Epilepsy in the Developing Brain

Focus on Neuropathology Research

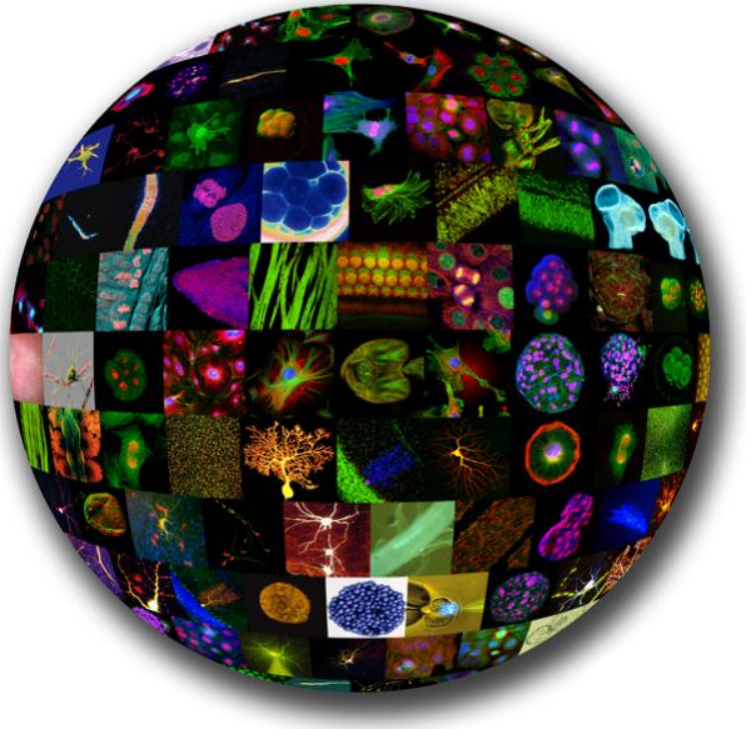
Past, Present and Future.

Maria Thom
Division of Neuropathology
UCL, Institute of Neurology, UK

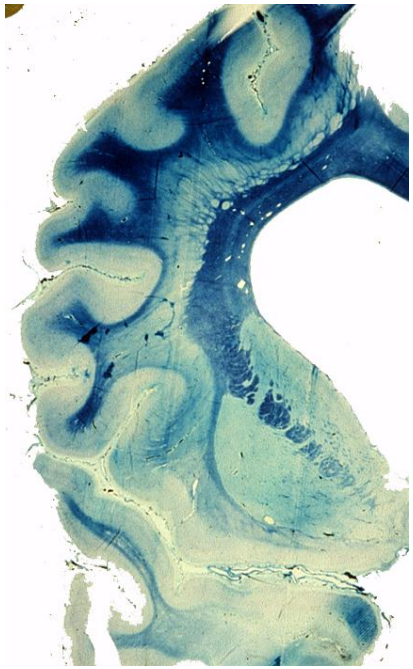
The Past → Present

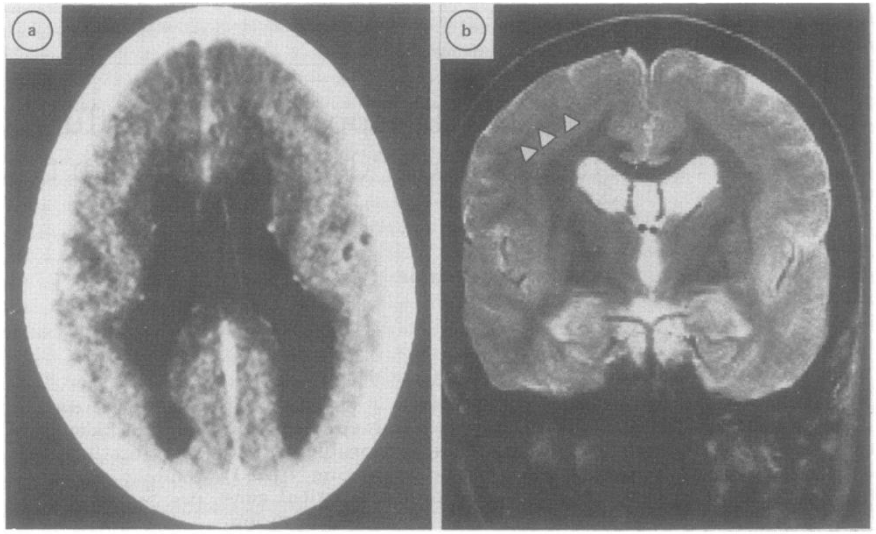
Neuropathology (cellular based / tissue studies) have played a vital part in understanding interactions of seizures and the developing brain.

→



The Doublecortin Story





Livingstone and Aicardi

Subcortical Laminar heterotopia

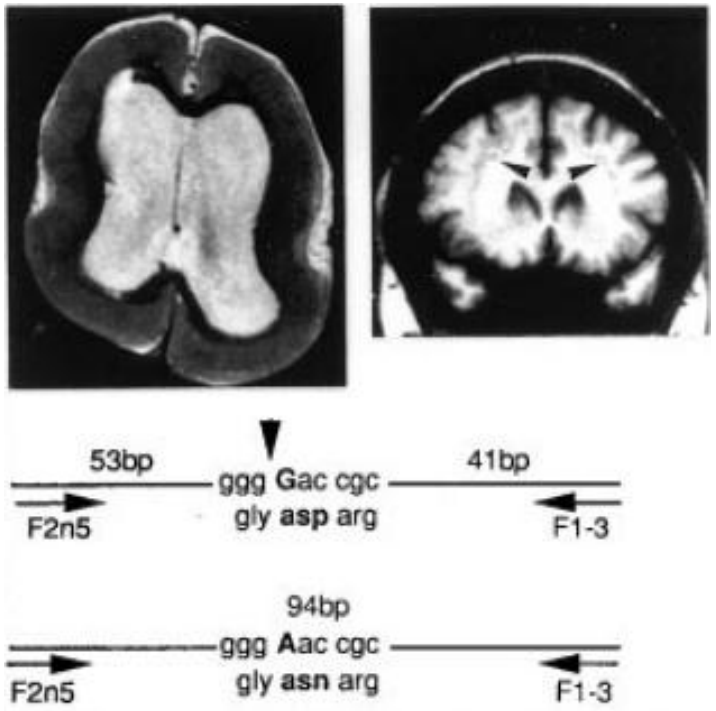
Pathology described ~1936

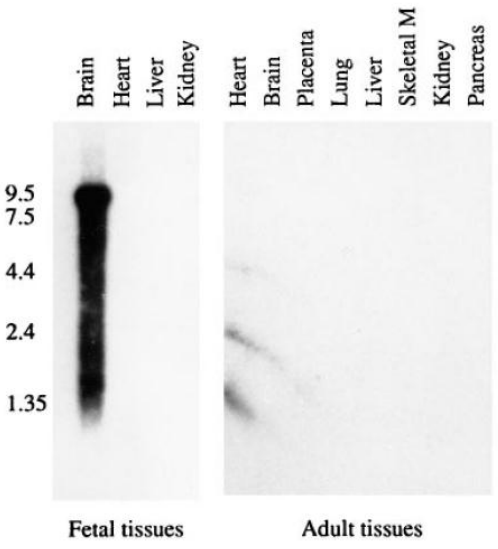
First neuroimaging reports ~1981

Cell, Vol. 92, 51–61, January 9, 1998, Copyright ©1998 by Cell Press

A Novel CNS Gene Required for Neuronal Migration and Involved in X-Linked Subcortical Laminar Heterotopia and Lissencephaly Syndrome

