

Approach to Focal Cortical Dysplasia in Epilepsy, Challenges and Lessons

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Focal dysplasia of the cerebral cortex in epilepsy

D. C. TAYLOR¹ AND M. A. FALCONER

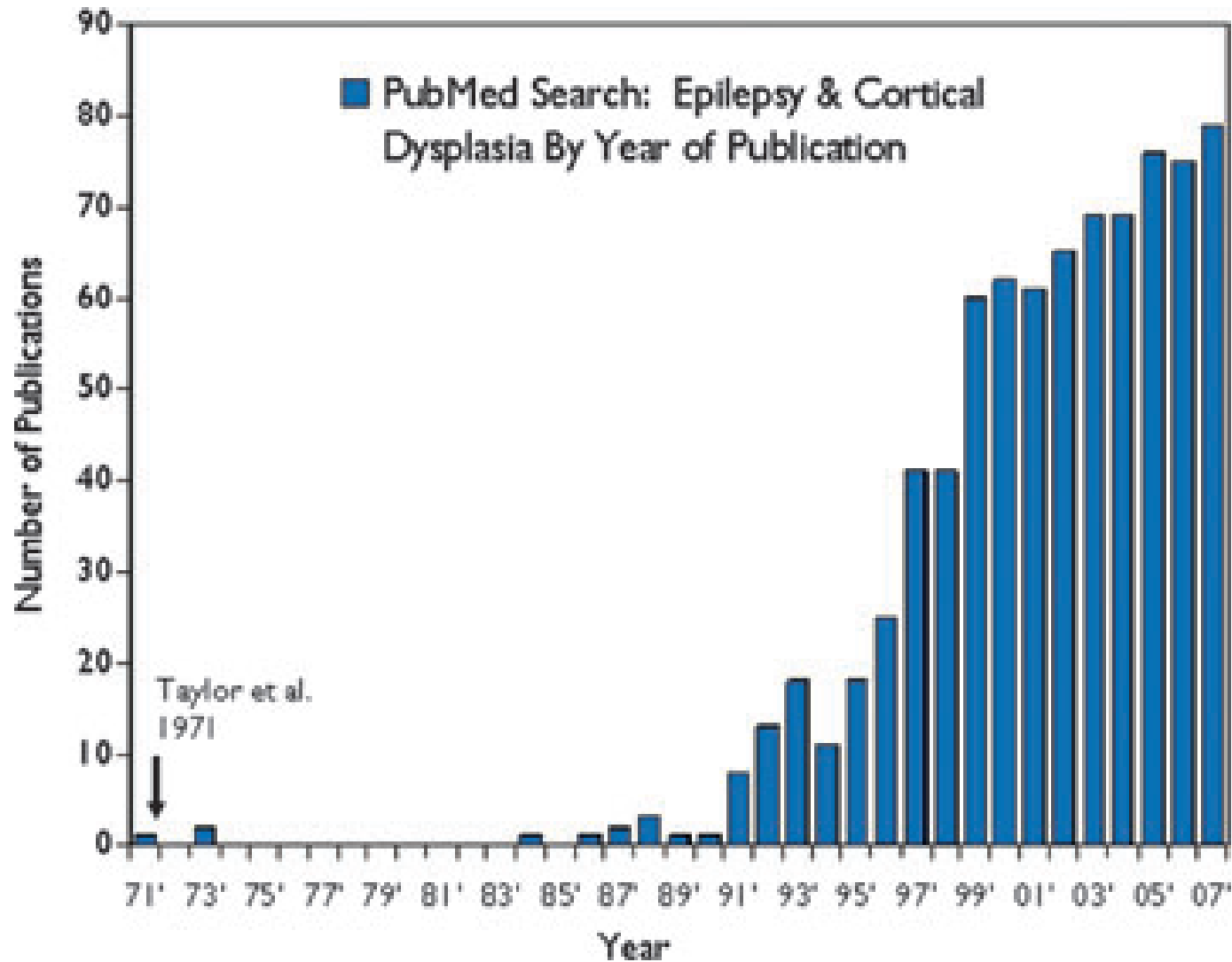
From the Neurosurgical Unit of Guy's, Maudsley, and King's College Hospitals, London

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 Megalencephalies
 - 1C Cortical dysgeneses with abnormal cell proliferation
 - Tuberous sclerosis*
 - Focal cortical dysplasia*

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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 abnormalities with dysmorphic neurons & balloon cells
 - *Imaging: commonly identified on MRI*

SPECIAL REPORT

The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission¹

^{*2}Ingmar Blümcke, †Maria Thom, ‡Eleonora Aronica, §Dawna D. Armstrong, ¶Harry V. Vinters, #Andre Palmi, **Thomas S. Jacques, ††Giuliano Avanzini, ‡‡A. James Barkovich, §§Giorgio Battaglia, ¶¶Albert Becker, ###Carlos Cepeda, ****³Fernando 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).

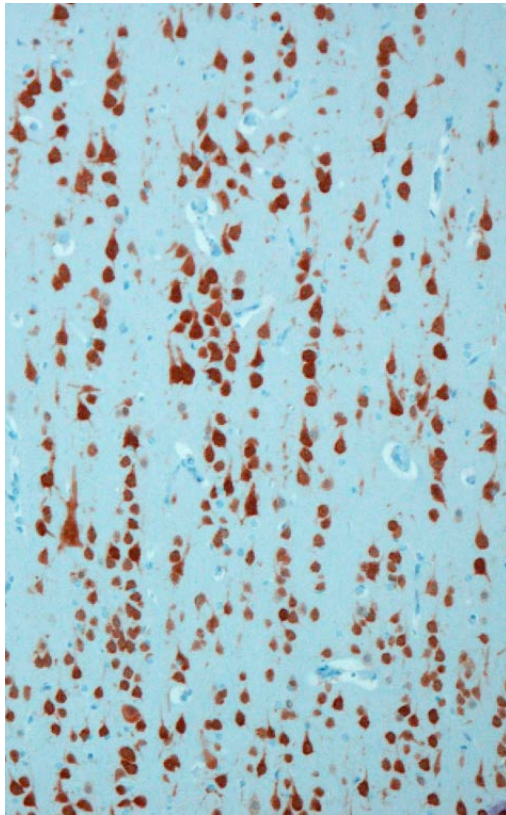
| | | | | |
|---|--|---|--|--|
| FCD Type I (isolated) | Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia) | Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib) | Focal cortical dysplasia with abnormal radial and tangential cortical lamination (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.

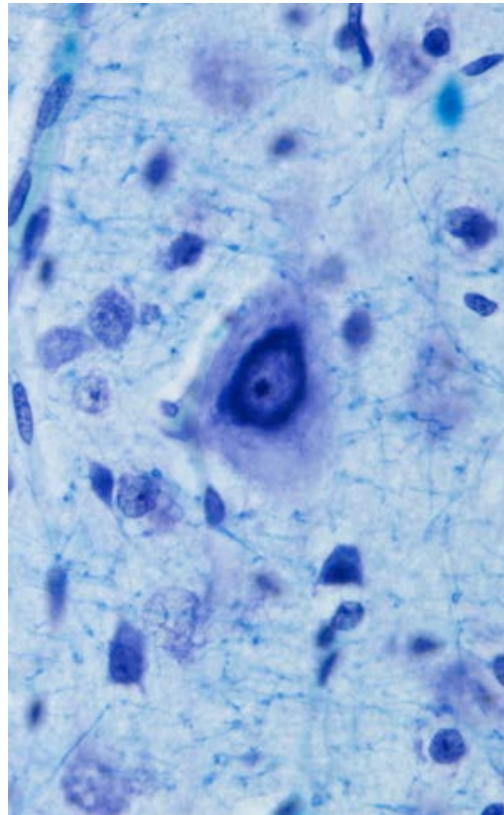
Three types of FCD

Type 1



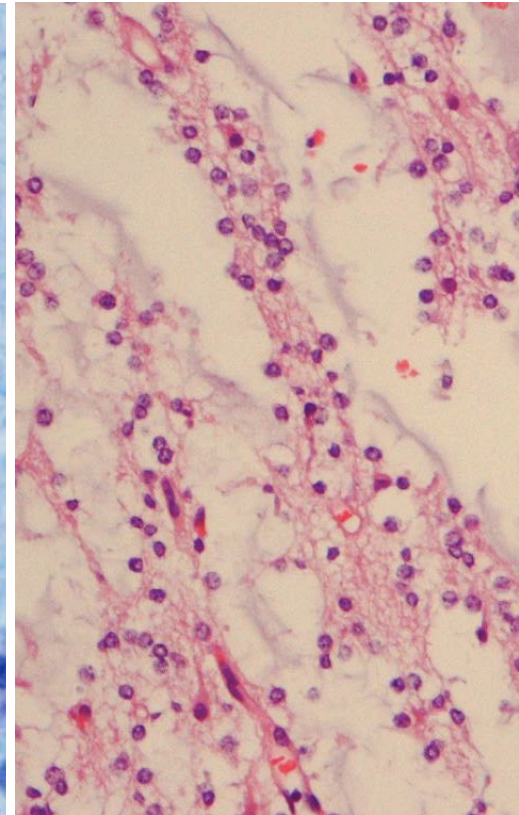
Architectural
Dysplasia

Type 2



Architectural
and Cytological
Dysplasia

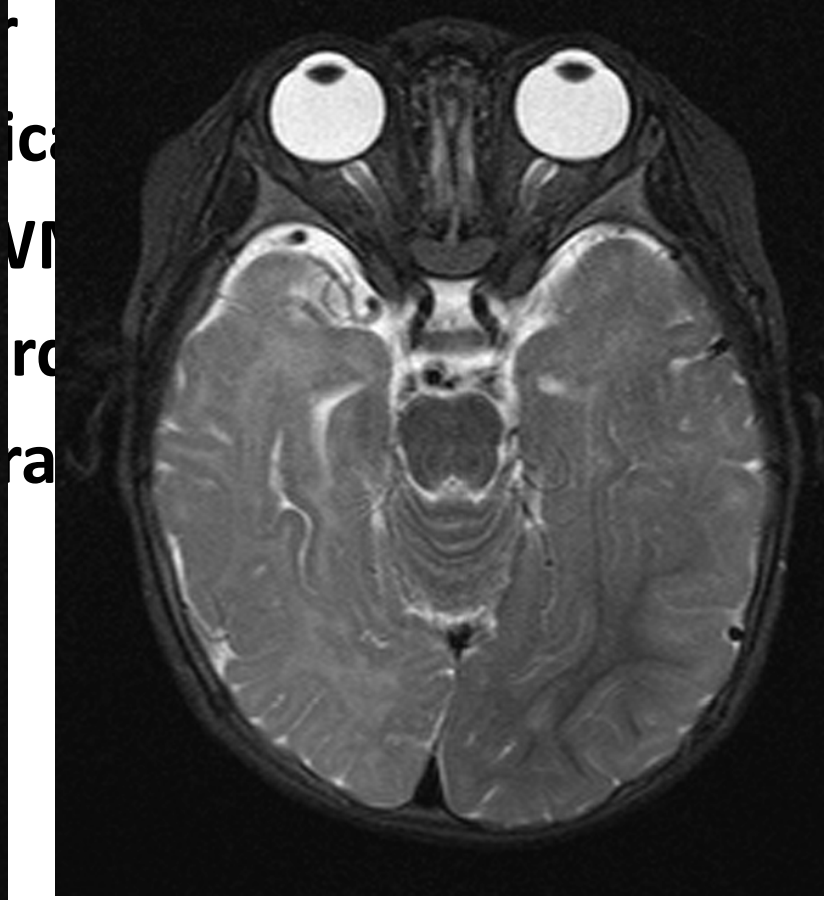
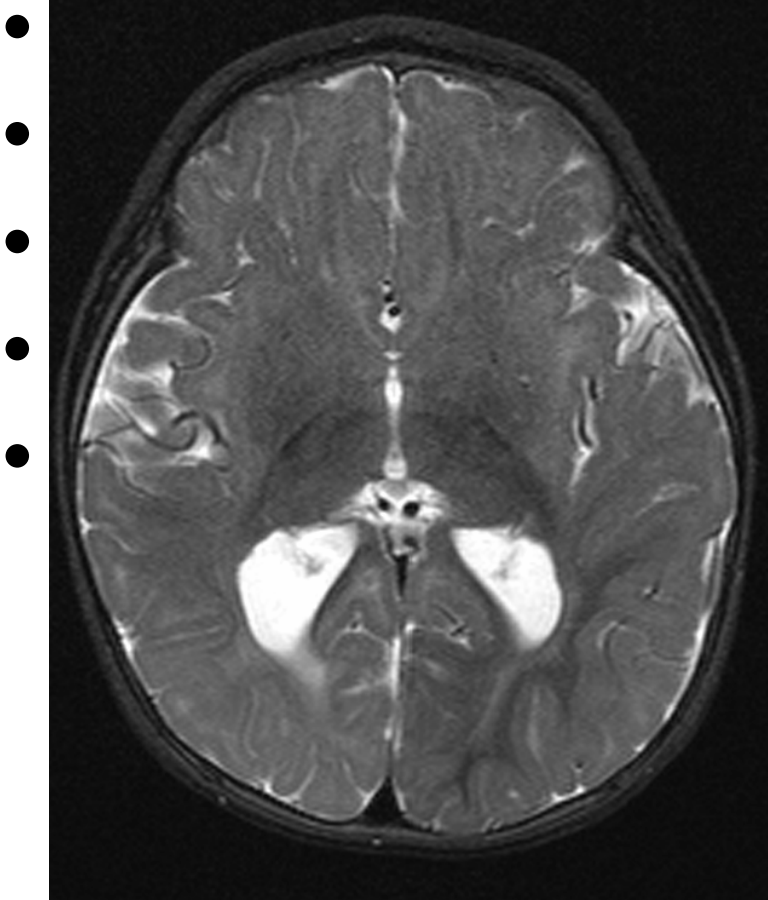
Type 3



Architectural
Dysplasia
+ 2nd pathology

Imaging Characteristics

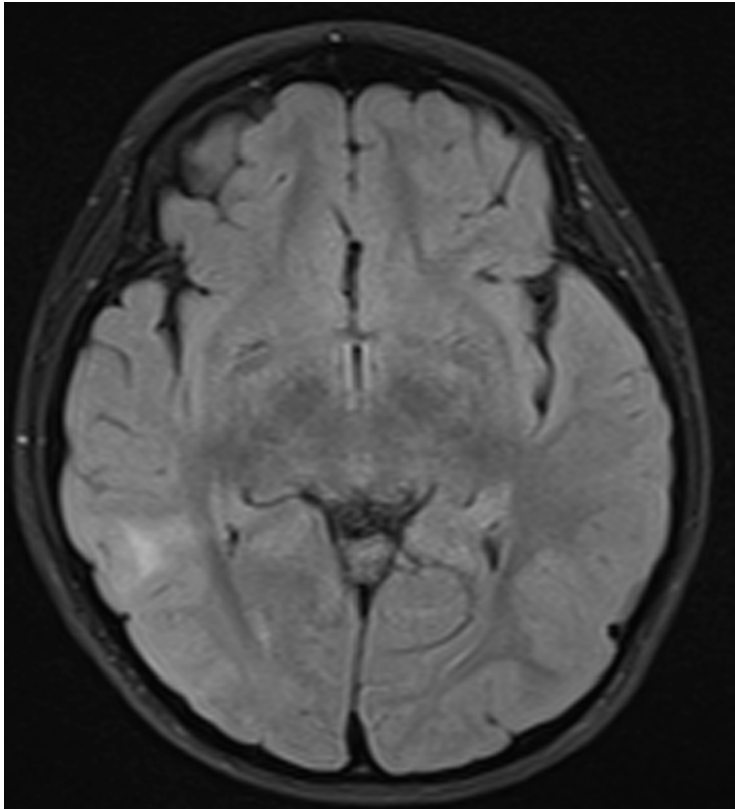
FCD Type I



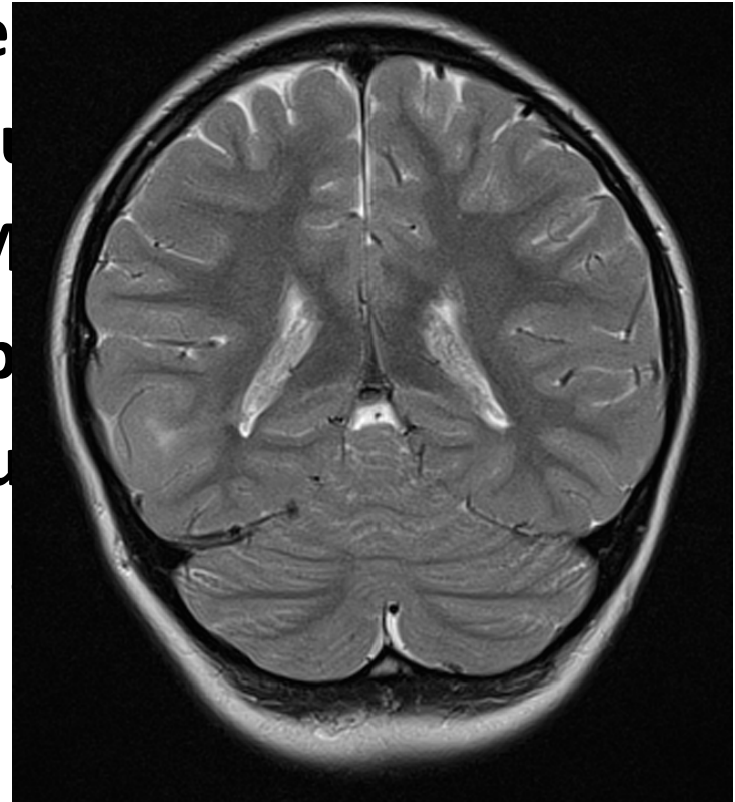
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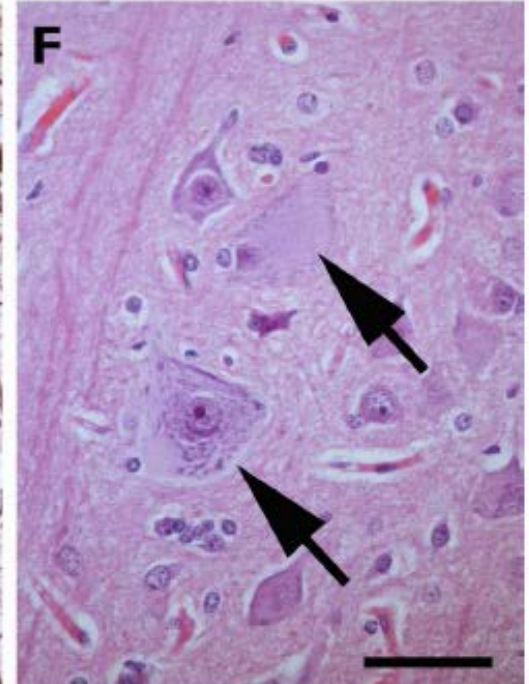
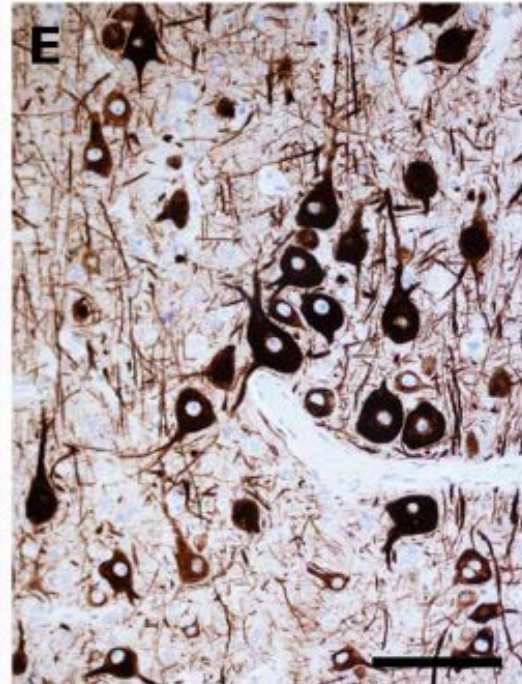
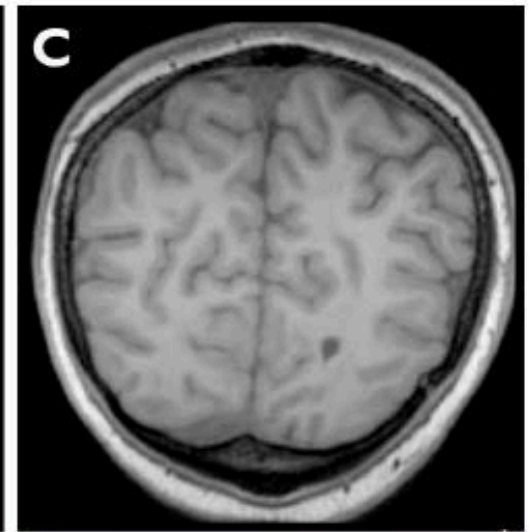
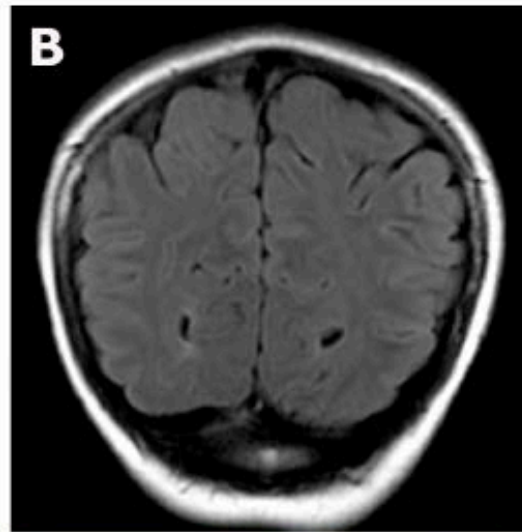
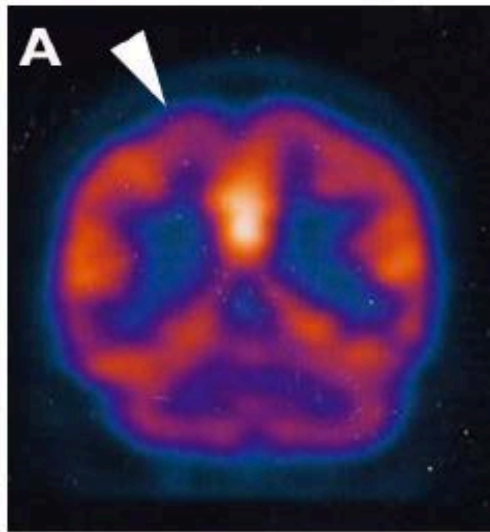
Imaging Characteristics

Type II

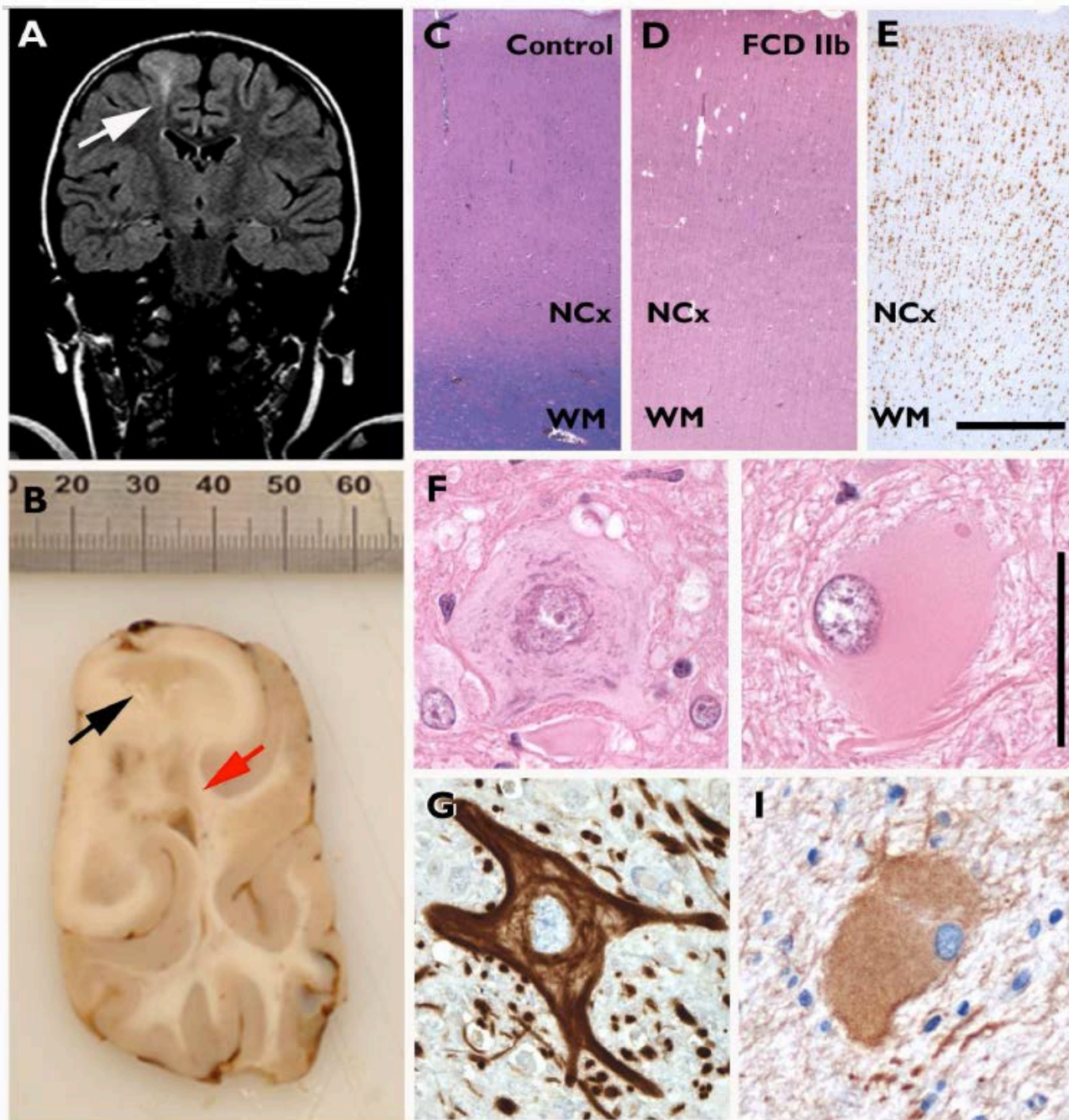


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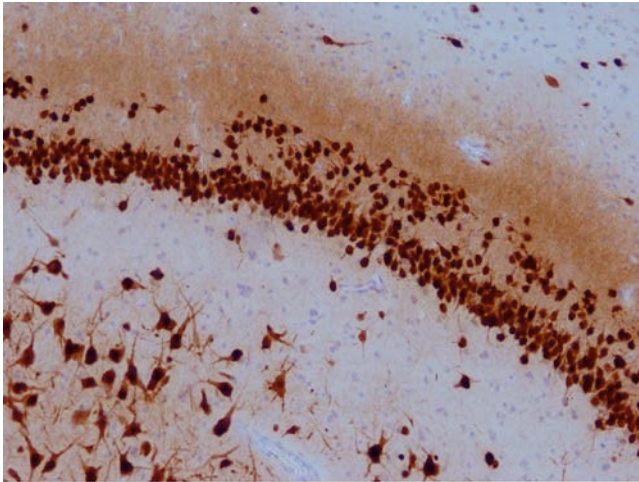
FCD Type II a



