Cleveland Clinic

Medically Intractability and Presurgical Evaluation

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Cleveland Clinic Epilepsy Center

Objectives:

1) To discuss the criteria used to define medical intractability (pharmacoresistance)
2) To discuss the methods used to confirm the diagnosis of focal epilepsy
3) To review the workup needed in patients with intractable epilepsy

Disclosures

- Advisory Board Speakers' bureau: Eisai
- Research funding: National Institutes of Health

The Clinical dilemma: The patient who does not seem to be responding to antiepileptic medication(s)

- **Clinical importance:**
  - **A patient is followed regularly**
  - **He/she reports recurrent seizures to his/her physician**
  - **The physician adjusts the medication doses upwards, monitors for side effects**
  - **Seizures continue: the physician and patient decide to try a new AED…**

When should we start to think about pharmacoresistance?

Predictors of pharmacoresistance

Clinical predictors

- **Frequent seizures prior to initial therapy (20 seizures or more before therapy): only 29% seizure free vs 51%[1]**
- **Symptomatic etiology (identifiable lesion): only 26% seizure free vs 40% of patients with so called idiopathic epilepsy[1,2]**
- **Early age at onset[2]**

[1]Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319.
[2]Ko TS, Holmes GL. *Clin Neurophysiol.* 1999;110:1245-1251.

Predictors of pharmacoresistance

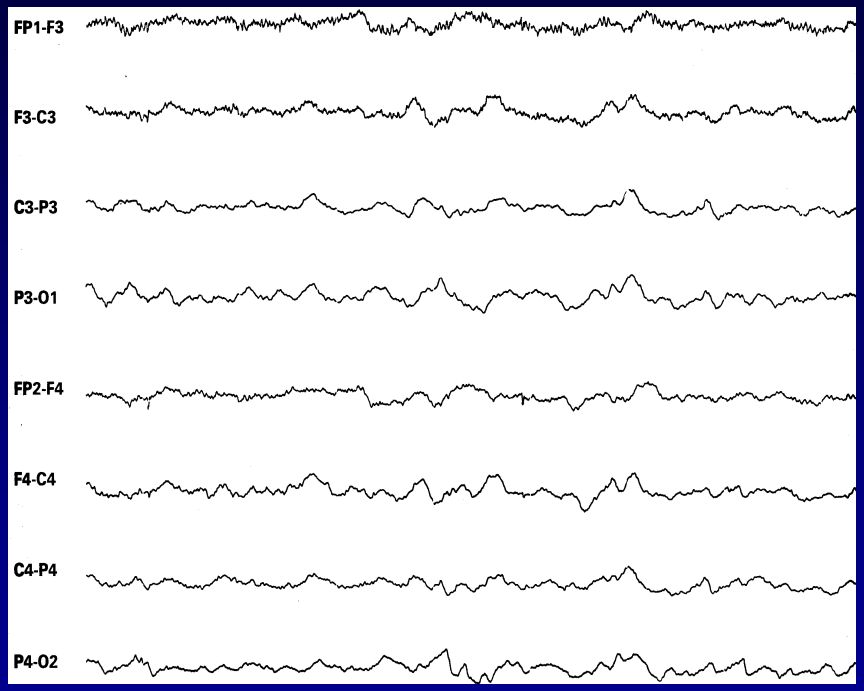
Response to the first AED

- **Response to first AED is a powerful predictor**
- **11% of patients whose first AED failed because of inadequate seizure control ever achieve seizure freedom <u>but:</u>**
  - **41% achieve seizure control if first AED failed due to intolerable side effects and,**
  - **55% achieve seizure control if first AED failed due to idiosyncratic reactions**

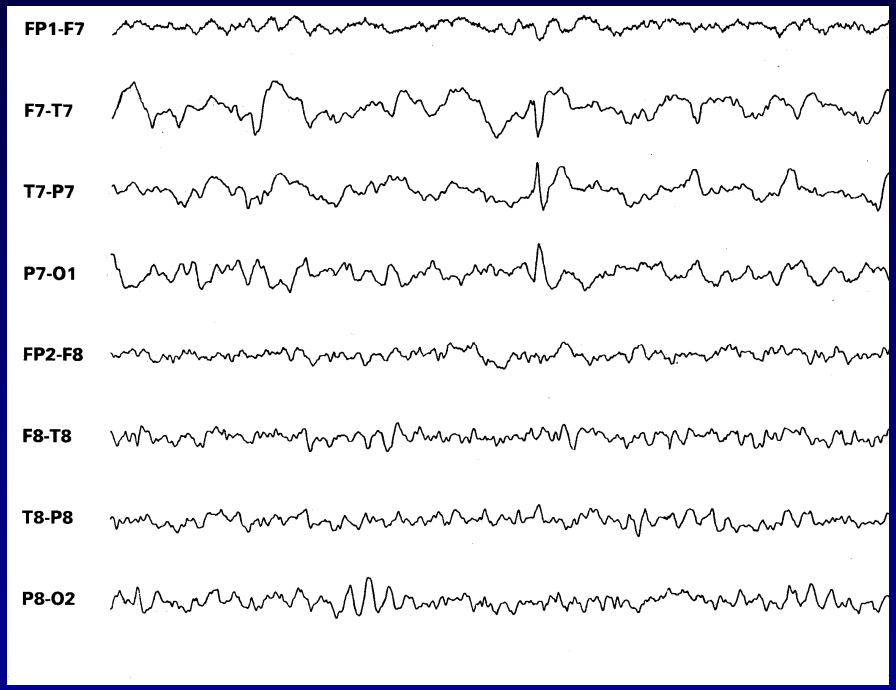
Kwan P, Brodie MJ. N Engl J Med. 2000;342:314-319.

Other Predictors of Pharmacoresistance

Abnormal EEG: Independent Predictor



Slowing



Sharp wave

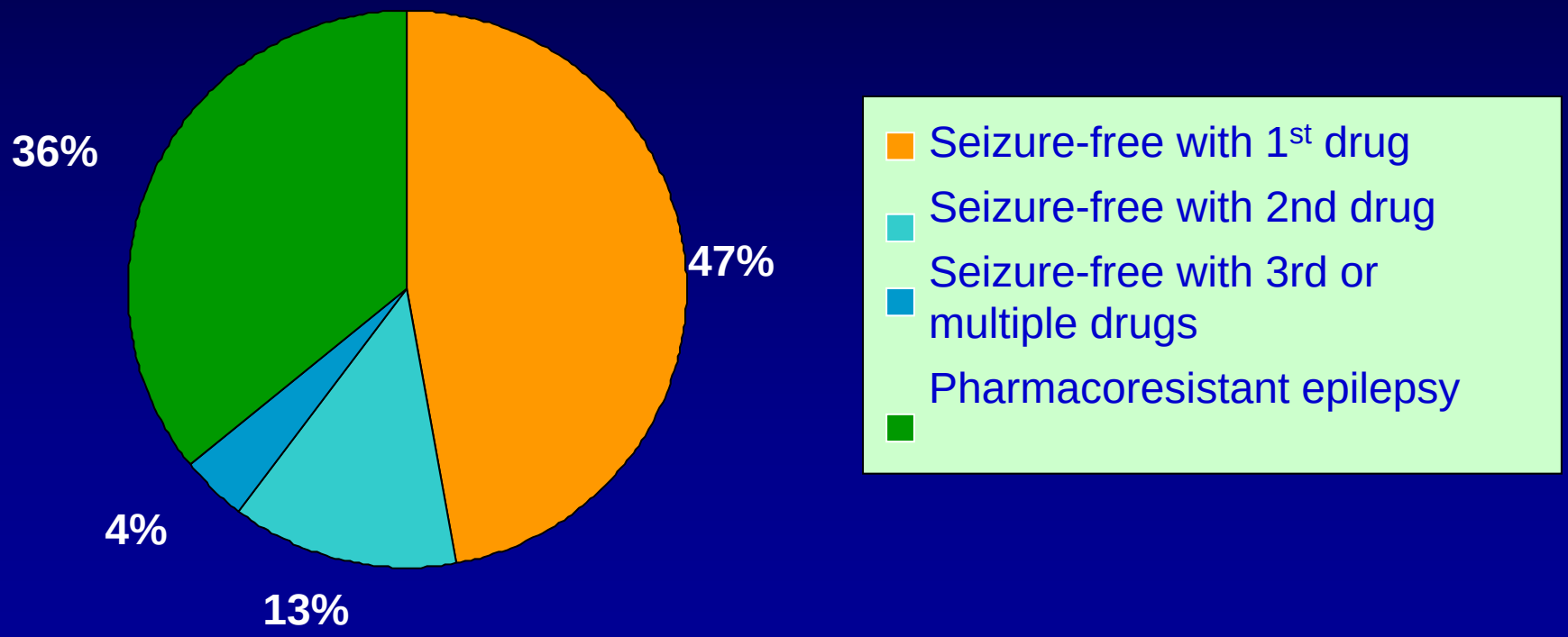
[1]Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319

What are the options after the patient fails two AEDs?

- More medications
- Epilepsy surgery:
  - If patient has focal epilepsy with resectable lesion
- Other options (If patient failed the above):
  - Responsive Neuro-Stimulation (RNS)
  - Deep Brain Stimulation (DBS)
  - Vagus Nerve Stimulation
  - Ketogenic diet

