizations.

Matchmaker Exchange is a federated network of databases whose goal is to find genetic causes of rare diseases by matching similar phenotypic and genotypic profiles.

The **BRCA Exchange (Challenge)** aims to advance understanding of the genetic basis of breast cancer and other cancers by pooling data on BRCA genetic variants from around the world, bringing together information on sequence variation, phenotype and scientific evidence. Improved understanding of genetic variation in these genes has the potential to improve patient diagnoses and prevention of disease.

Cancer Gene Trust

An emerging initiative in **Somatic Cancer** proposes to aggregate somatic cancer mutation data and some clinical data in order to improve the genomic landscape of actionability in some cancers and to enable greater personalized clinical care for individuals with rare cancer mutations.

BIPMed

BEACON

https://beacon-network.org

Find genetic mutations shared by these organizations

Beacon Adoption

Global Alliance for Genomics & Health

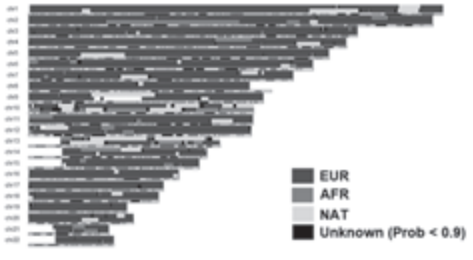
80+ Beacons

400+ Datasets

100,000+ Queries

250,000+ Individual Subjects

Genome-wide ancestral haplotypes



BRAIN

Acta Neurologica Scandinavica

DYSTONIA

New *THAP1* mutation and role of putative modifier in *TOR1A*

Piovesana LG, Torres FR, Azevedo PC, Amaral TP, Lopes-Cendes I, D'Abreu A. New *THAP1* mutation and role of putative modifier in *TOR1A*.
Acta Neurol Scand: DOI: 10.1111/ane.12379

L. G. Piovesana[1], F. R. Torres[2], P. C. Azevedo[2], T. P. Amaral[2], I. Lopes-Cendes[2], A. D'Abreu[1]

[1]Department of Neurology, University of Campinas (UNICAMP), Campinas, SP, Brazil, [2]Department of Medical Genetics, University of Campinas (UNICAMP), Campinas, SP, Brazil

BRAIN

In conclusion, our results indicate that although patients with dystonia in Brazil have clinical presentations similar to patients worldwide, the relative frequency of potentially deleterious mutations in *TOR1A* and *THAP1* is low. Interestingly, considering the results from our study as well as all studies performed previously in other Brazilian patients with dystonia, the frequency of DYT6 is higher than DYT1. These findings are relevant in clinical practice, since they are in conflict with the international recommendations for the genetic diagnosis of inherited isolated dystonia. Further studies, including samples from other Brazilian regions, as well as studies of additional genes recently implicated in dystonia may better answer which algorithm would be more appropriate for genetic testing of patients with dystonia in the Brazilian population.

ARTICLE IN PRESS

ELSEVIER

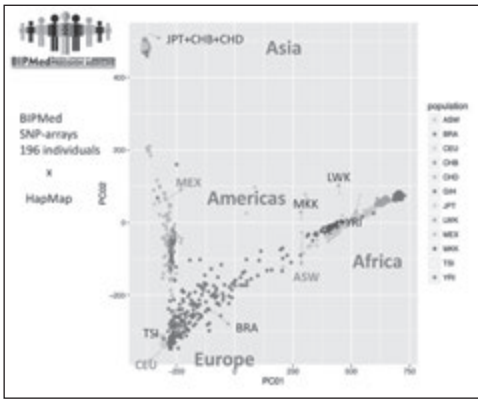
Cancer Genetics

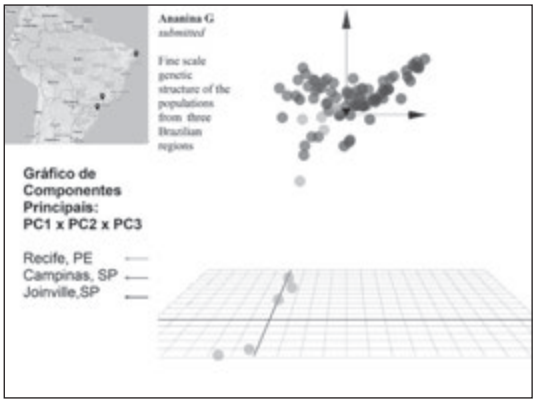
Cancer Genetics ■■ (2016) ■■–■■

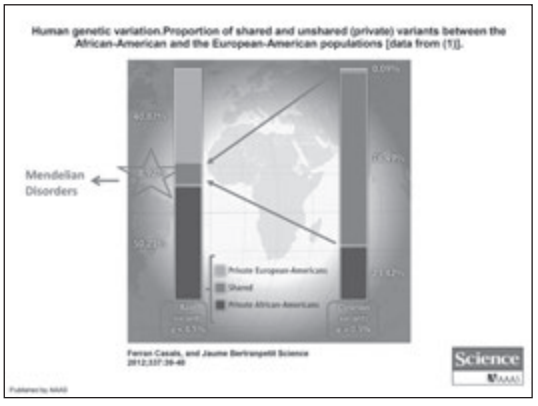
ORIGINAL ARTICLE

Prevalence of Hispanic *BRCA1* and *BRCA2* mutations among hereditary breast and ovarian cancer patients from Brazil reveals differences among Latin American populations

Bárbara Alemar [a,b], Josef Herzog [c], Cristina Brinckmann Oliveira Netto [d], Osvaldo Artigalás [e], Ida Vanessa D. Schwartz [a,d,f], Camila Matzenbacher Bittar [a], Patricia Ashton-Prolla [a,b,d,f,*], Jeffrey N. Weitzel [c]







LatinGen

- **AIM**: To support data-sharing in Latin America by fostering collaboration and integration among projects in different countries:
  - To facilitate integration between public databases already stablished in LA
  - To stimulate and support new initiatives by providing technical assistance (bioinformatics expertise) to implement and to integrate public databases in LA
  - Others ….

LatinGen

- Current participants
  - BRAZIL: BIPMed (www.bipmed.org)
  - CHILE: Dr. Gabriela Repetto
  - Mexico: Dr. Augusto Rojas-Martinez

- Additional groups that have demonstrated interest
- URUGUAY: Dr. Hugo Naya – (URUGENOMES)
- CHILE: Dr. Ricardo Verdugo – (CHILEGENOMICO)

GENÉTICA DE LAS ENCEFALOPATÍAS EPILÉPTICAS EN LA INFANCIA (EEI) EN AMÉRICA LATINA

Análisis molecular por secuenciación del exoma (Whole Exome Sequencing) para identificación de variantes potencialmente patogénicas.

UNICAMP

INTERNATIONAL LEAGUE AGAINST EPILEPSY ILAE

Iscia Lopes-Cendes, MD, PhD
Fernando Cendes, MD, PhD
Hebel Urquia-Osorio, PhD student

Laboratorio de Genética Molecular
Instituto Brasileiro de Neurociencias y Neurotecnologia (BRAINN)
Iniciativa Brasileña de Medicina de Precisión (BIPMed)
Faculdade de Ciencias Médicas, Universidad de Campinas (UNICAMP).

Conclusions

- Change in paradigm in Medicine
- Genomic Medicine is already a reality; however, to achieve Precision Medicine we need a higher level of integration of information from different sources (BIG Data). This includes Population Genetics!
- We are part of this global process with the launching of BIPMed and LatinGen, which is integrated within the GA4GH and other initiatives (HVP, IGM and others)

Visit us at

www.bipmed.org


Thank you
UNICAMP

Maria Roberta Cilio (USA)

PRECISION MEDICINE TREATMENT

Jaime Carrizosa (Colombia)

HOW DO HUMAN BEINGS CREATE? A NEURO-PSYCHOLOGICAL APPROACH TO CREATIVITY

¿Cómo crean los seres humanos?
Una aproximación neuro-psicológica a la creatividad

Jaime Carrizosa Moog
Profesor Titular
Neurología Infantil – Universidad de Antioquia
Medellín Colombia

LASSE 2018

Definición

La creatividad se define como el trabajo que produce algo novedoso, inesperado y original, que a su vez es útil en un contexto social determinado.

Dietrich A. The cognitive neuroscience of creativity. Psychon Bull Rev. 2004; 11 (6): 1011-1026.

PETER PAUL RUBENS
Los milagros de San Ignacio de Loyola – 1617, Amberes

¿Se puede medir la creatividad?

Tests de estimulación de pensamiento divergente

- Unusual Uses Test
- Torrance Test of Creative Thinking
- Remote Association Task
- Creative Achievement Test

¿Cuál es la relación entre inteligencia y creatividad?

BAGNI, PERUGIA – 1700
Exvoto - Per Grazia Ricevuta

SAN BENEDICTO CURA UN MONJE
Guarino Francesco, Campobasso
1700

Behavioral/Systems/Cognitive

Biochemical Support for the "Threshold" Theory of Creativity: A Magnetic Resonance Spectroscopy Study

Rex E. Jung,[1,2,3,4] Charles Gasparovic,[1,2] Robert S. Chavez,[1] Ranee A. Flores,[1] Shirley M. Smith,[1,2] Arvind Caprihan,[1] and Ronald A. Yeo[2]
[1]The Mind Research Network, and Departments of [2]Neurology, [3]Psychology, and [4]Neurosurgery, University of New Mexico, Albuquerque, New Mexico 87131

En personas creativas e inteligencia normal (IQ < 116), disminuye la expresión de NAA en la sustancia gris frontal derecha. Las personas más inteligentes y creativas (IQ >116) se diferenciaban por un incremento de NAA en la corteza frontal izquierda.

OPEN ACCESS Freely available online

PLoS one

Cerebral Blood Flow during Rest Associates with General Intelligence and Creativity

Hikaru Takeuchi[1]*, Yasuyuki Taki[2], Hiroshi Hashizume[2], Yuko Sassa[2], Tomomi Nagase[2], Rui Nouchi[2], Ryuta Kawashima[1,2,3]

[1]Smart Ageing International Research Center, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, [2]Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, [3]Faculty of Medicine, Tohoku University, Sendai, Japan, [4]Department of Functional Brain Imaging, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

El flujo sanguíneo cerebral en reposo se incrementa significativamente en la región perisilviana izquierda en personas inteligentes, mientas que se disminuye en el precuneo en personas creativas.

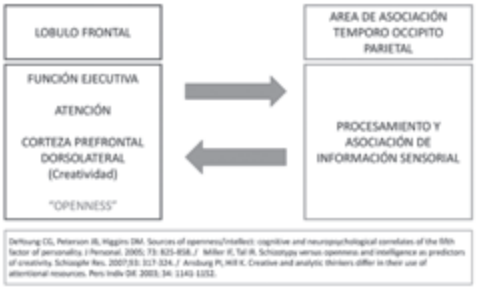
ELSEVIER

NeuroImage

Neural correlates of intelligence as revealed by fMRI of fluid analogies

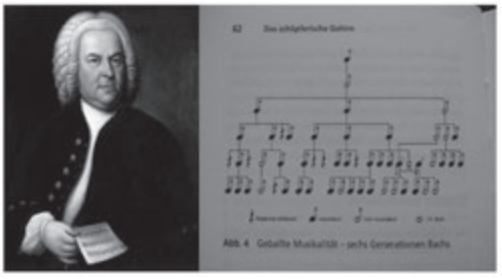
John G. Geake[a,c,*] and Peter C. Hansen[b,c]

Al realizar pruebas de analogías verbales, que requieren habilidades intelectuales y creativas, resalta la activación bilateral de los giros frontales superior, inferior y medio y de la corteza del cíngulo en la resonancia nuclear funcional. Estas zonas se han asociado con actividades de razonamiento abstracto como silogismos, sintaxis y creatividad lingüística.



DeYoung CG, Peterson JB, Higgins DM. Sources of openness/intellect: cognitive and neuropsychological correlates of the fifth factor of personality. J Personal. 2005; 73: 825-858. / Miller JF, Tal-Or N. Schizotypy versus openness and intelligence as predictors of creativity. Schizophr Res. 2007;93: 317-324. / Ansburg PI, Hill K. Creative and analytic thinkers differ in their use of attentional resources. Pers Indiv Dif. 2003; 34: 1141-1152.

¿CREATIVIDAD Y GENÉTICA??



Available online at www.sciencedirect.com
SciVerse ScienceDirect
Cortex

Clinical neuroanatomy

DRD2 polymorphisms modulate reward and emotion processing, dopamine neurotransmission and openness to experience

Marta Pecina[a], Brian J. Mickey[c], Tiffany Love[c], Heng Wang[a], Scott A. Langenecker[c], Colin Hodgkinson[b], Pei-Hong Shen[b], Sandra Villafuerte[a,c], David Hsu[c], Sara L. Weisenbach[c], Christian S. Stohler[a], David Goldman[b] and Jon-Kar Zubieta[a,c,d,*]

BRAIN RESEARCH

Research Report

Identification of first candidate genes for creativity: A pilot study

Martin Reuter*, Sarah Roth, Kati Holve, Jürgen Hennig

Genes DRD2 y TPH se asocian a creatividad en general

Alelo A1 de DRD2 se asocia a creatividad verbal

Alelo A del gen TPH1 se asocia a creatividad con figuras y números

OPEN ACCESS Freely available online

PLoS one

Musical Aptitude Is Associated with AVPR1A-Haplotypes

Liisa T. Ukkola[1*], Päivi Onkamo[2], Pirre Raijas[3], Kai Karma[4], Irma Järvelä[1,5]

1 Department of Medical Genetics, University of Helsinki, Helsinki, Finland, 2 Department of Biological and Environmental Sciences, University of Helsinki, Helsinki, Finland, 3 Sibelius Academy, Oodilka Department, Helsinki, Finland, 4 Sibelius Academy, Department of Music Education, Helsinki, Finland, 5 Laboratory of Molecular Genetics, Helsinki University Central Hospital, Helsinki, Finland

19 Familias, 343 personas, músicos profesionales o amateurs
Las funciones creativas musicales tienen una alta asociación genética.
Los haplotipos RS1 y RS2 de AVPR1A se asocia con varias pruebas musicales (Karma Music Test, Carl Seashores Test, Combined Music Test)
La percepción y producción musical se puede asociar a la teoría del apego relacionada con la vasopresina.

