Cleveland Clinic

Epilepsy Surgery Genetics

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History of “Epilepsy” surgery

Trepanation:
To relieve the brain from demons
To decrease pressure from depressed skull fractures

The skull was found in a dolmen in France by Pruniéres (Wellcome Library, London)

Transition from *skull surgery* to *Epilepsy surgery*

Late 1800's

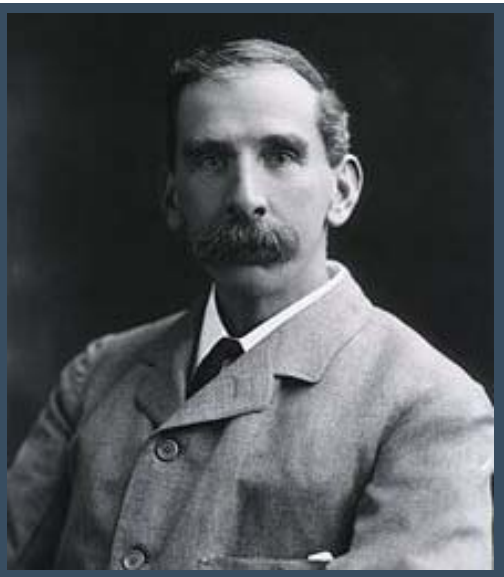
The transition from skull surgery to modern brain surgery was prompted by:

1) An increasingly critical view of trepanation

2) The emerging localization theories of the brain

3) The introduction of antisepsis and better pain treatment.

Late 19th Century: Resection of cortical lesion



Sir Victor Horsley:

Successful cortical resections with significant reduction in epileptic seizures in 3 patients (Horsley,1886)

?first association of epilepsy localization and “etiology” for the success of epilepsy surgery

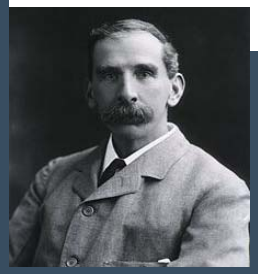
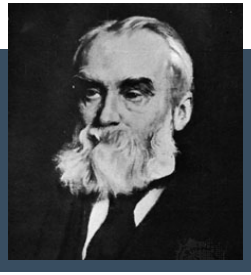
“…local commencement of the fit suggests that the disease causing them is at the surface of the brain…”

Sir William Gowers, 1881

Late 19th Century: Pathology (lesion) a possible cause of Epilepsy as a clinical "disease"

Pathology (lesion)

Sir Victor Horsley, J.H. Jackson and D. Ferrier: Macroscopic lesion (pathology) and/or cortex area which, on stimulation, reproduced the initial symptoms of the clinical seizure (semiology).

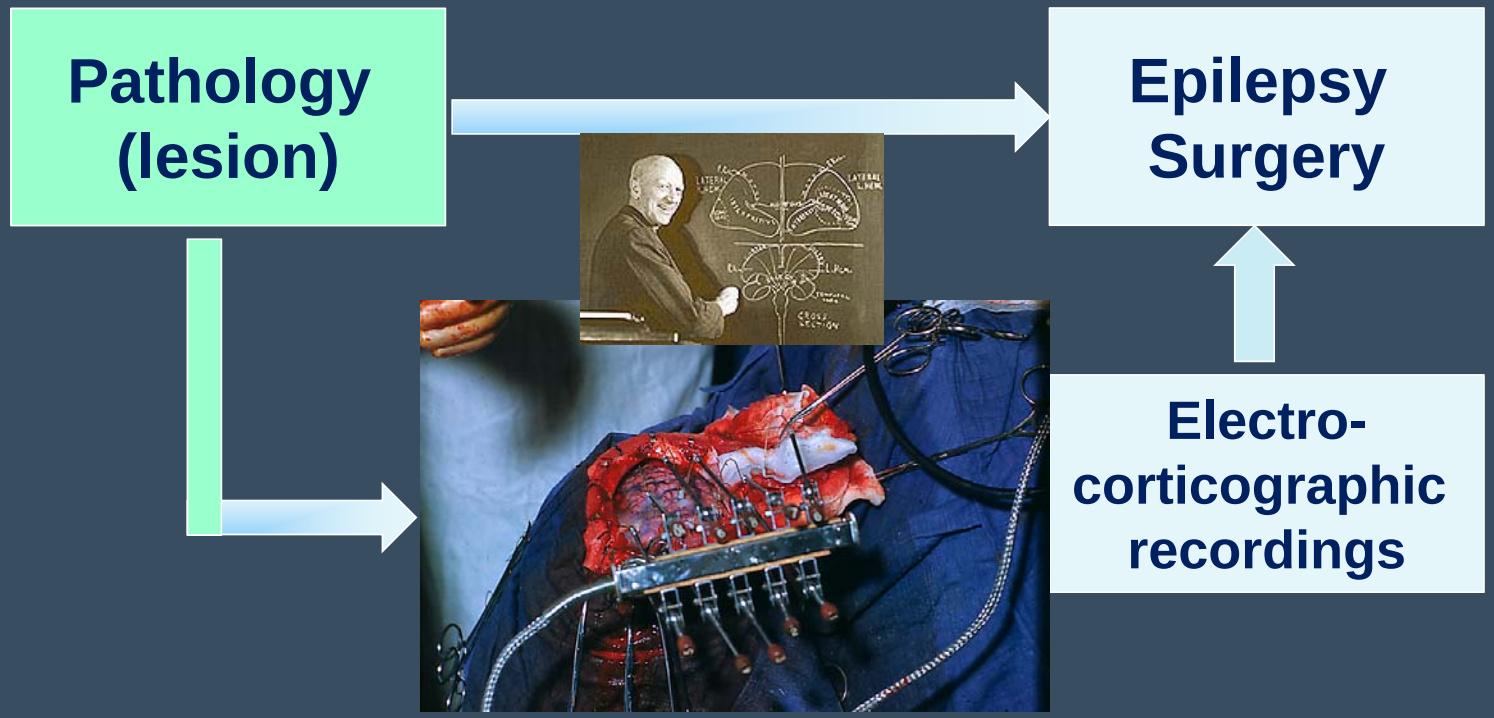




Direct cortical stimulation

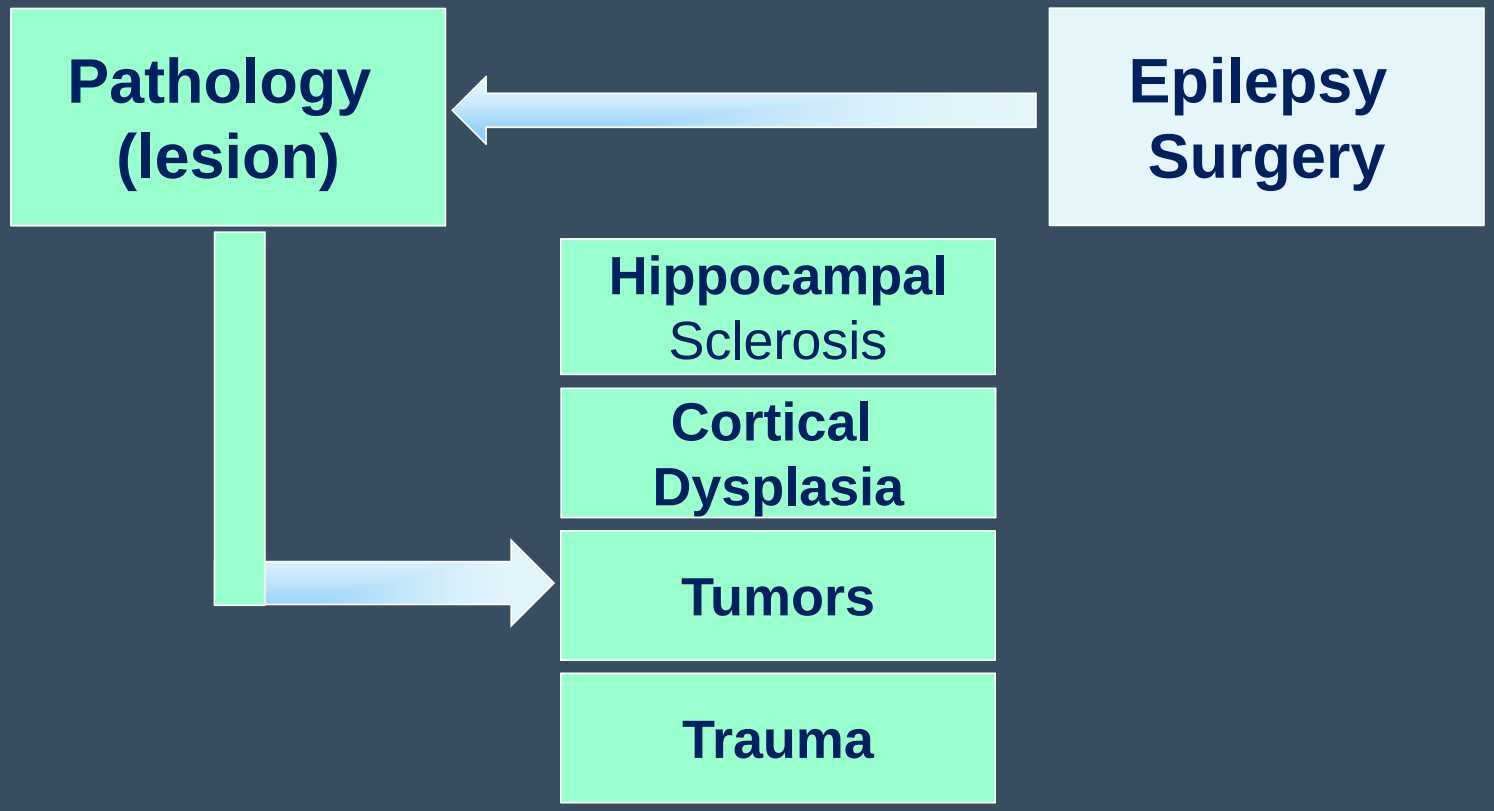
Seizure Semiology

Epilepsy Surgery

Mid 20th Century: Pathology a possible cause of Epilepsy as an electrical “disease”



Second half of 20th Century: Epilepsy Surgery helped in the microscopic characterization of Epileptic pathologies

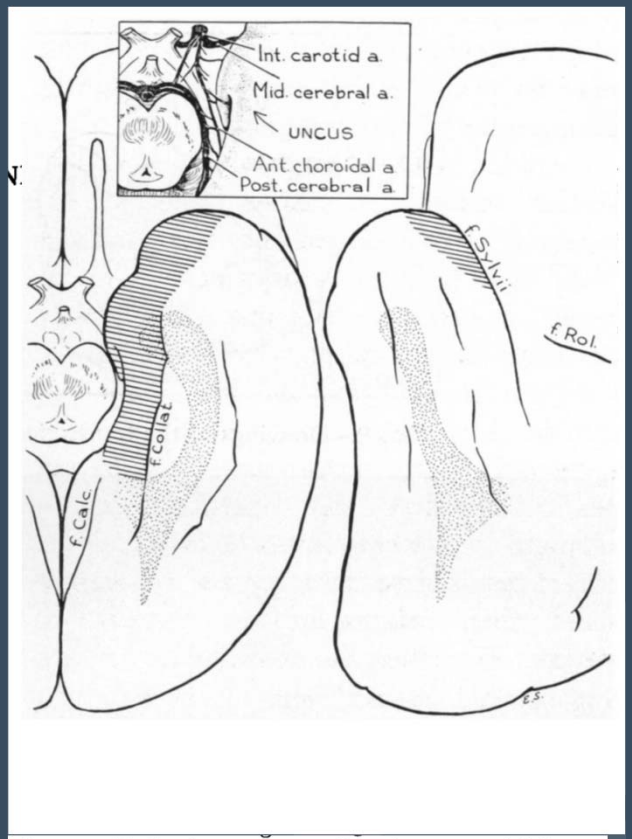


Pathology of Temporal lobe Epilepsy

Penfield reported “incisural sclerosis” in 100 out 157 patients he operated on for temporal lobe epilepsy.