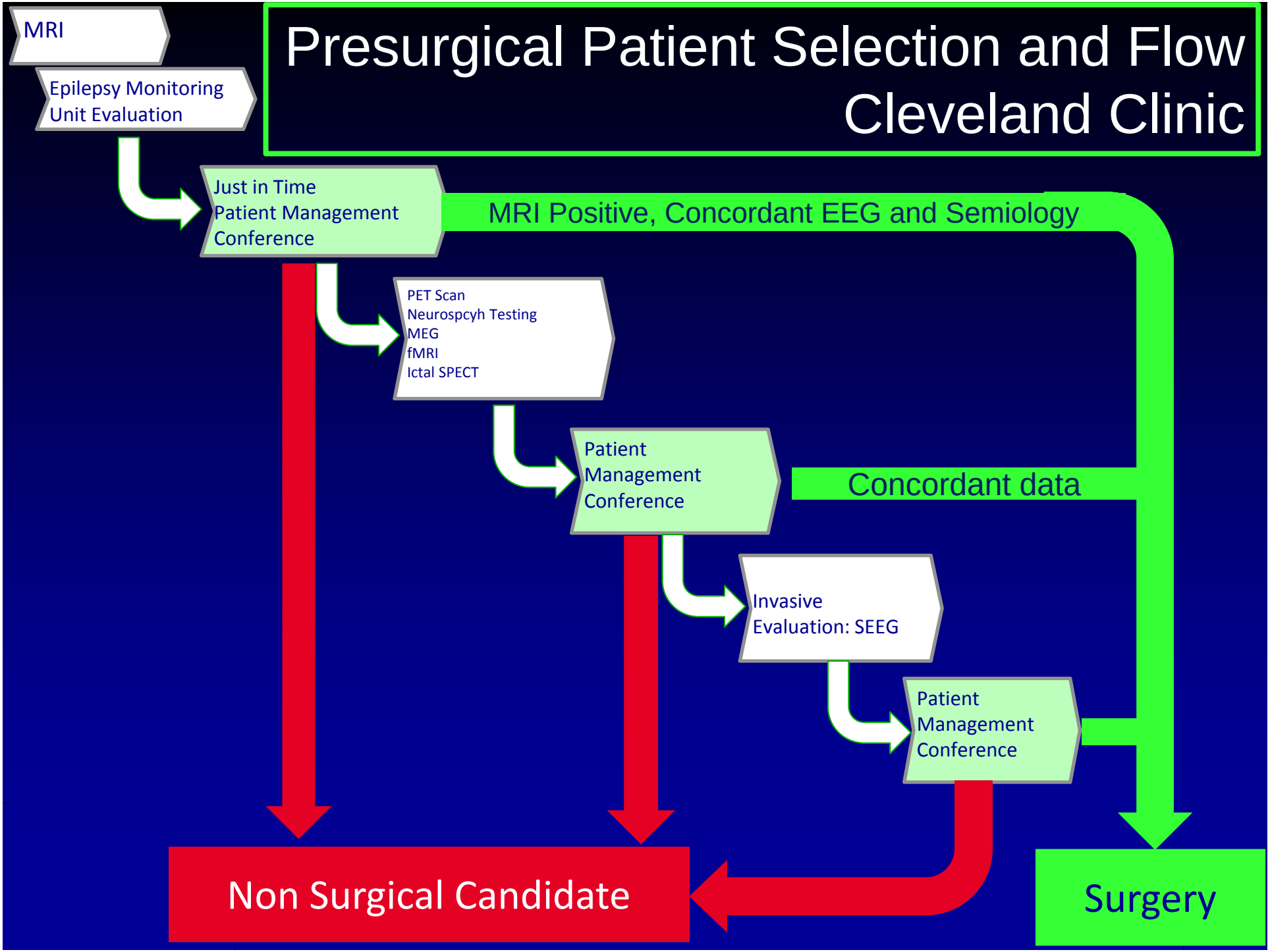
Option of more medications after the first 2-3 has minimal chance of success

Previously Untreated Epilepsy Patients (n=470)



Kwan P, Brodie MJ. N Engl J Med. 2000;342:314-319.

Epilepsy Surgery as a treatment option in patients with pharmacoresistant epilepsy?

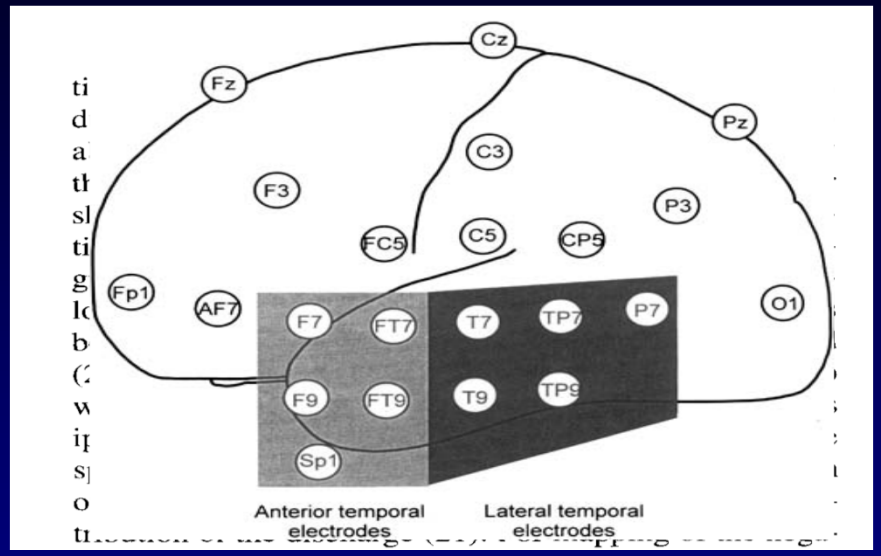

MRI
Epilepsy Monitoring Unit Evaluation
Presurgical Patient Selection and Flow
Cleveland Clinic
Just in Time Patient Management Conference
MRI Positive, Concordant EEG and Semiology
PET Scan
Neurospcyh Testing
MEG
fMRI
Ictal SPECT
Patient Management Conference
Concordant data
Invasive Evaluation: SEEG
Patient Management Conference
Non Surgical Candidate
Surgery

During the NON INVASIVE EVALUATION:

The diagnosis of focal epilepsy is confirmed through scalp Video EEG monitoring…

… and the possible cause (pathology) and its anatomical location are identified on MRI

Distribution of Interictal Spikes in MTLE: HS versus hippocampal tumors



quent posterior or extratemporal sharp waves may detract from the certainty of the diagnosis of HS.

These restricted anterior temporal discharges in our HS patients confirmed previous studies (15,16) and may suggest a smaller irritative zone (5,24) as compared with medial temporal lobe tumors. Alternatively, there may be more organized interictal activity associated with intrinsic hippocampal disease. These data are in agreement with previous hypotheses on the generators of interictal epileptiform activity in HS (25,26). By using three-dimensional multiple dipole modeling, Baumgartner et al. (26) identified two possible sources of interictal spikes in HS patients. The first source involved the mesiobasal aspect of the temporal lobe (hippocampus and parahippocampal gyrus) and was followed within 40 ms by activation of the anterior temporal lobe neocortex. The rare occurrence of lateral temporal and frontal

the two patients wh
surgery.

In extracranial El
may have a more r
changes in TLE (3
seizure origin if they
ant in a single region
patients in our study
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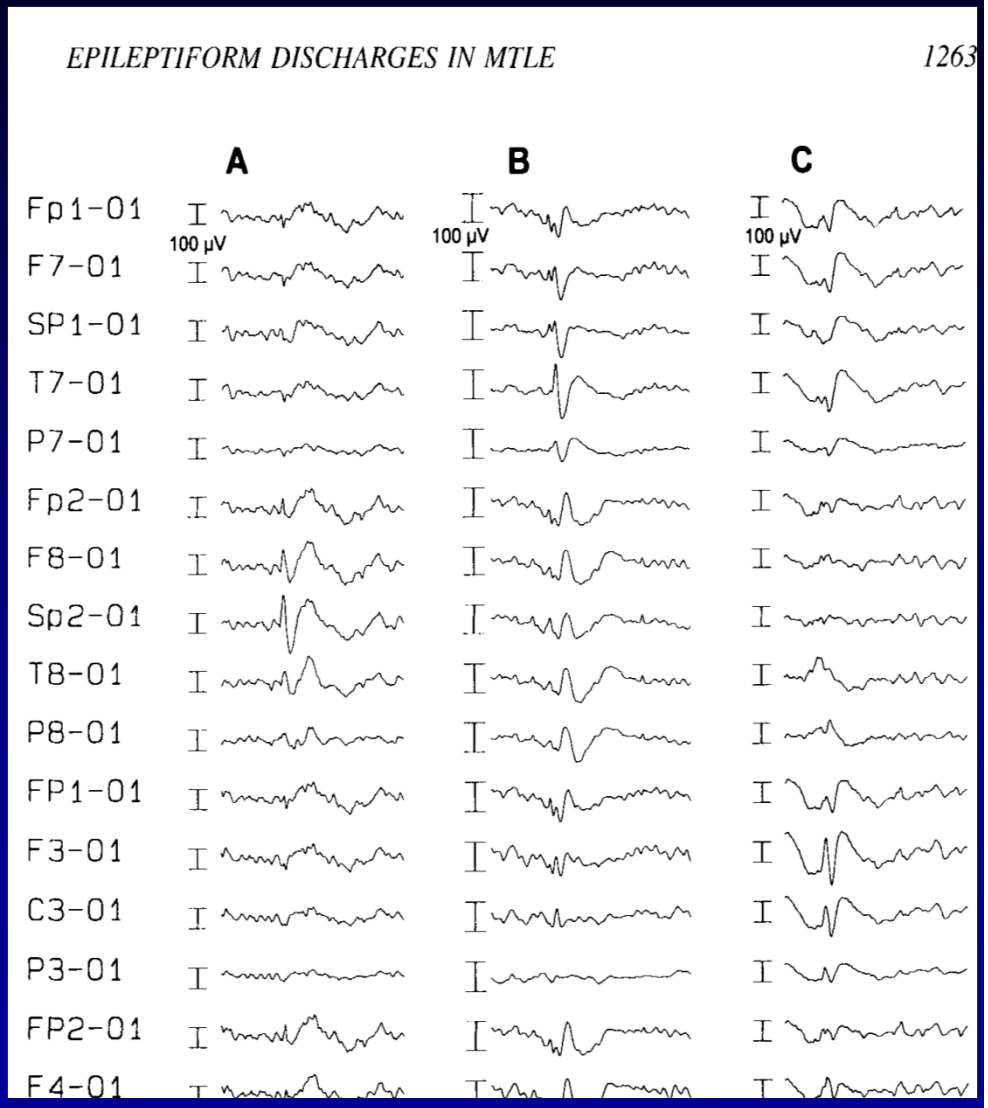
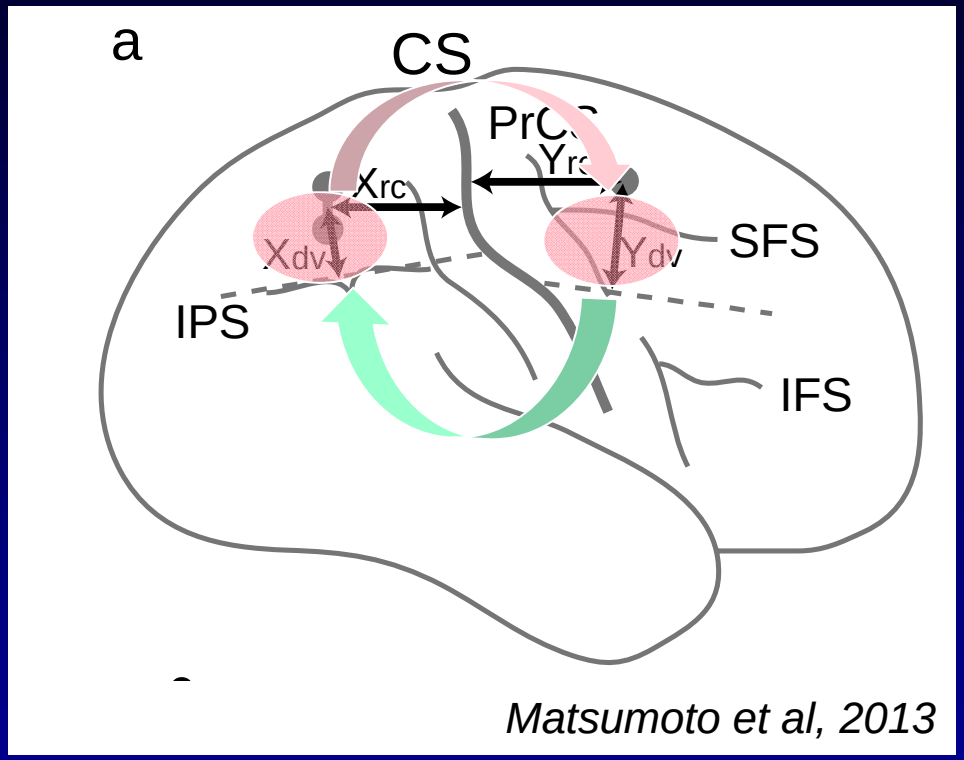