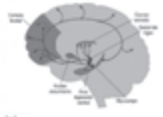
¿Y LA MOTIVACIÓN EN LA CREATIVIDAD?

La creatividad requiere de motivación además de inteligencia y apertura a experiencias nuevas

MOTIVACIÓN INTERNA

MOTIVACIÓN EXTERNA

MOTIVACIÓN INTERNA

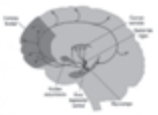


- Sistema mesolímbico dopaminérico
- Facilita comportamiento voluntario y propositivo
- Avidez por recompensa – satisfacción
- Inhibe otros intereses en competencia
- Estable hasta la adolescencia – aprendizaje
- Curiosidad exploratoria

⬆ Creatividad

Flaherty, 2005; Hamid et al, 2016; Mroß, Santucci & Baldassarre, 2013; Leppan, Greene & Nisbett, 1973; Deci, 1971; Prabhu, Sutton & Sauser, 2008; Hennessy

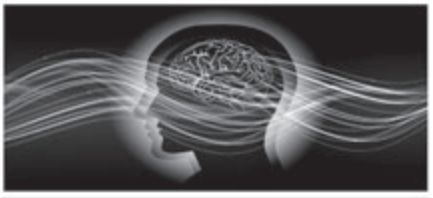
MOTIVACIÓN EXTERNA



- Una recompensa externa disminuye la magnitud del interés e ímpetu de una actividad propuesta

⬆ Eficiencia del trabajo

Amabile & Martinage, 1989; Bromberg-Martin & Hikosaka, 2009



"F L O W"

El estado de motivación intrínseca de mayor expresión atencional en una actividad, donde deja de lado la percepción del entorno y de si mismo, y el trabajo fluye sin mayor exigencia, ni sensación de laxitud, se denomina *flow*.

Características del "flow"

1. La actividad tiene un objetivo claro
2. Existe una retroalimentación inmediata sobre la efectividad de la acción
3. La exigencia de la actividad concuerda con la capacidad de la persona para realizarla
4. El pensamiento está totalmente ocupado con la acción
5. No existe temor al fracaso
6. Las necesidades personales/fisiológicas pasan a un segundo plano u "olvido"
7. No hay conciencia del tiempo
8. La actividad tiene una interés propio

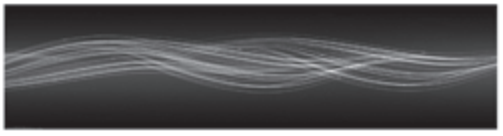
NEUROIMAGENES FUNCIONALES EN "FLOW"

Aumento de actividad en giro frontal anteroinferior y putamen izquierdos	• mayor control cognitivo • éxito probabilístico en la tarea asignada • afecto positivo, buena autoestima y satisfacción y bienestar psicológico
Reducción de la actividad en la corteza prefrontal medial y de la amígdala	• reducción en el procesamiento de la información autoreferencial • disminución de emociones negativas

Dietrich, 2004; Ulrich, Keller, Hoenig, Waller & Grön, 2014; de Manzano, Cervenka, Jucaite, Hellenäs, Farde & Ullén, 2013

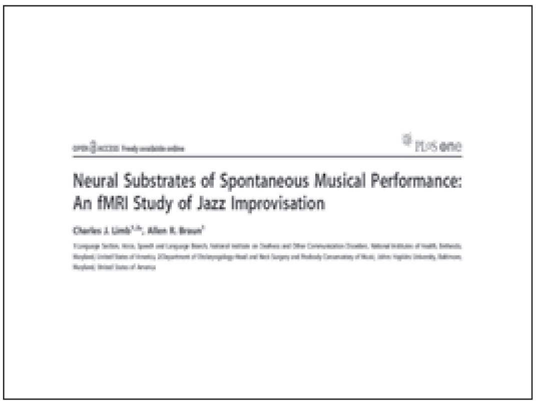
Hasta ahora la evidencia señala que el *flow* permite disfrutar de la creatividad, que incrementa la producción creativa, pero al parecer no genera las nuevas ideas propias de la creatividad

(MacDonald, Byrne & Carlton, 2006; Csíh, Philipps & Pearson, 2015).



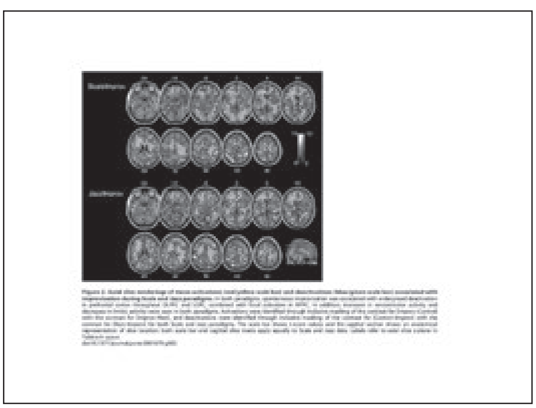
"A mis 38 años y ya con cuatro libros publicados desde mis 20 años, me senté en mi máquina de escribir y empecé: "Muchos años después, frente al pelotón de fusilamiento, el coronel Aureliano Buendía había de recordar aquella tarde remota en que su padre lo llevó a conocer el hielo". No tenía la menor idea del significado ni del origen de esa frase ni hacia dónde debía conducirme. Lo que hoy sé es que no dejé de escribir durante 18 meses hasta que terminé el libro. [...]"

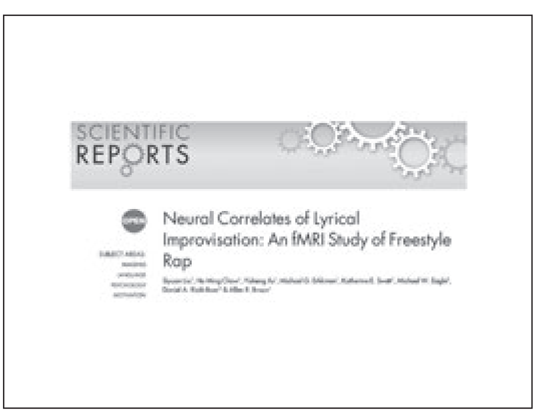
¿EXISTE UN HEMISFERIO CREATIVO?


PLoS one

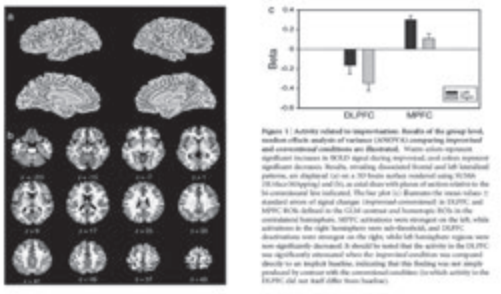
Neural Substrates of Spontaneous Musical Performance: An fMRI Study of Jazz Improvisation

Charles J. Limb, Allen R. Braun




SCIENTIFIC REPORTS

Neural Correlates of Lyrical Improvisation: An fMRI Study of Freestyle Rap



EUREKA

"¿Pero cuándo nació Harry?

" En un viaje de Manchester a Londres la asaltó la idea y le pareció que le sería divertido escribir una historia sobre un joven mago en una escuela de brujería. La desesperación le asaltó cuando se dio cuenta que no tenía una libreta a mano (siempre la tenía!)... pero ella comenta que así fue mejor, porque durante el viaje ideó gran parte de la serie... "

Algunos artistas y científicos obtienen sus creaciones de manera súbita, casi inesperada, como una especie de iluminación o revelación. A diferencia del pensamiento divergente, donde múltiples opciones se abren a una situación, en el discernimiento interior (*insight*), todo el pensamiento se vuelca de manera integral y sencilla a una sola salida o solución abrupta.

Kleibeuker, De Dreu & Crone, 2013; Jung-Beeman et al, 2004; Bowden & Beeman, 2003; Chi & Snyder, 2011

¿Y LA IMAGINACIÓN?

La **imaginación** es un proceso psicológico superior que permite al individuo manipular información generada intrínsecamente con el fin de crear una representación percibida por los sentidos de la mente. Esta representación (intrínsecamente generada) significa que la información se ha formado dentro del organismo en ausencia de estímulos del ambiente.

29

British Journal of Psychology (2003), 94, 29–44
© 2003 The British Psychological Society
www.bps.org.uk

Mental imagery and creativity: A meta-analytic review study

Nicholas LeBoutillier[1]* and David F. Marks[2]
[1]Middlesex University, UK
[2]City University London, UK

3 % ?

EJN

COGNITIVE NEUROSCIENCE

Brain networks underlying mental imagery of auditory and visual information

La imaginación demuestra la activación de áreas con funciones de atención (lóbulo frontal, ganglios basales), memoria (lóbulos temporales), preparación motora (corteza premotora) y áreas de asociación (corteza temporo occipito parietal).

La imaginación auditiva suprime parcialmente áreas de procesamiento visual y viceversa. La imaginación visual y auditiva disminuye la actividad de las cortezas primarias de la visión y audición

¿SE PUEDE PROMOVER LA CREATIVIDAD?

RESEARCH REPORT

Give Your Ideas Some Legs: The Positive Effect of Walking on Creative Thinking

Marily Oppezzo and Daniel L. Schwartz
Stanford University

Four experiments demonstrate that walking boosts creative ideation in real time and shortly after. In Experiment 1, while seated and then when walking on a treadmill, adults completed Guilford's alternate uses (GAU) test of creative divergent thinking and the compound remote associates (CRA) test of convergent thinking. Walking increased 81% of participants' creativity on the GAU, but only increased 23% of participants' scores for the CRA. In Experiment 2, participants completed the GAU when seated and then walking, when walking and then seated, or when seated twice. Again, walking led to higher GAU scores. Moreover, when seated after walking, participants exhibited a residual creative boost. Experiment 3 generalized the prior effects to outdoor walking. Experiment 4 tested the effect of walking on creative analogy generation. Participants sat inside, walked on a treadmill inside, walked outside, or were rolled outside in a wheelchair. Walking outside produced the most novel and highest quality analogies. The effects of outdoor stimulation and walking were separable. Walking opens up the free flow of ideas, and it is a simple and robust solution to the goals of increasing creativity and increasing physical activity.

La actividad física facilita la creatividad:

disipar la función ejecutiva por la multiplicidad de funciones a desarrollar (caminar y crear)

un buen ánimo por el ejercicio incentiva la ideación de nuevas ideas

la relajación en la supresión de memoria permite el surgimiento de nuevas ideas asociativas

el ejercicio incrementa la función de memoria en el hipocampo

Opezzo & Schwartz, 2014; Baas, De Dreu & Nijstad, 2008; Steinberg, Sykes, Moss, Le Boutillier & Dewey, 1997; Chrysikou & Thompson-Schill, 2011; Erickson et al, 2011

OPEN ACCESS Freely available online

PLOS ONE

Creativity in the Wild: Improving Creative Reasoning through Immersion in Natural Settings

Ruth Ann Atchley[1], David L. Strayer[2*], Paul Atchley[1]

[1]Department of Psychology, University of Kansas, Lawrence, Kansas, United States of America, [2]Department of Psychology, University of Utah, Salt Lake City, Utah, United States of America

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Multicultural Experience Enhances Creativity

The When and How

Angela Ka-yee Leung — *Singapore Management University*
William W. Maddux — *INSEAD*
Adam D. Galinsky — *Northwestern University*
Chi-yue Chiu — *University of Illinois at Urbana-Champaign*

NeuroImage 52 (2010) 319–327

Contents lists available at ScienceDirect

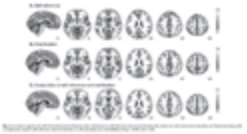
NeuroImage

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

Mapping the self in the brain's default mode network

Christopher G. Davey[a,b,c,*], Jesus Pujol[d], Ben J. Harrison[a]

En los momentos de relajación, distracción u ocio, en los que no se requiere una atención sostenida y dirigida, se activan las cortezas prefrontal medial, del cíngulo y el precuneo, constituyendo la denominada red neuronal por defecto (Default Mode Network – DMN).



La red está implicada en funciones de autoconciencia, autopercepción, autoreferenciación temporal y espacial, introspección, recuperación de la memoria autobiográfica y de los deseos, sueños, miedos.

Su actividad permite la ensoñación, "el soñar despierto". Su mayor actividad se relaciona con el cociente intelectual, la apertura a nuevas experiencias y la aparición de ideas libres de perjuicio moral; las condiciones previamente descritas son propicias para la creatividad.

Davey, Pujol & Harrison, 2016; Cavanna & Trimble, 2006; Baird, Smallwood, Mrazek, Kam, Franklin & Schooler, 2012; Hearne, Mattingley & Cocchi, 2016; Baety, 2016

La misma red mantiene la actividad durante la etapa del sueño de movimientos oculares rápidos o sueño MOR, y aquellas personas que logran recordarse con mayor frecuencia de sus sueños, tienen una apertura a experimentar cosas novedosas y una mayor creatividad.

Eichenlaub, Nicolas, Daltrozzo, Redouté, Costes & Ruby, 2014; Watson, 2003

EPILEPSIA Y CREATIVIDAD

Brainstorm in a teacup: can epilepsy fuel creativity?

