Neuropathology of epilepsy

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AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

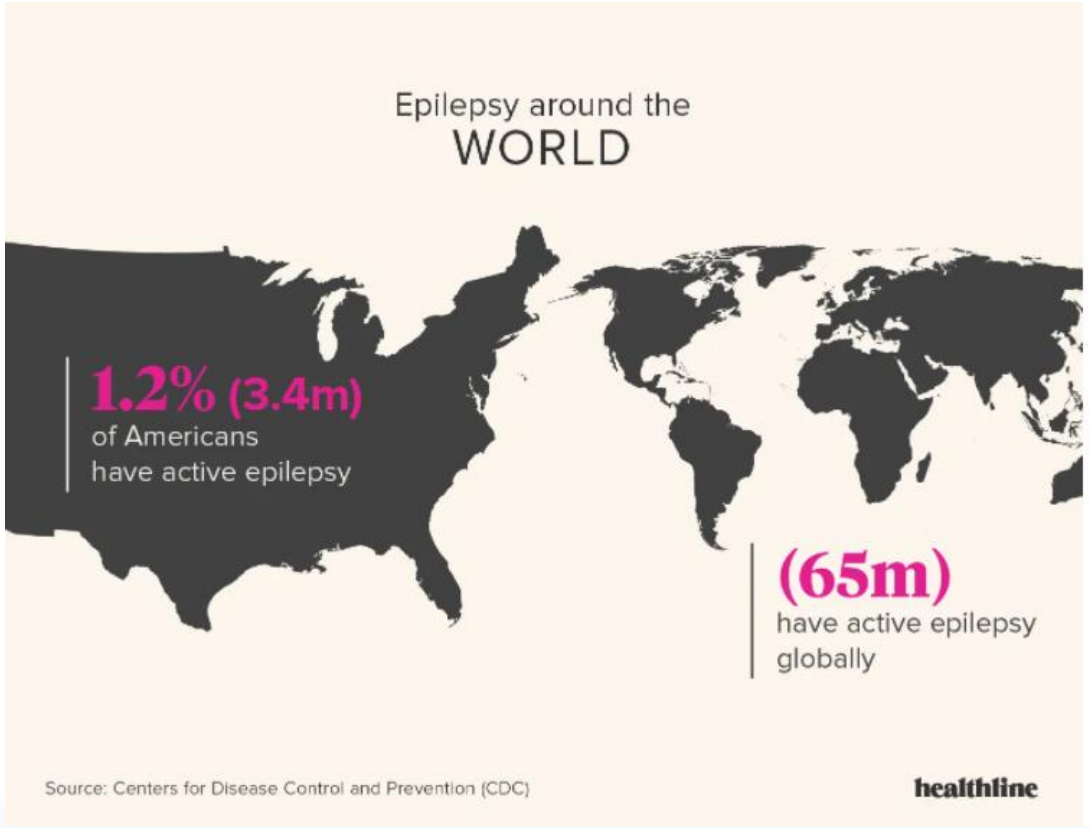
1. Describe the difference between seizures and epilepsy, and how epilepsy is diagnosed
2. Identify specific histologic patterns that can be observed in epilepsy surgical specimens
3. Outline the appropriate steps for tissue handing in the setting of epilepsy surgery

Outline

- Background
- Hippocampal sclerosis
- Focal cortical dysplasia
- Other lesions
- Practical considerations

Epilepsy

- Recurring, unprovoked seizures
  - At least 2, >24h apart
  - OR single unprovoked seizure if probability of recurrence is >60% over next 10 yrs
  - OR epilepsy syndrome
- 1.2% of US population has active epilepsy
- Can begin at any age, but more people are diagnosed at two distinct phases in life: early childhood and after age 55



https://www.healthline.com/health/epilepsy/facts-statistics-infographic#Prevalence

Zack MM, Kobau R. MMWR 2017;66:821-825

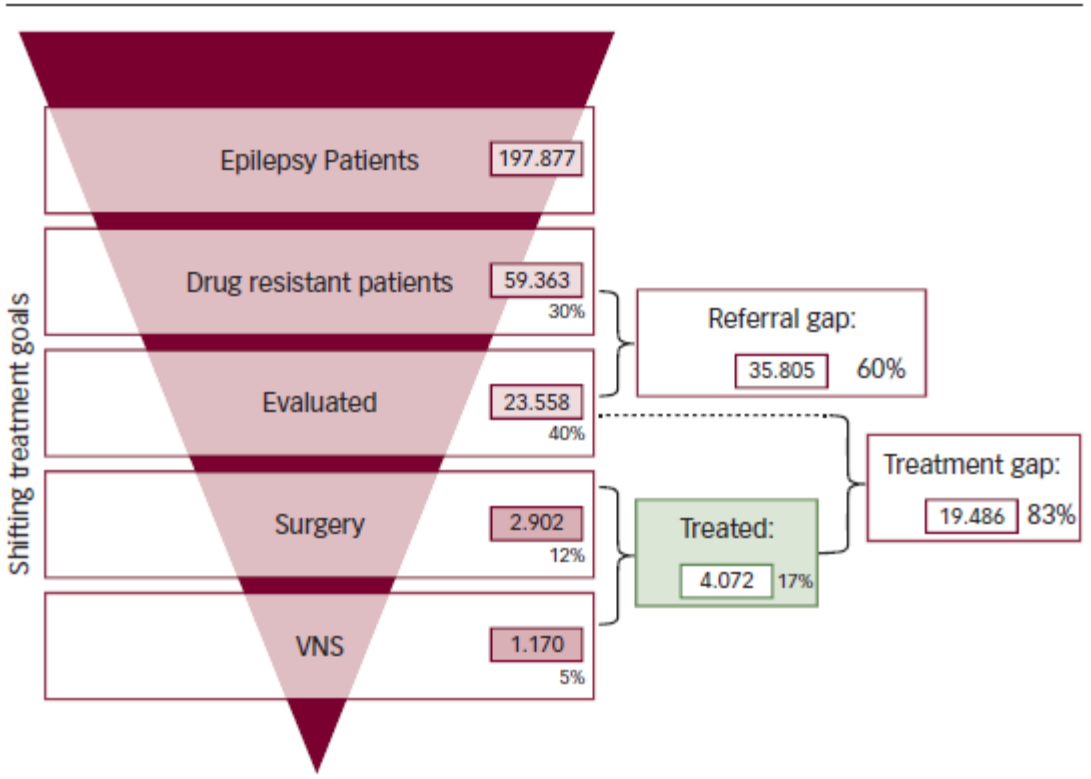
Epilepsy is common

- 1 in 26 people will develop epilepsy at some point during their lifetime
- More common than multiple sclerosis, muscular dystrophy, cerebral palsy, and Parkinson's disease combined

- Impacts the entire family and every activity
- Even seizure free epilepsy patients still report decreased QoL due to stress and uncertainty of when a seizure will occur

Drug-resistant epilepsy

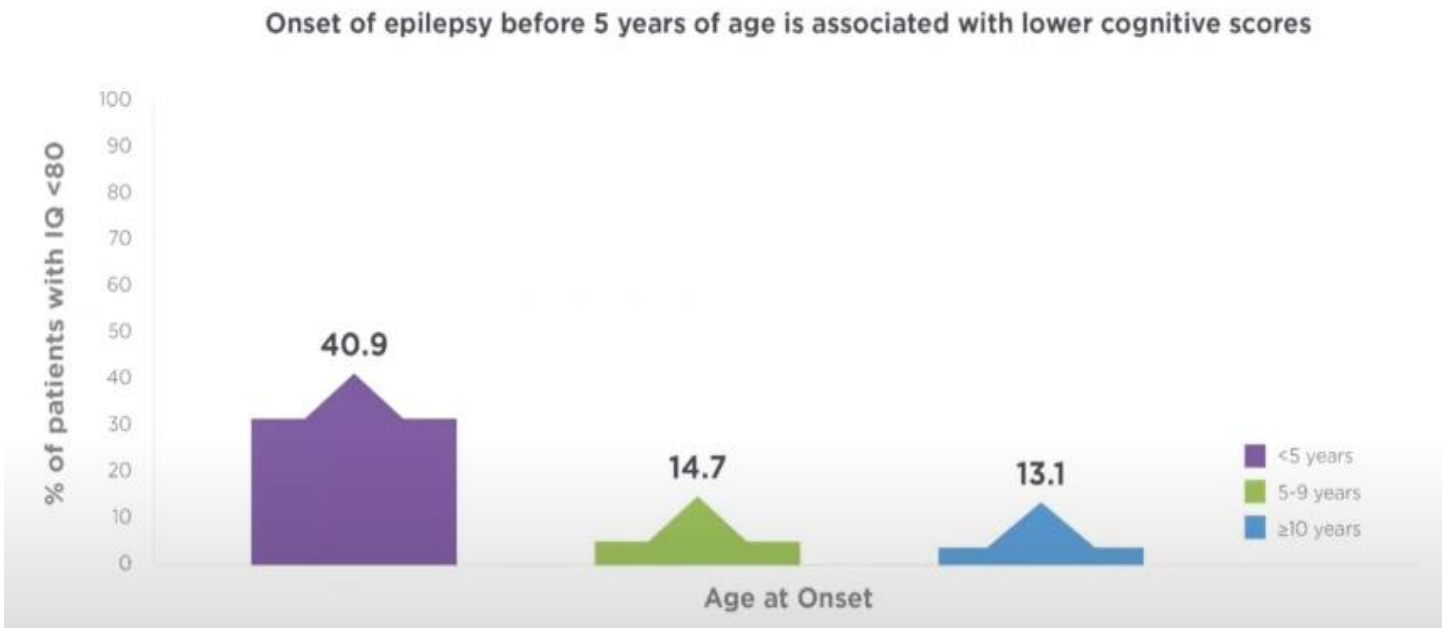
- 65-70% of patients respond to the first or second medication used, with near or complete seizure control.
- Patients who have failed 2 medications have less than ~5% chance of responding to a third
- **“medication resistant”**



Boon at al., Eur. Neurological Review 2015

Kids are differentially impacted

- In kids, a window of opportunity to learn key skills means urgency to arrive at accurate diagnosis
- Longer duration of epilepsy (>5 years) is associated with worse behavioral and psychosocial outcomes
  - Aggression, self-aggression
  - Attention deficit



Berg AT et al. Epilepsia 2008.
Valova et al. Neuropediatrics 2019.

Evaluations

Goal is to establish:

Type of epilepsy

- Focal
- Generalized
- Mixed

Underlying cause

- H&P, EEG, MRI, labs, genetic tests
- Drug resistant epilepsy should see an epileptologist
  - Video/EEG monitoring
  - MRI with an epilepsy protocol
  - Neuropsych testing (“thinking and learning”)
  - Genetic testing (WES)
  - PET, SPECT, MEG

ILAE 2017: Updated classification of seizure types

- Focal – start in one spot in the brain
  - Old system
    - complex partial (change in consciousness)
    - simple partial (no change in consciousness)
  - New system:
    - Focal-Aware and Focal-Impaired awareness
    - Motor vs. non-motor
- Any can secondarily become generalized convulsive type
- Generalized
  - Motor
  - Non-motor (absence)
- Determining the type
  - Video/EEG
  - 24 hour increases percent detection into 90s
  - Patients w focal seizures need MRI

ILAE 2017 Classification of Seizure Types Basic Version

From Fisher RS, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia, 58(4):531–542, 2017.

___ Focal Onset

(if focal onset, choose one or leave blank if unknown)

__ Aware
__ Impaired Awareness

(if focal onset, choose one or leave blank if unknown)

__ Motor Onset
__ Nonmotor Onset
__ Focal to bilateral tonic-clonic

___ Generalized Onset

(if generalized onset, choose one or leave blank if unknown)

__ Motor
__ Nonmotor (absence)

___ Unknown Onset

(if unknown onset, choose one or leave blank if unknown)

__ Motor
__ Nonmotor

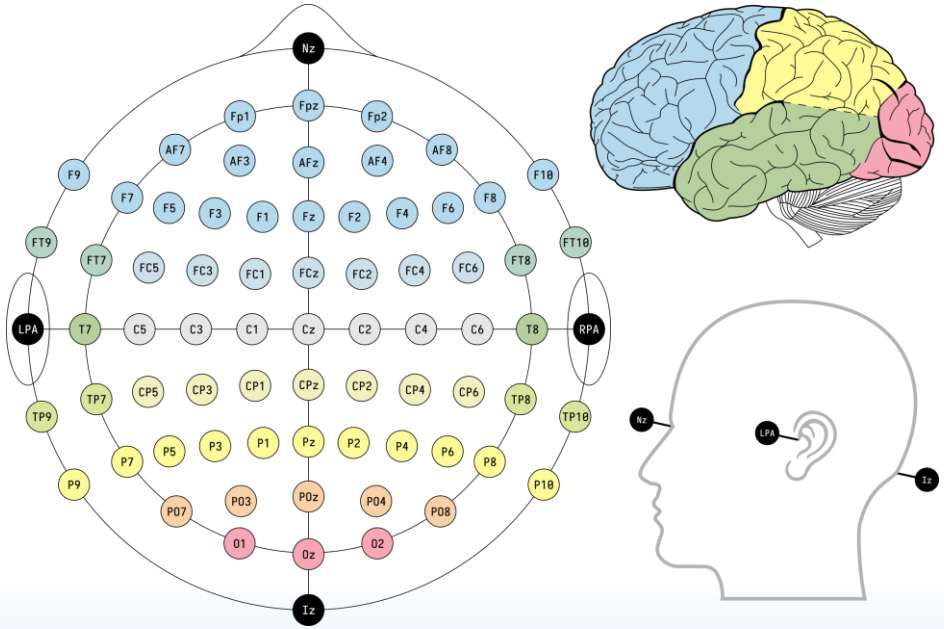
EEG

Electrical patterns of the brain

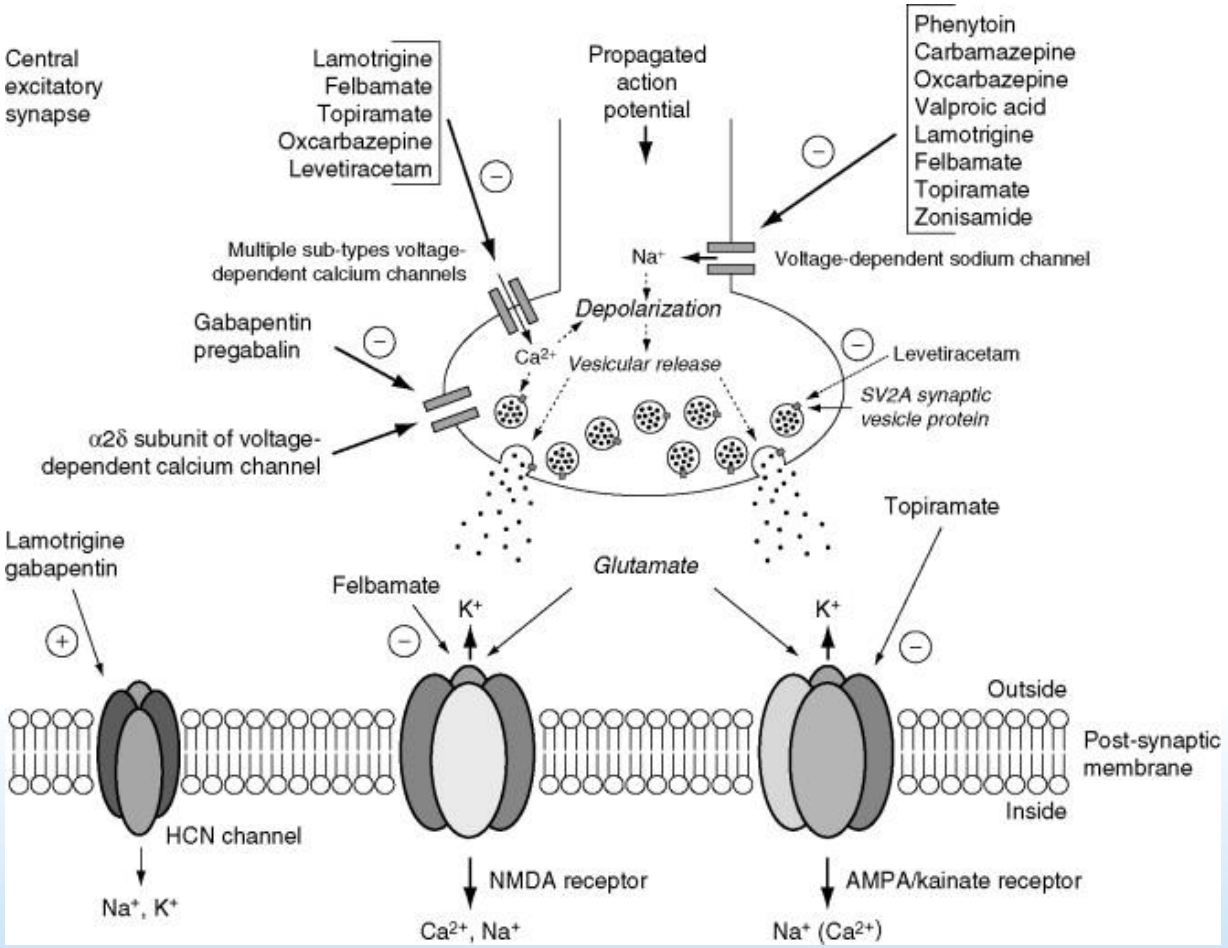
- Awake (normal)
- Closed eyes (normal)
- Drowsy (normal)
- Early sleep (normal)
- Deeper sleep (normal)
- REM sleep (normal)
- Some brains don’t make any normal patterns (global disabilities)

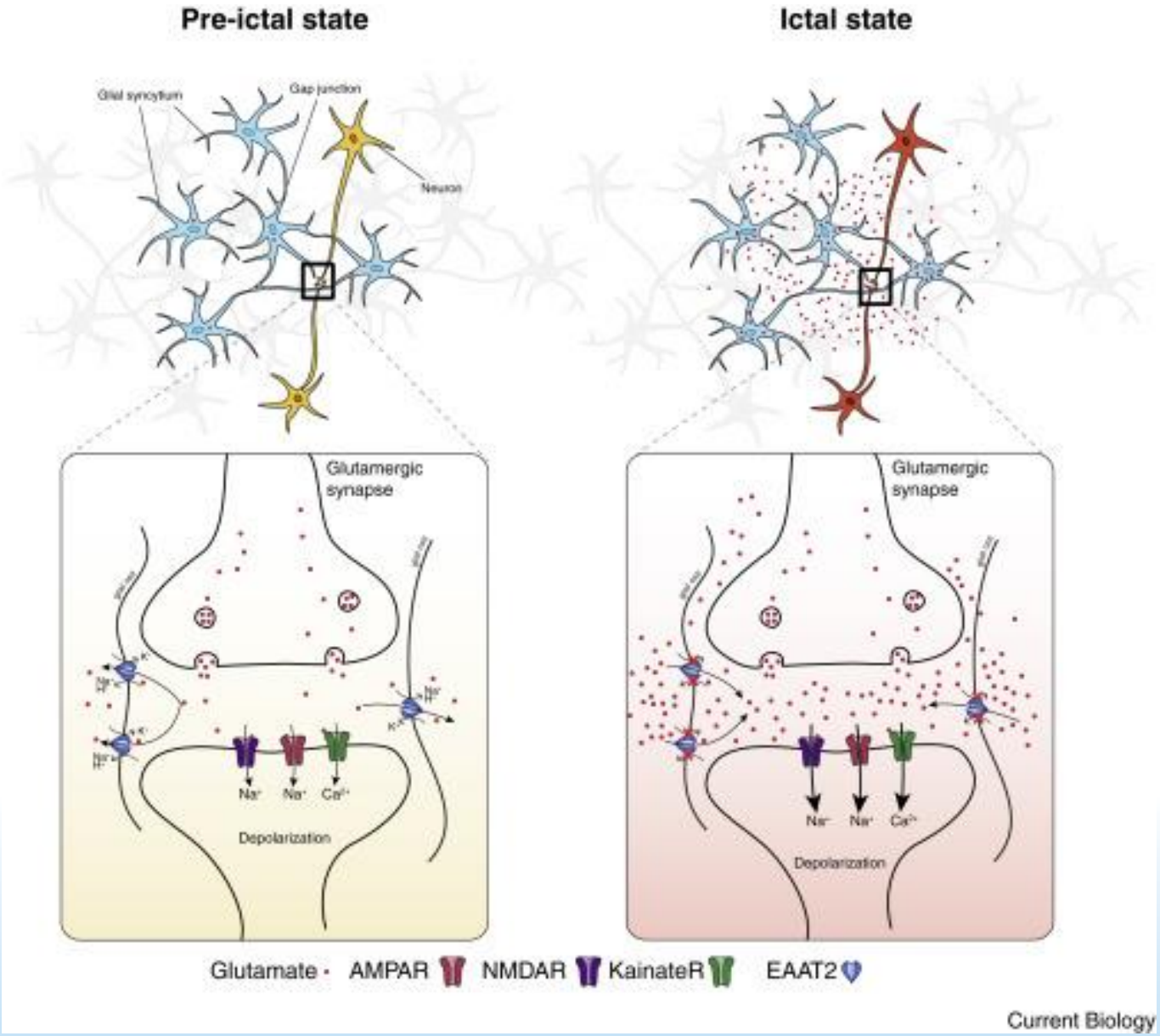
Activations

- Flashing lights
- Breathing deeply
- Sleep deprivation



Seizure: mechanism and drug actions





Rosch et al. 2019. PMID: 31794761

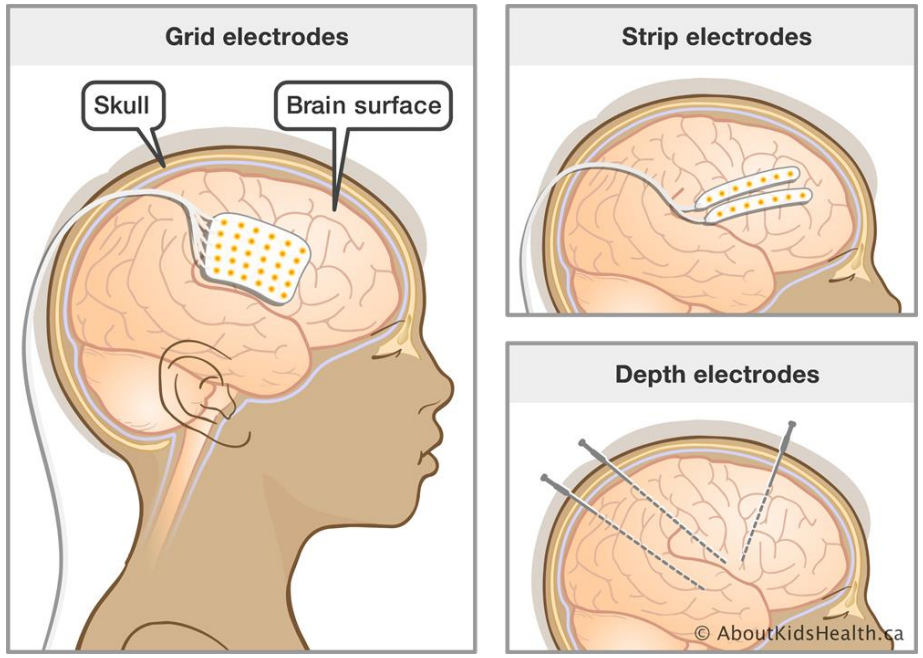
Epilepsy surgery: Pre-surgical evaluation

Phase I

- Non-invasive
- Outpatient monitoring
- Inpatient/video EEG
- Neuroimaging
- Neuropsych testing

Phase II

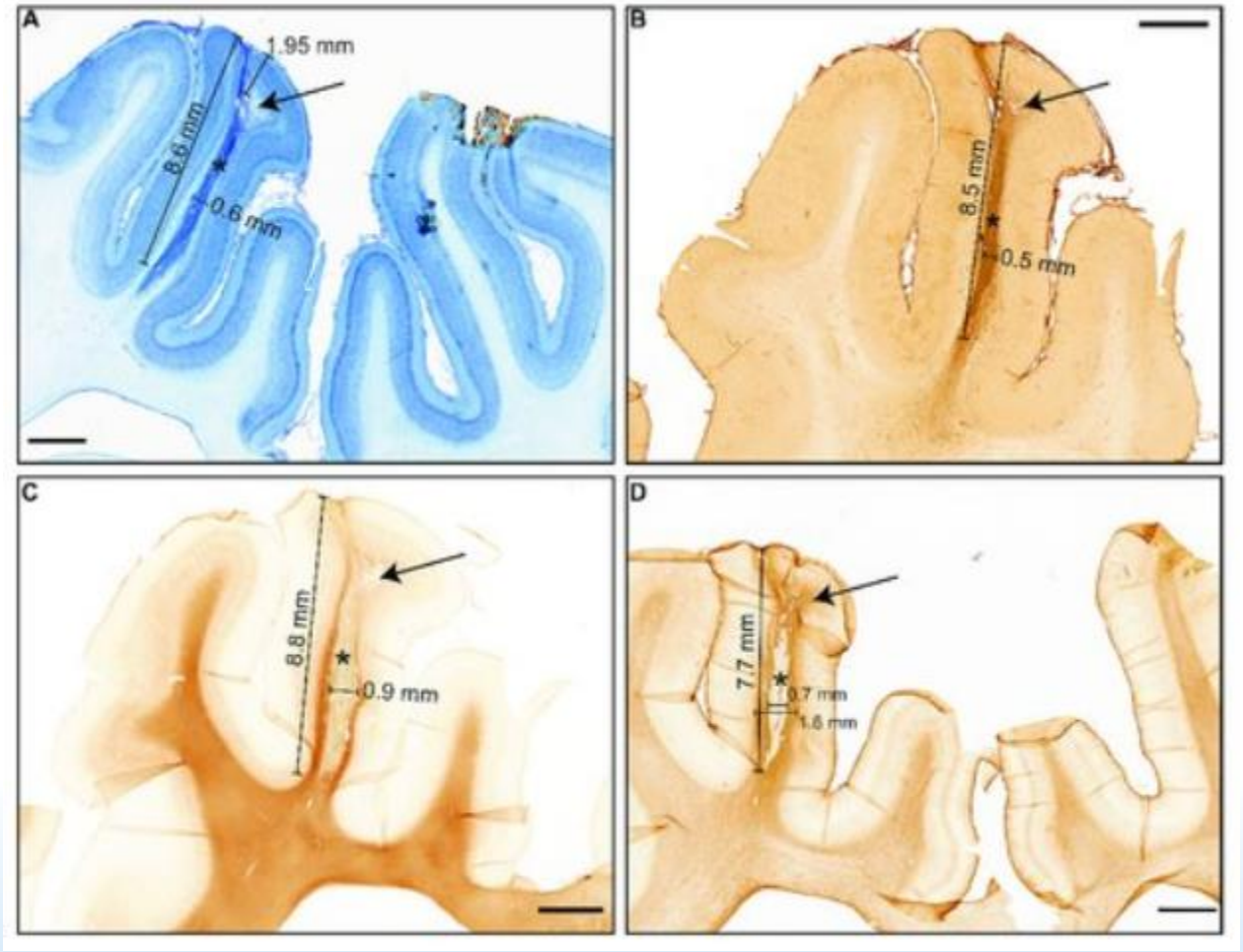
- Anesthesiology
- Neurosurgery
- Pre-op tests
- Intracranial depth electrodes
- Subdural strip/grid electrodes
- Electrocorticography



www.aboutkidshealth.ca/article?contentid=2056

Electrode tract histology

isolectin



myelin

GFAP

Zaer H et al. Front Hum Neurosci. 2021; PMID: 33613212

Surgery if indicated after Phase I/II

Phase I	Phase II	Phase III	Phase IV
• Workup • Imaging • Neuropsych	• Intracranial monitoring	• Resection • Disconnection • Ablation • Neuromodulation	• Recovery

Causes of epilepsy

- Migrational anomalies
- Temporal lobe structural abnormalities
- Brain tumors
- Neurocutaneous disorders
- Infections
- Vascular diseases
- Brain injury

Table 1 Neuropathological findings in epilepsy surgery

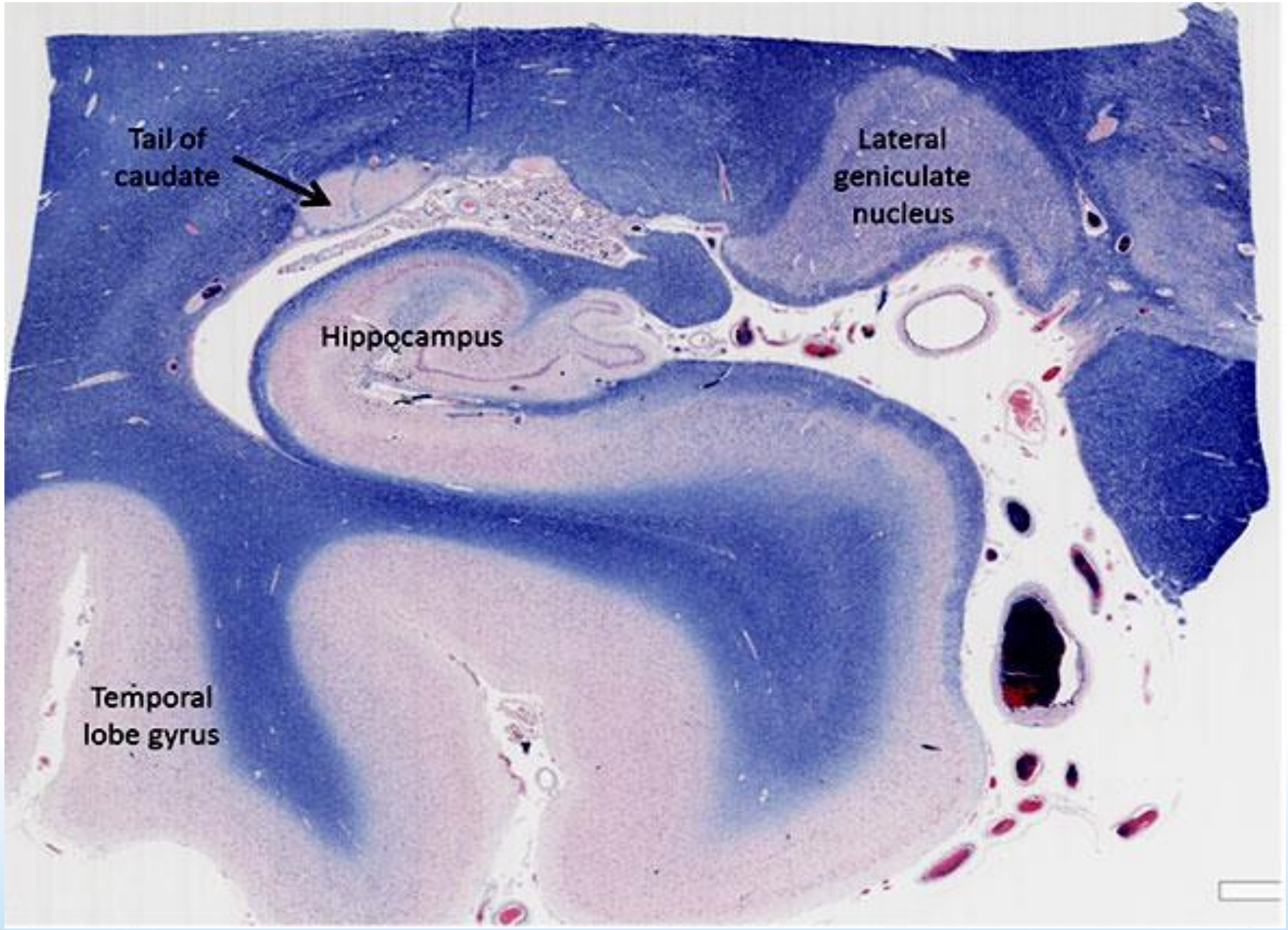
Category	Numbers (%)	Age OP	Onset	Duration
HS	1,908 (32.7 %)	33.9 + 10.4	11.3 + 7.7	22.7 + 10.0
Dual	294 (5.0 %)	25.5 + 12.8	9.5 + 7.8	15.9 + 9.9
LEAT	1,551 (26.5 %)	27.9 + 12.3	16.5 + 10.1	11.8 + 8.8
MCD	930 (15.9 %)	18.2 + 12.0	5.9 + 5.7	12.3 + 9.1
Vascular	328 (5.6 %)	36.1 + 12.3	23.4 + 11.4	12.7 + 9.0
Glial scars	284 (4.9 %)	25.6 + 12.4	10.3 + 8.0	14.7 + 8.6
Encephalitis	96 (1.6 %)	20.4 + 12.6	13.3 + 9.4	8.2 + 7.1
No lesion	451 (7.7 %)	29.2 + 10.8	12.6 + 7.7	16.1 + 8.0
Total	5,842	28.6 + 12.5	12.4 + 8.9	16.5 + 10.1