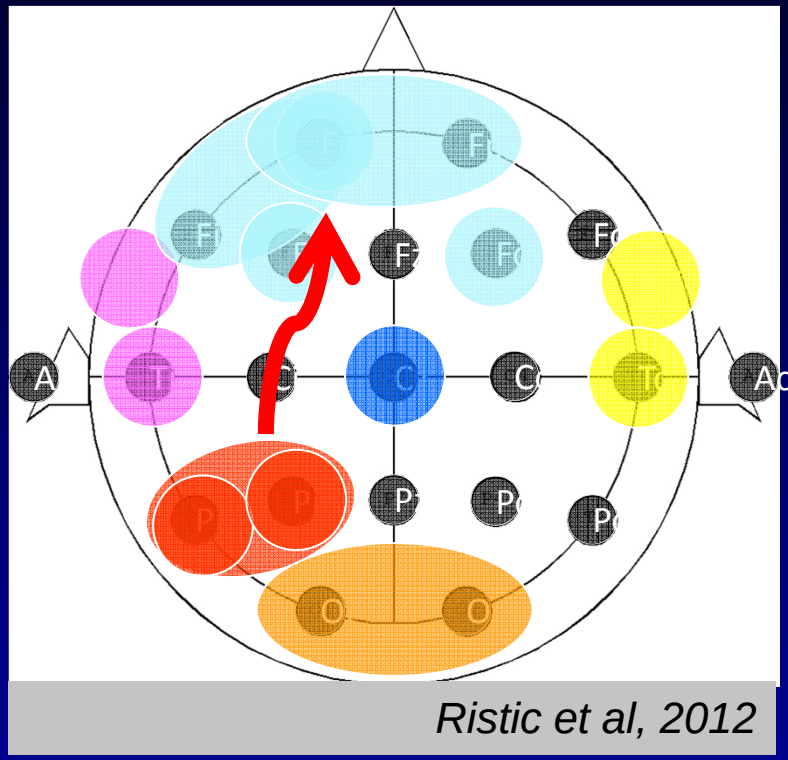
Hamer et al, Epilepsia (1999)

Parietal Lobe Epilepsy:

Scalp EEG may be frontal, temporal or bilateral



Matsumoto et al, 2013



Ristic et al, 2012

…therefore, in the absence of a lesion, Parietal lobe epilepsy may be mislocalized or mislateralized

The localizing value of ictal EEG in focal epilepsy

N. Foldvary, DO; G. Klem, REEGT; J. Hammel, MS; W. Bingaman, MD; I. Najm, MD; and H. Lüders, MD, PhD

NEUROLOGY 2001;57:2022–2028

MTLE,	NTLE,	Temporal,	MFLE,	LFLE,	PLE,	OLE,	Extratemporal,	Total,

MFLE, n = 51	LFLE, n = 125	PLE, n = 56	OLE, n = 29	Extratemporal, n = 261
12 (24)	81 (65)	26 (46)	12 (41)	131 (50)
1 (1)	8 (6)	—	2 (7)	11 (4)

† Localized seizures more common in temporal lobe than extratemporal epilepsy, and in MTLE vs LFLE, MFLE, and OLE ($p < 0.001$).

‡ Lateralized seizures more common in NTLE ($p = 0.03$).

§ Generalized seizures more common in extratemporal epilepsy than temporal lobe epilepsy ($p < 0.001$) and in MFLE than the other subgroups ($p = 0.003$).

Ictal EEGs yield correct localization in **50.2% of extratemporal** epilepsy cases and **74.5% of neocortical TLE** cases.

Scalp Video EEG evaluation: Advantages

"Concordant" Electro-clinical manifestations

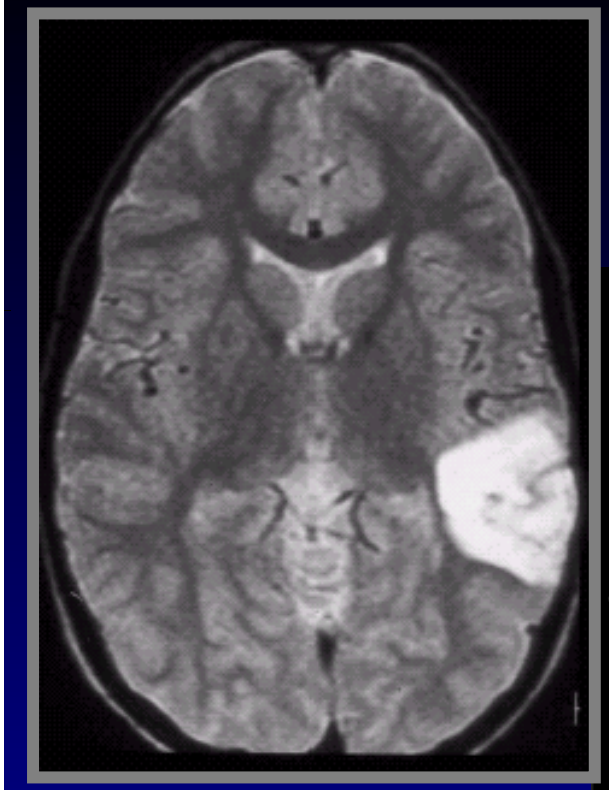
- **Clinical manifestations:**
  - Mostly stereotypical:
    - Abdominal aura in mesial temporal lobe or insular epilepsy
    - Visual aura in occipital lobe epilepsy
    - Contralateral somatosensory aura in central lobe epilepsy…
- **EEG:**
  - Mostly predictable in its location:
    - Anterior temporal in mesial temporal lobe epilepsy
    - Posterior quadrant in Occipital lobe epilepsy
    - Fronto-central in central lobe epilepsy

Scalp Video EEG evaluation: Pitfalls

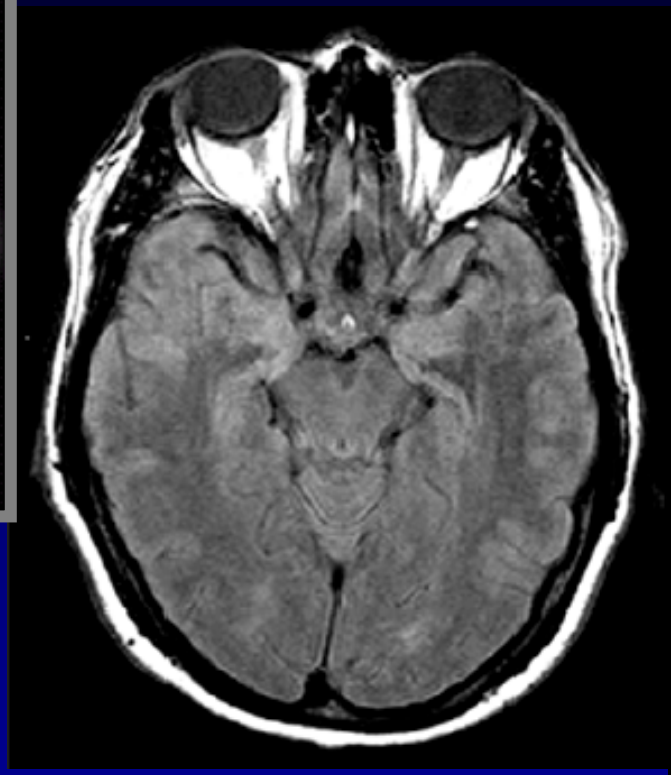
"Discordant" Electro-clinical manifestations Network activation

- **Clinical manifestations:**
  - Visual aura in perisylvian epilepsy
  - Contralateral upper extremity motor seizure in parietal lobe epilepsy (pseudofrontal)
- **EEG (**Mislocalizing or mislateralizing):
  - Interhemispheric
  - Insular/opercular
  - Basal temporal,
  - Mesial frontal
  - Parietal lobe

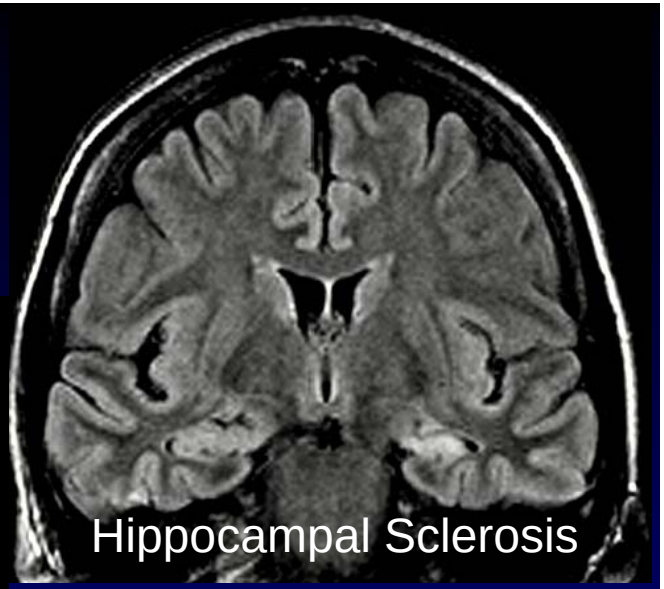
MRI



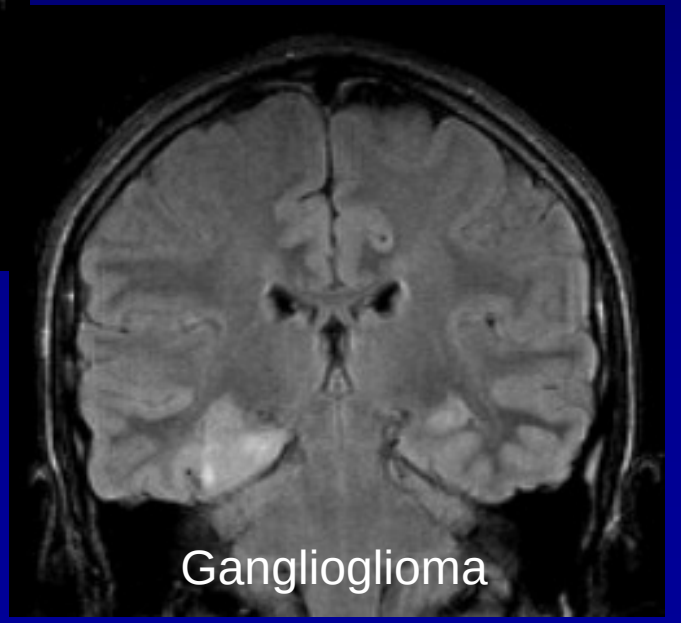
DNET



Cortical Dysplasia



Hippocampal Sclerosis



Ganglioglioma

Why is the identification of a lesion important in Epilepsy Surgery?