"Having controlled my epilepsy myself for years, without medication and with reasonable success, I recently made the decision to start taking medication again. And it worked. More or less. I've had a couple of seizure in the past couple of years, but only under extreme pressure.

But the big ideas have also stopped. The weird and wonderful connections that made my work different have seemingly dried up. It could be writers block or it could be coincidence, but I suspect that it has something to with the meds.

The question is, am I willing to risk stability for wild ideas? The ability to get up early for bleary-eyed gibberish? And the truth is – I don't know."

Dan Mitchell is a comedian and actor, and is on Twitter as @epsilyptic

Epilepsy and Creativity: Finding My Voice

"One particular aspect of my life that the brain fog has affected has been my creativity. Along with many people with epilepsy who are drawn to the arts, I've always wanted to be a creative writer. Some neurologists have said that those with temporal lobe epilepsy in particular have a "disorder" called a hypergraphia, a nearly uncontrollable compulsion to write. Whether I have a disorder or not, I know only that I feel a need, a calling, to write and that the side effects of my medications have inhibited my ability to find the right words."

Under the Hood
Could Prince's Epilepsy Have Contributed To His Creativity? How The Seizure Disorder Can Affect Artists

"Prince himself once said his colorful onstage personality was a way to compensate for his illness. It's no surprise then, as Slate correspondent Katy Waldman pointed out, his songs often evoked "a hallucinatory scene" and "invited you into an altered state of consciousness." Some experts and patients suggest epilepsy can spur creative impulses in the brain, where the chronic disorder originates."

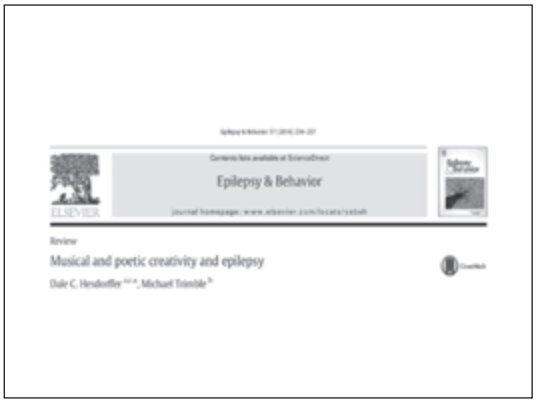
In the Temporal Lobes, Seizures and Creativity

By NATALIE ANGIER
Published: October 12, 1993

"Although the seizures may be undetectable to observers, they can prompt symptoms like hallucinations, powerful religious sensations, fury, fear, joy and -- a blessing for those in the arts -- an unquenchable desire to write or draw, a desire that persists even after the seizure is over."

Epilepsy & Behavior

Is there a creative functional paradoxical facilitation in juvenile myoclonic epilepsy?



Epilepsy & Behavior

Review

Musical and poetic creativity and epilepsy

Dale C. Hesdorffer, Michael Trimble

Epilepsy & Behavior

Review

Epilepsy treatment and creativity

Sarah Zublov, Daniel Friedman

Epilepsy & Behavior

Effect of vagus nerve stimulation on creativity and cognitive flexibility

Georges A. Ghazleh, Joel I. Shenker, Brian Shenal, Basim M. Uthman, Kenneth M. Heilman

Epilepsy & Behavior

Letters to the Editor

Dramatic changes in artistic preference after left temporal lobectomy

Fernando Cendes (Brazil)

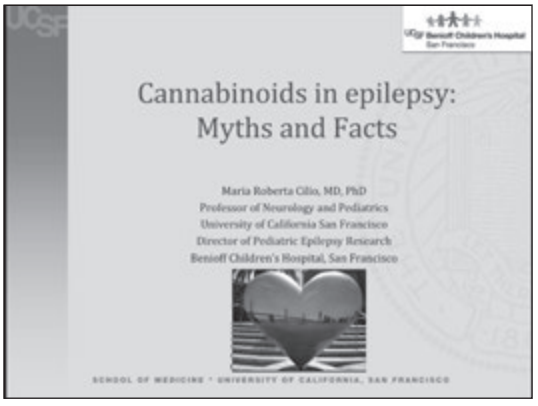
ABERRANT 'IN VIVO' FUNCTIONAL CONNECTIVITY IN EPILEPSY AND ITS RELATIONSHIP WITH COGNITION

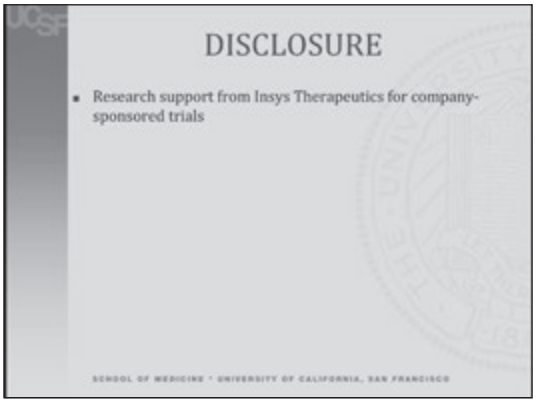
Fulvio Scorza (Brazil)

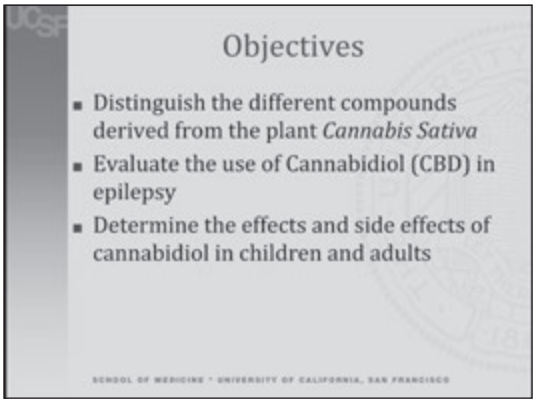
SUDDEN DEATH IN EPILEPSY ON THE HORIZON: ARE WE SPEAKING THE SAME LANGUAGE?

Maria Roberta Cilio (USA)

CANNABINOIDS IN THE TREATMENT OF EPILEPSIES







CONTROVERSY IN EPILEPSY

The case for assessing cannabidiol in epilepsy

*Maria Roberta Cilio, †Elizabeth A. Thiele, and ‡Orrin Devinsky

- The media hype: high expectations for cannabidiol as a potential therapy for epilepsy
- The naturalistic fallacy
  - It is natural and organic: it must be good
    - Not perceived as a drug but a natural remedy
    - It works better alone
- Impact on increased placebo rate in trials
- Perception that the medication used is novel or has very potent characteristics
- The degree of positivity with which a treatment is presented

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The case and the challenges for assessing cannabidiol in epilepsy

- CBD ≠ Marijuana
- DEA Schedule 1 substance – license and safe
- Children
- FDA approval
- Internal approval
- Import from the UK
- Traveling within the US
- Foundations have expressed "legal" concerns – study is unfunded


epilepsy.com

NEW TREATMENT FOR INTRACTABLE SEIZURES IN CHILDREN BEGINS CLINICAL TRIALS

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The context

September 2013

" This is a very sensitive issue for those of us practicing in Colorado as we have kids streaming in from all over the country whose parents bring them here to get "Charlotte's web". We are aware of more kids who have not responded than the few who have and made CNN.

I would love to refer some of these patients to be a part of a good clinical study instead of being given it in an uncontrolled and in my opinion unsafe fashion by someone in Colorado Springs with no knowledge or experience in care of epilepsy patients."

AES member

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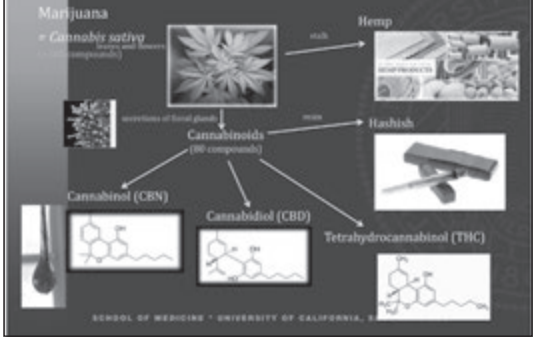
What is CBD?



SCHOOL OF MEDICINE • UNIVERSITY OF CALIFORNIA, S

Cannabis-based compounds

Product	Content
Recreational marijuana	THC >> CBD
Most "medical" marijuana	THC >> CBD
CBD-enriched cannabis extracts (e.g. Charlotte's Web™)	CBD >> THC
Epidiolex© (GW Pharma)	Almost pure (98%) CBD, plant-derived –pharmaceutical preparation
Oral Solution (Insys)	Synthetic CBD, pure – pharmaceutical preparation

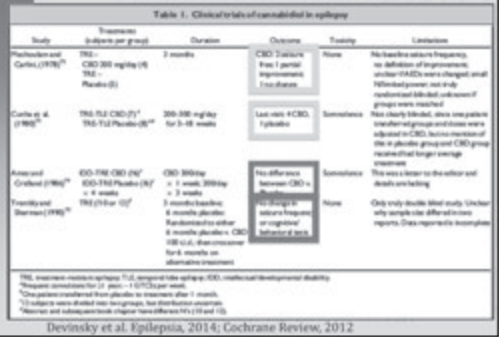
Cannbidiol is not "medical marijuana"

- Significant variability in artisanal "medical marijuana" preparations
- What about those >500 other chemical in cannabis?
  - Could some of them or some combination be more effective?
  - Be more toxic?
  - Need for reproducible, pharmaceutical-grade, CBD

- A 2015 FDA analysis showed that six (33%) of 18 over the-counter cannabidiol preparations contained no cannabinoid.

US Food and Drug Administration. Warning letters and test results.2015. http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm (accessed May 6, 2015)

Little RCT evidence



Devinsky et al. Epilepsia, 2014; Cochrane Review, 2012

The pharmacological basis of cannabis therapy for epilepsy

- CBD is anticonvulsant, but it has a low affinity for the cannabinoid receptors CB1 and CB2
- Despite its low affinity for CB receptors, CBD can produce effects at reasonably low concentrations and in fact, in the low nanomolar range CBD it alters the binding of agoniststo the CB1/CB2 receptors (Thomas et al, 1998)
- Identification of mechanisms underlying the anticonvulsant efficacy of CBD is also critical for identifying other potential treatment options

Reddy and Golub, *J Pharmacol Exp Ther.*, 2016

Cannabidiol: possible mechanisms of action

- The exact mechanism by which it affects seizures remains poorly understood
- Decreases presynaptic release of glutamate
- Inhibits adenosine reuptake
- Activate %HT 1A receptors
- Anti-inflammatory?
- Antioxidant?
- Modulation of mTOR pathway?
- ????
- A rigorous clinical evaluation of pharmaceutical CBD products is needed to establish the safety and efficacy of their use in the treatment of epilepsy


Epilepsy & Behavior

Brief Communication

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

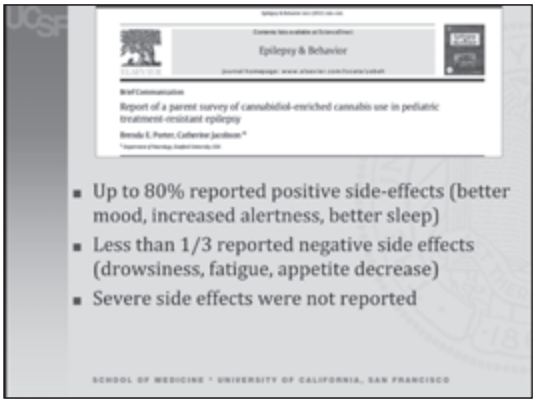
- US survey of 19 parents using artisanal preparations of CBD-enriched cannabis to treat their children with treatment-resistant epilepsy aged 2-16 years
- 12/19 had Dravet syndrome
- 4 patients had Doose syndrome
- 1 had Epilepsy in Females with Mental Retardation
- 1 had Lennox-Gastaut Syndrome
- 1 had idiopathic epilepsy


Epilepsy & Behavior

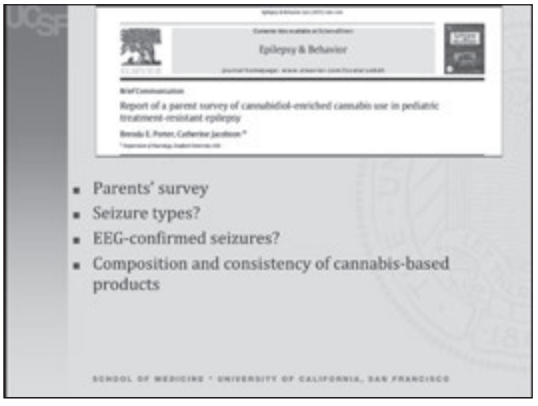
Brief Communication

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

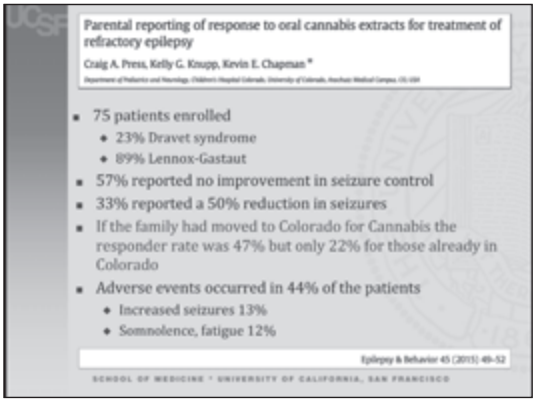
- 2 patients were reported to be seizure-free (1 Doose, 1 Dravet syndrome)
- 8 had a reduction in seizure frequency > 80% (5/12 patients with Dravet syndrome)
- 3 had a reduction > 50% (Dravet syndrome)
- 3 had a reduction > 25%
- 3 patients experience no change (2 Dravet syndrome, 1 Doose)