Data retrieved from the European Epilepsy Brain Bank

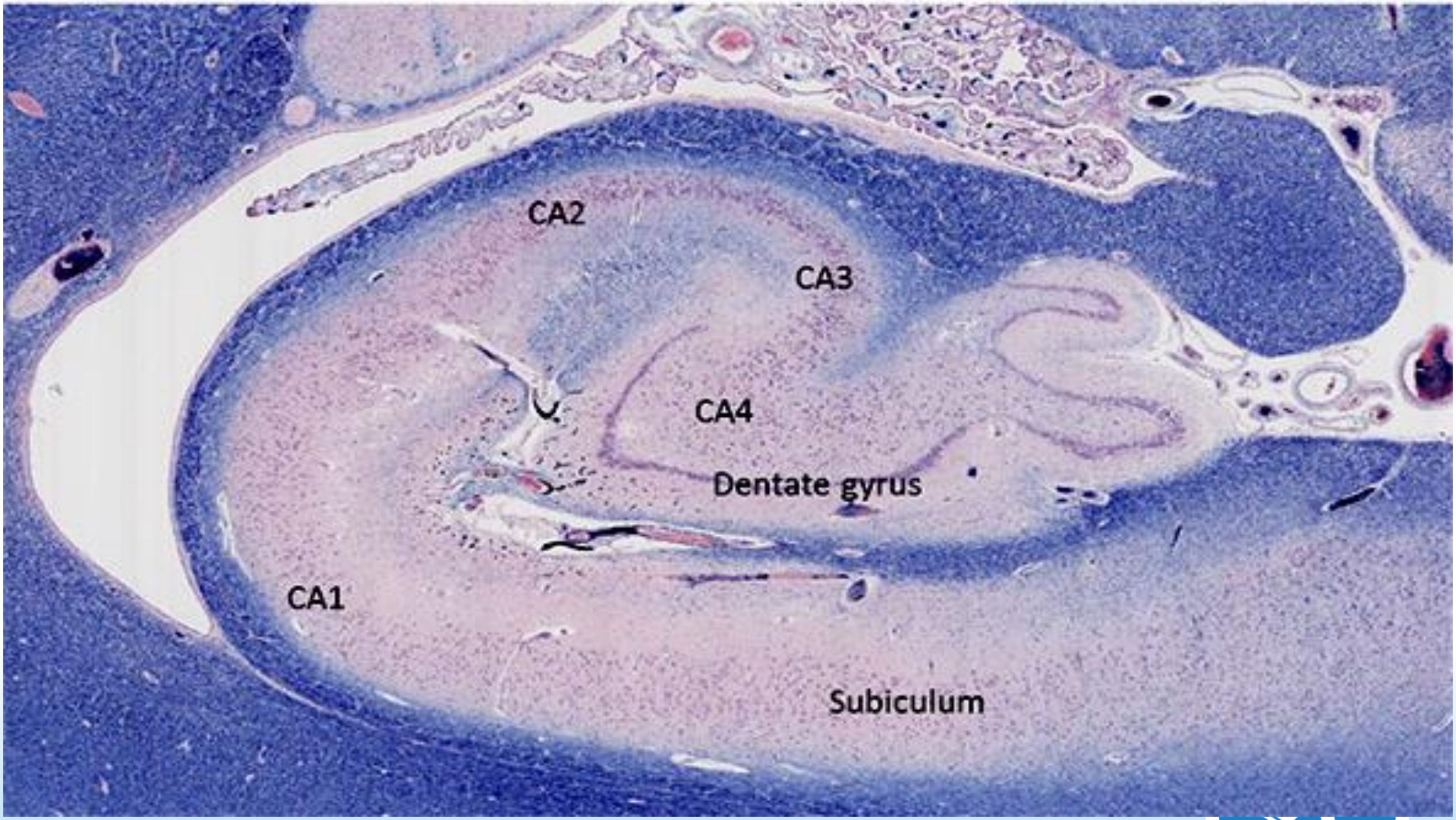
HS hippocampal sclerosis, *Dual* dual pathology, *LEAT* long-term epilepsy-associated tumors, *MCD* malformations of cortical development, *Age OP* age of patients at surgery (in years), *Onset* age at onset of spontaneous seizure activity (in years), *Duration* duration of seizure disorder before surgical treatment (in years)

Hippocampal sclerosis

- HS is the pathologic pattern in ~56% of MTLE cases
- Recognized since 1880 (Sommer)
- Overall loss of hippocampal volume
- Surgical resection results in post-op seizure freedom in 60-80%
- Neuronal loss and gliosis involving CA1, CA4/3 subfields
  - Granule cell dispersion
  - Axonal reorganization (mossy fiber sprouting)

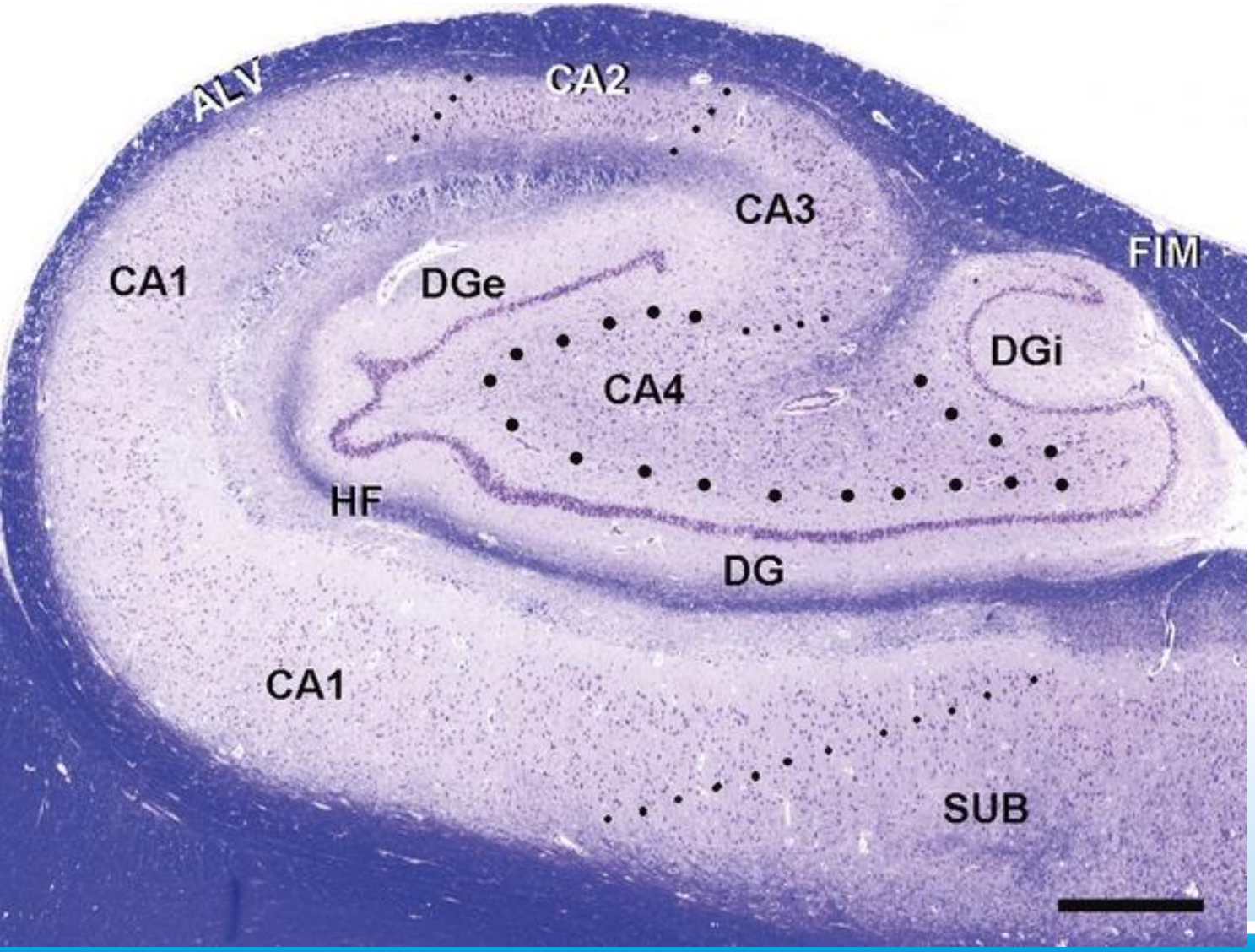


https://www.med.umich.edu/digitallab/m2pathlabs/neuro/review.html



https://www.med.umich.edu/digitallab/m2pathlabs/neuro/review.html

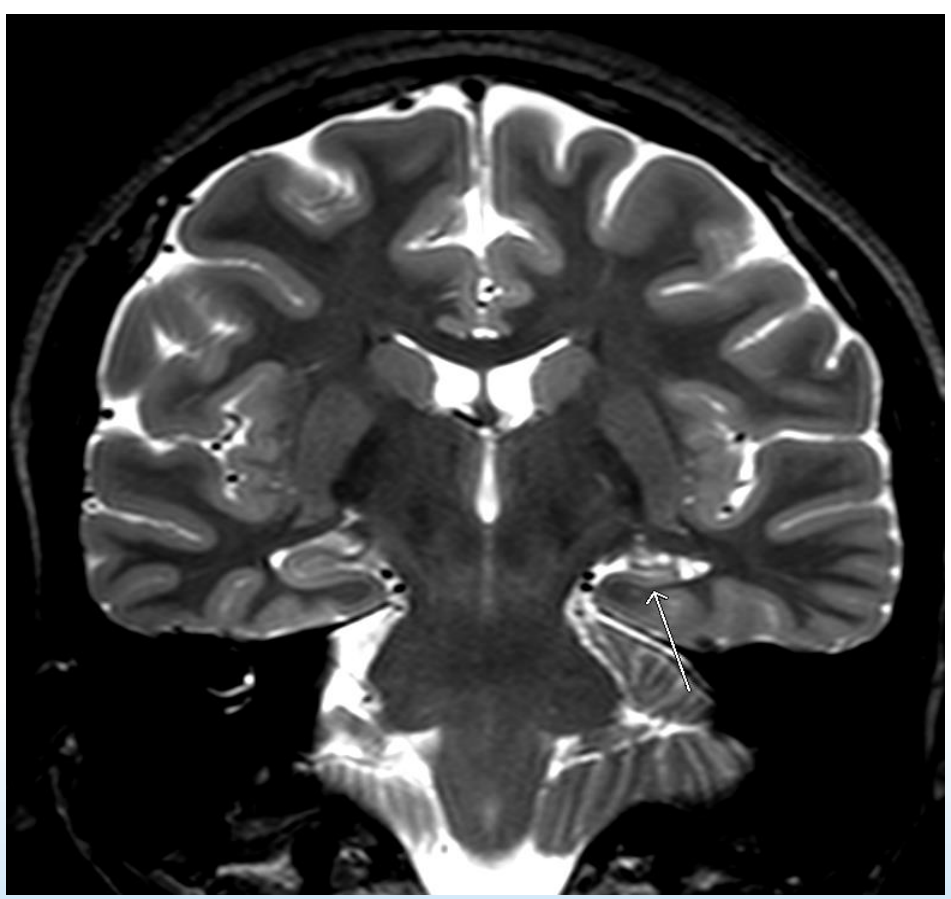
ILAE hippocampal sclerosis evaluation

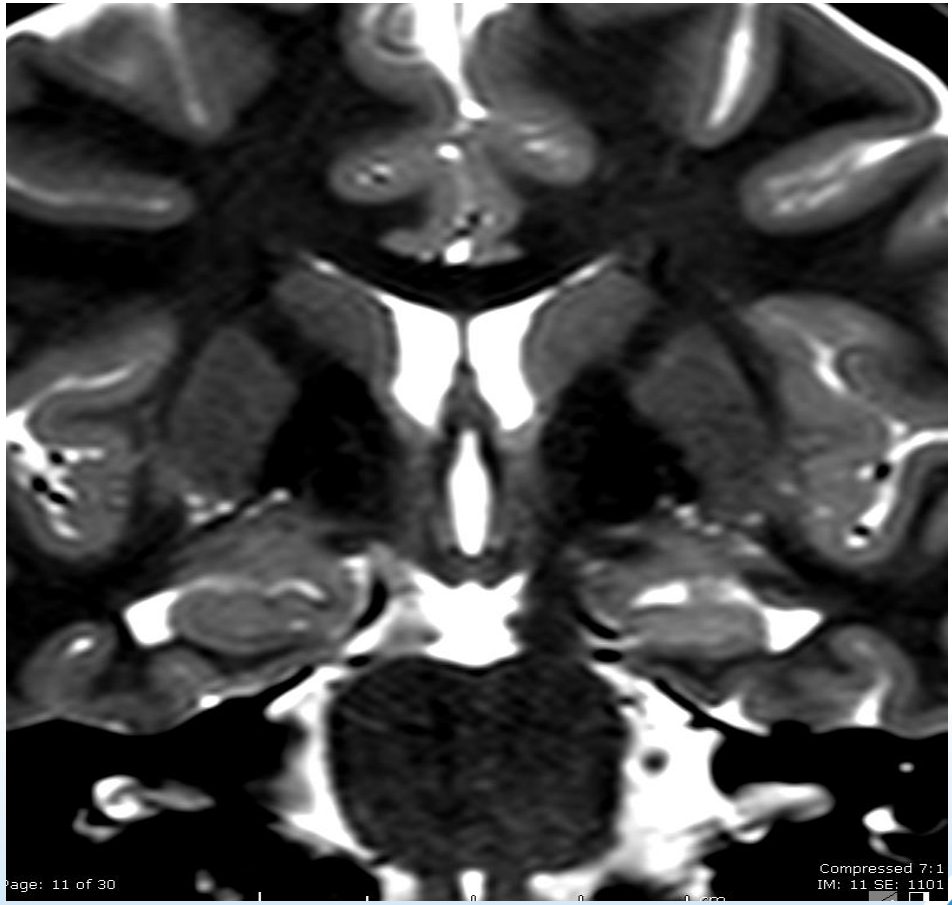


- Dotted lines circumscribe anatomic boundaries between CA sectors
- First detectable neuronal loss by visual inspection ~30-40%
- Quantification should be performed at the center of these regions

Blumcke I Thom M et al. Epilepsia 2013. PMID: 32692496

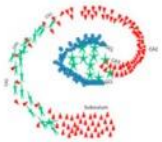
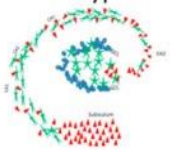
Hippocampal sclerosis





Hippocampal sclerosis pathology

- Types of HS are distinguished by patterns of pyramidal cell loss
- Highest rate of seizure freedom in Classical HS (type 1)
- Atypical patterns of HS associate with poorer outcomes
- No known genetic susceptibility to HS

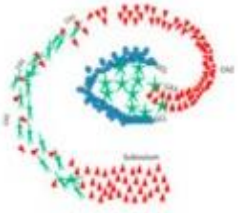
	Main pathology findings					
	No HS  No HS	Gliosis only  End folium gliosis	ILAE type 3  End folium sclerosis	ILAE type 2  CA1 predominant	ILAE type 1  Classical HS	ILAE type 1 
Classification system/era	*No neuronal loss and no gliosis*	*Gliosis only (often involving the subgranular zone)*	*Neuronal loss and gliosis in CA4 subfield (endplate/hilus)*	*Neuronal loss and gliosis predominant in CA1 subfield*	*Neuronal loss and gliosis in CA1 > CA4, CA3 with sparing of CA2*	*Extensive neuronal loss (and gliosis) in all subfields including the dentate gyrus*
Corsellis/Bruton (1966 to 1988)	No HS		End folium sclerosis	Not identified	Classical Sclerosis	Total Sclerosis
Wyler (1996)	Grade 0	Grade 1	Grade 2 (end folium pattern)	Grade 2	Grade 3	Grade 4
Blumcke/ILAE (2007 to 2013)	No HS	Gliosis only	ILAE type 3 HS	ILAE type 2 HS	ILAE type 1 HS	
Approximate proportion*	10–30%	Unknown	3–7.4%	5–10%	60–80%	
Clinicopathological correlations in temporal lobe epilepsy surgical series†	(1) Poorer postsurgical seizure-free outcomes (42–58% seizure free) (2) FS – less common	Unknown specificity for TLE	(1) Pattern of HS most often associated with a second (dual) pathology (e.g. DNT, cavernoma) (2) Older age at onset of epilepsy† (3) Poorer postsurgical seizure-free outcomes in some series	(1) Older age at onset of epilepsy in some series (2) Poorer postsurgical seizure-free outcomes in some series	(1) Highest rates of seizure freedom (~70–85% seizure freedom post-operatively at 2 years, ~50% at 10 years) (2) Common association with febrile seizures 50–76%	

*This refers to the relative incidence of the patterns of sclerosis in surgical epilepsy series where HS/mesial temporal lobe sclerosis is considered, both electroclinically and/or by MRI, to be the cause of epilepsy.
†Clinicopathological correlations for different subtypes have been reported in some, but not all, epilepsy surgical series.
In the diagrams pyramidal neurones of hippocampal subfields and subiculum are shown in red, granule cells in blue and astrocytosis in green.
ILAE, International League Against Epilepsy; FS, febrile seizures; DNT, dysembryoplastic neuroepithelial tumour.

Patterns of neuronal cell loss by sector

Sector	HS type 1	HS type 2	HS Type 3	No-HS/Gliosis only
CA1	2	1-2	0-1	0
CA2	0-2	0-1	0-1	0
CA3	0-2	0-1	0-1	0
CA4	2	0-1	1-2	0
DG	0-2	0-1	0-2	0-1

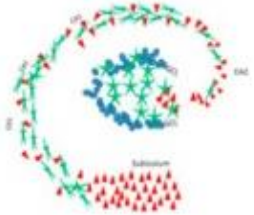
ILAE type 1



Classical HS

Neuronal loss and gliosis in CA1 > CA4, CA3 with sparing of CA2

ILAE type 1



Extensive neuronal loss (and gliosis) in all subfields including the dentate gyrus

ILAE type 2

CA1 predominant

Neuronal loss and gliosis predominant in CA1 subfield

ILAE type 3

End folium sclerosis

Neuronal loss and gliosis in CA4 subfield (endplate/hilus)

No HS

No HS

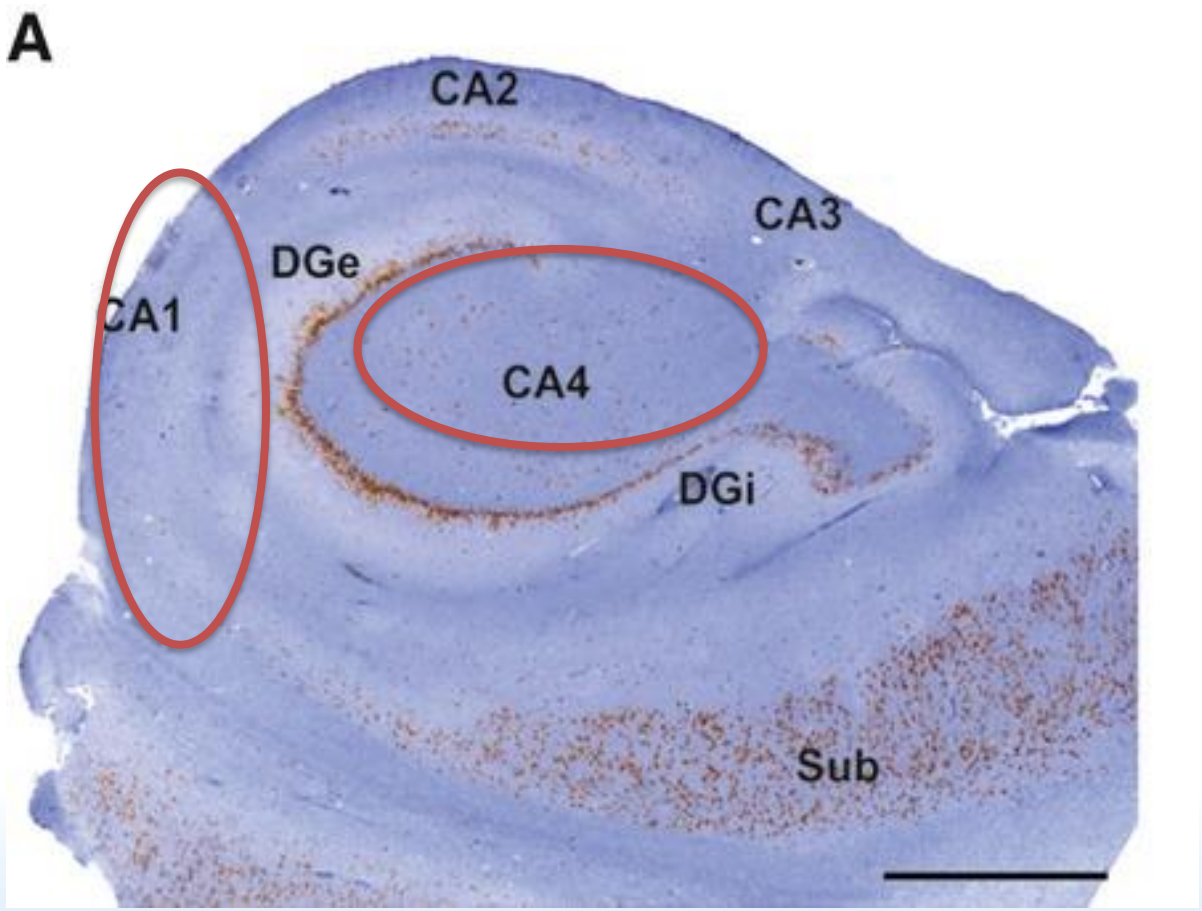
No neuronal loss and no gliosis

Gliosis only

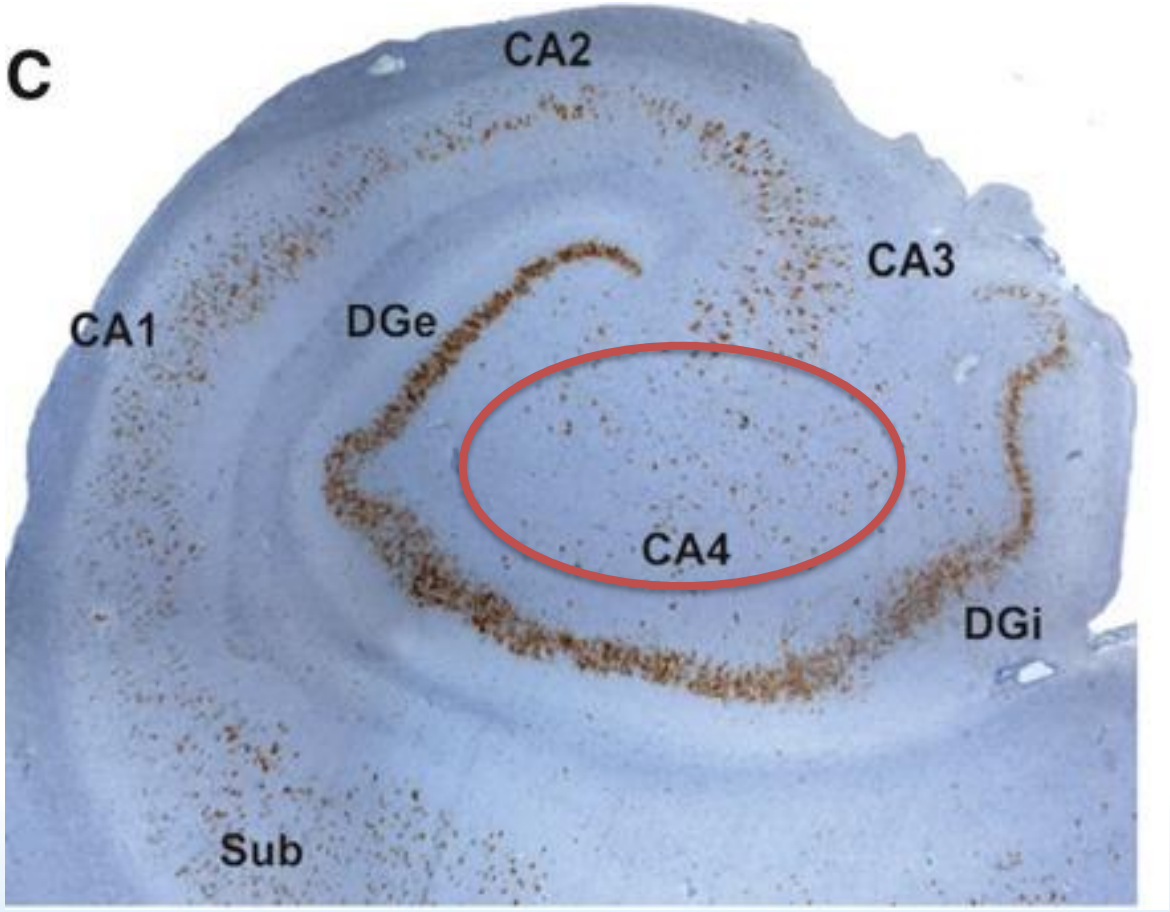
End folium gliosis

Gliosis only (often involving the subgranular zone)

Which type of HS? Where is the neuronal loss?

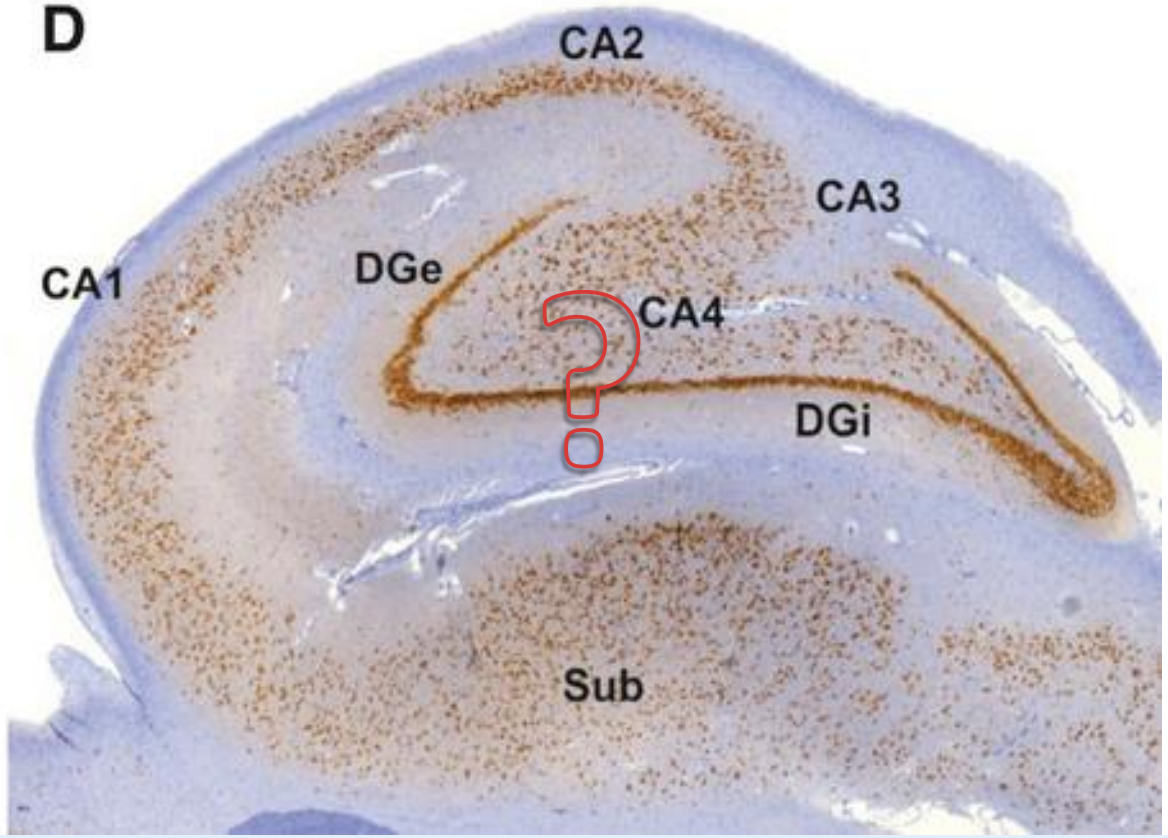


Classical HS (ILAE type 1)

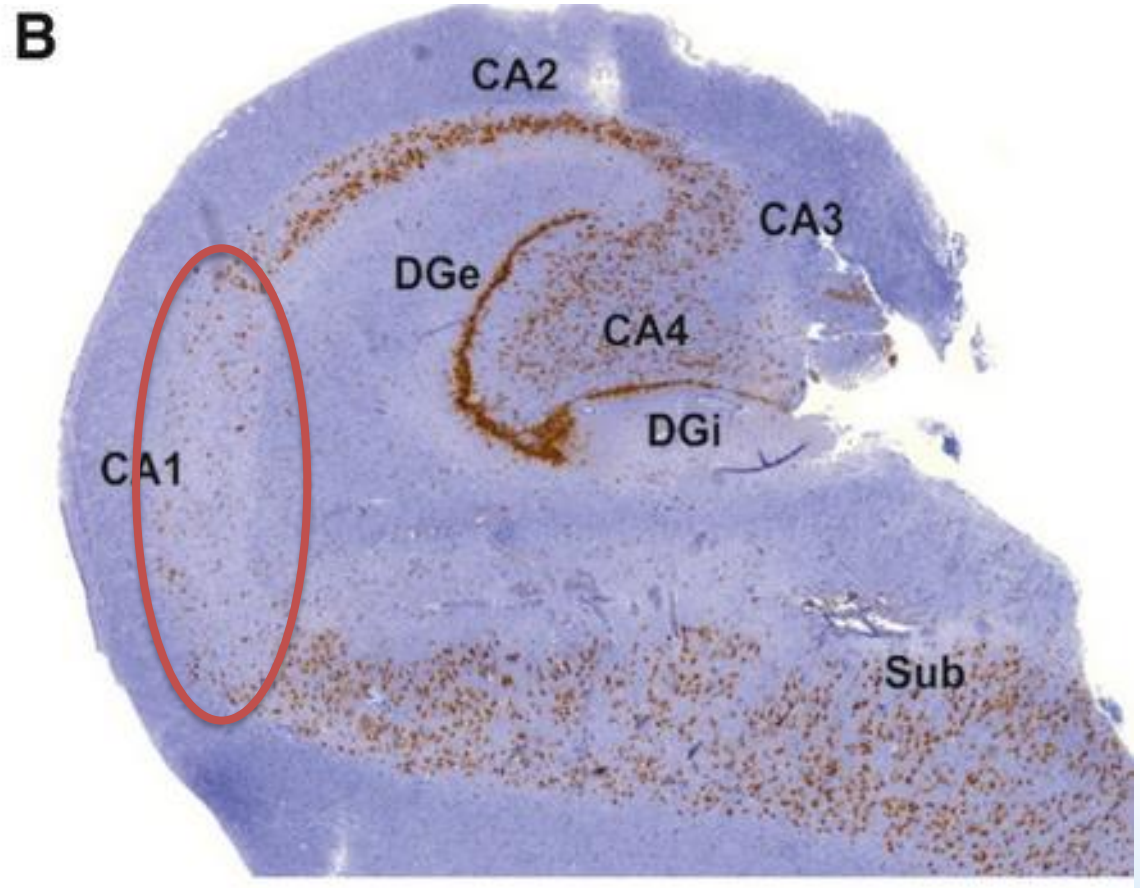


CA4-predominant (ILAE type 3)

Which type of HS? Where is the neuronal loss?