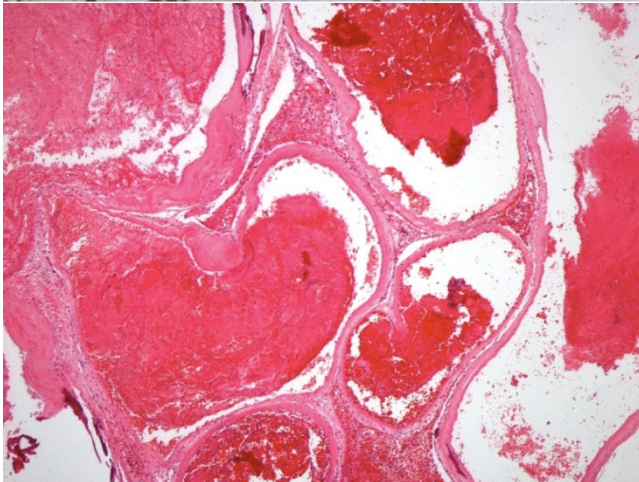
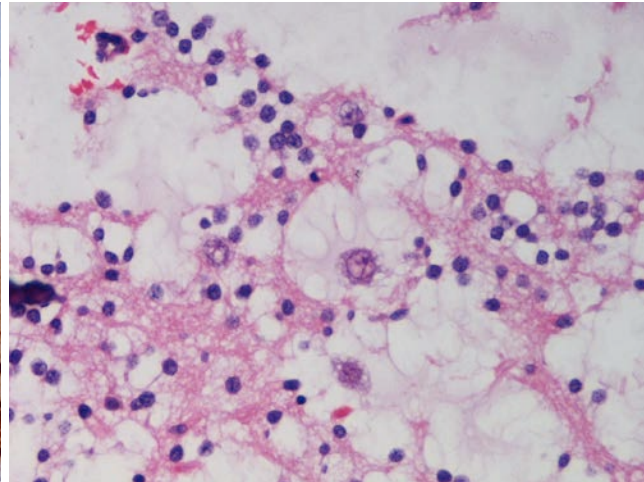
FCD Type II b

Focal Cortical Dysplasia Type III

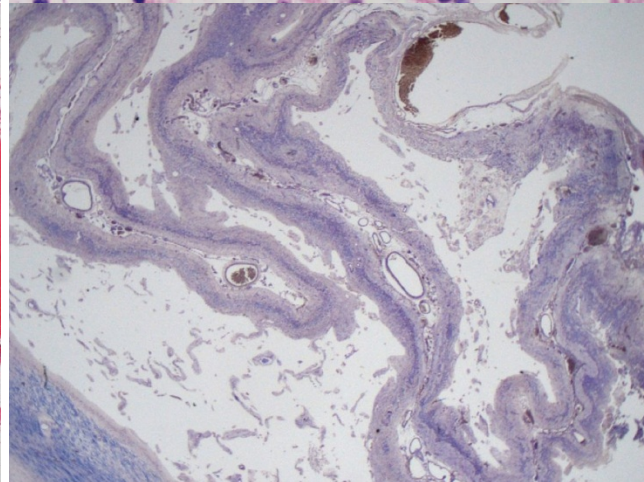
IIIa
Associated with HS



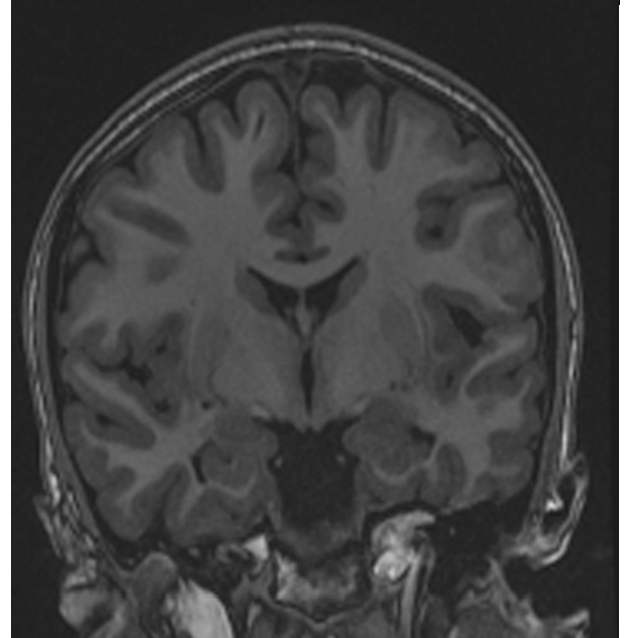
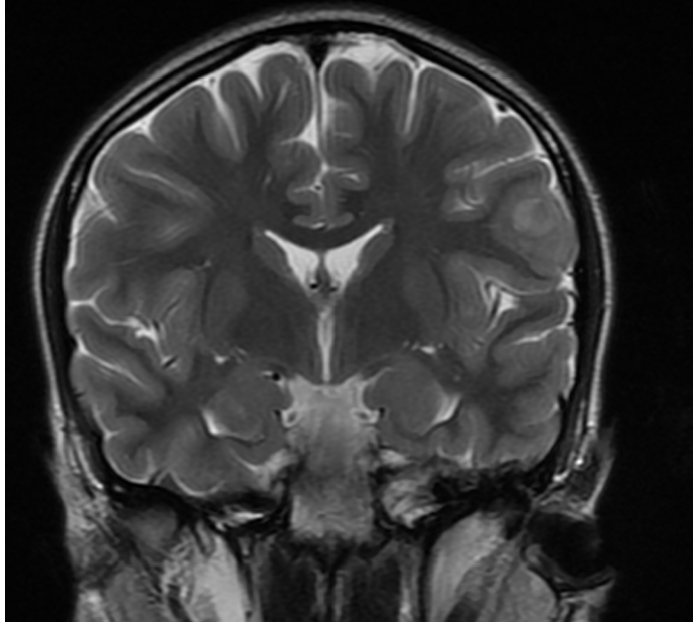
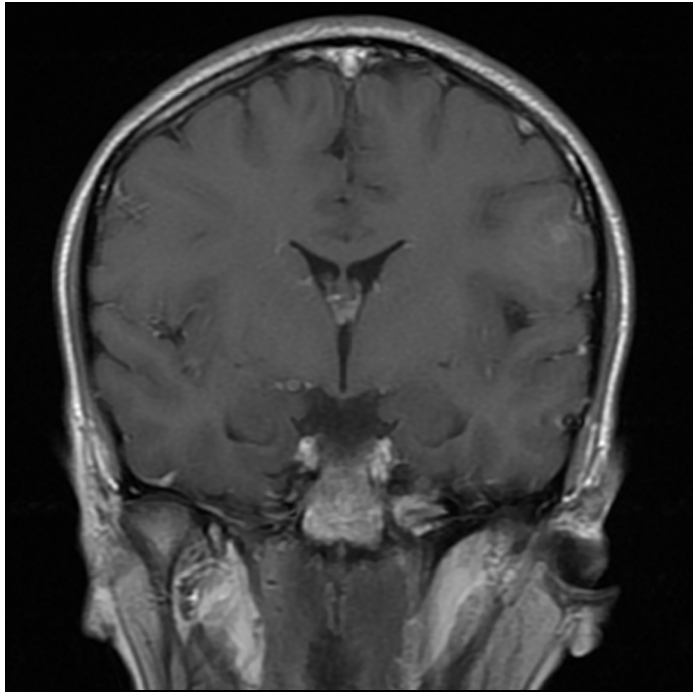
IIIb
Adjacent to a tumour



IIIc
Adjacent to a vascular malformation



IIId
Adjacent to an acquired lesion from early life

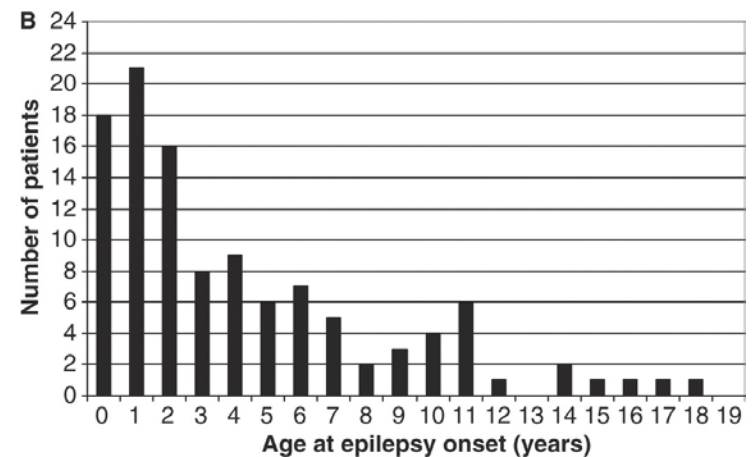
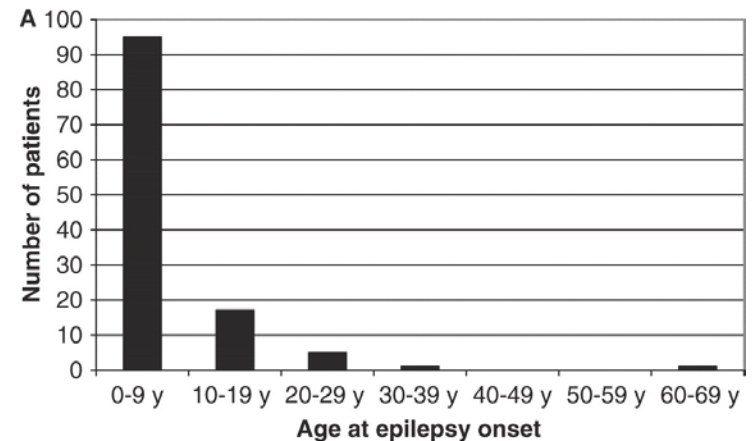


Clinical Characteristics of FCD

- **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

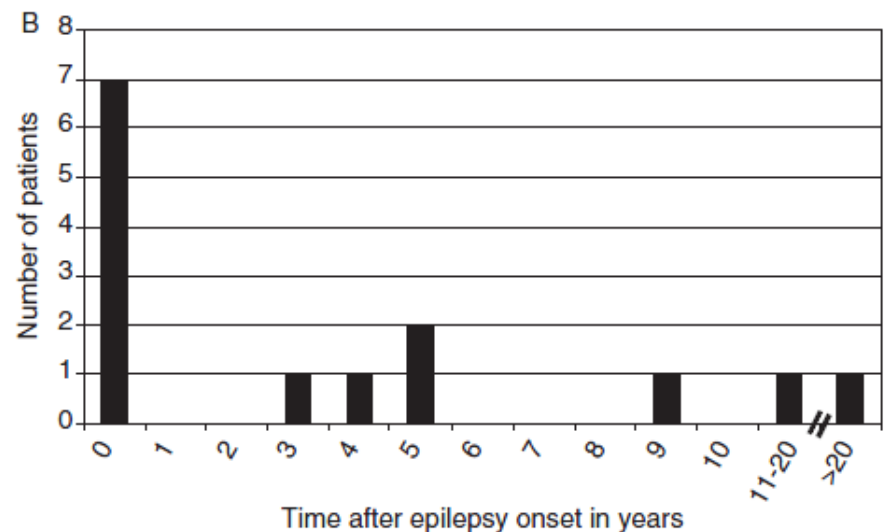
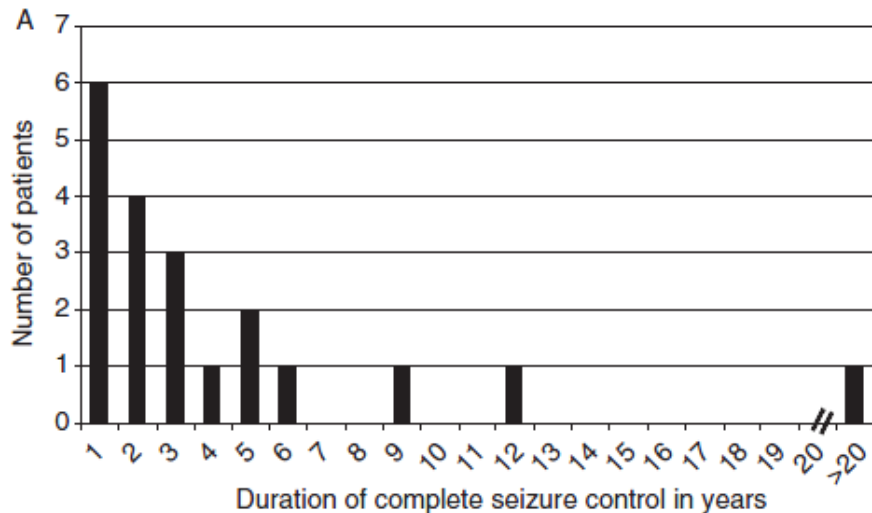
2200 patients, 8% first seizure, over 7 years

96 (8%) cortical dysgenesis

23 (24%) seizure free

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 Volk² and Andreas Schulze-Bonhage¹



Responsiveness to antiepileptic drugs

Medical Treatment

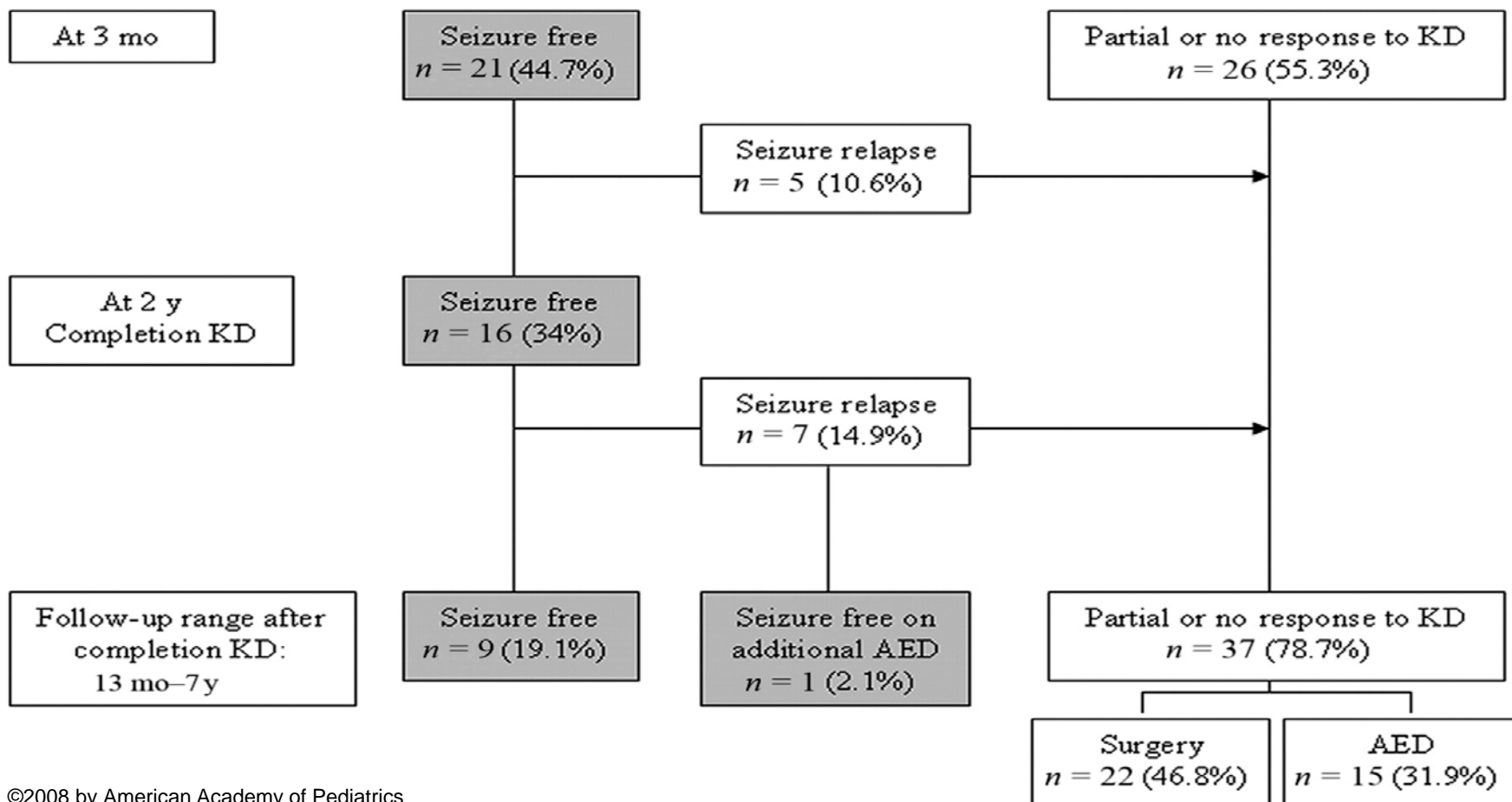
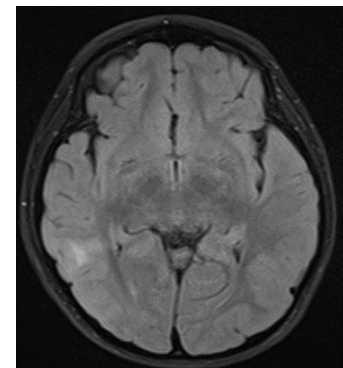
Vigevano & Koivikko *Epilepsia* 1997;38:1275-1282

Vigabatrin vs ACTH for Infantile Spasms N=47

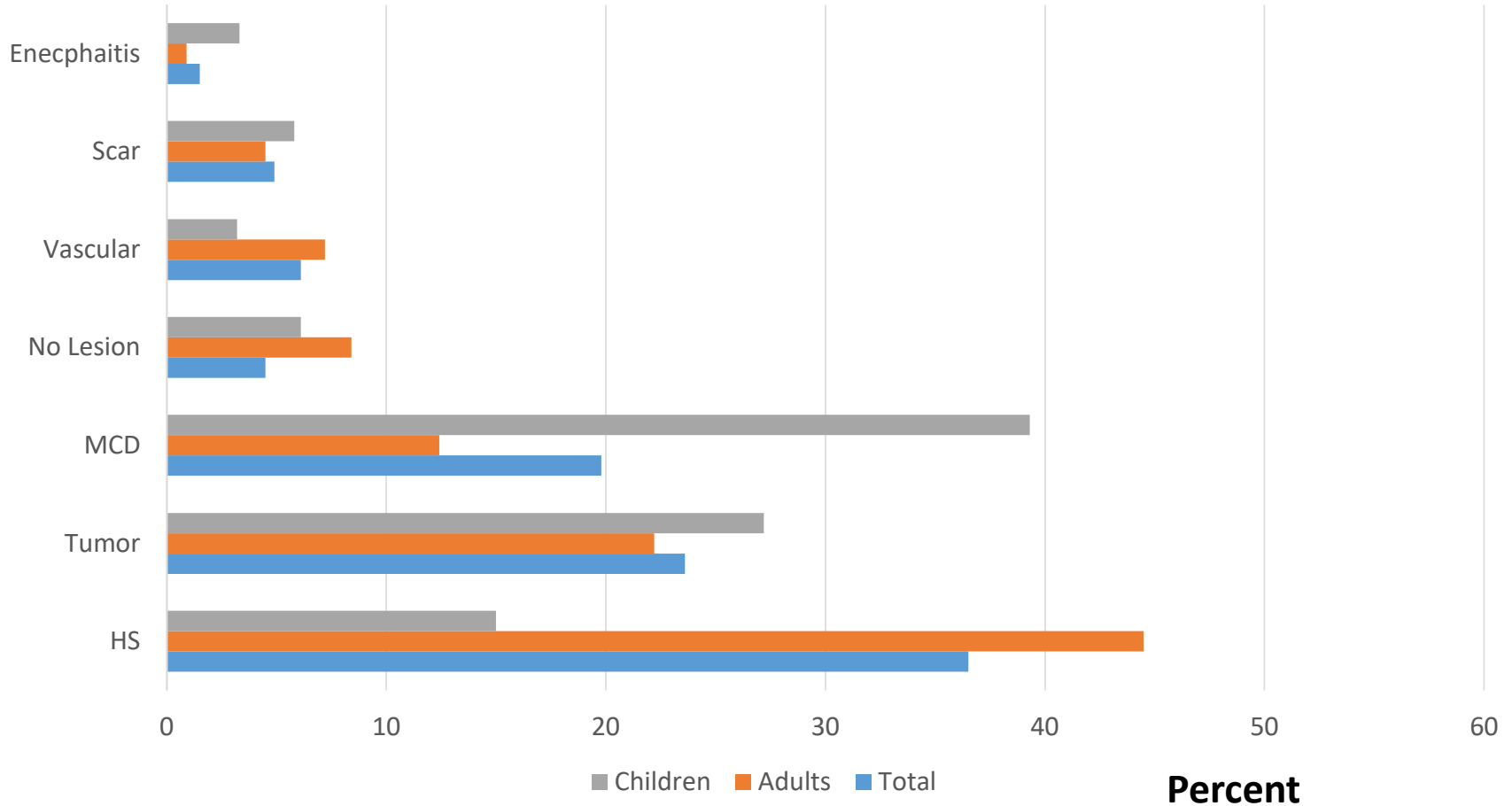
| | VGB | ACTH |
|------------------------------|--------------------|--------------------|
| Cessation of spasms | 11/23 (48%) | 14/19 (74%) |
| Cerebral malformation | 3/4 (75%) | 0/3 (0%) |
| Tuberous sclerosis | 3/3 (100%) | 1/1 (100%) |

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*

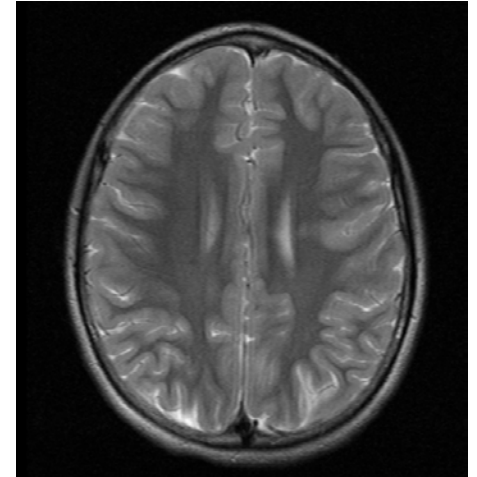
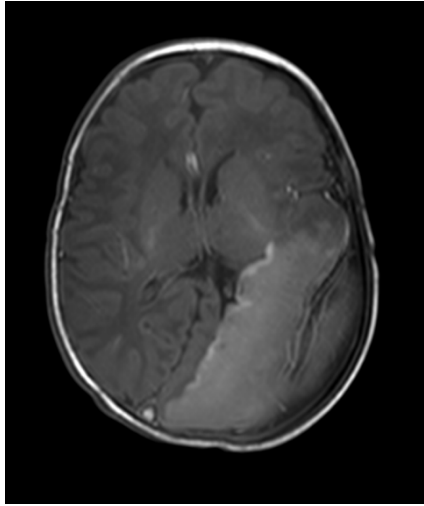


Major aetiological categories



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

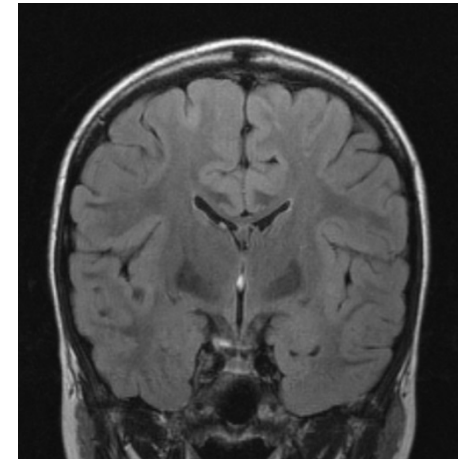
Epileptogenic zone often from around rather than within lesion

