American Association of Neuropathologists, Inc.

Focal cortical dysplasias: a neuropathological and molecular perspective

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Department of (Neuro)Pathology, AMC, University of Amsterdam

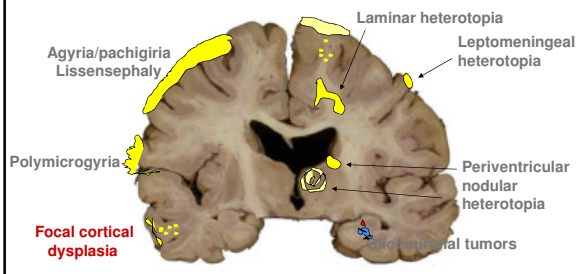
Learning Objectives

- Explain the new consensus classification of distinct FCD subtypes based on histopathological features
- Discuss the recently emerging hypotheses on the molecular pathogenesis of FCD
- Explain the mechanisms of epileptogenesis in FCD

American Association of Neuropathologists (AANP)| **2014 Annual Meeting**

Malformations of cortical development
Classification and Pathogenesis

Focal cortical dysplasias (FCD) represent localised malformative brain lesions of unknown cause



Primary/ idiopathic (genetic origin)

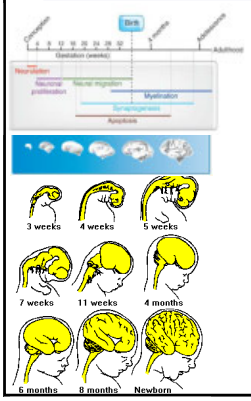
Secondary/symptomatic (environmental insults)

Malformations of cortical development

Key issues

- **How are the distinct focal malformations formed?**
  - When does the malformative process begin ?
  - Can we identify common pathogenetic pathways?
- **Relationship to epilepsy:**
  - Why epileptogenic?
  - Can we identify common epileptogenic pathways ?
- **Relationship to cognitive abnormalities**

Alteration of different stages of brain development produce specific pathologies



Embryonic period (3-6 weeks)
Dorsal induction (3-4 w)
Formation and neural tube closure
Anencephaly, Encephalocele
Ventral induction (4-6 w)
Development of prosencephalon
Holoprosencephaly

Fetal period (6-24 weeks)
Neurogenesis
Proliferatieve disorders
(Micro-, macro-cephaly, cortical dysplasias)
Migration
Migration disorders

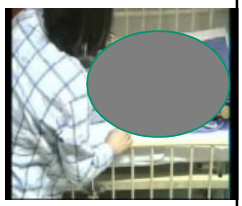
Perinatal period (24 -postnatal)
Organization
Polymicrogyria/Cortical dysplasias (specific subtypes)
Myelinisation (24 tot 2 yrs)

Malformations of cortical development
Focal cortical dysplasias (FCD)
Clinical Issues

FCD are a recognized cause of epilepsy:
Virtually all seizure subtypes have been described

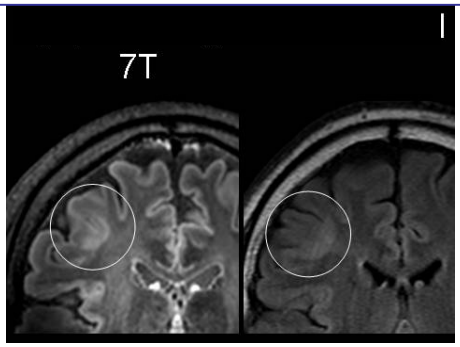
Age distribution:
Infants, children and adults

Pharmacoresistance:
Population of completely refractory patients



Surgery:
- *20-40 % surgical resections*
- *surgery improved seizure control in ≤ 50% of patients*

Focal Cortical Dysplasia

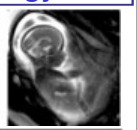


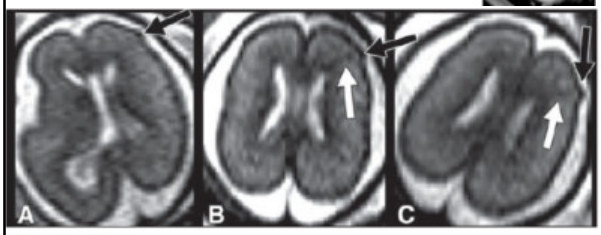
In children and adolescents cortical dysplasia is the most frequent etiology (42%) Epilepsia ILAE

Epileptic Disord 2009; 11 (3): 194-205; Lancet Neurol. 2009 Sep;8(9):830-43. Review.

