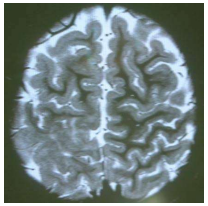


Approach to Focal Cortical Dysplasia in Epilepsy, Challenges and Lessons

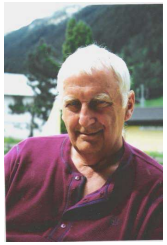
J Helen Cross

UCL Great Ormond Street Institute of Child Health, London & Youug Epilepsy, Lingfield, UK

Young Epilepsy

Great Ormond Street Hospital for Children NHS Trust

Great Ormond St Institute of Child Health UCL



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

Focal dysplasia of the cerebral cortex in epilepsy

D. C. TAYLOR[1] AND M. A. FALCONER

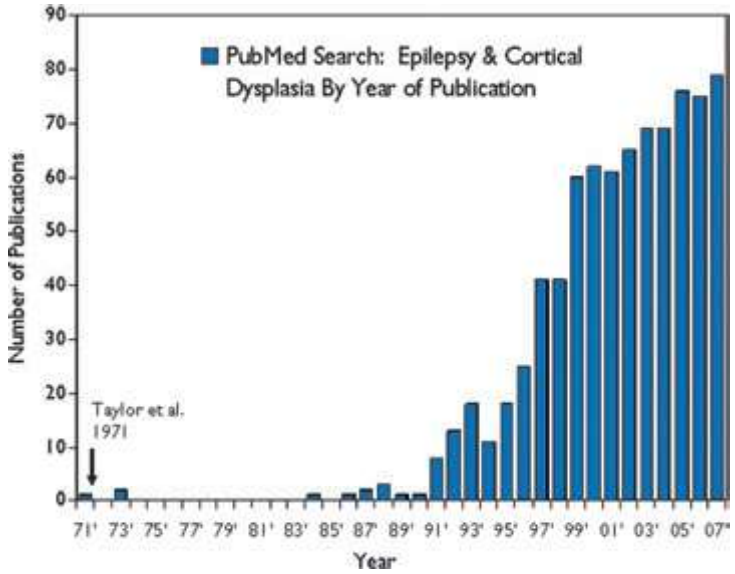
From the Neurosurgical Unit of Guy's, Maudsley, and King's College Hospitals, London

and

C. J. BRUTON AND J. A. N. CORSELLIS

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

- **Pathology reports 1951-1960**
- **Unusual findings in 10 individuals undergoing lobar resection for epilepsy**
- ***'consisted of congregations of large, bizarre neurones which were littered through all but the first cortical layer. In most, but not in all cases, grotesque cells, probably of glial origin, were also present in the depths of the affected cortex and in the subjacent white matter.....reminiscent of tuberous sclerosis'***
- **3% operative cases**



Lerner et al Epilepsia 2009;50:1310-1335

Classification of MCD

I. **Malformations secondary to abnormal neuronal and glial proliferation of apoptosis**
   - **1A Microcephaly**
   - **1B Megalancephalies**
   - **1C Cortical dysgeneses with abnormal cell proliferation**

II . **Malformations due to abnormal neuronal migrations**
   - **IIA Heterotopia**
   - **IIB Lissencephaly**
   - **IIC subcortical heterotopia and sublobar dysplasia**
   - **IID Cobblestone malformations**

III. **Malformations secondary to abnormal postmigrational development**
   - **IIIA. Polymicrogyria and schizencephaly**
   - **IIIC Focal cortical dysplasia**
   - **IIID Postmigrational microcephaly**

Barkovich et al 1996,2002
Neurology 2005;65:1873–1887
Brain 2012;135:1348-1369

Classification of MCD

I. Malformations secondary to abnormal neuronal and glial proliferation of apoptosis
   - 1A Microcephaly
   - 1B Megalancephalies
   - 1C Cortical dysgeneses with abnormal cell proliferation
     - *Tuberous sclerosis*
     - *Focal cortical dysplasia*

II . Malformations due to abnormal neuronal migrations
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Barkovich et al 1996,2002
Neurology 2005;65:1873–1887
Brain 2012;135:1348-1369

Focal cortical dysplasias

- **Type I: No dysmorphic neurons or balloon cells**
  - **IA: isolated architectural abnormalities (dyslamination)**
  - **IB: architectural abnormalities + giant of immature neurons**
  - ***Imaging: ?can be seen by current techniques***
- **Type II: Taylor type FCD (dysmorphic neurons with or without balloon cells)**
  - **IIA: architectural abnormalities with dysmorphic neurons without balloon cells**
  - **IIB: architectural abnormalties with dysmorphic neurons & balloon cells**
  - ***Imaging: commonly identified on MRI***

Palmini et al
Neurology 2004;62(Suppl 3):S2–S8

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[1]

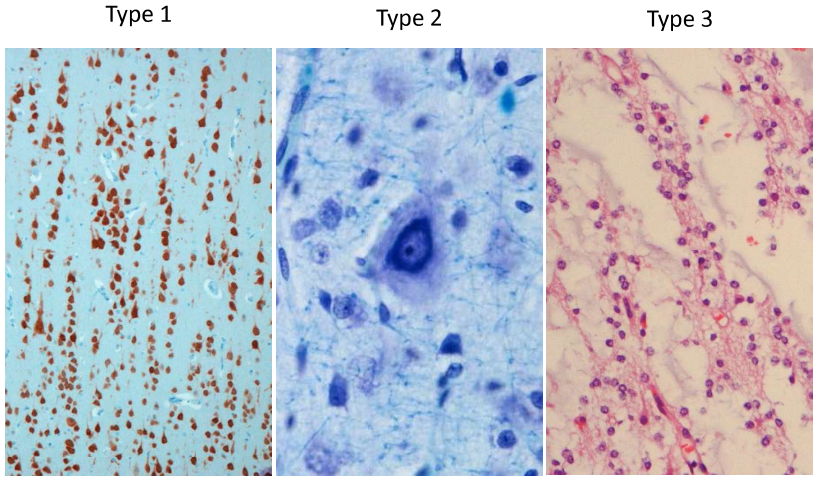
*[2]Ingmar Blümcke, †Maria Thom, ‡Eleonora Aronica, §Dawna D. Armstrong, ¶Harry V. Vinters, #Andre Palmini, **Thomas S. Jacques, ††Giuliano Avanzini, ‡‡A. James Barkovich, §§Giorgio Battaglia, ¶¶Albert Becker, ##Carlos Cepeda, ***[3]Fernando Cendes, †††Nadia Colombo, ‡‡‡Peter Crino, §§§J. Helen Cross, ¶¶¶Olivier Delalande, ###François Dubeau, ****John Duncan, ††††Renzo Guerrini, ‡‡‡‡Philippe Kahane, §§§§Gary Mathern, ¶¶¶¶Imad Najm, ####Çiğdem Özkara, *****Charles Raybaud, †††††Alfonso Represa, ‡‡‡‡‡Steven N. Roper, §§§§§Noriko Salamon, ¶¶¶¶¶Andreas Schulze-Bonhage, #####Laura Tassi, ******Annamaria Vezzani, and ††Roberto Spreafico

Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

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

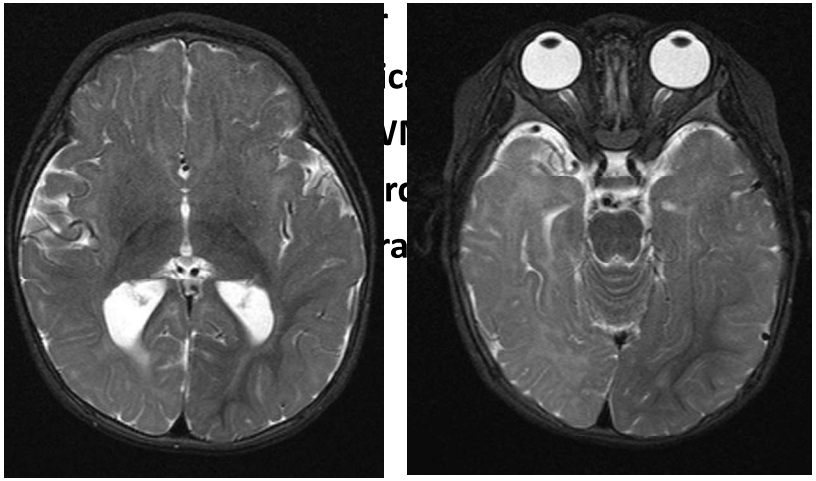
FCD Type III (not otherwise specified, NOS): if clinically/radiologically suspected principal lesion is not available for microscopic inspection.
Please note that the rare association between FCD Types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variant.