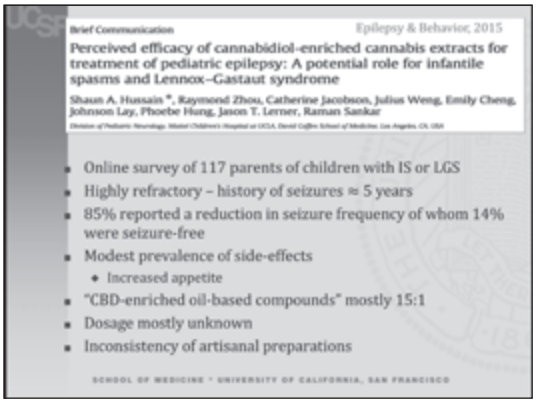
- Up to 80% reported positive side-effects (better mood, increased alertness, better sleep)
- Less than 1/3 reported negative side effects (drowsiness, fatigue, appetite decrease)
- Severe side effects were not reported



- Parents' survey
- Seizure types?
- EEG-confirmed seizures?
- Composition and consistency of cannabis-based products



- 75 patients enrolled
  - 23% Dravet syndrome
  - 89% Lennox-Gastaut
- 57% reported no improvement in seizure control
- 33% reported a 50% reduction in seizures
- If the family had moved to Colorado for Cannabis the responder rate was 47% but only 22% for those already in Colorado
- Adverse events occurred in 44% of the patients
  - Increased seizures 13%
  - Somnolence, fatigue 12%



- Online survey of 117 parents of children with IS or LGS
- Highly refractory – history of seizures ≈ 5 years
- 85% reported a reduction in seizure frequency of whom 14% were seizure-free
- Modest prevalence of side-effects
  - Increased appetite
- "CBD-enriched oil-based compounds" mostly 15:1
- Dosage mostly unknown
- Inconsistency of artisanal preparations

FULL-LENGTH ORIGINAL RESEARCH

Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients

- 18-month retrospective chart review of 119 children with epilepsy whose parents indicated they were administering cannabis-derived compound
- Parental report of seizure frequency
- Responders > 50% reduction in seizure frequency
- 49% reported some improvement
- 24% were responders
- Best responders: LGS
- 19% adverse events

FULL-LENGTH ORIGINAL RESEARCH

Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients

- Adverse events:
  - 8% seizure worsening
  - 6% somnolence
  - 5% gastrointestinal
- 71% discontinued cannabis extract during the study period
  - 13% had an adverse event
  - 10% had Dravet diagnosis
- 57% of the 23 patients with AD discontinued

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FULL-LENGTH ORIGINAL RESEARCH

Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients

- Discontinuation of oral cannabis extracts is common in pediatric epilepsy patients
- Continuation of use is predicted by perception of benefits on seizure burden
- Only factor predicting perceived benefit was relocation to Colorado
  - 67% vs 38% *p=0.001*
- Factors associated with shorter use included adverse events (*p=0.03*) and Dravet syndrome (n=17) (*p=0.02*)

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Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

- Cannabidiol 98% – Epidiolex® GW Pharma in sesame oil
- Age: 1-22 years
- 1-7 concomitant AEDs
- Starting dose: 2-5 mg/kg/day
- Weekly increased by 5 mg/kg/day up to 25 mg/kg/day
- In most cases, doses of concomitant AEDs were kept constant
- Motor seizures were counted
- Seizure diary

www.thelancet.com/neurology Published online December 23, 2013


Patients enrolled in Epidiolex Expanded Access Program as of 1/15/2015 (N=214)
Enrolled after 9/23/15 – did not have 12 weeks of follow-up after 1st dose of CBD (N=52)
Analysis for safety and tolerability (N=162)
Excluded from efficacy analysis
Age < 1 (N=1)
Progressive disorder (NCL) (N=2)
No "motor" seizures (N=23)
Analysis for efficacy (intention to treat) (N=137)
Patients stopped Epidiolex before 12 weeks (N=10)
Devinsky et al, The Lancet Neurology 2015
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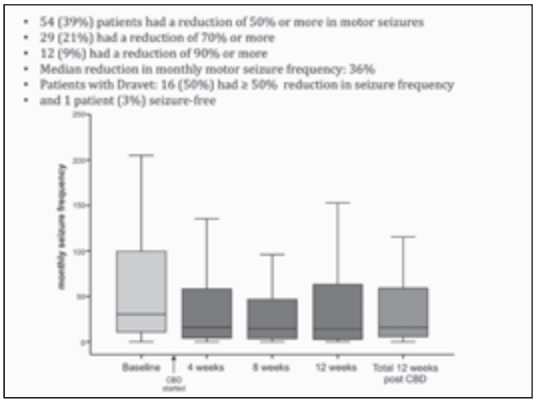
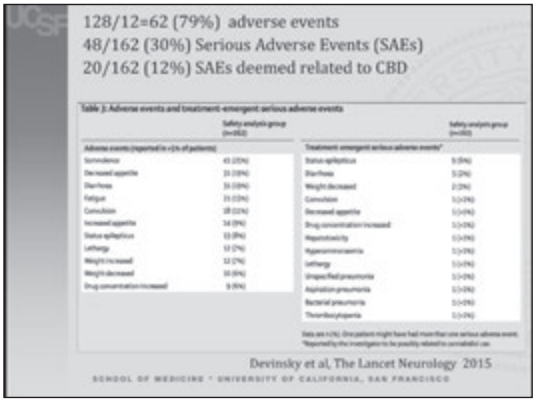

54 (39%) patients had a reduction of 50% or more in motor seizures
29 (21%) had a reduction of 70% or more
12 (9%) had a reduction of 90% or more
Median reduction in monthly motor seizure frequency: 36%
Patients with Dravet: 16 (50%) had ≥ 50% reduction in seizure frequency
and 1 patient (3%) seizure-free
monthly seizure frequency
Baseline
CBD started
4 weeks
8 weeks
12 weeks
Total 12 weeks post CBD


128/12=62 (79%) adverse events
48/162 (30%) Serious Adverse Events (SAEs)
20/162 (12%) SAEs deemed related to CBD
Table 3: Adverse events and treatment-emergent serious adverse events
Devinsky et al, The Lancet Neurology 2015
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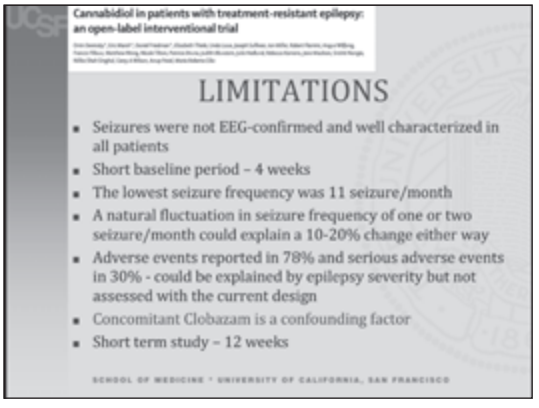
Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial
LIMITATIONS
Seizures were not EEG-confirmed and well characterized in all patients
Short baseline period – 4 weeks
The lowest seizure frequency was 11 seizure/month
A natural fluctuation in seizure frequency of one or two seizure/month could explain a 10-20% change either way
Adverse events reported in 78% and serious adverse events in 30% - could be explained by epilepsy severity but not assessed with the current design
Concomitant Clobazam is a confounding factor
Short term study – 12 weeks
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DRUG-DRUG INTERACTIONS

- 57 patients
- Following the addition of CBD, several patients required dose reduction of one of their background AEDs because of sedation attributed to elevated levels of the drug or the effect of combined medication
- There was significant variability in the change in clobazam, valproate, felbamate and levetiracetam levels
- 7/17 patients on clobazam had an increase of > 40% in their clobazam level

Friedman et al. AES, 2014

Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy

[1]Alexandra L. Geffrey, [1]Sarah F. Pollack, Patricia L. Bruno, and Elizabeth A. Thiele

- Cannabidiol and clobazam are both metabolized by cytochrome P450
- Clobazam and norclobazam were measured in 13 patients with pure CBD (Epidiolex) in add-on to clobazam at baseline, week 4, and week 8
- Mean increase of clobazam level was not statistically significant
- Mean Norclobazam level was increased by 60% compared to baseline
- 9/13 had a > 50% decrease of seizure frequency
- Side effects drowsiness and ataxia

ARTICLES

Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial

C Chiron, M C Marchand, A Tran, E Rey, P d'Athis, J Vincent, O Dulac, G Pons, and the STICLO study group*

Background Stiripentol is an inhibitor of cytochrome P450 that showed antiepileptic efficacy in severe myoclonic epilepsy in infancy (SMEI) in association with clobazam and valproate in an open study. To confirm these results, 41 children with SMEI were included in a randomised, placebo-controlled, add-on trial.

Methods After a baseline period of 1 month, placebo (n=20) or stiripentol (n=21) was added to valproate and clobazam during a double-blind period of 2 months. Patients then received stiripentol in an open fashion. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double-blind period compared with baseline.

Findings 15 (71%) patients were responders on stiripentol (including nine free of clonic or tonic-clonic seizures), whereas there was only one (5%) on placebo (none were seizure free; stiripentol 95% CI 52·1–90·7 vs placebo 0–14·6). The 95% CI of the difference was 42·2–85·7. Percentage of change from baseline was higher on stiripentol (−69%) than on placebo (+7%), p<0·0001. 21 patients on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of comedication was decreased in 12 of the 21 cases.

The Lancet, 2000

IN VITRO AND IN VIVO INHIBITORY EFFECT OF STIRIPENTOL ON CLOBAZAM METABOLISM

Carole Giraud, Jean-Marc Tréluyer, Elisabeth Rey, Catherine Chiron, Jean Vincent, Gérard Pons, and Agnès Tran

- Stiripentol is a potent inhibitor of clobazam's metabolism both in vitro and in vivo
- Increased CLB and NCLB plasma concentrations were seen in children treated with the association CLB/STP
- The inhibitory effect of stiripentol on cytochrome P450 potentiates the effect of clobazam
- Stiripentol can be considered a 'booster' of clobazam
- A drug interaction should not always be regarded as an adverse effect

Comments to the Lancet Neurology

" Long-term safety data are also much needed and eagerly anticipated. Hopefully, the premature enthusiasm of patients, parents, and the media for products related to marijuana is slowly being replaced by rational, evidence-driven behavior. There remains reason for cautious optimism as the haze begins to clear."

Detyniecki and Hirsch, 2016 Comment to The Lancet Neurology

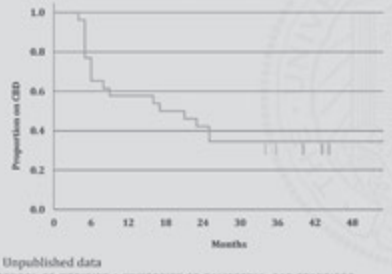
Long-term efficacy and tolerability - UCSF

Feature	n = 26
Sex (F)	13 (50 %)
Age of seizure onset, range (mean)	Neonatal period – 8 years (1.5 years)
Age at enrollment, range (mean)	1- 18 years (9 years)
Number of AEDs tried, range (mean)	4-11 (7)
Concurrent therapies:	Number of AEDs, range (mean) 0-3 (2) Ketogenic diet 4 Vagal nerve stimulator 5
Duration of CBD treatment, range (mean):	4-53 months (21.8 months)
Epilepsy syndrome:	Dravet syndrome 6 (23 %) Epilepsy with myoclonic-absences 5 (19 %) CDKL5 epileptic encephalopathy 5 (19 %) Lennox-Gastaut syndrome 4 (15 %) Other 6 (23 %)
Seizure types:	Generalized tonic-clonic 16 (61.5 %) Tonic 6 (23 %) Myoclonic 5 (19 %) Myoclonic-absence 5 (19 %) Hypermotor tonic spasms 5 (19 %) Focal/multifocal 3 (11.5%) Focal with generalization 2 (7.7 %) Atypical absence 2 (7.7 %) Tonic-atonic 1 (3.8 %)

Results at 3 months

- 6 patients with Dravet
  - Seizure-free: 2
  - 25-50% reduction: 3
  - Increased seizure frequency : 1
- 5 patients Epilepsy with Myoclonic Absences
  - 75-90% reduction:
  - Ineffective: 3
- 5 patients with CDKL5 (3 F, 2 M)
  - Seizure-free: 1 (M)
  - 20-30% reduction: 3
  - Ineffective: 1
- 4 patients with LGS
  - 50% reduction: 3
  - Ineffective: 1
- Ineffective in 1 patient with MPSI KCNT1+

RETENTION RATE



Unpublished data

3 months

- Response rate 16/26 (62%)
- Seizures-free: 3/26 (12%)
- ≥ 50% seizure reduction 7/26 (27%)
- < 50% seizure reduction 6/26 (23%)
- No effect or seizure increase: 10/26 (38%)

Follow-up (34-52months)

- Response rate 9/26 (35%)
- Seizure-free: 3/26 (12%)
  - 1 Dravet syndrome
  - 2 Epilepsy with Myoclonic Absences
- ≥ 50% seizure reduction 4/26 (15%)
- < 50% seizure reduction 2/26 (8%)
- Inefficacy or adverse events: 17/26 (65%)

Unpublished data

Long-term results

- 6 patients with Dravet
  - Seizure-free: 1
  - 25-50% reduction: 4
  - Increased seizure frequency : 1
- 5 patients Epilepsy with Myoclonic Absences
  - Seizure-free on VPA and CBD: 2 (1 patient on CBD monotherapy for 19 months)
  - Ineffective: 3
- 5 patients with CDKL5 (3 F, 2 M)
  - Seizure-free: none
  - > 50% seizure reduction: 1
  - 20-30% reduction: 2
  - Ineffective: 1
  - Discontinued for severe weight loss: 1
- 4 patients with LGS
  - 50% reduction: 1
  - < 50% reduction: 2
  - Ineffective: 1
- Ineffective in 1 patient with EMFSI KCNT1+