He called the lesion probably ischemic and involving at times the anterior part of the “first temporal convolution”

In the remaining 57cases: tumors or the sequelae of head injury or infection.



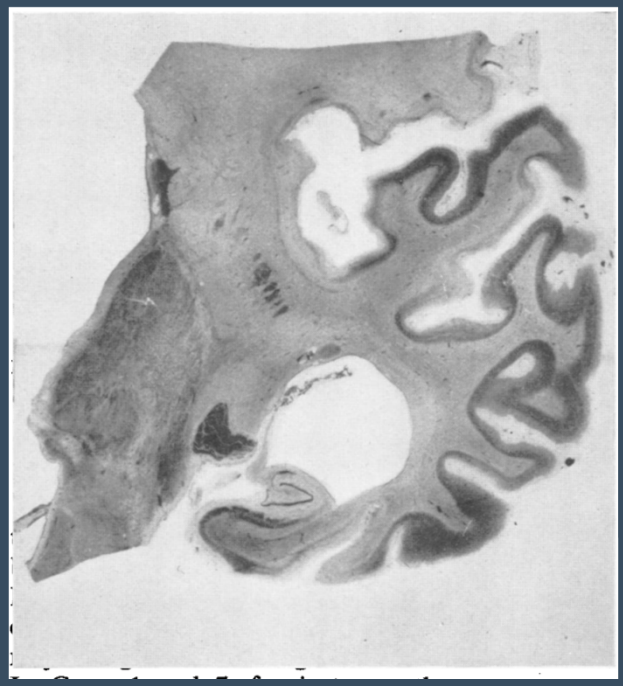
ade it possible for the surgeon ations in temporal lobe epi

an cooperate

emporal lobe epilepsy. It had been found by
n in 100 out of 157 patients (63%) submitted
peration. The extent of this sclerosis ranged from
olvement of a single gyrus to involvement of the
re temporal lobe, but the mesial and inferior
tions of the lobe (uncus, hippocampal gyrus)
first temporal gyrus were the areas most fre-

have already been reviewed by Hill, Falconer, a
Pampiglione (1953). Several other cases of tempo
lobe epilepsy due to large structural lesions, su
as readily recognizable tumours, porencepha
cysts, and angiomas, were also operated on during
same period, but these were excluded as the operat
intervention in them was limited to an excision

27



Hippocampal
Sclerosis

J Neurol Neurosurg Psychiatry 1971;34:369-387 doi:10.1136/jnnp.34.4.369

Articles

Focal dysplasia of the cerebral cortex in epilepsy

D. C. Taylor[1], M. A. Falconer, C. J. Bruton, J. A. N. Corsellis

Neurosurgical Unit of Guy's, Maudsley, London
King's College Hospitals, London
Department of Neuropathology, Runwell Hospital, Wickford, Essex

Abstract

An unusual microscopic abnormality has been identified in the lobectomy specimens removed surgically from the brains of 10 epileptic patients. The abnormality could seldom be identified by palpation or with the naked eye. Histologically, it consisted of congregations of large, bizarre 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. This kind of abnormality appears to be a malformation. The picture is reminiscent of tuberous sclerosis but too many distinguishing features, both in the clinical and in the pathological aspects, make this diagnosis untenable. The cases are therefore looked on provisionally (since all but one are still alive) as comprising a distinct form of cortical dysplasia in which localized, exotic populations of nerve cells underlie the electrical and clinical manifestations of certain focal forms of epilepsy.

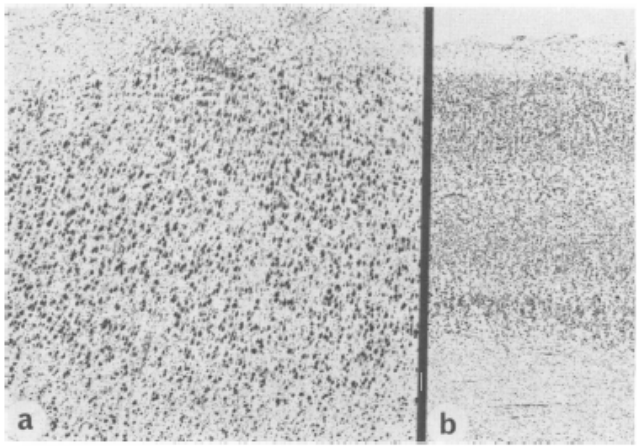


FIG. 3. a. *Case 1. Vast population of large anomalous neurones spread through all but the first cortical layer. The cortex is widened and the lamination is lost.* b. *Normal striate cortex for comparison with, and at the same time magnification as,* a. *Cresyl violet, a and b, ×30.*

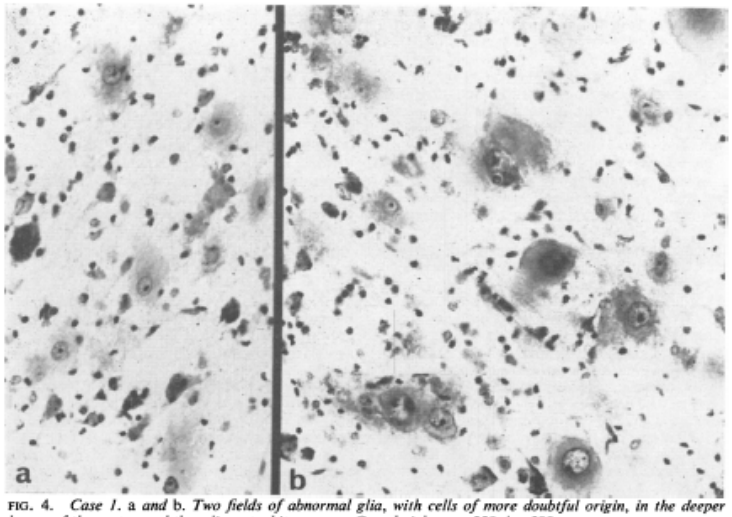
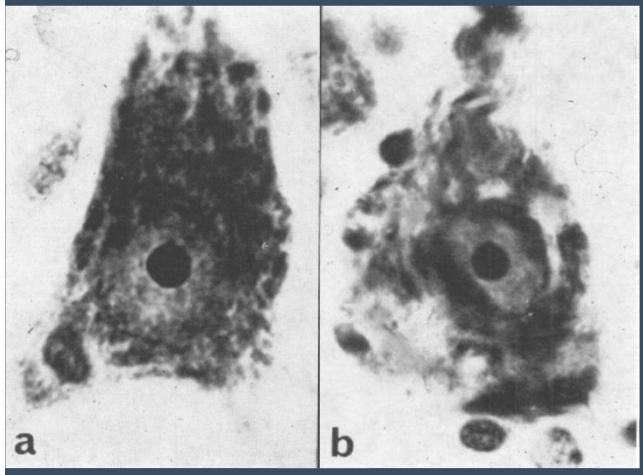


FIG. 4. *Case 1.* a *and* b. *Two fields of abnormal glia, with cells of more doubtful origin, in the deeper layers of the cortex and the adjacent white matter. Cresyl violet, a × 250, b × 500.*

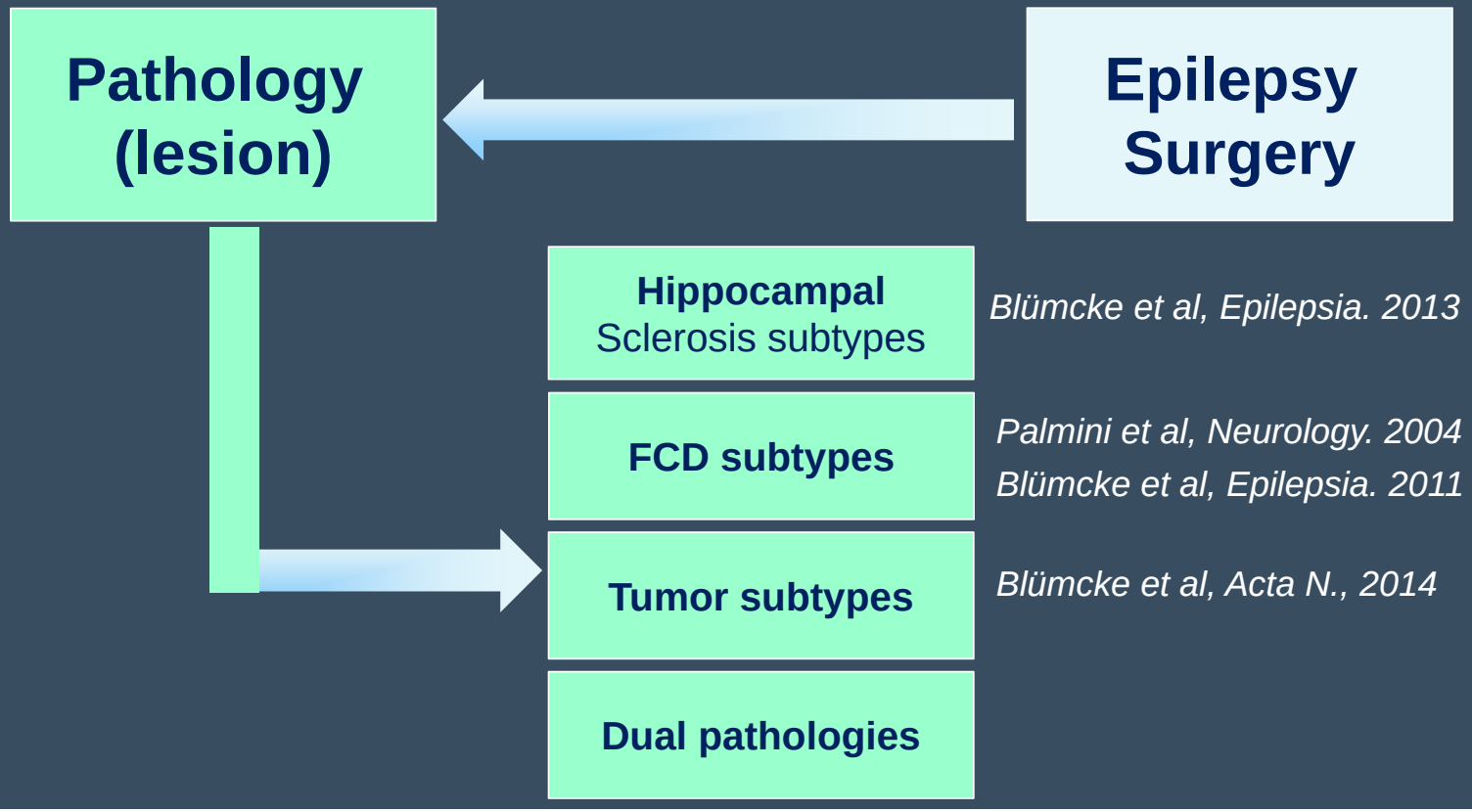
Cortical Dysplasia

Main features:
1. Architectural disorganization
2. Dysmorphic cells
3. Giant cells in white matter and cortex
4. Gliosis