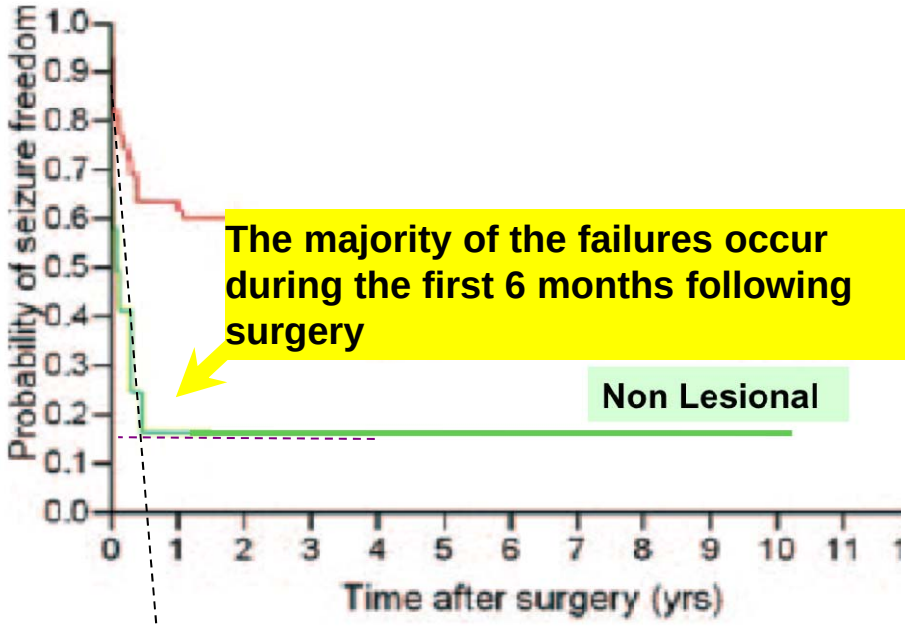
OUTCOME

The lack of a lesion on MRI has consistently been shown to be one of the predictors for surgical failure

[1]*Tellez-Zenteno et al, 2010, Epilepsy Research*
[2]*Bien et al, 2009, Arch Neurol.*
[3]*Jeha et al, 2007, Brain*
[4]*Bulacio et al, 2012, Epilepsia*

Long term seizure outcome following Epilepsy Surgery (Cleveland Clinic)

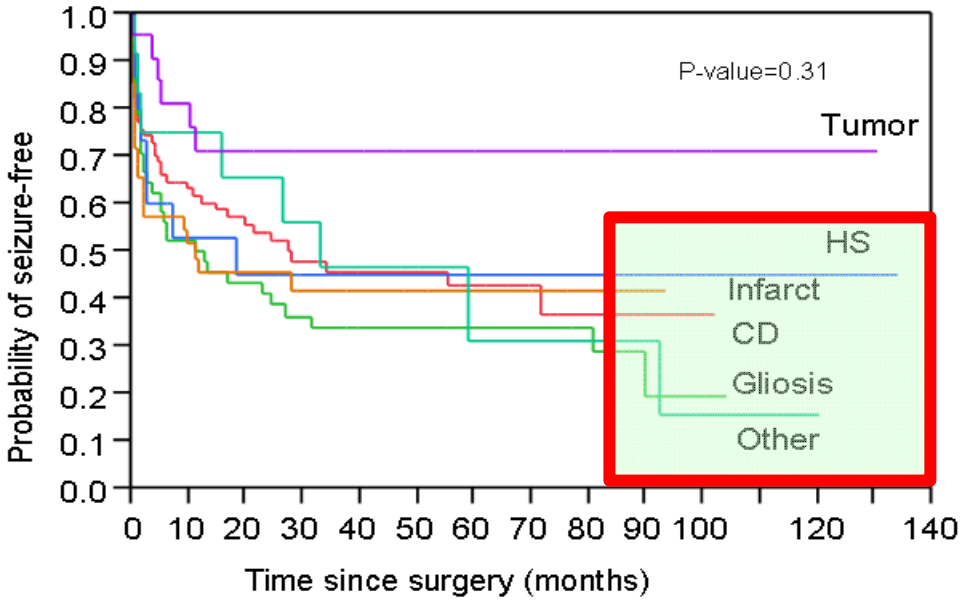
Frontal lobe Surgery
(n=153)



The majority of the failures occur during the first 6 months following surgery

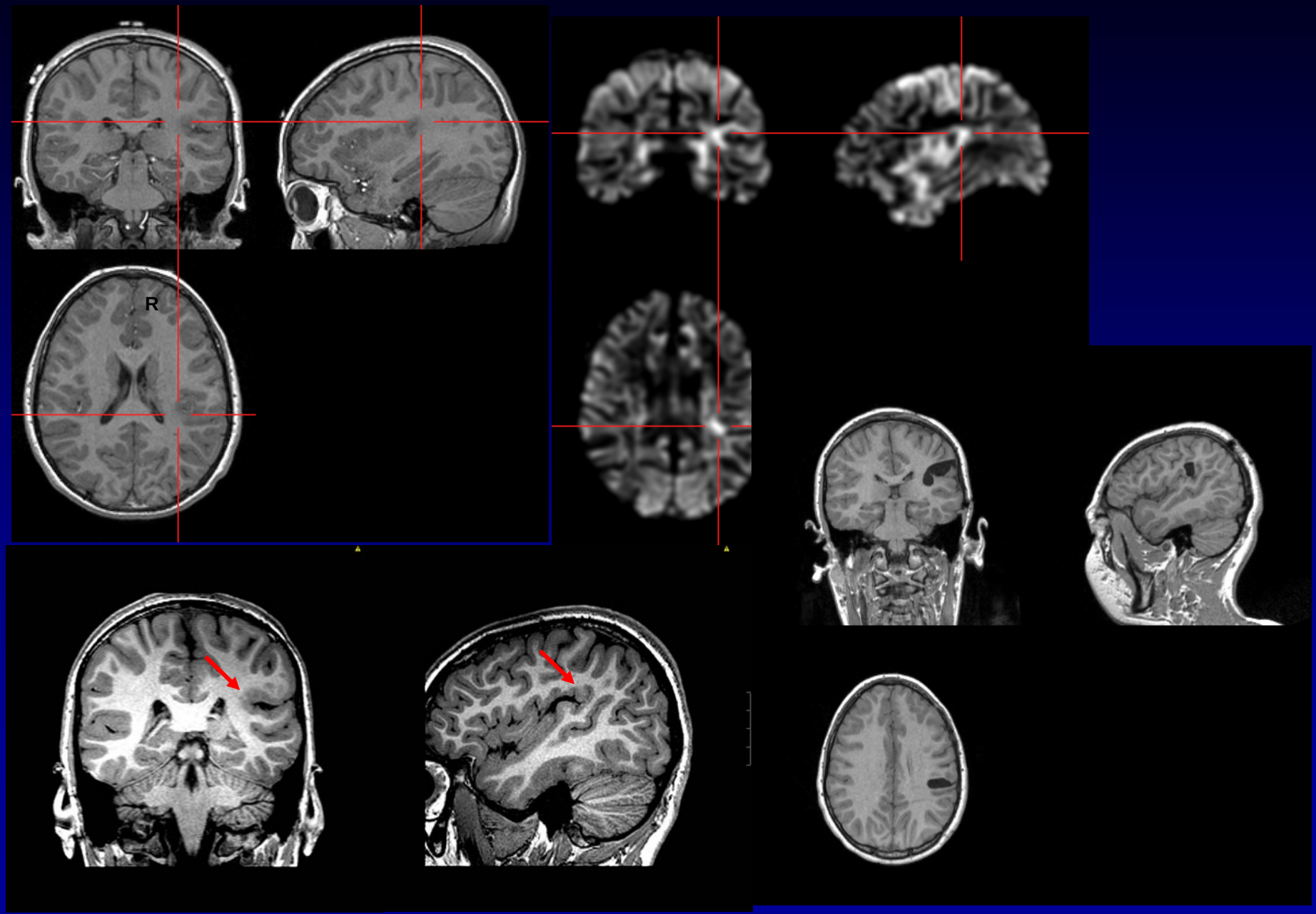
Non Lesional

Surgery following invasive evaluation
N= 350 patients



Jeha et al, Brain, 2007
Bulacio et al, Epilepsia, 2012

VBM in MRI negative epilepsy



Ann Neurol. 2014 Jan 2. doi: 10.1002/ana.24097. [Epub ahead of print]

Linking MRI post-processing with Magnetic source imaging in MRI-negative epilepsy.

Wang Z, Alexopoulos A, Jones S, **Najm** I, Ristic A, Wong C, **Prayson** R, Schneider F, Kakisaka Y, **Wang** S, Bingaman W, Gonzalez-Martinez J, Burgess R.

Author information

Abstract

Objective: MRI-negative (MRI-) pharmacoresistant focal epilepsy (PFE) patients are most challenging for epilepsy surgical management. This study utilizes a voxel-based MRI post-processing technique, implemented using a morphometric analysis program (MAP), aiming to facilitate detection of subtle focal cortical dysplasia (FCD) in MRI-patients. Furthermore, the study examines the concordance between MAP-identified regions and localization from magnetic source imaging (MSI). Methods: Included in this retrospective study were 25 MRI-surgical patients. MAP was performed on T1-weighted MRI, with comparison to a normal database. The pertinence of

Results: The detection rate of subtle changes by MAP was 48% (12/25). Once MAP+ areas were resected, patients were more likely to be seizure-free (p = 0.02). There were no false positives in the 25 age-matched normal controls. Seven patients had a concordant MSI correlate. Patients in

conventional MRI visual analysis in presurgical evaluation of PFE. Concordant MRI post-processing and MSI analyses may lead to the noninvasive identification of a structurally and electrically abnormal subtle lesion that can be surgically targeted. ANN NEUROL 2013. © 2013 American Neurological Association.