Three types of FCD

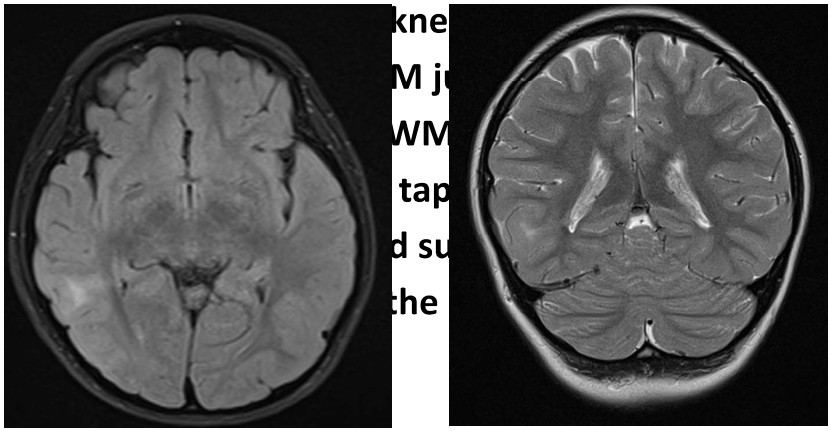


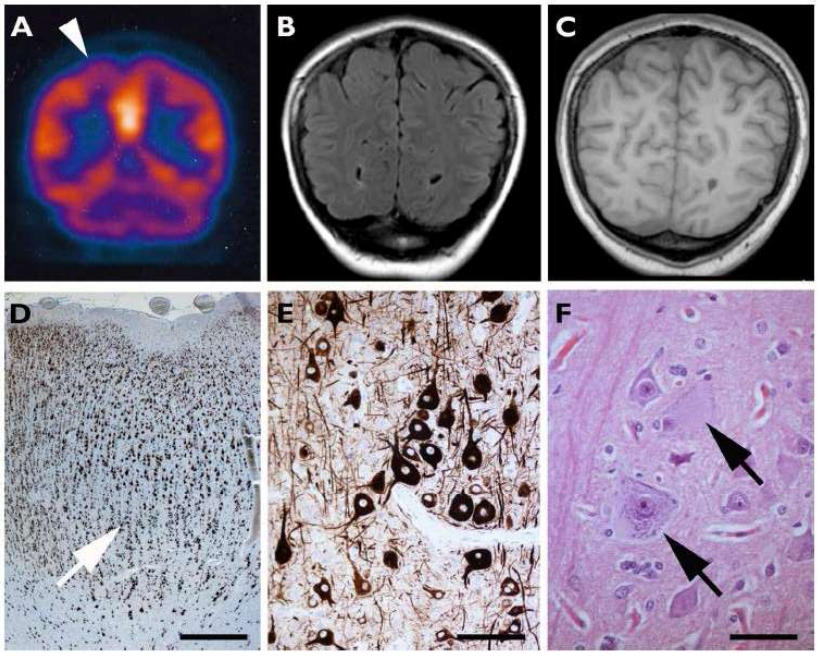
Imaging Characteristics
FCD Type I

-
-
-
-
-

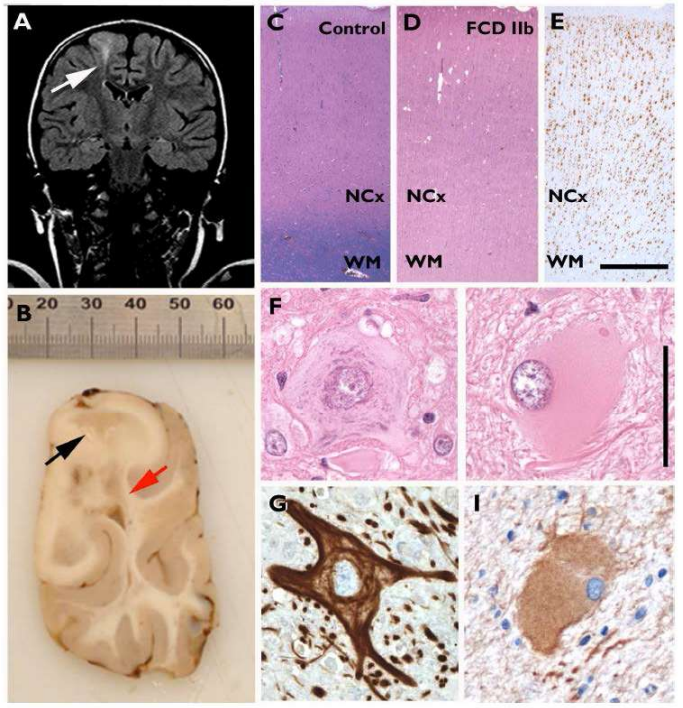


Imaging Characteristics
Type II



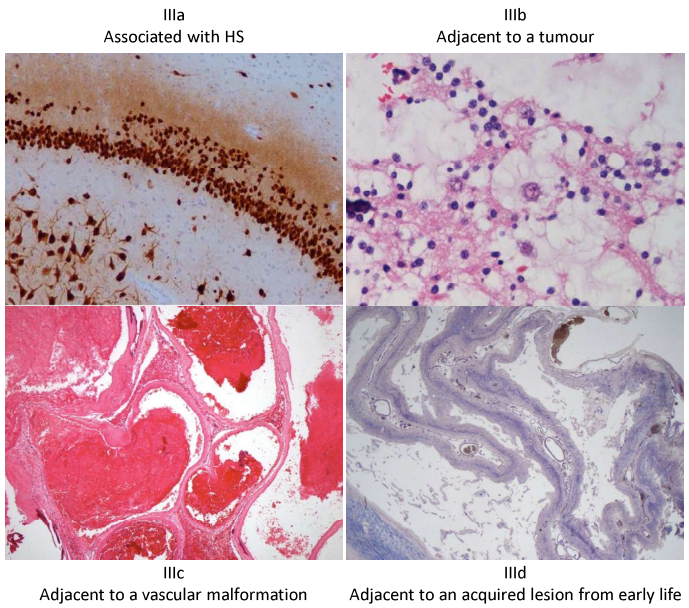


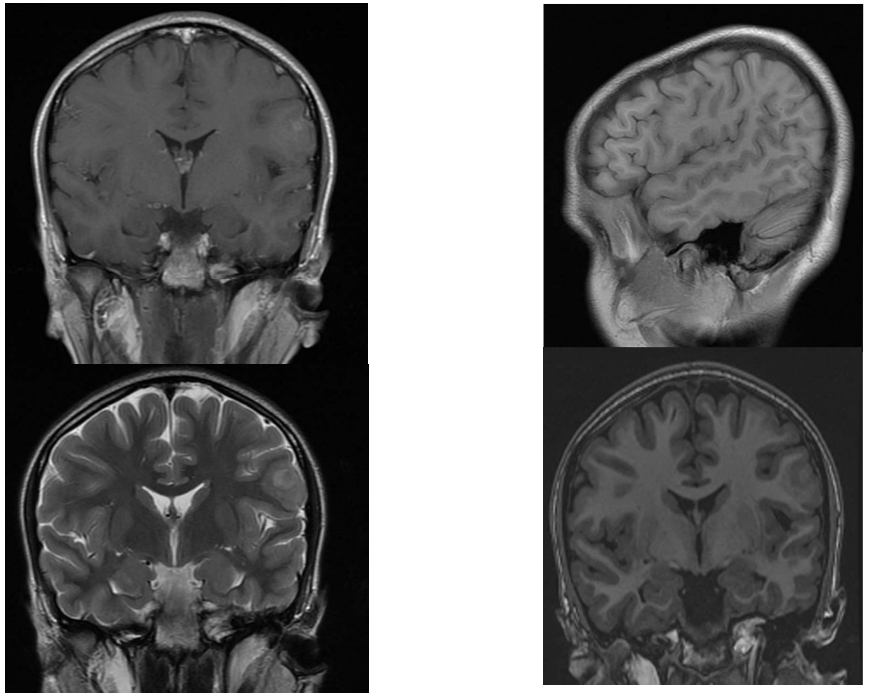
FCD Type II a



FCD Type II b

Focal Cortical Dysplasia Type III



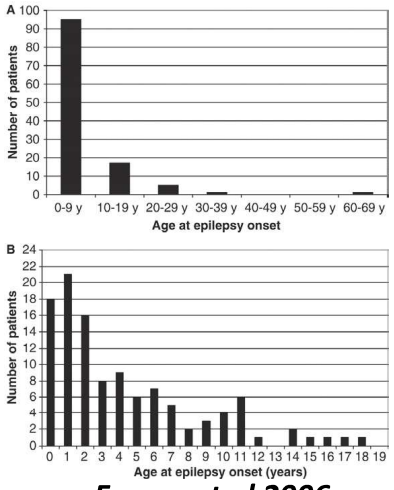


Clinical Characteristics of FCD

- Present early
- Vary in size and location
- May be multilobar
- Seizures very resistant to treatment
- Minimal focal neurology
- Neuropsychological and developmental impact
- Focal rhythmic electrical discharges on scalp EEG

Age of onset of epilepsy

- Most series suggest early onset epilepsy in the majority
- Cascino et al 2005, surgical series, 7 centres; 21/213 (10%) onset >18 years
- Fauser et al 2006, 120 patients surgical series, 61% <5 yrs, 92.5% <16 years



Fauser et al 2006

Medical Treatment

Stephan, Kwan and Brodie, *Epilepsia* **2001; 42:357-362**

550 patients; 70% newly diagnosed focal epilepsy over 13 years ***Minimum 2yr review***

63(12%) cortical dysplasia

34 (54%) seizure free AEDs (none) 5, (1) 22

Semah et al, *Neurology* **1998; 51: 1256-1262**

2200 patients, 8% first seizure, over 7 years

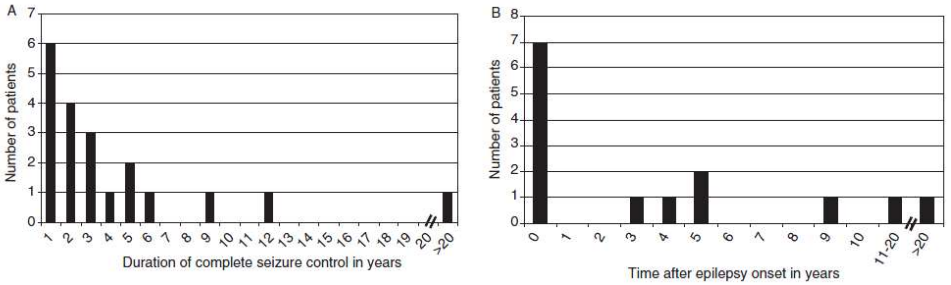
96 (8%) cortical dysgenesis

23 (24%) seizure free

doi:10.1093/brain/awl133 *Brain* (2006), **129**, 1907–1916

Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients

Susanne Fauser,[1] Hans-Juergen Huppertz,[1] Thomas Bast,[4] Karl Strobl,[5] Georgios Pantazis,[2] Dirk-Matthias Altenmueller,[1] Bertram Feil,[1] Sabine Rona,[1] Christoph Kurth,[5] Dietz Rating,[4] Rudolf Korinthenberg,[3] Bernhard J. Steinhoff,[5] Benedikt Volk[2] and Andreas Schulze-Bonhage[1]



Responsiveness to antiepileptic drugs

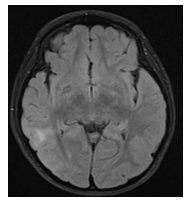
Medical Treatment

Vigevano & Koivikko *Epilepsia* 1997;38:1275-1282

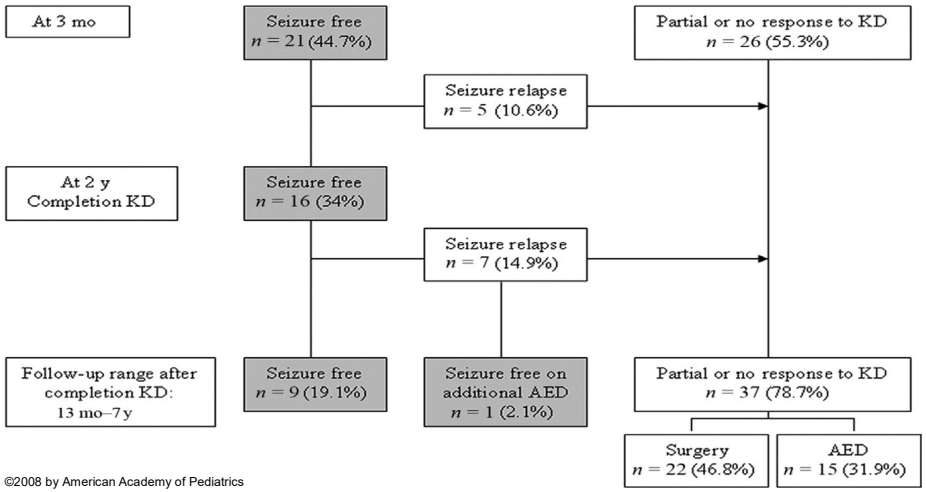
Vigabatrin vs ACTH for Infantile Spasms N=47

	VGB	ACTH
Cessation of spasms	**11/23 (48%)**	**14/19 (74%)**
Cerebral malformation	**3/4 (75%)**	**0/3 (0%)**
Tuberous sclerosis	**3/3 (100%)**	**1/1 (100%)**

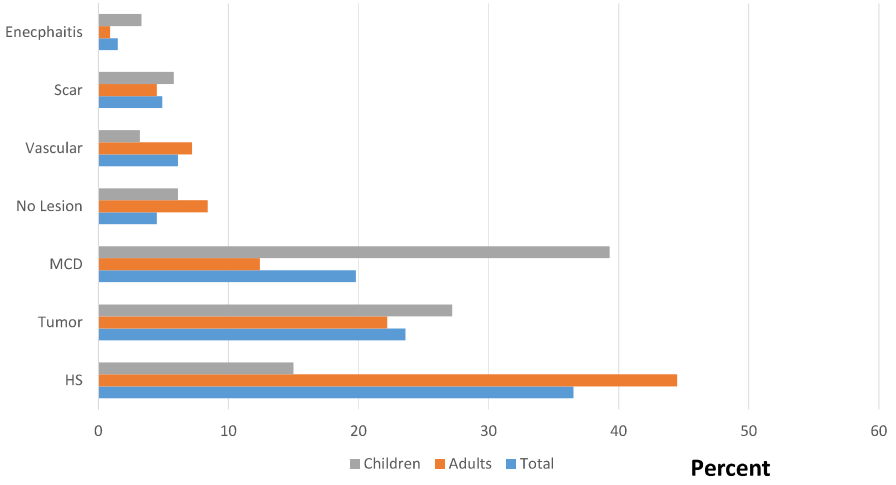
Ketogenic diet



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***

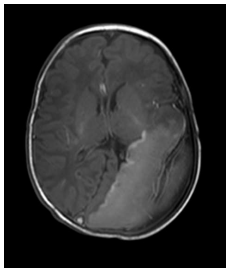


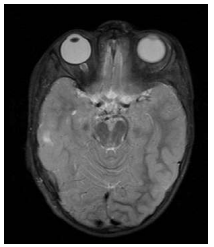
Major aetiological categories

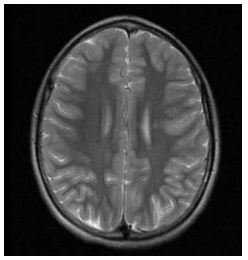


European Epilepsy Brain Bank 1990-2014, N = 7286, *Blumcke et al 2017*

Surgical resection







Evaluation required will depend on extent & location of FCD, as well as age of child

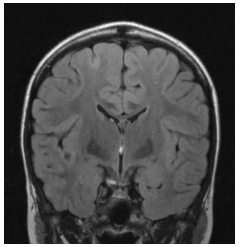
Epileptogenic zone often from around rather than within lesion

?Role for ECoG

Role of invasive EEG – grids/SEEG

-Limits of lesion

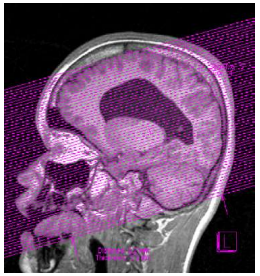
-Dysplastic tissue often located in eloquent cortical regions



Optimised imaging

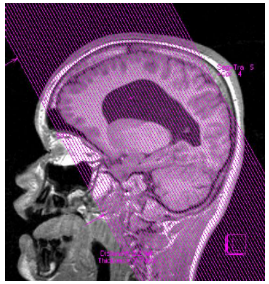
Protocols

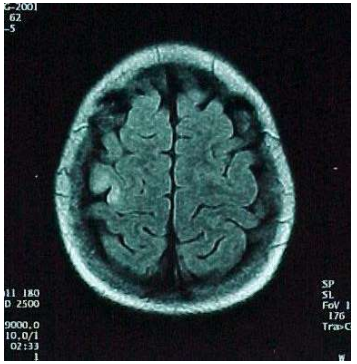
- **Anatomic thin slice volumetric T1**
- **Axial & coronal T2**
- **3D FLAIR**

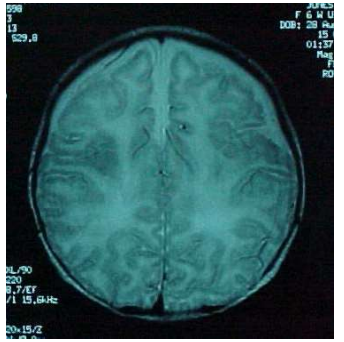


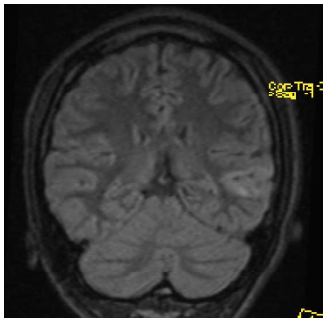
Children <2yrs

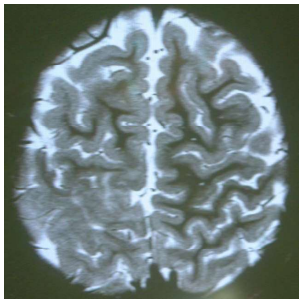
- **3D data set,**
- **Sagittal, axial & coronal T1**
- **Axial & coronal T2**

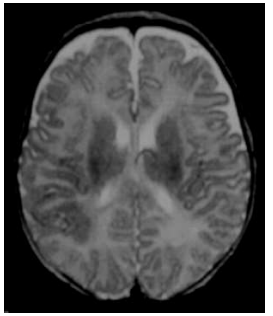








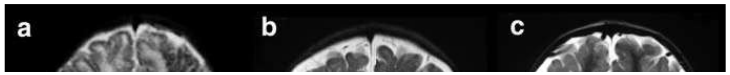




Are the MRI Findings Specific?