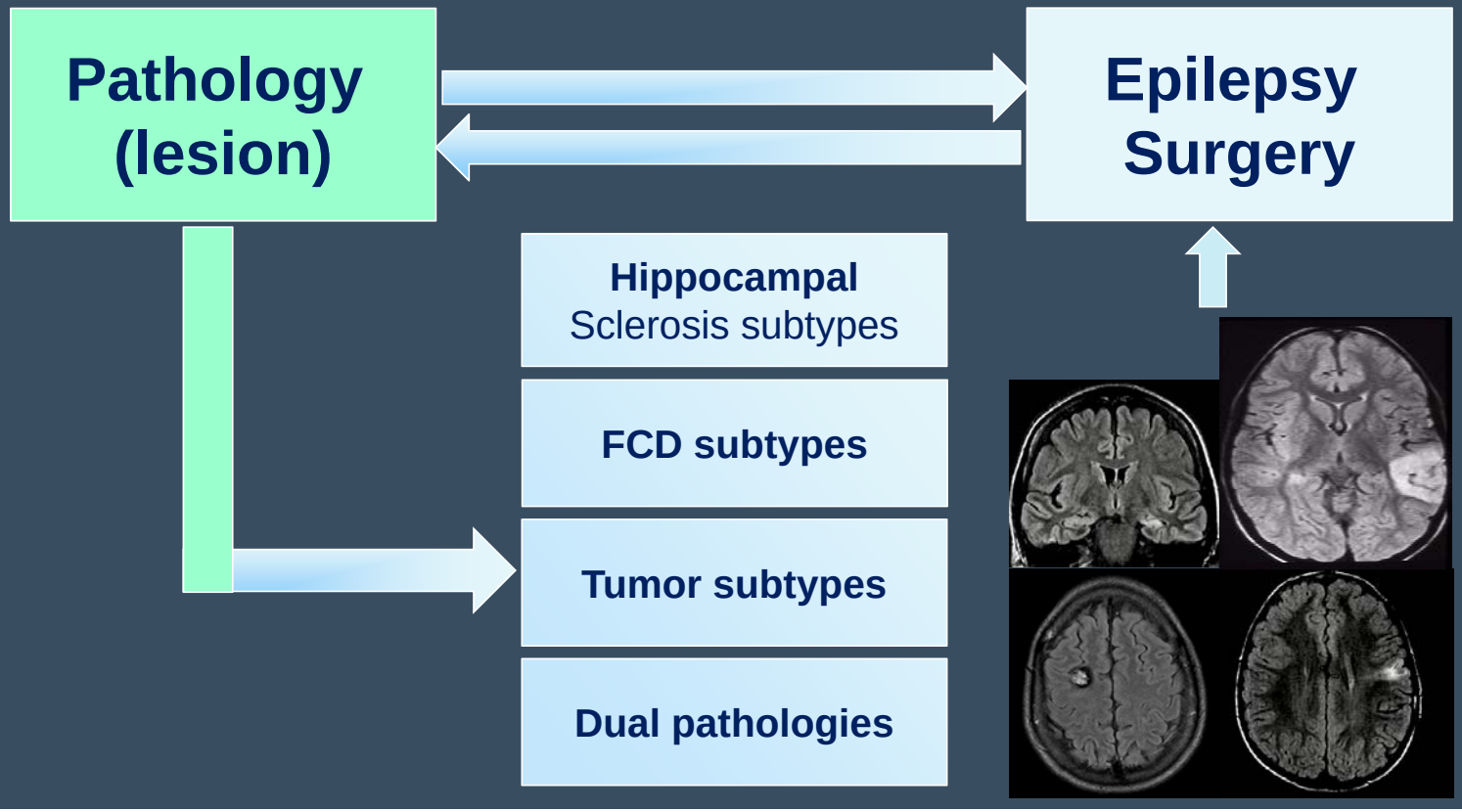


Taylor et al, 1971

Late 20th Century: Epilepsy Surgery helped in microscopic sub-characterization of Epileptic pathologies



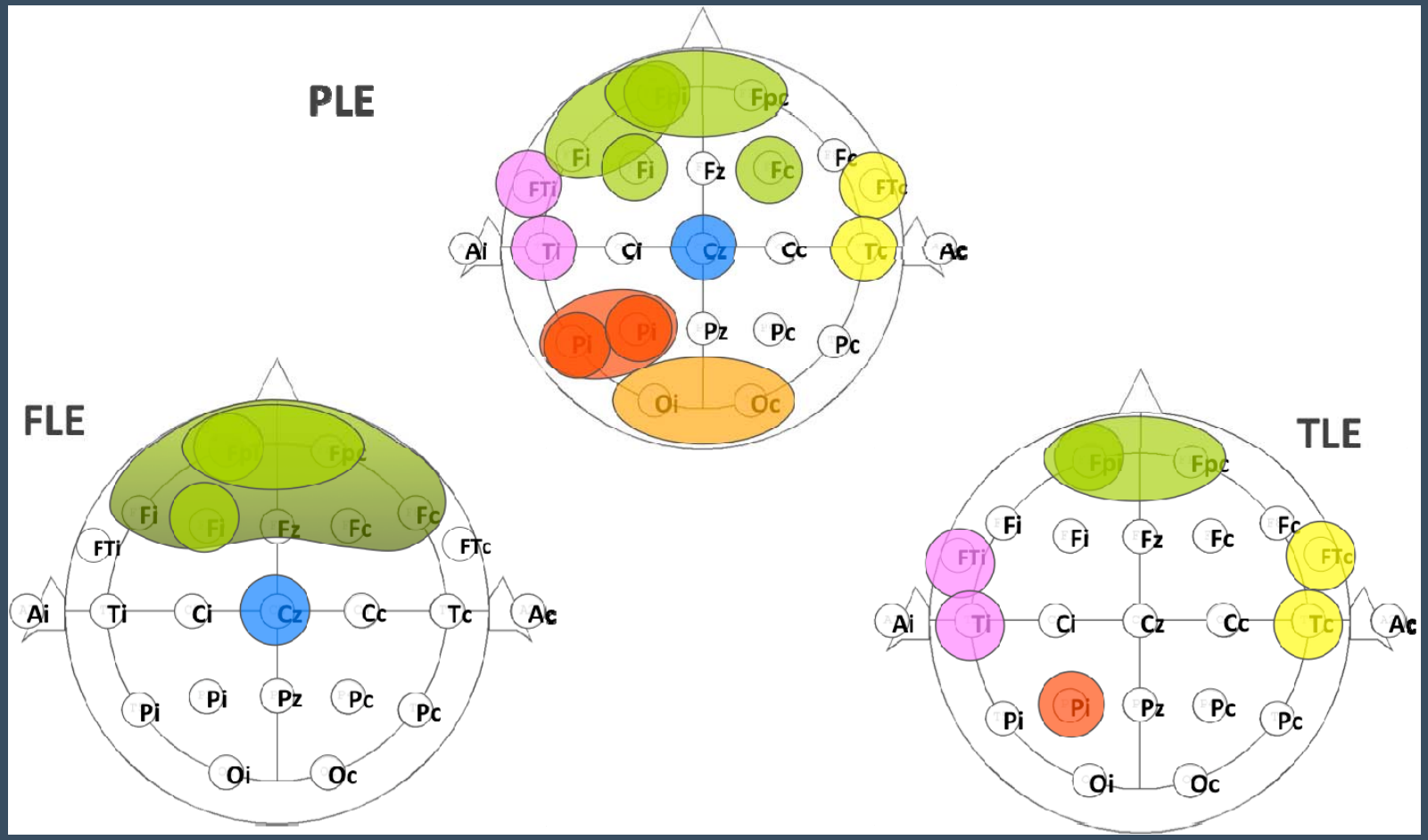
Late 20th Century: Pathology helped in imaging characterization of epileptic lesions