?Role for ECoG

Role of invasive EEG – grids/SEEG

-Limits of lesion

-Dysplastic tissue often located in eloquent cortical regions



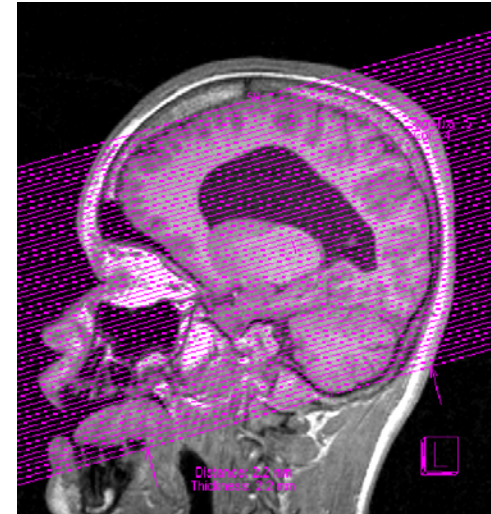
Optimised imaging

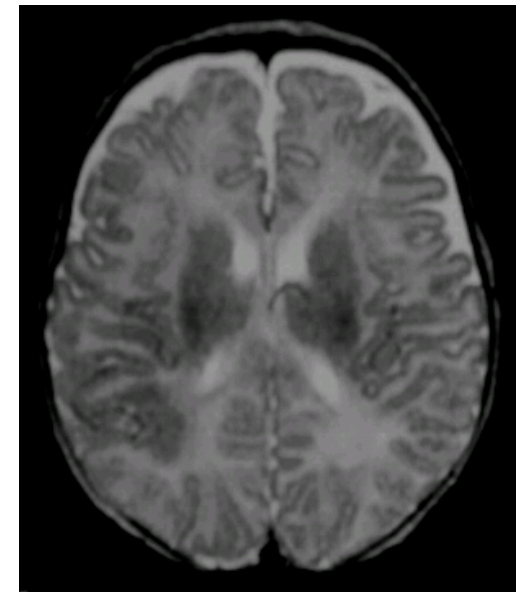
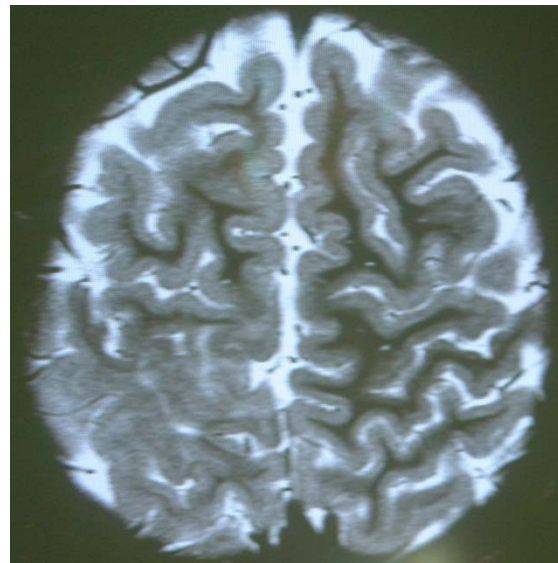
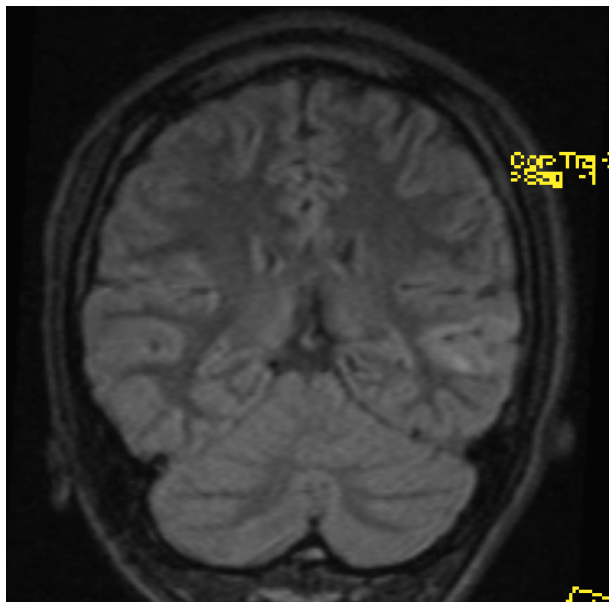
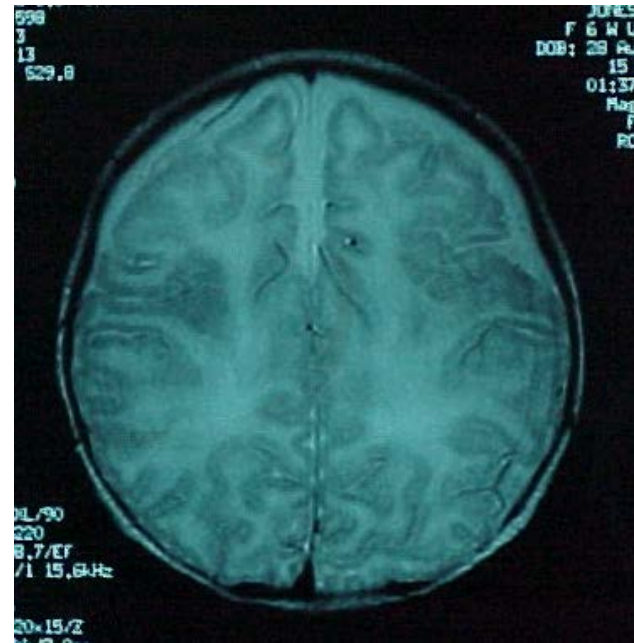
Protocols

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

Children <2yrs

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

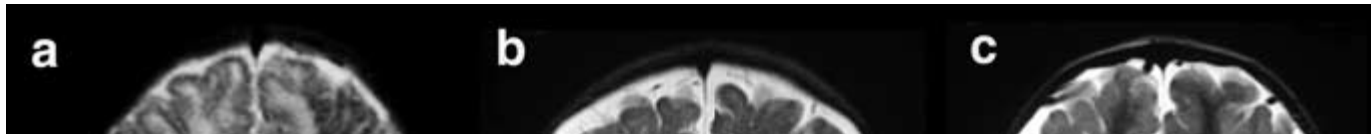




Are the MRI Findings Specific?

| 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 |

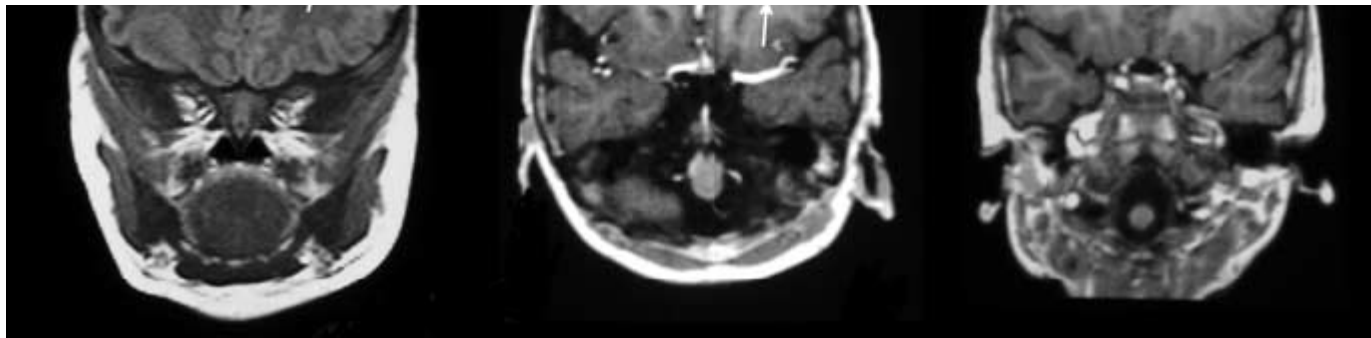
Timing of Scan & Maturation



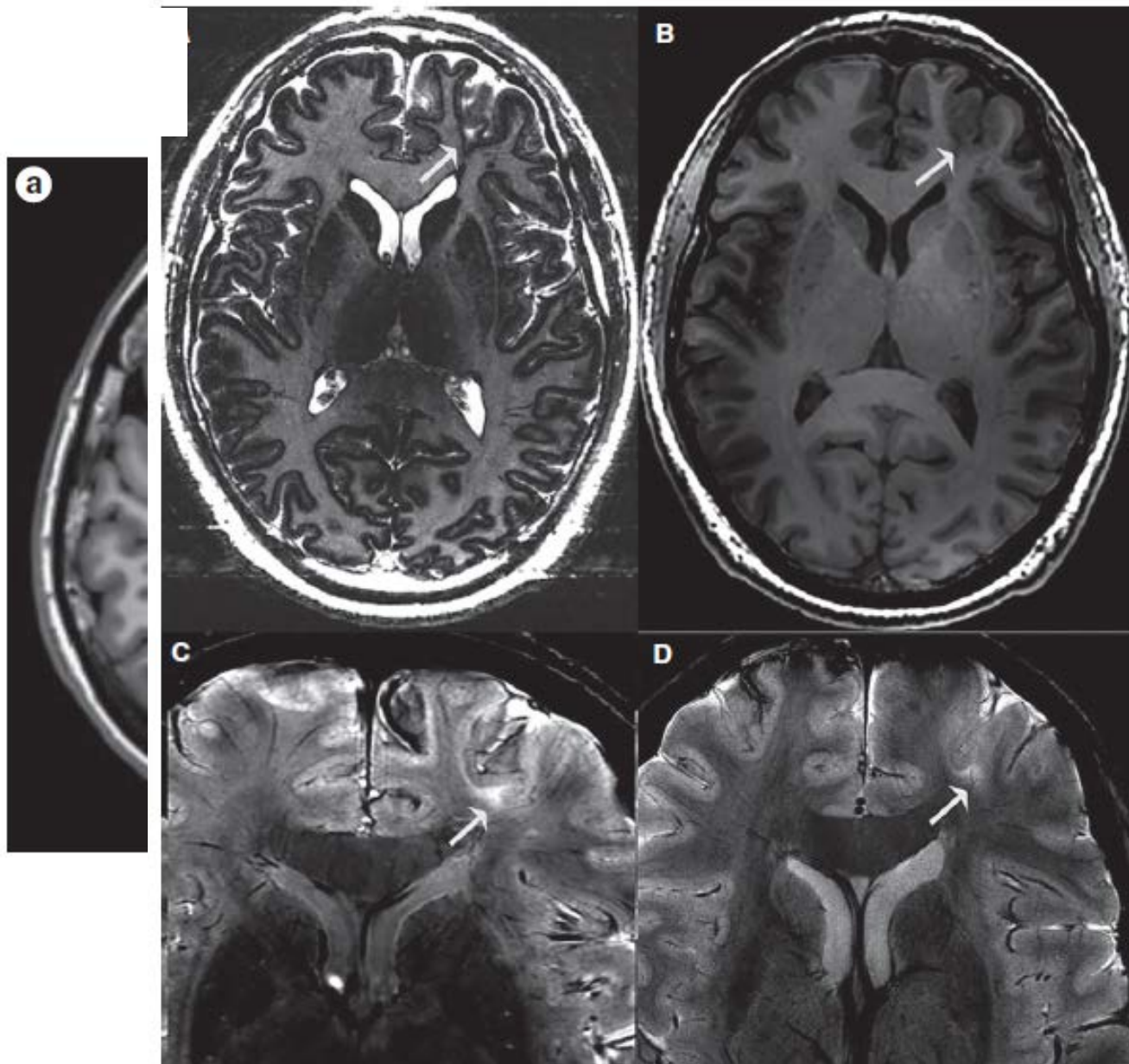
Taylor-type Focal Cortical Dysplasia in Infants: Some MRI Lesions Almost Disappear with Maturation of Myelination

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

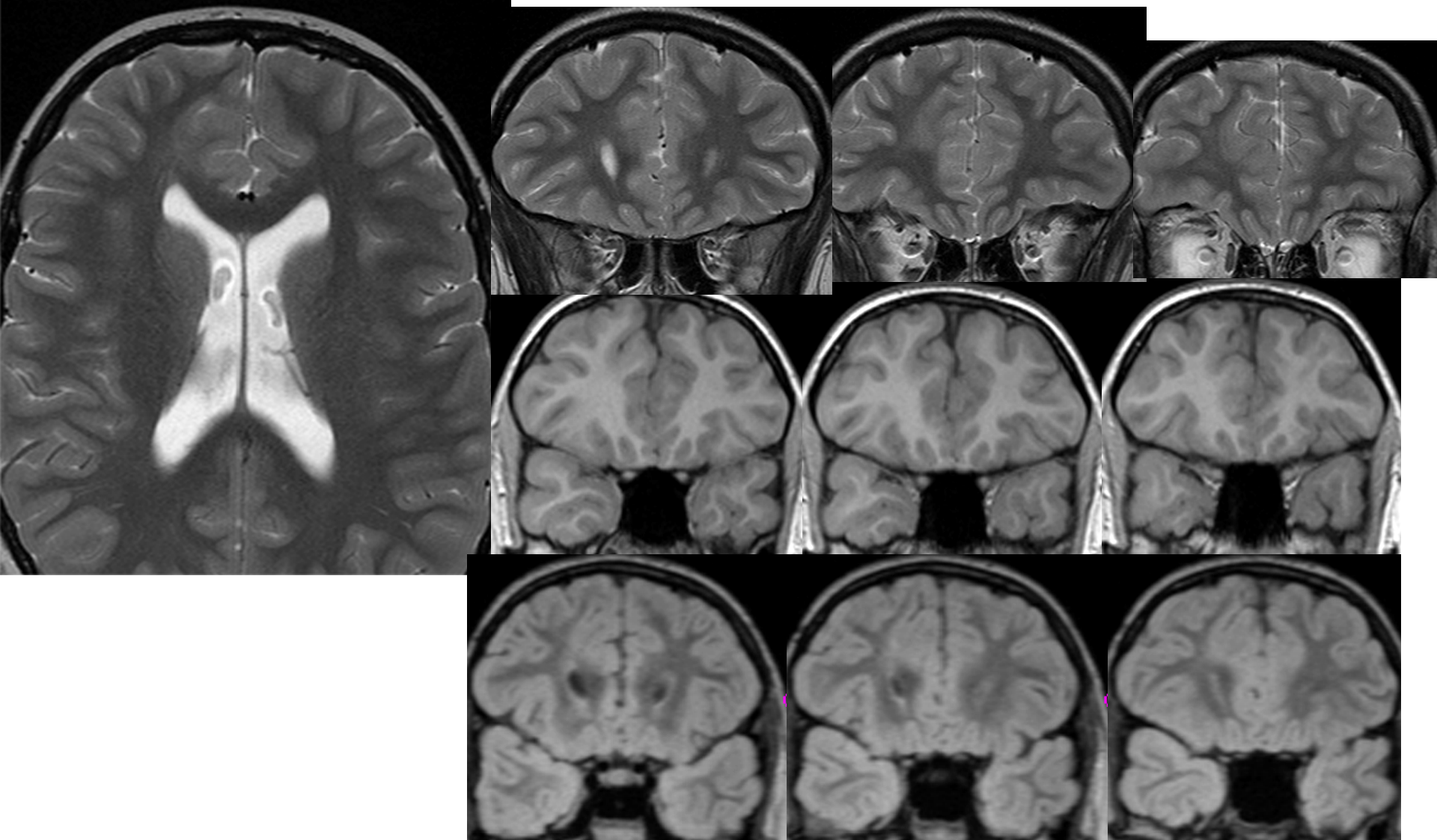
**Institute of Child Health, University College London, United Kingdom; and †Great Ormond Street Hospital for Children, London, United Kingdom*

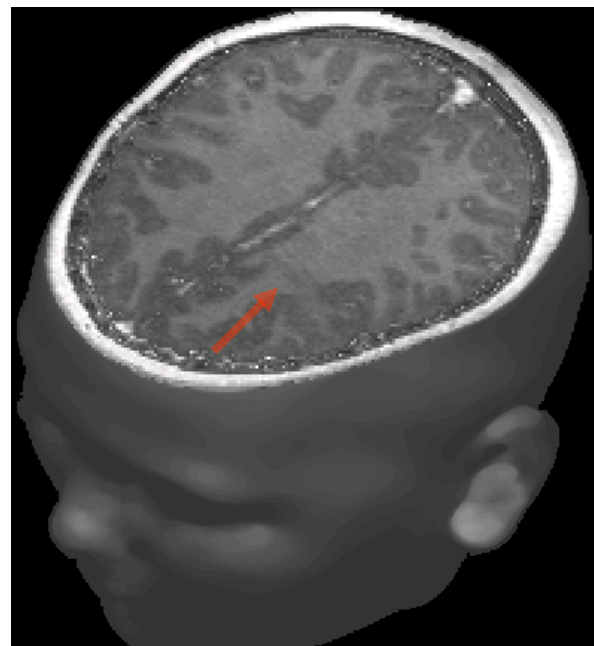
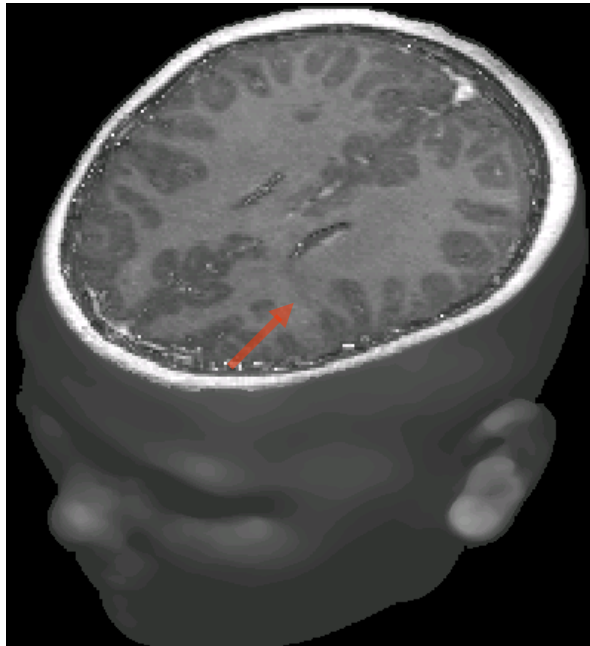
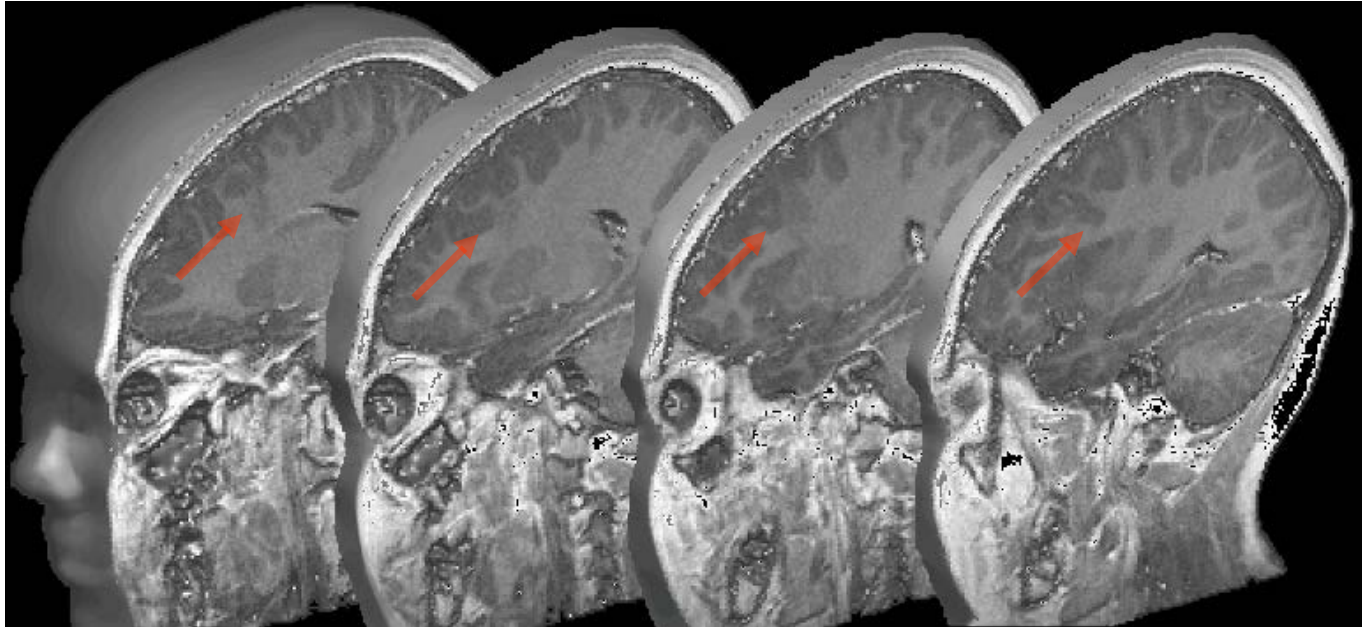


7T



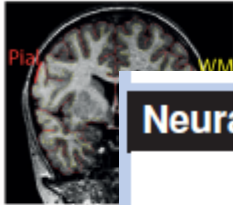
F 12 yr R frontal seizures





Doughnut Method

1. FreeSurfer Reconstruction



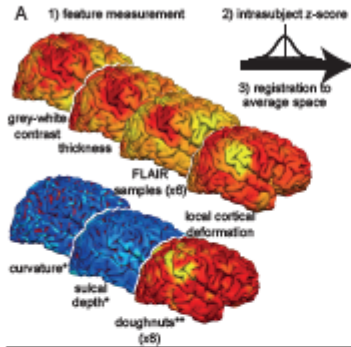
2. Calculation of Cortical Thickness, GM/WM Intensity Contrast & FLAIR Signal Intensity



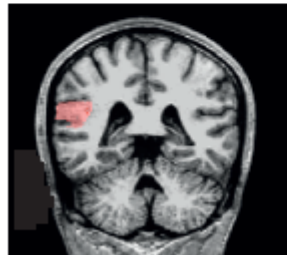
5. Smoothed Doughnut



Neural Network

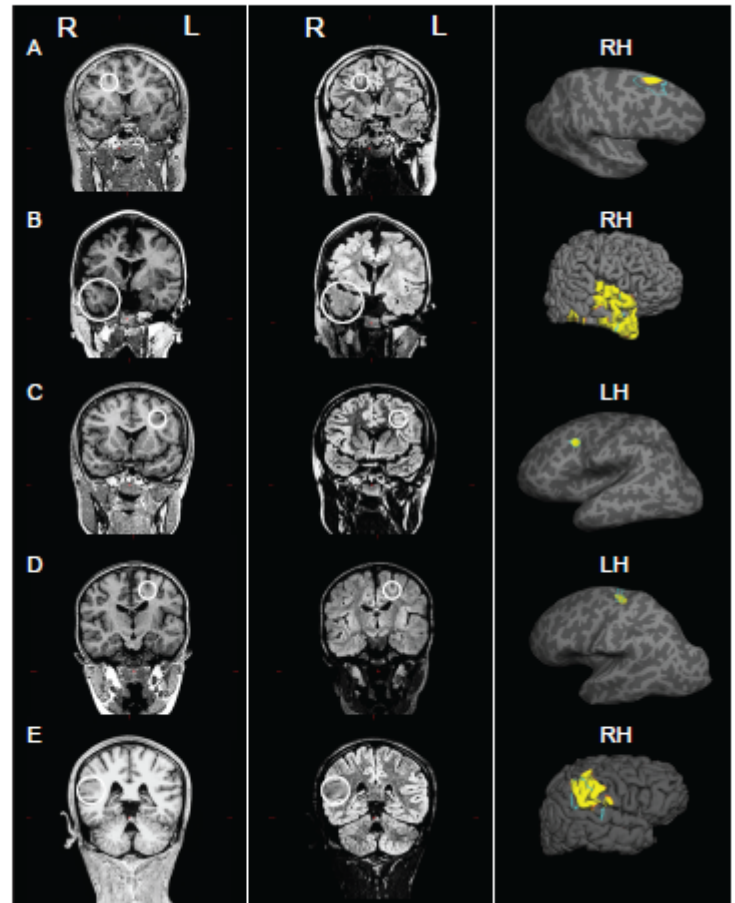


B 1) lesion masks on volumetric T1 and FLAIR 2) masks on template space



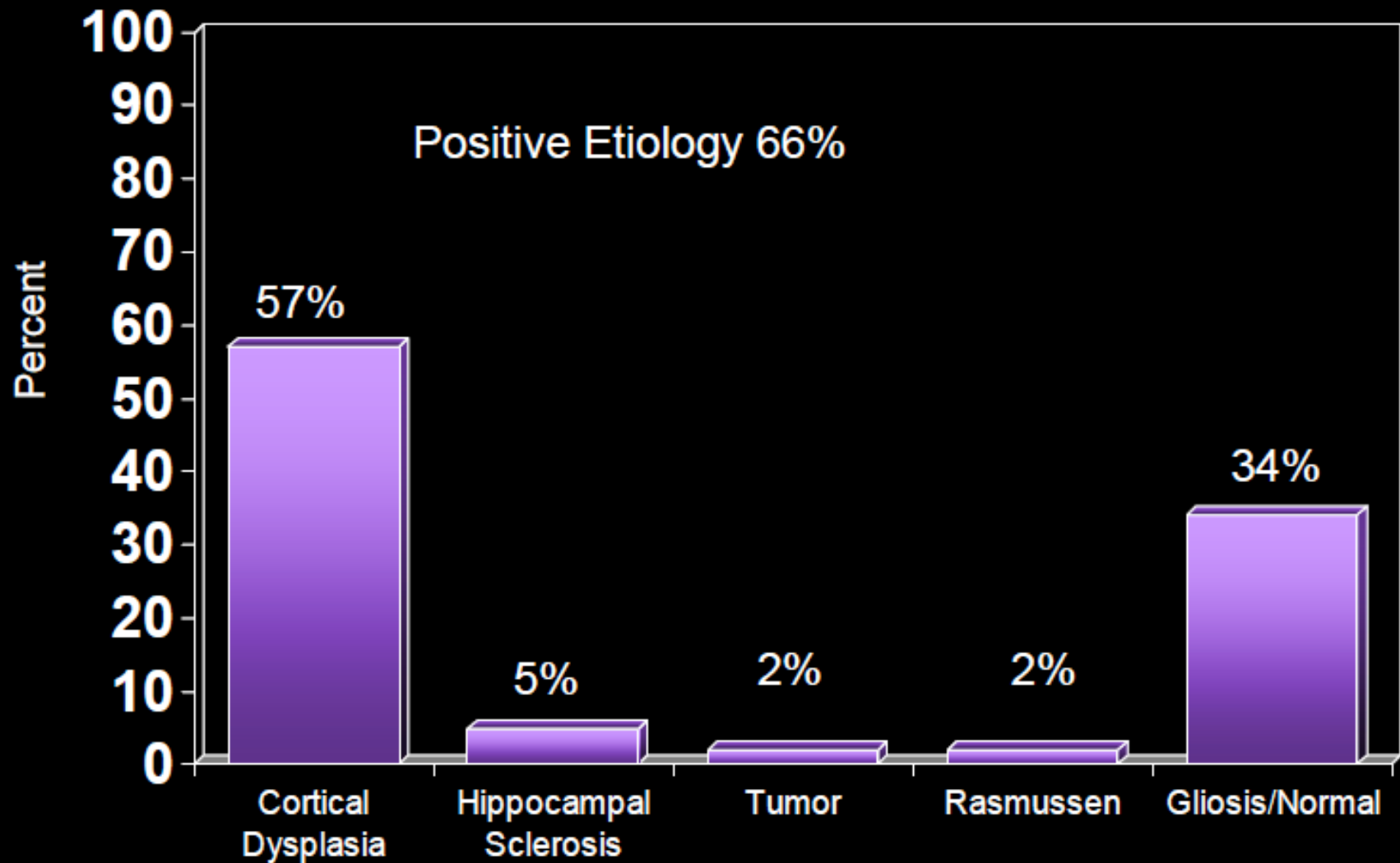
Lesion label

Classifier Results

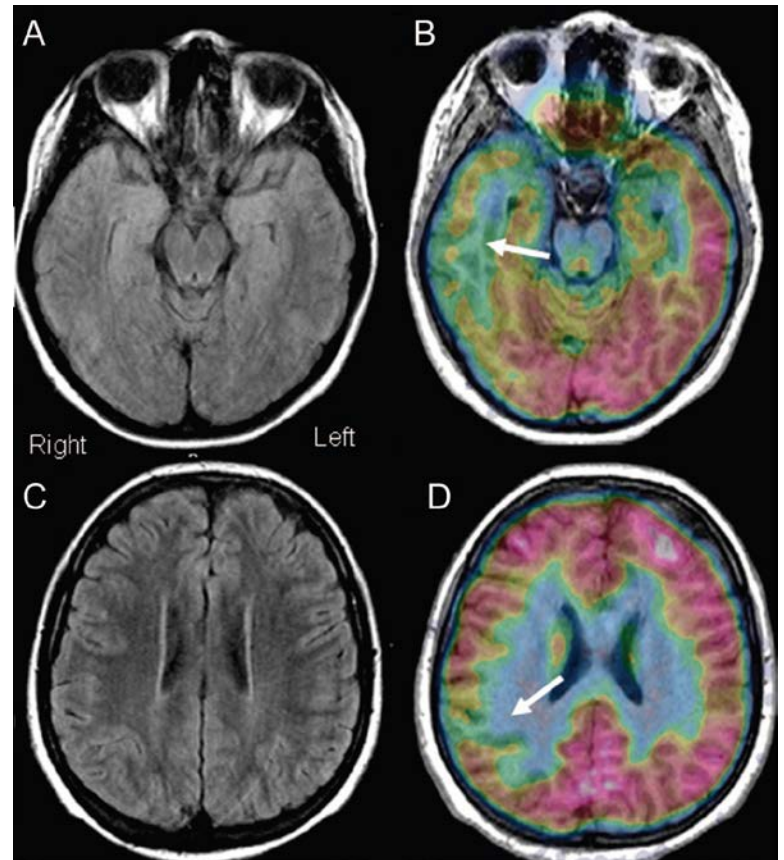
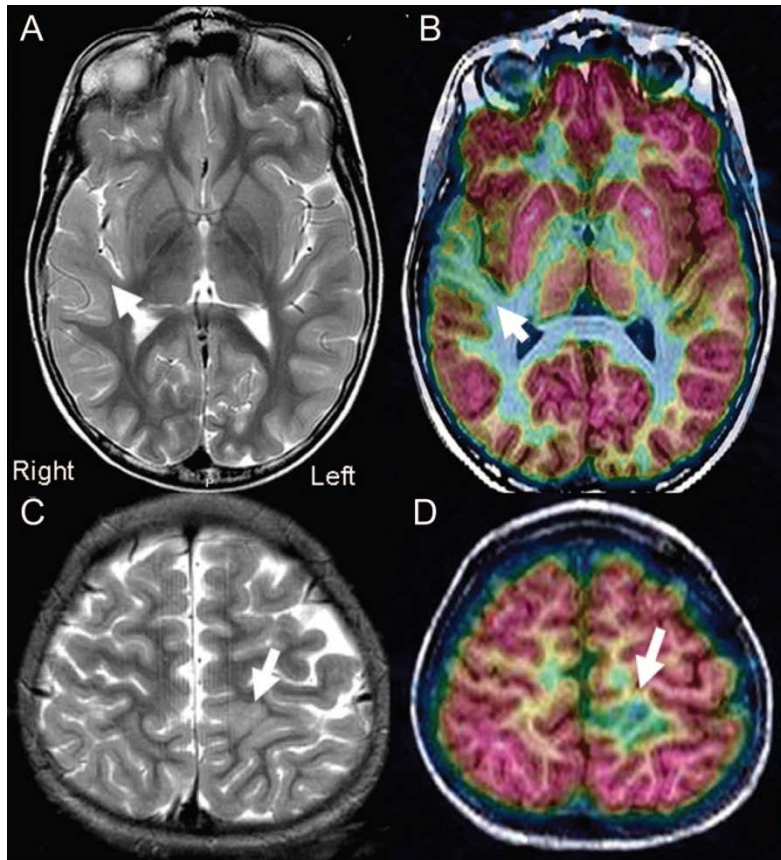