Mod Pathol. 2013 Aug;26(8):1051-8. doi: 10.1038/modpathol.2013.52. Epub 2013 Apr 5.

The pathology of magnetic-resonance-imaging-negative epilepsy.

Wang ZI, Alexopoulos AV, Jones SE, Jaisani Z, **Najm** IM, **Prayson** RA.

Patients with MRI-negative refractory epilepsy who underwent surgical resection (n=89)

- Focal cortical dysplasia (N=40, 43%): 37 Type 1
- Gliosis (N=21, 22%)
- Hamartia + gliosis (N=12, 13%)
- Hippocampal sclerosis (N=9, 10%)
- No identifiable pathology: Seven patients

Video EEG monitoring confirms focal epilepsy… leads to a localizing/lateralizing hypothesis... and MRI is done and analyzed...

MRI

MRI + (a lesion is identified)

Issues of mapping (+/- localization):

1. The extent of epileptogenicity
2. The functional status of the lesion (and its surroundings)

MRI – (no Lesion is identified)

Issues of localization and mapping:

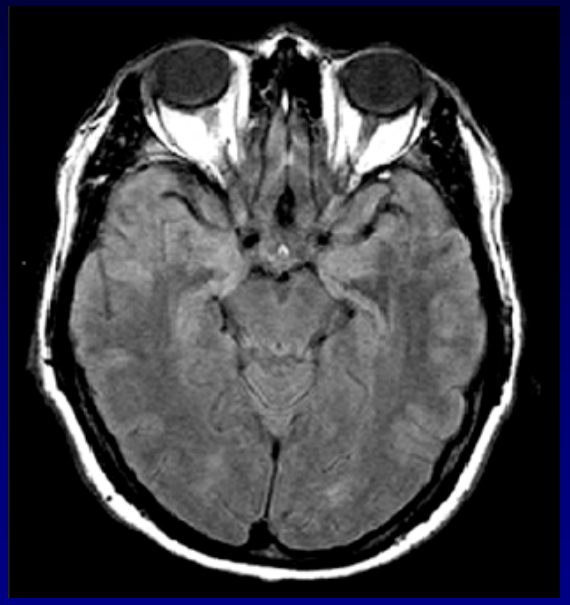
1. The localization of epilepsy
2. The extent of epileptogenicity
3. The functional status of the epileptic region

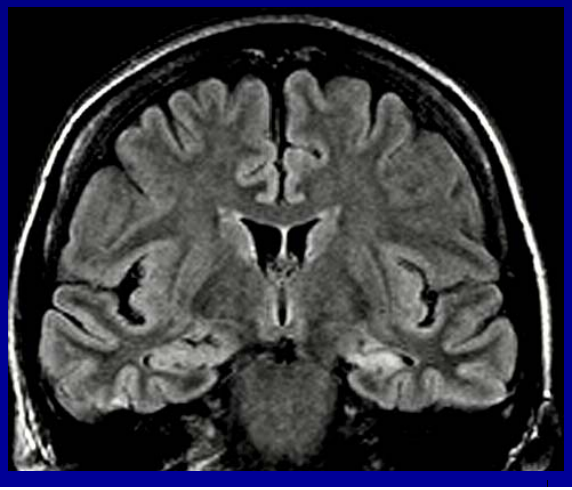
When the MRI is positive!

1. The lesion is in a NON ELOQUENT region
2. The lesion is in or close to an ELOQUENT AREA
3. Special situations of DEPTH OF SULCUS LESION
4. More than one lesion

When there is a lesion in a NON ELOQUENT CORTEX…

- **No need for an invasive evaluation** (if good electro-clinico-anatomical correlations)
- Neuropsychological testing
- +/- Intraoperative electrocorticography





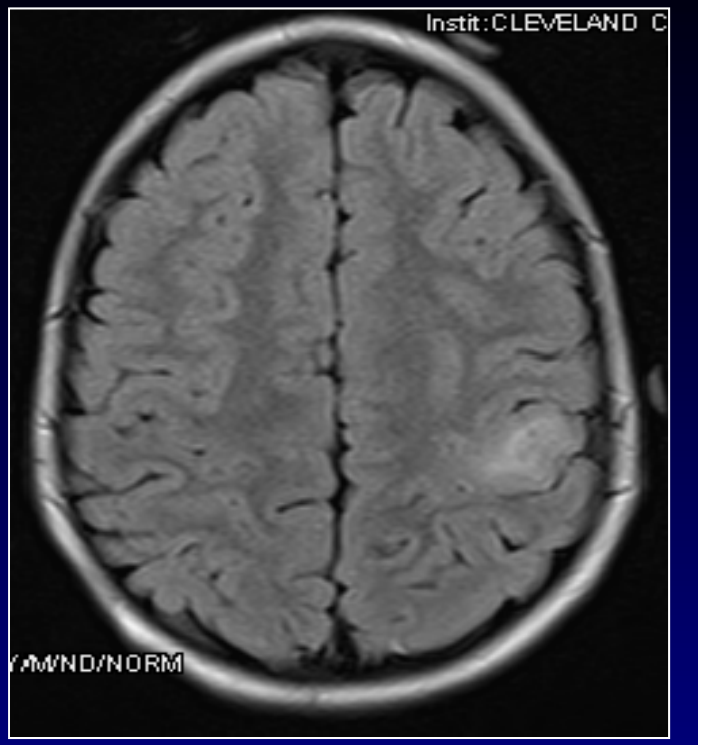
Lesion is *close or within an ELOQUENT area*

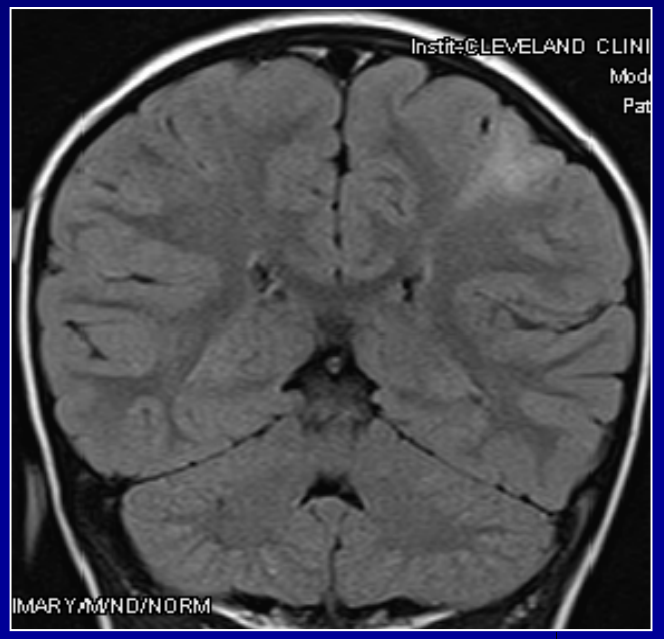
6 year old male patient, Left handed

Onset Age: 8 months

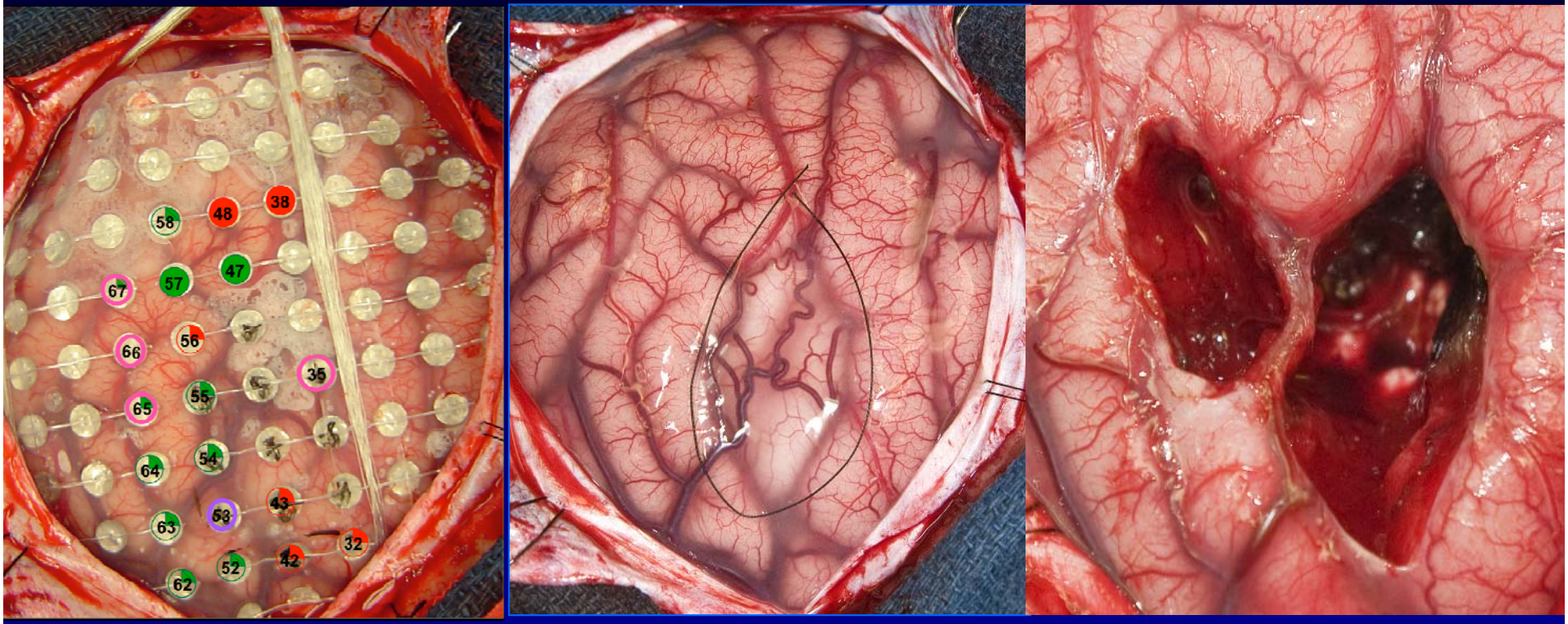
Seizures:

Aura-→ bilateral asymmetric tonic-→Right arm clonic





Epileptic regions and eloquent areas are outside the anatomical border of the lesion