MRI Appearance	+	-	Positive %
Subcortical white matter signal change	24	0	100
Well-defined margins	21	3	87.5
Blurring of gray-white matter junction	20	4	83.3
Abnormal cortical gyration/sulcation	20	4	83.3
Single lobe involvement	20	4	83.3
Apparent cortical thickening	13	11	54.2
Signal intensities on MRI scans			
•Hyperintense on T2W & Hypointense on T1W images	10	14	42
•Hypointense on T2W & T1W images	8	16	33

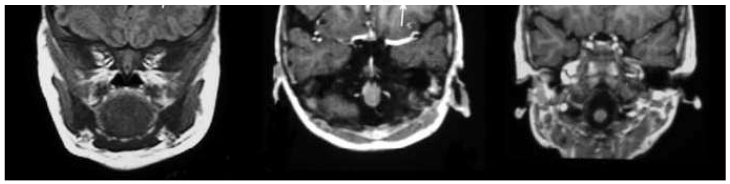
Timing of Scan & Maturation



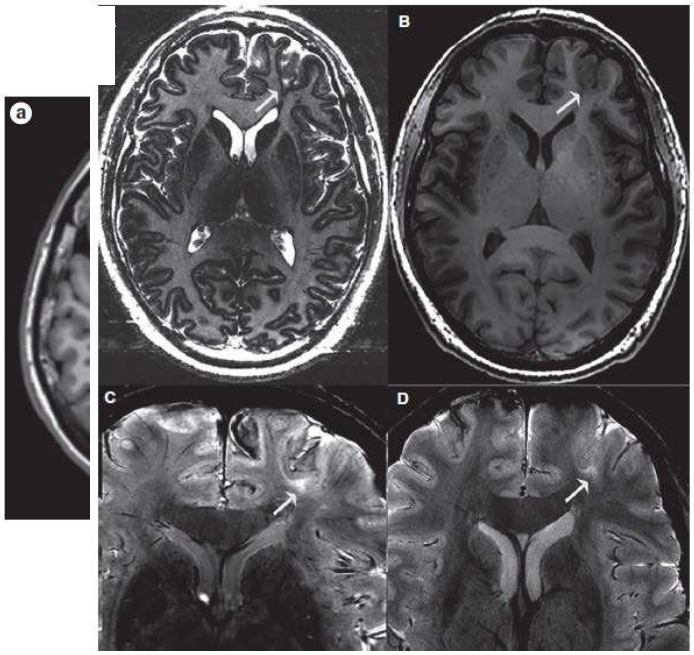
Taylor-type Focal Cortical Dysplasia in Infants: Some MRI Lesions Almost Disappear with Maturation of Myelination

*Christin M. Eltze, *†Wui K. Chong, †Sanjay Bhate, *†Brian Harding, *†Brian G. R. Neville, and *†J. Helen Cross

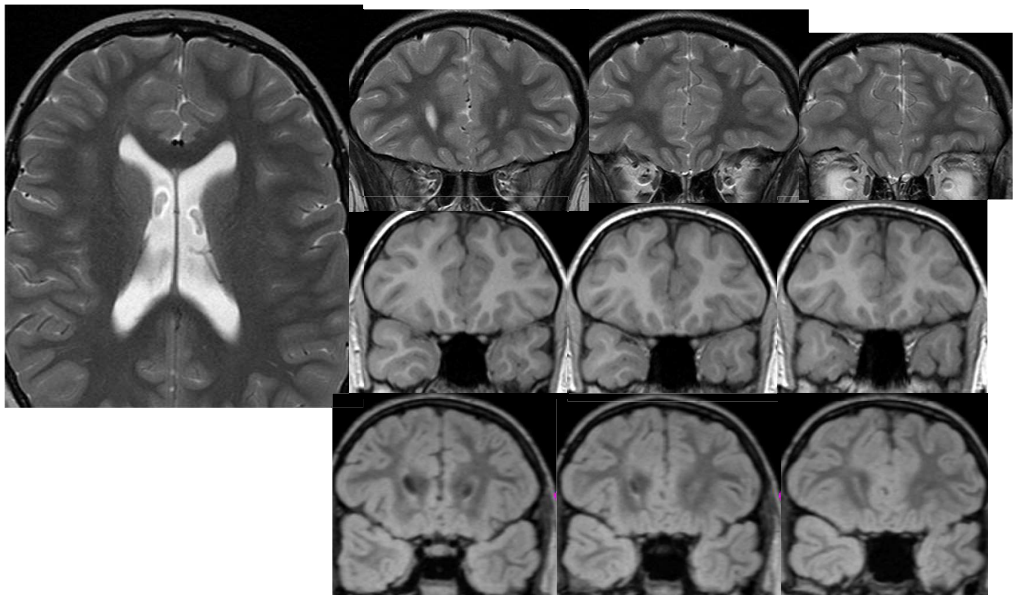
*Institute of Child Health, University College London, United Kingdom; and †Great Ormond Street Hospital for Children, London, United Kingdom

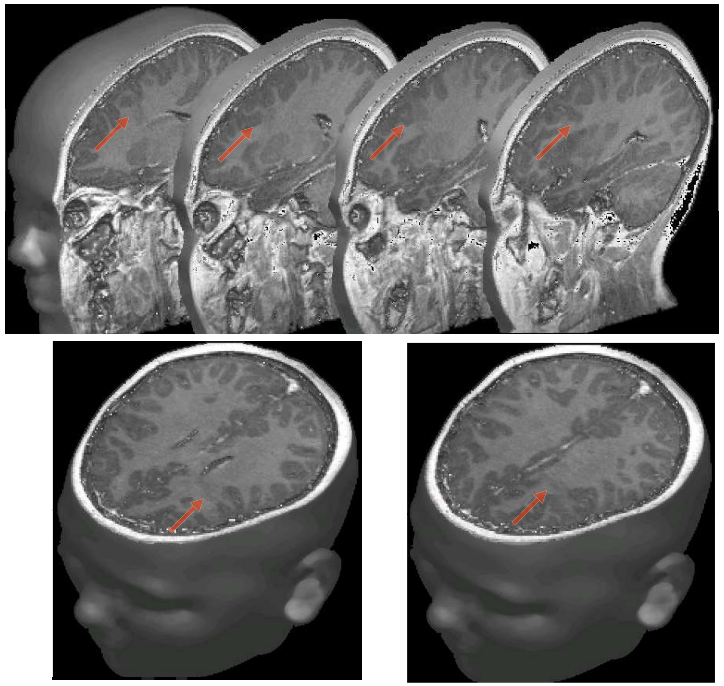


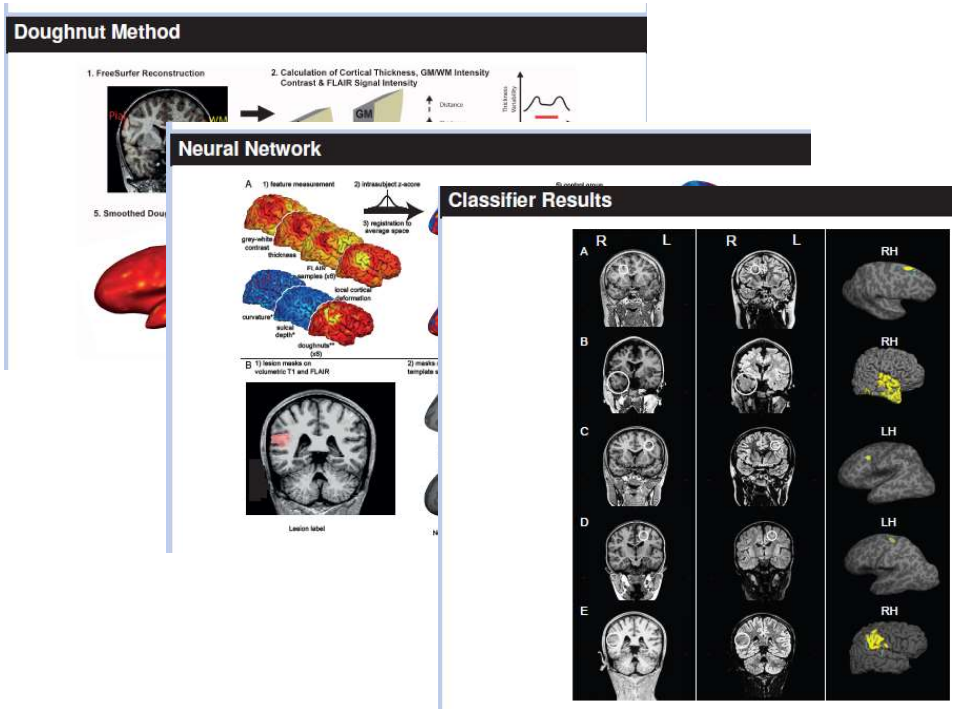
7T

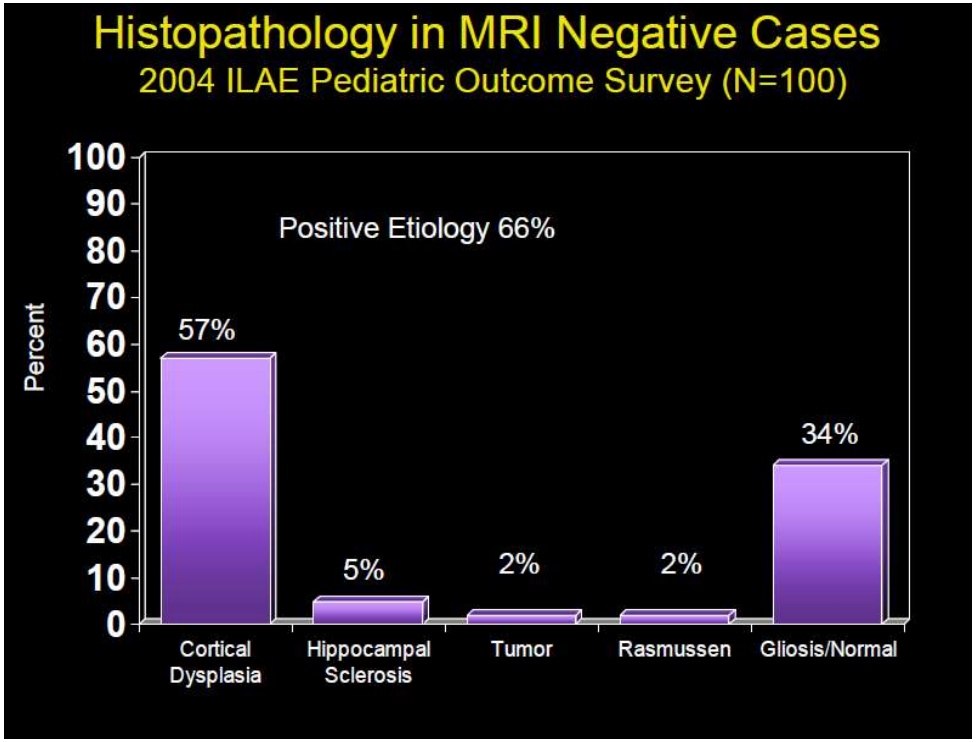


F 12 yr R frontal seizures

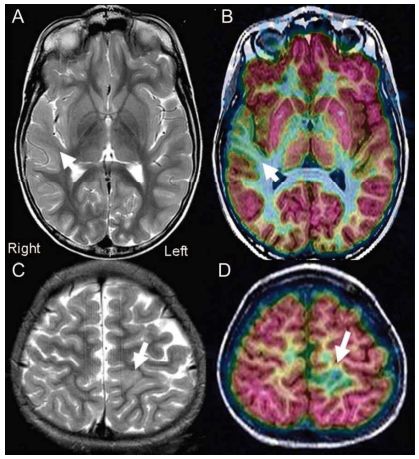


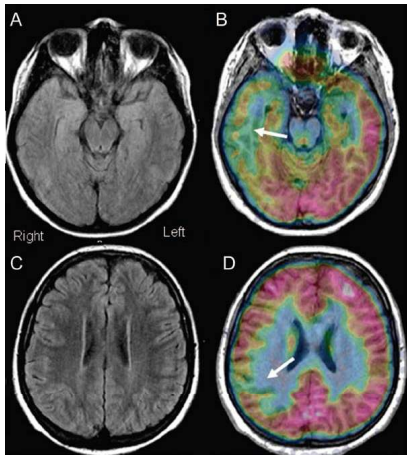






FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy





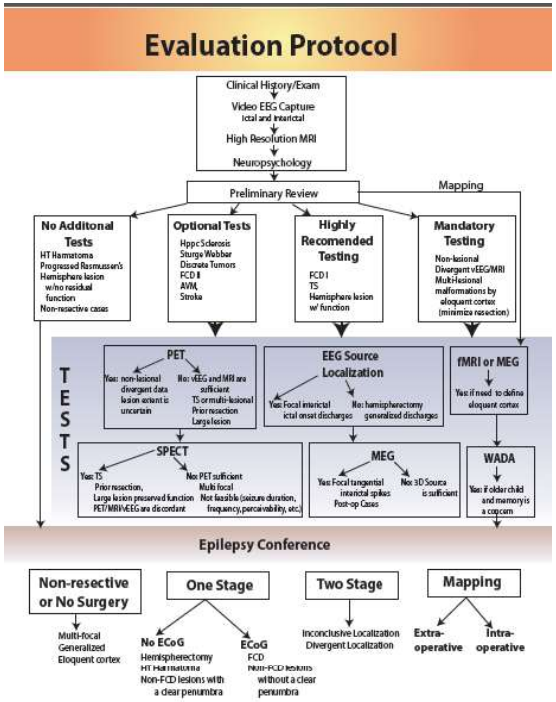
Salamon et al Neurology 2008;71:1594-1601