Histopathology in MRI Negative Cases

2004 ILAE Pediatric Outcome Survey (N=100)



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



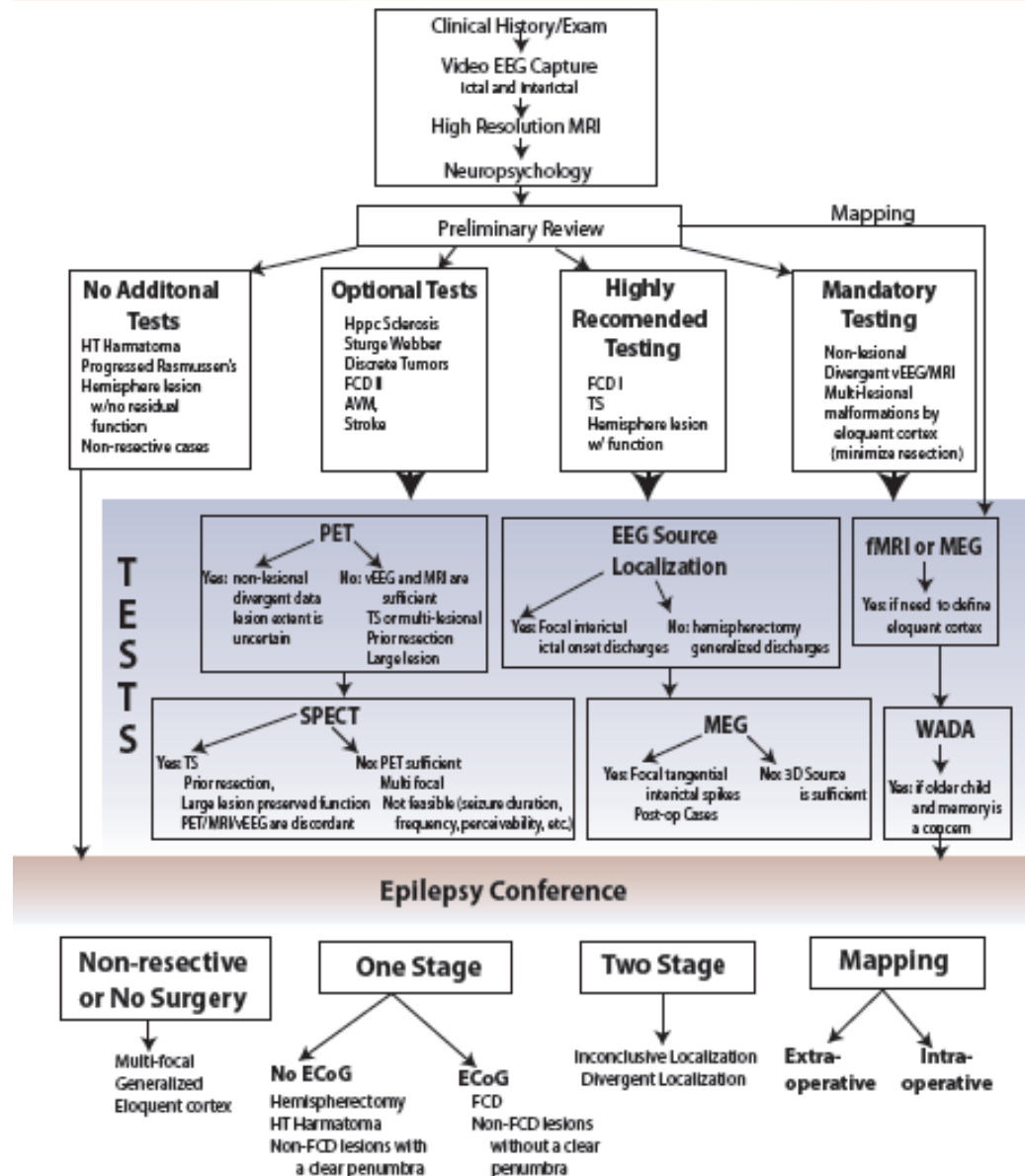
The role of additional investigations

| Cohort | II EEG | Video EEG | MRI | 3D EEG/MEG | PET | SPECT | ECoG | IEM | Comments |
|----------------------------|--------|-----------|-----|------------|-----|-------|------|-----|-----------------------------------|
| Single Lesion | | | | | | | | | |
| <i>Dev Tumors</i> | M* | H | M* | O | O | O | O | O | |
| <i>FCD I</i> | M* | M* | M* | H | H | H | H | H | |
| <i>FCD II</i> | M* | M* | M* | O | O | O | M/H | O | |
| <i>HS</i> | M* | M | M* | O | O | O | O | O | Consider possibility of dual path |
| <i>SWS</i> | M* | M | M* | L | O | O/L | O/L | L | |
| <i>Hyph Hamar</i> | M* | H | M* | L | L | L | L | L | IEM not justified |
| <i>Vascular</i> | M* | M | M* | O | O | O | O | O | |
| Post-infec/Ischemic | M* | M | M* | O | O | O | O | O | Lesions may be bilateral |
| Hemispheric | | | | | | | | | |
| <i>No Function</i> | M* | H | M* | L | L | L | L | L | Possible EEG false lateralization |
| <i>Function ++</i> | M* | M* | M* | H | H | H | H | H | Tailored resection |
| <i>PMG</i> | M* | M* | M* | H | H | O | O | O/H | Tailored resection |
| <i>Rasmussen</i> | 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 |

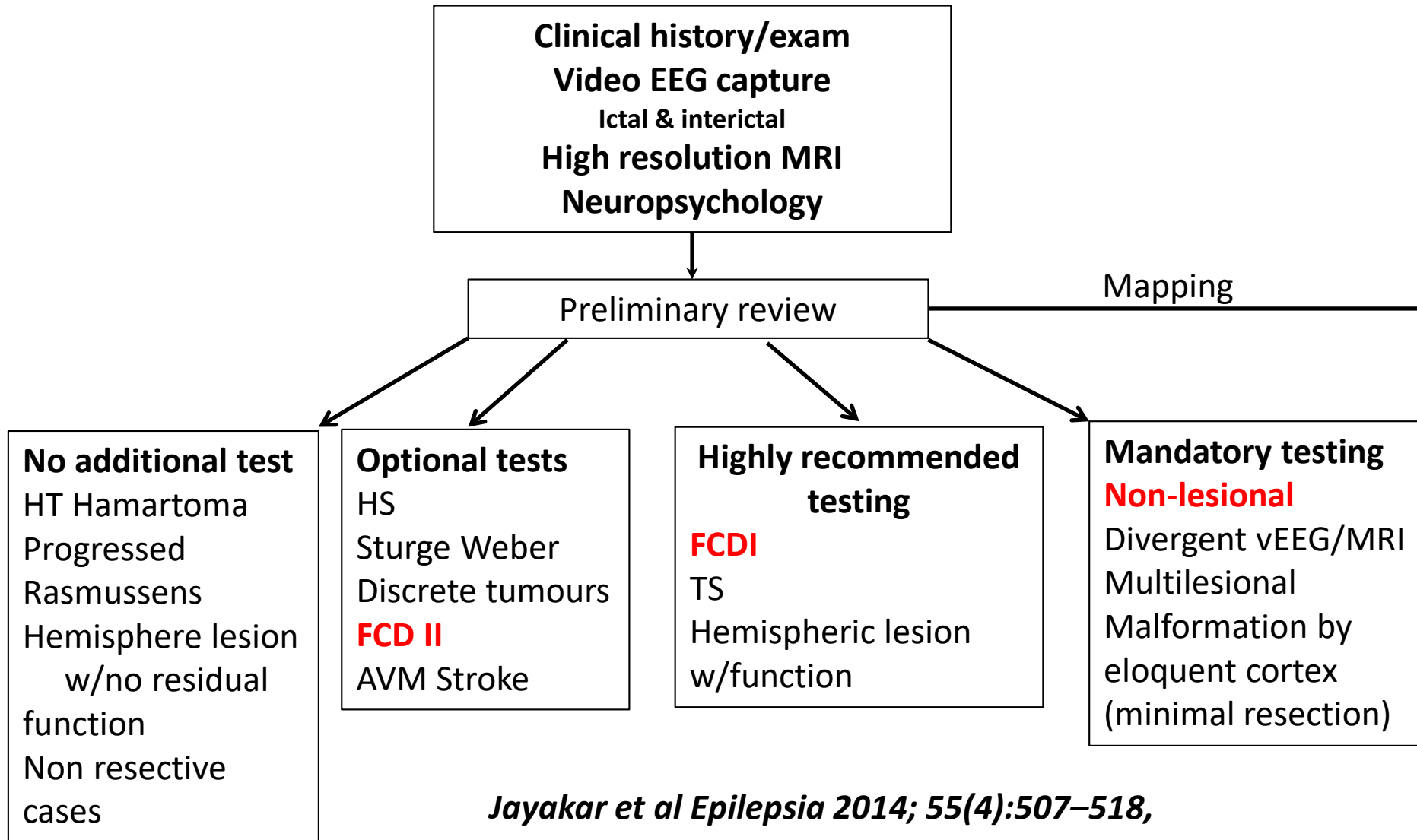
Treatment Paradigm GOSH



Evaluation Protocol



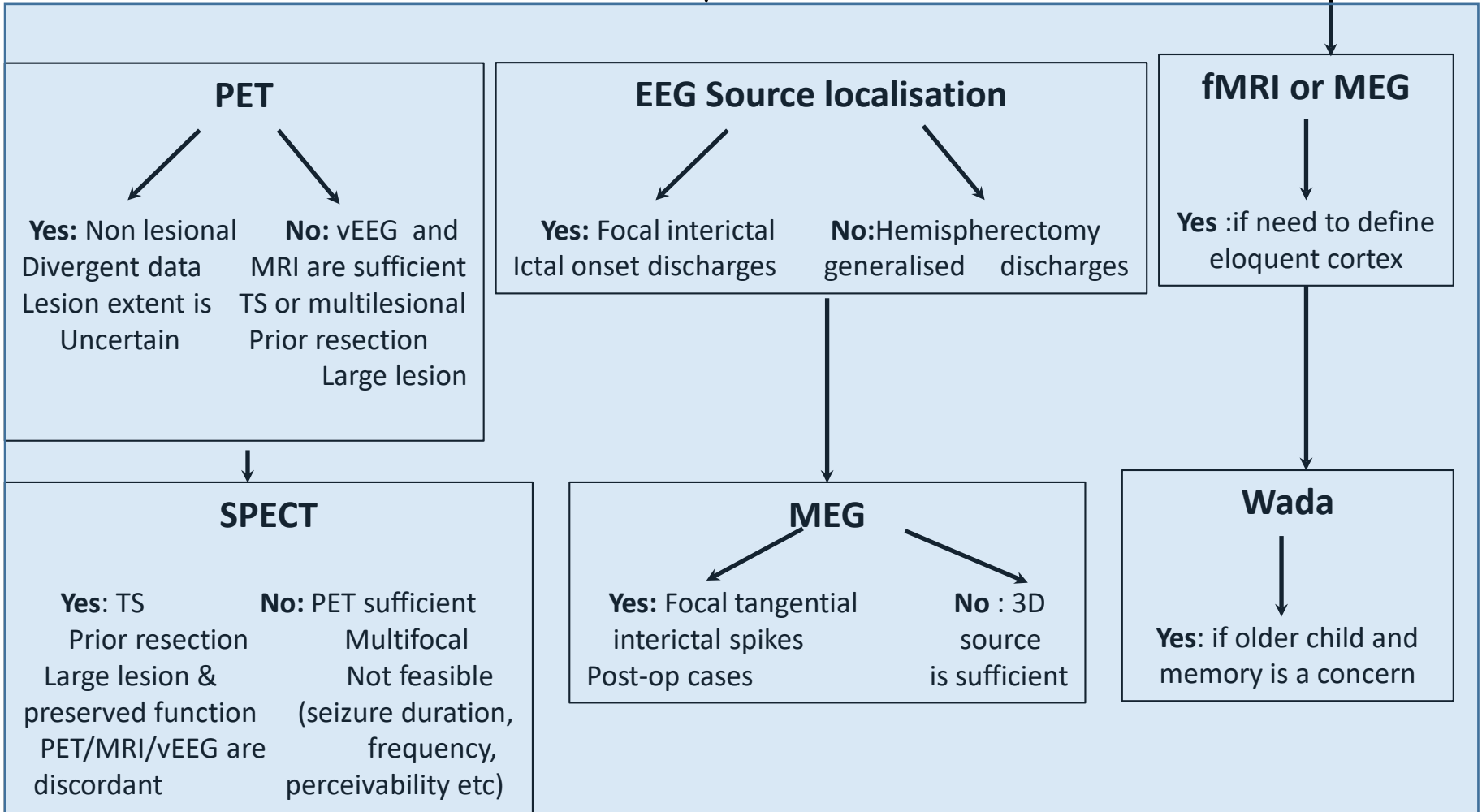
Evaluation Protocol



No additional tests

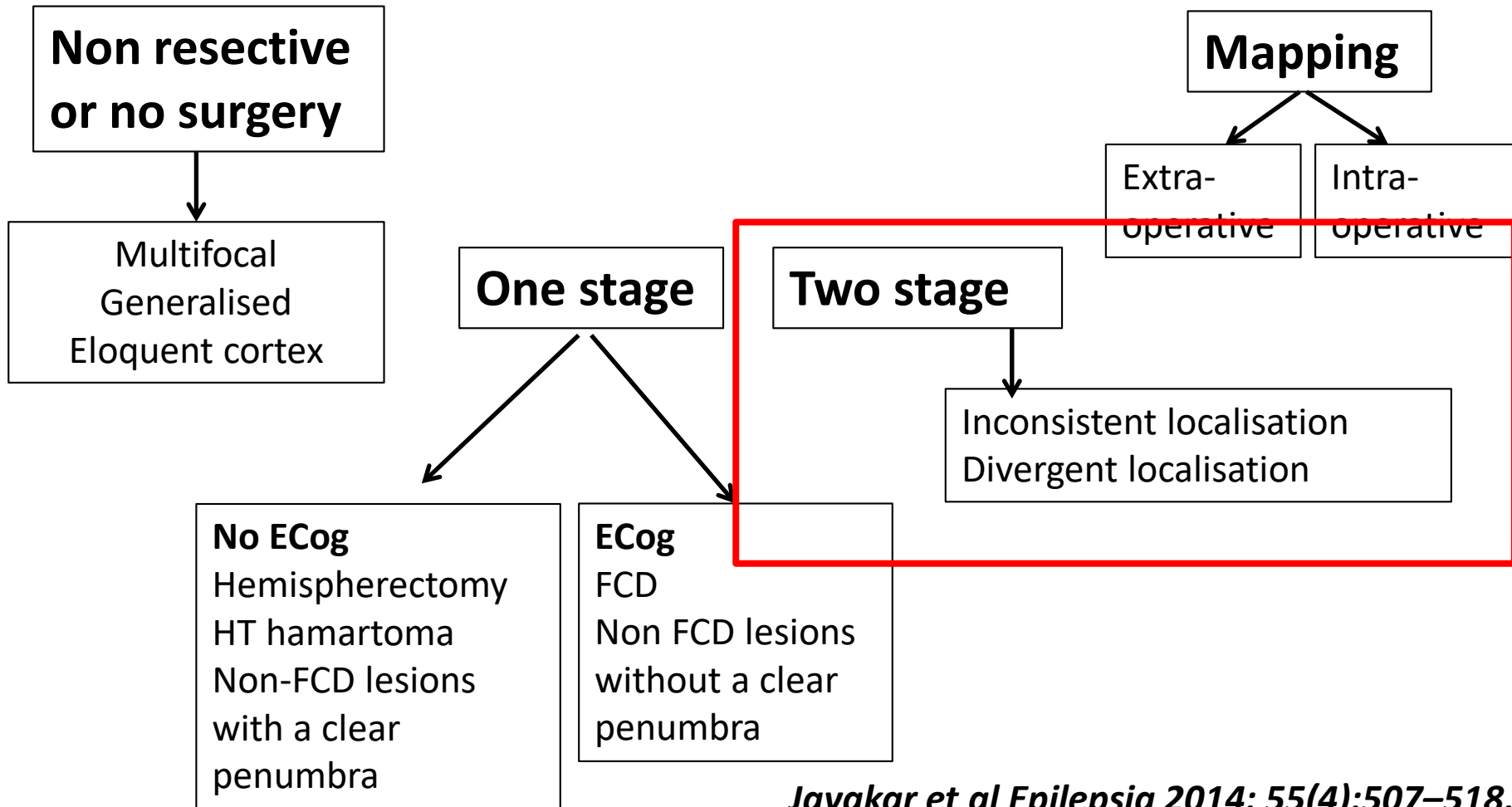
TESTS

Mapping



Epilepsy Conference

Epilepsy Conference

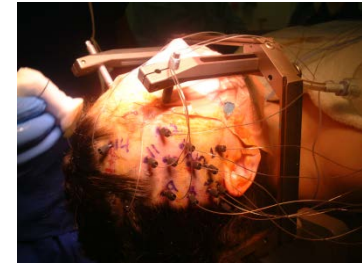
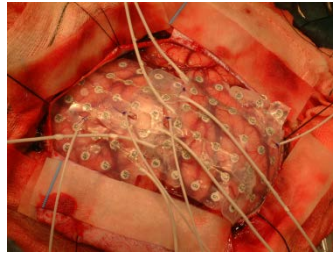


Threshold for invasive evaluation

Extent of resection

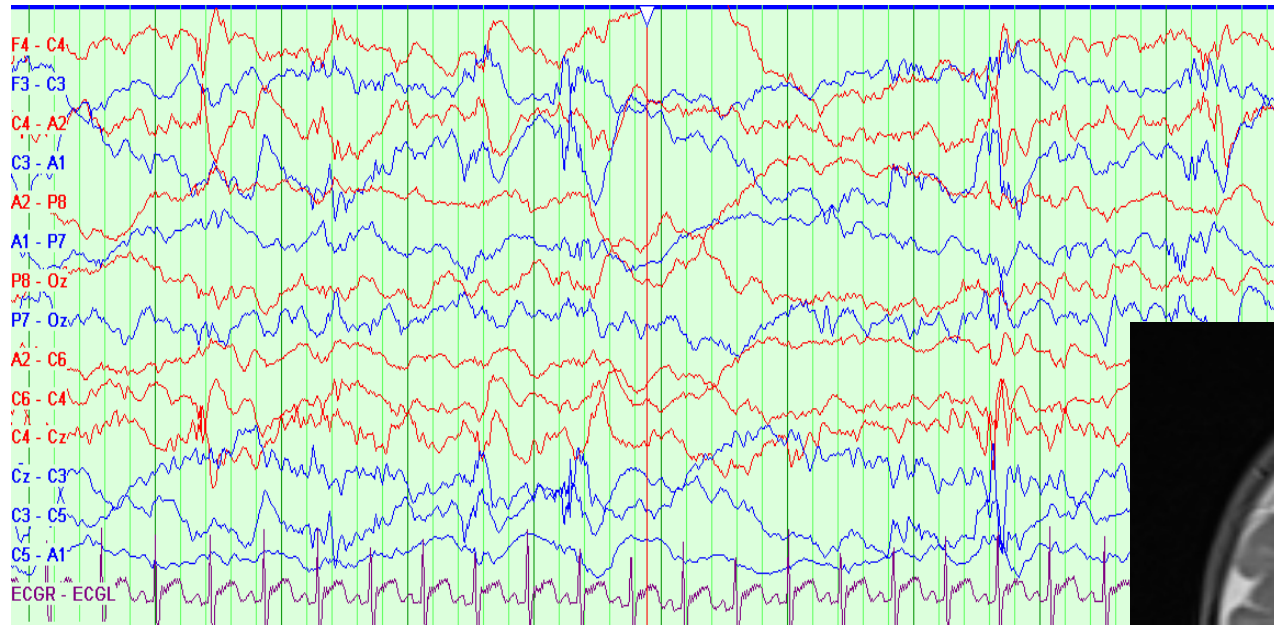
Plasticity

Choosing an invasive strategy

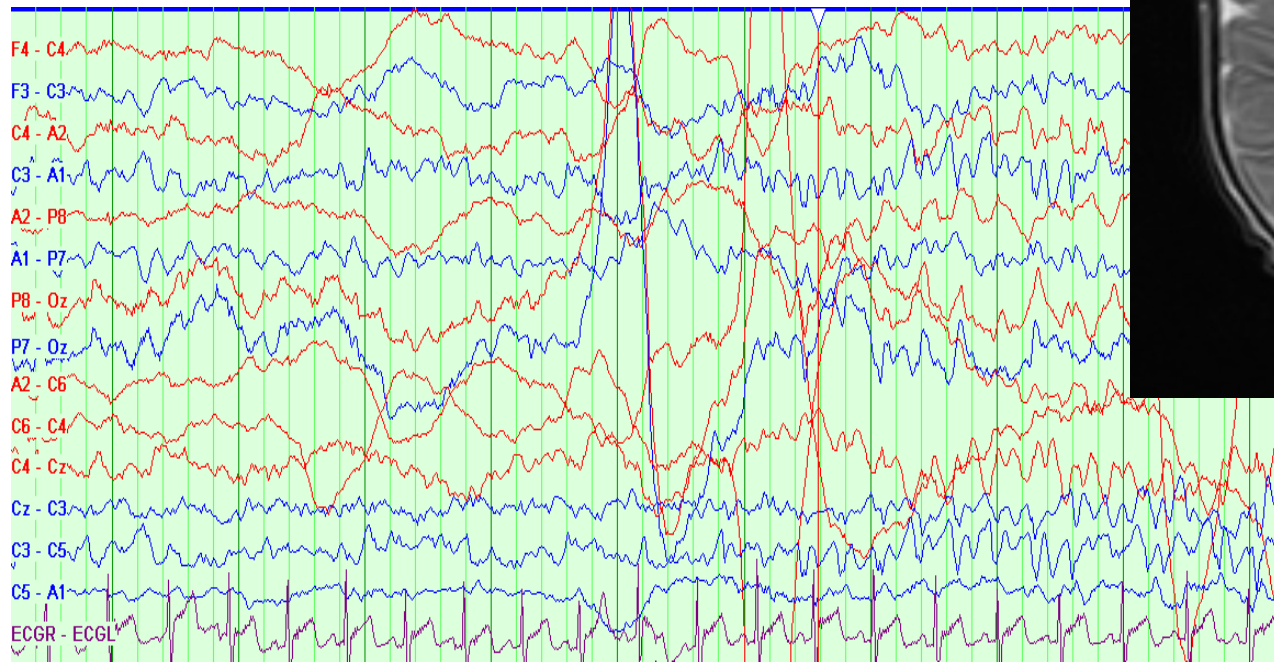
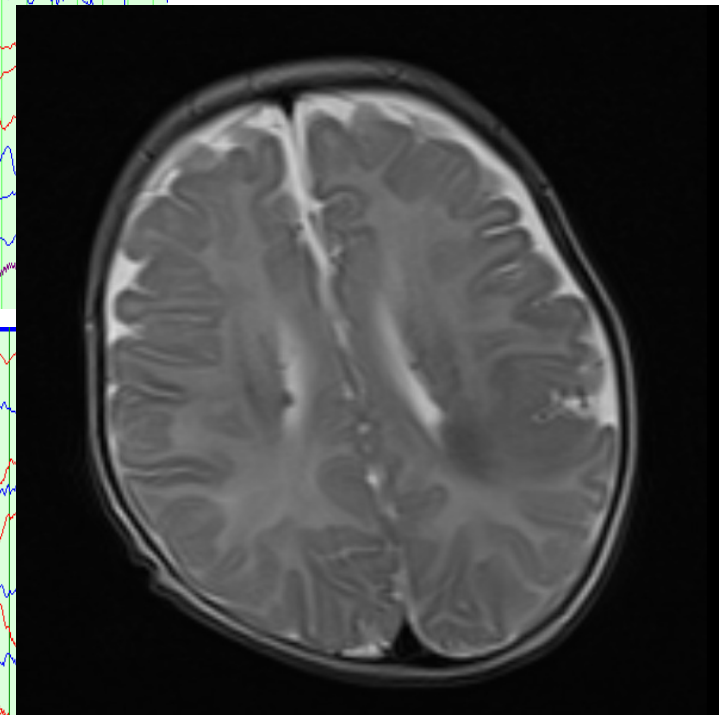


| | SUB –DURAL GRID | sEEG |
|---|-----------------|------|
| MRI negative | ✗ | ✓ |
| Multiple lesions | ✓ | ✓✓ |
| Deep structures involved | ✗ | ✓ |
| Defining limits of cortical malformations | ✓ | ✗ |
| Functional mapping | ✓ | ✗ |
| Morbidity | ✗ | ✓✓ |