Unpublished data

Adverse events:

Adverse Events		
No side effects	4	15 %
Decreased appetite/food aversion	9	34.6 %
Diarrhea/loose stools	7	26.9 %
Weight loss	7	26.9 %
Increased seizures	4	15.4 %
Increased AED levels	3	11.5 %
Increased transaminases with VPA	2	7.7 %
Nausea/vomiting	2	7.7 %
Somnolence/drowsiness	2	7.7 %
Agitation	2	7.7 %
Insomnia	2	7.7 %
Anxiety	1	3.8 %
Fatigue/lethargy	1	3.8 %
Serious Adverse Events		
Hyponatremia	1	3.8 %
Status epilepticus	3	11.5 %
Catatonia/psychosis	2	7.7 %

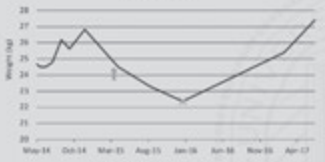
Unpublished data

Adverse events

- 9/27 (35%) Appetite loss, food aversion – dose dependent
- 7/26 (27%) Diarrhea, loose stools –dose dependent
- 6/26 (23%) Weight loss up to > 10% – dose dependent
- 3/26 (11%) Explosive diarrhea –dose dependent
- 2/26 (8%) Agitation, insomnia
- 2/26 Catatonia
- Drug-drug interaction
  - Increased levels of Phenobarbital
  - Increased levels of Clobazam

Unpublished data

Case 10



Maximum weight loss

Unpublished data

The NEW ENGLAND JOURNAL of MEDICINE

JULY 25, 2017

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

- Multinational randomized double-blind trial – 32 centers – Industry-funded
- Children and young adults 2-18 years
- Dravet Syndrome with seizures uncontrolled by current AED regimen
- No change in AED regimen for previous 4 weeks and trial period
- Cannabidiol 20 mg/kg/day versus placebo
- 14 week period, 14-day titration period
- Seizures number and type recorded daily by patients and/or caregivers
- Primary endpoint: seizure reduction
- Secondary endpoint: Caregiver Global Impression of Change (CGIC)

Cannabidiol in Dravet syndrome

- 120 patients with Dravet syndrome
- 9.2 years median age (2.3-18.4)
- 48% F, 52% M
- 4.6 +/- 3.8 prior AEDs
- 2.9 +/- 1 concomitant AEDs
- Randomized to CBD (20 mg/kg/day) or placebo
  - Primary endpoint: Change in convulsive seizure frequency over 14-week treatment period compared to 4-week baseline

Cohort characteristics:

- 120 patients randomized
- 108 completed the study (85% CBD group – 95% placebo group)
- 105 entered the OLE (open label extension study)

- Mean age 9.8 years (2.3 – 18.4) – 52% males
- Median number of seizures: 13 per month

- Previous AED regimen:
- Patients were taking median of 3 drugs (1-5) and had tried median of 4
- Most common drugs: clobazam (65%), valproates (59%), stiripentol (42%), levetiracepam (28%), topiramate (26%)

- Most common seizure types: generalized tonic-clonic, secondarily generalized tonic-clonic
- Non convulsive seizures: 61% of CBD group, 69% placebo group

Primary End Point Results: Seizure Frequency

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 171.7)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2139)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 317)	−13.3 (−91.3 to 230)	−22.8 (−41.1 to −5.4)	0.01

* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

Devinsky O et al. N Engl J Med 2017;376:2011-2020.

Proportion becoming seizure-free: 5% CBD vs 0% placebo ($p=0.08$)

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Secondary End-Point Results

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).*

End Point	Cannabidiol vs. Placebo		P Value†
	Difference (95% CI)	Odds Ratio (95% CI)	
Change from baseline in CGIC score	−1.0 (−1.9 to 0.0)		0.02
Reduction in convulsive seizures from baseline‖			
≥25% reduction		2.19 (1.01 to 4.75)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.99)	0.11
100% reduction	4.9 (−0.5 to 10.3)		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	−16.20 (−39.25 to −1.77)		0.03
Total nonconvulsive seizures	0.00 (−21.36 to 31.59)]		0.88
Reduction from baseline in duration of seizure subtypes††			
Tonic-clonic seizures		2.48 (0.94 to 6.51)	0.07
Tonic seizures		3.40 (0.53 to 22.23)	0.20
Clonic seizures		1.25 (0.13 to 10.57)	0.84
Atonic seizures		7.44 (0.27 to 204.78)	0.24
Myoclonic seizures		2.89 (0.58 to 14.47)	0.20
Countable partial seizures		6.01 (0.83 to 43.21)	0.08
Other partial seizures		1.00 (<0.01 to >999.99)	1.00
Absence seizures		0.61 (0.14 to 2.66)	0.50
Change from baseline in other variables‡‡			
Sleep-disruption score	−0.4 (−1.5 to 0.7)		0.45
Epworth Sleepiness Scale score	1.5 (−0.2 to 3.2)		0.08
Quality-of-Life in Childhood Epilepsy score	1.5 (−1.8 to 4.8)		0.38
Vineland-II score	−2.6 (−6.8 to 1.6)		0.21
Inpatient hospitalizations due to epilepsy	0.0 (0.0 to 0.1)		0.54

Devinsky O et al. N Engl J Med 2017;376:2011-2020.

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Adverse Events

Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N=41)	Placebo (N=39)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (51)	4 (10)
Vomiting	9 (25)	3 (8)
General		
Fatigue	12 (33)	2 (5)
Pyrexia	9 (25)	5 (8)
Infections—upper respiratory tract infection	7 (21)	5 (8)
Metabolism: decreased appetite	17 (39)	3 (5)
Nervous system		
Convulsion	7 (21)	3 (5)
Lethargy	8 (23)	2 (5)
Somnolence	22 (56)	4 (10)

* Events were classified according to the Medical Dictionary for Regulatory Activities, version 17.0.

AE 93% CBD vs. 75% placebo

SAE 16% CBD vs 5% placebo

AE leading to discontinuation 8 CBD vs 1 placebo

Devinsky et al. NEJM, 2017

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Cannabidiol in Dravet syndrome

- Primary endpoint: % change in median seizure frequency
  - CBD -38.9% vs placebo -13.3%
  - Adjusted mean difference: -22.8%
- >50% reduction in convulsive seizures:
  - CBD 43% vs placebo 27%
- Caregiver Global Impression of Change scale
  - CBD 62% improvement in >1 category vs placebo 34%

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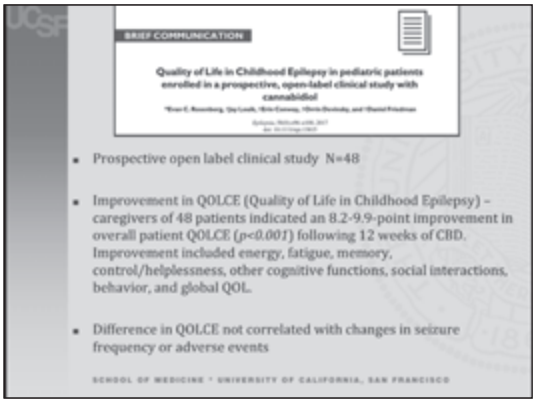

- Prospective open label clinical study N=48
- Improvement in QOLCE (Quality of Life in Childhood Epilepsy) – caregivers of 48 patients indicated an 8.2-9.9-point improvement in overall patient QOLCE ($p<0.001$) following 12 weeks of CBD. Improvement included energy, fatigue, memory, control/helplessness, other cognitive functions, social interactions, behavior, and global QOL.
- Difference in QOLCE not correlated with changes in seizure frequency or adverse events

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Cannabidiol in treating refractory epilepsy in Lennox-Gastaut Syndrome

- Key inclusion criteria
  - Patients aged 2-55 years
  - Clinical diagnosis of LGS inadequately controlled by ≥ 1 AED, and slow (< 3 Hz) spike-and-wave pattern on EEG
  - ≥ 2 drop seizures (atonic, tonic, or tonic-clonic seizures that led, or could have led, to a fall or injury) each week during the 8-day baseline period
- Treatment groups
  - 20 mg/kg/day of CBD or placebo as add-on to current AEDs
  - Dose started at 2.5 mg/kg/day, titrated to 20 mg/kg/day over two weeks, followed by a 12-week dose maintenance period

Primary endpoint

- Percentage change from baseline in drop seizures during the 14-week treatment period

Thiele et al, The Lancet, in press, presented at AES 2017

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Cannabidiol in Lennox-Gastaut syndrome

- 170 patients (CBD=86; Placebo=85)
- 113 pediatric age 2-17 years
- 58 adult age 18-55 years
- 51% M, 49% F
- Median number of prior AEDs: 6 (min 1, max 18)
- Median number of current AEDs: 3 (min 1, max 4)
- Median drop seizure frequency (per 28 days) during baseline: 71 CBD and 75 placebo
- Median total seizure frequency (per 28 days) during baseline: 145 CBD and 177 placebo

94% of patients were on multiple concomitant AEDs; most common were clobazam (49%), valproic acid (40%), and lamotrigine (37%)

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Median % reduction in monthly drop and non-drop seizure frequency

CBD treatment period
- Drop seizures: 44

p=0.0135

CBD 4-week maintenance period
- Drop seizures: 49

p=0.0096

CBD treatment period
- Non-drop seizures: 49

p=0.0044

CBD 4-week maintenance period
- Non-drop seizures: 55

p=0.0008

Placebo treatment period
- Drop seizures: 22

Placebo 4-week maintenance
- Drop seizures: 20

Placebo treatment period
- Non-drop seizures: 23

Placebo 4-week maintenance
- Non-drop seizures: 24

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Cannabidiol in Lennox-Gastaut syndrome: Safety

Treatment-Emergent Adverse Events (TEAEs)	CBD (n=86) n (%)	Placebo (n=85) n (%)
All-causality TEAEs	74 (86)	59 (69.4)
Treatment-related TEAEs	53 (61.6)	29 (34.1)
TEAEs leading to withdrawal	12 (14)	1 (1.2)
Serious TEAEs	20 (23.3)	4 (4.7)
Treatment-related serious TEAEs	9 (10.5)	1 (1.2)
TEAEs reported in > 10% of patients in	either groups	by preferred term
Diarrhea	16 (18.6)	7 (8.2)
Somnolence	13 (15.1)	8 (9.4)
Pyrexia	11 (12.8)	7 (8.2)
Decreased appetite	11 (12.8)	2 (2.4)
Vomiting	9 (10.5)	14 (16.5)

- There was 1 death in the CBD group, not deemed treatment related
- Of those who reported TEAE, 78% of CBD and 97% of placebo reported it as mild or moderate

Cannabidiol in Lennox-Gastaut syndrome: Laboratory investigations

- Increases in ALT or AST (>3 x ULN) occurred in 20 CBD patients and 1 placebo
- 16 CBD patients with increases were on concomitant valproic acid
- No patient met standard criteria for drug-induced liver injury (Hy's law) with concurrent elevated bilirubin >2 xULN
- 6 CBD patients withdrew from treatment; a 7th patient met criteria for withdrawal but was discontinued for non compliance
- All elevations resolved

Impact of CBD on Clinical Care and Practice

- CBD has efficacy in some patients with medically refractory epilepsy
  - RTCs in Dravet and Lennox-Gastaut syndromes
- Actual responders and seizure freedom rate similar to those reported with other new drugs
- High rate of adverse events
- Multiple interactions with other AEDs
- Retention rate?
  - Open label
  - No solid data yet form the RCTs open label extension phase
- Concerns about effects on brain development in the young

CONCLUSIONS

- Determine whether the efficacy and safety profile of CBD is similar to other AEDs, better, or worse
- Drug-drug interactions – consider it with all cannabis-based product
- Is it syndrome-specific?
- Broad spectrum or narrow spectrum?
- Does it target a seizure type better than another
- Best combinations
- On the long run, cannabidiol will prove to be a good drug but it is unlikely the magic bullet

Impact of CBD on Clinical Care and Practice

- CBD is a valuable addition to our treatment options in epileps
- It is not a first, or second, or third line drug
- It is a drug to try after our current mainstays rather than early in the course
- This may change as we gain more experience with its use and can identify those most likely to benefit

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- Linda Laux – Children's Hospital Chicago

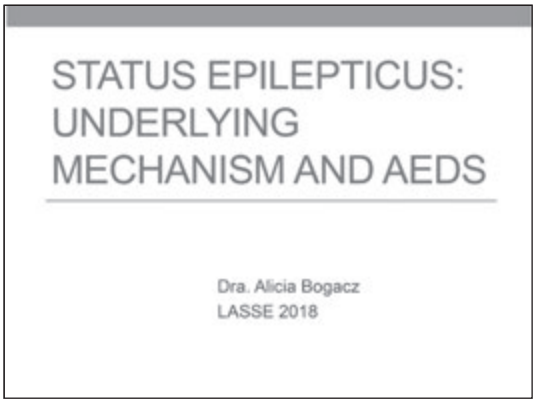
- GW Pharma

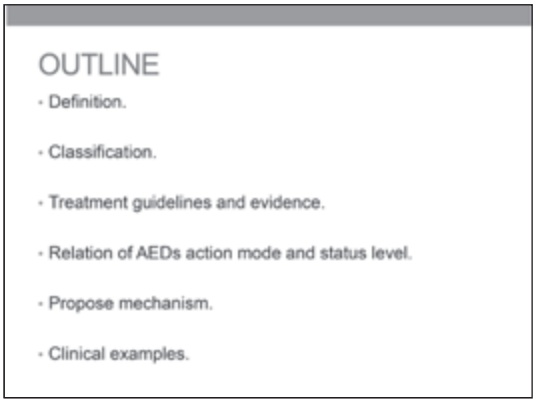
" My intention is not to prove I was right but to find out whether I was right….and if we find anything which would suit us, that thing we will eye with particular distrust…"

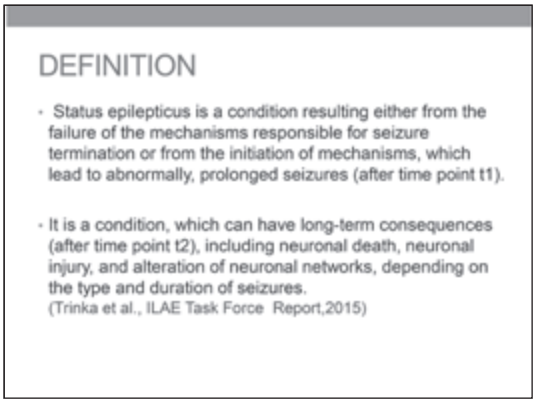
"Galileo", Bertold Brecth, 1966

Alicia Bogacz (Uruguay)

AEDS IN STATUS EPILEPTICUS: A SITUATION OF EXTREME HYPEREXCITABILITY







DEFINITION

- This definition is conceptual, with two operational dimensions: the first is the length of the seizure and the time point (t1) beyond which the seizure should be regarded as "continuous seizure activity."
- The second time point (t2) is the time of ongoing seizure activity after which there is a risk of long-term consequences.

