Imaging of excitotoxicity and functional connectivity in Pediatric Epilepsy

Dr Sidney KRYSTAL

09/06/2022

HÔPITAL FONDATION
Adolphe de ROTHSCHILD
LA RÉFÉRENCE TÊTE ET COU

NeuroSpin

neuroimaging of epilepsy laboratory
noel

CHU
LILLE

Imaging of excitotoxicity and Functional connectivity in Pediatric epilepsy

1- Excitotoxicity and epilepsy

- Pathophysiology
- DW imaging
- differential

2- Functional connectivity and epilepsy

- resting-state functional MRI
- applications in epilepsy

Imaging of excitotoxicity and Functional connectivity in Pediatric epilepsy

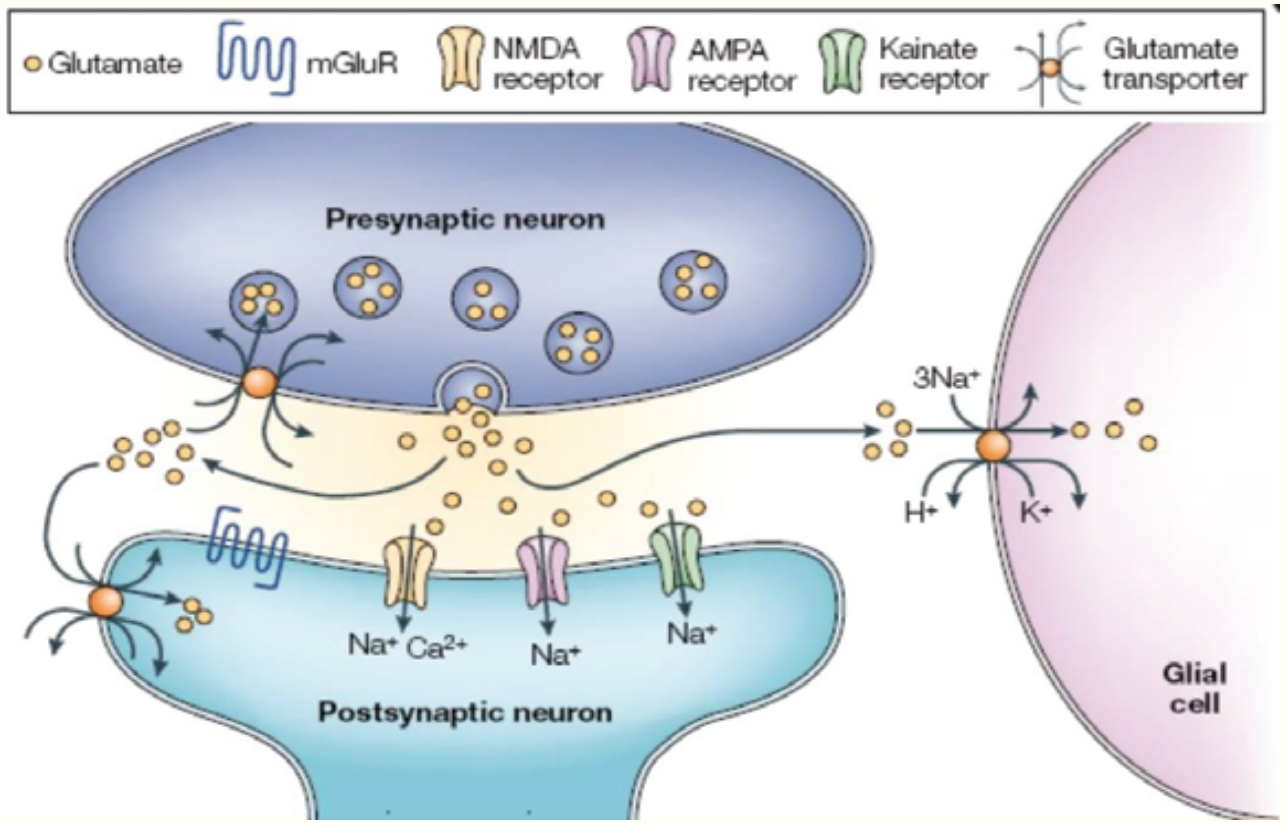