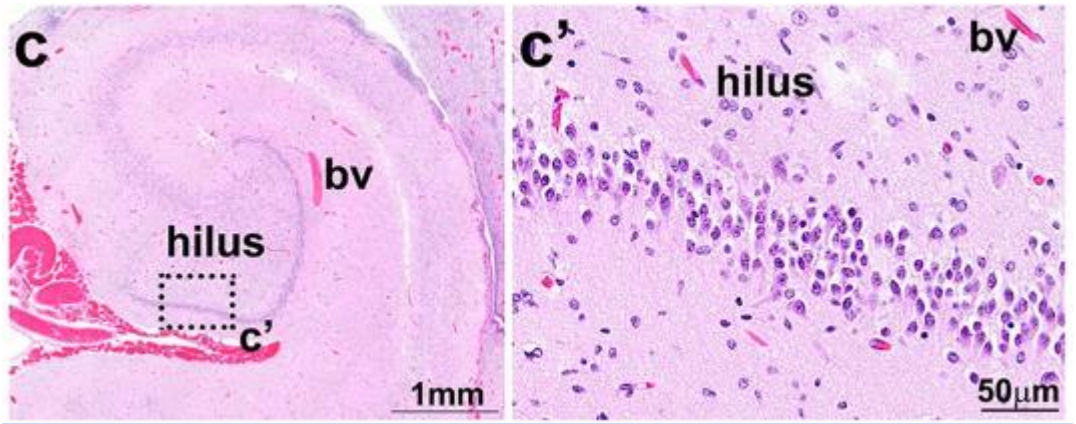
No HS/gliosis only



HS ILAE Type 2 (CA1 predominant)

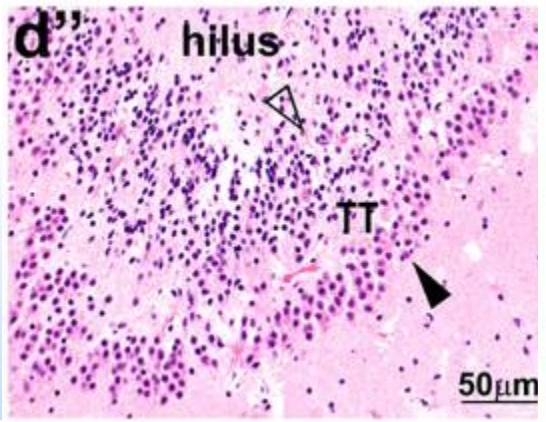
Granule cell dispersion

- Seen in 50% of TLE cases
  - Variably present in HS types 1, 2, and 3
- Abnormal clustering or bi-lamination
- Proposed definition of >10 layers, ill-defined boundary with molecular layer, and ectopic granule cells
  - Important to avoid tangentially cut sections
- Mechanisms proposed
  - Seizures create pro-neurogenic environment
  - Mature neurons migrate due to local effects (reelin deficiency)
- **Pediatric series suggest GCD is not specific to seizure-affected brains**

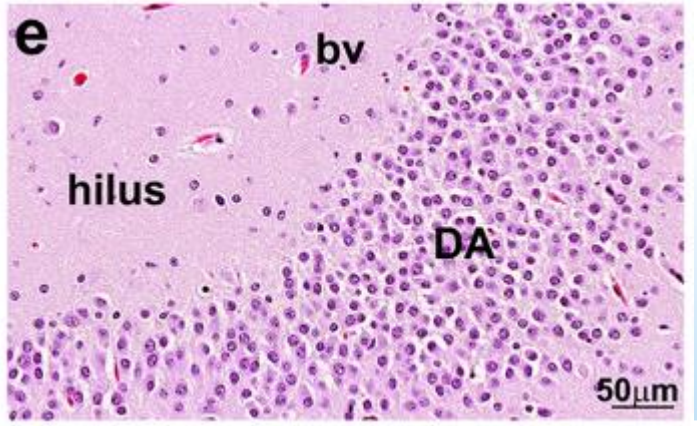


compact/"normal"

"tram-track"

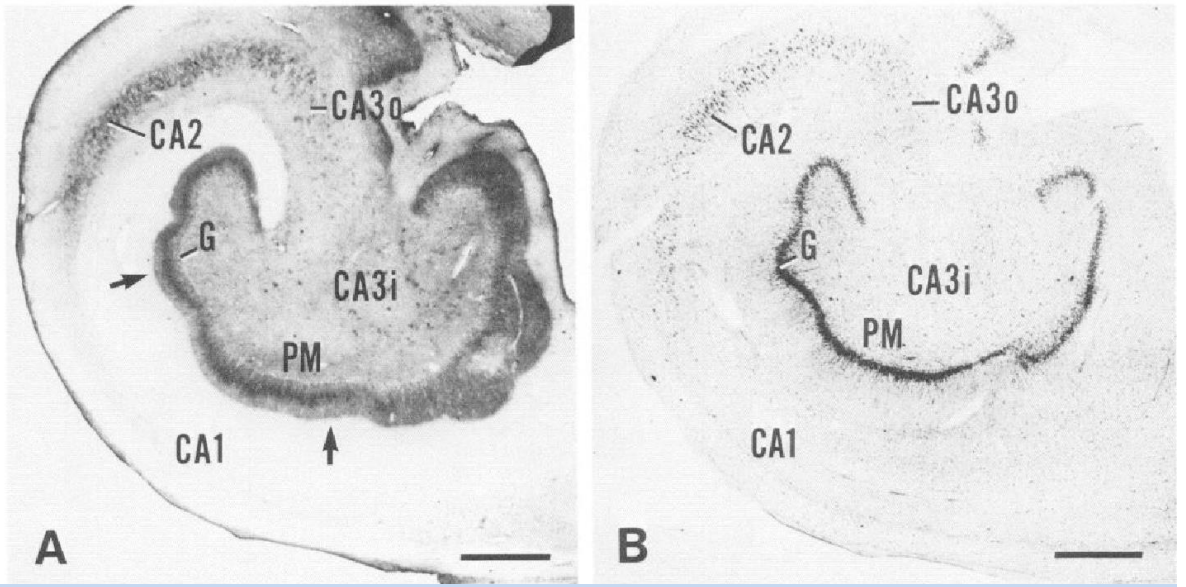


disaggregated



Mossy fiber sprouting

- Outgrowth of dentate granule cells' axons into the inner molecular layer
- Thought to result in aberrant microanatomy which can be epileptogenic
- Animal models with status epilepticus show mossy fiber sprouting
  - Common morphologic marker for hippocampal change/reorganization



TLE case, dynorphin immunoreactivity in inner molecular layer around the dentate gyrus (A) compared to CV (B)

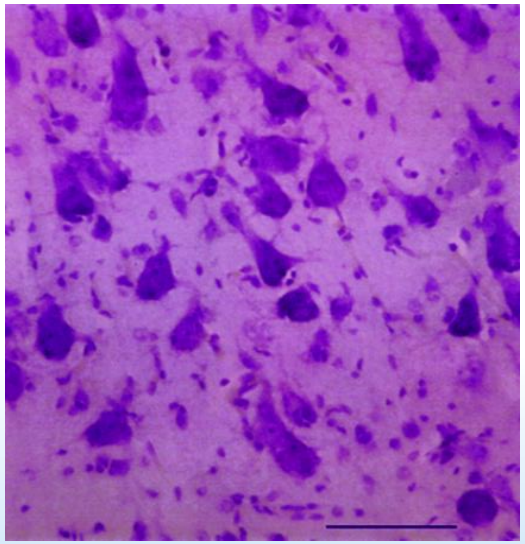
Houser C, Miyashiro J et al. J Neurosci 1990.

Focal cortical dysplasia

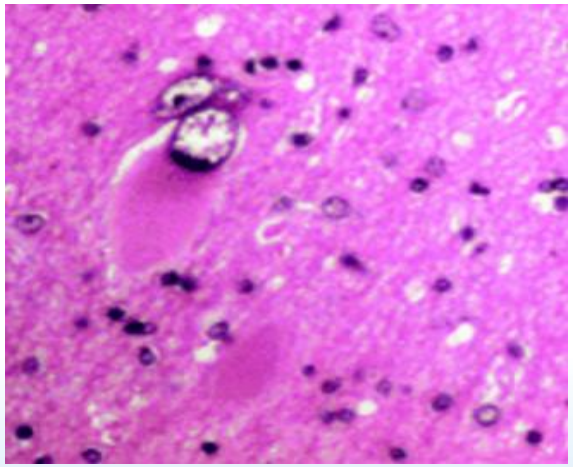
- “microscopically discernable architectural disorganization of the neocortex in patients with focal epilepsies”
- Associated with drug-resistant epilepsy
- Classification has changed several times
  - Challenge of interobserver reproducibility in more subtle lesions

Palmini classification of cortical dysplasias

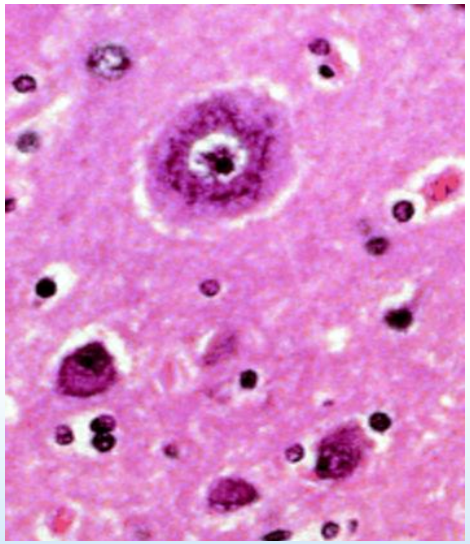
- Panel of neurologists, neuropathologists, neuroradiologists
- “Malformations due to abnormal cortical development”
  - “cortical dysplasia”/FCD – if malformation restricted to or mostly in the cortex
  - “neuronal migration disorder”
  - ~~“microdysgenesis”~~
  - Mild MCDs
    - with ectopically placed neurons in layer I
    - with abnormalities outside layer I



Dysmorphic neuron



Balloon cell



Giant neuron

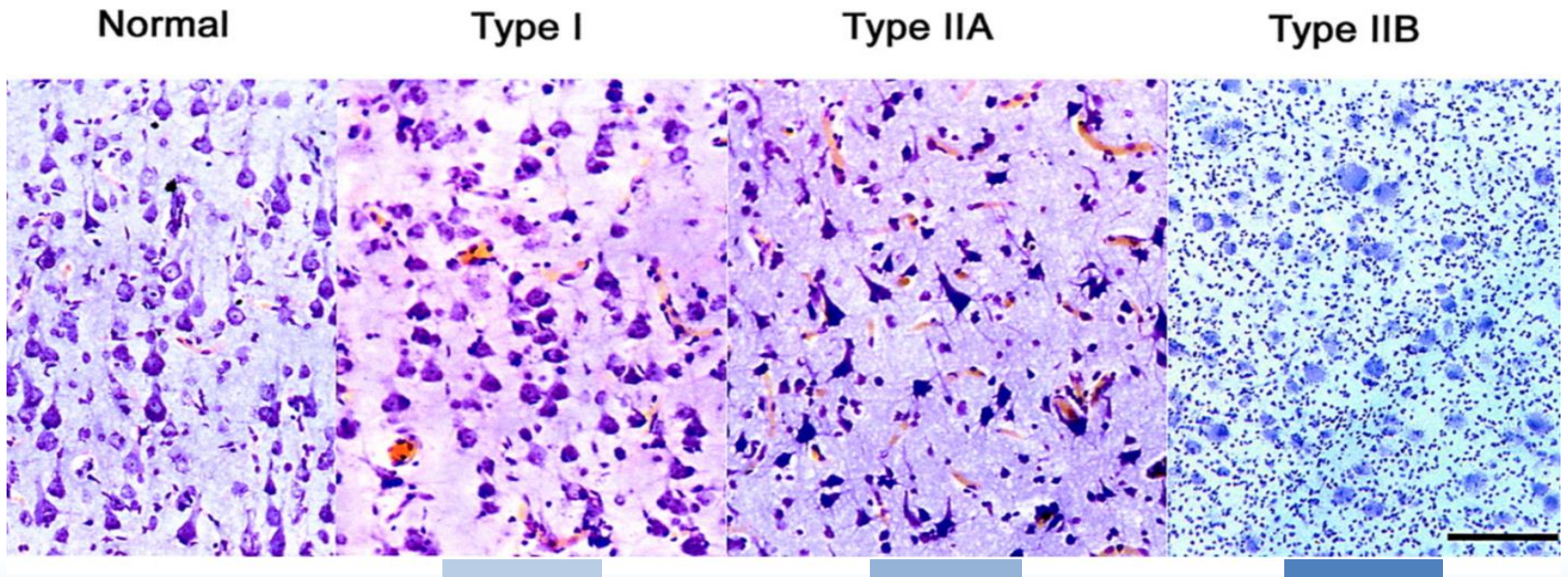
Palmini A et al. Neurology 2004 PMID: 15037671.

Palmini classification of cortical dysplasias

Mild MCD

Type I (ectopic neurons in/adj to layer I)

Type II (microscopic neuronal heterotopia outside layer I)



-DN -BC

+DN -BC

+DN +BC

IA: isolated architectural abnormalities
Dyslamination +/- mild MCD

IB: architectural abnormalities
+ giant or immature neurons

DNET and Ganglioglioma can be associated with epilepsy and dyslamination in surrounding cortex

MCD: malformation of cortical development
DN: dysmorphic neurons
BC: balloon cells

ILAE Diagnostic Methods Commission 2011

Palmini et al. 2004	Blumcke et al. 2011 #
Mild MCD, type I	*mMCD type I*
Mild MCD, type II	*mMCD type II*
FCD, type IA	Type I
FCD, type IB **	Type I
FCD, type IIA	Type IIa
FCD, type IIB	Type IIb
Adjacent to LG tumor	Type III (category also includes association with entities other than tumors)

** Not reproducible among 9 North American neuropathologists (Chamberlain et al. 2009)
# 30 international neuropathologists achieved good inter- and intra-observer agreement

Palmini A et al. Neurology 2004 PMID: 15037671; Blumcke I et al. Epilepsia 2011 PMID: 2129302

ILAE classification 2011

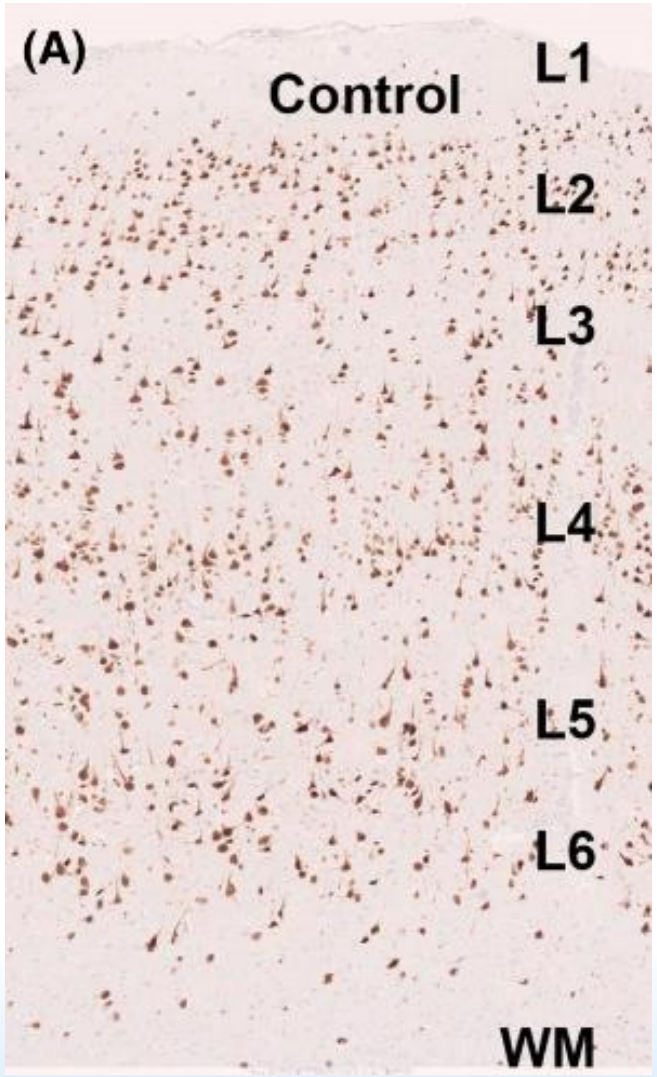
mMCD: ectopic/heterotopic neurons

FCD I: architectural disorganization without cytologic change

FCD II: dysmorphism of neuronal cells

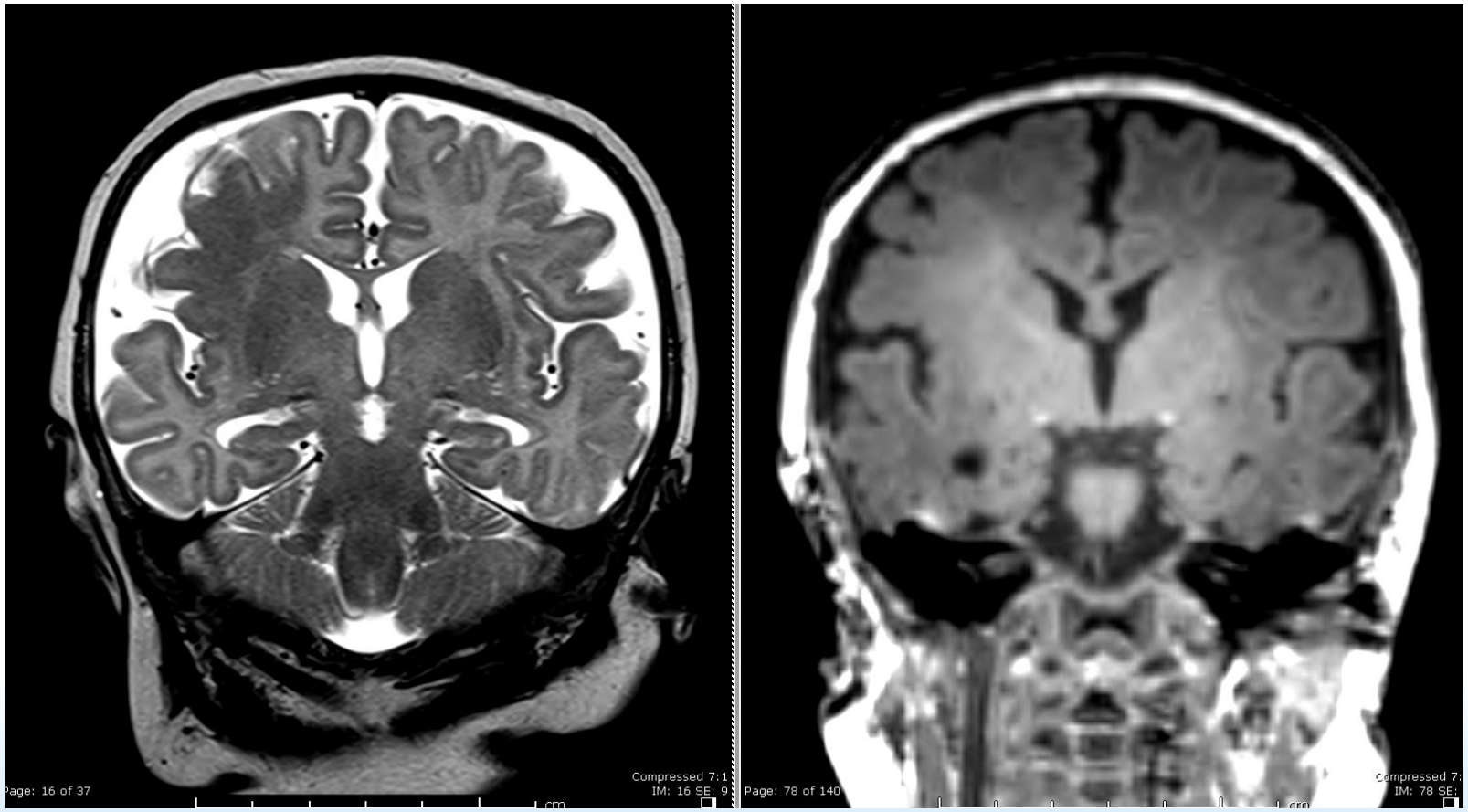
- IIa: no balloon cells
- IIb: with balloon cells

FCD III: architectural abnormalities in association with another 'principal' lesion (e.g., HS, tumor, vascular, or acquired)



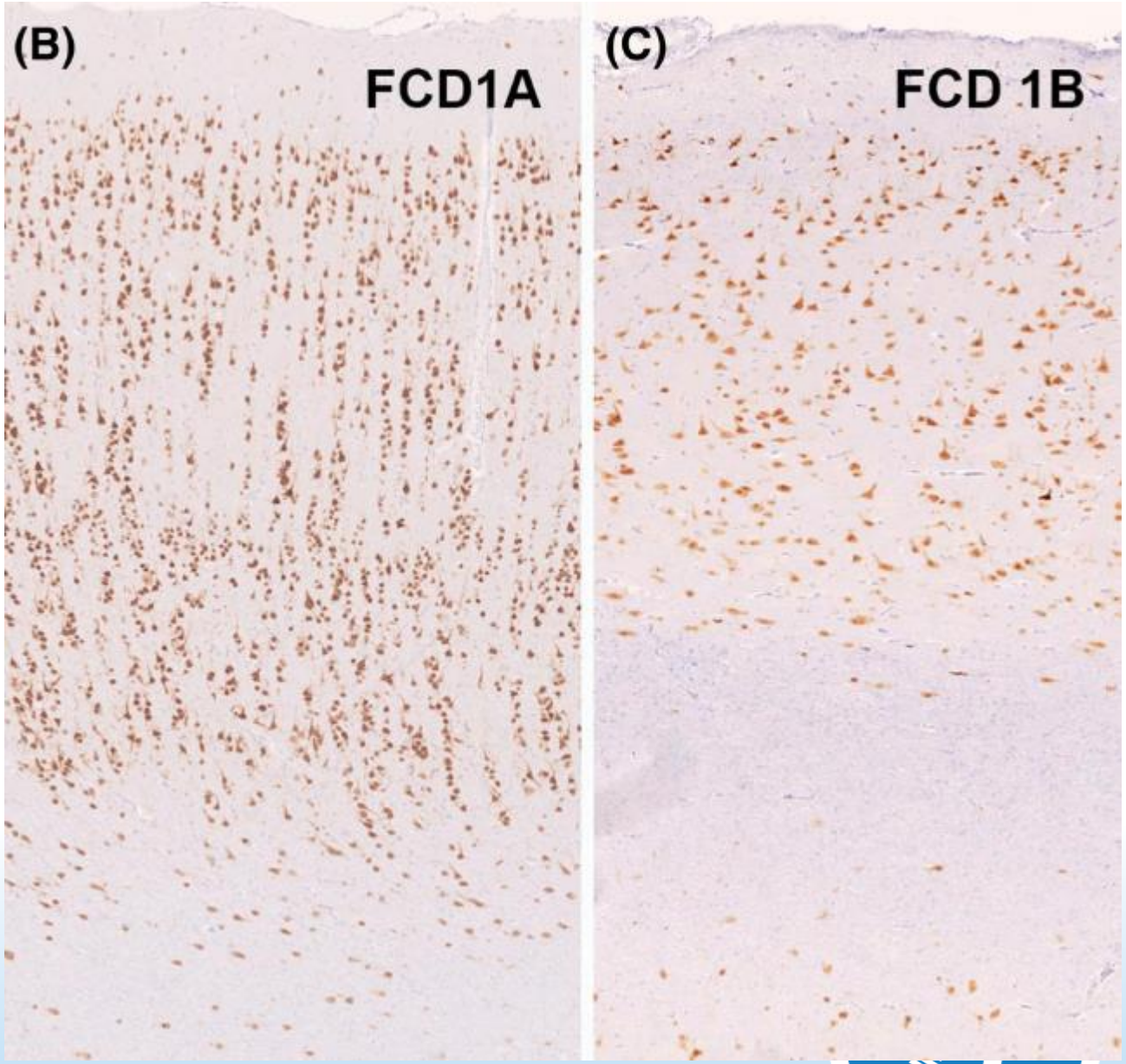
Blumcke I et al. Epilepsia 2011; Najm I et al. Epilepsia 2022

Mild MCD (histo: ectopic neurons in layer 1 and WM)