(Trinka et al., ILAE Task Force Report,2015)

In the case of convulsive (tonic-clonic) SE time points (t1 at 5 min and t2 at 30 minutes) are based on animal experiments and clinical research.

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

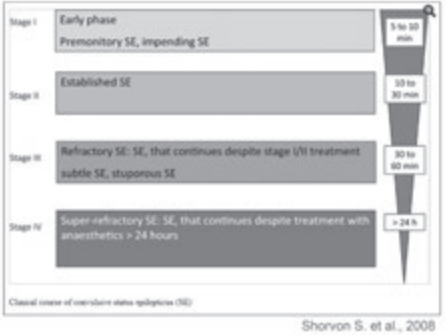
Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

(Trinka et al., ILAE Task Force Report,2015)

- Current knowledge of the pathophysiology of status epilepticus is uncomplete.
- Both clinical and animal studies indicate that SE is a dynamic condition during which a progressive sequence of events occurs.
- It is a complex process and can be visualized as a cascade of changes that perpetuate and intensify seizures throughout SE.
- This concept would explain the clinician impression that the longer SE persists, the harder it is to control.

(Lothman,1990 and Delgado-Escueta et al.,1983)



Shorvon S. et al., 2008

Why 5 minutes?

- Generalized convulsive SE in adults and children older than 5 years was defined as: "…≥5 min of(1) continuous seizure or (2) two or more discrete seizures between which there is incomplete recovery of consciousness," (Lowenstein DH, Bleck T, Macdonald RL, 1999)
- Data from populations with refractory epilepsy undergoing video–EEG monitoring indicate that most convulsive seizures last <5 min. (Gastaut H, Broughton R., 1972; Shinnar S et al, 2001)
- In community-based populations, the data suggest that the estimated duration of seizures >5 min is more common than suggested by inpatient monitoring. (Hauser WA et al, 1990)
- Observations from a pediatric population show that there are two subgroups of patients, one with a tendency to brief seizures (<5 min) and the other subgroup that represents a significant minority of patients with a propensity to more prolonged seizures. (Shinnar S et al, 2001)
- Taken together, these findings led the Task Force to reach a consensus opinion that treatment of convulsive seizures should be initiated at around 5 min. (Trinka et al., ILAE Task Force Report,2015)

Why 30 min?

- Early works suggested that 82 min or longer of ongoing seizure activity in baboons can cause irreversible neuronal injury due to excitotoxicity. (Meldrum BS et al, 1973)
- Other animal models of SE have been employed to demonstrate that ongoing epileptic activity in the brain can affect both excitatory and inhibitory synapses and thus neuronal plasticity .. (Sperk G. et al, 2009. Rajasekaran K. et al, 2015)
- Given the experimental evidence indicating irreversible brain damage after prolonged seizures and the potential threat of brain damage in humans, the task force suggest the time of t2 at 30 min in convulsive SE, in line with previous definitions of SE. (Trinka et al., ILAE Task Force Report,2015)

CLASSIFICATION

- 1 Semiology
- 2 Etiology
- 3 EEG correlates
- 4 Age

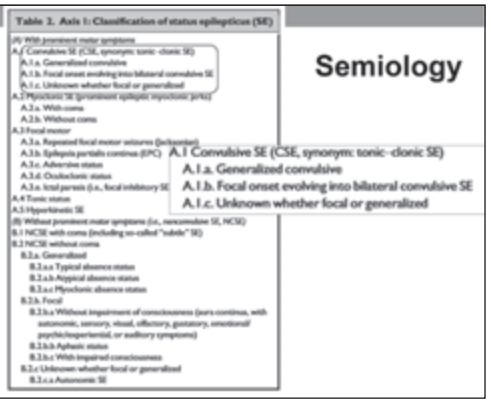


Table 4. Etiology of status epilepticus

Known (i.e., symptomatic)
Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
Progressive (e.g., brain tumor, Lafora's disease and other PMEs, dementias)
SE in defined electroclinical syndromes
Unknown (i.e., cryptogenic)

- At least half of the patients presenting with SE do not have epilepsy.
- SE is not a disease but rather a symptom with a great number of etiologies.

EEG

- EEG will affect choice and aggressiveness of treatment, prognosis, and clinical approaches.
- EEG should be sought where possible and as early as possible.
- Some forms of SE may only be reliably diagnosed by EEG. (Bauer G, Trinka E. 2010)

(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
B.2.a: Generalized
B.2.a.a Typical absence status
B.2.a.b Atypical absence status
B.2.a.c Myoclonic absence status

GENERAL PRINCIPLES OF TREATMENT

- All protocols emphasize prompt recognition and treatment of persisting seizure activity to prevent death or irreversible brain damage and reduce morbidity and mortality.
- Because of the circumstances during status epilepticus, it is difficult to assess the effect of each treatment.
- The patient's critical condition requires the use of several therapeutic treatments, either simultaneously or one after the other.

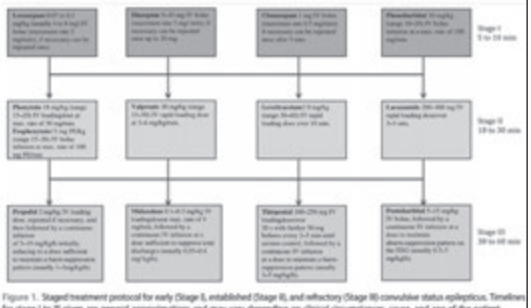


Figure 1. Staged treatment protocol for early (Stage I), established (Stage II), and refractory (Stage III) convulsive status epilepticus. Timelines for stage I to III given are general approximations and may vary depending on clinical circumstances, cause, and age of the patient.

Trinka E et al. 2016

- Clinical practice defines the first stage with a time frame (5 min of convulsive and 10 min of focal non-convulsive), and the later stages by treatment response.
- In adults, compared to the first therapy, the second therapy is less effective while the third therapy is substantially less effective (Level A).
- In children, the second therapy appears less effective and there are no data about third therapy efficacy (Level C). (Glauser T, 2016)

EARLY STATUS TREATMENT

- The treatment of early SE relies on the use of benzodiazepines.
- These drugs exert their antiepileptic properties by enhancing the inhibitory neurotransmission through increasing channel opening frequency of the GABA-A receptors, with subsequent increased chloride conductance and neuronal hyperpolarization.(Trinka E et al. 2015)
- In adults with convulsive status epilepticus, intramuscular midazolam, intravenous lorazepam, intravenous diazepam and intravenous phenobarbital are established as efficacious as initial therapy. (Glauser T et al.2016)
- Early treatment of status epilepticus (SE) is effectively controlled in with intravenous lorazepam or intramuscular midazolam in 64 to 73%. (Trinka E et al. 2016)

$GABA_A$ receptor structure

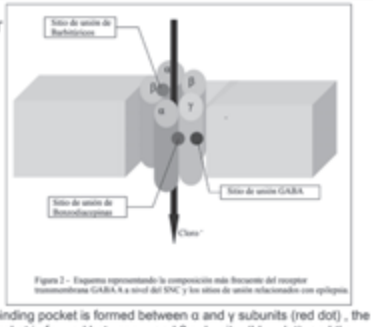


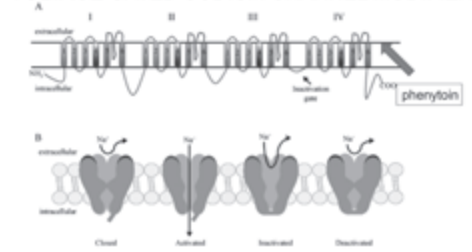
Figura 2 – Esquema representando la composición más frecuente del receptor transmembrana GABA A a nivel del SNC y los sitios de unión relacionados con epilepsia.

The benzodiazepine binding pocket is formed between α and γ subunits (red dot) , the barbiturates binding pocket is formed between α and β subunits (blue dot), and the GABA binding pocket is formed in γ subunits (green dot). From Braga P. et al. 2014.

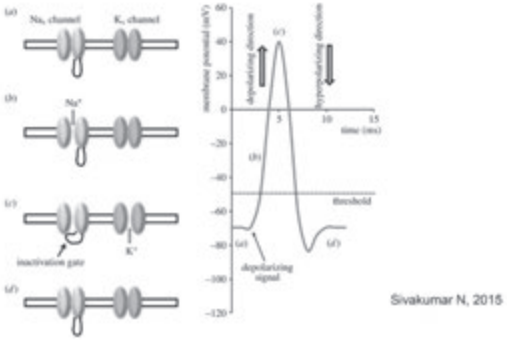
ESTABLISH STATUS TREATMENT

- The efficacy of benzodiazepines reduces as the seizure activity persists over time.
- Approximately 40% of patients with GCSE are refractory to benzodiazepine treatment.
- It was recommended to start after 30–120 minutes of ongoing seizure activity Stage II treatment, but now a faster treatment escalation is recommend, even within 10 minutes after failure of benzodiazepines. (Shorvon S et al 2011; Trinka E et al 2015)
- Phenytoin (or fosphenytoin), valproate, levetiracetam, phenobarbital, and lacosamide are use, after failure of benzodiazepines in the early stage.
- There is no high-class evidence available to prefer one to the other; valproate and levetiracetam have a favorable safety profile compared to phenobarbital and phenytoin.
- Lacosamide is available as I/V, but there is only limited evidence for its use in SE from small case series. (Trinka E et al. 2016)

VOLTAGE GATED SODIUM CHANNEL MODIFIERS



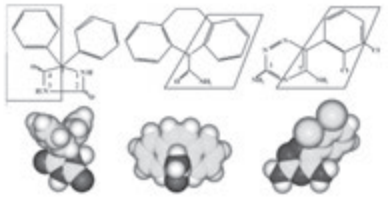
The VGSC is composed of four homologous domains that contain six transmembrane segments. Its function is to elicit conformational alterations during depolarization and repolarization phases. The S4 helices can translate upward or downward depending on the polarity of the electric field thus causing channel activation or deactivation.



Sivakumar N, 2015

- Voltage-gated sodium channels activate and start to conduct Na current in a voltage and time dependent manner.
- The counteracting process where Na entry ceases is known as inactivation and occurs in a time-dependent manner.
- In the brain, VGSC can cycle through this process in a few milliseconds, thus being able to sustain high frequency trains of action potentials.
- Anticonvulsants, such as phenytoin, carbamazepine, and lamotrigine, exert their action over short time scale.

PHENYTOIN



Anticonvulsants like phenytoin (left), carbamazepine (middle) and Lamotrigine (right) share common molecular structures. (Lipkind GM, 2010)

LACOSAMIDE

- Another mechanism of inactivation is known as slow-inactivation in which channels inactivate at slow time constant extending to a few seconds.
- Lacosamide stabilizes the slow-inactivated state in contrast to other anticonvulsants that exhibit their effects primarily on the fast-inactivation state.
- Another effect of lacosamide is blocking neuronal channels without any shifts in the voltage-dependent curves of activation.

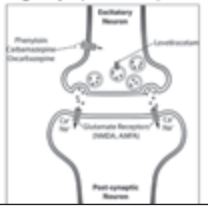
(Sheets PL et al, 2008)

VALPROATE

- The broad spectrum of antiepileptic efficacy of valproate is reflected in preclinical in vivo and in vitro models, including a variety of animal models of seizures or epilepsy.
- VPA exhibits its effects increasing GABA levels, it may also have antiepileptic activity by reducing the high-frequency firing of neurons by blocking voltage-gated sodium, potassium, and calcium channels. (Ghodke-Puranik, 2013)
- Maximum plasma concentrations were reached within minutes, and onset of action is quick. (Trinka E et al., 2015)

LEVETIRACETAM

- Levetiracetam is a drug with a broad spectrum of efficacy against all seizure types and a low potential for interactions due to minimal hepatic metabolism and low plasma protein binding.
- The precise mechanism by which levetiracetam exerts its antiepileptic effect is unknown.
- Levetiracetam binds to the synaptic vesicle protein SV2A, which is thought to be involved in the regulation of vesicle exocytosis.The molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not complete understood. (Lynch BA et al., 2004)



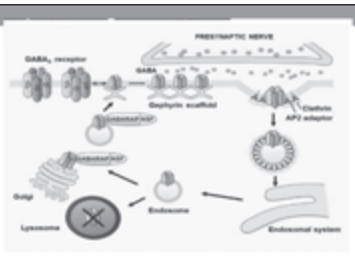
Pre and post excitatory neuron with neurotransmitter, glutamate. (Mrak A. 2015)

PHENOBARBITAL

- It promotes binding to inhibitory GABA subtype receptors, and modulates chloride currents through receptor channels. It also inhibits glutamate induced depolarizations.
- The central depressive effect of phenobarbital, especially following the use of benzodiazepines, limits its clinical utility.
- It has been used for decades in the treatment of SE and a wide experience has been gained in adults, children and newborn.