1- Excitotoxicity and epilepsy

- Pathophysiology
- DW imaging
- differential

2- Functional connectivity and epilepsy

- resting-state functional MRI
- applications in epilepsy

Excitotoxicity / Epilepsy



- Neuronal seizure activity

  => **increased release of Glu**

- Prolonged seizure: **uncoupling between hypermetabolism and CBF**

  => Na-K-ATPase dysfunction + decrease in glutamate reuptake

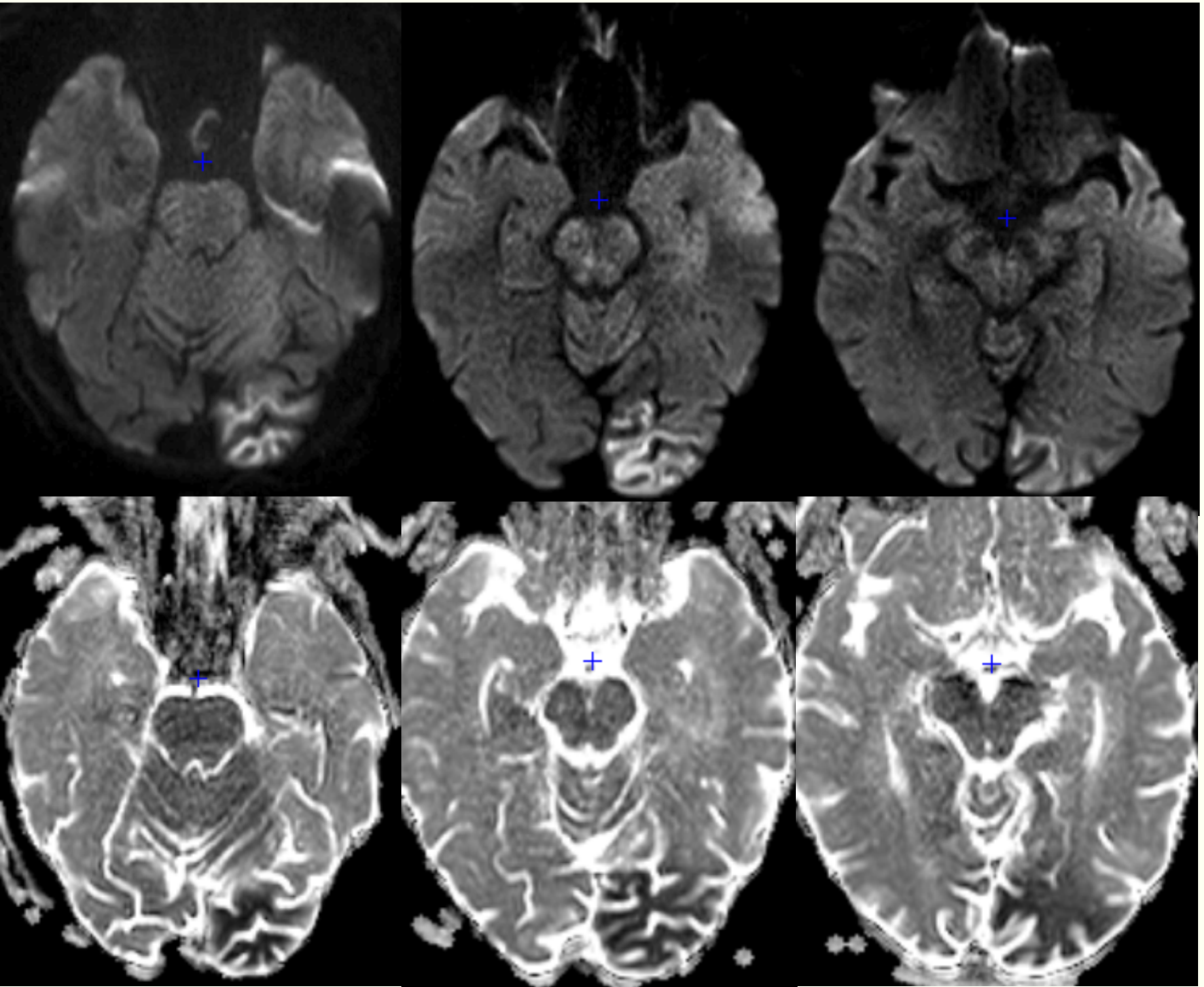
- Binding to receptors

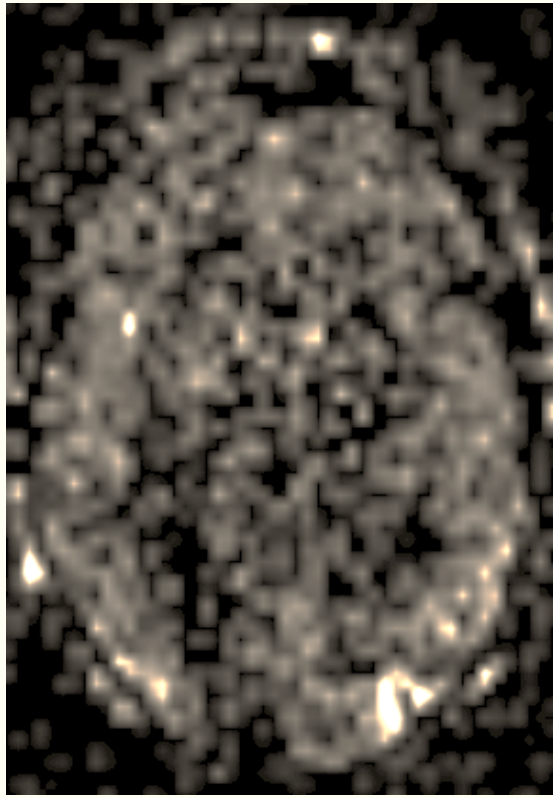
  => **Cytotoxic edema**

- **Hippocampus,** thalamus, cerebellum

Noebels JL et al., 2012.
Brison, 2013