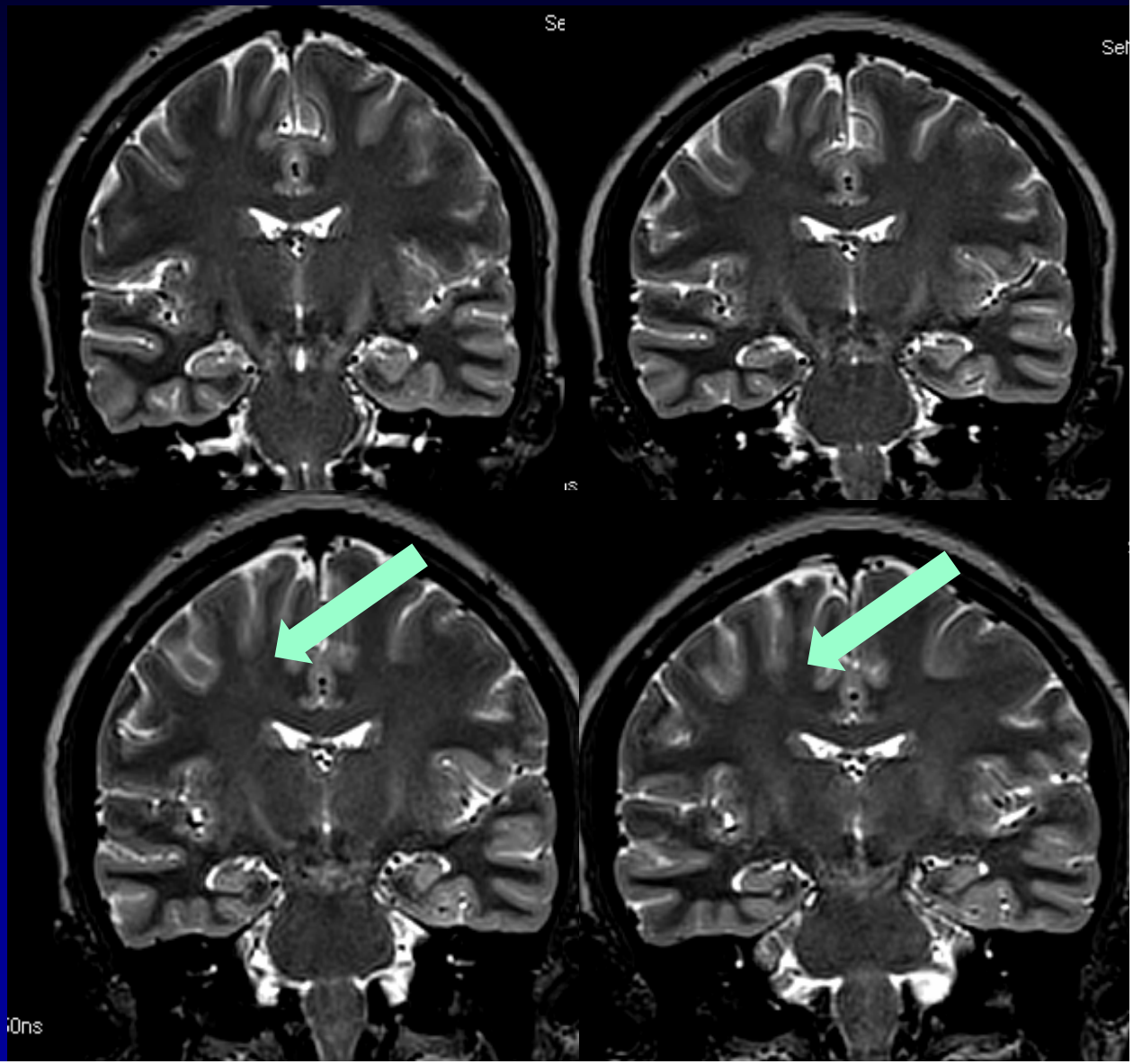
Pathology: Type II B FCD
Outcome: Seizure free
Mild transient right hand weakness

When the lesion is in the *depth of sulcus*

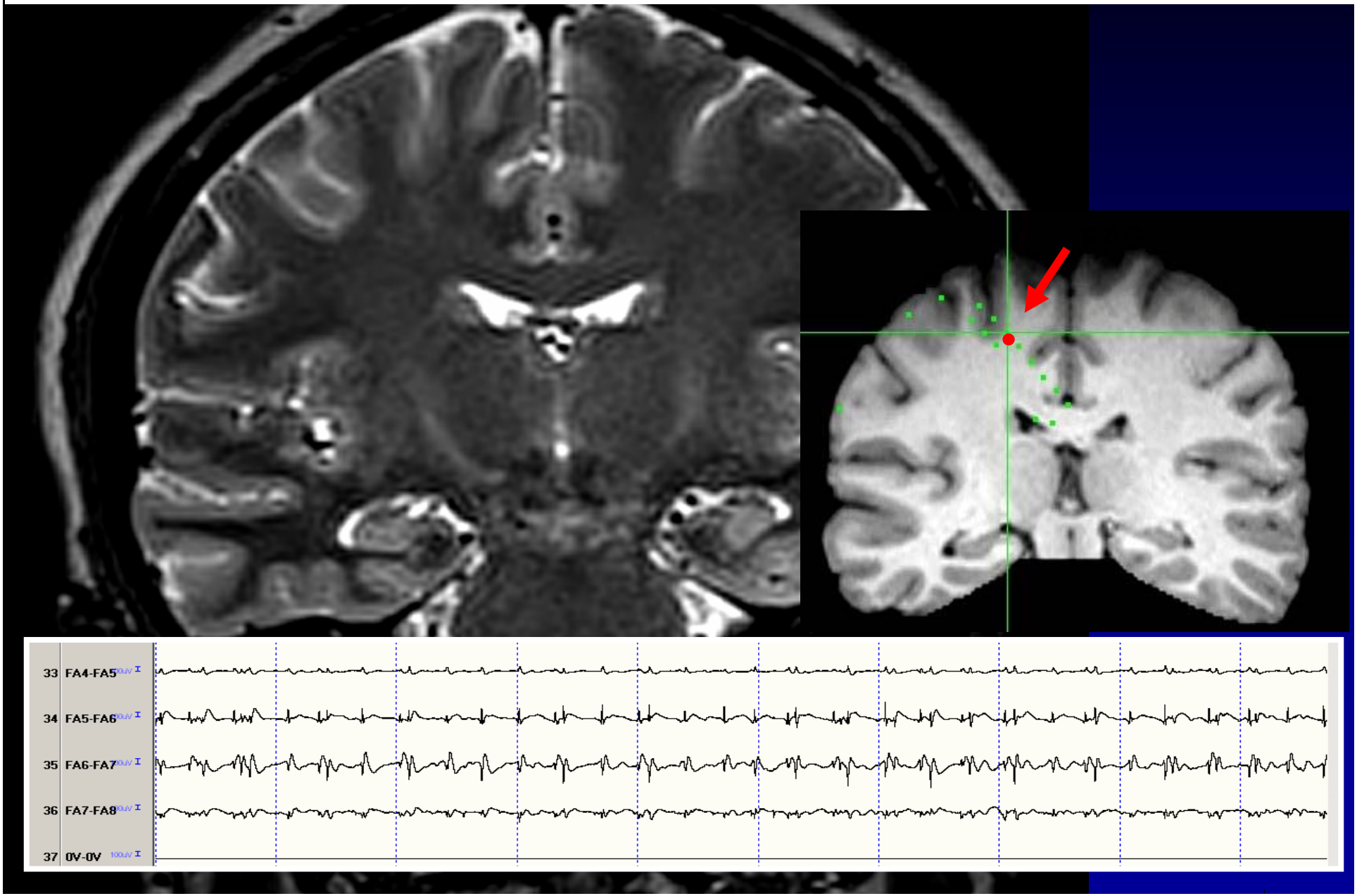
29 years old female, RH

Sz onset 8 y

Aura -→ left arm elevation →left leg elevation

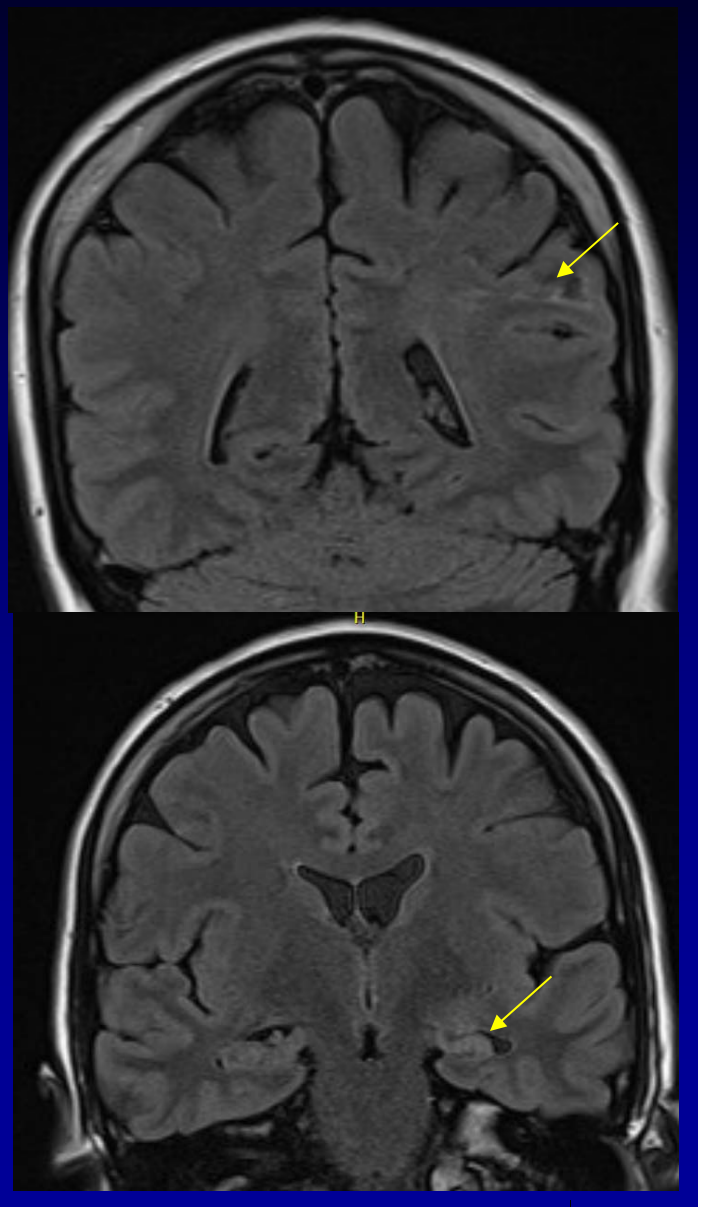


Interictal Continuous Rhythmic Spiking from deep sulcal lesion with mild T2/FLAIR signal increase