REFRACTORY STATUS TREATMENT

- With increasing duration of seizure, a decrease in motor activity occurs, while the patient remains in coma.
- This phase is called refractory SE, referring to the failed treatment of early and established SE.
- The efficacy of benzodiazepines reduces as the seizure activity persists over time.
- This pharmaco-resistance to benzodiazepines has been attributed to a reduction of GABA-A postsynaptic receptors, leading to failure of GABAergic inhibition with seizure activity becoming self-sustaining.
- Time-dependent internalization of synaptic GABA receptors explains, in part, the loss of inhibition and the loss of response to benzodiazepines
- Receptor trafficking with relocation of GABA-A receptors subunits from synapses to the cell interior has been reported to occur after SE. (Niquet J et al., 2016)



- **Model of hypothesis of $GABA_A$ receptor trafficking during the transition of single seizures to status epilepticus.** (Niquet J et al., 2016)
- After repeated seizures, the synaptic membrane of $GABA_A$ receptors forms clathrin-coated pits, which internalize as clathrin-coated vesicles, inactivating the receptors because they are no longer within reach of the neurotransmitter.
- These vesicles develop into endosomes, which can deliver the receptors to lysosomes, where they are destroyed, or to the Golgi apparatus, from where they are recycled to the membrane.

- **Model of hypothesis of NMDAR trafficking during the transition of single seizures to SE.** (Niquet J et al., 2016)
- After repeated seizures, in NMDA synapses, subunits are mobilized to the synaptic membrane and assemble into additional receptors.
- They may move initially to the perisynaptic area, then laterally to the synaptic area.
- As a result of this trafficking, the number of functional NMDARs per synapse increases.

- The increase in NMDA receptors may contribute to the runaway excitation and excitotoxicity of SE. (Niquet J et al., 2016)
- *N*-methyl-D-aspartate receptor (NMDAR) blockers remain potent, even in late SE.
- These changes could have therapeutic implications.
- Ketamine has a strong antagonistic effect on the NMDA-glutamate receptor.
- Animal models (hippocampal electrical stimulation or pilocarpine animal models) have demonstrated the efficacy of ketamine in refractory SE in rats.
(Mazarati AM et al, 1999 and Gaspard N et al. 2013)

- In refractory SE anaesthetics have been commonly used for over 50 years.
- Propofol, continuous midazolam infusion, thiopental/pentobarbital are more commonly used.
- There is no randomized trial available, but retrospective series suggest a higher morbidity with thiopental / pentobarbital, compared to midazolam or propofol.

SUPER-REFRACTOTY STATUS

- At Super-refractory SE seizures continue despite maximal treatment with intravenous anesthetics for more than 24 h in an intensive care unit. (Shorvon S et al, 2011)
- These patients have ictal EEG discharges when anesthesia is lessened.
- In super-refractory SE, ketamine, magnesium, and immunomodulatory treatments should be considered early.
- Corticosteroids and other immunomodulators have their place in the treatment of SE even in the absence of an autoimmune etiology, since SE may be associated with an inflammatory response and with a disruption of the BBB. (Li G et al, 2011)
- The identification of a cause and its appropriate treatment is of greatest importance at this stage.

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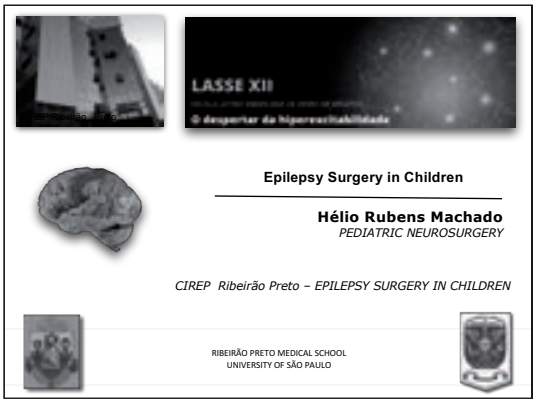
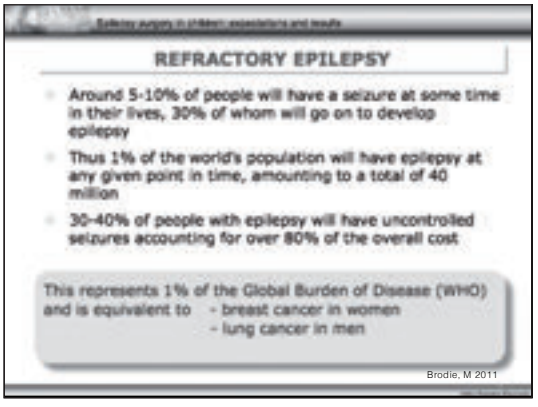
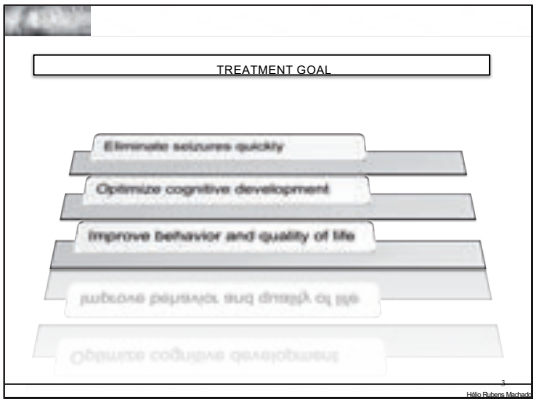
SURGICAL TREATMENT OF THE EPILEPSIES

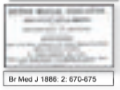






HISTORICAL NOTE





Br Med J 1886; 2: 670-675

McKenzie KC: The present status of a patient who had the right cerebral hemisphere removed...

HISTORICAL NOTE


R A Krynauw


T Rasmussen

Krynauw RA: Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatry 13:243; 1950

Papers	N	Age	Surgery	Results
Davidson & Falconer, 1975	40	<15	Temporal	80%
Rasmussen, 1977	77	6-15	Temporal	73%

Outline

1. Children are not small adults - the surgical challenge
2. Epidemiology - Temporal X Extra-temporal surgery
3. Definition of refractoriness
4. ILAE recommendation for evaluation
5. Indications for surgery - invasive evaluation
6. Surgical techniques
7. Specific etiology
8. Outcome

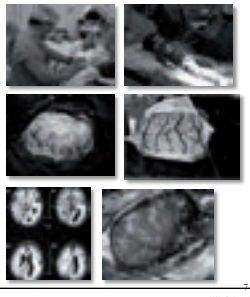
1. Children are not small adults - the surgical challenge

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

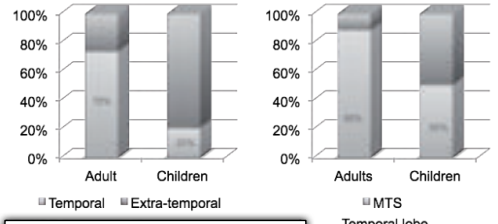


2. Epidemiology - Temporal X Extra-temporal surgery

Holland K, 2002

2. Epidemiology - Temporal X Extra-temporal surgery

Epidemiology – ADULTS X CHILDREN



CIREP 1996 -2013 : 1610 patients

Peculiarities of Surgery in Children – Early Surgery

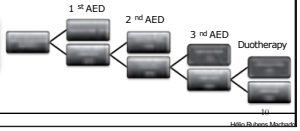
Defining Refractoriness in Children

Brodie, M 2011

...as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules ...to achieve sustained seizure freedom.

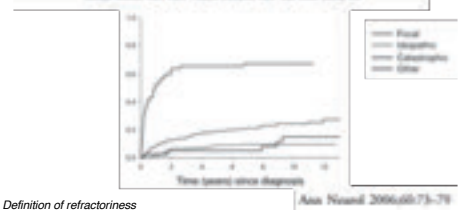
Kwan & Brodie NEJM 2000; 342: 314-9

New drugs have not altered the number of intractable cases in children
Holland, 2002; Duchowny, 2008



3. Definition of refractoriness

How Long Does It Take for Epilepsy to Become Intractable? A Prospective Investigation



Ann Neurol 2006;60:73–79

3. Definition of refractoriness

Catastrophic epilepsy

Seizures 666,9 / mês
Status epilepticus 40,7%

Refractory epilepsy

Progressive neurologic deficit

spastic hemiplegia

Developmental delay

Behavior deterioration

3. Definition of refractoriness

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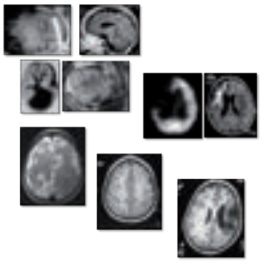
Catastrophic epilepsy

- Sturge Weber syndrome
- Hemimegalencephaly
- Rasmussen encephalitis
- Tuberous Sclerosis complex
- Cortical dysplasia
- Porencephaly



3. Definition of refractoriness

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4. ILAE recommendation for evaluation

Original Research

Proposed Criteria for Referral and Evaluation of Children for Epilepsy Surgery: Recommendations of the Subcommission for Pediatric Epilepsy Surgery

- Rationale for pediatric epilepsy surgical services
- Typical surgical syndromes
- Pediatric epilepsy unit
- Outcome assessment for pediatric surgical patients

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4. ILAE recommendation for evaluation

Diagnostic test utilization in evaluation for resective epilepsy surgery in children

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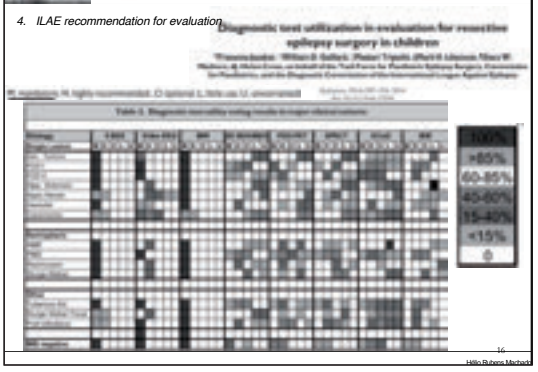
4. *ILAE recommendation for evaluation*



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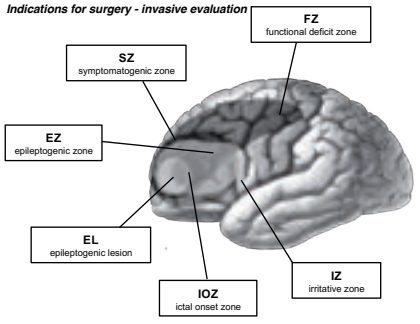
5. *Indications for surgery - invasive evaluation*



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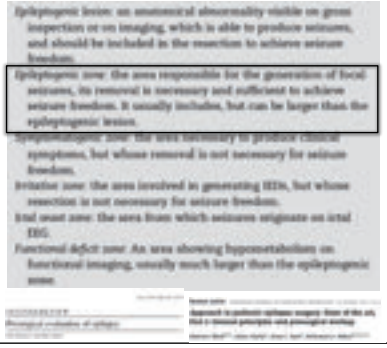
5. *Indications for surgery - invasive evaluation*



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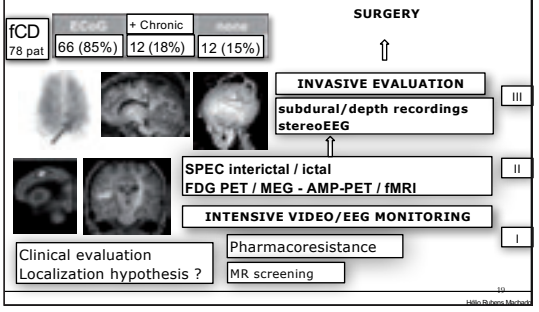
5. *Indications for surgery - invasive evaluation*

Patient management



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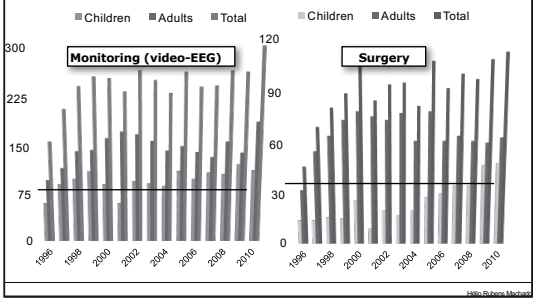
5. *Indications for surgery - invasive evaluation*

■ Presurgical evaluation



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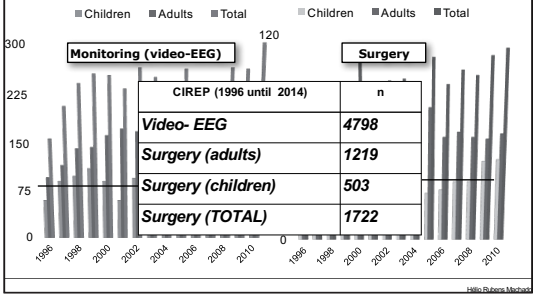
5. *Indications for surgery - invasive evaluation*