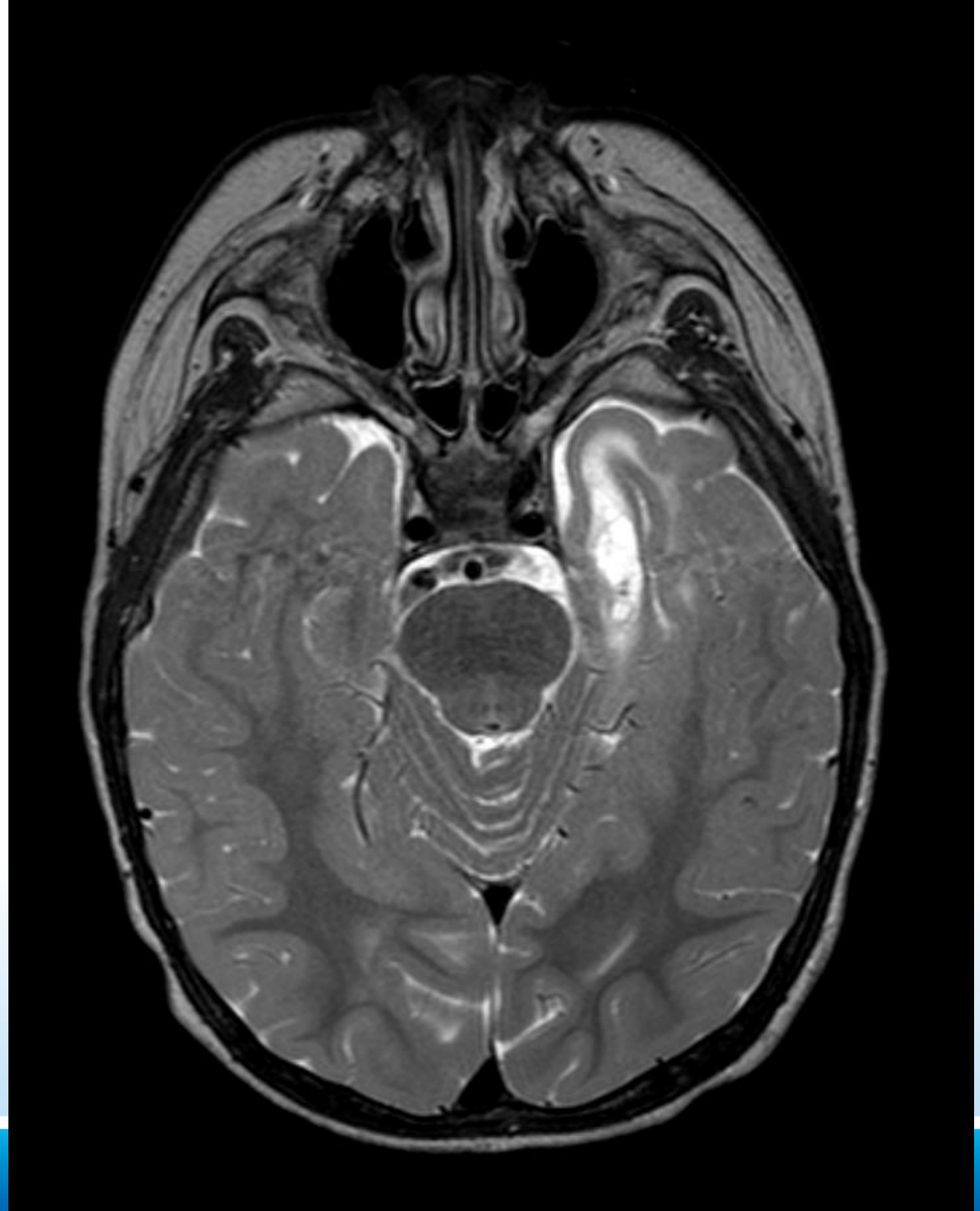
FCD 1A and 1B

- 1A
  - Micro-columns
  - “string of pearls”
- 1B
  - Lack of lamination

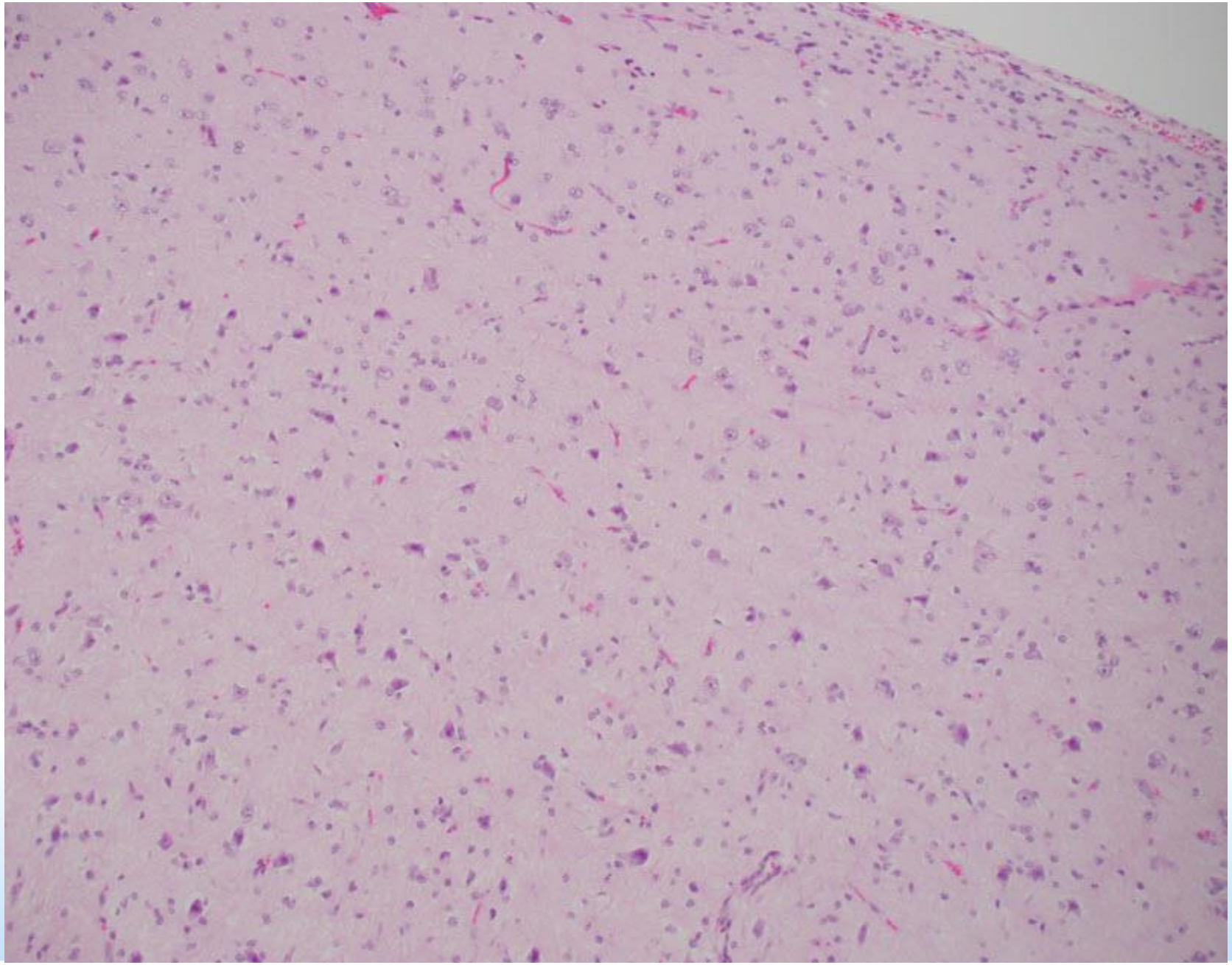


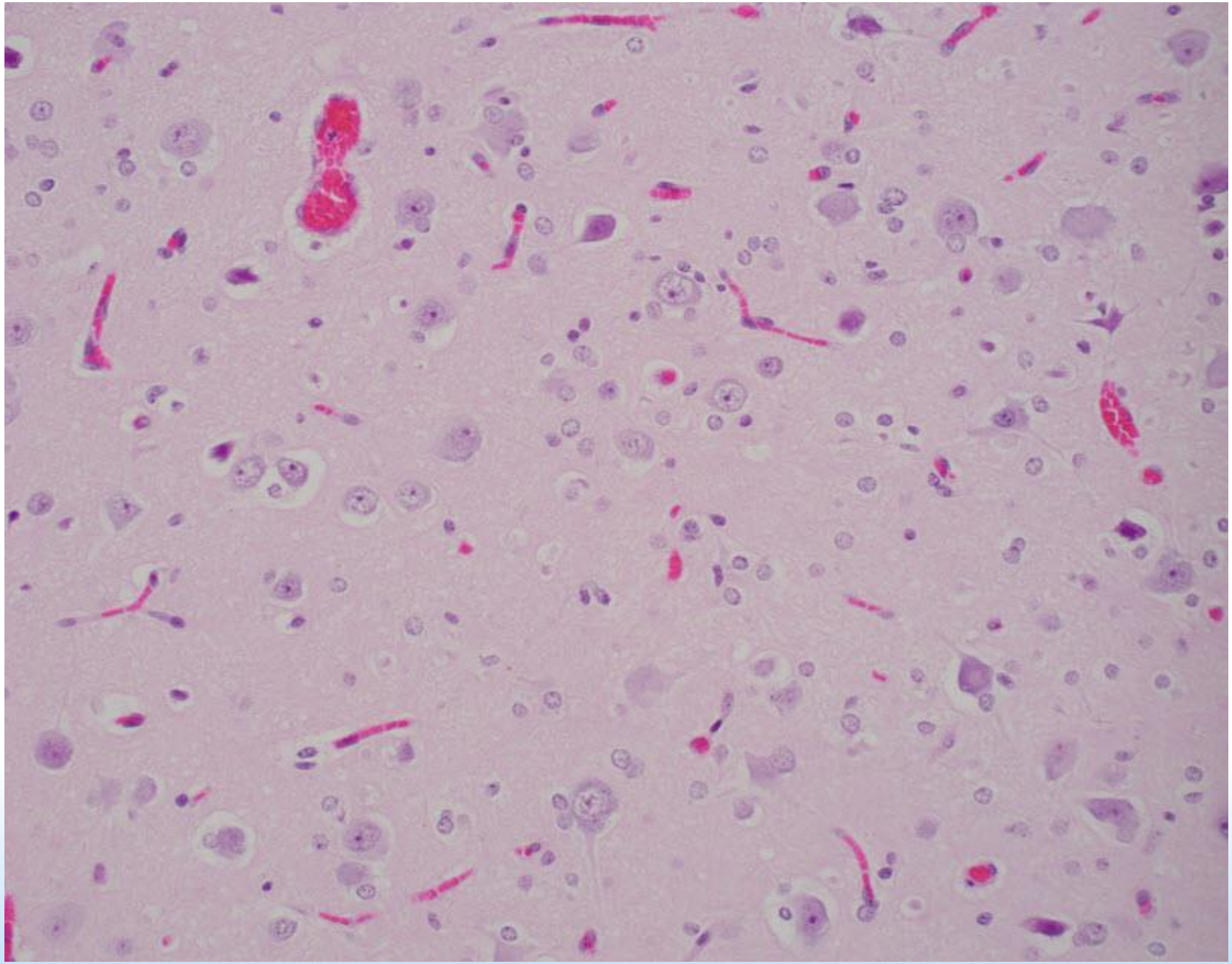
Najm I et al. Epilepsia 2022

FCD2A

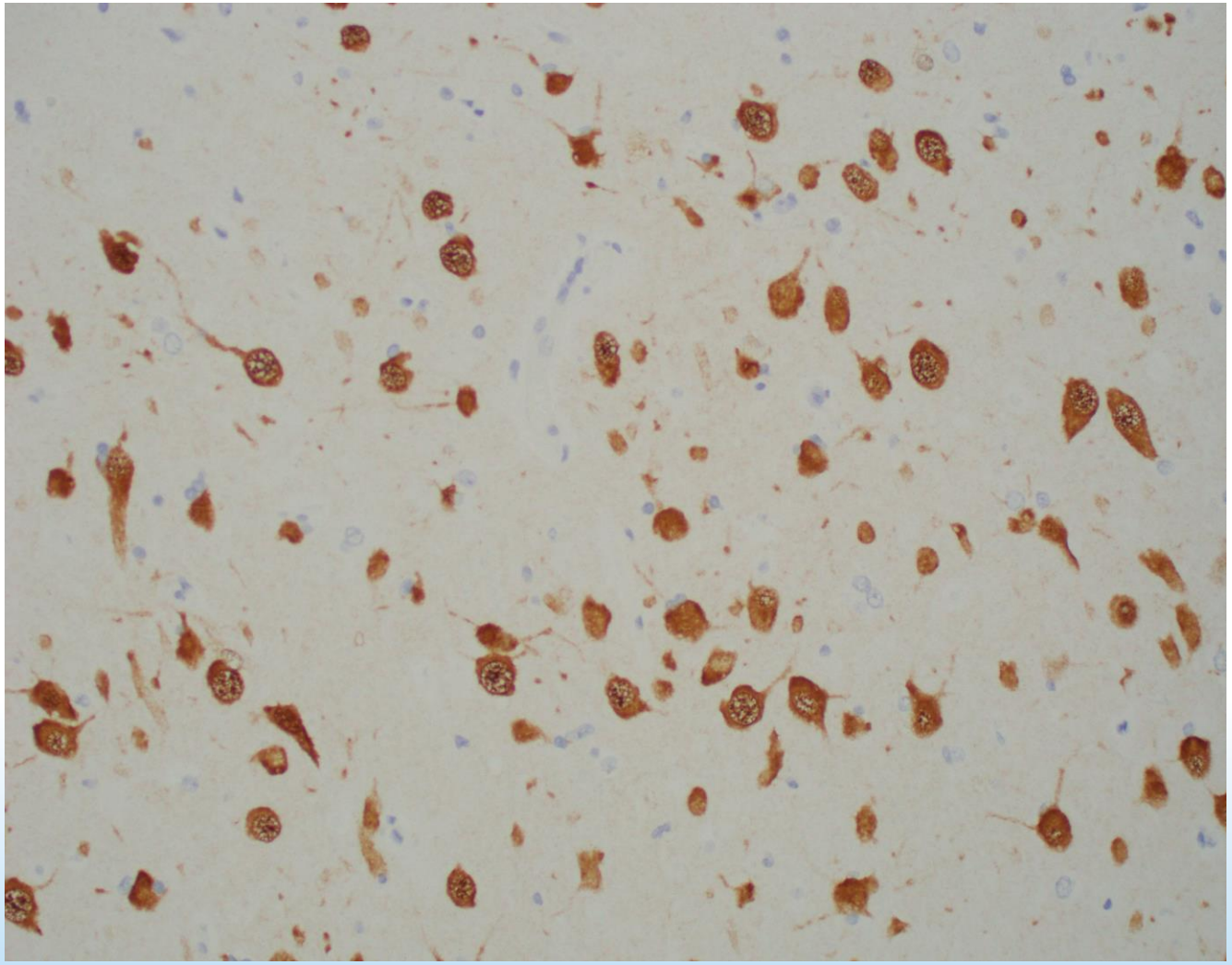


Dr. C. Jason Liu

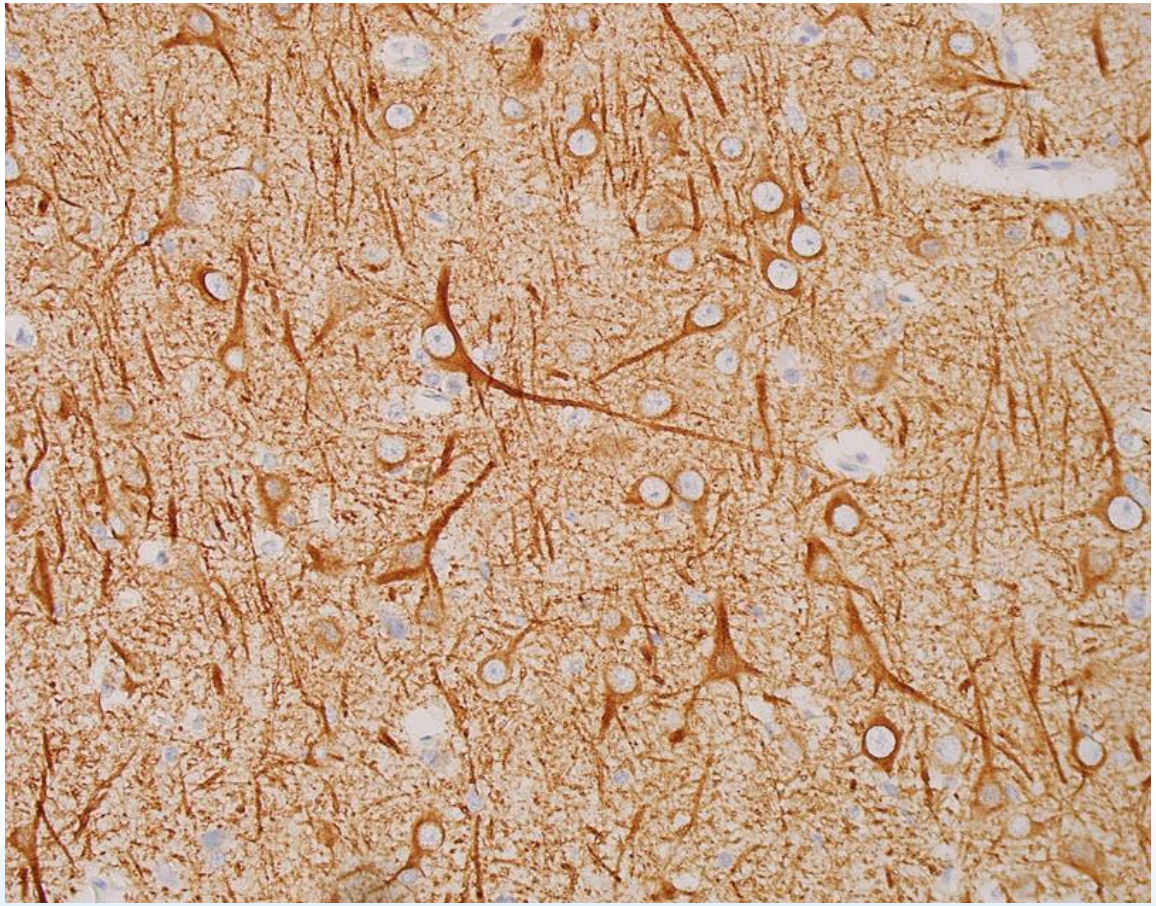


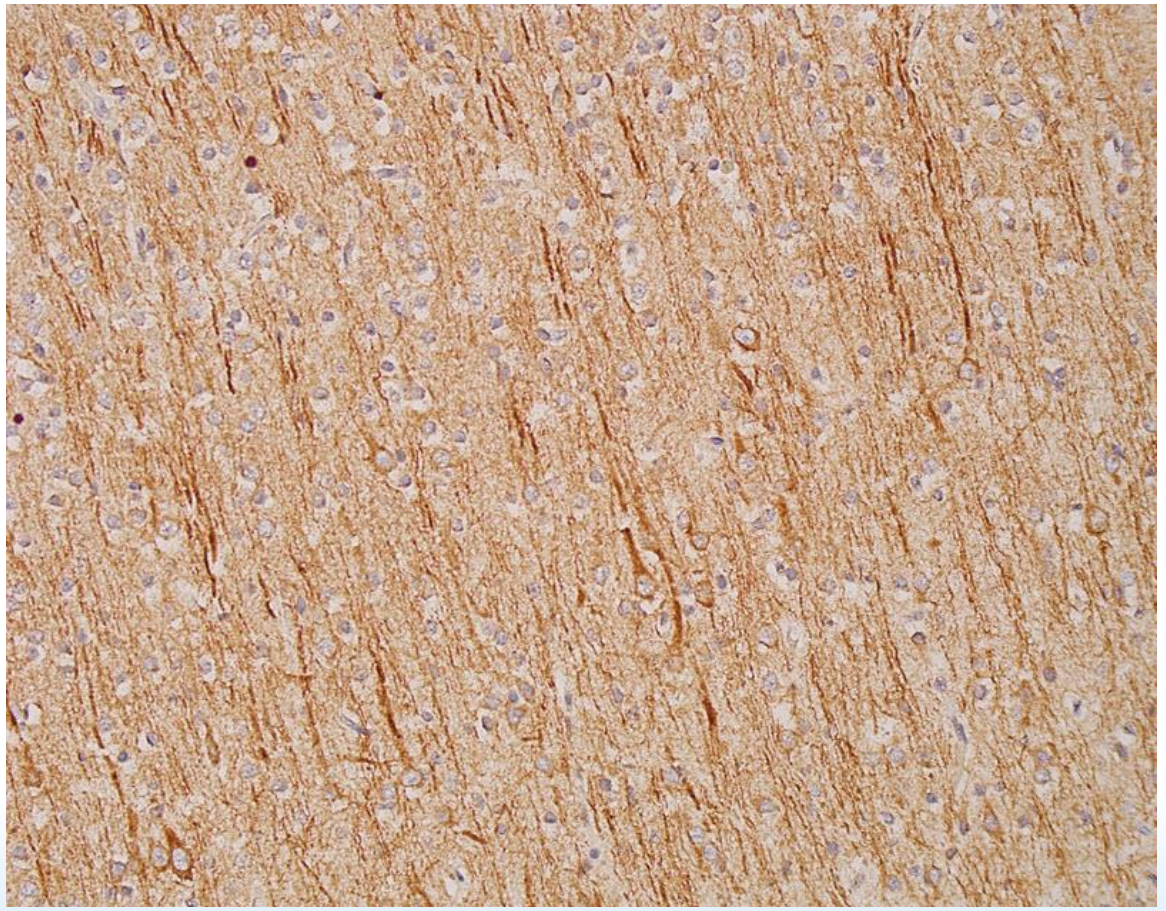


Loss of laminar pattern (NeuN)