Moritani et al, 2005

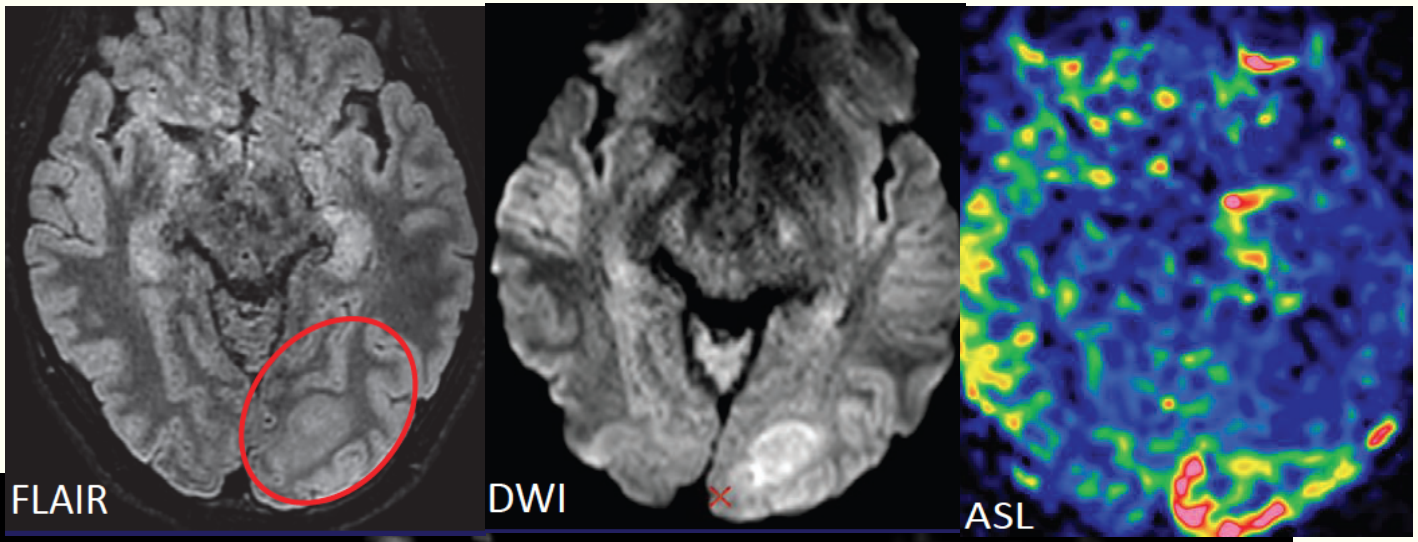
17 yo, right homonymous hemianopia





Cortical + adjacent white matter hyperintensity

DWI / ASL

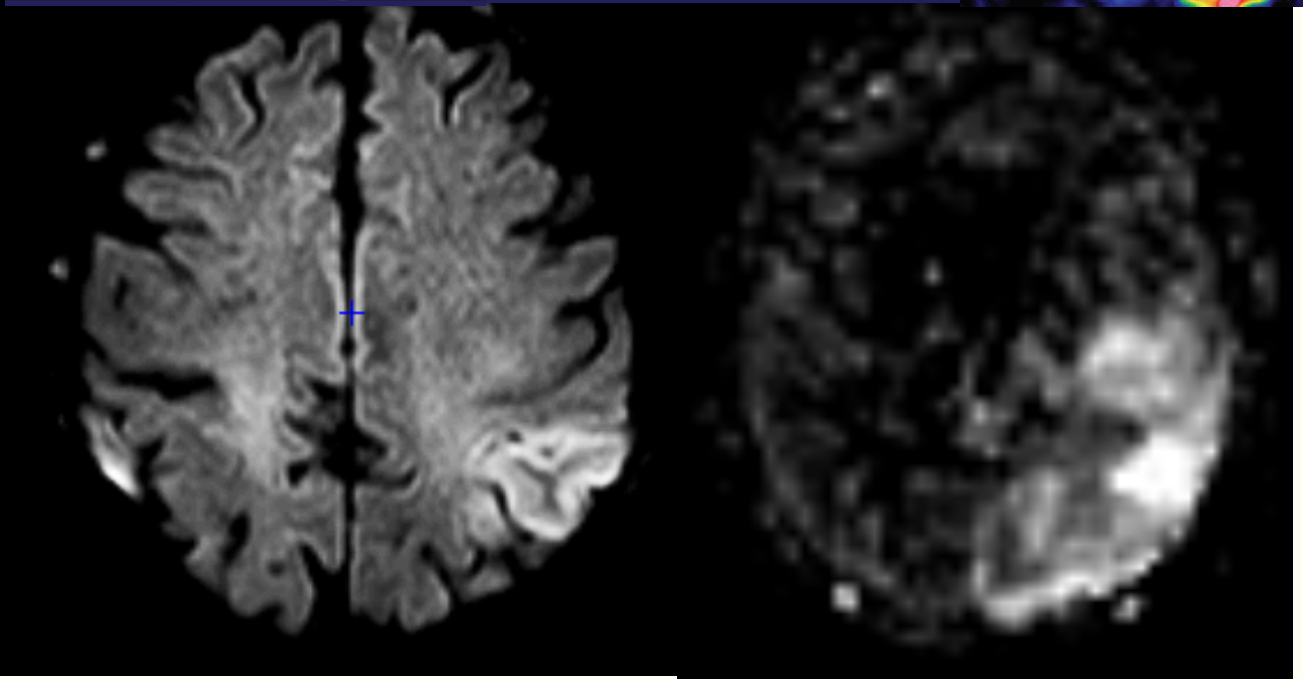


12 yo, drug-resistant epilepsy
Immediate post-ictal MRI

- Epilepsy assessment: DWI + ASL useful to **localize the epileptogenic lesion** (no etiologic orientation)
- Stroke suspicion: DWI hyperintensity does not mean stroke…

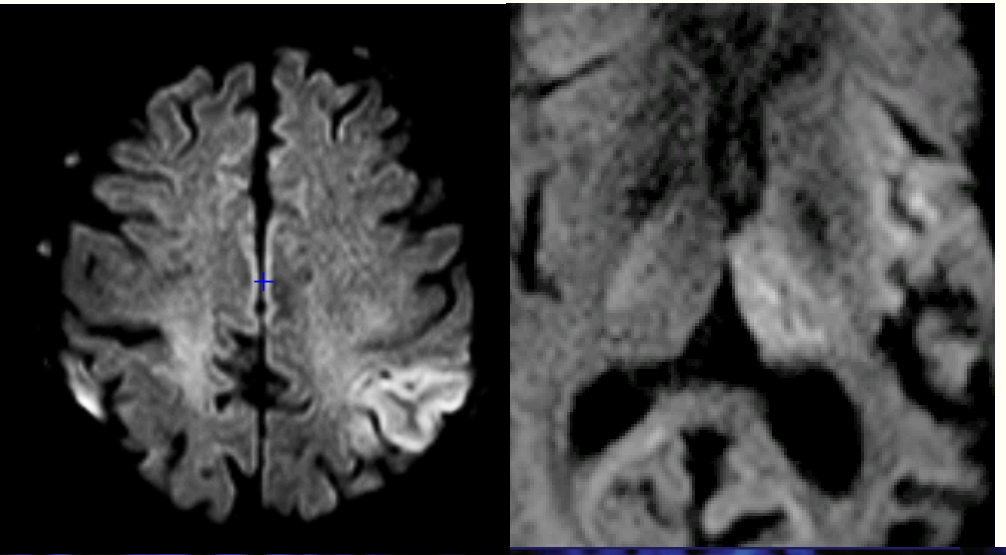
⇒no vascular territory

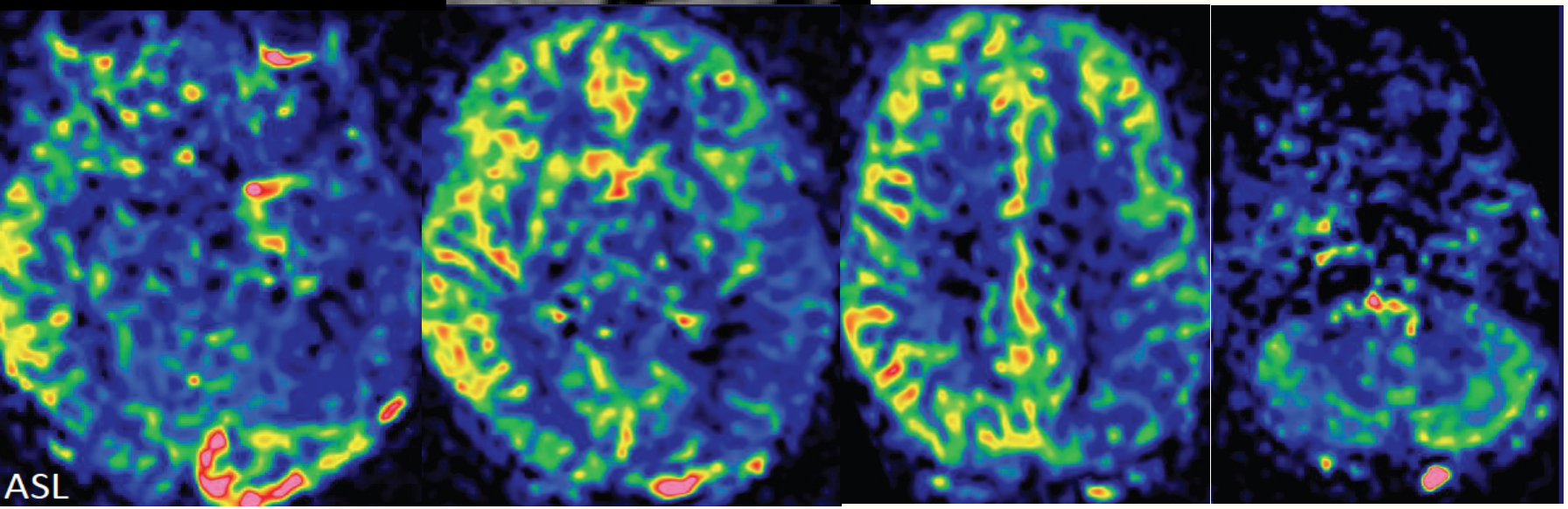
⇒ASL if doubt (increased)



14 yo, acute motor aphasia: stroke?