The role of additional investigations

Cohort	II EEG	Video EEG	MRI	3D EEG/ MEG	PET	SPECT	ECoG	IEM	Comments
Single Lesion									
Dev Tumors	M*	H	M*	O	O	O	O	O	
FCD I	M*	M*	M*	H	H	H	H	H	
FCD II	M*	M*	M*	O	O	O	M/H	O	
HS	M*	M	M*	O	O	O	O	O	Consider possiblilityof dual path
SWS	M*	M	M*	L	O	O/L	O/L	L	
Hypth Hamar	M*	H	M*	L	L	L	L	L	IEM not justified
Vascular	M*	M	M*	O	O	O	O	O	
Post-infec/Ischemic	M*	M	M*	O	O	O	O	O	Lesions may be bilateral
Hemispheric									
No Function	M*	H	M*	L	L	L	L	L	Possible EEG false lateralization
Function ++	M*	M*	M*	H	H	H	H	H	Tailored resection
PMG	M*	M*	M*	H	H	O	O	O/H	Tailored resection
Rasmussen	M*	M	M*	L	L	L	L	L	Serial MRI required
TS	M*	M*	M*	H/O	O	H	H	H/O	AMT PET useful
MRI negative	M*	M*	M*	H	H	H	H	H	Serial Tests

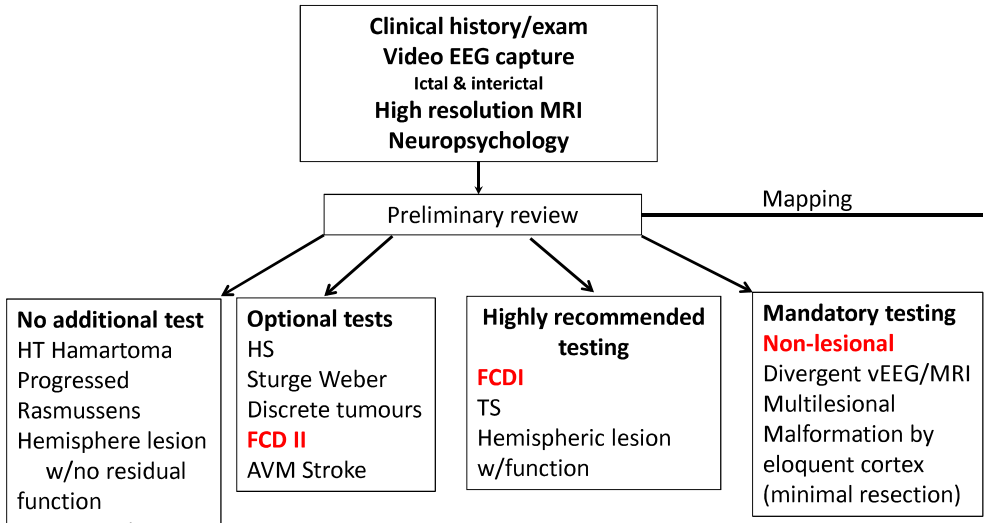
Jayakar et al Epilepsia 2014; 55(4):507–518,

Treatment Paradigm GOSH

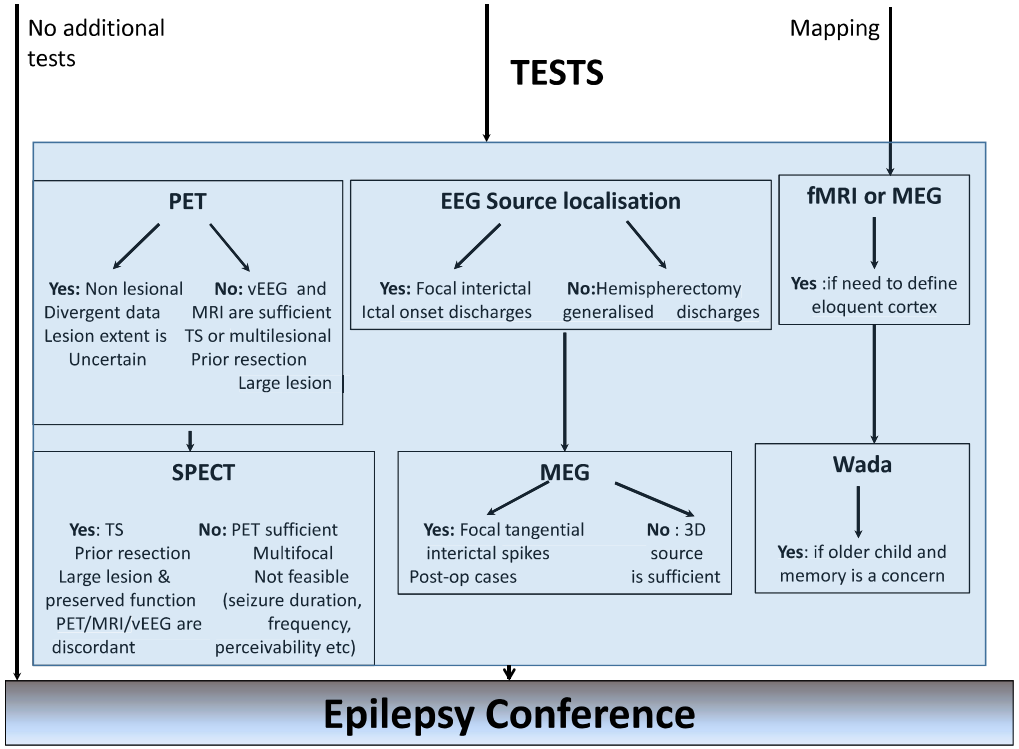


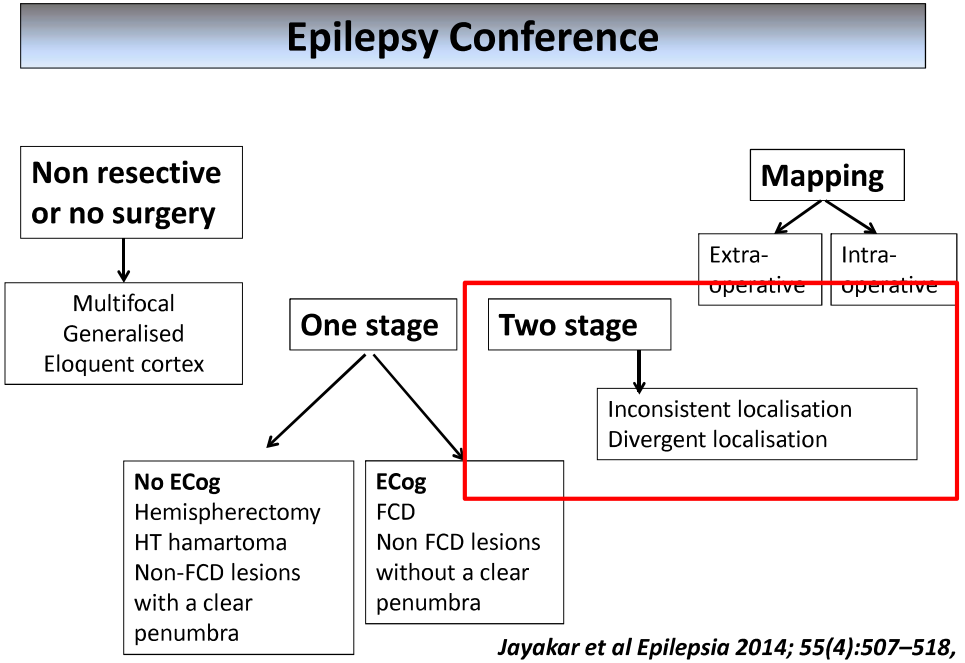
Jayakar et al Epilepsia 2014; 55(4):507–518,

Evaluation Protocol



Jayakar et al Epilepsia 2014; 55(4):507–518,





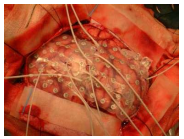
Jayakar et al Epilepsia 2014; 55(4):507–518,

Threshold for invasive evaluation

Extent of resection

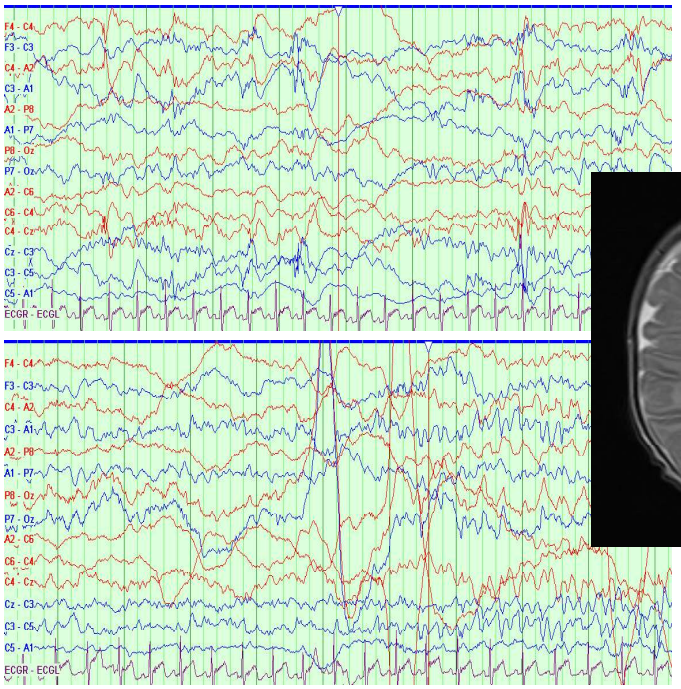
Plasticity

Choosing an invasive strategy

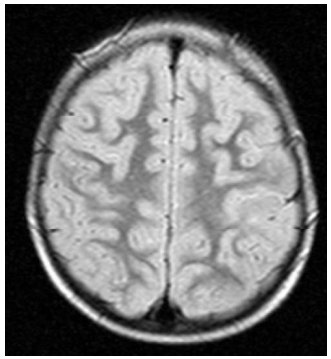


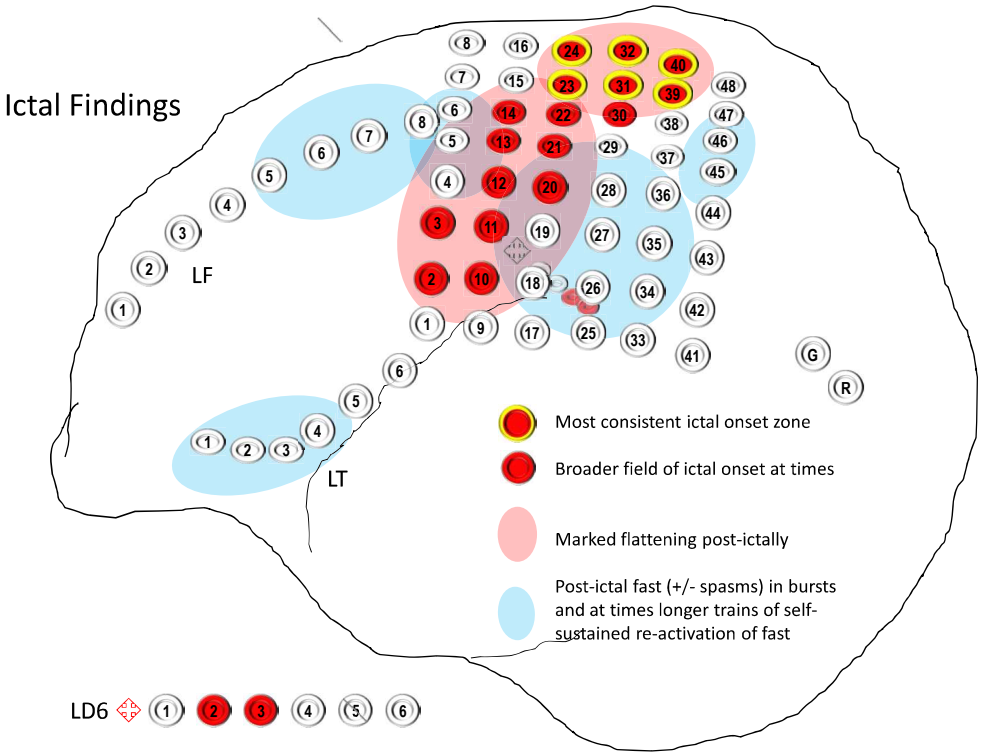
	SUB –DURAL GRID	sEEG
MRI negative	✗	✓
Multiple lesions	✓	✓✓
Deep structures involved	✗	✓
Defining limits of cortical malformations	✓	✗
Functional mapping	✓	✗
Morbidity	✗	✓✓