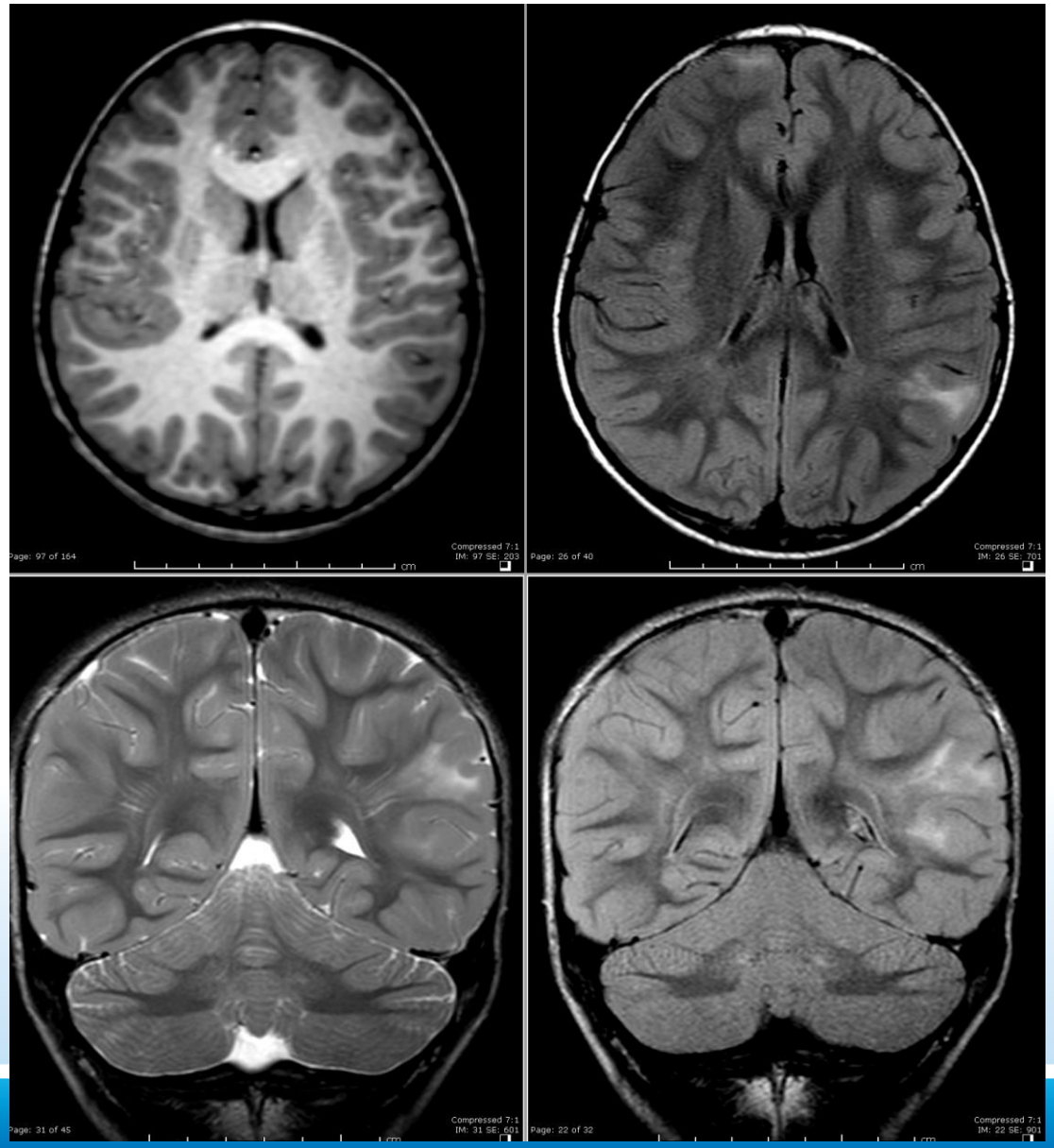


MAP 2: FCD 2A vs. Normal

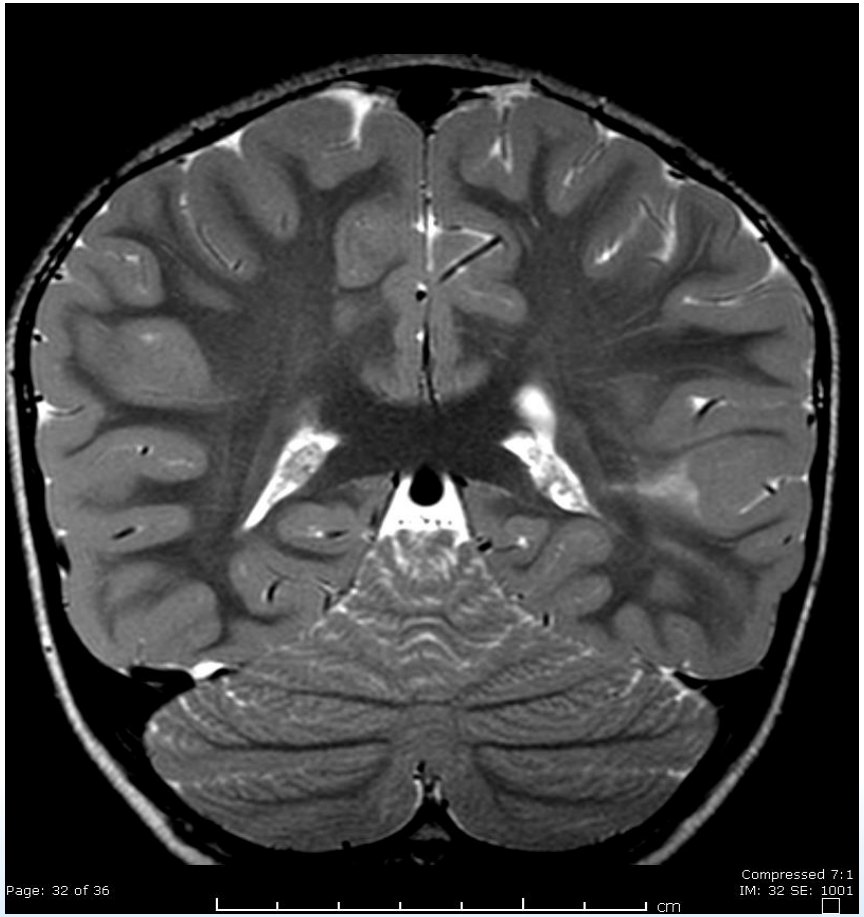


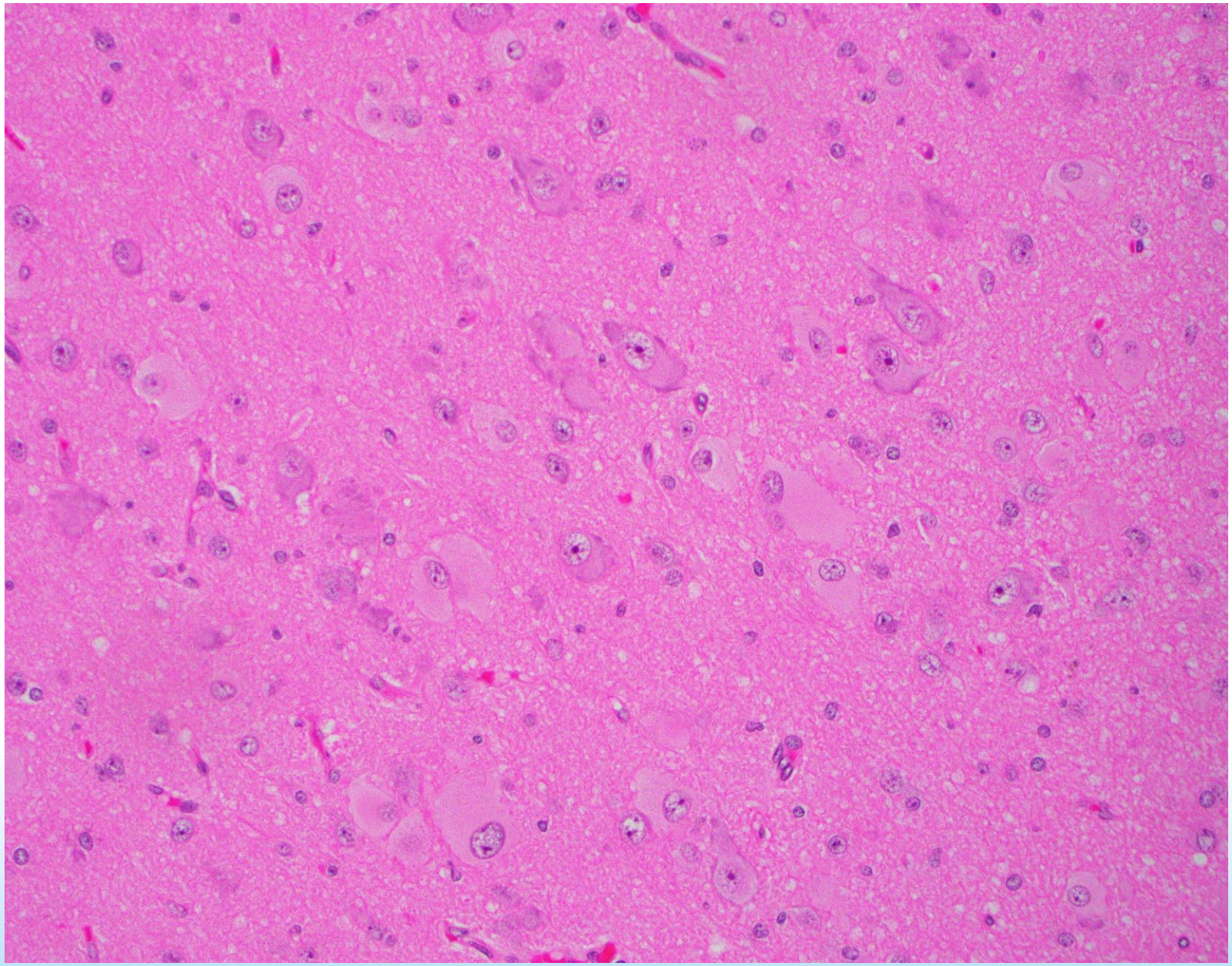


FCD2b transmantle sign

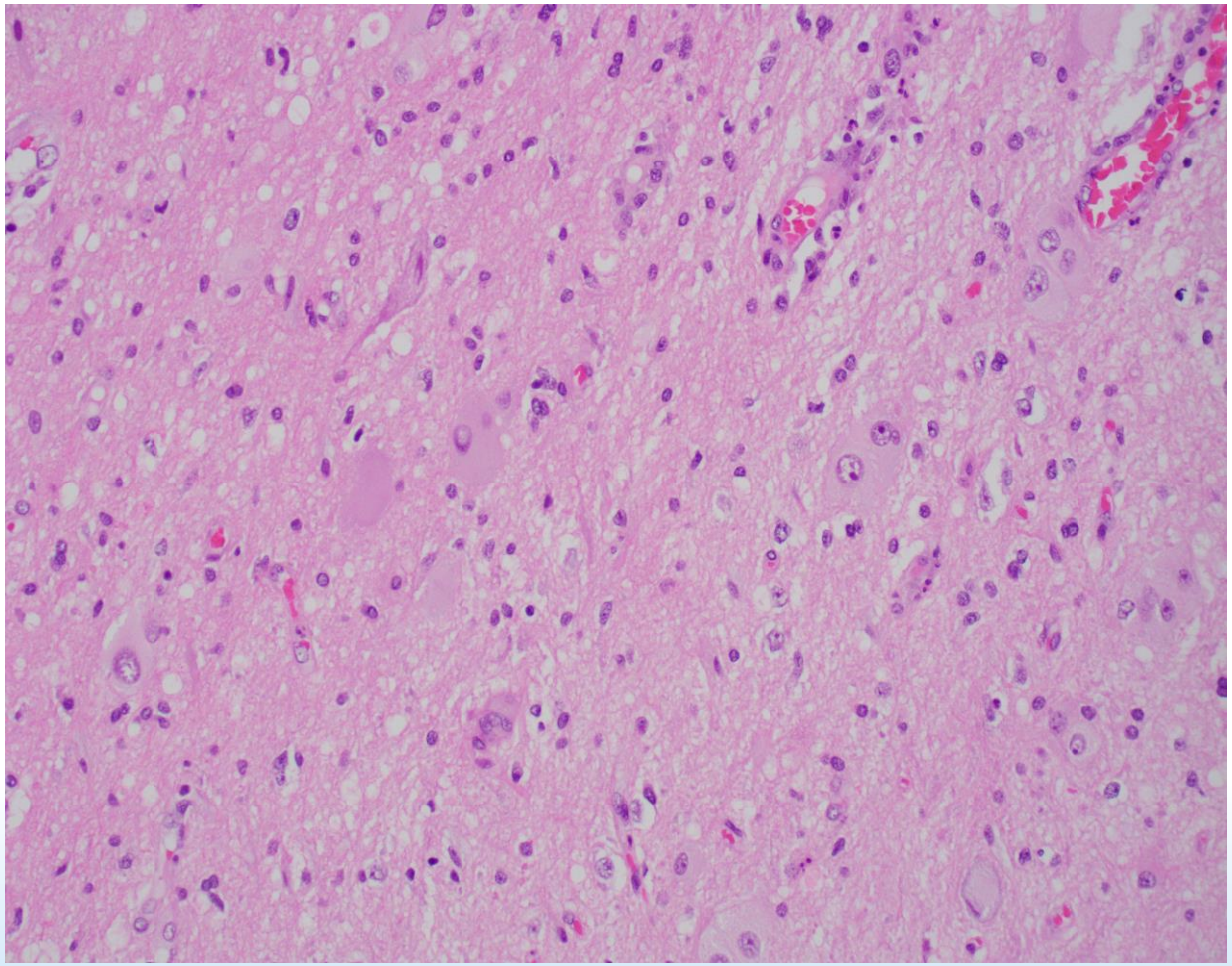


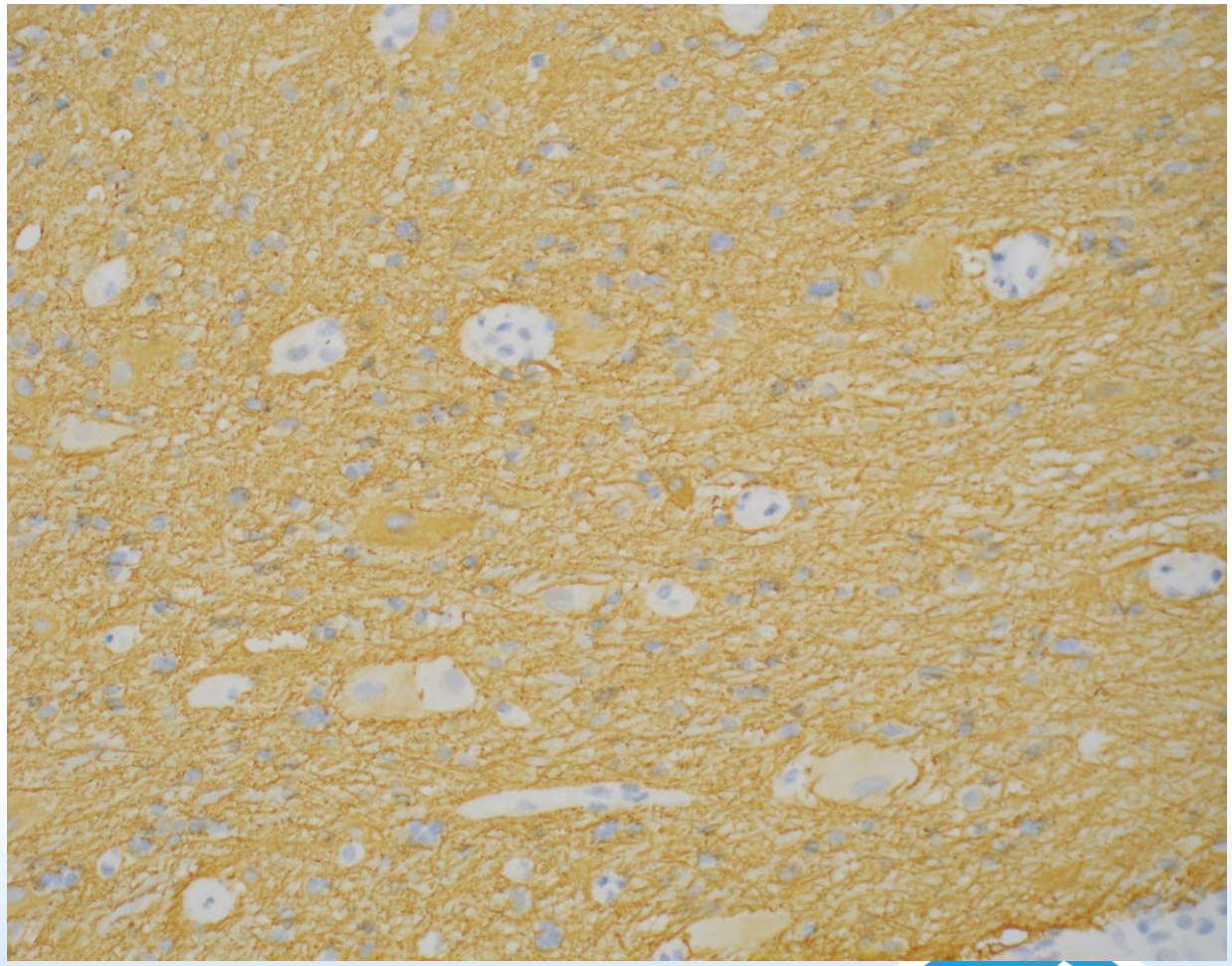
FCD2b transmantle sign





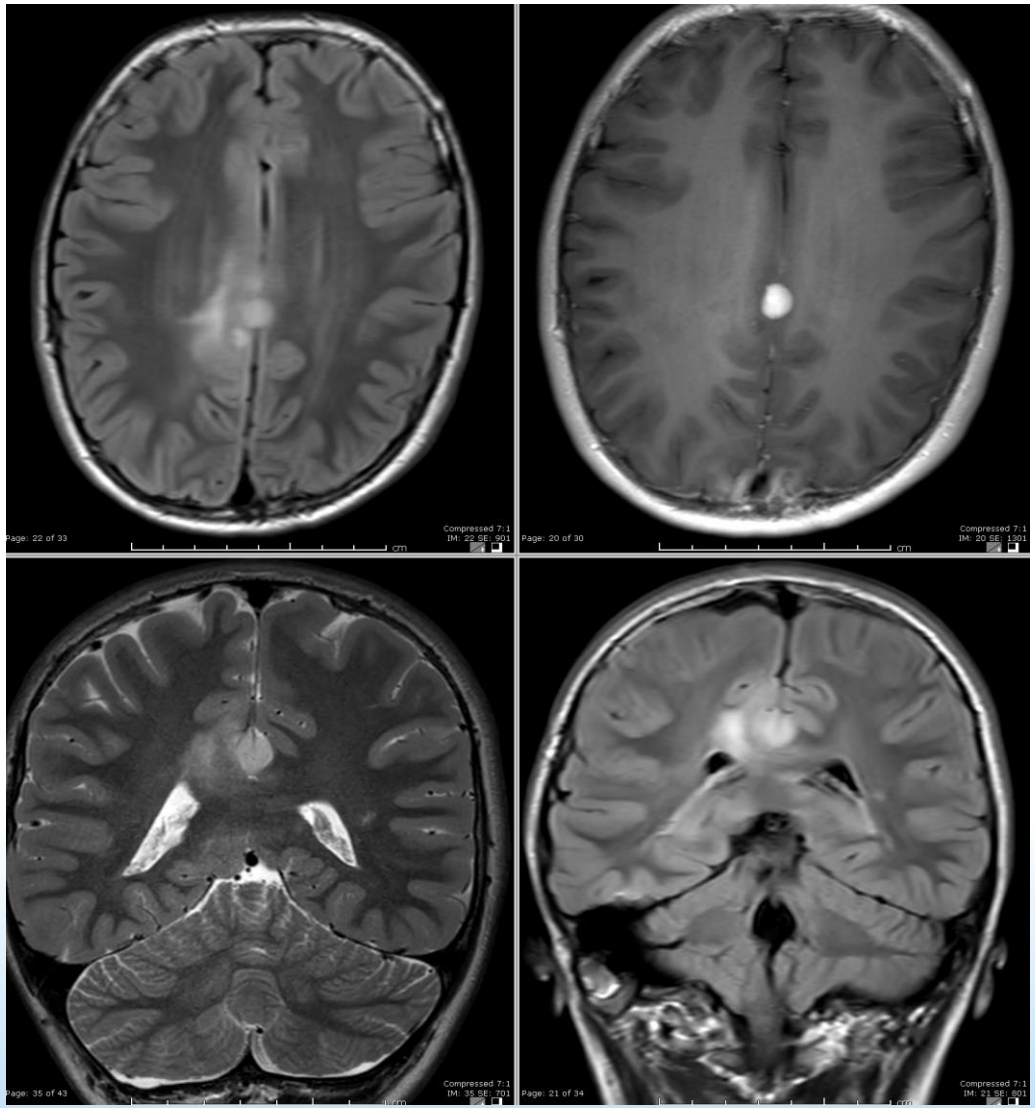
FCD2b

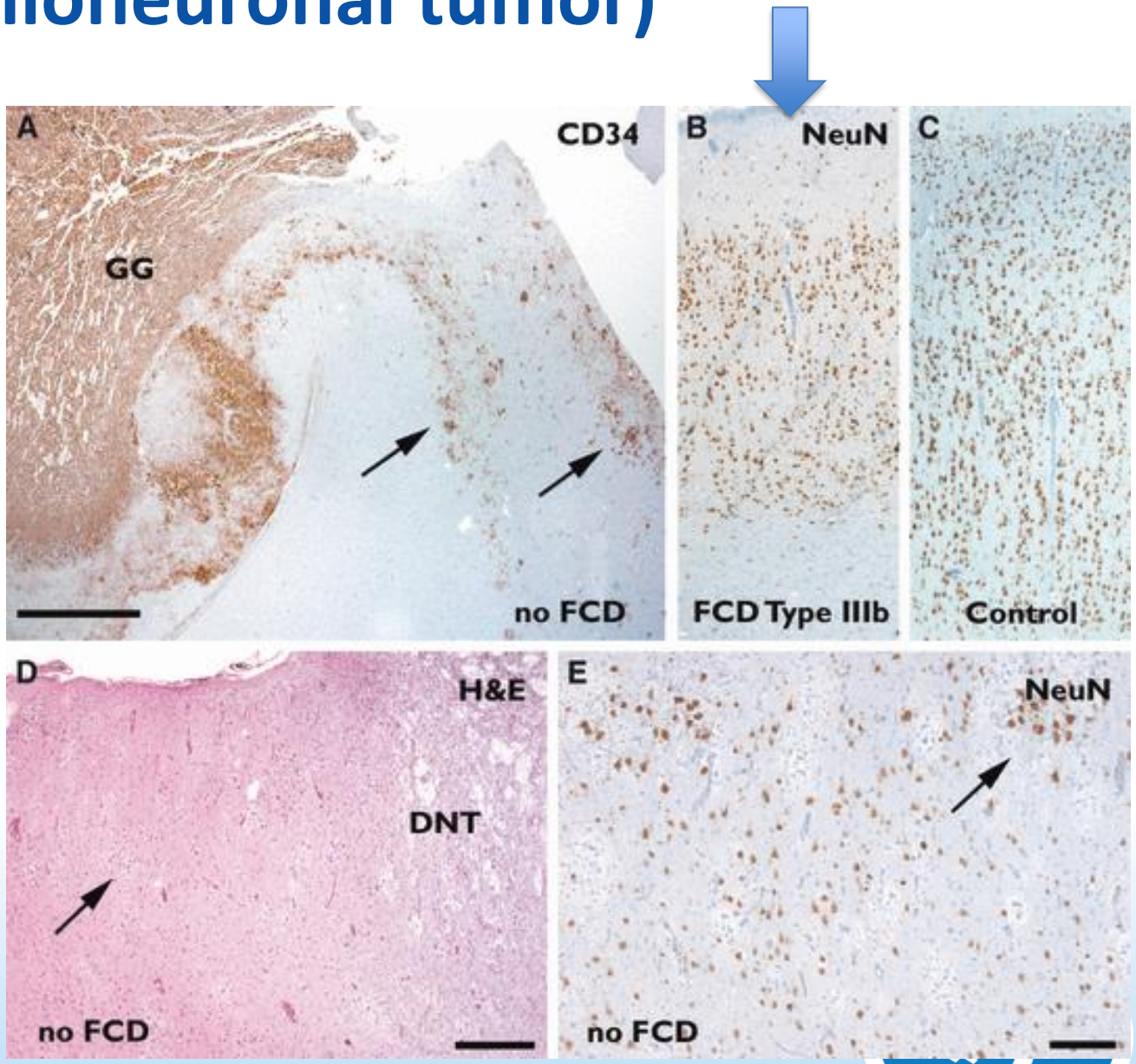




Variable GFAP expression in BC

FCD 3b (associated with glioneuronal tumor)





Dr. C. Jason Liu (MRI), Blumcke I et al., Epilepsia 2011

Relationship of FCD to hemimegalencephaly (HME)

- HME: enlargement of one hemisphere
- Structure of the brain on one side may be markedly abnormal or show subtle changes
- PIK3CA variants are more common than mTOR variants (same pathway)
- Spectrum from FCD to HME proposed by recent studies

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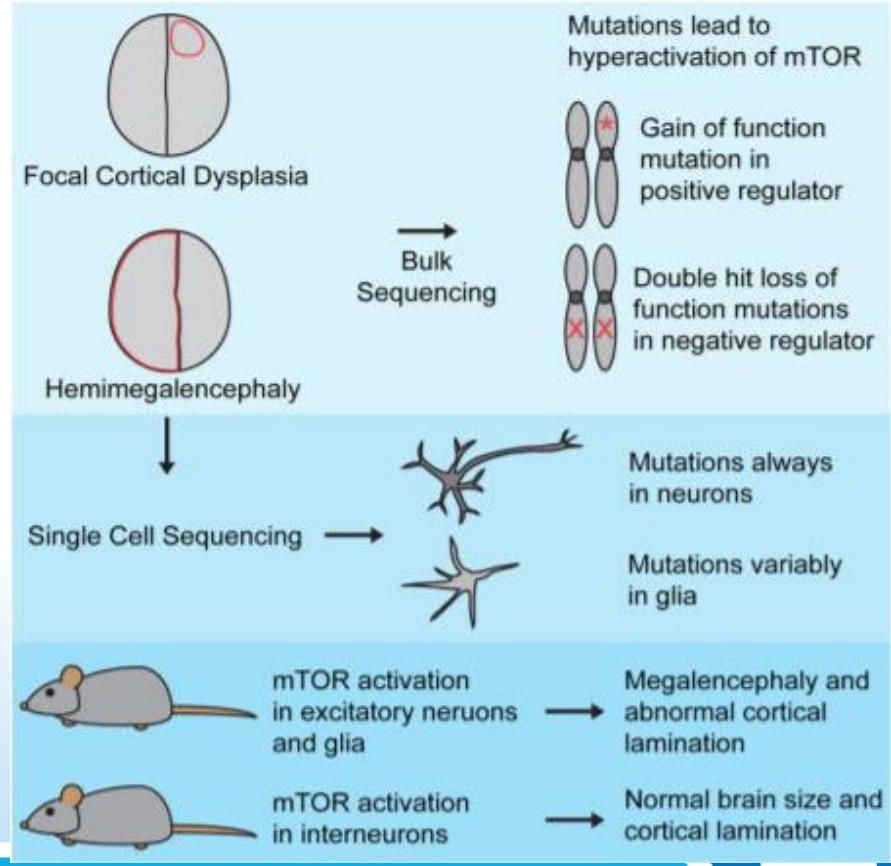
Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias

Alissa M. D'Gama[1,2,3], **Mollie B. Woodworth**[1,2,3], **Amer A. Hossain**[1,2,3], **Sara Bizzotto**[1,2,3], **Nicole E. Hatem**[1,2,3], **Christopher M. LaCoursiere**[4], **Imad Najm**[5], **Zhong Ying**[5], **Edward Yang**[6,7], **A. James Barkovich**[8], **David J. Kwiatkowski**[9], **Harry V Vinters**[10], **Joseph R. Madsen**[11], **Gary W. Mathern**[12], **Ingmar Blümcke**[5,13], **Annapurna Poduri**[4,14], and **Christopher A. Walsh**[1,2,3,*]



Relationship of FCD to hemimegalencephaly (HME)

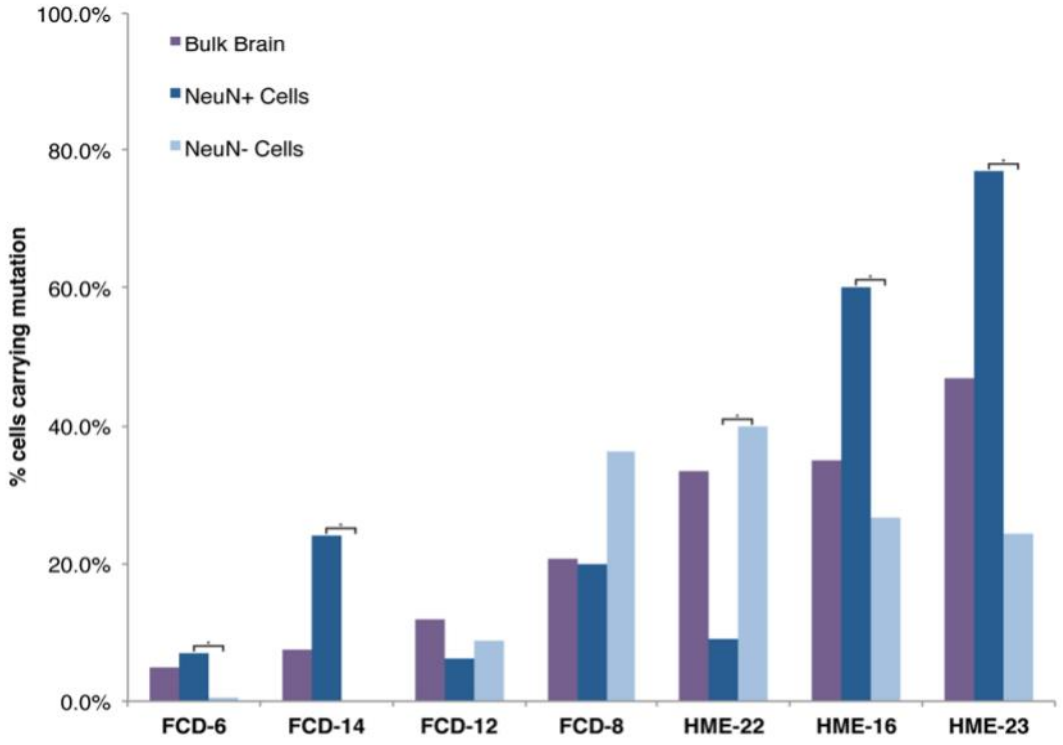


Figure 3. Pathogenic somatic mutations in FCD and HME are always present in the neuronal lineage

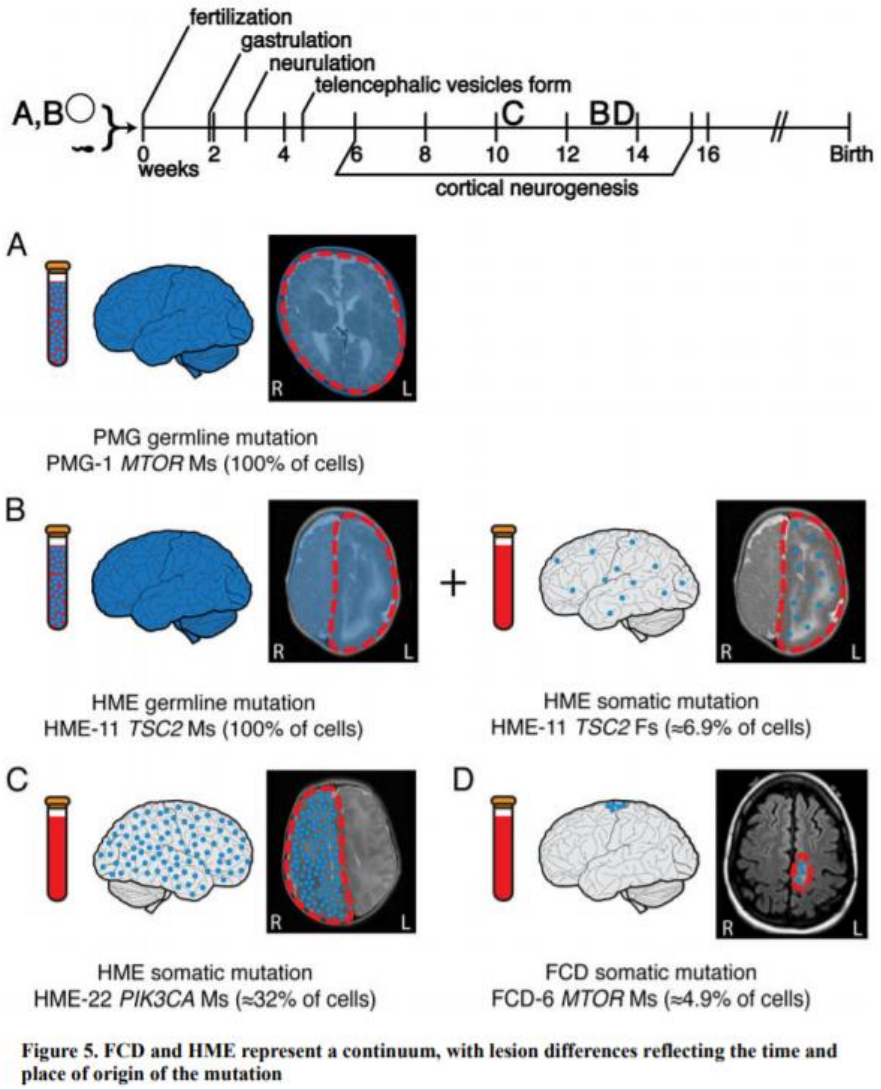
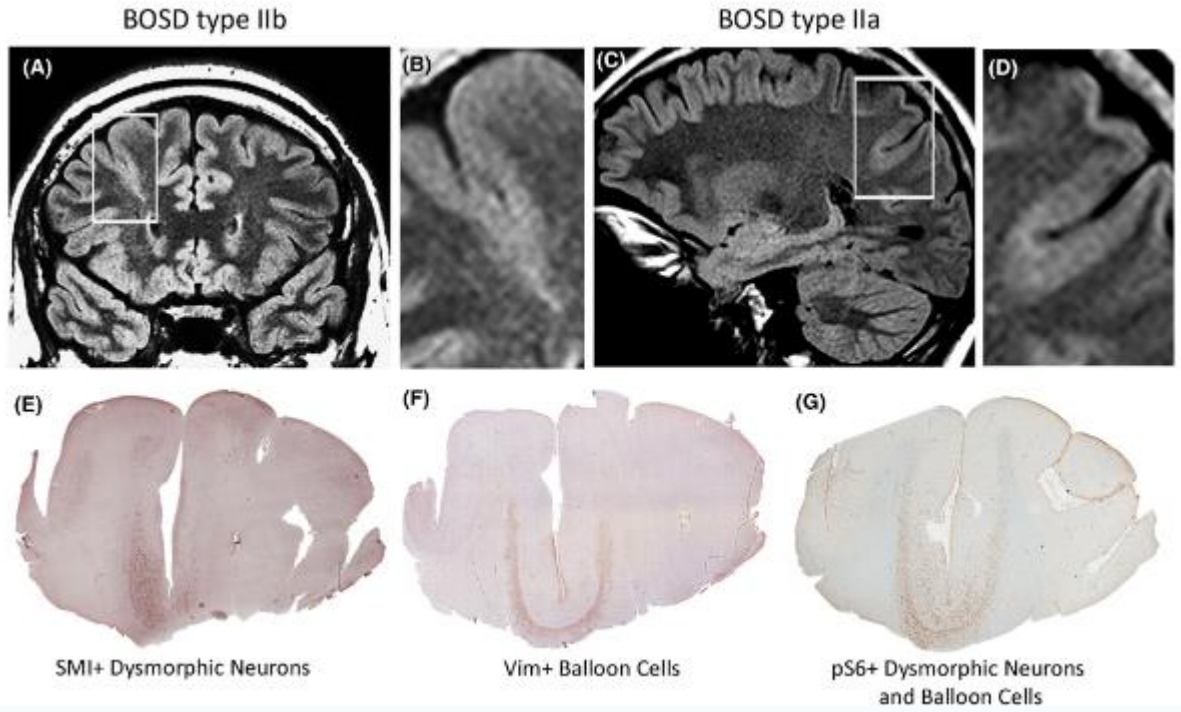


Figure 5. FCD and HME represent a continuum, with lesion differences reflecting the time and place of origin of the mutation

Bottom of sulcus dysplasia

- Focal, epileptogenic cortical malformation
- May be type IIa or IIb
- Maximal abnormalities at bottom of sulcus
- Associated with somatic variants in *MTOR*, *DEPDC5*, *NPRL3*



Studer et al. Epilepsia 2022; PMID: 3592101; Lee et al. Neurology 2020; PMID: 3287954

MOGHE

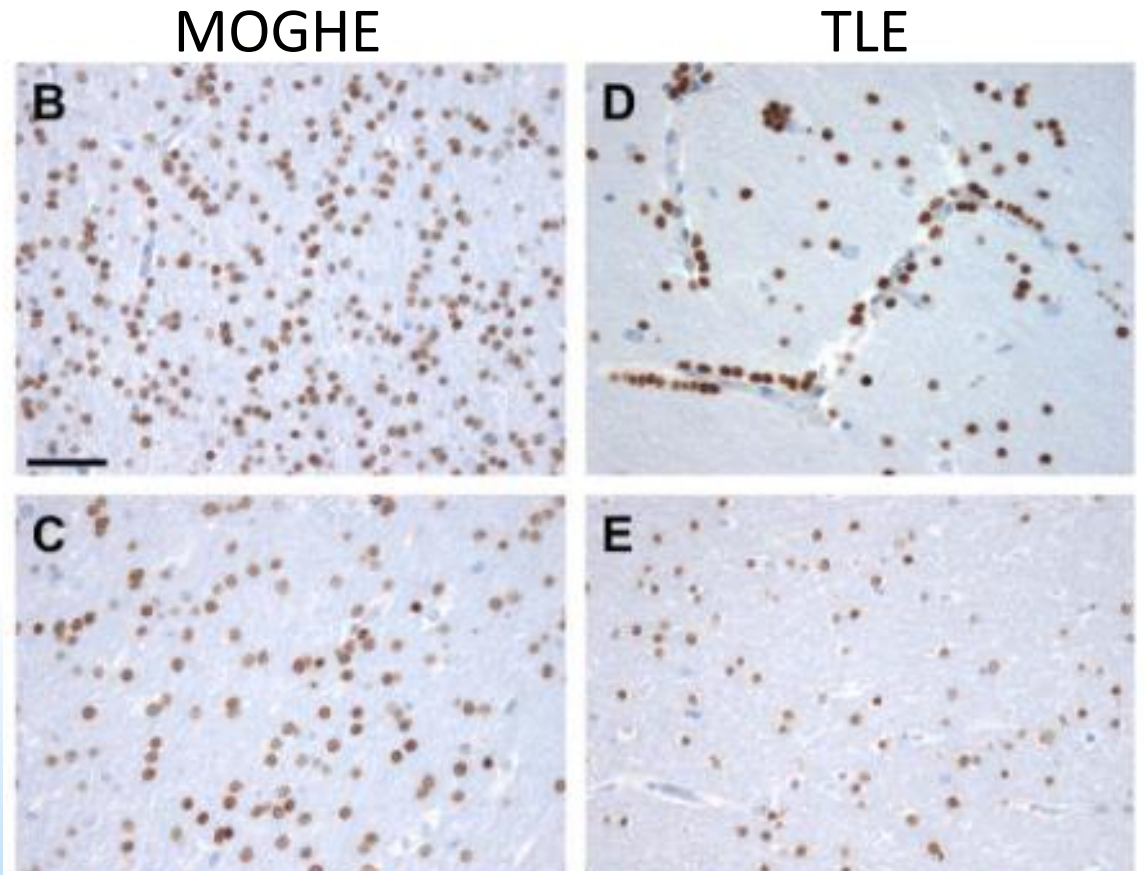
- Early onset FLE
- Hyperintense cortical lesions (suspected FCD)
- “non-lesional” pathology findings
  - Blurred g/w boundary
  - Increase in subcortical oligodendroglial cells
  - Proliferative cells (Ki-67)
- Proposed mild malformation of cortical development

Brain Pathology ISSN 1015–6305

RESEARCH ARTICLE

Mild Malformation of Cortical Development with Oligodendroglial Hyperplasia in Frontal Lobe Epilepsy: A New Clinico-Pathological Entity

Johannes Schurr[1]*; Roland Coras[1]*; Karl Rössler[2]; Tom Pieper[3]; Manfred Kudernatsch[3]; Hans Holthausen[3]; Peter Winkler[3]; Friedrich Woermann[4]; Christian G. Bien[4]; Tilman Polster[4]; Reinhard Schulz[4]; Thilo Kalbhenn[5]; Horst Urbach[6,7]; Albert Becker[8]; Thomas Grunwald[9]; Hans-Juergen Huppertz[9]; Antonio Gil-Nagel[10]; Rafael Toledano[10]; Martha Feucht[11]; Angelika Mühlebner[11,12]; Thomas Czech[13]; Ingmar Blümcke[1]



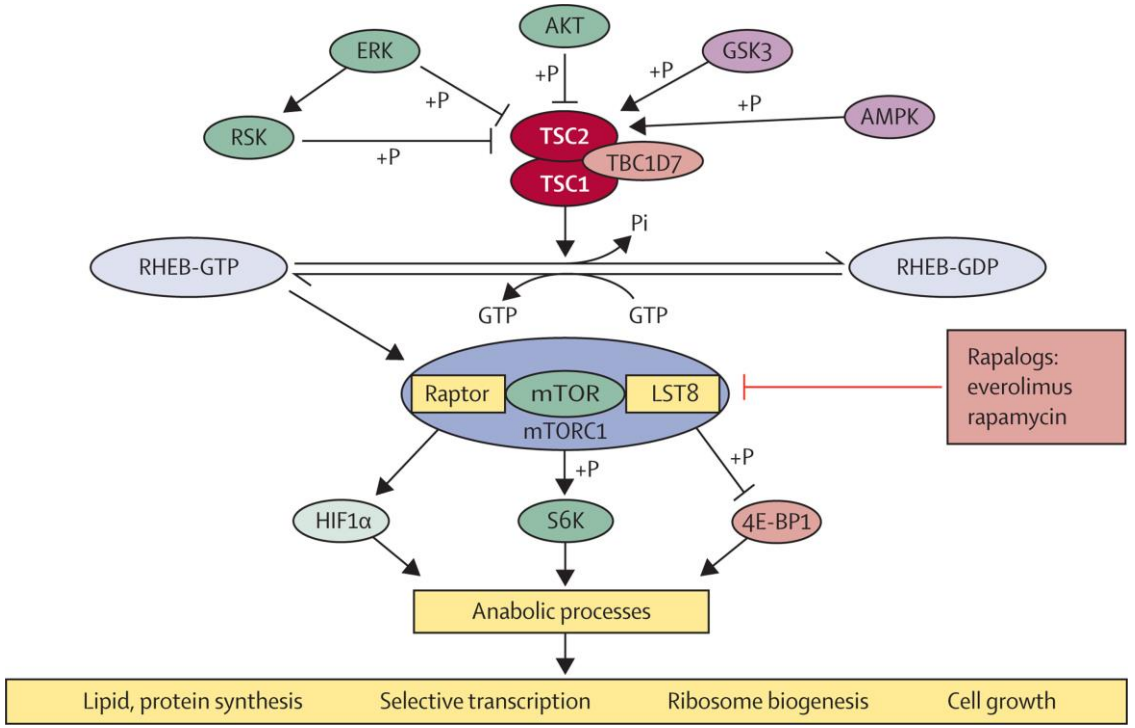
Schurr et al. Brain Pathol 2017; PMID: 2678554