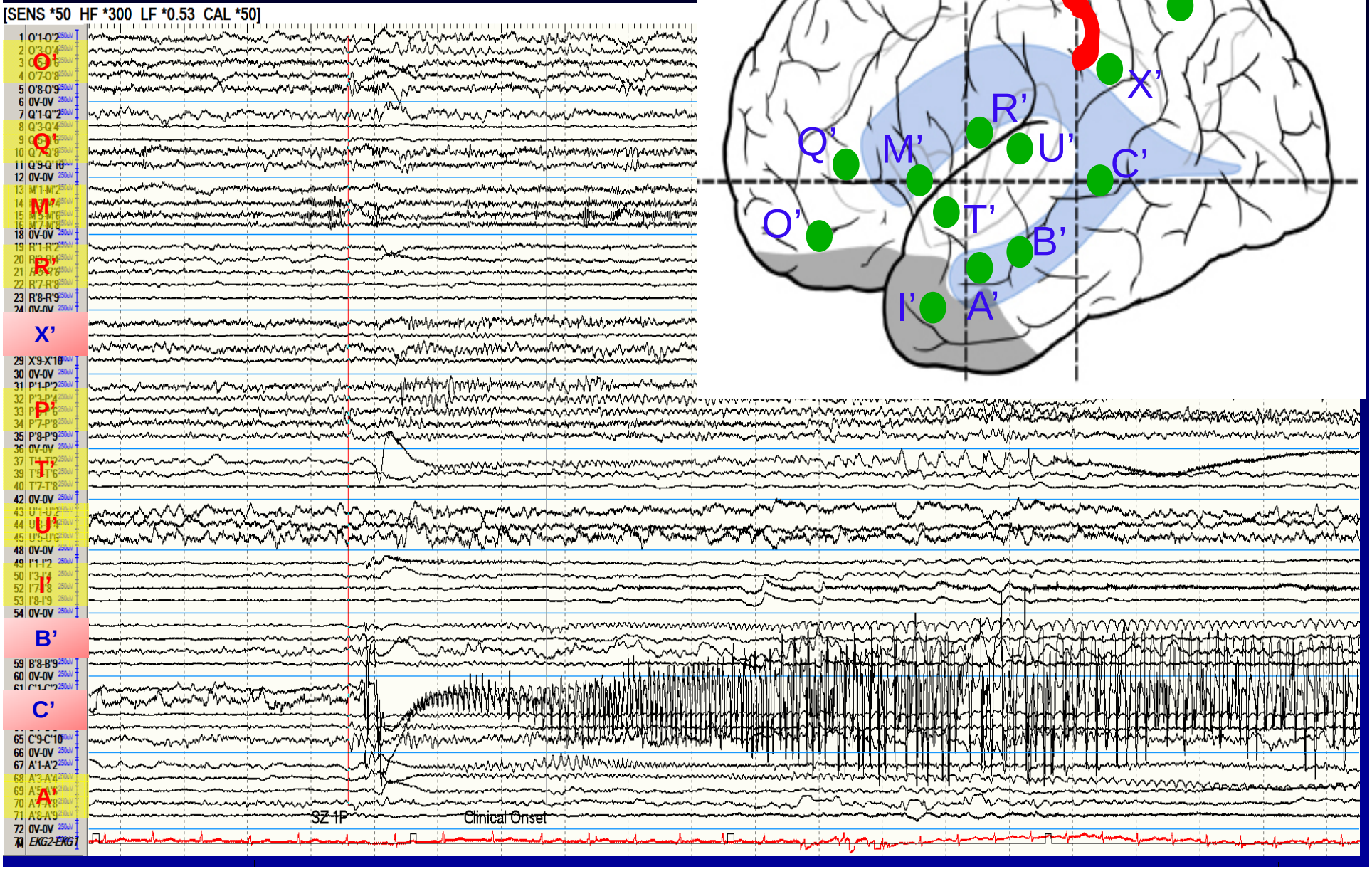


Dual pathology
Parietal vs mesial temporal vs parietal and mesial temporal

- 43 y/o, Right handed F
- Age at onset : 32 y
- Febrile seizure (1 year of age)
- Seizure description:
  - Aura: “sick feeling” like she is going to die
  - Staring
  - Jaw locks, tongue moves side to side
  - Groans repetitively



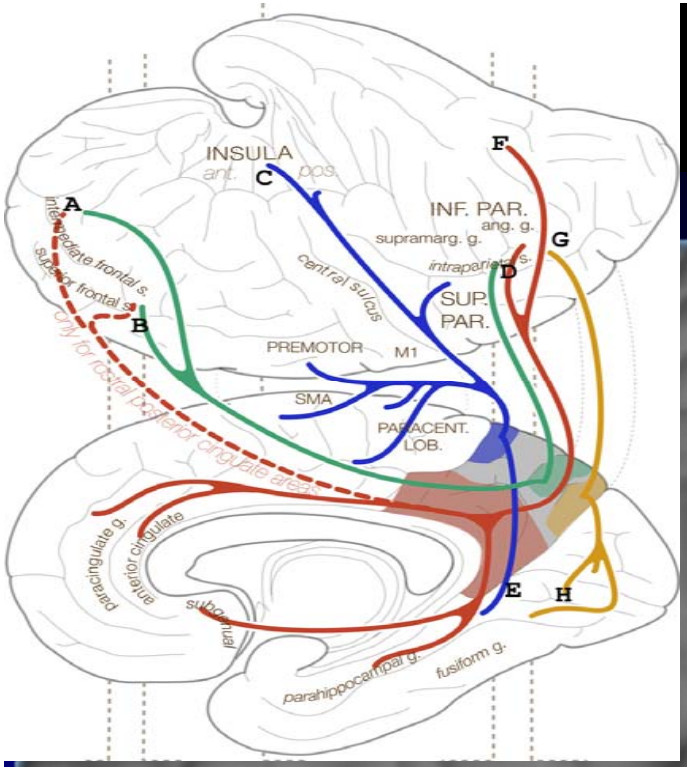
Epileptogenic area: HIPPOCAMPUS

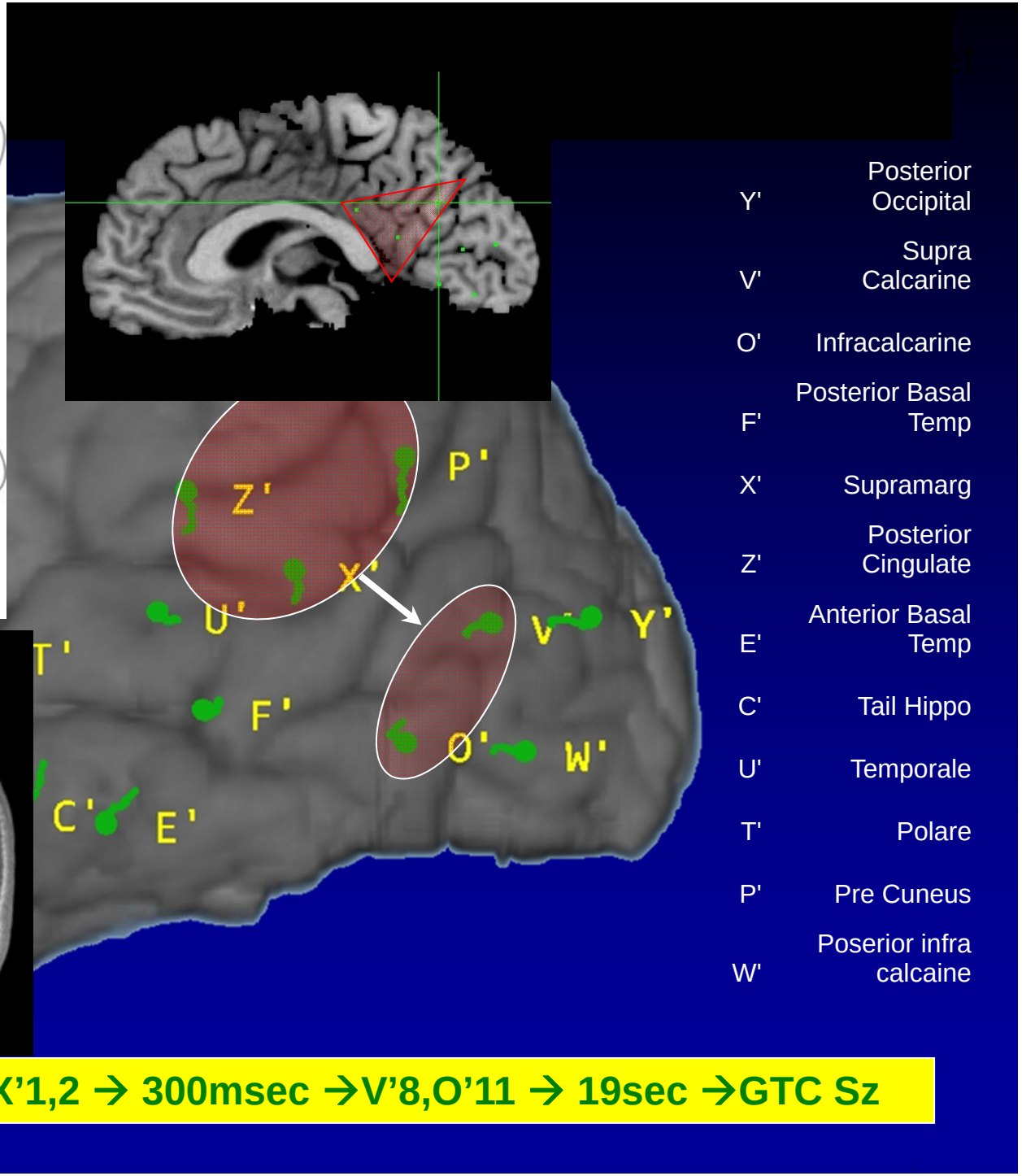


MRI negative
Mesial (Precuneus/Cingulate)

- INTERICTAL: Sharp waves, **left frontal**
- ICTAL: Aura (unclassified) -> Bilateral asymmetric tonic (Right head deviation) -> Complex motor -> GTC (2 recorded)

  EEG seizure: Lateralized **left hemisphere**
- MRI: Negative
- Ictal SPECT: Left lateral parietal, lateral temporal and dorsal frontal
- PET: Left mesial P-O, lateral TPO
- MEG: Not done (2007)





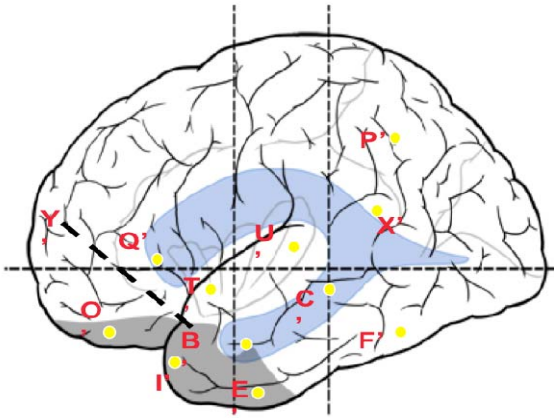
Y'	Posterior Occipital
V'	Supra Calcarine
O'	Infracalcarine
F'	Posterior Basal Temp
X'	Supramarg
Z'	Posterior Cingulate
E'	Anterior Basal Temp
C'	Tail Hippo
U'	Temporale
T'	Polare
P'	Pre Cuneus
W'	Poserior infra calcaine