DWI/ASL discordance





- Diffusion hyperintensity without ASL abnormalities (focal aware seizure)
  => **ipsilateral pulvinar**

- ASL hyperperfusion without DWI abnormality: ASL systematic when stroke suspicion with negative DWI

Why do some patients have DWI/ASL abnormalities?
Seizure length, interval btw seizure and MRI
Task force

Hypoxic ischemic encephalopathy (HIE)

Energy depletion in neurons and glial cells

=> decreased reuptake of glutamate

Developing brain vulnerable to excitotoxicity injury

Putamen, thalamus, peri-rolandic cortex, internal capsule

Cerebral peduncles and corpus callosum secondary involved (wallerian and transneuronal degeneration)

DWI abnormalities (7 days)

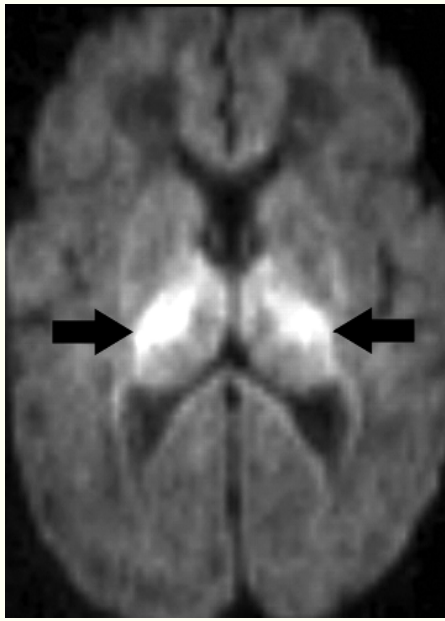
=> bilateral

=> no underlying cortical lesion

T1 and T2 hyperintensity (several months)

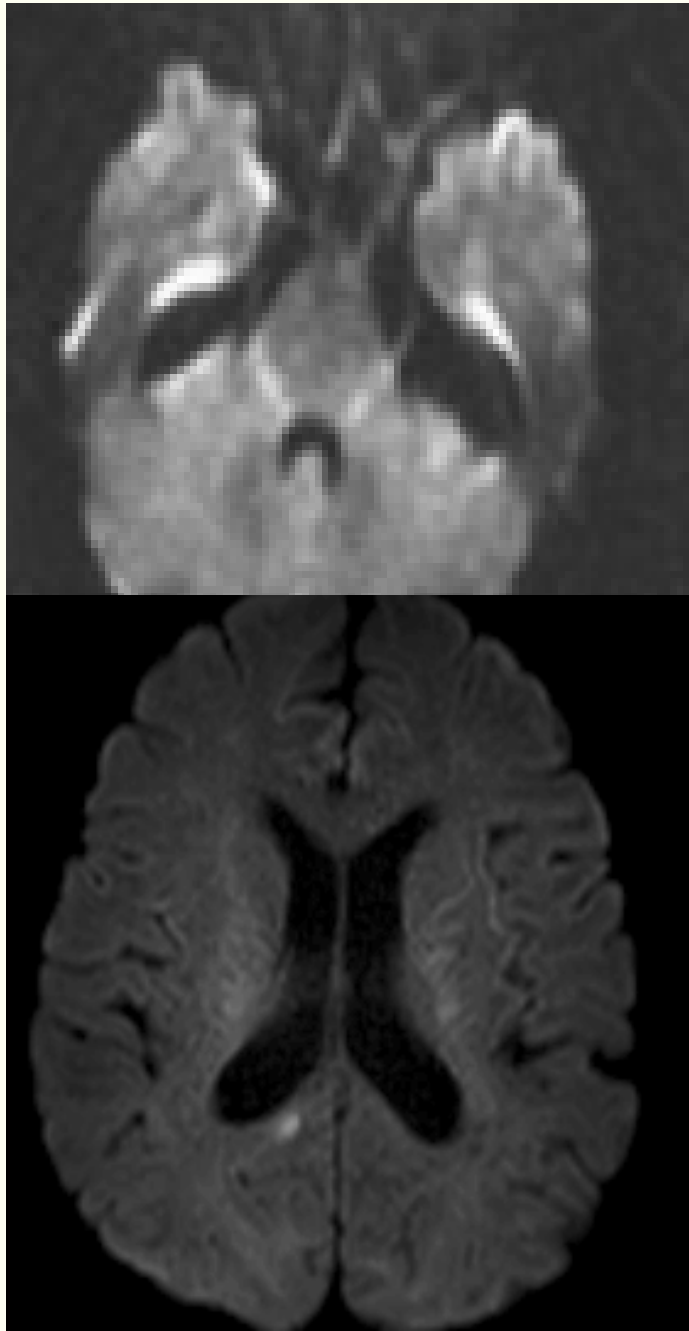
Sequelae (can lead to drug-resistant epilepsy) :

Posterior putaminal and ventrolateral thalamic atrophy and T2 hyperintensity



Differential

- **HSV**: Free radicals generated during the immune response to infections => excessive glutamate release (neonatal HSV2: widespread anomalies in both hemispheres including the basal ganglia and thalami)
- **CLOCCS** (seizure, sudden decrease in drugs, drugs)
- **Diffuse axonal injury**
- **Baby shaken syndrome**: glumamate levels increased (widespread parenchymal injury)
- **Osmotic myelinolysis**
- **Vigabatrin**