Vincent des Portes,[1] Jean Marc Pinard,[2] Pierre Billuart,[1] Marie Claude Vinet,[1] Annette Koulakoff,[3] Alain Carrié,[1] Antoinette Gelot,[4] Elisabeth Dupuis,[5] Jacques Motte,[6] Yoheved Berwald-Netter,[3] Martin Catala,[7] Axel Kahn,[1] Cherif Beldjord,[1] and Jamel Chelly[1,8]

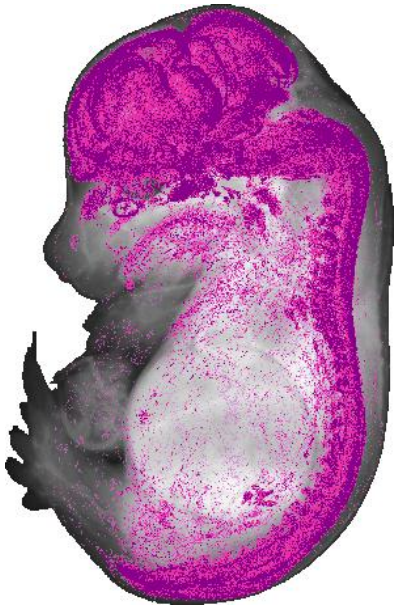




Doublecortin gene identified - 1998

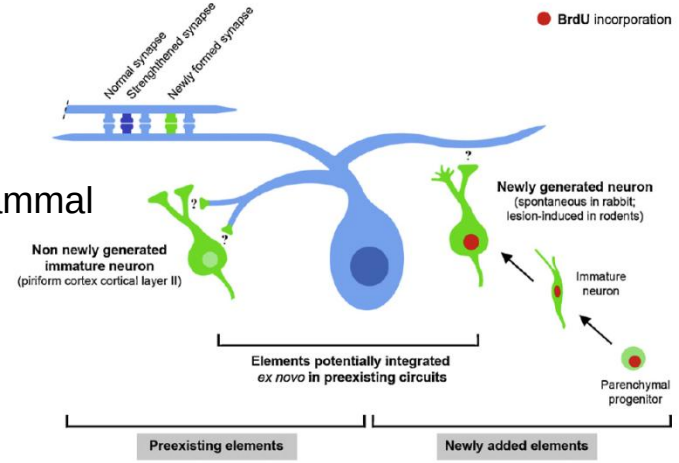
Doublecortin (DCX) and normal brain development

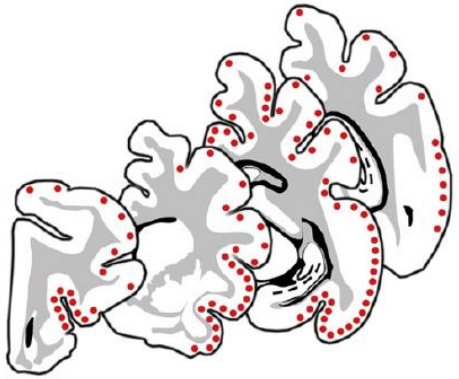
Fetal — Birth — Adult



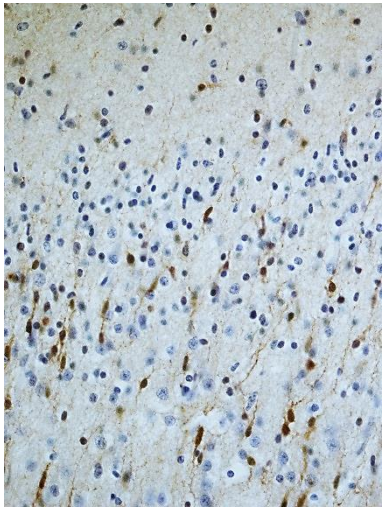
DCX Human 15 days gestation
http://www.hudsen.org/