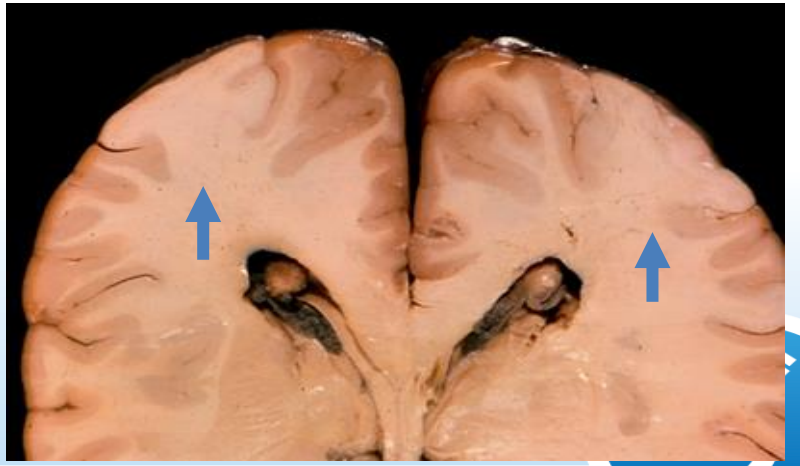
Whole slide image – case 1

- https://pathpresenter.net/public/display?token=e027e3c7

Tuberous sclerosis

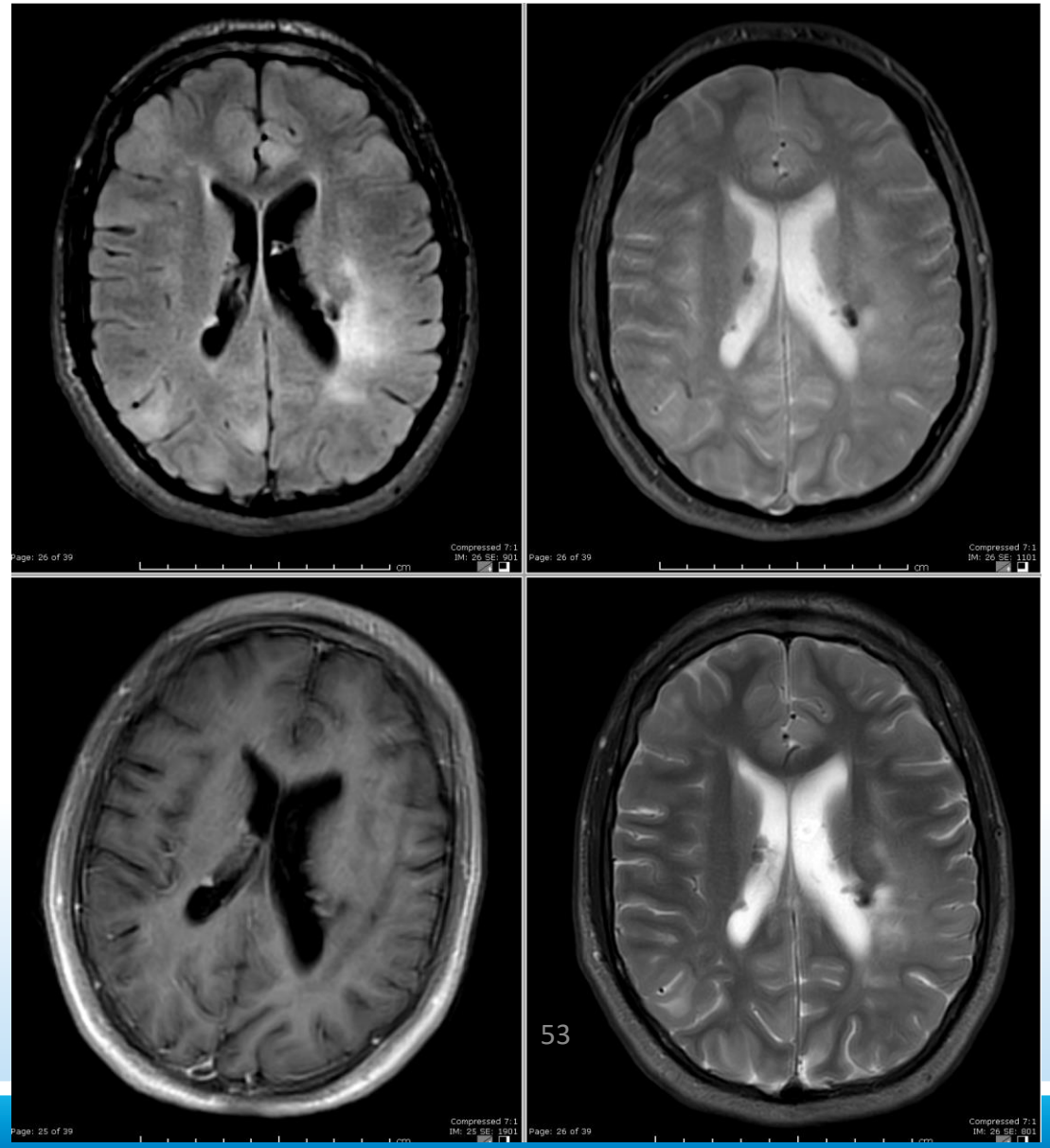
- 1:6,000 births in U.S.
- Autosomal dominant
  - TSC1 9q34 or TSC2 16p13.3
  - 1/3 familial, 2/3 de novo
- Loss of function of either TSC gene leads to increased mTOR1 signaling
  - Facial angiofibromas
  - Hypomelanotic macules
  - Shagreen patches
  - Retinal nodular hamartomas
  - Angiomyolipoma of kidney
  - Rhabdomyoma of heart
- Cortical tubers present in utero by 20 weeks gestation (embryonic cortical development)

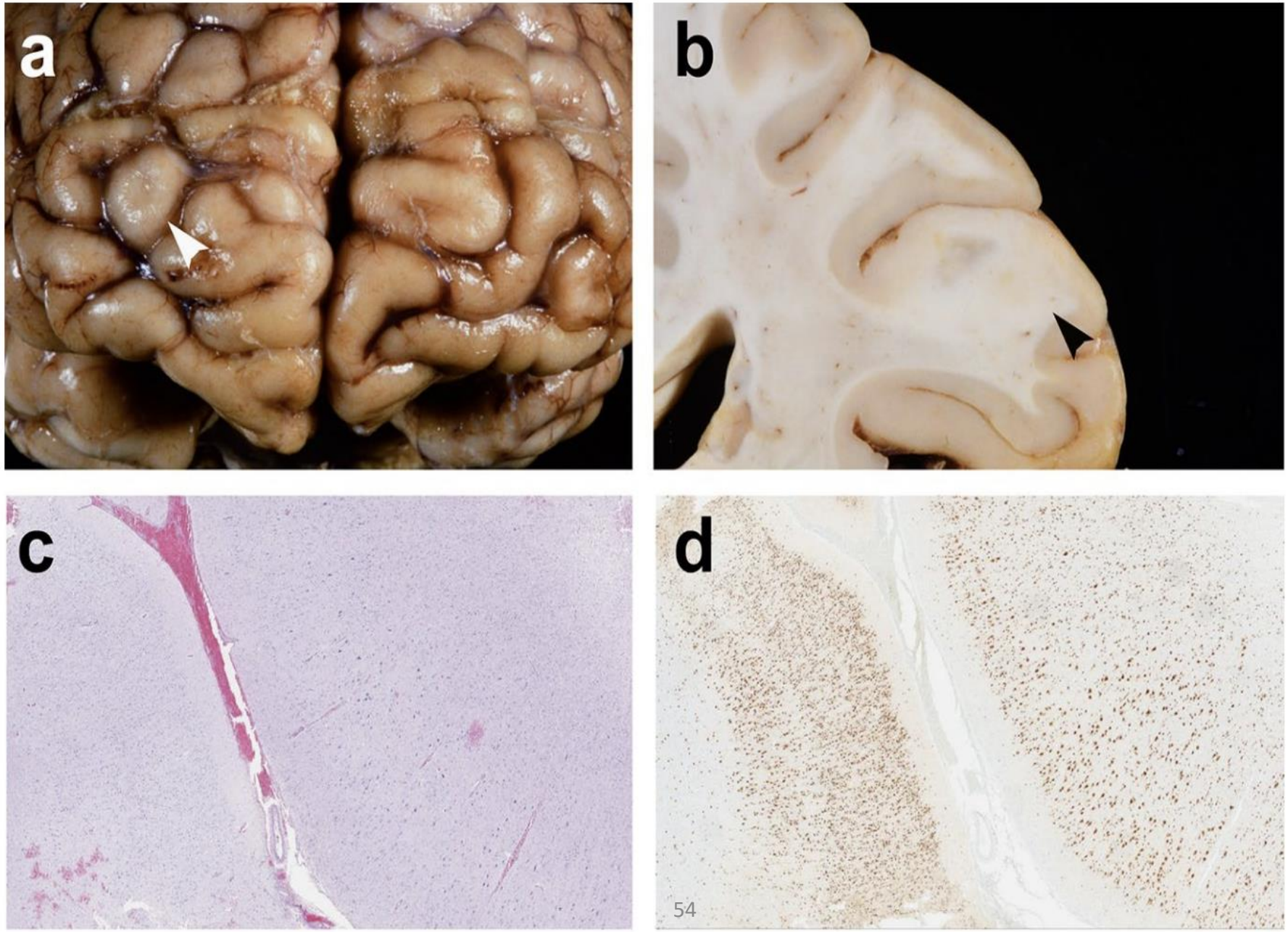




Roach and Kwiatkowski, Lancet 2016. PMID: 27613522; Dr. D. Agamanolis, neuropathology-web.org

Tuberous sclerosis

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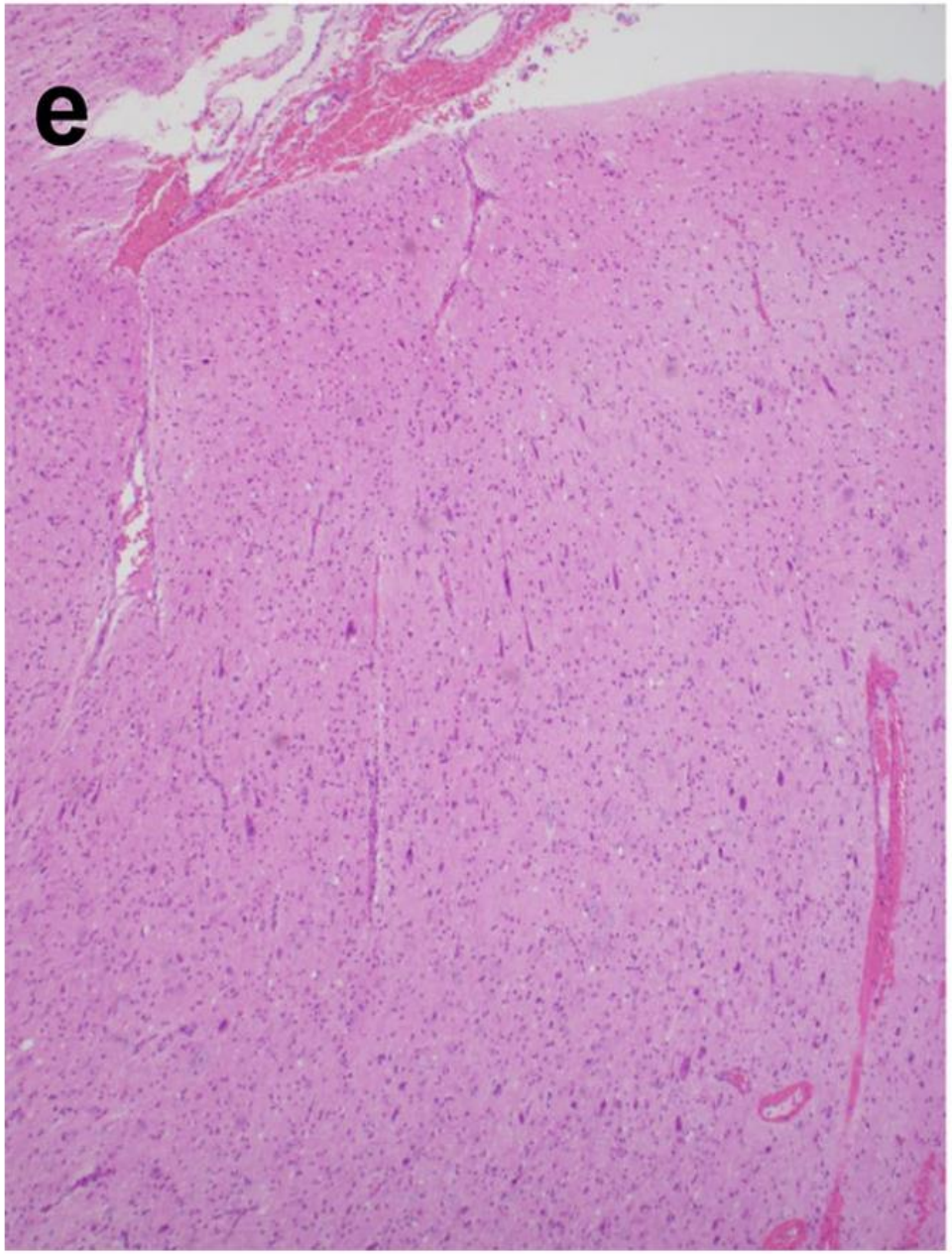
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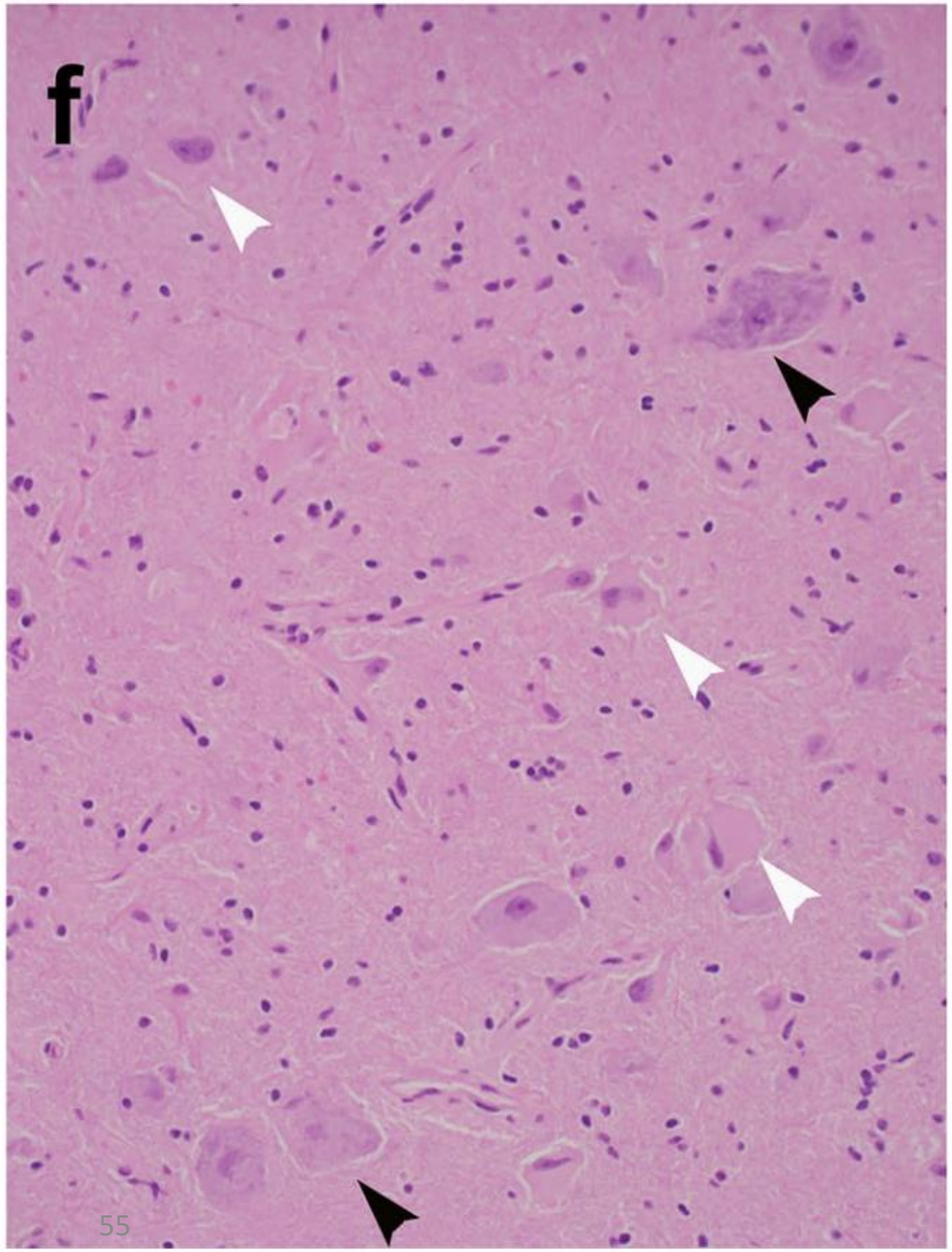
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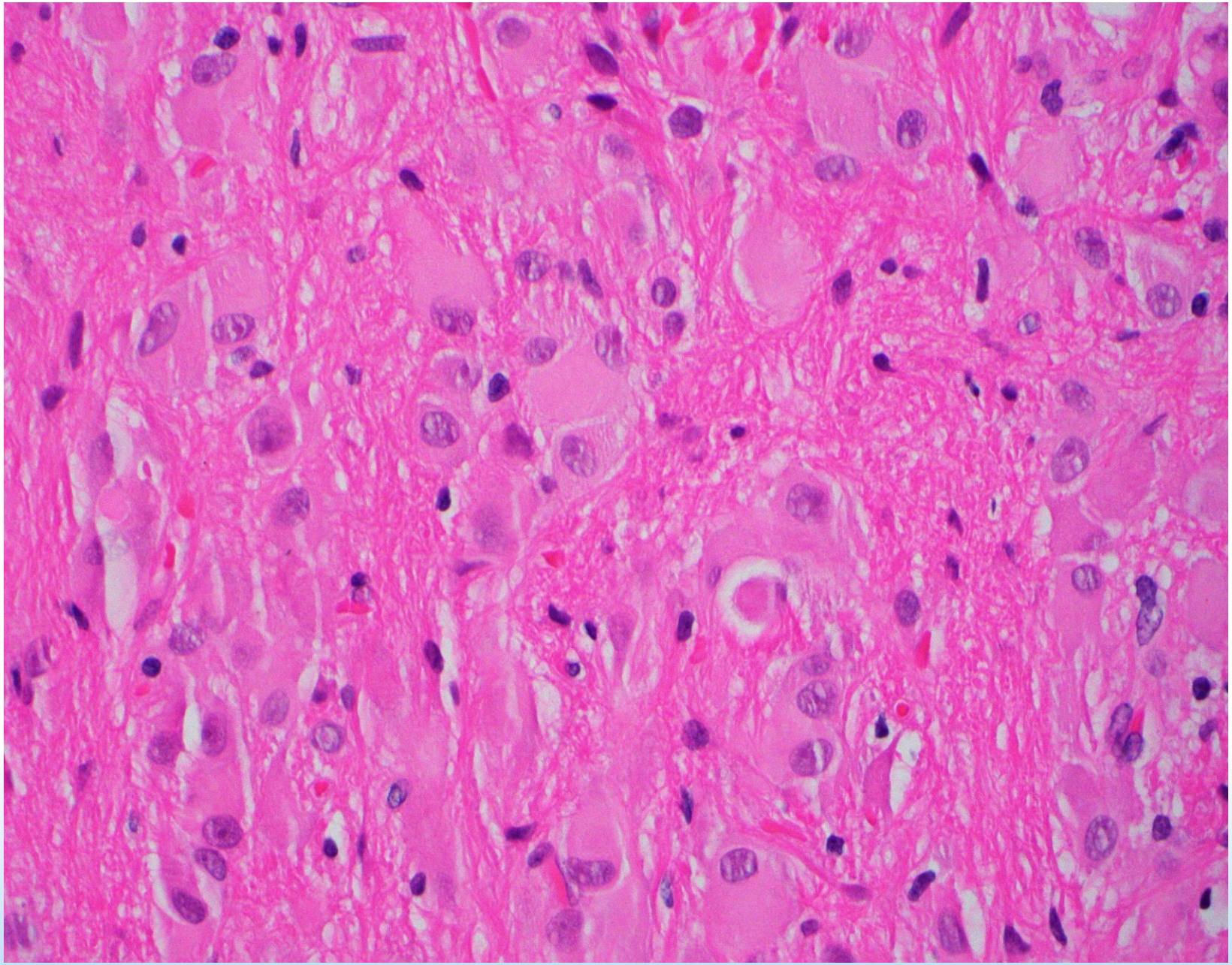
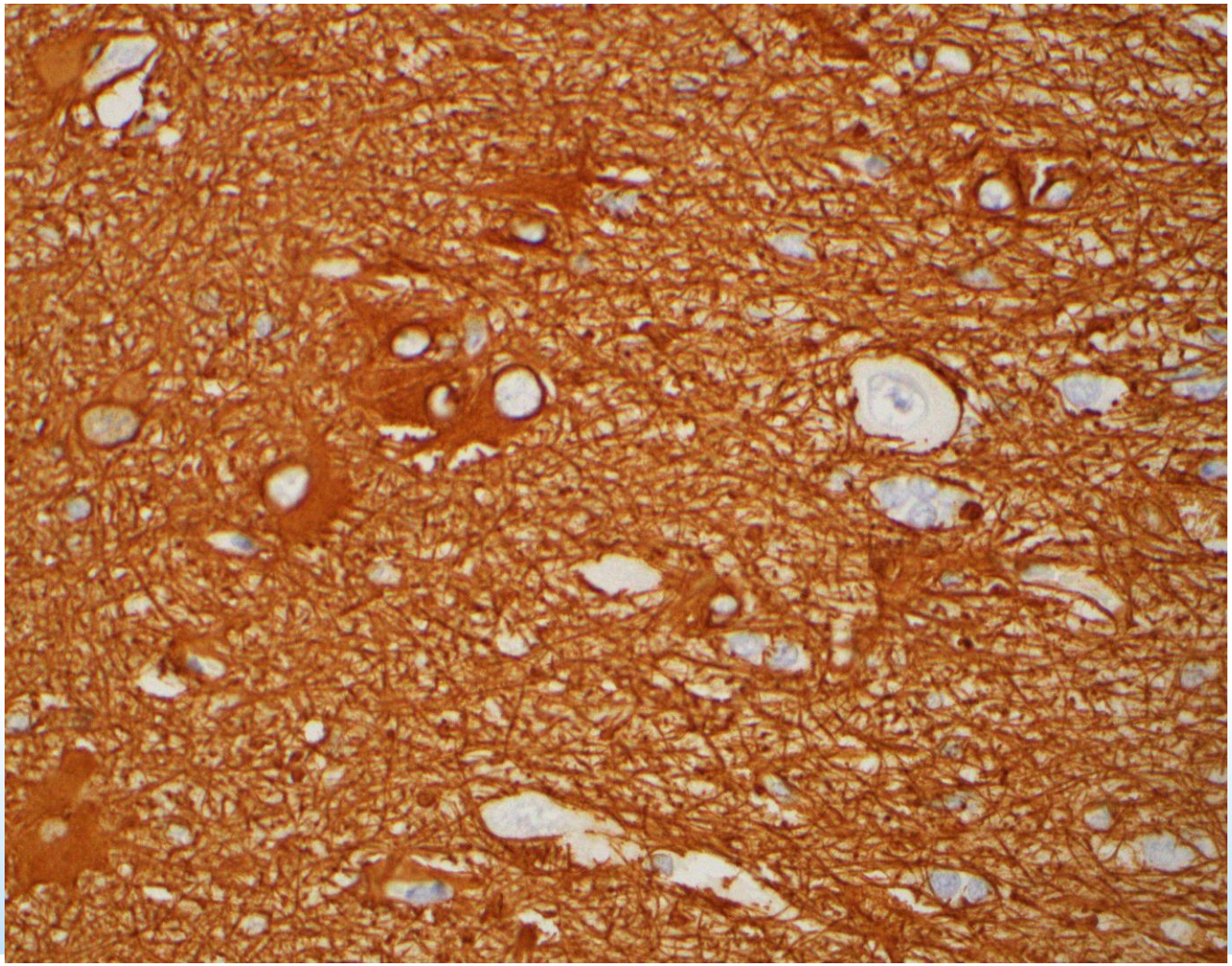
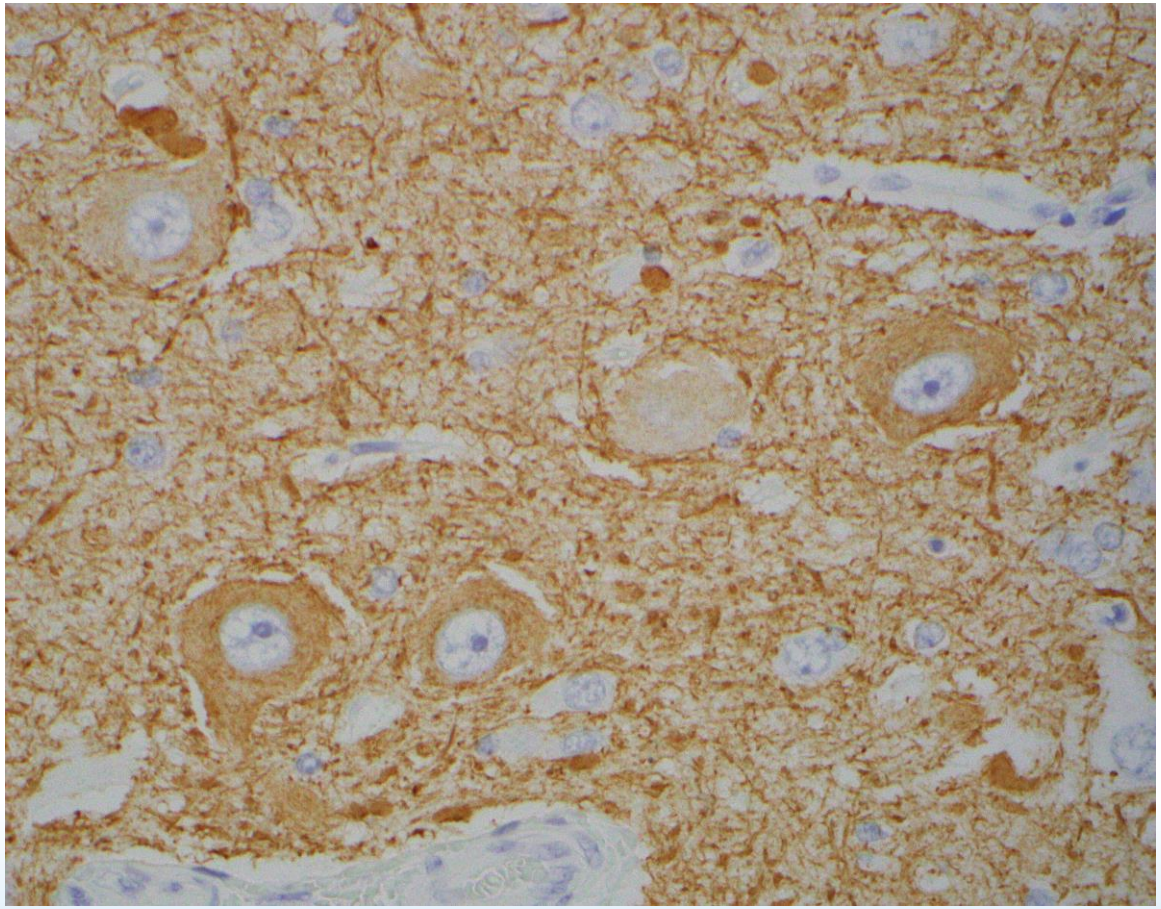
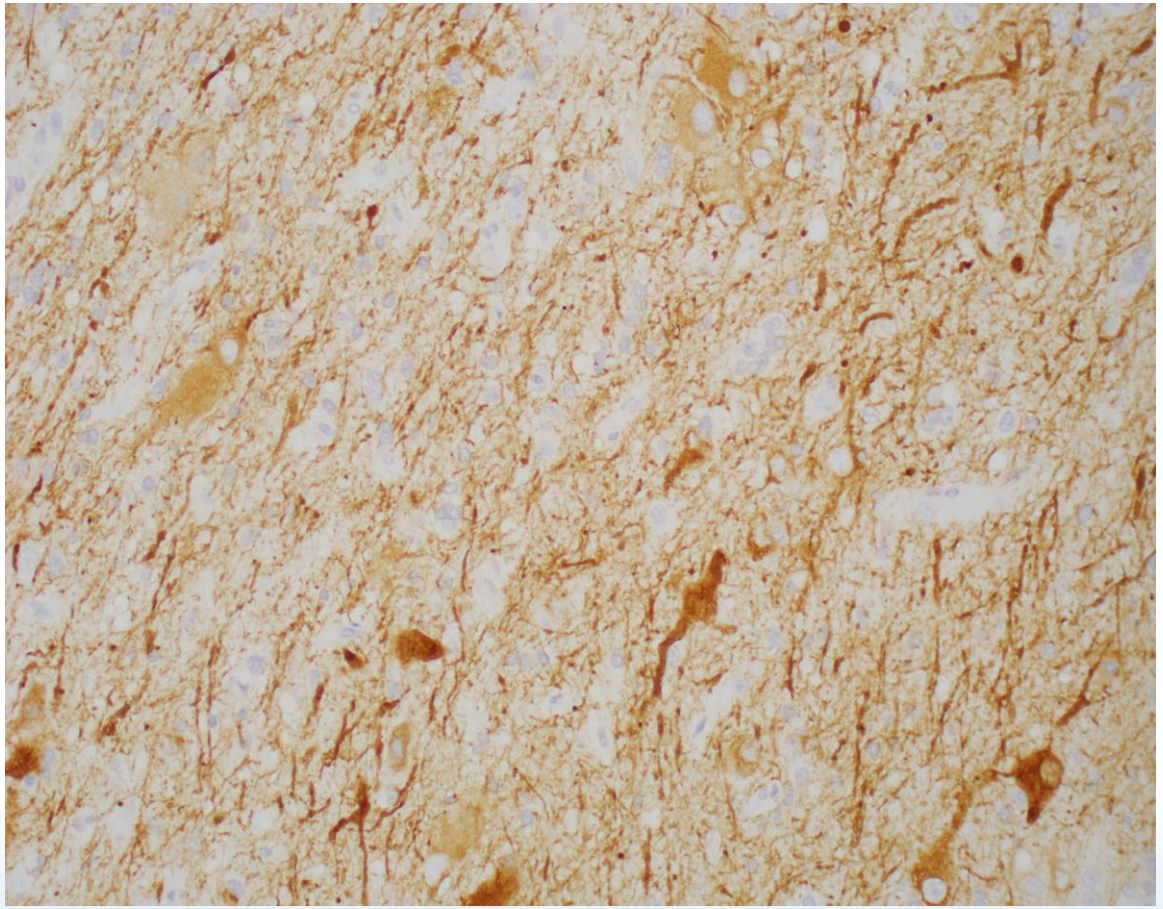