- **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**



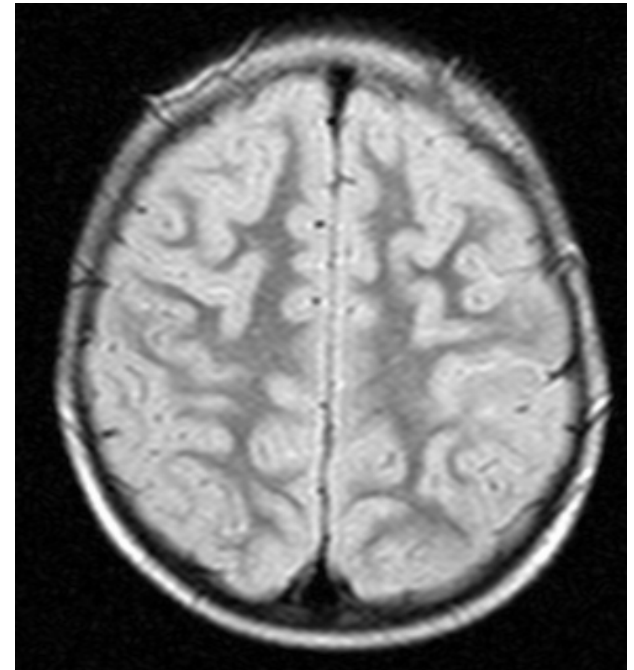
Interictal



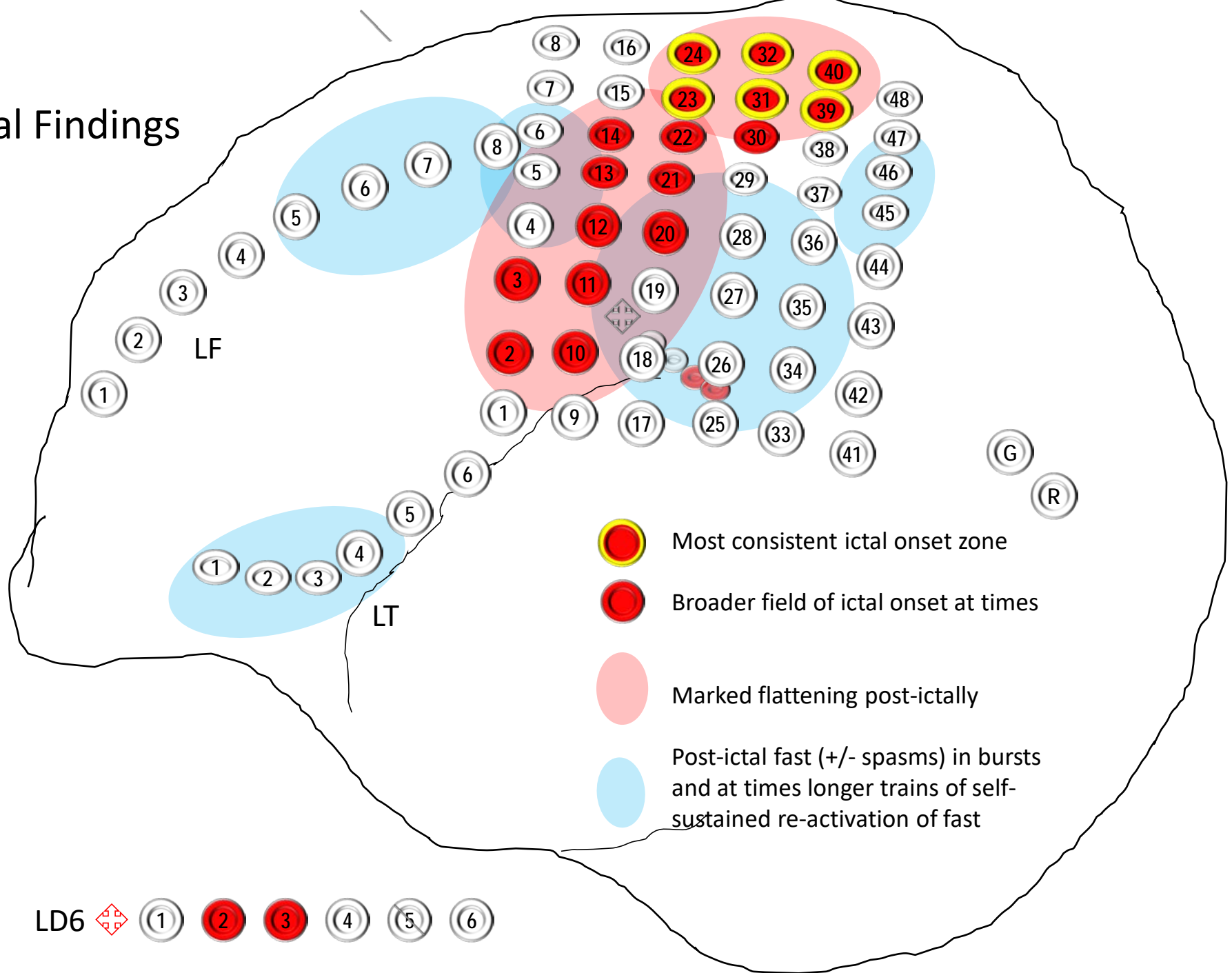
Ictal

- **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**

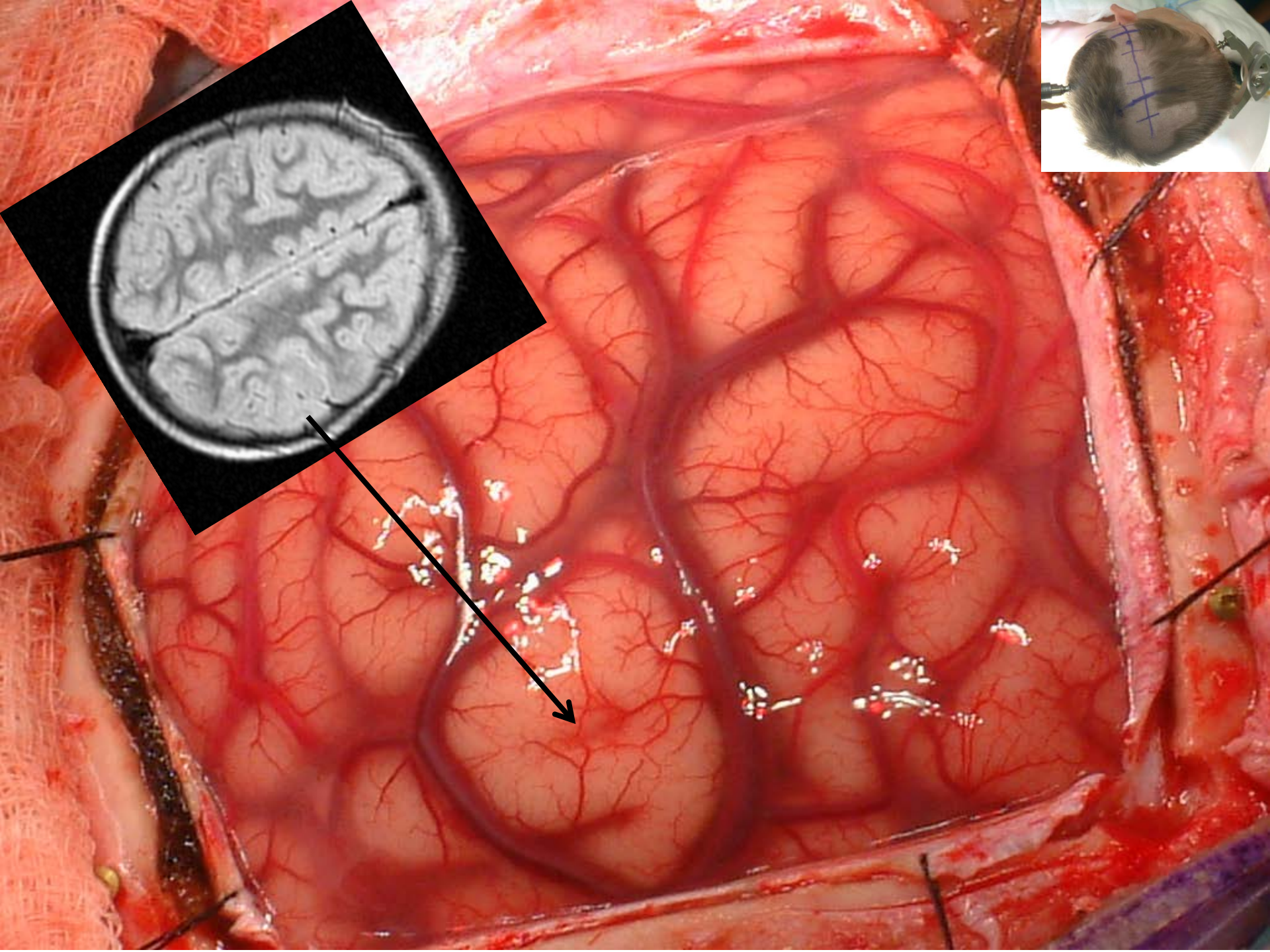
- **Continued seizures; cognitively low average but days where less interactive, poor oral intake and drooling**



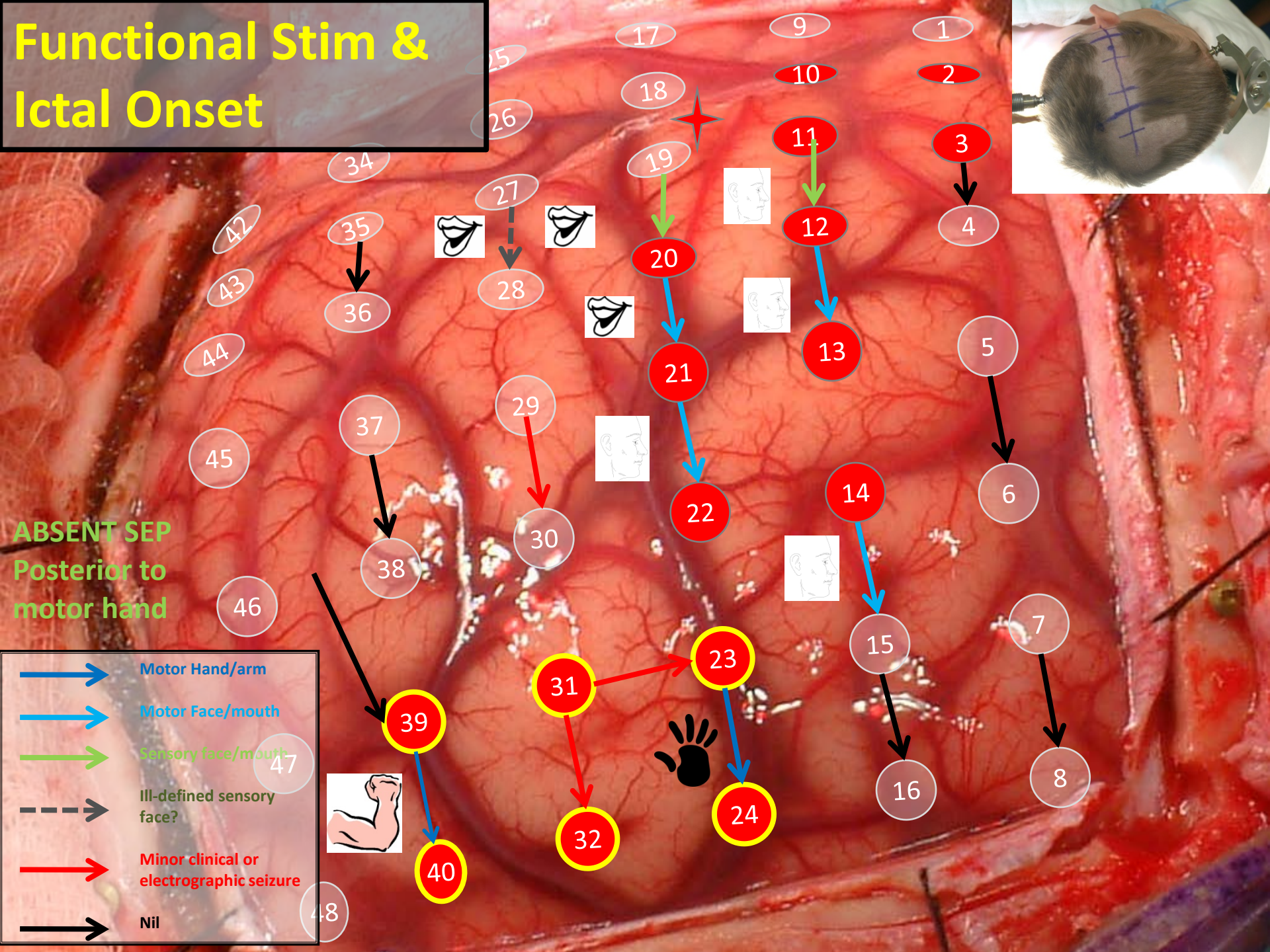
Ictal Findings



LD6       



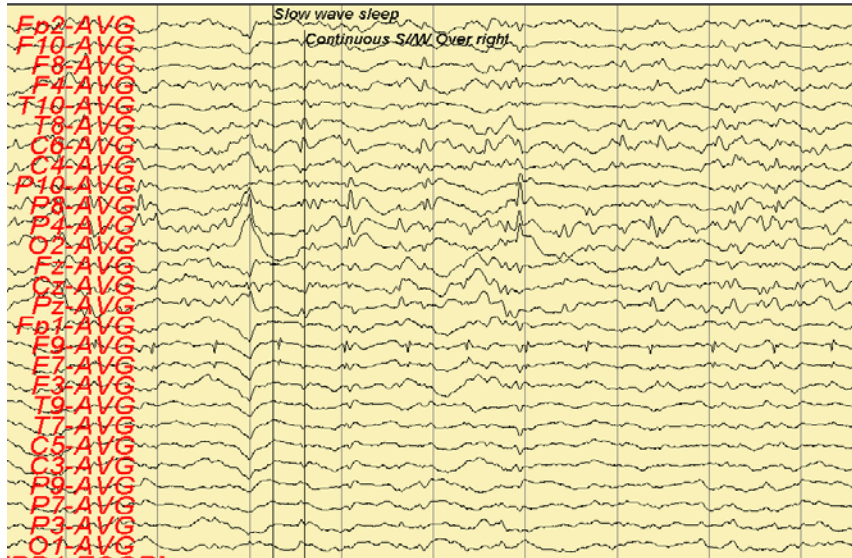
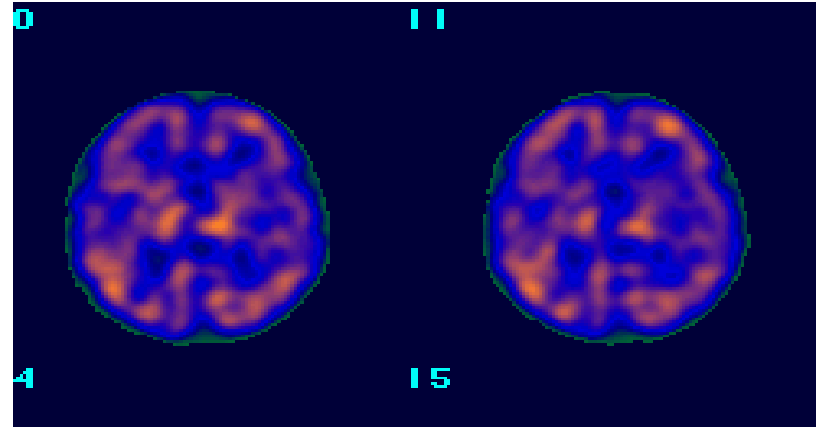
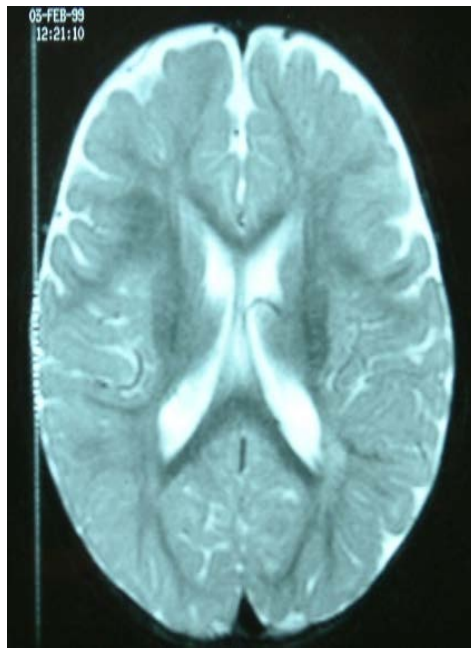
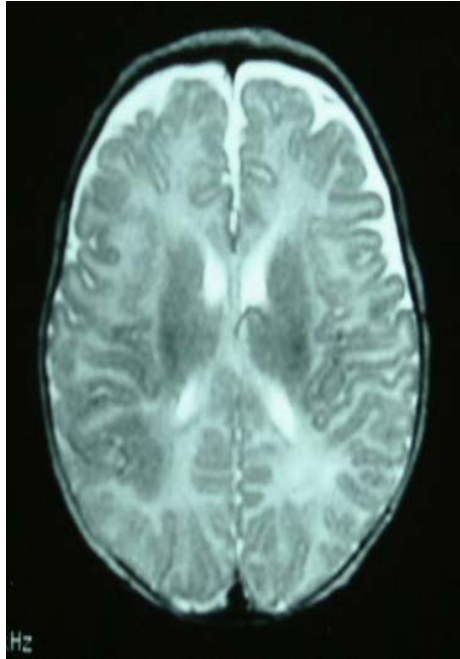
Functional Stim & Ictal Onset

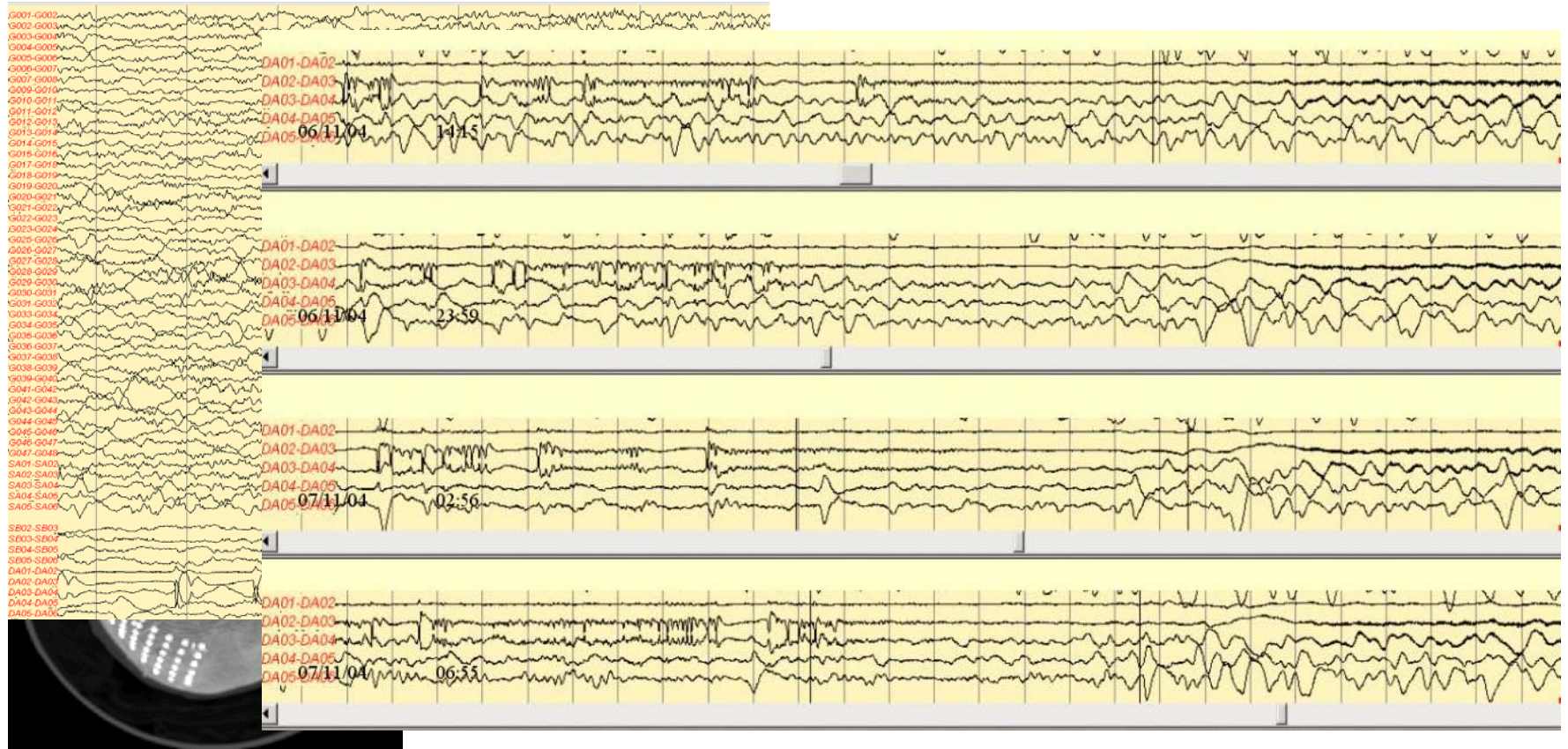
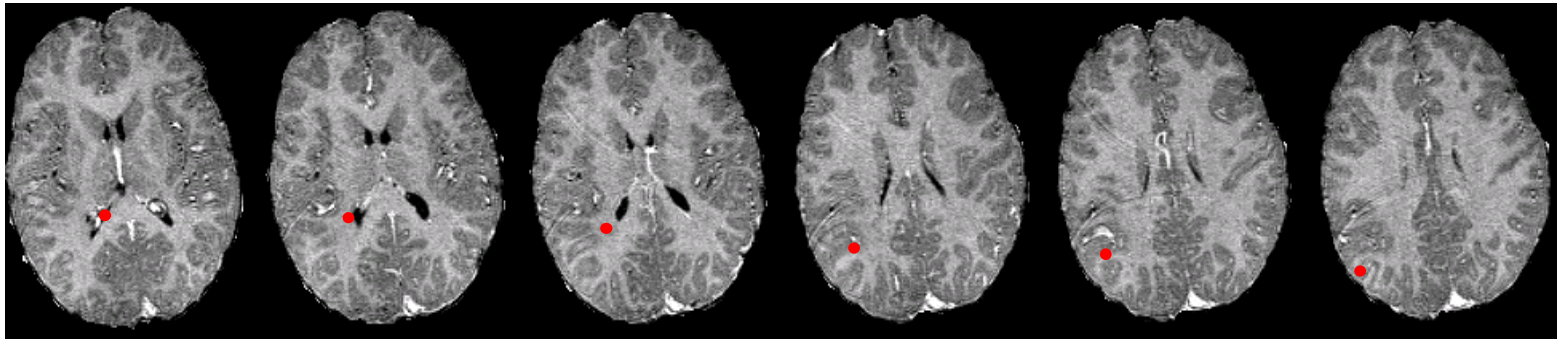


ABSENT SEP
Posterior to
motor hand

| | |
|--|--|
| | Motor Hand/arm |
| | Motor Face/mouth |
| | Sensory face/mouth |
| | Ill-defined sensory face? |
| | Minor clinical or electrographic seizure |
| | Nil |

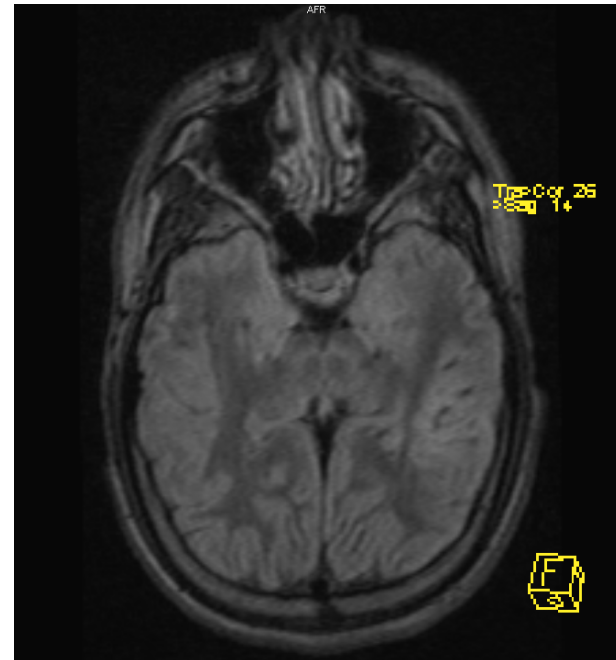
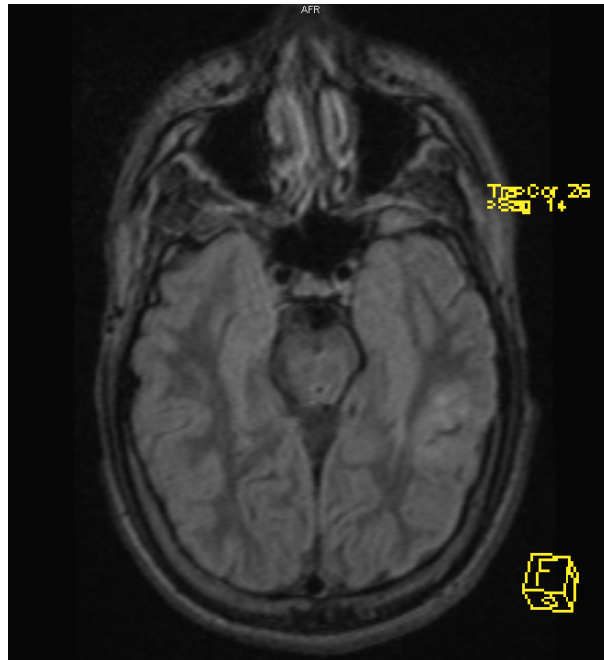
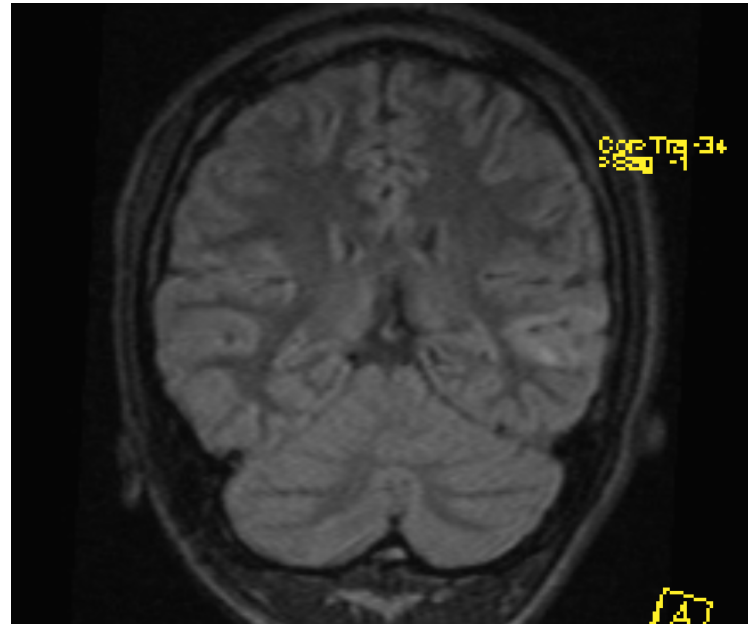