Mammal

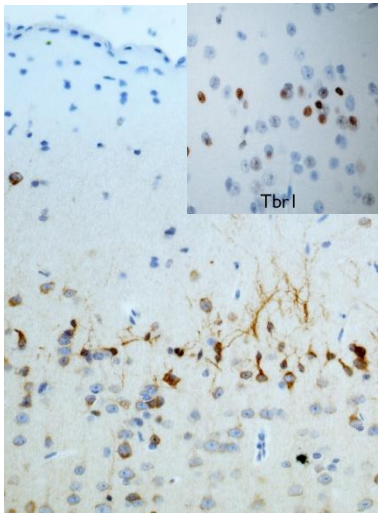




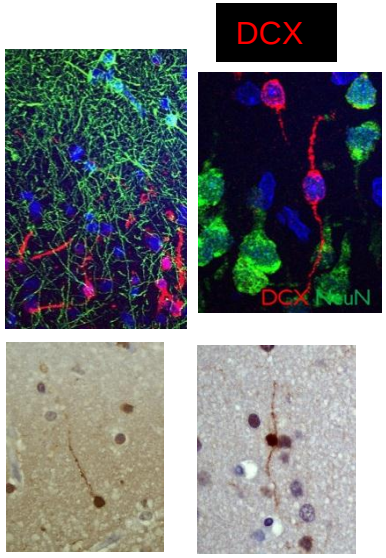
Human



Day 2, layer II cortex



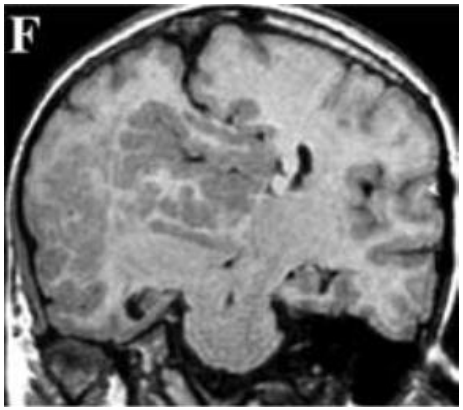
Age 2, Epilepsy

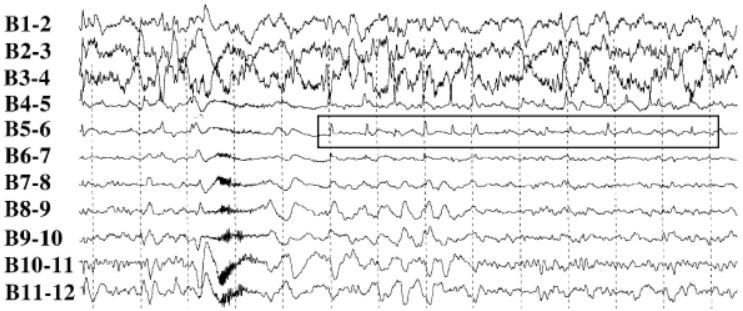


Age 42, Epilepsy

Srikandarajah, 2009

Epileptogenesis mechanisms, 2007





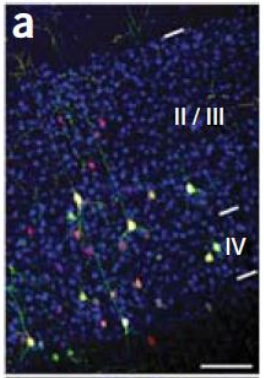
Bataglia, 2007

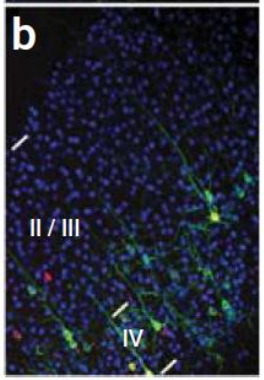
Doublecortin – experimental replacement, 2008

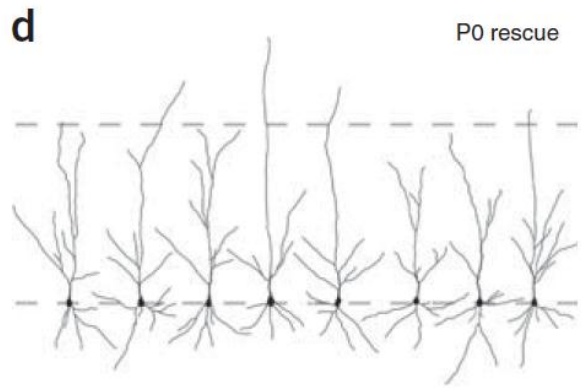
nature medicine

Dcx reexpression reduces subcortical band heterotopia and seizure threshold in an animal model of neuronal migration disorder

Jean-Bernard Manent[1], Yu Wang[1], YoonJeung Chang[1], Murugan Paramasivam[1] & Joseph J LoTurco[1]

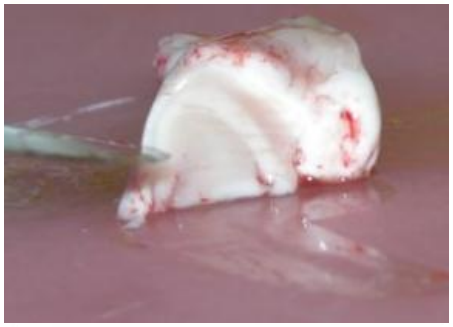


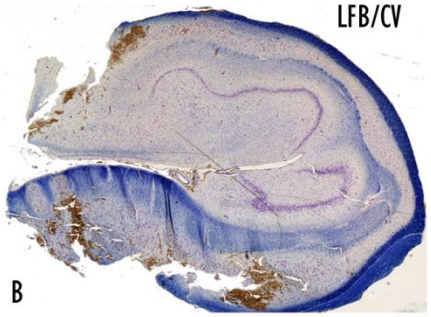


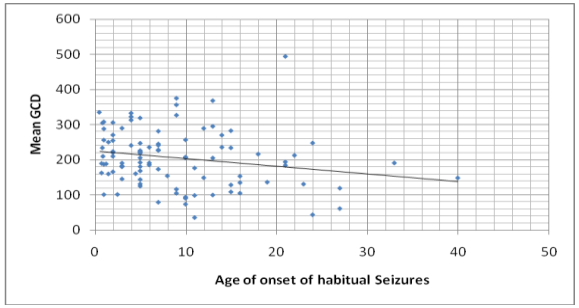


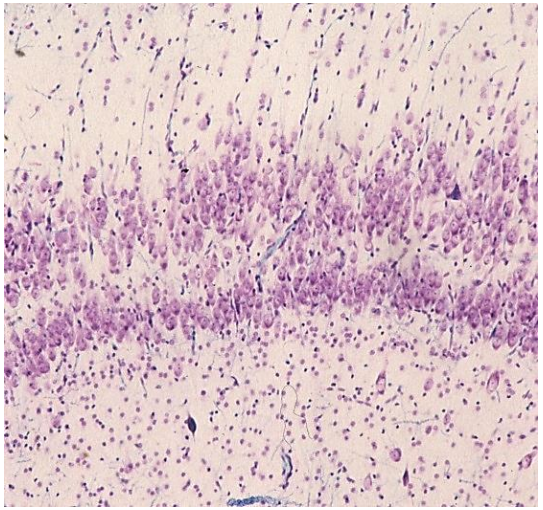
‘An immature brain is not a small adult brain’

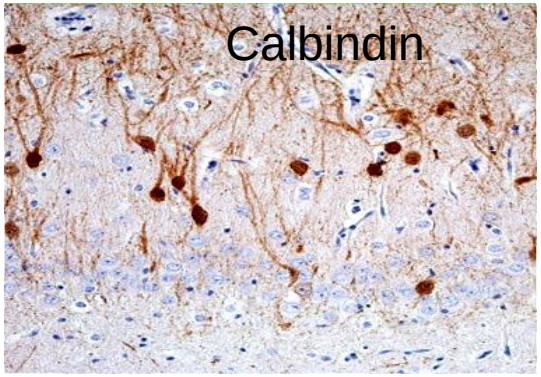
Granule cell dispersion in Hippocampal sclerosis / TLE









