11ª. ESCOLA LATINO-AMERICANA DE VERÃO EM EPILEPSIA
11ª. ESCUELA LATINO-AMERICANA DE VERANO EN EPILEPSIA
11th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 2 – 11 DE MARÇO DE 2017
Centro de Convenções Santa Mônica

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Prof. Dr. Esper A. Cavalheiro

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EPILEPSIA NA AMÉRICA LATINA: LASSE XI INAUGURA UMA NOVA DÉCADA

LASSE XI DEDICADA A DIETER JANZ (1920-2016)

A 11ª. 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 11ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) realizada em Cabuçu, Serra da Cantareira, São Paulo entre 02 e 11 de março de 2017 aborda o tema Malformações do Desenvolvimento Cortical e Epilepsia e inaugura 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-XI, razão maior do nosso trabalho.

A COMISSÃO ORGANIZADORA

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11th Latin-American Summer School on Epilepsy - LASSE XI
02 – 11 March 2017 – São Paulo – Brazil

PROGRAM

Esper Cavalheiro (Brazil)

WELCOME ADDRESS

Marcelo Rodrigues Masruha (Brazil)

EMBRYOLOGIC DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM

Escola Paulista de Medicina

LASSE XI

Neurodevelopmental Disorders and Epilepsy

Embryologic Development of the Central Nervous System

Marcelo Masruha Rodrigues, M.D., Ph.D.

Professor of Child Neurology

Department of Neurology and Neurosurgery

Escola Paulista de Medicina

Overview

1. Major stages in the development of the human CNS
2. Basic aspects of the first 4 weeks of development
3. Neurulation
4. Development of the spinal cord
5. Early development of the encephalon
6. Fetal development of the encephalon
7. Myelination

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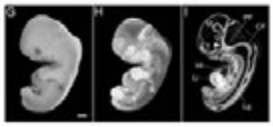
Importance of neuroembriology

Kyoto Collection of Human Embryo

- Initiated by Dr. Hideo Nishimura in 1961
- Comprises over 44.000 human embryo specimens
- Mainly derived from therapeutic abortions

Modern techniques of imaging



MRI microscopy
35 µm/pixel

Importance of neuroembriology

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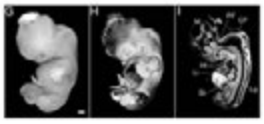

Episcopic fluorescence capture
2.3 to 13.4 μm/pixel

Importance of neuroembriology

Kyoto Collection of Human Embryo

- Initiated by Dr. Hideo Nishimura in 1961
- Comprises over 44.000 human embryo specimens
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Modern techniques of imaging

Optical projection tomography

Blue: HNF3b protein
Green: neurofilament-a
Red: non-specific autofluorescence

Major Stages in the Development of the Human Brain and Spinal Cord

Postfertilization or postconceptional x gestational age

Embryonic period – the first 8 weeks of development

- 23 stages – the Carnegie stages

Carnegie stages	Length (mm)	Age (days)	External features	Internal features (with emphasis on the nervous system)
1		1	Fertilization	
2		2–3	From 2 to about 16 cells	
3		4–5	Free blastocyst	Inner cell mass and trophoblast
4		6	Attaching blastocyst	Cytotrophoblast and syncytiotrophoblast distinguishable
5	0.1–0.2	7–12	Implantation; embryonic disk circular	Amniotic cavity; primary yolk sac; extra-embryonic mesoderm
6	0.2	17	Embryonic disk elongated	Chorionic villi; primitive streak and node; prechordal plate appears; secondary yolk sac
7	0.4	19	Embryonic disk oval	Notochordal process visible; hematopoiesis starts
8	1.0–1.5	23	Primitive pit appears; neural folds may begin to form	Notochordal and neurenteric canals detectable
9	1.5–2.5	25	First somites appear; mesencephalic flexure begins; otic disc forms	Neural groove evident; 3 major subdivisions brain distinguishable; heart begins to develop
10	2–3.5	28	Neural folds begin to fuse; otic pit develops; 4–12 somites; pharyngeal arches 1 and 2 visible	Optic primordium begins to develop; cardiac loop appears; intermediate mesoderm
11	2.5–4.5	29	Rostral neuropore closes; 13–20 somites	Optic vesicles develop
12	3–5	30	Caudal neuropore closes; 21–29 somites; 4 pharyngeal arches visible; upper limb buds appearing	Secondary neurulation starts
13	4–6	32	Otic vesicle closed; lens disc not yet indented; 30 or more somites; 4 limb buds visible	Retinal and lens discs develop; primordium of cerebellum

14	5–7	33	Lens pit appears; upper limb buds elongated	Future cerebral hemispheres, pontine flexure, optic cup developes, adenohypophysial pouch defined
15	7–9	36	Lens pit closed; nasal pit appearing; hand plate forming	Future cerebral hemispheres become defined; retinal pigment visible
16	8–11	38	Retinal pigment visible; nasal sacs face ventrally; auricular hillocks beginning; foot plate appears	Epiphysis cerebri develops; neurohypophysial evagination; olfactory subsicle
17	11–14	41	Head relatively larger; trunk straighter; auricular hillocks distinct; finger rays	Internal and external cerebellar swellings; chondrification begins in humerus, radius and ulna; vertebral centra
18	13–17	44	Body more cuboidal; elbow region and toe rays appearing	Otomucal membrane develops; 1–3 semicircular ducts in mental ear
19	16–18	46	Trunk elongating and straightening	Olfactory bulb develops; cartilaginous otic capsule; choroid plexus of fourth ventricle
20	18–22	49	Upper limbs longer and bent at elbows	Optic fibers reach optic chiasm; choroid plexus of lateral ventricle
21	22–24	51	Fingers longer; hands approach each other, foot rhomboid	Cortical plate becomes visible; optic tract and lateral geniculate body
22	23–28	53	Eyelids and external ear more developed	Olfactory tract, internal capsule, adenohypophysial stalk incomplete
23	27–31	56	Head more rounded; limbs longer and more developed	Insula indented, caudate nucleus and putamen recognizable; humerus presents all cartilaginous stages

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Major Stages in the Development of the Human Brain and Spinal Cord

Postfertilization or postconceptional x gestational age

Embryonic period – the first 8 weeks of development

- 23 stages – the Carnegie stages
- The first 4 embryonic weeks – blastogenesis
- The last 4 embryonic weeks – organogenesis

Fetal period – from the ninth week of development to the time of birth

- Can not be divided into a series of morphologically defined stages
- Phenogenesis

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Major Stages in the Development of the Human Brain and Spinal Cord

Embryonic period – three in time overlapping phases

- Formation and separation of the germ layers
- Dorsal induction – neurulation and neuromeres formation
- Ventral induction – telencephalization

Fetal period

- The fetal period proper (9 – 24 gestational weeks)
- The perinatal period (extending from the 24th week)

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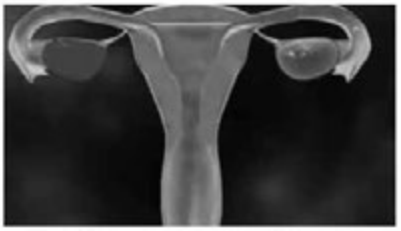
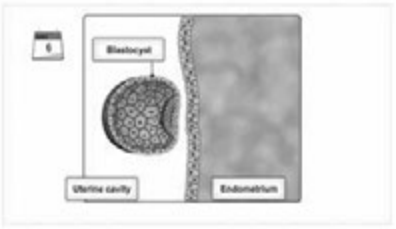
Basic Aspects of the First 4 Weeks of Development

First week – cleavage and blastocyst formation



Moore, K.L., Persaud T.V.N., Torchia, M.G. Before We Are Born: Essentials of Embryology and Birth Defects. 8th ed. Elsevier / Saunders, Philadelphia, 2012.

Second week – implantation



Second Week of development – Primal Anatomy & Physiology Online Course. http://primalonlinelearning.com

Third week – gastrulation

Moore, K.L., Persaud T.V.N., Torchia, M.G. Before We Are Born: Essentials of Embryology and Birth Defects. 8th ed. Elsevier / Saunders, Philadelphia, 2012.

Forth week – folding of the embryo

Moore, K.L., Persaud T.V.N., Torchia, M.G. Before We Are Born: Essentials of Embryology and Birth Defects. 8th ed. Elsevier / Saunders, Philadelphia, 2012.

Neurulation

Neurulation

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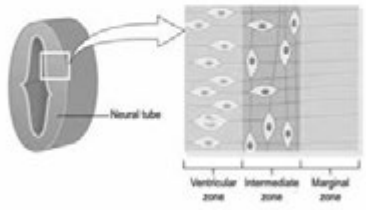
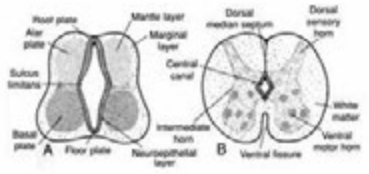
Neurulation



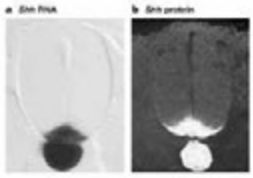
Development of the Spinal Cord

Development of the Spinal Cord



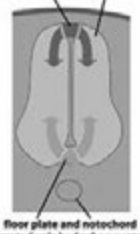
Development of the Spinal Cord

Extracellular signaling molecules



roof plate and adjacent cells secrete BMP proteins

neural tube

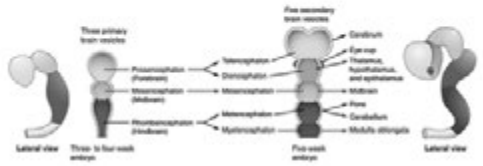


floor plate and notochord secrete Sonic hedgehog protein

Early Development of the Encephalon

Early Development of the Encephalon

The neural tube become bent by three flexures



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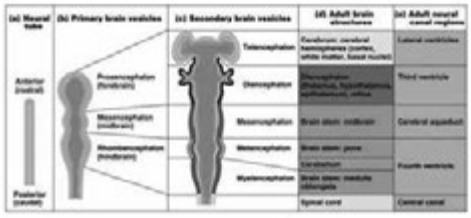
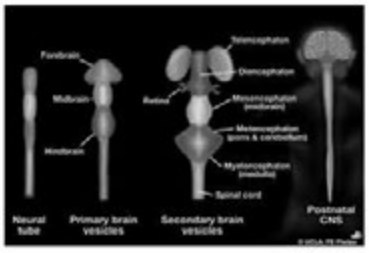
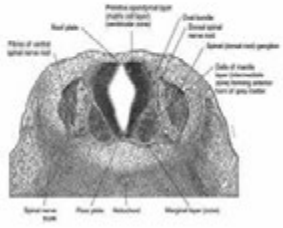


Early Development of the Encephalon



Pattern Formation of the Encephalon

Mediolateral or ventrodorsal pattern formation

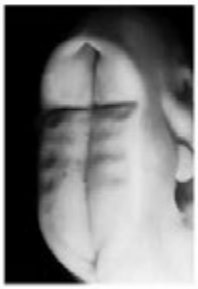


Pattern Formation of the Encephalon

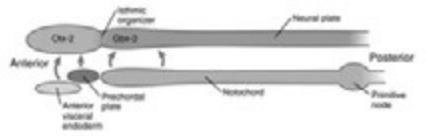
Mediolateral or ventrodorsal pattern formation

Rostrocaudal pattern formation – transverse zones

Neuromeres: segmentally arranged transverse bulges along the neural tube, particularly evidente in the hindbrain (rhombomeres)

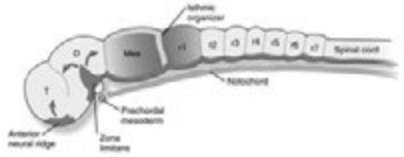


Early Development of the Encephalon



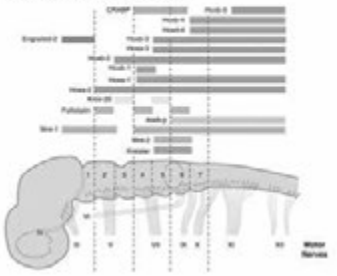
In response to signals (green arrows) from the anterior visceral endoderm, the prechordal plate, and the notochord, the neural tube express Otx-2 in the future forebrain and midbrain regions and Gbx-2 in the hindbrain and spinal cord

Early Development of the Encephalon

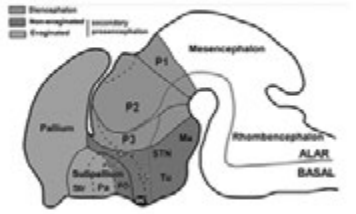


Later in development, signals (FGF-8 – green; Wnt-1 – yellow) from the isthmic organizer induce decreasing gradients of En-1 and En-2 (blue) on either side. Another organizer – the anterior neural ridge – secrets sonic hedgehog (red) and FGF-8 (green), and both the zona limitans and the ventral part (floor plate) of the neural tube secrete sonic hedgehog

Early Development of the Encephalon

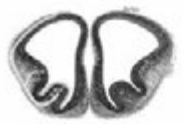


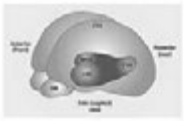
Early Development of the Encephalon

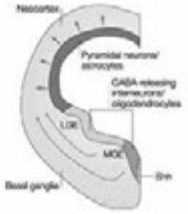


Ma: mammillary area; oc: optic chiasm; Pa: pallidum; PO: preoptic region; POC: commissural preoptic area; SC: suprachiasmatic area; SPV: supraoptic/paraventricular area; STN: subthalamic nucleus; Str: striatum; Tu: tuberal hypothalamus

Early Development of the Encephalon







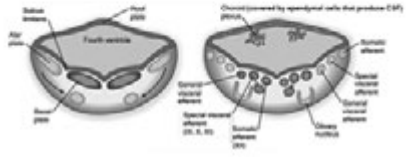
Fetal Development of the Encephalon

Fetal Development of the Encephalon

The myelencephalon

Alar plate develops into 4 sensory tracts:

- Olivary nucleus (cerebellar input)
- Somatic afferent (general sensation from the face, external ear, auditory meatus, and eardrum - CN V, IX, X)
- Special visceral afferent (taste – CN IX, X)
- General visceral afferent (autonomic input – CN IX, X)

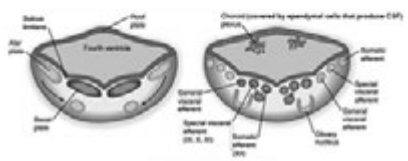


Fetal Development of the Encephalon

The myelencephalon

Basal plate develops into 3 motor tracts:

- General visceral efferent (autonomic output – CN IX, X)
- Special visceral efferent (innervation of pharyngeal arch muscles of the larynx and pharynx - CN IX, X)
- Somatic efferent (CN XI, XII)

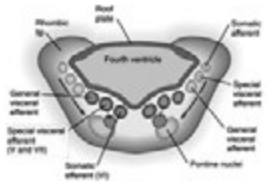


Fetal Development of the Encephalon

The metencephalon

Rhombic lip develops into cerebellum

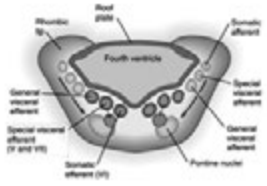
Alar plate develops into 4 sensory tracts:
- Pontine nuclei (cerebellar input)
- Somatic afferent (general sensation from the face and tongue - CN V)
- Special visceral afferent (taste – CN VII)
- General visceral afferent (soft palate and pharynx – CN V, VII)



Fetal Development of the Encephalon

The metencephalon

Basal plate develops into 3 motor tracts:
- General visceral efferent (autonomic output to salivary and lacrimal glands – CN VII)
- Special visceral efferent (innervation of muscles of the face – CN VII, and of mastication - CNV)
- Somatic efferent (innervation of lateral rectus muscule of the eye – CN VI)



Fetal Development of the Encephalon

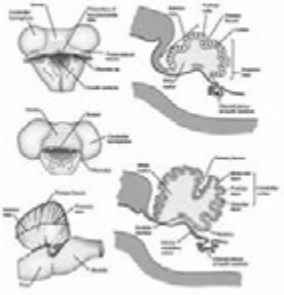
The cerebellum

Alar layers of the first rhombomere

6th week - tuberculum cerebelli

7th week - posterolateral fissure

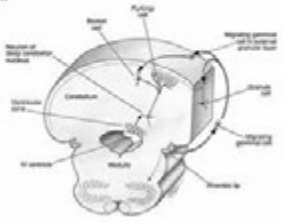
12th week – vermis, fissures (transverse pattern)

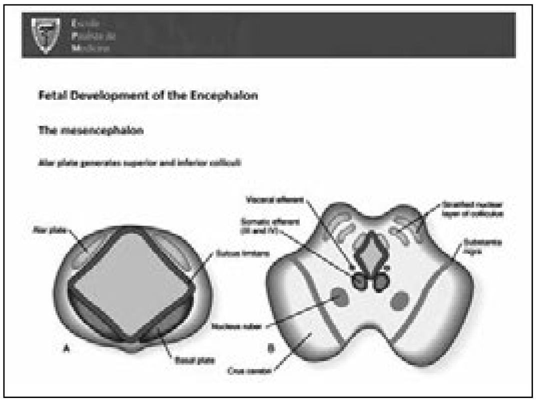


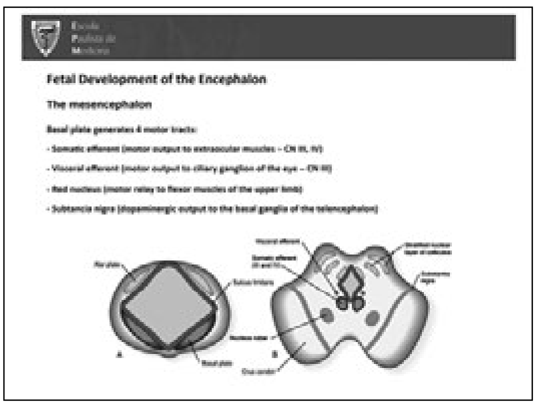
Fetal Development of the Encephalon

The cerebellum

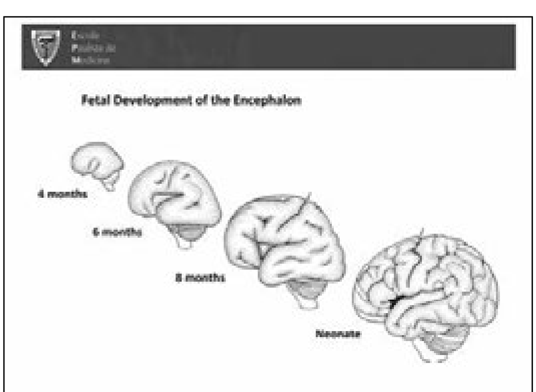
1. Direct migration from the ventricular zone to the primordial cerebellum (cerebellar plate)
2. Migration from the rhombic lip to the outer surface (external granular layer) of the cerebellar plate



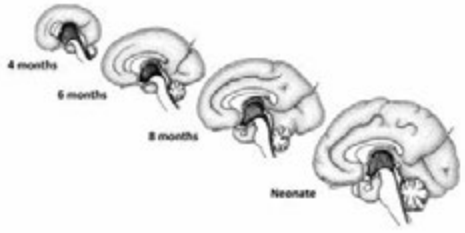

Escola
Paulista de
Medicina
Fetal Development of the Encephalon
The mesencephalon
Alar plate generates superior and inferior colliculi
Visceral efferent
Somatic efferent (III and IV)
Stratified nuclear layer of colliculus
Alar plate
Sulcus limitans
Substantia nigra
Nucleus ruber
A
B
Basal plate
Crus cerebri


Escola
Paulista de
Medicina
Fetal Development of the Encephalon
The mesencephalon
Basal plate generates 4 motor tracts:
- Somatic efferent (motor output to extraocular muscles – CN III, IV)
- Visceral efferent (motor output to ciliary ganglion of the eye – CN III)
- Red nucleus (motor relay to flexor muscles of the upper limb)
- Subtancia nigra (dopaminergic output to the basal ganglia of the telencephalon)
A
B


Escola
Paulista de
Medicina
Fetal Development of the Encephalon
Between weeks four and eight,
the embryo grows rapidly and the
face becomes recognizably human.
Prenatal Brain Development: From Conception to Birth.

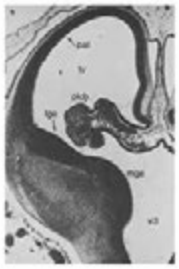

Escola
Paulista de
Medicina
Fetal Development of the Encephalon
4 months
6 months
8 months
Neonate

Fetal Development of the Encephalon



Fetal Development of the Encephalon

The plexus choroideus of the lateral ventricle arises in the lower part of the medial wall of the telencephalic vesicle



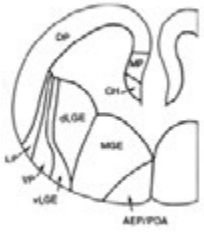
Fetal Development of the Encephalon

Medial pallium or archipallium – hippocampal cortex

Dorsal pallium or neopallium

Lateral pallium or paleopallium – olfactory cortex

Ventral pallium – claustroamygdaloid complex



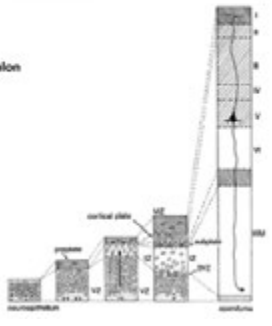
MP: medial pallium; DP: dorsal pallium; LP: lateral pallium; VP: ventral pallium; AEP/POA: anterior entopeduncular/preoptic area; CH: cortical hem; dLGE: dorsal part of lateral ganglionic eminence; MGE: medial ganglionic eminence

Fetal Development of the Encephalon

Neuron Production

Symmetrical cell divisions – 4 to 6 weeks

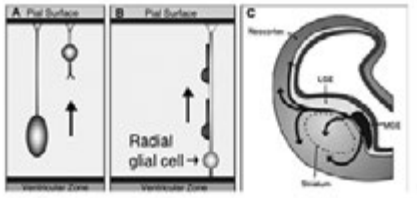
Asymmetrical cell divisions – 6 to 16 weeks



VZ: ventricular zone; IZ: intermediate zone; SVZ: subventricular zone; MZ: marginal zone; WM: white matter

Fetal Development of the Encephalon

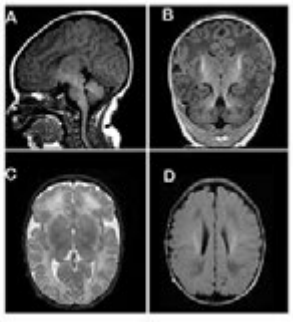
Neuron Migration – 12 to 24 weeks



Myelination

Myelination

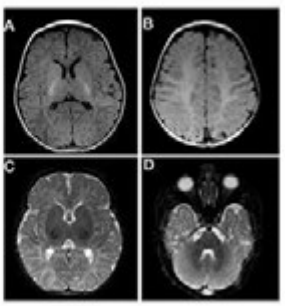
Newborn – 1,5 Tesla field strength



(A) Sagittal **T1-weighted** image demonstrating high-signal myelin within the dorsal medulla, pons, and midbrain. **Compare with the** unmyelinated low-signal white matter in the ventral pons and hemispheric white matter. **(B)** Coronal **T1-weighted** three-dimensional gradient echo image demonstrates high signal myelin in the posterior limbs of the bilateral internal capsules and the superior cerebellar peduncles. **(C) Axial T2-weighted** fast spin echo inversion recovery image demonstrating low signal myelin in the bilateral ventral lateral thalami. **(D)** Axial T2-weighted fluid attenuation inversion recovery image demonstrates patchy low signal in the deep frontal and parietal white matter due to high water content with signal suppression.

Myelination

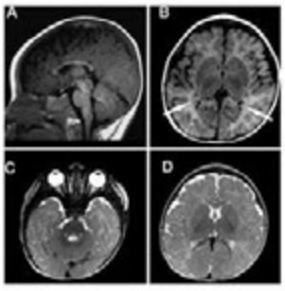
2 months – 3 Tesla field strength



(A) Axial **T1-weighted** image demonstrates prominent high-signal myelination of the posterior limbs of the internal capsules and early myelination within the anterior limbs. **(B)** Axial **T2-weighted** fluid attenuation inversion recovery image shows uniform high signal throughout the deep hemispheric white matter. The low-signal regions characteristic of the newborn have resolved by this age. **(C)** Axial **T2-weighted** fast spin echo inversion recovery (FSE-IR) image demonstrating low-signal myelin within the posterior limbs of the internal capsules, the anterior thalami, and to a lesser extent, the bilateral optic radiations. **(D)** Axial **T2-weighted** FSE-IR image displays myelin involving the brachium pontis bilaterally with early involvement of the deep cerebellar white matter.

Myelination

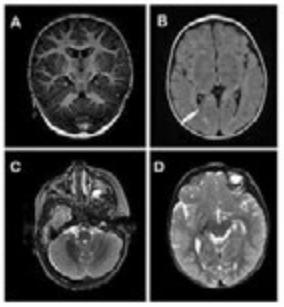
6 months – 3 Tesla field strength



(A) Sagittal T1-weighted image demonstrates high-signal myelin throughout the entire corpus callosum. **(B)** Axial T2-weighted FLAIR image showing low signal in the posterior limbs of the internal capsules and optic radiations (arrows). **(C)** Axial **T2-weighted** fast spin echo (FSE) image confirms complete myelination of the ventral pons. **(D) Axial T2-weighted** FSE image demonstrating low-signal myelin in the splenium of the corpus callosum and the posterior limbs of the internal capsules.

Myelination

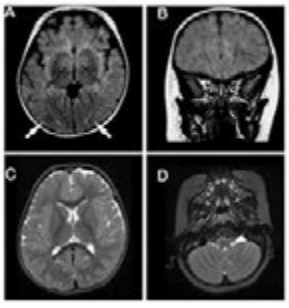
12 months – 3 Tesla field strength



(A) Coronal **T1-weighted** three-dimensional gradient echo image demonstrates an adult pattern of myelination with high-signal myelin extending into the subcortical U-fibers of the frontal and temporal lobes as well as throughout the cerebellum. **(B)** Axial **T2-weighted** fluid attenuation inversion recovery image shows early low-signal myelin in the deep white matter of the anteromedial occipital lobes best seen on the right (arrow). **(C)** Axial **T2-weighted** fast spin echo inversion recovery (FSE-IR) image demonstrates low-signal myelin in the deep white matter of the cerebellar hemispheres. **(D)** Axial **T2-weighted** FSE-IR image at a more superior level demonstrating early hypointense myelination of the occipital subcortical U-fibers. **There is low-signal myelin in the deep temporal white matter; however,** the subcortical white matter of the temporal lobes demonstrates persistent high signal.

Myelination

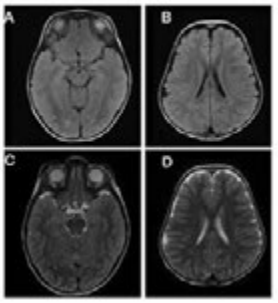
18 months – 1.5 Tesla field strength



(A) Axial T2-weighted fluid attenuation inversion recovery (FLAIR) image shows early low-signal myelin in the subcortical white matter of the occipital lobes (arrow). **(B)** Coronal axial T2-weighted FLAIR image demonstrating low-signal myelin in the deep white matter of the frontal lobes. **(C)** Axial **T2-weighted** fast spin echo inversion recovery (FSE-IR) **image demonstrates** prominent subcortical white matter myelination posteriorly and significantly less subcortical myelination in the frontal lobes. **(D) Axial T2-weighted** FSE-IR **image demonstrates** complete peripheral myelination in the cerebellum.

Myelination

24 months – 1.5 Tesla field strength



(A) Axial T2-weighted fluid attenuation inversion recovery (FLAIR) image demonstrating near complete low signal white matter myelination with the exception of the anterior temporal poles. Persistent high signal in the occipital lobes adjacent to the occipital horns of the lateral ventricles represents a normal FLAIR variant. **(B)** Axial T2-weighted FLAIR image confirms complete low-signal myelination of the frontal and parietal lobes with terminal zones of high signal in the periatrial regions as a normal variant. **(C,D)** Axial fast spin echo **T2-weighted** images demonstrate complete low-signal myelination throughout the brain with the exception of the periatrial terminal zones.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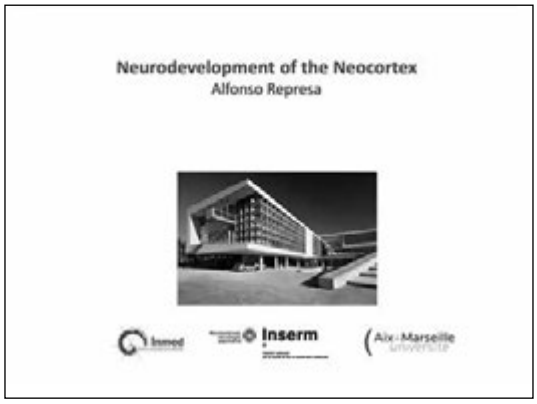
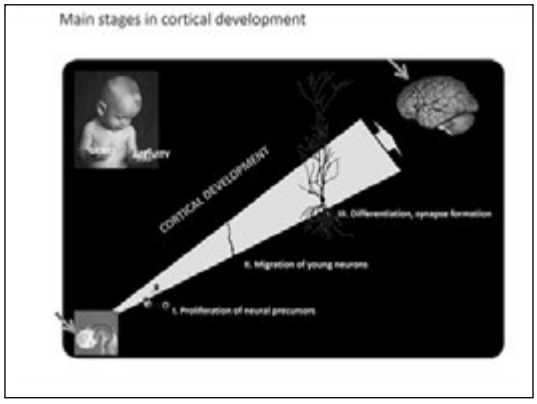
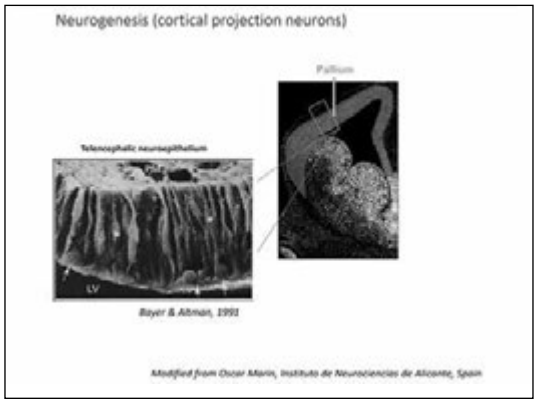
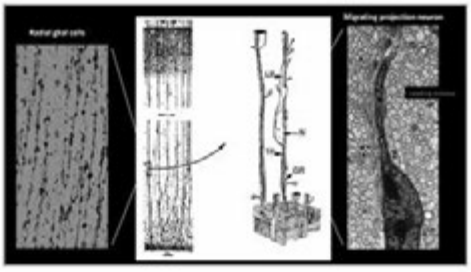
NEURODEVELOPMENT OF THE NEOCORTEX





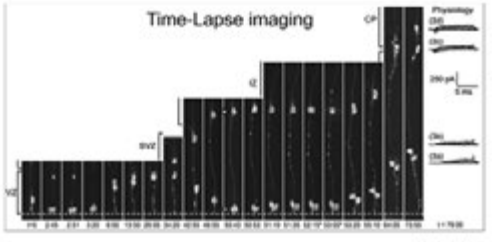


Cortical projection neurons migrate along radial glial fibers



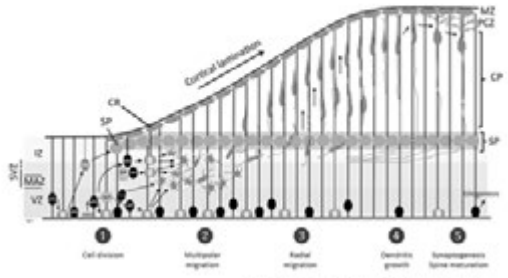
From Pasko Rakic, Yale School of Medicine, USA

Time-Lapse Imaging of cortical progenitors proliferation and migration



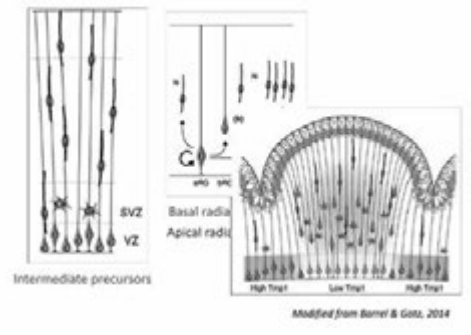
Kriegstein lab.

Neocortical histogenesis: a continuum of developmental stages



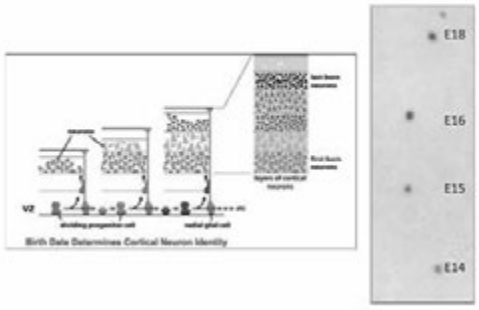
Ohtaka-Maruyama and Okado , Front Neurosci 2015

Novel types of neural precursor cells

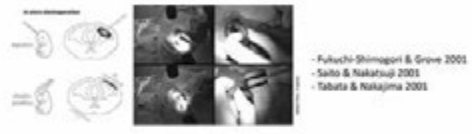


Modified from Borrel & Gotz, 2014

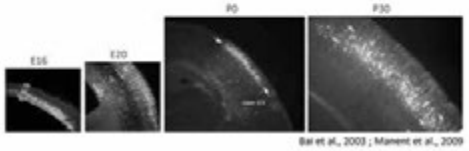
Cortical projection neurons migrate in an 'inside-to-outside' fashion to form columns and layers



The position of neurons in the cortical plate is dependent on the date of birth?



- Fukuchi-Shimogori & Grove 2001
- Saito & Nakatsuji 2001
- Tabata & Nakajima 2001

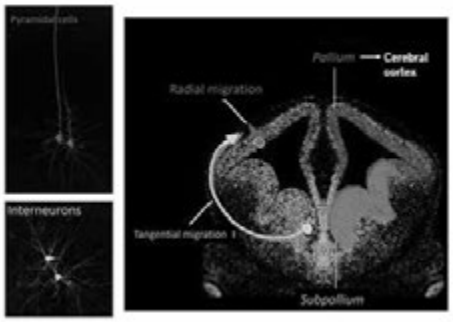


Bai et al., 2003 ; Monent et al., 2009

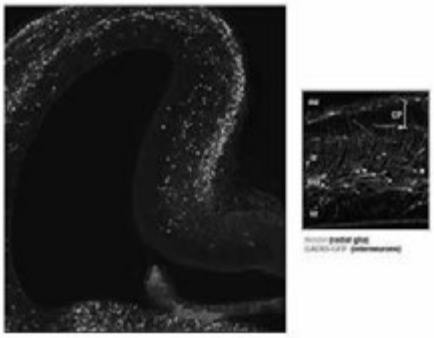
Cortical projection neurons migrate in an 'inside-to-outside' fashion to form columns and layers

Adult mouse somatosensory cortex. (Maureen P. Boyle, et al. 2011)

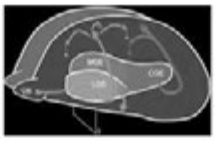
Two modes of migration in the cerebral cortex



Tangential migration (cortical interneurons)

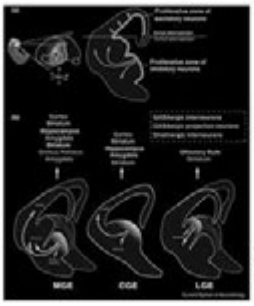


Origin and migration of cortical interneurons



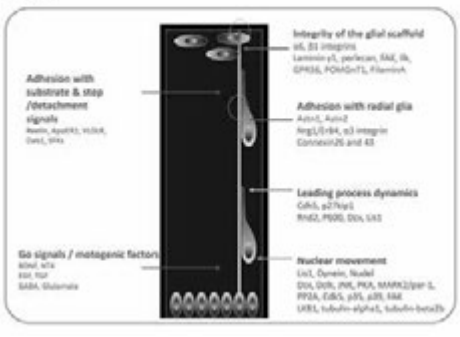
Faux et al. Neurosignals 2012

Ganglionic eminence produces GABAergic interneurons and projection neurons.

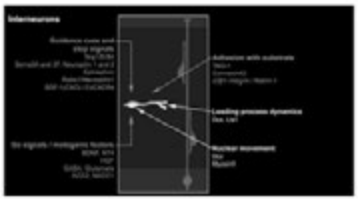


RC Bandler, C Mayer, G Fishell: Current Opinion in Neurobiology 2017

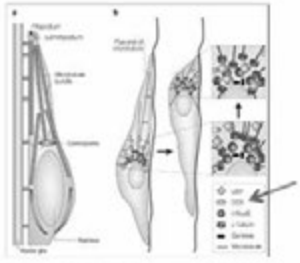
Cell-autonomous and cell-to-cell signaling events controlling radial migration



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

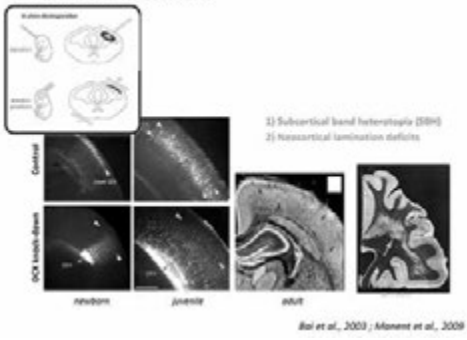


Microtubule-based nuclear translocation in neuronal migration



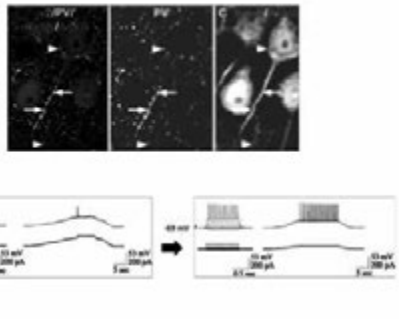
1) Microtubules extension in the leading process (DCX + MAPs)
2) Lis1 recruitment at the centrosome and microtubules shortening (= pulling forces)

Dcx loss of function generates a brain malformation (SBH: subcortical brain heterotopia)

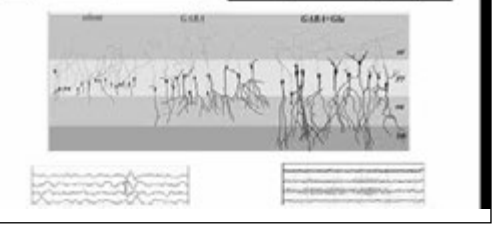


Bai et al., 2003 ; Manent et al., 2009

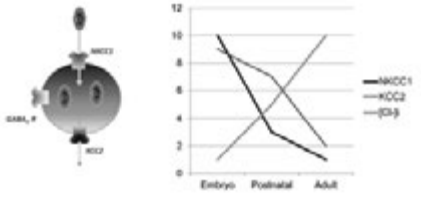
Neuronal maturation: axon maturation and genesis of action potentials



Neuronal maturation: Synaptogenesis and network activity maturation

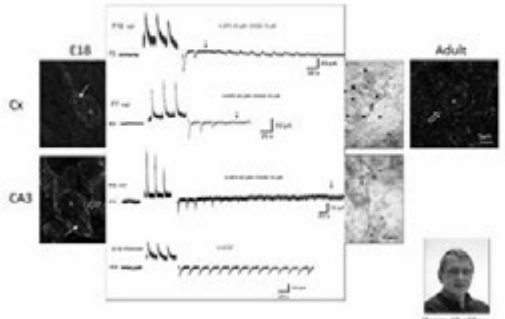


$[Cl^-]_i$ in developing brain



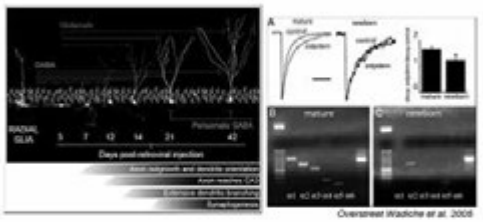
Tyzio et al., 2006 Science; 2007 Epilepsia; 2008 Eur. J. Neurosci.
Valeeva et al., 2010 Front. Cell. Neurosci.

KCC2 and Dynamic Regulation of choride



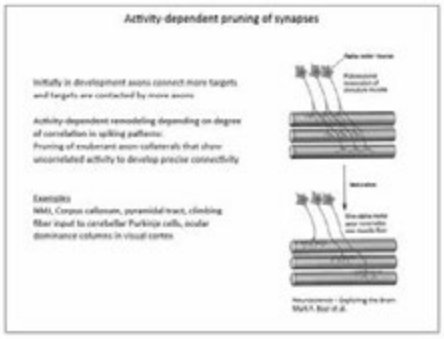
Ilgam Khalilov

Dendritic and synaptic maturation

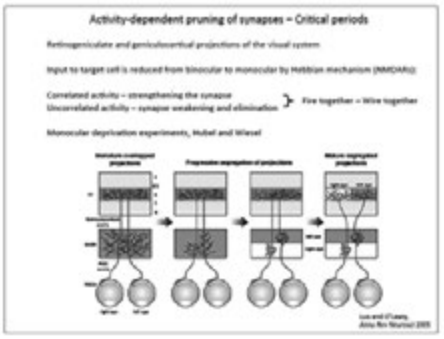


Overstreet Wadiche et al. 2005

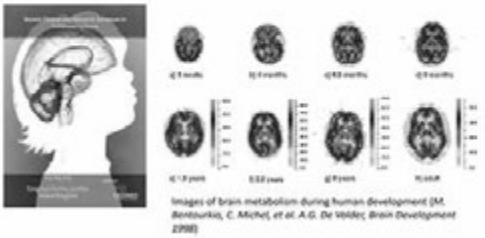
Developmental plasticity



Developmental plasticity

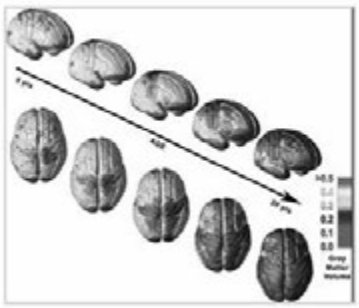


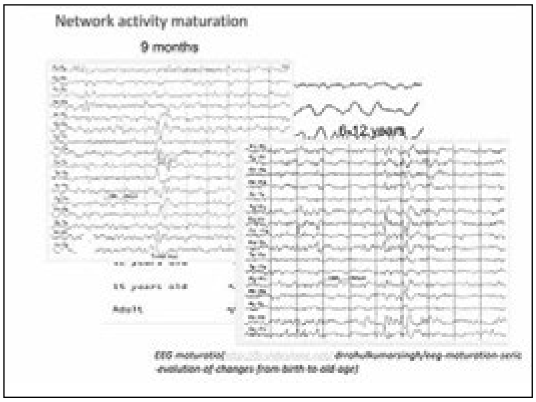
Developmental brain changes

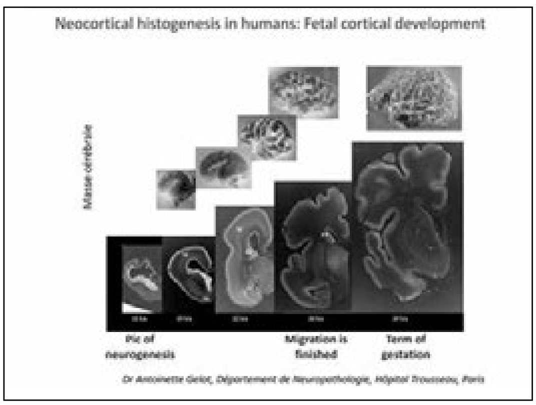


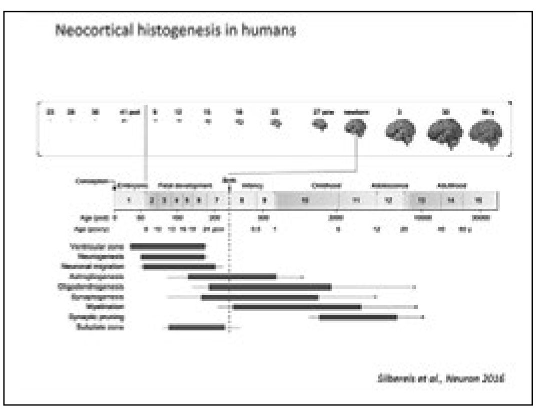
Images of brain metabolism during human development (*M. Bentourkia, C. Michel, et al. A.G. De Volder, Brain Development 1998*)

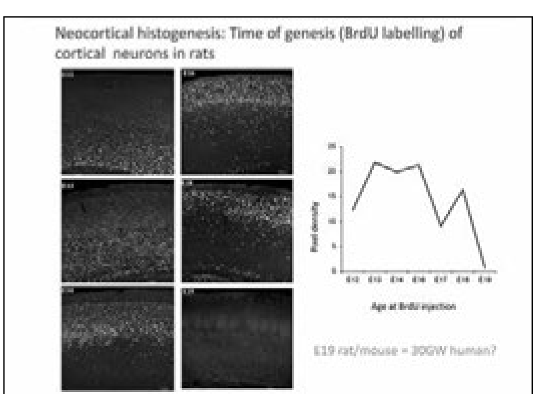
Brain development: regional maturation of cortical thickness



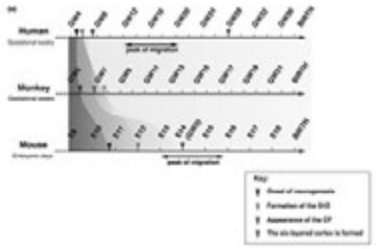

Network activity maturation
9 months
6-12 years


Neocortical histogenesis in humans: Fetal cortical development
Masse cérébrale
Pic of neurogenesis
Migration is finished
Term of gestation
Dr Antoinette Gelot, Département de Neuropathologie, Hôpital Trousseau, Paris


Neocortical histogenesis in humans
Silbereis et al., Neuron 2016


Neocortical histogenesis: Time of genesis (BrdU labelling) of cortical neurons in rats
Pixel density
Age at BrdU injection
E19 rat/mouse = 30GW human?

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



Xavier H. Joglin, Jamel Chelly; Trends in genet. 2009

Relative timelines of conserved cortical development hallmarks in human and mouse

Kindly provided by Dr Khazipov (INMED)

Marina Bentivoglio (Italy)

NEURODEVELOPMENT OF THE LIMBIC CIRCUITRY

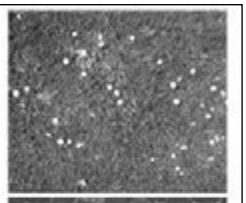
CHRISTOPHE BERNARD (FRANCE)

DEVELOPMENTAL CHANGES IN RECEPTOR CHANNELS

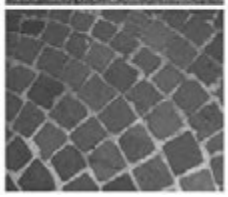
Giuseppe Bertini (Italy)

WHAT IS IMPORTANT WHEN DESIGNING A RESEARCH PROJECT

LASSE



Out there…



1. question/general idea
2. background search
3. design/hypotheses
4. grant writing
5. experiments
6. data analysis
7. paper writing
8. fame and glory

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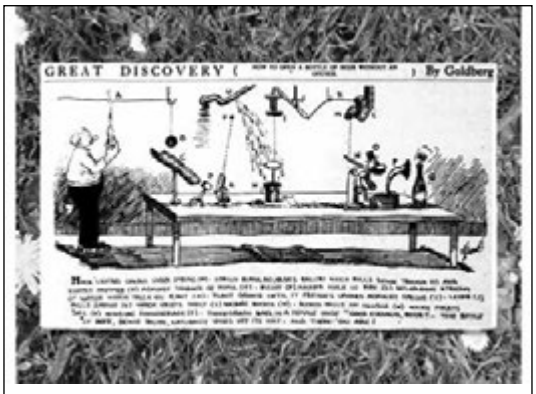
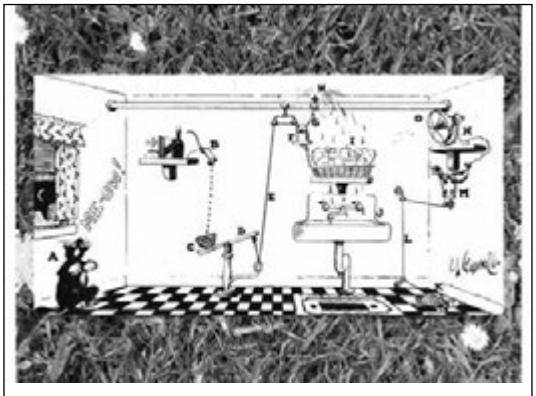
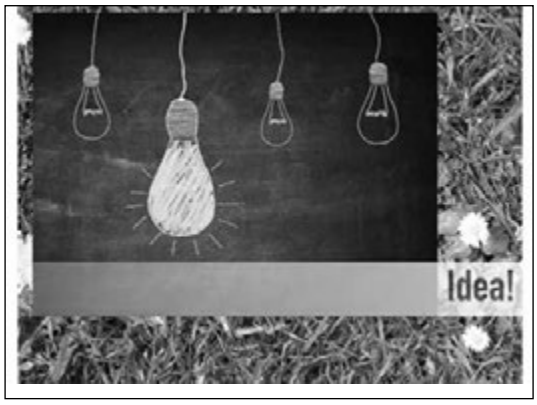
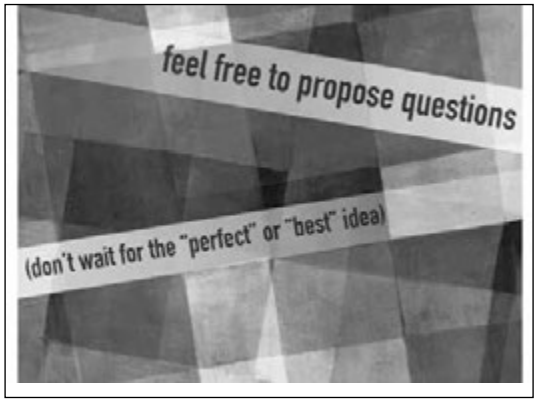


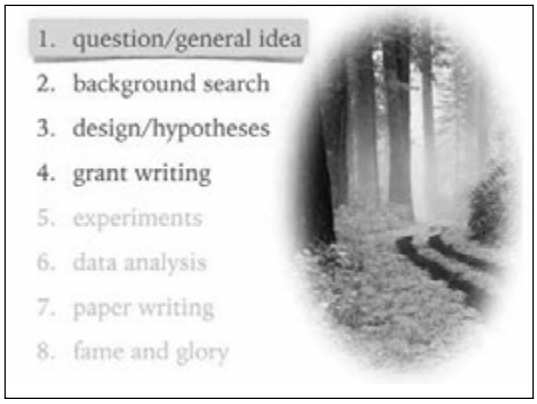


ideas


"cascading" ideas


Idea!


feel free to propose questions
(don't wait for the "perfect" or "best" idea)


1. question/general idea
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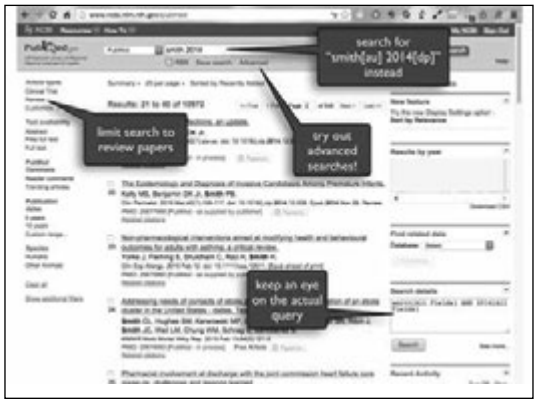
7. paper writing
8. fame and glory


Literature search

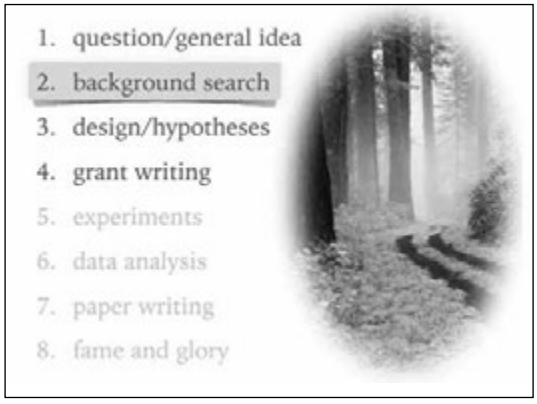

PubMed
Google
scholar


PubMed
Google


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


Paperpile - collaborative reference management


add references
to your Paperpile
collection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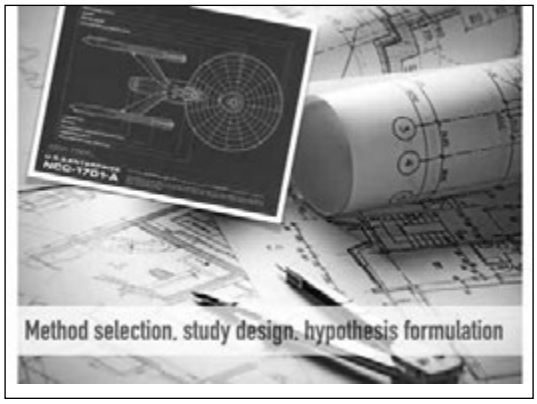
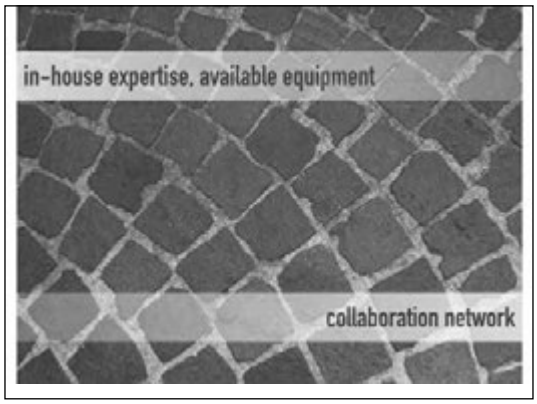
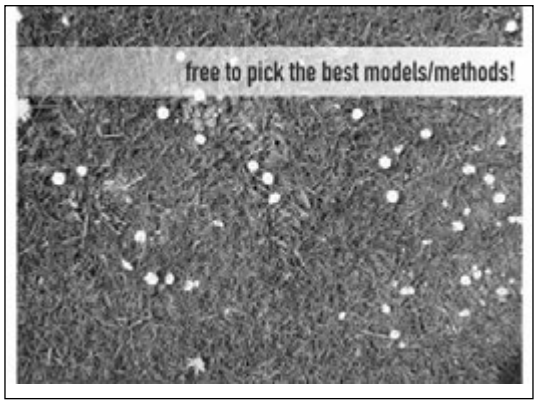
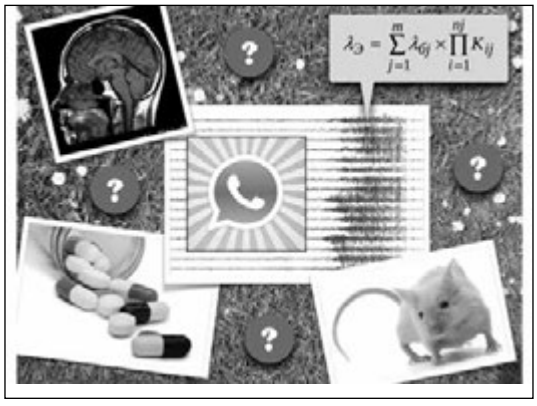
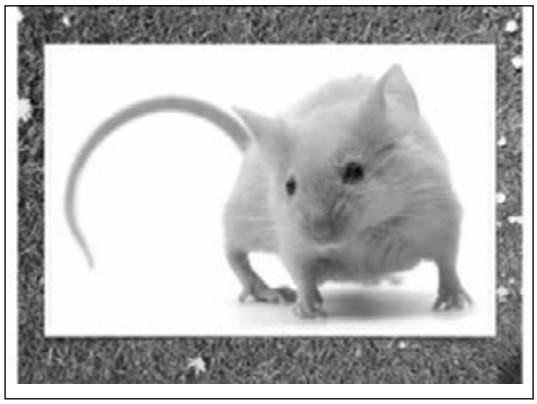

Method selection, study design, hypothesis formulation


in-house expertise, available equipment
collaboration network


free to pick the best models/methods!

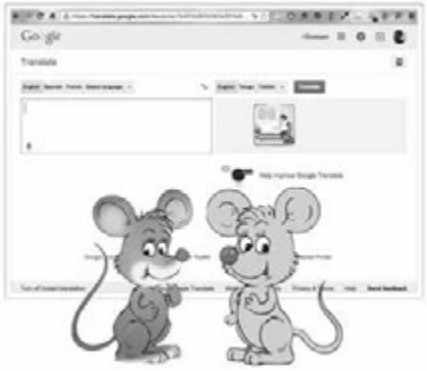

but make sure you are choosing the right tools...


$\lambda_{\ominus} = \sum_{j=1}^{m} \lambda_{\ominus j} \times \prod_{i=1}^{nj} K_{ij}$



our focus…

ANIMAL MODELS OF NEUROLOGICAL DISORDERS



COMMENTARY

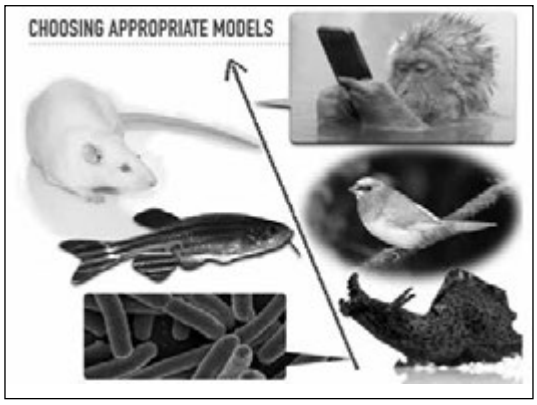
JAMA The Journal of the American Medical Association

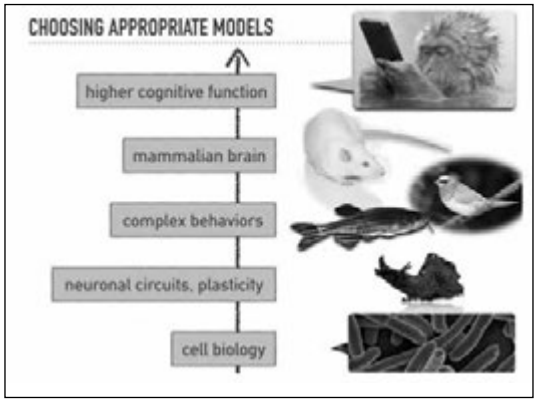
The Meaning of Translational Research and Why It Matters

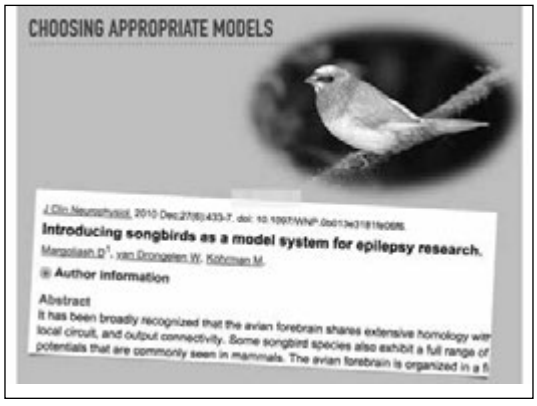
T1: the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans

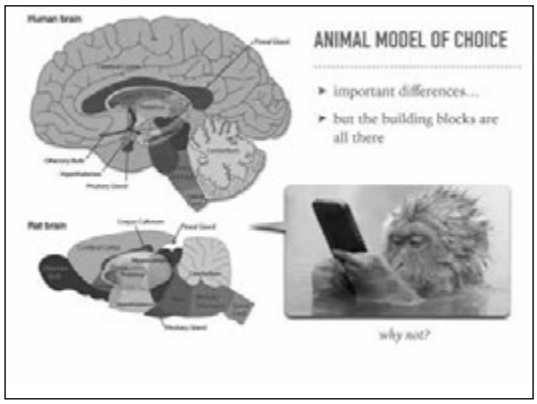
T2: the translation of results from clinical studies into everyday clinical practice and health decision making


ways to do translational research with animal models


CHOOSING APPROPRIATE MODELS

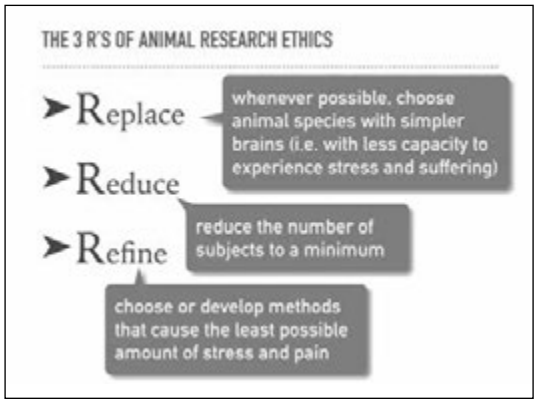

CHOOSING APPROPRIATE MODELS
higher cognitive function
mammalian brain
complex behaviors
neuronal circuits, plasticity
cell biology

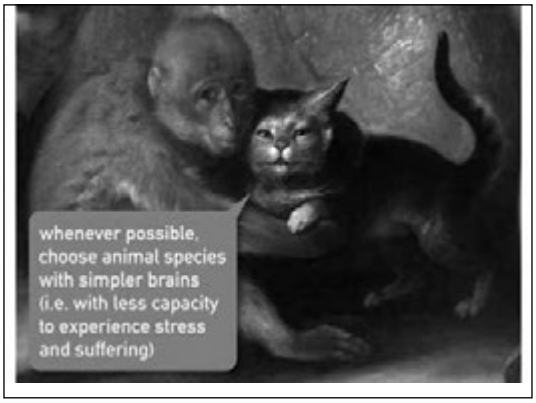

CHOOSING APPROPRIATE MODELS
J Clin Neurophysiol. 2010 Dec;27(6):433-7. doi: 10.1097/WNP.0b013e3181fe0685.
Introducing songbirds as a model system for epilepsy research.
Margoliash D[1], van Drongelen W, Kohrman M.
Author information
Abstract
It has been broadly recognized that the avian forebrain shares extensive homology wit
local circuit, and output connectivity. Some songbird species also exhibit a full range of
potentials that are commonly seen in mammals. The avian forebrain is organized in a fi


Human brain
Rat brain
ANIMAL MODEL OF CHOICE
important differences...
but the building blocks are all there
why not?


WHEN PLAID GOES BAD
FUR
WHEN PLAID GOES BAD
FUR
RESEARCH ETHICS
the ethical treatment of animals is a serious, widely-felt theme
fanaticism destroys constructive dialogue
scientists need strategies to move from "defensive" to "propositive"


NC 3Rs
https://www.nc3rs.org.uk
The 3Rs
Our science
Our resources
Funding
Welfare assessment e-learning resource launched


THE 3 R'S OF ANIMAL RESEARCH ETHICS
Replace
whenever possible, choose animal species with simpler brains (i.e. with less capacity to experience stress and suffering)
Reduce
reduce the number of subjects to a minimum
Refine
choose or develop methods that cause the least possible amount of stress and pain

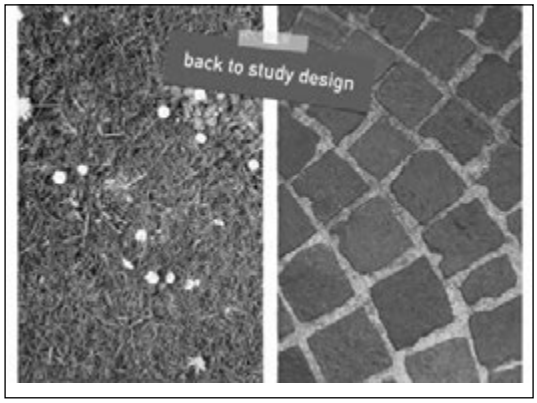


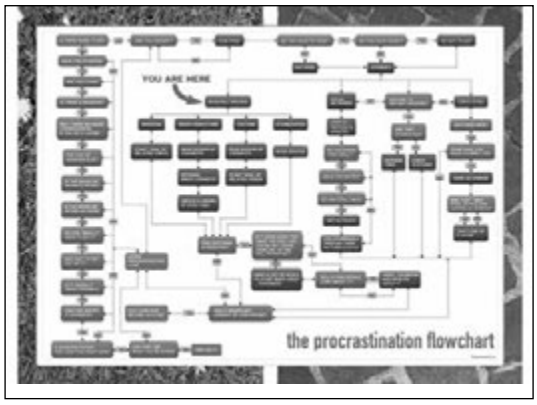
THE 3 R'S OF ANIMAL RESEARCH ETHICS

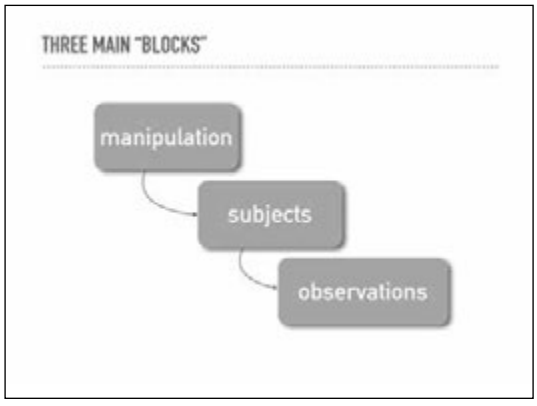
- Replace
- Reduce — reduce the number of subjects to a minimum
- Refine

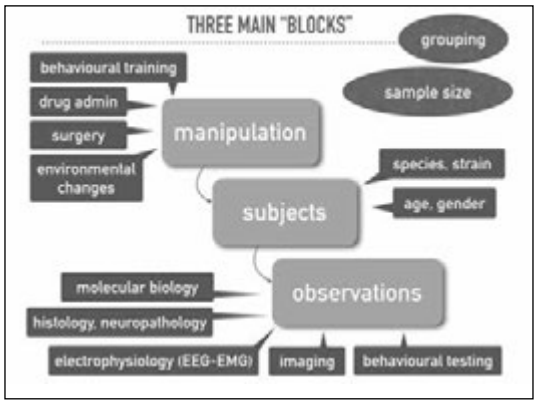
THE 3 R'S OF ANIMAL RESEARCH ETHICS

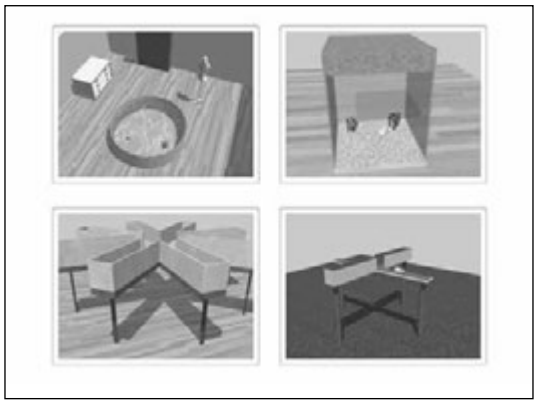
- Replace
- Reduce
- Refine — choose or develop methods that cause the least possible amount of stress and pain


back to study design

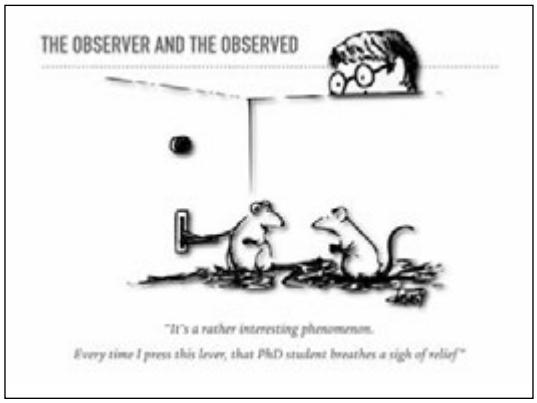

YOU ARE HERE
the procrastination flowchart


THREE MAIN "BLOCKS"
manipulation
subjects
observations

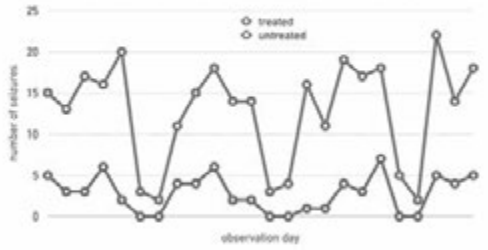

THREE MAIN "BLOCKS"
grouping
behavioural training
sample size
drug admin
manipulation
surgery
environmental changes
species, strain
subjects
age, gender
molecular biology
observations
histology, neuropathology
electrophysiology (EEG-EMG)
imaging
behavioural testing




BEWARE
hidden variables, experimental bias,
confounds, flaws, etc.

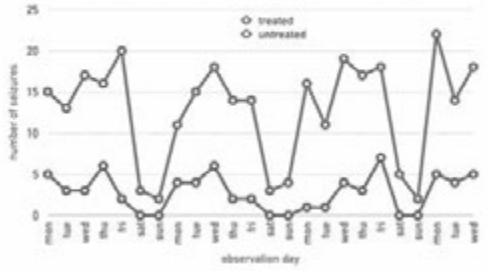

THE OBSERVER AND THE OBSERVED
"It's a rather interesting phenomenon.
Every time I press this lever, that PhD student breathes a sigh of relief"

A HIGHLY SIGNIFICANT EFFECT?



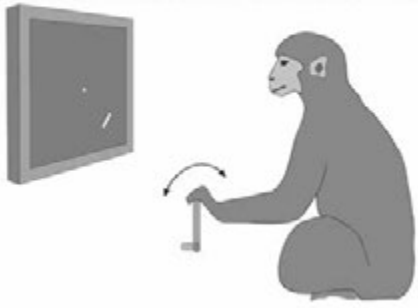
Paolo Fabene et al, unpublished observations

A HIGHLY SIGNIFICANT EFFECT?



Paolo Fabene et al, unpublished observations

IS THE MODEL BEHAVING AS EXPECTED?



1. question/general idea
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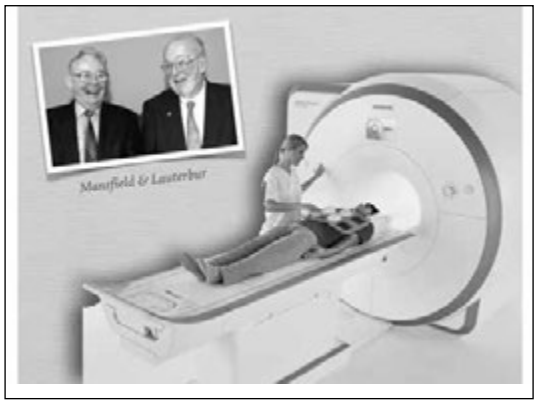
6. data analysis
7. paper writing
8. fame and glory

UP AND DOWN THE MOUNTAIN…

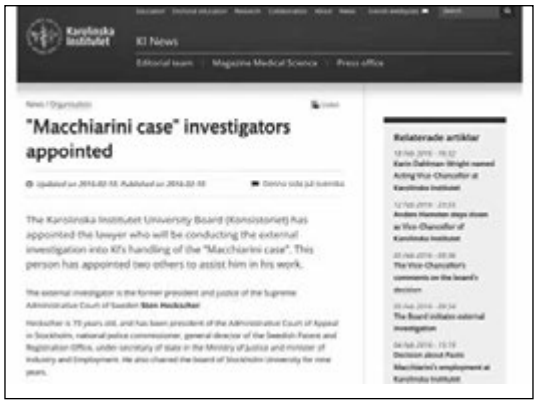
- tight resources, need to justify investments
- extreme competition: focus on "excellence", strategic questions, large networks
- exaggerated claims on what can be accomplished
- often disappointing results
- bureaucratic checks increased, repeat from start


Mansfield & Lauterbur

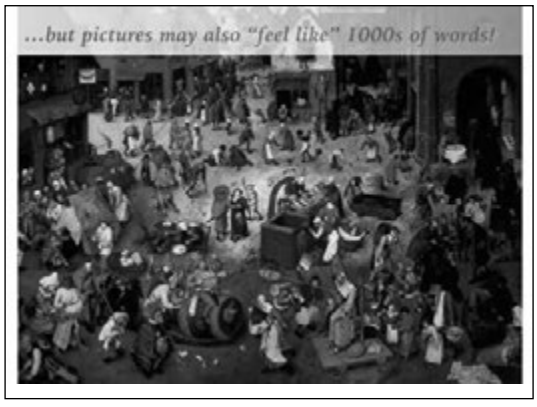

MONEY

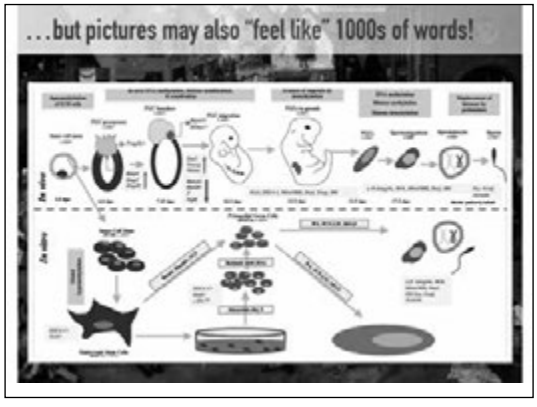

the stardom factor

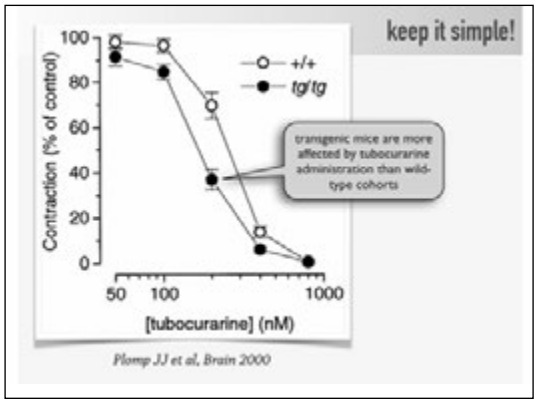

The Celebrity Surgeon Who Used Love, Money, and the Pope to Scam an NBC News Producer


Karolinska Institutet
KI News
Editorial team
Magazine Medical Science
Press office
"Macchiarini case" investigators appointed
The Karolinska Institutet University Board (Konsistoriet) has appointed the lawyer who will be conducting the external investigation into KI's handling of the "Macchiarini case". This person has appointed two others to assist him in his work.
Relaterade artiklar


a picture worth a thousand words

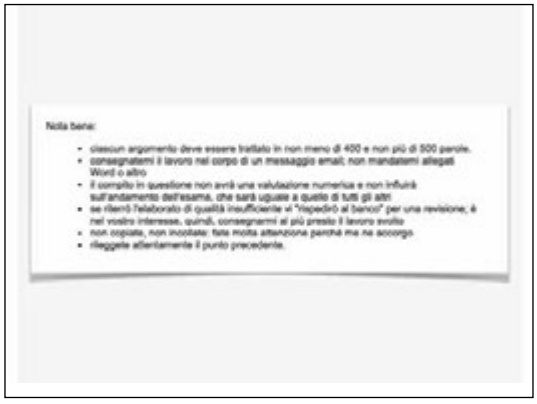

...but pictures may also "feel like" 1000s of words!


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


keep it simple!
100
80
60
40
20
0
Contraction (% of control)
+/+
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


the noble art of copying

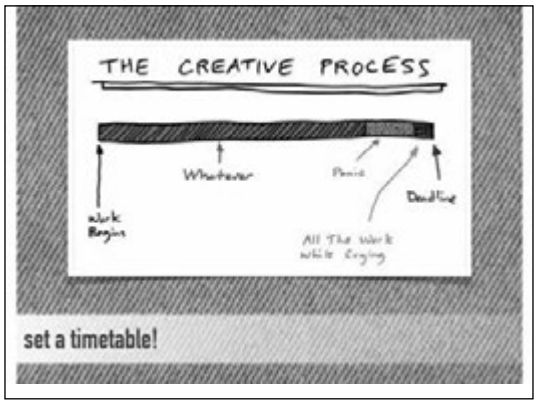

Epilepsy
the slightly less noble approach…

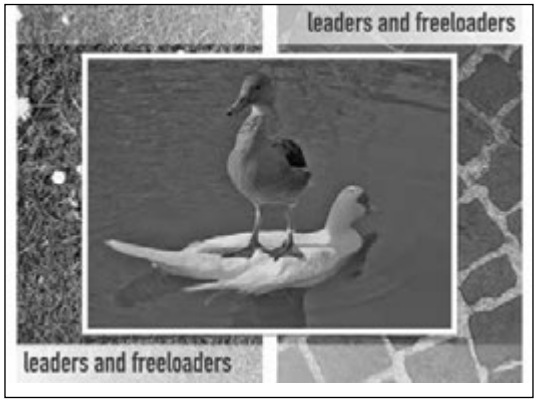

Nota bene:
classun argomento deve essere trattato in non meno di 400 e non più di 500 parole.
consegnatemi il lavoro nel corpo di un messaggio email; non mandatemi allegati Word o altro
il compito in questione non avrà una valutazione numerica e non influirà sull'andamento dell'esame, che sarà uguale a quello di tutti gli altri
se riterrò l'elaborato di qualità insufficiente vi "rispedirò al banco" per una revisione, è nel vostro interesse, quindi, consegnarmi al più presto il lavoro svolto
non copiate, non incollate: fate molta attenzione perché ma na accorgo
rileggete attentamente il punto precedente.