■ Presurgical evaluation



CIREP (1996 until 2014)	n
Video- EEG	*4798*
Surgery (adults)	*1219*
Surgery (children)	*503*
Surgery (TOTAL)	*1722*

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5. *Indications for surgery - invasive evaluation*

- KSF, 2 yo, normal milestones until sz that started at 1 y 4 mo, EPC, tonic and clonic sz. R Hemiplegia. Refractory to AED. Rasmussen encephalitis

- Video EEG

sleep

- Video – EEG
  - Characterization of seizures
  - Frequency of seizures
  - Ictal semiology
  - Lateralization / localization EZ
- Define
  - Ictal onset zone - < than EZ
  - Irritative zone – interictal epileptiform discharges
  - Symptomatogenic zone – Clinical semiology

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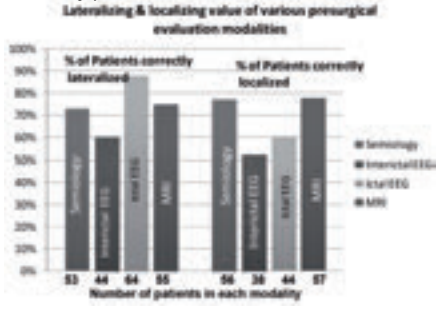
5. *Indications for surgery - invasive evaluation*



Elwan S, Alexopoulos A, Silviera D, Kotagal P. AES abstract 2010

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5. Indications for surgery - invasive evaluation

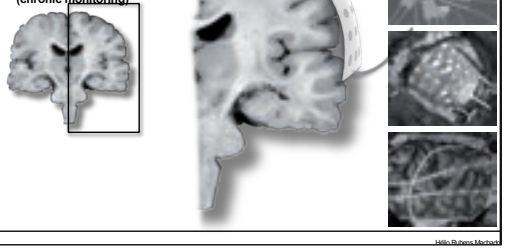
- **Invasive monitoring in children epilepsy**
  - **Indications**
    - **Inconclusive Preoperative Data**
      - Normal or Non-specific MRI
      - Structural lesion – CD, SSW or multiple lesions (TSC)
    - **Seizure localization**
      - Routine long term video EEG monitoring do not give sufficient data
      - Video EEG shows noncongruent data
      - Partial seizures and normal or nonlocalizing imaging data
    - **Involvement of eloquent cortex – *Functional Cortical Mapping***
      - Sensorimotor Mapping
      - Language Mapping

DIVERGENT DATA

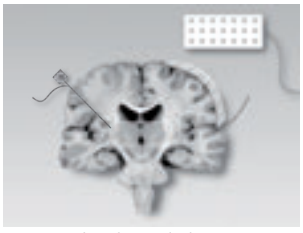
Clinical Semiology , EEG, and Functional/ Structural imaging data implicate separate regions

5. Indications for surgery - invasive evaluation

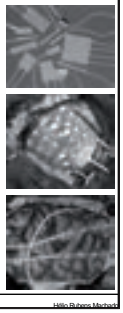
- Invasive monitoring
  - **ECoG (acute monitoring)**
  - **ECog + subdural electrodes (chronic monitoring)**



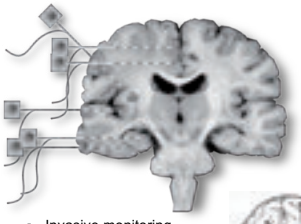
5. Indications for surgery - invasive evaluation



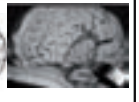
- Invasive monitoring
  - **Depth recordings**
  - **Stereo EEG (chronic monitoring)**



5. Indications for surgery - invasive evaluation



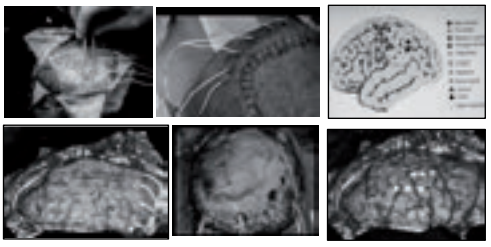
Anatomic – Electro Clinical correlation



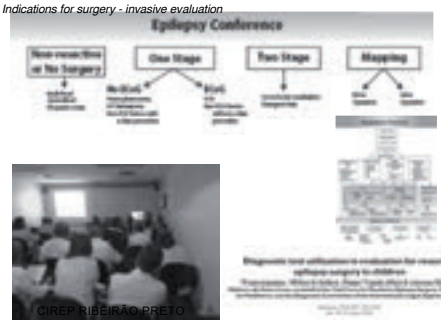
- Invasive monitoring
  - **Depth recordings**
  - **Stereo EEG (chronic monitoring)**

5. Indications for surgery - invasive evaluation

▪ Chronic electrodes implantation



5. Indications for surgery - invasive evaluation



6. Surgical technique

SURGERY

1996 to 2017

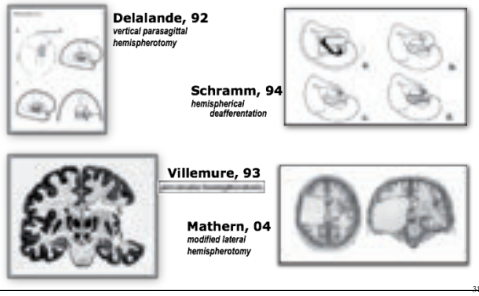
Patients 627

CIREP Children – Ribeirão Preto
Ribeirão Preto Medical School
UNIVERSITY OF SÃO PAULO
BRAZIL

Surgical technique	
Hemispherotomy (24%)	**152**
Temporal Lobectomy	**127**
Lesionectomy	**130**
VNS	**49**
Frontal Lobectomy	**36**
Posterior(par-occipital) cortex	**41**
Callosotomy	**38**
Occipital Lobectomy	**15**
Multilobar Resection	**3**
Focal Corticectomy	**17**
other	**19**
Total	**627**

6. Surgical technique

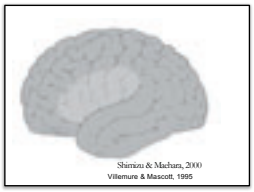
❑ Hemispherotomy – surgical technique



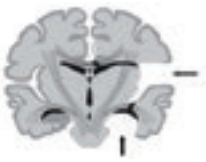
Hemispherotomy and pediatric epilepsy

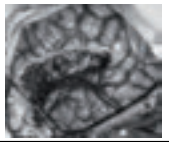
6. *Surgical technique*

- Hemispherotomy – surgical technique



Shimizu & Maehara, 2000
Villemure & Mascott, 1995





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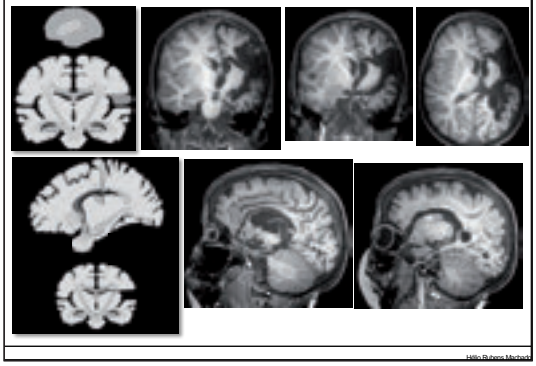
Hemispherotomy and pediatric epilepsy



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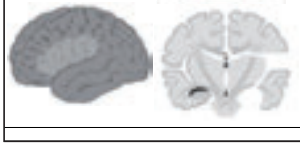
6. *Surgical technique*

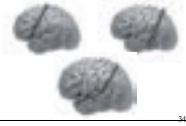
Temporal lobe surgery

Lesionectomy

Hemispherotomy



Disconnective surgery



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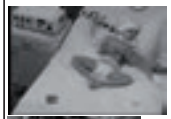
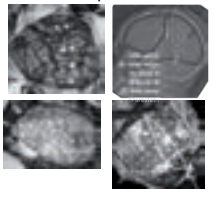
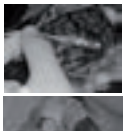
6. *Surgical technique*

- Surgical technique
  - Functional mapping
    - Intra-operative monitoring
    - Extra-operative







- Invasive monitoring
- Brain stimulation

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7. Specific etiology

- Clinical characteristics
  - Symptomatic etiologies

1996 to 2017 — Children 627

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

Pathology	
Cortical Dysplasia	**199**
Tumor	**80**
Gliosis	**70**
Mesial temporal sclerosis	**66**
Rasmussen encephalitis	**45**
Tuberous sclerosis	**25**
Porencephaly	**27**
Difuse atrophy	**21**
MR normal	**14**
Sturge-Weber	**11**
AVM	**3**
(other 66) Total	**627**

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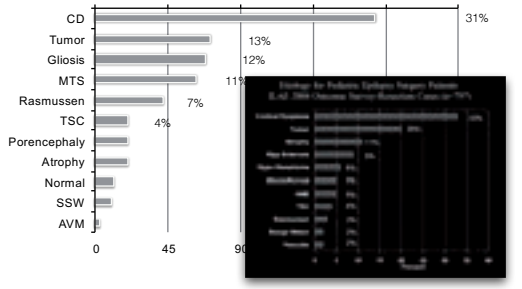
7. Specific etiology

Etiology of cases operated at CIREP (RP) - 1996 to 2017 (n= 627)



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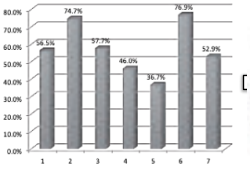
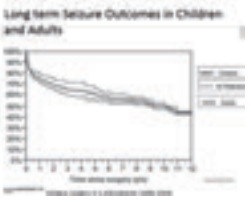
8. Outcome

Seizure-free



Cirep - Ribeirão Preto outcomes in children and adults 1996 - 2014



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8. Outcome

8. Outcome

- Improving the outcome
  - Centralization of epilepsy program
  - Time to surgery
  - Rehabilitation program

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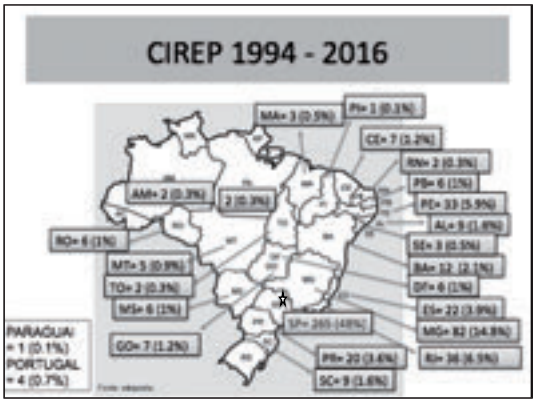
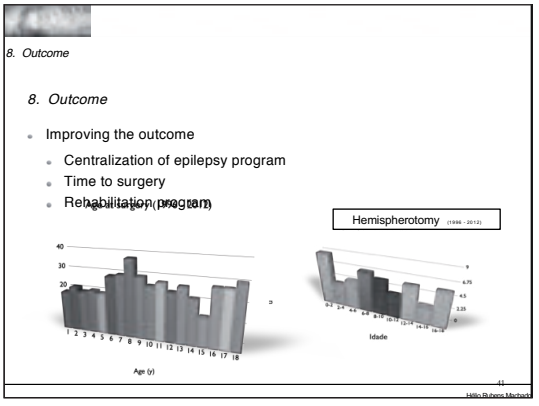

CIREP 1994 - 2016
MA= 3 (0.5%)
PI= 1 (0.1%)
CE= 7 (1.2%)
RN= 2 (0.3%)
PB= 6 (1%)
PE= 33 (5.5%)
AL= 9 (1.6%)
SE= 3 (0.5%)
BA= 12 (2.1%)
DF= 6 (1%)
ES= 22 (3.9%)
MG= 82 (14.8%)
RJ= 36 (6.5%)
AM= 2 (0.3%)
2 (0.3%)
RO= 6 (1%)
MT= 5 (0.9%)
TO= 2 (0.3%)
MS= 6 (1%)
SP= 265 (48%)
GO= 7 (1.2%)
PR= 20 (3.6%)
SC= 9 (1.6%)
PARAGUAI = 1 (0.1%)
PORTUGAL = 4 (0.7%)


8. Outcome
8. Outcome
Improving the outcome
Centralization of epilepsy program
Time to surgery
Rehabilitation program
Hemispherotomy (1996 - 2012)
Age (y)
Idade
41
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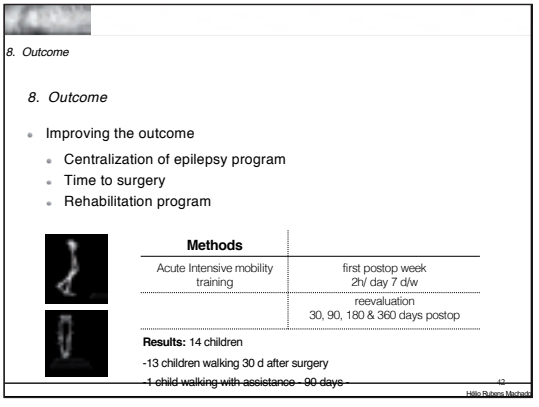
8. Outcome
8. Outcome
Improving the outcome
Centralization of epilepsy program
Time to surgery
Rehabilitation program
Methods
Acute Intensive mobility training
first postop week
2h/ day 7 d/w
reevaluation
30, 90, 180 & 360 days postop
Results: 14 children
-13 children walking 30 d after surgery
-1 child walking with assistance - 90 days -
42
Hélio Rubens Machado


Thank you
CIREP – CENTER FOR EPILEPSY SURGERY
2 w post op
RIBEIRÃO PRETO MEDICAL SCHOOL
UNIVERSITY OF SÃO PAULO

GROUP WORKING

PRESENTATION OF RESEARCH PROJECTS