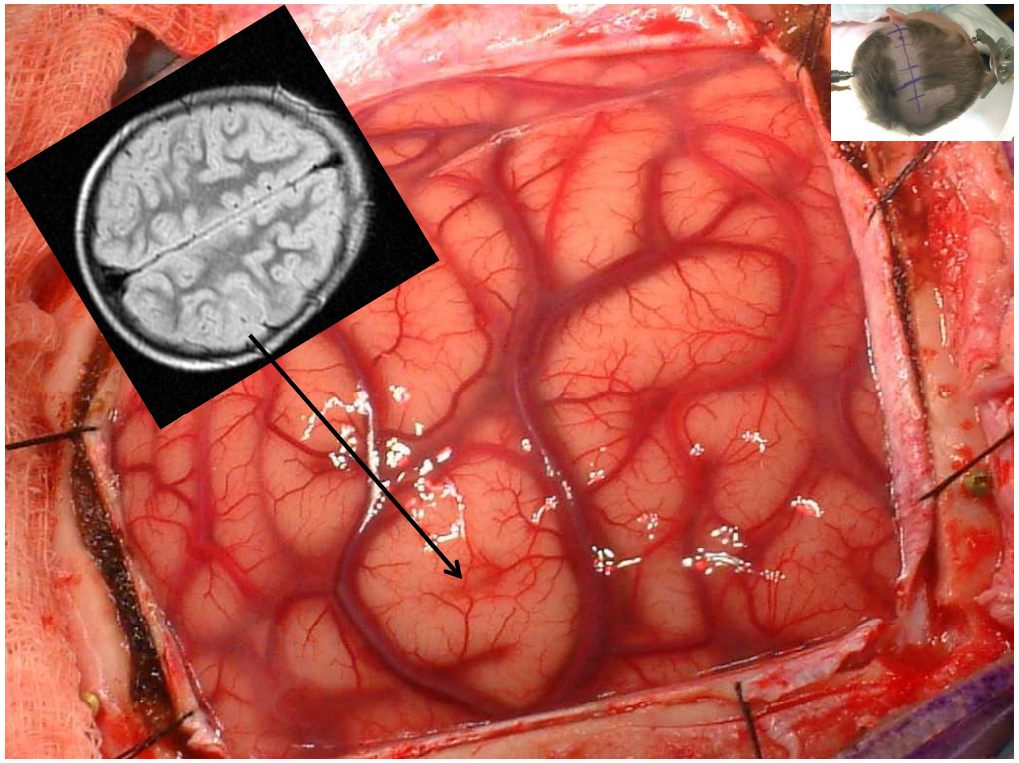
- FTND
- Day 1:Twitching right arm and leg
- Day 6: Jerking right, spread to involve both sides
- Short, frequent. Need for rescue medication
- Further seizures subtle behaviour change, eye flickering, deviation, some with right upper limb involvement; 50-100/day
- PB, CBZ, VPA, CLB, PHT, VGB, LVT
- Clonazepam infusion x2
- At 10 weeks unable to wean CLN infusion
- When well, fixing, following, smiling

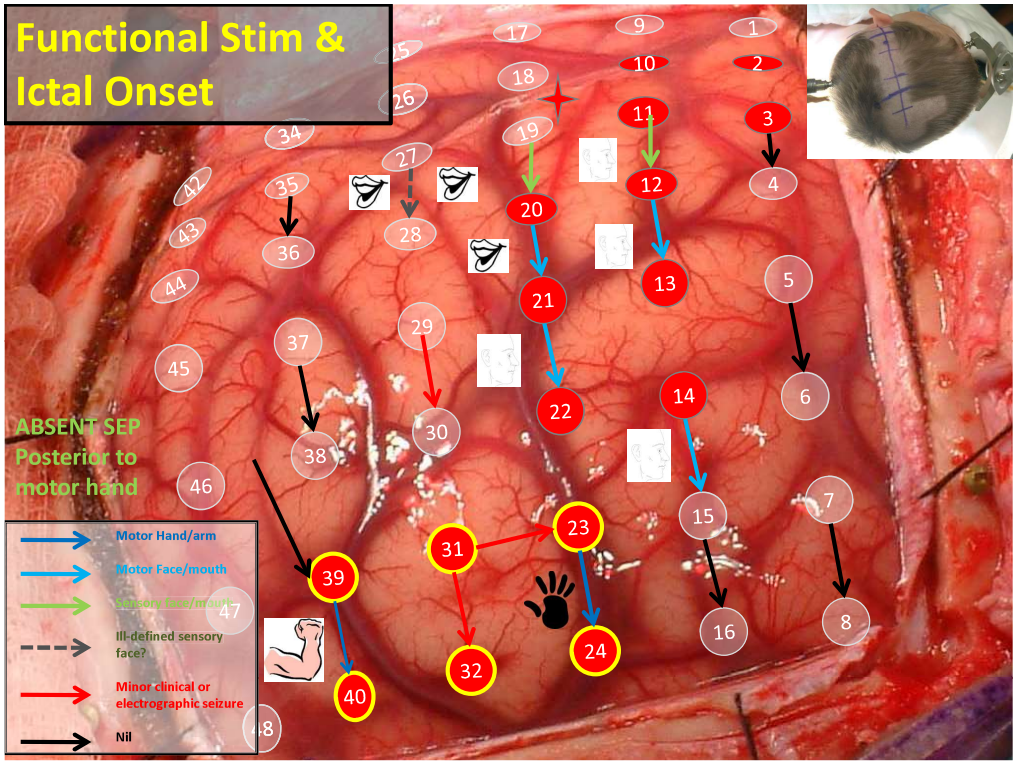


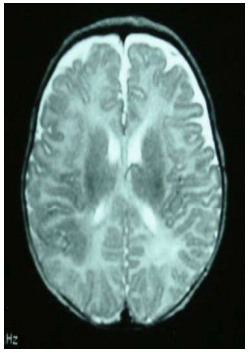
- Age 8 years
- FTND; no early concerns
- First seizure age 21m; prolonged
  - •Right focal UL>LL, speech affected, 2 to 4/night
  - • Right focal with sec Generalised, 1 / fortnight
  - • Right focal (face), mild and with aura, 1 to 2/week
- Variable upper limb function but no fine finger movement since presentation
- Multiple medications
- MRI: cortical dysplasia
- Decision made 'not surgical candidate'
- VNS inserted
  - •No benefit
- Continued seizures; cognitively low average but days where less interactive, poor oral intake and drooling

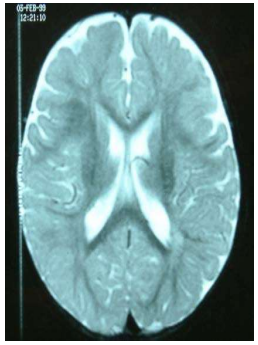


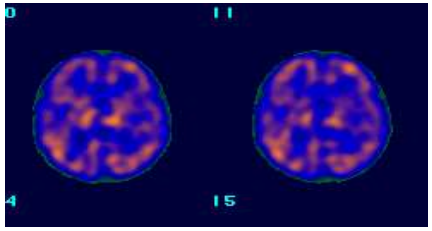


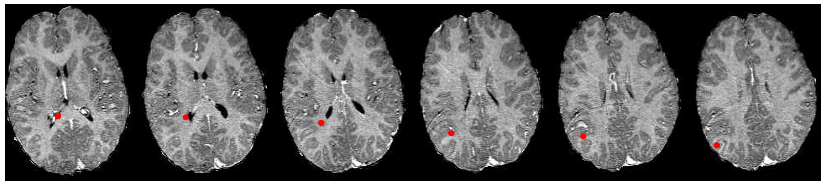


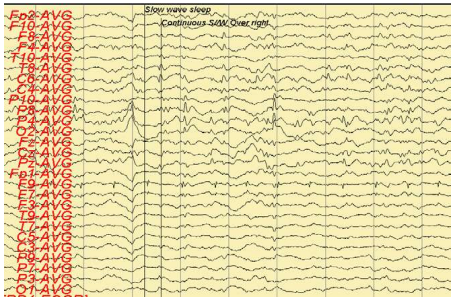

Functional Stim & Ictal Onset
ABSENT SEP Posterior to motor hand
Motor Hand/arm
Motor Face/mouth
Sensory face/mouth
Ill-defined sensory face?
Minor clinical or electrographic seizure
Nil

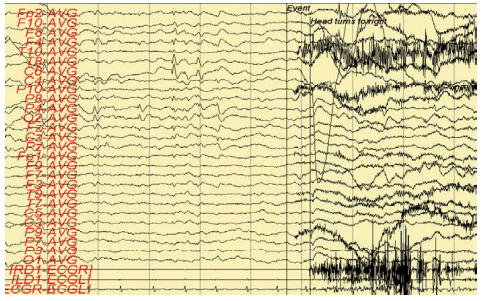


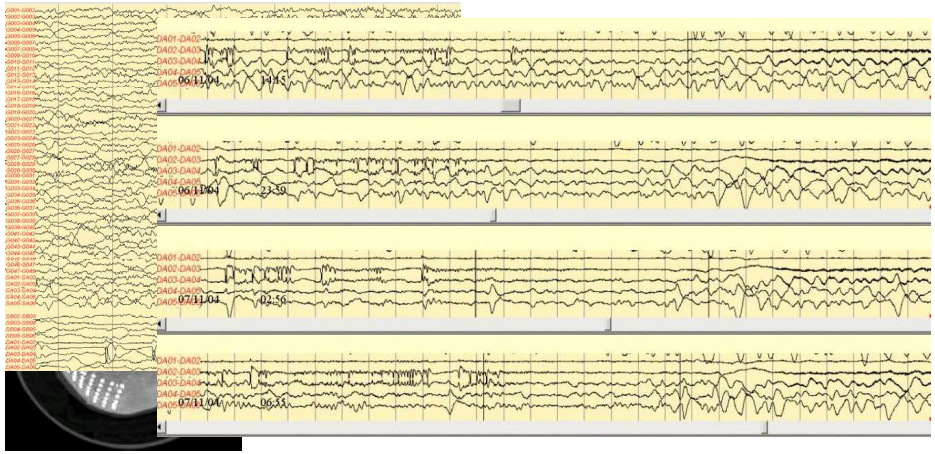






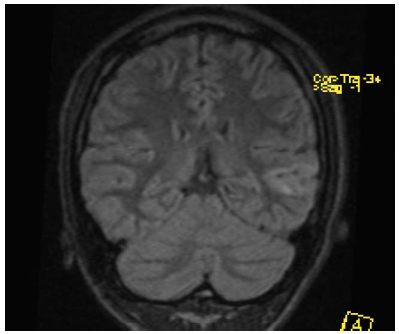


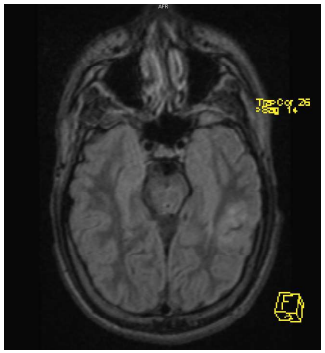


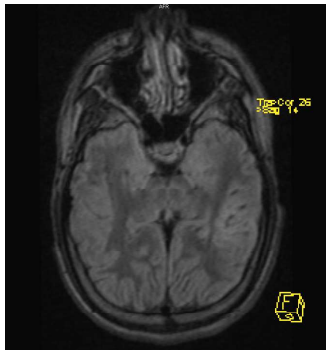


14 yr old boy

- First seizure 2 yrs
- Warning, appears agitated, fumbles, noncommunicative
- 4 previous AEDs
- Mainstream education
- Increasing difficulty