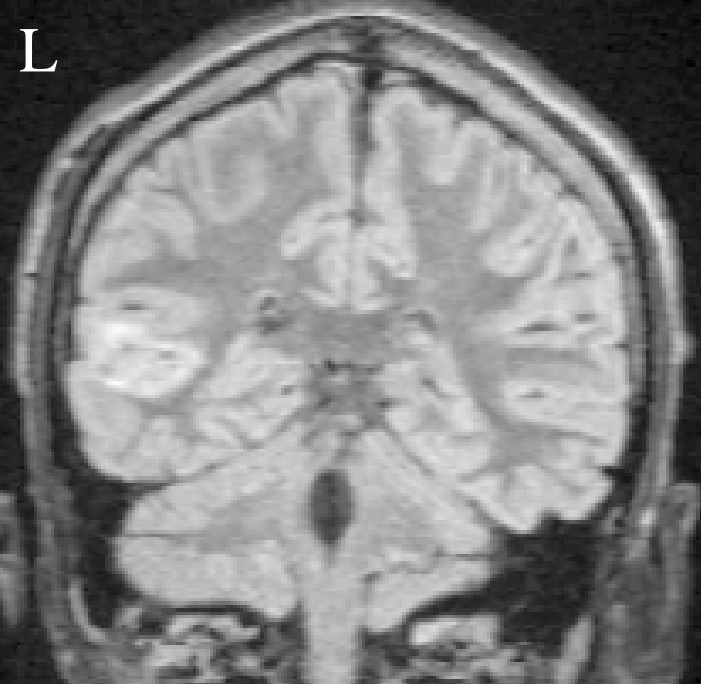
14 yr old boy

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

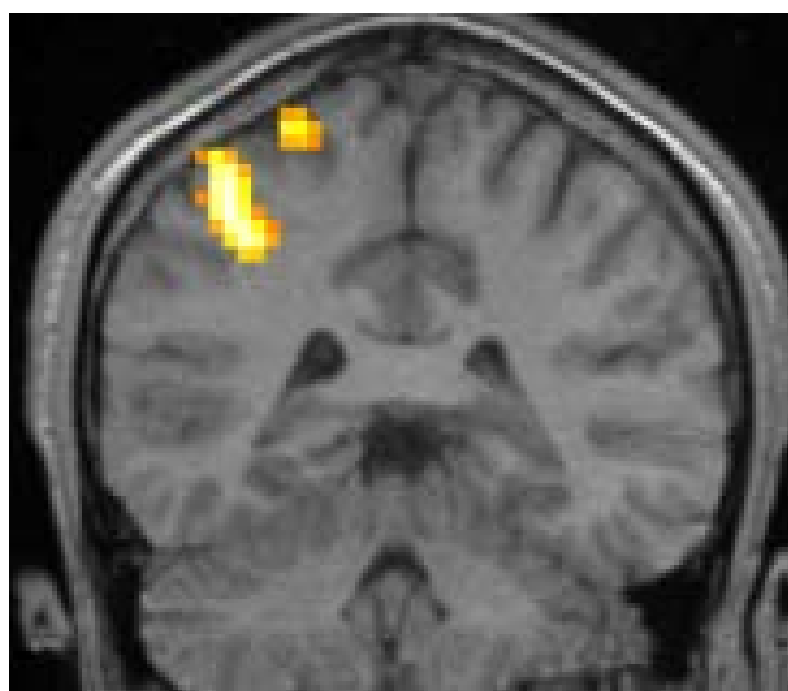
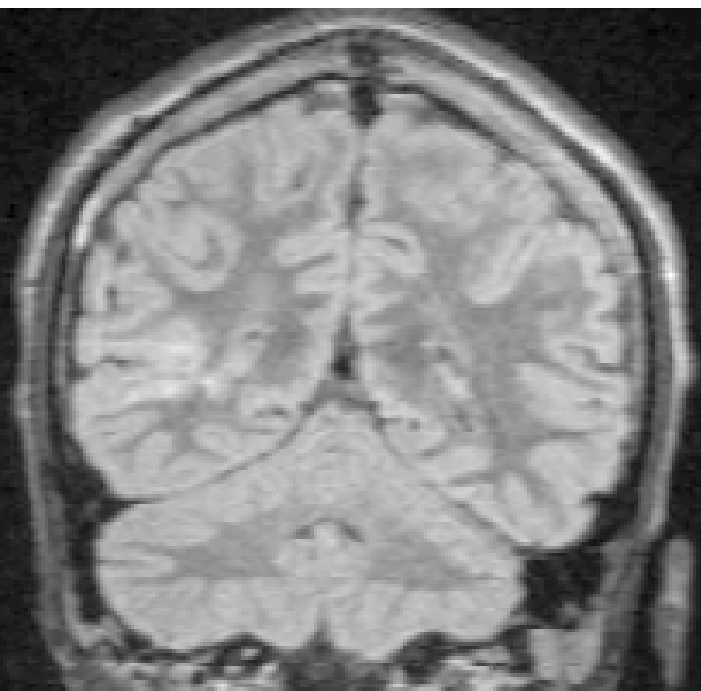
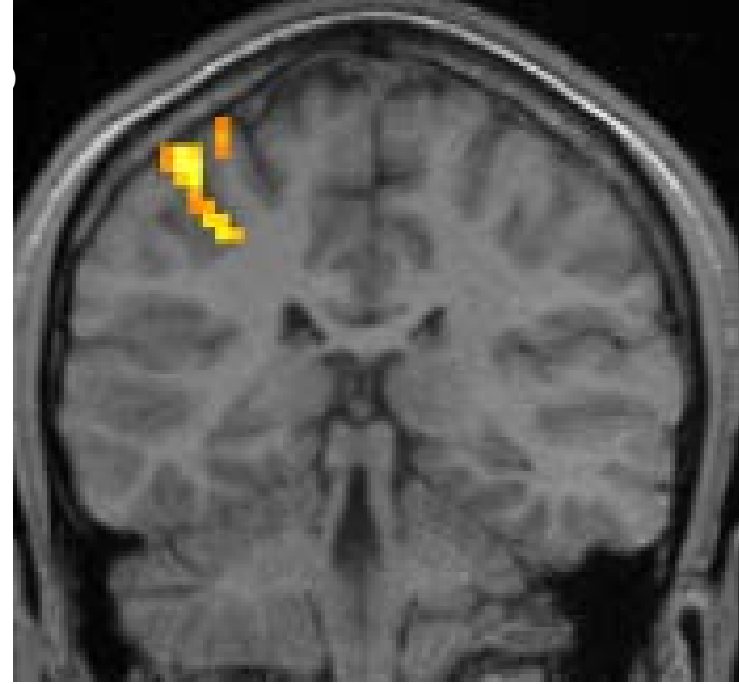


Surface EEG

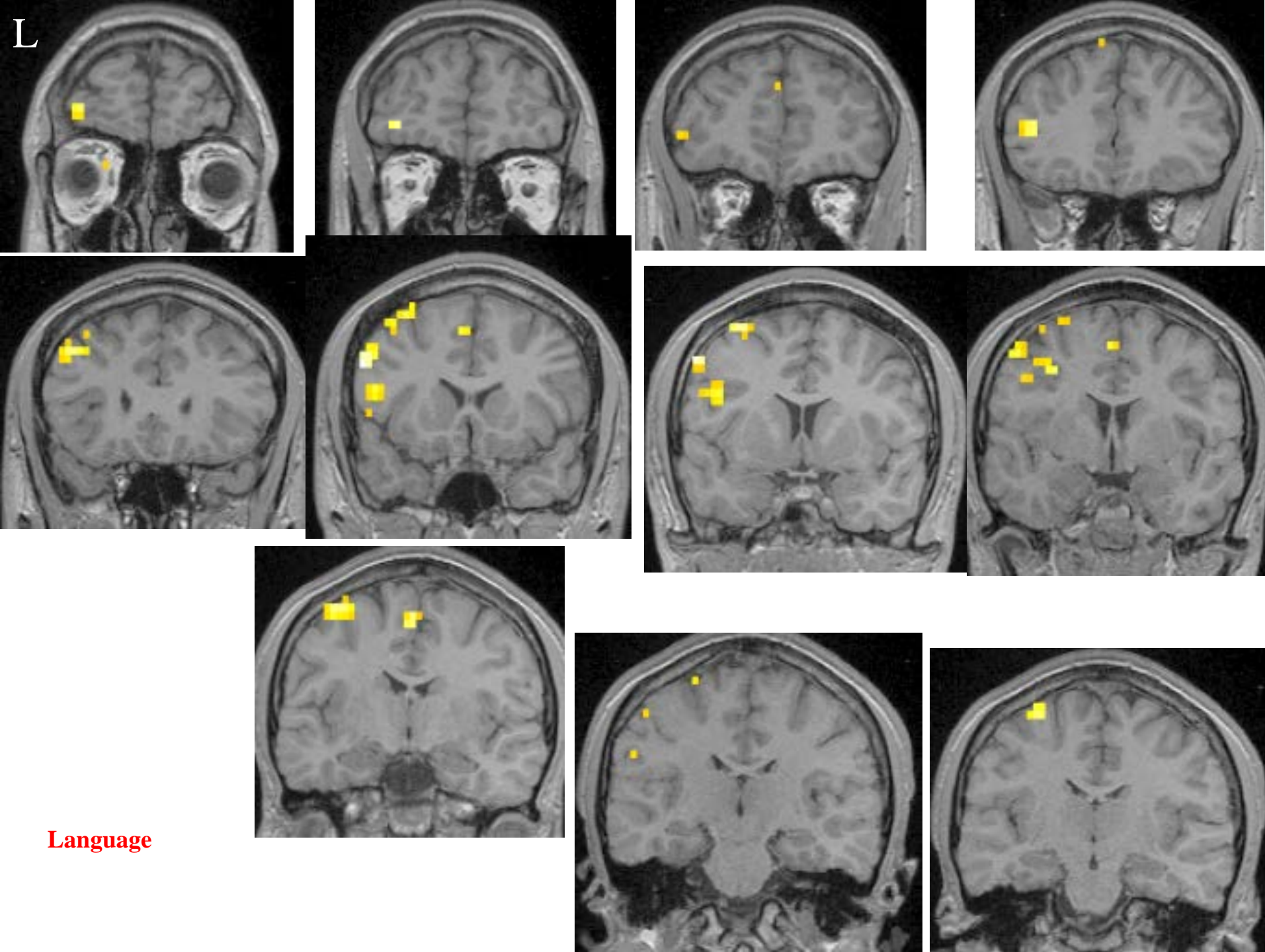
- **Mild background slowing**
- **Occ discharges over the left temporal region in sleep**
- **Three similar seizures; EEG changes lagged behind clinical change**
- **Attenuation at onset in two & right fronto temporal discharges late in event in third**



Right hand motor



L



Language

No lesion?

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

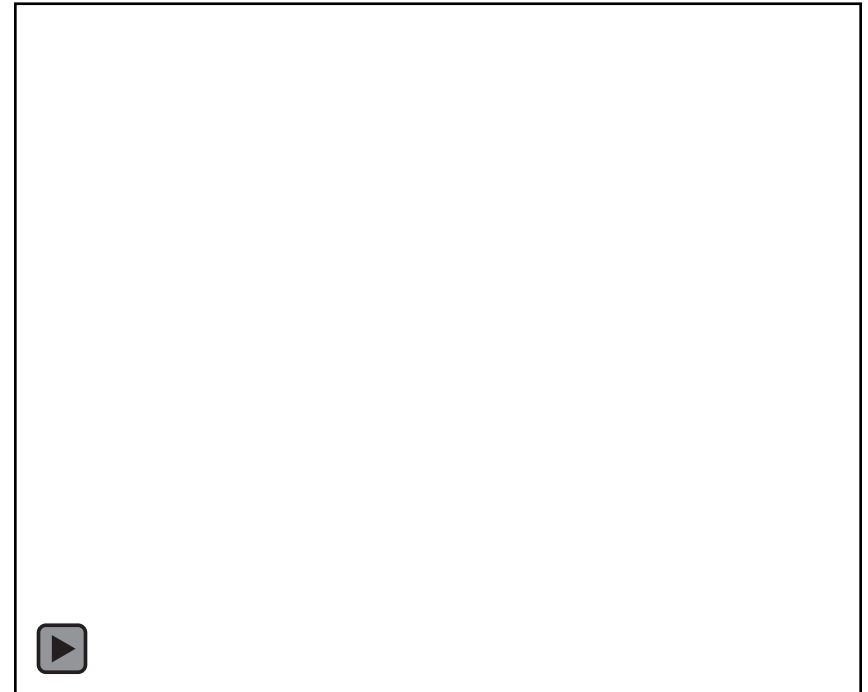
- Seizures fairly stereotypic

Short events

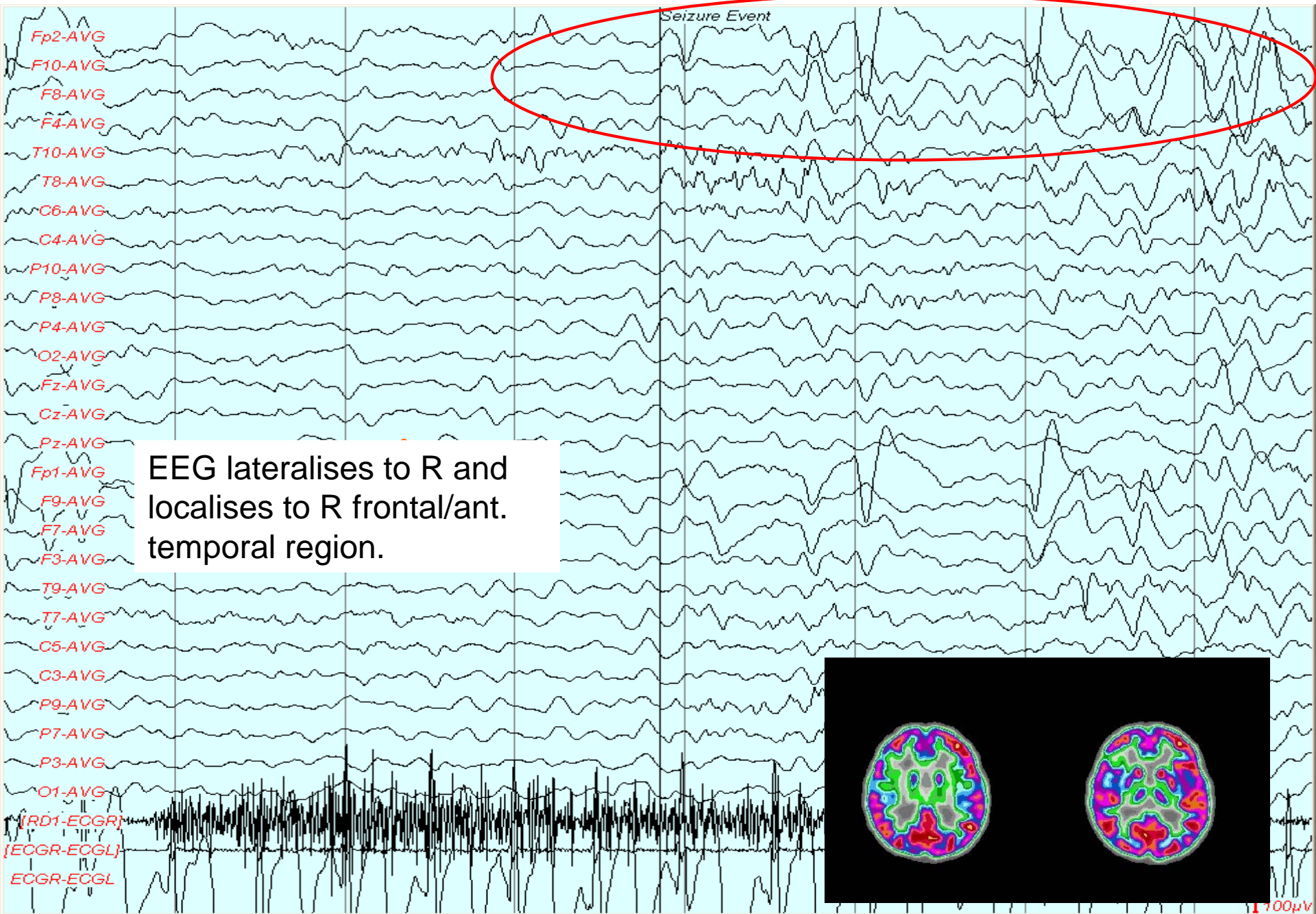
- Behavioural arrest
- Leans to side and grabs parents

Long events

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

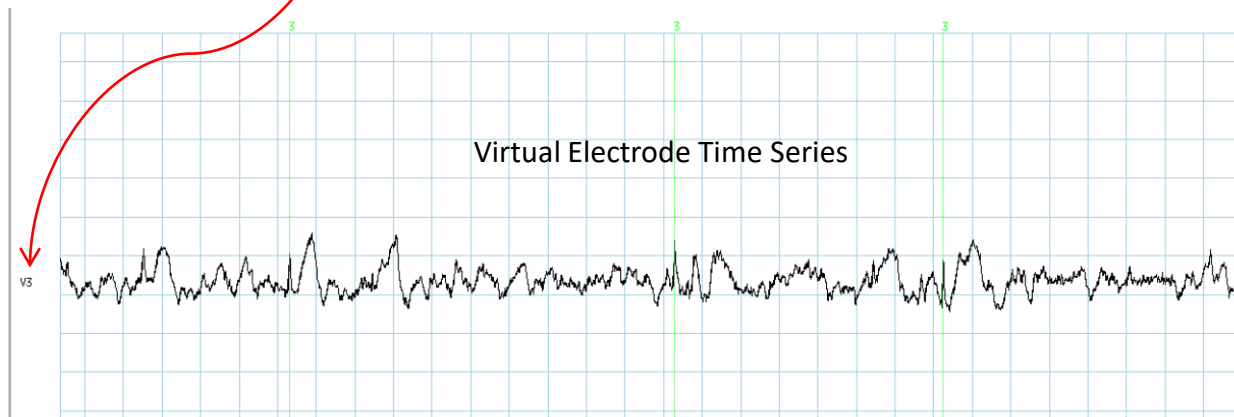
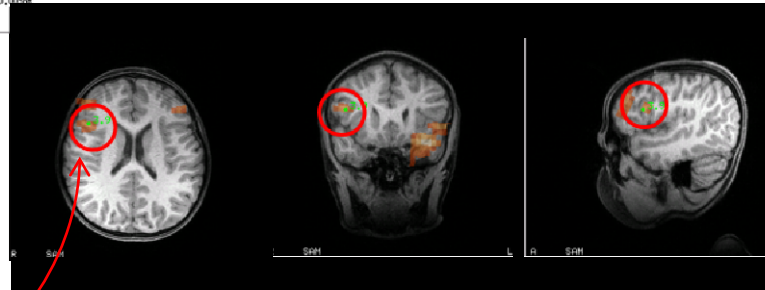
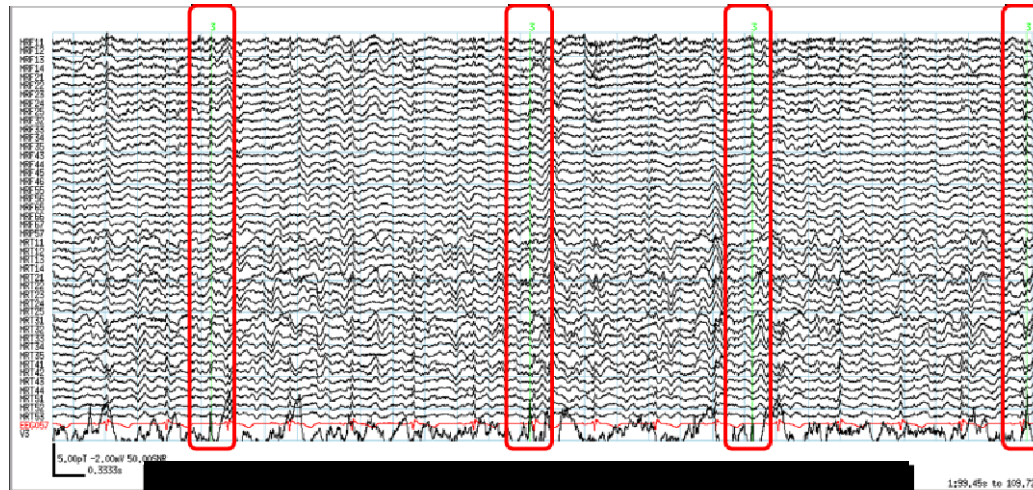


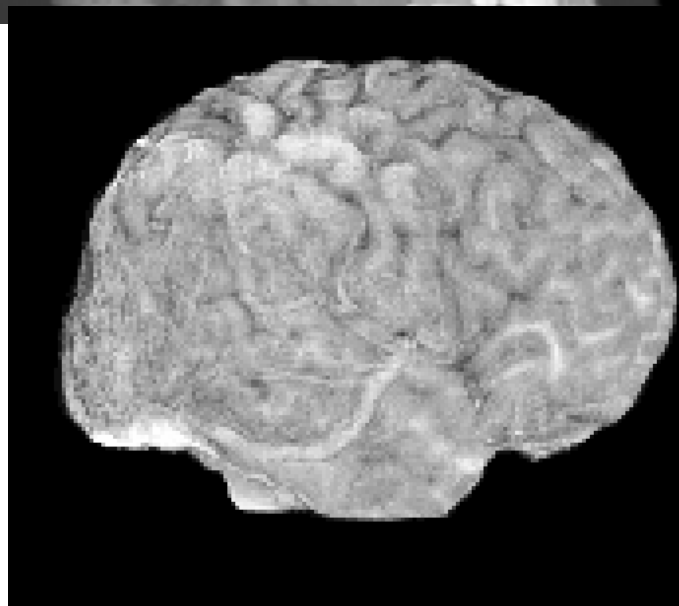
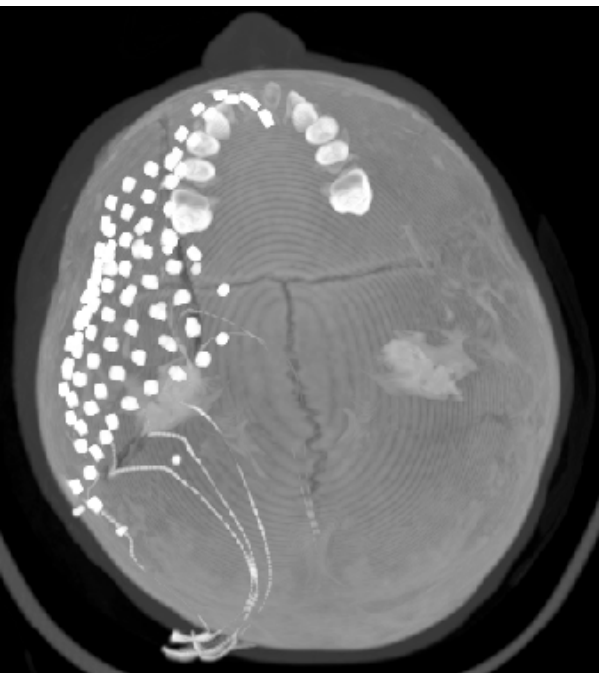
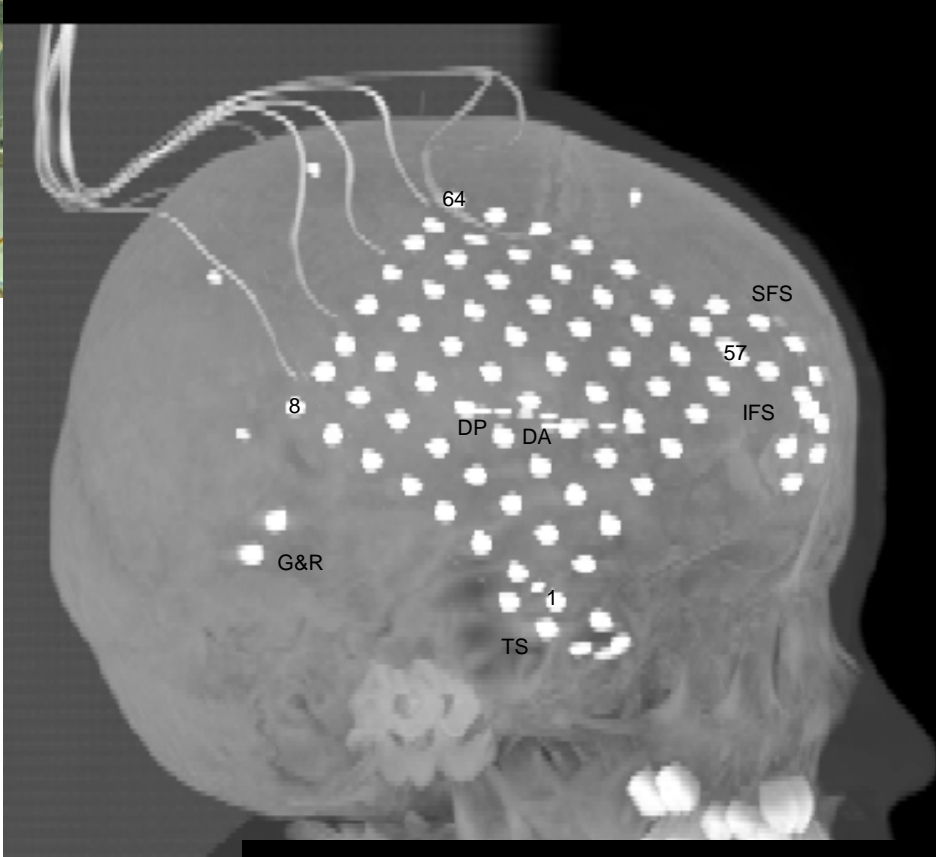
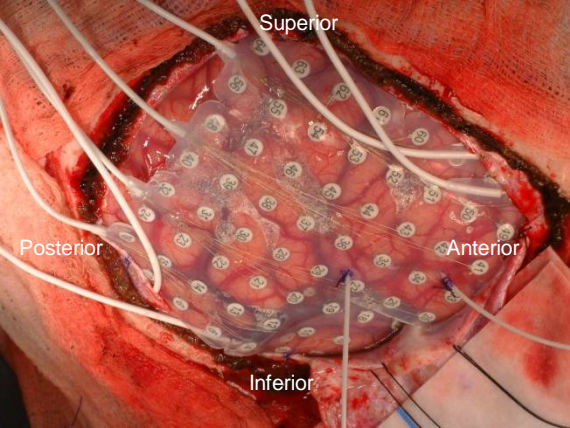
Onset of seizure -slow activity over Right frontal and Ant. Temporal region