Developmental Neuropathology

Early Formative Stage of Human Focal Cortical Gyration Anomalies: Fetal MRI



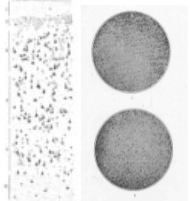


AJR 2012; 198:439–447

Historical background
Focal cortical dysplasias (FCD)

Pathologic studies on brains of patients with epilepsy

Roncoroni L (1896) La fine morfologia del cervello degli epilettici e dei delinquenti. Arch Psich Scienze penali Antropol Criminale 17:92–116



"Abundant **gliosis**.... **large pyramidal neurons** haphazardly arranged.....**abnormal orientation** of their apical dendrites, **.....polymorphous giant cells**" (in 13 patients with epilepsy) "**numerous nervous cells in the white matter and large disruption of cortical organization**" (in 10 patients)

Ronconi: "**a disorder of the development of the nervous system**".

Lombroso: "This form of degeneration, [the epilepsy], is related to an **embryonic development arrest** that has acquired atavic features....

Historical background
Focal cortical dysplasias (FCD)

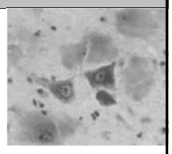
J. Neurol. Neurosurg. Psychiat., 1957, **20**, 117.

INFANTILE CEREBRAL GLIOSIS WITH GIANT NERVE CELLS

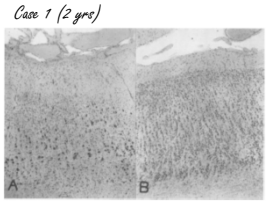
BY

L. CROME

From the Department of Neuropathology, the Fountain Hospital, Tooting, London



Case 1 (2 yrs)



"Fibrous **gliosis**... **Cortical lamination was disrupted** and totally unrecognizable in the worst areas. **Nerve cells** were reduced in number, those remaining showing many changes....., **enlargement with distortion of the cell outlines and formation of giant cells**"

"The details of the histological picture and, particularly, the giant nerve cells, were reminiscent of tuberous sclerosis (localized tuberous sclerosis).....It is, however, improbable that the condition is TSC.. .....omatic manifestations of TSC are absent".

Historical background
Focal cortical dysplasias (FCD)

D. C. TAYLOR.

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

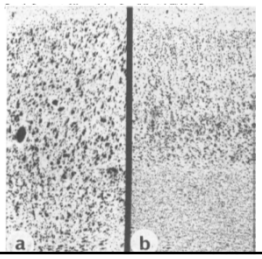
Focal dysplasia of the cerebral cortex in epilepsy

D. C. TAYLOR[1] 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



M. A. FALCONER

Historical background
Focal cortical dysplasias (FCD)

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

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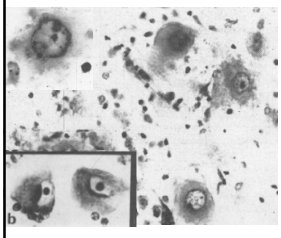
From the Department of Neuropathology, Runwell Hospital, Wickford, Essex



First comprehensive description of FCD

"**An unusual microscopic abnormality** has been identified in lobectomy specimens removed surgically from brains of 10 epileptic patients. The abnormality could seldom be identified by palpation or with the naked eye.

Histologically, it consisted of congregations of **large, bizarre neurons** which were littered through all but first layer. In most but not in all cases, **protoplasmic cells**, probably of glial origin were also present in the depth of the affected cortex and in the subjacent white matter"

"No report of closely similar observations have been traced"

Historical background
Acquired dysplasias

Journal of Neuropathology and Experimental Neurology
Copyright © 1999 by the American Association of Neuropathologists
Vol. 58, No. 5
May, 1999
pp. 487–429

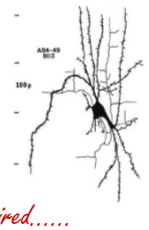
Developmental Neuropathology and Impact of Perinatal Brain Damage. III: Gray Matter Lesions of the Neocortex

Miguel Marín-Padilla, MD

Acquired dysplasias

Acquired Minimal GM Damage

The combined use of various staining procedures (RG, NF, GFAP, PV, and SY) has shown postinjury alterations in primarily undamaged cortical regions far from the injured site, as well as in regions adjacent to small cortical lesions (e.g. marginal heterotopias). Often, these alterations are unrecognizable in routine preparations. These postinjury alterations include partial obliteration of layer I, cytoarchitectural disorganization, partial laminar obliteration, columnar and/or circular arrangement of neurons around cell-free zones, focal reparative gliosis, and the presence of isolated and strongly NF+ hypertrophic neurons. The abnormal morphology of hypertrophic neurons can only be recognized using RG preparations (Figs. 3E,



Hypertrophic neurons:posty-injury acquired.....