Buongiorno, come da accordi le invio il mio elaborato sugli argomenti da lei assegnati.
Mi faccia gentilmente sapere se lo scritto corrisponde ed esaudisce le sue richieste.
Distinti saluti,

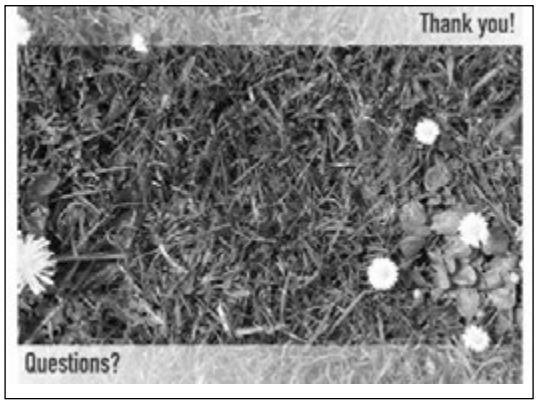

5. experiments
6. data analysis


Developing and presenting a well-designed research project in one week


THE CREATIVE PROCESS
Whatever
Panic
Deadline
work Begins
All the work while crying
set a timetable!

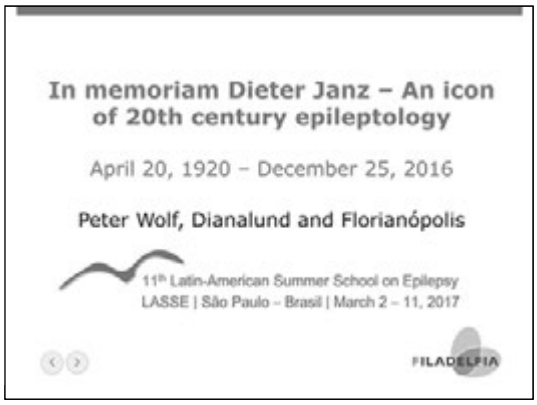

leaders and freeloaders
leaders and freeloaders

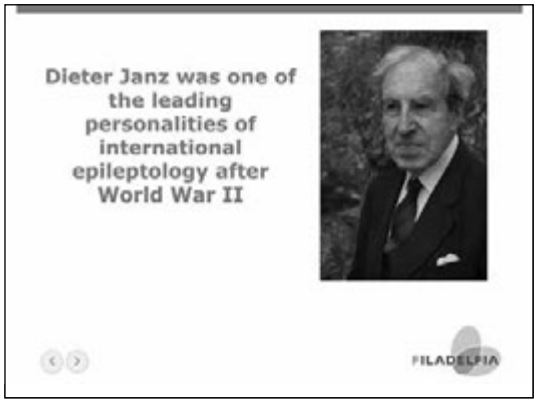

Google
Drive
Lasse15 abstract
File Edit View Insert Format Tools Table Paperpile Help

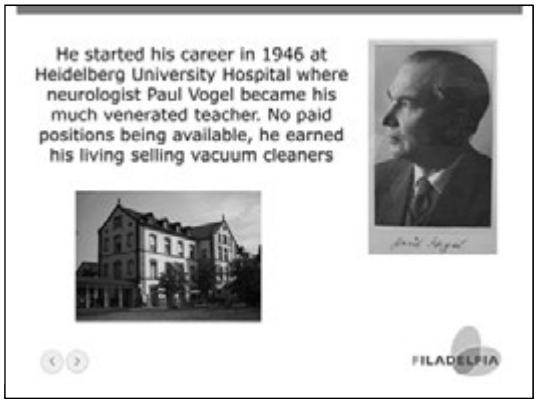

Thank you!
Questions?

Peter Wolf (Denmark)

IN MEMORIAM DIETER JANZ – AN ICON OF 20TH CENTURY EPILEPTOLOGY







- Became soon interested in epilepsy which at the time was a rather amorphous concept.
- Efforts to structure it by delineation of syndromatic entities.
- No EEG available, based on clinical and biological features
  - Semiology and seizure combinations
  - Motor patterns
  - Biorhythms
  - Age relations
  - Psychological traits and behaviour
  - Reaction to environmental stimuli
  - Treatment response

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1950ies: types of Grand Mal epilepsies

GM on awakening:

- combination with absences and myoclonic seizures
- juvenile onset
- sensitive to lack of sleep, alcohol
- best response to barbiturates
  - later, with EEG: syndrome of idiopathic generalized epilepsy

GM during sleep:

- combination with psychomotor (complex partial) szs
- circumstantial, pedantic personalities
- best response to phenytoin
  - later, with EEG: belonging to temporal lobe epilepsies

No circadian binding: no clear syndromatic features

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Juvenile myoclonic epilepsy

- Onset around puberty
- Szs: myoclonic, GTC, absences
- Awakening phase!
- Sleep deprivation alcohol!
- Personality traits (volatile, forgetful, "promise more than they hold")
- EEG: poly-spike wave (PSW), photo-sensitivity
- Good response to primidone
- Familiar occurrence!

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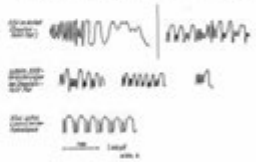
1957: Juvenile myoclonic epilepsy

Walter Christian



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1969 monograph "The Epilepsies"

Last single-author book about the entire clinical epilepsy

Comprehensive literature review

20 years of own experience with patients

Wealth of subtle, precisely described observations and their interpretation

The art of listening: from the patients we can learn most!

One of the masterworks of epileptology of the 20th Century

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Antiepileptic drug (AED) treatment

- In 1950/60ies standard treatment was with fixed combination pills (DPH, PB + x)
- Nobody cared about pharmacokinetics
- Janz found this completely irrational
- The Heidelberg standard:
  - First approach monotherapy with the most promising AED, if necessary dose increase until first toxic effects
  - In case of failure, 2nd monotherapy
  - Combination only in 3rd place and individual

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1973 Prof. of Neurology, Free University Berlin

Establishment of a new Department of Neurology

Among the (West) Berlin neurological departments, it stood out by its focus on therapy and rehabilitation (most others focused on diagnostics)

Dieter Janz represented the Heidelberg school of anthropological medicin which tries to comprehensively understand disease in its psycho-physical and social dimension.

This found a vivid echo in the young generation, and Janz became a much venerated teacher.

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The Berlin FU Department

Epilepsy was a priority with involvement in the most up-to-date developments:

- Video-EEG diagnostics
- AED measurement in serum for optimization of treatment, and research

Activities on international level

1973- 1981 Dieter Janz became Vice President of the International League against Epilepsy (ILAE)

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Genetic research

- Prospective longterm investigation of off-spring of the patients in his continuous personal care
- Clinical and EEG
- Begun in Heidelberg 1970 and continued in Berlin >20 years
- Kick-off for modern epilepsy genetics

with Antonio Delgado-Escueta

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ILAE Genetics Commission

Established in 1985
(President Harry Meinardi)
Dieter Janz became first Commission Chair
Period 1985-1991

H. Meinardi – P. Wolf – D. Janz

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Janz and epilepsy care

- 1957 instrumental in establishment of German Chapter of ILAE
- 1960 first German epilepsy clinic
- Followed by development of a country-wide network of seizure clinics, high impact on epilepsy care in Germany
- 1973 German Research Foundation: Memorandum on Epilepsy, resulting in improvement of conditions for epileptology

For Dieter Janz, the task to improve the situation for epilepsy and those affected by it always was multidimensional

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The Michael Foundation Sept 5, 1962

With Dieter Janz as its mentor, the Foundation became a highly important instrument to improve epileptology on all levels

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Janz and the Michael Foundation

- Training fellowships in epilepsy
  - for doctors
  - for paramedicals
- Equipment for epilepsy clinics
- Start help for self-help groups
- Meetings for specialisation of social workers
- Information brochures for patients, families, general public on many aspects of epilepsy
- Dieter Janz found this information program particularly important to assist patients with their typical life problems

STIFTUNG MICHAEL

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Rehabilitation

- One of the biggest challenges for patients with epilepsy is independent living
- Discrimination at the workplace because of irrational fears of possible damage
  - Cooperation with rehabilitation centres in Heidelberg, Berlin, to give PWE adequate vocational training
  - Establishment of commission of neurologists and statutory industrial accident insurances
  - ⇒ scales based on seizure symptoms and seizure frequencies to define in detail which workplaces are possible for PWE without increased risk

STIFTUNG MICHAEL

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Other public health initiatives

- Establishment of Information Centre for Epilepsy in Germany
- Epilepsie-Kuratorium: expert panel to monitor situation of epilepsy in Fed. Republic Germany and publish national epilepsy reports

STIFTUNG MICHAEL

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The Gargnano Seminars since 1989

- Not exactly a LASSE but …
- a 3 day seminar for 50-60 practicing neurologists / pediatricians and staff of neurological departments
- On Lake Garda, Italy but in German language
- Intensive working atmosphere in pleasant surroundings
- Dieter Janz loved it, never missed it, contact with young generation
- After 1989 strong participation of representatives of former DDR

Gargnano: teaching and relaxing

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The Michael Prize

- Established in 1963 as one of the very first initiatives of the new Foundation, proposed to the founder by Dieter Janz
- Original purpose: stimulation of epilepsy research in Germany
- 1963 – 1978 a German award
  - (including Austria, Switzerland)

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Michael Prize 1963-1978

The German period

Laureates in the fields of

- Clinical neurology/neuropediatrics/neurosurgery
- Experimental epilepsy research
- Psychiatry/psychology/neuropsychology
- Clinical neurophysiology
- Neuropathology
- Genetics
- Pharmacology

Michael Prize 1969

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Michael Prize after 1978

The international period

- Young researchers (< 45 yrs)
- Now one of the most prestigeous awards
- Biennial, 20.000 €
- Laureates: who is who in international epileptology?
  - predominantly experimental epileptology
- Recently more focus on clinical research
- 2017: laureate from neuroimaging field

Michael Prize 1984

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Michael Foundation new initiatives

- Support for Virepa students
- Focused Michael Fellowships:
- ≥ 6 weeks stay in a German institute or epilepsy centre
- Strategic workshops about future strategies for epilepsy in Germany
  - professionals
  - lay organisations

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Honours

Lifetime Achievement Award of ILAE and IBE 1999

2015 Michael Foundation Honorary Chair (with Michael's sister Dr. Agathe Bühler)

2004 Otfrid Foerster Medal German Epilepsy Society

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Dieter Janz as a cosmopolitan

- Cordial relations especially to Japan and to Latin America (Chile, Uruguay, Brasil)
- To some extent related to philosophy

Bin Kimura, Kyoto

Otto Dörr, Santiago

Heidelberg school of anthropological medicine

- Medicine not just applied natural science
- To understand a patient's disease you have to see the entire person, body and soul, in the person's social context
- Janz' teacher Paul Vogel represented this school

- » Janz most prominent representative in his generation in Germany
- » Strong echo in Japanese and Chilean neuropsychiatry

Victor v. Weizsäcker 1886 - 1957

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Janz and anthropological medicine

- As academic teacher:
  - In Berlin strong positive echo of the young generation to this approach
- As emeritus:
  - Co-Founder of Victor v. Weizsäcker Society
  - Co-Editor of his Collected Works in 10 volumes
  - In his last years working on edition of Weizsäcker's correspondence

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Dieter Janz' epileptological legacy

Juvenile Myoclonic Epilepsy (Janz syndrome)

1799 - 1865

Proposed name: *Impulsiv-Petit Mal*

In first case description by Théodore Herpin (1867) the myoclonic jerks of the patient were described by parents as "impulsions".

Name and description at first not well accepted outside the German-speaking community.

JME was a compromise which Janz never really liked

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Dieter Janz' epileptological legacy: JME

Original description

- Comprehensive clinical syndrome including psychosocial aspects
- EEG including photosensitivity
- Good treatment response
- Heredity

Additions

- Micromorphology and functional imaging
- Reflex epileptic traits
- Sophisticated neurophysiology (MEG, EP etc)
- Neuropsychology, psychiatry
- Genetics
- Long-term prognosis

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Dieter Janz' epileptological legacy

JME, the Brasilian connection:

at UNIFESP large, well-investigated cohort

- MR spectroscopy, morphometry
- Endophenotypes, cognitive testing
- Psychiatry
- Prognostic criteria

Project Theory of Mind in JME (São Paulo & Florianópolis)

Janz' legacy: present nosological concept

REVIEW

Juvenile myoclonic epilepsy:
A system disorder of the brain

Peter Wolf[a,b,*], Elza Márcia Targas Yacubian[c], Giuliano Avanzini[d], Thomas Sander[e], Bettina Schmitz[f], Britta Wandschneider[g], Matthias Koepp[g]

Dieter Janz' 95th birthday gift

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Thank you for your kind attention!

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MEET THE TUTORS

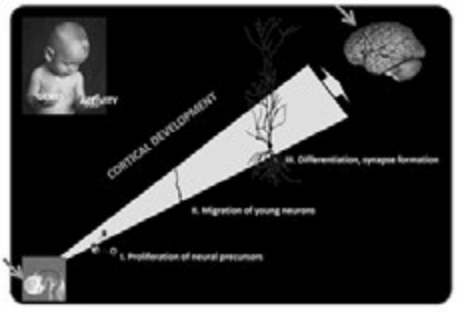
Alfonso Represa (France)

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

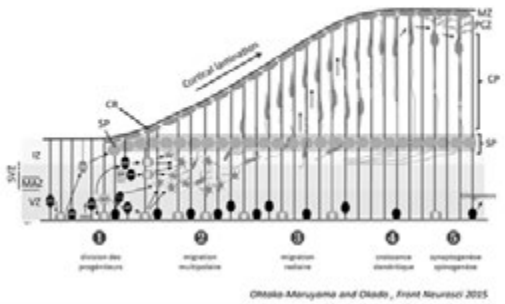
Molecular mechanisms that underlie cortical network development and function in health and disease

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

Main stages in cortical development

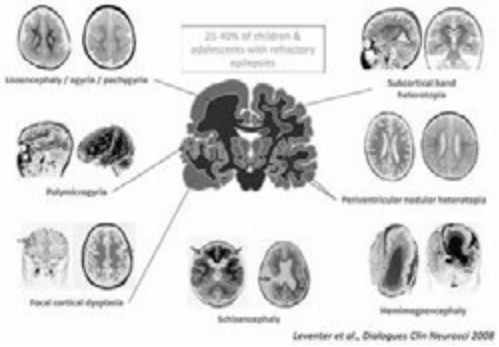


L'histogenèse néocorticale : a continuum of developmental steps



Ohtaka-Maruyama and Okado , Front Neurosci 2015

Cortical malformations



Leventer et al., Dialogues Clin Neurosci 2008

Neuronal migration disorders: clinical manifestations

- **Epilepsy**
- **developmental delay**
- **mental retardation**
- poor muscle tone and motor function
- failure to grow and thrive
- difficulties with feeding
- swelling in the extremities,
- smaller than normal head

- **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

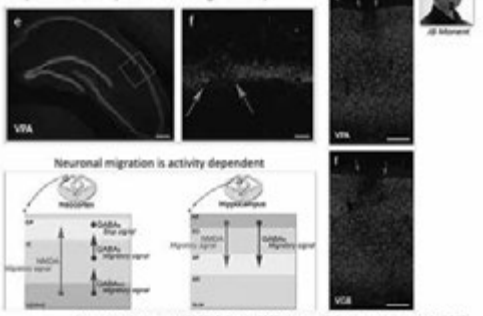
Cellular and molecular mechanisms depend on the
- Genetic or Environmental causes
- The cell type affected
- The developmental period concerned

Environmental factors and conditions which can potentially influence the developing brain

Therapeutic drugs	Catecholamines
Retinoic acid	Thyroid hormones
Anti-thyroid drugs	Diabetes
Oestroprogerstative drugs	Non treated phenylketonuria
Testosterone and derivatives	Coagulopathies
Anti-mitotic drugs	Peptides (vasoactive intestinal peptide)
Lithium and psychotropic drugs	Hormones from placenta and decidua
Benzodiazepines	Hypoxic-ischemic conditions
Anti-epileptic drugs	Chorioamnionitis
Recreational drugs	Hyperthermia
Tobacco	Infectious agents (human pathogens)
Caffeine	Herpes simplex virus I and II
Ethanol	Varicella zoster
Cocaine	Human cytomegalovirus
Heroin	Benign lymphocytic choriomeningitis virus
LSD	Rubella virus
Marijuana	Parvovirus B19
Physical and chemical agents	Coxsackie virurs (B group)
Dioxins	Pestivirus
Heavy metals	HIV
Organic solvents	Influenza virus
Ionizing radiations	BK and JC viruses
Head trauma	Toxoplasma gondii
Repeated head shaking	Listeria monocytogenes
Maternal factors and conditions	Treponema pallidum (syphilis)
Sexual hormones	

Grossens et al, 2001

Antiepileptic drugs affects cortical development (in utero exposure to Valproate and Vigabatrin)



Neuronal migration is activity dependent

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

Genetic basis of cortical development disorders

Genes involved on migration defects		Type of malformation
TSC1 *TSC2*		Abnormal proliferation/differentiation (Tuberosclerosis and FCDs)
ARX *DCX* *TUBA1A* *LIS1* *RELN* *VLDLR*	*YWHAE* *KIF2A* *TUBG1*	Abnormal migration : lissencephaly , Subcortical band heterotopia
FLNA *ARGEF2*		Abnormal migration : Periventricular Heterotopia
FCMD *FKRP* *LARGE* *POMGNT1* *POMT1* *POMT2* *TMEM5*	*GPR56* *SNAP29* *B3GALNT2* *B3GNT1* *GTDC2* *GPD* *LAMB1*	Cobblestone, Syndrome Walker-Warburg, Syndrome Muscle-eye-brain
SRPX2 *TRB2* *PAX6* *GPR56* *DYNC1H1* *TUBB2B, B3 and B5*		Abnormal cortical organization/Gyration

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

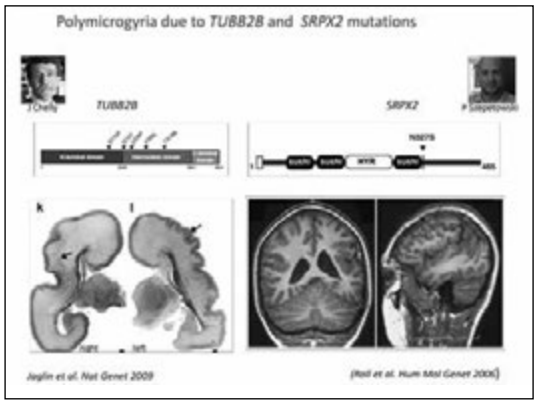
- (A) SEVERE CONGENITAL MICROCEPHALY (MIC), pre-migrational reduced proliferation or excess apoptosis
- (B) MEGALENCEPHALY (MEG) including both congenital and early postnatal
- (C) CORTICAL DYSGENESIS WITH ABNORMAL CELL PROLIFERATION BUT WITHOUT NEOPLASIA
- (D) CORTICAL DYSPLASIAS WITH ABNORMAL CELL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

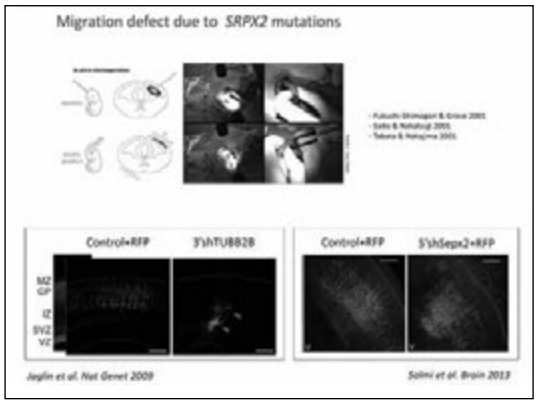
(II) MALFORMATIONS DUE TO ABNORMAL NEURONAL MIGRATION

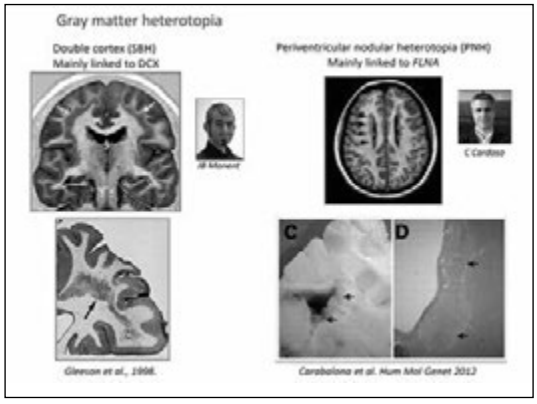
- (A) MALFORMATIONS WITH NEUROEPENDYMAL ABNORMALITIES: PERIVENTRICULAR HETEROTOPIA
- (B) MALFORMATIONS DUE TO GENERALIZED ABNORMAL TRANSMANTLE MIGRATION (radial and non-radial)
- (C) (C) MALFORMATIONS PRESUMABLY DUE TO LOCALIZED ABNORMAL LATE RADIAL OR TANGENTIAL TRANSMANTLE MIGRATION

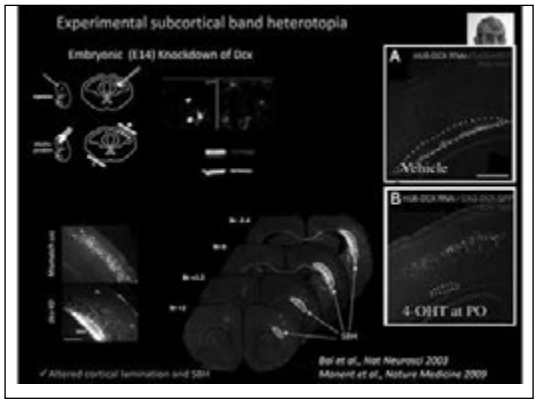
(III) MALFORMATIONS DUE TO ABNORMAL POSTMIGRATIONAL DEVELOPMENT

- (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


Polymicrogyria due to TUBB2B and SRPX2 mutations
TUBB2B
SRPX2
Jaglin et al. Nat Genet 2009
(Roll et al. Hum Mol Genet 2006)

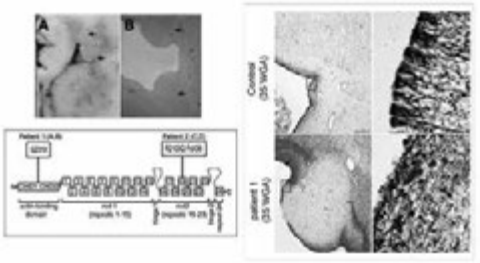

Migration defect due to SRPX2 mutations
Control+RFP
3'shTUBB2B
Control+RFP
5'shSepx2+RFP
MZ
CP
IZ
SVZ
VZ
Jaglin et al. Nat Genet 2009
Salmi et al. Brain 2013


Gray matter heterotopia
Double cortex (SBH)
Mainly linked to DCX
Periventricular nodular heterotopia (PNH)
Mainly linked to FLNA
C Cardoso
JB Moment
C
D
Gleeson et al., 1998.
Carabalona et al. Hum Mol Genet 2012


Experimental subcortical band heterotopia
Embryonic (E14) Knockdown of Dcx
A
Vehicle
B
4-OHT at PO
SBH
Bai et al., Nat Neurosci 2003
Moment et al., Nature Medicine 2009

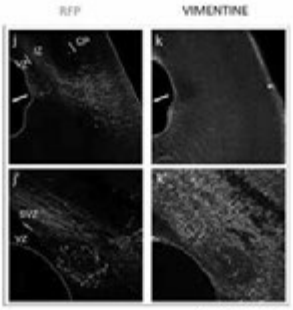
Radial glia disruption in PNH patients with *FLNA* mutations

E Carabalona



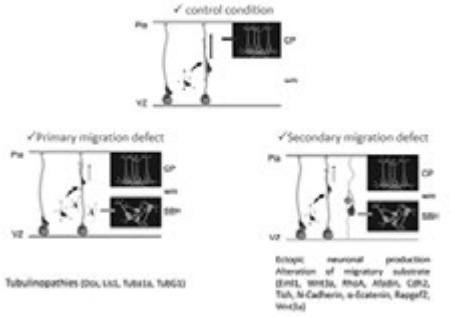
Carabalona et al. Hum Mol Genet 2012

FlnA periventricular nodular heterotopia: Glialopathy?



Carabalona et al. Hum Mol Genet 2012

Gray matter heterotopia (SBH and PNH): Primary or secondary migration alteration



Tubulinopathies (Dcx, Lis1, Tuba1a, Tubb3)

Ectopic neuronal production
Alteration of migratory substrate
(Ephb1, Wnt3a, RhoA, Afadin, Cdh2, Tiam, N-Cadherin, α-Catenin, Rapgef2, Vim-/-)

Questions:

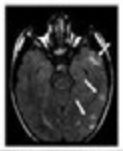
1. Link between cause and phenotype: understanding the pathophysiology of cortical development disorders

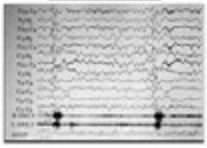
2. Link between the developmental alteration and the epileptic condition

Questions:

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

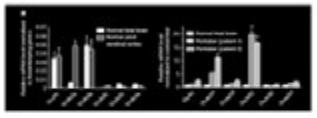
Cell autonomous changes: exploring human postsurgical samples and animal models for Tuberous sclerosis

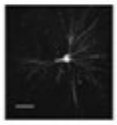




Recordings from postoperational human brain tissue from TSC patient

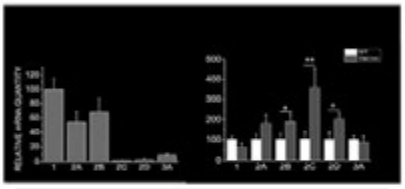
N Bernashev

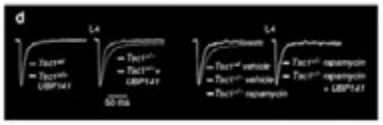




Lozovaya et al. Nat. Comm. 2014

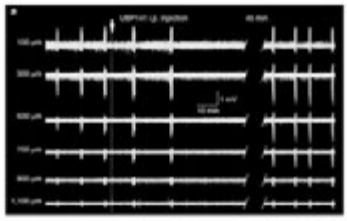
Relative expression of NMDAR subunits in wild type and *Tsc1* $^{+/-}$ mice





Lozovaya et al. Nat. Comm. 2014

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



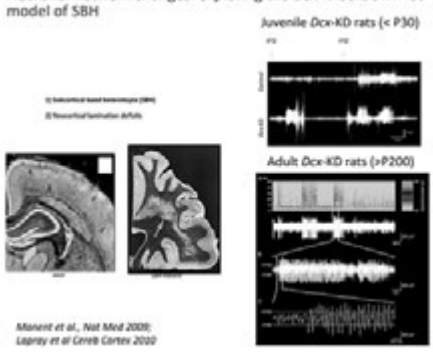
Losonsya et al. Nat. Comm. 2014

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 patients (a new therapeutic target)

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



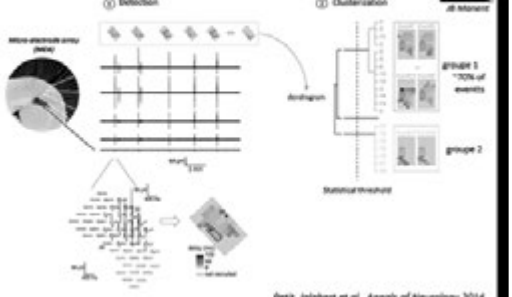
Juvenile *Dcx*-KD rats (< P30)

Adult *Dcx*-KD rats (>P200)

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

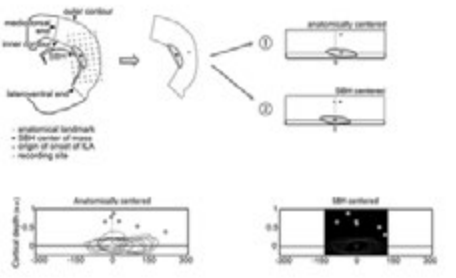
Characterization of interictal activities using MEA recordings and cluster analysis

JB Manent



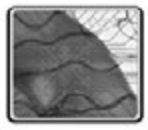
Peiti, Jalabert et al., Annals of Neurology 2014

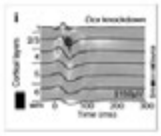
Origin of interictal activity



Petit, Jalabert et al., Annals of Neurology 2014

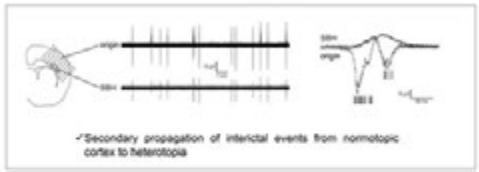
The epileptogenic focus on the cortical slices of DCX-KD rats is out of the heterotopia



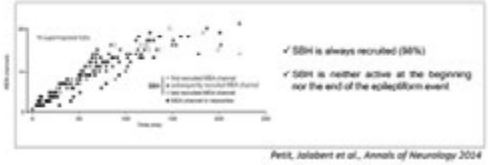


Petit, Jalabert et al., Annals of Neurology 2014

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



✓Secondary propagation of interictal events from normotopic cortex to heterotopia

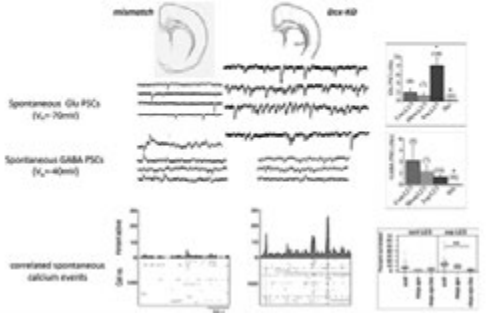


✓SBH is always recruited (96%)

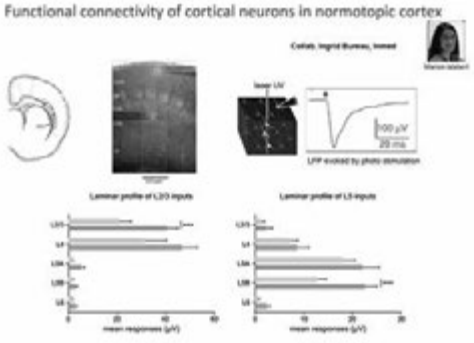
✓SBH is neither active at the beginning nor the end of the epileptiform event

Petit, Jalabert et al., Annals of Neurology 2014

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

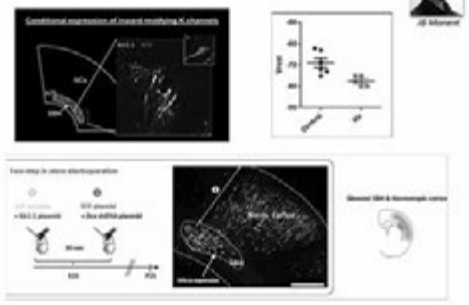


Functional connectivity of cortical neurons in normotopic cortex

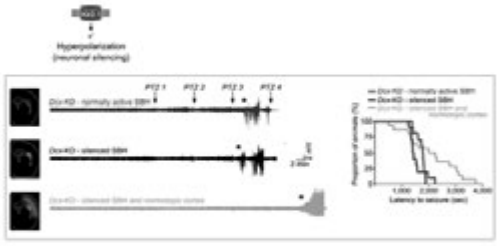


Jelabert et al, preliminary data

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



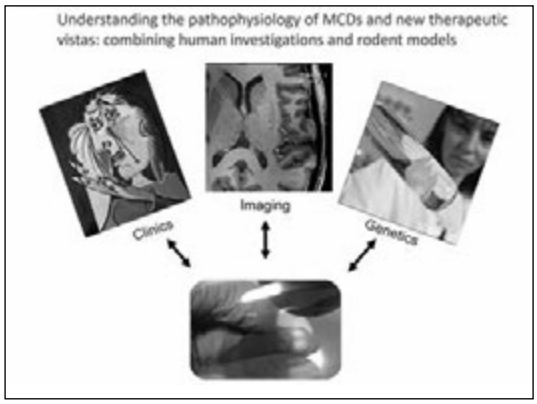
Supression of neuronal network excitability



Paoli, Jelabert 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 MCDs and new therapeutic vistas: combining human investigations and rodent models
Clinics
Imaging
Genetics

MATTEO CALEO (ITALY)

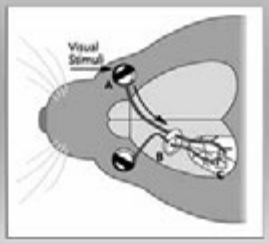
CRITICAL PERIODS FOR BRAIN PLASTICITY AND EPILEPSY

CRITICAL PERIODS
FOR BRAIN PLASTICITY
AND EPILEPSY

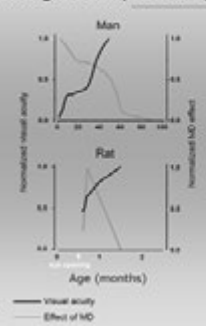
Matteo Caleo

CNR Neuroscience Institute
Pisa, Italy

The visual system: a classical model to study activity-dependent plasticity



The visual cortex is immature at birth, and gradually develops its functional properties



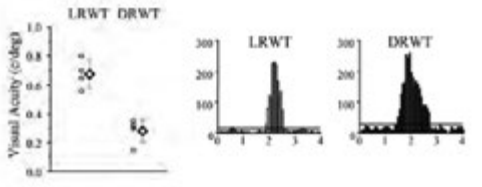
During the "critical period":

- Increase of visual acuity
- Decreased plasticity

Visual afferent input is required for proper cortical development during the critical period

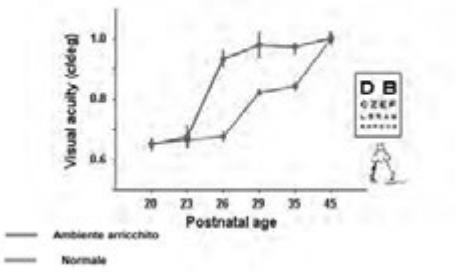
Functional development of the visual cortex: effects of dark rearing

Impaired development of visual acuity Increased receptive field sizes

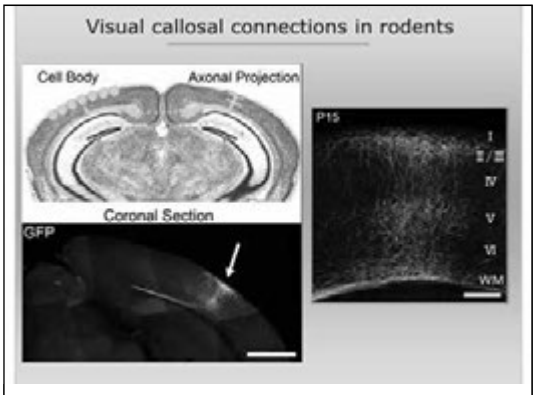


Functional development of the visual cortex: effects of enriched environment

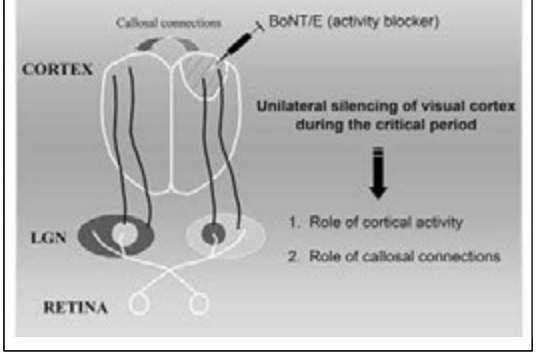
Functional maturation of the visual cortex: effects of enriched environment



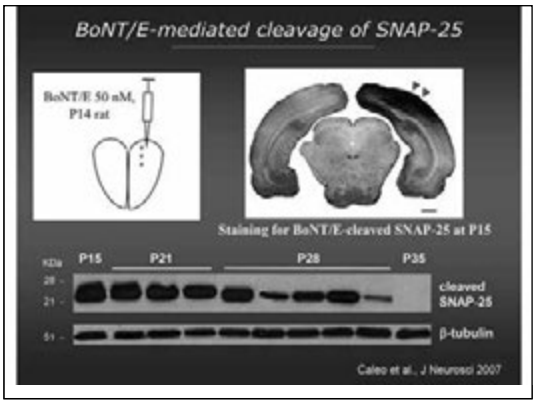
Visual callosal connections in rodents



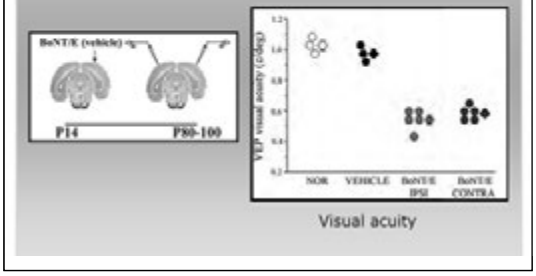
Role of neural activity in cortical development



BoNT/E-mediated cleavage of SNAP-25

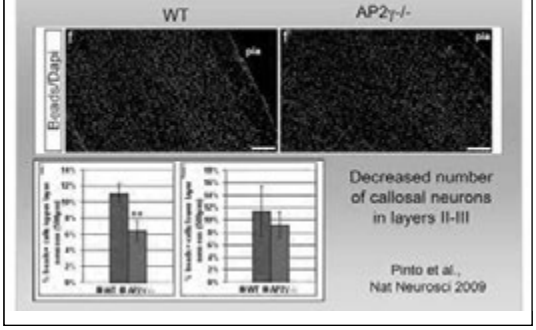


Unilateral, transient activity blockade has persistent effects on both hemispheres



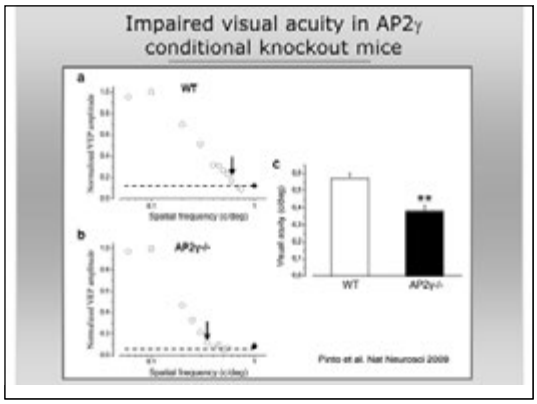
Visual acuity

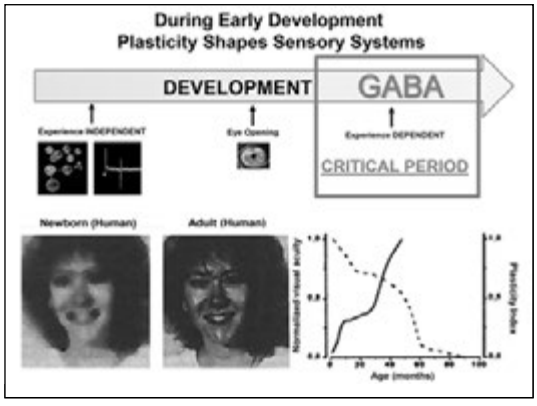
Reduced callosal projections in AP2γ conditional knockout mice

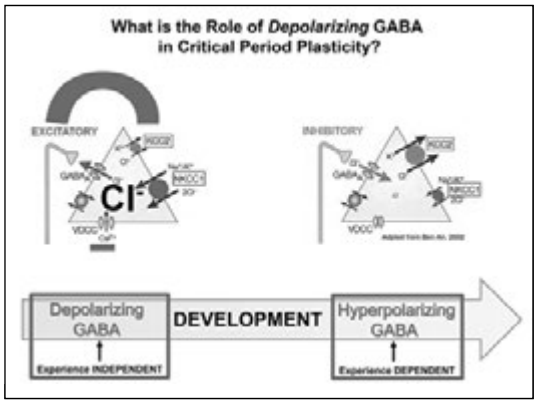


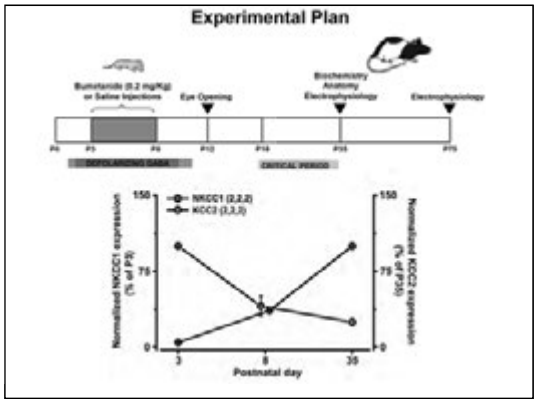
Decreased number of callosal neurons in layers II-III

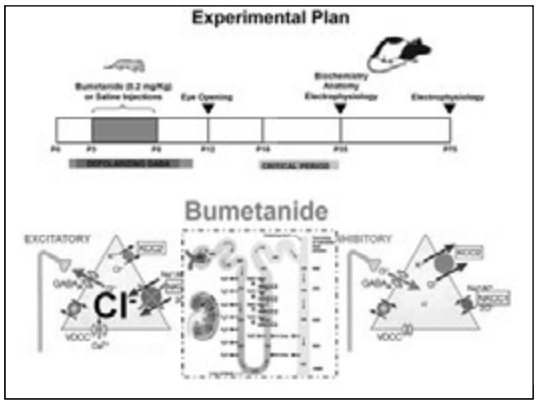
Pinto et al., Nat Neurosci 2009

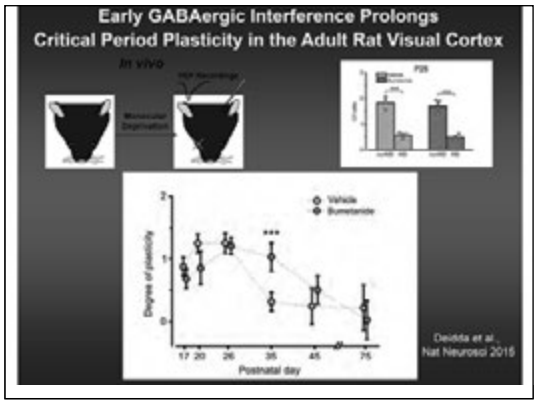

Impaired visual acuity in AP2γ conditional knockout mice
a
WT
b
AP2γ-/-
c
**
WT
AP2γ-/-
Pinto et al. Nat Neurosci 2009

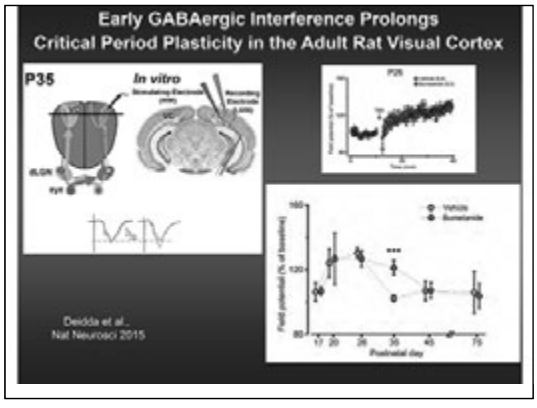

During Early Development
Plasticity Shapes Sensory Systems
DEVELOPMENT
GABA
Experience INDEPENDENT
Eye Opening
Experience DEPENDENT
CRITICAL PERIOD
Newborn (Human)
Adult (Human)
Age (months)

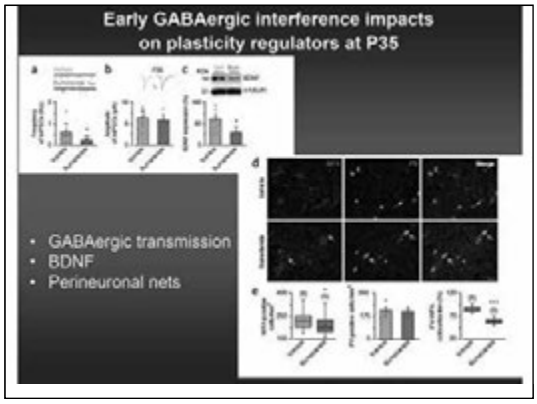

What is the Role of Depolarizing GABA in Critical Period Plasticity?
EXCITATORY
INHIBITORY
Cl-
Depolarizing GABA
DEVELOPMENT
Hyperpolarizing GABA
Experience INDEPENDENT
Experience DEPENDENT


Experimental Plan
Bumetanide (0.2 mg/Kg) or Saline Injections
Eye Opening
Biochemistry
Anatomy
Electrophysiology
Electrophysiology
NKCC1 (2,2,2)
KCC2 (1,1,1)
Postnatal day


Experimental Plan
Bumetanide (0.2 mg/Kg) or Saline Injections
Eye Opening
Biochemistry Anatomy Electrophysiology
Electrophysiology
P4
P5
P6
P12
P14
P35
P75
Bumetanide
EXCITATORY
INHIBITORY
GABA
Cl-
KCC2
NKCC1
VDCC

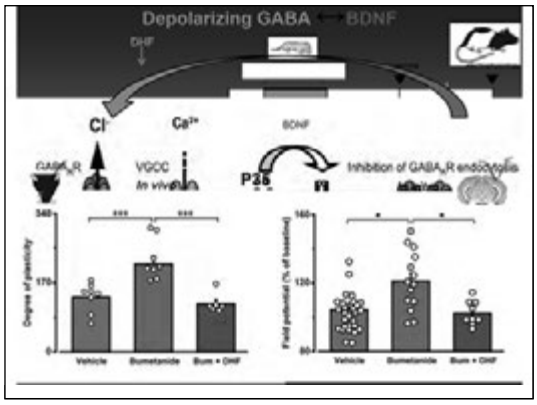

Early GABAergic Interference Prolongs
Critical Period Plasticity in the Adult Rat Visual Cortex
In vivo
Monocular Deprivation
P35
Vehicle
Bumetanide
Degree of plasticity
Postnatal day
17 20 26 35 45 75
***
Deidda et al.,
Nat Neurosci 2015

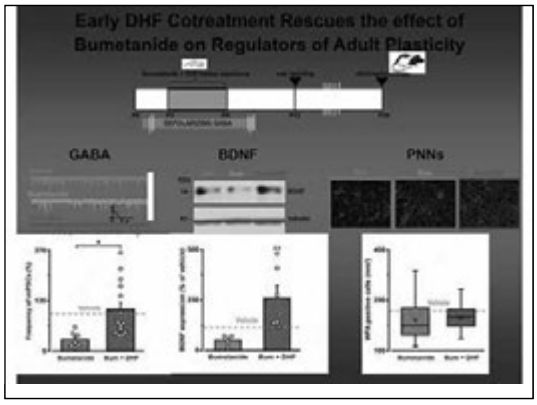

Early GABAergic Interference Prolongs
Critical Period Plasticity in the Adult Rat Visual Cortex
P35
In vitro
dLGN
V1
P25
Vehicle
Bumetanide
Field potential (% of baseline)
Postnatal day
***
Deidda et al.,
Nat Neurosci 2015


Early GABAergic interference impacts
on plasticity regulators at P35
• GABAergic transmission
• BDNF
• Perineuronal nets

Questions….

What are the mediators that link early depolarizing GABA with regulation of cortical plasticity later in development?

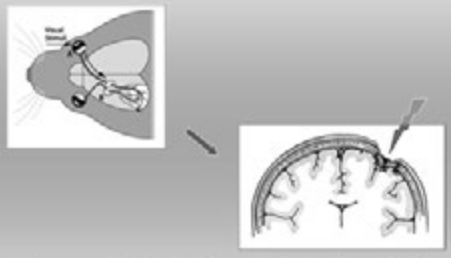




Conclusions

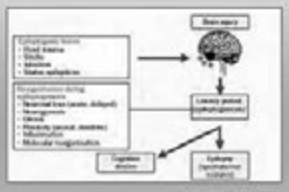
- A brief interference with depolarizing GABA prolongs critical period plasticity, with no effect on overall development of the visual system
- Prolongation of plasticity is accompanied by release of "plasticity brakes", i.e. dampened inhibitory neurotransmission and reduced density of PNNs
- TrkB activation during GABA interference rescues the effects on plasticity and its regulators
- These results drive attention on the possible long-term consequences of GABAergic drugs in infants

Translational perspectives....



Can we exploit the plasticity mechanisms learned in the visual cortex to understand plastic mechanisms underlying epileptogenesis?

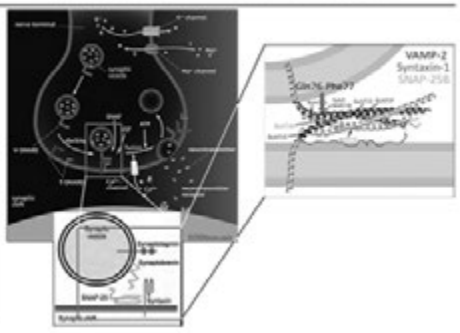
Natural history of symptomatic epilepsy



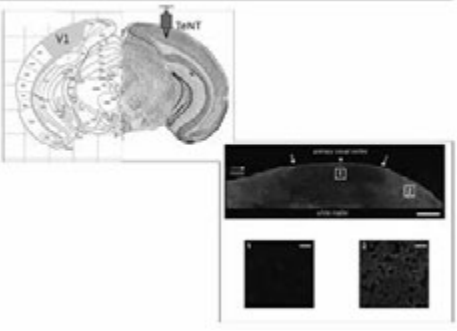
Pitkanen and Sutula, 2002

Brain insult ⟶ **Epileptogenesis** ⟶ **Seizures**

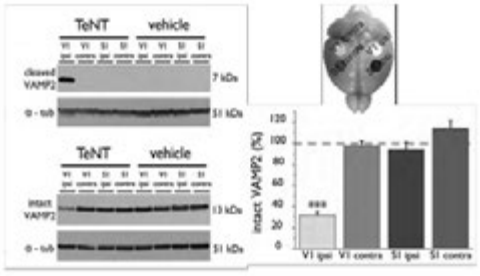
Tetanus neurotoxin: mechanism of action



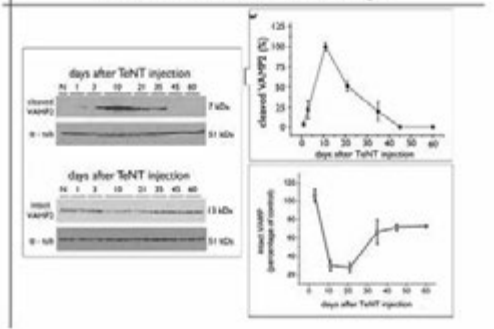
TeNT intracortical injection



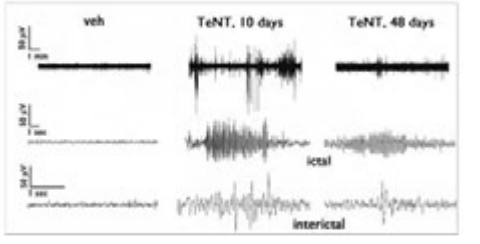
Regional specificity of VAMP-2 cleavage



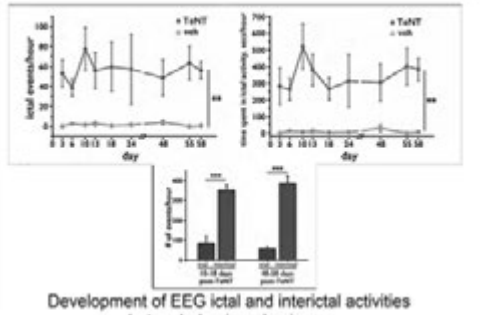
Time course of VAMP-2 cleavage



Epileptiform activity in the acute and chronic phase

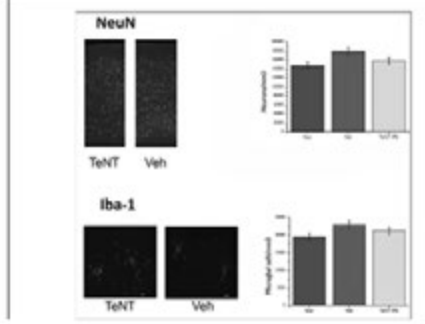


Quantification of epileptiform activity



Development of EEG ictal and interictal activities
but no behavioural seizures

Lack of histopathological alterations



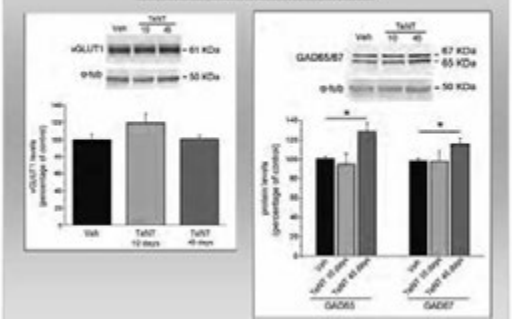
Conclusions (I)

Epileptiform activity is observed both during and after the time window of TeNT action

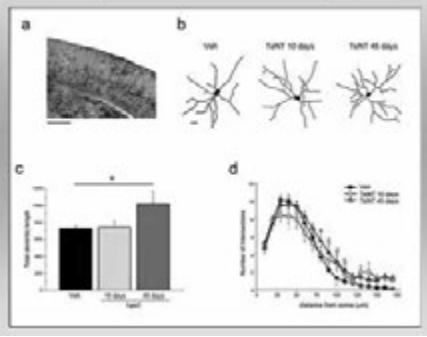
What are the persistent circuit changes that maintain network hyperexcitability?

Does epileptogenesis impair sensory processing in visual cortex?

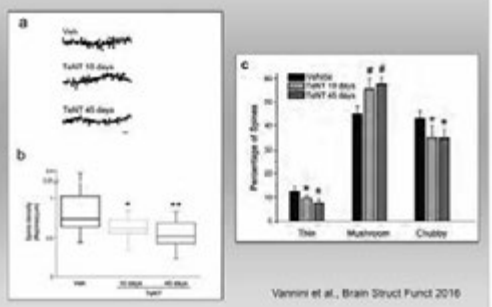
Enhanced GABAergic markers within the epileptic focus



Structural alterations within the epileptic focus



Structural alterations within the epileptic focus



Vannini et al., Brain Struct Funct 2016

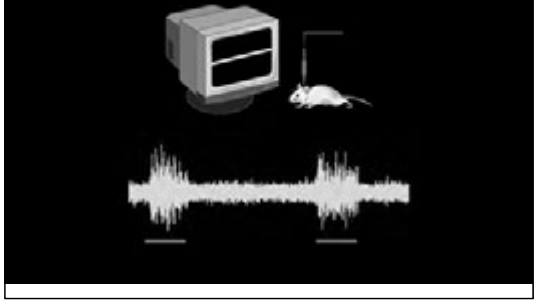
Conclusions (II)

Enhanced GABAergic markers

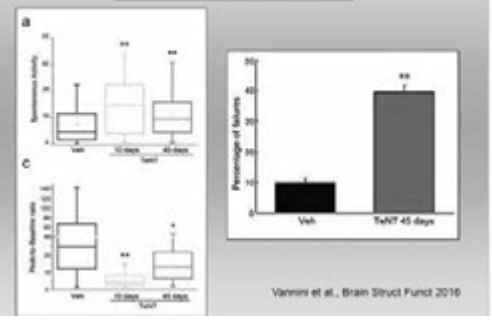
and structural remodeling of denditic spines

underlie long-term network hyperexcitability

Study of neuronal responses within the epileptic focus

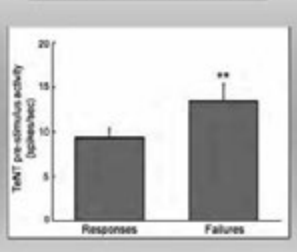


Altered neuronal responses within the epileptic focus

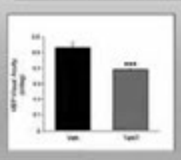


Vannini et al., Brain Struct Funct 2016

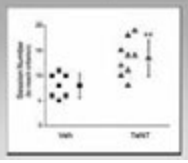
Spontaneous activation of the epileptic network interferes with stimulus-evoked firing



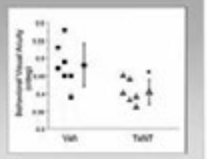
Reduced visual acuity in epileptic mice



Electrophysiology



Behavior

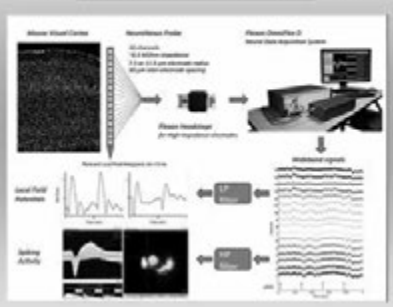


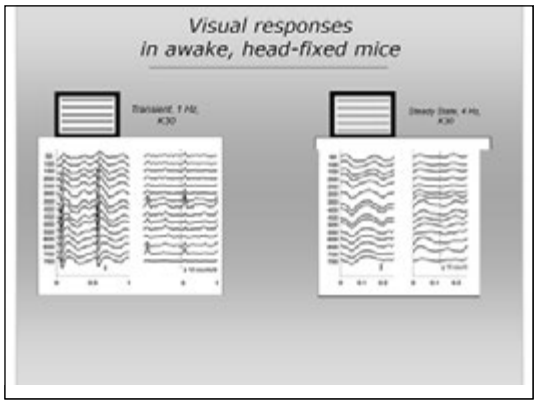
Conclusions (III)

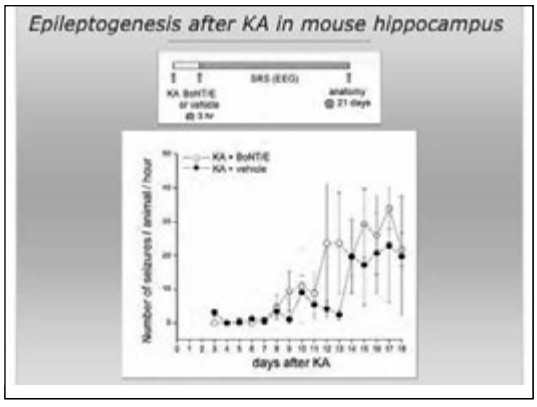
Long-term disturbances in information processing within the epileptic cortex:

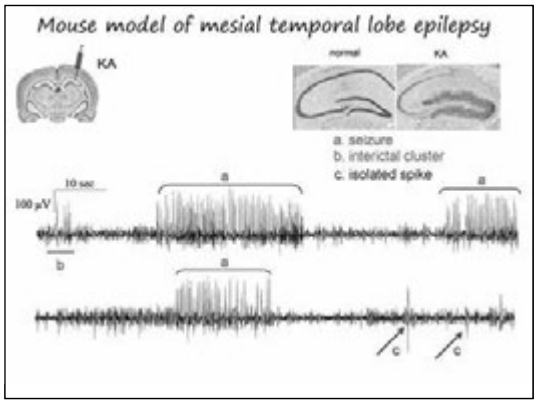
- **Higher baseline discharge**
- **Reduced response reliability**
- **Reduced spatial resolution (acuity)**

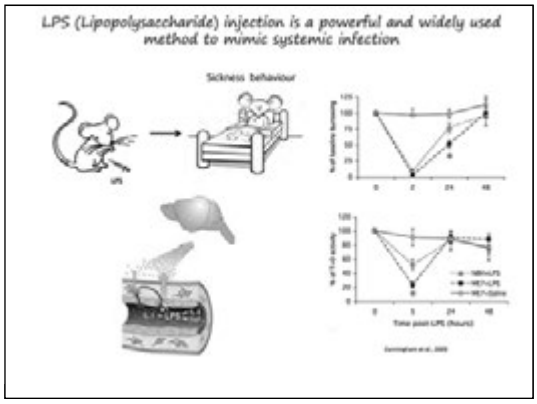
Multichannel recordings of epileptic activity in awake, head-fixed mice



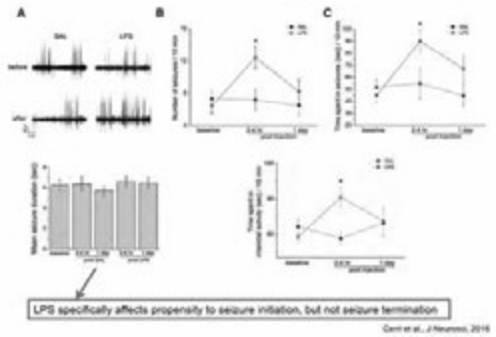

Visual responses
in awake, head-fixed mice


Epileptogenesis after KA in mouse hippocampus
SRS (EEG)
KA BoNT/E
or vehicle
@ 3 hr
@ 21 days
KA + BoNT/E
KA + vehicle
Number of seizures / animal / hour
days after KA


Mouse model of mesial temporal lobe epilepsy
KA
normal
KA
a. seizure
b. interictal cluster
c. isolated spike
10 sec
100 µV


LPS (Lipopolysaccharide) injection is a powerful and widely used method to mimic systemic infection
Sickness behaviour

Systemic inflammation enhances spontaneous seizures



Corti et al., J Neurosci, 2016

Expression of inflammatory molecules in the epileptic hippocampus following LPS

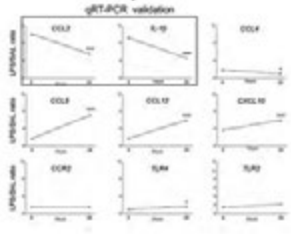
533 genes differentially expressed in epileptic hippocamp at both 4 and 24 h after LPS

↓

most genes belong to chemokine/cytokine pathways

↓

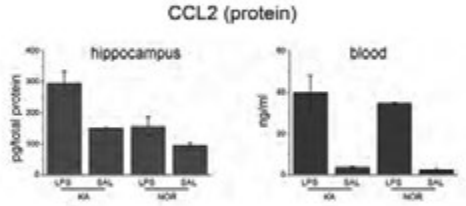
qRT-PCR validation



Strong increase of CCL2 and IL-1β expression at the time of LPS-induced seizure aggravation (4 h) points to a possible involvement of these molecules in mediating LPS effects

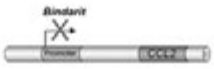
Corti et al., J Neurosci, 2016

Expression of CCL2 in the epileptic hippocampus following systemic LPS



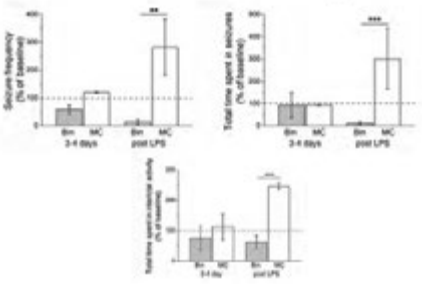
Does interference with CCL2 signalling prevent the enhancement of chronic seizures following systemic LPS treatment?

1)Inhibition of CCL2 transcription



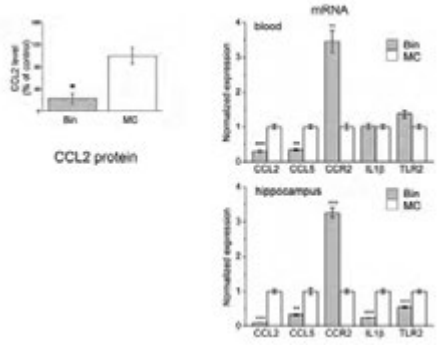
Corti et al., J Neurosci, 2015

1)Inhibition of CCL2 transcription

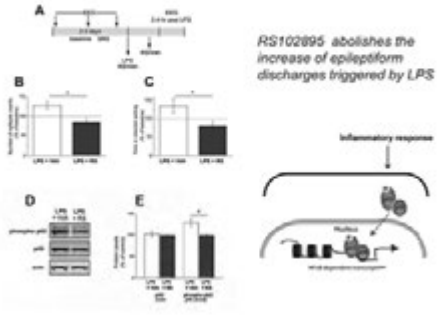


Bindarit abolishes the seizure-enhancing effect of LPS

Effect of bindarit on CCL2/CCR2 expression

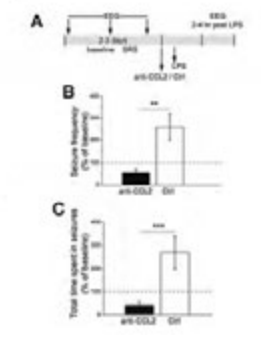


2) Effects of the selective CCR2 antagonist, RS102895

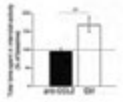


RS102895 abolishes the increase of epileptiform discharges triggered by LPS

3) Selective interference with CCL2 within the epileptic focus



Intrahippocampal injection of a CCL2 neutralizing antibody abrogates the increase in seizures following LPS



Conclusions

-A systemic inflammatory challenge exacerbates the epileptic phenotype, enhancing SRS frequency in KA-injected, chronically epileptic mice

-LPS triggers an exaggerated CCL2 up-regulation in the epileptic brain

-Both systemic and local interference with CCL2/CCR2 signaling yields potent anti-convulsant effects following systemic inflammation

⇩

CCL2 mediates seizure up-regulation following systemic inflammation

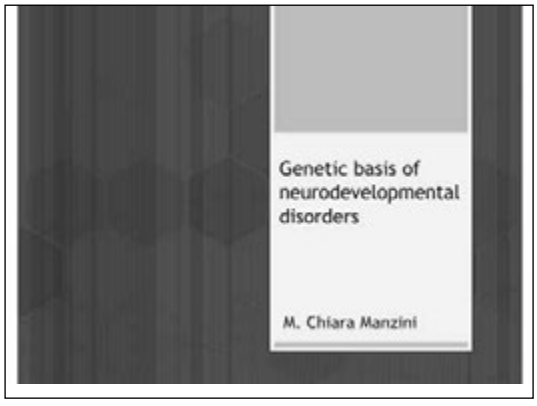
Drugs interfering with CCL2 signalling may be tested in epileptic syndromes that remain resistant to currently available medications

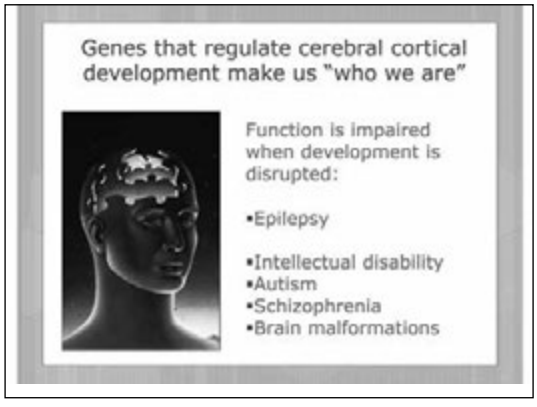
CHRISTOPHE BERNARD (FRANCE)

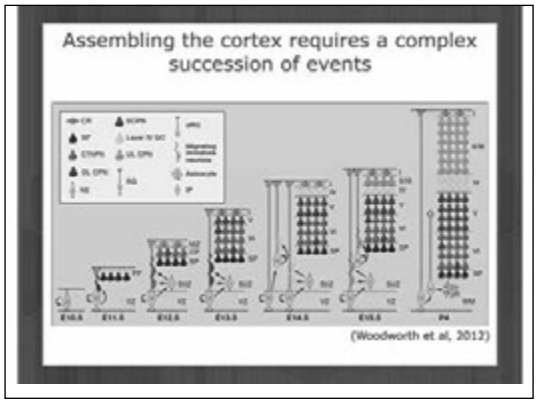
WHAT IS EPILEPSY? HOW CAN WE STUDY IT?

Maria Chiara Manzini (USA)

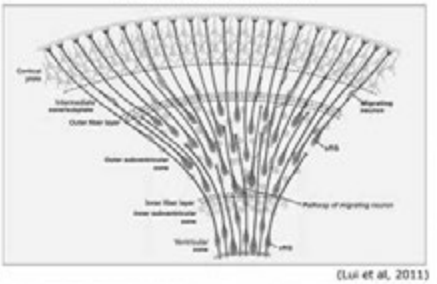
GENETIC BASIS OF NEURODEVELOPMENTAL DISORDERS







Assembling the cortex requires a complex succession of events



(Lui et al, 2011)

Plan for today:

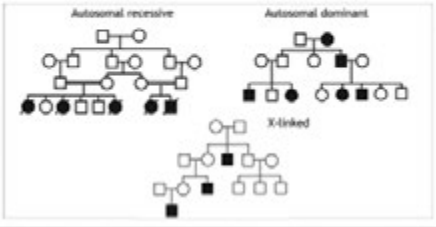
1. What kind of genetic mutations are linked to neurodevelopmental disorders (NDDs)?
2. How do we identify the mutated genes?
1. How do we study their function?

What is the genetic architecture of NDDs?

- Common causes of small effect – variants common in the population which increase your risk of contracting a disease
- Rare causes of large effect – mutations in several different genes each causing the disease

How is disease inherited?

- Monogenic disease is inherited in stereotypical fashion, depending on the mutation



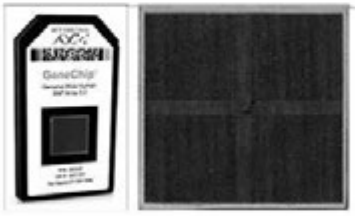
Plan for today:

1. What kind of genetic mutations are linked to neurodevelopmental disorders (NDDs)?
2. How do we identify the mutated genes?
   1. Common risk variants
1. How do we study their function?

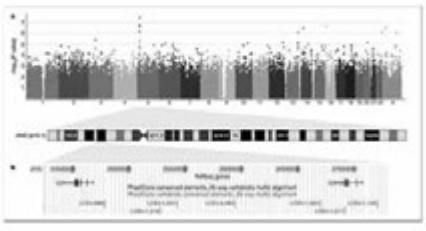
Disease risk can be determined with genetic association studies

- Genome-wide association studies (GWAS) take into account the entire genome of each individual
- Variants across the genome are assayed
- Association of specific variants with the disease condition is determined
- Each variant is just a place marker pointing to a gene or a genomic region associated with the disease

Genome-wide SNP array



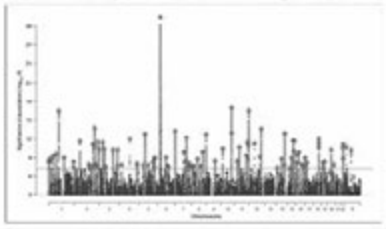
A locus on chromosome 5 associated with autism



(Wang et al, Nature, 2009)

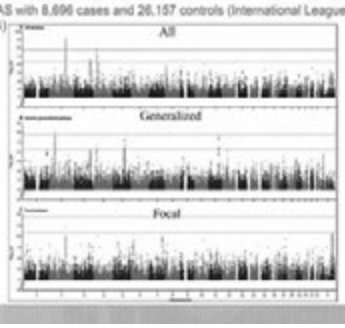
One of the largest GWAS yet for schizophrenia identified 108 loci

- GWAS with 36,989 cases and 113,075 controls of Asian and European ancestry (Schizophrenia Working Group, 2014)



Meta-analysis of GWAS for epilepsy

- GWAS with 8,696 cases and 26,157 controls (International League, 2014)



Common variants may not be the only answer

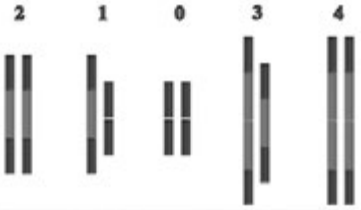
- GWAS has pointed to multiple loci, but few have been validated in different cohorts
- Large studies with tens or hundreds of thousands of individuals are needed
- Sample size and "population stratification" have been a huge problem
- Follow-up studies are difficult because SNPs are often non-coding

Plan for today:

1. What kind of genetic mutations are linked to neurodevelopmental disorders (NDDs)?
2. How do we identify the mutated genes?
   1. Common risk variants
   2. Copy-number variants
1. How do we study their function?

Developmental delay is often associated with copy-number variants (CNV)

- CNV are variations from the normal (N=2) number of copies in the genome:



The CNV revolution of 2006

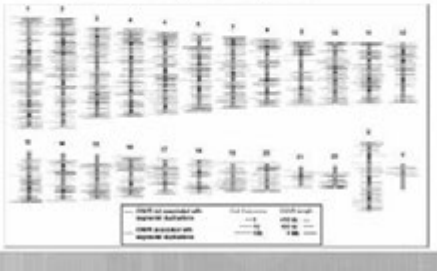
- Measure copy-number in human controls (HapMap) using SNP arrays

ARTICLES

Global variation in copy number in the human genome

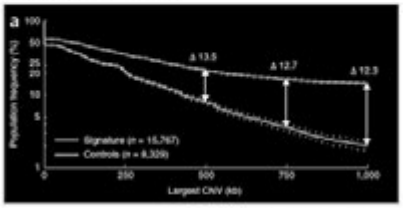
The human genome is full of "holes"

- Multiple CNVs throughout the genome



CNV analysis identified dozens of CNV associated with developmental delay

- CNV tend to be more common in patients with developmental delay

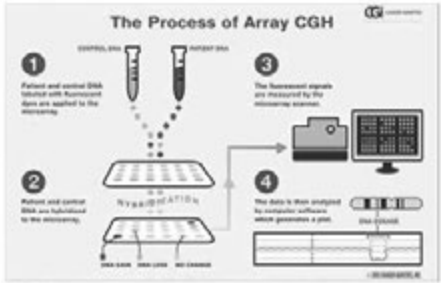


(Cooper et al, Nat Genet, 2011)

CNVs account for 10-15% of developmental delay cases

- 14% of developmental delay can be explained by large CNVs (>400kb) often de novo (Cooper et al, Nat Genet, 2011)
- This size is easily detectable via array CGH (comparative genomic hybridization) which has a resolution in the few 10^3 bp
- The cohorts are usually very heterogeneous
- 5% of epilepsy cases have possibly pathogenic CNVs

How array CGH works

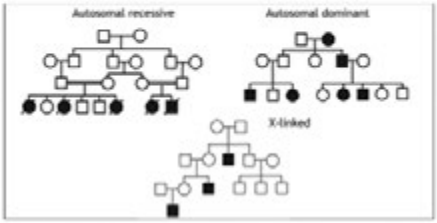


Plan for today:

1. What kind of genetic mutations are linked to neurodevelopmental disorders (NDDs)?
2. How do we identify the mutated genes?
   1. Common risk variants
   2. Copy-number variants
   3. Monogenic mutations
1. How do we study their function?

Family-based studies

- Monogenic disease is inherited in stereotypical fashion, depending on the mutation



Are all possible genes mutated?

- Mutational saturation test in lab animals:
  - Induce mutations with chemicals
  - If there are 3 independent mutations in the same gene, then 95% of other genes are mutated
  - 5 independent alleles in the same gene implies that 99% of all genes have been mutated

7×10^9 humans saturate the genome for detectable mutations in any gene

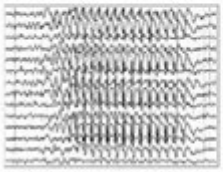
- Human genes have many independent mutations:
  - Haemophilia A (Factor VIII) 1/5,000 males
    267 alleles
  - Rett Syndrome (MECP2) 1/15,000 girls
    614 alleles
  - β Thalassemia (hemoglobin β) 1/100,000
    497 alleles
  - Merosin-deficient MD (LAMA2) 1/100,000
    86 alleles
- Therefore, mutations in any gene with a detectable phenotype are already present among humans

How do we identify these genes?