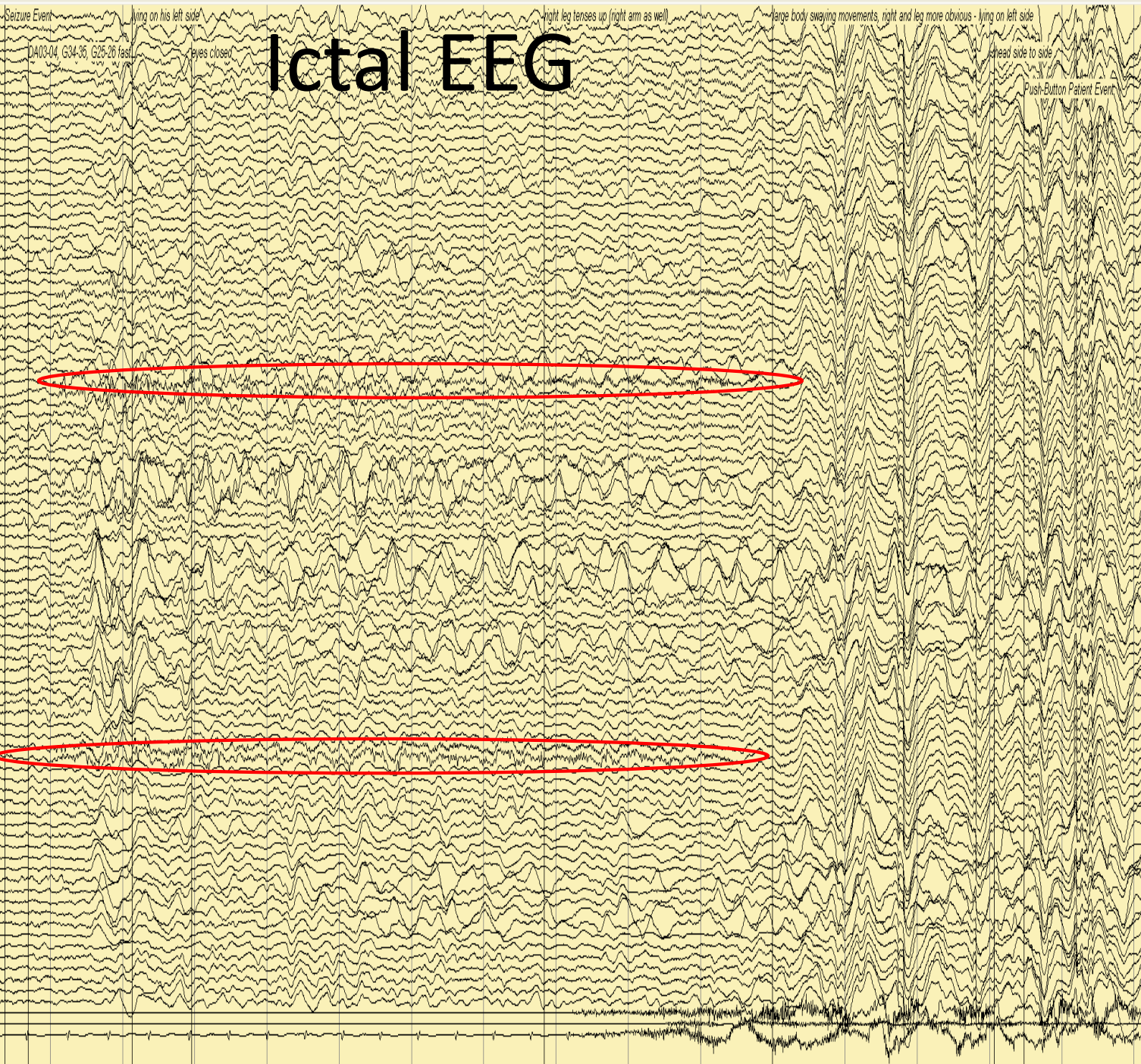
EEG lateralises to R and localises to R frontal/ant. temporal region.

Magnetoencephalography

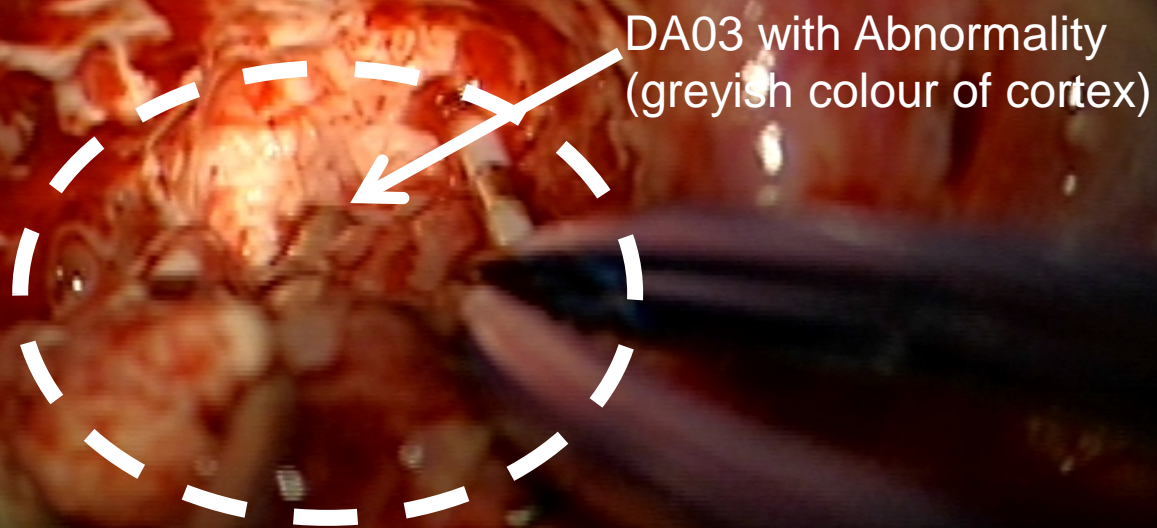


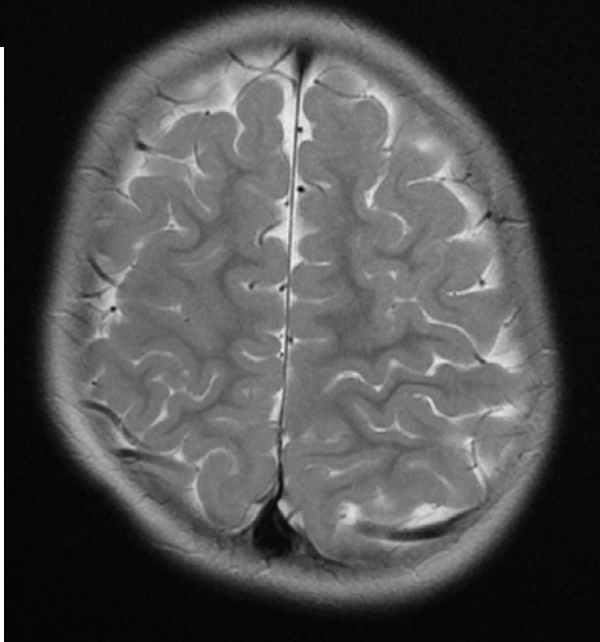
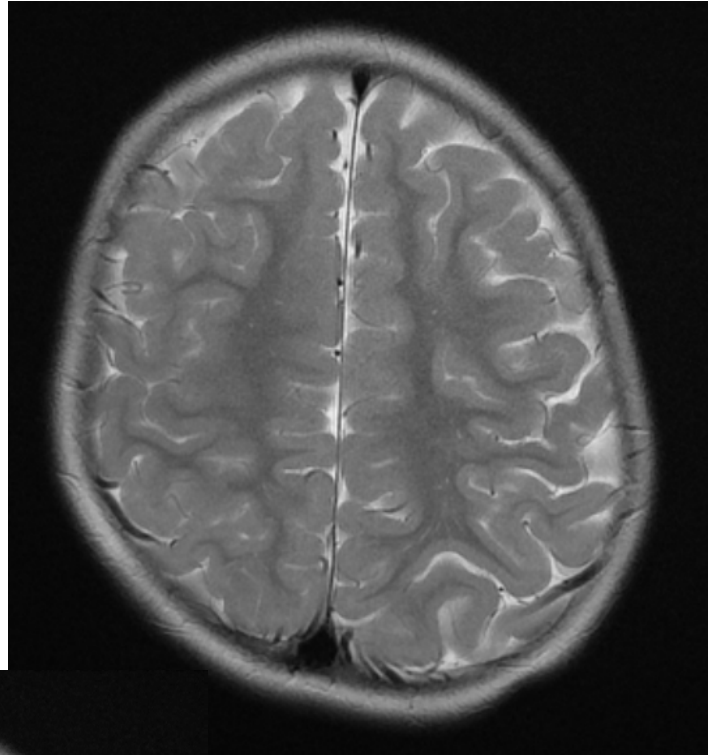
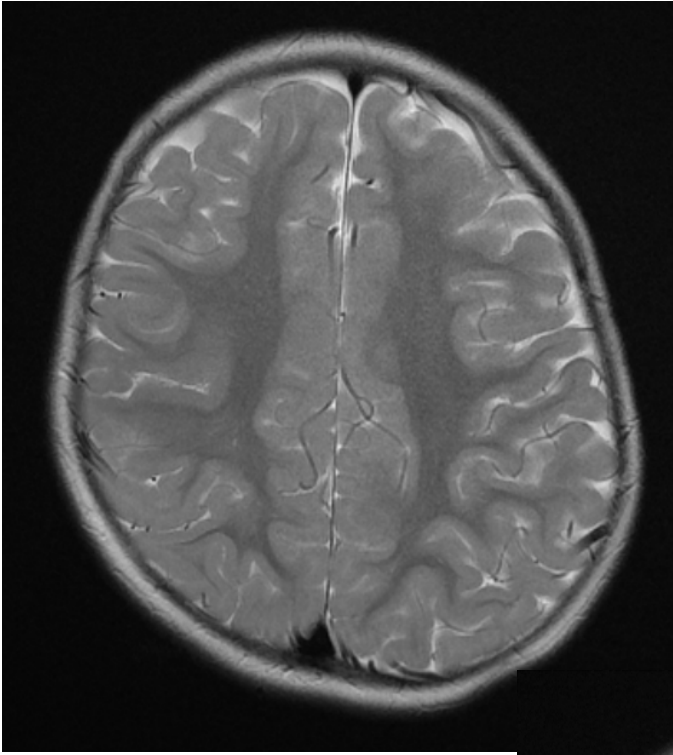


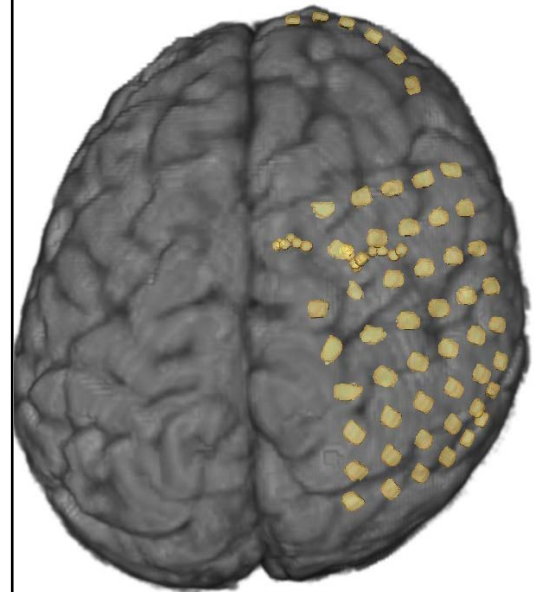
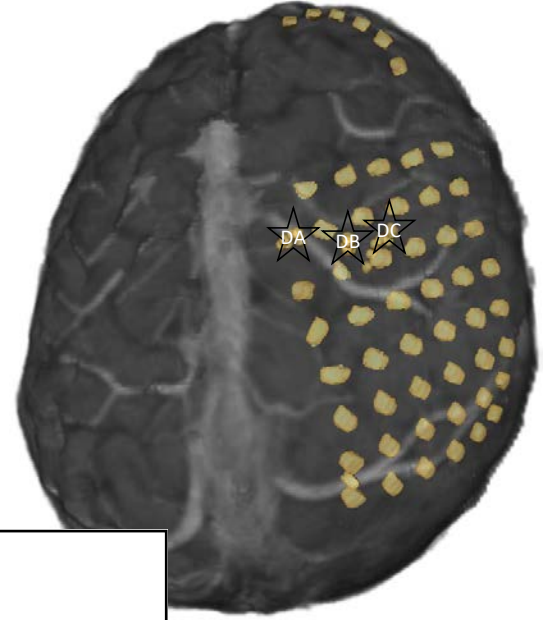
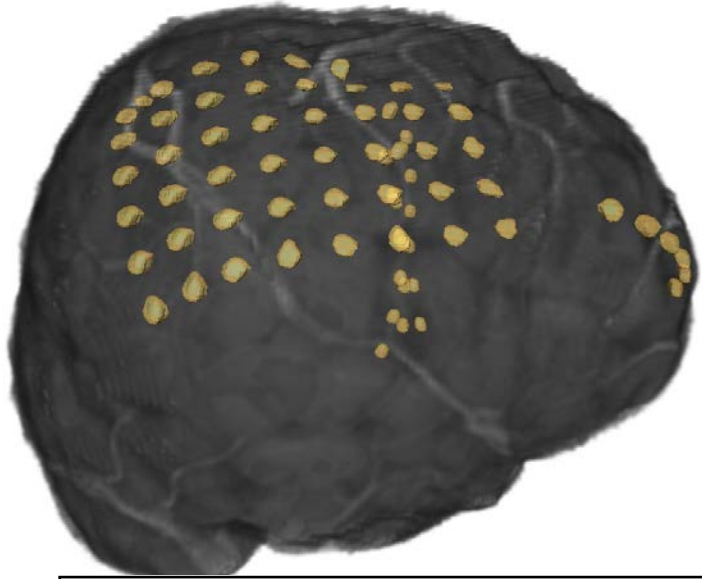
Ictal EEG



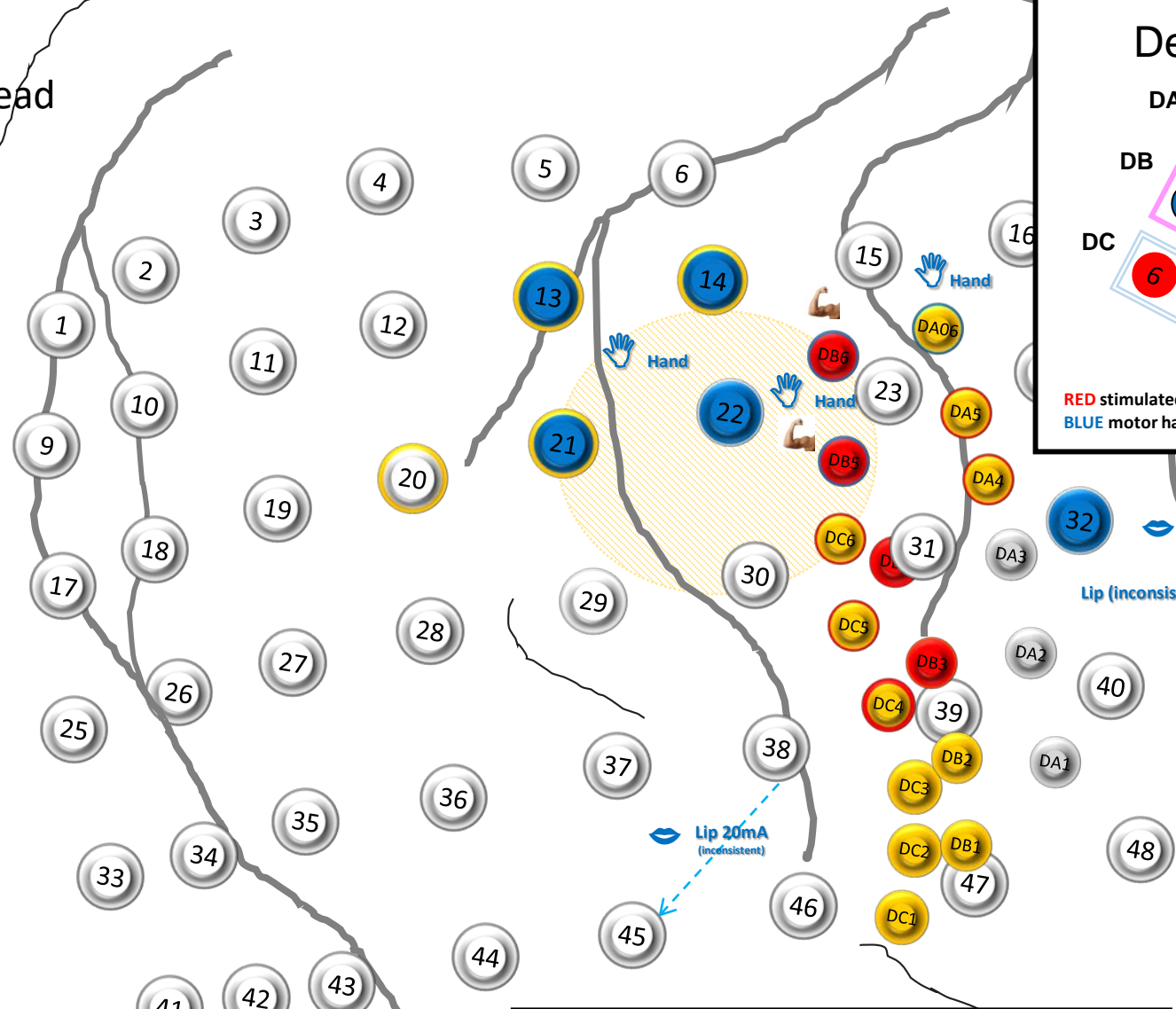
Abnormality found in Surgery – adjacent to DA03 and running posteriorly







Ictal Onset/spread

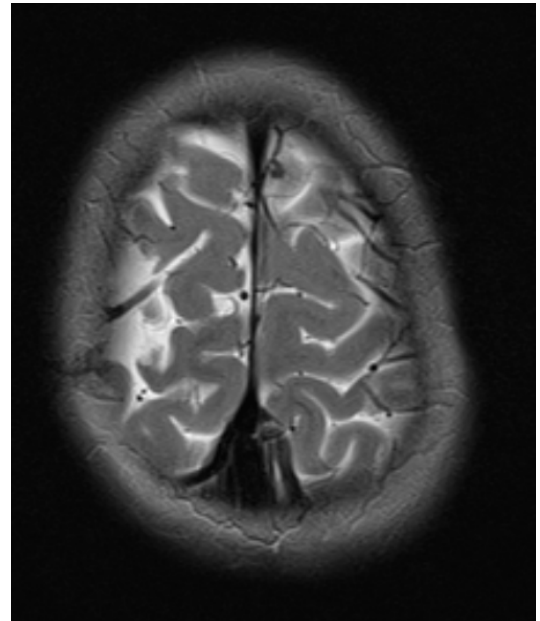
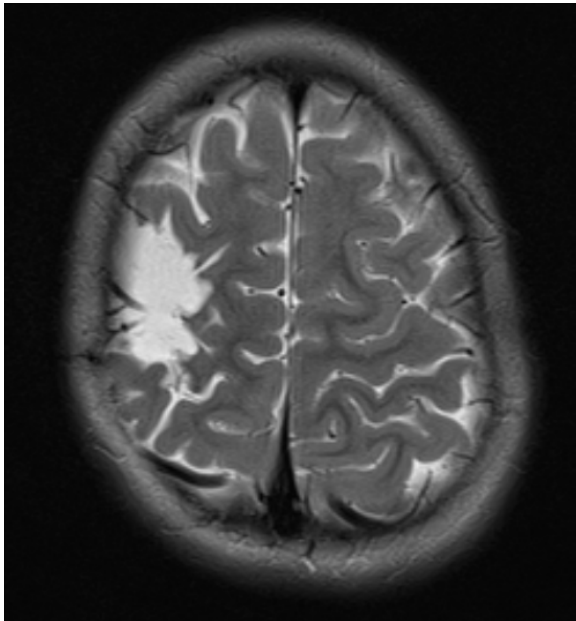
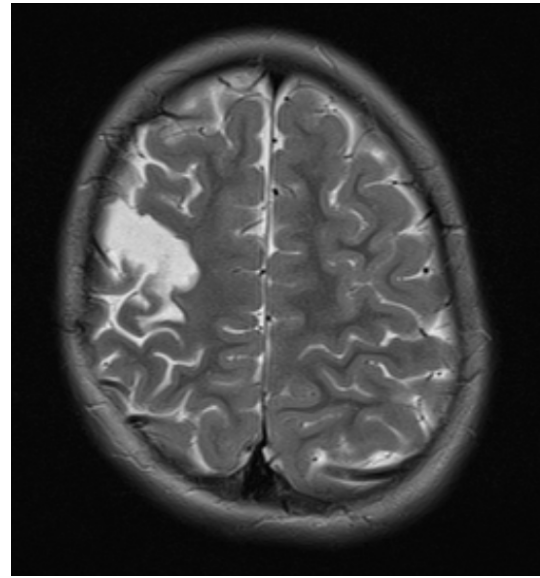
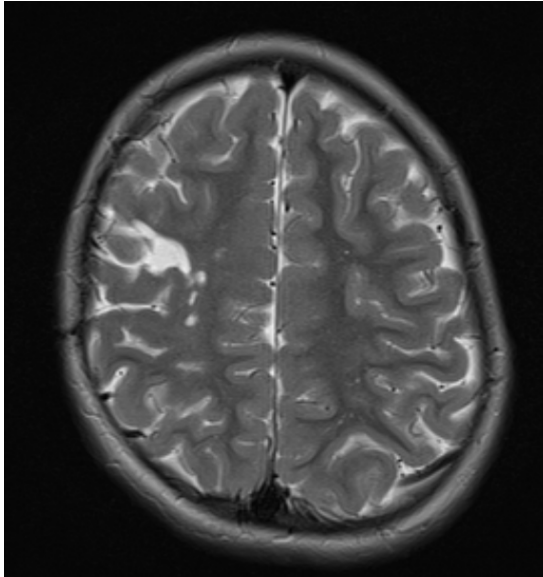