Imaging of excitotoxicity and functional connectivity in epilepsy

1- Excitotoxicity

- principles
- diffusion MRI

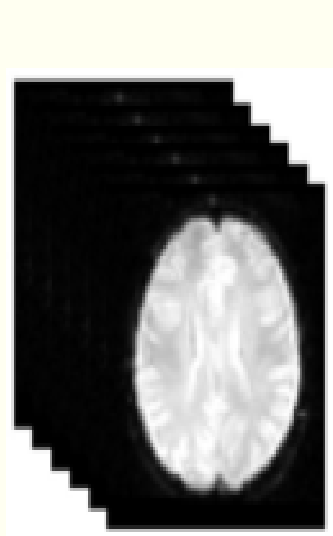
2- Functional connectivity and epilepsy

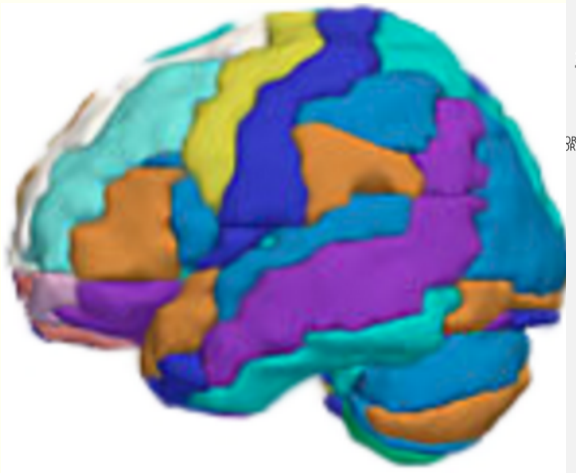
- resting-state functional MRI

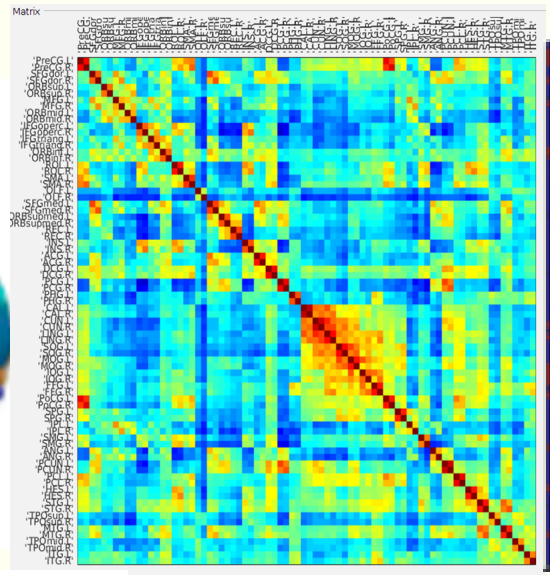
- applications in epilepsy

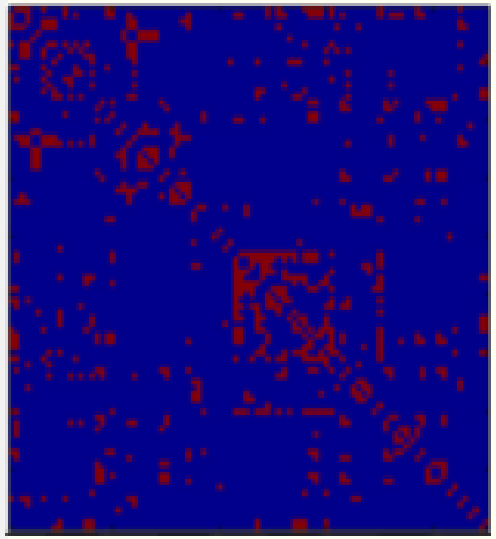
Resting-state functional MRI (rs-fMRI)

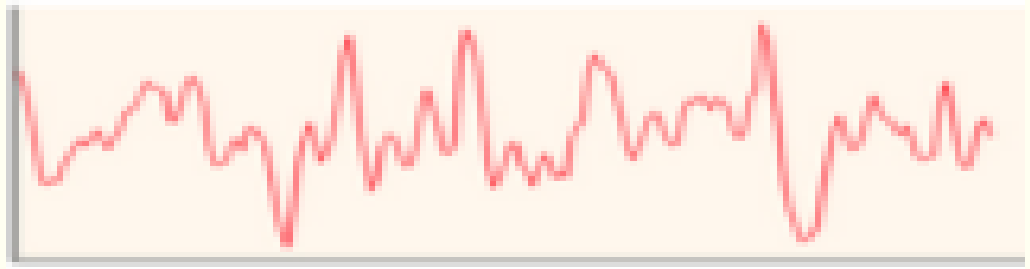
Functional networks

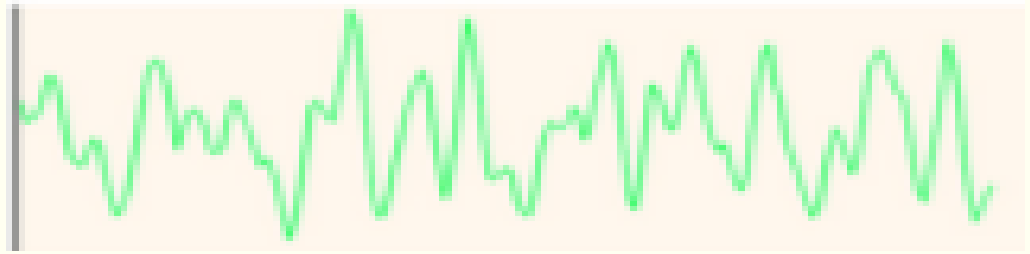


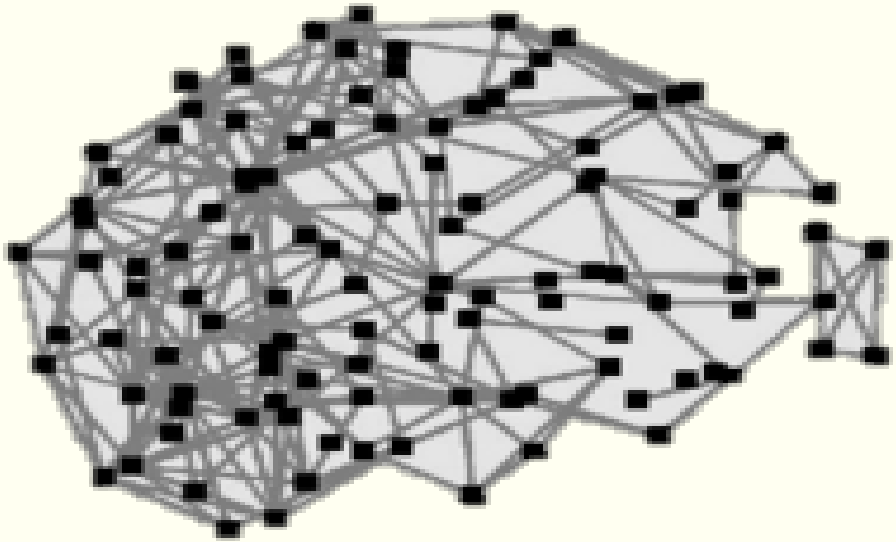












Imaging of excitotoxicity and functional connectivity in epilepsy

1- Excitotoxicity

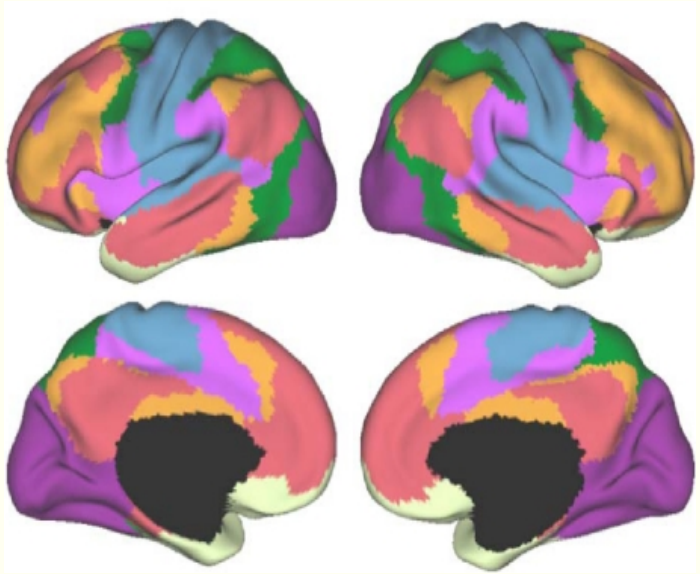
- principles
- diffusion MRI

2- Functional connectivity and epilepsy

- resting-state functional MRI
- **applications in epilepsy**
  - Independent Component Analysis
  - Seed-based Analysis
  - Graph Theory

Independent Component Analysis

- Determination of the epileptogenic zone by ICA (350 patients) then application to 40 patients:
  - Concordance rs-fMRI / sEEG : 90%
  - 2 « sEEG – » operated from rs-fMRI : seizure-free at 1 year
  - 8 children operated based on sEEG while an additional area had been detected in rs-fMRI: 25% seizure-free vs 96% if no add epileptic zone detected



- Total resection of the epileptogenic zone detected on pre-operative rs-fMRI + normalisation of the rs-fMRI 1 year after surgery: seizure-free biomarker (Se = 96% ; Sp = 93%)