Localization of the epileptic region in the 21st Century

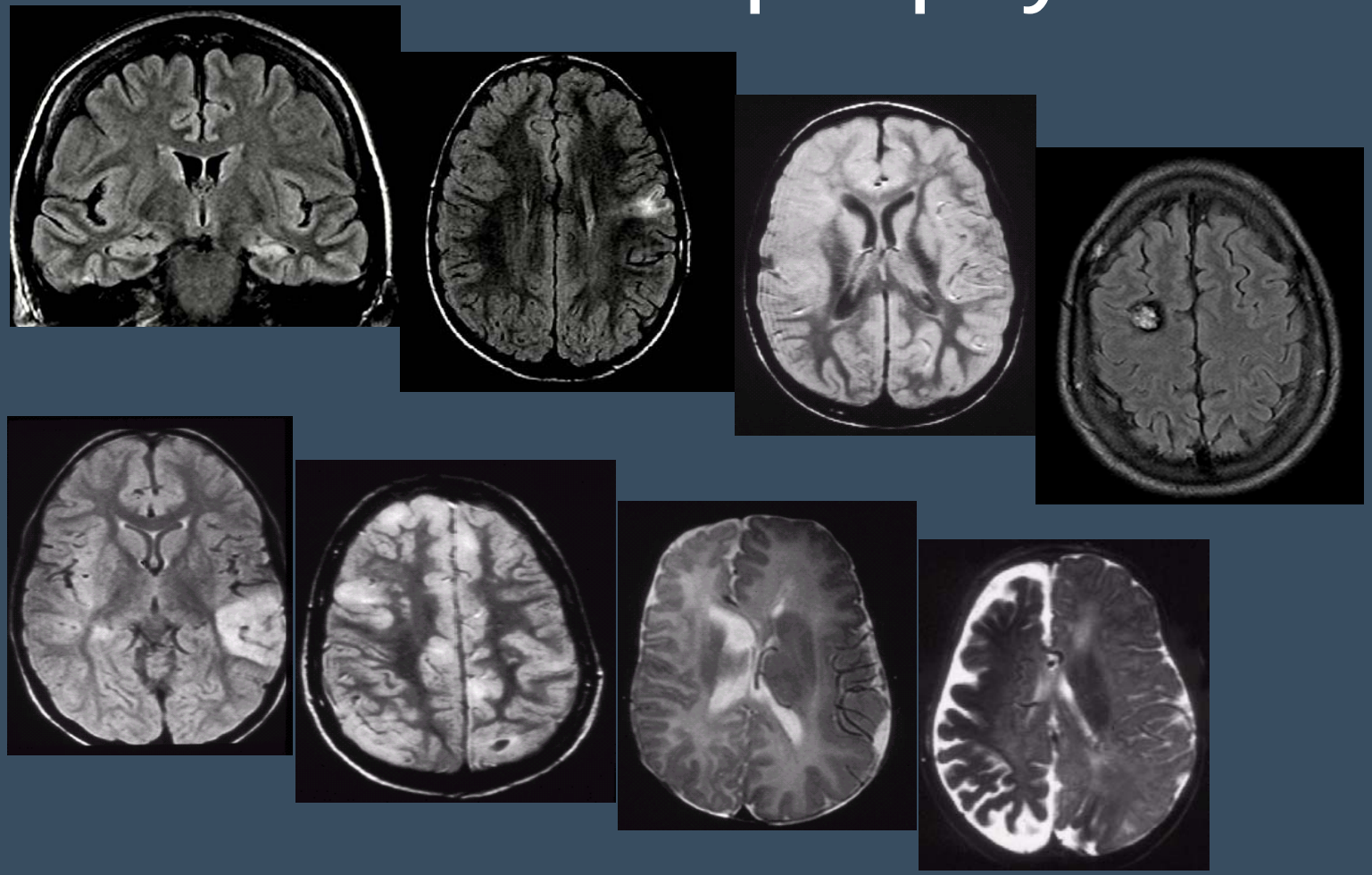
- SCALP EEG
- MRI
- FDG-PET
- ICTAL SPECT
- MEG
- INVASIVE

EEG does not adequately localize the Epileptic region



Ristic et al, Epileptic Disorders, 2012

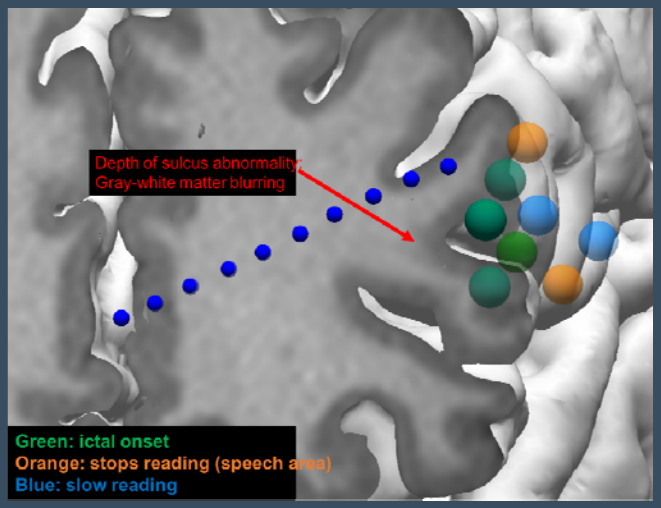
MRI in Epilepsy

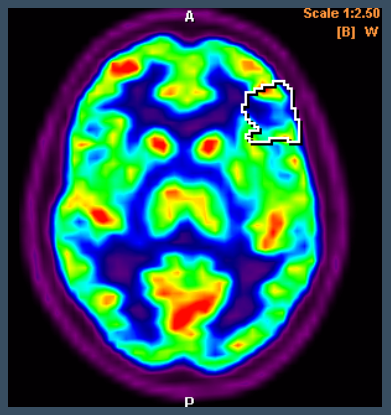


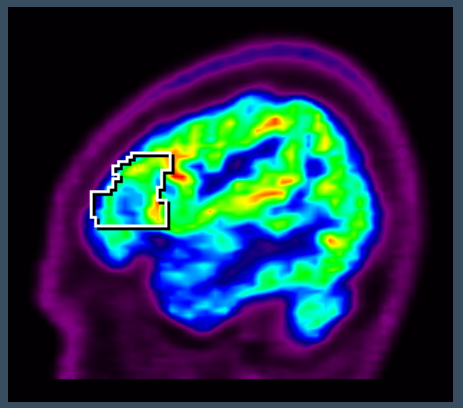
…but up to 25% of patients with medically intractable epilepsy do not show ”lesions’ on MRI!

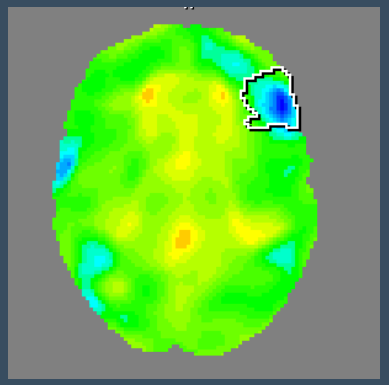
FDG-PET scan:

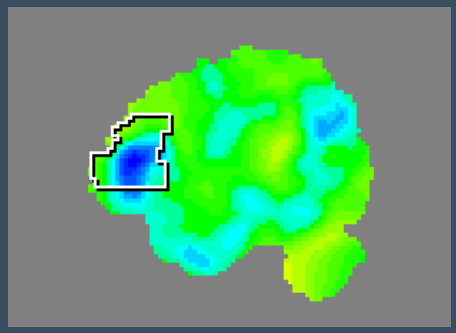
High sensitivity, low specificity, not a good predictor of pathology





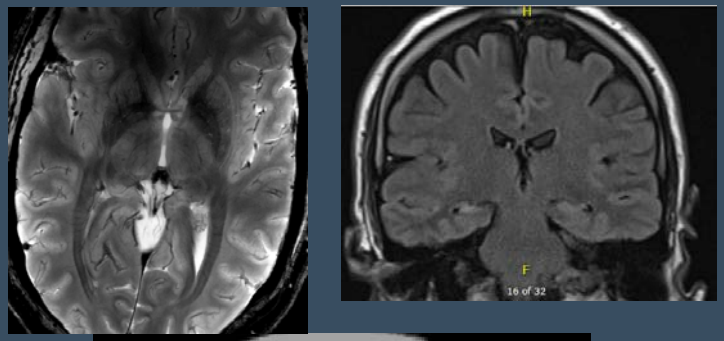


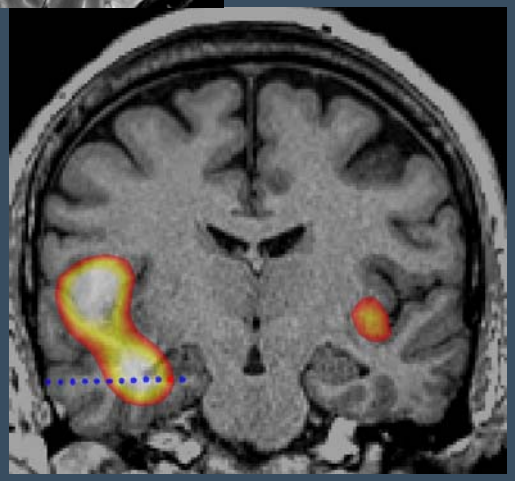




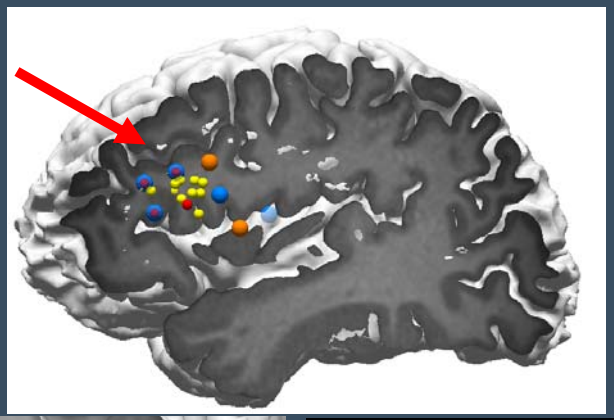
Ictal SPECT:
Maps network of ictal activation

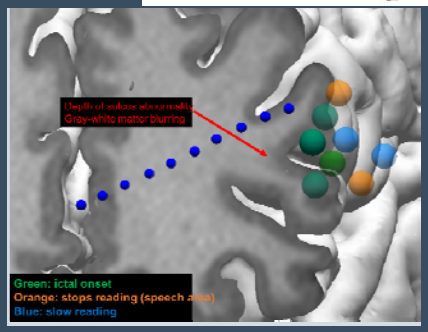
HS+ Insular FCD2A

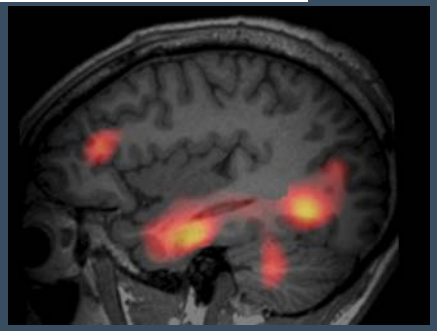




BOS FCD

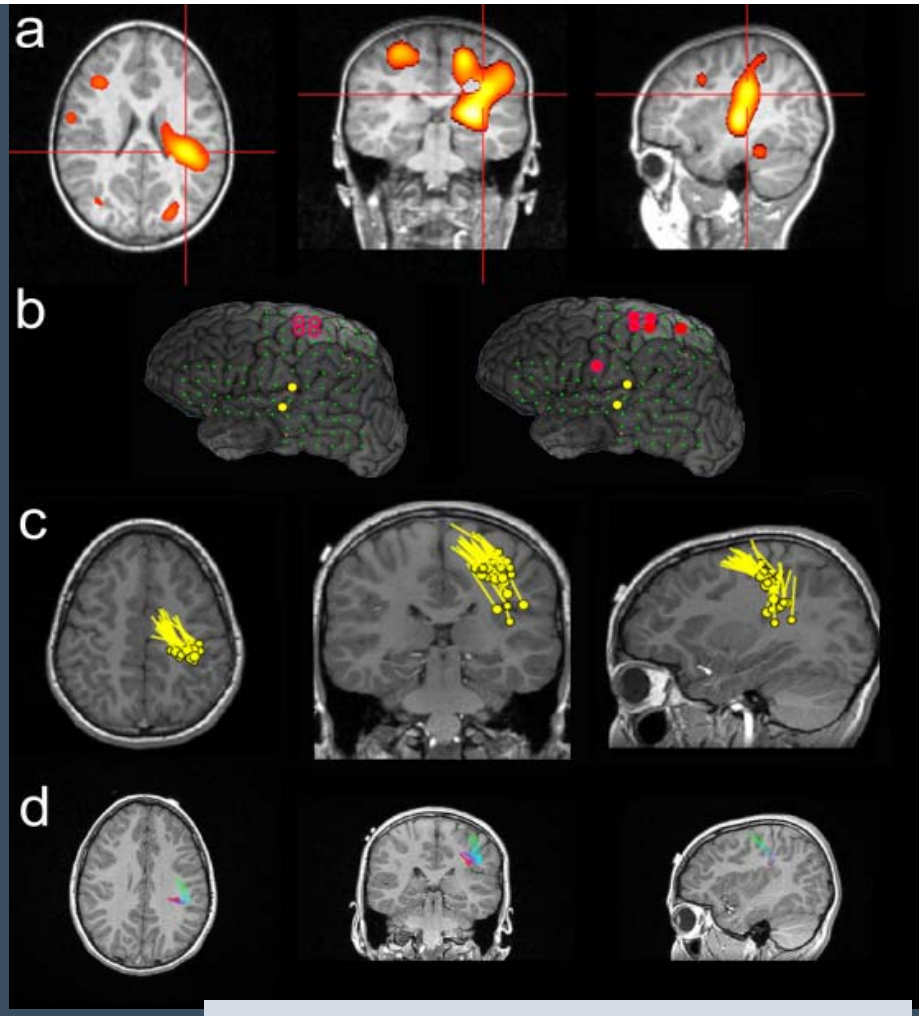






…but does not point to the epileptogenic zone

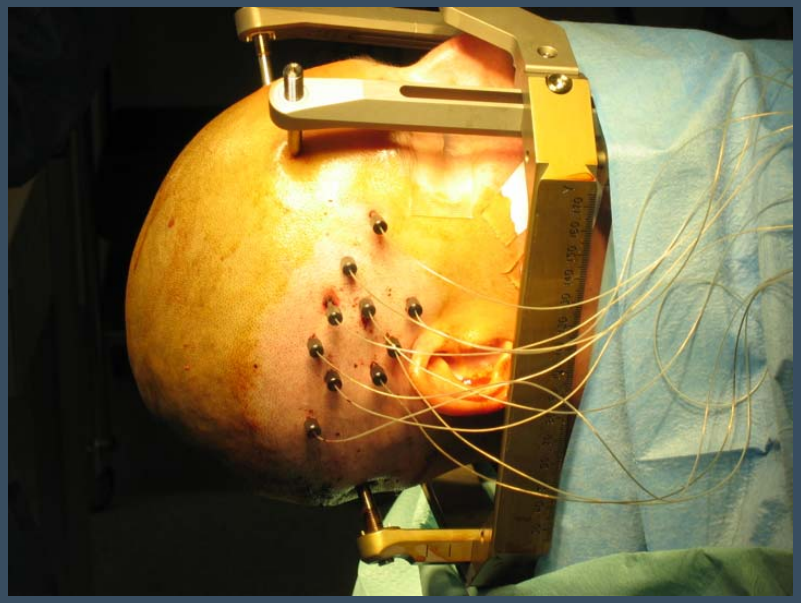
MEG may localize the interictal focus and its spread