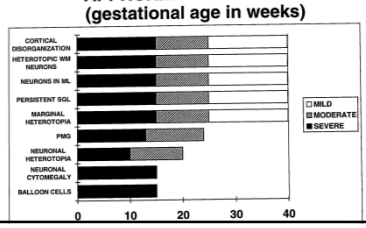
Historical background
Different Classification Systems of Focal Cortical Dysplasias

Journal of Neuropathology and Experimental Neurology
Copyright © 1995 by the American Association of Neuropathologists
Vol. 54, No. 2
March, 1995
pp. 137–153

Cerebral Cortical Dysplasia Associated with Pediatric Epilepsy. Review of Neuropathologic Features and Proposal for a Grading System

Paul S. Mischel, M.D., Loan P. Nguyen, M.D., and Harry V. Vinters, M.D., FR.C.P. (C)

APPROXIMATE TIME LINE (gestational age in weeks)



Historical background
Different Classification Systems of Focal Cortical Dysplasias

Brain. 2002 Aug;125(Pt 8):1719-32.

Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome.

Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, Cardinale F, Cossu M, Ferrario A, Galli C, Bramerio M, Citterio A, Spreafico R.

Three subgroups were identified:

(i) Architectural dysplasia: abnormal cortical lamination and ectopic neurones in white matter

(i) Cytoarchitectural dysplasia: giant neurofilament-enriched neurones in addition to altered cortical lamination

(i) Taylor-type cortical dysplasia: giant dysmorphic neurones and balloon cells associated with cortical laminar disruption

Historical background
Different Classification Systems of Focal Cortical Dysplasias

Articles

Terminology and classification of the cortical dysplasias

A. Palmini, MD, PhD, I. Najm, MD, G. Avanzini, MD, T. Babb, PhD, R. Guerrini, MD, N. Foldvary-Schaefer, DO, G. Jackson, MD, H.O. Lüders, MD, PhD, R. Preyser, MD, PhD, R. Spreafico, MD, PhD, and H.V. Vinters, MD

Tassi et al. *Brain* 2002	Architectural dysplasia: abnormal cortical lamination and ectopic neurons in WM		Cytoarchitectural dysplasia: ... plus NFP-positive giant neurons outside layer V	Taylor-Typ ... plus dysmorphic neurons and balloon cells
Palmini et al. Neurology 2004	mMCD type I: Ectopic neurons in layer I; mMCD type II: Neuronal heterotopia outside layer I	FCD type IA: Isolated architectural abnormalities	FCD type IB: ... plus giant, not dysmorphic neurons	FCD type IIa: dysmorphic neurons, no balloon cells; FCD type IIb: dysmorphic neurons and balloon cells
Barkovich et al. Neurology 2005	Not visible at MRI	Abnormal cortical organization	Abnormal cortical organization	Abnormal neuronal and glial proliferation

Historical background
Palmini's classification and postsurgical outcome

Favorable post-surgical seizure relief in patients with FCD Type II

References	# Patients	Classification	Surgical outcome
Taylor et al. 1971	10	Histology	60%[a]
Urbach et al. 2002	22	Histology	100%[b]
Tassi et al. 2002	15	Histology	75%
Fauser et al. 2004	14	Histology	70%
Kresk et al. 2008[c]	35	Histology	75%
Kresk et al. 2009[c]	16	Histology	75%
Total	112		76%

[a] Patients reported as "ilt free".
[b] Seizure relief obtained in all patients with complete resection of MRI visible lesion.
[c] This author reported two independent patient cohorts from Germany and Florida, respectively.

"Controversial" postsurgical outcome prediction in patients with FCD Type I

References	# Patients	Classification	Surgical outcome
Tassi et al. 2002	31	Histology	43%[a]
Fauser et al. 2004	38	Histology	55-67%[b]
Kresk et al. 2008[c]	79	Histology	45-49%[d]
Kresk et al. 2009[c]	24	Histology	21%[c]
Total	172		21-67% (47%)

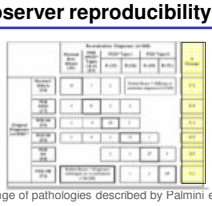
[a] 43% of patients presented with hippocampal sclerosis; mean age of operation was 27 years.
[b] 67% of patients presented with hippocampal sclerosis; mean age at operation was 21.3 years.
[c] No patient presented with hippocampal sclerosis; mean age at operation was 6.8 years.
[d] 67% of patients presented with hippocampal sclerosis; mean age at operation was 10.7 years.
[e] This author reported two independent patient cohorts from Germany and Florida, USA.