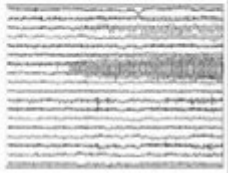
- Most of these diseases are very rare and seldom described
- You must identify families to perform genetic analyses
- You need an extended network of collaborating physicians all over the world

Electroencephalogram classification

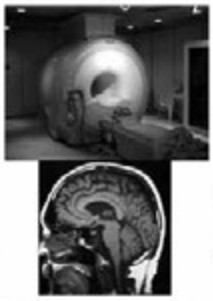
Generalized



Focal/partial

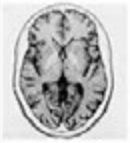


Magnetic Resonance Imaging



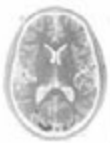
- Uses a strong magnetic field to align hydrogen atoms
- Allows for clear visualization of soft tissue
- Uses harmless radiation
- Has multiple applications

Different types of MR available for brain research



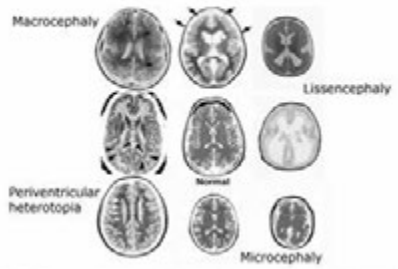
Classic MRI: for morphology and structure

Diffusion Tensor Imaging (DTI): to follow projections

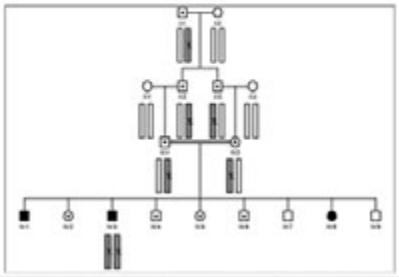


Functional MRI (fMRI): to study brain activity

Developmental disorders of the cerebral cortex

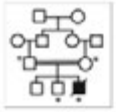


Homozygosity mapping to identify founder mutations in families

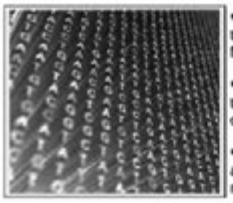


Regions of homozygosity may cover many genes

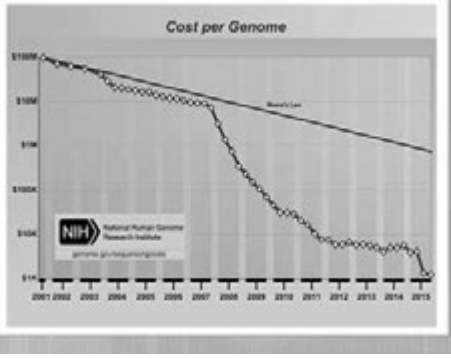
- 9.6% homozygosity - 2480 genes



Whole-exome sequencing revolutionized how we identify rare disease genes



- *Next-generation sequencing technologies to analyze each family individually
- *Whole-exome sequencing targets coding sequences (1% of genome)
- *85% of disease mutations are predicted to be in coding regions



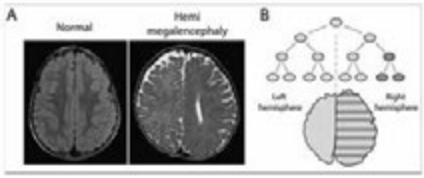
Homozygosity mapping and exome sequencing to identify disease genes

- Exome sequencing yields 30-50,000 variants per individual
- A need for an appropriate filtering strategy
  - In region of homozygosity: focus on the 2480 genes
  - Rare or novel
  - Pathogenic: missense, stop, splicing, frameshift
- This approach reduced the number of candidate genes from 2480 to 6!
- A stop codon in the glycosyltransferase *GTDC2* appeared to be the best candidate (Manzini *et al*, 2012)

Plan for today:

1. What kind of genetic mutations are linked to neurodevelopmental disorders (NDDs)?
2. How do we identify the mutated genes?
   1. Common risk variants
   2. Copy-number variants
   3. Monogenic mutations
   4. Somatic mutations
1. How do we study their function?

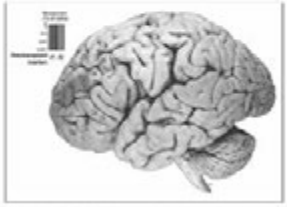
What about somatic mutations?



- Deep sequencing in post-mortem brains reveals possible somatic mutations in a few cases (D'Gama et al, Neuron, 2015)

How do you find somatic mutations?

- Deep sequencing: sequence the same base multiple times and find very rare changes (D'Gama et al, Neuron, 2015)
- Single-cell sequencing: identify a clonal change in the brain (Evrony et al, Neuron, 2015)

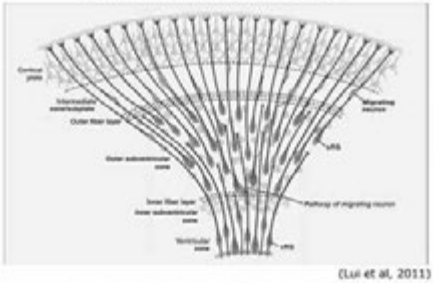


Take-home message 2:

There are multiple types of genetic mutation that cause NDDs and epilepsy

- There may be human mutants out there for any possible viable mutation in the genome
- These may be so rare that they require specialized clinical studies to identify
- Family studies have been the most informative but next-generation sequencing is speeding gene identification
- Epilepsy can be caused by common or rare variants, somatic mutations or CNVs

The genes responsible may affect early developmental processes



(Lui et al, 2011)

Plan for today:

1. What kind of genetic mutations are linked to neurodevelopmental disorders (NDDs)?
2. How do we identify the mutated genes?
1. How do we study their function?

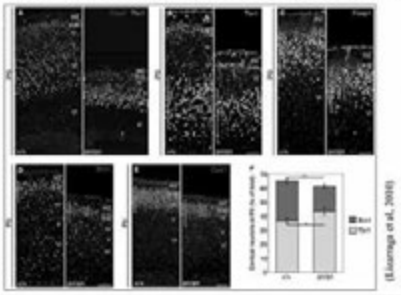
What is the best animal model to study brain development?

The mouse to study cortical size and organization

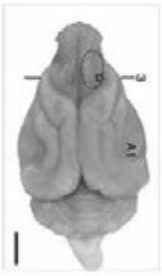
Epilepsy can also be induced in the mouse

Mouse epilepsy video

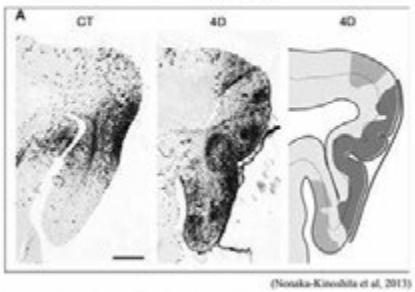
Analysis of cortical size and organization



Ferrets to analyze gyration

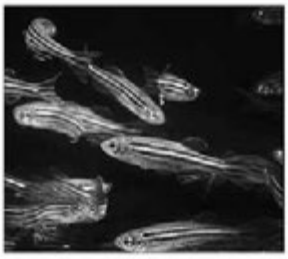


Ferrets to analyze gyration



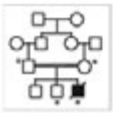
(Nonaka-Kinoshita et al, 2013)

How about the zebrafish?



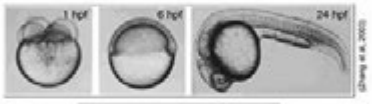
Back to the family we saw at the beginning

- 9.6% homozygosity - 2480 genes
- Cobblestone lissencephaly

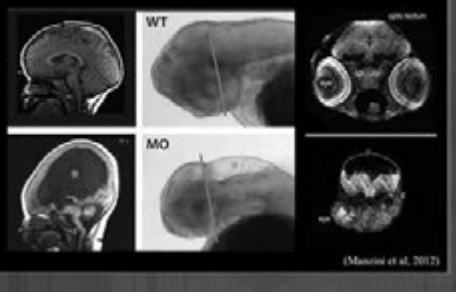


The zebrafish larva as a functional model for variant validation

- The zebrafish larva develops over just a few days



Hydrocephalus can be modeled in the zebrafish



Epilepsy can also be studied in the zebrafish

Zebrafish epilepsy video

How about the marmoset?

(Niu et al, 2010)

- CRISPR/Cas technology has generated double mutants (Niu et al, 2014)

Take-home message 3:

You need to find the appropriate model for the question you are asking

- Mouse to look at seizures, neuronal proliferation, neuronal/axonal differentiation in the brain
- Ferret to look at cortical gyrus formation and lamination
- Zebrafish to rapidly screen genes for seizures, head size, hydrocephalus, lamination defects
- Marmoset or other primates? (Rett Syndrome macaque, Liu et al, Nature 2016)

Questions?

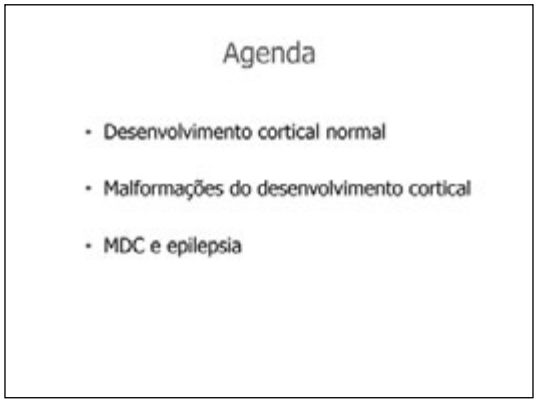
chiara.manzini@gmail.com

Maria Chiara Manzini (USA)

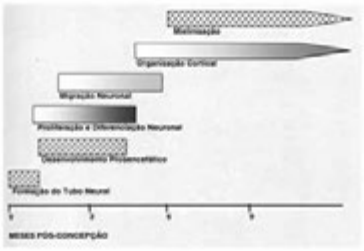
METTING WITH ALFONSO REPRESA/MATTEO CALEO

Marilisa Guerreiro (Brazil)

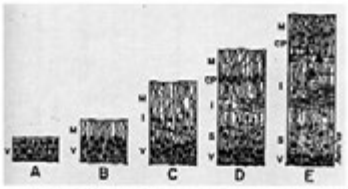
MALFORMATIONS OF CORTICAL DEVELOPMENT



Desenvolvimento do SNC

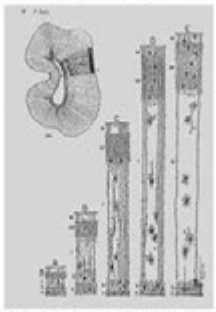


Formação de Camadas



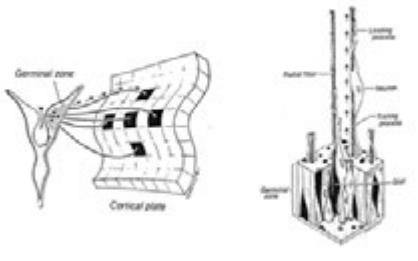
A figura mostra o desenvolvimento cerebral com a formação progressiva de camadas. Abreviaturas: V = zona ventricular, M = zona marginal, I = zona intermediária, S = zona subventricular, CP = lâmina cortical. Inicialmente a zona ventricular é densamente celularizada e regressivamente a lâmina cortical passará a ficar preenchida. *Retirado de Sidman & Rakic, Brain Research 1973.*

Migração Neuronal



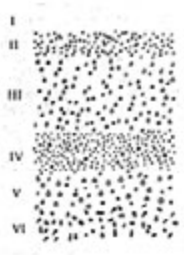
Rakic, P. Neuronal migration and contact guidance in the primate telencephalon. Postgrad Med J 1978; 54: 25-37.

Unidade Radial



Barkovich A.J. et al. MR of Neuronal Migration Anomalies. AJNR 1987; 8:1009-1017.

Citoarquitetura Cortical



Agenda

- Desenvolvimento cortical normal
  - Proliferação e diferenciação
  - Migração neuronal
  - Organização cortical
- Malformações do desenvolvimento cortical
- MDC e epilepsia

Malformações do Desenvolvimento Cortical

- Distúrbios da proliferação
- Distúrbios da migração neuronal
- Distúrbios da organização cortical

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

A. James Barkovich,[1] Renzo Guerrini,[2,3] Ruben I. Kuzniecky,[4] Graeme D. Jackson[5,6] and William B. Dobyns[7,8]

1 Departments of Radiology and Biomedical Imaging, Neurology, Paediatrics and Neurosurgery, The University of California at San Francisco and the Benioff Children's Hospital at UCSF, San Francisco, CA 94143-0628, USA
2 Child Neurology Unit, A. Meyer Children's Hospital, University of Florence, Florence 50100, Italy
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4 Department of Neurology and NYU Comprehensive Epilepsy Center, New York University, New York, NY 10016, USA
5 Florey Neuroscience Institutes, Austin Hospital, Heidelberg, 3084 Victoria, Australia
6 Department of Medicine, University of Melbourne, Melbourne Brain Centre, Heidelberg, 3084 Victoria, Australia
7 Departments of Paediatrics and Neurology, University of Washington, Seattle, WA 98195, USA
8 Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA 98101, USA

Proliferação Anormal

- Displasia cortical focal
- Hamartomas corticais da esclerose tuberosa
- Hemimegalencefalia

Displasia Cortical Focal

- Desorganização focal da arquitetura cortical
- Neurônios displásicos (gigantes e bizarros) dispostos de forma desorganizada
- Células em balão (intermediárias entre glia e neurônio)

J. Neurol. Neurosurg. Psychiat., 1971, 34, 369-387

Focal dysplasia of the cerebral cortex in epilepsy

D. C. TAYLOR AND M. A. FALCONER
From the Neurosurgical Unit of Guy's, Maudsley, and King's College Hospitals, London
and
C. J. BRUTON AND J. A. N. CORSELLIS
From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

Epilepsia, 52(1):158–174, 2011
doi: 10.1111/j.1528-1167.2010.02777.x

SPECIAL REPORT

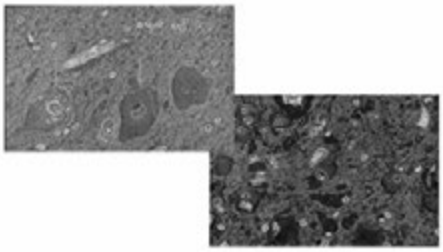
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[†]

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

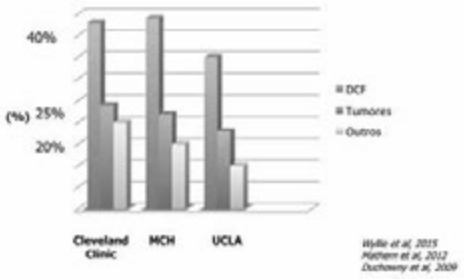
Displasias Corticais Focais

- DCF tipo I
  - Tipo Ia: dislaminação radial
  - Tipo Ib: dislaminação tangencial
- DCF tipo II
  - Tipo IIa: neurônios dismórficos
  - Tipo IIb: células em balão
- DCF tipo III
  - Tipo IIIa: DCF com esclerose hipocampal
  - Tipo IIIb: DCF com tumor

Histologia da DCF



Etiologia

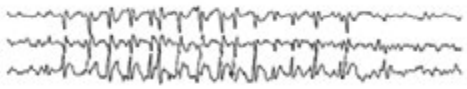


Wyllie et al, 2015
Mathern et al, 2012
Duchowny et al, 2009

Diagnóstico

Intrinsic Epileptogenicity of Human Dysplastic Cortex as Suggested by Corticography and Surgical Results

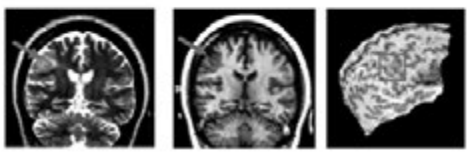
- Eletrencefalograma
  - Descargas epileptiformes contínuas
  - Surtos repetitivos de espículas
  - Padrão eletrográfico semelhante a crises ictais



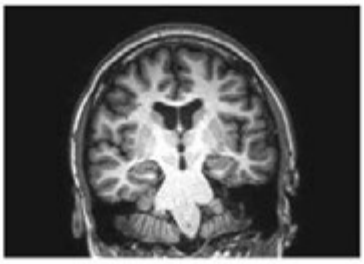
Ann Neurol 1995; 37:476-487

Displasia Cortical Focal

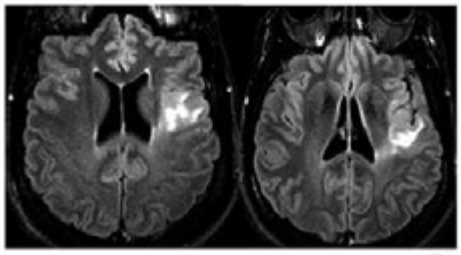
- Neuroimagem
  - Áreas de espessamento cortical
  - Hipersinal
  - Atrofia focal
  - Borramento entre substância branca e cinzenta



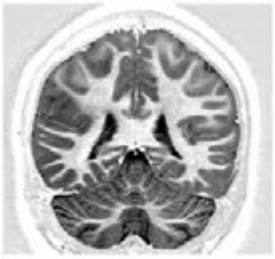
DCF – Borramento entre substância branca e cinzenta

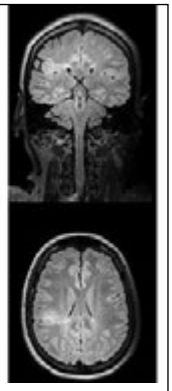


DCF – Hipersinal subcortical em imagens T2 / FLAIR

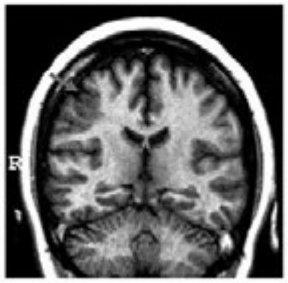


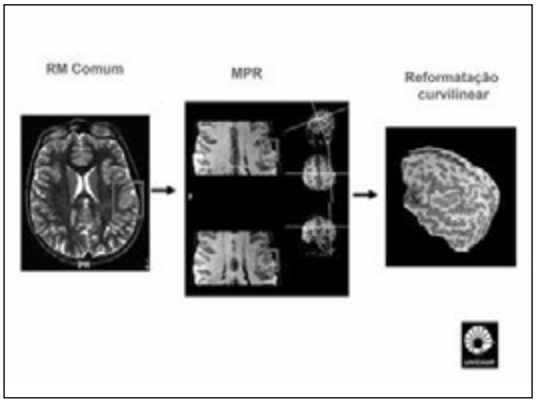
DCF – Sinal "transmantle"





DCF – Anomalias na anatomia dos sulcos e circunvoluções e aumento do espaço subaracnoideo adjacente





Tratamento

- Medicamentoso
  - DAE
- Cirúrgico
  - Extensão do córtex comprometido
  - Localização cortical

Incomplete resection of focal cortical dysplasia is the main predictor of poor postsurgical outcome

P. Kwok, MD, PhD
B. Mann, MD
P. Jayakar, MD, PhD
P. Dean, ARNP
B. Kerman, MS
G. Ito, PhD
C. Duncan, MD
E. Pathan-Jaome, MD
G. Morrison, MD
J. Raphi, MD
H.Y. Yiannis, MD, PhD
T. Resnik, MD
M. Duchowny, MD

ABSTRACT

Background: Focal cortical dysplasia (FCD) is recognized as the major cause of focal intractable epilepsy in childhood. Various factors influencing postsurgical seizure outcome in pediatric patients with FCD have been reported.

Objective: To analyze different variables in relation to seizure outcome in order to identify prognostic factors for selection of pediatric patients with FCD for epilepsy surgery.

Methods: A cohort of 149 patients with histologically confirmed mild malformations of cortical development or FCD with at least 2 years of postoperative follow-up was retrospectively studied. 113 subjects had at least 5 years of postoperative follow-up. Twenty-eight clinical, EEG, MRI, neuropsychological, surgical, and histopathologic parameters were evaluated.

Results: The only significant predictor of surgical success was completeness of surgical resection, defined as complete removal of the structural MRI lesion (if present) and the cortical region exhibiting prominent ictal and interictal abnormalities on intracranial EEG. Unfavorable surgical outcomes are mostly caused by overlap of dysplastic and eloquent cortical regions. There were nonsignificant trends toward better outcomes in patients with normal intelligence, after hemispherectomy and with FCD type II. Other factors such as age at seizure onset, duration of epilepsy, seizure frequency, associated pathologies including hippocampal sclerosis, extent of EEG and MRI abnormalities, as well as extent and localization of resections did not influence outcome. Twenty-five percent of patients changed Engel's class of seizure outcome after the second postoperative year.

Conclusions: The ability to define and fully excise the entire region of dysplastic cortex is the most powerful variable influencing outcome in pediatric patients with focal cortical dysplasia. *Neurology*® 2009;73:217–223

Prognóstico Cirúrgico

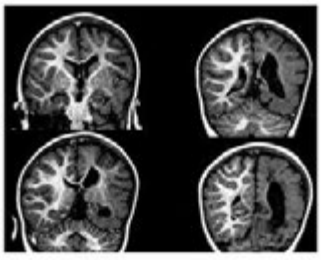
- Ressecção completa: 80%
- Ressecção incompleta: 20%

Hauptman & Mathern, Epilepsia, 2012

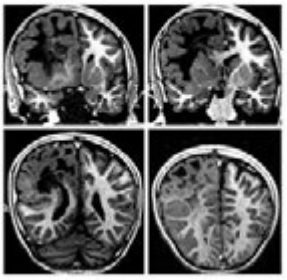
Considerações

- Principal etiologia (juntamente com tumores do desenvolvimento) de epilepsia refratária na infância em séries cirúrgicas
- Principal localização: frontal
- Com os progressos da neuroimagem: principal etiologia no grupo das epilepsias sintomáticas
- Resultados cirúrgicos : 60-80% de sucesso

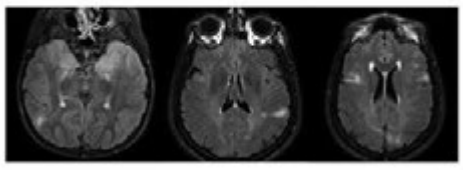
Hemimegalencefalia



Hemimegalencefalia



Esclerose Tuberosa



Distúrbios da Migração Neuronal

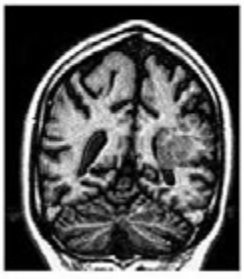
Migração Neuronal Anormal

- Heterotopia nodular periventricular
- Heterotopia em banda (Córtex duplo)
- Complexo agiria/pachigiria (Lissencefalia)

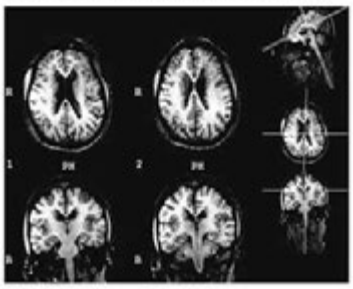
Heterotopia Nodular Periventricular

- Agrupamentos de neurônios heterotópicos na região periventricular (neurônios maduros e céls. da glia)
- HNP
  - Bilateral: nódulos periventriculares simétricos
    - Predominância no sexo feminino
    - Herança ligada ao X: Xq28, com mutação no gene *filamina 1*
  - Unilateral
    - Não está associada à HF
    - Associa-se a eventos pré-natais que causem falha perfusional

Heterotopia Nodular



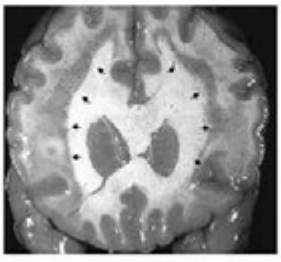
Heterotopia Nodular Periventricular



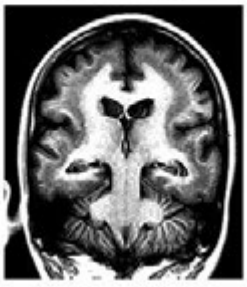
Heterotopia Subcortical em Banda (Córtex Duplo)

- Neurônios heterotópicos dispostos em banda
- Associa-se a mutações nos genes *LIS1* ou *DCX*
- Herança ligada ao X
  - Sexo feminino apresenta forma mais leve
  - Sexo masculino apresenta forma mais grave (lissencefalia)
- Quadro clínico proporcional à espessura da banda
  - Epilepsia
  - Déficit cognitivo

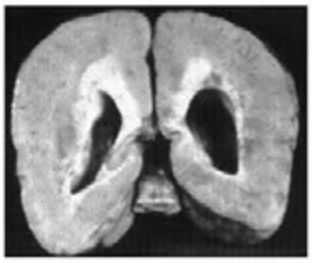
Córtex Duplo



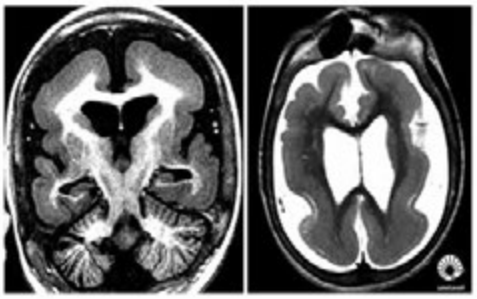
Córtex Duplo



Lissencefalia



Lissencefalia



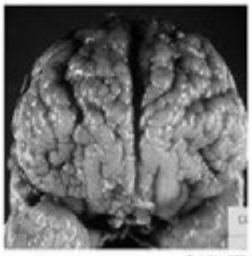
Organização Cortical Anormal

- Polimicrogiria
- Esquizencefalia

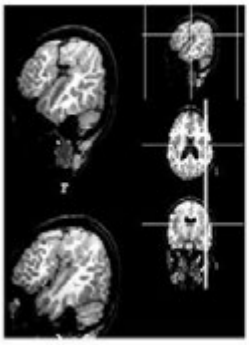
Polimicrogiria

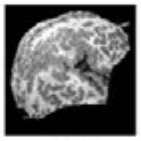
- Presença de vários pequenos giros em decorrência de insulto vascular
- Quadro clínico
  - Depende da localização e extensão do córtex afetado
  - Epilepsia tratável com DAE

Polimicrogiria envolvendo os dois hemisférios



Polimicrogiria Perisylviana Bilateral



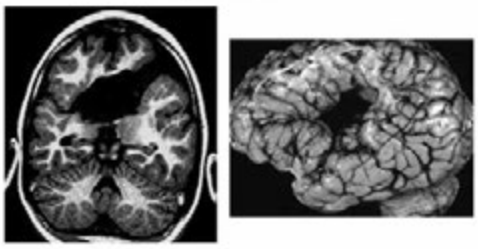


12 mm

Polimicrogiria e Epilepsia

- Kuzniecky et al: 87%
  - CBPS
  - 31 pacientes
- Guerreiro et al: 43%
  - Famílias
  - 42 pacientes
- Teixeira et al: 32%
  - 40 pacientes (Unicamp)
  - Predomínio de cças com DEL

Esquizencefalia



Esquizencefalia

- 44 pacientes (24 pac com fenda unilateral e 20 pac com fendas bilaterais)
- Epilepsia: 63% x 55%
- A extensão do córtex comprometido não se correlaciona com a gravidade do quadro epiléptico, ao contrário do quadro cognitivo e motor

Lopes et al., J Child Neurol, 2006

Agenda

- Desenvolvimento cortical normal
- Malformações do desenvolvimento cortical
- MDC e epilepsia

MDC e Epilepsia

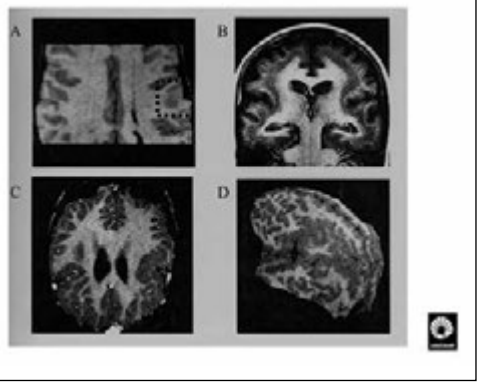
ORIGINAL CONTRIBUTION

Interrelationship of Genetics and Prenatal Injury in the Genesis of Malformations of Cortical Development

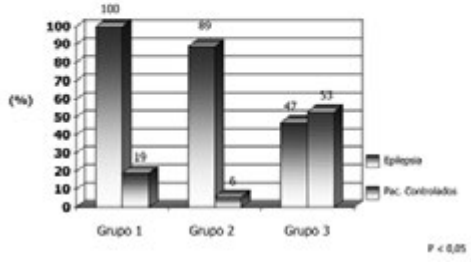
Maria Augusta Montenegro, MD; Marilisa M. Guerreiro, MD, PhD; Iscia Lopes-Cendes, MD, PhD; Carlos A. M. Guerreiro, MD, PhD; Fernando Cendes, MD, PhD.

Arch Neurol, 2002

Desenho do Estudo



MDC - Epilepsia



Epilepsia X MDC

- Grupo I. DCF apresenta epileptogenicidade intrínseca: epilepsia frequente e refratária
- Grupo II. Depende
- Grupo III. PMG e esquizencefalia associam-se menos à epilepsia

Conclusões

- O córtex displásico é bastante epileptogênico e insultos ambientais ou predisposição genética não estão associados à epilepsia
- O córtex polimicrogírico é menos epileptogênico e insultos ambientais ou predisposição genética estão associados à epilepsia

Agenda

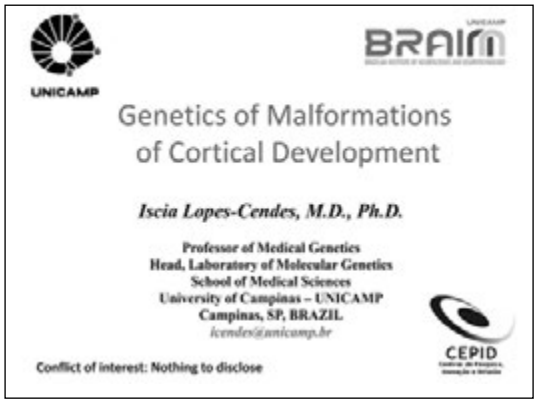
- Desenvolvimento cortical normal
- Malformações do desenvolvimento cortical
- MDC e epilepsia

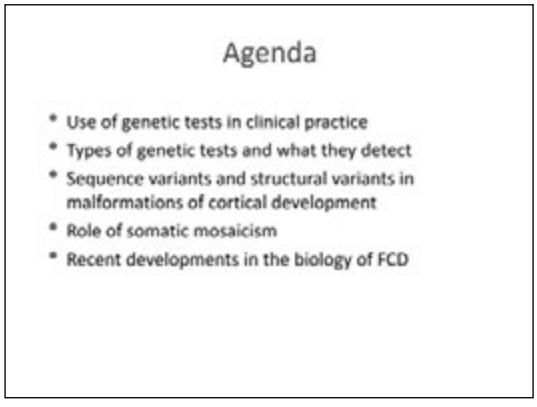
" Curar quando possível,
Aliviar quase sempre,
Consolar sempre."

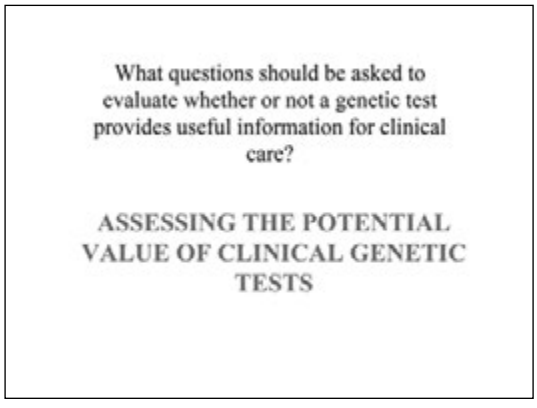
Hipócrates

Iscia Cendes (Brazil)

GENETICS OF MALFORMATIONS OF CORTICAL DEVELOPMENT







ILAE Genetics Commission

(2006 -2009)

Members (2006-2009):

Ruth Ottman, Ph.D., USA (Chair)
Shinichi Hirose, M.D., Ph.D., JAPAN
Satish Jain, M.D., D.M., F.R.C.P., INDIA
Holger Lerche, M.D., GERMANY
Iscia Lopes-Cendes, M.D., Ph.D., BRAZIL
Jeffrey L. Noebels, M.D., Ph.D., USA
Ingrid E. Scheffer, M.B.B.S. Ph.D. F.R.A.C.P., AUSTRALIA
José Serratosa, M.D., Ph.D., SPAIN
Federico Zara, Ph.D., ITALY

Genetic testing in the epilepsies--report of the ILAE Genetics Commission

Epilepsia Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE. Epilepsia. 2010 Apr;51(4):655-70.

When evaluating the appropriate use of genetic tests, clinicians must consider

- the accuracy with which a test identifies a patient's clinical status (clinical validity)
- the risks and benefits resulting from test use in the clinical setting, as well as the potential do improve health outcomes (clinical utility)
- the accuracy and other test properties that may be influenced by testing technology (analytic validity)

Burke W. Curr Protoc Hum Genet. ; 81: 9.15.1-9.15.8. (2015)
Holtzman, NA.; Watson, MS. Final report of the Task Force on Genetic Testing. Baltimore: Johns Hopkins University Press; 1998. Promoting safe and effective genetic testing in the United States

Clinical Validity

The term clinical validity was proposed by the NIH-DOE Task Force on Genetic Testing to describe the accuracy with which a genetic test identifies a particular clinical condition. It is described in terms of sensitivity, specificity, positive predictive value, and negative predictive value

Test Properties Measuring Clinical Validity

Test parameter	Definition
Sensitivity	Among people with a specific condition, the proportion who have a positive test result
Specificity	Among people who do not have the condition, the proportion who have a negative test result
Positive predictive value	Among people with a positive test result, the proportion who have the condition
Negative predictive value	Among people with a negative test result, the proportion who do not have the condition

Burke W. Curr Protoc Hum Genet. ; 81: 9.15.1-9.15.8. (2015)
Holtzman, NA.; Watson, MS. Final report of the Task Force on Genetic Testing. Baltimore: Johns Hopkins University Press; 1998. Promoting safe and effective genetic testing in the United States

Clinical Utility

- The term refers to the risks and benefits resulting from genetic testing
- The most important considerations in determining clinical utility are:

(i) whether the test and any subsequent interventions lead to an improved health outcome among people with a positive test result; and
(ii) what risks occur as a result of testing

- Complete measurement of clinical utility requires evaluation of the medical and social outcomes associated with testing, and subsequent interventions for people with both positive and negative test results
- When treatment is unavailable, a genetic test with high clinical validity may be useful to establish a diagnosis or provide prognosis; in this situation, the value of testing is determined mainly by clinical validity

Burke W. Curr Protoc Hum Genet. ; 81: 9.15.1-9.15.8. (2015)

Potential Risks

- Psychological distress
- Discrimination in health insurance, life insurance, employment
- Effects on family communication dynamics and social relationships
- Exacerbation of stigma (may extend to family members of affected individual)

Phelan JC. J Health Soc Behav. 2005 dec;307-322.

Potential Benefits

- Clarify the diagnosis
- Provide information about prognosis
- Changes in course of treatment
- Save patient and family from expensive and uncomfortable or invasive tests
- Provide an answer to the questions about what caused the disorder
- Provide information on risk of recurrence which can help with reproductive decisions

Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE. Epilepsia. 2010 Apr;51(4):655-70.

Analytic Validity

- Analytic validity depends on the molecular aspects of detecting a gene variant in a DNA sample rather than on the disease
- Even when a test for a specific change within a gene is accurate, the test could still miss other important changes it is not designed to detect
- No single test currently available examines all aspects of variation within a gene

Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE. Epilepsia. 2010 Apr;51(4):655-70.

Analytic validity

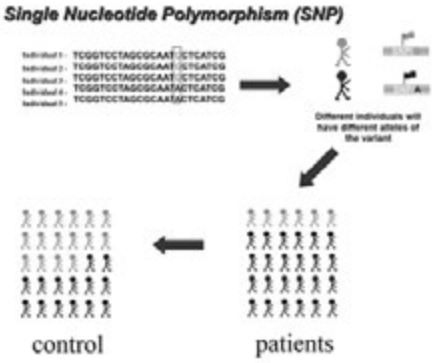
Refers to the accuracy with which a particular genetic characteristic, such as a DNA sequence variant, chromosomal abnormality, or biochemical indicator, is identified in a given laboratory test

- Most genetic characteristics of clinical interest can be tested by a variety of protocols
- Technical issues arising in the evaluation of analytic validity include:

(i) the specific technical requirements of the assay chosen,
(ii) its reliability,
(iii) the degree to which reliability varies from laboratory to laboratory, and
(iv) the complexity of test interpretation.

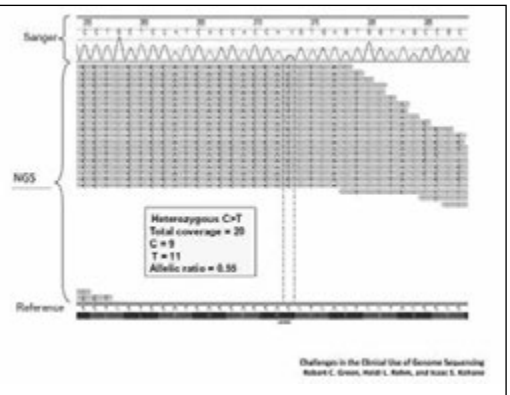
Technical Consideration

- Type of molecular changes to be detected



DNA Sequencing

- The nucleotide sequence of the DNA is determined



A New Look into Genes Involved in Malformations of Cortical Development Reveals a Complex Relationship between Molecular Findings and Phenotype

*Fábio Torres[1], Maria Montenegro[2], Vera Terra[2], Marilisa Guerreiro[2], Fernando Cendes[2], Iscia Lopes-Cendes[1] **

1. Department of Medical Genetics - Faculty of Medical Sciences –UNICAMP – Brazil
2. Department of Neurology - Faculty of Medical Sciences –UNICAMP – Brazil
3. Department of Neurology - USP Ribeirão Preto – Brazil

A New Look into Genes Involved in Malformations of Cortical Development Reveals a Complex Relationship between Molecular Findings and Phenotype

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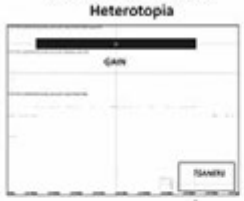
3. Department of Neurology - USP Ribeirão Preto – Brazil

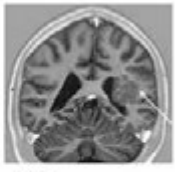
MCD

- Low frequency of sequence variants (SNVs) (8/110 ; 7.2%)
- Searching for CNVs could reveal new candidate genes for MCD and seems to yield good results in terms of finding causal variants for diagnostic purposes (18/40, 45%)

Rossi F. et al 2016

Periventricular Nodular Heterotopia



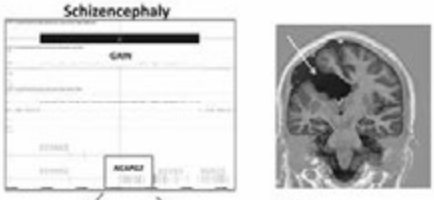


Male
63 years old

Vesicle Mediated Transport

Mutations in *ARFGEF2* implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex

Schizencephaly



Male
29 years old

Cell division
Mitosis
Chromosome Condensation

Microcephalin/MCPH1 Associates with the Condensin II Complex to Function in Homologous Recombination Repair*

NATURE GENETICS VOLUME 44 | NUMBER 8 | AUGUST 2012

De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly

Jeong Ho Lee[1,19], My Huynh[2,9], Jennifer L Silhavy[2,3], Sangwoo Kim[2], Tracy Dixon-Salazar[2,3], Andrew Heiberg[2,3], Eric Scott[2,3], Vincet Bafna[4], Kiley J Hill[2,3], Adrienne Collazo[2,3], Vincent Fenoy[5,6], Carsten Bue[8], Stacey B Gabriel[9], Gary W Mathern[3,4,10] & Joseph G Gleeson[1,2,10]

VOLUME 44 | NUMBER 8 | AUGUST 2012 NATURE GENETICS

De novo germline and postzygotic mutations in *AKT3*, *PIK3R2* and *PIK3CA* cause a spectrum of related megalencephaly syndromes

Jean-Baptiste Rivière[1], Ghazia M Mirzaa[2], Brian J O'Roak[3], Margaret Beddaoui[2], Diana Alcantara[2], Robert L Conway[4], Judith St-Onge[5], Jeremy A Schwartzentruber[6], Karen W Gripp[7], Sarah M Nikkel[8], Thea Worthylake[4], Christopher T Sullivan[2], Thomas R Ward[2], Hadly E Butler[2], Nancy A Kramer[10], Beate Albrecht[11], Christine M Armour[12], Linlea Armstrong[13], Osnat Caluseriu[14], Cheryl Cytrynbaum[15], Beth A Dvorkin[16,17], A Micheil Innes[18], Julie L Lauzon[18], Angela E Lin[19], Gracia M S Mancini[20], Wendy S Meschino[20], James D Reggin[21], Anand K Saggar[22], Telly Lerman-Sagie[23], Gökhan Uyanik[24], Rosanna Weksberg[25], Birgit Zirn[26], Chandree L Beanlands[4], Finding of Rare Disease Genes (FORGE) Canada Consortium[20], Jacek Majewski[27], Dennis E Bulman[28], Mark O'Driscoll[3], Jay Shendure[3], John M Graham Jr[29], Kym M Boycott[4,5] & William B Dobyns[1,20,30]

UNICAMP

PhD Project - 2016

FCM

Searching for mutations associated with focal cortical dysplasia using genomic approaches

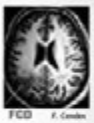
Y.S. de Almeida[1], S.M. Avansini[1], M. Borges[1], F.R. Torres[1], F. Rogerio[1], B.S. Carvalho[1], F. Cendes[1], I. Lopes-Cendes[1]

Project is part of CEPID-BRAINN. Process FAPESP #: 2013/07559-3

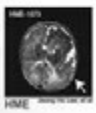
PhD: Vanessa Simão de Almeida
Advisor: Prof. Dra. Iscia Lopes-Cendes
Co-advisor: Dr. Fabio Rossi Torres

➢ FCD

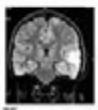
- Is a brain malformation frequently associated with refractory seizures;
- Characterized by cytoarchitecture abnormalities and dysmorphic cells.
- These characteristics are observed in other cortical malformations, such as Hemigalencefaly and Tuberous Sclerosis.



FCD F. Cendes



HME



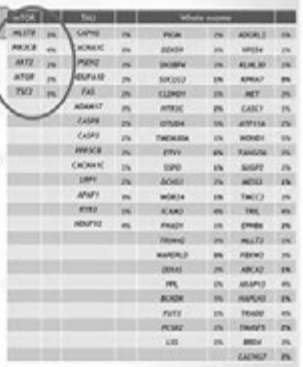
TE

Results

- Exoma -> MuTect

Filters:

- ✓ consequences: frameshift, missense, splicing site mutations
- ✓ SIFT: deleterious
- ✓ PolyPhen2: damaging
- ✓ Reported: rs e COSM
- ✓ MAF < 0.1
  - IGV → mosaic
    - Blood = 0
    - Tissue < 100%

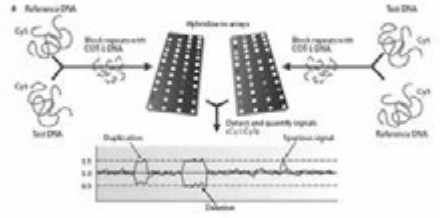


Copy Number Variations (CNVs)

- Contain >1 kb deletions or duplications of DNA
- Cause significant changes in gene expression due to variation in the number of gene copies present or disruption in gene(s) sequences
- CNVs can contain zero, one, or many genes and have been increasingly recognized as an important source of both normal genetic variation and pathogenic mutations

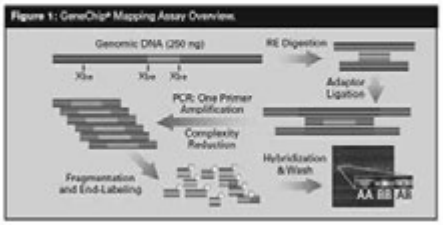
Mefford, HC. *Curr Genet Med Rep* (2014) 2:162–167

Array-CGH



Feuk et al., 2006

SNP array



MCD

- **Low frequency of sequence variants (SNPs) in candidate genes (8/110 ;** 7.2%)
- **Searching for CNVs could reveal new candidate genes for MCD and seems to yield good results in terms of finding causal variants for diagnostic purposes (18/40,** 45%)

Rossi F. et al 2015 (unpublished data)

Challenges in the clinical use of WES/WGS

- Incidental findings
- Dynamic results
- Genomic counselling

Genetic Testing: important recommendation

- No genetic test should be ordered without the patient's informed consent. Since genetic information can be complex, it is important to make sure the patient understands the ramifications of testing in order to make an informed choice

Conclusions

- Genetic testing has many potential benefits
- Potential harms should also be considered, such as genetic discrimination
- Clinicians should consider clinical validity, clinical utility and analytic validity
- Progress in genetic research with the introduction of genomic techniques are changing rapidly the way clinical tests are used

BRAIN FAPESP

PIBMed - Brazilian Initiative on Precision Medicine

BIPMed Brazilian Initiative on PRECISION MEDICINE

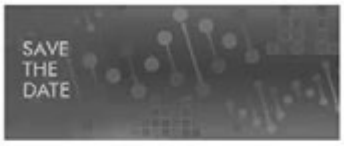
bipmed.iqm.unicamp.br

Global Alliance for Genomics & Health

THE NEW ENGLAND JOURNAL of MEDICINE

Perspective

A New Initiative on Precision Medicine



FAPESP

BIPMED: ONE YEAR AND FORWARD

November 10th, 2016

8:45am to 12:30pm

A meeting to celebrate the one-year launching of the Brazilian Initiative on Precision Medicine (BIPMed)

UNICAMP

BRAIN

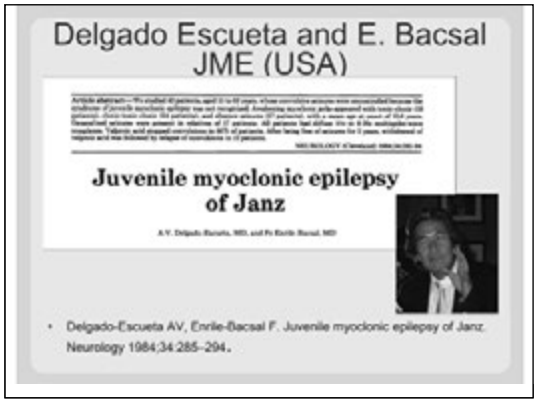

FAPESP
BRAIN

Eleonora Aronica (The Netherlands)

NEUROPATHOLOGY AND EPILEPSY IN NEURODEVELOPMENTAL DISORDERS

Marco Tulio Medina (Honduras)

NEURODEVELOPMENTAL DISORDER, GENETICS AND JME



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

Constancio Castells

- Carlos Mendilaharsu

Descubrimiento Clínico

Herpin, 1867
"secousses"
"impulsions"

Rabot, 1899
"sacudidas breves"
"mioclonias"

Sole-Sagarra, 1952
"benigno"

Janz, 1955
"impulsiv petit mal"

TH. Herpin 1867

Experts'Definition

- Class I criteria encompass myoclonic jerks without loss of consciousness exclusively occurring on or after awakening and associated with typical generalized epileptiform EEG abnormalities, with an age of onset between 10 and 25

Kasteleijn-Nolst Trenité DG et al 2013

Experts'Definition

- Class II criteria allow the inclusion of myoclonic jerks predominantly occurring after awakening, generalized epileptiform EEG abnormalities with or without concomitant myoclonic jerks, and a greater time window for age at onset (6-25 years).

- Kasteleijn-Nolst Trenité et al 2013

Experts'Definition

- For both sets of criteria, patients should have a clear history of myoclonic jerks predominantly occurring after awakening and an EEG with generalized epileptiform discharges supporting a diagnosis of idiopathic generalized epilepsy

Kasteleijn-Nolst Trenité et al 2013

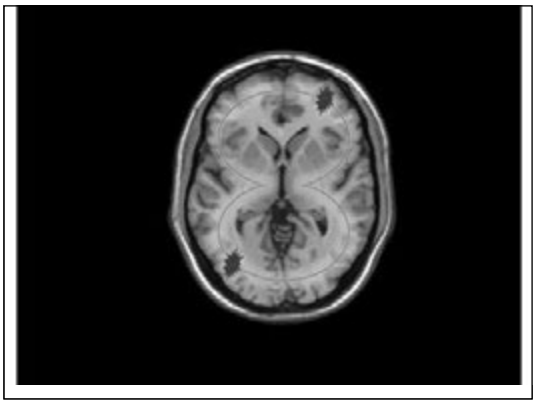
JME ICD-11 proposed definition

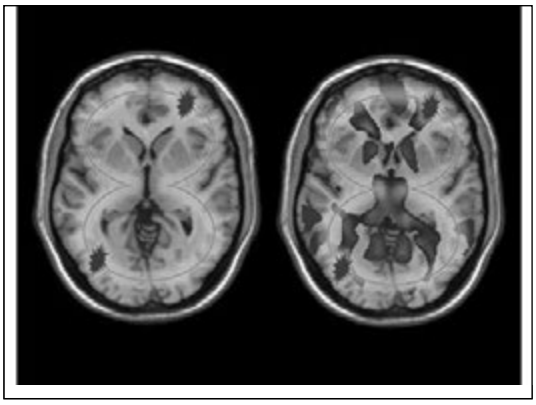
- The onset is between the ages of 6 and 25 years with myoclonic jerks without loss of consciousness predominantly occurring early in the morning. Intelligence is generally not affected, though mild cognitive and social dysfunction can occur. Jerks may be facilitated by sleep deprivation, stress, or certain visual stimuli. Convulsive seizures may occur and may be preceded by myoclonic jerks.

- Berger, Ettore, Jette, Medina, WHO 2013

Generalized - reconceptualized

- For seizures
  - *Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. …can include cortical and subcortical structures, but not necessarily include the entire cortex.*





Recommended terminology for etiology

Use terms which mean what they say:

- Genetic
- Structural-Metabolic
- Unknown

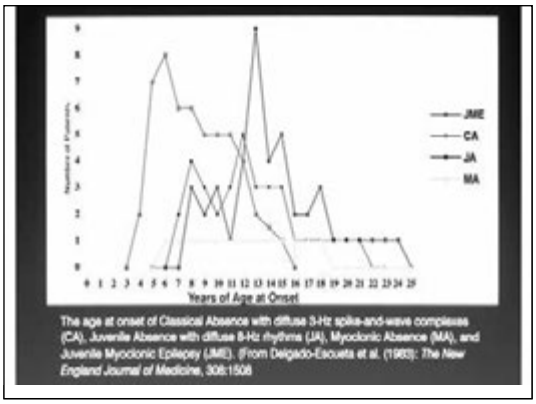
Previously used terms denoting old concepts:
Idiopathic, cryptogenic, symptomatic

Genetic

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

Pedro I Brazil

- **Dom Pedro I of Brazil and IV of Portugal: epilepsy and peculiar behavior**
- **Dom Pedro de Alcântara Bragança e Bourbon (1798-1834), first Emperor of Brazil. . Dom Pedro presented familiar incidence of epilepsy. His seizures were relatively benign and scattered, supposedly started at the age of 13. The diagnosis: juvenile myoclonic epilepsy.**
- **Gomes and Chalub. Arq Neuropsiquiatr 2007 Sep;65(3A):710-5**



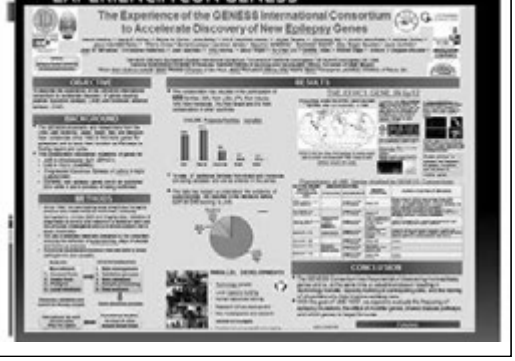
The age at onset of Classical Absence with diffuse 3-Hz spike-and-wave complexes (CA), Juvenile Absence with diffuse 8-Hz rhythms (JA), Myoclonic Absence (MA), and Juvenile Myoclonic Epilepsy (JME). (From Delgado-Escueta et al. (1983): *The New England Journal of Medicine*, 308:1508

GENESS Consortium in the Americas

*Laforin;GABRb3;EFHC1;JCK;IPO8;PROSER1;MYOFERL

Fundadores:
Delgado Escueta
ME Alonso
MT Medina
F Rubio-Donnadieu

EXPERIENCIA CON GENESS

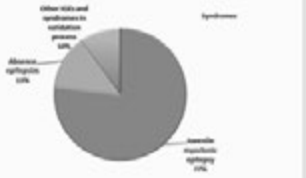


Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up

Iris E. Martínez-Juárez,[1,2] María Elisa Alonso,[3] Marco T. Medina,[4] Reyna M. Durón,[1,4] Julia N. Bailey,[1,5] Minerva Lopez-Ruiz,[3] Ricardo Ramos-Ramírez,[6] Lourdes León,[3] Gregorio Pineda,[7] Ignacio Pascual Castroviejo,[8] Rene Silva,[9] Lisardo Hija,[9] Katerina Perez-Goniengfiao,[1] Jesús Machado-Salas[10] and Antonio V. Delgado-Escueta[1]

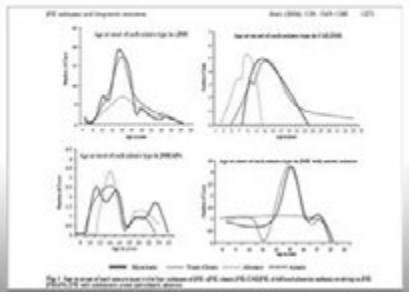
[1]David Geffen School of Medicine at UCLA and VA GLAHS Epilepsy Center of Excellence, Epilepsy Genetics/Genomics Laboratories, Comprehensive Epilepsy Program, [2]Semel Institute for Neuroscience, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [3]National Institute of Neurology and Neurosurgery, [4]Neurology and Neurosurgery Unit, Mexico General Hospital, Mexico City, [5]Angel Leaños Hospital, Guadalajara, Mexico, [6]National Autonomous University of Honduras, Tegucigalpa, Honduras, [7]Pediatric Neurology, University Hospital La Paz, Madrid, Spain, [8]Nuestra Señora de La Paz Hospital, San Miguel, El Salvador and [9]Institute of Neurological Sciences, Lima, Peru

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



Medina et al 2005

SUBSINDROMES



Sindrome de Janz o JME

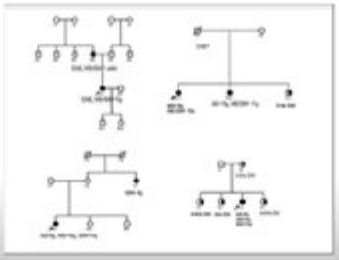
13

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

Marco T. Medina,*† Reyna M. Durón,*† María E. Alonso,‡ Charlotte Dravet,§ Lourdes León,‡ Minerva Lopez-Ruiz,‡ Ricardo Ramos-Ramírez,‖ Ignacio Pascual Castroviejo,¶ Karen Weissbecker,# B. Westling, Katerina Tanya Perez-Goniengfiao,** Sonia Khan,†† Gregorio Pineda, Ryoji Morita,‡‡ Astrid Rasmussen,§§ Jose Ramos Peek,‖ Sergio Cordova,‖ Iris Martínez-Juarez,*‖ Francisco Rubio-Donnadieu,‖ Adriana Ochoa,‖ Aurelio Jara-Prado,‖ Julia N. Bailey,*¶ Miyabi Tanaka,* Donsheng Bai,* Jesús Machado-Salas,* and Antonio V. Delgado-Escueta*

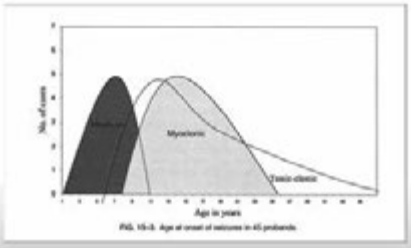
- Medina et al Advances of Neurology 2005

Patron de Herencia



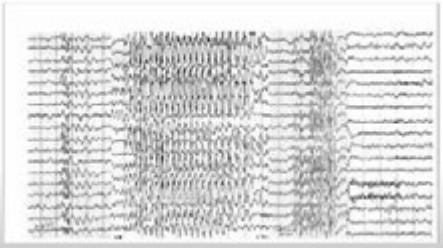
- Medina et al Advances of Neurology 2005

PATRON CLINICO



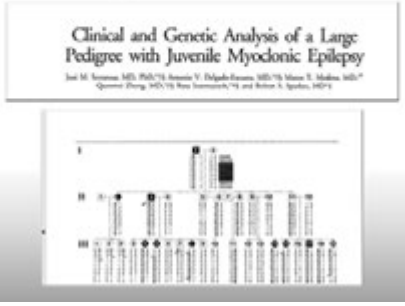
- Medina et al Advances of Neurology 2005

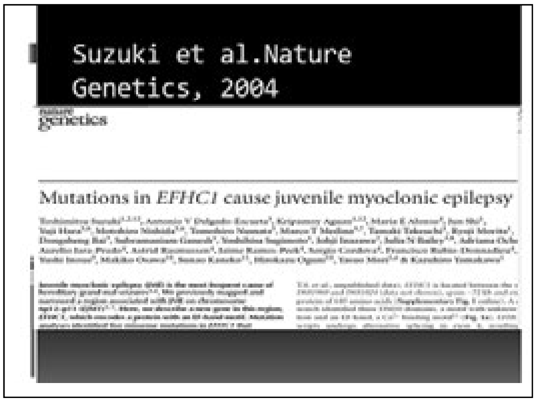
Patron EEG

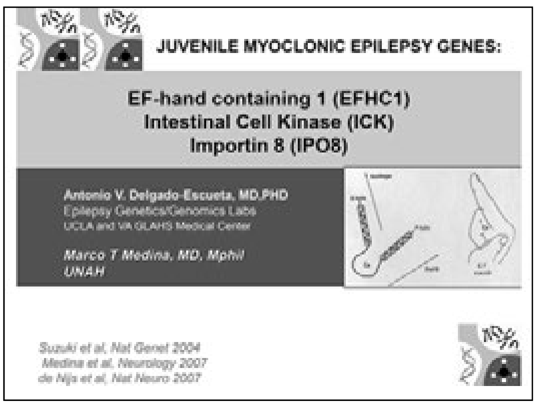


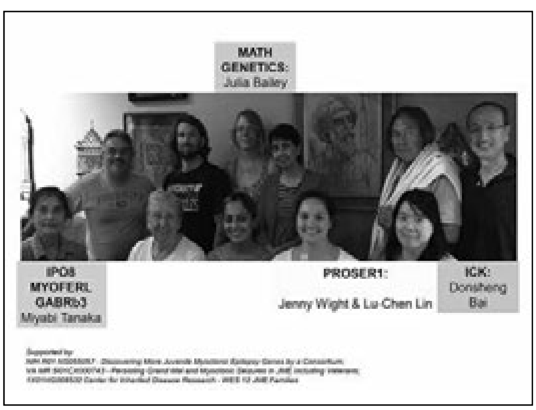
- Medina et al Advances of Neurology 2005

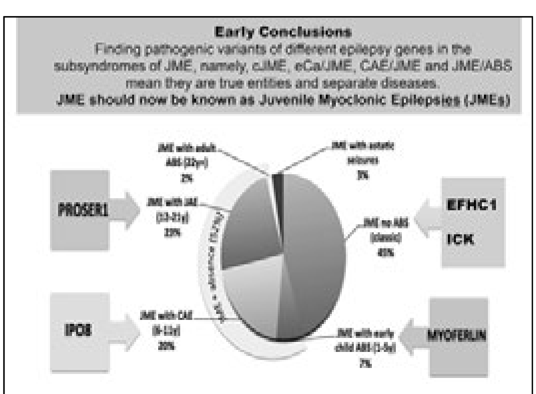
Searching the JME Genes


Clinical and Genetic Analysis of a Large Pedigree with Juvenile Myoclonic Epilepsy


Suzuki et al.Nature Genetics, 2004
nature genetics
Mutations in EFHC1 cause juvenile myoclonic epilepsy


JUVENILE MYOCLONIC EPILEPSY GENES:
EF-hand containing 1 (EFHC1)
Intestinal Cell Kinase (ICK)
Importin 8 (IPO8)
Antonio V. Delgado-Escueta, MD,PHD
Epilepsy Genetics/Genomics Labs
UCLA and VA GLAHS Medical Center
Marco T Medina, MD, Mphil
UNAH
Suzuki et al, Nat Genet 2004
Medina et al. Neurology 2007
de Nijs et al, Nat Neuro 2007


MATH GENETICS:
Julia Bailey
IPO8
MYOFERL
GABRb3
Miyabi Tanaka
PROSER1:
Jenny Wight & Lu-Chen Lin
ICK:
Donsheng Bai


Early Conclusions
Finding pathogenic variants of different epilepsy genes in the subsyndromes of JME, namely, cJME, eCa/JME, CAE/JME and JME/ABS mean they are true entities and separate diseases.
JME should now be known as Juvenile Myoclonic Epilepsies (JMEs)
JME with adult ABS (22yr) 2%
JME with astatic seizures 3%
PROSER1
JME with JAE (13-21y) 23%
JME no ABS (classic) 45%
EFHC1
ICK
IPO8
JME with CAE (6-11y) 20%
JME with early child ABS (1-5y) 7%
MYOFERLIN

RESEARCH STRATEGY in JME

CLINICAL STRATEGY – JME probands with absence: 12 Mg/Mx JME families with **>8 members affected with same JME** phenotype across 3-5 generations. CIDR scanned the whole genome of these 12 families looking for linkage and haplotype loci using 6500 SNPs.
SEQUENCING STRATEGY – (1) REDUCE SIZE OF GENOME: WES affected siblings (share 50% of DNA), affected first cousins (share 12.5% of DNA), affected second cousins (share 6.25% of DNA), an affected individual who is 'distant' plus a 'married in' as control.
(2) CONFIRM: After GATK processing of BAM files and ANNOVAR identifies candidate variants from VCF located in linkage & hapiotype locus, –Confirm by Sanger sequencing co-inheritance of variants in all JME-affected members.
(3) Screen by amplicon/MiSeq 190-380 GGE and JME families to detect in exonic and non-exonic regulatory regions: 5' and 3' areas, transcription binding sites, CPG islands, intergenic regions and introns.
(4) **Vett** variants of candidate JME genes of through NHGRI and ACMG guidelines to assign pathogenicity or benign status.

RESULTS
(Bailey et al.,Gen. in Med.,2016)

EFHC1 is more common in Classic JME (cJME): We vetted, through NHGRI and ACMG guidelines, 54 EFHC1 (EF hand containing 1 gene) exonic variants observed in 73 JME families from 17 cohorts worldwide and classified 23 EFHC1 variants as pathogenic or likely pathogenic in classic JME (cJME). Of these, 16 cJME cases and 1 case CAE/JME from our GENESS consortium.

Epilepsy Genes in Latin America

JME in chromosome 6p12

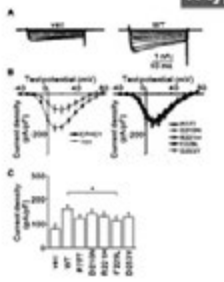
Studying calcium functions: Myoclonin/EFHC1

- Baby Hamster Kidney Cells
  - Co-transfected with various types of VDCC
  - Significant increase in currents of R type VDCC by EFHC1
  - Human JME mutations reduce the increased R type VDCC currents

[Suzuki et al., 2004]

Epilepsy Genes in Latin America

Myoclonin/EFHC1 enhances R type VDCC currents



JME mutations reverse myoclonin effects.

[Suzuki et al., 2004]

ICK VARIANTS IN 6% of 265 probands with cJME

ICK-632 aa protein

INTESTINAL CELL KINASE: 0.58 Mb away from EFHC1 in 6p12 (cis position)

Originally cloned by Nagase et al in 1999. By 2005,Fu et al.,showed ICK may control G1 cell cycle progression by regulating cell cycle regulators,cyclin D1,cMyc,and p21Cip1.

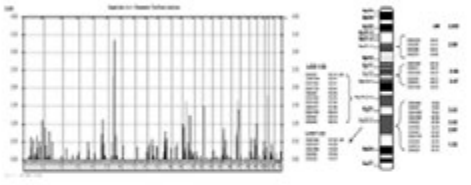
ICK activates mTOR complex 1 by phosphorylating Raptor Thr-90823

ICK phosphorylates Scythe (BAT3),the reaper binding nuclear protein which downregulates apoptosis and cell proliferation.

Thus, ICK is involved in apoptosis, cell proliferation, and cell-cycle regulation.

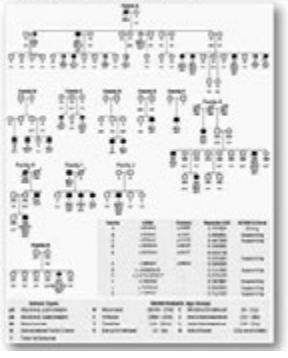
MYOCLONIN3/ICK IN LA/BELIZE FAMILY

(ANCESTRAL ORIGIN-ALSACE-LORRAINE)



Dongsheng Bai

Pedigrees studied, Bayesian LOD scores

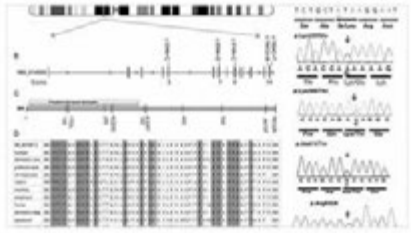


PEDIGREES OF JME FAMILIES WITH *ICK* MUTATIONS
Bayesian lod scores

Family	cDNA	Protein	Bayesian LOD	ACMG Criteria
A	c.914A>C	p.K305T	3.737004	Strong
B	c.304A>C	p.I102L	1.085652	Supporting
C	c.658A>G	p.K220E	0.487396	Supporting
D	c.1843G>A	p.A615T	0.186986	
E	c.1843G>A	p.A615T	-0.033702	
			0.153284	Supporting
F	c.1894C>T	p.R632X	0.000000	
G	c.-20960A>G	.	0.111366	Supporting
H	c.[-1772>T;2991C>T		-0.335294	
I	c.*102A>G	.	0.787887	Supporting
J	c.*1936A>G	.	0.560965	Supporting
K	c.*169A>T	.	0.412469	Supporting
L	c.1434G>A	p.T478T	-0.021167	Benign
	c.1581A>G	p.K527K	0.000000	

RESULTS

ICK is also more common in cJME: Previously, we also vetted 5 pathogenic or likely pathogenic exonic ICK (Intestinal cell kinase) variants in cJME (6 families), and 2 ICK deletions, 3 novel and 3 rare variants in 3'UTR or promoter areas in 2 families with CAE/JME, 1 family with CAE, 1 JME with adolescent ABS, and 4 families with cJME.



Odds Ratios of 5 variants of ICK with JME cases (# chromosomes) by all and ethnic matched ExAC control groups.

Family	cDNA	Protein	Index Cases		ExAC Allele Counts		OR	P-value	
C	c.658A>G	p.K220E							
	Latino		1	174	0	11,578	∞	0.0118	*
	All		1	666	0	121,404	∞	2.779E-06	***
A	c.914A>C	p.K305T							
	Latino		1	332	4	11,510	8.69	0.0406	*
	All		1	658	4	121,124	49.08	0.0023	**
D,E	c.1843G>A	p.A615T							
	East Asian		2	188	2	8,650	46.49	0.0079	**
	All		2	664	4	120,938	91.34	4.291E-05	***
F	c.1894C>T	p.R632X							
	East Asian		1	188	0	8,642	∞	0.0080	**
	All		1	664	3	121,277	60.97	0.0016	**
B	c.304A>C	p.I102L							
	Latino		1	170	2	11,566	15.67	0.0433	*
	All		1	640	2	121,232	94.86	0.0006	***

Summary of evidentiary data implicating variants of ICK based on NHGRI criteria

Variants	Bayesian lod score	Odds Ratio	Minor allle frequencies	Prediction algorithms		
				conservation	aminoacid damage	splice site
p.I102L	- 0.021	✓	✓	✓	✓	✓
p.S174S	-	✓	✓	✓		✓
p.T478T	-	✓	✓	-		✓
p.K527K	-	✓	✓	✓		✓
369-373 del	-	-	-	✓		-
p.K305T	✓	✓	✓	✓	✓	✓
p.T152L	✓	✓	✓	✓	✓	✓
p.K220E	✓	✓	✓	✓	✓	✓
p.A615T	✓	✓	✓	✓		✓
p.R632X	✓	✓	✓	✓	✓	✓

✓ *significant or novel depending on population*

Evidentiary Summary of ICK Variants and ACMG Guidelines

Pathogenic Variants

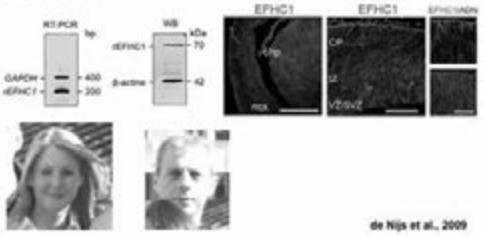
c.430A>G	p.K220E
Strong	•Experimental functional studies demonstrate impaired radial migration of neurons during development, mitotic cells, and cell cycle index while increasing the rate of apoptosis. (PS3) •Prevalence significantly increased in JME over Ctrl/C allele counts for both Latinos (OR: ∞, $p \leq 0.0118$) and all populations (OR: ∞, $p \leq 7.7705E-06$). (PS4)
Moderate	•Absent in all populations in ExAC database. (PM2)
Supporting	•Found in compound with 2 clinically affected individuals in 1 family (Bayesian LOD Score: 0.3874). (PP1)

c.1504C>T	p.R502X
Strong	•Experimental functional studies demonstrate impaired radial migration of neurons during development, mitotic cells, and cell cycle index while increasing the rate of apoptosis. (PS3) •Prevalence significantly increased in JME over Ctrl/C allele counts for both Latinos (OR: 0.01, $p \leq 0.0002$) and all populations (OR: 49.46, $p \leq 0.0023$). (PS4)
Supporting	•Found in compounds with 2 clinically affected and 2 asymptomatic individuals with splice-wave complexes in 1 family (Bayesian LOD Score: 1.7578). (PP1)

c.1808C>T	p.A603V
Strong	•Experimental functional studies demonstrate impaired radial migration of neurons during development, mitotic cells, and cell cycle index while increasing the rate of apoptosis. (PS3) •Prevalence significantly increased in JME over Ctrl/C allele counts for both Latinos (OR: ∞, $p \leq 0.0008$) and all populations (OR: 10.77, $p \leq 0.0013$). (PS4)
Moderate	•Absent in East Asian populations in ExAC database. (PM2) •Protein length changes due to in-frame deletion/insertions in a non-repeat region or stop-loss variants. (PM4)
Supporting	•Predicted to have effect on splicing mechanism by creating a new Donor (+) by Human Splicing Finder. (PP3)

Expression of EFHC1 during brain development

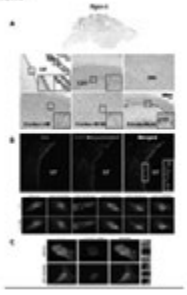
E17 rat brain (term: E21)



de Nijs et al., 2009

Genetically Implicated ICK variants in Cerebral Cortex Development

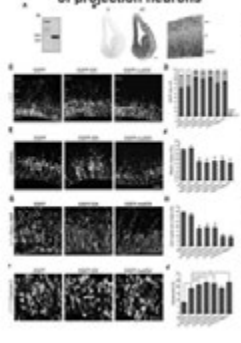
JME/ICK heterozygous mutations (p.K220E,p.K305T,p.A615T,p.R832X) do not impair centrosome association; only R272Q of ECO syndrome causes loss of nuclear localization.



A. ICK mRNA at E.14.5 developing Telencephalon.
B. ICK is in soma of ependymal cells but not cilia;EFHC1 is in soma and cilia
C. Intense fluorescent spots close to nuclei are positive for γ-tubulin,a centrosome marker. **No change for mutants except R272Q.**

ICK variants' dominant negative effect on radial migration of projection neurons

EGFP tagged neurons introduced into neocortex by ex vivo electroporation at E.14.5.Three days later analyse distribution in VZ/SVZ,IZ, and cortical plate., f.Caspase3 for apoptosis at E.14.5.ICK overexpression increased apoptosis.ICK mutants but not A625T further incressed apoptosis.

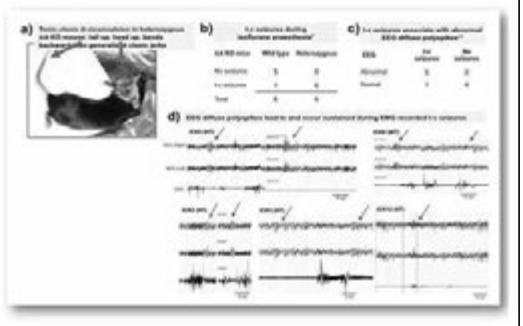


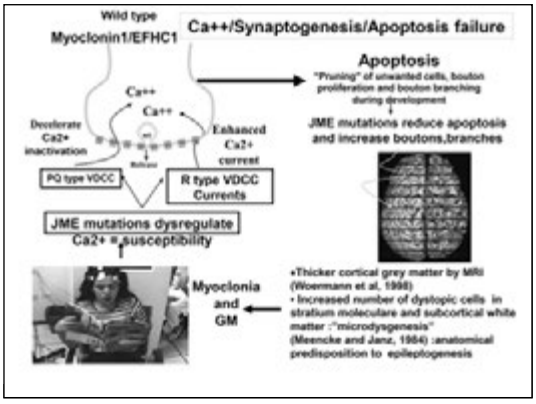
C.Radial migration.No differences in distribution between EGFP and EGFP-ICK. But ICK mutants reduce number of neurons reaching cortical plate except for the Japanese mutation A615T.

E. Mitotic M- phase imarker by phospho-histone H3decreased by ICK mutants.

G.Cell cycle exit index by triple labels-GFP ,BrdU and Ki67. decreased by ICK mutants.

ick knock out mouse – from Riken BSI





JME: One Common Disease Pathway for Three Myoclonin Genes

- **Myoclonin1/EFHC1 for cJME: Microtubule binding protein involved in apoptotic pruning of synaptic boutons and dendrites, increased R type VDCC influx, cell division and** neuroblast migration
- **Myoclonin3/ICK for cJME: Also a neurodevelopmental gene involved in** neuroblast migration
- **ALONSIN/IPO8- for photosensitive CAE/EM evolve JME: Also involved** in neuroblast migration.**Variants-no effects on functions of (1) MicroRNA-silencing mRNA and (b) cytoplasm to nucleus s nucleusinformation transfer/ signalling**

/ /

MEETING WITH MARILISA GUERREIRO, ISCIA CENDES, ELEONORA ARONICA, MARCO TULIO MEDIN

Peter Wolf (Denmark)

ICTOGENESIS OF FOCAL AND GENERALIZED EPILEPSIES

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Generalized and focal ictogenesis

Peter Wolf, Dianalund & Florianópolis

11th LASSE, Guarulhos
March 2 - 11, 2017

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The historical concepts

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

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Focal seizures

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

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

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

New nosological understanding ⇒ therapeutic consequence

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"Generalized"

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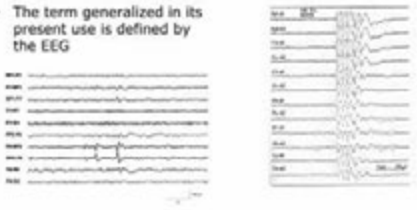
- The term generalized in its present use is defined by the EEG



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Concepts of ictogenesis: 1970 Classification

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

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The common view of generalized epilepsy

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

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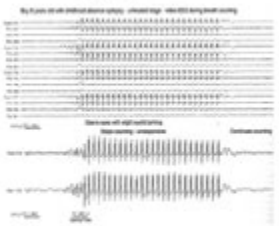
Generalised SW discharges typically are symmetric, synchronous and widespread -

but typically also have a frontal accentuation, especially at onset



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

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

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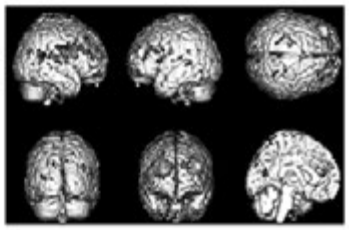
JME:
Global ⇑ of FMZ binding ($GABA_A$ receptors), especially in dorso-lateral pre-frontal cortex -

but also PO



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

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Morphological findings

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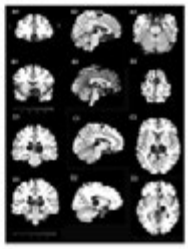
Cao et al (2013): meta-analysis of 7 studies of JME with voxel-based morphometry:

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



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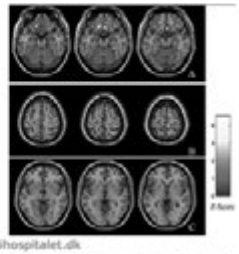
Voxel-based morphometry: JME, absence epilepsy, healthy controls: *Betting et al NeuroImage 2006; 32:498-502*

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



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"pseudofocal" discharge

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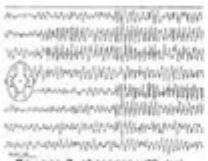
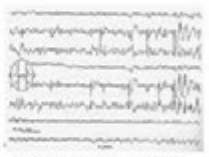


Boy age 7, absences with eye deviation to left. Benign course.