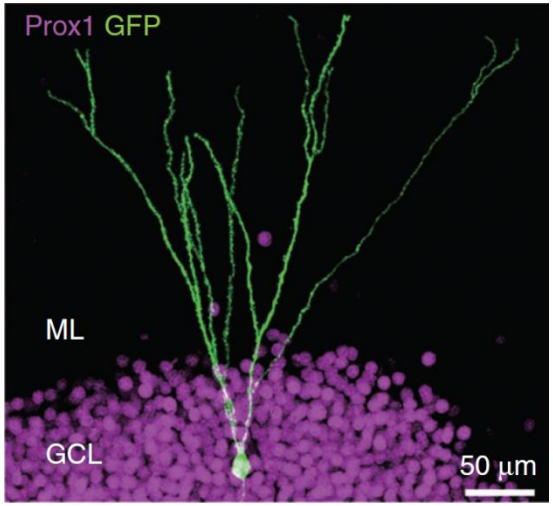


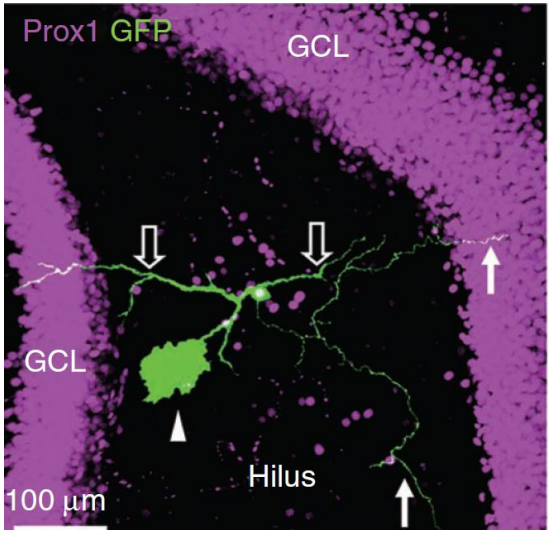
Martinian, 2012

nature medicine

GABAergic excitation after febrile seizures induces ectopic granule cells and adult epilepsy

Ryuta Koyama[1], Kentaro Tao[1,2], Takuya Sasaki[1,2], Junya Ichikawa[1], Daisuke Miyamoto[1], Rieko Muramatsu[1], Norio Matsuki[1] & Yuji Ikegaya[1]



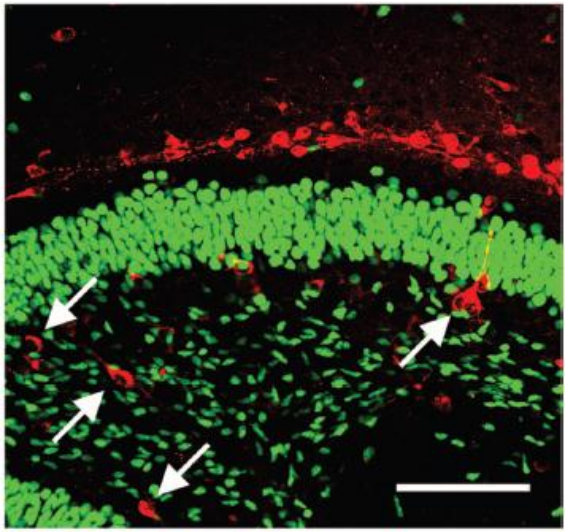


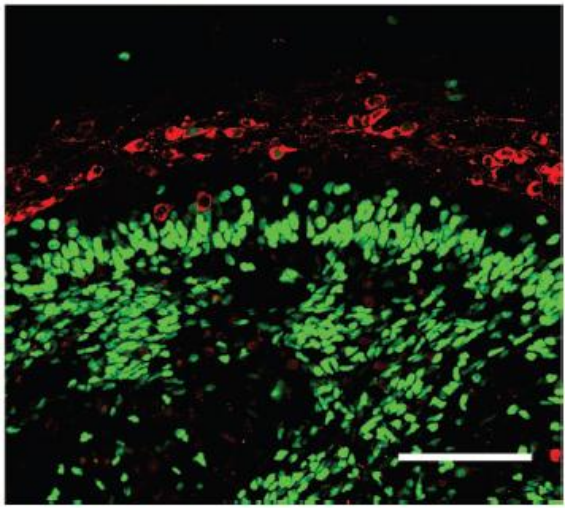
Cerebral Cortex Advance Access published March 15, 2013

Cerebral Cortex
doi:10.1093/cercor/bht067

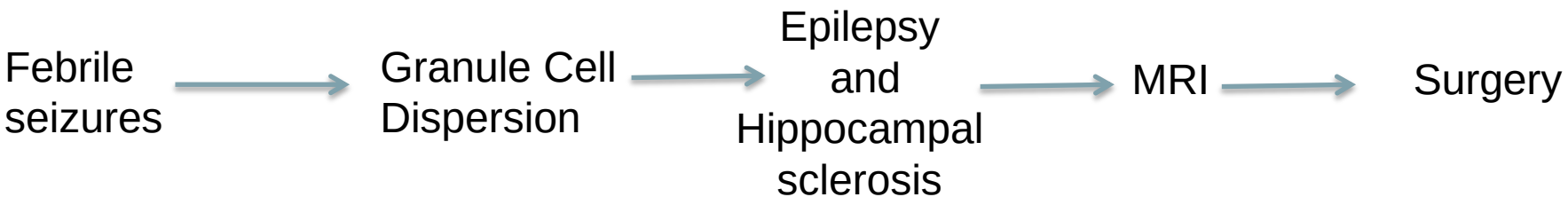
Epilepsy-Induced Motility of Differentiated Neurons

Xuejun Chai[1,†], Gert Münzner[2,†], Shanting Zhao[1], Stefanie Tinnes[2], Janina Kowalski[3], Ute Häussler[2], Christina Young[4], Carola A. Haas[2,†] and Michael Frotscher[1,†]