Palmini's classification
Interobserver agreement and intraobserver reproducibility

FULL-LENGTH ORIGINAL RESEARCH

Interobserver and intraobserver reproducibility in focal cortical dysplasia (malformations of cortical development)

*Wendy A. Chamberlain, †Mark L. Cohen, ‡Kymberly A. Gyure, §Bette K. Kleinschmidt-DeMasters, ¶Aric Perry, ‖Suzanne Z. Powell, **Jiang Qian, ††Susan M. Staugaitis, and *Richard A. Prayson



Methods: 26 epilepsy resections were selected to represent the range of pathologies described by Palmini et al.2004.

- **Interobserver concordance using this approach was moderate (κ value of 0.4968)**
- **The classification categories with the greatest concordance were FCD type IIa/b and the least, mild MCD and FCD types Ia/b.**
- **Difficulty in differentiating mild MCD/FCD type I lesions from normal and/or gliotic tissue was observed**

Focal Cortical Dysplasia

SPECIAL REPORT

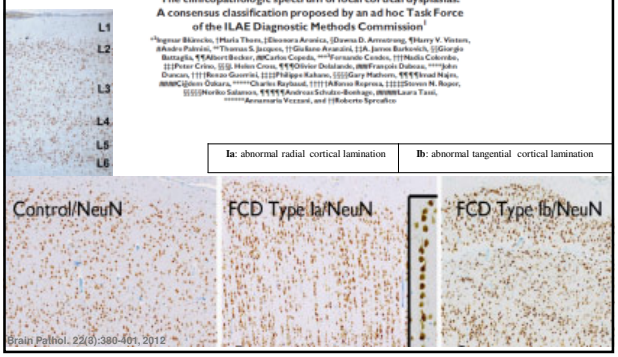
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

FCD Type I (isolated)	Focal Cortical Dysplasia with abnormal radial cortical lamination (FCD Ia)	Focal Cortical Dysplasia with abnormal tangential cortical lamination (FCD Ib)	Focal Cortical Dysplasia with abnormal radial and tangential cortical lamination (FCD Ic)
FCD Type II (isolated)	Focal Cortical Dysplasia with dysmorphic neurons (FCD IIa)	Focal Cortical Dysplasia with dysmorphic neurons and balloon cells (FCD IIb)	
FCD Type III (associated with principal lesion)	Focal Cortical Dysplasia in the temporal lobe associated with Hippocampal sclerosis (FCD IIIa)	Focal Cortical Dysplasia adjacent to a glial or glio-neuronal tumor (FCD IIIb)	Focal Cortical Dysplasia adjacent to vascular malformation (FCD IIIc)	Focal Cortical Dysplasia adjacent to any other lesion acquired during early life, e.g., trauma, porencephaly, encephalitis (FCD IIId)

Focal Cortical Dysplasia:FCD I

SPECIAL REPORT

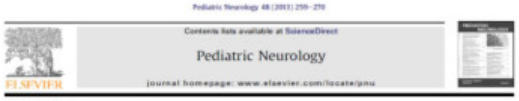
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]



Brain Pathol. 22(3):380-401, 2012

Focal Cortical Dysplasia: FCD Ia

Radial Microcolumnar Cortical Architecture
is normal in the cortical plate in the first half of gestation


Contents lists available at ScienceDirect

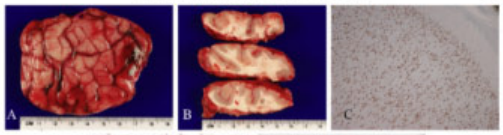
Pediatric Neurology

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

Review Article

Radial Microcolumnar Cortical Architecture: Maturational Arrest or Cortical Dysplasia?

Harvey B. Sarnat MS, MD, FRCPC[a,b,c,*], Laura Flores-Sarnat MD[a,c]

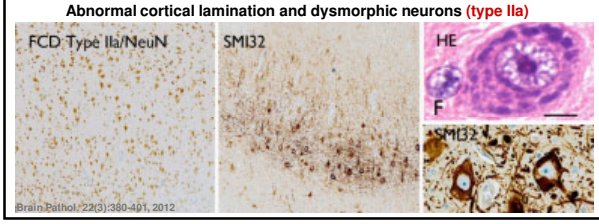


Focal Cortical Dysplasia: FCD IIa

SPECIAL REPORT

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

Abnormal cortical lamination and dysmorphic neurons (type IIa)