Tuber: GFAP

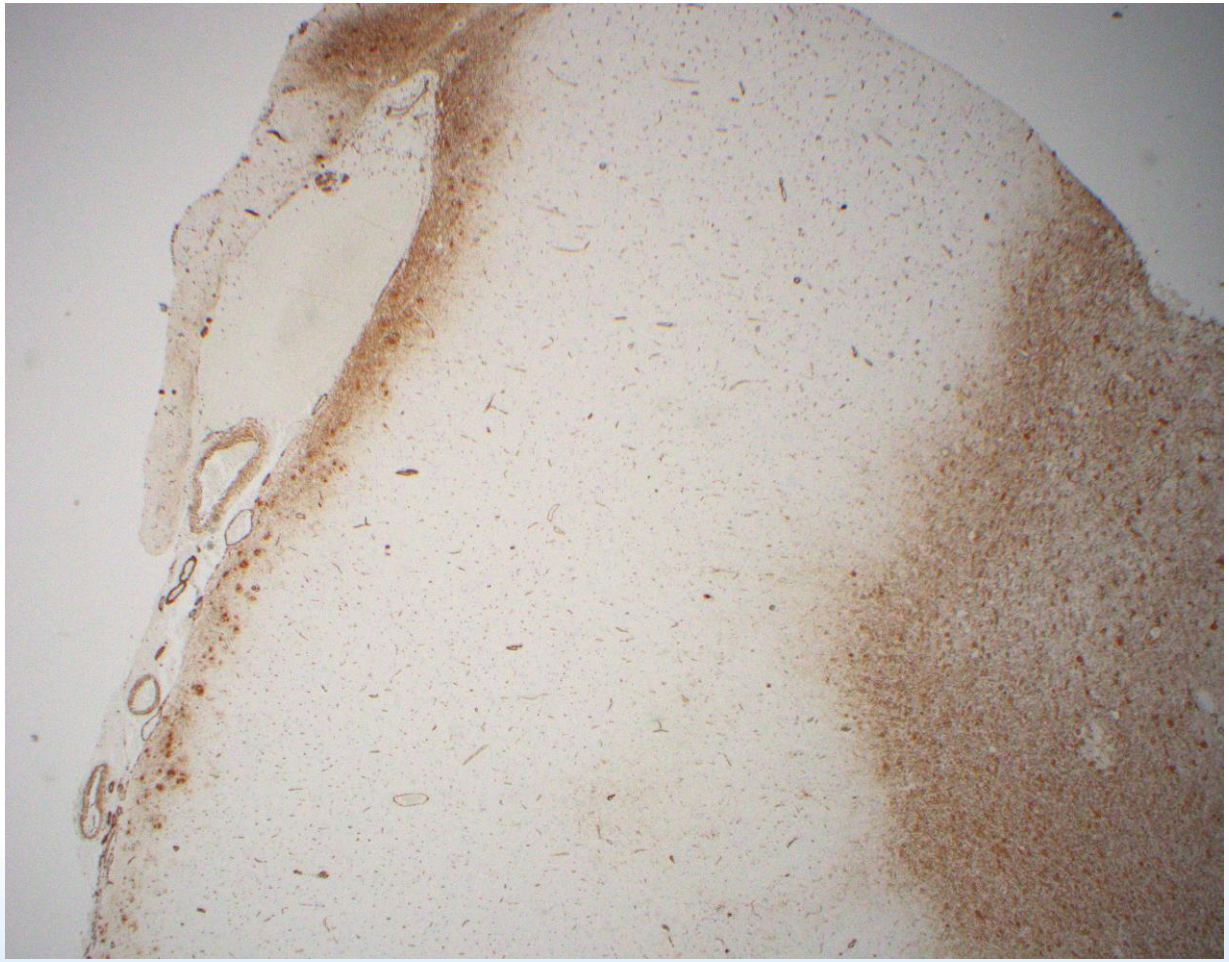


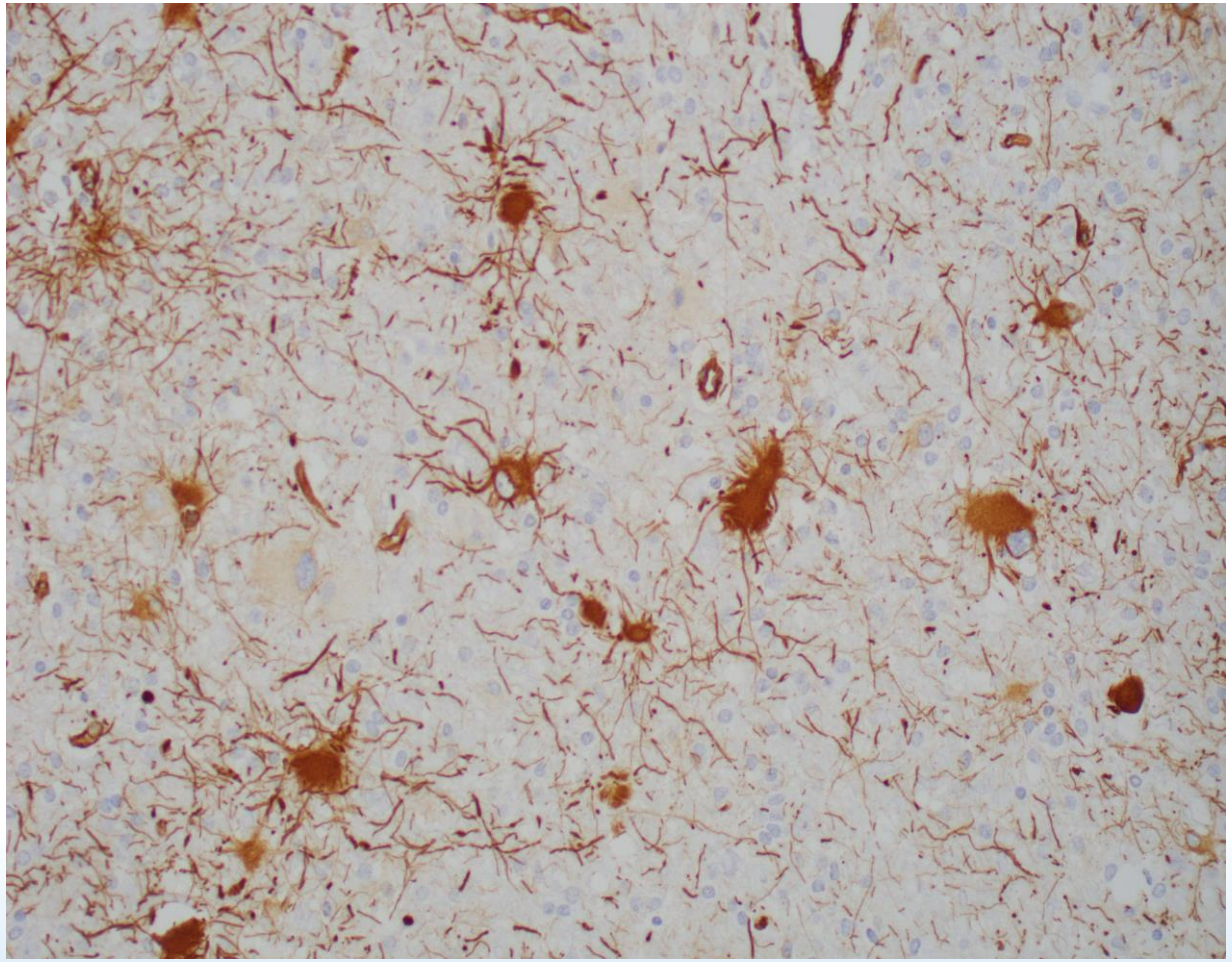
Tuber: neurofilament

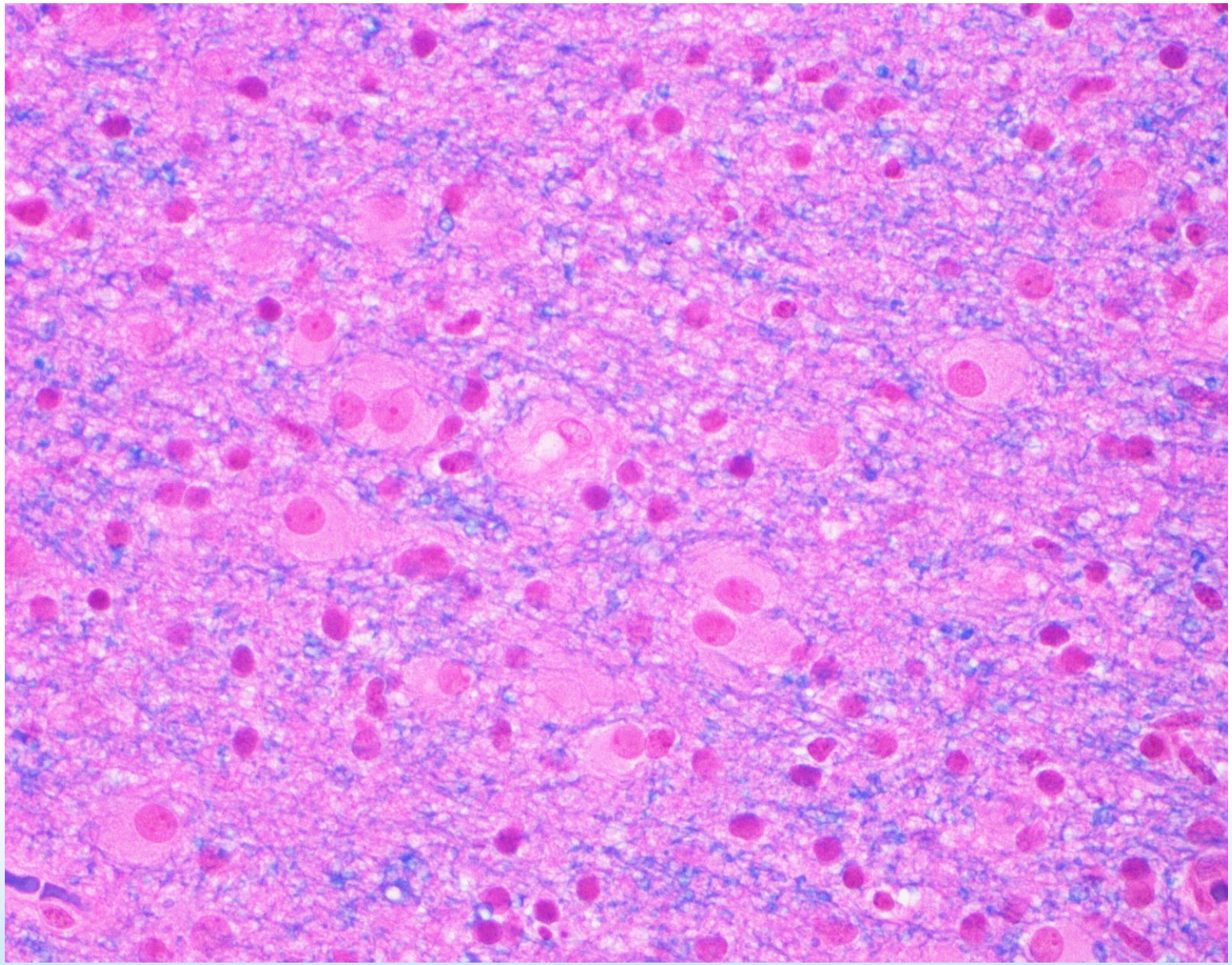




Tuber: vimentin





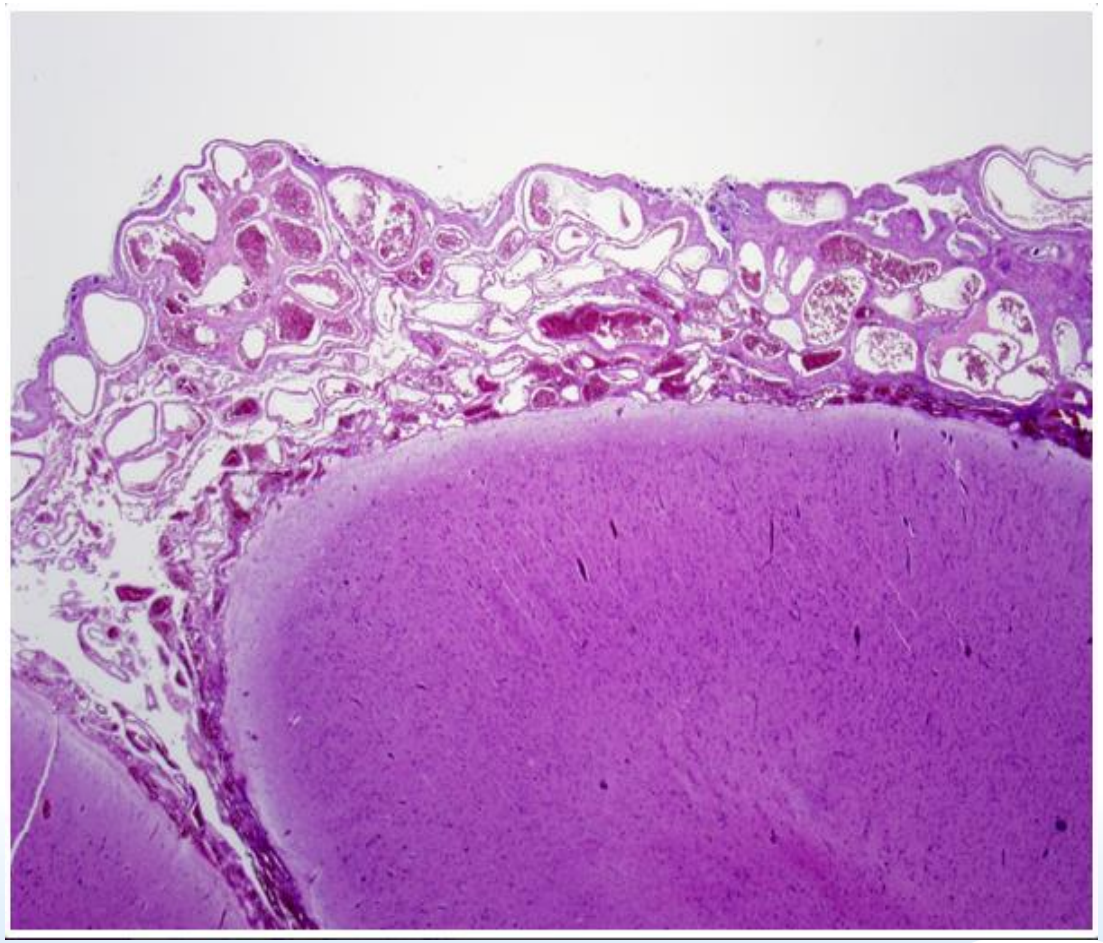


Whole slide image – case 2

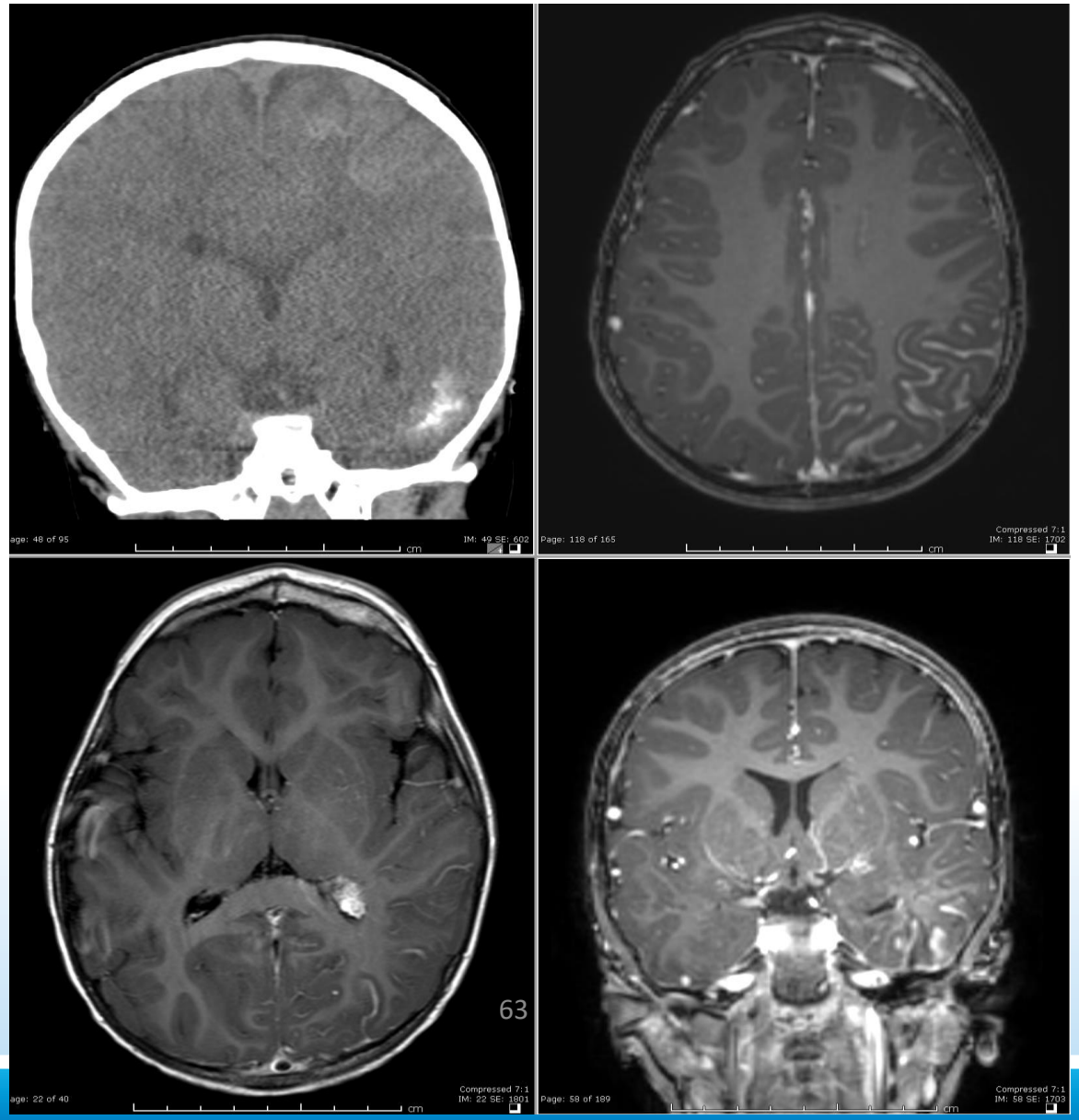
- https://pathpresenter.net/public/display?token=af7ee0d6

Sturge-Weber syndrome

- Encephalofacial angiomatosis
- Incidence 1:20,000-50,000 births
- Angiomas of the face, leptomeninges, and eye
- Almost always sporadic, *GNAQ* mutation
- Leptomeningeal vascular malformation thought to result from incomplete involution of embryonal vasculature, usually unilateral
- Can be associated with FCD 3c

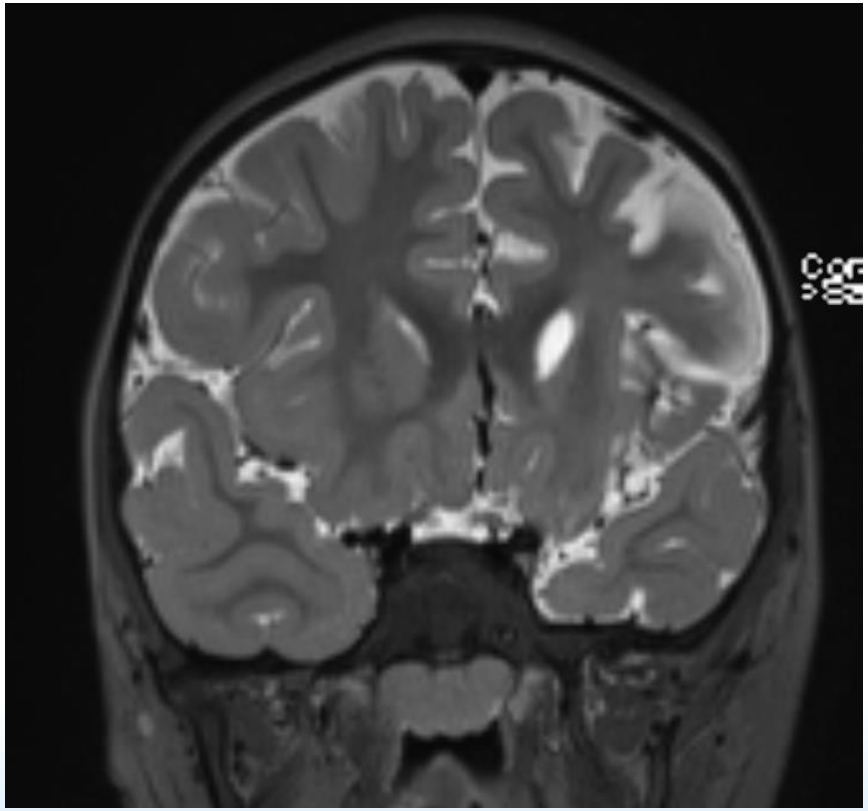


Sturge–Weber syndrome

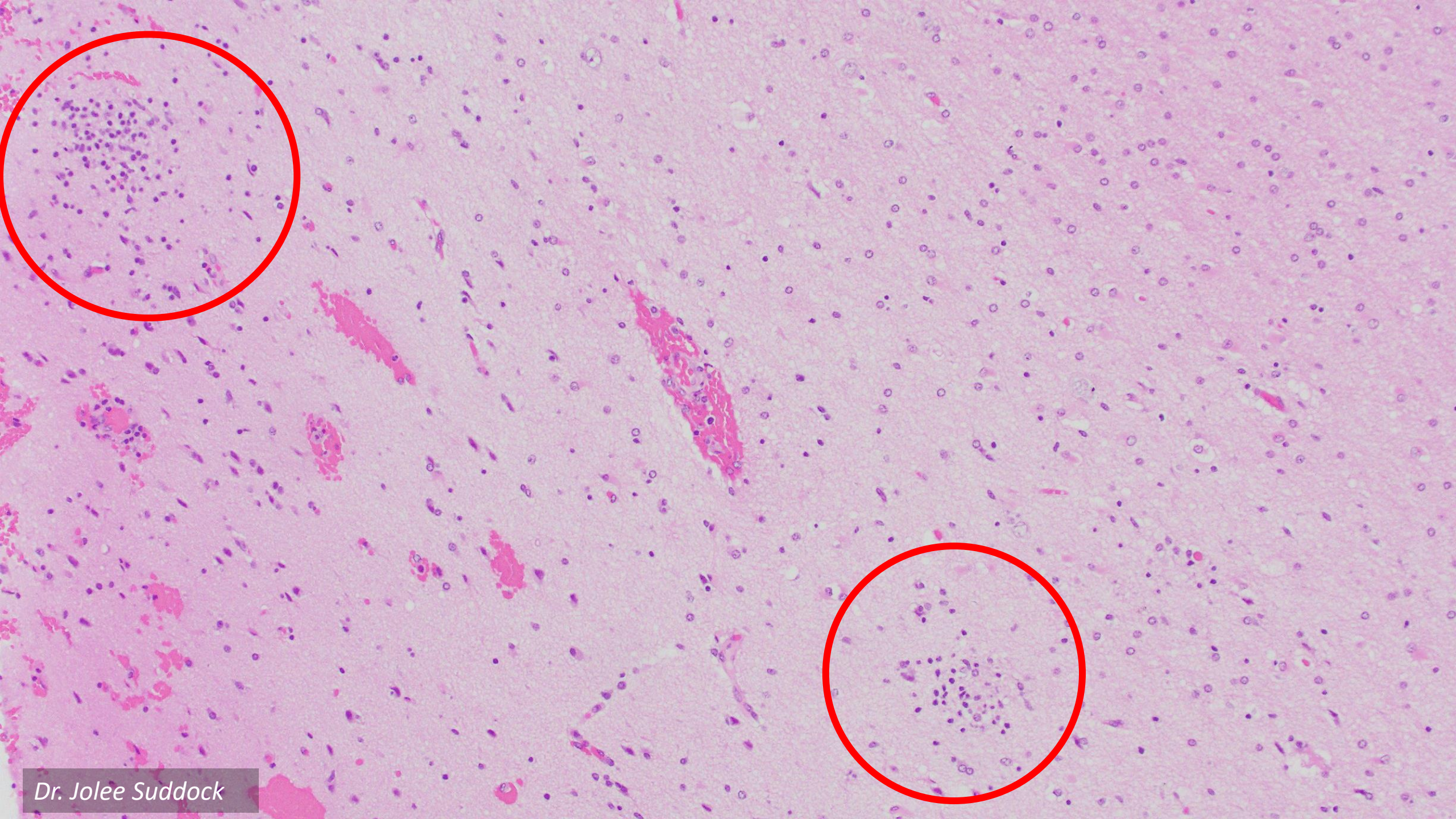


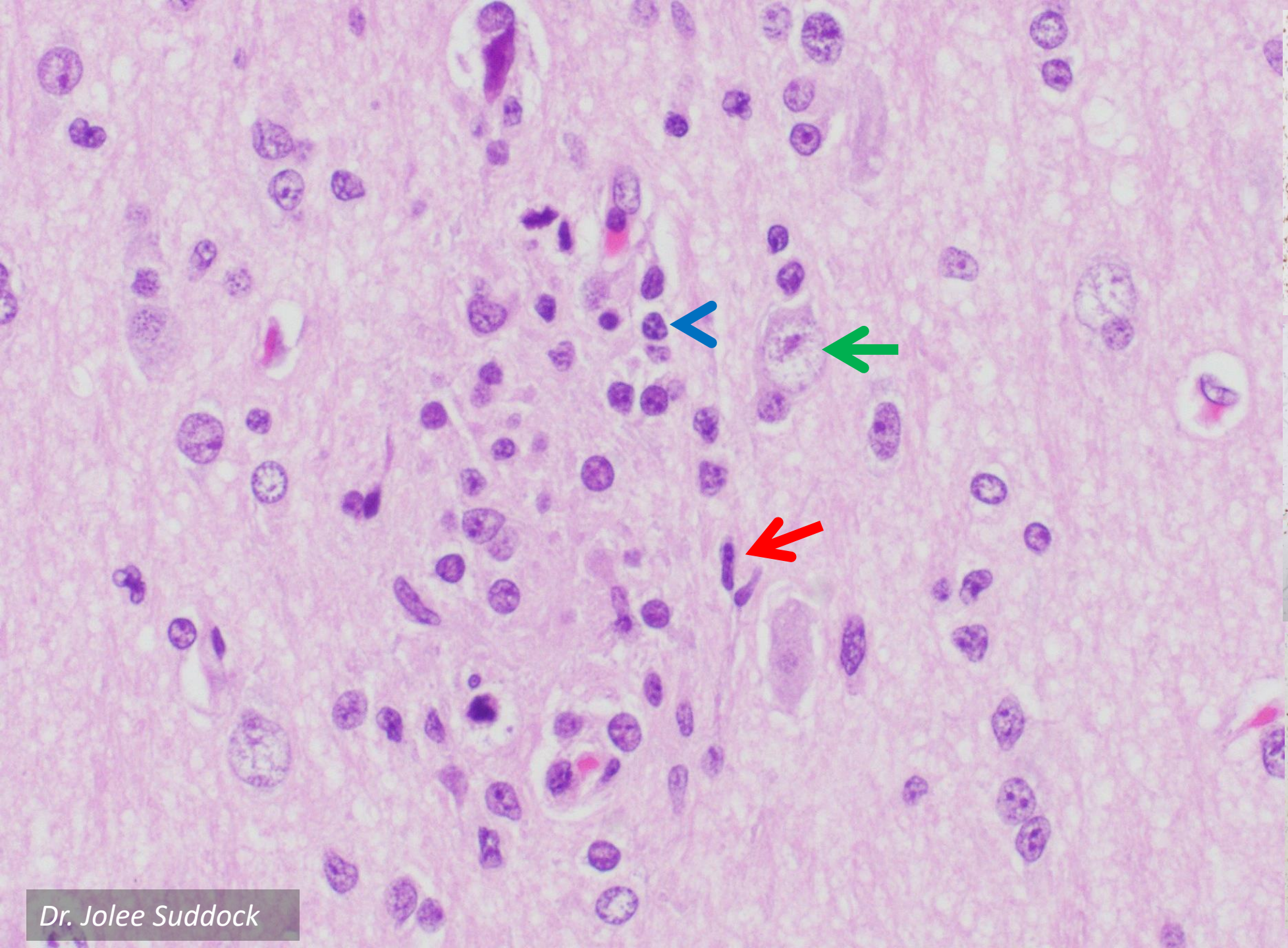
Rasmussen encephalitis

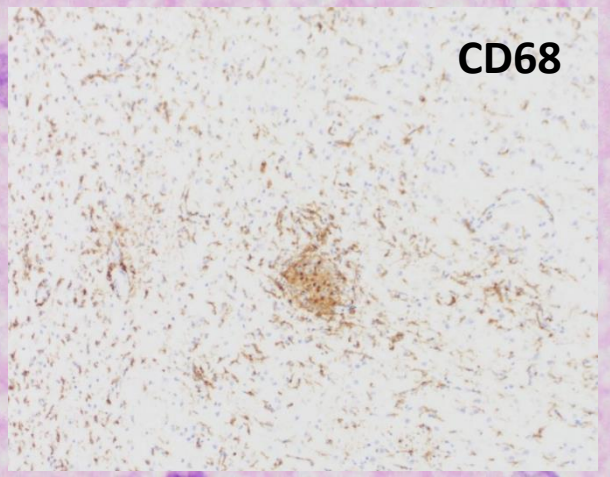
- Focal/multifocal encephalitis
- Drug-resistant epilepsy
- “epilepsia partialis continua”
  - Retained awareness, occur over hours/days/years?
- Cortical pathology can be heterogeneous over disease course
  - Early: T cells and gliosis
  - Late: neuronal cell death, cavitation

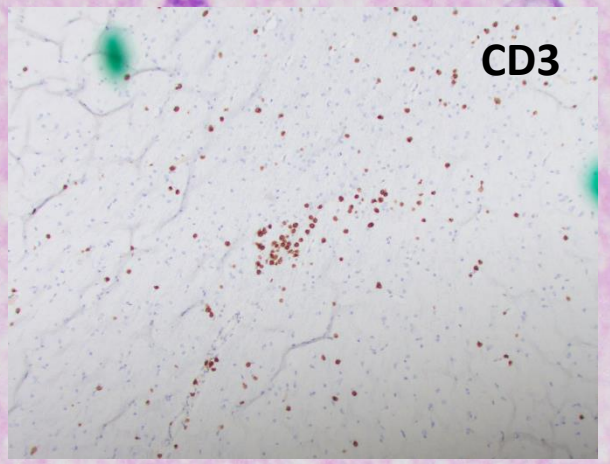


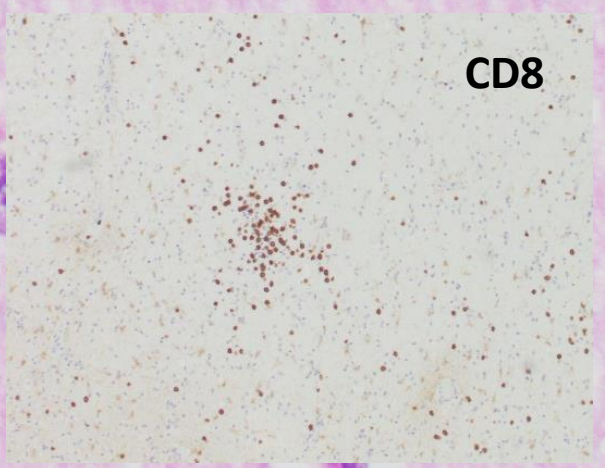
Pardo et al. Epilepsia 2004. PMID: 1510833