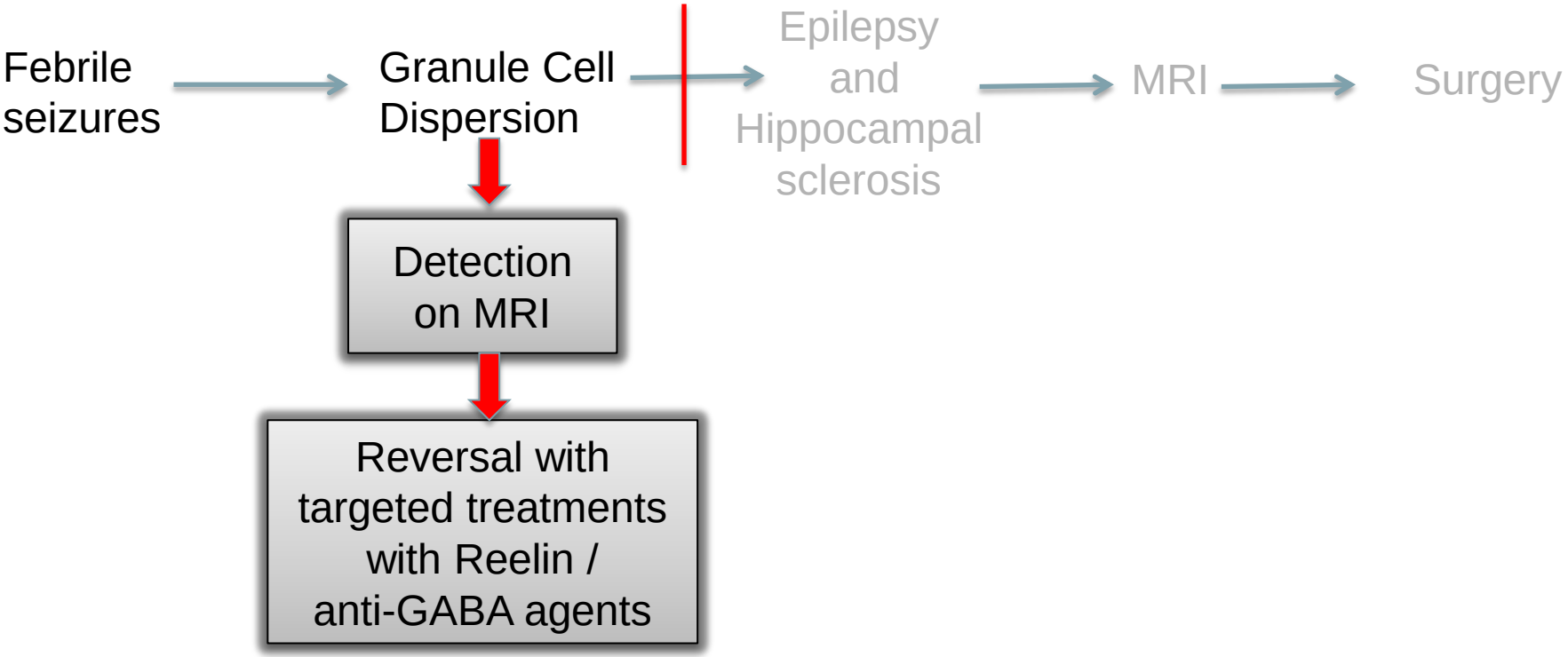




Natural history of refractory mTLE/hippocampal sclerosis



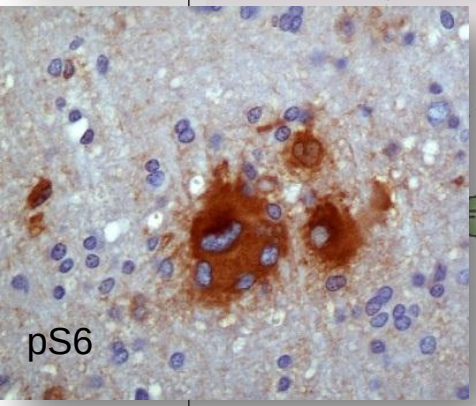
Future : Natural History refractory mTLE/HS ?



mTOR Pathway Activation in Tubers and Focal Cortical Dysplasia

mTOR Cascade Activation Distinguishes Tubers from Focal Cortical Dysplasia

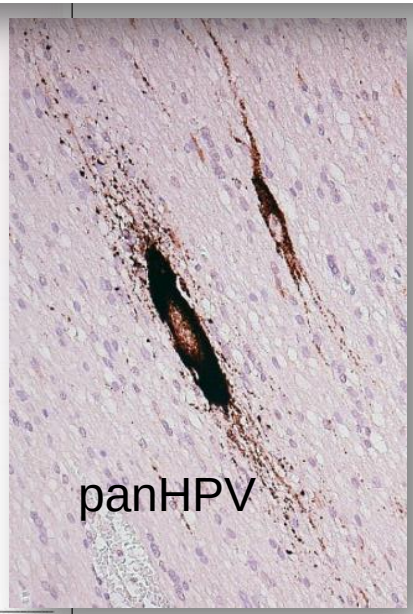
Marianna Baybis, MS,[1] Jia Yu, MD,[1] Allana Lee, BA,[1] Jeff A. Golden, MD,[2] Howard Weiner, MD,[3] Guy McKhann II, MD,[4] Eleonora Aronica, MD,[5] and Peter B. Crino, MD, PhD[1]



RAPID COMMUNICATION

Detection of Human Papillomavirus in Human Focal Cortical Dysplasia Type IIB

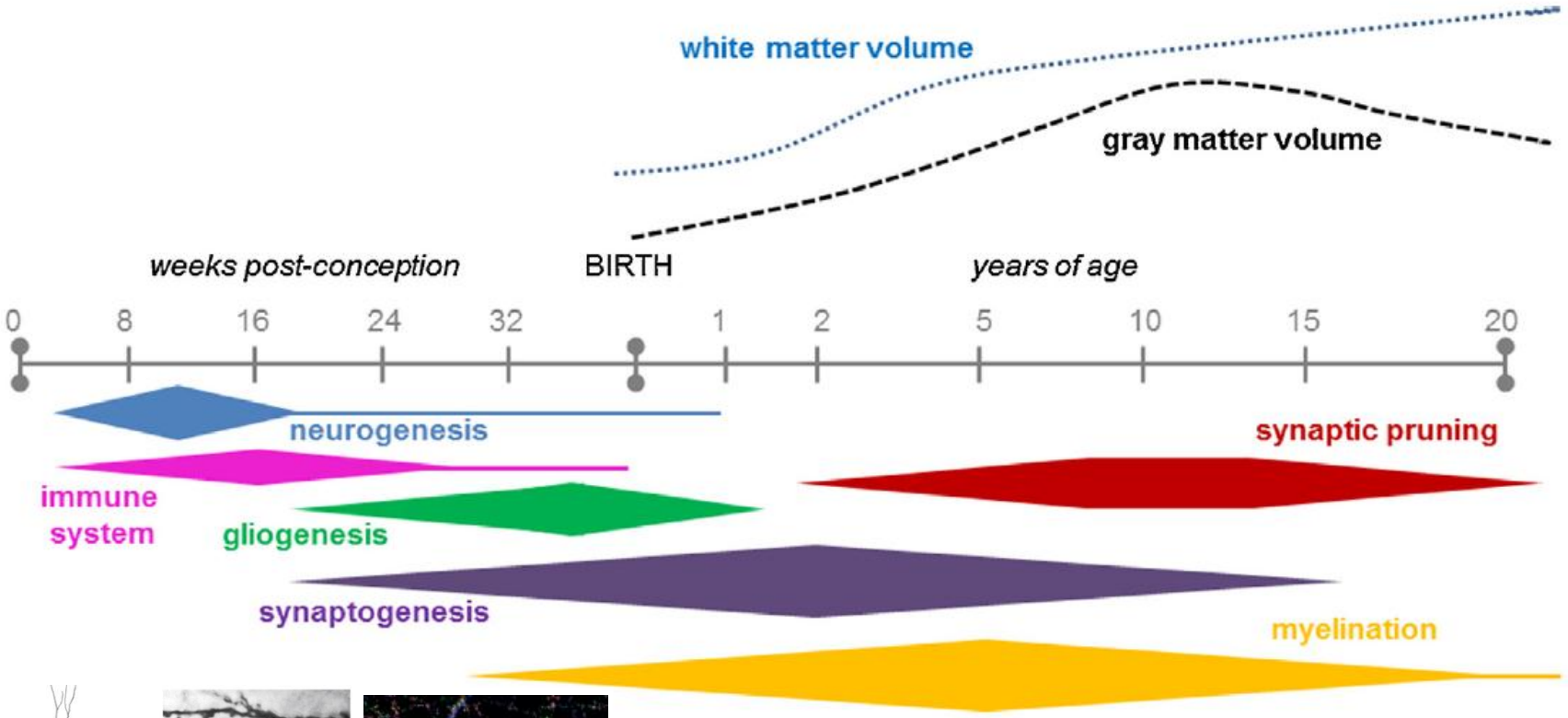
Julie Chen, BA,[1] Victoria Tsai, MS,[1] Whitney E. Parker, BA,[1] Eleonora Aronica, MD, PhD,[2,3] Marianna Baybis, MS,[1] and Peter B. Crino, MD, PhD[1,4]