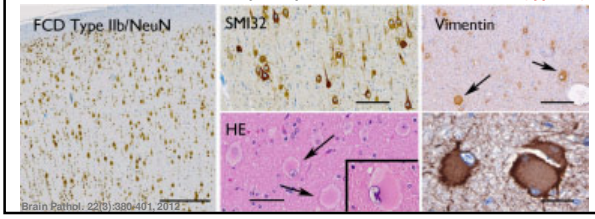
Brain Pathol. 22(3):380-401, 2012

Focal Cortical Dysplasia: FCD IIb

SPECIAL REPORT

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

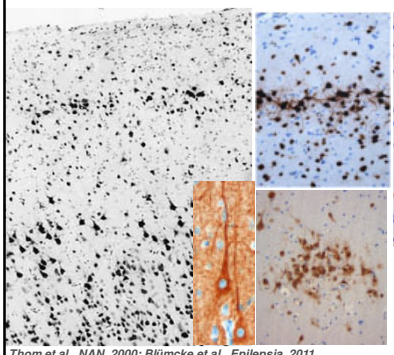
Abnormal cortical lamination, dysmorphic neurons and balloon cells (type IIb)



Brain Pathol. 22(3):380-401, 2012

Focal Cortical Dysplasia: FCD IIIa

Hippocampal sclerosis

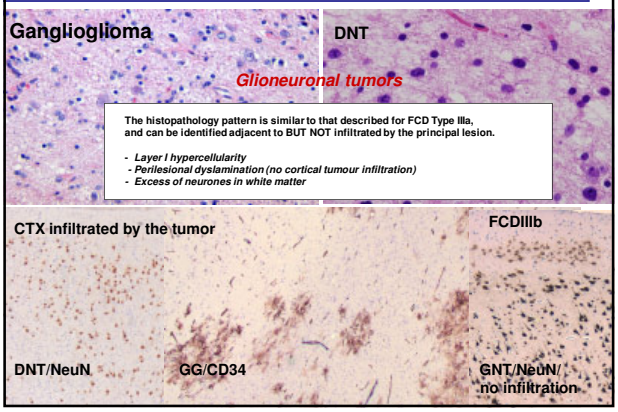


Dyslamination and cytoarchitectural changes

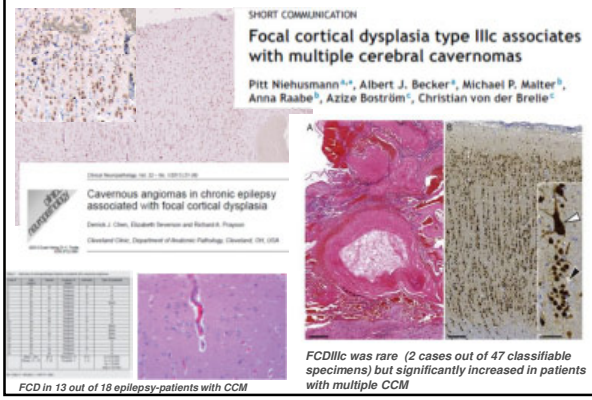
layer II disorganisation
Excess of neurones in white matter
Blurred interface between grey/wm

Thom et al., NAN, 2000; Blümcke et al., Epilepsia, 2011

Focal Cortical Dysplasia: FCD IIIb



Focal Cortical Dysplasia: FCD IIIc



FCD in 13 out of 18 epilepsy-patients with CCM

FCDIIIc was rare (2 cases out of 47 classifiable specimens) but significantly increased in patients with multiple CCM

2011 ILAE FCD consensus classification
Interobserver agreement and intraobserver reproducibility

Methods: 25 cases; Internet-based microscopy review; Nine experienced Neuropathologists; In a third evaluation round, 21 additional neuropathologists with different experience.

- **Interobserver agreement was good (κ = 0.6360) and consensus was obtained in 24 (96%) of 25 cases.**
- **Overall intraobserver reproducibility was also good (κ = 0.7824, ranging from 0.4991 to 1.000).**
- **In the third evaluation round, interobserver agreement was reflected by the level of experience of each neuropathologist (0.5056; >40 cases/year); (0.3265; <10 cases/year).**

2011 ILAE FCD consensus classification
Clinical differences

In silico transformation from *Palmini* into the ILAE classification ?

31 patients FCD type I
50 patients with FCD type IIIa
9 patients with temporal FCD type II

Clinical features in this cohort did not allow to clear separation of temporal FCD types I and IIIa.

Epilepsia. 2013 Aug;54(8):1506-7.

Proper evaluation requires microscopic review of surgical specimens

2011 ILAE FCD consensus classification
Clinical differences

Modern Pathology , (18 April 2014) | doi:10.1038/modpathol.2014.64

Post-surgical outcome for epilepsy associated with type I focal cortical dysplasia subtypes.
Simpson SL, Prayson RA.