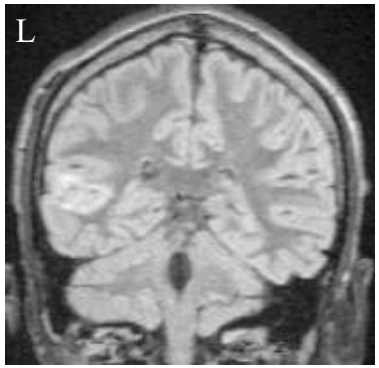




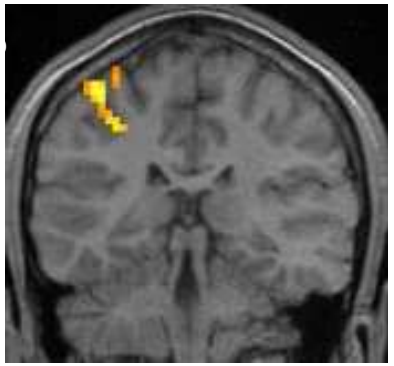


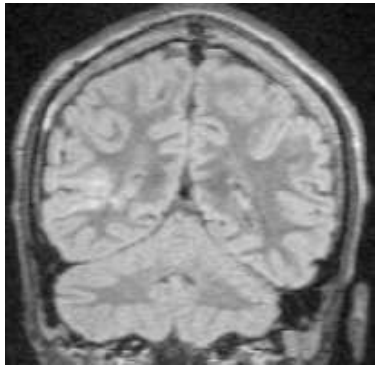
Surface EEG

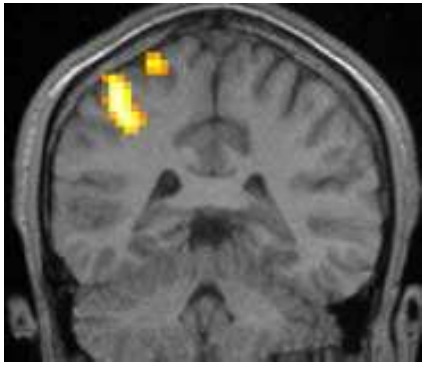
- Mild background slowing
- Occ discharges over the left temporal region in sleep
- Three similar seizures; EEG changes lagged behind clinical change
- Attenuation at onset in two & right fronto temporal discharges late in event in third

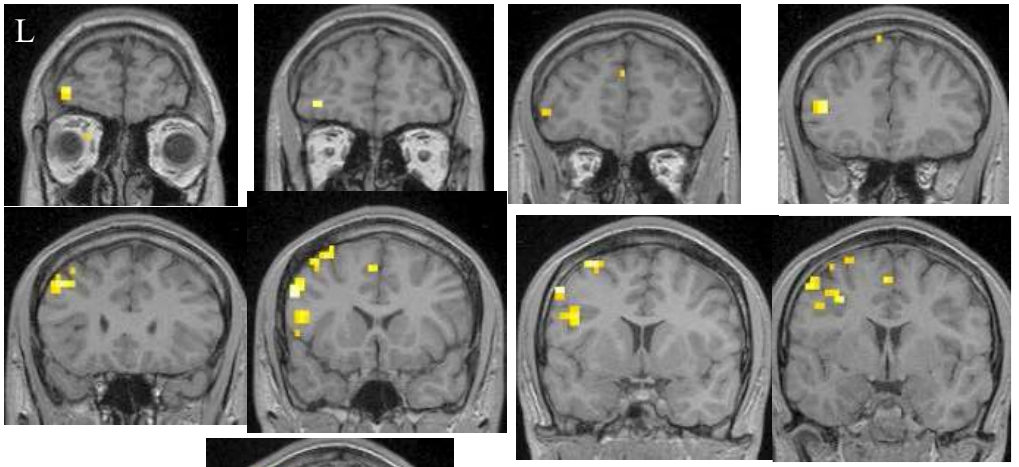


Right hand motor

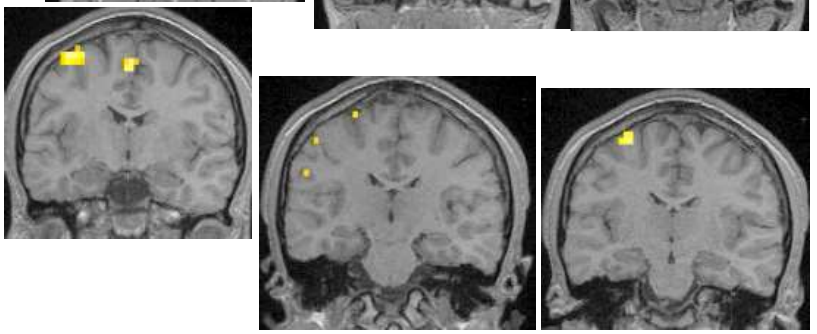








Language



No lesion?

6 year old boy , seizure onset 3 years, cluster of seizures, aura with partial awareness – long seizure free periods. Developmentally normal

- Seizures fairly stereotypic

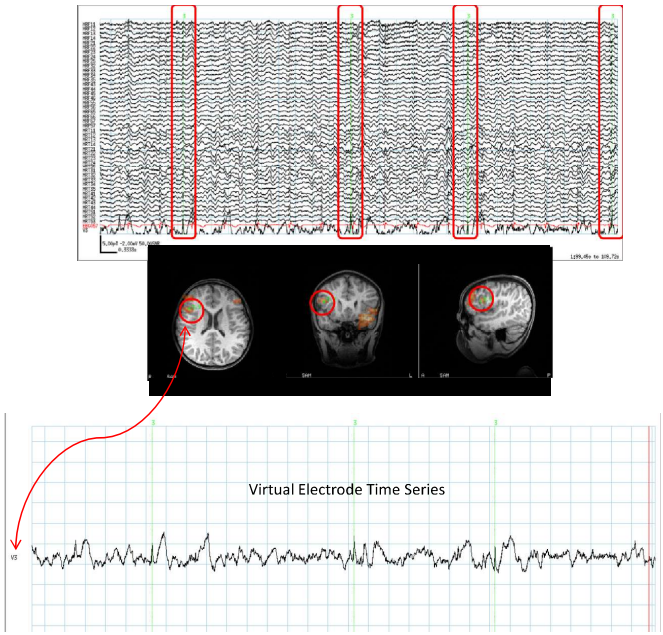
Short events

- Behavioural arrest
- Leans to side and grabs parents

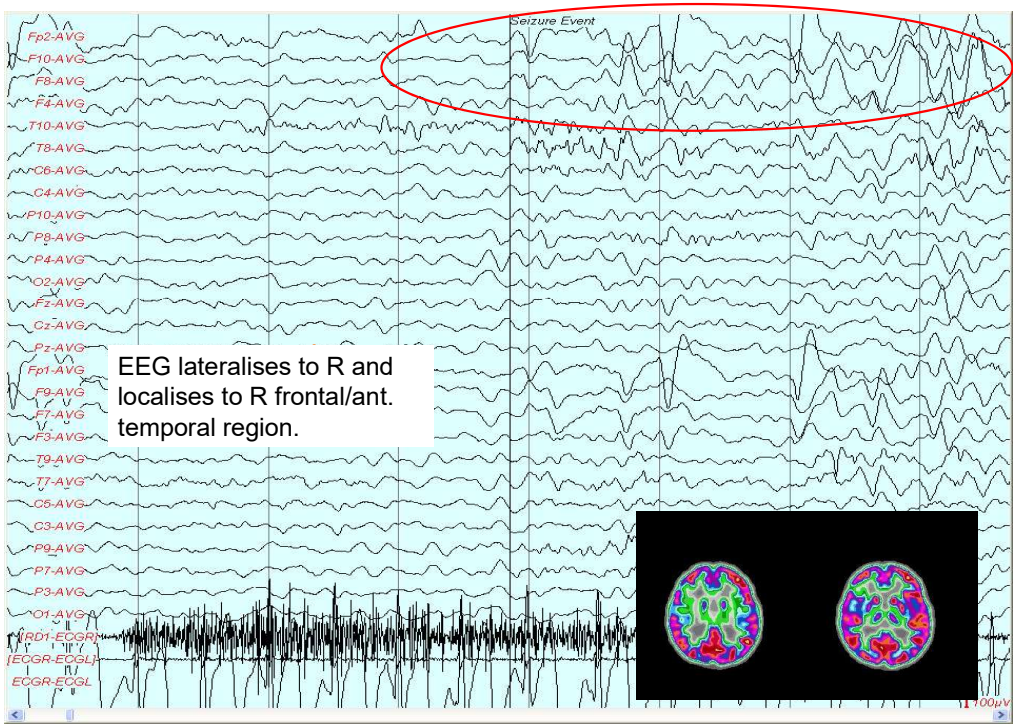
Long events

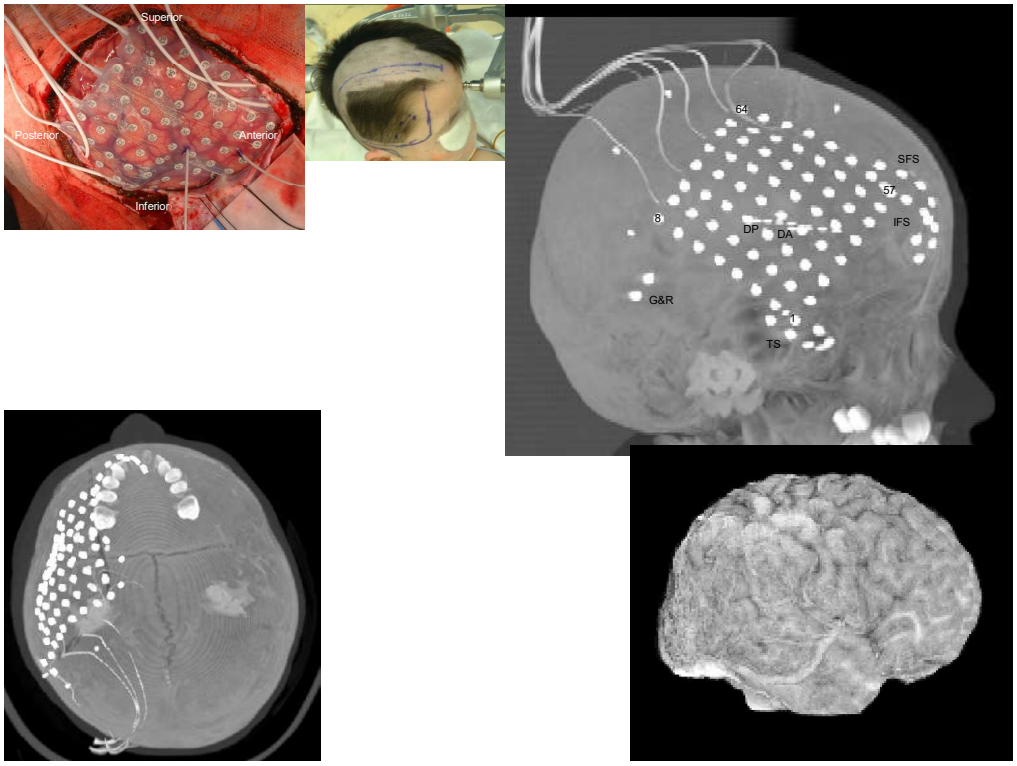
- Behavioural arrest
- Rubbing nose in the pillow
- Flipping over
- Thrashing movements.