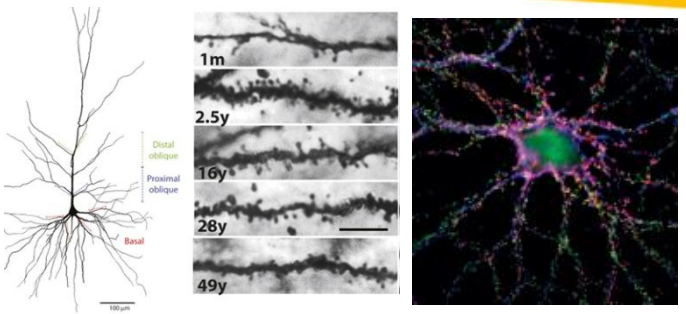


Epilepsy neuropathology studies in the developing brain have highlighted

1. Reciprocal influences between seizures and continuing brain development
2. Pro-epileptogenetic processes
3. New biomarkers and novel treatment pathways

Time course of brain development





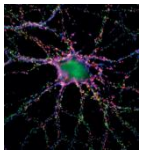
Semple 2013

Cortical cytoarchitecture

Neurochemical maturation

Apoptosis

Synaptogenesis



Myelination

Neuronal proliferation

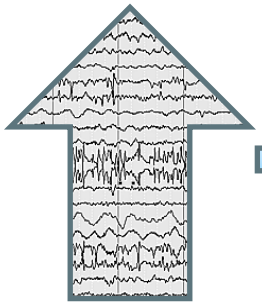
Neuronal migration

4 8 12 16 20 24 28 32 36 Birth 4 months Adolescence Adulthood

PAX6
DCX
LIS1

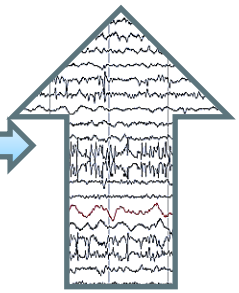
Developmental genes
Migration
Cell specification
Regional expression

Seizures



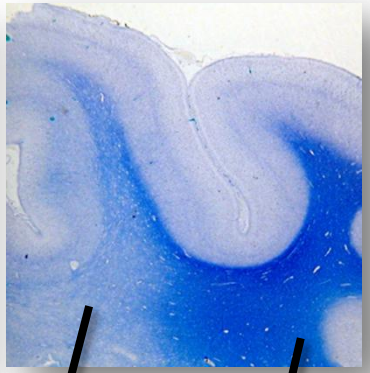
‘EPILEPTOGENESIS’
Neurotransmitters
Cell signalling
Astroglia
Microglia
BBB
Structural changes