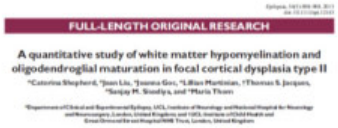
91 patients FCD type I
50 patients with ILAE FCD type Ib
41 with ILAE FCD type Ic

After surgery, 44 patients (48%) were seizure-free.

No significant difference concerning surgical outcome with respect to seizure frequency for the histologic subtypes of ILAE focal cortical dysplasia type I **(Ib vs Ic)**

Focal Cortical Dysplasia
Additional findings: WM abnormalities

FCD II: increased cortical thickness
FCD Ia: smaller cortical ribbon
FCD IIb: loss of myelin content
Compromised oligodendroglial lineage differentiation?



The primary pathologic process underlying WM abnormalities in FCD IIb: Reduction of myelinated axons (possibly influenced by duration of seizures), rather than dysmyelination

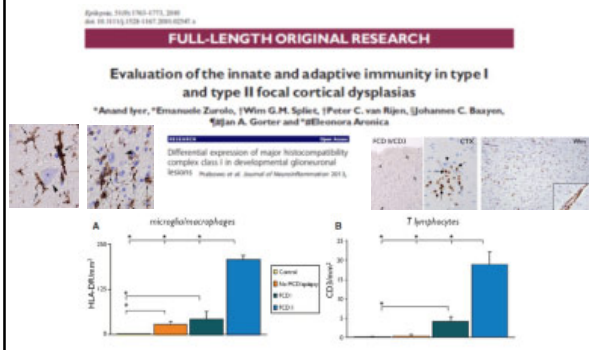
Focal Cortical Dysplasia
Additional findings: heterotopic neurons

In all FCD variants: increased number of heterotopic neurons

Heterotopic neurons:

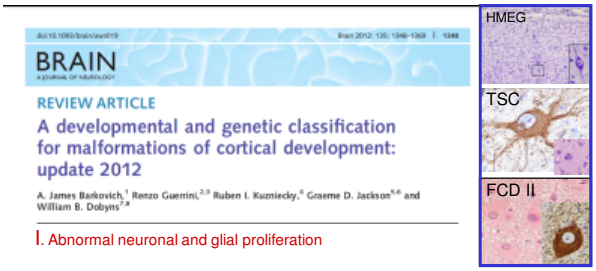
- Developmental abnormalities:
  - failure of normal migration
- Maturational abnormalities:
  - abnormal persistance of subplate neurons
  - Neurogenesis
- Functional significance: unkown

Focal Cortical Dysplasia
Additional findings: inflammatory cell components



Malformations of cortical development

- *When does the malformative process begin?*



I. Abnormal neuronal and glial proliferation

Histopathological features in FCD II indicate a primary "*unknown*" defect in the early stage of cortical development that coincides with the onset of neurogenesis

Malformations of cortical development

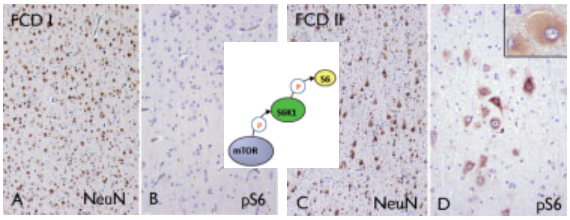
Key issues

- **How are the distinct focal malformations formed?**
  - When does the malformative process begin ?
  - Can we identify common pathogenetic pathways?
- **Relationship to epilepsy:**
  - Why epileptogenic?
  - Can we identify common epileptogenic pathways ?
- **Relationship to cognitive abnormalities**

mTOR Signaling Pathway and FCD

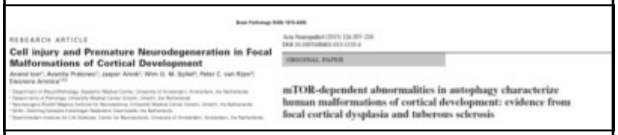
Immunohistochemical studies provide evidence of enhanced mTOR signaling in FCD II

(Baybis et al., 2004; Miyata et al., 2004; Schick et al., 2007; Orlova et al., 2010; Iyer et al., 2010)

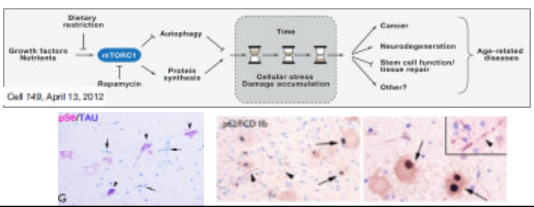


Iyer et al., 2010

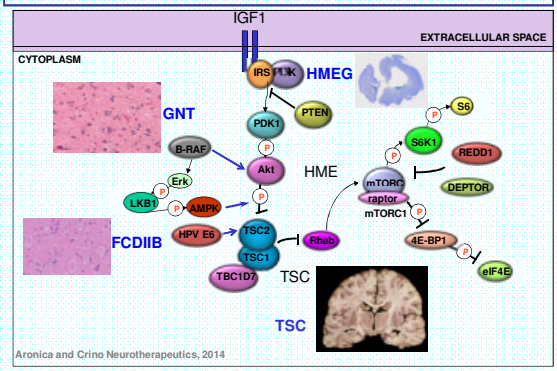
Focal Cortical Dysplasia
Additional findings: neurodegeneration and autophagy