Yeo et al, 2014
Boerwinkle et al, 2017-2018-2022

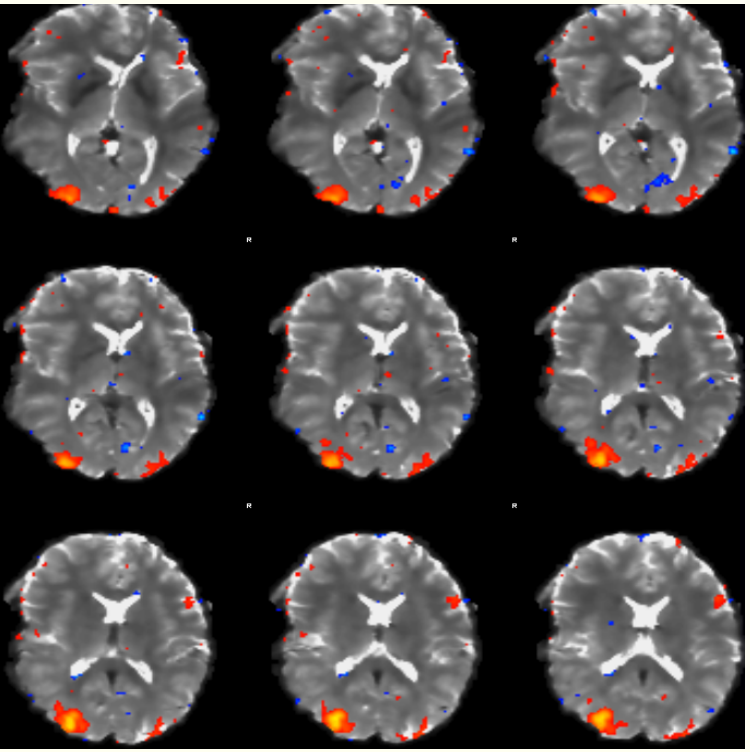
Independent Component Analysis

- Meta-analysis: non-inferiority of rs-fMRI (ICA) / sEEG

=> Alternative to more invasive techniques in pre-surgical planning?

- Implementation in the standard pre-surgical protocol in Phoenix:
  - Change of epileptogenic area based on rs-fMRI (44/50)
  - Modification of the resection area (22/38)
  - sEEG number decreased
  - Increase in the number of operated children (+26%)