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

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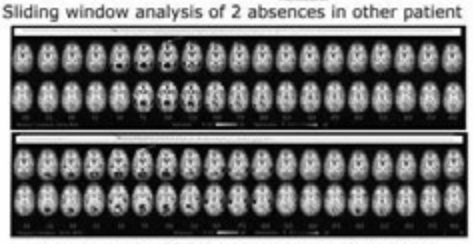
Sliding window analysis of 2 absences in other patient



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

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

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

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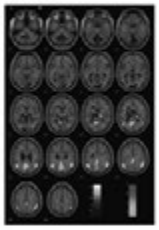
Benuzzi F et al, Epilepsia 2012; 53: 622-630: Changes of BOLD signal before and during absences: 15 Pat

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

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



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Conclusion at present

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

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Reflex epileptic mechanisms in IGEs

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

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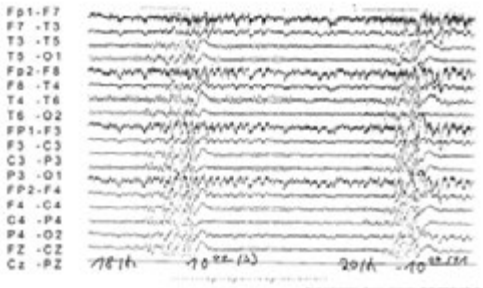
TV-induced seizures: photoparoxysmal EEG response



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

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

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

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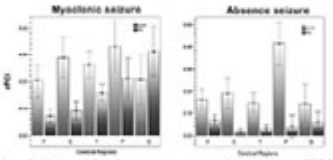
rPCI = relative phase clustering index



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

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

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

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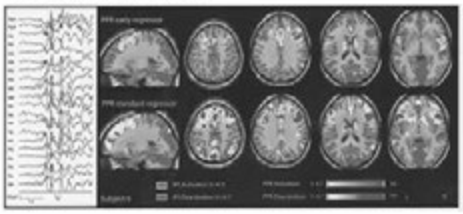
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2 years. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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Authors' conclusion

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

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Eye closure sensitivity:

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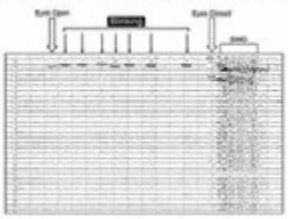
Vaudano et al Ann Neurol 2014; 76:412-27
Patients with Jeavons syndrome, all photosensitive



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

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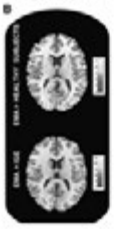
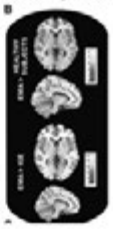
At eye closure



Following 3 sec



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Praxis induction

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- Precipitation of seizures by cognition-guided complex motor tasks
- Most typical: complex visuo-motor coordination
- Matsuoka et al (2000): closely related to IGE. Found in 50% of JME patients in Japan
- 25 – 30% of JME patients in Germany (Mayer et al 2006) and Brasil (Sao Paolo group: Yacubian et al)
- Pathophysiology: interaction of complex functional anatomical network subserving visuomotor coordination with short reflex loop (proprioception ⇒ myocloni) in active musculature
- Focal myocloni in a "generalized" epilepsy!

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Focal seizures in a generalized epilepsy

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Connectivity in JME

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

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

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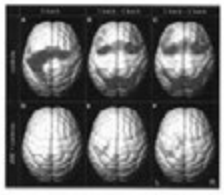
"Working memory paradigm": a spot appears in random sequence in one of 4 fields: where is it now? where was it last time? where the time before?

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



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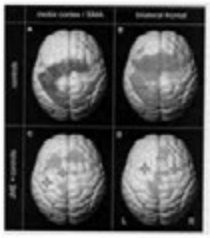
Vollmar et al. Motor system hyperconnectivity in JME: a cognitive fMRI study. Brain 2011; 134:1710-1719



Study: fMRI with an executive frontal lobe paradigm

Findings:

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

C+D: increased connectivity in JME patients

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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

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Conclusion on IGE: areas involved in corticothalamic and intracortical networks

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

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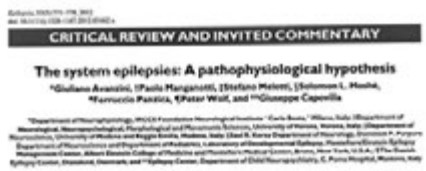

CRITICAL REVIEW AND INVITED COMMENTARY

The system epilepsies: A pathophysiological hypothesis

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

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

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The new view of IGEs: system epilepsies

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

Examples of neurological system disorders?

Motoneuron disease – Polyneuropathies - Myasthenia gravis

System epilepsies

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Development of view of focal ictogenesis

- Traditional view: there is an epileptic focus, i.e. a small aggregate of abnormally functioning neurons that start to produce spikes which spread from there.
- Usually there is also a local lesion, the more likely to be found the better your tools of investigation.
- More recent view: in focal lesional epilepsies seizures originate in consequence of an interplay of ictogenic tissues in or adjacent to the lesion, with normal tissue more or less close by.

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Focal ictogenesis: investigation methods

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

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Focal ictogenic networks

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

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

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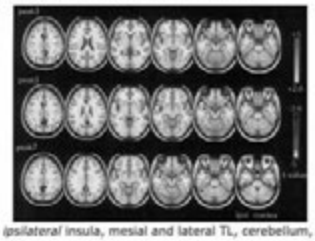

Activation: *ipsilateral* insula, mesial and lateral TL, cerebellum, *bilateral* mid-cingulate gyrus
Deactivation: *bilat.* inferior parietal lobules, posterior cingulate gyrus, precuneus, *contralat.* post. temp. cortex

Fahoum et al Epilepsia 2012

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14 pts with frontal lobe epilepsy

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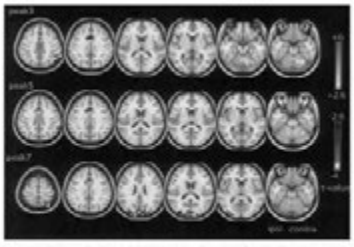

Activation: *bilateral* cingulate gyrus, *ipsilat* frontal operculum,medial thalamus, internal capsule, *contralat* cerebellum
Deactivation: *bilateral* cuneus, *contralat inf* and sup parietal lobules

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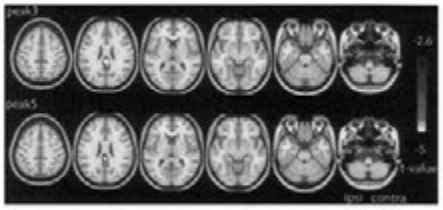
20 pts with posterior cortical epilepsies



Bilateral deactivation clusters in posterior cingulate cortex and precuneus

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Conclusion on focal lesional epilepsies

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

How are the focal ictogenic networks established?

Possibility for prospective connectivity studies after brain trauma

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Focal ictogenesis in idiopathic LREs

- There is no lesion or constant epileptic focus
- Seizures can be generated in alternate sides
- Very little investigated
- Ictal EEG in BECTS, topographic mapping (Jung et al 2003): Rolandic spikes originate from sulcal or gyral cortices on either side of the central sulcus, propagation from central to mid-temporal locations across the central sulcus by intracortical spreading

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Ictogenesis in idiopathic LREs

Components

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

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Conclusion

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

Uses physiological functional anatomical networks

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

Examples of neurological system disorders

Motoneuron disease

Polyneuropathies

Myasthenia gravis

System epilepsies

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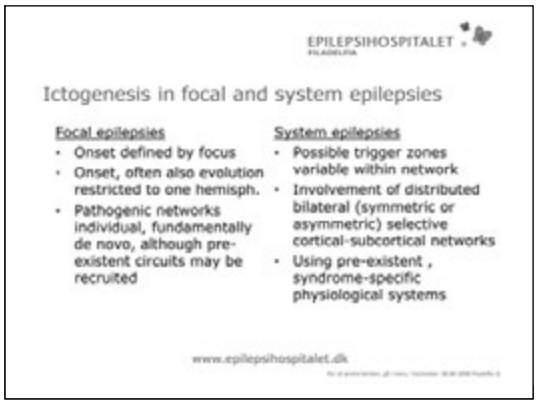
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Ictogenesis in focal and system epilepsies
Focal epilepsies
• Onset defined by focus
• Onset, often also evolution restricted to one hemisph.
• Pathogenic networks individual, fundamentally de novo, although pre-existent circuits may be recruited
System epilepsies
• Possible trigger zones variable within network
• Involvement of distributed bilateral (symmetric or asymmetric) selective cortical-subcortical networks
• Using pre-existent , syndrome-specific physiological systems
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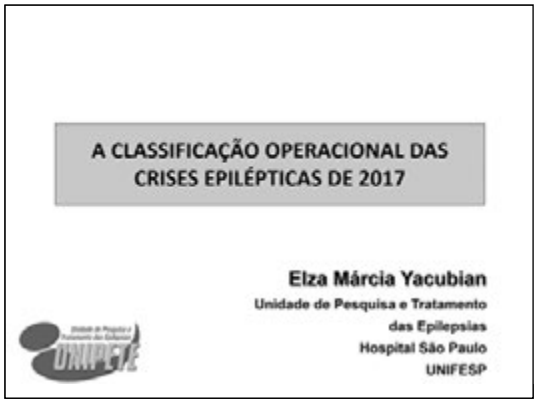
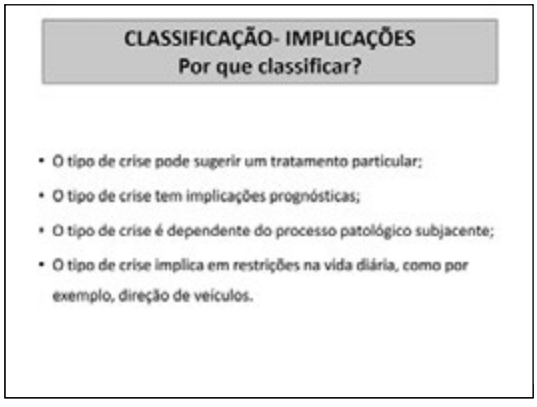
Elza Márcia Yacubian (Brazil)

THE NEW CLASSIFICATION OF EPILEPTIC SEIZURES





A CLASSIFICAÇÃO DAS CRISES EPILÉPTICAS DE 2017

A Classificação das Crises Epilépticas e das Epilepsias é um instrumento fundamental que promove significativo impacto em nossa atividade clínica diária.

Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures

From the Commission on Classification and Terminology of the International League Against Epilepsy*

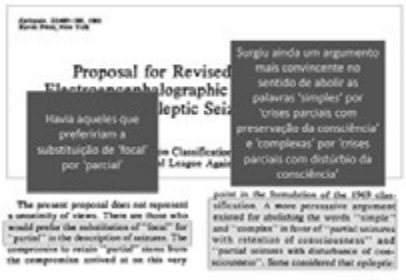
1981

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], Flora E. Jansen[6], Lieven Lagae[7], Solomon L. Moshé[8], Jukka Peltola[9], Elinor Roulet Perez[10], Ingrid E. Scheffer[11], Samuel M. Zuberi[12]

2017

1981- 2017. Um hiato de 35 anos



Proposal for Revised Electroencephalographic Classification of Epileptic Seizures

Havia aqueles que prefeririam a substituição de 'focal' por 'parcial'

Surgiu ainda um argumento mais convincente no sentido de abolir as palavras "simples" por 'crises parciais com preservação da consciência' e 'complexas' por 'crises parciais com distúrbio da consciência'

The present proposal does not represent a unanimity of views. There are those who would prefer the substitution of "focal" for "partial" in the description of seizures. The compromise to retain "partial" stems from the compromise arrived at on this very point in the formulation of the 1969 classification. A more persuasive argument existed for abolishing the words "simple" and "complex" in favor of "partial seizures with retention of consciousness" and "partial seizures with disturbance of consciousness". Some considered that epileptic

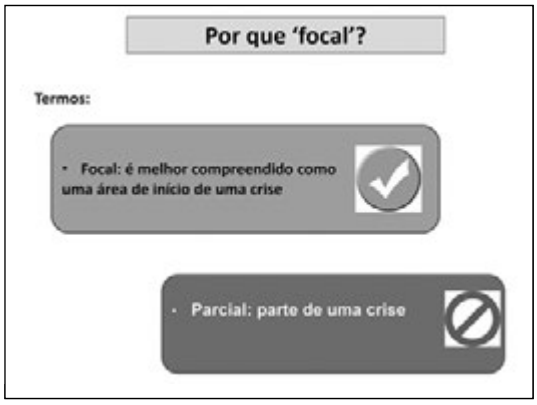
---

- **Crise parcial simples** pode banalizar seu impacto a um paciente que não crê que as manifestações e consequências das crises sejam de forma alguma simples.
- **Crise parcial complexa** pode implicar que esse tipo de crise é mais complicado ou difícil para entender que outros tipos de crises.

Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501.


Epilepsy classification: a cycle of evolution and revolution
Volume 26 • Number 2 • April 2013


1981- 2017. Um hiato de 35 anos
SPECIAL REPORT
Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009


Por que 'focal'?
Termos:
• Focal: é melhor compreendido como uma área de início de uma crise
• Parcial: parte de uma crise


The 2016 ILAE Seizure Classification

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- Dois documentos

Operational Classification of Seizure Types by the International League Against Epilepsy

Robert S. Fisher[1], J. Helen Cross[2], Jacqueline A. French[3], Norimichi Higurashi[4], Edouard Hirsch[5], Floor 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]

Instruction manual for the ILAE 2017 Operational Classification of Seizure Types

Robert S. Fisher[1], J. Helen Cross[2], Carol D'Souza[3], Jacqueline A. French[4], Sheryl Haut[5], Norimichi Higurashi[6], Edouard Hirsch[7], Floor E. Jansen[8], Lieven Lagae[9], Solomon L. Moshé[10], Jukka Peltola[11], Elaine Roulet Perez[12], Ingrid E. Scheffer[13], Andreas Schulze-Bonhage[14], Emera Somerville[15], Carol D'Souza[16] Herbert Spetlag[17], Elin Maria Trevathan[18], Sameer M. Zuberi[19].

Classificação
Dificuldades: definir consciência

Robert Fisher Chair

Consciência é um fenômeno complexo que engloba componentes subjetivos e objetivos

Os cinco tipos de envolvimento de consciência

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)- 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.

Crise focal evoluindo para tônico-clônica generalizada

Crise focal disperceptiva

FICS e FACS

1. FACS: Focal Aware Conscious Seizures
   - FACS sem disfunção perceptiva
   - FACS com disfunção perceptiva seletiva
2. FICS: Focal Impaired Consciousness Seizures *(propuseram evitar os termos crises discognitivas e dialépticas por considerá-los confusos)*
3. Crises de ausências
4. Crises tônico-clônicas generalizadas

Epilepsia 2014;55(8):1145-50.

Determinação retrospectiva da consciência

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

Consciousness
Consciência

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: percepção de si próprio e do meio, responsividade e memória.

Awareness
Percepção

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

Crises sem comprometimento da consciência= termo substituto- crises focais perceptivas

Como em várias línguas, aware=consciência **e** unaware=inconsciência, **usar com ou sem comprometimento (alteração) da consciência**

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.

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.

Robert Fisher
Chair

Classificação dos Tipos de Crises da ILAE 2017 [1]

Esquema simplificado

* Definições, outros tipos de crises e descritores estão listados no artigo e no glossário de termos
† Por informação inadequada ou impossibilidade de inserir nas outras categorias

Robert Fisher
Chair

Classificação dos Tipos de Crises da ILAE 2017 [1]

Esquema expandido

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.

Atualização do Glossário de 2001

ausência típica	evento de natureza súbita, com interrupção das atividades, olhar vago, possivelmente desviado para cima. Há dificuldade na responsividade, durando em geral menos de 30 segundos, com rápida recuperação. Se EEG disponível, registro de descargas epileptiformes generalizadas durante o evento. Uma crise de ausência é por definição uma crise de início generalizado, não sendo o termo "ausência" sinônimo de olhar vago, que também pode ocorrer em crises com início focal	Adaptado de [1]
ausência atípica	crise de ausência com mudanças de tônus mais pronunciadas que na ausência típica ou crise com início e/ou final não abruptos. EEG: registro descargas do tipo espícula-onda lenta, generalizadas e irregulares	Adaptado de Gastaut [2]
parada	ver parada comportamental	novo
atônica	redução ou perda súbita do tônus muscular não precedida por crise mioclônica ou clônica. Duração de aproximadamente 1-2 segundos, envolvendo a musculatura da cabeça, fronte, queixo ou membros	[1]
automatismos	atividade motora mais ou menos coordenada ocorrendo quando a cognição está alterada. Em geral, mas nem sempre, com recordação posterior (amnésia). Automatismos sempre imitam um movimento voluntário, podendo consistir em uma continuação inapropriado da atividade motora pré-ictal	[1]
crises autonômicas	rápida alteração da função do sistema nervoso autonômico envolvendo função cardiovascular, pupilares, gastrointestinais, sudomotoras, vasomotoras e termorregulatórias	Adaptado de [1]
aura	fenômeno ictal subjetivo, do vasto precedendo manifestações clínicas observáveis por circunstantes (aura é um termo de uso popular)	[1]
percepção	percepção de si próprio e do ambiente	novo
tônicas	ambos os lados, direito e esquerdo, apesar das manifestações de crises bilaterais poderem ser simétricas ou assimétricas	novo
clônicas	abalos, simétricos ou assimétricos, que se repetem de forma regular, envolvendo os mesmos grupos musculares	Adaptado de [1]

Atualização do Glossário de 2001

cognitivo	relativo a pensamento e funções cognitivas superiores como linguagem, percepção espacial, memória e praxis. O termo similar utilizado previamente era "psíquico"	novo
consciência	estado da mente que inclui ambos os aspectos subjetivos e objetivos, englobando a percepção de si mesmo como uma entidade única, a perceptividade, a responsividade e a memória	novo
disfórica	episódios de choro, que pode ou não estar associado ao sentimento de tristeza	[1]
distônica	contração sustentada dos músculos agonistas e antagonistas produzindo movimentos alentidos e de torção, que podem produzir posturas anormais	Adaptado de [1]
crises emocionais	crises que se apresentam com uma emoção ou que aparentam ter componente emotivo como uma característica proeminente, tais como medo, angústia espontânea ou euforia, gargalhadas (gelásticas) ou choro (dacrísticas)	novo
espasmos epilépticos	súbita flexão, extensão, ou combinação de extensão-flexão dos músculos predominantemente proximais e do tronco, frequentemente mais sustentada que os movimentos mioclônicos mas não tão mantida como nas crises tônicas. Formas mistas podem ocorrer: caracteristicamente, queda da cabeça ou movimentos oculares tonic. Espasmos epilépticos frequentemente ocorrem em grupos. Espasmos infantis são a forma mais conhecida, mas espasmos podem ocorrer em qualquer idade	Adaptado de [1]
epilepsia	doença cerebral definida por qualquer das seguintes condições: 1. Pelos menos duas crises não provocadas (ou reflexas) ocorrendo com intervalo superior a 24 horas 2. Uma crise não provocada (ou reflexa) e uma probabilidade de recorrência igual ou superior ao risco de recorrência geral nos próximos 10 anos após a segunda crise não provocada (que seria de pelo menos 60%) 3. Diagnóstico de uma síndrome epiléptica. A epilepsia é considerada resolvida para indivíduos que apresentaram uma síndrome epiléptica idade dependente, e que agora já passaram da idade de susceptibilidade ou aqueles que permaneceram livres de crises nos últimos 10 anos, sem medicação antiepiléptica nos últimos 5 anos	[1]

Lista de abreviaturas

TIPO DE CRISE	ABREVIATURA
Crise focal perceptiva	CPT
Crise focal disperceptiva	CPD
Crise focal motora	CPM
Crise focal não motora	CPNM
Espasmo epilético focal	EEF
Focal evoluindo para tônico-clônica generalizada	FTCG
Focal para bilateral outra	FBO
Crise tônico-clônica generalizada	CTCG
Crise de ausência generalizada	CAG
Crise generalizada motora	CGM
Espasmo epilético generalizado	EEG
Crise tônico-clônica de início desconhecido	TCGD

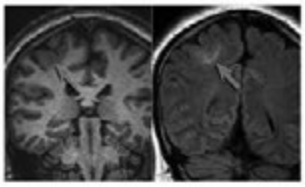
10 exemplos

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.

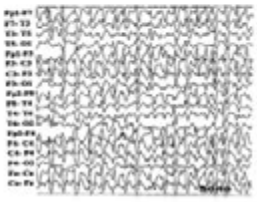
2. Num cenário alternativo do caso #1, o EEG mostra um alentecimento claro parietal esquerdo. A RM mostra uma área displásica parietal direita.



2. Num cenário alternativo do caso #1, o EEG mostra um alentecimento claro parietal esquerdo. 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. Uma criança tem diagnóstico de síndrome de Lennox-Gastaut de etiologia desconhecida. O EEG mostra surtos de ponta-onda lenta. Os tipos de crises incluem ausências e outras. Como classificar estas crises de ausência com este EEG?



3. Uma criança tem diagnóstico de síndrome de Lennox-Gastaut de etiologia desconhecida. O EEG mostra surtos de ponta-onda lenta. Os tipos de crises incluem ausências e outras. Como classificar estas crises de ausência?

3. Neste caso as crises de ausência são classificadas como **ausências atípicas** (a palavra 'generalizada' pode ser presumida pelo padrão EEG e síndrome epiléptica). As crises de ausência teriam tido a mesma classificação no sistema de 1981.

4. A mesma criança do caso #3 tem crises com hipertonia do braço e perna direitos, durante a qual a responsividade e a percepção são mantidas.

4. A mesma criança do caso #3 tem crises com hipertonia do braço e perna direitos, durante a qual a responsividade e a percepção são mantidas.

4. Esta crise é uma **crise focal perceptiva tônica** (a palavra 'motora' pode ser presumida). No sistema antigo, as crises seriam chamadas crises tônicas, talvez com uma suposição incorreta de início generalizado.

5. 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'.

5. 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'.

5. As crises seriam classificadas como **crises focais disperceptivas cognitivas**. 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**.

6. 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.

6. 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.

6. 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.

7. Um menino de 4 anos com epilepsia com crises mioclono-atônicas (síndrome de Doose) tem crises com alguns abalos nos braços seguidos de queda flácida.

crise generalizada mioclono-atônica

7. Um menino de 4 anos com epilepsia com crises mioclono-atônicas (síndrome de Doose) tem crises com alguns abalos nos braços seguidos de queda flácida.

7. Estas crises são agora classificadas como **crises mioclono-atônicas** (a palavra "generalizada" pode ser inferida). A antiga classificação chamaria estas crises não classificadas ou, não oficialmente, crises mioclono-astáticas.

8. Uma adolescente de 16 anos com epilepsia mioclônica juvenil tem crises que se iniciam com alguns abalos nos braços bilaterais, seguidos de enrijecimento dos 4 membros e depois abalos rítmicos dos 4 membros.

crise generalizada mioclono-tônico-clônica

---

8. Uma adolescente de 16 anos com epilepsia mioclônica juvenil tem crises que se iniciam com alguns abalos nos braços bilaterais, seguidos de enrijecimento dos 4 membros e depois abalos rítmicos dos 4 membros.

8. Esta seria classificada como **crise generalizada mioclono-tônico-clônica**. Não há um tipo de crise único na Classificação antiga, mas ela poderia ser considerada como uma crise mioclônica seguida por uma crise tônico-clônica.


The jerks can introduce a generalized tonic-clonic seizure suddenly or, when they repeatedly increase and decrease, at irregular intervals, recur in a crescendo. After a *major discharge*, which is

Juvenile myoclonic epilepsy of Janz

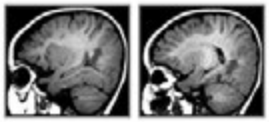

Instruction manual for the ILAE 2017 Operational Classification of Seizure Types

Robert S. Fisher[1], J. Helen Cross[2], Carol D'Souza[3], Jacqueline A. French[4], Sheryl Haut[5], Norimichi Higurashi[6], Edouard Hirsch[7], Floor E. Jansen[8], Lieven Lagae[9], Solomon L. Moshé[10], Jukka Peltola[11], Eliane Roulet Perez[12], Ingrid E. Scheffer[13], Andreas Schulze-Bonhage[14], Ernest Somerville[15], Michael Sperling[16], Elza Márcia Yacubian[17], Sameer M. Zuberi[18].

- Generalized myoclonic-tonic-clonic seizures begin with a few myoclonic jerks followed by tonic-clonic activity. These seizures are commonly seen in patients with juvenile myoclonic epilepsy and occasionally with other generalized epilepsies. It is arguable whether the initial jerks are myoclonic or clonic, but they are rarely sufficiently sustained to be considered clonic.

Fisher et al., em preparação

9. 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, mais proeminentes na região parietal esquerda. A RM mostra uma displasia parietal esquerda.



9. 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, mais proeminentes na região parietal esquerda. A RM mostra uma displasia parietal esquerda.

Classificação dos tipos de crises ILAE 2017

Início focal		Início generalizado	Início desconhecido
Perceptiva	Disperceptiva	Motor	Motor
Início motor automatismos atônicas clônicas espasmos epilépticos hipercinéticas mioclônicas tônicas		clônico-clônicas clônicas tônicas mioclônicas mioclônico-tônico-clônicas mioclônico-atônicas atônicas espasmos epilépticos	clônico-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 classificados**

9. Pela informação auxiliar, o tipo de crise deve ser considerado como **espasmos epilépticos focais** (o termo "motor" pode ser inferido). A Classificação prévia os denominaria espasmos infantis, sem a informação da focalidade.

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

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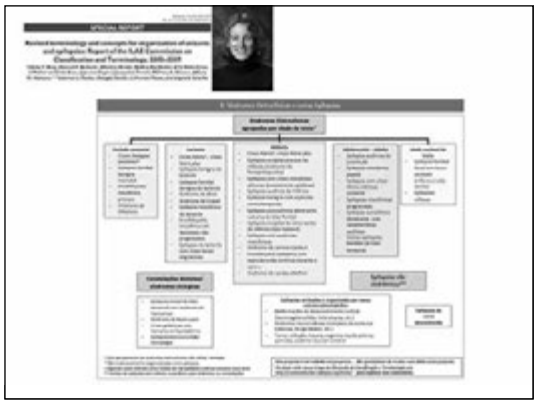
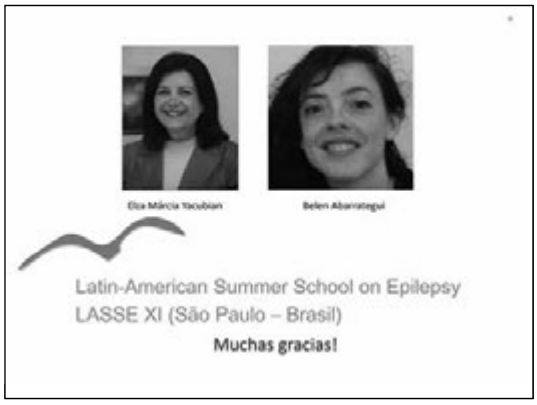
Classificação dos tipos de crises ILAE 2017

Início focal		Início generalizado	Início desconhecido
Perceptiva	Disperceptiva	Motor	Motor
Início motor automatismos atônicas clônicas espasmos epilépticos hipercinéticas mioclônicas tônicas		clônico-clônicas clônicas tônicas mioclônicas mioclônico-tônico-clônicas mioclônico-atônicas atônicas espasmos epilépticos	clônico-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 classificados**

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

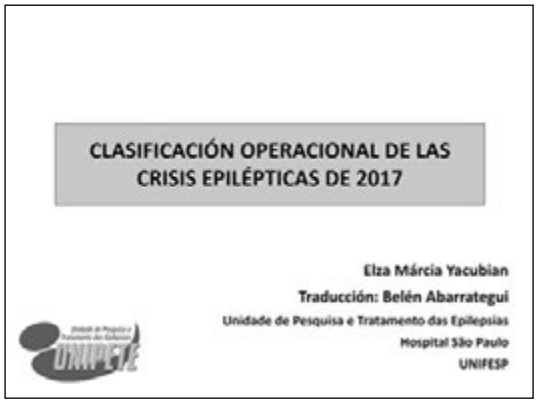


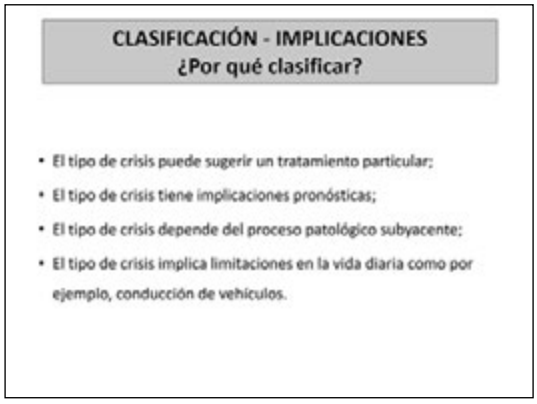

Márcia Morita
Lúcio Figueira
Elza Márcia Yacubian
Mirian Fabíola Mendes
LBE
COMISSÃO DE CONSENSO DA LBE
Muito obrigada!


Elza Márcia Yacubian
Belen Abarrategui
Latin-American Summer School on Epilepsy
LASSE XI (São Paulo – Brasil)
Muchas gracias!

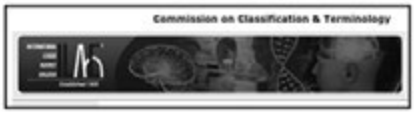
Elza Márcia Yacubian (Brazil)

THE NEW CLASSIFICATION OF EPILEPTIC SEIZURES





CLASIFICACIÓN DE LAS CRISIS EPILÉPTICAS DE 2017



La clasificación de las Crisis Epilépticas y de las Epilepsias es un instrumento fundamental con significativo impacto en nuestra actividad clínica diaria.

Epilepsia, 22:489–501, 1981
Raven Press, New York

Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures

From the Commission on Classification and Terminology of the International League Against Epilepsy*

1981

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], Flora E. Jansen[6], Lieven Lagae[7], Solomon L. Moshé[8], Jukka Peltola[9], Elinor Roulet Perez[10], Ingrid E. Scheffer[11], Samuel M. Zuberi[12]

2017

1981- 2017. Un lapso de 35 años

Epilepsia, 22:489–501, 1981
Raven Press, New York

Parte de la Comisión prefería sustituir 'parcial' por 'focal'

Se propuso cambiar el término 'simple' por 'crisis parcial con conciencia preservada' y 'compleja' por 'crisis parcial con alteración de la conciencia'

The present proposal does not represent a unanimity of views. There are those who would prefer the substitution of "focal" for "partial" in the description of seizures. The compromise to retain "partial" stems from the compromise arrived at on this very point in the formulation of the 1969 classification. A more persuasive argument existed for abolishing the words "simple" and "complex" in favor of "partial seizures with retention of consciousness" and "partial seizures with disturbance of consciousness". Some considered that epileptic

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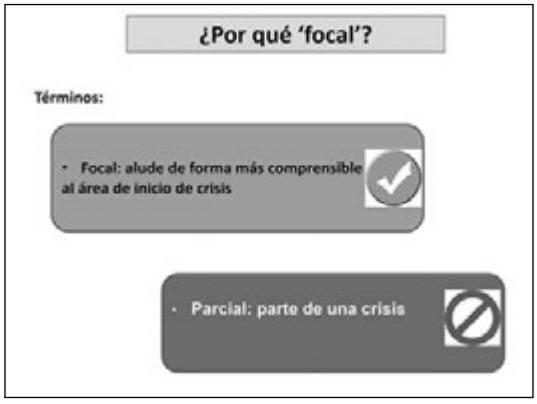
- **Crisis parcial simple** puede banalizar su impacto a un paciente que no cree que las manifestaciones y consecuencias de la crisis son de ninguna manera simple.

- **Crisis parcial compleja** puede implicar que este tipo de crisis es más complicado o difícil de entender que los otros tipos de crisis.

Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501.


Epilepsy classification: a cycle of evolution and revolution
Volume 26 • Number 2 • April 2013


1981- 2017. Un lapso de 35 años
SPECIAL REPORT
Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009


¿Por qué 'focal'?
Términos:
• Focal: alude de forma más comprensible al área de inicio de crisis
• Parcial: parte de una crisis


The 2016 ILAE Seizure Classification

Classificación- Intenciones

Robert Fisher Chair

- Desarrollar una clasificación de las crisis completamente nueva, basada en la anatomia, redes neurales o fisiopatologia;
- El conocimento cientifico actual no es suficiente para permitir esto
- Actualización de los esquemas existentes: una clasificación observacional- **clasificación operacional**.

Clasificación- Dos documentos

Operational Classification of Seizure Types by the International League Against Epilepsy

Robert S. Fisher[1], J. Helen Cross[2], Jacqueline A. French[3], Norimichi Higurashi[4], Edouard Hirsch[5], Floor 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]

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Clasificación
Dificultades: definir consciencia

Robert Fisher Chair

La Consciencia es un fenómeno complejo que engloba componentes subjetivos e objetivos

Los cinco tipos de afectación de la consciencia

CONTROVERSY IN EPILEPSY

CINCO TIPOS DE ALTERACIONES DE CONSCIENCIA

1. Auras: ilusiones e alucinaciones;
2. Crisis discognitivas: alteraciones de funciones cognitivas superiores con consciencia intacta. Ejemplo: crisis afásica;
3. Delirium ictal epiléptico (status no convulsivo)- amnesia completa del evento;
4. Crisis dialépticas (verbo gr. *dialepein* « *epilepein*» parar, interrumpir)- interrupción de la respuesta a estímulos externos, amnesia completa del evento;
5. Coma o estupor epiléptico.

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

Crisis focal con evolución a tónico-clónica bilateral

Crisis focal disperceptiva

FICS e FACS

CONTROVERSY IN EPILEPSY

1. FACS: Focal Aware Conscious Seizures
   - FACS sin disfunción perceptiva
   - FACS con disfunción perceptiva selectiva
2. FICS: Focal Impaired Consciousness Seizures (proponen evitar los términos *discognitiva* y *dialéptica*, que consideran confusos)
3. Crisis de ausencias
4. Crisis tónico-clónicas generalizadas

Epilepsia 2014;55(8):1145-50.

Determinación retrospectiva de la consciencia

Un clasificador no entrenado podría considerar que, para mostrar **alteración de la consciencia,** una persona precisaría estar en el suelo, inmóvil y arreactiva ('desmayada').

Consciousness
Consciencia

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

Consciencia: estado mental con aspectos objetivos y subjetivos, que comprende la percepción de uno mismo como ser independiente, percepción del entorno, reactividad y memoria.

Awareness
Percepción

Awareness: knowledge of self and environment.
Percepción: reconocimiento de uno mismo y del entorno.

Crisis sin alteración de consciencia= término substitutivo percepción

Como en varias lenguas aware=consciencia **e** unaware=inconsciencia, **también se puede utilizar *con* o *sin alteración de consciencia***

Focal aware seizure
Crisis focal perceptiva

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

Percepción: aspecto de la conciencia que permite el conocimiento de uno mismo y del entorno

Focal Seizure with Impaired Awareness
Crisis 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: la alteración de la percepción es una característica de las crisis focales disperceptivas, previamente denominadas crises parciales complejas. La alteración de la percepción aparece también en otros tipos de crisis.

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: perteneciente al pensamiento y funciones corticales superiores, como lenguaje, percepción espacial, memoria, praxia. El término previamente indicado para uso similar era psíquica.

Robert Fisher
Chair

Clasificación de los Tipos de Crisis ILAE 2017 [1]

[1] Definiciones, otros tipos de crisis y descriptores están listados en el artículo y en el glosario de términos
[2] Por información inadecuada o imposibilidad de clasificar en otras categorías

Clasificación de los Tipos de Crisis ILAE 2017 [1]

Robert Fisher
Chair

[1] Definiciones, otros tipos de crisis y descriptores están en el artículo y en el glosario de términos
[2] Estas pueden ser focales o generalizadas, con o sin alteración de la percepción
[3] Por información inadecuada o imposibilidad de clasificar en otras categorías

Clasificación de los tipos de crisis ILAE 2017

Inicio focal		Inicio generalizado	Inicio desconocido
Perceptiva	Disperceptiva	Motor	Motor
Inicio motor automatismos atónicas clónicas espasmos epilépticos hipercinéticas mioclónicas tónicas **Inicio no motor** autonómicas parada comportamental cognitivas emocionales sensoriales		tónico-clónica clónica tónica mioclónica mioclono-tónico-clónica mioclono-atónicas atónica espasmos epilépticos **No motor (ausencias)** típicas atípicas mioclónicas mioclonías palpebrales	tónico-clónica espasmos epilépticos **No motor** parada comportamental
Focal con evolución a tónico-clónica bilateral			**No clasificables**

Reglas para clasificar

- Al clasificar las crisis, al decidir si las crisis tienen inicio focal o generalizado, el médico debe usar el **intervalo de confianza de 80%**;
- Si la percepción está comprometida en qualquier momento durante una crisis focal, será clasificada como **crisis focal disperceptiva**;
- El **primer signo o síntoma prominente** de una crisis focal debe ser usado para la clasificación, con excepción de la parada comportamental transitoria. Una crisis focal sólo será considerada **crisis de parada comportamental** si éste signo fuera la característica más prominente de toda la crisis;
- Se anima a los clínicos a ampliar la descripción de otros signos y síntomas;
- Es posible usar **pruebas complementarias** para la clasificación;
- Las crisis pueden ser **no clasificables** por información inadecuada o incapacidad de clasificación en otras categorías.

Actualización del Glosario de 2001

ausencia típica	evento de inicio súbito, con interrupción de la actividad, mirada perdida y en ocasiones desviada en supraversión. La respuesta está disminuida y dura en general menos de 30 segundos, con recuperación rápida y completa. Si se dispone de EEG, registrará descargas epileptiformes generalizadas durante el evento. Una crisis de ausencia es por definición de inicio generalizado: el término "ausencia" no es sinónimo de mirada perdida, que también puede darse en crisis de inicio focal	Adaptado de [1]
ausencia atípica	crisis de ausencia con cambios de tono más pronunciados que en una ausencia típica o crisis con inicio y/o final no abruptos. EEG: registra descargas de tipo espiga-onda lenta, generalizadas e irregulares	Adaptado de Dravet [2]
parada	Ver parada comportamental	nuevo
atónica	reducción o pérdida súbita del tono muscular no precedida por crisis mioclónica o tónica. Duración de aproximadamente 1-2 segundos, afectando a musculatura de la cabeza, troncos, miembros superiores o miembros inferiores	[1]
automatismos	actividad motora más o menos coordinada que ocurre usualmente cuando la conciencia está alterada. En general, pero no siempre, sin recuerdo posterior (amnesia). Los automatismos siempre imitan un movimiento voluntario, pudiendo consistir en una continuación inapropiada de la actividad motora pre-ictal	[1]
crisis autonómicas	crisis con predominio de la alteración de la función del sistema nervioso autonómico afectando a las funciones cardiovasculares, pupilares, gastrointestinales, sudomotoras, vasomotoras y/o termorreguladoras	Adaptado de [1]
aura	fenómeno ictal subjetivo, o crisis precediendo manifestaciones clínicas objetivables por los testigos (aura es un término de uso popular)	[1]
percepción	percepción de uno mismo y del entorno	nuevo
bilateral	afectando ambos lados, derecho e izquierdo. Las manifestaciones de crisis bilaterales podrían ser además síncrónicas ou asincrónicas	nuevo
clónicas	sacudidas, síncrónicas o asincrónicas, que se repiten de forma regular, afectando a los mismos grupos musculares	Adaptado de [1]

Actualización del Glosario de 2001

cognitivo	relativo al pensamiento y las funciones cognitivas superiores como lenguaje, percepción espacial, memoria y praxias. El término equivalente previo era "psíquico"	nuevo
conciencia	estado de la mente que incluye ambos aspectos subjetivos y objetivos, englobando la percepción de uno mismo como entidad única, la percepción del entorno, la capacidad de respuesta y la memoria	nuevo
disrítmica	episodios de llanto, que pueden estar o no asociados a sentimiento de tristeza	[1]
distónica	contracción sostenida de los músculos agonistas e antagonistas produciendo movimientos alternativos y de torsión, que pueden producir posturas anormales	Adaptado de [1]
crisis emocionales	crisis que se presentan como una emoción o que aparentan tener componente emotivo como característica precoz prominente, tales como miedo, alegría espontánea o euforia, carcajadas (gelásticas) o llanto (dacrísticas)	nuevo
espasmos epilépticos	súbita flexión, extensión, o combinación de flexo-extensión de los músculos predominantemente proximales y del tronco, frecuentemente más sostenida que los movimientos mioclónicos pero no tan mantenida como en las crisis tónicas. Puede tener formas limitadas: muecas, caída de cabeza o movimientos oculares cutáneos. Los espasmos epilépticos frecuentemente ocurren en salvas. Los espasmos infantiles son la forma más conocida, pero pueden aparecer a cualquier edad	Adaptado de [1]
epilepsia	dolencia cerebral definida por cualquiera de las siguientes condiciones: 1. Al menos 2 crisis no provocadas (no reflejas) separadas por un intervalo superior a 24 horas 2. Una crisis no provocada (o no refleja) y una probabilidad de recurrencia igual o superior al riesgo de recurrencia en los 10 años posteriores a una segunda crisis no provocada (que sería de al menos 60%) 3. Diagnostico de un síndrome epiléptico La epilepsia se considera resuelta en individuos que presentaron un síndrome epiléptico edad dependiente y que ya superaron la edad de susceptibilidad, o aquellos que permanecieron libres de crisis en los últimos 10 años, sin medicación antiepiléptica en los últimos 5 años	[1]

Lista de abreviaturas

TIPO DE CRISIS	ABREVIATURA
Crisis focal perceptiva	CPT
Crisis focal disperceptiva	CPD
Crisis focal motora	CFM
Crisis focal no motora	CFNM
Espasmo epiléptico focal	EEF
Focal con evolución a tónico-clónica generalizada	FTCG
Focal con evolución a otro tipo de crisis bilateral	FBO
Crisis tónico-clónica generalizada	CTCG
Crisis de ausencia generalizada	CAG
Crisis generalizada motora	CGM
Espasmo epiléptico generalizado	EEG
Crisis tónico-clónica de inicio desconocido	TCGD

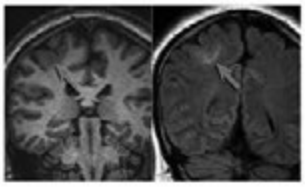
Ejemplos

1. Una mujer se despierta y encuentra a su marido teniendo una crisis en la cama. No pudo observar el inicio, pero es capaz de describir rigidez global seguida de sacudidas bilaterales. Su EEG y RM son normales.

1. Una mujer se despierta y encuentra a su marido teniendo una crisis en la cama. No pudo observar el inicio, pero es capaz de describir rigidez global seguida de sacudidas bilaterales. Su EEG y RM son normales.

1. Esta crisis se clasifica como de **inicio desconocido tónico-clónica**. No hay información suficiente para determinar si el inicio fue focal o generalizado. En la Classificación de 1981, esta crisis sería inclasificable.

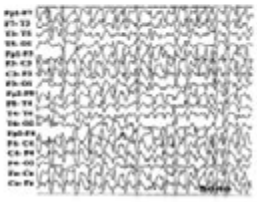
2. En un escenario alternativo al del caso #1, el EEG muestra un enlentecimento claro parietal derecho. La RM mostra un área displásica parietal derecha.



2. En un escenario alternativo al del caso #1, el EEG muestra un enlentecimento claro parietal derecho. La RM mostra un área displásica parietal derecha.

2. En esta circunstancia, la crisis puede clasificarse **como focal con evolución a tónico-clónica bilateral** a pesar de que su inicio no fue presenciado, porque se identificó una etiología focal. En la Clasificación de 1981, esta crisis sería clasificada como de inicio parcial, secundariamente generalizada.

3. Un niño tiene diagnóstico de síndrome de Lennox-Gastaut de etiología desconocida. El EEG muestra descargas de punta-onda lenta. Los tipos de crisis incluyen ausencias y otras. ¿Cómo clasificar estas crisis de ausencia?



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3. En este caso las crisis de ausencia se clasifican como **ausencias atípicas** (la palabra 'generalizada' puede asumirse por el patrón EEG y el síndrome epiléptico). Las crisis de ausencia se habrían clasificado igual por el sistema de 1981.

4. El mismo niño del caso #3 tiene crisis con hipertonía de brazo y pierna derechos, durante las cuales la capacidad de respuesta y la percepción están conservadas.

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4. Esta crisis es una **crisis focal perceptiva tónica** (la palabra 'motora' puede sobreentenderse). En el sistema antiguo, las crisis se llamarían crisis tónicas, quizás asumiendo incorrectamente un inicio generalizado.

5. Una mujer de 25 años describe crisis que se inician con 30 segundos de una sensación intensa de que 'están tocando una música familiar'. Ella puede oír a las personas hablar, pero después no puede determinar lo que están diciendo. Después de los episodios, está discretamente confusa, y necesita ' reorientarse'.

5. Una mujer de 25 años describe crisis que se inician con 30 segundos de una sensación intensa de que 'están tocando una música familiar'. Puede oír a las personas hablar, pero después no puede determinar lo que están diciendo. Después de los episodios, está discretamente confusa, y necesita ' reorientarse'.

5. Las crisis serían clasificadas como **focales disperceptivas cognitivas**. Aunque la paciente fuese capaz de interactuar con el medio, no puede interpretarlo, y queda después discretamente confusa.

6. Un hombre de 22 años tiene crisis durante las cuales permanece completamente perceptivo, con 'los pelos de punta en los brazos' y se siente ruborizado.

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6. Se clasificarían como **crisis focales perceptivas no motoras autonómicas**, o, más sencillamente, crisis focales perceptivas autonómicas. La clasificación de 1981 las llamaría crisis parciales simples autonómicas.

7. Un niño de 4 años con epilepsia con crisis mioclono-atónicas (síndrome de Doose) tiene crisis en las que presenta sacudidas en los brazos y cae flácido al suelo.

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7. Estas crisis se clasifican ahora como **mioclono-atónicas** (la palabra "generalizada" se sobreentiende). La antigua clasificación llamaría a estas crisis no clasificadas o, no oficialmente, crisis mioclono-astáticas.

8. Una adolescente de 16 años con epilepsia mioclónica juvenil tiene crisis que se inician com sacudidas bilaterales en brazos, seguidas de rigidez de las 4 extremidades y posteriormente sacudidas de las mismas.

8. Una adolescente de 16 años con epilepsia mioclónica juvenil tiene crisis que se inician com sacudidas bilaterales en brazos, seguidas de rigidez de las 4 extremidades y posteriormente sacudidas de las mismas.

8. Esta sería clasificada como **crisis generalizada mioclono-tónico-clónica.** En la Clasificación antigua no aparece como un tipo específico, pero podría considerarse una crisis mioclónica seguida por una crisis tónico-clónica.

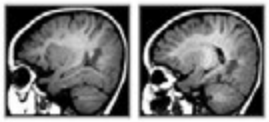
Instruction manual for the ILAE 2017 Operational Classification of Seizure Types

Robert S. Fisher[1], J. Helen Cross[2], Carol D'Souza[3], Jacqueline A. French[4], Sheryl Haut[5], Norimichi Higurashi[6], Edouard Hirsch[7], Floor E. Jansen[8], Lieven Lagae[9], Solomon L. Moshé[10], Jukka Peltola[11], Eliane Roulet Perez[12], Ingrid E. Scheffer[13], Andreas Schulze-Bonhage[14], Ernest Somerville[15], Michael Sperling[16], Elza Márcia Yacubian[17], Sameer M. Zuberi[18].

- Generalized myoclonic-tonic-clonic seizures begin with a few myoclonic jerks followed by tonic-clonic activity. These seizures are commonly seen in patients with juvenile myoclonic epilepsy and occasionally with other generalized epilepsies. It is arguable whether the initial jerks are myoclonic or clonic, but they are rarely sufficiently sustained to be considered clonic.

Fisher et al., em preparação

9. Una niña de 14 meses tiene crisis con flexión de ambos brazos y flexión de la cabeza durante 2 segundos. Estas crisis ocurren en salvas. El EEG muestra hipsarritmia con descargas bilaterales, más prominentes en la región parietal izquierda. La RM muestra una displasia parietal izquierda.



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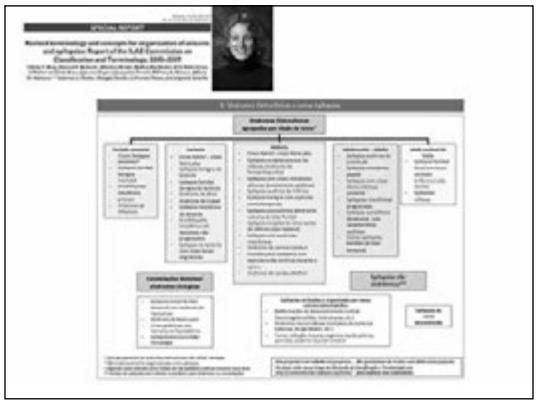
9. Por la información complementaria, el tipo de crisis debe ser considerado como **espasmos epilépticos focales** (el término "motor" se sobreentiende). La Clasificación previa los denominaría espasmos infantiles, sin la información de los datos focales.

10. Un hombre de 75 años refiere una sensación interna de temblor en el cuerpo. No se dispone de más información.

10. Un hombre de 75 años refiere una sensación interna de temblor en el cuerpo. No se dispone de más información.

10. Este es un evento no clasificable que puede no ser una crisis epiléptica.




Márcia Morita
Lúcio Figueira
Elza Márcia Yacubian
Mirian Fabíola Mendes
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COMISSÃO DE CONSENSO DA LBE
Muito obrigada!


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Latin-American Summer School on Epilepsy
LASSE XI (São Paulo – Brasil)
Muchas gracias!

Finbar O'Callaghan (UK)

SEMIOLOGY OF INFANTILE SEIZURES

KETTE VALENTE (BRAZIL)

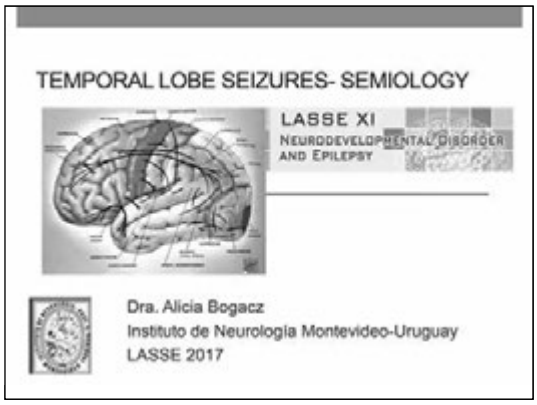
SEMIOLOGY OF DROP ATTACKS

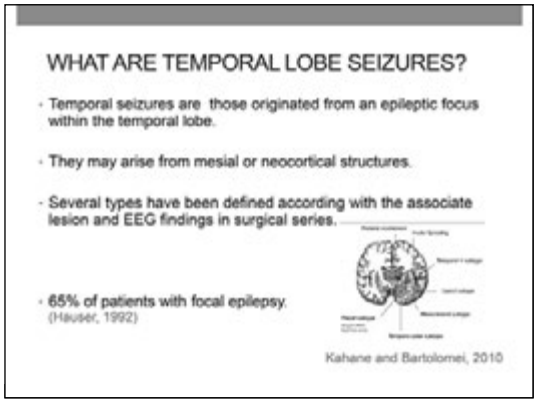
Peter Wolf (Denmark)

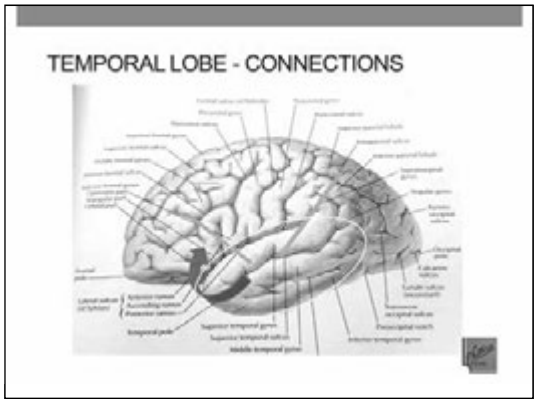
SEMIOLOGY OF ROLANDIC SEIZURES

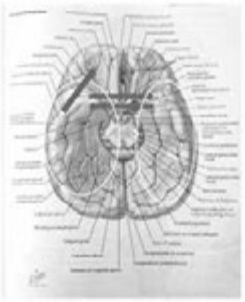
Alicia Bogacz (Uruguay), Ana Carolina Coan (Brazil), Guilca Contreras (Venezuela), Patricia Braga (Uruguay), Peter Wolf (Denmark)

SEMIOLOGY OF FRONTAL, TEMPORAL, PARIETAL AND OCCIPITAL SEIZURES









WHERE DOES IT COME INFORMATION ABOUT SEIZURES?

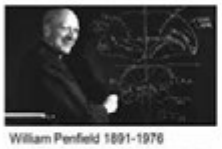
- ANATONOMICAL-CLINICAL CORRELATIONS
- CORTICAL STIMULATIONS
- VIDEO-EEG CORRELATIONS

ANATONOMICAL-CLINICAL CORRELATIONS

John Hughlings Jackson
1835-1911

- Proposed an association of ictal behaviour with pathological lesions involving temporal lobe structures.
- Introduced the term "dreamy state" to describe the alteration of patient's consciousness during the seizure.
- Correlate the olfactory auras with mesial temporal lobe structures.
  (Jackson and Colman, 1898)

CORTICAL STIMULATIONS

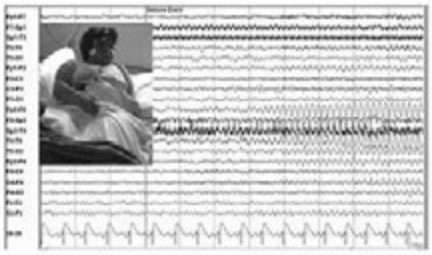


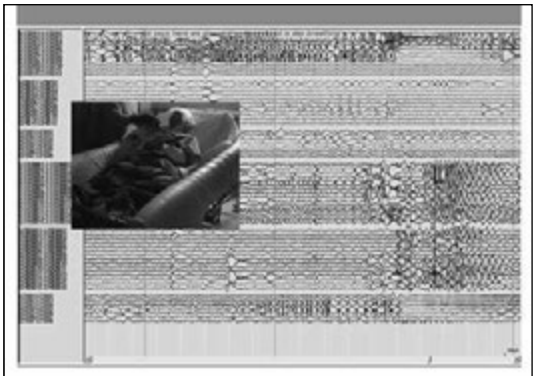
William Penfield 1891-1976

(Penfield and Rassussen,1950)

(Penfield and Jasper,1954)

VIDEO-EEG CORRELATIONS





Temporal lobe manifestations

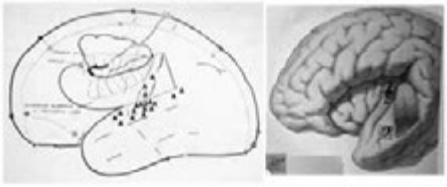
- AURAS or focal seizures without awareness impairment.
- MOTIONLESS STARE .
- AUTOMATISMS.
- DYSTONIC POSTURING

AURAS:
- **Auditory**
- **Olfactory**
- **Gustatory**
- **Autonomic**
- **Abdominal or epigastric**
- **Psychic or experiential**

They are frequent in temporal lobe epilepsy patients, but most of them are not specific.

Auditory auras

- These are simple auditory hallucinations, like hearing a "buzz" or a "noise".
- The symptomatogenic zone is Heschell's gyrus in the superior temporal gyrus.



(Penfield and Jasper,1954)

Olfactory and Gustatory auras

- Most of the time, these are hallucinations of unpleasant smells or taste.
- They are frequently seen in patients with mesial temporal lobe or basal frontal epilepsy.
- Olfactory sensation could only be induced by olfactory bulb or mesial temporal lobe electrical stimulation.
- Cortical stimulation studies have found the insula to be a symptomatogenic zone for gustatory aura.
- They are rare, associated with other types of aura and a relatively high percentage of these patients have neoplasms that involve the amygdala.

Autonomic auras

- These are subjective sensations suggesting possible autonomic alterations such as palpitations, sweating, "goose bumps".
- The symptomatogenic zone of most autonomic auras is most likely the insular cortex.
- Other autonomic signs like ictal vomiting, retching, hypersalivation are a rare signs that also occurs in temporal lobe .

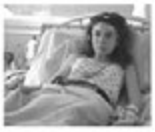
Abdominal or epigastric auras

- They are frequent in temporal lobe epilepsies.
- They may also be triggered by extra-temporal epilepsies (mainly mesial frontal lobe and insula).
- These auras are the result of either a sensation produced by increased peristalsis or as a sensory phenomena resulting from direct activation of the sensory cortical areas of the abdominal viscera.
- The sensation begins usually in the epigastrium or stomach in the midline and can remain localized there but not infrequently rises to the chest, throat.
- Epigastric sensations closely resembling epigastric auras can be elicited by electrical stimulation of the insula.
- There are also reports of abdominal auras elicited by electrical stimulation of other structures such as the mesial temporal structures.

Psychic auras

- These are complex hallucinations and/or illusions that usually affect different senses.
- They could be: -affective phenomena like fear, depression, happiness and exhilaration.
  - Mental phenomena like déjà vu/jamais vu, déjà vecu/jamais vecu, déjà entendu/jamais entendu.
- The temporal lobe is usually involved with these phenomena but they have no lateralizing value.
- Some of these sensations can be elicited by electrical stimulation of the temporal lobe convexity or the junction of the posterior temporal lobe with the occipital or parietal lobe.
- Mesial temporal structures were involved in most cases.

Motionless stare



- Arrest of activity, "blank expression", staring (widening of the palpebral fissures and pupillary dilatation) with awareness impairment.
- The alteration of awareness consisting of unresponsiveness during the seizure and amnesia of the episode post-ictally.
- The duration this alteration has a localizing value with seizures originating from the mesial temporal structures being of longer duration than the ones arising from the frontal lobe.

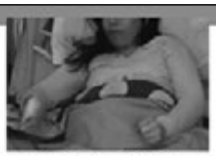
Motor manifestations

- AUTOMATISMS
- DISTONIC POSTURING
- HEAD TURNING

AUTOMATISMS

- They represent the main motor manifestation in temporal lobe seizures.
- Characterized by semi-purposeful motor activity, involving the distal segments of the hands, feet, mouth and tongue.
- These are typical of temporal lobe seizures but can also be seen with frontal lobe seizures.
- Frontal lobe automatisms tend to be of shorter duration than temporal lobe automatisms.
- They could be unilateral or bilateral; unilateral automatisms are more frequently an expression of an ipsilateral epileptogenic zone.
- 95% of the seizures with automatisms are associated with altered consciousness.
- Preservation of consciousness during seizures with automatisms has been observed almost exclusively in patients with non-dominant temporal epilepsy.

Dystonic posturing



- This is a sustained, forced, unnatural positioning of an upper extremity on one side of the body with a clear rotational component.
- In patients with temporal lobe epilepsy this is a reliable lateralizing sign to the contralateral hemisphere.
- Although more common in temporal lobe epilepsy this sign can occur in extra temporal lobe epilepsy as well.
- It is thought to be related to activation of the basal ganglia through spread of the epileptiform discharges.

HEAD TURNING

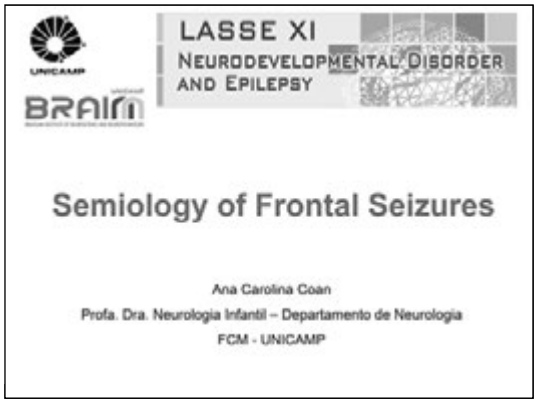
- It is important to differentiated between non-versive head turning and versive seizure.
- Versive seizures are defined as a forced and involuntary turning of the head and eyes in one direction with an associated neck extension resulting in a sustained unnatural position of both.
- Non-versive head turnings resemble natural movements, they are common in temporal lobe seizures.
- Versive seizures appear earlier in seizures of frontal lobe origin as opposed to temporal lobe origin.
- Versive seizures have a lateralizing value to the contralateral hemisphere, especially when they occur before secondary generalization.

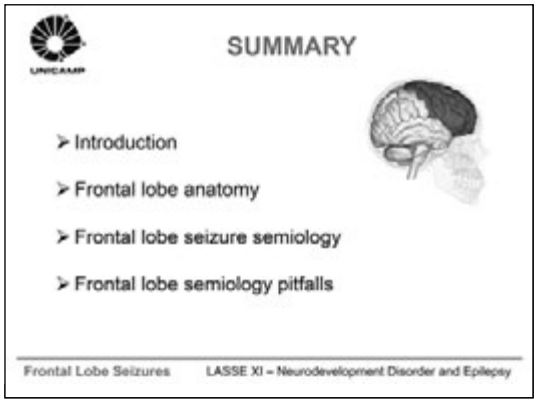
Post-ictal aphasia

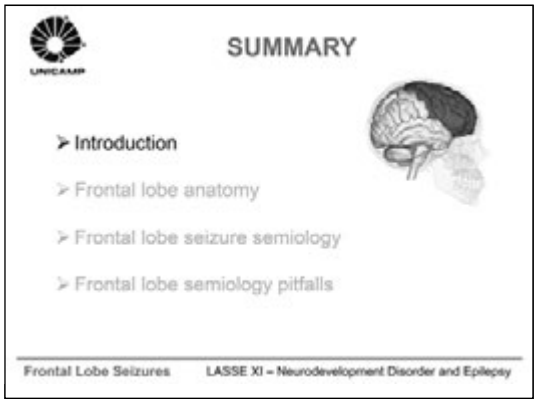
- Postictal aphasia lateralizes the epilepsy to the language dominant hemisphere in patients with temporal lobe epilepsy.
- Recovery of language function after the ictal EEG pattern has stopped was found to be significantly more delayed in patients with left temporal lobe epilepsy.
- To diagnose post-ictal aphasia it is essential to have a patient who is cooperative post-ictally (clearly tries to understand language and tries to talk) however, is aphasic.

Alicia Bogacz (Uruguay), Ana Carolina Coan (Brazil), Guilca Contreras (Venezuela), Patricia Braga (Uruguay), Peter Wolf (Denmark)

SEMIOLOGY OF FRONTAL, TEMPORAL, PARIETAL AND OCCIPITAL SEIZURES







FRONTAL LOBE EPILEPSY

- Frontal lobe: The largest lobe
- FLE:
  - 10-20% of patients in surgical series
  - Prevalence in non-surgical cohorts unknown (probably higher)

Kellinghaus & Lüders, Epil Disord 2004; Diehl, Sisodiya & Manford, 2015

FRONTAL LOBE SEIZURES

- Frontal lobe seizures:
  - Prominent motor features
  (hypermotor > asymmetric tonic posturing > clonic)
  - No aura or brief aura
  - Typically brief
  - May be exclusively nocturnal
  - Often cluster
  - Ictal EEG may be normal or obscured by artifacts

FRONTAL LOBE SEIZURES

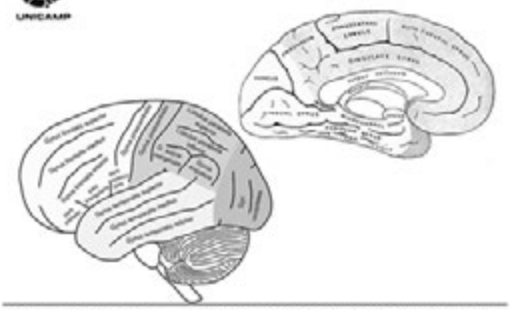
- "Typical" seizure semiology:
  - unilateral clonic
  - tonic asymmetric
  - hypermotor seizures

Whenever possible, subclassification of FLS to a specific frontal lobe region

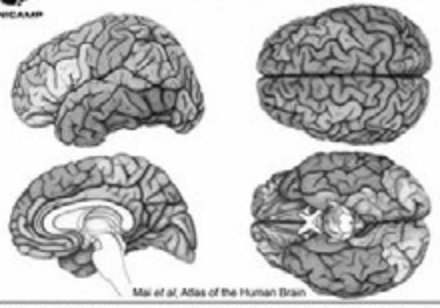
SUMMARY

- Introduction
- Frontal lobe anatomy
- Frontal lobe seizure semiology
- Frontal lobe semiology pitfalls

FRONTAL LOBE ANATOMY

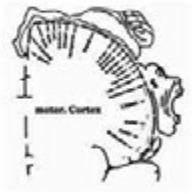


FRONTAL LOBE ANATOMY

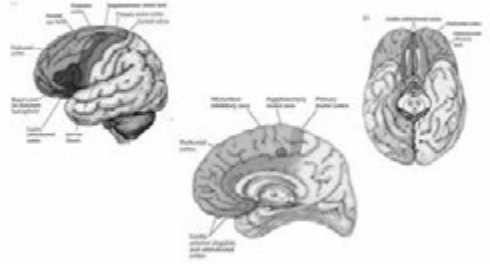


Mai *et al*, Atlas of the Human Brain

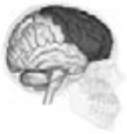
FRONTAL LOBE ANATOMY



FRONTAL LOBE ANATOMY

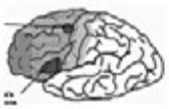


SUMMARY



- Introduction
- Frontal lobe anatomy
- **Frontal lobe seizure semiology**
- Frontal lobe semiology pitfalls

SUBCLASSIFICATION

Dorsolateral	*Mesial*	Basal (orbitofrontal)
		
Primary sensorimotor *Premotor (dorsolateral)* *Frontopolar* *Fronto-parietal operculum*	*Supplementary sensorimotor* *Cingulate*	

Beleza & Pinho, *J Clin Neurosc* 2011

SUBCLASSIFICATION

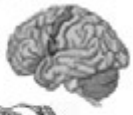
Dorsolateral

Primary sensorimotor (central)
Premotor (dorsolateral)
Frontopolar / Prefrontal

Beleza & Pinho, *J Clin Neurosc* 2011

Dorsolateral Frontal Lobe Seizures

Primary sensorimotor (central)



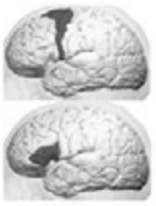
- "Central lobe": primary motor cortex
- Unilateral clonic or myoclonic seizures, more frequently affecting face and distal segments of the limbs

- Typical seizure evolution:
  - Jacksonian march, usually accompanied by ipsilateral head version and followed by postictal paresis (Todd)

Dorsolateral Frontal Lobe Seizures

Premotor

- Includes the secondary motor area, the frontal eye field and Broca's language area
- The premotor cortex projects to the primary motor cortex
  - role in motor preparation and motor learning



Rheims *et al.*, Epilepsia 2005; Goldberg-Stern *et al.*, Neurology 2004

Dorsolateral Frontal Lobe Seizures

Premotor

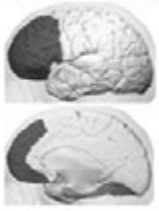
- Typical seizure evolution:
  - Early versive seizure, frequently followed by motor manifestation (automatisms or bilateral TCS)
  - Versive seizures: lateral deviation of the eyes, version of the head and, frequently, also of the trunk, especially when followed by a secondary bilateral TCS
- Aphasic seizures may occur if Broca's language area is involved

Rheims *et al.*, Epilepsia 2005; Goldberg-Stern *et al.*, Neurology 2004

Dorsolateral Frontal Lobe Seizures

Frontopolar / Prefrontal

- Emotion processing, moral behaviour, executive control, working memory, learning
- Responsible for the coordination of information processing and transfer / high-level cognitive operations

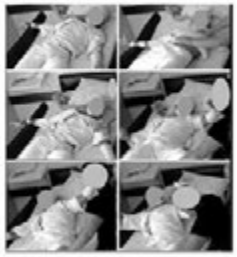


Luders et al, Acta Neurol Scand 1999; Bartolomei et al. Clin Neurophysiol 2005

Dorsolateral Frontal Lobe Seizures

Frontopolar / Prefrontal

- Hypermotor seizures: complex movements involving trunk and proximal limb segments, usually with preservation of consciousness



Coan & Cendes, Medlink

Dorsolateral Frontal Lobe Seizures

Frontopolar / Prefrontal

- Hypermotor seizures:
  - Eventual aura (fear, ill-defined feelings, and somatosensory)
  - Bizarre gestures, repetitive movements, bicycle peddling, pelvic thrusting and shouting
  - Often charged with emotional and aggressive features
  - Seizures are short and tend to occur during sleep

Luders et al, Acta Neurol Scand 1999; Bartolomei et al. Clin Neurophysiol 2005

Frontal Lobe Seizures

- Hypermotor seizures do not have a highly localizing value in the frontal lobe
  - orbitofrontal
  - dorsolateral
  - frontopolar
  - opercular–insular

Bancaud & Talairach, 1992; Harvey et al., Neurology 1993; Laskowitz et al., Neurology 1995

SUBCLASSIFICATION

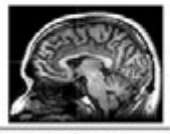
Mesial

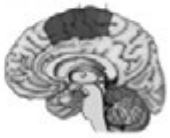
Supplementary sensorimotor
Cingulate

Beleza & Pinho, J Clin Neurosc 2011

Mesial Frontal Lobe Seizures

- Mesial surface of FL includes:
  - primary motor cortex for the lower limb
  - supplementary sensorimotor area (SSMA)
  - anterior cingulate cortex
  - prefrontal cortex

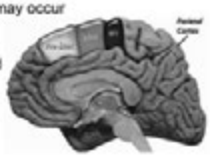




Mesial Frontal Lobe Seizures

Supplementary sensorimotor

- SSMA stimulation: bilateral and proximal tonic posturing predominanting on the contralateral side
  - contralateral sensory phenomena may occur
- Somatotopic distribution: the head and upper limbs are represented anteriorly and the lower limbs posteriorly



Donoghue & Sanes. J Clin Neurophysiol 1994; Unnwongse et al., Epilepsia 2009

Mesial Frontal Lobe Seizures

Supplementary sensorimotor

- Bilateral asymmetric tonic seizures: abrupt tonic posturing maintained for 10-40s and absence or minimal postictal confusion
  - Somatosensory aura may precede
  - Unilateral: highly lateralizing significance (contralateral)
  - Penfield & Jasper: "fencing posture"

- "M2e": tonic abduction and external rotation of the shoulder with flexion of the elbow

Penfield & Jasper, 1954; Ajmone-Marsan & Ralston, 1957; Werhahn et al., Epilepsia 2000

Mesial Frontal Lobe Seizures

Anterior Cingulate

- Hypermotor seizures: anterior cingulate region frequently proposed as responsible
- Affective aura and autonomic features
- "Frontal absences":
  - Repetitive vocalizations, rocking movements, subtle head and eye turning, brief postictal confusion
  - Staring may evolve to bilateral TCS
  - Bilateral cingulate involvement via callosal route?

Bancaud & Talairach, 1992; Huck et al., Acta Neurochir Suppl 1980

Mesial Frontal Lobe Seizures

- Negative myoclonic seizures:
  - short periods of muscle atonia (30–400 ms)
  - preceded by epileptiform discharges in the central region
  - sudden inhibition of tonic inervation of motor neurons
  - SSMA stimulation: silent periods, regardless stimulus intensity
  - premotor cortex or primary motor cortex: silent periods depended on the intensity of stimulation

Werhahn, et al., 2000

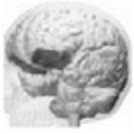
SUBCLASSIFICATION

Basal
(orbitofrontal)

Beleza & Pinho, J Clin Neurosc 2011

Basal Frontal Lobe Seizures

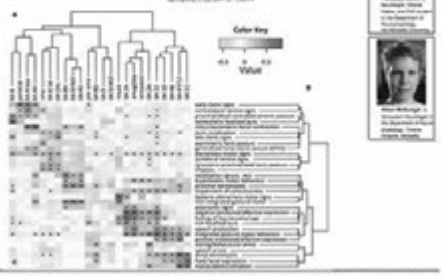
Orbitofrontal



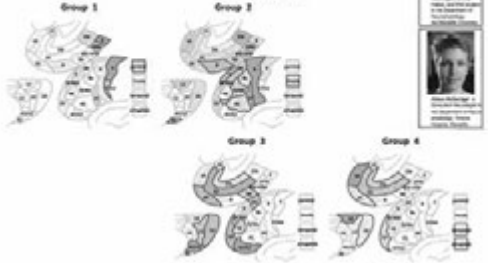
- 5 gyri:
  - Posterior part: continuous with insula ("limbic")
  - Rostral part: continuous with prefrontal cortex
- Olfactory auras (unpleasant)
- Dyscognitive features, initial repetitive gestural automatisms
- Autonomic seizures (tachycardia, bradycardia, hyperventilation, epigastric aura, vomiting, defecation, piloerection, pallor, flushing, mydriasis, miosis, urinary urge, sexual/orgasmic aura)
- Hypermotor seizures may also occur

Bancaud & Talairach, 1992; Cavada et al., Cereb Cortex 2000

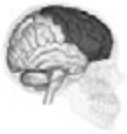
Frontal lobe seizures: From clinical semiology to localization



Frontal lobe seizures: From clinical semiology to localization



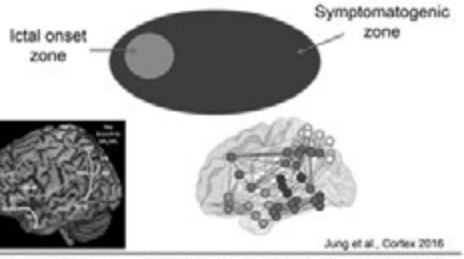
SUMMARY



- Introduction
- Frontal lobe anatomy
- Frontal lobe seizure semiology
- **Frontal lobe semiology pitfalls**

Frontal lobe semiology pitfalls

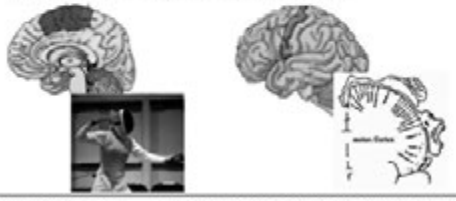
Seizure Semiology



Jung et al., Cortex 2016

Frontal lobe semiology pitfalls

- Seizure types considered as "typical" for frontal lobe origin may actually arise from different brain regions



Frontal lobe semiology pitfalls

- Frontal dyscognitive seizures *versus* absence seizures
- Nocturnal frontal lobe seizures *versus* parasomnias
  - Seizures: brief, stereotyped, preserved awareness, throughout the night
  - Parasomnias: longer, variable features, confusional state, 1-2 hours after falling asleep
- Frontal lobe seizures versus non-epileptic seizures
  - bilateral motor phenomena with preserved awareness
  - normal ictal EEG


Obrigada!
BRAIN
UNICAMP
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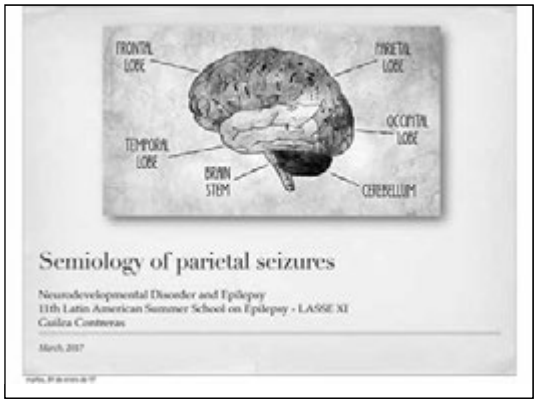
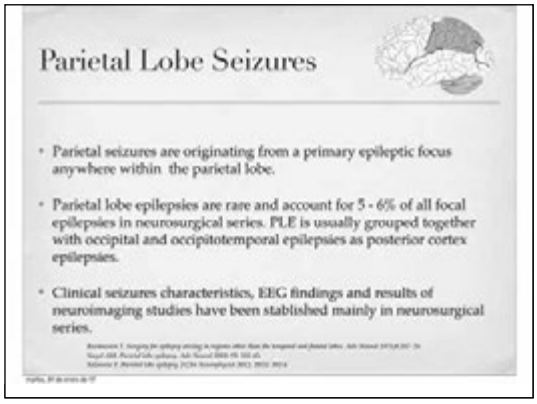
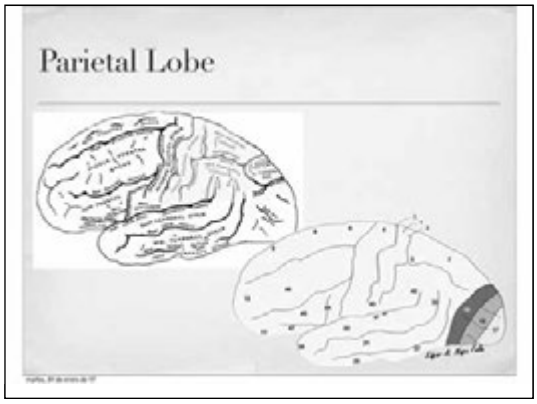
Frontal Lobe Seizures
LASSE XI – Neurodevelopment Disorder and Epilepsy

Alicia Bogacz (Uruguay), Ana Carolina Coan (Brazil), Guilca Contreras (Venezuela), Patricia Braga (Uruguay), Peter Wolf (Denmark)

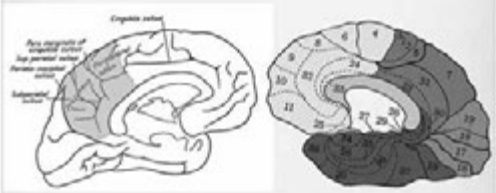
SEMIOLOGY OF FRONTAL, TEMPORAL, PARIETAL AND OCCIPITAL SEIZURES







Parietal Lobe



Parietal Lobe Seizures

- Clinical manifestations
- Somatosensory
  - Paresthesias
  - Pain
  - Thermal perception
  - Sexual manifestations
  - Ictal paralysis
  - Body image disturbances
- Visual symptomatology
  - Visual hallucinations
  - Visual illusions

Parietal Lobe Seizures

- Clinical manifestations
- Other seizure phenomenas
  - Vertiginous sensation
  - Anosognosia
  - Alexia
  - Acalculia
  - Aphemia
  - Gustatory seizures
  - Fear
  - Eye deviation
  - Receptive or conductive linguistic disturbances

Parietal Lobe Seizures

- Clinical manifestations
- Seizure spreading to extraparietal regions
  - Head and eye deviation
  - Tonic posture
  - Focal clonic
  - Automatism
  - Bilateral tonic-clonic
  - Visual symptoms

Parietal Lobe Seizures

- Clinical manifestations
- Eighty percent of patients report the presence of aura, of whom 72% report more than one kind of aura.
- Complex and simple partial seizures present a similar distribution among pediatric and adult patients, while spasms are exhibited exclusively by the youngest children.
- Loss of consciousness during seizures is not surprising since the associative parietal cortex is involved in the processing of normal consciousness.
- At least one secondary generalized seizure (SGS), more commonly within the first year following epilepsy onset, occurs in 70% of the patients.