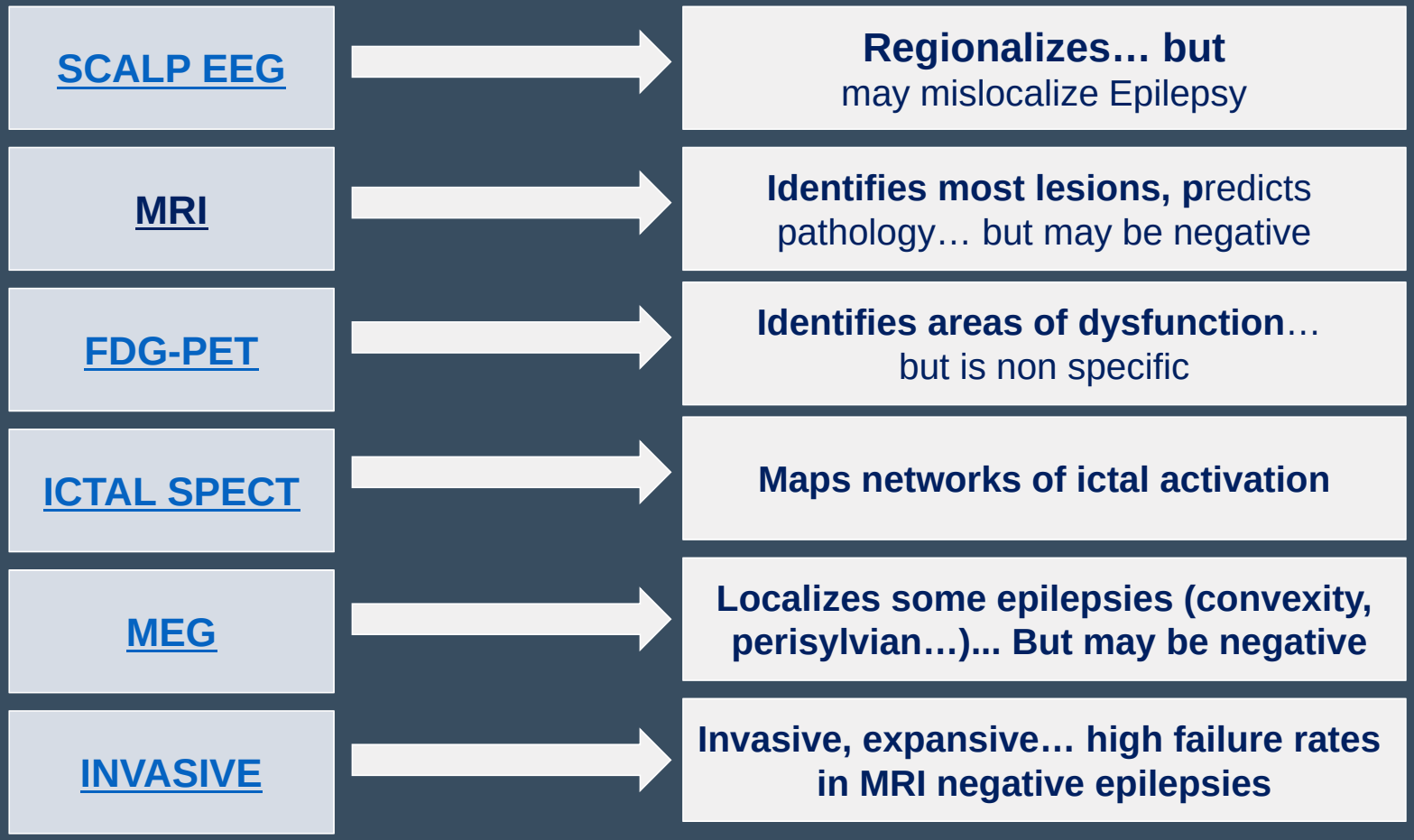
Wang et al, Hum Brain Mapp. 2012

…but does not always accurately localize the Epileptogenic Zone or may be negative

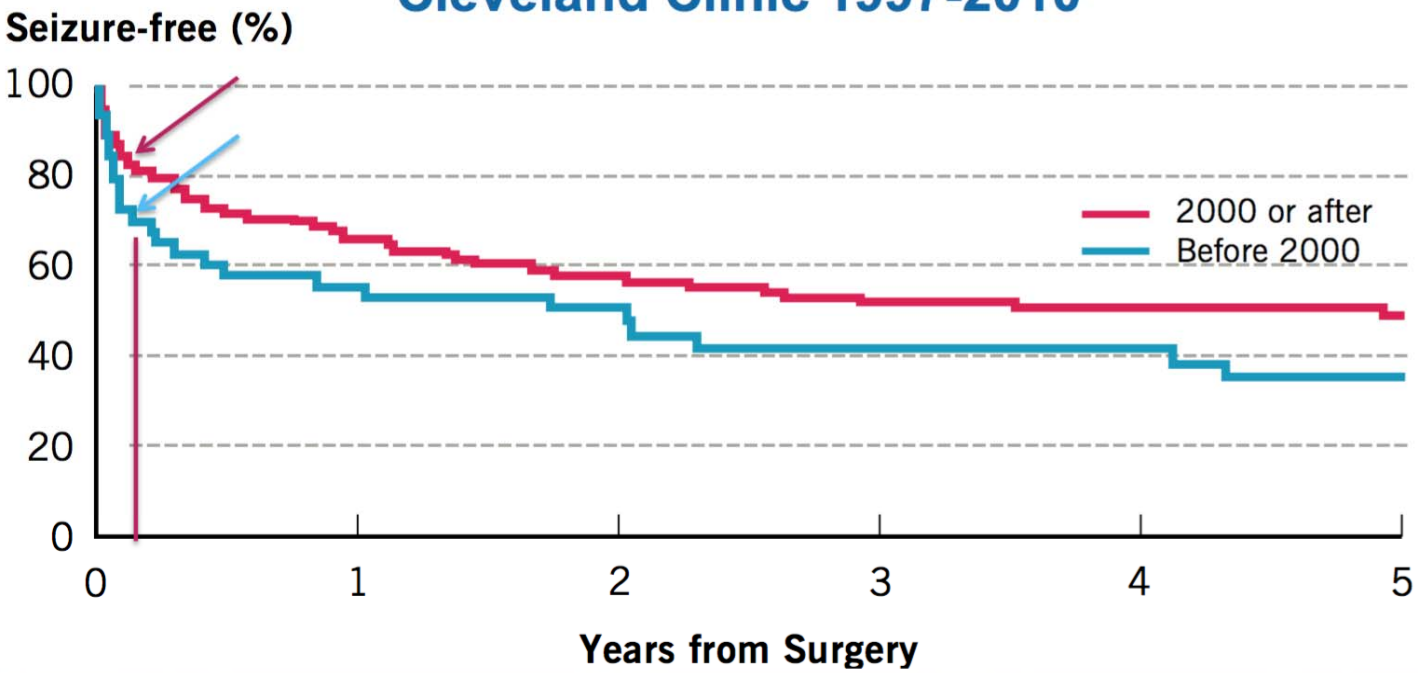
Invasive evaluations with SEEG or Subdural grids fail to localize the ictal onset in up to 15% of the cases



Localization of the epileptic region in the 21st Century



Does Technology help?
Improvement in Frontal Lobe Surgical Outcomes over the Years (N = 324)
Cleveland Clinic 1997-2010



Years from Surgery	1 Year	2 Years	5 Years
% Seizure-free - 2000 or After	65%	58%	47%
% Seizure-free - Before 2000	53%	48%	33%

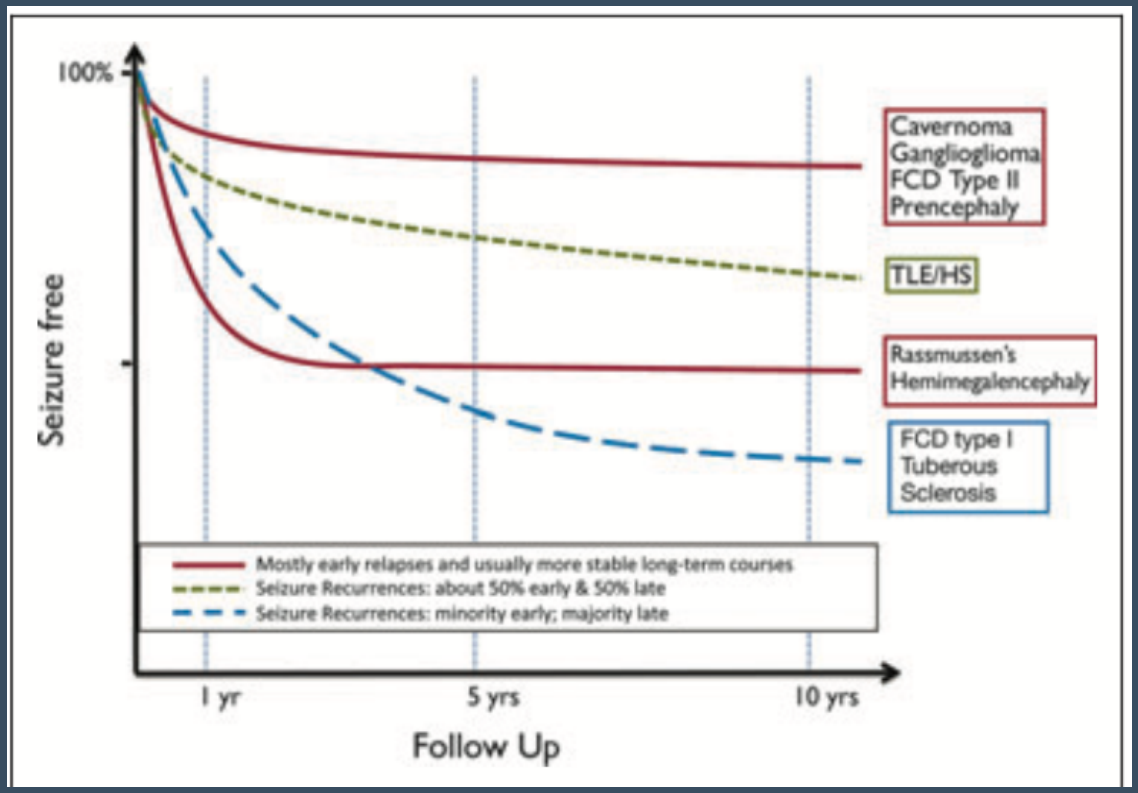
Why do we fail?

The main reason for the failure of the modern medical science is that it is dealing with results and not causes. Nothing more than the patching up of those attacked and the burying of those who are slain, without a thought being given to the real strong hold.

— Edward Bach —

1886-1936

Pathology-based outcome after Epilepsy Surgery



Focal lesions (when completely resected) have best outcome
HS failures: early and late
FCD type1 and TS have the worst outcome
Hemimegalencephaly and Rasmussen's encephalitis fail early

Najm et al, 2013

The role of genetics in Epilepsy Surgery

- Predict the pathology before surgery
- Predict the outcome
- Highlight opportunities for preventing failures

Can Genetics Predict Epileptic Pathologies?