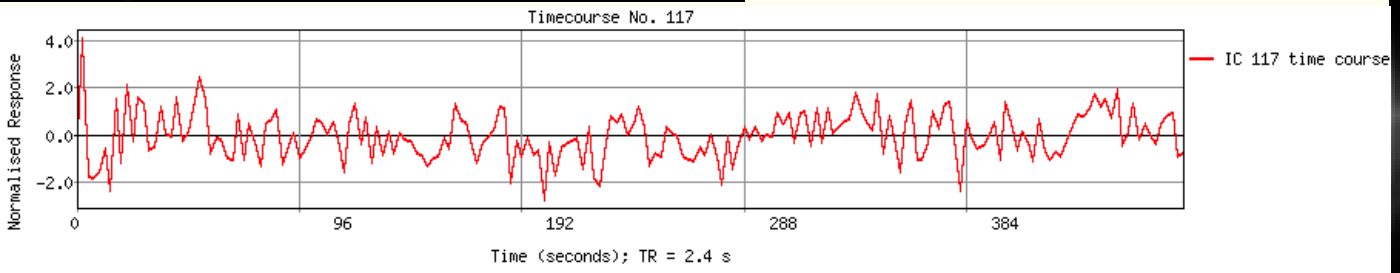
Boerwinkle et al, 2017-2018-2022

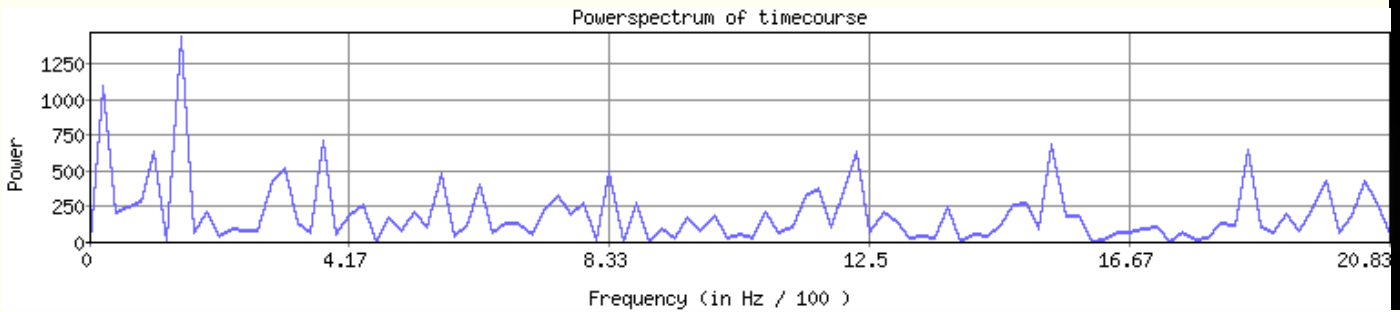


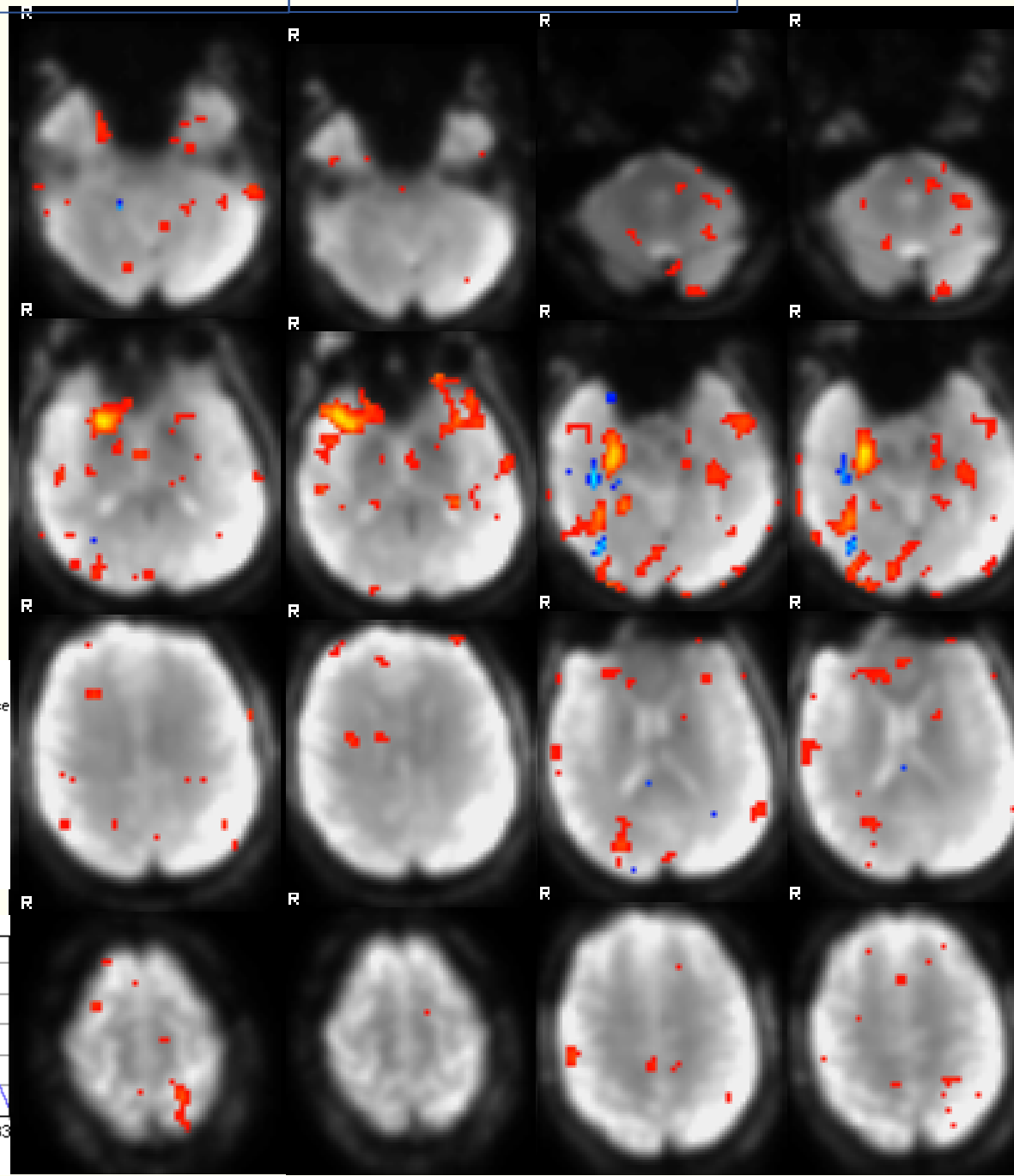
Mazzolo, Krystal, *in proc*

FCD 7 yo
TLE 21 yo

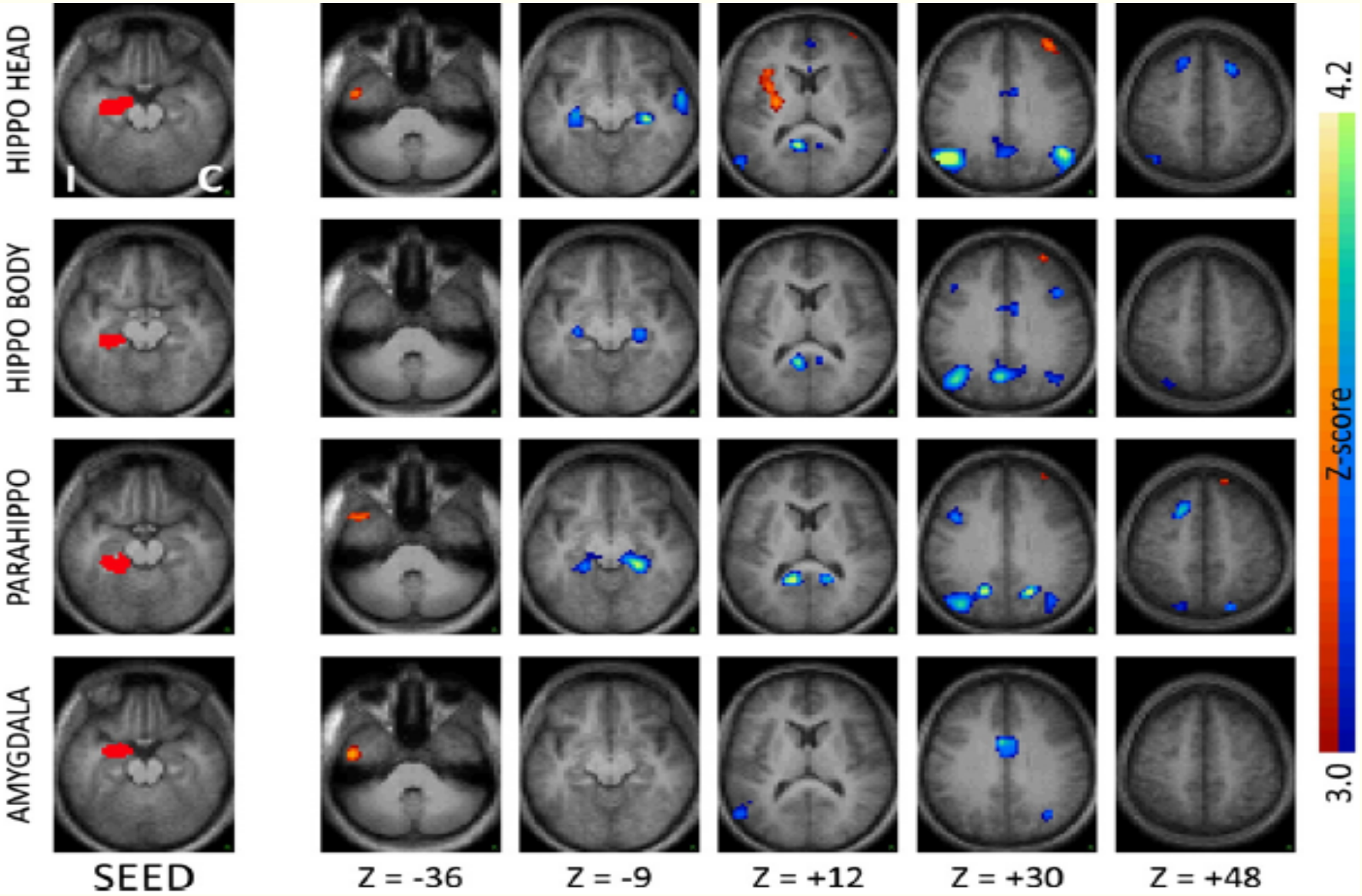
Systematic protocol







Seed-based Analysis



TEMPORAL-LOBE EPILEPSY

Ipsilateral/controlateral hemisphere;
Blue: decrease in functional connectivity
Red: increase in FC

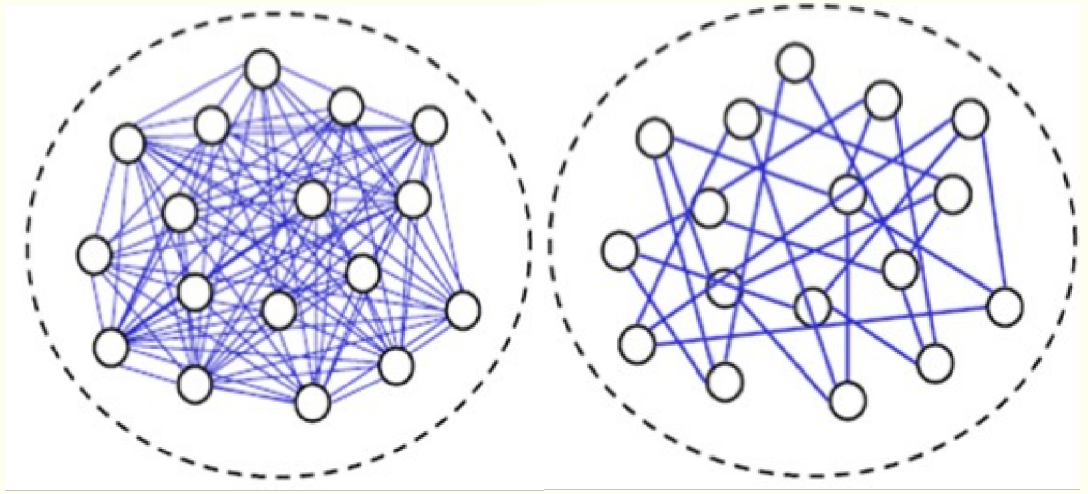
Maccotta et al, 2013

Graph Theory

- **PATH LENGTH** (PL) $$PL = \frac{1}{n}\sum_{i=1}^{n} L_i = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{\sum_{j=1}^{n} d_{ij}}{n-1}\right)$$
  - ✓ Locally: minimal number of links between two nodes
  - ✓ Whole-brain: **network integration** ⇔ network's ability to quickly transmit information between distant areas