Parietal Lobe Seizures

Parietal lobe epilepsy

Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988

V. Salanova, F. Andermann, T. Rasmussen, A. Olivier and L. F. Quesney

Table 1

Presence of aura in 77 out of 82 (94%)	%
Somatosensory (13 had painful sensations)	63
Disturbances of body image	[illegible]
Visual illusions	[illegible]
Vertiginous sensation	[illegible]
Aphasic aura	[illegible]
Feeling of inability to move one extremity	[illegible]
Complex visual or auditory hallucinations	[illegible]
Elementary visual hallucinations	[illegible]
Cephalic sensation	[illegible]
Epigastric (preceded by numbness of foot)	[illegible]

Parietal Lobe Seizures

Parietal lobe epilepsy

Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988

V. Salanova, F. Andermann, T. Rasmussen, A. Olivier and L. F. Quesney

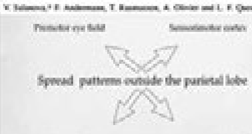


Table 2

Parietal Lobe Seizures

Drug-resistant parietal epilepsy: polymorphic ictal semiology does not preclude good post-surgical outcome

Parietal Lobe Seizures

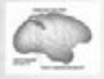


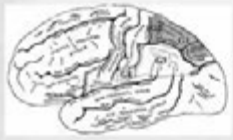
Table 6. Subjective vestibular and visual manifestations induced by intracerebral stimulations in the parietal lobe.

Stimulation site	Vestibular symptoms (N° of patients)	Visual symptoms (N° of patients)
Precuneus	"falling flat" (1) subjective vertigo (2) disequilibrium (1)	blurred vision (1) macropsia + object motion (1) "a moving object" (1)
Intraparietal sulcus	body oscillations "like being on the sea" (1)	double vision (1) blurred vision (1) metamorphopsia (1)
Superior parietal lobule	subjective vertigo (1) cephalic subjective vertigo (1) "sensation at the head" (1)	blurred vision + object motion (1) object motion (1)
Inferior parietal lobule	"falling into a vortex" (1)	blurred vision (1) object motion (1)
Supramarginal gyrus	"falling sort of head" (1) subjective vertigo (1) body oscillations "like being in a boat" (1)	blurred vision (1) "balls around the visual" (1)
Parietal congulum	"pulsation inside the head" (1)	blurred vision + object motion (1)

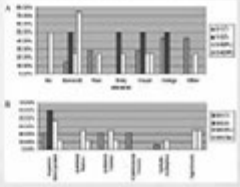
Hoffer, Et de vries de 17

Parietal Lobe Seizures

Neural networks underlying parietal lobe seizures: A quantified study from intracerebral recordings



- Epileptogenicity of brain structures was quantified according to the "epileptogenicity index" (EI), a way to quantify rapid discharges at seizure onset.

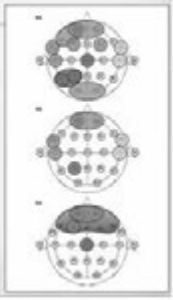


Hoffer, Et de vries de 17

Parietal Lobe Seizures

Parietal lobe epilepsy: the great imitator among local epilepsies

- The tendency toward multiple spread patterns (in particular to the temporal and frontal lobes), is characteristic of seizures originating in the parietal lobe.
- Interictal discharges in parietal lobe epilepsy showed the greatest magnitude of scatter outside the lobe of origin; the majority of patients with parietal lobe epilepsy had more than one spike population ($p<0.005$).
- Non-localizing ictal EEG patterns are more common than in frontal and temporal lobe epilepsies.



Hoffer, Et de vries de 17

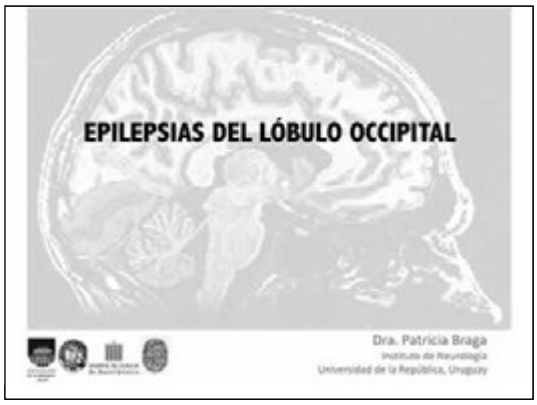
Parietal Lobe Seizures

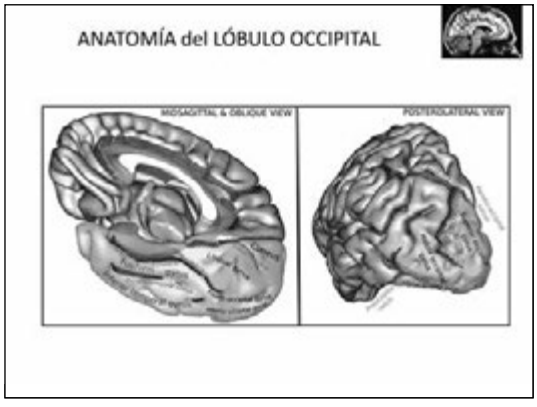
- The polymorphism of ictal manifestations accounts for the potential misdiagnosis of PLE, either with other localization-related epilepsies or even with non-epileptic psychogenic events.
- A large proportion of subjects (70%), exhibit secondarily generalized seizures, most commonly within the first year of illness.
- The presence of variable ictal patterns, such as focal tonic or clonic seizure activity and seizures with automatisms, reflects the rapid seizure spread outside of the PL, either to the frontal or to the temporo-limbic structures.

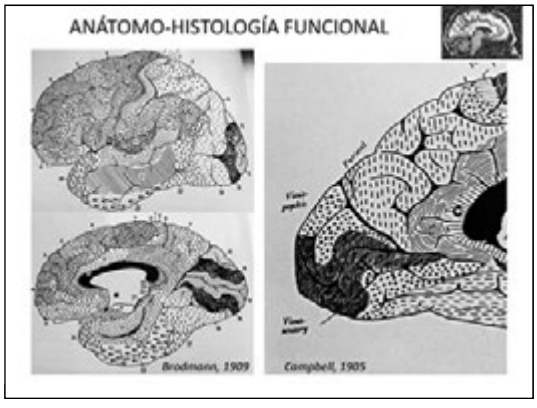
Hoffer, Et de vries de 17

Alicia Bogacz (Uruguay), Ana Carolina Coan (Brazil), Guilca Contreras (Venezuela), Patricia Braga (Uruguay), Peter Wolf (Denmark)

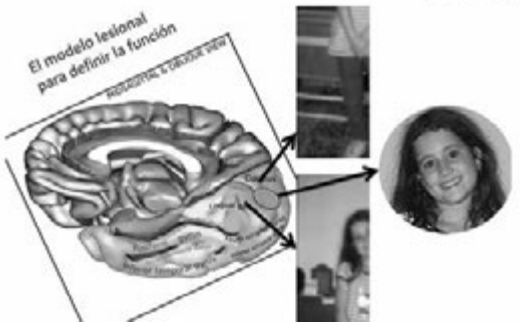
SEMIOLOGY OF FRONTAL, TEMPORAL, PARIETAL AND OCCIPITAL SEIZURES







ANATOMÍA FUNCIONAL: CENTROS



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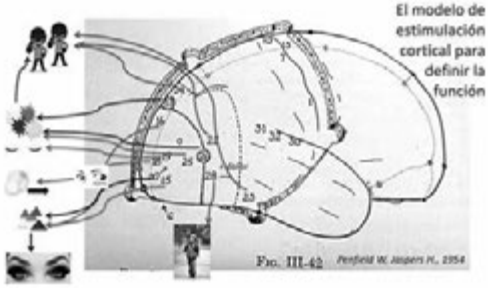


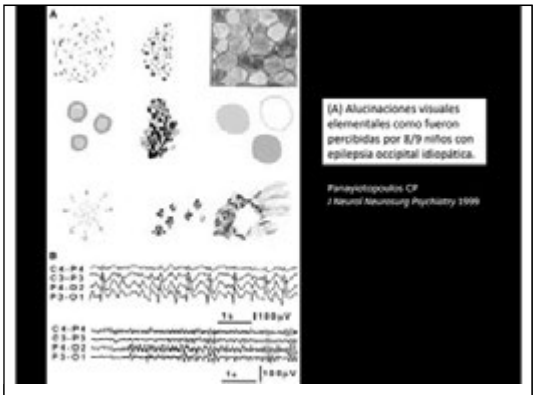
SEMIOLOGÍA ICTAL (I)
AURAS OCCIPITALES: sensoriales visuales

NEGATIVAS

- escotoma, hemianopsia
- amaurosis ictal
- visión borrosa

POSITIVAS

- Elementales
  - luces, formas geométricas, estrellas,
  - colores brillantes
  - generalmente múltiples, pequeños
  - estáticos o en movimiento: transversal, centrípeto, luces intermitentes; raramente con trayecto complejo o giratorio.
  - estereotipados en morfología, color, localización y movimiento



SEMIOLOGÍA ICTAL (I)
AURAS OCCIPITALES: sensoriales visuales

POSITIVAS

- Ilusiones perceptuales simples
  - cambio de tamaño: macropsia / micropsia
  - cambio de forma: metamorfopsia
  - cambios de color o luminosidad: discromatopsia, acromatopsia
  - cambio de inclinación: plagiopsia
  - alteración de visión estereoscópica
  - palinopsia (reverberación, persistencia o reaparición de objeto previamente visto)
- **Manifestaciones visuales complejas**
  - alucinaciones complejas como animales, personas u otras formas de colores, fijas o móviles

SEMIOLOGÍA ICTAL (II)
AURAS Y EPILEPSIA OCCIPITAL

- AURAS VISUALES EN OTRAS EPILEPSIAS
  - Auras visuales en **EGI**
  - Auras visuales en 3% de **ELTM**
  - Amaurosis ictal en epilepsia del lóbulo parietal
- OTRAS AURAS EN EPILEPSIA OCCIPITAL
  - **auras "temporales":** epigástricas, dismnésicas, auditivas
  - **auras vegetativas** y **signos autonómicos:**
    - **Náuseas y vómitos** (propagación a LT no-dominante y/o insula)
    - palidez, cianosis, dilatación pupilar, rubefacción facial, tos, incontinencia, respiración irregular

SEMIOLOGÍA ICTAL (III)
CEFALEAS

CEFALEA POST-ICTAL

- Cefalea unilateral contralateral a las alucinaciones visuales o bilateral.
- Pulsátil
- Moderada a severa
- Luego de 3-15 minutos del fin de la crisis visual
- A veces asociada con vómitos, foto y fonofobia
- Duración 30 min-24 horas

CEFALEA ICTAL

- Inicio precoz: en algunos pacientes los síntomas símil-migraña son parte de la crisis

SEMIOLOGÍA ICTAL (IV)
OTRAS CRISIS FOCALES OCCIPITALES

- CRISIS VERSIVAS
  - Desviación ocular *(Sveinbjornsdottirand Duncan, 1993; Andermann and Zifkin, 1998)*
  - Versión cefálica, generalmente contralateral *(Rosenbaum et al., 1996; Sveinbjornsdottir and Duncan, 1993)*
- CON SIGNOS OCULOMOTORES
  - Parpadeo forzado o flutter palpebral *(Sveinbjornsdottir and Duncan, 1993)*
  - Sensación de movimiento ocular *(Sveinbjornsdottir and Duncan, 1993)*
  - Nistagmus o movimientos óculo-clónicos *(Penfield and Jasper, 1954; Salanova et al., 1992; Sveinbjornsdottir and Duncan, 1993)*

SEMIOLOGÍA ICTAL (V)
SIGNOS LATERALIZADORES

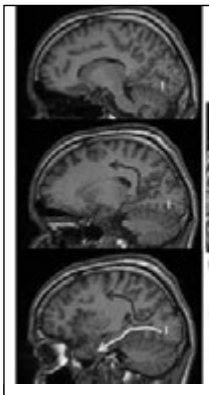
- **Lateralización a lóbulo occipital contralateral:**
  - Aura visual en un hemicampo
  - Desviación ocular/óculo-cefálica
  - Nistagmus epiléptico (fase rápida)
- **Alucinaciones visuales complejas** han sido asociadas a epilepsia del lóbulo occipital derecho *(Rasmussen 1992)*
- **Valor localizador:** La semiología de las crisis visuales no permite diferenciar crisis de origen occipital mesial y lateral *(Blume 2001)*

SEMIOLOGÍA ICTAL (VI)
CRISIS PARCIALES COMPLEJAS o DISCOGNITIVAS

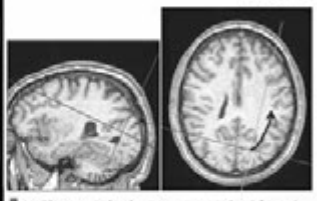
- Son frecuentes y reflejan patrones de propagación *(Williamson 1990)*.

> **Tipo Temporal:** crisis automotoras (trastorno de conciencia, automatismos).
>
> Tipo Frontal: crisis tónicas asimétricas o con componente motor clónico.

- 50% de pacientes combinan ambos tipos.
- Esta variabilidad puede hacer plantear una epilepsia multifocal.



ANATOMÍA FUNCIONAL: **REDES**



- Lesión **supracalcarina** propaga a parietal frontal: CPS motoras, sensitivas, tónicas asimétricas, CTCG.
- Lesión **infracalcarina** propaga a lóbulo temporal: auras y crisis temporales

(Ajmana-Marsan and Ralston, 1957)

ANATOMÍA FUNCIONAL: **REDES**

Research Article

The Classical Pathways of Occipital Lobe Epileptic Propagation Revised in the Light of White Matter Dissection

Francesco Latini,[1] Mats Hjortberg,[2] Håkan Aldskogius,[3] and Mats Ryttlefors[1]

- Diferentes vías anatómicas que conectan córtex occipital extra-estriado a frontal, parietal, o temporal.
- Haces con terminaciones parcialmente superpuestas.
- Excepto las radiaciones ópticas, son vías bidireccionales.

Latini F et al. Behav Neurol., 2015

Conexiones verticales

vSLF conecta giro supramarginal y angular con unión T-O

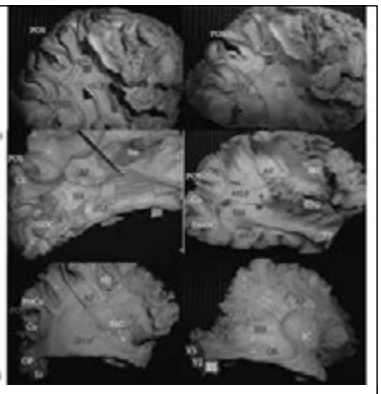
VO conecta el giro occipital superior con el fusiforme.

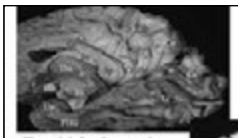
Conexiones longitudinales dorsolaterales

dILF- Fibras dorsales del fasciculo longitudinal inferior conectan cúneo y córtex occipital dorso-lateral (DLOC) al polo temporal.

IFOF- Fibras del fasciculo fronto-occipital inferior transcurren desde PreCu, Cu, OP y Ú por estrato sagital de Sachs (SSS) hacia el lóbulo frontal.

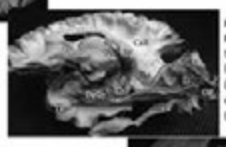
Latini F et al. Behav Neurol., 2015





Conexiones longitudinales mediales e inter-hemisféricas

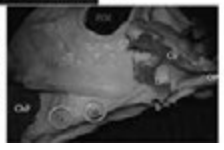
Fibras del cíngulo posterior alcanzan el córtex en cúneo y pre-cúneo, formando el sector medial del fórceps mayor (FM).



Fibras callosas del FM en el trígono terminan próximas a la radiación óptica (OR) a ambos lados de la cisura calcarina (CF).

Fibras del tapetum terminan siguiendo las radiaciones ópticas en la superficie medial del cúneo y lingula.

Latini F et al. Behav Neurol., 2015



CONCLUSIONES

- Son fuertemente sugestivos de Epilepsia Occipital:

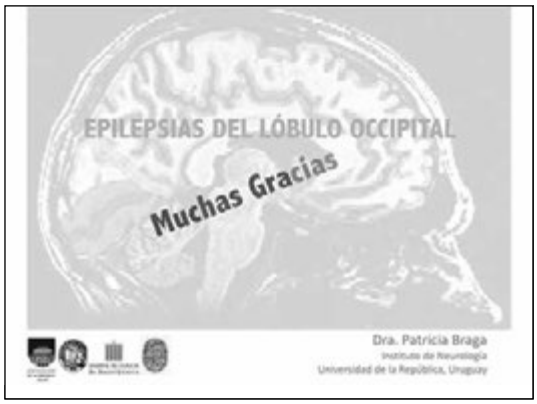
  alucinaciones visuales o amaurosis
  +/-
  movimientos oculares anormales (flutter, parpadeo, sensación)
  +
  déficit campimétrico

- Potencial de gran variabilidad de síntomas ictales: *"discharges arising from the visual region may possess the greatest potentiality for complexity of seizure formation".* *(Ajmone-Marsan, Ralston, 1957)*
- Múltiples tipos de crisis apoyan el diagnóstico. *(Williamson P et al, 1990)*

CONCLUSIONES

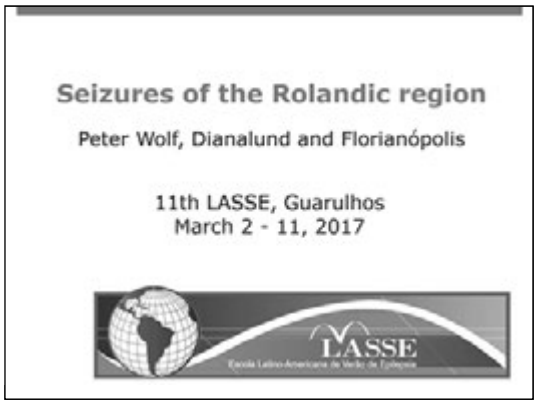
- Compleja conectividad funcional, con tractos verticales y longitudinales y potencial de propagación bidireccional. *(Latini F, 2015)*
- Conexiones verticales e interconexiones desafían el paradigma clásico de propagación ictal supra/infra-calcarina.
- Posibilidad de propagación retrógrada puede explicar los síntomas visuales en pacientes con epilepsia extra-occipital.

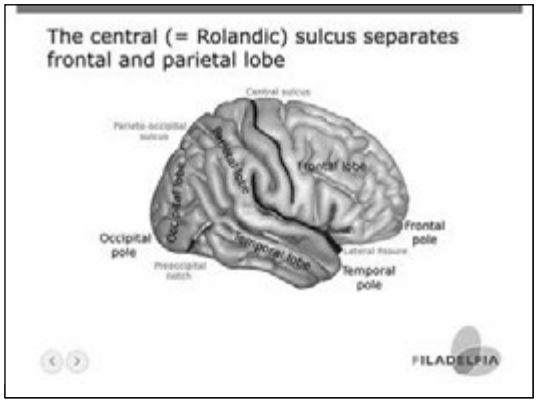
La fusión de información anatómica, imagenológica, neurofisiológica y clínica individualizada es fundamental para comprender las vías que subyacen a la fenomenología ictal en un alto porcentaje de pacientes con epilepsia occipital.

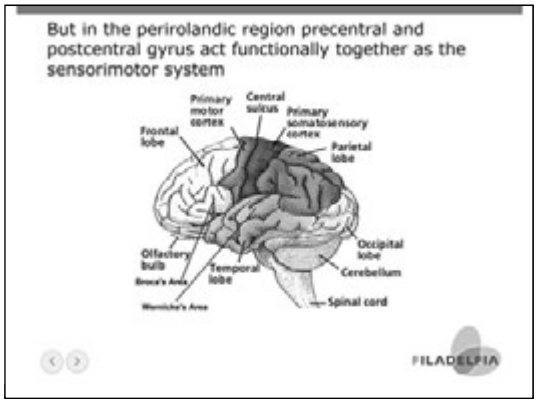

EPILEPSIAS DEL LÓBULO OCCIPITAL
Muchas Gracias
Dra. Patricia Braga
Instituto de Neurología
Universidad de la República, Uruguay

Alicia Bogacz (Uruguay), Ana Carolina Coan (Brazil), Guilca Contreras (Venezuela), Patricia Braga (Uruguay), Peter Wolf (Denmark)

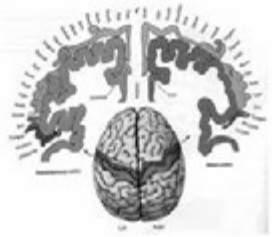
SEMIOLOGY OF FRONTAL, TEMPORAL, PARIETAL AND OCCIPITAL SEIZURES







Somatotopic organization of primary motor and sensory cortex



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Some history

- The rolandic region was the first brain region that got a seizure type attached when John Hughlings Jackson (1835 – 1911) in the 1870ies started to localize seizure signs anatomically
- These were motor seizures of the type which already had been described by Bravais (1801 – 1843)
- Jackson first understood their semiological meaning, and they are now called Jacksonian seizures

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More history

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.
The seizures "began by clonic spasmodic opposition of the thumb and forefinger".
No etiological clues
In monkeys this movement could be provoked by stimulation of "the ascending frontal and parietal convolutions at the line of junction of their lower and middle thirds".
At opening the skull at this place a tuberculoma was found and removed

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More history

- In consequence of Horsley's report a first big wave of epilepsy surgery developed in the 1890ies, with practically all interventions in the Rolandic area
- 50 reports and 7 doctoral theses between 1893 and 1898, one series of 146 cases
- In this period bromides only drug treatment
- German neurosurgeon Fedor Krause (1857 – 1937) became the leading expert performing about 400 epilepsy operations

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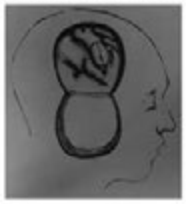
Fedor Krause's sketch of a cyst in the right precentral gyrus of a patient operated on November 16, 1893. Faradic stimulation produced myocloni in the left lower facial region below, and of shoulder and upper arm above the cyst.



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Fedor Krause's functional map of 1931 of the motor strip based on 142 epilepsy operations

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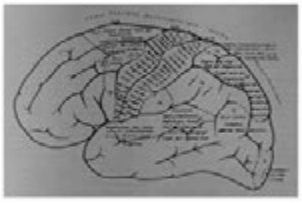
1930 map of cortical function by Otfrid Foerster (1873 – 1941)



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Conclusion

- In the first wave of epilepsy surgery perirolandic interventions were prevalent
  - Reliable anatomy before EEG based on semiology and sometimes radiology incl pneumencephalography
  - Semiology of neocortex best known
  - Not very much concern about postoperative deficits
    - ✓Most cases were symptomatic and there were deficits already before surgery

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Rolandic seizures are fundamentally sensorimotor!

Variants of Jacksonian seizures (analysis of 307 patients from 3 papers, 526 different seizures)

- Only motor 57 %
- Sensory ⇒ motor 19 %
- Sensorimotor (simultaneously) 16 %
- Motor ⇒ somatosensory 3 %
- Only somatosensory 5 %

Some motor involvement: 95%

Some sensory involvement: 43%

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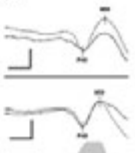
Variants of focal motor seizures

1. Classical Jacksonian seizure (precentral gyrus)
   - Clonic with local onset usually in periphery
   - Tonic component possible
   - March of convulsion, usually centripetal
   - May stop anywhere or spread over hemibody
   - Postictal paresis ("Todd's paresis") frequent
2. Clonic seizure without march
3. Tonic seizure (variable loci)
   - Flexor, extensor, versive
   - With pain: postcentral gyrus



Postictal SEP reduction after painful tonic st

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Somatosensory seizures

Contralateral

- Tingling, Numbness
- Sense of movement, desire to move
- Heat or cold, somatic pain, electric shock sensation
- Agnosia for body part, phantom sensations: post. parietal

Ipsilateral or bilateral symptoms of the same kind likely not rolandic but from secondary sensory areas (frontal or parietal operculum, inferior parietal lobule) and rarely other loci

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Epilepsia partialis continua (Epc)

- Variant of focal status epilepticus
- Stereotyped fragments of (sensori-)motor seizures, frequently repeated for > 1 hour (definition)
- May last up to many years
- May occur in repetitive episodes
- Multiple etiologies
- Epc due to chronic inflammation = Rasmussen syndrome

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How are perirolandic seizures generated?

- The classical focal seizure is generated in an ictogenic network around an epileptic focus
- How these networks are generated in the process of epileptogenesis is not yet known
- Most probably pathological *de novo* networks
- Seizure generation usually spontaneous
- rare: reflex szs precipitated by specific movements or touch of trigger zone (in focal cortical dysplasia)

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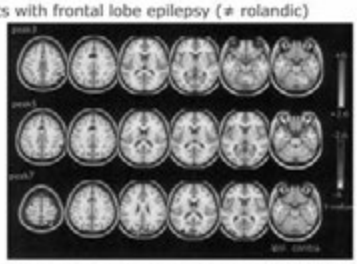
14 pts with frontal lobe epilepsy (≠ rolandic)



BOLD signal activations and deactivations in response to a single spike *(Fahoum et al Epilepsia 2012)*: ipsilateral and contralateral, cingulate, insula, TL, PL, precuneus, cerebellum

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Rolandic seizures are focal seizures but not all occur in focal epilepsies

Rolandic seizures also occur in

- Idiopathic Rolandic epilepsy of childhood
- Juvenile myoclonic epilepsy

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Idiopathic Rolandic epilepsy of childhood

- Seizures during sleep
- (Sensori-) motor seizures of the upper body quadrant (face + arm) with salivation
- No lesion
- Seizure and EEG spikes on alternate sides
- Spontaneous remission before puberty

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Idiopathic Rolandic szs: pathophysiology

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

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Rolandic seizures in juvenile myoclonic epilepsy

- Juvenile myoclonic epilepsy (Janz syndrome) is a system disorder of the brain
- Seizures are generated in an ictogenic network that abuses pre-existent functional anatomic brain systems
- Systems physiologically support vital functions like visuo-motor coordination

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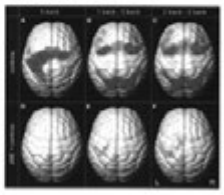
"Working memory paradigm": a spot appears in random sequence in one of 4 fields: where is it now? where was it last time? where the time before?

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



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Rolandic seizures in JME

- Visuomotor tasks in JME precipitate reflex myocloni in the hand active in the task
- "Praxis induction"
- The hyperexcited motor cortex responds to somatosensory input by myoclonic jerks
- 1/3 of JME patients (½ in Japan)

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Conclusions

- The perirolandic region consists of the primary motor and primary somatosensory cortex
- Together they function as the sensorimotor system
- Seizures reflect this double aspect, motor signs prevailing
- Szs can be generated in different ways dependent on the disease context
  - spontaneously in perifocal networks
  - sleep-induced in idiopathic Rolandic childhood epilepsy
  - as reflex myoclonі in JME

FILADELFIA

Roland Coras (Germany)

IMPACT OF THE NEW ILAE CLASSIFICATION ON FOCAL CORTICAL DYSPLASIA IN CHILDHOOD EPILEPSIES

Fernando Cendes (Brazil)

AGE-DEPENDENCE CHARACTERIZATION OF FCD NEUROIMAGING

Leila Chimelli (Brazil)

CHANGES IN BRAIN DEVELOPMENT RELATED TO ZIKA VIRUS INFECTION

CHANGES IN BRAIN DEVELOPMENT RELATED TO ZIKA VIRUS INFECTION

Leila Chimelli

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Federal University of Rio de Janeiro, Brazil

IECérebro

UFRJ

- Introduction
- Epidemiology/period of infection
- Diagnosis
- Radiological findings
- The ten first autopsies
- Macroscopic appearances
- Histological findings in the CNS
  - Topography of the lesions
  - Inflammation
  - Calcification
  - Neuronal migration disturbances
  - Search for the virus
- Other tissues, organs and placenta

INTRODUCTION

- Zika virus (ZIKV) a flavivirus transmitted by Aedes *aegypti*, recently arrived in Brazil and spread to many states and other countries in South and Central America in less than one year.
- Human infection varies from mild fever, arthralgia, rash, headache, and myalgia but may be asymptomatic.

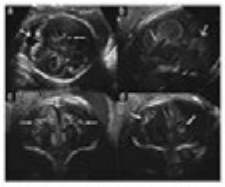
Zika outbreaks

- It has recently been established a relationship between ZIKV infection and microcephaly with frequent calcification on neuroimaging.

Ultrasound Obstet Gynecol 2016; 47: 6–7
Published online in Wiley Online Library (wileyonlinelibrary.com).

Physician Alert

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?



Microcephaly

Microcephaly Cases in Brazil

microcefalia e/ou alteração do SNC, Brasil, até a SE 08/2016.

CASOS CONFIRMADOS (n = 250 municípios)

The first neuropathological evidence linking ZIKV infection and microcephaly

BRIEF REPORT

Zika Virus Associated with Microcephaly

SUMMARY

The neuropathological findings in 10 autopsies

- Babies whose mothers reported a rash during the 1st or 2nd trimester of pregnancy and/or had ZIKV identified by PCR in the amniotic fluid or cord blood were followed intrauterus with ultrasound/CT, and were reported to have cerebral maturation and growth, drastically affected very early.
- Most were born with arthrogryposis
- Microcephaly was not always observed, sometimes due to a compensation of cephalic perimeter by ventriculomegaly.

Macroscopy

- Thickened leptomeninges, ventriculomegaly (ex-vacuo or obstructive), shallow sulci or agyria, thin cortex and white matter. Thin or absent corpus callosum. Abnormal hippocampi. Small basal ganglia and thalami.
- Cerebellar, brainstem and spinal hypoplasia.
- Calcification could be detected macroscopically in cerebral hemispheres, deep gray nuclei and brainstem.

Summary of histological features

- Abnormal clusters of germinal matrix along the ventricular surface and towards the cortex.
- Disturbances of neuronal migration in cerebral, cerebellar hemispheres and brainstem, including polymicrogyria, leptomeningeal glioneuronal heterotopia and cortical dysplasia, which are more severe in those who were infected earlier in pregnancy.
- Nerve cell degeneration, coarse and filamentous calcification in the hemispheres, basal ganglia, thalami, brainstem and spinal cord.
- Aqueduct stenosis, motor spinal nerve cell loss and small corticospinal tracts.
- Little inflammation (T lymphocytes CD8+)

The search for the virus

- ZikV was identified with *in situ* hibridization in the meninges, germinal matrix and neocortex.
- Electron microscopy also showed viral particles in the brain.
- In systemic organs, ZikV was frequently identified in the liver, spleen and kidney.
- ZikV was not detected in the placentas.

Acknowledgments

ASO Melo2,3; F Tovar-Moll4; R Madeiro4; PS Oliveira-Szejnfeld5; AHS Camacho1; GC Gomes1; FO Melo2; AGM Batista3; E Avvad 6; HN Machado6; C Viana6; D Dock6; ME Moreira6; V Silami Lopes7; A Carvalho7; O Ugarte7; AGM Batista3; TA Ferreira8; RD Andrade9; CA Wiley10; S Rehen4; MB Arruda11; RM Brindeiro11; R Delvechio11; RS Aguiar11; A Tanuri11

1- State Institute of Brain Paulo Niemeyer, Rio de Janeiro. 2- Research Institute Prof. Amorim Neto. 3- Health Secretary Campina Grande, PB. 4- D'Or Institute for Research (IDOR), UFRJ. 5- Fetal Medic Research, Foundation Institute Education Research Diagnostic Imaging (FIDI), São Paulo. 6- Fernandes Figueira Institute – FioCruz, Rio de Janeiro. 7- Dept Pathology, Fluminense Federal University; 8- Federal University of Campina Grande. 9- Health Institute Elpidio de Almeida - Campina Grande – PB. 10. University of Pittsburgh, USA. 11- Laboratory of Molecular Virology, Federal University of Rio de Janeiro.

Débora Silva; Diego Santos; Luciana Bitano For thecnical assistance

TO THE MOTHERS

Helen Cross (UK)

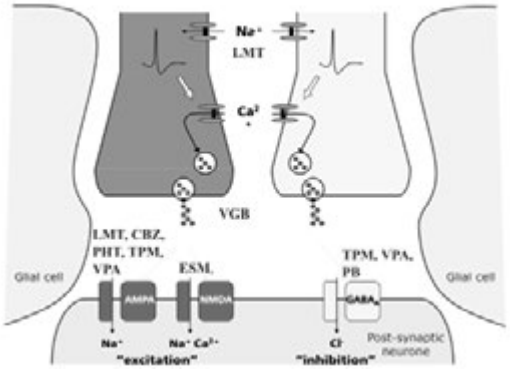
NOVEL THERAPEUTICS IN EARLY ONSET EPILEPSY

LASSE
LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY

Novel therapeutics in early onset epilepsy

J Helen Cross
UCL-Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London, & Young Epilepsy, Lingfield, UK

AED development



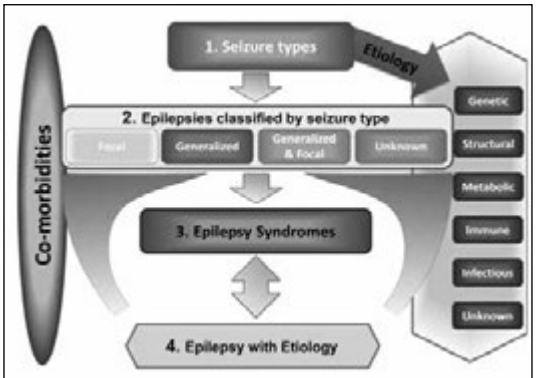
Concepts revisited

ILAE, Fisher et al Epilepsia 2014

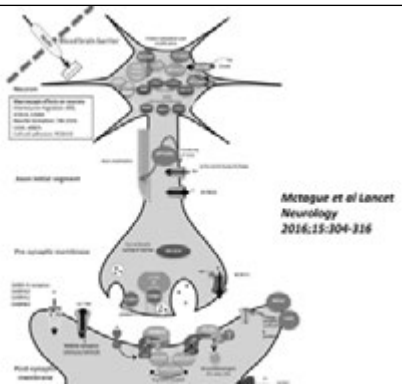
Epilepsy: A disease of the brain

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours 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.

Epilepsies = a group of diseases

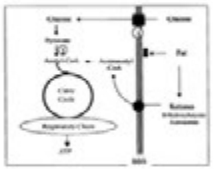


The epilepsies: a group of rare diseases



Metague et al Lancet Neurology 2016;15:304-316

GLUT 1 deficiency



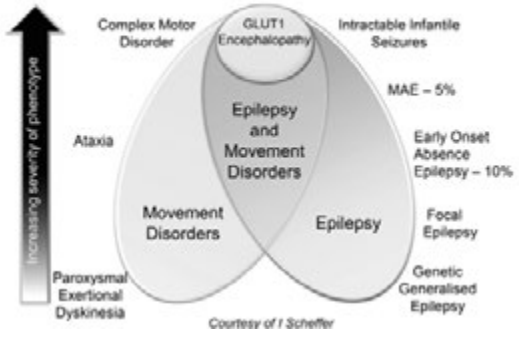
Glucose transporter

- 1 of 9 glucose transporters
- Blood-brain barrier, astrocytes, erythrocytes
- Brain is glucose dependent

SLC2A1

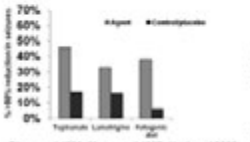
- Solute carrier family 2 (facilitated glucose transporter), member 1
- Encodes glucose transporter 1 – Glut1

Spectrum of GLUT 1 deficiency



The ketogenic diet

A high fat diet, designed to mimic the metabolic effects of starvation, used in the treatment of epilepsy.



Bitton et al 1998, Motte et al 1997, Neal et al 2008

- **Classical KD**
- **Medium chain triglyceride KD**
- **Modified KD**
- **Low GI**

A genetic basis to response?

Candidate genes

- Only one new case of GLUT1 deficiency (SLC2A1), from 246 cases
- Responder (R) vs non-responder (NR) association analysis
  - Responders = seizure-free at 3 month follow-up
- 8 R and 295 NR with *KCNJ11* sequencing data
- 8 R and 238 NR with *BAD* sequencing data
- 14 previously-reported and 9 novel variants found from Sanger sequencing

No variant significantly associated with KD response

DMCN 2015, Epilepsy Research

GWAS

- Genetic outliers excluded, single-variant analysis
- 5 R and 177 NR, 422230 SNPs post quality-control filtering
- Cluster of top SNPs lowest p=3.32x10-6

minor alleles present in the ONLY two patients with 100% seizure-freedom maintained over ≥2 years, and one individual with ≥50% seizure reduction

underpowered

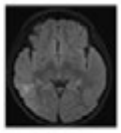
Exome sequencing

- **17 responders and 27 non-responders with whole exome-sequencing**

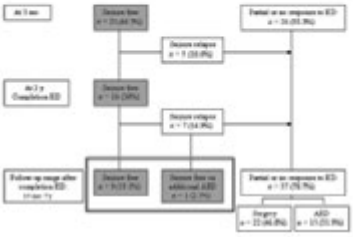
No differences validated so far, analysis ongoing

In collaboration with Sanjay Sisodiya, UCL-Institute of Neurology

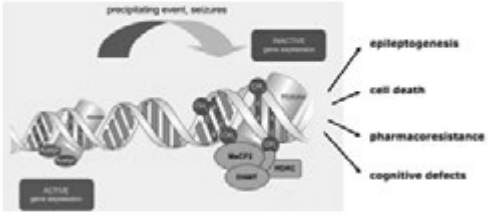
Structural epilepsies



Long term outcome of the ketogenic diet for intractable childhood epilepsy with focal malformation of cortical development *Jung et al Paediatrics 2008;122:e330-3*



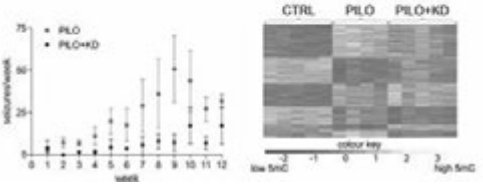
The „methylation hypothesis" in epilepsy



Kobow and Blümcke, Epilepsia 2011, 2012, 2013

Methylation hypothesis in epilepsy

Kobow and Blümcke, 2011, 2012, 2013

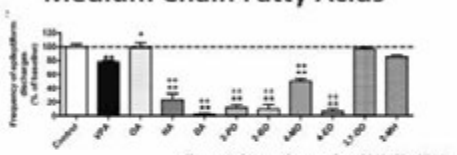


RCT of presurgical utilisation of ketogenic diet for FCD type II

Evaluation of Dietary Intervention Before surgical treatment of Epilepsy

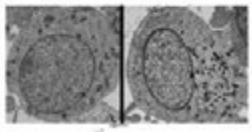
- **To determine whether resective surgery performed after ketogenic diet is more effective than not in the treatment of epilepsy associated with FCD II**

Medium Chain Fatty Acids



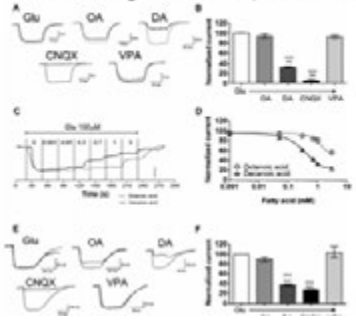
Chang et al Neuropharmacology 2013; 69:105-14

	CS Activity (nmol/min/mg protein)
MOA	6 Day Incubation
Control	111 ± 5.09
Control + Vehicle	113 ± 4.44
C8:0	115 ± 4.98
C10:0	146 ± 7.22**



Hughes et al J Neurochem 2014 130(3):426-33

Effect of Decanoic Acid on AMPA receptor mediated currents *Chang et al Brain 2016; 139: 431-443*

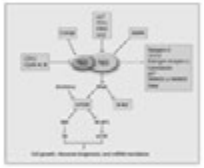


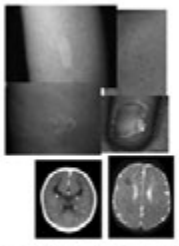
Decanoic acid in epilepsy

Matthew Walker, J Helen Cross, Sanjay Sisodiya

- **Patent applications GB1210699.3 and WO2012069790**
- **Betashot (Vitaflo)** **Tolerability trials**
- **Betashot with LGI diet**
  - **Children(3-18 years): Dravet, genetic epilepsies,**
  - **Adults: drug resistant epilepsy**
  - **12 week outcome**
    - **Gastrointestinal tolerance**
    - **Acceptability**
    - **Compliance**

Tuberous Sclerosis



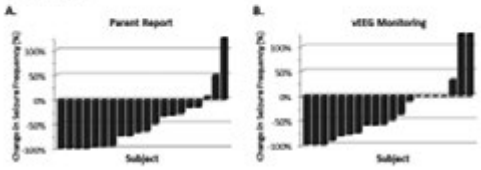


Franz et al 2006 **5 SEGAs regressed when treated; one regrowth when discontinued**

Zeng et al 2008 ***Early & late treatment in TSC1 CKO mouse caused reduced seizures & prolonged survival***

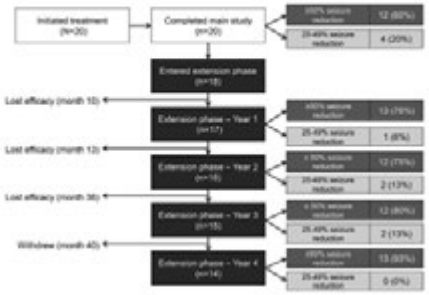
mToR inhibitors & epilepsy in Tuberous Sclerosis

- prospective, multicenter, open-label,phase I/II clinical trial Everolimus for epilepsy in TSC, > 2years age
- 23 subjects, 12 week treatment, 12/20 >50% reduction seizures



Krueger et al Ann Neurol 2013; 74:679-687

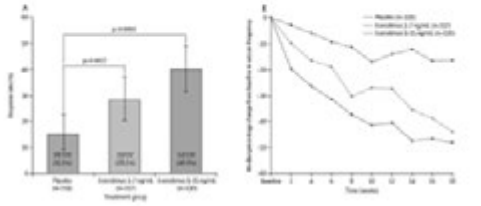
Long term follow up



Krueger et al Neurology 2016;87:2408-2415

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

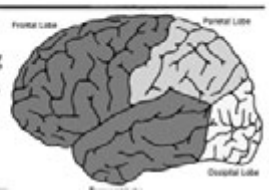
Lancet Neurol 2016;388:2153-2163



Familial Partial Epilepsy with Variable Foci: A New Partial Epilepsy Syndrome with Suggestion of Linkage to Chromosome 2

Ingrid E. Scheffer, FRACP,*†‡ Hilary A. Phillips, BSc,§ Catherine E. O'Brien, MA,‖ Michael M. Saling, PhD,‖ Jacqueline A. Wrennall, MSc,¶ Robyn H. Wallace, BSc(Hons),§ John C. Mulley, PhD,§ and Samuel F. Berkovic, FRACP*†

Focal epilepsy originating in different brain regions in different family members



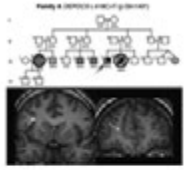
LETTERS

nature genetics

Mutations in *DEPDC5* cause familial focal epilepsy with variable foci

Leanne M Dibbens[1,2,23], Bonkje de Vries[3,23], Simona Donatello[4], Sarah E Heron[1,2], Bree L Hodgson[5], Satyan Chintawar[6], Douglas E Crompton[3,6], James N Hughes[7], Susannah T Bellows[8], Karl Martin Klein[3,9], Petra M C Callenbach[3], Mark A Corbett[10], Alison F Gardner[10], Sara Kivity[11], Xenia Iona[1], Brigid M Regan[4], Claudia M Weller[5], Denis Crimmins[12], Terence J O'Brien[13], Rosa Guerrero-López[14], John C Mulley[1,2,15], Francois Dubeau[16], Laura Licchetta[18], Francesca Bisulli[18], Patrick Cossette[16], Paul Q Thomas[7], Josef Gecz[1,2,6], Jose Serratosa[19], Oebele F Brouwer[20], Frederick Andermann[21], Eva Andermann[21], Ann M J M van den Maagdenberg[3,22], Massimo Pandolfo[4], Samuel F Berkovic[8] & Ingrid E Scheffer[8,17,23]

published online 31 March 2013;



Mutations in Mammalian Target of Rapamycin Regulator DEPDC5 Cause Focal Epilepsy with Brain Malformations

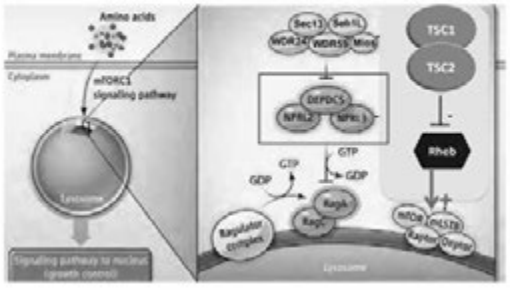
Scheffer et al Ann Neurol 2014;75: 782-787

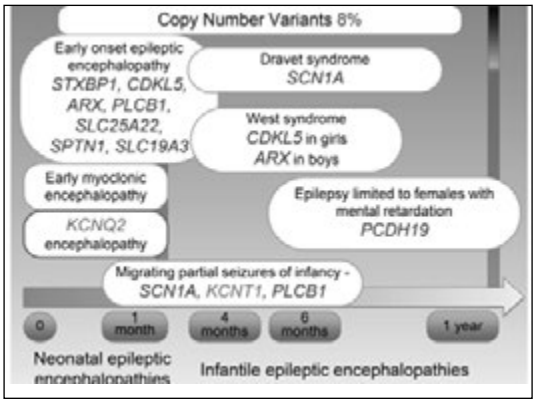
Familial Focal Epilepsy with Focal Cortical Dysplasia Due to *DEPDC5* Mutations

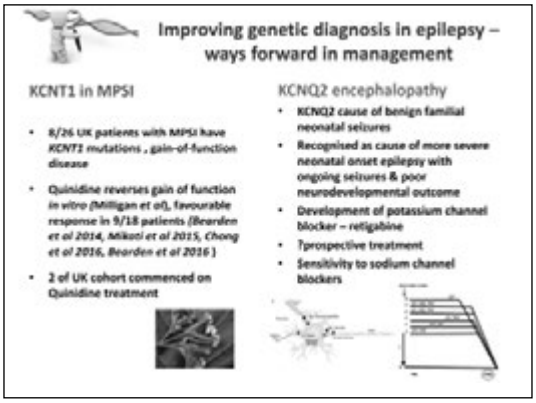
Stephanie Baulac, PhD,[1,2,3,4] Saeko Ishida, PhD,[1,2,3,4] Elise Marsan,[1,2,3,4] Catherine Miquel, MD,[5] Arnaud Biraben, MD,[6,7] Dang Khoa Nguyen, MD,[8] Doug Nordli, MD,[9] Patrick Cossette, MD, PhD,[8,10] Sylvie Nguyen, MD,[11] Virginie Lambrecq, MD,[1,2,3,4,12] Mikaela Vlaicu, MD,[4,13] Mollya Davies,[1,2,3,4] Franck Bielle, MD, PhD,[1,2,3,4,14] Eva Andermann, MD, PhD,[15,16] Frederick Andermann, MD,[17,18] Eric Leguern, MD, PhD,[1,2,3,4,19] Francine Chassoux, MD,[5,20] and Fabienne Picard, MD[1]

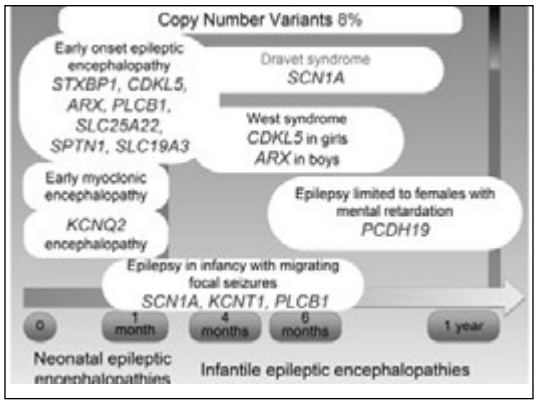
Ann Neurol 2015;77:675–683

mTOR inhibitors effective in epilepsy?



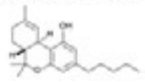






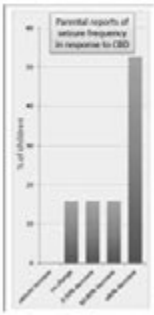
Cannabis

- Cannabis: for the most part, *Cannabis sativa*.
- One of the most widely used recreational and medicinal drugs worldwide.
  - ~150 million people smoking cannabis daily (WHO)
- Likely the first non-food plant cultivated by humans (~8000 BC)
- Best known for its psychoactive constituent, Δ^9-tetrahydrocannabinol ('THC').

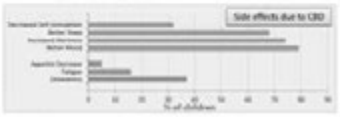



Use of cannabis in epilepsy

Parental survey

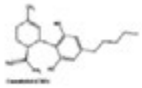


- **19 children** on CBD-enriched medical marijuana
  - 13x Dravet syndrome
  - 1x Lennox-Gastaut syndrome
  - 4x Doose syndrome
  - 1x idiopathic epilepsy
- Average of 12 antiepileptic drugs tried before CBD
- CBD reduced seizure frequency in majority of cases
- CBD had an excellent side effect profile
  - Better mood, increased alertness; better sleep; drowsiness; fatigue
  - Common negative side effects often associated with other AEDs notably absent after CBD exposure



Porter BE, Jacobson C. Epilepsy & Behavior 2013;29:574-577

Cannabidiol



- **Pure cannabis; almost insignificant THC**
- **In vitro, significant anti epileptic effects in hippocampal slices**
- **In vivo, anitconvulsant effects in five animal models of seizures**

- **CBD is one of two major cannabinoids in Sativex**
- **Human exposure to pure CBD in clinical trials is limited**

FDA IND; open label protocol

Epidiolex (CBD)

Devinsky, Sullivan, Friedman, Thiele, Marsh, Laux, Hedlund, Tilton, Bruno, Bluvstein, Cilio

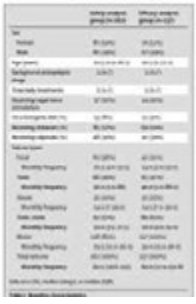
Inclusion criteria

- Intractable early onset epilepsy
- ≤ 3 AEDs (not including VNS or KD)
- Non progressive disorder
- No significant laboratory abnormalities

Protocol

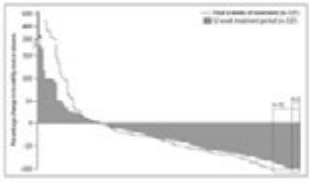
- 4 week baseline seizure diary
- CBD 5mg/kg/day
- Titrated at 2·5mg/kg increments until tolerance or max 25mg/kg/day
- Labs for FBC, Liver, kidney function & AED levels 4, 8 and 12 weeks

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial



Lancet Neurology 2016;15:270-8

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial



- 214 patients across 11 sites
- safety & tolerability 167
  - Adverse events 79%
- 137 efficacy analysis
  - 54 (39%) >50% reduction

Dravet N=32
49% responders, 3% SF
LGS N=30
37% responders, 3% SF

Lancet Neurology 2016;15:270-8

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial *Lancet Neurology 2016;15:270-8*

	Safety analysis (N=162)
Somnolence	41 (25%)
Decreased appetite	31 (19%)
Diarrhoea	31 (19%)
Fatigue	21 (13%)
Convulsion	18 (11%)
Increased appetite	14 (9%)
Status epilepticus	13 (8%)
Lethargy	12 (7%)
Weight increased	12 (7%)
Weight decreased	10 (6%)

Conclusion: cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy.

AED interaction; clobazam

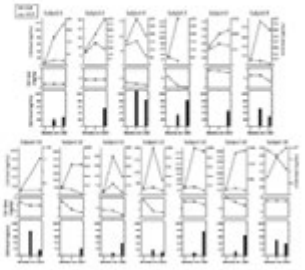
13/25 children CBD 2—25mg/kg/day

Mass General Hospital, Boston

Norclobazam increased in 12/13

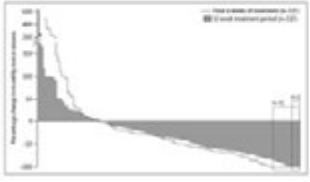
Side effects 10/13

- Drowsiness 6
- Ataxia 2
- Irritability 2
- Restless sleep 1
- Urinary retention 1
- Tremor 1
- Loss of appetite 1



Geffrey et al. Epilepsia. 56(8):1246–1251. 2015

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial



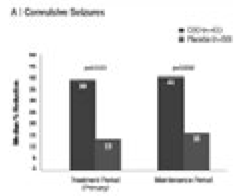
>50% reduction
- Clobazam 36/70 (51%)
- No clobazam 18/67 (27%)

Multiple logistic regression clobazam use only independent predictor of reduction >50% in motor seizures

Lancet Neurology 2016;15:270-8

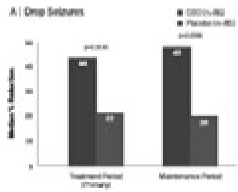
RCT CBD vs placebo

Dravet syndrome



Cross et al AES 2016

Lennox Gastaut syndrome



Thiele et al AES 2016

FULL-LENGTH ORIGINAL RESEARCH

Successful use of fenfluramine as an add-on treatment for Dravet syndrome

*†Berten Ceulemans, ‡†Marc Boel, *Katrien Leyssens, *Carolin Van Rossem, ‡Pieter Neels, §Philippe G. Jorens, and ‡†Lieven Lagae

12 patients, 3-35 yrs
Exposure 1-19 years
7 still receiving treatment at last visit seizure free >12m, mean 6 years

"Thickening" of the cardiac valves	4/12
Loss of appetite	6/12
Mild obesity	3/12
Weight <3rd centile	2/12
Fatigue	2/12
Behavioral problems	2/12
Somnolence	1/12

ORIGINAL ARTICLE

Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients

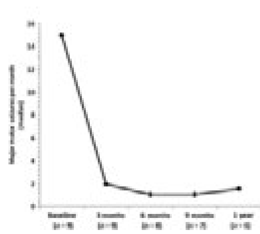
9 patients, Dravet syndrome, 1.2-29.8 yrs

Prospective open label observational study

Starting dose 0.25-1mg/kg/day
Dose adjusted to max 20mg/day

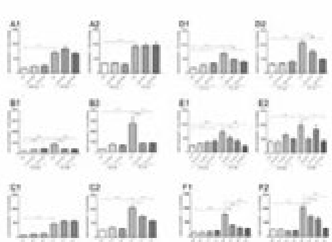
6/9 >50% reduction in seizures at 3m

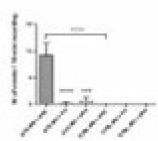
TEAEs
- *somnolence* *5*
- *anorexia* *4*
- *fatigue* *3*
- *sleep difficulties* *2*
- *non-convulsive SE* *3*



Fenfluramine in knockdown zebra fish model of Dravet syndrome

Zhang et al PLoS One 2016;10(5): e0125898





So where are we now?

- Traditional concepts of the epilepsies are now being challenged
  - Group of diseases
  - Rationale to treatments
- Older therapies more targeted in approach
  - Moving towards simplified approach
- Genetics providing an understanding of underlying pathophysiology, and perhaps revisiting of optimal treatment

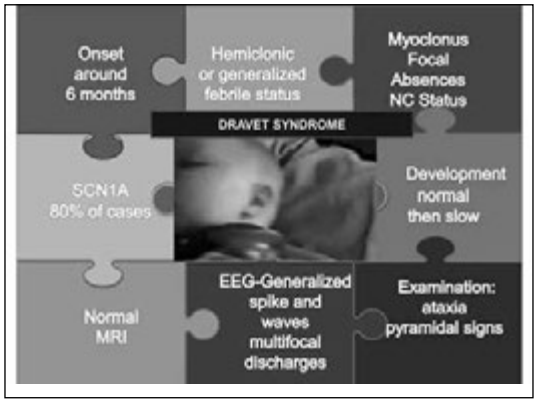
Anna Lecticia Pinto (USA)

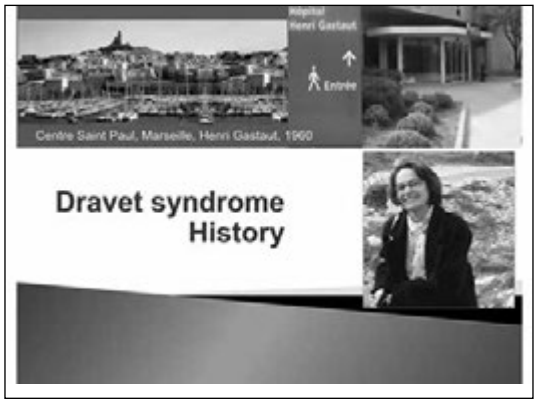
STURGE-WEBER SYNDROME: NEW APPROACH TO AN OLD DISEASE

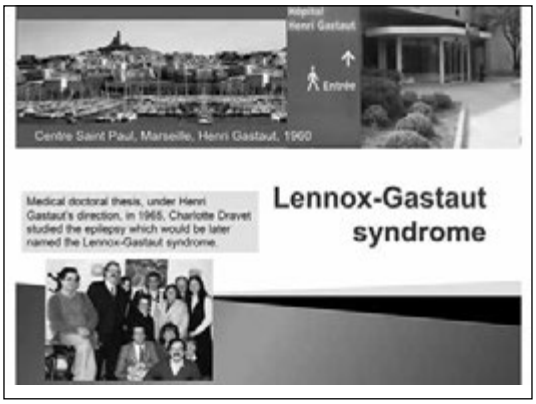
MEETING WITH LEILA CHIMELLI, ROLAND CORAS, FERNANDO CENDES, HELEN CROSS, ANNA LECTICIA PINTO

Elza Marcia Yacubian (Brazil)

DRAVET SYNDROME



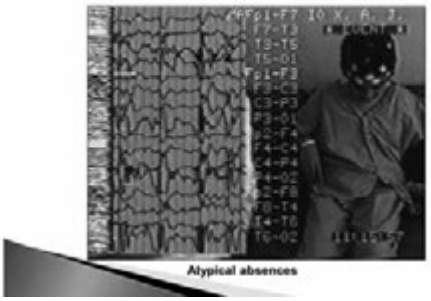




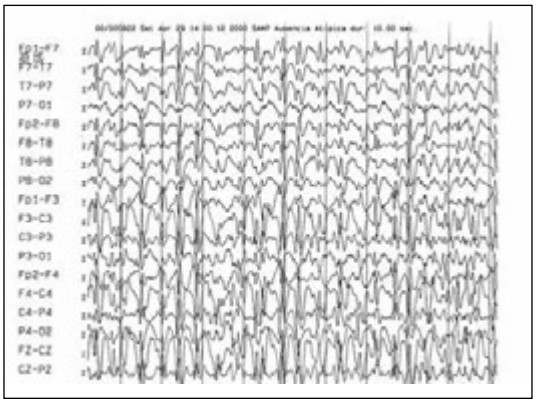
Lennox-Gastaut syndrome
Clinical aspects

- Onset between 1 and 7 years (peak 3-5 years);
- Cognitive and behavioural abnormalities (20-60% of patients);
- Boys more affected than girls (60%);
- Polymorphic seizures: atypical absences; tonic seizures; atonic seizures; myoclonic seizures (11-28% of cases);
- Neuropsychological deterioration.

Lennox-Gastaut syndrome
Clinical aspects

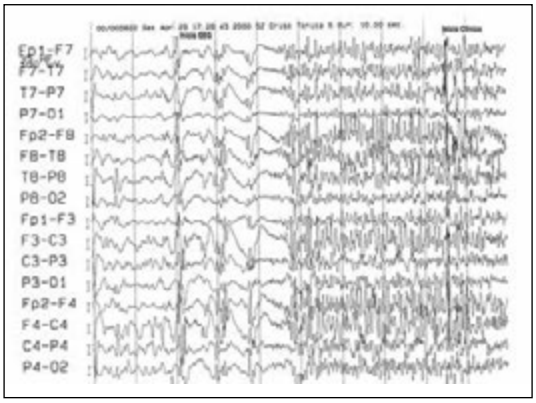


Atypical absences



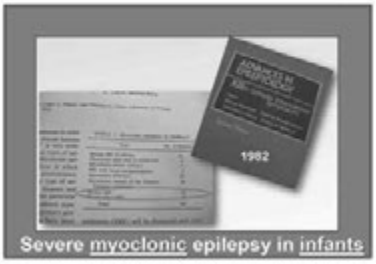
Lennox-Gastaut syndrome
Clinical aspects

Tonic seizures



Dravet syndrome spectrum

Why Dravet syndrome?



Severe myoclonic epilepsy in infants

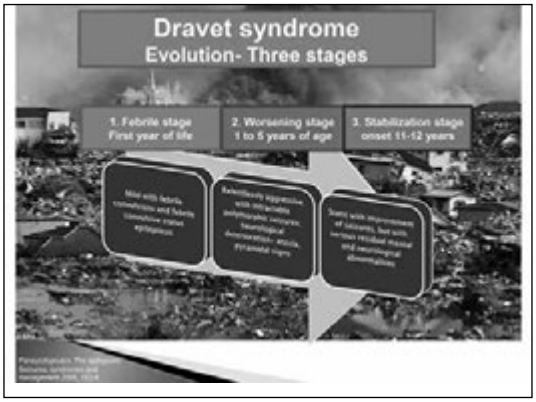
Myoclonia absent in over half of the cases= DRAVET SYNDROME

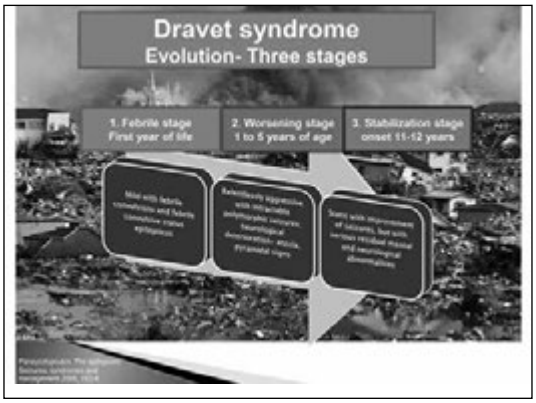
Dravet syndrome
Clinical aspects

- 1978-1982- Centre Saint Paul- specific epileptic encephalopathy different of the Lennox-Gastaut syndrome;
- Onset before 1 year (peak 5 months) in normal children, without any relevant antecedent;
- Severe, prolonged convulsive seizures, first febrile, then afebrile.

Dravet syndrome
Epidemiology

- Not well known;
- 1/15.700 to 1:40.000 (Wu et al., 2015); less rare as genetic tests become available; 1.4% of children with epilepsy;
- Its frequency is probably higher;
- Males are more frequently affected than females (ratio of 2 to 1);
- Family antecedents of epilepsy and febrile convulsions (> 25%).





Dravet syndrome
Febrile seizures

- Of early onset (usually between 4 and 8 months);
- Prolonged beyond 15 or 30 minutes;
- Unilateral; alternating hemiconvulsions;
- Mainly clonic; frequent (once a month);
- Triggers: low fever often below 38° C, vaccinations, abrupt change in temperature;
- Normal EEGs, normal development.

The diagnosis is nearly certain if intractable myoclonic jerks and mental deterioration appear within 1-2 years from onset

Dravet syndrome
Clinical aspects

- Prolonged unilateral clonic seizures.

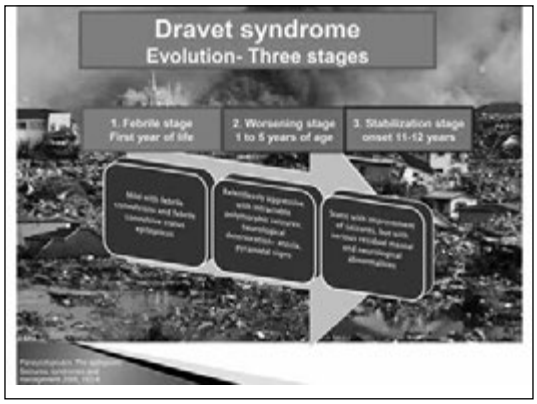
- Provoked by hyperthermia of around 38° C, temperature variations (body temperature unstable), minor infections, immunizations or hot baths

Dravet syndrome
Febrile seizures

- We must be worried
  - Prescribe rectal diazepam in case of other seizures;
  - Often fails to stop the seizure that requires admission to hospital;
  - Consider doing the genetic analysis.

Dravet syndrome
Is early development really normal?

- Studies showing early impaired visual function (tracking, visual attentiveness), prior to diagnosis, prior to seizure onset;
- Raises questions about the assumption that developemnt is always normal before onset of the epilepsy.



Dravet syndrome
Clinical aspects

- Afebrile seizures of mixed types including partial seizures;
- Shorter motor seizures- still triggering factors such as mild hyperthermia, physical exercise, emotion, light;
- Development regression or stagnation;
- Ataxua, ¼ autistic behavior, stereotypes;
- Normal neuroimaging.

Dravet syndrome
Clinical aspects

- Myoclonic seizures.

Dravet syndrome
Clinical aspects

- Atypical absences; obtundation status (40%).

Non-convulsive SE- confusion combined with erratic myoclonus of the extremities and around the mouth lasting several hours associated with pseudo-rhythmic slow wave activity encroached with irregular spikes.

Dravet syndrome
Clinical aspects

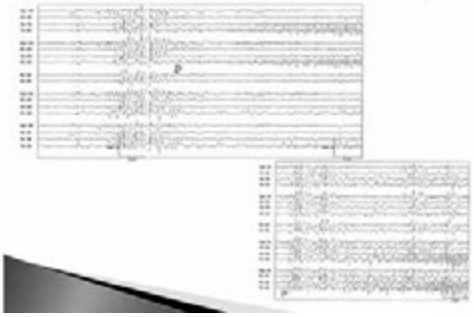
- Intractable seizures;
- Frequent and prolonged status epilepticus;
- Photosensitivity- eye closure, photic and pattern stimulation (50% of the cases-1/4 self-induced seizures)-environment ligh intensity.

Epileptic encephalopathy without known etiology

Different of the Lennox-Gastaut syndrome

Severe myoclonic epilepsy in infants

Dravet syndrome
EEG



Dravet syndrome
Evolution- Three stages

Dravet syndrome
Clinical picture

- Refractory convulsive seizures during sleep;
- Still precipitated by fever and infections;
- 8-16% adults seizure-free > 1year.

Death

- Mortality rate is high, reaching 10-18% of patients, with a peak at 3-7 years;
- SE used to be a significant cause of death (36%); acute encephalopathy;
- SUDEP is the main cause of death (56%) with two peaks:
  - At 1-3 years
  - Over 18 years, without evidence of worsening epilepsy.

Gataullina & Dulac, 2017

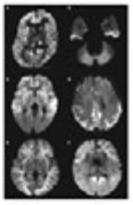
2012

FULL-LENGTH ORIGINAL RESEARCH

Acute encephalopathy in children with Dravet syndrome

- Prolonged SE followed by coma with or without other neurological symptoms, lasting for > 24 h in association with infections symptoms.

- Ischemic lesions and psychomotor impairment, mainly within the first 5 years of life;
- Patients chronically treated with VPA and BZD;
- Benzodiazepines, when administered chronically, may facilitate this condition. They should be restricted to SE.



Gataullina & Dulac, 2017

Dravet syndrome
Neuropathology

Morphometry in the second decade shows global volume reduction of gray and white matter in brainstem, cerebellum, corpus callosum, corticospinal fibers and association fibers.

BRIEF COMMUNICATION

A case of SUDEP in a patient with Dravet syndrome with SCN1A mutation

- Micronodular dysplasia left temporal lobe
- Bilateral gliosis CA4
- Global cerebral edema

Why Dravet spectrum?

Dravet syndrome
Clinical picture

- In the 70's a very characteristic picture, many patients presenting with the same features;
- End of the 80's: patients with a less typical picture were reported- variability between the patients particularly for the myoclonic symptoms which was often very slight, even absent (1/5 patients). Tonic seizures, the hallmark of LGS, are exceptional.

Which were the borderlines of the syndrome?

2001- 80% cases SCN 1A mutations- α subunit- it was an epileptic disease- 95% de novo; 5% familial;
> 1250 mutations described- ¼ involving the paternal chromosome

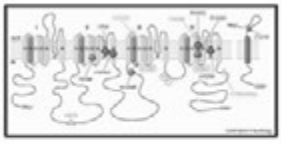
Claes et al., 2001
Gataullina & Dulac, 2017

Dravet spectrum

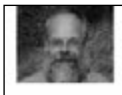
Febrile seizures → Genetic Epilepsy with Febrile Seizure (GEFS+) → Borderline type Intractable Childhood Epilepsy with Generalized TCS Severe Infantile Multifocal Epilepsy → Dravet syndrome

MILD → SEVERE

Dravet syndrome
Clinical picture



- Is this a single disease with different forms related to different mutation types?
- Is this disease a part of a large spectrum of channelopathies including other myoclonic and non-myoclonic epilepsies?



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

Ulrike Claes,[1] Jurgen Del-Favero,[1] Barbara Coulemans,[1,2] Doreen Lagae,[3] Christine Van Broeckhoven,[1] and Peter De Jonghe[1,2]

Am. J. Hum. Genet. 69:1327–1332, 2001

SCN1A mutation (70-80%) 95% *de novo* | PCDH19 (2-5%) | Otherino known mutation (15-20%)

Other: SCN1B, GABRA1, GABRG2, SCN 2A

Regardless the type of mutation the syndrome is the same!

Not all patient with a SCN1A variant have Dravet syndrome

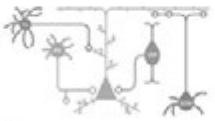
10-20% genetic cause remains unknown
Familial recurrence- 7% of the cases, paternal mosaicism

Not all patient with Dravet syndrome have a SCN1A variant

- Dravet syndrome is a clinical diagnosis.

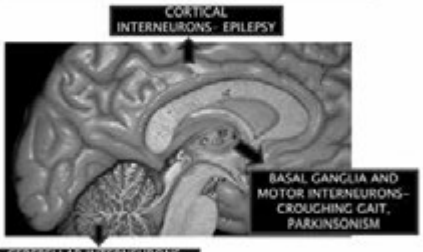
Dravet syndrome
Mechanisms

- Animal model: reduced sodium channel currents in GABAergic inhibitory interneurons but not in the excitatory pyramidal neurons;
- SCN1A mice- hyperactivity, stereotyped behavior, social deficits, cardiac arrhythmias, spatial memory impairment.

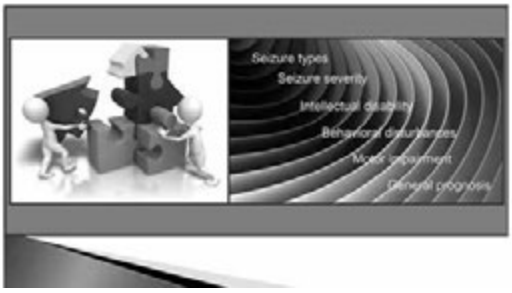


Yu FH et al., 2006

Dravet syndrome
Mechanisms- An interneuron disease



Dravet syndrome diagnosis as a progressive puzzle and spectrum



Dravet syndrome
Treatment

We must . . . feel a sense of therapeutic despair whenever a case of ordinary epilepsy appears for treatment. . . . The ingenuity of therapeutics has become bankrupt in the effort to find drug cures for epilepsy.

Mitchell SW A medical and surgical symposium: the medical treatment of epilepsy. *Ther Gaz.* 1912;36153- 157

Dravet syndrome
Treatment

The diagnosis is clinical- early diagnosis can be made by molecular approach

Algorithms- GTC seizures

1. Valproato(Depakote, Depakene)- even if the seizure had a focal component)
2. Clobazam (Frisium, Urbanil) (avoided in Germany)
3. Stiripentol (Diacomit)*- orphan drug- 2 RCT
4. Bromides (Germany, Japan)
5. Topiramato (Topamax)
6. Levetiracetam (Keppra)
7. Other benzodiazepines

Dravet syndrome
Treatment

The diagnosis is clinical- early diagnosis can be made by molecular approach

Algorithms- GTC seizures

1. Valproato(Depakote, Depakene)- even if the seizure had a focal component)
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Dravet syndrome
Treatment

The diagnosis is clinical- early diagnosis can be made by molecular approach

Algorithms

1. **Myoclonic seizures**
   - Valproate, benzodiazepines, levetiracetam
2. **Absences**
   - Valproate, benzodiazepines, ethosuximide
3. **Partial seizures**
   - Same treatment as for GTC seizures

Chiron et al., 2000; Thami et al., 2002; Striano et al., 2007

Dravet syndrome
BROMIDES

Bromides were used as hypno-inducer in asylums. Despite its unpleasant taste and considerable toxicity (therapeutic effect very close to the toxic dose) in the mid-1870s, about 2.5 tons of bromide were used annually at The National Hospital for the Relief and Cure of the Paralysed and the Epileptic in Queen Square, birthplace of the modern epileptology (Shorvon & Sander, 1996).

BROMIDES 1857

WILLIAM GOWERS (1845-1915)

Dravet syndrome
BROMIDES

DIBRO-BE
Mono
850mg tabletten

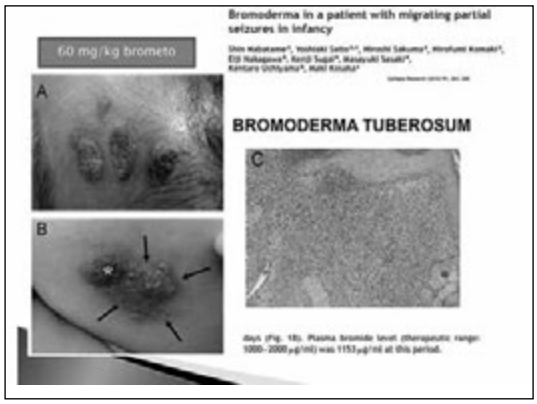
Kaliumbromid

60 tablets

DIBROPHARM GmbH Distribution & Co. KG
Gaisbuehlstrasse, 5a76532 Baden - Baden

Neuropediatrics 2012;43(1):17-21.
Bromide in patients with SCN1A-mutations manifesting as Dravet syndrome.
Lotte J, Haberlandt E, Neubauer B, Staudt M, Kluger GJ

- 32 patients with Dravet syndrome with SCN1A-mutations who received bromide;
- After 3 months of bromide treatment, 26 patients (81%) showed a relevant improvement with a reduction of seizure frequency by >50% (>75%) in 18 (12) patients (56 and 37%, respectively);
- After 12 months, we observed a reduction of >50% (>75%) in 15 (9) patients (47 and 28%, respectively);
- Long-term response was noted in 18 patients (56%);
- Adverse reactions were mainly mild or moderate leading to treatment termination in 5/32 patients; no aggravation was reported.



Dravet syndrome
Aggravation

- ❑ - Carbamazepina (Tegretol)
- ❑ - Fenitoína (Hidantal)
- ❑ - Lamotrigina (Lamictal)
- ❑ - Oxcarbazepina (Trileptal)
- ❑ - Vigabatrina (Sabril)

Dravet syndrome
Non DrugTreatment

- ❑Ketogenic diet
- ❑Stimulation of vagus nerve

Dravet syndrome
Rescue medication

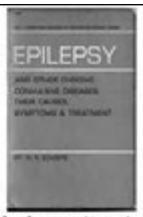
- ❑ Prolonged seizures or status epilepticus:
  - Early treatment of infectious diseases and hyperthermia, which are their triggering factors;
  - Benzodiazepines.