P'1,2,6,10 & Z'1,2 & X'1,2 → 300msec →V'8,O'11 → 19sec →GTC Sz

MRI Negative: limbic epilepsy (temporal-perisylvian)

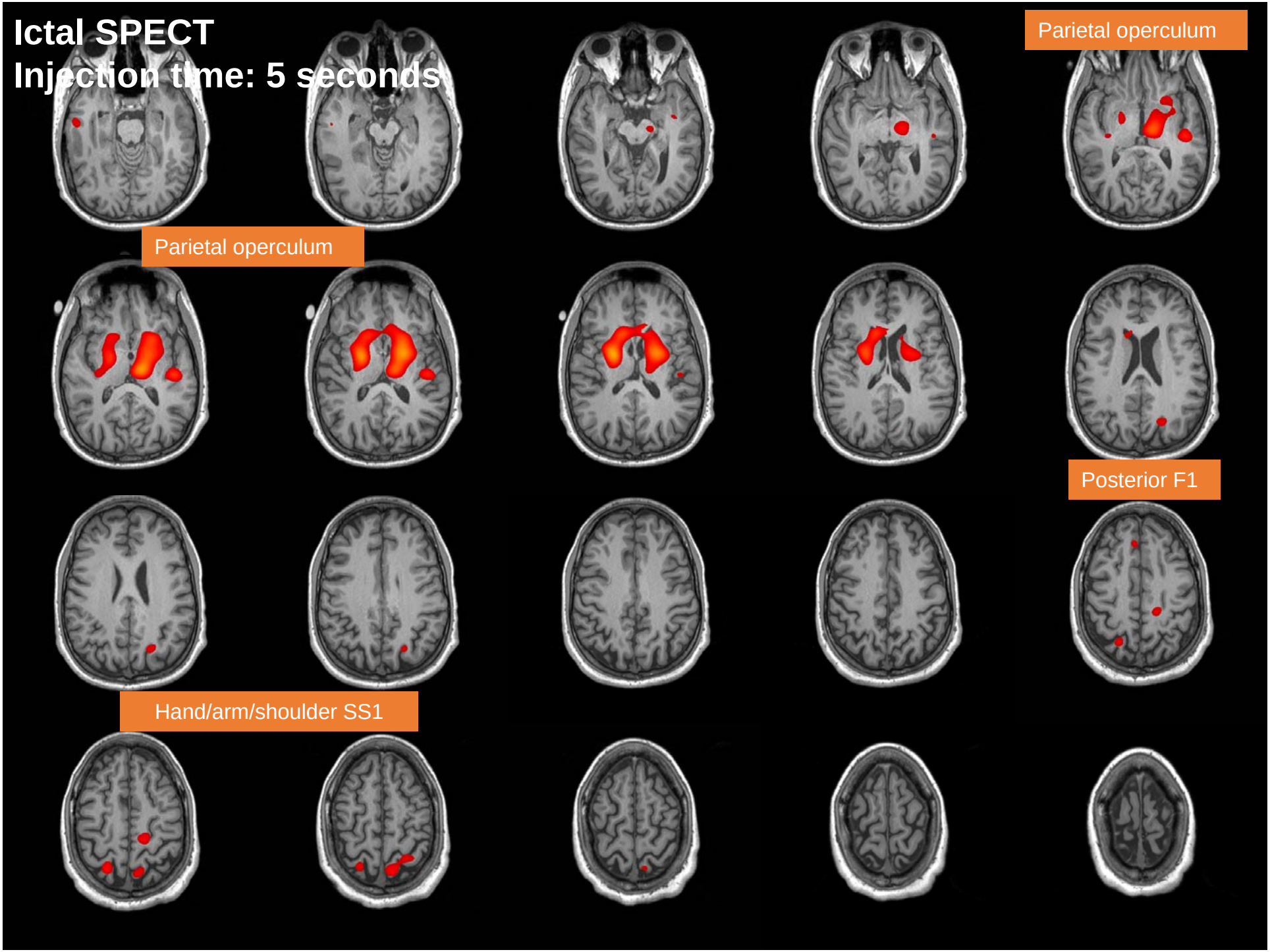
- 52 year old LHD woman with first seizure (convulsive) at age 50
- Seizures: Aura (psychic/autonomic) -> dialeptic or automotor seizure -> right versive seizure -> generalized tonic-clonic seizure
- MRI: Normal
- PET: Left temporal hypometabolism

Epileptogenic Zone: Hippocampus

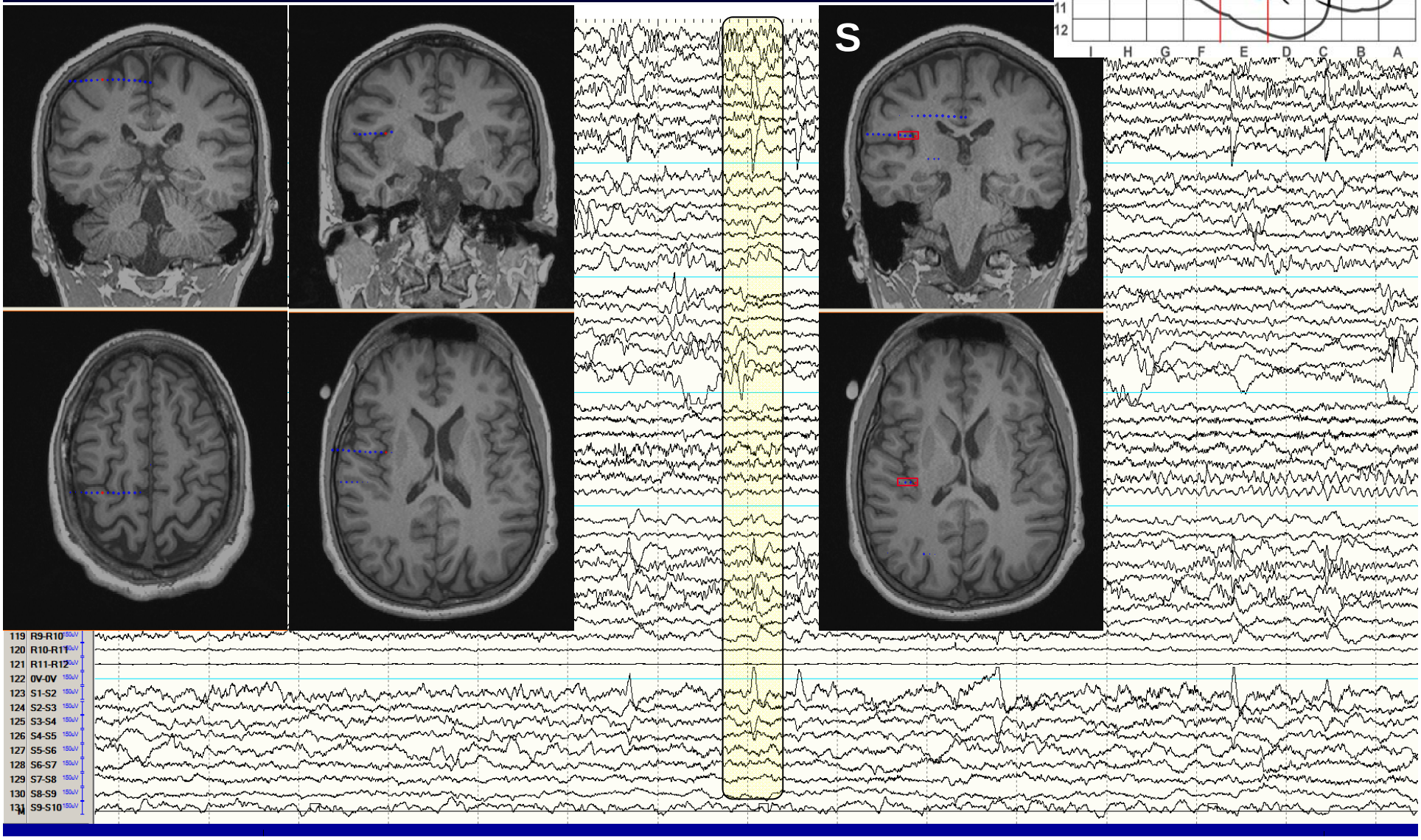


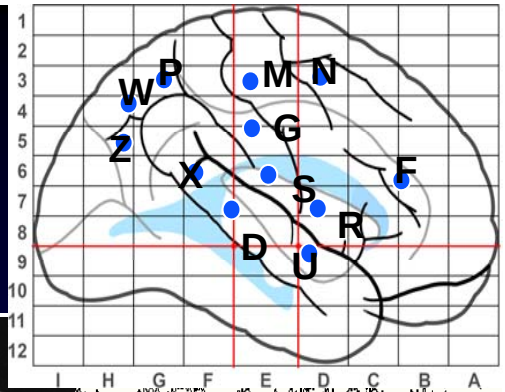
MRI negative epilepsy: posterior perisylvian

- Age: 18 years old, right handed, onset at 3 y
- Seizure description:
  - Describes sensation in his left arm as tingling, shock, pain which can move to left flank/leg, sometimes head. He will grab his left arm with his right and curl into a ball.
  - vEEG: Initially grabs his upper left arm with the right hand, rolls onto his left side, looks in pain, screams and kicks with his left leg. Becomes tachycardic (HR 66 > 138) no loss of awareness.
- Normal MRI/PET


Ictal SPECT
Injection time: 5 seconds
Parietal operculum
Parietal operculum
Posterior F1
Hand/arm/shoulder SS1

SZ3A: aura (sensory, facial tingling)
Onset R2-6, S1-4, synchronous spread
M10-13





Invasive evaluation in MRI negative Epilepsies

- Strong anatomo-electro-clinical hypothesis is needed
- Ictal SPECT may be helpful for ictal network mapping
- MEG could be helpful in some cases of perisylvian, dorsal convexity epilepsies
- Full network needs to be covered

Presurgical Evaluation

Focal Epilepsy
Video EEG Monitoring
MRI

Lesion Identified:
Complete resection of the lesion +/- intraoperative electrocorticography (invasive evaluation mainly for functional mapping)

No Lesion is identified:
PET, Ictal SPECT, MEG, followed by Invasive evaluation based on network hypothesis

Cleveland Clinic

Every life deserves world class care