Increasing evidence supports the role of this pathway in the mechanisms underlying cellular ageing and neurodegeneration



mTOR Signaling Pathway and Malformations



Focal Cortical Dysplasia: Familial cases

Six pedigrees with familial cortical dysplasia and related lesions.

Is focal cortical dysplasia sporadic? Family evidence for genetic susceptibility

*†‡Richard J. Leventer, §¶Floor E. Jansen, **††Simone A. Mandelstam, ‡‡Alice Ho, §§Ismail Mohamed, ¶¶Harvey B. Sarnat, ###Mitsuhiro Kato, ***Tatsuya Fukasawa, †††Hirotomo Saitsu, †††Naomichi Matsumoto, ‡‡‡Masayuki Itoh, §§§¶¶¶Renate M. Kalnins, ‡###Chung W. Chow, *†‡A. Simon Harvey, ¶**Graeme D. Jackson, ****Peter B. Crino, ¶Samuel F. Berkovic, and *‡¶**Ingrid E. Scheffer

Epilepsia, 55(3):e22–e26, 2014
doi: 10.1111/epi.12533

Clinical evidence suggesting that FCD, HME, glioneuronal tumors may share common genetic determinants

mTOR Signaling Pathway and FCD Mechanisms

Upstream activators of mTOR:

✓ microenvironmental factors: growth factors (VEGF)

✓ glutamate receptors (mGluR5)

Seizures *(Galanopoulou et al., Epilepsia 2012; Vezzani, Nature, 2012)*

Mutations or a germ-line predisposition (polymorphisms) in TSC genes:

FCD IIb: TSC1 sequence alterations in FCD IIb *(Becker et al. Ann Neurol, 2002; Epilepsia, 2007)*

Another study could not confirm the hypothesis of a germ-line predisposition (increased polymorphisms) in the TSC1 gene, as causative for FCD II (*Gumbinger et al, Epilepsia, 2009)*

Somatic mosaicism or mutations in other components of the Pi3K-mTOR pathway ?

Reviewed in Aronica and Crino Neurotherapeutics, 2014

New etiology of FCD ?

The high-risk human papillomavirus type 16 oncoprotein E6 was identified as a potent activator of mTORC1 signaling

New aetiology of FCD ?

Interpretations of data

✓ HPV and potentially CMV, HHV, and HSV, may serve as **pathogenic agents** for FCDII, intra-uterine infection ? **routes of infection, and mechanisms of viral attachment and internalization**

✓ Viruses may serve as **cofactors** or transactivators in neural progenitor cells during brain development that **cause or facilitate pathogenic somatic gene mutations**

✓ The cell subtypes within FCD may be somehow trophic for a select group of **viruses** that are **sequestered** within the lesions

The presence of these sequences may be **non-pathogenic** and reflect detection of relatively common viral isotypes in human brain tissue

Ann. Neurol, 2013 doi: 10.1002/ana.24032

Malformations of cortical development

Key issues

❑ **How are the distinct focal malformations formed?**

- When does the malformative process begin ?
- Can we identify the developmental origin of the abnormal large cells ?
- Can we identify common pathogenetic pathways?

❑ **Relationship to epilepsy:**

- Why epileptogenic?
- Can we identify common epileptogenic pathways ?
- Contribution of peri-lesional brain?

❑ **Relationship to cognitive abnormalities**

Intrinsic epileptogenicity

FULL-LENGTH ORIGINAL RESEARCH

High frequency oscillations mirror disease activity in patients with focal cortical dysplasia

Activity of high frequency oscillations mirrors the higher epileptogenicity of FCD type 2 lesions compared to type 1 lesions.

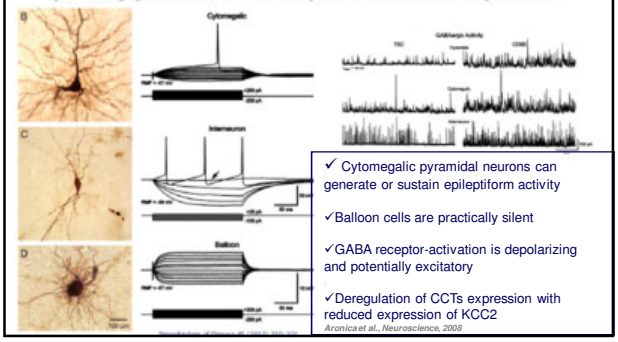
Rates of high frequency oscillations can reflect disease activity of a lesion

High frequency oscillations as biomarkers for epileptogenic areas?