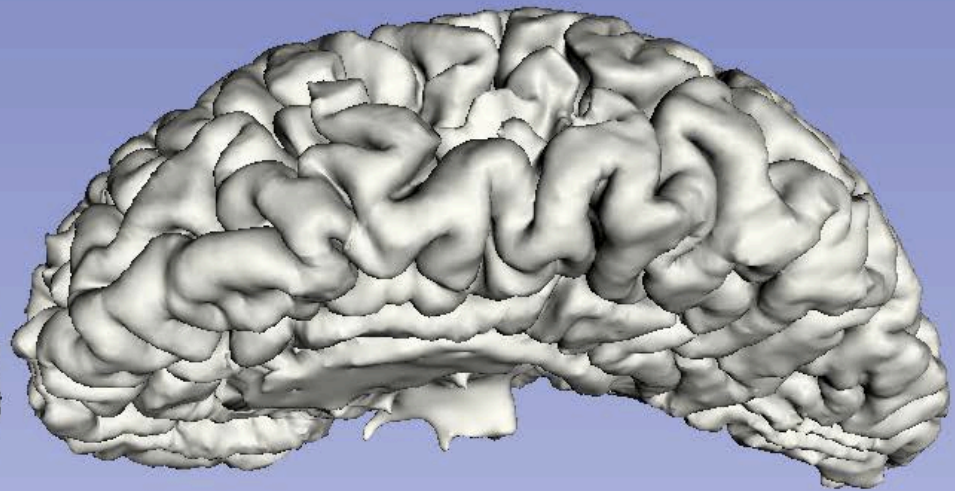
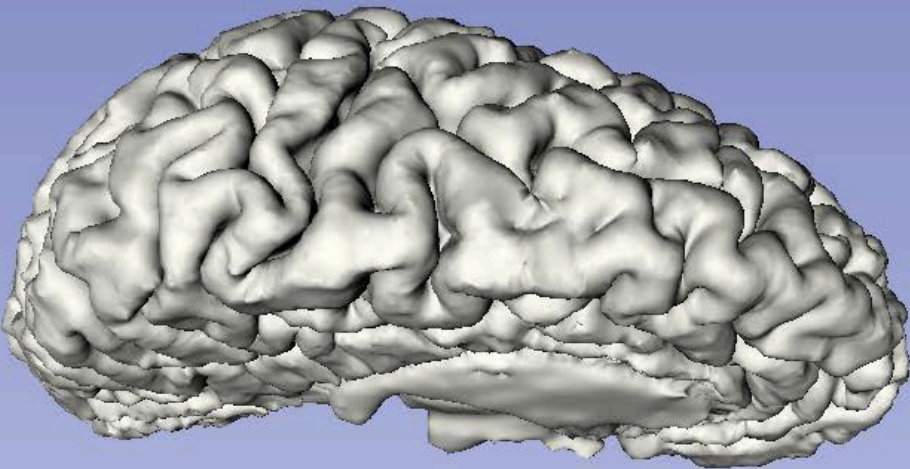
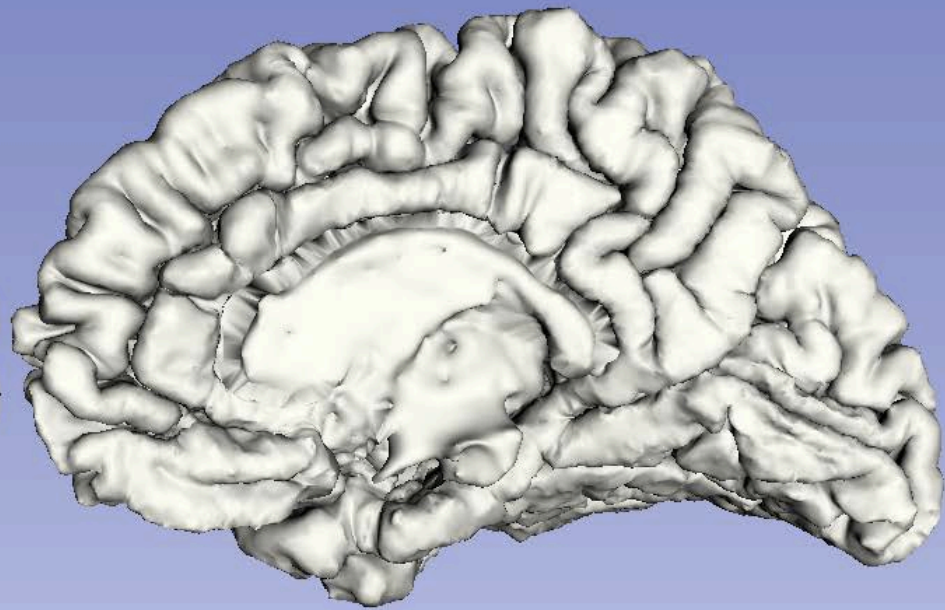
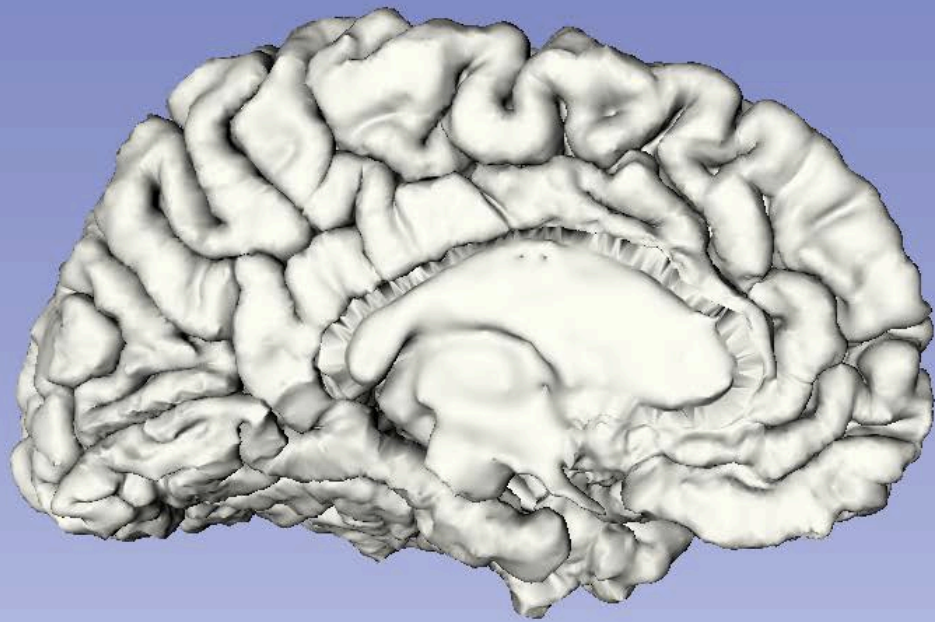
Depth electrodes

DA [6, 5, 4, 3, 2, 1]
 DB [6, 5, 4, 3, 2, 1]
 DC [6, 5, 4, 3, 2, 1]

RED stimulated seizures
 BLUE motor hand/face

| | | | |
|--|-----------------------------------|--|--|
| | Ictal onset | | Ictal onset or early spread/overlap with motor |
| | Early spread | | |
| | Wider spread with bigger seizures | | Ictal onset/early spread & stimulated seizures |





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

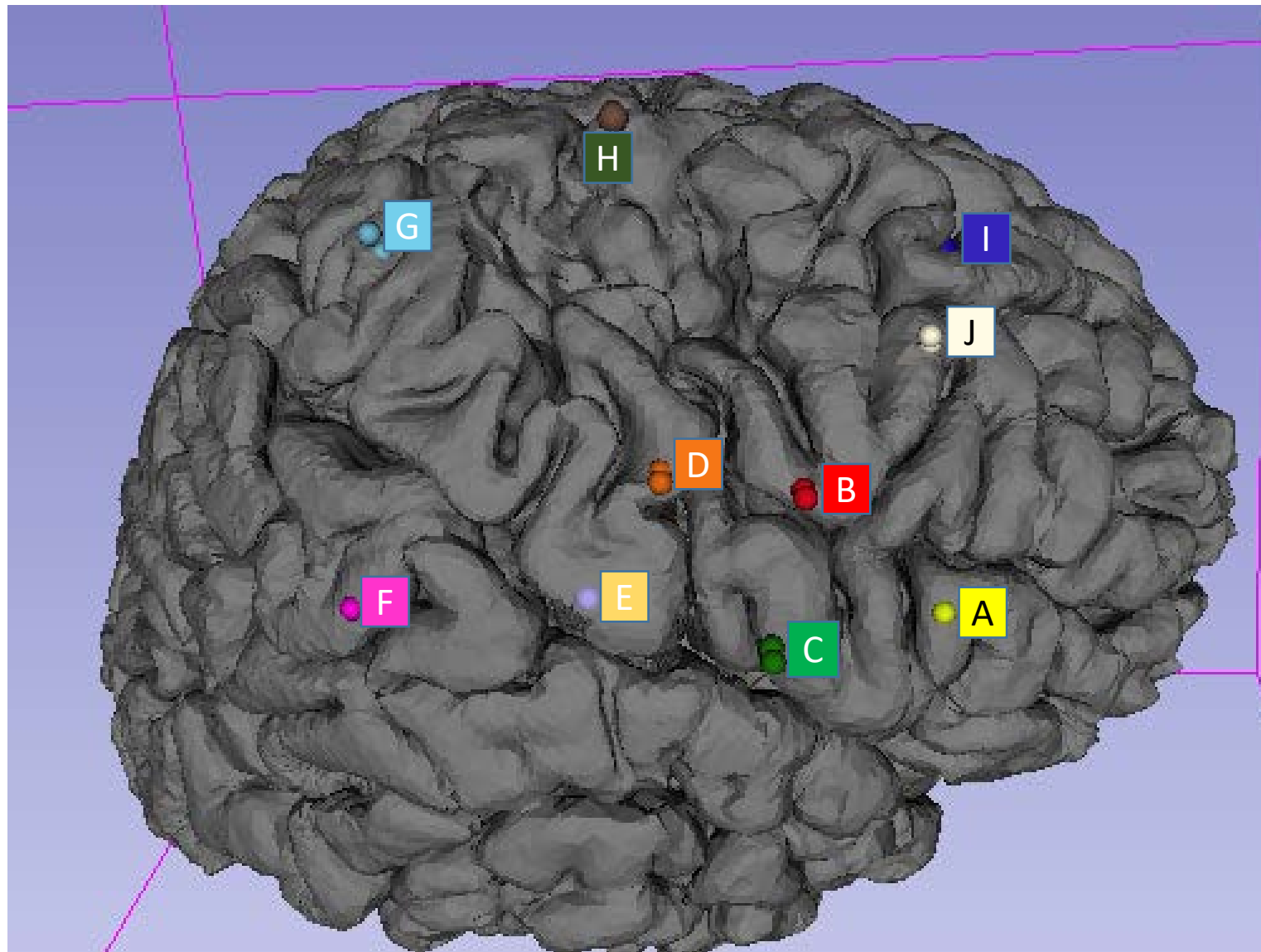
F – Parietal 1-18

G – S1 1-15

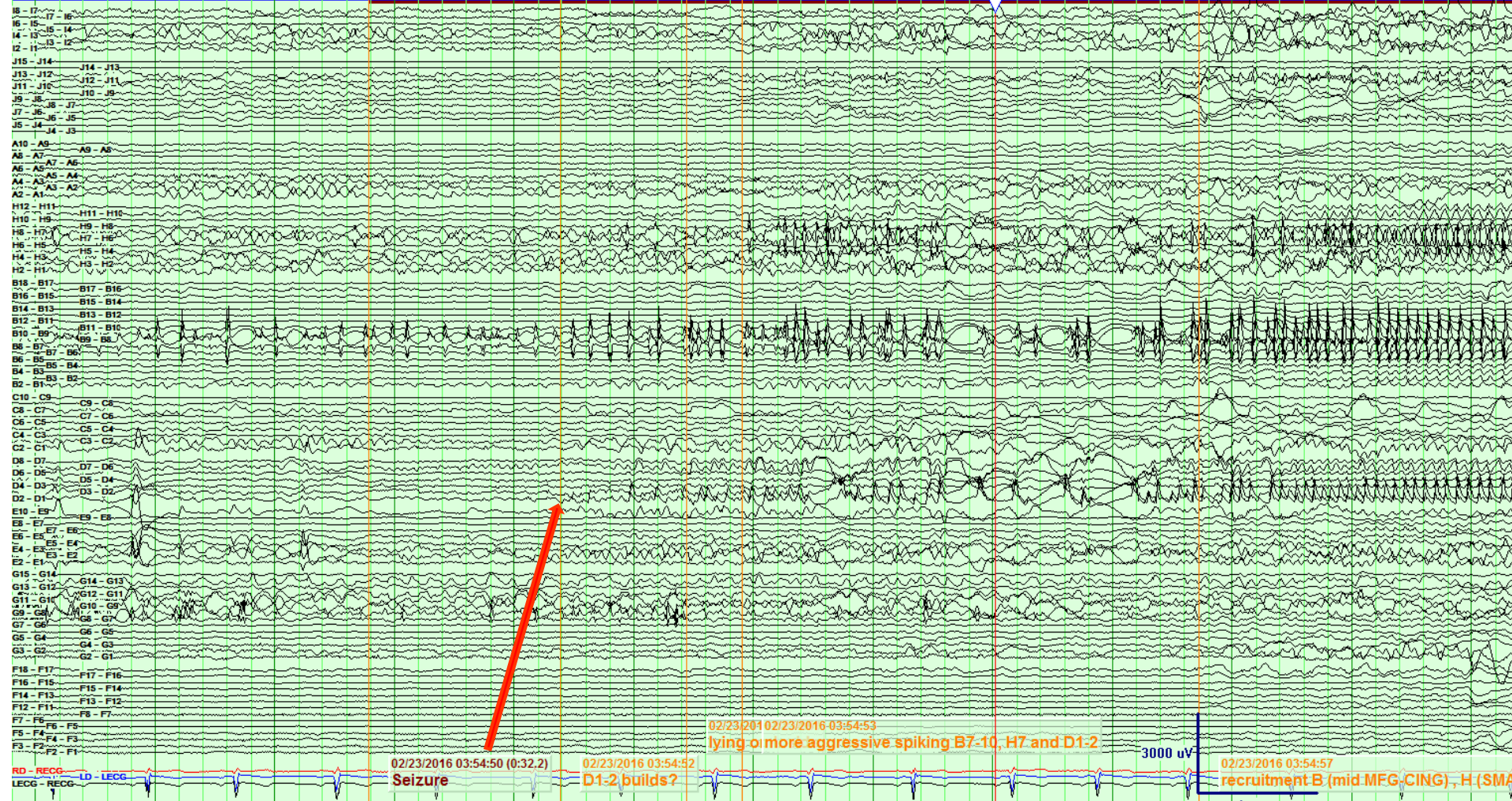
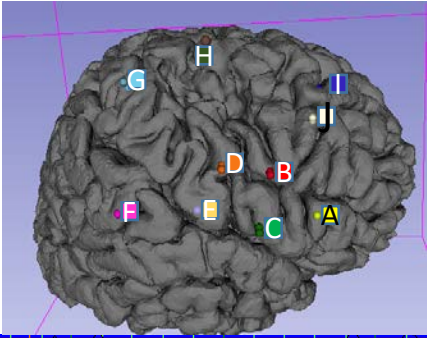
H – SMA 1-12

I – A-SFG 1-8

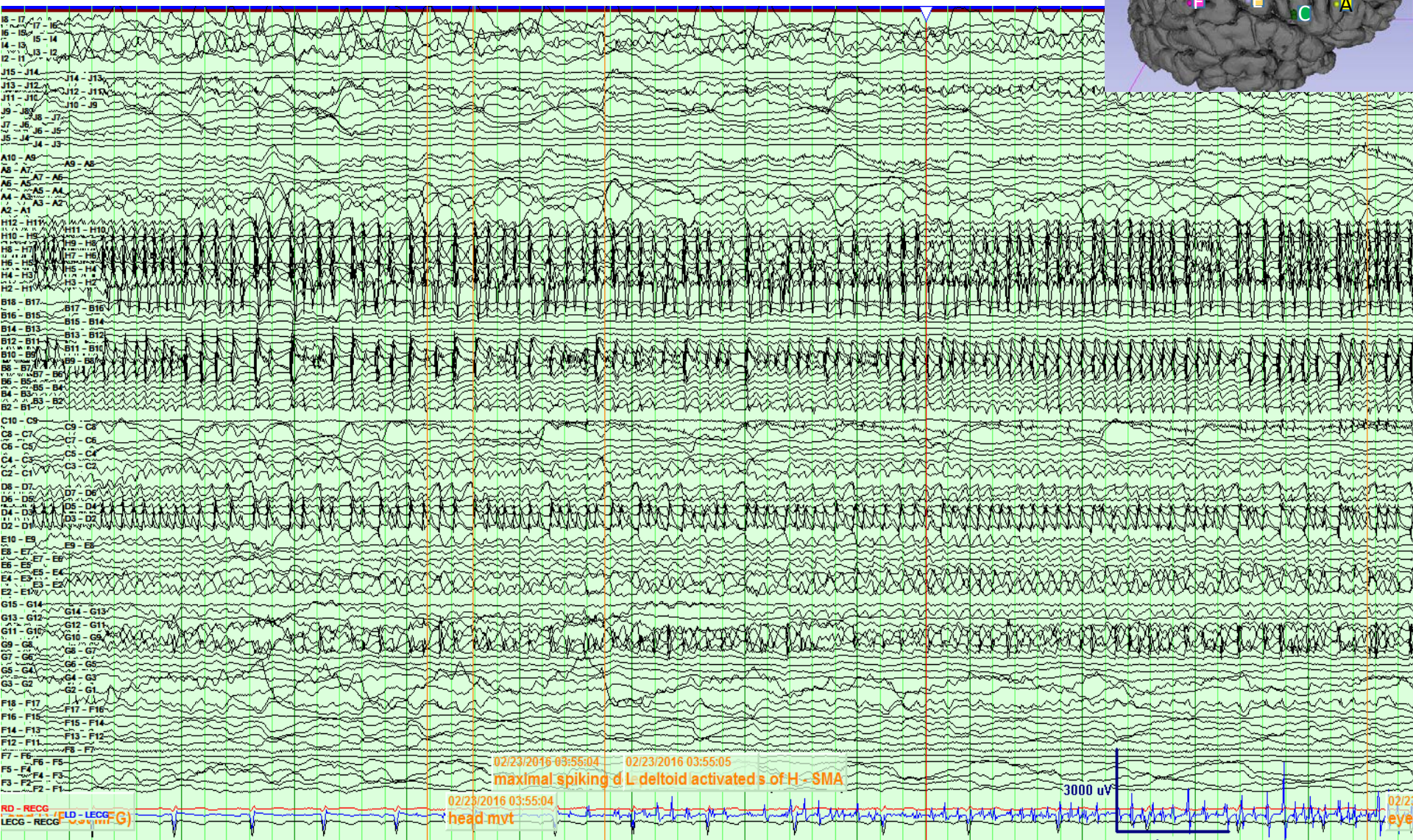
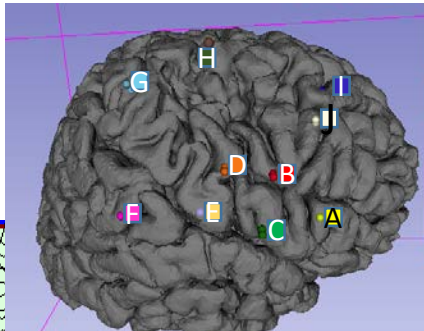
J – A-MFG 1-15

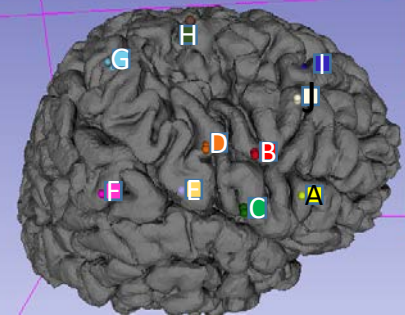


Seizure From sleep: D1-2 rhythmic

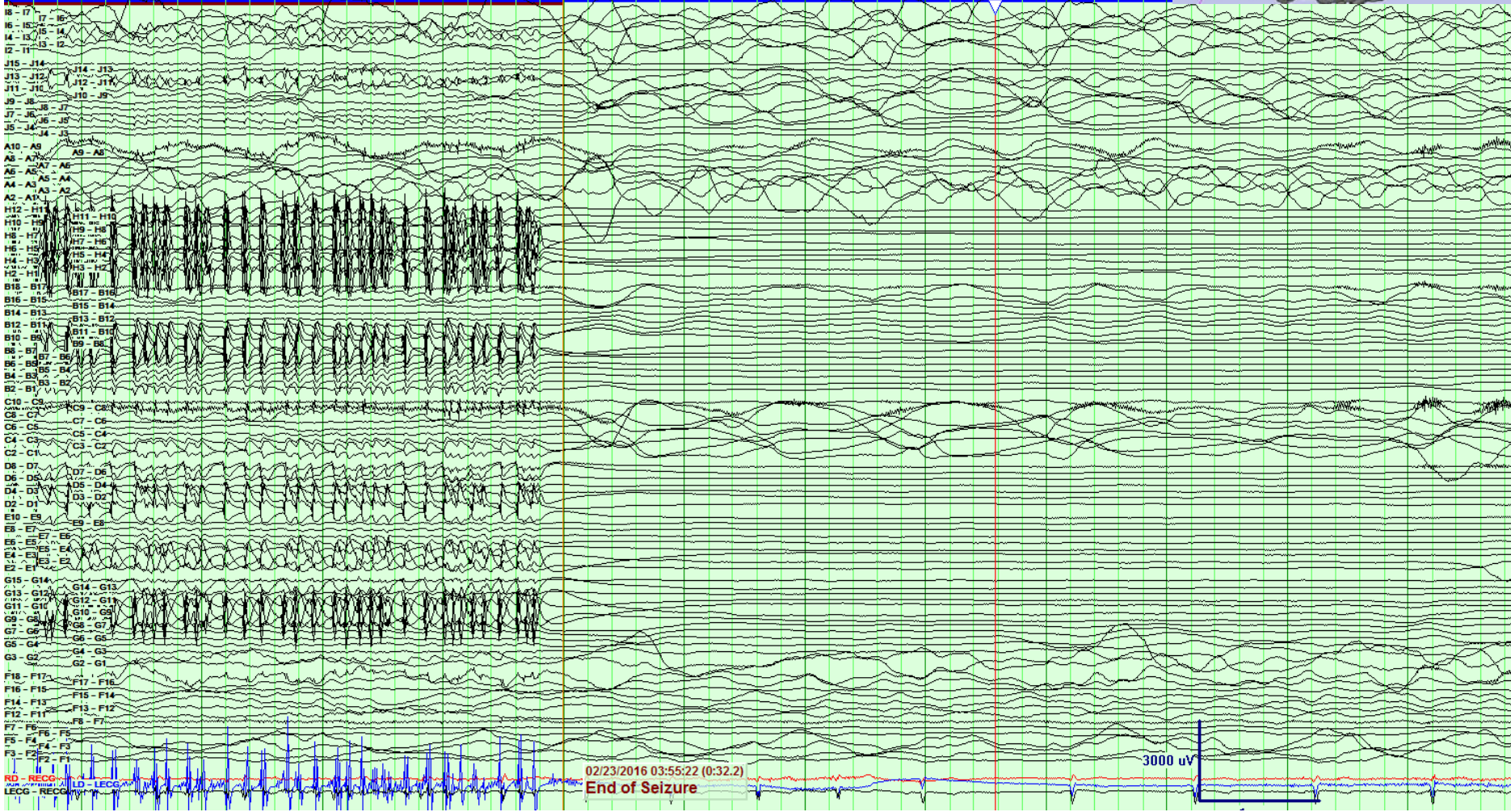


Seizure continued – spread H1-7, B6-10, G8-10

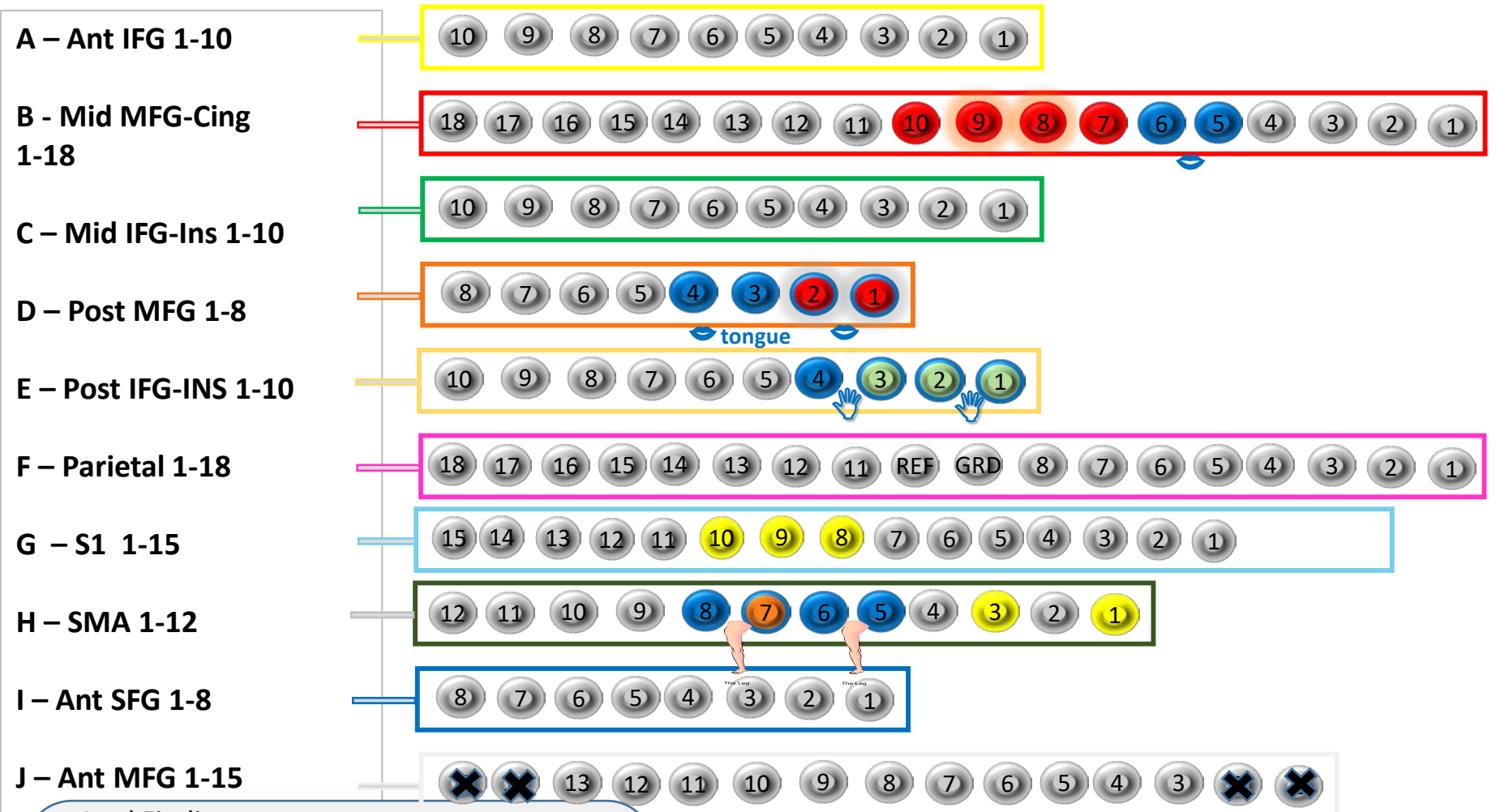




end



Functional Stim & Ictal Findings

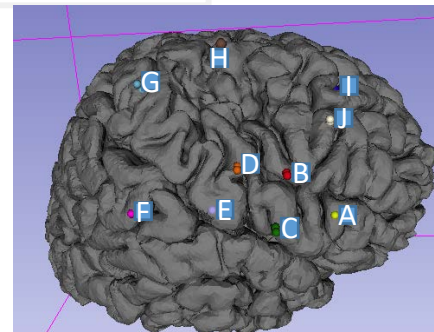


Ictal Findings

- Initial change
- Enhanced discharges
- Subsequent spread
- Subsequent spread
- Subsequent spread

Motor

Faulty contact/outside of cortex



D



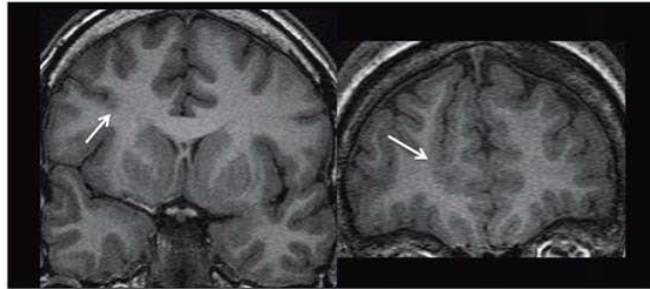
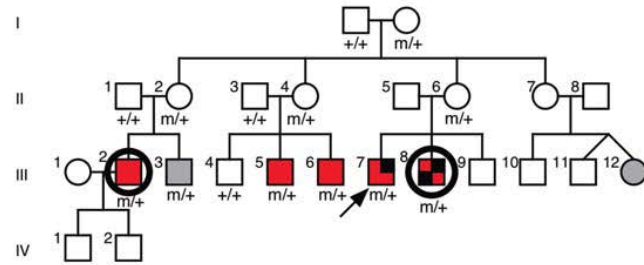
Seizure outcome following surgery

| | 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

A

Family A *DEPDC5* c.418C>T (p.Gln140*)



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

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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**