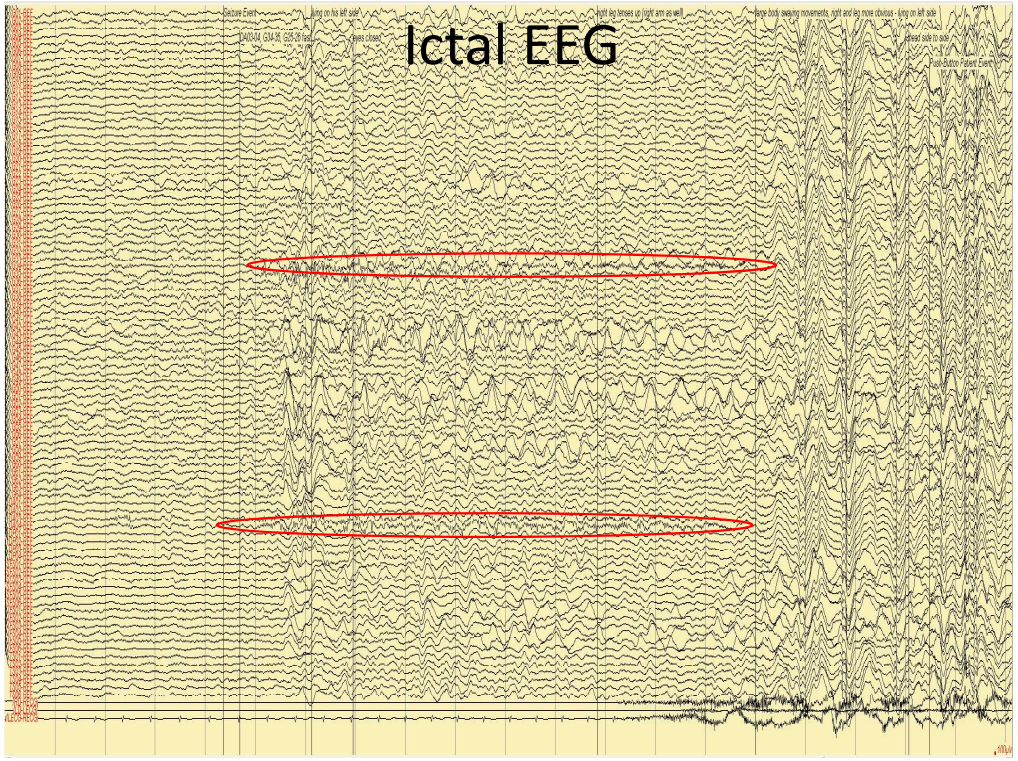
Magnetoencephalography

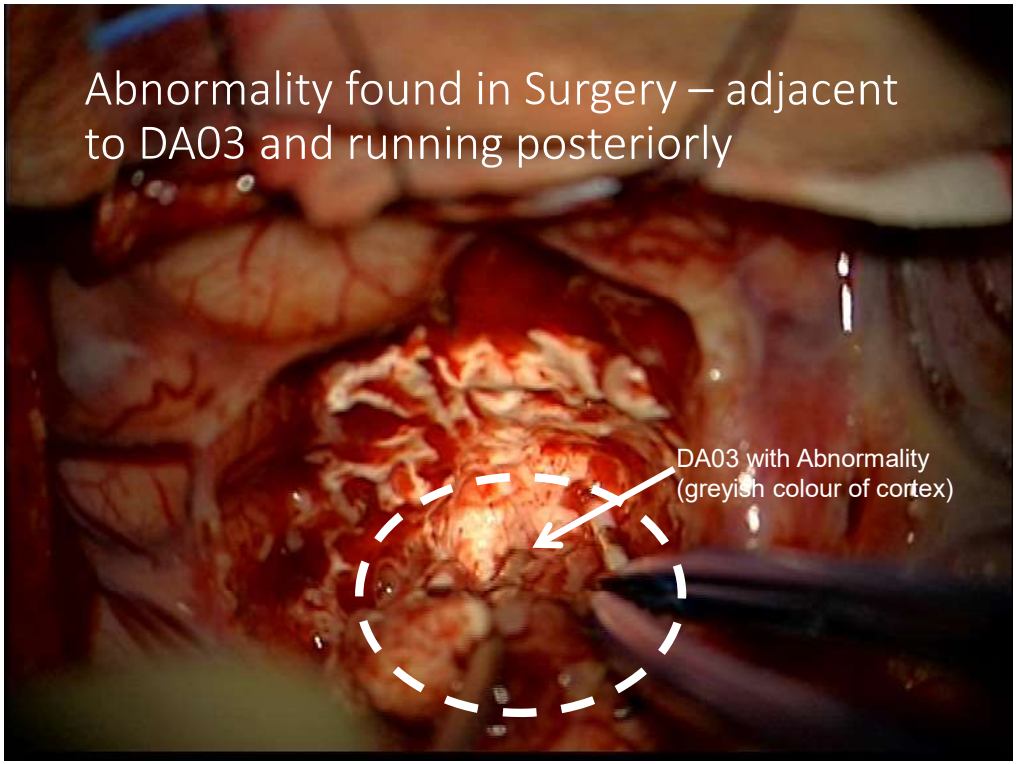


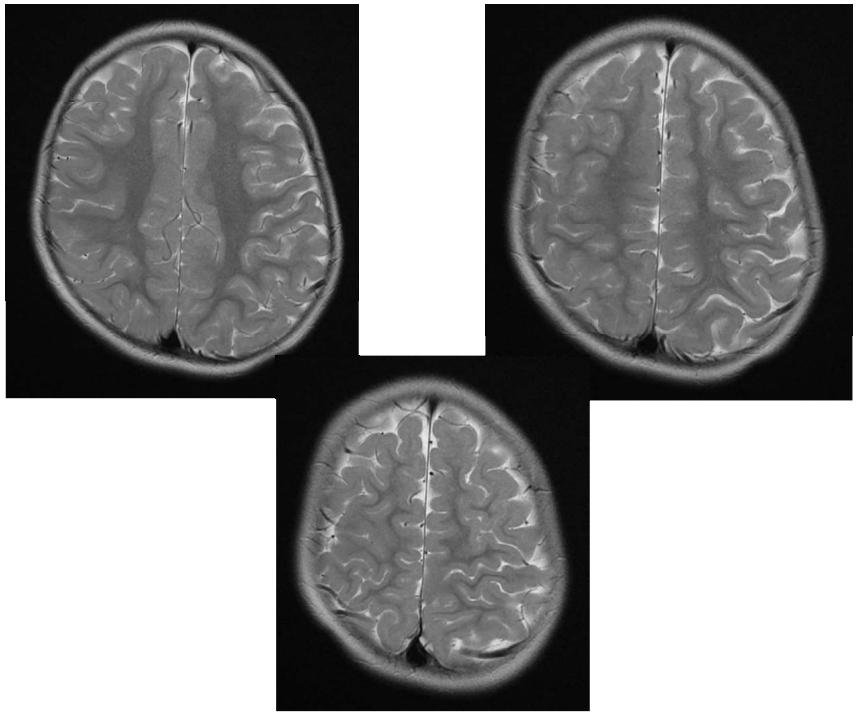
Onset of seizure -slow activity over Right frontal and Ant. Temporal region

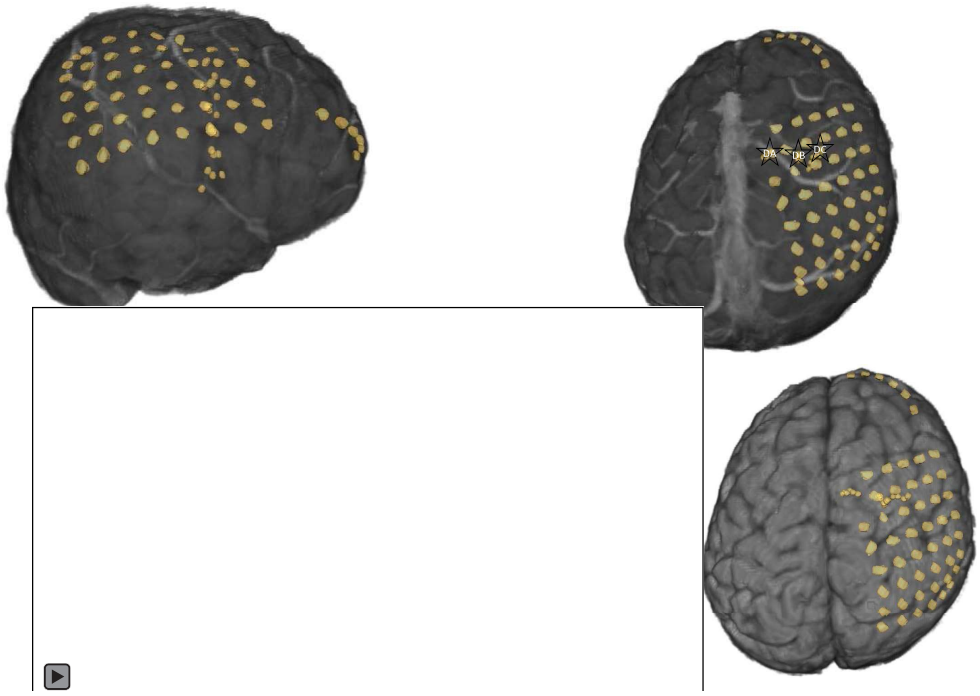




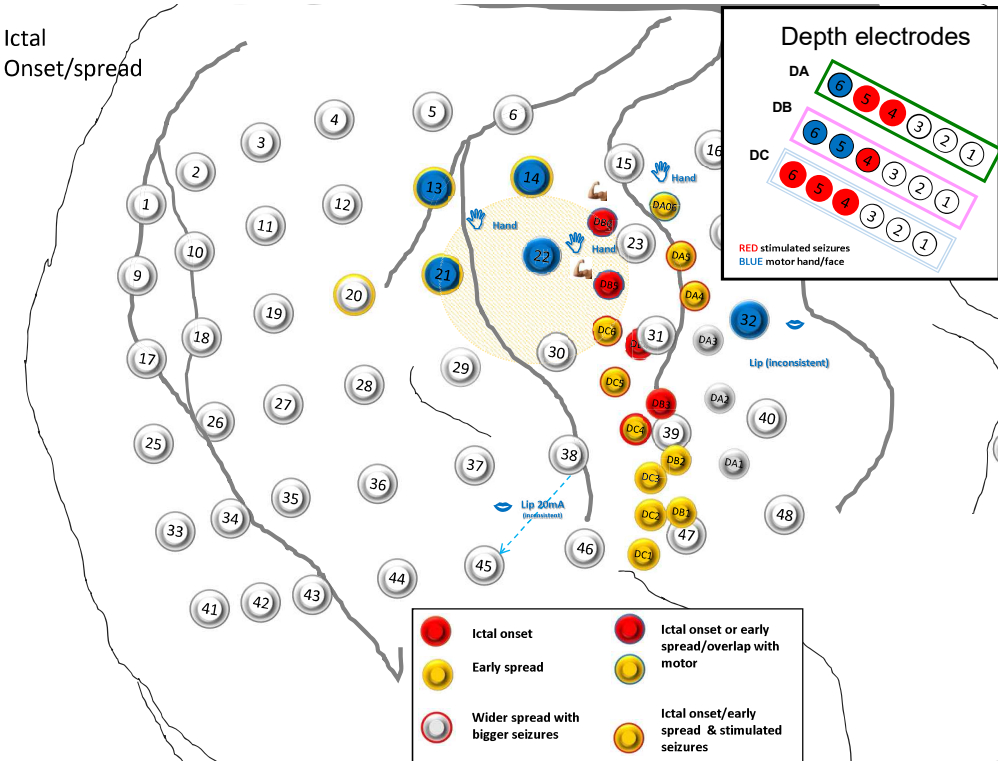

Ictal EEG

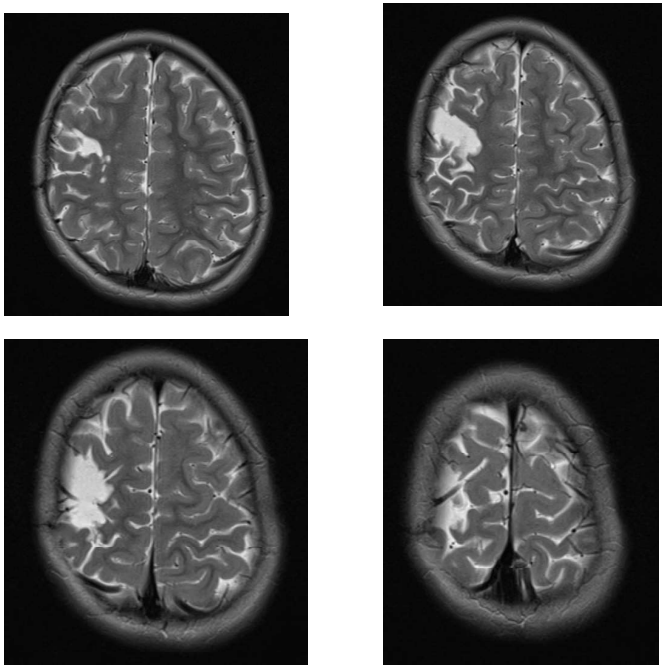

Abnormality found in Surgery – adjacent to DA03 and running posteriorly
DA03 with Abnormality (greyish colour of cortex)