Epileptiform activity

Cytomegalic pyramidal neurons/Balloon cells

Enhanced GABAergic network and receptor function in pediatric cortical dysplasia Type IIB compared with Tuberous Sclerosis Complex



✓ Cytomegalic pyramidal neurons can generate or sustain epileptiform activity

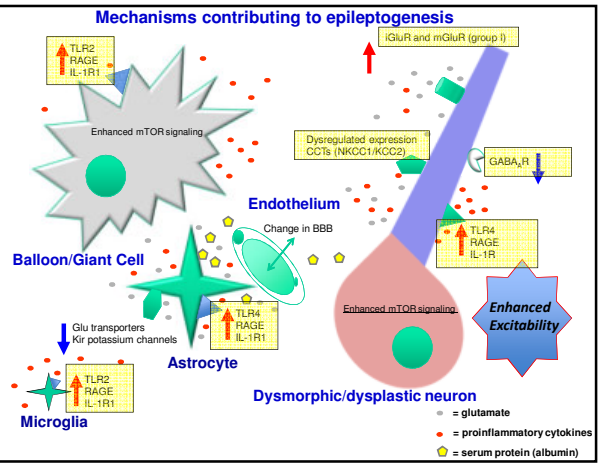
✓Balloon cells are practically silent

✓GABA receptor-activation is depolarizing and potentially excitatory

✓Deregulation of CCTs expression with reduced expression of KCC2

Aronica et al., Neuroscience, 2008

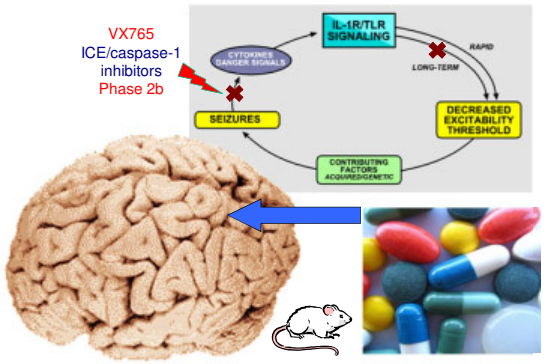
Mechanisms contributing to epileptogenesis



Mechanisms contributing to epileptogenesis

Inflammation: ictogenesis & epileptogenesis

VX765
ICE/caspase-1 inhibitors
Phase 2b

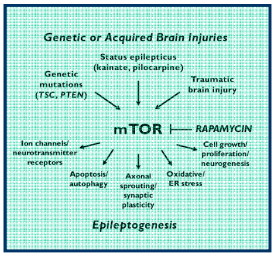


Vezzani et al, Nature Rev Neurol, 2011; BBI, 2011; Vezzani et al, Brain Behav Immun, 2011; Aronica and Crino, Epilepsia, 2011

Antiinflammatory drugs

Mechanisms contributing to epileptogenesis

Enhanced mTOR signaling



Everolimus Treatment of Refractory Epilepsy in Tuberous Sclerosis Complex

The Mammalian Target of Rapamycin Signaling Pathway Mediates Epileptogenesis in a Model of Temporal Lobe Epilepsy

Pharmacological inhibition of the mammalian target of rapamycin pathway suppresses acquired epilepsy

Xiaoxing Huang [a,1], Hailong Zhang [a,1], Jun Yang [a,1], Jingfan Wu [a,1], John McMahon [a], Yufan Lin [a], Zhonglian Cao [a], Michael Gruenthal [b], Yunfei Huang [a,*]

Conclusions and Future Goals

Multidisciplinary approach

Neurology

Neurogenetics

Neurophysiology

Neuroradiology

Neurosurgery

Neuropathology

Basic research

- Increased knowledge in the pathogenesis *(new classifications)*
- Development of clinical genetic testing *(genetic prenatal counseling)*
- Modulation of selected pathways *(targeted drug design)*
- Patient-specific therapeutic approach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EPISTOP
AMC Academic Medical Center, University of Amsterdam
UMCU University Medical Center Utrecht
VUMC Vrije Universiteit Medical Center, Amsterdam
SILS Swammerdam Institute for Life Sciences
SEIN Stichting Epilepsie Instellingen Nederland
UPENN University of Pennsylvania Medical Center, USA
Nationaal Epilepsie Fonds
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