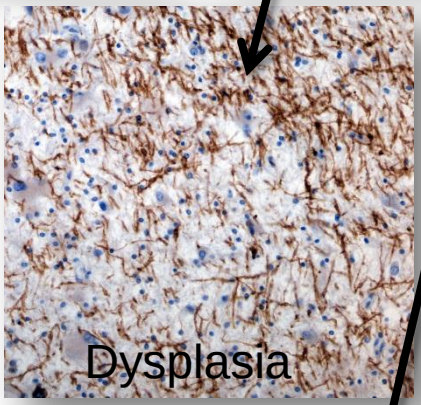
Seizures

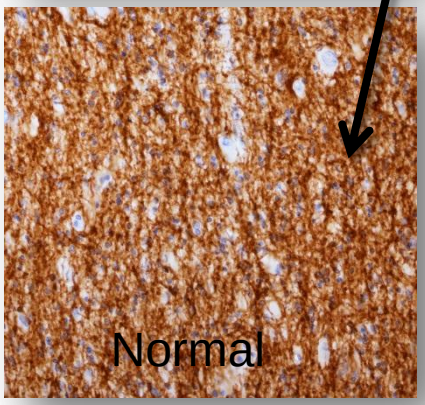


Gene mutation
epigenetic factors

Dysmyelination in Focal Cortical Dysplasia FCDIIB

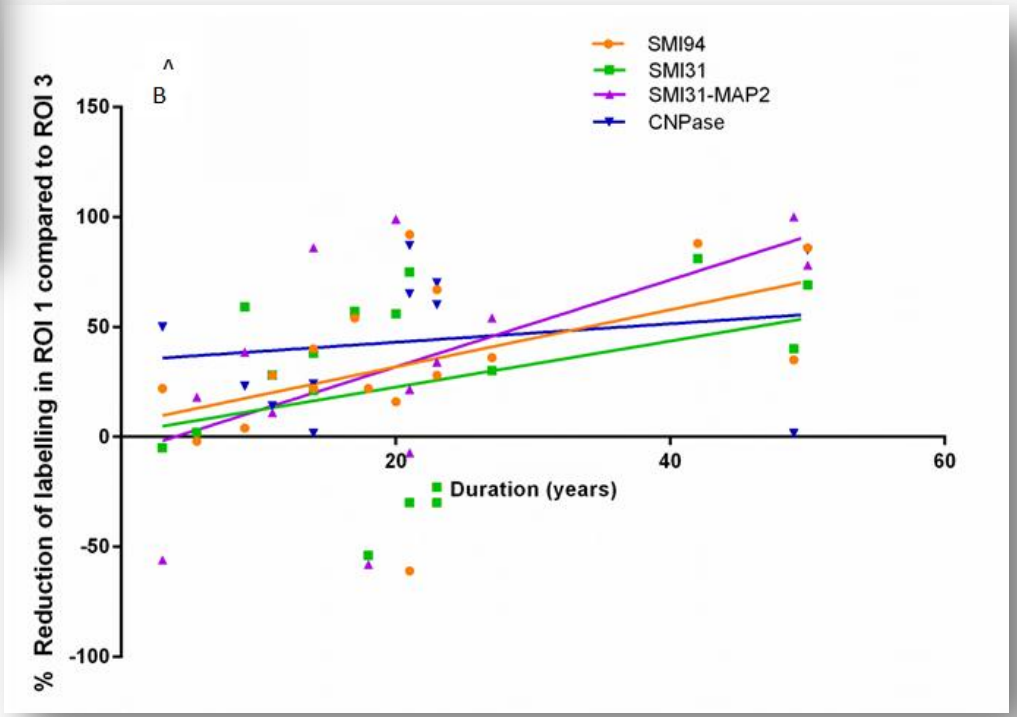


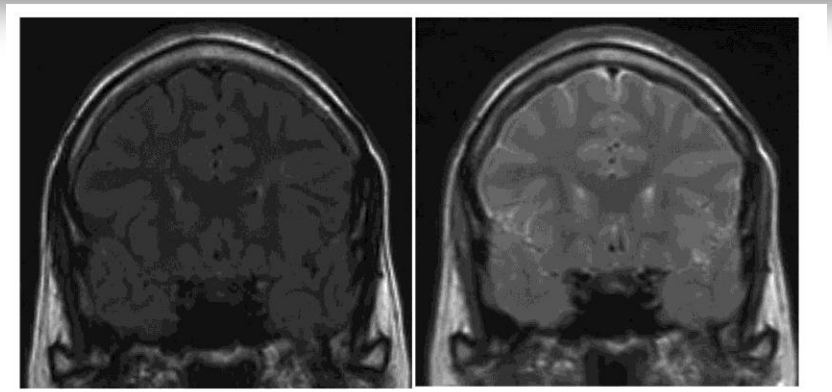


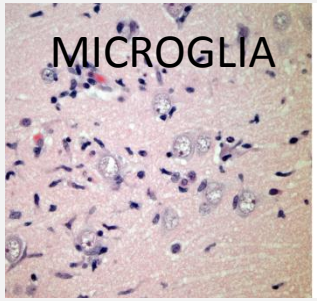


Myelin basic protein

Shepherd 2013







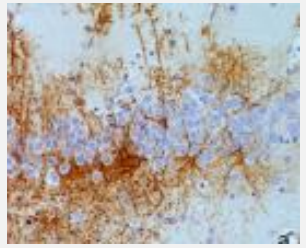
Inflammatory cells
Interleukins, cytokine synthesis, complement

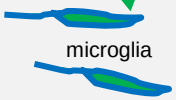
Dendritic and synpatic plasticity

Astrocyte dysunction
Glutamate metabolism and transport

Alteration of K+homeostasis

Inflammatory mediators
Synaptic transmission





Precipitating injury or initial event

Background genes

Developmentally regulated genes

Epigenetic factors

Neuronal hypertrophy & altered morphology (in tumours and dysplasias)

Pyramidal neurone

Neuronal degeneration

Gliosis
Physical interrutpion of axon repair

Channelopathy
•Acquired changes to ligand-gated and receptor-gated ion channels
• Emergence of 'Pacemaker cells'

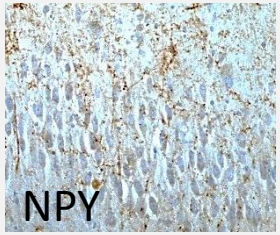
FUNCTIONAL OUTCOME

Epilepsy

Memory impairment

Drug resistance

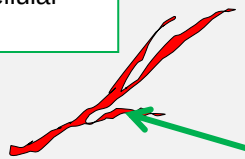
Developmental delay



Axonal sprouting

Alteration of extracellular matrix

Neurogenesis
Integration of new neurones into circuits
Abnormal physiology



Interneuronal alterations
Loss
Sprouting
Dormancy
Altered networks

Neuronal loss
? essential for epileptogenesis

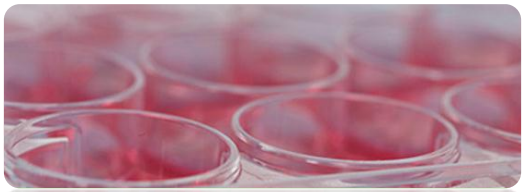
Blood brain barrier alteration
angiogenesis

EPILEPTOGENESIS MECHANISMS !

Current and future tissue technologies

Fresh

Functional properties

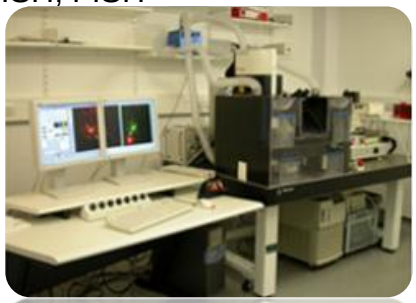


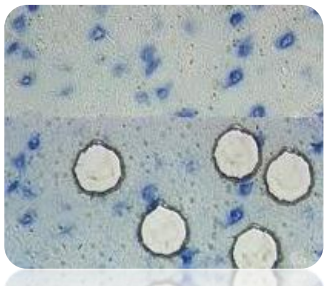
Cell culture / slice culture / electrophysiology

Morphology

Lineage
Differentiation
Distribution

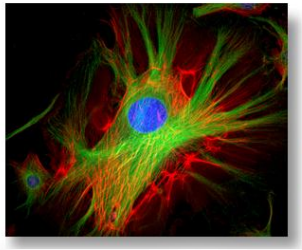
Immunohistochemistry,
Confocal
ISH, FISH