Why predicting pathology?
Hippocampal sclerosis

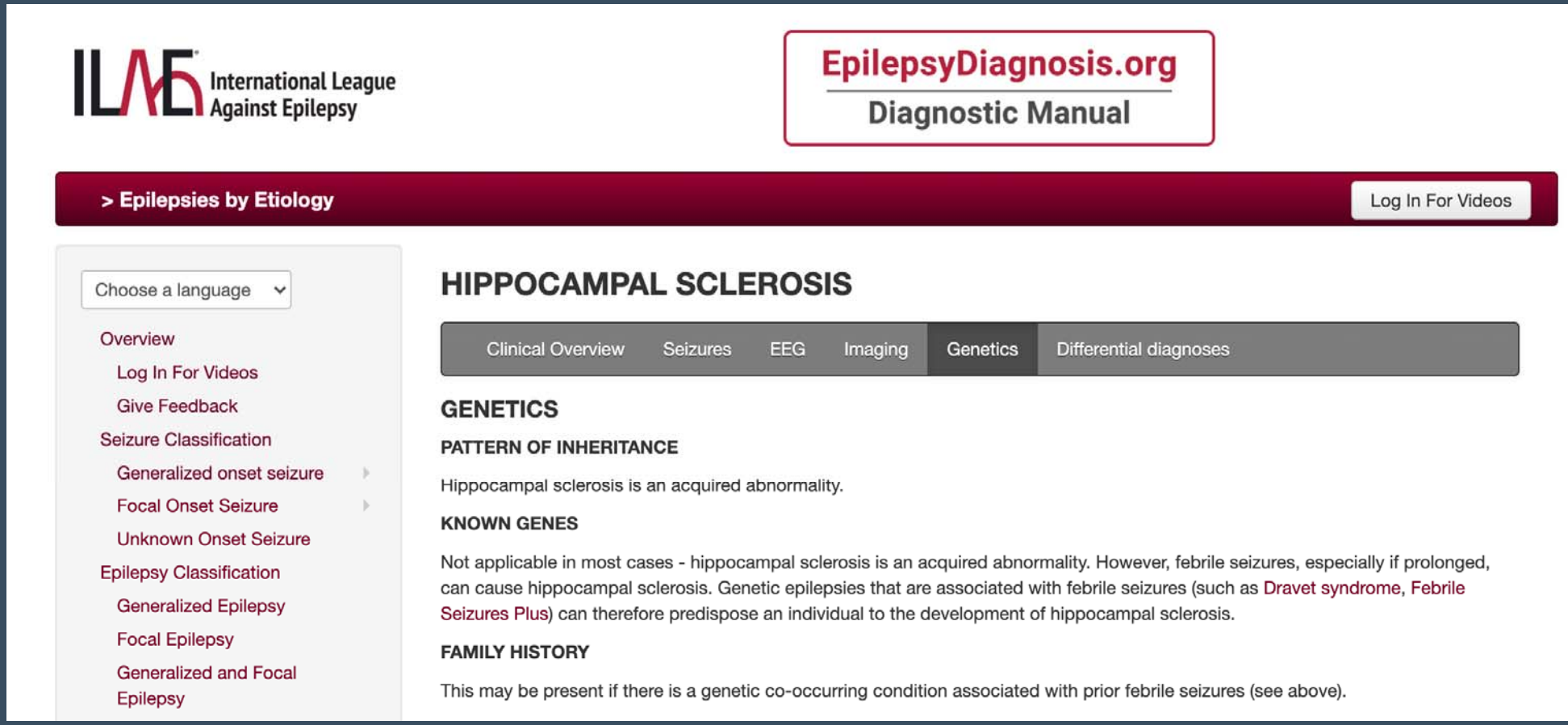
- Large number of patients with pathologically confirmed HS have normal MRI
- Early Detection of hippocampal sclerosis increases the likelihood of surgical intervention and improved seizure freedom
- Patients with HS continue to fail over time

Why predicting pathology?
Hippocampal sclerosis

Age of onset	Epilepsy Duration	SEEG Indication	SEEG seizure onset
5	17	Normal MRI	Hippocampus
14	17	Basal occipital encephalomalacia (s/p Ganglioglioma resection, new seizures)	Hippocampus
13	8	Frontal encephalomalacia (s/p LGG resection F2/F3/opercularis, new seizures)	Hippocampus
32	11	Parietal lesion (IPL, post-traumatic lesion)	Hippocampus/Amygdala
47	3	Visual and auditory auras	Hippocampus/entorhinal gyrus/Temporal pole
25	29	Normal MRI	Hippocampus/Amygdala
35	10	Left HS and Right temporal seizures	Hippocampus
16	33	Bilateral HS on MRI	Hippocampus
10	20	MRI abnormality anterior insula and posterior perisylvian semiology	Hippocampus/Amygdala/Temporal pole
15	18	Bilateral hip atrophy on MRI	Hippocampus/PHG
4	15	Hemispheric congenital abnormalities	Hippocampus

In a large number of patients,MRI does not uncover HS or may point to other pathologies

Genetics of Hippocampal sclerosis



…but why patients with HS exhibit seizure recurrence years after successful epilepsy surgery

Why predicting pathology?

Malformations of cortical development

- Surgical outcomes depend on the type and subtype of FCD: *The type of FCD is confirmed after surgical resection… no presurgical diagnosis*
- A large number of patients with FCDs have normal MRIs: *This leads to surgical resection for some patients who could have been excellent candidates*

Outcome of surgery with patients with FCD following invasive implantation

- 139 patients (1999-2011)
- Baseline characteristics:
  - Mean age at onset: 11 y (0.1-55 y, median: 9 y)
  - Mean age at surgery: 27 y (4-66 y, median: 25 y)
  - Mean duration of epilepsy: 16 years (0-55 y)
  - Mean follow-up: 2 y (0.5-13, median 1 y)
  - MRI: Non lesional in 40% of patients

Pinheiro Martins et al, In Preparation

Four Predictors of Early Surgical Failures

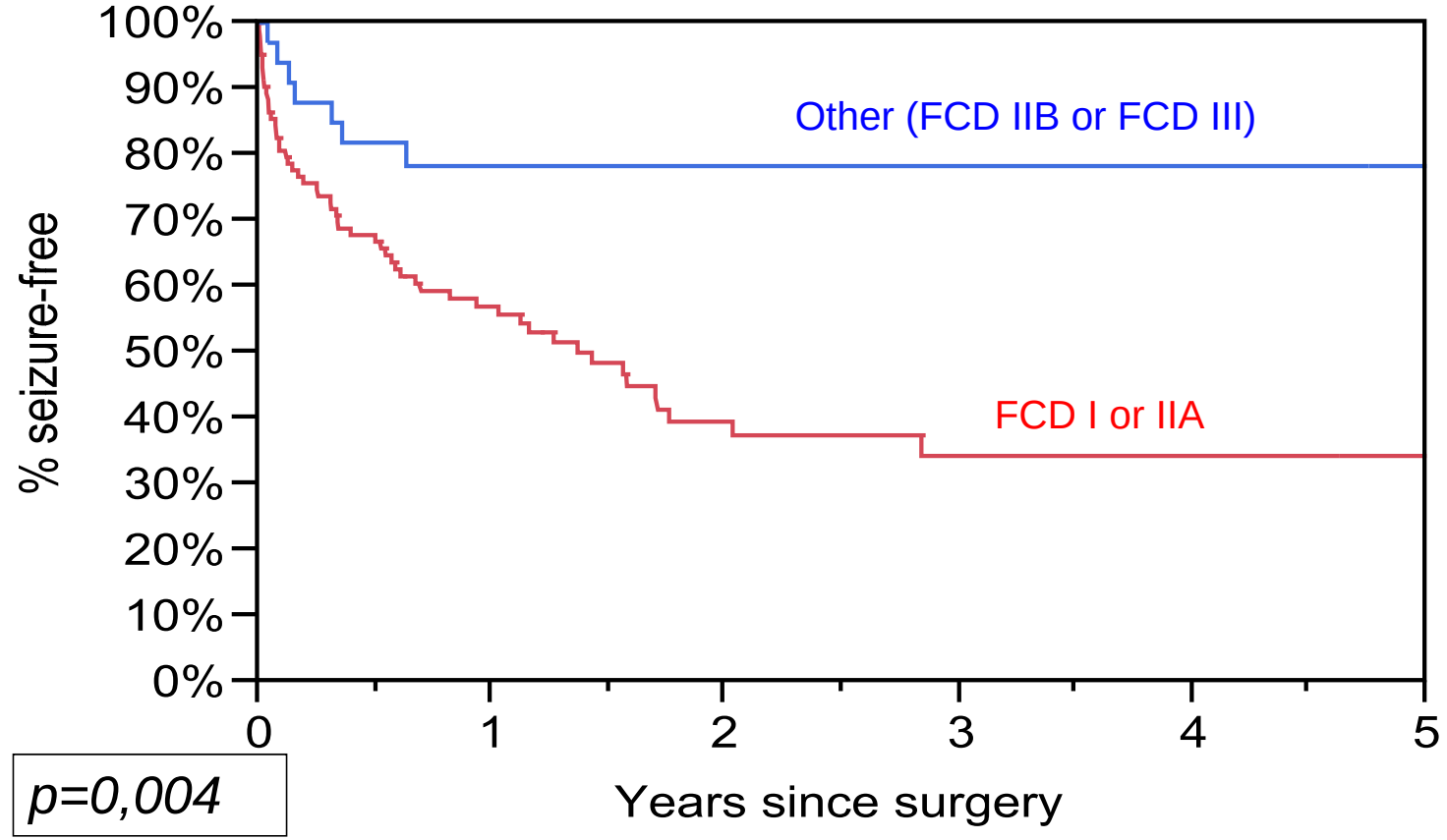
Multivariate analysis

(whole model logrank test <0.0001)

Predictor	Risk Ratio	95% CI	Adjusted p-Value
Pathology: FCD type I or IIA	3.99	1.52-12.97	0.004
Semiology: More than one type	2.35	1.07-5.07	0.036
Size of the ictal onset zone	2.17	1.04-4.61	0.04
Function: Overlap with eloquent cortex	2.74	1.09-6.60	0.03

Pinheiro Martins et al, In Preparation

Pathological Subtype:
FCD Type IIB and Type III have the best Outcome



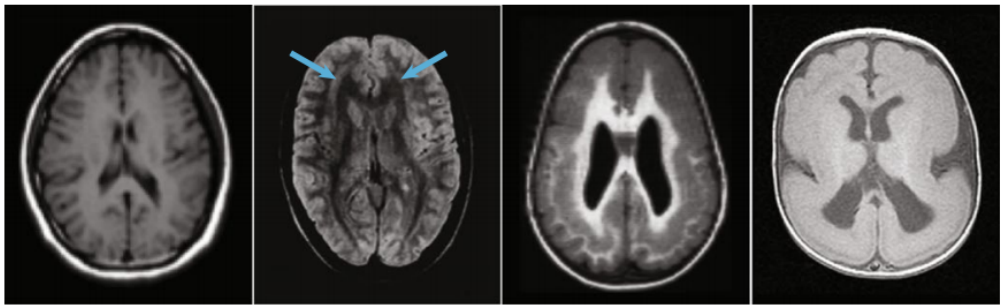
Pinheiro Martins et al, In Preparation

REVIEW ARTICLE
https://doi.org/10.1038/s41593-018-0257-3

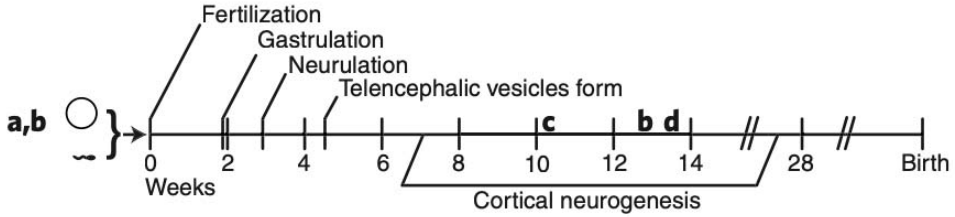
nature neuroscience

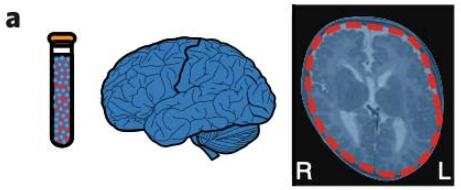
Somatic mosaicism and neurodevelopmental disease

Alissa M. D'Gama[1,2,3] and Christopher A. Walsh[1,2,3*]