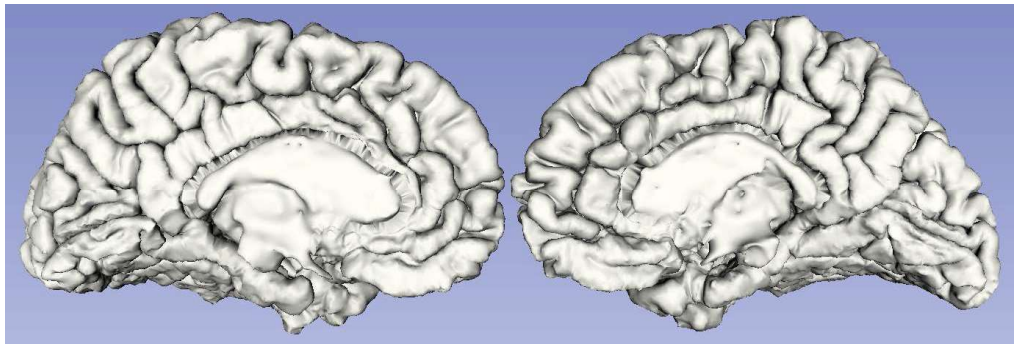


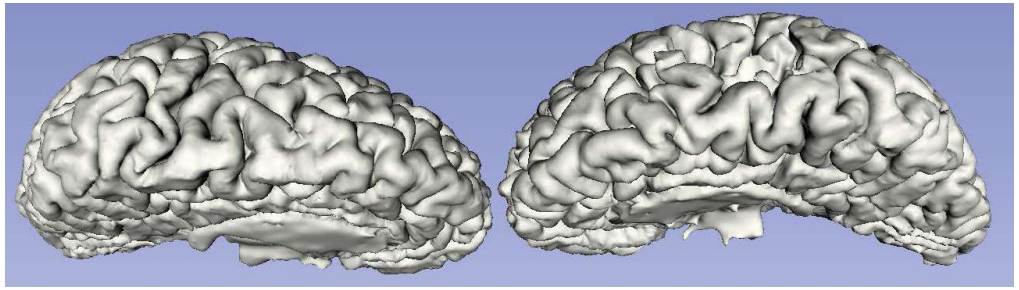


Ictal
Onset/spread









3D Reconstruction

A – A-IFG 1-10

B – M-MFG-CING 1-18

C – M-IFG-INS 1-10

D – P-MFG 1-8

E – P-IFG-INS 1-10

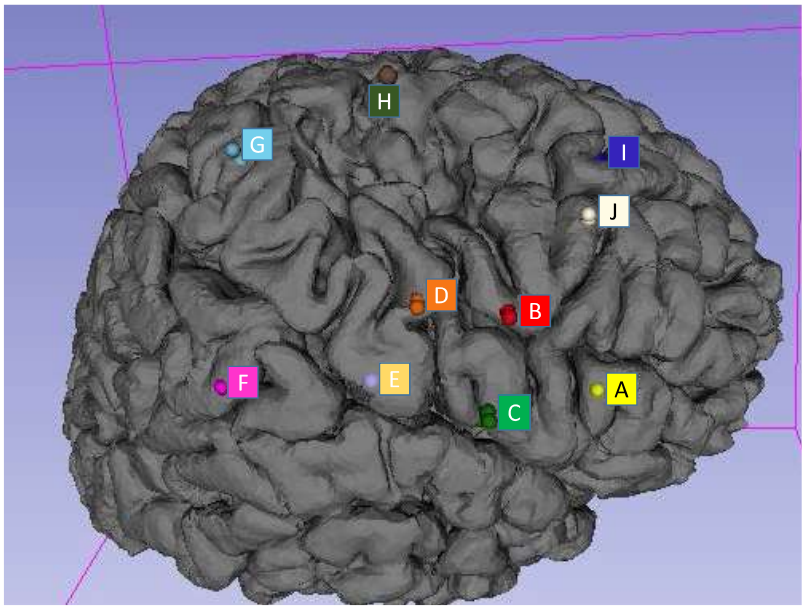
F – Parietal 1-18

G – S1 1-15

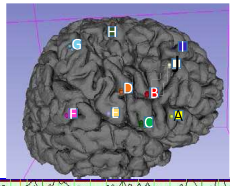
H – SMA 1-12

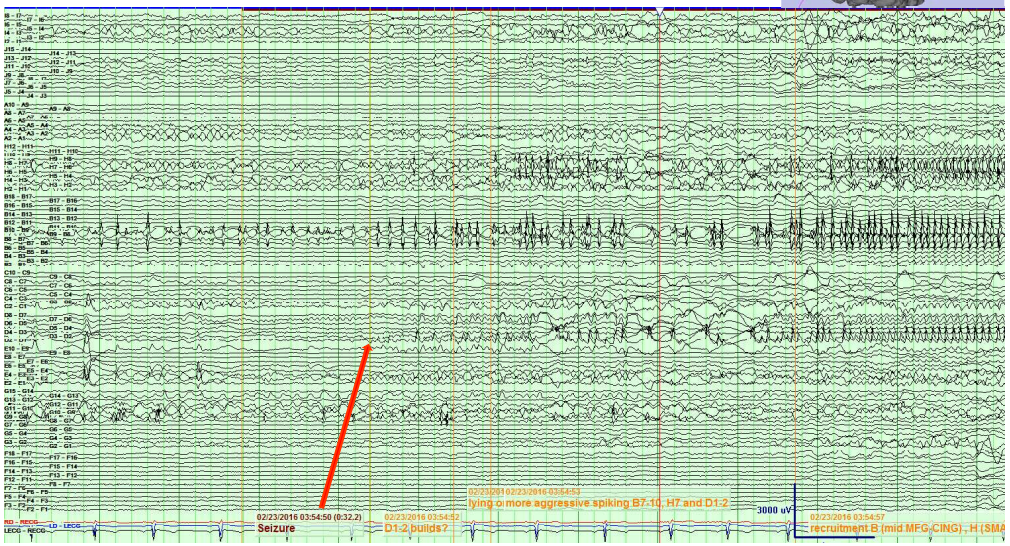
I – A-SFG 1-8

J – A-MFG 1-15

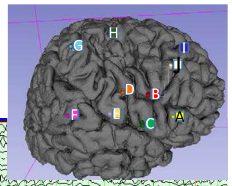


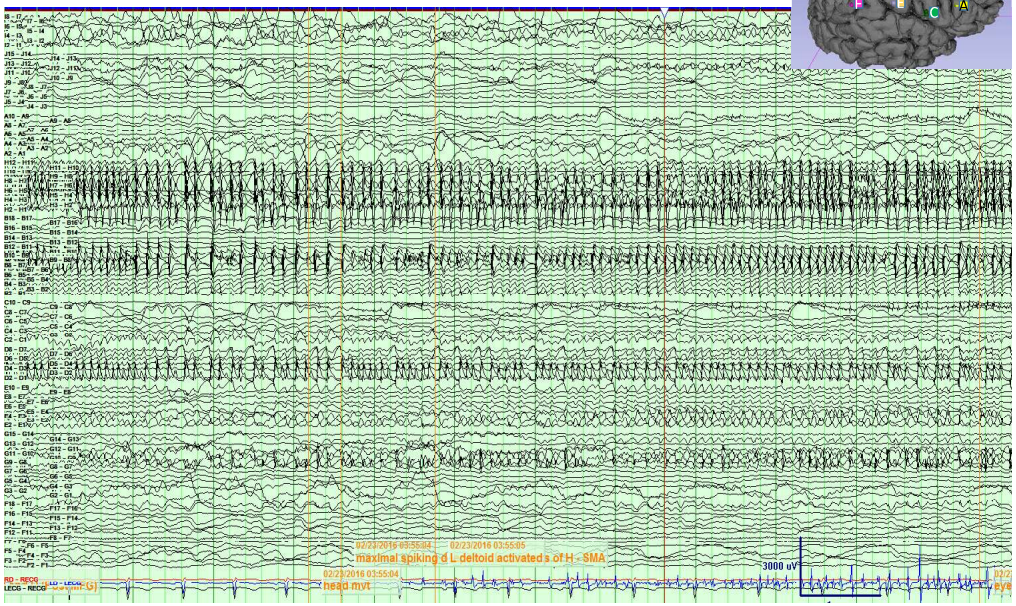
Seizure From sleep:
D1-2 rhythmic



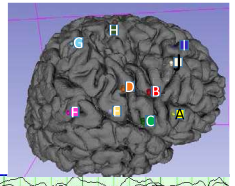


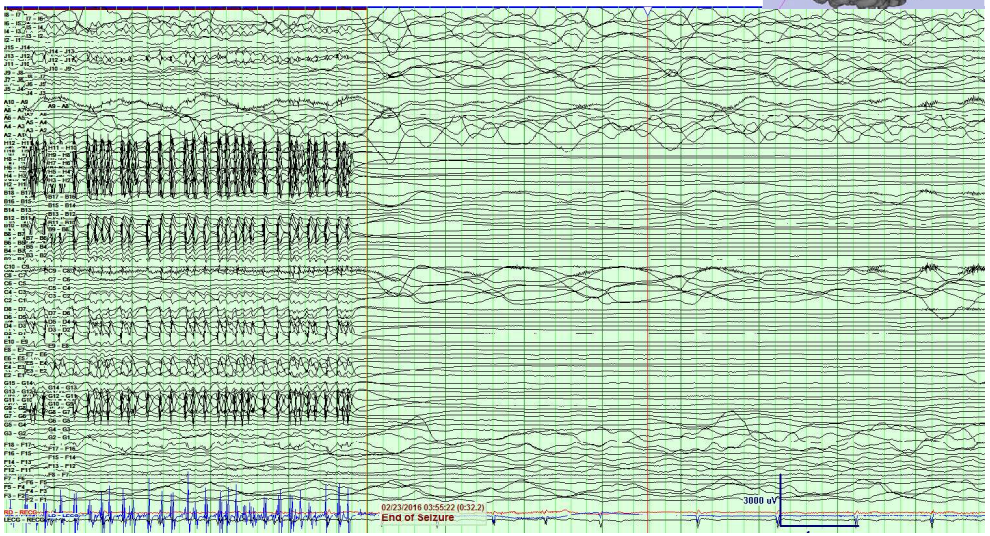
Seizure continued – spread H1-7, B6-10, G8-10



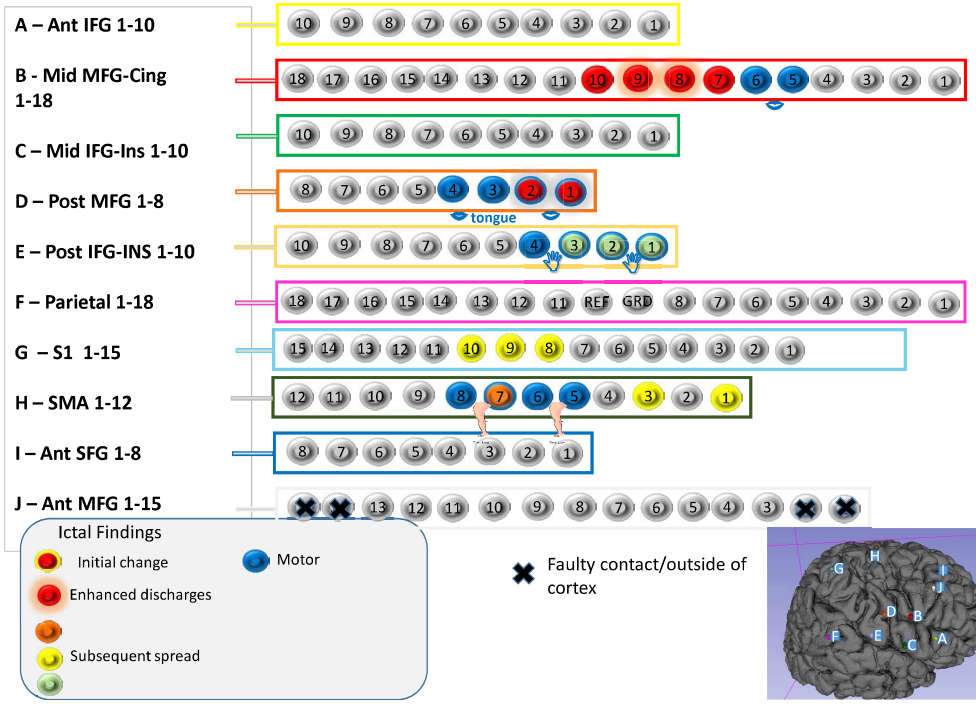


end





Functional Stim & Ictal Findings



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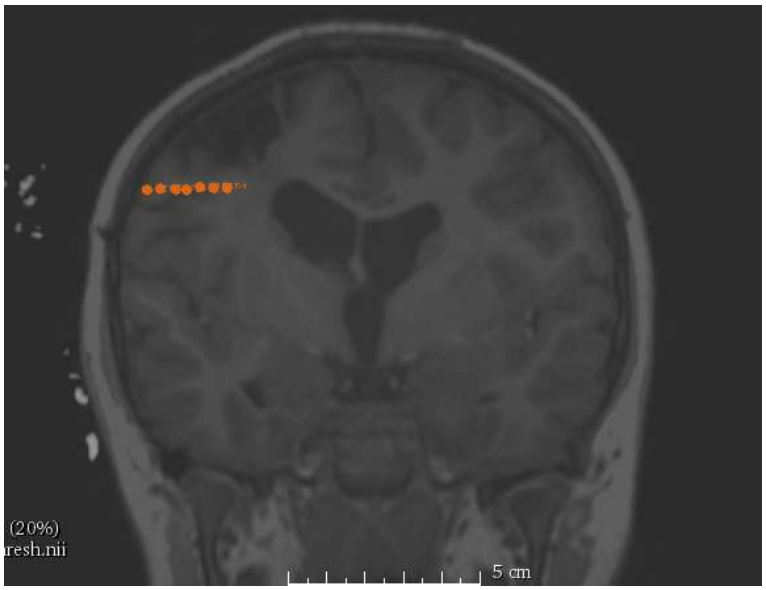
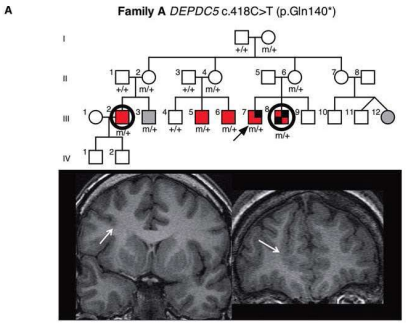


Seizure outcome following surgery

	FCD type 1 (%)	FCD type 2 (%)	FCD type 3a (%)
(B)			
Postoperative outcome (last follow-up)			
Engel class I	37 (56)	52 (61)	34 (64)
Engel class Ia	32 (48)	42 (49)	26 (49)
Engel class II	11 (17)	13 (15)	10 (19)
Engel class III	12 (18)	13 (15	3 (6)
Engel class IV	6 (9)	7 (8)	6 (11)
	FCD type 1 (%)	FCD type 2 (%)	FCD type 3a (%)
Postoperative outcome (5 years)			
Engel class I	17 (61)	26 (67)	17 (65)
Engel class Ia	13 (46)	22 (56)	15 (58)
Engel class II	4 (14)	4 (10)	4 (15)
Engel class III	5 (18)	7 (18)	2 (8)
Engel class IV	2 (7)	2 (5)	3 (11)

There was no statistically significant difference between FCD types 1, 2, and 3a concerning postoperative outcome (log-rank test $p = 0.46$).
[a]Statistically significant value.

Fauser et al Epilepsia 2015;56:66-76



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

Stéphanie 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] Mihaela Vlaicu, MD,[4,13] Maïlys Daniau,[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,[21]

Ann Neurol 2015;77:675–683

Conclusions

- **Focal cortical dysplasia most common pathology in paediatric surgical series**
  - **Challenges & rewards**
  - **Early referral required for consideration of surgery**
- **Structured approach to evaluation within complex epilepsy team**
- **Optimise information available prior to surgical decision**
- **Specific consideration to need or type of invasive evaluation that may be required**