Dr. Jolee Suddock









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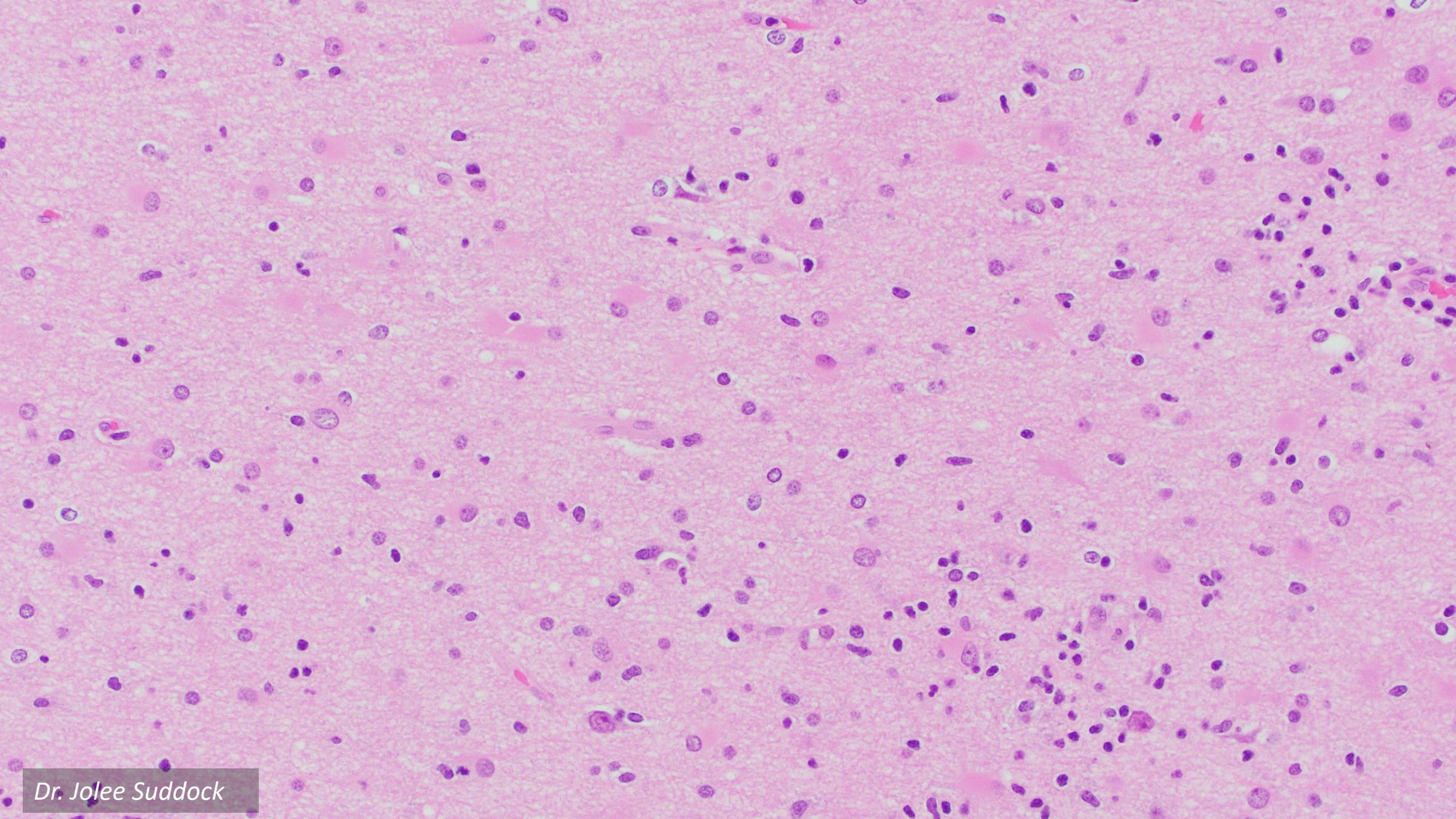
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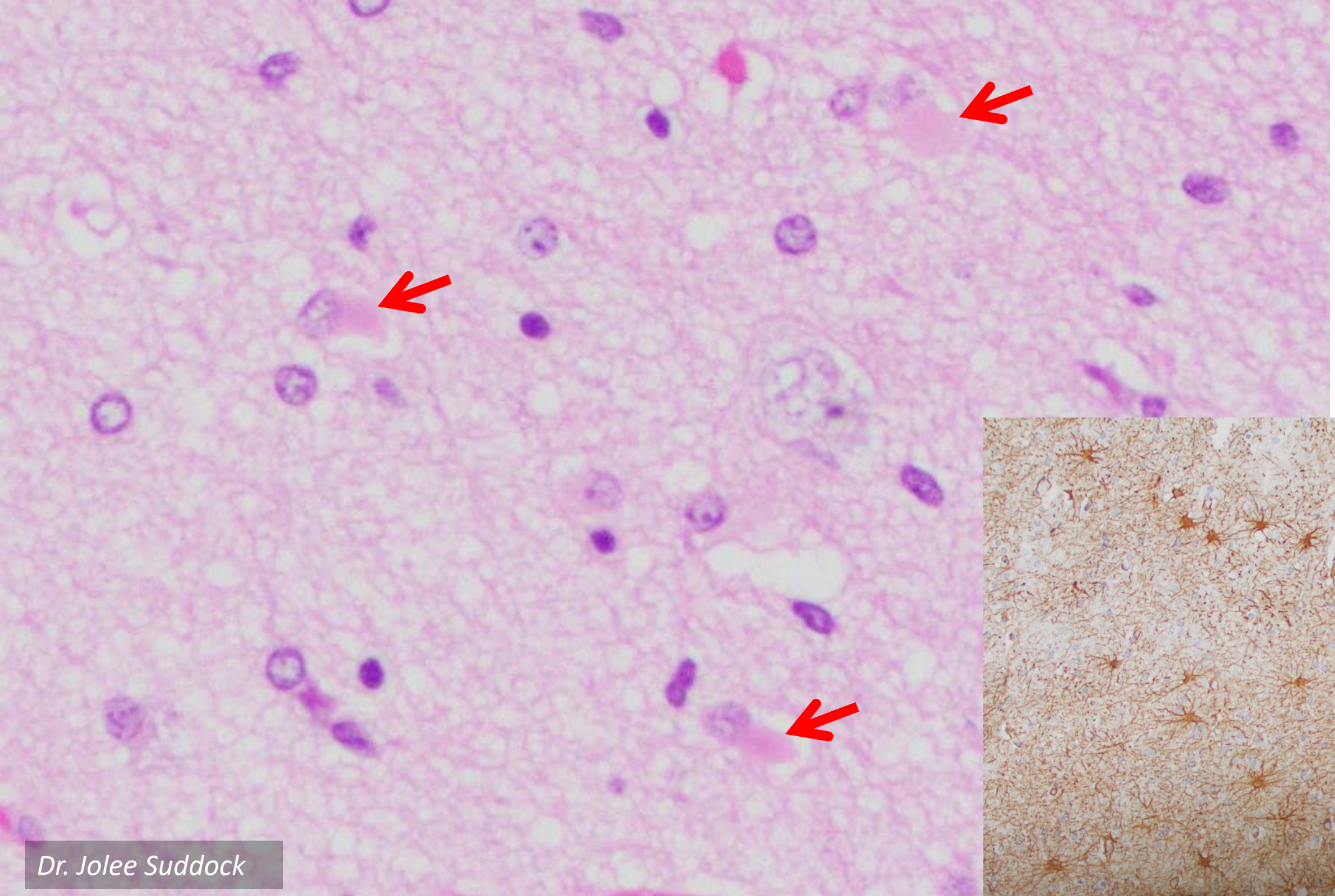

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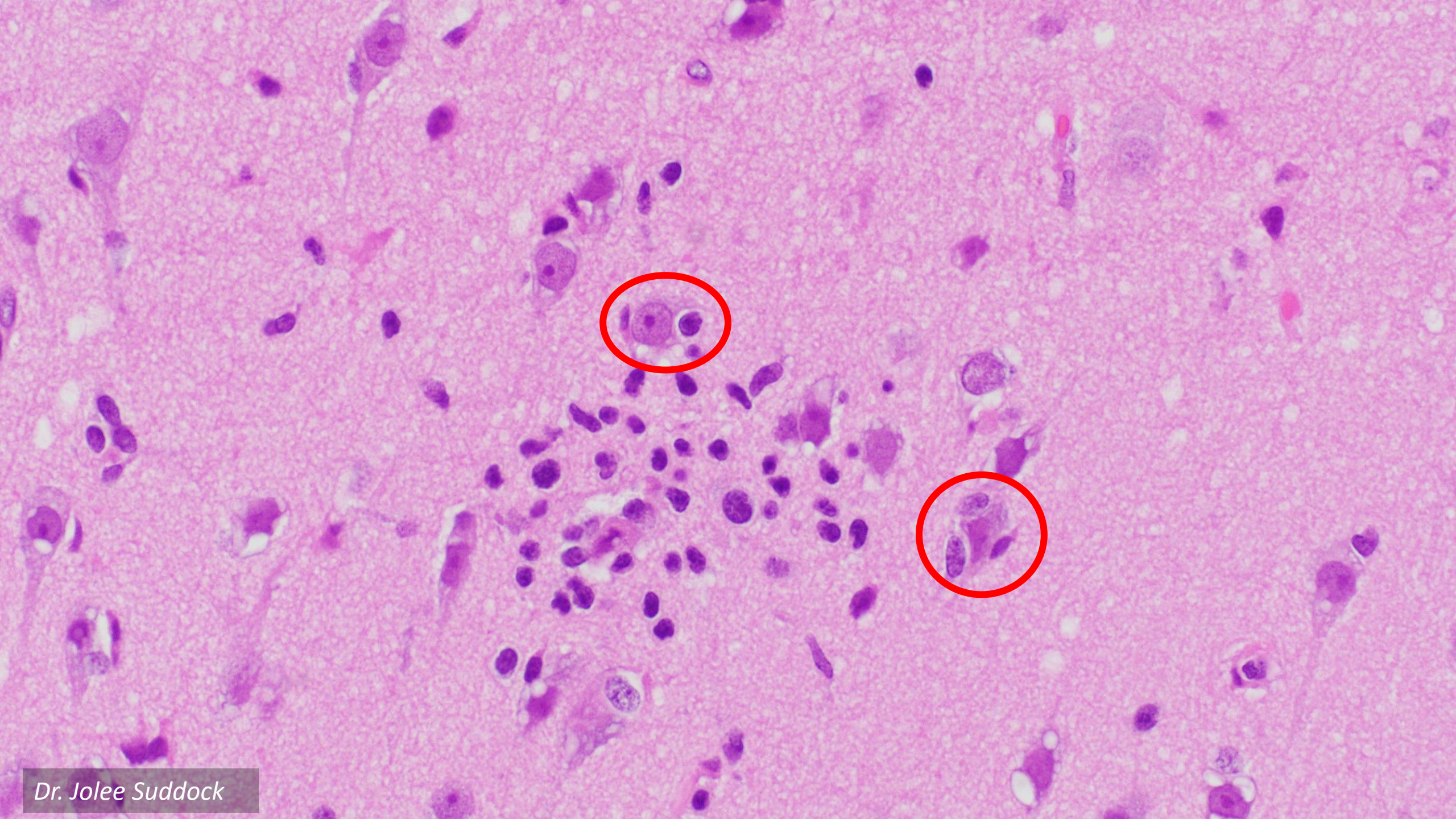
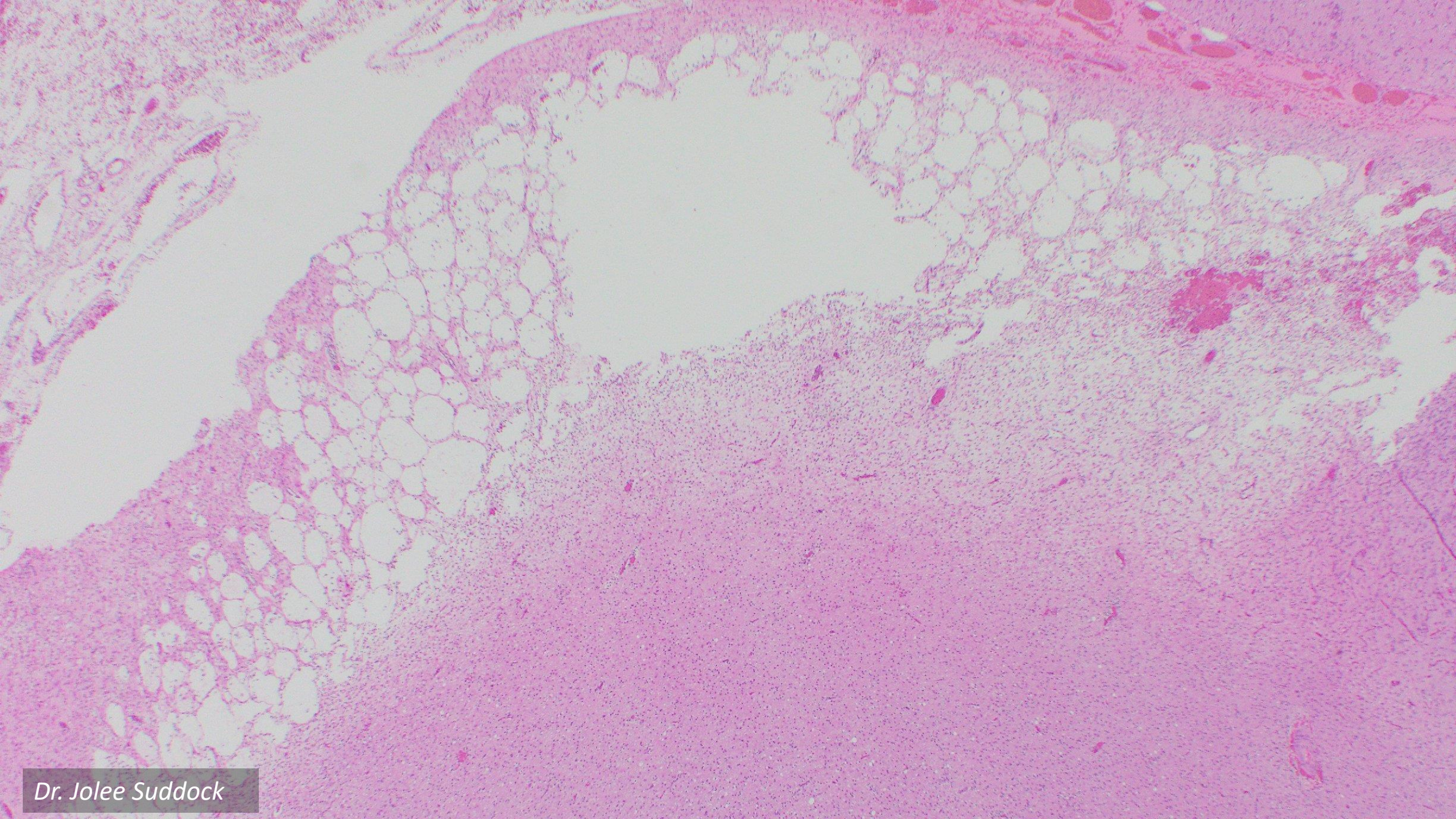

Dr. Jolee Suddock



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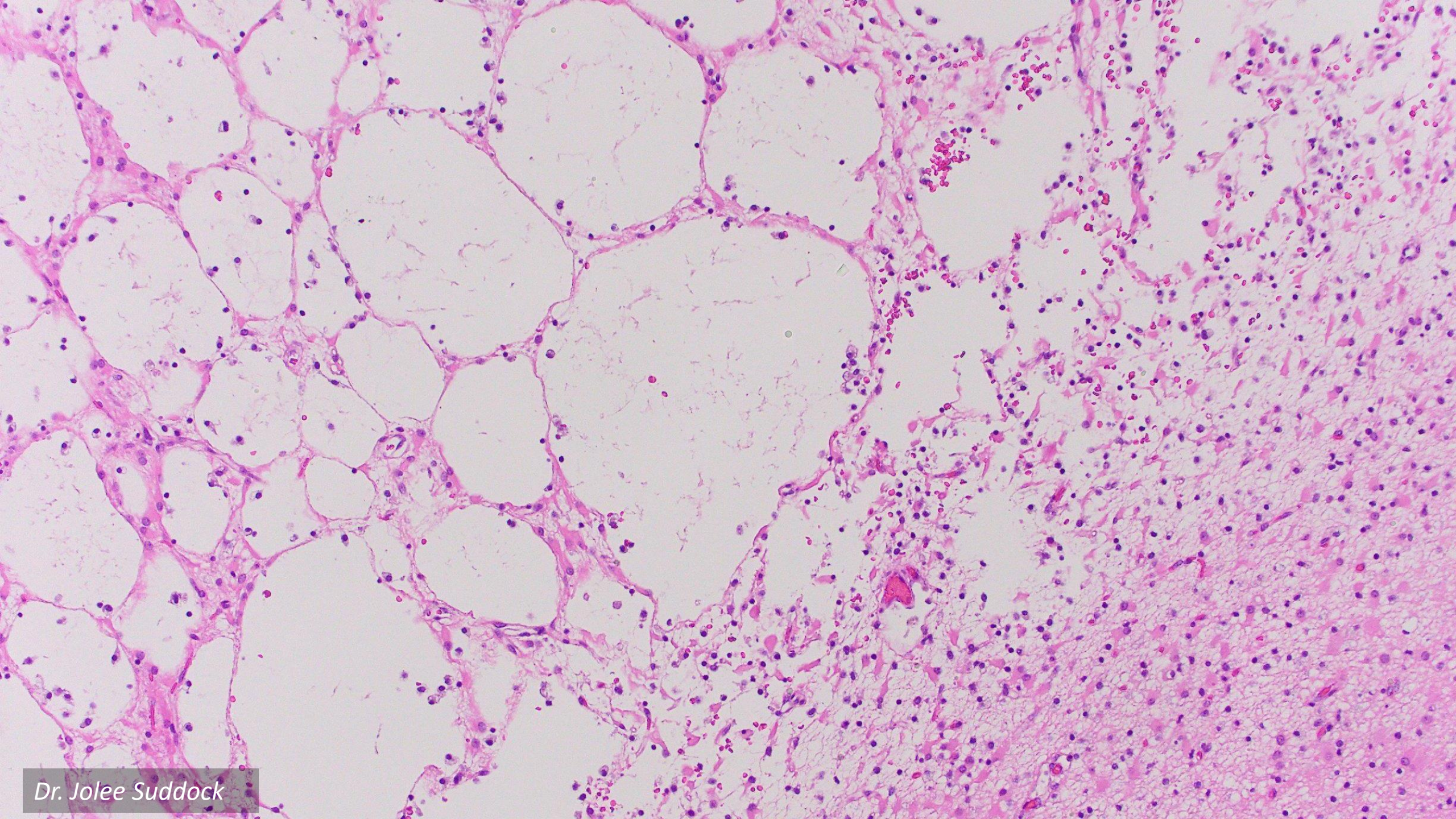
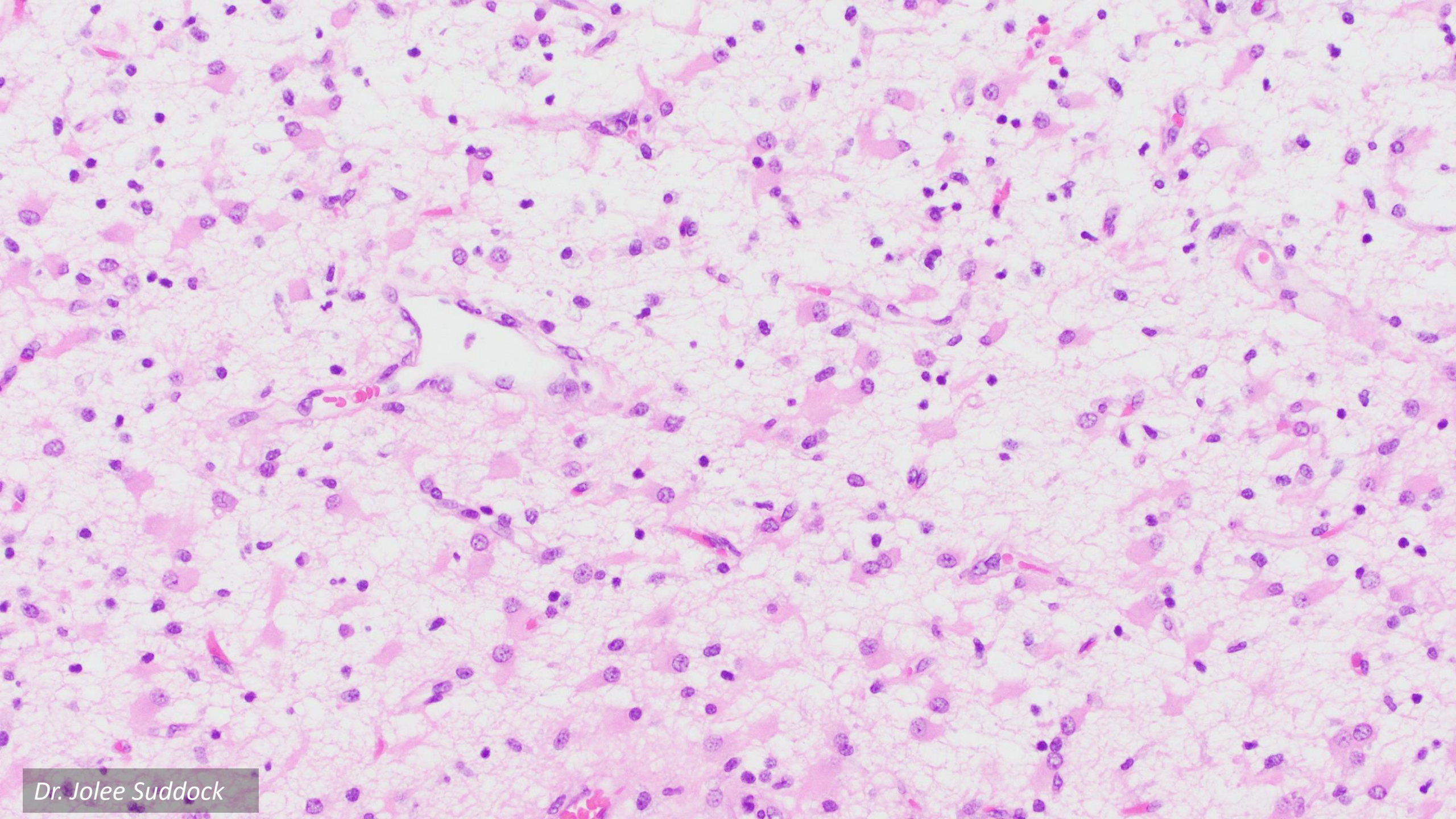
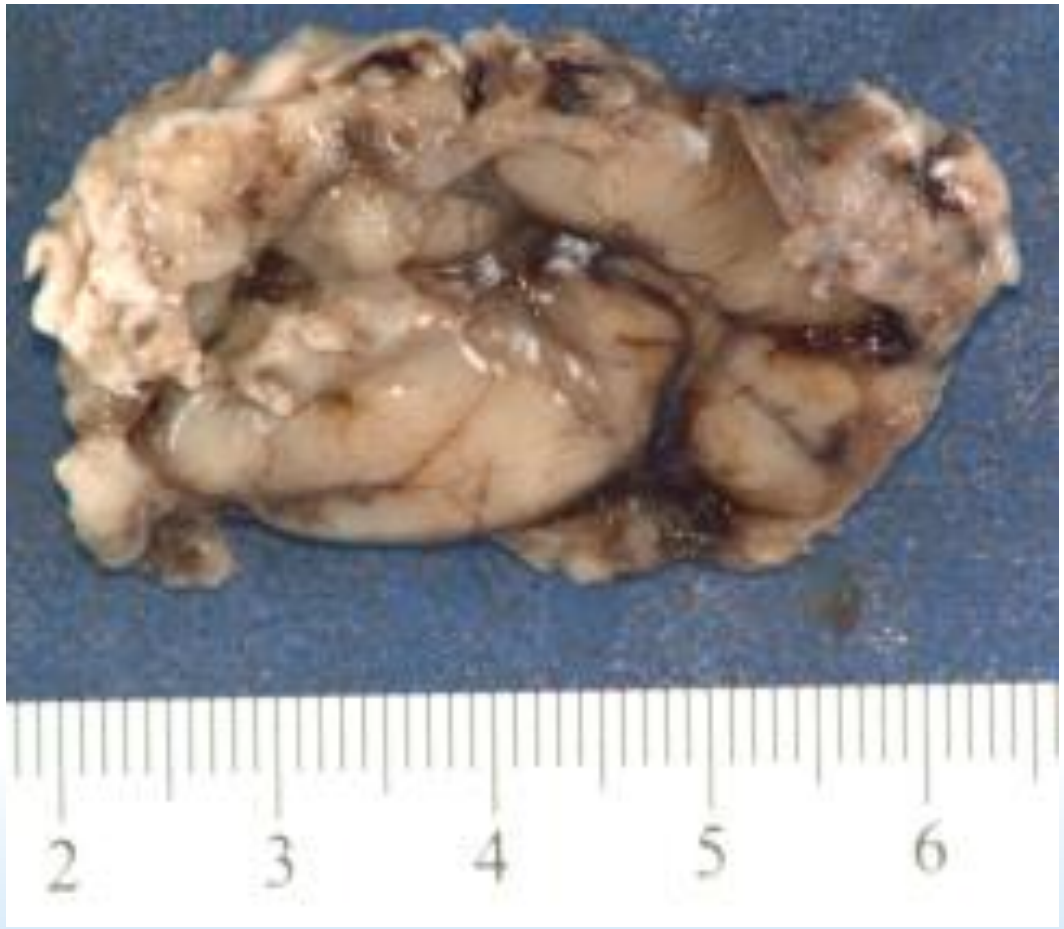

Dr. Jolee Suddock

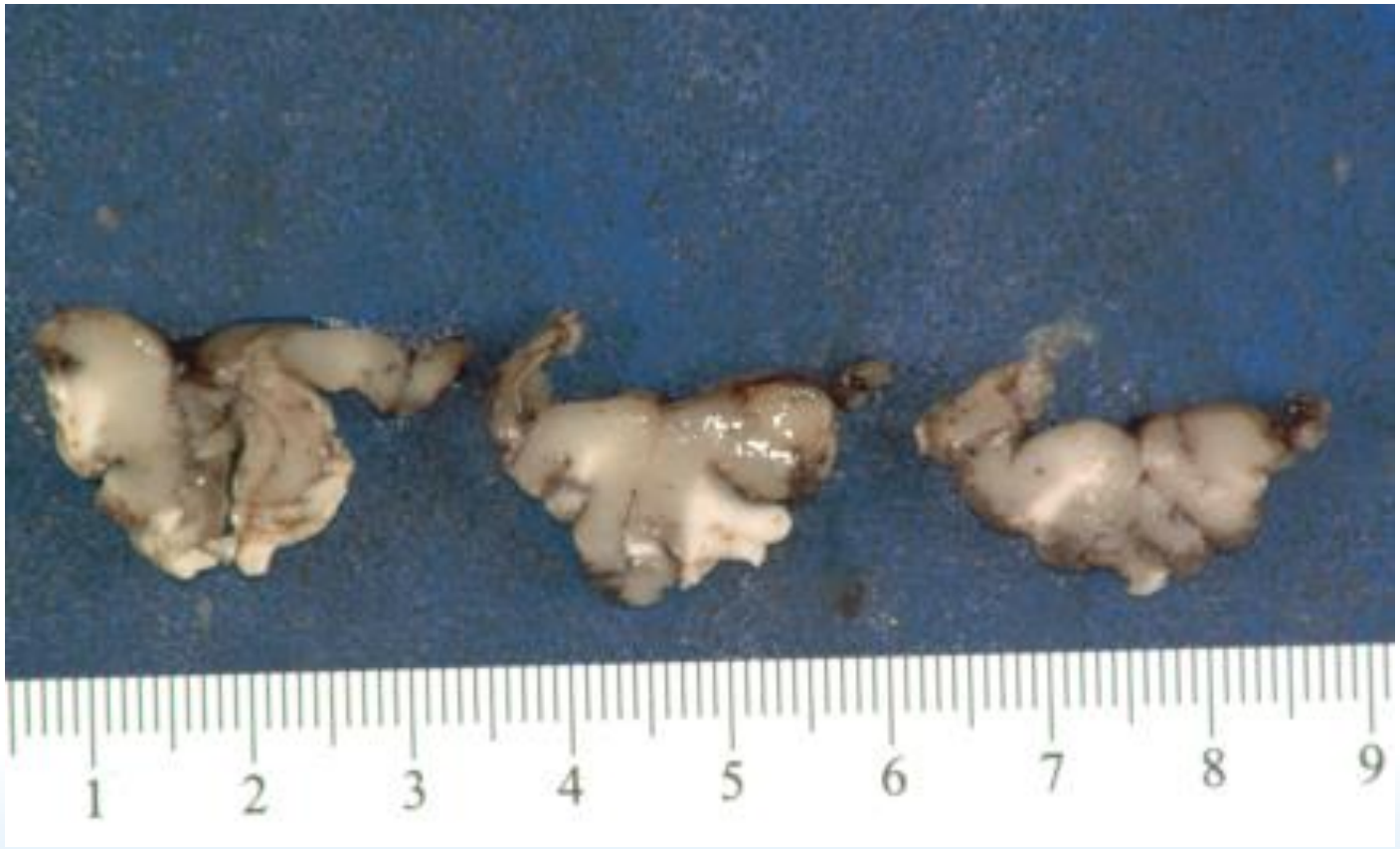

Dr. Jolee Suddock

Tissue handling

- Photography is recommended for en bloc samples
  - Optimal correlation to ECOG and MRI
  - Cortical/subcortical lesions can be macroscopically subtle
  - Track samples procured for research/banking: snap frozen tissue

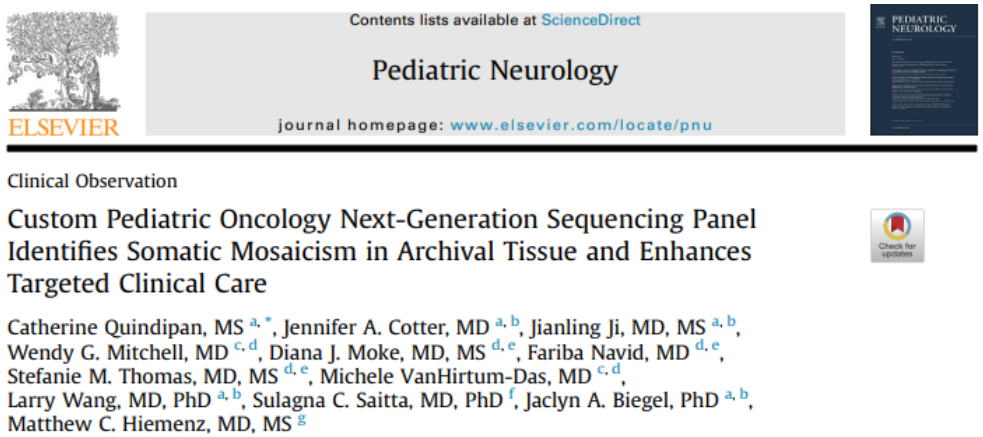
Sample photography





Tissue handling

- Photography is recommended for en bloc samples
  - Optimal correlation to ECOG and MRI
  - Cortical/subcortical lesions can be macroscopically subtle
  - Track samples procured for research/banking: snap frozen tissue
- Ensure samples available for potential genetic testing
  - Key to sample affected tissue in the setting of mosaicism



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Clinical Observation

Custom Pediatric Oncology Next-Generation Sequencing Panel Identifies Somatic Mosaicism in Archival Tissue and Enhances Targeted Clinical Care

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2 patients with HME

PIK3CA mosaicism detected from routine frozen tissue

VAF 20-32% in affected brain tissue

Learning Objectives

1. Describe the difference between seizures and epilepsy, and how epilepsy is diagnosed
2. Identify specific histologic patterns that can be observed in epilepsy surgical specimens
3. Outline the appropriate steps for tissue handing in the setting of epilepsy surgery

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Q&A