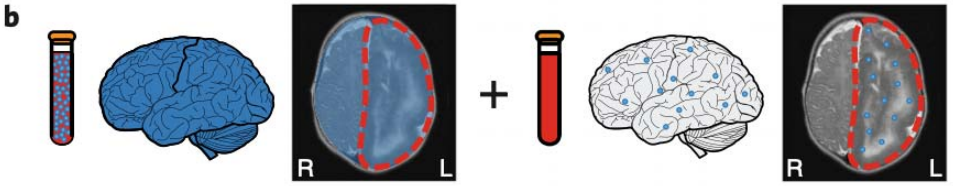


Normal | Low mosaic *DCX* mutation 10% mutant cells | High mosaic *LIS1* mutation ~50% mutant cells | Germline *DCX* mutation (M) or *LIS1* mutation (M and F) 100% mutant cells



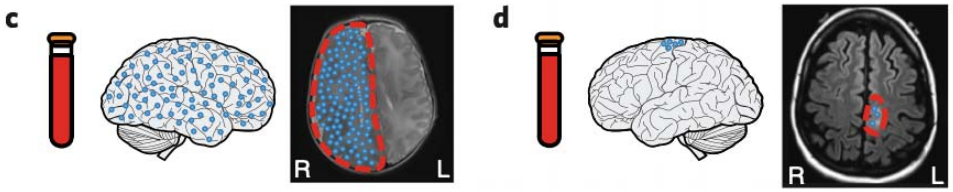


PMG germline mutation
PMG-1 *MTOR* Ms (100% of cells)



HME germline mutation
HME-11 *TSC2* Ms (100% of cells)

HME somatic mutation
HME-11 *TSC2* Fs (~6.9% of cells)



HME somatic mutation
HME-22 *PIK3CA* Ms (~32% of cells)

FCD somatic mutation
FCD-6 *MTOR* Ms (~4.9% of cells)

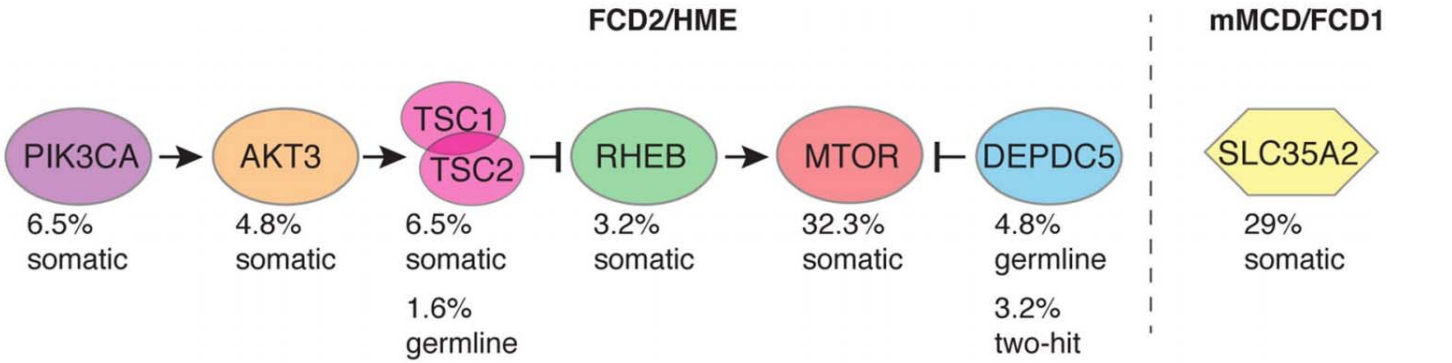
Acta Neuropathologica
https://doi.org/10.1007/s00401-019-02061-5

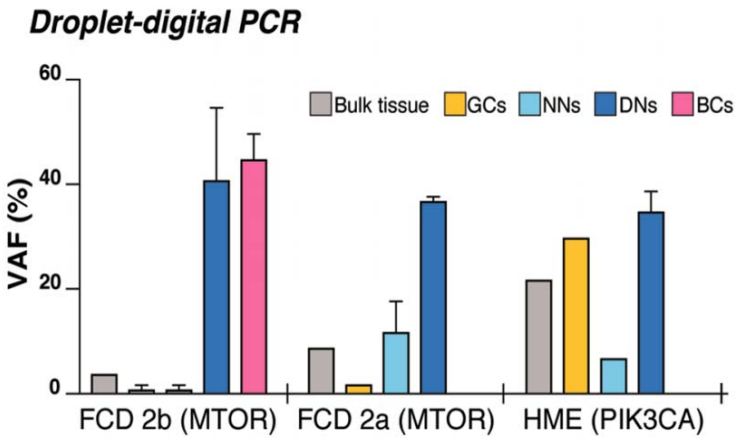
ORIGINAL PAPER

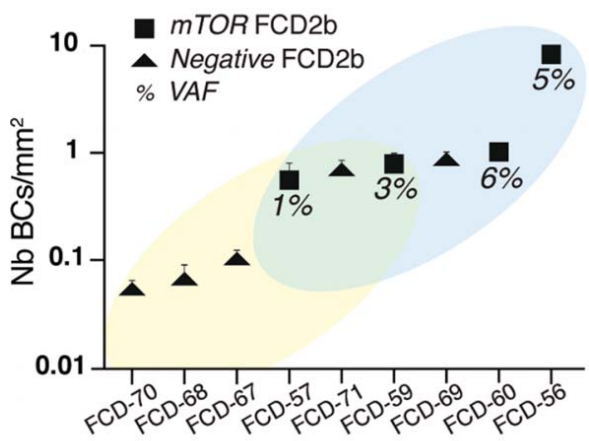
Dissecting the genetic basis of focal cortical dysplasia: a large cohort study

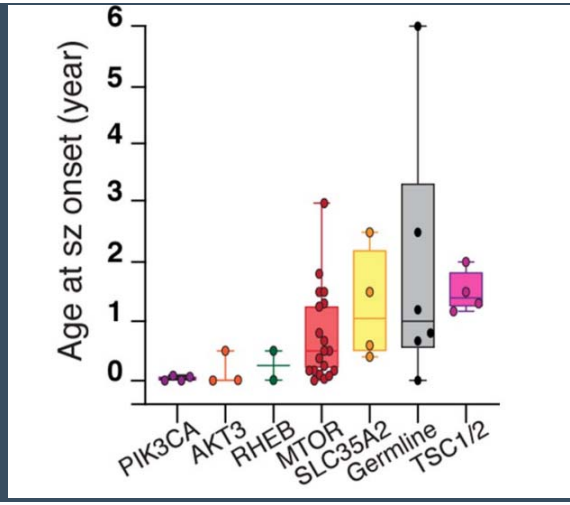
Sara Baldassari[1,2,3,4] · Théo Ribierre[1,2,3,4] · Elise Marsan[1,2,3,4] · Homa Adle-Biassette[5,6,7] · Sarah Ferrand-Sorbets[8] · Christine Bulteau[8] · Nathalie Dorison[8] · Martine Fohlen[8] · Marc Polivka[7] · Sarah Weckhuysen[1,2,3,4,9] · Georg Dorfmüller[8] · Mathilde Chipaux[8] · Stéphanie Baulac[1,2,3,4]

80 children subjected to surgery for the treatment of drug-resistant epilepsy at the Rothschild Foundation Hospital (Paris, France) between 2015 and 2018



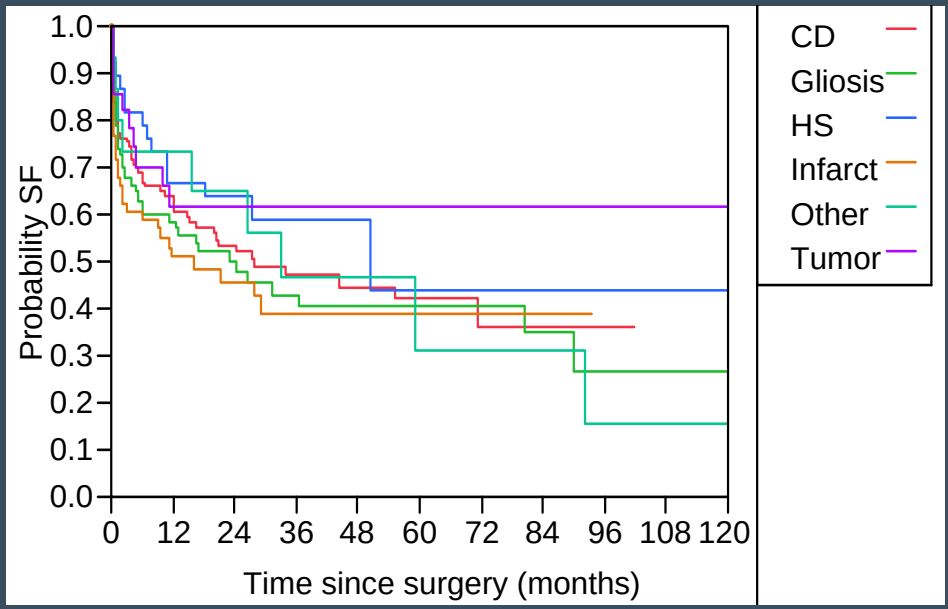






Why predicting pathology?
Glioneuronal tumors

Glioneuronal tumors: gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumors (DNTs), represent a well-recognized cause of intractable epilepsy.
Histologically, they are characterized by mixed neuroepithelial cell types, including aberrantly shaped neuronal cells and glial elements, in coexistence with cortical dysplasia



RESEARCH ARTICLE

BRAF V600E Mutation Is Associated with mTOR Signaling Activation in Glioneuronal Tumors

Avanita S. Prabowo[1]; Anand M. Iyer[1]; Tim J. Veersema[3,4]; Jasper J. Anink[1]; Antoinette Y. N. Schouten-van Meeteren[2]; Wim G. M. Spliet[5]; Pieter C. van Rijen[3]; Cyrille H. Ferrier[4,6]; David Capper[7,8]; Maria Thom[9]; Eleonora Aronica[1,10,11]

Brain Pathology **24** (2014) 52–66

Table 4. BRAF V600E, CD34 and pS6 expression in glioneuronal tumors and clinical features: tumor recurrence and postoperative seizure outcome. Abbreviations: GGs = gangliogliomas; DNTs = dysembryoplastic neuroepithelial tumors.

Parameters (positive/negative)	Recurrence (No. of patients)			Postoperative seizure outcome			Diagnosis		
	Without	With	*P*-value†	Engel I	Engel II-IV	*P*-value†	GG	DNT	*P*-value†
BRAF V600E	63/105	0/6	0.088	43/90	17/16	0.040	38/55	23/54	0.137
pS6-DN	96/72	2/4	0.406	61/72	29/4	<0.001	83/10	12/65	<0.001
CD34	107/60	0/6	0.003	80/53	21/11	0.568	66/27	39/38	0.008
pS6 & CD34	73/38	0/4	0.016	47/39	20/3	0.005	62/7	9/35	<0.001
BRAF V600E & pS6-DN	47/56	0/4	0.129	27/56	17/4	<0.001	38/10	7/49	<0.001
BRAF V600E & CD34	55/53	0/6	0.028	39/49	14/9	0.157	32/22	22/37	0.020
BRAF V600E & pS6-DN & CD34	40/37	0/4	0.116	24/38	14/3	0.001	32/7	7/34	<0.001

The presence of BRAF is a predictor of worse post resection outcome in patients with glioneuronal tumors

Can Genetics Predict Surgical Outcomes?

Epileptic Disord 2018; 20 (2): 99-115

Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review

Remi Stevelink [1], Maurits WCB. Sanders [1], Maarten P. Tuinman [1], Eva H. Brilstra [2], Bobby PC. Koeleman [2], Floor E. Jansen [1], Kees PJ. Braun [1]

Meta-analysis of 24 articles of 82 patients who underwent surgical resection for medically intractable epilepsy and had genetic studies:

Three types of gene mutations were reported:

1. Channel function and synapses
2. mTOR pathway
3. Other genetic mutations

Table 1A. Success rates of epilepsy surgery for patients with different genetic causes (**germline mutations**) of epilepsy.