Dravet syndrome
Adjunctive treatment

- Photosensitivity
  - Sunglasses
  - Avoid light stimulation (videogames, TV)
- Prevention of accidents related to seizures
  - Bath, swimming pools, falls, agitation, etc.
- Educational treatment and training measures

Treatment

WILLIAM GOWERS (1845-1915)



...Cannabis indica is sometimes, though not very frequently, useful. It is of small value as an adjunct to bromide, but is sometimes of considerable service given separately ... It is also capable of causing delirium and sleep, first depression and then acceleration of the heart, and also dilates the pupil... The cerebral excitement is relatively more marked than in the case of belladonna...

Epilepsy and Other Chronic Convulsive Diseases: their Causes, Symptoms & Treatment, 1881 pp. 223-4

Cannabinoids- Medical marijuana

Gloss D, Vickrey B. Cochrane Database of Systematic Reviews. 2012; Issue 6.

Desperate parents turn to medical marijuana in last-ditch effort to improve their children's lives

- More specifically a specific component of marijuana known as cannabidiol (CBD). This component of the marijuana plant does not produce the psychoactivity that tetrahydrocannabinol (THC) does;
- Medical marijuana- High in CBD but low in THC.

Brief Communication

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter, Catherine Jacobson *

* Department of Neurology, Stanford University, USA

- Parents belonging to a Facebook group
- Diagnosis of epilepsy-use of cannabidiol-enriched cannabis;
- 13 Dravet syndrome; 4 Doose syndrome; 1 Lennox-Gastaut syndrome, 1 idiopathic epilepsy;
- 16/19 parents reported reduction in seizure frequency;
- 2(11%) seizure free; 8 (42%) > 80% seizure reduction; 6 (32%) reported 25-60% seizure reduction;
- Increased alertness; better mood; improved sleep;
- Side effects: drowsiness and fatigue.

FDA; open study Epidiolex®

A purified 98% oil-based CBD extract

Omri Devinsky

- Inclusion criteria
  - Intractable early onset epilepsies;
  - ≤ 3 AEDs (not including VNS and KD);
  - Non progressive disorders;
  - No significant laboratory abnormalities.
- Study design
  - 4 weeks baseline seizure diary;
  - Dose 5 mg/kg/day. Increases 2-5 mg/kg/day, intervals 1-2 weeks until tolerance or up to 25 mg/kg/day;
  - Laboratory tests and AED levels 4, 8 and 12 weeks.

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.

Lancet Neurol 2016; 15(3): 270-8

- 214 patients were enrolled;
- 162 (76%) patients who had at least 12 weeks of follow-up were included in the safety and tolerability analysis;
- 137 (64%) patients were included in the efficacy analysis;
- In the safety group:
  - 33 (20%) patients had Dravet syndrome
  - 31 (19%) patients had Lennox-Gastaut syndrome.
  - The remaining patients had intractable epilepsies of different causes and type.
- The median monthly frequency of motor seizures was 30.0 (IQR 11.0-96.0) at baseline and 15.8 (5.6-57.6) over the 12 week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR 0-64.7).
- 12 weeks; 9% of total and 16% of those with DS seizure free.

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.

Lancet Neurol 2016; 15(3): 270-8

- Adverse events were reported in 128 (79%) of the 162 patients within the safety group;
- Adverse events reported in more than 10% of patients were:
  - somnolence- 25%
  - decreased appetite- 19%
  - diarrhoea- 19%
  - fatigue- 13%
  - convulsion- 11%
- Five (3%) patients discontinued treatment because of an adverse event;
- Serious adverse events were reported in 48 (30%) patients, including one death- a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]).

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.

Lancet Neurol 2016; 15(3): 270-8

- Expectations fuelled by the media; a timely study;
- A third of the patients had increased seizure frequency and another third ≤ 50% reduction;
- Adverse effects in 79% (serious in 30%);
- Similar or worse than other AEDs.

Bauer & Sander, May 2016

- CBD is a potent inhibitor of CYP3A4 and CYP2C19;
- Increased serum level of CLB- 10% - 40%;
- Increases the levels of N-desmethyl clobazam.

Mandelbaum, May 2016

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.
Lancet Neurol 2016; 15(3): 270-8

Bertold Brecht

"My intention is not to prove I was right but to find out whether I was right"..."

Galileo Galilei

Mandelbaum, May 2016

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.
Lancet Neurol 2016; 15(3): 270-8

Randomized, double blind, placebo controlled trials

We endorse Brecht's and Thomas Huxley's views: "the great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact." And we welcome the facts as they come—whether they are good, bad, or ugly.

Orrin Devinsky

Devinsky, Marsh and Friedman, May 2016

Where are we now with cannabinoids?

Neither miracle, nor fairy tail

- Anecdotal and open label evidence of possible benefit- short term tolerability evident;
- Need for further trial data:
  - Efficacy
  - Safety
- Long term safety/tolerability & sustained efficacy requires evaluation- pure CBD vs? THC?

Dravet syndrome
When to think about Dravet syndrome

- Any child < 1 year of age with prolonged febrile seizures, unexplained seizures with or without febrile susceptibility;
- Any child with early onset epilepsy and development regression;
- FS may be misleading, but there is a higher incidence of FS in families of Dravet syndrome children.


Thank you for your attention!

Laura Guilhoto (Brazil)

LENNOX-GASTAUT SYNDROME

Helen Cross (UK)

IMPROVING OUTCOMES IN EARLY ONSET EPILEPSY

LASSE
LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY

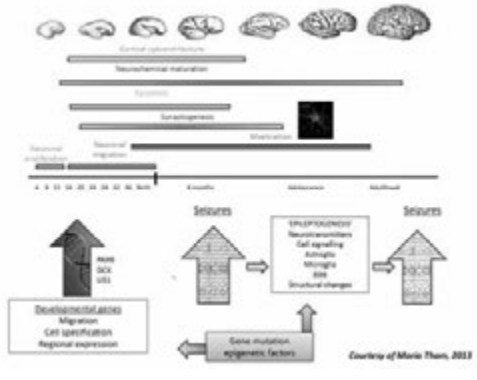
Improving outcomes in early onset epilepsies

J Helen Cross

UCL-Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London & Young Epilepsy, Lingfield, UK

Is there a problem -can we make a difference?

- The prognosis of early onset epilepsies
- What is the role of aetiology vs epilepsy?
- Evidence from standard treatments
- New ways of thinking?



Recurrent seizures in the first year - outcome

	Chevrie&Aicardi, 1977, 1979, 1979 n=334	Cavazzuti et al, 1984 n=484*	Cocchiarella et al, 1994 n=133	Battaglia et al, 1999 n=150
Population	Hospital / Clinic 1963-1974	Hospital / Clinic 1971-1976	Hospital / Clinic 1979-1987	Hospital / Clinic
Design	retrospective	"prospective"	"prospective"	"prospective"
Follow up	1-24years (median 3.4y)	5- >10y	3->7y	4-10y
Persisting Epilepsy	56 % (cumulative % a years)	55%	44%	46%
Developmental Delay Severe-moderate	55%	40%	54% (IQ<70)	58% (IQ < 70)
Symptomatic cases	60%	44%	43%	66%
Mortality	12%	4%	11%	10%

* Febrile convulsions and some symptomatic seizures included

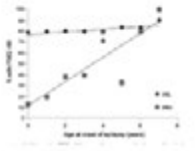
Outcome of early onset epilepsy

Longitudinal study of a cohort with epilepsy onset < 3 years

TABLE 1. Mean Vineland Scores at Initial Study Entry and Over Time for the Full Study Sample (n = 172)

Domain	Baseline, Mean (SD)	1 Year, Mean (SD)	2 Years, Mean (SD)	3 Years, Mean (SD)	*P* Value for Trend
Composite	92.0 (11.5)	86.6 (12.0)	82.9 (12.4)	81.5 (13.7)	<.0001
Communication	93.6 (13.3)	90.4 (13.0)	87.2 (12.0)	85.2 (13.3)	.0003
Daily Living	89.6 (11.4)	79.0 (11.4)	76.5 (12.6)	74.4 (13.4)	<.0001
Motor	96.6 (13.7)	90.0 (12.2)	85.1 (12.5)	86.9 (13.3)	<.0001
Social	96.1 (13.7)	93.7 (13.6)	90.0 (12.2)	88.8 (13.4)	.0013

Berg et al Pediatrics 2004;114: 645-650



Longitudinal study to 8-9 years following seizure onset <8 years

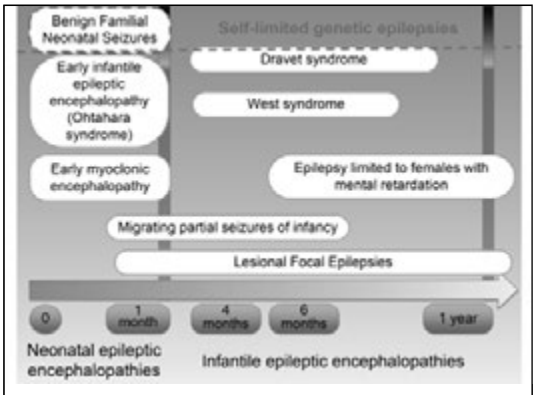
Dichotomous IQ indicator strongly correlated with age at onset in pharmacoresistant group (p<0.0001), not pharmacoresponsive group (p=0.61)

Berg et al Neurology 2012;79:1384-1391

'Epileptic Encephalopathy'

'the epileptic activity itself contributes to cognitive and behavioral impairments beyond that expected from the underlying pathology alone (e.g. cortical malformation)' Berg et al 2010

Reversible

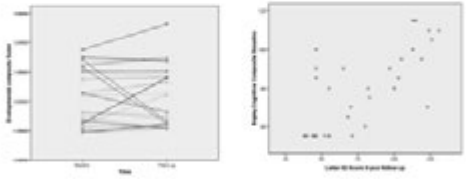


Prevalence of syndromes

N London Epilepsy in Infancy Study N= 57
Incidence ≤ 2 years 53.6/100,000

Eltze et al Epilepsia 2013;54:437-445

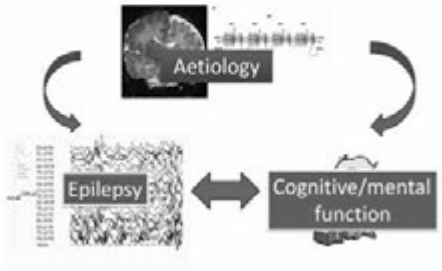
Seizure onset under 2 years; natural history?

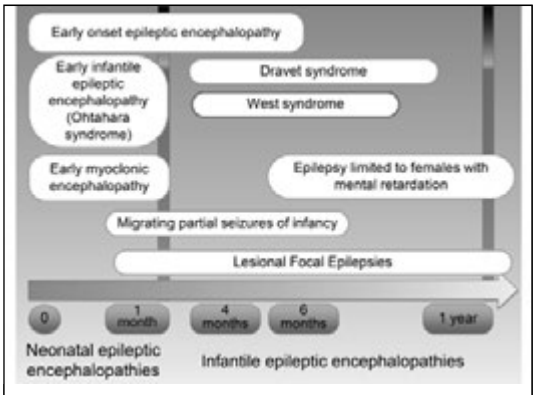


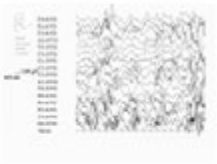
12 months **3 years**

Eltze et al Epilepsia 2013;54:437-445
O'Reilly et al submitted

Can we influence outcome?







'West Syndrome'

- *Infantile Spasms*
- *Hypsarrhythmia*
- *Developmental plateau*

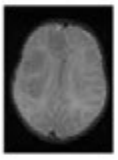
85% developmental compromise, 60% ongoing seizures

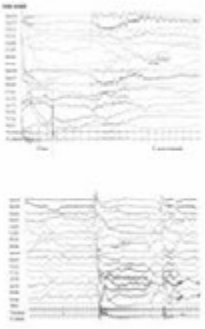
Treatment choices in Infantile Spasms

- **Vigabatrin – TS** *Sabril Investigator group 1996*
- **Steroids > vigabatrin** *UKISS Lux et al 2004*
- **Vigabatrin + steroids> steroids alone** *ICISS O'Callaghan et al 2011*

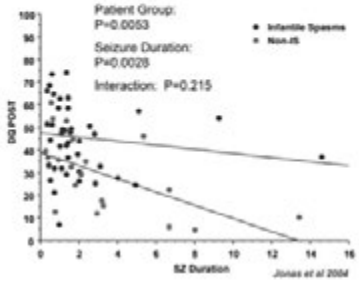
Potential to influence outcome

- **Impact of aetiology**
  - **Cryptogenic >symptomatic** *Riikonen et al 2001*
  - **ARX mutations impact on autistic outcome** *Turner et al 2002*
- **Impact of treatment**
  - **Short treatment lag** *Kivity et al 2004, O'Callaghan et al 2011*
  - **Prompt response to treatment**
    - **TS** *(Lombroso et al 2000),* **Trisomy 21** *Eisermann et al 2003*
  - **Short duration of hypsarrythmia** *Hrase-Primec et al 2006*





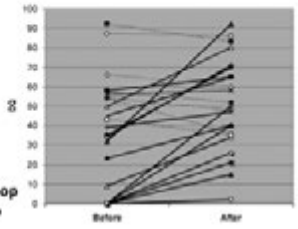
Longer seizure duration's associated with lower Vineland DQ



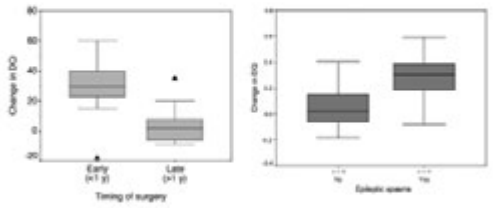
Developmental progress after early surgery

Loddenkemper, T. et al. Pediatrics 2007;119:930-935

- 24/50 children <3 yrs
- 2 yr followup
  - Hemispherectomy 14
  - Focal resection 10
- Median DQ preop 3m (mean 5.83)
- Median DQ post op 9m (mean 11.94)
- Developmental status preop predicted function postop



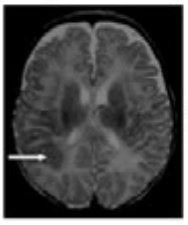
Developmental progress after early surgery

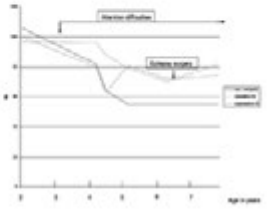


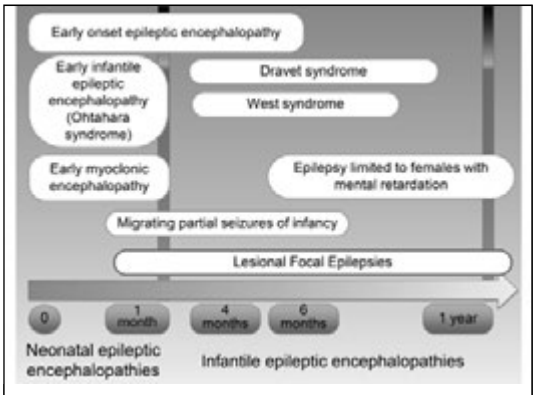
Loddenkemper, T. et al. Pediatrics 2007;119:930-935

Should we wait?

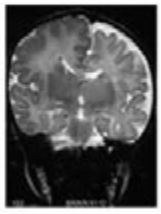
6 year old boy, presentation with infantile spasms at 4m; control with vigabatrin
Subsequent focal seizures, variable periods of control







Hemimegalancephaly

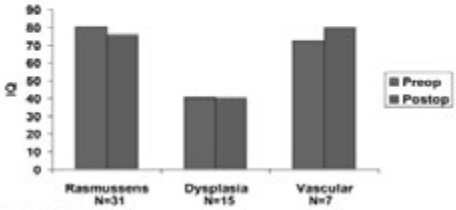


Pre-op

Post-op

Cognitive outcome following hemispherectomy

53/79 children, hemispherectomy for epilepsy The Johns Hopkins Hospital 1968-1997, mean age 7.2 yrs, mean f/up 5.4 yrs, 65% seizure free



Pulsifer et al Epilepsia 2004;45:243-254

Extratemporal epilepsy

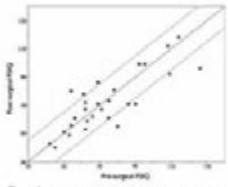


Figure 1.

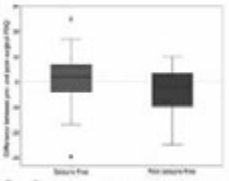
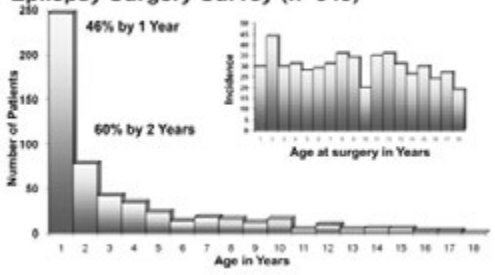


Figure 2.

D'Argenzio et al Epilepsia 2011;52:1966-1972

Age at Seizure Onset ILAE 2004 Paediatric Epilepsy Surgery Survey (n=543)



Harvey et al., Epilepsia 2008;49:146-155

preoperative cognitive level

Freitag & Tuxhorn Epilepsia 2005;46: 561-7

50 consecutive children age 3-7 yrs

preoperative IQ<70 70%

85-115 16%

Postoperatively

- Short term (6-12m) : **82% showed stable developmental velocity ; 3 gains >15, 3 not assessable to assessable**
- Longer term (2-3 yrs): **73% showed stable developmental velocity; 8 gains >15**
- **Gains only seen where SF, ass with shorter duration epilepsy**

Cognitive outcome after temporal lobe surgery in childhood

IQ change across the post-op period

- Variability in IQ changes until 4-6 years post-op
- IQ improvements detectable >6 years post-op

63% 26% 40% 29% 58%

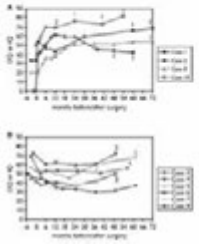
>1-2 years >2-4 years >4-6 years >6-8 years 8+ years

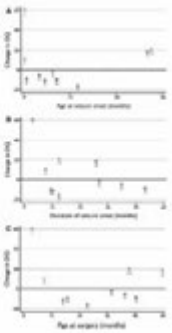
Time after surgery (years)

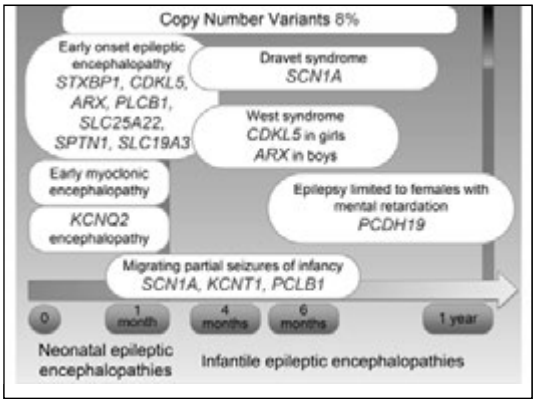
Skirrow et al Neurology 2011;76:1330-1337

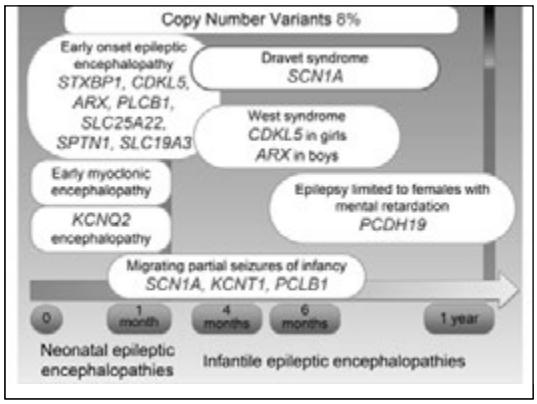
Developmental progress after early surgery

Roulet –Perez et al Epilepsia 2010;51:1266-1276

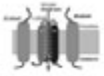








Dravet syndrome



- 1% of the epilepsy population
- Normal early development/imaging
- Febrile and afebrile general and unilateral prolonged clonic or tonic-clonic s. 1st year of life (100%)
- Later appearance of myoclonus (80%), atypical absences (40%), focal seizures (46%)
- Developmental delay progressively apparent
- All seizure types resistant
- Interictal EEG: normal initially, generalized discharges
- Prognosis always unfavorable, for seizures, cognitive development, high mortality rates (up to 15%)
- *>80% mutation SCN1A*

Dravet Syndrome
Long term course

- **Intellectual disability**
  - **Severe 50%, moderate 25%, mild 25%**
- **Most dependent and cannot live independently**
- **Risk of death**
  - **15% by 20 years**
  - **SUDEP, status with multiorgan failure**

Dravet syndrome
Optimised treatment

Effective anti-epileptic treatment

- Valproate
- Clobazam

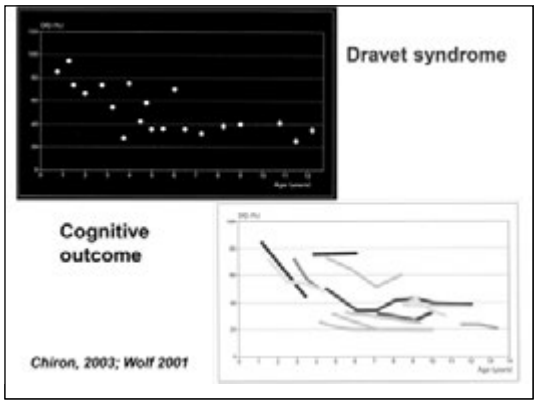
} +/- Stiripentol

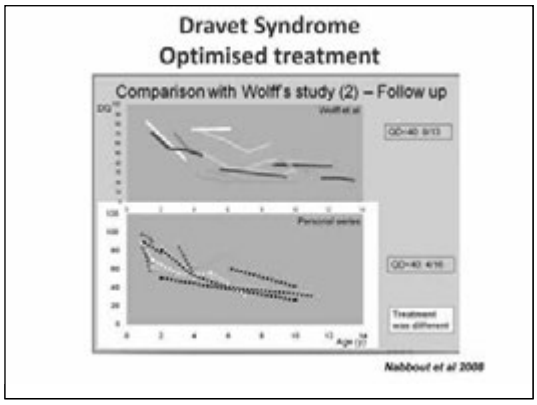
- Topiramate
- Levetiracetam
- Ketogenic diet

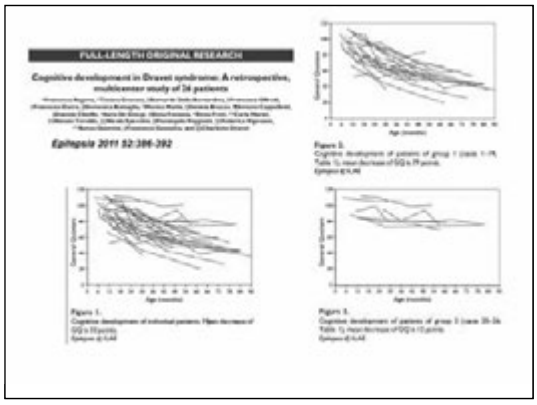
Drugs on the horizon
- Cannabidiol
- Fenfluramine

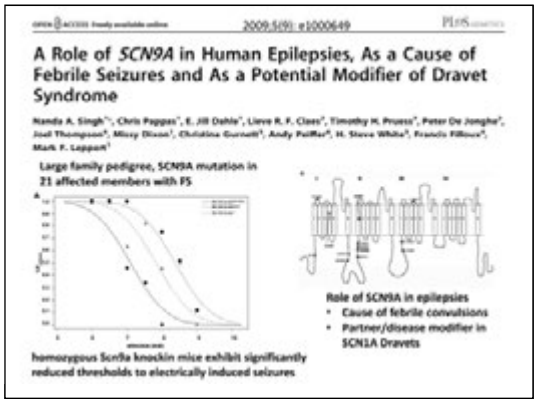
Avoidance of
- Carbamazepine, phenytoin
- Lamotrigine - *Guerrini et al 1996*

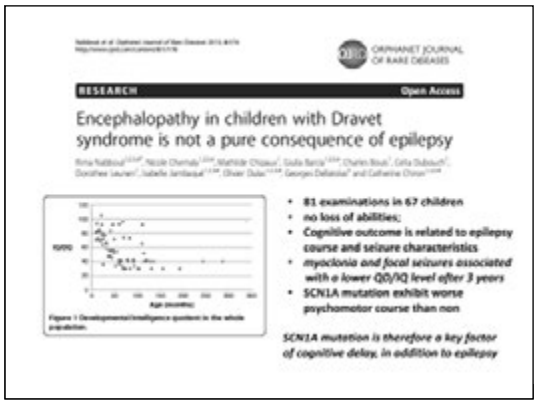
Active treatment of fever
Prompt individualised treatment of prolonged seizures


Dravet syndrome
Cognitive outcome
Chiron, 2003; Wolf 2001


Dravet Syndrome
Optimised treatment
Comparison with Wolff's study (2) – Follow up
Wolff et al
Personal series
QD<40 9/13
QD<40 4/16
Treatment was different
Age (Y)
Nabbout et al 2008


FULL-LENGTH ORIGINAL RESEARCH
Epilepsia 2011 52:380-392


2009 5(9): e1000649
A Role of SCN9A in Human Epilepsies, As a Cause of Febrile Seizures and As a Potential Modifier of Dravet Syndrome
Large family pedigree, SCN9A mutation in 21 affected members with FS
Role of SCN9A in epilepsies
Cause of febrile convulsions
Partner/disease modifier in SCN1A Dravets
homozygous Scn9a knockin mice exhibit significantly reduced thresholds to electrically induced seizures



ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy

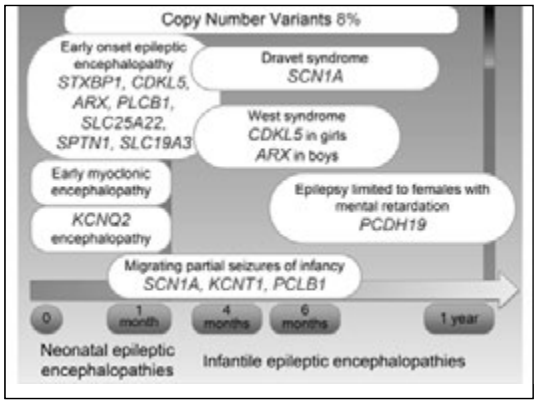
- 81 examinations in 67 children
- no loss of abilities;
- Cognitive outcome is related to epilepsy course and seizure characteristics
- *myoclonia and focal seizures associated with a lower QD/IQ level after 3 years*
- SCN1A mutation exhibit worse psychomotor course than non

SCN1A mutation is therefore a key factor of cognitive delay, in addition to epilepsy

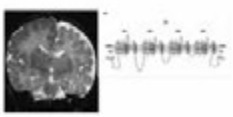
Dravet syndrome– epileptic encephalopathy?

Catarino et al Brain 2011;134(Pt 10):2982-3010

- **22 adult cases – oldest 60 years**
- **Neurological deterioration occurred throughout life**
- **7 had drug changes following diagnosis**
- **3 meaningful follow-up – 2 improvement in cognition, one spontaneous language**
- **PM no consistent cerebral structural changes, cell loss or neurodegeneration**



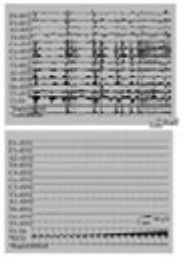
Targeting aetiology?



Metabolic epilepsies

Pyridoxine-dependent epilepsy: Outcome

- Life-long treatment
  - 15 mg/kg/day (up to 500mg daily)
  - Learning difficulties (particularly language)
- Delayed treatment (months/years)
  - Severe motor disorder, learning difficulties, sensory impairment
- Treatment in utero may lead to improved cognitive outcome *Bok et al 2009*



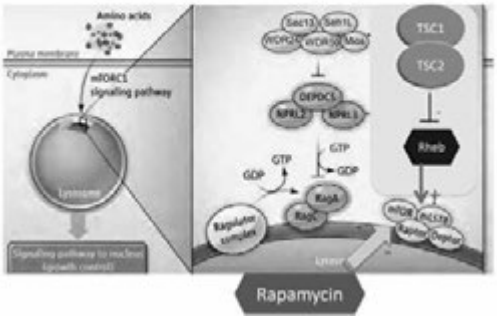
Glut 1 Deficiency

- Glut 1; 1 of 9 glucose transporters. Coded by SLC2A1
- Wide range clinical presentation – early onset absence epilepsy to later onset movement disorder
- Treatment with ketogenic diet
  - 86% epilepsy respond to KD
  - Less frequent for movement disorder

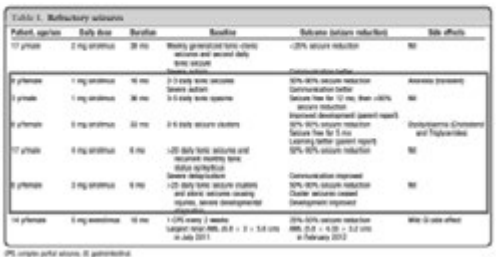
Leen et al Brain 2010;133:655-70

- Early diagnosis and intiation of KD may improve outcome *Ramm-Pettersen et al Dev Med Child Neurol 2013;55:440-447*

mTOR inhibitors effective in epilepsy?

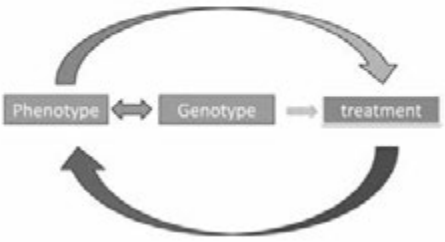


mToR inhibitors & epilepsy in Tuberous Sclerosis

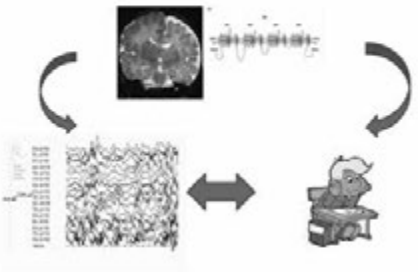


Cardamone et al J Peds 2014; 164(5):1195-200

Targeted treatments
Closing the loop



Can we influence outcome?



Developmental and/or Epileptic Encephalopathy

- For many encephalopathies, there is a developmental component *independent* of epileptic encephalopathy
- Developmental delay may precede seizure onset
- Co-morbidities eg. cerebral palsy, autism spectrum disorder, ID
- Outcome poor even though seizures stop
  eg. KCNQ2, STXBP1 encephalopathies

Scheffer et al (ILAE) Epilepsia in press

Developmental and/or *Epileptic* Encephalopathy

- Developmental **encephalopathy**
  - *May begin in utero*
  - *Post birth*
- Epileptic **encephalopathy**
  - *Can occur at any age, any syndrome*
  - *May be remediable component – right vs wrong AED*
- Move towards *GENE* encephalopathy
  - *eg. CDKL5 encephalopathy, SCN2A encephalopathy*

Scheffer et al (ILAE) Epilepsia in press

Summary

- Early onset epilepsy poor prognosis for long term seizure remission & neurodevelopmental outcome
- Major impact from aetiology, compounded by seizures
- Accurate diagnosis, with appropriate intervention likely to have greatest impact on outcome
- Impact on neurodevelopment from early surgery in appropriately selected candidates
- New ways of thinking with regard to treatment, related to aetiology, are likely to have further impact in other epilepsies

A problem can never be solved on the same level of thinking that identified it....

Einstein

Jaime Carrizosa (Colombia)

"DR. JECKYLL AND MR HYDE": ANTAGONISM IN FEBRILE SEIZURES

"Dr. Jeckyll and Mr Hyde":
antagonism in febrile seizures

Jaime Carrizosa Moog

Neurólogo Infantil
Universidad de Antioquia – Medellín
Colombia

LASSE 2017

Dr. Jekyl - "Benign" Febrile Seizures

CLASSIFICATION FEBRILE SEIZURES

Table 1. Classification of Febrile Seizures

Simple (all of the following)
Duration of less than 15 minutes
Generalized
No previous neurologic problems
Occur once in 24 hours
Complex (any of the following)
Duration of more than 15 minutes
Focal
Recurs within 24 hours

Adapted with permission from Miller JS. Evaluation and treatment of the child with febrile seizure. Am Fam Physician. 2005;72(10):1965, with additional information from reference 1.

RISK FACTORS FOR FS

- Discharge from neonatal unit after 28 days
- Day care attendance
- Viral infections: HHV 6
- Vaccinations: MMR,DPT
- Child´s temperature

RISK FACTORS FOR FS

- Temperature rise
- Fe or Zn deficiency
- Genetics
  - IL 6 gene
  - GABA A receptor Ɣ subunit mutations

Pediatric Neurology 2012; 46:36-38.
Pediatric Neurology 2014; 50:353 – 356.
Am Fam Phys 2012; 85:149 – 153.

LP – AA Pediatrics

- Children 6 – 12 months with incomplete immunization for H. inflenzae type b and S. pneumoniae.
- Children pretreated with antibiotics
- Meningeal signs or other findings indicating intracraneal infection.

MENINGITIS ??

704 SIMPLE FEBRILE SEIZURES – 0 CASES

Pediatrics. 2009;123(1):6-12

526 COMPLEX FEBRILE SEIZURES – 3 CASES

Pediatrics. 2010;126(1):62-69

136 COMPLEX FEBRILE SEIZURES – 1 CASE

West J Emerg Med; 14(3): 206 - 2011

Electroencephalography in SFS

"Electroencephalography has not been shown to predict recurrence of febrile seizures or future epilepsy in patients with simple febrile seizures."

AAP, Pediatrics. 2011;127(2):389-394
AAP, Pediatrics. 1996;97(5):769-772
Arch Dis Child. 2004;89(3):290

Electroencephalography in CFS

Clinical and EEG risk factors for subsequent epilepsy in patients with complex febrile seizures

Hunmin Kim*, Sung Hwan Byun*, Jin Soo Kim*, Byung Chan Lim*, Jong-Hee Chae*,**, Jieun Choi*,**, Ki Joong Kim*,**, Yong Seung Hwang*,**, Hee Hwang*,**

Original article

Risk for developing epilepsy and epileptiform discharges on EEG in patients with febrile seizures

Suet Byol Wa*, Jun Hwa Lee*, Yong Ju Lee*, Tae-Jung Sung*, Kon Hee Lee*, Sung Koo Kim*,**

Electroencephalography in CFS

The Odds ratio and 95% confidence interval of significant factors were; prolonged seizure (3.04, 1.11—8.32), multiple seizures (3.63, 1.12—11.8) and epileptiform discharges (5.15, 1.84—14.5).

The odds ratio of subsequent epilepsy according to the presence of epileptiform discharges in patients with multiple seizures was 4.98 (95% confidence interval, 2.04—12.15)

and 10.9 (95% confidence interval, 3.4—34.5) for patients with prolonged seizure.

However, the presence of epileptiform discharges in patients with complex febrile seizures due to focal or lateralized seizures was not significantly different between the two groups ($p = 0.151$).

Routine neuroimaging

"Routine neuroimaging after simple febrile seizures is discouraged; it also has no additional diagnostic or prognostic value, and in the case of computed tomography, carries a small increased risk of cancer.

Even after first complex febrile seizures, neuroimaging is not likely to be helpful in well-appearing children."

Routine neuroimaging

"In a review of 71 patients with first complex seizures, none had intracranial findings necessitating acute medical or surgical intervention."

Emerg Med Clin North Am. 2011;29(1):83-93
Pediatrics. 2006;117(2):528-530
Pediatrics. 2006;117(2):304-308

Treatment (acute)

"A Cochrane review found lorazepam to be as effective as diazepam, with fewer adverse effects and less need for additional antiepileptic agents. The same study found buccal midazolam to be superior to rectal diazepam when intravenous administration is not possible."

Prognosis

"Physicians can play a vital role in reassuring families about the good prognosis after a febrile seizure.

Parents should be reassured that children without underlying developmental problems do not seem to have lasting neurologic effects from febrile seizures."

Prognosis

"A population-based study in the United Kingdom that included 381 children with febrile seizures reported that those with febrile seizures perform as well as others academically, intellectually, and behaviorally when assessed at 10 years of age.

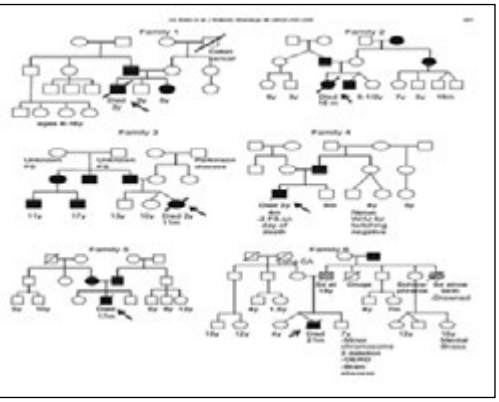
Parents should be told that mortality from febrile seizures is very rare—so rare that it is difficult to assess accurately."

Pediatric Neurology

Original Article

Inheritance of Febrile Seizures in Sudden Unexplained Death in Toddlers

Ingrid A. Holm MD, MPH[a,*], Annapurna Poduri MD, MPH[b], Laura Crandall PT, MA[c], Elisabeth Haas MPH[d], Marjorie R. Grafe MD, PhD[e], Hannah C. Kinney MD[f], Henry F. Krous MD[g]



Death in children with febrile seizures: a population-based cohort study

Findings We identified 8172 children who died, including 232 deaths in 55 215 children with a history of febrile seizures. The mortality rate ratio was 80% higher during the first year (adjusted mortality rate ratio 1·80 [95% CI 1·31–2·48]) and 90% higher during the second year (1·89 [1·27–2·70]) after the first febrile seizure; thereafter it was close to that noted for the general population. 132 of 100 000 children (95% CI 102–163) died within 2 years of a febrile seizure compared with 67 (57–76) deaths per 100 000 children without a history of this disorder. In the nested case-control study, children with simple (<15 min and no recurrence within 24 h) febrile seizure had a mortality rate similar to that of the background population (adjusted mortality rate ratio 1·08 [95% CI 0·72–1·64]), whereas mortality was increased for those with complex (>15 min or recurrence within 24 h) febrile seizures (1·99 [1·24–3·21]). This finding was partly explained by pre-existing neurological abnormalities and subsequent epilepsy.

Interpretation Long-term mortality is not increased in children with febrile seizures, but there seems to be a small excess mortality during the 2 years after complex febrile seizures. Parents should be reassured that death after febrile seizures is very rare, even in high-risk children.

Lancet 2008; 372:457 - 463

Prognosis

"Parents should be warned that febrile seizures reoccur frequently. One cohort study found that 32 percent of children presenting with an initial febrile seizure later had additional febrile seizures, 75 percent of which occurred within one year."

N Engl J Med. 1998;338(24):1723-1728
Lancet. 2008;372(9637):457-463
Arch Pediatr Adolesc Med. 1997;151(4):371-378

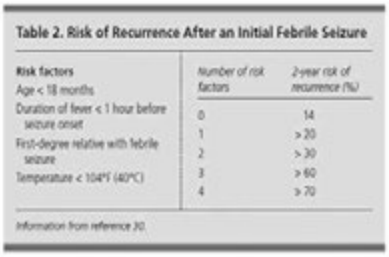


Table 2. Risk of Recurrence After an Initial Febrile Seizure

Risk factors	Number of risk factors	2-year risk of recurrence (%)
Age < 18 months	0	14
Duration of fever < 1 hour before seizure onset	1	> 20
First-degree relative with febrile seizure	2	> 30
Temperature < 104°F (40°C)	3	> 60
	4	> 70

Information from reference 30.

Epilepsy development after FS??

"A Danish cohort study of 1.54 million persons found that the long-term risk of epilepsy is increased 5.43-fold after febrile seizures, but did not distinguish between simple and complex febrile seizures."

Am J Epidemiol. 2007;165(8):911-918.

Epilepsy development after FS??

"Parents can be reassured that the risk of epilepsy after an initial simple febrile seizure is approximately 2 percent.

In one study, children with one complex seizure feature had a risk of 6 to 8 percent. In those with two or three complex features, the risk was 17 to 22 percent and 49 percent, respectively."

BMJ. 1991;303(6814):1373-1376. *N Engl J Med.* 1987;316(9):493-498. *J Child Neurol.* 2002;17(suppl 1):S44-S52.

Table 3. Risk Factors for Future Epilepsy After a Febrile Seizure

Complex febrile seizure*
Family history of epilepsy
Fever duration < 1 hour before seizure onset
Neurodevelopmental abnormality (e.g., cerebral palsy, hydrocephalus)

*—Febrile seizures with multiple complex features are a possible risk factor.

Adapted with permission from Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. 2002;17(suppl 1):S44–S52.

TABLE 1. Risk Factors for Developing Epilepsy After Febrile Seizures

Risk Factors
"Complex" febrile seizures—prolonged, partial or repetitive during a single febrile illness
Family history of nonfebrile seizures
History of cerebral palsy
Low Apgar scores at 5 minutes
Abnormal EEG
Remote symptomatic etiology

Epilepsy Currents, Vol. 13 (3)2013:143–145

RISK OF AFEBRILE SEIZURES AFTER FS

STUDY	No PATIENTS FS	FOLLOW UP TIME YEARS	% AFEBRILE SEIZURES
Anneggers, USA	687	25	7%
Danemark	?	23	5,43%
Nellingen	?	22	9,7%
FEBSTAT	199	4	11% (22/199)
DUKE	23	7	30%
Columbia	157	3	5,7%

Epilepsy Currents, Vol. 13 (3)2013:143–145

Pediatric Neurology

Original Article

Increased Association Between Febrile Convulsion and Allergic Rhinitis in Children: A Nationwide Population-Based Retrospective Cohort Study

Wen-Ya Lin MD[a], Chih-Hsin Muo MS[b,*], Yi-Chia Ko MD[c], Fung-Chang Sung PhD[d], Chia-Hung Kao MD[e,f,g]

Pediatric Neurology

Original Article

Risk of Subsequent Asthma in Children With Febrile Seizures: A Nationwide Population-Based Retrospective Cohort Study

Wen-Ya Lin MD[a], Chih-Hsin Muo MSc[b,c], Yi-Chia Ko MD[c], Fung-Chang Sung PhD[d], Chia-Hung Kao MD[e,f,g,*]

Chronic / intermitent treatment ??

"Continuous use of phenobarbital, primidone, and valproic acid has proved effective in reducing recurrence of simple febrile seizures.

However, these agents are not recommended because of associated adverse effects, the burden of long-term compliance, and a lack of data showing a reduced risk of future epilepsy with prevention of recurrent simple febrile seizures."

Chronic / intermitent treatment ??

"Intermittent use of antipyretics or anticonvulsants at the onset of fever is not recommended.

Although intermittent use of oral diazepam at the onset of fever is effective at reducing recurrence of simple febrile seizures, the AAP does not recommend it because of potential adverse effects and because many recurrent febrile seizures occur before recognition of fever."

Chronic /intermitent treatment ??

"If parental anxiety is high, oral diazepam given at the onset of a child's fever may be considered.

Additionally, rectal administration of diazepam for abortive use at home may be considered in those with an initial prolonged febrile seizure and in those at highest risk of recurrence."

Pediatrics. 2008;121(6):1281-1286. *Arch Pediatr Adolesc Med.* 2009;163(9):799-804. *J Paediatr Neurol.* 2004;8(3):131-134. *N Engl J Med.* 1993;329(2):79-84. N Engl J Med 1990;322(6):364–9. Brain & Development 32 (2010) 42–50

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References	Comments
Routine laboratory tests, electroencephalography, and neuroimaging are not recommended in patients with simple febrile seizures.	C	17, 19–21, 24, 25	Consensus guideline and retrospective cohort studies
Parents should be reassured after a simple febrile seizure that there is no negative impact on intellect or behavior, and no increased risk of death.	B	1, 28, 29	Consensus guideline and prospective cohort studies
Use of long-term continuous or intermittent antiepileptic medication after a first simple febrile seizure is not recommended because of potential adverse effects.	B	1, 32, 33	Consensus guideline and randomized controlled trials
Use of antipyretic agents at the onset of fever is not effective at reducing simple febrile seizure recurrence.	A	1, 31	Consensus guideline and randomized controlled trial

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SOMF evidence rating system, go to http://www.aafp.org/afpsort.xml.

Mr Hyde – "Worrying" Febrile Seizures

FULL-LENGTH ORIGINAL RESEARCH

Design and phenomenology of the FEBSTAT study

*[Dale C. Hesdorffer,][‡][,¶¶]Shlomo Shinnar, #Darrell V. Lewis, **Solomon L. Moshé, ††Douglas R. Nordli Jr, ‡‡‡,¶¶John M. Pellock, §§James MacFall, ‖Ruth C. Shinnar, ‡David Masur, ***L. Matthew Frank, ††Leon G. Epstein, ^Claire Litherland, ‡‡‡‡Syndi Seinfeld, †††Jacqueline A. Bello, ‡‡‡Stephen Chan, §§§Emilia Bagiella, ¶¶¶Shumei Sun, and the FEBSTAT study team'

PURPOSE:

The FEBSTAT study was designed to prospectively examine the association between prolonged febrile seizures and development of HS and associated temporal lobe epilepsy

FEBSTAT Study

METHODS:

- prospective,multicenter study
- age 1 month to 6 years of age
- febrile seizure lasting 30 min or longer
- at baseline: MRI study and EEG recording within 72 h of FSE
- detailed history and neurologic examination
- baseline development and behavior are assessed at 1 month.
- baseline assessment is repeated at 1 and 5 years
- assesment at the development of epilepsy and 1 year after that
- telephone calls every 3 months document additional seizures

FEBSTAT Study

METHODS:

"Control" groups consisting of children with a first febrile seizure ascertained at Columbia University and with almost identical baseline and 1-year follow-up examinations and a pilot cohort of FSE from Duke University.

FEBSTAT Study

KEY FINDINGS

Number	199
Median age	16 months
Continuos seizures	57,3%
Intermitent seizures	31,2%
Partial seizures	2%
Secondarly generalized	65,8%
GTCS	98%
Normal development	86,4%
Prior febrile seizures	20%
Unrecognized FCSE	1/3

FEBSTAT Study

CONTROL GROUPS

Duke: 23 patients, mean age 18 months, mean duration FCSE 90 minutes

Columbia: 159 patients, SFS 64,2%, CFS 26,4%, FCSE 9,4% (14 months, 43 minutes)

FEBSTAT - **Risk Factors for Febrile Status Epilepticus: A Case-Control Study** *J Pediatr.* 2013 October ; 163(4): 1147–51

	FSE	SFS	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age < 18 m	107	40	2,7(1,6-4,4)	2,8(1,47-5,43)
Familial History FS	42	20	1,3(0,7-2,4)	3,0(1,28-6,88)
Female	87	43	1,5(0,9-2,4)	2,2(1,14-4,43)
Abn. MRI	21	3	4,6(1,30-16,0)	4,6(1,17-18,39)
T < 104 F	136	57	3,4(1,9-5,8)	3,7(1,80-7,50)
Fever 1 – 24 Hs	139	53	2,2(1,2-4,2)	2,4(1,10-5,33)

FEBSTAT - **Cerebrospinal Fluid Findings in Children with Fever-Associated Status Epilepticus** - *J Pediatr. 2012 December ; 161(6): 1169–1171*

Prospective multicenter study of 200 patients with fever-associated status epilepticus (FSE) patients of whom 136 had nontraumatic lumbar punctures confirms that:

- FSE rarely causes cerebrospinal fluid (CSF) pleocytosis.
- CSF glucose and protein were unremarkable.
- Temperature, age, seizure focality, and seizure duration did not affect results.
- CSF pleocytosis should not be attributed to FSE.

FEBSTAT - **Acute EEG findings in children with febrile status epilepticus** - *Neurology 2012;79:2180–2186*

Table 2 Frequency of EEG abnormalities in the FEBSTAT cohort

	No.	%
Overall	90	45.2
Nonepileptiform	85	42.7
Slowing	58	29.1
Focal	47	23.6
Temporal	45	22.6
Diffuse	22	11.1
Focal attenuation	25	12.6
Epileptiform		
Focal spikes	13	6.5
Temporal	6	3.0
Generalized spike and wave	1	0.5

Logistic regression for the association with focal slowing on EEG in 199 children with FSE

	Focal slowing (%)	No focal slowing (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Focal seizure	42 (89.4)	93 (61.2)	5.3 (2.0–14.2)	4.5 (1.6–12.6)
MRI any abnormity	17 (38.6)	29 (19.7)	2.6 (1.2–5.3)	-
T > 104 F	4 (8.5)	51 (33.6)	0.18 (0.06–0.5)	0.2 (0.06–0.69)

	No. with focal attenuation (%)	No. without focal attenuation (%)	Crude OR (95% CI)
Hippocampal T2 signal abnormality	5 (20.8)	12 (7.3)	3.3 (1.1–10.5)

Focal EEG slowing or attenuation are present in EEGs obtained within 72 hours of FSE in a substantial proportion of children and are highly associated with MRI evidence of acute hippocampal injury. These findings may be a sensitive and readily obtainable marker of acute injury associated with FSE.

FEBSTAT - **Human Herpesvirus 6 and 7 in Febrile Status Epilepticus Epilepsia.** *September 2012 ; 53(9): 1481–1488*

- HHV-6 or HHV-7 status in 169/199 patients (84.9%).
- HHV-6B viremia at baseline: 54 subjects (32.0%).
- No HHV-6A infections were identified.
- HHV-7 viremia at baseline: 12 (7.1%) subjects
- Co-infection at baseline: 2 HHV-6/HHV-7.
- There were no differences in age, characteristics of illness or fever, seizure phenomenology or the proportion of acute EEG or imaging abnormalities in children presenting with FSE with or without HHV infection.

FEBSTAT - **Human Herpesvirus 6 and 7 in Febrile Status Epilepticus**
Epilepsia. 2012 September ; 53(9): 1481–1488

Significance—HHV-6B infection is commonly associated with FSE. HHV-7 infection is less frequently associated with FSE. Together, they account for one third of FSE, a condition associated with an increased risk of both hippocampal injury and subsequent temporal lobe epilepsy.

FEBSTAT - **MRI abnormalities following febrile status epilepticus in children** ***Neurology 2012;79:871–877***

- 22/199 (11.5%) children had abnormal increased T2 signal in the hippocampus following FSE compared with none in the control group (*p* 0.0001).
- Developmental abnormalities of the hippocampus were more common in the FSE
- group (20, 10.5%) than in controls (2, 2.1%) (*p* 0.0097) with hippocampal malrotation being the most common (15 cases and 2 controls).
- Extrahippocampal imaging abnormalities were present in 15.7% of the FSE group and 15.6% of the controls.
- However, extrahippocampal imaging abnormalities of the temporal lobe were more common in the FSE group (7.9%) than in controls (1.0%) (*p* 0.015).

FEBSTAT - **Hippocampal Sclerosis After Febrile Status Epilepticus**
Ann Neurol. 2014 February ; 75(2): 178–185

Hippocampal T2 hyperintensity, maximum in Sommer's sector, occurred acutely after FSE in 22 of 226 children (9,7%) in association with increased volume.

Follow-up MRIs obtained on 14 of the 22 with acute T2 hyperintensity showed HS in 10 and reduced hippocampal volume in 12.

In contrast, follow-up of 116 children without acute hyperintensity showed abnormal T2 signal in only 1 (following another episode of FSE).

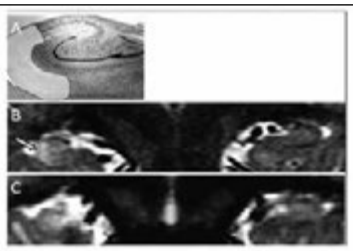


Figure 1.
Increased Hippocampal T2 Signal Following FSE. A) Nissl stain of hippocampal body outlining area of Sommer's sector (Courtesy O. Mathern). B) Acutely swollen and hyperintense right hippocampus of a 13 month old male 3 days after a 120 min long episode of FSE. Note the right hippocampus is larger and has increased T2 signal most prominent in Sommer's sector (Arrow). C) Follow up MRI 6 months later of same child showing the right hippocampus now smaller and the T2 signal increase is persistent but no longer maximum in Sommer's sector.

FEBSTAT - **Hippocampal Sclerosis After Febrile Status Epilepticus**
Ann Neurol. 2014 February ; 75(2): 178–185

Furthermore, compared to controls with simple febrile seizures, FSE subjects with normal acute MRIs had abnormally low right to left hippocampal volume ratios, smaller hippocampi initially and reduced hippocampal growth.

Interpretation—Hippocampal T2 hyperintensity after FSE represents acute injury often evolving to a radiological appearance of HS after one year. Furthermore, impaired growth of normal appearing hippocampi after FSE suggests subtle injury even in the absence of T2 hyperintensity. Longer follow-up is needed to determine the relationship of these findings to TLE.

Imaging-related biomarkers of human epileptogenesis

Hippocampal volumetry and T2 relaxometry are proposed as candidate biomarkers of epileptogenesis in temporal lobe epilepsy following febrile status epilepticus.

Biomark Med. 2011 October ; 5(5): 599–606

FEBSTAT - **Emergency Management of Febrile Status Epilepticus**
Epilepsia. 2014 March ; 55(3): 388–395

- 179 received at least one antiepileptic drug.
- More than one AED was required in 140 patients (70%).
- Median time from the seizure onset to first AED was 30 minutes.
- Mean seizure duration was 81 minutes for subjects given medication prior to ED and 95 minutes for those who did not (p=0.1).
- Median time from the first dose of AED to end of seizure was 38 minutes.
- Lorazepam/diazepam was suboptimal in 32/166 patients (19%).
- Reducing the time from seizure onset to AED initiation was significantly related to shorter seizure duration.
- FSE rarely stops spontaneously, is fairly resistant to medications and even with treatment persists for a significant period of time.

Prolonged febrile seizures, clinical characteristics, and acute management *Epilepsia, 54(6):1092–1098, 2013*

60 children, median age 18.3 months, median seizure duration of 35 min, 43 (71.7%) lasting 30 min, focal onset in 34 infants (57%)

33 (61%) were medically treated by the ambulance paramedic, of whom 15 (45%) responded to treatment. Twelve children with active seizures did not receive medications.

Even timely treatment does not prevent status epilepticus in the majority of cases.

ELSEVIER

The American Journal of Emergency Medicine

Brief Report

Lack of efficacy of phenytoin in children presenting with febrile status epilepticus☆

Salima Ismail MD[a], Arielle Lévy MD[b], Helena Tikkanen MB[a], Marcel Sévère MD[a], Franciscus Johannes Wolters MD[a], Lionel Carmant MD[a,*]

ELSEVIER

Pediatric Neurology

Original Article

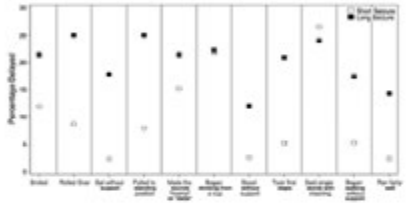
Midazolam Fails to Prevent Neurological Damage in Children With Convulsive Refractory Febrile Status Epilepticus

Hiroaki Nagase MD, PhD[1,*], Masahiro Nishiyama MD[1], Taku Nakagawa MD[1], Ryoko Fujita MD[1], Yohsuke Saji MD[2], Azusa Maruyama MD[1]

FEBSTAT- **Distribution Of Febrile Seizure Duration And Associations With Development** *Ann Neurol. 2011 July ; 70(1): 93–100*

- Long FS were significantly associated with developmental delay (p=0.010) and delays and younger age at first FS (p=0.048).
- Support to defining 10 minutes as the upper limit for a simple FS.

FEBSTAT- Distribution Of Febrile Seizure Duration And Associations With Development *Ann Neurol. 2011 July ; 70(1): 93–100*



Comparison of the percentage of children with delayed completion of developmental milestones between children with short seizures and those with long seizures

FEBSTAT- **Cognitive functioning one month and one year following febrile status epilepticus** *Epilepsy & Behavior 64 (2016) 283–288*

- Children with FSE did not differ dramatically on tasks compared with FS controls at one month.
- Slightly weaker motor development (p = 0.035) and receptive language (p = 0.034) at one year after FSE.
- Performances were generally within the low average to average range.
- Within the FSE cohort, non-White children performed weaker on many of the tasks compared with Caucasian children.
- At the one-year visit, acute hippocampal T2 findings on MRI were associated with weaker receptive language skills (p=0.0009)
- Human herpes virus 6 or 7 (HHV6/7) viremia was associated with better memory performances (p = 0.047).

FEBSTAT- **Risk factors for subsequent febrile seizures**
Epilepsia, 57(7):1042–1047, 2016

- The risk for recurrence of a second FS of any type was 42.9% (83/193) in FSE versus 28.9% (29/101) in SFS (Wilcoxon p = 0.094)
- The risk for a subsequent FSE was 9.9% (19/193) in FSE versus 2.3% (2/101) in SFS (Wilcoxon p = 0.024)
- Any magnetic resonance imaging (MRI) abnormality increased the risk 3.4-fold (p < 0.05)
- Rectal diazepam was administered at home to 5 (23.8%) of 21 children with subsequent FS lasting ≥10 min.

Prognostic factors for subsequent epilepsy in children with febrile seizures *Epilepsia, 54(12):2101–2107, 2013*

560 children with a first FS - 5.4% epilepsy

(1) complex FS increased the risk for epilepsy 3.6 times
(2) age at onset of FS beyond the third year raised the risk 3.8 times
(3) positive family history of epilepsy 7.3 times
(4) multiple episodes of FS about 10 times.
(5) focality at the first and the second FS recurrence increased the risk of epilepsy about 9.7 and 11.7 times, respectively.

Utility of initial EEG in first complex febrile seizure
Epilepsy & Behavior 52 (2015) 200–204

154 children, 20 (13%) children developed epilepsy

Epileptiform EEGs were noted in 20% (4/20) of patients with epilepsy and 13% (17/134) of patients without epilepsy (p = 0.48).

PPV of an epileptiform EEG for subsequent epilepsy was 15%. None of the clinical variables (presence of more than 1 complex feature, family history of epilepsy, or status epilepticus) predicted epilepsy.

FSE and Epileptogenesis

Implicated mechanisms:

- Genetics (SCN1B, SCN1A, SCN2A, gamma 2 subunit of the GABA A receptor)
- Epigenetics: virus type, duration FS,
- Cortical displasia (microdysgenesis, dual pathology)
- Prior injury
- Inflammatory response to fever and seizures (TNF, IL)
- Ion channels (SCN A), temperature sensitive channels: TRPV,HCN,Cav 1.2
- Increased expression of excitatory amino acid receptors
- Developmentally regulated depolarizing activity of -aminobutyric acid (GABA)
- Immaturity of seizure suppressing networks compared to adults
- IL-1 could reduce GABA A receptor currents

FSE and Epileptogenesis

Implicated mechanisms:

- IL-1 promotes glutamatergic mediated excitatory effects
- IL-1 proconvulsant; IL 6, IL ra, IL 10 anticonvulsant
- Fever reduces presynaptic GABA release
- Hypocarbia prolonges the latency and duration of FS
- Elevated pH in the immature brain leads to hyperexcitability
- Inflammation activates the (excitatory) Toll-like receptor 4 (TLR4)

FSE and Epileptogenesis

Implicated mechanisms:

- Transient cell injury post-hyperthermia, normal cell counts
- TNF-α has been found to increase surface expression of AMPA receptors and decreasing GABA receptors
- Upregulation AMPA receptors leads to abnormal function or expression of ion channels or receptors.
- Increase in the hippocampal levels of NMDA receptorNR2A subunit (excitability)
- Increased number of cannabinoid type 1 receptors (inhibits GABA)

FSE and Epileptogenesis

FSE → Epilepsy

*Neurosci Lett. 2011 June 27; 497(3): 155–162. Epilepsy Research (2010) **89**, 27—33. Epilepsy Curr 2014, 14; 15–22. Epilepsy Curr 2013, 13;143–145. Neurobiol Dis 32 (2008) 176–182. Brain Devel 31 (2009) 383–387. Neurobiol Dis 43 (2011) 312–321. Neurotherapeutics (2014) 11:242–250.*

FSE and Epileptogenesis

Predisposing Factors ⟶ FSE ⟶ Epilepsy

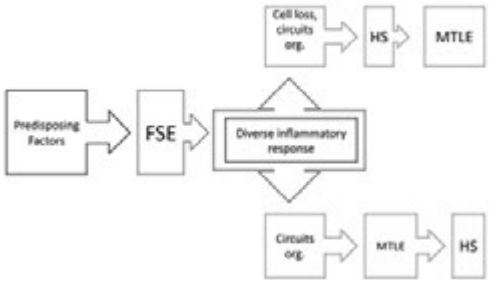
FSE and Epileptogenesis

FSE ⟶ HS ⟶ MTLE

FSE and Epileptogenesis

FSE ⟶ MTLE ⟶ HS

FSE and Epileptogenesis

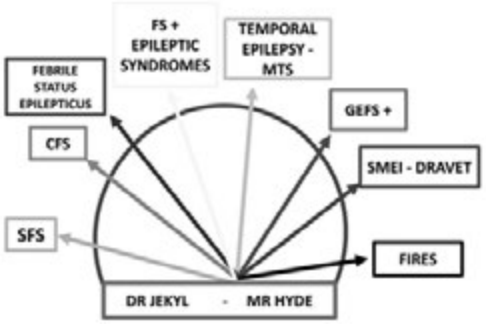


HIPPOCAMPAL SCLEROSIS - HS

HS may follow CSE or repetitive afebrile seizures, not only FSE or PFS

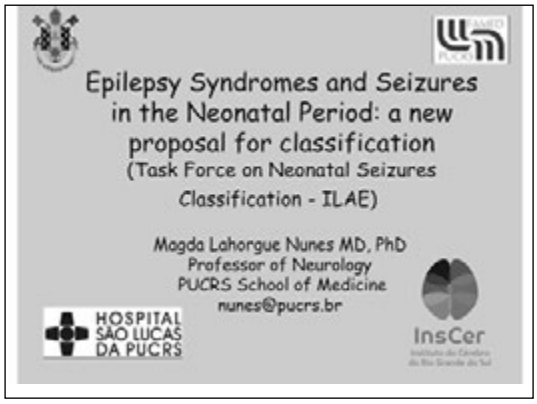
Epilepsia, 54(12):2108–2115, 2013

FS - SPECTRUM

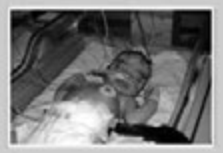


Magda Lahorgue Nunes (Brazil)

SEIZURES AND EPILEPTIC SYNDROMES IN THE NEONATAL PERIOD: A NEW PROPOSAL FOR CLASSIFICATION (TASK FORCE ON NEONATAL SEIZURES CLASSIFICATION - ILAE)



Full - Term x Premature



Challenges

- Age dependent mechanisms of neurotransmitter

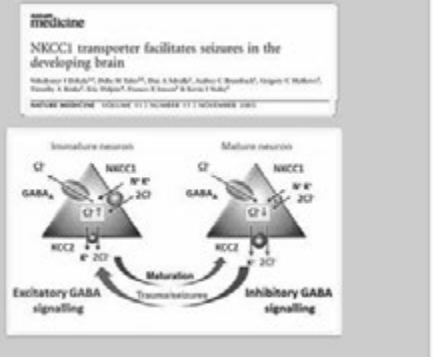
I am not just a little adult!

Neonatal Seizures: Gaps Between the Laboratory and the Clinic

TABLE 2. Ideas from the laboratory

- In animal models, neonatal seizures cause both acute effects and long-term sequelae.
- These may occur also if exogenous factors are excluded, such as hypoxia or hypoglycemia, and if the animals are paralyzed.
- These long-term effects can occur even without histological evidence of neuronal lesions.
- The acute and long-term deleterious effects are due either to
  a) Energy failure,
  b) Excitotoxicity,
  c) Neurogenesis with consequent formation of new excitatory circuitry,
  d) Disorders in "programmed cell death" (apoptosis), and
  e) EEP or repetitive shorter seizures place the brain for epileptogenesis, and for cognitive, behavioral problems.

*Status epilepticus



NKCC1 transporter facilitates seizures in the developing brain

Challenges

- Age dependent mechanisms of neurotransmitter
- Variable incidence

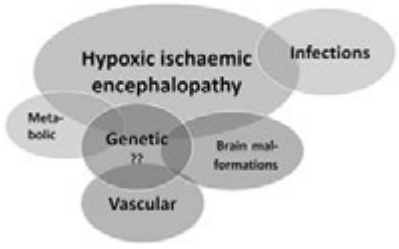
Incidence

- Neonatal Seizures
- 24.2/1000 RN - selected population in NICU (Silva et al. 2004)
- 1.0 -3.5 / 1000 newborns - population based studies (Lanska et al. 1995, Saliba et al. 1999, Ronen et al. 1999)
- Neonatal Epilepsies
- Benign Neonatal Familial Seizures : 14.4 : 100.000 live births (Ronen et al. 1999)
- Neonatal encephalopathies (Ohtahara, Aicardi): ?

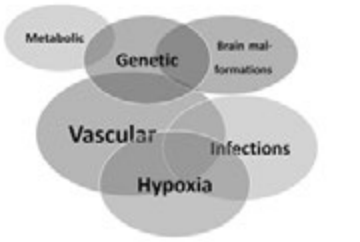
Challenges

- Age dependent mechanisms of neurotransmitter
- Variable incidence
- Variable etiology

Prevalence of etiologies in term babies



Prevalence of etiologies in preterm babies
(little data availed)



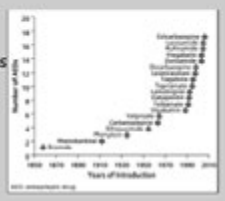
ILAE Task Force on Neonatal Seizures

Challenges

- Age dependent mechanisms of neurotransmitter
- Variable incidence
- Variable etiology
- Choice of treatment

Current practice

- Phenobarbital 1st line drug for neonatal seizures
- No evidence base for current management of neonatal seizures (Boots and Evans, 2004; WHO, 2011)
- No new AED developed for neonatal seizures
- Risk due to frequent off-label use of antiepileptic drugs



New AED trials for neonatal seizures

- **Lignocaine** (Malingre 2006, Rademaker & de Vries 2008, van de Broek 2011, 2013)
  - Local anaesthetic/antiarrhythmic drug.
  - Narrow therapeutic window, PK prolonged with cooling.
- **Topiramate** (Filipi et al 2009, 2010)
  - Neuroprotective properties,
  - Unfavourable safety profile in children.
- **Levetiracetam** (Ramantani et al 2010; Ledet et al 2010, Fürwentsches et al 2010)
  - Safety and PK/PD studied in newborns.
  - Case reports and retrospective studies (mostly without EEG)
  - No RCT
- **Bumetanide** (Kahle 2009; Pressler et al 2016)
  - Loop diuretic, good safety profile as diuretic.
  - Feasibility study: NEMO (EU)

Challenges

- Age dependent mechanisms of neurotransmitter
- Variable incidence
- Variable etiology
- Choice of treatment
- Variable outcome

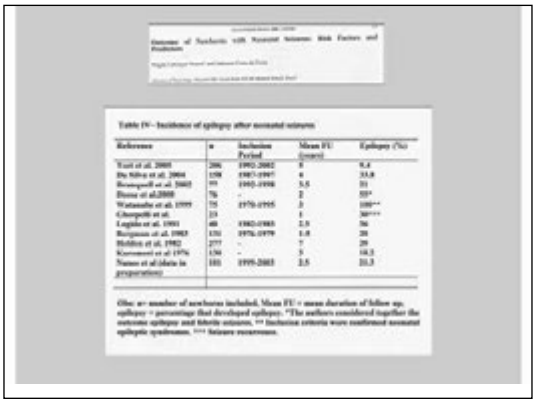


Table IV – Incidence of epilepsy after neonatal seizures

Reference	n	Inclusion Period	Mean FU (years)	Epilepsy (%)
Yuri et al. 2005	206	1992-2002	5	9.4
Da Silva et al. 2004	158	1987-1997	6	33.8
Bourgeoll et al. 2002	??	1992-1998	5.5	31
Ilioia et al.2000	76	-	2	55*
Watanabe et al. 1999	75	1976-1995	3	100**
Ghergelli et al.	23		1	30***
Legido et al. 1991	48	1982-1985	2.5	56
Bergman et al. 1983	131	1976-1979	1.5	28
Holden et al. 1982	277	-	7	29
Kurtzweil et al 1976	130	-	3	16.2
Nunes et al (data in preparation)	181	1995-2003	2.5	21.3

Obs: n= number of newborns included, Mean FU = mean duration of follow up, epilepsy = percentage that developed epilepsy. *The authors considered together the outcome epilepsy and febrile seizures, ** Inclusion criteria were confirmed neonatal epileptic syndromes, *** Seizure recurrence.


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

Pediatrics 2006;117:1270-1280

- Retrospective design
- Seizures diagnosis based on NICU staff observation, confirmed by Neurologist
- Volpe classification
- Included :100 term newborns, followed up 89
- Neonatal mortality 7%
- Etiology : 40% global hypoxia-ischemia, 18% focal HI
- Relationship between type of seizure and outcome not statistically significant


Risk Factors for Developing Epilepsy After Neonatal Seizures

- Retrospective study (January 1987-December1997)
- 6528 nb admitted :158 diagnosed with seizures (2.4%), 127 followed
- Diagnose criteria: Clinical observation of at least 2 episodes, Volpe Classification of sz (39.4%clonic, 26%subtle, 11.8 tonic, 5.5%mioclonic).
- More than one sz type RR 3.02 for CNS infection
- 56% male, 65.4% term
- Etiology: 33.8% HIE (15 preterm and 28 term), 30% electrolytic imbalance
- Mortality: 24 decease in NICU (15%)
- Morbidity: 25.4% cerebral palsy, 33.8% post neonatal epilepsy


NEUROLOGICAL OUTCOME OF NEWBORNS WITH NEONATAL SEIZURES

A cohort study in a tertiary university hospital

- Prospective study (January 1999-Decemebr 2003)
- 3659 nb admitted :101 diagnosed with seizures (2.7%)
- Diagnose criteria: Clinical observation of at least 2 episodes, Volpe Classification of sz.
- 57% male, 71.4% term
- Etiology:51% HIE
- Mortality: 25 decease in NICU (24.7%), 9 during the 1st year of life.
- Morbidity: 35 developmental delay, 19 post neonatal epilepsy (10 had HIE), 11 both outcomes
- Prematurity increased the risk for developmental delay
- Among all neonates seizures increased the risk of post neonatal epilepsy (19.3/100 vs. 1.8/100, p<0.001)


Impacto das crises convulsivas neonatais no prognóstico neurológico durante os primeiros anos de vida

Impact of neonatal seizures in the neurological outcome during the early years of life

- Cross sectional: period January 2004 to December 2009
- Diagnosis: sz confirmed by EEG or video-EEG
- 42 newborns with seizures: 52.3 %male (n=22), 71.4%term (n=30), 40.4 % HIE
- Neonatal mortality 9.2%
- 22 with follow up (12 male, 14 term)
- Morbidity: 45% (n=10) post neonatal epilepsy, 40% (n=9) developmental delay

Comparison 3 cohorts PUCRS

	1987-1997	1999-2003	2004-2009
Number patients	127	101	22*
Sex	56% male	58% male	54.6% male
Term/preterm (%)	65.4/34.6	71.4/29.6	72.7/27.3
Incidence (per 1000 live births)	24.2/1000	27.6/1000	11.2/1000
Mortality (neonatal)	15%	25%	9.2%
Post Neonatal Epilepsy	33.8%	29.6%	45.5%

(*confirmed by video-EEG)

Challenges

- Age dependent mechanisms of neurotransmitter
- Variable incidence
- Variable etiology
- Choice of treatment
- Variable outcome
- Issues on recognition and classification

Neonatal epilepsies: classification

- Proposal ILAE 2001
- Focal familiar epilepsies:
  Benign familial neonatal convulsions
- Epileptic encephalopaties:
  Early Myoclonic Encephalopathy
  Early Infantile epileptic encephalopathy
- Seizures that do not permit a syndrome diagnosis:
  Benign neonatal convulsions (idiopathic)

SPECIAL REPORT

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

Table 1. Electroclinical syndromes and other epilepsies

Electroclinical syndromes arranged by age at onset*
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome

Benign Familial Neonatal Seizures

- 1st description Rett & Teubel, 1964
- Sz starts around the 3rd day , healthy term neonates, positive family hx for epilepsy.
- Sz types: clonic, apnea ,SE
- Genetics:

Autossomal dominant heritage

⬇

Cromossome 20 (q 13.3)

⬇

Molecular biology : Channelopathies (mutations on KCNQ).

Benign Familial Neonatal Seizures

- **KCNQ2 and KCNQ3 mutations are known to be responsible for benign familial neonatal seizures (BFNS).**
- Claes LR et al. Neurology 2004. De novo KCNQ2 mutations in patients with benign neonatal seizures..
- Yalçin O et al. Turk J Pediatr. 2007. A novel missense mutation (N258S) in the KCNQ2 gene in a Turkish family afflicted with benign familial neonatal convulsions (BFNC).
- Herlenius E et al. Epilepsia 2007. **SCN2A** mutations and benign familial neonatal-infantile seizures: the phenotypic spectrum..
- Striano P .Epilepsia 2006. A novel **SCN2A** mutation in family with benign familial infantile seizures.

Neonatal Encephalopathies

- Early Myoclonic Encephalopathy (Aicardi & Goutiéres , 1978)

⬍

- Early Infantile Epileptic Encephalopathy (Ohtahara et al. 1976)

- Refractory seizures
- Multiple etiologies

EME -more associated to IEM

EIEE - more associated to cerebral dysgenesis, HIE

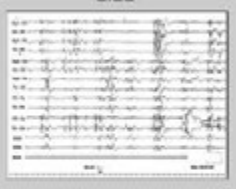
- Semiology

EME- fragmentary erratic or massive myoclonus, partial motor sz.

EIEE-tonic spasms in cluster or singly

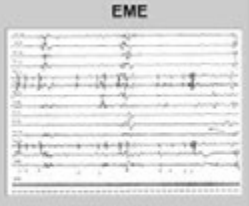
- No response to conventional AEDs
- EEG with suppression-burst pattern
- High morbidity/mortality

EIEE



SB pattern identical during awake and sleep, latter SB is more evident during sleep, bursts 2-6s, suppression phase 3-5s

EME



Awake and Sleep, brevity of bursts and marked interburst flattening , myoclonias follow EEG burst

Neonatal Encephalopathies

- Weckhuysen S et al. Ann Neurol. 2012. *KCNQ2* encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy.,
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- Okumura A et al. Epilepsia 2011. Refractory neonatal epilepsy with a de novo **duplication of chromosome 2q24.2q24.3**.

Classification of neonatal seizures based on clinical findings

- Burke,1954; Craig 1960; Keen 1969, McInerny & Schubert 1969)
- EEG and cinematography – Dreyfus-Brisac & Monod, 1964
- Consolidation and confirmation of clinical findings (early 70s)
  Rose & Lombroso, 1970
  Volpe, 1973

Classification of neonatal seizures based on clinical findings

- Volpe 1973
- Subtle
- Clonic (focal, multifocal)
- Tonic (focal, generalized)
- Myoclonic (focal, multifocal, generalized)

Classification of neonatal seizures based on electroclinical findings

Mizhari & Kellaway , 1984

1)Clinical seizures with a consistent electro cortical signature (pathophysiology: epileptic)

- Focal clonic (unifocal: multifocal: alternating, migrating: hemi convulsive, axial)
- Focal tonic (asymmetrical truncal posturing, limb posturing, sustained eye deviation)
- Myoclonic (generalized, focal)
- Spasms (flexor,extensor, mixed)

Classification of neonatal seizures based on electroclinical findings

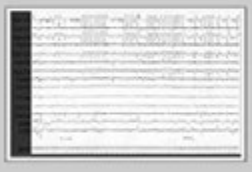
(Mizhari EM, Kellaway P. Diagnosis and Management of Neonatal Seizures, 1998)

2) Clinical seizure without a consistent electro cortical signature (presumed pathophysiology: non epileptic -primitive brainstem and spinal cord motor patterns released from tonic inhibition normally exerted by forebrain- reflex origin).