- **CLUSTERING COEFFICIENT** (CC) $$CC(k) = \frac{Vi(k)}{V(k)}$$
  - ✓ Locally: number of node's neighbors that are themselves connected
  - ✓ Whole-brain: **network segregation** ⇔ network's ability to get organized in dense subnetworks

- « NORMAL BRAIN »: short PL, high CC

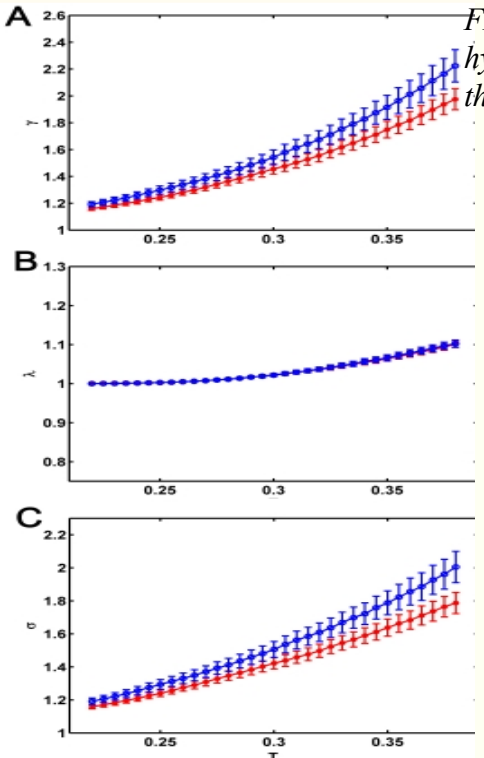


Graph Theory

TEMPORAL-LOBE EPILEPSY

- Small-world topology maintained
- But more regularized inter-ictal network topology
  - ⇔less shortcuts between nodes
- Decrease in CC in the final stages of sclerosis
  - ⇔ sparser local brain connections
  - ⇔ decreased level of functional segregation
- Interictal increase in PL
  - ⇔ Decreased global integration

FLAIR MRI coronal view showing a small and hyperintense right hippocampus, consistent with the diagnosis of mesial sclerosis (or TLE)



Blue: TLE
Red: Controls

(A): normalized clustering coefficient
(B): normalized path length
(C): small-worldness of network

Liao et al, 2010

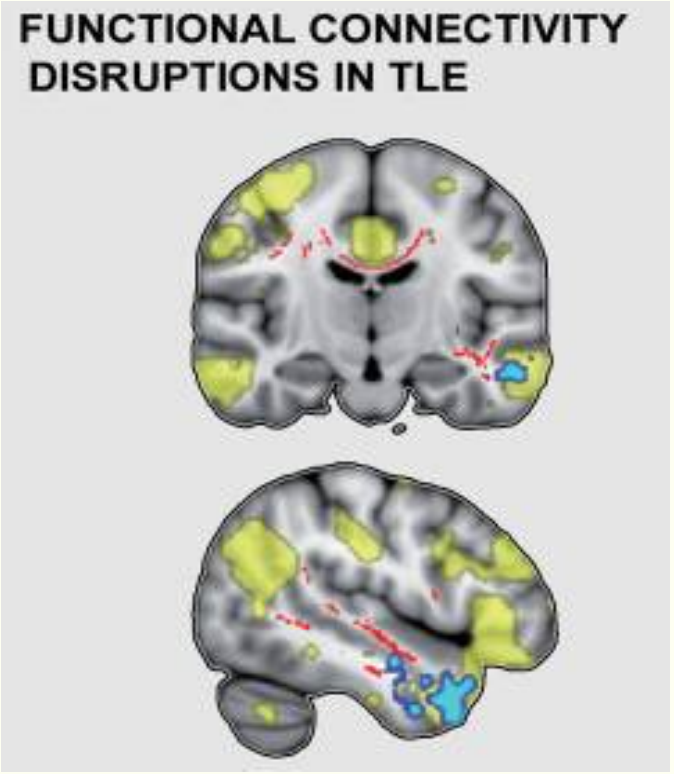
Graph Theory

TEMPORAL-LOBE EPILEPSY

- Topological changes mostly seen within the temporal lobe and the Default Mode Network (DMN)
- **Involvement of extratemporal structures**
- **>80% accuracy (TLE vs controls) using graph theory**
- Mesiotemporal increased PL

  ⇔ disconnection between the hippocampus and the other structures

  <u>Potential application: isolated hippocampus (with higher PL) could be easier to neutralize surgically</u>



Bernhardt et al, 2013

- Regularized network configuration + redistribution of network hubs toward the temporal lobe and paralimbic association cortices may provide an environment conducive to ictogenesis
- *In proc:* graph theory on the epileptogenic network to predict the surgical outcome

Conclusion

- Imaging of epilepsy: very challenging
  - Very small lesions to detect
  - Need for accurate and early diagnosis (dramatic consequences of DRE)

- Every tool that could help us must be used
  - DWI, ASL, SWI
  - Resting-state functional MRI
  - Help for better understanding of ictogenesis and drugs' mode of action

- Do not forget the basis:
  - Clinic, EEG
  - T1, T2, asymmetry
  - Take time for interpretation
  - If « MRI-negative », 2nd advice, expert center

Thank you

- Pediatric neuroimaging task force:
  - **Pr Maria ARGYROPOULOU, Dr Volodia DANGOULOFF-ROS**
- Montreal Neurological Institute
  - **Pr Neda LADBON-BERNASONI, Pr Andrea BERNASCONI**
- CHU TOURS
  - **Pr Jean-Philippe COTTIER**
- Hôpital-Fondation Rothschild
  - **Dr Julien SAVATOVSKY, Dr Jerry BLUSTAJN, Neuroimaging department**
  - **Dr Gilles HUBERFELD, Pr Georg DORFMULLER, Pediatric neurosurgery department**
- CHU Lille
  - **Pr Jean-Pierre PRUVO**
  - **Dr Quentin VANNOD-MICHEL, Dr Renaud LOPES, Dr Cécile BORDIER**
- **Leïla MAZZOLO**

Thank you

Excitotoxicity and functional connectivity in pediatric epilepsy

Dr Sidney KRYSTAL

09/06/2022

skrystal@for.paris