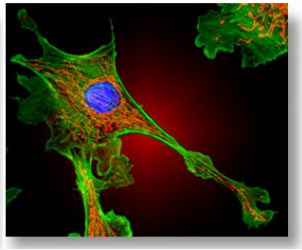




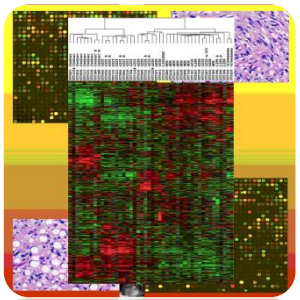
Laser cell microdisection

Fixed

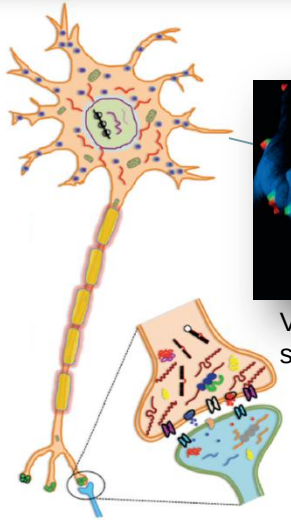


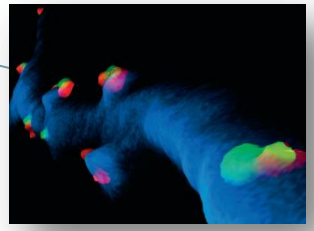


Proteomics

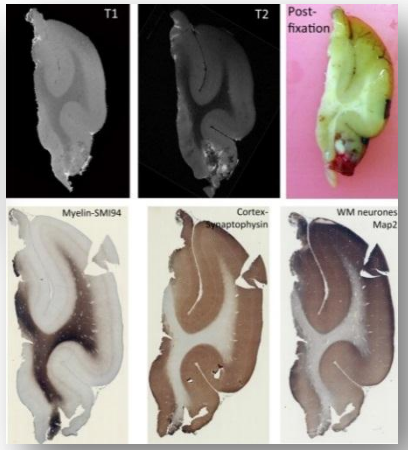


Cell gene expression





Visualising synpases *Yuki Goda*



Tissue 9T MRI

Value of human tissue research

- Exploration of complexity
  - Compared to animal models of epilepsy
- Localistion
  - Cell subtype, cortical layer, region, networks
- Greater resolution
  - Compared to neuroimaging
- Effects of local environment
  - ECM, glia, inflammatory cells, BBB
- Pathology diagnosis and classification
  - Benchmark or ‘gold standard’

‘Fine tuning’ neuropathology diagnostic criteria.
ILAE neuropathology task force 2010-13

FCD and HS - reclassification

Virtual microscopy

Teaching / training our workforce

http://community.ilae-epilepsy.org/diagnosticmethods/MEMBERS/NeuropathologyTaskForce/

Value of post-mortem brain tissue in epilepsy research

- Can compare epileptogenic and normal regions in focal epilepsies
- Enables the study of ‘non-surgical’ epilepsies
- Investigations into SUDEP
- Study of secondary or long term effects of seizures and co-morbidities

Epilepsy Brain/Tissue Banks

Problems

Few dedicated epilepsy brain banks

Decline in autopsy rate

Public perception of organ retention

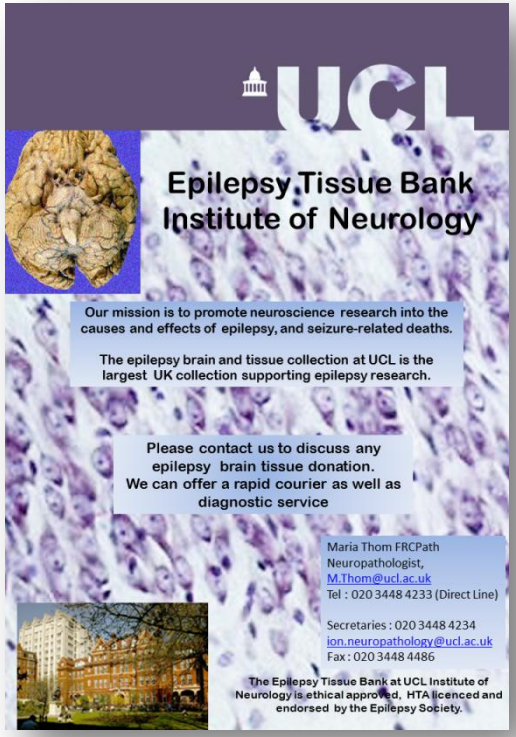
Collection of atypical cases

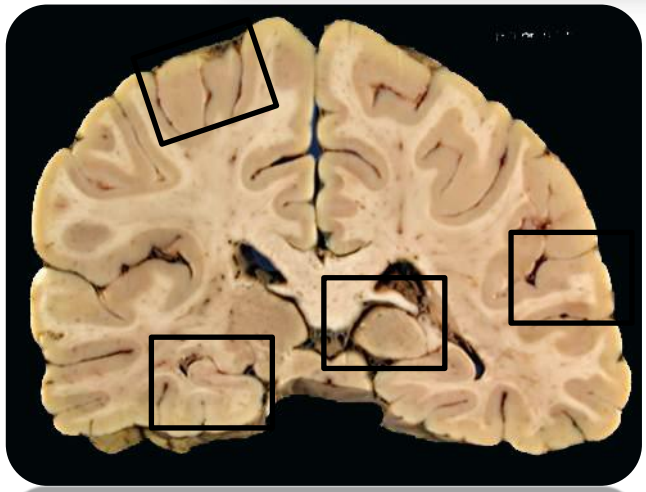
Advantages

Enables collection/sharing of rare pathologies

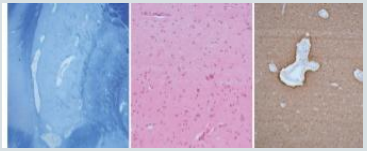
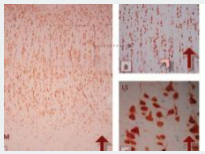
Specific brain regions sampled, collected relevant to condition

Relevant clinical data collected



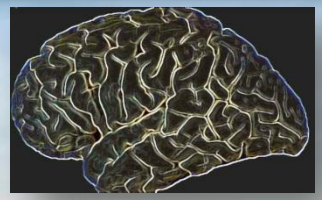


Epilepsy Syndromes in Neonatal Period – Total Post Mortem studies last 15 years

	Case Reports	Series	Positive neuropathology reported
Epilepsy of infancy with migrating focal seizures	Frielich 2013 Copola 2007 Fasulo 2012	McTague 2013 	Microcephaly Hippocampal scerlosis PMG FCD Putaminal atrophy
West syndrome	Weckhuysen, 2013 Vinters 1993		FCDI Cystic encephalomalacia FCDII
Myoclonic epilepsy in infancy (MEI)	0	0	0
Benign infantile epilepsy	0	0	0
Benign familial infantile epilepsy	0	0	0
Dravet syndrome		Catarino 2011 Guerrini 2011	Pathology negative Cortical malformations Hippocampal sclerosis Cerebellar atrophy
Myoclonic encephalopathy in non-progressive disorders	0	0	0

On Our Horizon

Prevention of epilepsy



Clinical
Neuroimaging
Neurogenetics
Electrophysiology
Experimental models
Human Tissue Based studies
(Neuropathology)

Acknowledgments

All the patients and relatives who donate tissue for epilepsy research

Clinical and Research teams at National Hospital for Neurology and Department of Clinical and Experimental Epilepsy Institute of Neurology & Great Ormond Street Hospital

Members of the Neuropathology Task Force of ILAE