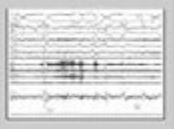
- Myoclonic (generalized, Focal, fragmentary
- Generalized tonic (flexor/extensor/ mixed)
- Motor automatisms (oro-buccal-lingual movements, ocular signs, progression movements, complex purposeless movements)

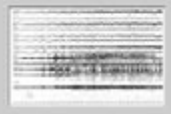
3) Electrical seizures without clinical seizure activity

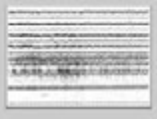
Clinical seizures with a consistent electro cortical signature



Clinical seizure without a consistent electro cortical signature







Electrical seizures without clinical seizure activity

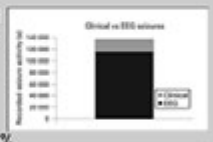
Seizures a clinical diagnosis?

- 20 video clips of 11 seizures and 9 other events
- Evaluated by 137 health professionals (US, Ire, UK) - 91 doctors (consultants, fellows, residents), 46 NICU nurses / midwifes
- Asked to identify seizures vs non-seizures
- Correctly identified events: 10/20 in average
  - Clonic seizures most frequently identified
  - Others poorly
- Poor agreement with correct diagnosis
- Poor inter-observer agreement

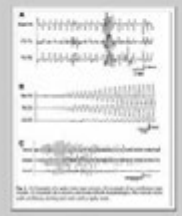
Malone et al 2008

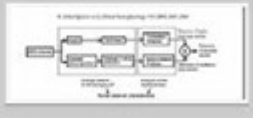
Clinical seizure detection

- 51 high risk babies with cEEG
- 12 babies with electro-clinical clinical or electrical seizures
- Clinical diagnosis of seizures
  - Under diagnosis in ~90%
  - Over diagnosis in ~70%
- Clinical seizures activity in 20% of total EEG seizure burden

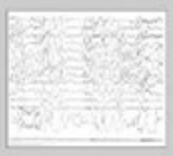


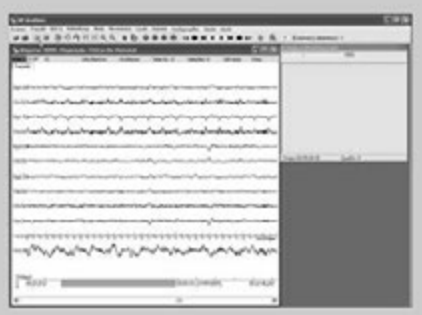
Murray et al 2009

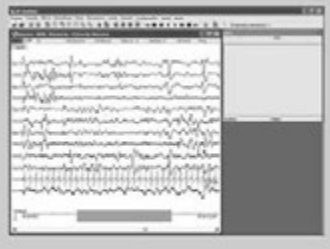


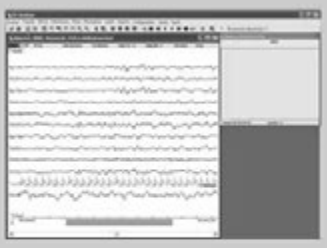


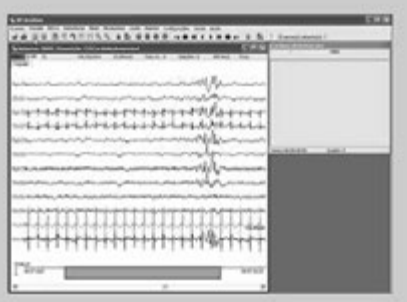
Different types of seizure- same neonate

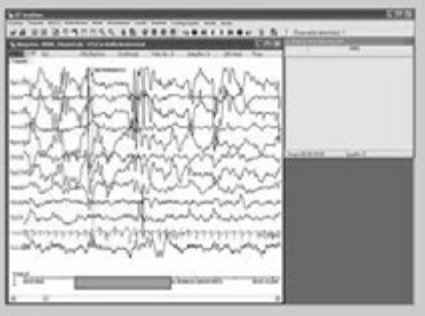










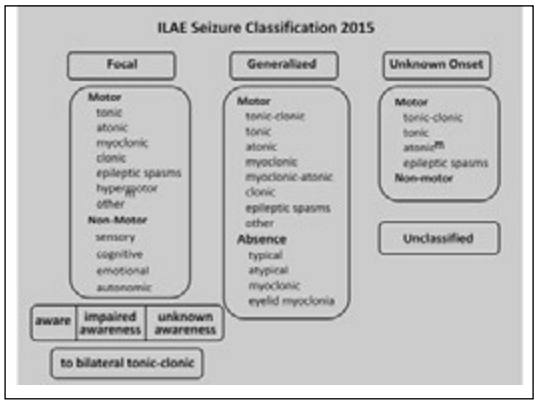


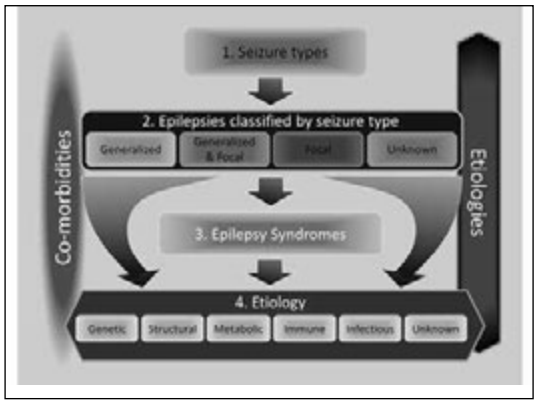
ILAE Commission on Classification & Terminology - 2013

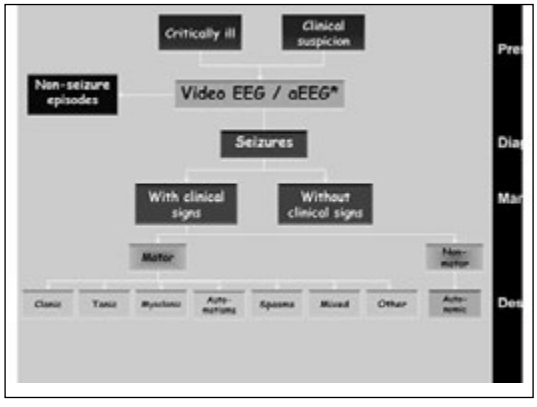
Aims of the Task Force

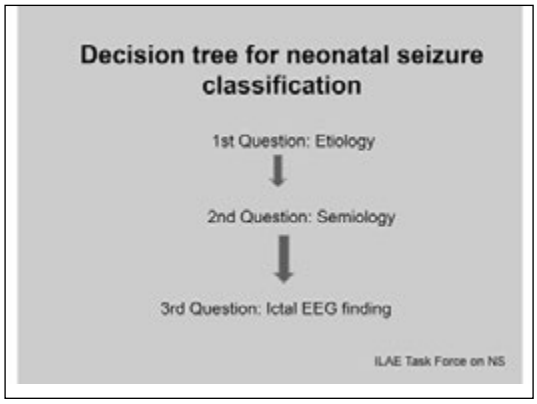
Develop a framework of seizures in neonates through detailed characterisation of electro-clinical phenotypes

- Take into account the specificities of neonatal seizures
- Clinically useful in different health care settings
- Have implication on management and treatment of events
- Acceptable to neonatologists, paediatricians and neurologists alike
- Relevant for clinical and translational research


ILAE Seizure Classification 2015
Focal
Motor
tonic
atonic
myoclonic
clonic
epileptic spasms
hyperkinetic
other
Non-Motor
sensory
cognitive
emotional
autonomic
Generalized
Motor
tonic-clonic
tonic
atonic
myoclonic
myoclonic-atonic
clonic
epileptic spasms
other
Absence
typical
atypical
myoclonic
eyelid myoclonia
Unknown Onset
Motor
tonic-clonic
tonic
atonic[f]
epileptic spasms
Non-motor
Unclassified
aware
impaired awareness
unknown awareness
to bilateral tonic-clonic


1. Seizure types
2. Epilepsies classified by seizure type
Generalized
Generalized & Focal
Focal
Unknown
3. Epilepsy Syndromes
4. Etiology
Genetic
Structural
Metabolic
Immune
Infectious
Unknown
Co-morbidities
Etiologies


Critically ill
Clinical suspicion
Non-seizure episodes
Video EEG / aEEG*
Seizures
With clinical signs
Without clinicol signs
Motor
Non-motor
Clonic
Tonic
Myoclonic
Epasms
Mixed
Other
Pre
Dia
Ma
Des


Decision tree for neonatal seizure classification
1st Question: Etiology
2nd Question: Semiology
3rd Question: Ictal EEG finding
ILAE Task Force on NS

Special thanks to Ronit Pressler MD
and
all members of
ILAE Task Force on Neonatal Seizures

BraIns

/ /

MEETING WITH ELZA MARCIA YACUBIAN, LAURA GUILHOTO, HELEN CROSS, JAIME CARRIZOSA, MAGDA LAHORGUE NUNES

Guilca Contreras (Venezuela)

VNS IN CHILDHOOD EPILEPSY: FROM THEORY TO PRACTICE

Fabio Rogério (Brazil)

PATHOLOGICAL CHARACTERISTICS OF OTHER ETIOLOGIES OF REFRACTORY CHILDHOOD EPILEPSIES: DEVELOPMENTAL TUMORS AND TUBEROUS SCLEROSIS

LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY - LASSE

LASSE IX - NEURODEVELOPMENTAL DISORDER AND EPILEPSY

"PATHOLOGICAL CHARACTERISTICS OF OTHER ETIOLOGIES OF REFRACTORY CHILDHOOD EPILEPSIES: DEVELOPMENTAL TUMORS AND TUBEROUS SCLEROSIS"

Fabio Rogerio, MD, PhD.
University of Campinas - Unicamp
Campinas - Brazil

Developmental Tumors

1. Gangliocytoma and ganglioglioma

Well-differentiated, slow-growing neuroepithelial tumors composed of isolated dysplastic ganglion-like cells (gangliocytoma) or associated with neoplastic glial cells (ganglioglioma). These are the tumors most frequently associated with chronic epilepsy in children and young adults.

Gangliocytoma and ganglioglioma together account for 0.4% of tumors of the nervous system and 1.3% of brain tumors. Age at presentation and mean age at diagnosis widely vary (2 months to 70 years and 8 to 25 years, respectively). Males and females are affected with approximately equal frequency, with slight variations among series of cases. Any region of the central nervous system (CNS) may be affected. Particularly, around 70% of all gangliogliomas occur in the temporal lobes and, in decreasing order, in the frontal, parietal and occipital lobes.

Clinical features depend on tumor localization and size. Brain lesions are classically associated with long history of focal seizures (from years to decades).

On neuroimaging analyses, classic features are cortical cysts with a mural nodule, which can show calcifications on computed tomography (CT). Magnetic resonance imaging (MRI) shows circumscribed lesions, hypointense in T1- and, hyperintense in T2-weighted scans. Contrast enhancement is variable. Mass effect and perilesional edema are not common, since the tumors grow very slow. Grossly, both tumors may present as well-circumscribed cystic or solid lesions. Calcification and hemorrhage may be observed.

Microscopically, gangliocytomas are composed of groups of frequently dysplastic multipolar neurons. Gangliogliomas present neural and glial neoplastic elements with striking heterogeneity. Dysplastic neurons are large, with predominant perimembranous distribution of Nissl substance and may exhibit binucleation. They tend to be arranged in groups without cytoarchitectural organization. The glial component is the proliferative population and may show astrocytic or oligodendroglial features. Calcification and perivascular lymphoid infiltrates are commonly observed. Adjacent cortex - not containing tumor cells - may show focal cortical dysplasia (FCD), which is then classified as FCD Type IIIb according to the International League Against Epilepsy (ILAE) classification. Gangliogliomas that show glial component with increased cellularity, pleomorphism, elevated number of mitosis, vascular proliferation and necrosis are designated as anaplastic. Immunostainings for neuronal proteins (chromogranin-A, synaptophysin, neurofilament and MAP2) identify the neuronal counterpart. Antibody to an astrocytic protein - glial fibrillary acidic protein (GFAP) - highlights the proliferative glial component in ganglioglioma, which is also positive for S100 protein and vimentin. Immunopositivity for the oncofetal marker CD34 is detected in 70-80% of gangliogliomas and helps

to identify satellite lesions in adjacent cortex. Ki-67/MIB1 index is used to estimate cellular proliferation (mean values range from <1 - 3%).

Both gangliocytoma and ganglioglioma have favorable prognosis, thus corresponding histologically to WHO grade I. Anaplastic gangliogliomas show a more reserved prognosis and are WHO grade III lesions.

2. Dysembryoplastic neuroepithelial tumor (DNT)

DNT is a benign glioneuronal neoplasm typically located in the temporal lobe of children or young adults with early-onset epilepsy. Frequency ranges from around 1.0 to 25% of the lesions removed in epilepsy surgery centers. Mean age at presentation and mean age at surgery are 15 and 25.8 years, respectively. Predominance is slightly higher in males. DNT may occur in any supratentorial cortical region, mainly the temporal and frontal lobes. Chronic (until decades) drug-resistant focal seizures, with or without secondary seizure generalization is the most common clinical setting.

On CT the tumor is hypodense, well-demarcated and located in the cortex. Calcifications and deformity of the bone adjacent to exophytic lesions may occur. On MRI, the lesion is intracortical, hypo-/isointense in T1 and hyperintense in T2, without edema. Contrast enhancement may be observed in ~30% of the cases. Macroscopically, the lesion is mainly intracortical, (multi)nodular and its consistency varies from viscous to firm.

Histologically, the "specific glioneuronal element", which spans the entire cortical thickness, is a hallmark. This tissue has characteristic columnar appearance, the columns being oriented perpendicular to the cortical surface and formed by bundles of axons, lined by small glial cells, positive for S100 protein and OLIG2 and negative for GFAP. Among the columns, normal neurons seem to float in a mucoid interstitial fluid, palely eosinophilic (floating neurons). GFAP-positive astrocytes are also identified. Dysplastic ganglion cells are not detected. CD34 protein expression is variable. Areas adjacent to the specific glio-neuronal element may show focal cortical dysplasia. ILAE FCD Type IIIb should be diagnosed only when no neoplastic cells are observed. Ki-67/MIB1 index varies from 0% to 8%. DNT has a favorable diagnosis and corresponds histologically to WHO grade I.

3. Angiocentric glioma (monomorphous angiocentric glioma, angiocentric neuroepithelial tumor)

Angiocentric glioma is an epilepsy-associated, stable or slow-growing cerebral tumor primarily affecting children and young adults. This lesion is uncommon, its real frequency being still undetermined. Males and females seem to be equally affected. The superficial topography in the cerebral cortex (frontal, parietal or temporal) is typical. Clinically, this neoplasm is associated with chronic epilepsy lasting for years. On MRI, angiocentric gliomas present as solid and well-circumscribed cortical thickening, extending to the white matter. They are hyperintense in T2 and FLAIR and are not enhanced by contrast in T1 images. Blurring of the gray matter/white matter boundary has been described as a gross finding. Histological evaluation shows an angiocentric pattern of growth, monomorphous bipolar cells, and features of ependymal differentiation. Cells may be isolated or arranged in cords/palisades, nests or sheets in subpial and/or intraparenchymatous regions, occasionally forming a trabecular pattern with clefts. Tumor cells are immunopositive for GFAP, vimentin and S100 protein, but not for neuronal antigens (synaptophysin, chromogranin-A or NeuN). Ependymal features are noted as EMA-positive small cytoplasmic spots. Ki-67 index varies from <1% to 5%. Angiocentric gliomas seem to be stable tumors and correspond histologically to WHO grade I.

Tuberous sclerosis

Tuberous sclerosis is a group of autosomal dominant disorders caused by an inactivating mutation in *TSC1* or *TSC2* genes, which lead to production of hamartin or tuberin proteins, respectively. Most tuberous sclerosis cases (approximately 60%) are sporadic, suggesting the occurrence of a high rate of *de novo* mutations. Under physiological conditions, hamartin and tuberin interact and form a complex that integrates growth factor signals from the PI3K/AKT pathway to coordinate cellular processes, including proliferation and cell size. The complex negatively regulates the mTOR pathway. Disruption of the tuberin-hamartin complex, as determined by genetic mutations, leads to upregulation of the mTOR pathway and increase in proliferation and cell growth. Consequently, tuberous sclerosis is characterized by hamartomas and neoplastic lesions that affect not only the CNS but also various non-neural tissues (such as skin, lungs, heart, kidneys and digestive system). Around 2 million individuals are affected worldwide, the estimated prevalence being 1:6000 - 1:10000 live births. The diagnosis is performed primarily according to clinical features. Genetics tests are particularly helpful when clinical criteria for a definite diagnosis are not found.

In the CNS, tuberous sclerosis causes cortical hamartomas (tubers), subependymal nodules and subependymal giant cell astrocytoma. Neurologic manifestations include

chronic seizures, cognitive/behavioral disorders and raised intracranial pressure.

Cortical tubers resemble sporadic cortical malformations on neuroimaging. MRI scans show blurring of the grey matter/white matter boundary on T1- and subcortical hypersignal on FLAIR and T2-weighted images. Microscopically, tubers consist of dysmorphic neurons, giant cells, gliosis and calcification. Particularly, dysmorphic neurons present with abnormal lamination (extending from the meningeal surface to the white matter), irregular shape, cytoplasmic vacuolation and perikarial accumulation of fibrils. Giant cells show prominent nucleolus, eosinophilic glassy cytoplasm and may be arranged in groups. The adjacent white matter exhibits loss of myelin, heterotopic neurons and giant cells.

Subependymal hamartomas are nodular periventricular lesions that frequently calcify. Histologically, they are indistinguishable from cortical tubers.

Subependymal giant cell astrocytoma (SEGA) is the most common CNS tumor in tuberous sclerosis patients. Its incidence ranges from 5%–15% in individuals with confirmed diagnosis of tuberous sclerosis and typically occurs during the first two decades of life. In general, the tumor develops in the walls of the lateral ventricles, close to the foramen of Monro. Patients usually present with chronic epilepsy and/or symptoms of increased intracranial pressure. On CT scans, the lesion is solid and calcified. Lateral ventricles may be enlarged. On MRI, the neoplasm is heterogeneous, iso- or hypointense on T1- and hyperintense on T2-weighted images, with contrast enhancement. Macroscopically, the tumor is circumscribed, nodular and firm, with cysts and calcifications.

Microscopically, SEGA is characterized by a heterogenous population of cells with astroglial features in a fibrillar background: large polygonal cells with glassy cytoplasm and smaller spindled cells arranged in fascicles, sheets or nests. Giant cells with a ganglionic appearance are common; their nuclei are vesicular with a finely granular chromatin and distinct nucleoli. They are essentially similar to the giant cells seen in cortical tubers and balloon cells observed in focal cortical dysplasia Type IIb of the ILAE classification. There may be multinucleated and/or pleomorphic cells. Vessels with hyalinized walls and infiltration of lymphocytes and mast cells are common.

A variable proportion of cells may be immunopositive for GFAP and S100 protein. Some neuronal markers (NeuN, tubulin, neurofilament and synaptophysin) may be demonstrated as well. Glial and neuronal proteins can be identified in similar cell populations. Such findings suggest cellular lineages with divergent phenotypes, including glial, neuronal and mixed differentiation. Ki-67 labelling index is usually low (mean: 3.0%).

Despite the operative morbidity, these tumors have favorable prognosis, even with atypia, mitosis and occasional vascular proliferation and necrosis. SEGA rarely recurs and, even in this case, no malignant transformation has been reported. Thus, SEGA corresponds histologically to WHO grade I.

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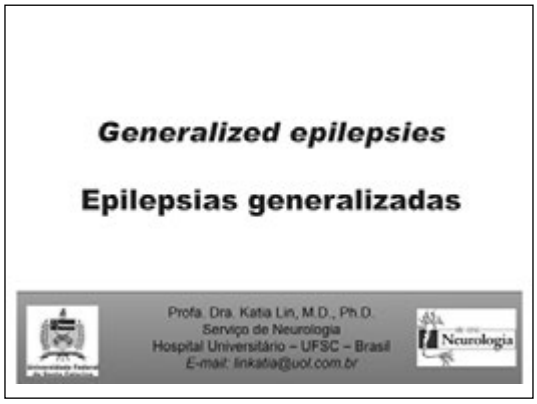
Thom M, Blümcke I, Aronica E. Long-term epilepsy-associated tumors. Brain Pathol. 2012 22(3):350-379. doi: 10.1111/j.1750-3639.2012.00582.x.

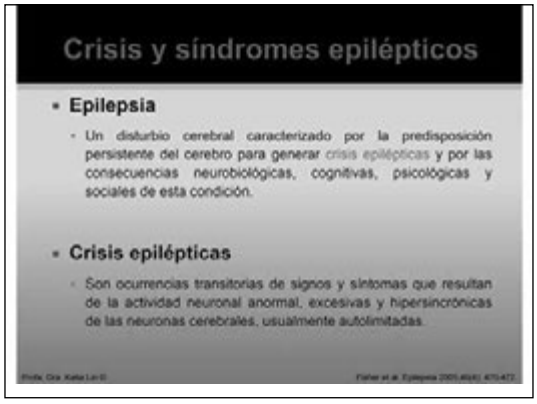
Finbar O'Callaghan (UK)

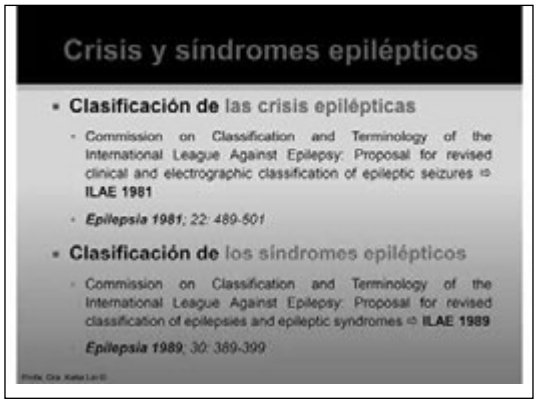
CLINICAL CHARACTERIZATION OF TUBEROUS SCLEROSIS

Katia Lin (Brazil)

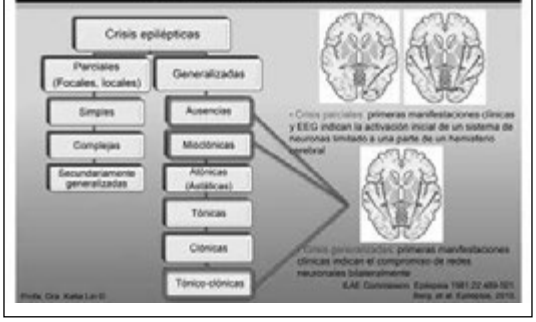
SEMIOLOGY OF IDIOPATHIC/GENETIC GENERALIZED EPILEPSIES



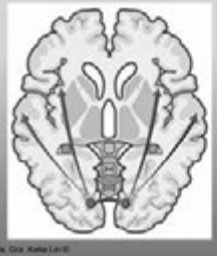




Clasificación de las crisis epilépticas, 1981 ILAE



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



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

Berg, et al. Epilepsia, 2010.
Avanzini, et al. Epilepsia, 2012.

Epilepsias Generalizadas Idiopáticas/Genéticas (EGI)

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

Proposal for Revised Classification of Epilepsies and Epileptic Syndromes

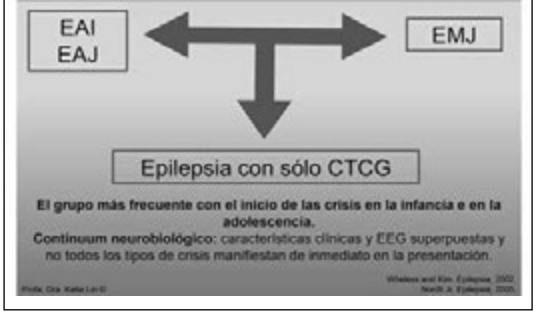
Commission on Classification and Terminology of the International League Against Epilepsy

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

Edad	Epilepsias/Síndromes epilépticos
Recién nacido a 2 meses	Convulsiones neonatales familiares benignas Convulsiones neonatales benignas
3 meses a 3 años	Epilepsia mioclonica benigna del nino
3 años a pubertad	Epilepsia ausencia infantil
Pubertad a adulto	Epilepsia ausencias juvenil Epilepsia mioclonica juvenil Epilepsia con crisis de gran mal del despertar
Cualquier edad	Otras epilepsias generalizadas idiopaticas no definidas Epilepsia con crisis caracterizadas por modos especificos de precipitación (epilepsiafotogenica)

ILAE Commission. Epilepsia 1989;30:389-399.

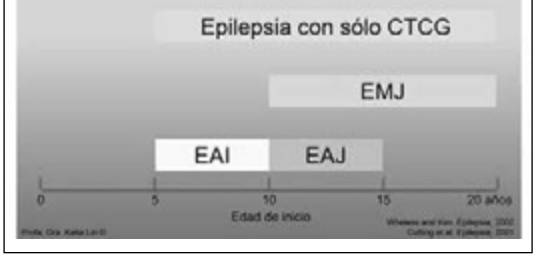
Epilepsias Generalizadas Idiopáticas/Genéticas



El grupo más frecuente con el inicio de las crisis en la infancia e en la adolescencia.
Continuum neurobiológico: características clínicas y EEG superpuestas y no todos los tipos de crisis manifiestan de inmediato en la presentación.

Epilepsias Generalizadas Idiopáticas/Genéticas

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

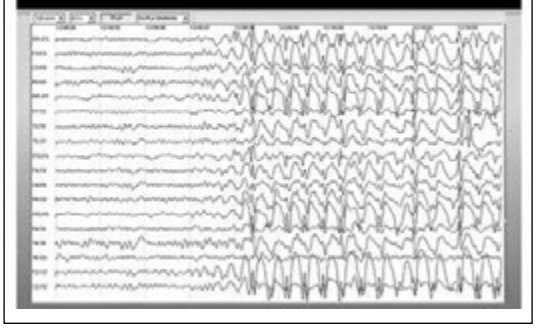


Crisis de ausencia típicas Picnolépticas

VÍDEO

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

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



Crisis de ausencia típicas Espaniolépticas

VÍDEO

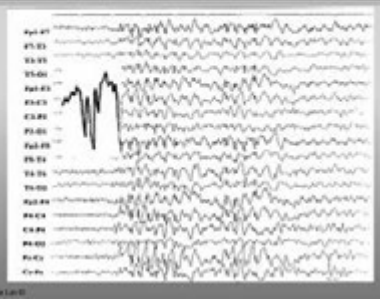
La alteración de la consciencia puede ser total o parcial, con el mantenimiento de la actividad en curso de forma automática. Al inicio y al final son graduales, pudiendo haber dificultad en la identificación de ellas.

Crisis de ausencia

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

Asadi-Pooya et al., 2012
Obeid, 1994

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



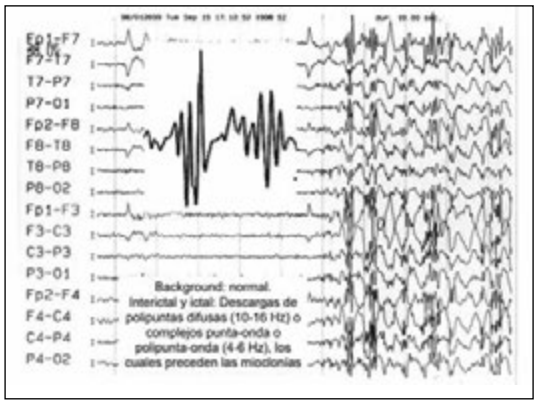
Crisis mioclónicas

Myoclonus (gr.) = músculo + perturbación

VÍDEO

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

Blume, et al. Epilepsia, 2001



Crisis tónico-clónicas generalizadas (CTCG)

VÍDEO

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

Crisis tónico-clónicas generalizadas (CTCG)

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

Gastaut & Broughton, 1974
Scaramelli et al., 2006

Crisis tónico-clónicas generalizadas (CTCG)

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

Gastaut & Broughton, 1974

Crisis tónico-clónicas generalizadas (CTCG)

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

Crisis tónico-clónicas generalizadas (CTCG) – EEG

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

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

Epilepsia ausencia infantil

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

Epilepsia ausencia juvenil

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

Ausencias precipitadas por la hiperventilación

VÍDEO

Epilepsia mioclónica juvenil

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

Síndrome de Janz

Prof. Dieter Janz

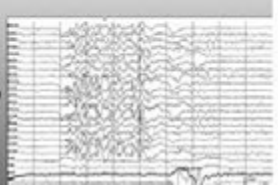
Impulsiv-Petit mal (1957)

VÍDEO

Descargas epileptiformes y convulsiones precipitadas por fotoestimulación

Fotosensibilidad

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



Epilepsia com sólo CTCG

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

Investigación

Diagnóstico

SUGESTIVO DE EGI

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

SUGESTIVO DE EPILEPSIAS FOCALES

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

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

Investigación

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

Tratamento farmacológico

2013

SPECIAL REPORT

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

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

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

Revisión de la literatura: 1940-2012

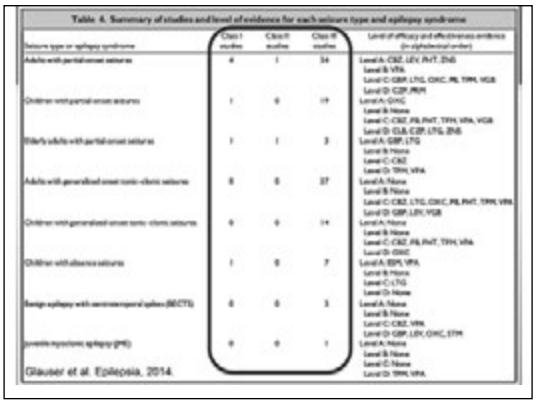


Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Glauser et al. Epilepsia, 2014.

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

Glauser et al. Epilepsia, 2013. UFSC

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

Glauser et al. Epilepsia, 2013. UFSC

Guidelines

- Falta de RCT bien diseñados
  - Niños y epilepsias generalizadas

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

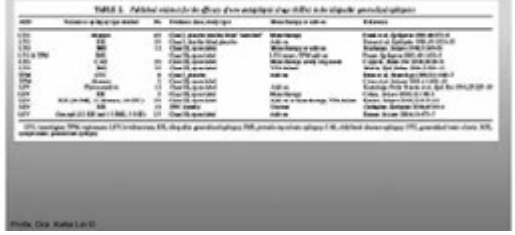
Glauser et al. Epilepsia, 2013.

UFSC

Dilemas en el tratamiento

Valproato – MAE de elección

Practical Management Issues for Idiopathic Generalized Epilepsies



Practical Management Issues for Idiopathic Generalized Epilepsies

TABLE 1. *Published evidence that some antiepileptic drugs (AEDs) are not effective in idiopathic generalized epilepsies and may exacerbate some seizure types (Modified with permission [11])*

AED	Seizure or epilepsy type studied	Reference
CBZ	IGE	*N Engl J Med* 1985;313:916–21
CBZ	JME	*Neurology* 2000;55:1106–9
CBZ	Unclear	*Epilepsia* 1994;35:1154–9
GBP	Childhood absence	*J Child Neurol* 1996;11:470–5
TGB	IGE	*Seizure* 1999;8:314–7
CBZ	Unclear	*Neurology* 1983;33:1487–9
CBZ	Mixed	*Pediatr Neurol* 1988;2:340–5
CBZ	Unclear	*Epilepsia* 1994;35:1026–8
CBZ	Unclear	*Epilepsia* 1994;35:1134–9
PHT	IGE	*Neurology* 1965;15:716–22
PHT, CBZ	JME	*Epilepsia* 1994;35:285–96
PHT, CBZ	JME	*Neurology* 2000;55:1106–9
OXC	IGE	*Epilepsia* 2002;43(suppl 7):308 [abstract]
OXC	IGE	*Epilepsia* 2004;45:1282–6


Obrigada!
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Neurologia

Jean Faber (Brazil)

BASIC STATISTICS FOR SCIENTIFIC RESEARCH

/ /

MEETING WITH FABIO ROGERIO, FINBAR O'CALLAGHAN, KATIA LIN

Helio Rubens Machado (Brazil)

SURGICAL TREATMENT OF TUBEROUS SCLEROSIS

LASSE XI
NEURODEVELOPMENTAL DISORDER AND EPILEPSY

TUBEROUS SCLEROSIS
Surgical treatment of epilepsy

Hélio Rubens Machado
PEDIATRIC NEUROSURGERY

CIREP – EPILEPSY SURGERY IN CHILDREN

RIBEIRÃO PRETO MEDICAL SCHOOL
UNIVERSITY OF SÃO PAULO

TREATMENT GOAL

- Eliminate seizures quickly
- Optimize cognitive development
- Improve behavior and quality of life

Hélio Rubens Machado

- History

Perot P, Weir B, Rasmussen, T: Tuberous Sclerosis. MNI, 1966

focus.[11,12] During the past 16 years at the Montreal Neurological Institute, surgical treatment for epilepsy has been carried out on seven patients in each of whom the cerebral lesion responsible for the seizure disorder was that of typical tuberous sclerosis. All of the patients presented with epilepsy; four patients had seizures with

had associated skin lesions. Two patients have been seizure free since operation (an average follow-up interval of 15 years), and a third patient operated on in January 1966 has been seizure free to date. Because of these encouraging results plus the increasing awareness that tuberous sclerosis is not necessarily a progressively fatal or debilitating disease, we have felt that it would be useful to review the clinical course of these seven patients in some detail.

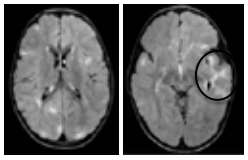
Hélio Rubens Machado

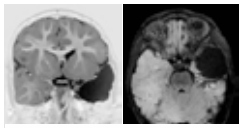
- History

1. Up to the 1990's surgery was usually discarded in cases of TSC "because that condition was notoriously diffuse"(Erba & Duchowny, 1990).
2. Occasionally a single tuber was unexpectedly found (so called "formes frustes") f.i in 2% of 503 consecutive cases at the MNI (Mathieson, 1975) or 2,3% in the UCLA series of 129 temp lobectomies (Babb & Brown, 1987).
3. At the Mayo Clinic 9 patients w TSC were operated between 1986 and 1990 and 6 cases became sz free (Bebin et al, 1993).
4. After 1986 the UCLA started a program considering possible candidates for surgery children with Infantile Spasms including TSC
5. In the Miami Children's Hospital 3 cases of TSC were reported as "cortical resection with excellent results"in spite of "unequivocal evidence of neuro-imaging of multiples areas of signal abnormalities" (Erba & Duchwony, 1990).
6. Between 1981 and 1993 six patients w TSC underwent resective surgery at the Cleveland Clinic, five after invasive monitoring with subdural grids.Five patients remained sz free (Acharya et al, 1995; Kotagal & Tuxhorn, 1997).

Hélio Rubens Machado

TSC surgery: focal surgery indicated for apparent multifocal or generalized epilepsy





Pediatric Neurol 2007

Pediatric Epilepsy Surgery in Focal Lesions and Generalized Electroencephalogram Abnormalities

- ARBAR, 3 yo. Sz free

Hélio Rubens Machado

Tuberous Sclerosis Complex

- Multi-system genetic disease: benign tumors in brain, skin, heart, eyes, lungs, kidneys

Diagnostic criteria for tuberous sclerosis complex

Major	Minor
Cardiac rhabdomyoma	Multiple pits in dental enamel
Cortical tuber	Hamartomatous rectal polyps
Facial angiofibroma	Bone cysts
Hypomelanotic macule	Radial migration lines in cerebral white matter
Lymphangioleiomyomatosis	Gingival fibromas
Renal angiomyolipoma	Retinal achromatic patches
Retinal hamartoma	"Confetti" skin lesions
Shagreen patch	Multiple renal cysts
Subependymal giant-cell tumor	
Subependymal nodule	
Cortical fibromas	

Definite TSC: Two majors or one major plus two minor criteria.

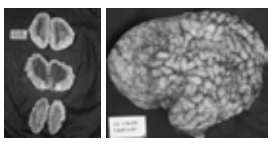
Probable TSC: One major plus one minor criteria

Possible TSC: One major or two minor features

THE TUBEROUS SCLEROSIS COMPLEX

Hélio Rubens Machado

- Prenatal diagnosis in TSC
  - Tubers form during embryonic brain development, probably between 9 - 20 w of human gestation (Glenn & Barkovich, 2006)



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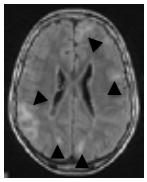
- Neurological Manifestations of TSC
  - Cortical tubers are collections of dysmorphic neurons, large astrocytes and giant cells
  - Epilepsy occurs in over 90% of patients and is associated with the presence of cortical tubers
  - Behavioral and cognitive impairments are common in children with TSC including such disorders as ASD(17%-68%) or ADHD(>50%)



ADHD – attention deficit- hyperactivity disorder
ASD- autism spectrum disorder

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- Epilepsy in Tuberous Sclerosis Complex
  - Present in >90% of TSC patients (many seizure types, many intractable)
  - >70% have focal or multifocal epileptiform EEG abnormalities
  - The tuberal / perituberal region of the cortex is the focus of seizures
  - AED may not be successful; epilepsy surgery is effective in many patients

Curatolo, 08

Hélio Rubens Machado

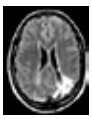
- Epilepsy in Tuberous Sclerosis Complex
  - 63% of patients experience seizure onset in the 1st year of life
  - 38% have infantile spasms
  - Focal seizures may precede, coexist with or evolve into infantile spasms
  - The likelihood of developing epilepsy after a first seizure is 100%
  - Vigabatrin is the drug of choice in TSC-related Infantile spasms

Curatolo, 08

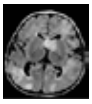
Hélio Rubens Machado

Tuberous Sclerosis Complex - Pathology

- SENs - subependymal nodules
  - Found in approximately 90% of cases
  - Sen often contain calcifications and are composed of glial cells
  - Small usually multiple, benign proliferative lesions lining the ventricular system that are believed to develop in fetal life and to be asymptomatic
  - Sen may grow and develop into SEGAs



- SEGAs - subependymal giant cell astrocytomas
  - Low-grade, slow-growing tumors that arise from the periventricular region and can cause obstructive hydrocephalus, frequently located at the foramen of Monro. Associated with morbidity and mortality
  - Found in 15% of cases.



Sarnat HB & Blumcke I: Malformations of cortical development. In: Surgical Neuropathology of focal epilepsies. 2015

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Tuberous Sclerosis Complex - Pathology

- CORTICAL TUBERS
  - Focal developmental malformations detected as single or multiple lesions in more than 80% of patients (Orlova & Crino, 2010)
  - Tubers display cortical dyslamination with cell types including dysmorphic neurons, reactive astrocyte and giant cells
  - No difference between dysmorphic neurons observed in tubers and in patients w FCD II a/b or HME. Similarly the giant cells in TSC are histologically identical to balloon cells detected in FCD IIb
  - Tubers are not static lesions, but are dynamic exhibiting evolving features overtime
  - Perituberal cortex, histologically normal, may show dysregulation of mTOR signaling and aberrant synaptic connectivity enabling intrinsic epileptogenicity (Philippe Major et al, 2009; Ruppe et al, 2014)

Sarnat HB & Blumcke I: Malformations of cortical development. In: Surgical Neuropathology of focal epilepsies. 2015

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7. Specific etiology

- Clinical characteristics
  - Symptomatic etiologies

TSC CHILDREN EVALUATED
total : 44 children
selected for surgery: 21 children

1996 to 2016 — Children 576

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

Pathology	
Cortical Dysplasia	**181**
Tumor	**73**
Gliosis	**70**
Mesial temporal sclerosis	**65**
Rasmussen encephalitis	**42**
Tuberous sclerosis	**21**
Porencephaly	**21**
Difuse atrophy	**20**
MR normal	**11**
Sturge-Weber	**10**
AVM	**3**
(other 59) Total	**576**

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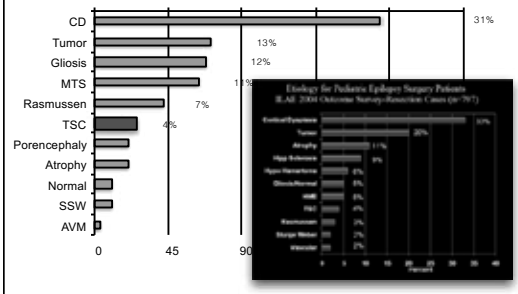
Etiology of cases operated at CIREP (RP) - 1996 to 2016 (n= 576)



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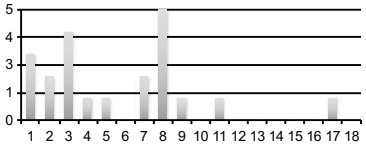
Age at surgery – 20 patients



DEFINING THE TARGET OF SURGERY

- Main objective identify epileptogenic tuber and evaluate benefits and risks of resection as early as possible

- tuber
- perituberal cortex
- SEGA

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Epilepsy Surgery - different approaches

Noninvasive			
FDG PET/ MRI MEG Intraop ECoG	**UCLA** **Toronto**	AMT PET GRIDS	**WAYNE STATE**
Invasive			
Phased surgery Intracranial GRIDS/ STRIPS	**NYU**	SPECT + MEG GRIDS Intraop ECoG SEEG	**CCF** **Miami** **Netherlands**

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Patient management

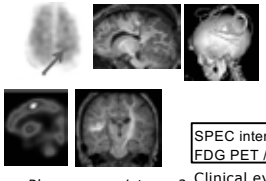
ECoG	Invasive	none
8	10	3

1. Temporal lobe
2. Hemispheric
3. VNS

INVASIVE EVALUATION

subdural / depth recordings

⇧



SPEC interictal / ictal
FDG PET / (AMP-PET)

Pharmacoresistance? Clinical evaluation
Localization hypothesis ? ***MR screening***

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- UCLA – ictal video EEG localized to a quadrant in 39%, hemisphere in 36 %
- All patients FDG-PET and MRI + MSI
- 67% Sz free after surgery

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Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex

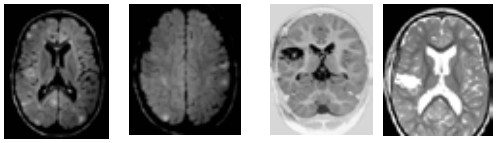
- UCLA – ictal video EEG localized to a quadrant in 39%, hemisphere in 36 %
- All patients FDG-PET and MRI + MSI
- 67% Sz free after surgery

Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with alpha-[11C]methyl-L-tryptophan positron emission tomography (PET).

- AMT PET detects dysplasia around tubers
- AMT PET a tracer of tryptophan metabolism, can differentiate between epileptogenic and nonepileptogenic tubers interictally in two-thirds of TSC patients with intractable epilepsy

Tuberous Sclerosis

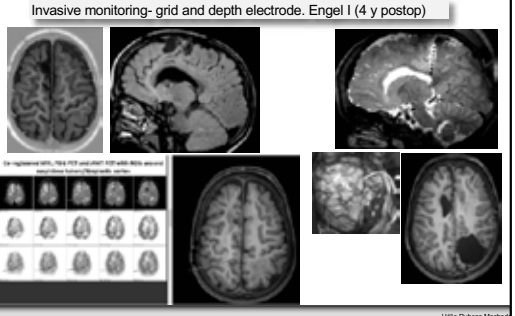
- ASRPF, 2 yo, sz since 6 mo old w eye blink and at 8 mo w head fall. TSC complex was diagnosed. Infantile spasms started at 11 mo age. Video-monitoring and invasive monitoring demonstrated sz starting at R insula



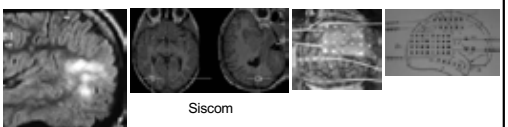
- Surgery: Resection of the tuber
- Outcome: Seizure free. Mild L deficit (cleared 6 mo after surgery)

- PLT, 4 yo, TSC, submitted to surgery elsewhere, sz persisted.

Invasive monitoring- grid and depth electrode. Engel I (4 y postop)

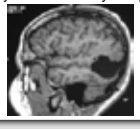


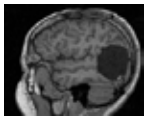
- **FAFC, 7 yo. sz since 2 mo , Infantile Spasms**



Siscom

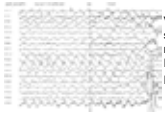
- 1st surgery – Lesionectomy . Sz persisted



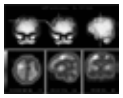


- 2nd surgery – Engel I (7y)

- JLBN, 1 year 5 mo, sz since 3 mo old, Infantile Spasms, developmental delay. Video-EEG : L frontal. Ictal SPECT: hiperperfusion L Frontal. Surgery:L Frontal lobectomy + resection of SEGA. Engel I (10 y fu).

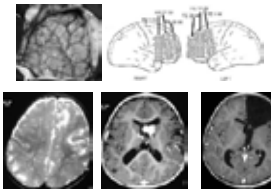


Video EEG – Sz starting in the L frontal region. Spike-wave FP1, F7, max activity F3

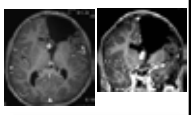


Ictal Spect – inj at 34 sec – hyperperfusion R frontal

Hypoperfusion L



Invasive monitoring – L frontal



10 y fu – SEGA R Frontal

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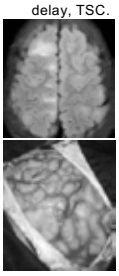
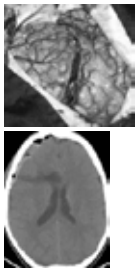
- JJBCF, 5 y old, sz since 6 mo age, refractory to AED, mild cognitive delay, TSC.





R Frontal Disconnection + resection of tuber Engel I

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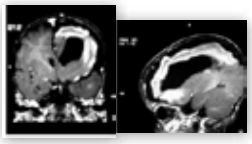
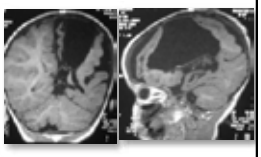
- **FAPS,10 mo old, Infantile spasms, TSC (hemimegalencephaly). Engel I**
- Vertical hemispherotomy

postop





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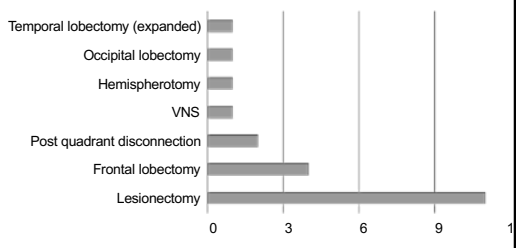
SURGICAL TECHNIQUES APPLIED TO TSC PATIENTS



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- **TSC Natural History Database Project: Epilepsy Surgery (Nakagawa J, AES,2009)**
  - 28% surgery (173 incl SEGA, VNS); 72% medical
  - Brain surgery (multiple procedures)
    - VNS 51%
    - Resective Surgery 49%
      - 28 % lesionectomies; multilobar resections 20%; hemispherectomy 2%
      - corpus callosotomy 7,5%
      - SEGA resection 22%

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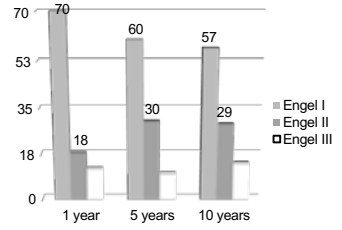
Results of surgical treatment in TSC patients



- mortality – 1 case

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Conclusions

1. **Children with TSC should be evaluated for surgery as early as possible.**
2. **Although non-invasive methods are attractive in the majority of cases invasive evaluation will be needed.**
3. **When carefully selected surgical candidates will have a good prognosis.**

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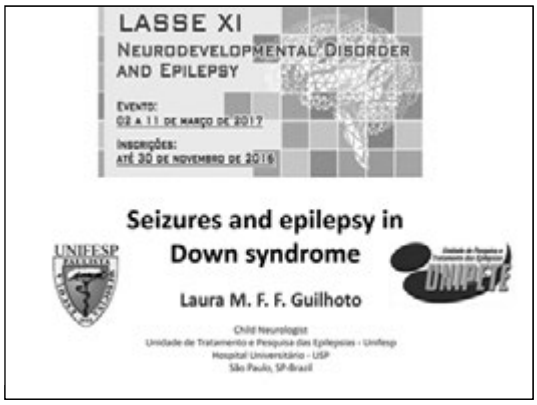
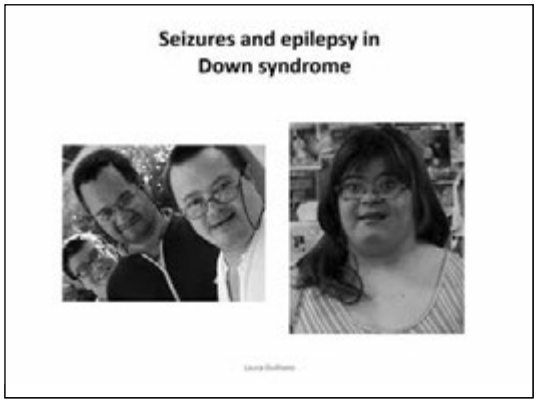
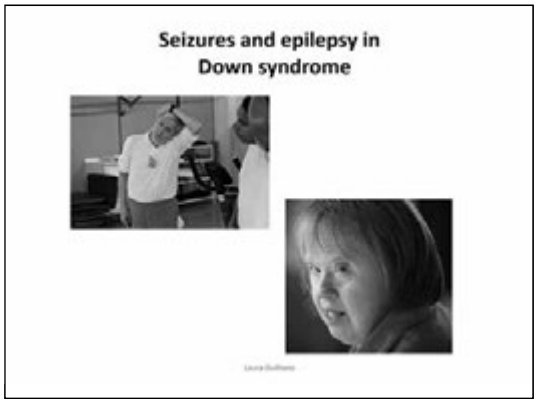
Laura Guilhoto (Brazil)

SEIZURES AND EPILEPSY IN DOWN SYNDROME







Seizures and epilepsy in Down syndrome

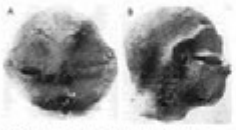
1. **History**
2. Down syndrome
3. Down syndrome and epilepsy – early years
4. Down syndrome, aging and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

History: Down syndrome

- Descriptions with possible allusions to the physical characteristics of Down syndrome in old objects (pre and post Christianity)
  - Ancient Greece
  - Pre-Colombian America
  - Europe: middle age and Renascence

History: Down syndrome

Neolithic idol - Greece - 5.000 b.C.



(Diamandopoulos et al., 1997)

Egyptian figure - 100 A.D.

(Kunze & Nippert, 1996)

History: Down syndrome

- Olmec figures - Meso-America 1500 b.C.
  (Milton & Gonzalo, 1974)

History: Down syndrome

- Peru – 1.200-1.500 b.C. (Wells, 1964; Ebbin et al., 1968)

- Culture Tumaco-La Tolita - Colombia and Ecuador – c. 500 b.C. (Bernal & Brecino, 2006)

Starbuck. J Contemp Anthropol 2011;2(1):19-43

Laura Guilfoile

History: Down syndrome

- Monte Alban – Mexico - 400-800 A.D. (Kunze & Nippert , 1986)

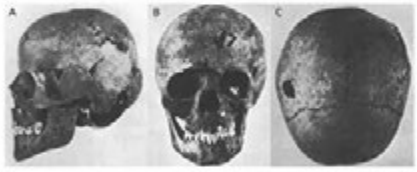
- Terracotta figure – culture Tolteca - Mexico – c. 500 A.D. (Martinez-Frias, 2005)

Starbuck. J Contemp Anthropol 2011;2(1):19-43

Laura Guilfoile

History: Down syndrome

- Breedon-on-the-Hill – England (700-900 A.D.) (Brothwell, 1960)



Starbuck. J Contemp Anthropol 2011;2(1):19-43

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History: Down syndrome

The Adoration of the Christ Child
Jan Joest of Kalkar (Netherland, c. 1515)

Starbuck. J Contemp Anthropol 2011;2(1):19-43

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History: Down syndrome

Lady Cockburn and her children
Joshua Reynolds (1723-1792)

The Adoration of the Shepherd
Jacob Jordaens (1593-1678) (c. 1618 A.D.)

Starbuck. J Contemp Anthropol 2011;2(1):19-43

Laura Guilhoto

History: Down syndrome

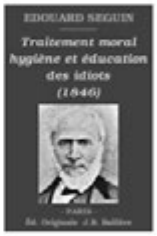
- First clinical descriptions are considered those done in 1838 by French Psychiatry Jean-Étienne Dominique Esquirol
  - Difference: mental disease X mental deficiency

Laura Guilhoto

Wehmeyer 2013. The history of Intellectual Disability. Brookes Co.

History: Down syndrome

- French physician Onésime-Édouard Séguin
  - 1846: publication of first treaty of education in children with intellectual disability
  - description of some features found in Down syndrome



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Wehmeyer 2013. The history of Intellectual Disability. Brookes Co.

History: Down syndrome

- 1866 English physician Longdon Down, contemporaneously to Mendelian laws discovery, described in details the features of the children called mongoloids, how were named the people with Down syndrome

—[...] when placed side by side, it is difficult to believe that the specimens compared are not children of the same parents. (Down, 1866).

Laura Guilhoto

History: Down syndrome

OBSERVATIONS ON AN ETHNIC CLASSIFICATION OF IDIOTS.

By J. LANGDON H. DOWN, M.D., Lond.

- Down JL. Observations on an Ethnic Classification of Idiots. London Hospital Reports, 3:259-262, 1866.

"....The life expectancy, however, is far below the average,....."

History: Down syndrome

- 1959 Jerôme Jean Louis Marie Lejeune, French geneticist, published with his group, after the description of DNA by Watson & Crick in 1953, the genetic abnormality in Down syndrome, the **trisomy of chromosome 21**

History: Down syndrome

- Lejeune J. Le mongolism: premier exemple d'aberration autosomique humaine. Ann. Genet. 1, 41-9 (1959)
- Lejeune J, Turpin R, Gautier M. Chromosomic diagnosis of mongolism. Arch Fr Pediatr. 16:962-3 (1959)

History: Down syndrome

- Terminology:
  - In 1961 the term mongolism was replaced by **trisomyc anomaly of chromosome 21** or **Down syndrome**
  - Down syndrome (USA)
  - Trisomy of chromosome 21 (Europe)

History: Down syndrome

- In 2012 UNESCO promulgated the International day of Down syndrome celebrated in March 21

http://www.worlddownsyndromeday.org/

Seizures and epilepsy in Down syndrome

1. History
2. **Down syndrome**
3. Down syndrome and epilepsy – early years
4. Down syndrome, aging and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

Down syndrome

- Down syndrome (DS) : trisomy of chromosome 21
- 1-3/1.000 live births
- Longer life expectancy nowadays, better clinical characterization
  - Early aging
  - Dementia as in Alzheimer disease

Down syndrome

Most common genetic cause of intellectual disability

- Trisomy 21 (HSA21) (47, +21): 95%
  - ✓ Frequency of trisomy increases with increasing maternal age
- Robertsonian translocation involving chromosome 21: ± 3%, not related to maternal age
- Trisomy 21 mosaicism – 2% cases

Relationship Of Down Syndrome Incidence To Mothers Age

Mothers Age	Incidence Down Syndrome
Under 30	Less then 1 in 1,000
30	1 in 900
35	1 in 400
36	1 in 300
37	1 in 230
38	1 in 180
39	1 in 135
40	1 in 105
42	1 in 60
44	1 in 35
46	1 in 20
48	1 in 16
49	1 in 12

Hook & Lindsjo 1978. Am J Hum Genet.30(1):19-27

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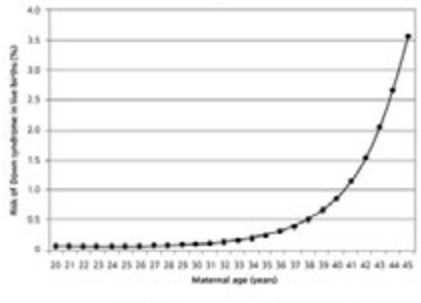
Down syndrome



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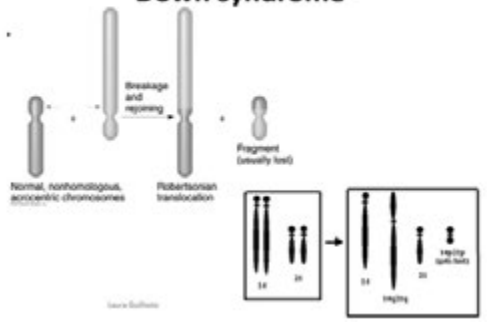
Cuckle et al 1987. Br J Obstet Gynaecol 94:387-402

Down syndrome



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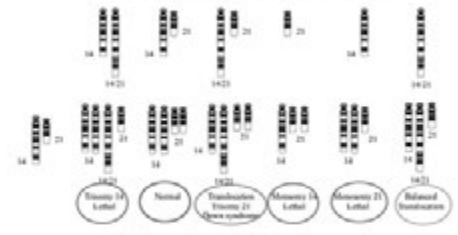
Translocation

Possible gametes from translocation



Offspring when combined with normal gamete

Human genomic project

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Down syndrome

Trisomy 21 mosaicism – 2% cases

International Mosaic Down Syndrome Association

Down syndrome

-40% of known causes of Intellectual Disability
-Related to maternal age during gestation
-Intellectual disability within a spectrum
-Typical facial features
-Abnormalities: cardiac, metabolic (thyroid), orthopedic (ligament laxity), ocular and immunological dysfunction

Down syndrome

- Single phenotype, variable expression and epigenetic influence
- Clinical characteristics
  - Oblique eyelid folds , epicanthus, acromicia, tongue protrusion, brachydactyly, hypotonia, single palmar crease, etc..
- Pre-natal diagnosis (95%)
  - Human chorionic gonadotropin
  - Nuchal translucency
  - Alpha-fetoprotein
  - Amniocentesis
  - Chorionic villus sampling
  - Detection of cells with trisomy in maternal blood

Karyotyping in Down syndrome

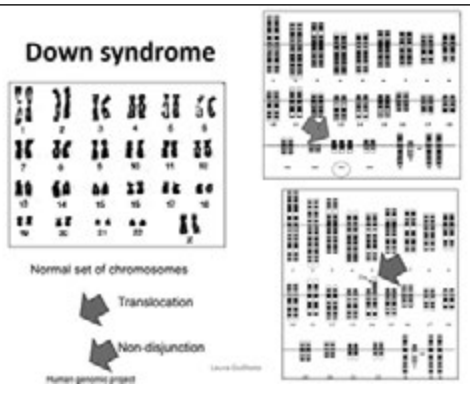
Non-disjunction trisomy 21	95%
Robertsonian translocation	3%

Recurrence risk by karyotype

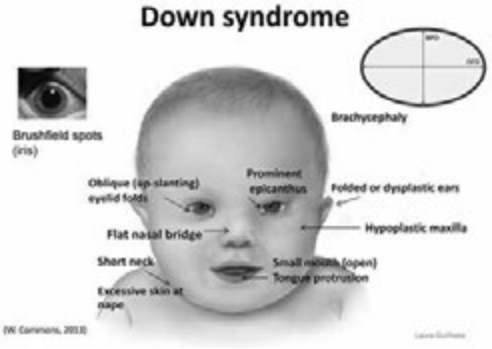
Non-disjunction trisomy 21	
47(XX or XY) + 21	1%
Translocation	
both parents normal	<1%
father carrier	3%
mother carrier	12%
mosaics	<1%

(Benke et al. 1995. http://www.ds-health.com/benke.htm)

Down syndrome



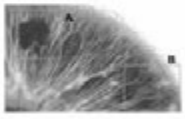
Down syndrome



Down syndrome

- Epicanthal folds are prominent

- The iris has the light smudgy opacities of Brishfield spots



Down syndrome

Extremities

- Short broad hands
- Short fifth finger
- Incurved fifth finger
- Transverse palmer crease
- Space between first and second toe
- Hyper flexibility of joints

Down syndrome

Dental Anomalies

- Microdontia in 35-55%
- Hypoplasia and hypocalcification are common
- Congenitally missing teeth (partial anodontia) occur in 50% of people with Down syndrome
- Delay in the eruption of dentition

Desai. 1997. Oral Surg Oral Med Oral Pathol Oral Radiol Endod;84(3):279-85.

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Down syndrome

Newborn

- cardiac defects
- gastrointestinal: duodenal atresia, tracheo-oesophageal fistula, anorectal malformation, pyloric stenosis and Hirshsprung disease
- vision: congenital cataracts, glaucoma
- hypotonia & joint laxity
- feeding problems
- congenital hypothyroidism
- congenital dislocation of the hips

Hickey et al. 2012. Adv Pediatr;59(1):137-57
Bull 2011. Pediatrics. 2011;128(2):393-406

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Down syndrome

Infancy and Childhood

- hypothyroidism (10%) (prev. increases with age)
- short stature
- congenital heart disease
- coeliac disease
- nutritional inadequacy due to feeding problems and thyroid hormone deficiency
- over/underweight
- recurrent respiratory infections
- leukemia (relative risk: 15 to 20 times): incidence 1%

Hickey et al. 2012. Adv Pediatr;59(1):137-57
Bull 2011. Pediatrics. 2011;128(2):393-406

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Down syndrome

Infancy and Childhood

- delayed developmental milestones
- mild to moderate intellectual impairment (IQ 25 to 50)
- epileptic seizures (6%)
- hearing loss (>60%) due to secretory otitis media, sensorineural deafness, or both
- visual impairment – squint (50%), cataract (3%),
- nystagmus (35%), glaucoma, refractive errors (70%)
- sleep related upper airway obstruction

Hickey et al. 2012. Adv Pediatr;59(1):137-57
Bull 2011. Pediatrics. 2011;128(2):393-406

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Down syndrome

Infancy and Childhood

- Atlantoaxial instability
  - children with Down syndrome should not be barred from taking part in sporting activities
  - appropriate care of the neck
    - under general anesthesia
    - after road traffic accident

Hickey et al. 2012. Adv Pediatr 59(1):137-57
Burt 2011. Pediatrics. 2011;128(2):393-406

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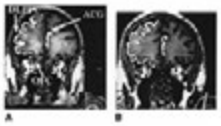
Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: Evidence from MRI morphometry



A B

Neurology 1995;45:356-366

A: DS B: control

Down syndrome

Smaller: cerebral and cerebellar hemispheres, pons, mammillary bodies, hippocampal formation, cerebellar vermis: smaller lobules VI- VIII; decreased dorsolateral prefrontal cortex, anterior cingulate gyrus, inferior parietal and temporal cortex, parietal white matter and pericalcarin cortex;

Larger: parahippocampal gyrus

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Down syndrome

- Why the phenotipical spectrum?

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Seizures and epilepsy in Down syndrome

1. History
2. Down syndrome
3. **Down syndrome and epilepsy – early years**
4. Down syndrome, aging and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

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Down syndrome and epilepsy

- Epilepsy: approximately 5-13%
- Epilepsy incidence

  General Population < DS < ID
- Bimodal pattern
  - Early childhood (infantile spasms, reflex seizures, Lennox-Gastaut syndrome)
  - Adults (focal seizures, tonic-clonic, reflex seizures, late onset myoclonic epilepsy - LOMEDS)
    - 18-35 yrs.
    - >35yrs.

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Down syndrome and epilepsy

- High prevalence of EEG abnormalities (20-25%) even in the absence of seizures
- No distinctive EEG pattern or correlation with behavioural phenotype

Ellingson et al. 1973. Electroencephalogr Clin Neurophysiol;34(2):193-6

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Down syndrome and epilepsy

Putative mechanisms of epileptogenesis in DS

Neuronal or synaptic anatomy
- Fewer inhibitory inter-neurons - Decreased neuronal density - Abnormal neuronal lamination - Persistence of dendrites with foetal morphology - Primitive synaptic profiles
Membrane channel dysfunction
- Altered membrane potassium permeability - Decreased voltage threshold for spike generation - Smaller hyperpolarization following spikes - Altered action potential duration

Arya et al. Epileptic Disord 2011; 13 (1): 1-7

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Down syndrome and epilepsy

Epilepsy & Behavior

Cerebral overinhibition could be the basis for the high prevalence of epilepsy in persons with Down syndrome

Bruno Henrique Silva Araujo, Leila Brito Torres, Laura Maria F.F. Guilhoto

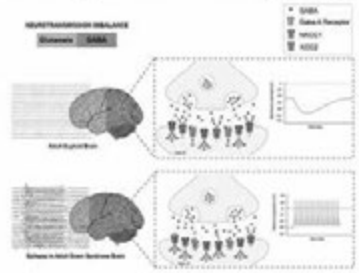
Araújo et al. Epilepsy & Behavior 2015;53:120-5

Down syndrome and epilepsy

- Hypotheses underlying increased seizure susceptibility:
  - Structural brain abnormalities
  - Abnormal cortical lamination
  - Disruption of normal dendritic morphology
  - Underdeveloped synaptic profiles
  - Deficiency or loss of GABA inhibition
  - Excessive inhibitory brain function
    - Paradoxically, enhanced GABA inhibition has also been reported to promote seizures

Araújo et al. Epilepsy & Behavior 2015;53:120-5

Down syndrome and epilepsy



Araújo et al. Epilepsy & Behavior 2015;53:120-5

Down syndrome and epilepsy

Infantile Spasms

- The most important type of seizures in children with DS
- Onset usually at 6-8 months of age (range 4-18 m) (Eisermann et al., 2003; Goldberg-Stern et al., 2001; Nabbout et al., 2001; Pollack et al., 1978; Silva et al., 1996; Stafstrom and Konkol, 1994; Wolcott and Chun, 1973)
- Male preponderance (Goldberg-Stern et al., 2001; Stafstrom and Konkol, 1994)

Arya *et al.* Epileptic Disord 2011; 13 (1): 1-7

Down syndrome and epilepsy

Infantile Spasms

- May be associated to secondary lesions
- Risk factors
  - Prematurity
  - Congenital heart disease
  - Cardiac surgery
  - Perinatal hypoxia-ischaemia

Goldberg-Stern *et al.* 2001. Brain Dev;23(6):376-8

Down syndrome and epilepsy

Infantile Spasms

- EEG characteristics in Infantile spasms and DS (Silva et al., 1996)
  - Symmetrical hypsarrhythmia
  - No focal activity
  - Single rather than clustered spasms on ictal EEG
- When associated to other lesions
  - No interictal paroxysmal activity between consecutive spasms
  - EEG seizure initiated by or combined with focal discharges

Lopes *et al.* Epilepsia 1998;37:977-82

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Down syndrome and epilepsy

Infantile Spasms

- Classical hypsarrhythmia

Eisermann *et al.* 2003. Epilepsy Res;55:21-7
Pollack *et al.* 1978. Ann Neurol;3:406-8

- Other EEG patterns without structural correlate
  - Focal discharges
  - Hypsarrhythmia variants
  - Burst suppression patterns and hemi-hypsarrhythmia

Goldberg-Stern *et al.* 2001. Brain Dev;23(6):373-8
Stafstrom & Konkol. 1994. Dev Med Child Neurol;36(7):576-85

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Down syndrome and epilepsy

Infantile Spasms

Treatment

- Vigabatrine
- Steroids
  - ACTH
  - Predinosolone
- Sodium valproate
- Benzodiazepines
- Pyridoxine

Arya *et al.* Epileptic Disord 2011;13(1):1-7

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Down syndrome and epilepsy

Infantile Spasms

Prognosis

- Relative better evolution than other etiologies

Menendez. Brain Dev 2005;27:246-52

- Predictors
  - Early treatment of spasms for
    - Seizure remission
    - Developmental quotient
    - Autistic score
  - Delayed response to treatment

Eisermann *et al.* Epilepsy Res 2003;55:21-7

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Down syndrome and epilepsy

Infantile Spasms

Prognosis

- Evolution to other seizure types
  - Focal, myoclonic, generalised tonic clonic and atonic seizures (Goldberg-Sternetal.,2001; Silva et al., 1996)
  - Progression to Lennox-Gastaut syndrome (Stafstrom and Konkol, 1994)
  - Response to conventional medications including VPA and benzodiazepines

Eisermann *et al.* Epilepsy Res 2003;55:21-7

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Down syndrome and epilepsy

Lennox-Gastaut syndrome

- 13 patients (8 males)
- Mean age at onset : 9.1 yrs. (range 5-16)
  - 62% experienced seizure onset > age 8 yrs.
- None had IS
- Predominance of reflex seizures, precipitated by sudden unexpected sensory stimulation
  - Common sensory triggers: noise, touch, emotions
  - Tonic, atypical absence, myoclonic, generalized tonic-clonic, atonic (most refractory to treatment)
- Majority had normal neuroimaging

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Fenaccio *et al.* Epilepsia 2009;50:1587-95

Down syndrome and epilepsy

Reflex seizures

Reflex Seizures are Frequent in Patients with Down Syndrome and Epilepsy

*Ilkasso Guerrini, *Pierre Genton, †Michelle Bureau, *Charlotte Dravet, and *Joseph Roger

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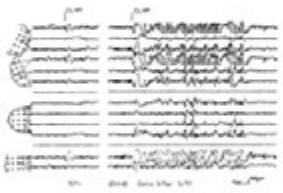
Guerrini *et al.* Epilepsia 1990;31(4):406-17

Down syndrome and epilepsy

Reflex seizures

- Onset 2.5-24 yrs
- Differences from other etiologies
  - Usually detected without other spontaneous seizures
  - Occur without spasticity or focal motor deficits



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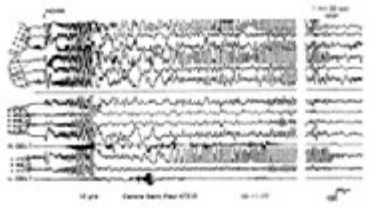
Guerrini *et al.* Epilepsia 1990;31(4):406-17

Down syndrome and epilepsy

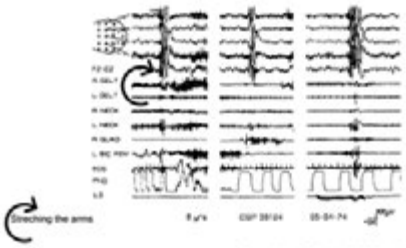
Reflex seizures



Guerrini et al. Epilepsia 1990;31(4):408-17

Down syndrome and epilepsy

Reflex seizures



Guerrini et al. Epilepsia 1990;31(4):408-17

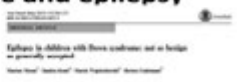
Down syndrome and epilepsy

Other seizure types

- Gelastic features evolving with typical flexor spasms
  Pollack *et al.* 1978. Ann Neurol 3(5):406-8
- Mainly present in other secondary causes
  - Stroke or hypoxic-ischaemic encephalopathy
  - Associated genetic causes (phenylketonuria, neurofibromatosis-1
    Goldberg-Stern *et al.* 2001. Brain Dev;23(6):375-8
  - A symptomatic basis could be demonstrated in 61%
    - Additional causes: bacterial and viral neurological infections, cerebrovascular disease including moya-moya syndrome, intracranial bleed and chemotherapy related neurotoxicity
      Stafstrom *et al.* 1991. Dev Med Child Neurol;33(3):191-200

Down syndrome and epilepsy

Prognosis



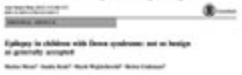
- 130 children with DS
- Followed up by a multidisciplinary team at the Antwerp University Hospital
- 12 (9.2 %; 8 boys) had epileptic seizures
  - 8 infantile spasms
  - 4 other seizure types

  (2 other had spike-like activity in 24-h video-EEG, without clinical signs of seizures)

Meeus et al. Acta Neurol Belg 2015;115:569-73

Down syndrome and epilepsy

Prognosis



Infantile spasms (8/12)

- VGB or VPA 1st line
- All received VGB (4/8 controlled seizures)
- Steroids after - 5/8 (1 controlled seizures)
- Time to seizure control - 3 to 13 m

Other seizure types (4/12)

- VPA 1st line (3/4) - all seizure free in 3 month
- 1/4 politheray - seizure free after 140 m (LTG)

Meeus et al. Acta Neurol Belg 2015;115:569-73

Seizures and epilepsy in Down syndrome

1. History
2. Down syndrome
3. Down syndrome and epilepsy – early years
4. **Down syndrome, aging and Alzheimer disease**
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

Down syndrome and epilepsy
Epilepsy Prevalence

>50 yrs. and DS

46% (McVicker et al., 1994)

Non-SD and Alzheimer Disease

10-12% (Bernardi et al., 2009)

Down syndrome and aging

Early aging

- Life expectancy 12 yrs. in 1949 to 60 yrs. in 2010 (Bittles & Glasson, 2004; Penrose, 1949)
- Skin/hair abnormalities
- Early menopause
- Visual and auditory abnormalities
- Late epilepsy
- Thyroid dysfunction
- Diabetes, obesity
- Sleep apnea
- Muscle and skeletal abnormalities

Esbensen 2010. Int Rev Res Ment Retard;39(C):107-26

Down syndrome
Mortality

- Life expectancy still below the general population
  - Women with DS: shorter than men (premature menopause?)
- Predictive factors: previous functional abilities, age, worsening of behavior disorders
- Common causes of death: leukemia, respiratory disease, circulatory congenital malformations, dementia
- In children with DS: leukemia (after respiratory problems and congenital heart defects)
- Mortality due to the risk of cancer in adults with DS is equal to or lower than in general population or in other causes of ID
  - In particular, risk of mortality from solid tumors among adults with DS is considerably lower

Esbensen 2010. Int Rev Res Ment Retard;39(C):107-26

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Down syndrome - Adult life

- Respiratory problems and birth defects: more common
- Ischemic CV disease: less common
- High frequency of mitral valve prolapse
- Decreased risk for CV and cerebrovascular disease
- Lower frequency of emphysema, fractures, hypercholesterolemia and heart disease compared to adults with ID from other causes
- Lower resting heart rate and lower blood pressure than the general population

Esbensen 2010. Int Rev Res Ment Retard;39(C):107-26

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Comparison of Intima-Media Thickness of the Carotid Artery and Cardiovascular Disease Risk Factors in Adults With Versus Without the Down Syndrome

Christopher C. Draheim, PhD*, Justin B. Geijer, MS*, and Donald R. Dengel, PhD*†‡

Adults with DS lower arterioscleorsis levels ?

- CV disease risk: intima-media thickness of carotid artery (IMT)
- Method: B-mode imaging L common carotid
- 52 adults with DS (25 male, mean age 42yrs.) x controls

DS

- lower levels
  - IMT (0.43±0.07 vs 0.48±0.09 mm, p <0.001)
  - Systolic BP (116±15 vs 125±17 mm Hg, p <0.011)
  - Diastolic BP (69±10 vs 73±9 mm Hg, p <0.001)
- Higher levels
  - Protein C-reactive (0.58±0.55 vs 0.30±0.42 mg/dl, p <0.001)
  - Triglycerides (126.5±55.2 vs 103.8±53.2 mg/dl, p <0.048)
  - Total fat (37.8±10.2% vs 32.4±11.2%, p <0.002)
- Males (p <0.001) and physical activity (p=0.020) predictors of IMT for adults with DS
- Fasting insulin (p <0.001), age (p <0.001), gender (p <0.001), fruit and vegetable intake (p=0.001), LHDL cholesterol (p=0.004), smoking (p=0.023) for controls

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Draheim et al., 2010. Am J Cardiol;106(10):1510-4.