Genetic cause		MRI-positive seizure-free/total	MRI-negative seizure-free/total	Total group seizure-free/total
Pathogenic variants of genes related to ion channel function and synaptic transmission	*SCN1A*	FCD: 0/2 HS: 0/2 Encephalomalacia: 0/1 Subcortical area of abnormal signal: 0/1	0/2	0/8
	SCN1B	HS: 1/1	1/1	2/2
	CNTNAP2	HS: 0/2	0/1	0/3
	STXBP1	-	0/1	0/1
	Overall	**1/9**	**1/5**	**2/14 (14%)**
Pathogenic variants of mTOR pathway genes	*DEPDC5*	FCD: 3/6	2/3	5/9
	PTEN	HME: 1/1	-	1/1
	NPRL2	-	0/1	0/1
	NPRL3	FCD: 1/1	-	1/1
	Overall	**5/8**	**2/4**	**7/12 (58%)**
Other genetic causes of epilepsy	Microdeletions	HS: 9/10	0/2	9/12
	Neurofibromatosis type 1	FCD: 2/2 HS: 4/6 Polymicrogyria: 0/1 Tumour: 5/11	1/1	12/21
	Fragile-X syndrome	HS: 2/2	-	2/2
	Mitochondrial mutations	HS: 1/3	-	1/3
	Overall	**23/35**	**1/3**	**24/38 (63%)**
Total		**29/52 (56%)**	**4/12 (33%)**	**33/64(52%)**

Epileptic Disord 2018; 20 (2): 99-115

Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review

Remi Stevelink [1], Maurits WCB. Sanders [1], Maarten P. Tuinman [1], Eva H. Brilstra [2], Bobby PC. Koeleman [2], Floor E. Jansen [1], Kees PJ. Braun [1]

Meta-analysis of 24 articles of 82 patients who underwent surgical resection for medically intractable epilepsy and had genetic studies:

Three types of gene mutations were reported:

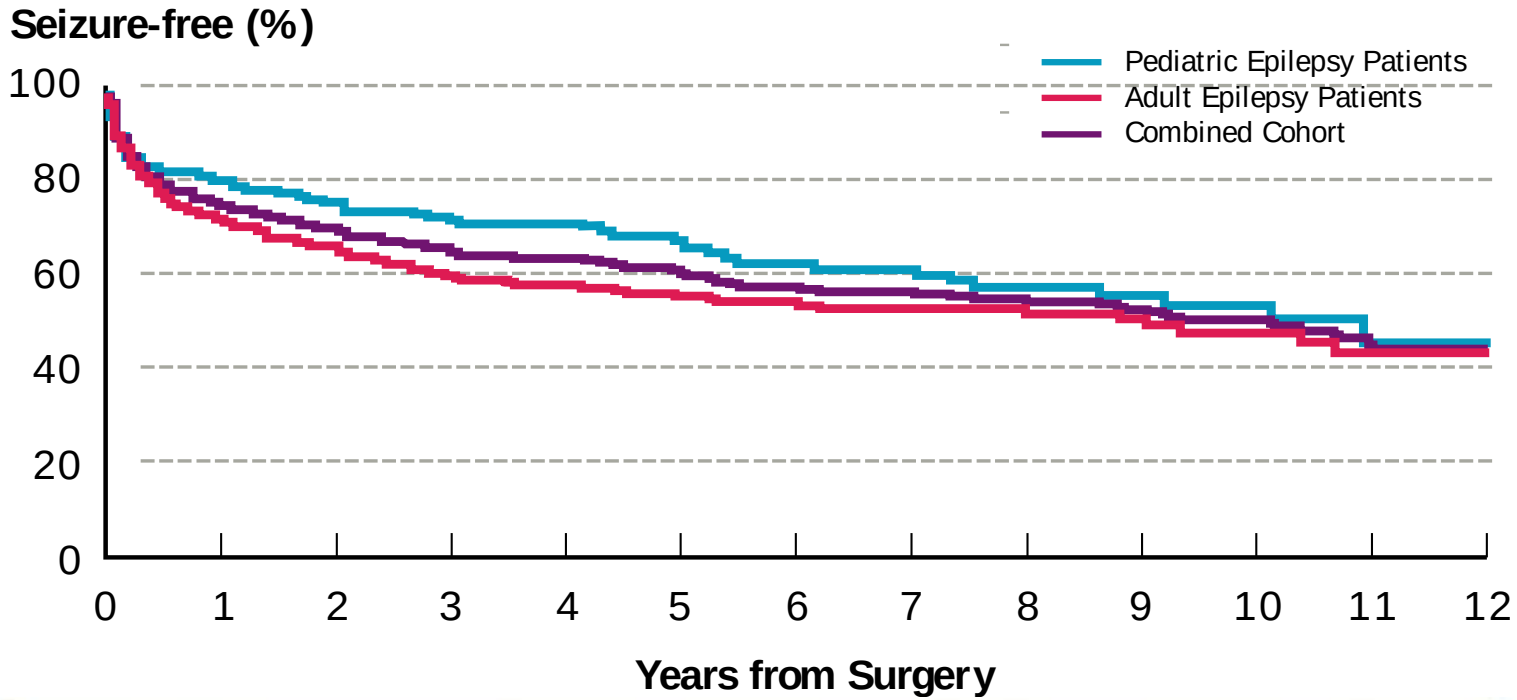
1. Channel function and synapses
2. mTOR pathway
3. Other genetic mutations

Table 1B. Success rates of epilepsy surgery for patients with different genetic causes (**somatic mutations**) of epilepsy.

Genetic cause		MRI-positive seizure-free/total	MRI-negative seizure-free/total	Total group seizure-free/total
Pathogenic variants of mTOR pathway genes	*PIK3CA*	HME: 5/5 FCD: 1/1	-	6/6
	AKT3	HME: 1/3 FCD: 1/1	-	2/4
	mTOR	HME: 1/1 FCD: 6/7	-	7/8
Total		**15/18 (83%)**	**-**	**15/18 (83%)**

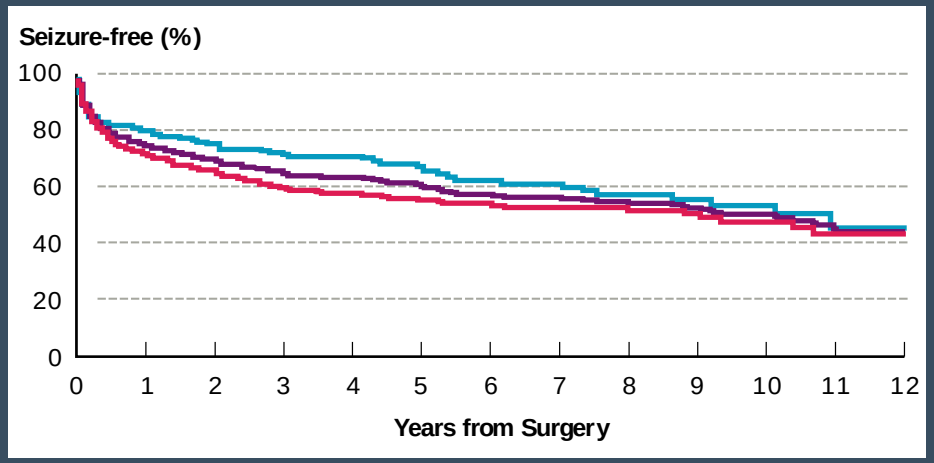
Long Term Seizure Freedom in Adult and Pediatric Patients Following Epilepsy Surgery

Cleveland Clinic (N = 1,594)



Years from Surgery	1 Year	2 Years	5 Years	10 Years	12 Years
% Seizure-free (overall group)	76%	71%	62%	50%	44%
% Seizure-free (adult epilepsy)	72%	66%	56%	48%	43%
% Seizure-free (pediatric epilepsy)	80%	76%	67%	50%	44%

Can genetics play a role in some epilepsy surgery failures?



Early recurrences are due to failure in epilepsy localization

Late recurrences are due to failure to understanding epileptogenesis

Najm et al, 2013

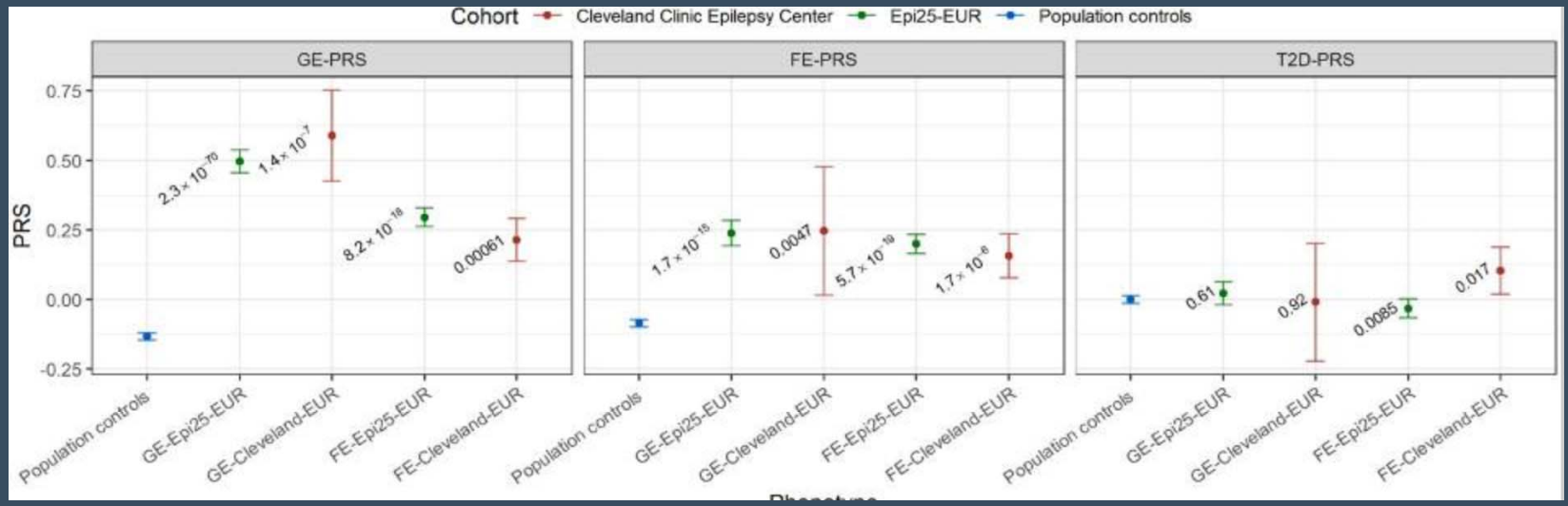
Genetic Susceptibility for seizure recurrence?

doi:10.1093/brain/awz292 BRAIN 2019: 0; 1–9 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Polygenic burden in focal and generalized epilepsies

Costin Leu,[1,2,3] Remi Stevelink,[4] Alexander W. Smith,[2] Slavina B. Goleva,[5,6] Masahiro Kanai,[2,7,8,9,10] Lisa Ferguson,[11,12,13] Ciaran Campbell,[14,15] Yoichiro Kamatani,[10,16] Yukinori Okada,[10,17,18] Sanjay M. Sisodiya,[3,19] Gianpiero L. Cavalleri,[14,15] Bobby P.C. Koeleman,[4] Holger Lerche,[20] Lara Jehi,[11,13] Lea K. Davis,[5,6] Imad M. Najm,[11,13] Aarno Palotie,[2,21] Mark J. Daly,[2,7,21] Robyn M. Busch,[11,12,13] Epi25 Consortium and Dennis Lal[1,2,11,22]



Conclusion

- Recent genetic observations show promise in the presurgical diagnosis of various epileptic pathologies, and in the possible prediction of surgical outcome
- There is a need for large multicenter/multinational studies to address the challenges through the inclusion of large number of patients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