Seizures and dementia in Down's syndrome

1. History
2. Down syndrome
3. Down syndrome and aging
4. **Down syndrome and Alzheimer disease**
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

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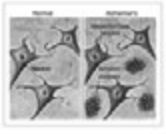
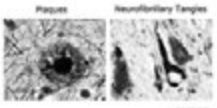
Down syndrome and aging

- Up to 35 yrs. mortality rate similar to other causes of intellectual disability
  - After 35 yrs.: mortality rate doubles each 6.4 yrs. vs each 9.6 yrs. in people without Down syndrome (Strauss & Eyman, 1996; Head et al., 2012)
  - Down syndrome involves the overexpression of amyloid precursor protein in chromosome 21

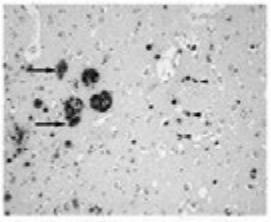
Alzheimer's Disease Plaques and Tangles

- Cause or symptom ?
- Amyloid plaques are deposits of beta-amyloid protein that build up in the spaces between nerve cells
- Neurofibrillary tangles are twisted fibres of tau protein that build up inside cells
- Neocortical atrophy with neuronal loss, synaptic loss
- Neurochemical changes – cholinergic deficits in cortical and limbic regions





Aβ immunization in Alzheimer disease induces amyloid plaque phagocytosis by activated microglia



Perry, V. H. et al. (2010) Microglia in neurodegenerative disease. *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2010.17

nature REVIEWS NEUROLOGY

Down syndrome and Alzheimer disease

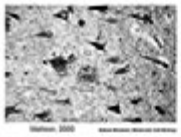
- Age
- Gender (even when controlling for longevity)
  - Females increased AD likelihood
- Vascular risk factors (smoking, vascular disease, diabetes, etc) even in AD
- Head trauma
- Education? Cognitive reserve
- Family history
- Apolipoprotein E (ApoE) status

McCullagh *et al.* 2001. Adv Psychiatr Treat;7:24-31

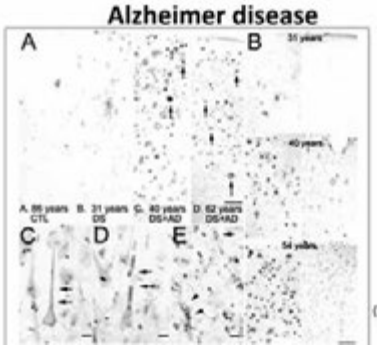
Down syndrome and Alzheimer disease

- Plaques and tangles in the brain tissue present in the brains of nearly all adults with Down syndrome by the age of 40

(Malamud, 1972; Wisniewski et al. 1985)



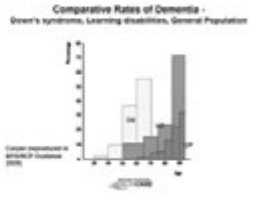
Down syndrome and Alzheimer disease



(Head & Lott, 2001)

Down syndrome and Alzheimer disease

- Increased life expectancy
- Link between chromosome 21 and amyloid production
- Average age of onset is 55 yrs.
- 9 years (on average) from diagnosis to death
- Virtually all people with DS >40 yrs. show characteristic brain changes of AD - although not all show clinical signs



Chromosome 21

Panel 1: 16 genes on chromosome 21 with a role in energy and reactive oxygen species metabolism

Symbol	Name
BTG3	BTG family, member 3
MRPL39	Mitochondrial ribosomal protein L39
ATP5J	Mitochondrial coupling factor 6
GABPA	GA binding protein transcription factor, alpha subunit 60kDa
BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor 1
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))
CRYZL1	Crystallin, zeta (quinone reductase)-like
ATP5O	ATP synthase H+ transporting, mitochondrial F1 complex, O subunit (oligomycin sensitivity conferring protein)
MRPS6	Mitochondrial ribosomal protein S6
DSCR3	Down syndrome critical region 3
CBR1	Carbonyl reductase 1
CBR3	Carbonyl reductase 3
SH3BGR	SH3 domain binding glutamic acid-rich protein
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 3, 10kDa
SNF1LK	SNF1-like kinase
C21orf2	Chromosome 2 open reading frame (mitochondrial protein)

Genes involved with energy and reactive oxygen species metabolism

Rozen & Patterson 2003 Lancet;361(9365):1281-9

Chromosome 21

Genes involved possibly in brain development, neuronal loss, AD

Panel 2: **Genes localised to chromosome 21 that possibly affect brain development, neuronal loss, and Alzheimer's type neuropathology**

Symbol	Name	Possible effect in Down's syndrome
SIM2	Single-minded homolog 2 (Drosophila)	Brain development: required for synchronised cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A	Brain development: expressed during neuroblast proliferation and believed important homologue in regulation of astrocyte kinetics during cell division
GART	Phosphoribosylglycinamide formyltransferase, Phosphoribosylglycinamide synthetase, Phosphoribosylaminoimidazole synthetase	Brain development: expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development: function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart disease: expressed in all molecular regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system
GRIK1	Glutamate receptor, ionotropic, kainate 1	Neuronal loss: function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer's type neuropathy: seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein, beta (neural)	Alzheimer's type neuropathy: stimulates glial proliferation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated ageing? Scavenges free superoxide molecules in the cell and might accelerate ageing by producing hydrogen peroxide and oxygen

Rozen & Patterson 2003. Lancet;361(9365):1281-9

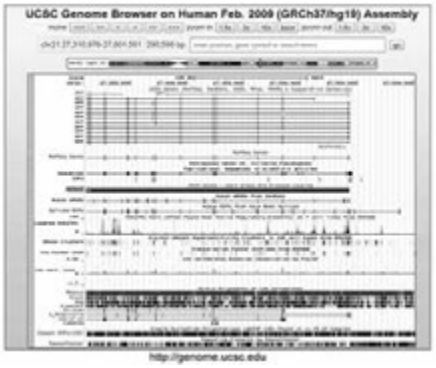
Chromosome 21

Panel 3: **Six genes with a role in folate and methyl group metabolism**

Symbol	Name
N6AMT1	Putative N6 DNA methyltransferase
CBS	Cystathionine-beta-synthase
DNMT3L	DNA (cytosine-5-)-methyltransferase-like
SLC19A1	Solute carrier family 19 (folate transporter), member 1
FTCD	Formiminotransferase cyclodeaminase
HRMT1L1	HMT1 hnRNP methyltransferase-like 1 (S cerevisiae)

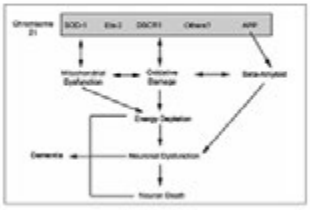
Genes are listed in order from the centromere to the telomere on chromosome 21. There might be additional genes in the group that have not yet been identified.

Rozen & Patterson 2003. Lancet;361(9365):1281-9



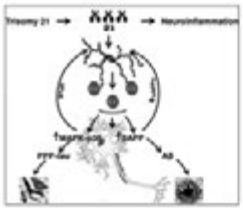
http://genome.ucsc.edu

Down syndrome and Alzheimer disease



Lott et al. 2006. Curr Alzheimer Res;3(5):521-8

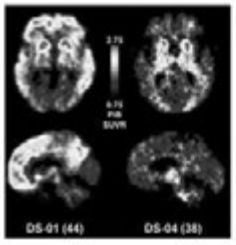
Down syndrome and Alzheimer disease

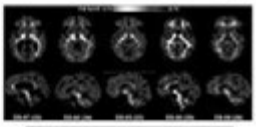


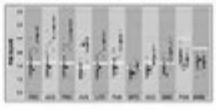
(Wilcock & Griffin, 2013)

(Head & Lott, 2004)

Imaging brain amyloid in nondemented young adults with Down syndrome using Pittsburgh compound B







Down syndrome and Alzheimer disease

Neuroscience Letters

Association of variants within APOE, SORL1, RUNX1, BACE1 and ALDH18A1 with dementia in Alzheimer's disease in subjects with Down syndrome

Down syndrome and Alzheimer disease

Obesity

– Individuals with Down syndrome are more likely to be overweight or obese than other individuals with intellectual disability

- Intellectual disability & DS – mean BMI 30.40
- Intellectual disability only – mean BMI 28.55
- Intellectual disability & autism/PDD – mean BMI 27.42
- Intellectual disability & CP – mean 24.53

	Obese (BMI ≥ 30)	Overweight or Obese (BMI ≥ 25)
Down syndrome	44.3%	72.7%
U.S. population	33.8%	68.0% Flegal et al. 2010 JAMA 303(3):235-241

Stancliffe 2011, Am J Intellect Dev Disabil,116(6):401-18

Down syndrome and Alzheimer disease

Sedentary Lifestyle

- Levels of physical activity in non-athletic adults without intellectual disability were twice as high compared to adults with an intellectual disability
- No significant difference between Down syndrome and other causes of intellectual disability

Vis et al. Int J Cardiol. 2012;26;156(3):367-93

Laura Gulfhane

Down syndrome and Alzheimer disease

Alzheimer disease in the general population
- Roughly 10% of people 65 yrs. and older
- Nearly 50% of people 85 yrs. and older

Clinical symptoms of dementia in Down syndrome
- <10% between 30-39 yrs. of age
- 10-25% between 40-49 yrs.
- 20-50% between 50-59 yrs.
- 50-70% by 60-70 yrs.
- Variable, however seems to progress more quickly than in general population

(Mann & Esiri, 1989; Prasher, 1994; Holland et al., 1998)

Laura Gulfhane

Down syndrome and Alzheimer disease

Compared to younger non-demented with Down syndrome

- More irritation
- Fear
- Restlessness at night
- Sadness
- Suspiciousness
- Loss of appetite

Laura Gulfhane

Heveman et al. J Intellect Disabil Res. 1994;38(Pt 3):341-50

Seizures and epilepsy in Down syndrome

1. History
2. Down syndrome
3. Down syndrome and epilepsy – early years
4. Down syndrome, aging and Alzheimer disease
5. **Down syndrome and late onset myoclonic epilepsy**
6. Conclusions

Laura Gulfhane

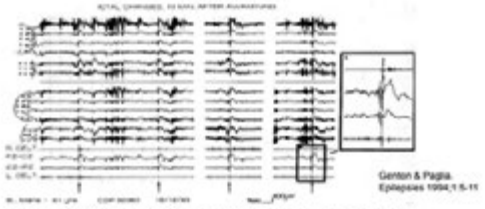
Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)

- Pedersen, 1990 (AES abstract): first report of myoclonic seizures in adults with DS
- Genton & Paglia, 1994: 2 patients with LOMEDS
  - Beginning after the 4th decade of life
  - Myoclonic seizures on awakening and generalized tonic-clonic seizures
- EEG: generalized discharges of spike-wave complexes
- Clinical picture similar to juvenile myoclonic epilepsy
- Myoclonic seizures usually unnoticed
- Diagnosis of importance: evolution to convulsive seizures and falls: ⟹ worse prognosis

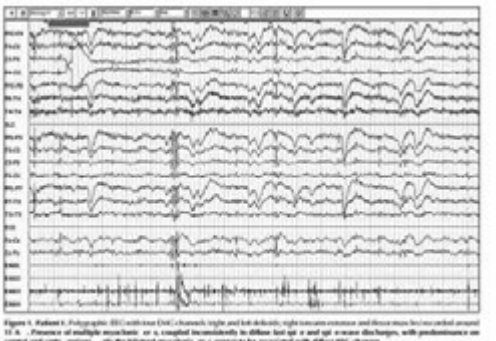
Genton & Paglia. Epilepsies 1994;1:5-11

Epilepsie myoclonique sénile ?
Myoclonies épileptiques d'apparition tardive dans le syndrome de Down

Pierre Genton*, Gabriella Paglia*

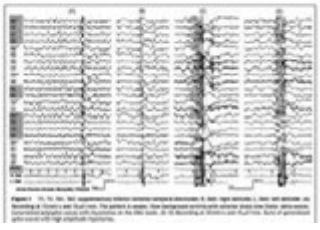


Genton & Paglia. Epilepsies 1994;1:5-11

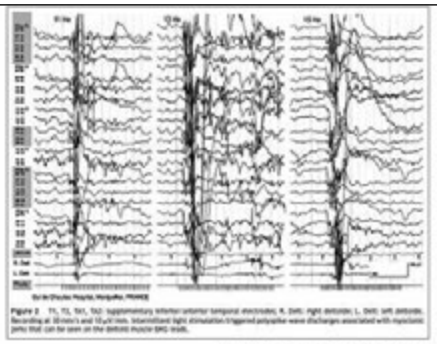


De Simone *et al*. Epileptic Disord 2006;8(3):223-7

Senile myoclonic epilepsy of Genton: Two cases in Down syndrome with dementia and late onset epilepsy

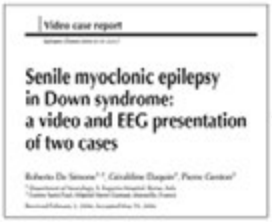


Crespel *et al*. Epilepsy Res. 2007;77(3-3):165-8



Crespel *et al.* Epilepsy Res. 2007;77(2-3):165-8

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)



Video case report

Senile myoclonic epilepsy in Down syndrome: a video and EEG presentation of two cases

- Both aged 56 years with seizures
  - 1 female : before dementia
  - 1 male : after dementia
- Myoclonic epilepsy (resemble in its clinical expression, the classical juvenile myoclonic epilepsy)

De Simone et al.. Epileptic Disord 2006;8(3):223-7

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)

Epilepsy in adult patients with Down syndrome: a clinical-video EEG study

22 patients with epilepsy and Down syndrome

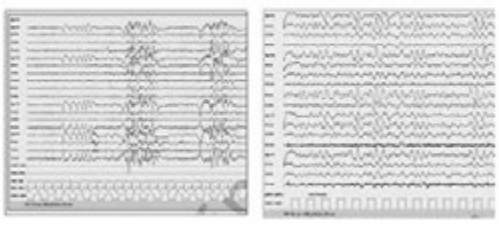
- mean age: 46 yrs.
- onset of epilepsy: 36.8 yrs.
- 9 patients – focal seizures
- **9 patients – LOMEDS**
- 4 patients – non classified

LOMEDS

- Mean age at epilepsy onset: 50.2 yrs.
- Cognitive decline preceded any obvious seizure 6-18 months (5/9) or occurred at seizure onset (4/9)
- Brain imaging: cerebral atrophy
- EEG: slow background activity and diffuse spike waves or polyspike waves
- Video-EEG: in a few cases, possible to record myoclonias, mainly involving upper limbs

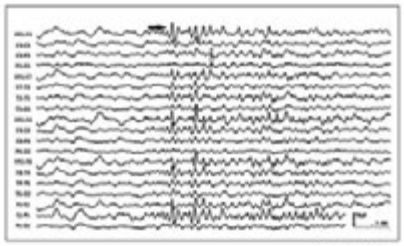
Vignoli *et al.* Epileptic disorders 2011;13(2):125-32

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)



Vignoli *et al.* Epileptic disorders 2011;13(2):125-32

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)



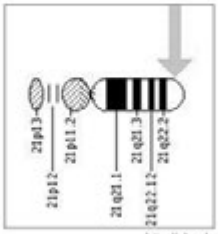
62 yrs., male

Unverricht-Lundborg syndrome.....

- Onset 6-15 yrs.; stimulus-sensitive myoclonus, and tonic-clonic epileptic seizures
- Late symptoms: ataxia, incoordination, intentional tremor, dysarthria
- May have normal lifespan, mentally alert
- Emotional liability, depression, and mild decline in intellectual performance over time
- **Associated to chromosome 21 in a gene in region 21q22.3**

Genton 2005. Rev Neurol (Paris).161(9 Pt):919-26
Lehesjoki 2002. Adv Neurol;89:193-7

"Cystatin B gene (stefin B)"



http://ghr.nlm.nih.gov/gene/CSTB

Cytogenetic Location: 21q22.3
Molecular Location on chromosome 21: base pairs 45,193,830 to 45,196,258

Seizures and dementia in Down's syndrome

1. History
2. Down syndrome
3. Down syndrome and aging
4. Down syndrome and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. **Conclusions**

http://www.fondationlejeune.org/

- http://www.youtube.com/watch?v=jt9o4JPibBI

Famous people with Down syndrome

Chris Burke | Jane Cameron | Sujeet Desai | Bernadette Resha

??
Phenotipical variation
Mosaicism
Environment

Thank you for your attention!

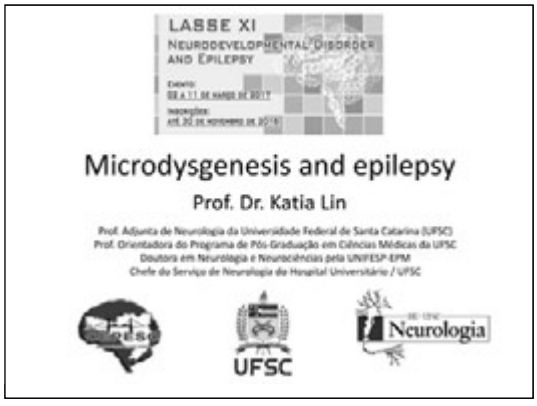
Laura M. F. F. Guilhoto
lauragui@gmail.com

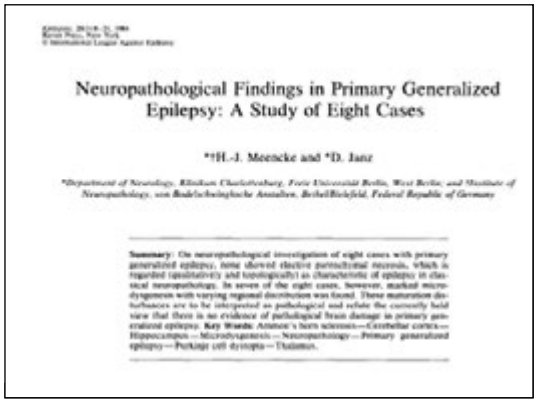
Alberto Costa (USA)

ON THE POTENTIAL PATHOGENIC ROLE OF NMDA RECEPTORS ON DEVELOPMENTAL ASPECTS OF DOWN SYNDROME

Katia Lin (Brazil)

PRIMARY GENERALIZED EPILEPSY AND MICRODYSGENESIA – A NEURODEVELOPMENTAL DISTURBANCE



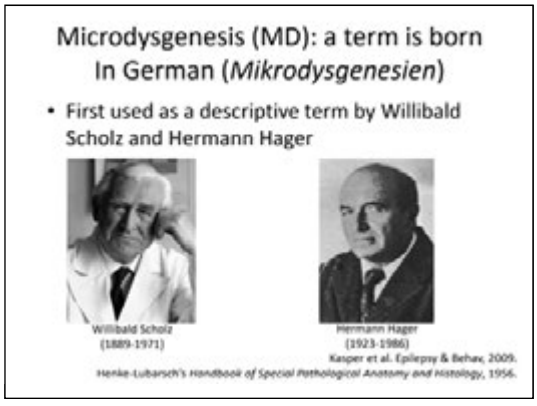


Neuropathological Findings in Primary Generalized Epilepsy: A Study of Eight Cases

*†H.-J. Meencke and *D. Janz

*Department of Neurology, Rhinkum Charlottenburg, Freie Universität Berlin, West Berlin; and Institute of Neuropathology, von Bodelschwinghsche Anstalten, Bethel/Bielefeld, Federal Republic of Germany

Summary: On neuropathological investigations of eight cases with primary generalized epilepsy, some showed ectopic pyramidal neurons, which is regarded (qualitatively and topologically) as characteristic of epilepsy in classical neuropathology. In seven of the eight cases, however, marked microdysgenesis with varying regional distribution was found. These maturation disturbances are to be interpreted as pathological and refute the currently held view that there is no evidence of pathological brain damage in primary generalized epilepsy. **Key Words:** Ammon's horn sclerosis—Cerebellar cortex—Hippocampus—Microdysgenesis—Neuropathology—Primary generalized epilepsy—Perikaryal cell dyscopia—Thalamus.

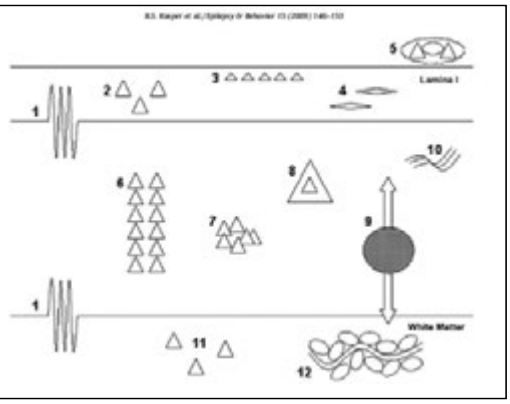


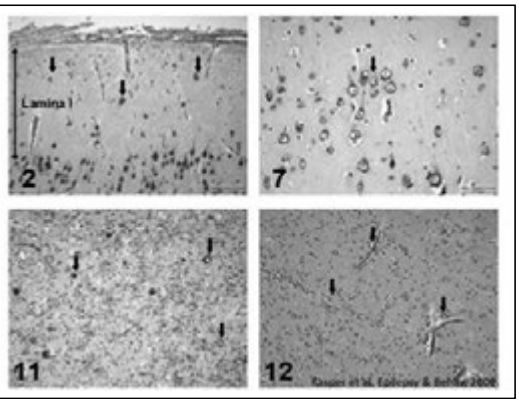
What is microdysgenesis (MD)?

- A microscopic malformation of cortical development characterized by heterotopic neurones and abnormal cortical architecture
- Initially described in primary generalized and partial epilepsy
- Controversial significance
  - Lack of consensus of diagnostic criteria and clinical significance
    - Normal variation? Pathological? Epileptogenic? An epilepsy epiphenomenon?
  - Different terms used for the same malformations

What is microdysgenesis (MD)?

- Other terms
  - *Mild cortical dysplasia*
  - *Minor dysgenetic changes*
  - *Glioneuronal hamartia*
  - *Mild glioneuronal heterotopias*
  - *Microscopic cortical dysplasia*
  - *Architectural dysplasia*
  - *Mild malformations of cortical development (MCD)*





Diverse histopathological criteria used for microdysgenesis Qualitative studies

Table 1 Histopathological criteria used for microdysgenesis

Study	Irregular cortical nerve cell distribution	Irregular or blurred border between layers I and II	Increased frequency of nerve cells in layer I	Increased frequency of nerve cells in white matter	Other
Meencke and Janz	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Nordborg et al.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hardiman et al.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Eriksson et al.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Kasper et al.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Kilpatrick et al.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Nishio et al.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Eriksson et al. Acta Neurol Scand, 2005.

Quantitative studies in microdysgenesis

Eriksson et al. Acta Neurol Scand, 2005.

SPECIAL REPORT

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

BRAIN

REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

A. James Barkovich, Renzo Guerrini, Ruben I. Kuzniecky, Graeme D. Jackson and William B. Dobyns

Group I: malformations secondary to abnormal neuronal and glial proliferation or apoptosis

Group II: malformations due to abnormal neuronal migration

Group III: malformations secondary to abnormal postmigrational development

SPECIAL REPORT

International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods

†‡Ingmar Blümcke, ‖¶Eleonora Aronica, §Hajime Miyata, #Harvey B. Sarnat, **Maria Thom, ††Karl Roessler, ‡‡§§Bertil Rydenhag, ¶Lara Jehi, ¶¶Pavel Krsek, ##Samuel Wiebe, and ***Roberto Spreafico

Epilepsia, ***(*):1–11, 2016
doi: 10.1111/epi.13319

- ✓ Neuropathology in epilepsy surgery: an interdisciplinary diagnostic approach is required for successful epilepsy surgery
- ✓ Recommendations for consensus protocols in the neuropathology workup
- ✓ Neuropathology Task Force of the ILAE Commission on Diagnostic Methods

Microdysgenesis in Mesial Temporal Lobe Epilepsy: A Clinicopathological Study

Burkhard S. Kasper, MD,[1] Hermann Stefan, MD,[1] and Werner Paulus, MD[2]

The interrelationship of mesial temporal lobe epilepsy (MTLE), hippocampal sclerosis, and febrile convulsions still remains an enigma. Additional microscopical cortical dysplasia or microdysgenesis has been suggested as pre-existent susceptibility factor rendering the affected brain vulnerable to the development of MTLE after initial precipitating injuries such as febrile convulsions. Twenty-four MTLE cases with histopathologically definite hippocampal sclerosis were examined for closely defined features of microdysgenesis and further signs of neocortical dysplasia. Although unequivocal signs of dysplasia were absent, 29.2% of cases showed cortical neuronal clustering, 25.0% showed perivascular clustering, and 20.8% showed increased white matter neurones. The features of microdysgenesis studied here were not linked with each other and were not related to initial precipitating injuries, positive family history, or any other clinical parameter. Their suggested fundamental role as dysplastic factor within development of hippocampal sclerosis and MTLE is not confirmed.

Ann Neurol 2003;54:501–506

Brain (2001), **124**, 2299–2309

Microdysgenesis in temporal lobe epilepsy
A quantitative and immunohistochemical study of white matter neurones

Maria Thom,[1] Sanjay Sisodiya,[2] William Harkness[3] and Francesco Scaravilli[1]

[1]Departments of Neuropathology, [2]Neurology and [3]Neurosurgery, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK

Correspondence to: M. Thom, Department of Neuropathology, Institute of Neurology, Queen Square, London, WC1N 3BG, UK
E-mail: M.Thom@ion.ucl.ac.uk

Neuroimaging and microdysgenesis

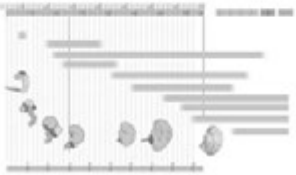
Regional gray matter abnormalities in juvenile myoclonic epilepsy: A voxel-based morphometry study

Epilepsy & Behavior

Voxel-by-Voxel Comparison of Automatically Segmented Cerebral Gray Matter—A Rater-Independent Comparison of Structural MRI in Patients with Epilepsy

Causes of microdysgenesis

- Disturbance late in gestational life or postnatally
- No studies correlating possible causal prenatal incidents and MD



Clinical significance

- Controversy 1: microdysgenesis in other conditions than epilepsy and in normal controls
- Controversy 2: role in epileptogenesis

Since the pioneering investigation of autopsy cases in patients with IGE which was motivated by the clinical observation of strongly age-dependent phenotypes and hereditary traits in various forms of IGE (*Janz, personal communication*)...

1984

Neuropathological Findings in Primary Generalized Epilepsy: A Study of Eight Cases

H.-J. Meencke and D. Janz

...To *EFHC1* variants – the most common mutations in inherited myoclonic and grand mal clonic-tonic-clonic (CTC) convulsions of JME – explaining CTC convulsions and microdysgenesis neuropathology of JME.

2017 SYSTEMATIC REVIEW | Genetics in Medicine

***EFHC1* variants in juvenile myoclonic epilepsy: reanalysis according to NHGRI and ACMG guidelines for assigning disease causality**

Julia N. Bailey, PhD[1,2], Christopher Patterson, BA[1], Laurence de Nijs, PhD[3,4], Reyna M. Durón, MD[5,6], Viet-Huong Nguyen, PharmD, MPH[7,8], Miyabi Tanaka, MD[1,2], Marco T. Medina, MD[7,9], Aurelio Jara-Prado, PhD[7,9], Iris E. Martínez-Juárez, MD, MSc[7,9], Adriana Ochoa, MSc[7,9], Yolli Molina, MSc[7,9], Toshimitsu Suzuki, PhD[7,10], Maria E. Alonso, MD[7,9], Jenny E. Wight, MPH[1,2], Yiu-Chen Lin, MPH[1,2], Laura Guilhoto, MD[11,12], Elza Marcia Targas Yacubian, MD[11,12], Jesús Machado-Salas, MD, PhD[5,6], Andrea Daga, PhD[13], Kazuhiro Yamakawa, PhD[14], Thierry M. Gilsar, MD, PhD[3,4], Bernard Lakaye, PhD[3,4] and Antonio V. Delgado-Escueta, MD[1,2]

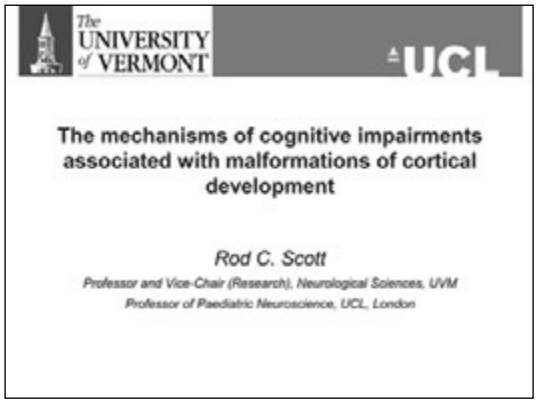
SYSTEMATIC REVIEW

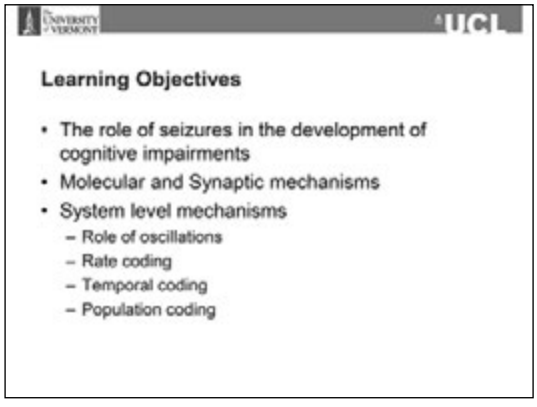
Future perspectives

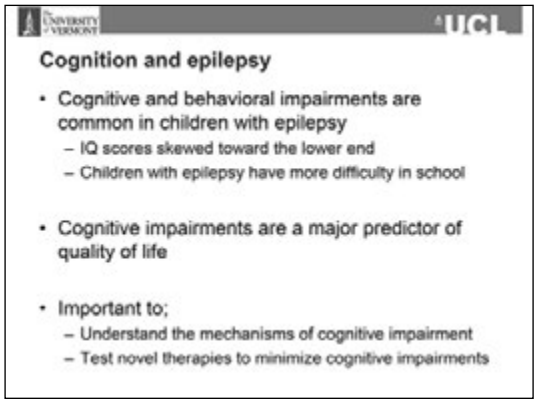
- Clear and definite consensus on diagnostic criteria of microdysgenesis
  - Stereological and qualitative morphological assssments
- Histopathological findings and clinical data
- Multicentric studies

Rodney Scott (USA)

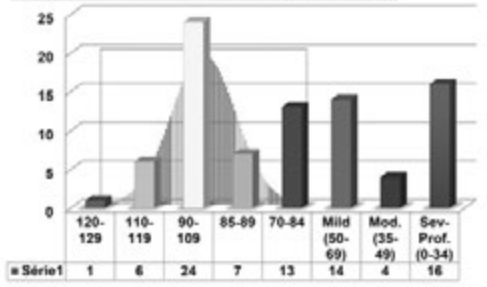
THE MECHANISMS OF COGNITIVE IMPAIRMENTS ASSOCIATED WITH MALFORMATIONS OF CORTICAL DEVELOPMENT



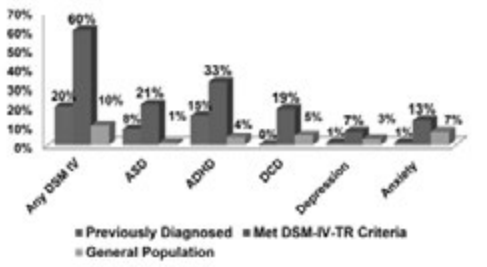




Global Cognitive Functioning (CHESS)



Behaviour Diagnosis



Factors associated with Impairments

- Intellectual Disability
  - Seizures in the first 24 months compared with first seizures at 24-60 or 61+ months
  - Polytherapy (OR 7.7)
  - Generalised seizures (OR 5.6)
  - Status epilepticus (OR 7.3) were independently associated with ID.
- Behavioural Disorders
  - Epilepsy related factors did not independently predict the presence of behavioural disorders.

Academic Achievment

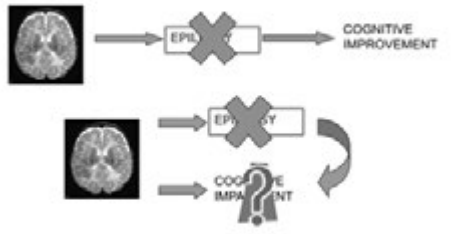
- 65 of 85 children were able to complete subtest of WRAT-4
  - 72% displayed 'low achievement' (1SD below test mean)
  - 42% displayed 'underachievement' (1SD below assessed IQ)
- More frequent seizures, polytherapy and presence of ADHD were associated with lowered performance

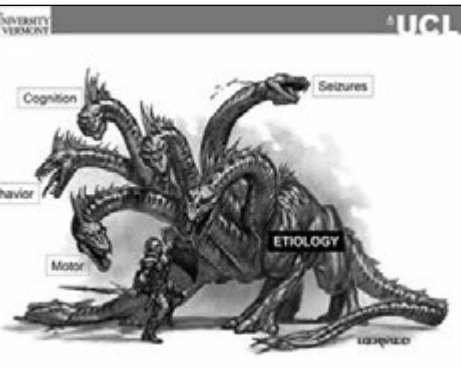
Quality of Life

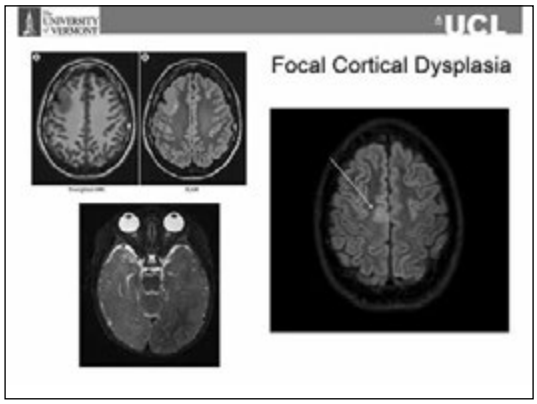
- QOLCE used to measure factors associated with parent reported health related quality of life (HRQOL).
- Factors independently significantly associated ($p<.05$) with total QOLCE scores were seizures before 24 months, cognitive impairment (<85), anxiety, depression and parent reported school attendance difficulty.
- These factors were also significantly associated with total QOLCE when children with IQ<50 were excluded.

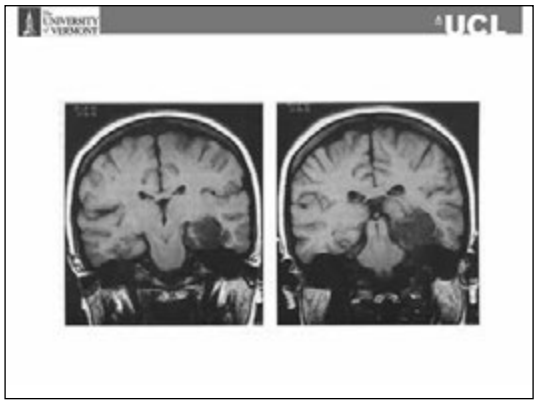
Cognitive outcomes

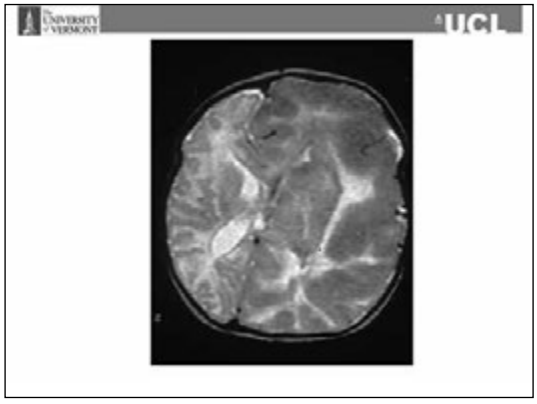
- Strong correlation between cognitive abilities ~3 months after diagnosis and 1 year after diagnosis
  - Not dependent upon seizure freedom of at least 6 months
  - Not dependent on whether on AEDs

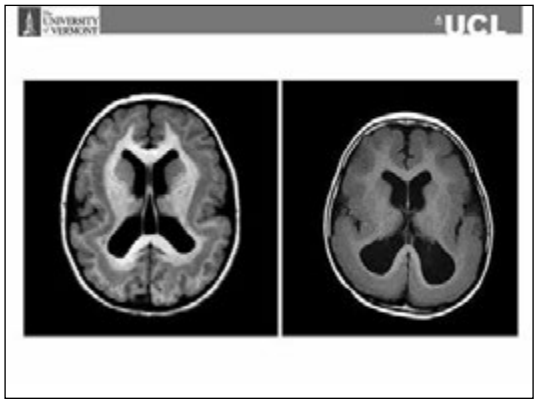





UCL
Focal Cortical Dysplasia


UCL


UCL


UCL

Clinical Relevance of MCD

- MCD result from a variety of genetic and environmental insults
- ~75% of people with MCDs have seizures and/or cognitive impairment
- ~40% of children with refractory epilepsy have MCD and the majority of children with refractory epilepsy have cognitive difficulties
- Treatment
  - Surgical – focal resections improve seizures but not cognition
  - Medical – AEDs often have little impact on either seizures or cognition

Clinically relevant animal model

- Structural brain abnormality commonly identified in children with epilepsy

BUT

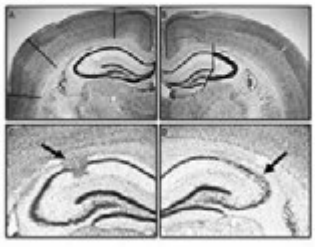
- No (few) spontaneous seizures
- In which seizures can be induced

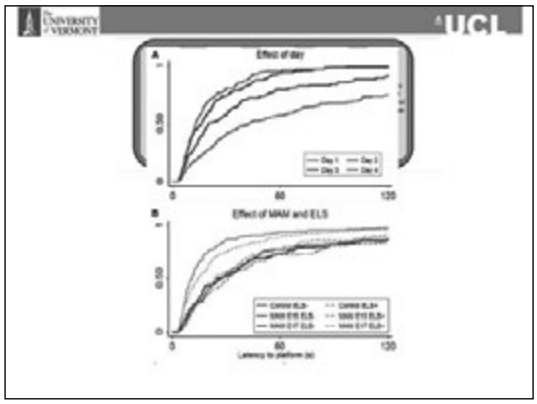
MAM model of cortical dysplasia

MAM model of MCD (E17)

- Malformations are structurally similar at a histological level to human malformations
- Animals have significant learning impairments
  - Spatial along with many others (used as a model of schizophrenia)
- Few to no clinical seizures (usually considered a weakness of the model)
  - Allows us to dissociate seizures and cognition

Histology

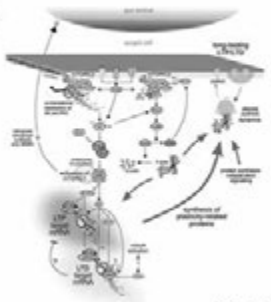




Molecular mechanisms of cognitive impairment

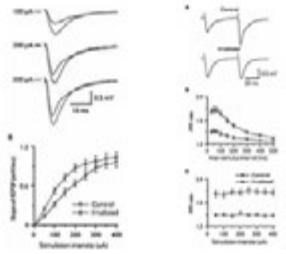
- Many genes associated with MCDs
  - Abnormal neurogenesis
  - Abnormal neuronal migration
  - Abnormal arrest of neuronal migration
  - Abnormal neuronal organization
- Question
  - Do these genes modify synaptic transmission and plasticity in a way that modifies cognition?

mTOR signaling



Graber et al, 2013

Synaptic Mechanisms – acquired MCD



Zhou et al, 2012

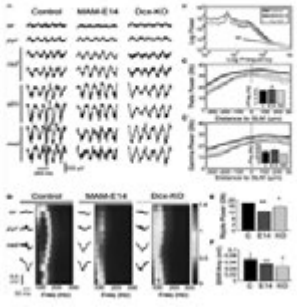
System level mechanisms

- At the level of the oscillation
  - Theta oscillations
  - Gamma oscillations
  - Oscillatory coherence
- At the level of multiple simultaneously recorded single neurons in awake behaving animals
  - Rate coding
  - Temporal coding
  - Population coding

Oscillations

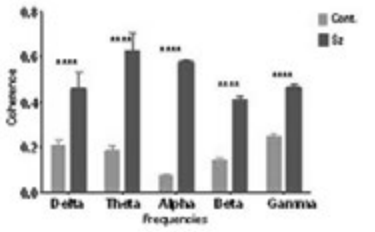
- Theta (4-12 Hz) is the dominant frequency in rodents
  - Most observed during locomotion
- Disruption to theta frequency or power impairs spatial cognition
- Gamma is a marker of local network function
- Coherence is a marker of synchrony between brain regions

Hippocampal oscillations in MAM



Cid et al, 2014

Coherence (hippocampus to PFC)

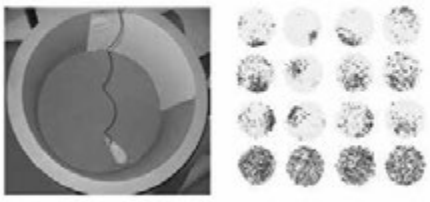


Holmes et al, 2015

System mechanisms of information processing

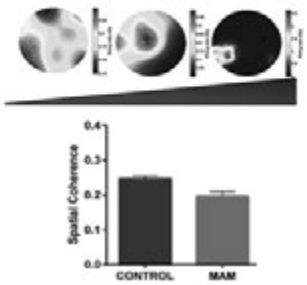
- Rate coding
  - Place cells
- Timing coding
- Population coding

Single Unit Recordings

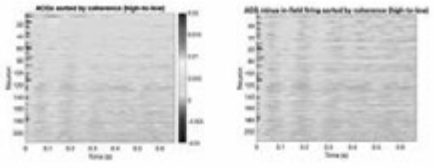


Rate coding

Spatial Coherence of Pyramidal Cells



Relationship between temporal coding and coherence



GLM approach to timing coding

- Mathematically principled way of obtaining timing information
- Not dependent upon firing rate of cells
- Explicitly distinguishes between the place field and structure of timing of action potentials

GLMs for spike train modeling

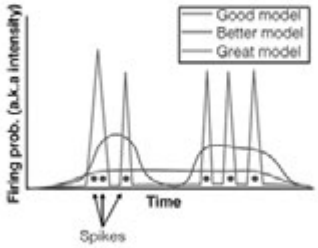
Want to predict spike times:

$$\text{Prob}(\text{spike @ time} = t)$$

This probability is called the intensity, denoted λ_t.

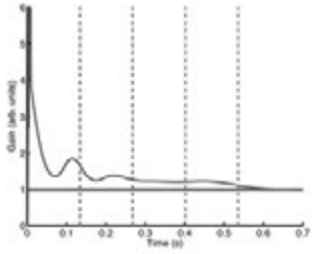
Depends on:
- Behavior (place cells)
- Network structure (oscillations, firing history)
- Stimuli (experimentally controlled inputs)
- etc.

Cartoon data

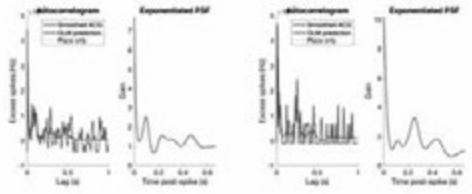


Good models localize high probability around actual spikes.

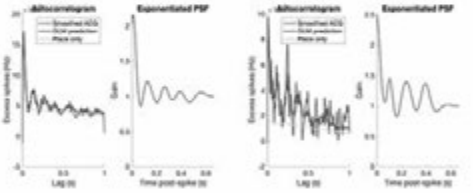
Example post-spike filter



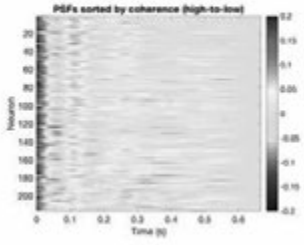
Relationship between ACG and PSF



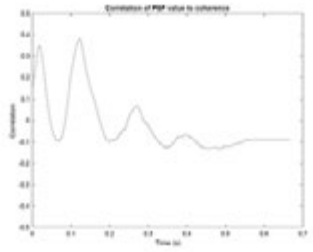
Relationship between ACG and PSF



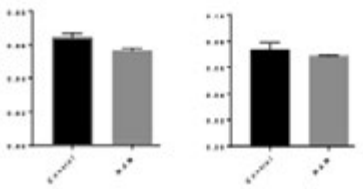
Relationship between coherence and PSF



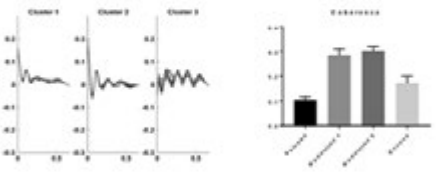
Relationship between coherence and PSF time



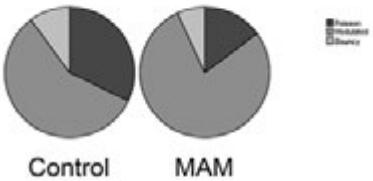
Theta Modulation



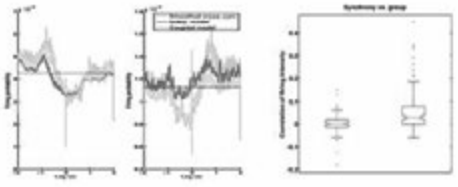
Different firing structures

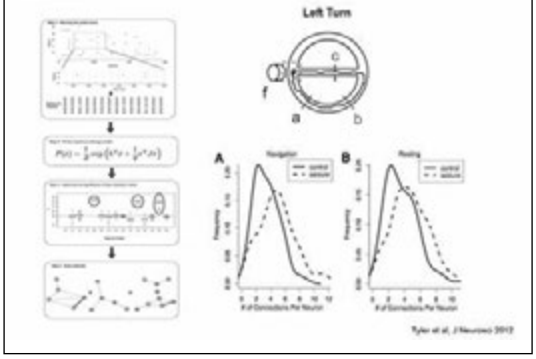


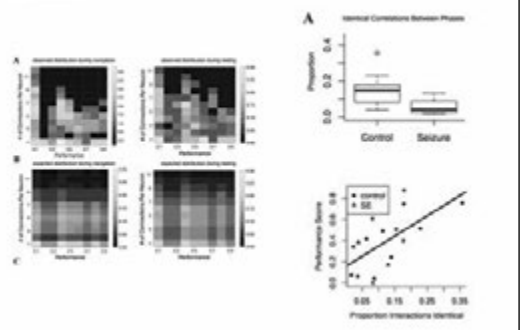
Endophenotypes



Population coding







Conclusions

- MCDs are common in epilepsy and associated with cognitive impairment
- Seizures are likely not the primary driver of cognitive outcomes
- Understanding mechanisms of adverse cognitive outcome could inform development of novel therapies
  - Molecular, plasticity or network levels

Marilisa Guerreiro (Brazil)

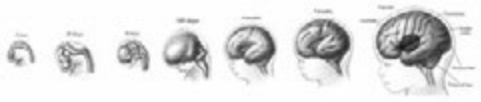
MALFORMATIONS DUE TO ABNORMAL POSTMIGRATIONAL DEVELOPMENT

Malformações/Anormalidades do Desenvolvimento Pósmigracional

Marilisa M. Guerreiro
Departamento de Neurologia

LASSE 2017

Desenvolvimento do SNC



Formação do tubo neural

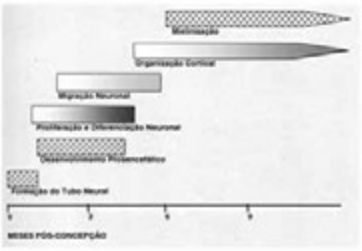
Segmentação

Desenvolvimento cortical

Desenvolvimento Cortical

- Desenvolvimento cortical normal
- Malformações do desenvolvimento cortical

Desenvolvimento do SNC

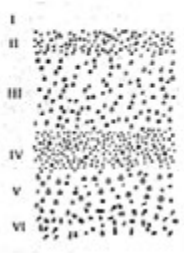


Malformações do Desenvolvimento Cortical

- Distúrbios da proliferação
- Distúrbios da migração neuronal
- Distúrbios da organização cortical/

Anormalidade do desenvolvimento pósmigracional

Citoarquitetura Cortical



BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

A. James Barkovich,[1] Renzo Guerrini,[2,3] Ruben I. Kuzniecky,[4] Graeme D. Jackson[5,6] and William B. Dobyns[7,8]

Annals of NEUROLOGY

REVIEW

Malformations of Cortical Development

Rahul S. Desikan, MD, PhD and A. James Barkovich, MD

Malformations of cortical development (MCDs) comprise a diverse range of disorders that are common causes of neurodevelopmental delay and epilepsy. With improved imaging and genetic methodologies, the underlying molecular and pathobiological characteristics of several MCDs have been recently elucidated. In this review, we discuss genetic and molecular alterations that disrupt normal cortical development, with emphasis on recent discoveries, and provide detailed radiological features of the most common and important MCDs.

Group III: malformations secondary to abnormal portmigrational development

- Grupo III.A
  - 1. Polimicrogiria e esquizencefalia (com calcificações)
  - 2. PMG (sem calcificações e classificadas pelo local)
  - 3. PMG com síndromes (geneticamente determinadas)
- Grupo III.B PMG com erros inatos do metabolismo
- Grupo III.C DCF tipo I e tipo III
- Grupo III.D Microcefalia pósmigracional

Organização Cortical Anormal/ Desenvolvimento Pósmigracional Anormal

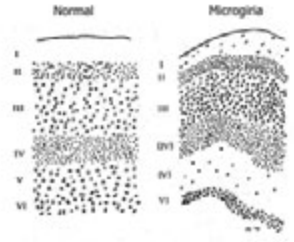
- Polimicrogiria
- Esquizencefalia

Polimicrogiria Etiologias

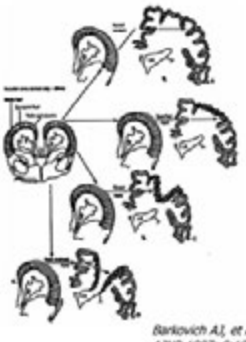
- Isquemia prénatal
- Infecção congênita (CMV)
- Teratogenia

Desikan & Barkovich, Ann Neurol, 2016

Polimicrogiria (PMG)



Insulto vascular

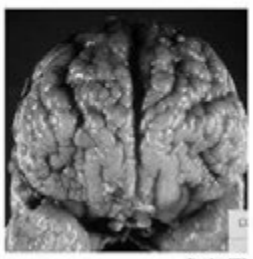


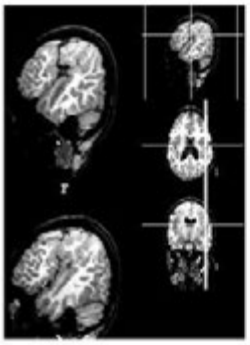
Barkovich AJ, et al.
AJNR 1987; 8:1009-1017.

Polimicrogiria

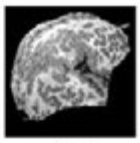
- Presença de vários pequenos giros em decorrência de insulto vascular
- Quadro clínico
  - Depende da localização e extensão do córtex afetado
  - Epilepsia tratável com DAE

Polimicrogiria envolvendo os dois hemisférios





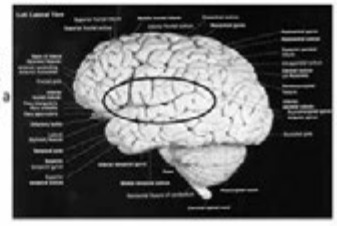
Polimicrogiria Perisylviana Bilateral



12 mm

S. Perisylviana - Definição

- Diversas manifestações clínicas que podem acompanhar lesões que comprometem a região perisylviana ou opercular



Síndrome Perisylviana
Caracterização clínica e de neuroimagem (n=40)

- A gravidade das manifestações clínicas se correlaciona com a extensão do envolvimento cortical
- A maioria dos pacientes apresenta atraso de fala ou dificuldades de linguagem e não tem epilepsia
- A SP pode apresentar-se de forma familial
- Existe um contínuo entre DEL e dislexia em casos familiares

Ecila Oliveira, 2006;
Iara Brandão-Almeida, 2005;
Karine Teixeira, 2006.

S. Perisylviana
Caracterização Clínica e de Neuroimagem

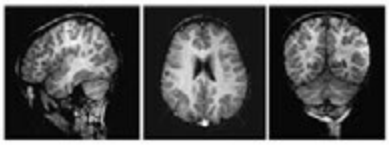
Espectro de neuroimagem PMG perisylviana

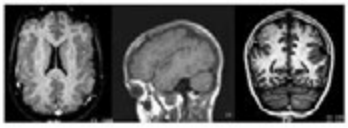
Posterior — Difusa

Espectro clínico da síndrome perisylviana

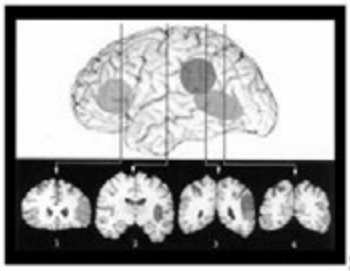
Distúrbio de linguagem — Epilepsia, Déficit cognitivo, Sinais pseudobulbares

Polimicrogiria parietal posterior





Principais Áreas Relacionadas à Linguagem



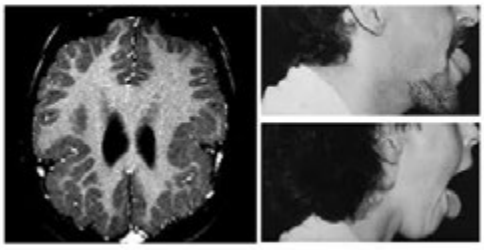
S. Perisylviana - Histórico

CONGENITAL SUPRABULBAR PARESIS*

By C. WORSTER-DROUGHT (London)

- Anos 50: Worster-Drought usou o termo "Paresia Suprabulbar Congênita" para descrever crianças com problemas de fala e alterações neurológicas sugestivas de comprometimento em áreas corticais motoras
- Recentemente um desses pacientes foi submetido à RM: PMG perisylviana

Síndrome Perisylviana



Guerreiro et al, Ann Neurol, 2000

CME **Developmental language disorder associated with polymicrogyria**

M.M. Guerreiro, MD, PhD; S.R. Hage, PhD; C.A. Guimarães, BSc;D.V. Abramides, BSc; W. Fernandes, MD; P.S. Pacheco, MD; A.M.S.G. Piovesana, MD,PhD; M.A. Montenegro, MD; and F. Cendes,MD, PhD

NEUROLOGY 2002;59:245–250

Resultados

História de dificuldades pseudobulbares dificuldade à sucção e deglutição sialorréia	50%
Sinais de paralisia pseudobulbar dificuldade para movimentar a língua, fala disártrica, alteração do reflexo nauseoso, sialorréia, disfagia	50%
História familial de DEDL	60%
RM PMG perisylviana difusa PMG bilateral posterior parietal outros	 40% 40% 20%

Síndrome Perisylviana e Epilepsia

- Kuzniecky et al: 87% *Kuzniecky et al, Neurology, 1994*
  - CBPS
  - 31 pacientes
- Guerreiro et al: 43% *Guerreiro et al, Ann Neurol, 2000*
  - Famílias
  - 42 pacientes
- Teixeira et al: 32% *Teixeira et al, J Clin Neurophysiol, 2007*
  - 40 pacientes (Unicamp)
  - Predomínio de cças com DEL
- Leventer et al: ~70% *Leventer et al, Brain, 2010*
  - 328 pacientes

BRAIN

Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients

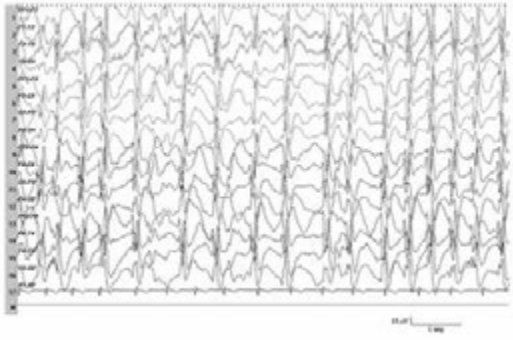
Richard J. Leventer,[1,2,3] Anna Jansen,[4,5,6] Daniela T. Pilz,[7] Neil Stoodley,[8] Carla Marini,[9] Francois Dubeau,[6,10] Jodie Malone,[11] L. Anne Mitchell,[12] Simone Mandelstam,[13] Ingrid E. Scheffer,[1,2,3,11] Samuel F. Berkovic,[11] Frederick Andermann,[6,10,14] Eva Andermann,[6,7] Renzo Guerrini[9] and William B. Dobyns[14]

Síndrome Perisylviana
Caracterização neurofisiológica

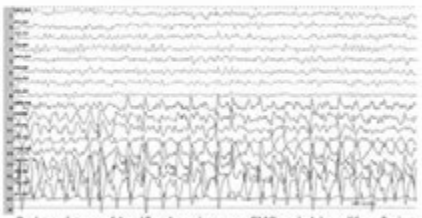
Síndrome Perisylviana
Caracterização neurofisiológica

- 34 pacientes com PMG perisylviana
  - Difusa = 20 (DEL = 12); BPPP = 14 (DEL = 12)
- O EEG é normal na maioria dos pac
- 30% com atividade epileptiforme
  - Principalmente fronto-temporal
  - Correlação positiva com a extensão do córtex comprometido e com quadro neurofisiológico

EMES

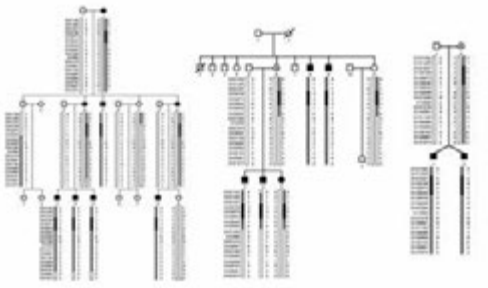


Atividade Epileptiforme
Contínua Focal

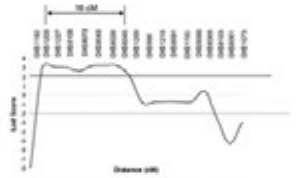


Registro eletroencefalográfico de paciente com PMG perisylviana difusa. Paciente em vigília. Complexos espícula e polespícula onda lenta contínuos na região fronto-centro-temporal direita. Filtro:70 Hz, Constante de tempo:0,3s, Sensibilidade: 10mv/mm.

Síndrome Perisylviana
Caracterização genética



Identificação de um novo Locus para Síndrome Perisylviana no Cromossomo Xq27 – q28



Santos et al, 2008

AJMG American Journal of medical genetics

A New Candidate Locus for Bilateral Perisylvian Polymicrogyria Mapped on Chromosome Xq27

S. Perisylviana – "CBPS" Quadro Clínico

- Manifestações pseudobulbares
  - Dificuldade para sugar e deglutir
  - Disfagia (dificuldade para alimentar-se)
  - Engasgo fácil
  - Sialorréia (às vezes por toda a vida)
  - Disartria
  - Distúrbios de linguagem
  - Pé torto
- Epilepsia
- Déficits cognitivos variáveis

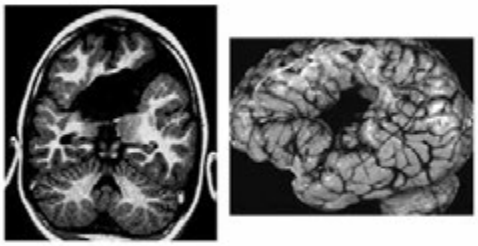
Kuzniecky et al, Lancet, 1993
Kuzniecky et al, Neurology, 1994

The Clubfoot, Jusepe de Ribera, 1642

Organização Cortical Anormal/ Desenvolvimento Pósmigracional Anormal

- Polimicrogiria
- Esquizencefalia

Esquizencefalia



Esquizencefalia
Etiologias

- Idade materna precoce
- Uso de álcool
- Ausência de seguimento prénatal

Dies et al, J Child Neurol, 2013

Esquizencefalia

- 44 pacientes (24 pac com fenda unilateral e 20 pac com fendas bilaterais)
- Epilepsia: 63% x 55%
- A extensão do córtex comprometido não se correlaciona com a gravidade do quadro epiléptico, ao contrário do quadro cognitivo e motor

Lopes et al, J Child Neurol, 2006

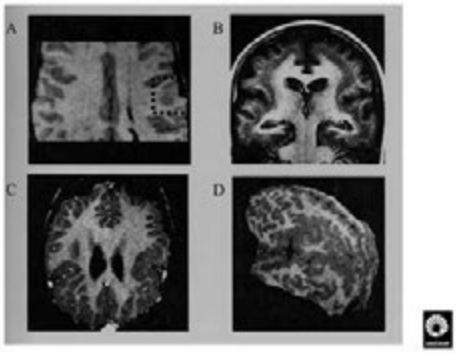
ORIGINAL CONTRIBUTION

Interrelationship of Genetics and Prenatal Injury in the Genesis of Malformations of Cortical Development

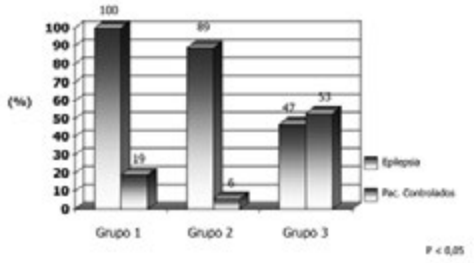
Maria Augusta Montenegro, MD; Marilisa M. Guerreiro, MD, PhD; Iscia Lopes-Cendes, MD, PhD; Carlos A. M. Guerreiro, MD, PhD; Fernando Cendes, MD, PhD

Arch Neurol, 2002

Desenho do Estudo



MDC - Epilepsia



Epilepsia X MDC

- Grupo I. DCF apresenta epileptogenicidade intrínseca: epilepsia frequente e refratária
- Grupo II. Depende
- Grupo III. PMG e esquizencefalia associam-se menos à epilepsia

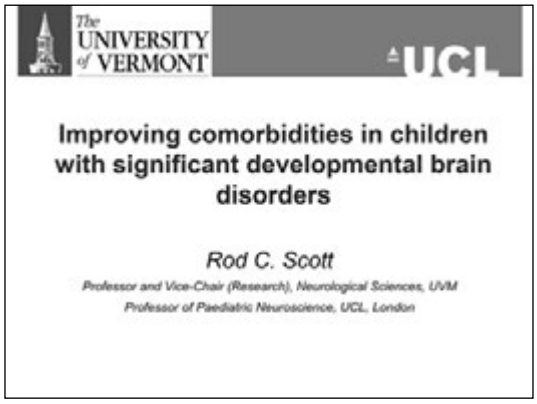
Conclusões

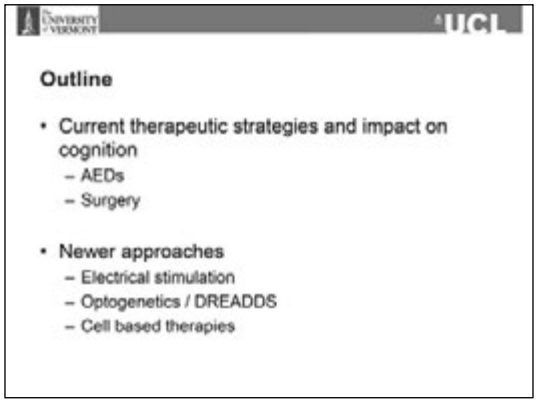
- O córtex displásico é bastante epileptogênico e insultos ambientais ou predisposição genética não estão associados à epilepsia
- O córtex polimicrogírico é menos epileptogênico e insultos ambientais ou predisposição genética estão associados à epilepsia

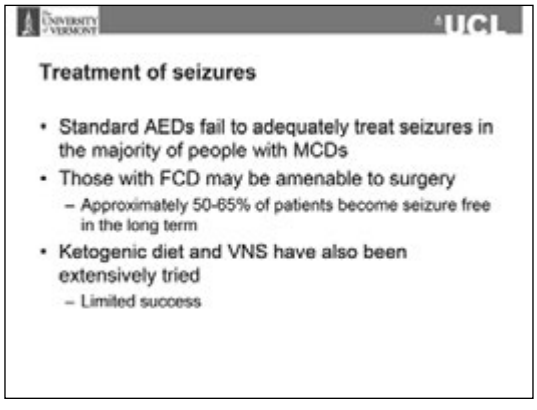

Muito obrigada
pela atenção!

Rodney Scott (USA)

IMPROVING COMORBIDITIES IN CHILDREN WITH SIGNIFICANT DEVELOPMENTAL BRAIN DISORDERS



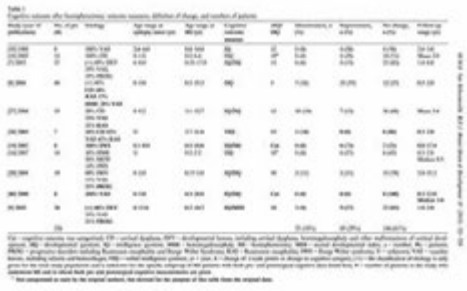




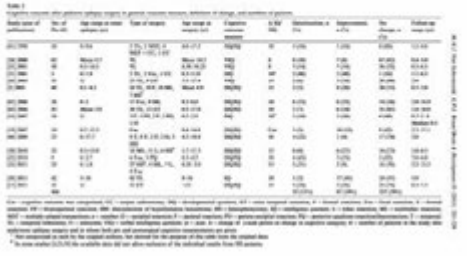
Cognitive outcomes

- Few data specifically addressing MCD outcomes
- Surgical studies including patients with MCD are conflicting
  - Improvements in DQ associated with seizure freedom, predominantly in children with very low baseline
  - No change in DQ or IQ following surgery
  - Increase in IQ in patients treated for TLE
    - Greatest effect seems to be reduction in AEDs

Cognitive impact of epilepsy surgery



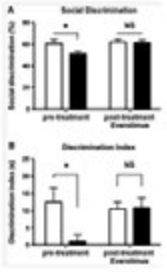
Cognitive impact of epilepsy surgery



Therapies based on molecular knowledge

- Example of tuberous sclerosis
- Rapaymcin (and analogues) modulates mTOR signaling known to be abnormal in TS
  - Plasticity changes may be responsible for seizures and cognitive impairments

Social interaction improved with Everolimus

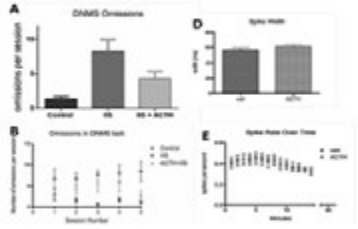


Schneider et al, 2016

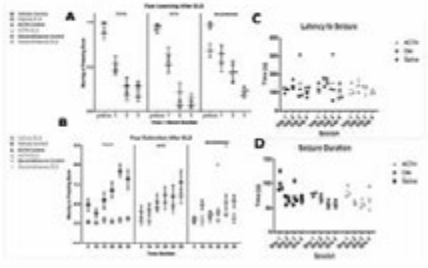
Therapies based on seredipity

- ACTH is widely used for treatment of infantile spasms
- Children with IS and no identified etiology, treated with hormonal therapies, have better cognitive outcomes
- Outcome measure is always seizures in clinical studies

Serendipity



Serendipity

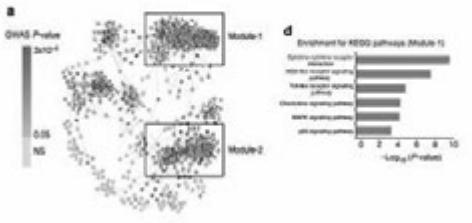


The Importance of System Level Mechansims An Analogy

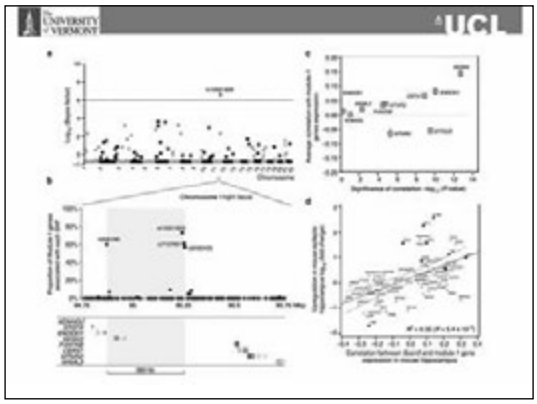
Analogy

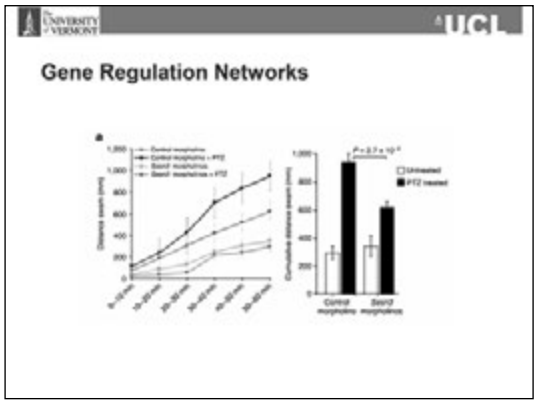
Analogy

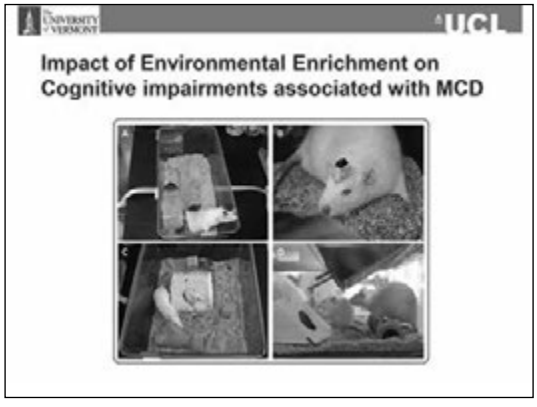
Gene Regulation Networks

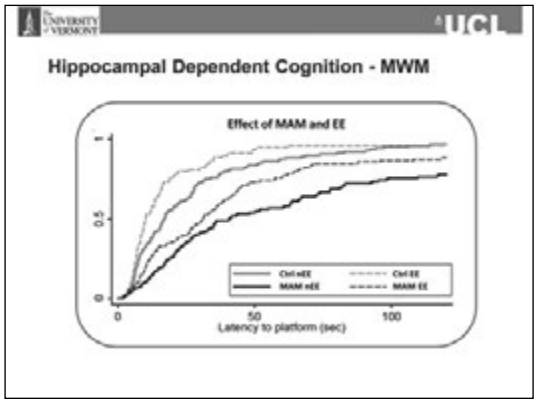


Johnson et al, Nat Comm 2015

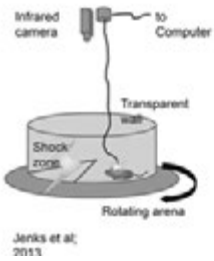



Gene Regulation Networks

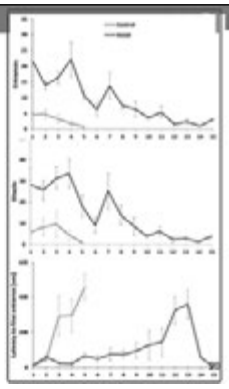

Impact of Environmental Enrichment on
Cognitive impairments associated with MCD


Hippocampal Dependent Cognition - MWM
Effect of MAM and EE
Ctrl nEE
MAM nEE
Ctrl EE
MAM EE
0
0.5
1
0
50
100
Latency to platform (sec)

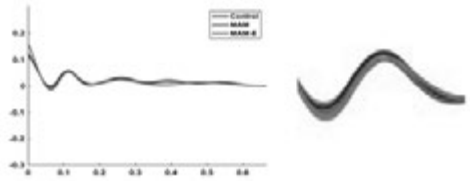
Overtraining



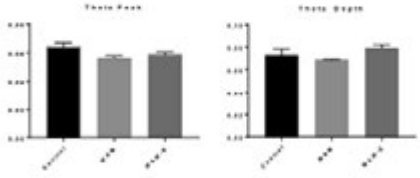
Jenks et al; 2015



System level mechanisms of cognitive improvement



Theta Modulation

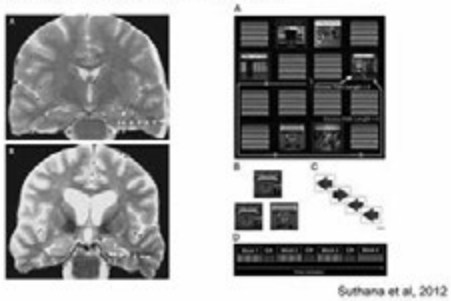


Firing endophenotypes of pyramidal cells

Is it possible to drive neural networks in a way that recapitulates the effect of enrichment and thereby improve cognition?

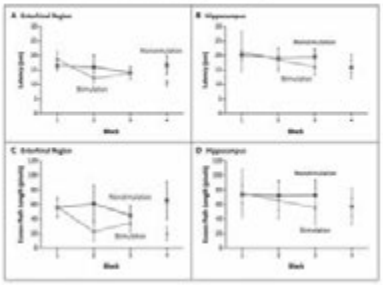
- Electrical stimulation
- Optogenetics
- DREADDS
- Cell-based therapies

Electrical stimulation - Humans

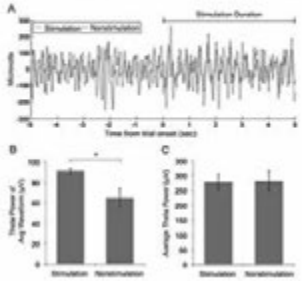


Suthana et al, 2012

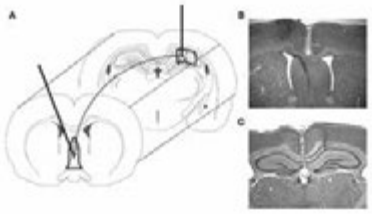
Behavioral Performance on Spatial Learning Tasks.



Theta Modulation

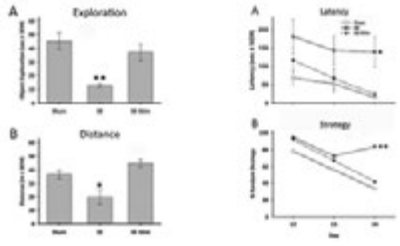


Electrical Stimulation - Animals



Lee et al, 2017

MSDB stimulation (7.7 Hz) improves performance



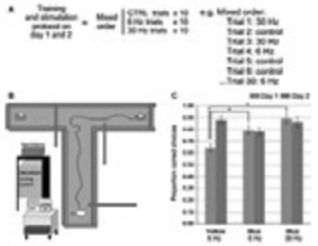
Optogenetics and epilepsy

- Optogenetics primarily used for dissection of circuits
- More recently being considered as a therapeutic tool
- In epilepsy, used to terminate seizures
  - Thalamo-cortical, cortical and hippocampal seizures
  - On-demand and closed loop systems
- Not obvious that terminating seizures will have significant impact on cognition
- Alternative view – modify background networks to improve cognition and determine whether this reduces seizure propensity

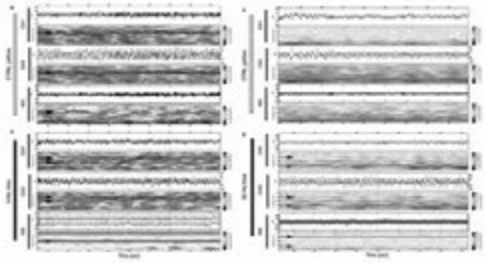
Optogenetics and Cognition

- In activation of nucleus acumbens improves behavioral flexibility (Aquili et al, 2014)
- Activation of central amygdala enhances fear memory consolidation (Andero et al, 2016)
- Activating dorsal raphe serotonergic neurons improves patience (Miyazaki et al, 2014)

MSDB stimulation with optogenetics



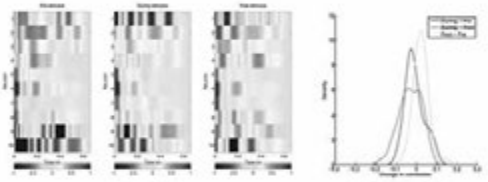
Modulation of theta



6Hz stimulation

30 Hz stimulation

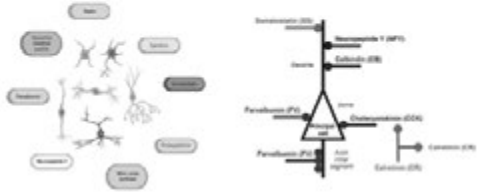
Single Units



Timing Coding

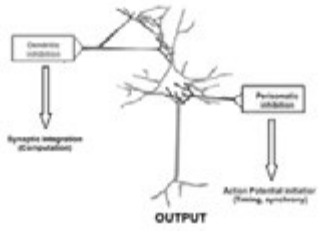
Population Coding

Cell-based therapies - The role of interneurons in the hippocampus



Owens & Kriegstein, 2002

Interneuron functional diversity



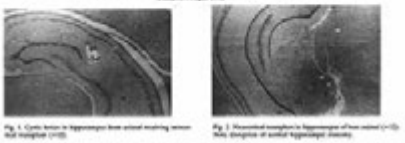
Interneuron development

Rat E11 - 17

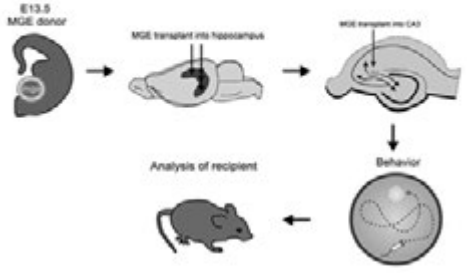
- *Dlx1/2 (differentiation, migration, and process formation)*
- *Sox6 & Nkx2.1 (controls subtype differentiation)*
- *Shh (maintains Nkx2.1 expression)*

Prev

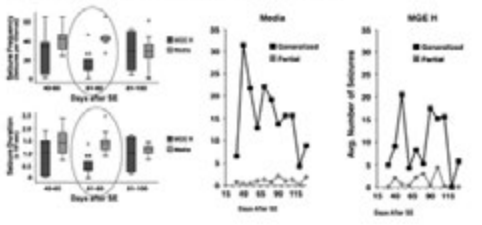
Effect of neural transplants on seizure frequency and kindling in immature rats following kainic acid



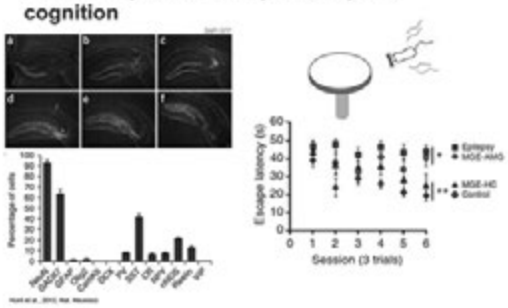
Experimental paradigm



MGE transplantation into dentate gyrus modestly improves seizure outcome



MGE transplantation improves spatial cognition



Conclusions

- Treatment of seizures may result in some cognitive improvements, but these are modest
- Structurally abnormal brains can be functionally modified to improve cognition independently of seizures
- Timing and population coding are critical for cognition and appear to be modifiable
- WATCH THIS SPACE