2023 GW Epilepsy Board Review & Best Practices

Functional Imaging Patients with Epilepsy

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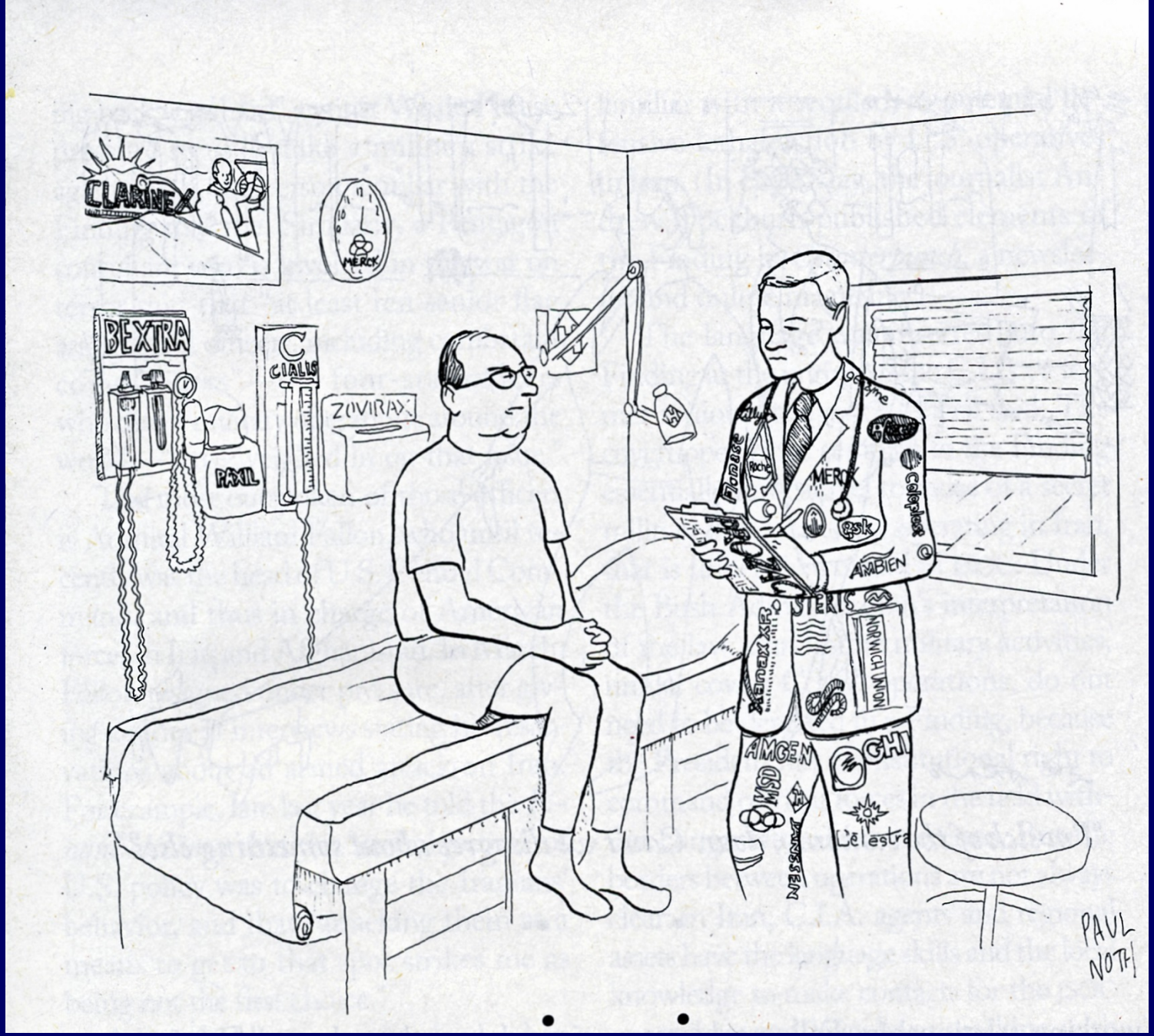
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Disclosure Slide: William Davis Gaillard

- Supported by Federal Grants R01 NS44280 NINDS, RO1 MH65395 NIMH, P30HD40677 NICHD, U54 MH066417 & Clinical Epilepsy Section NINDS, NIH.
- Co-Investigator (Not PI, no salary support) on several Pharmaceutical Industry supported AED clinical trials: Rectal Diazepam, Oxcarbazine, Lamotrigine, Zonisimide, Vigabatrin, Tiagabine, Gabapentin, Clobazam, Rufinimide.
- I do use pens and flashlights from industry with logo.
- I WILL discuss off label use of PET ligands used on a research basis under FDA IND.

Question 1

- The single most helpful test for evaluating the cause of epilepsy and for identifying the epilepsy focus is:
- 1. FDG-PET
- 2. functional MRI
- 3. High resolution structural MRI
- 4. Low radiation CT
- 5. HMPAO ictal SPECT
- 6. MEG source imaging

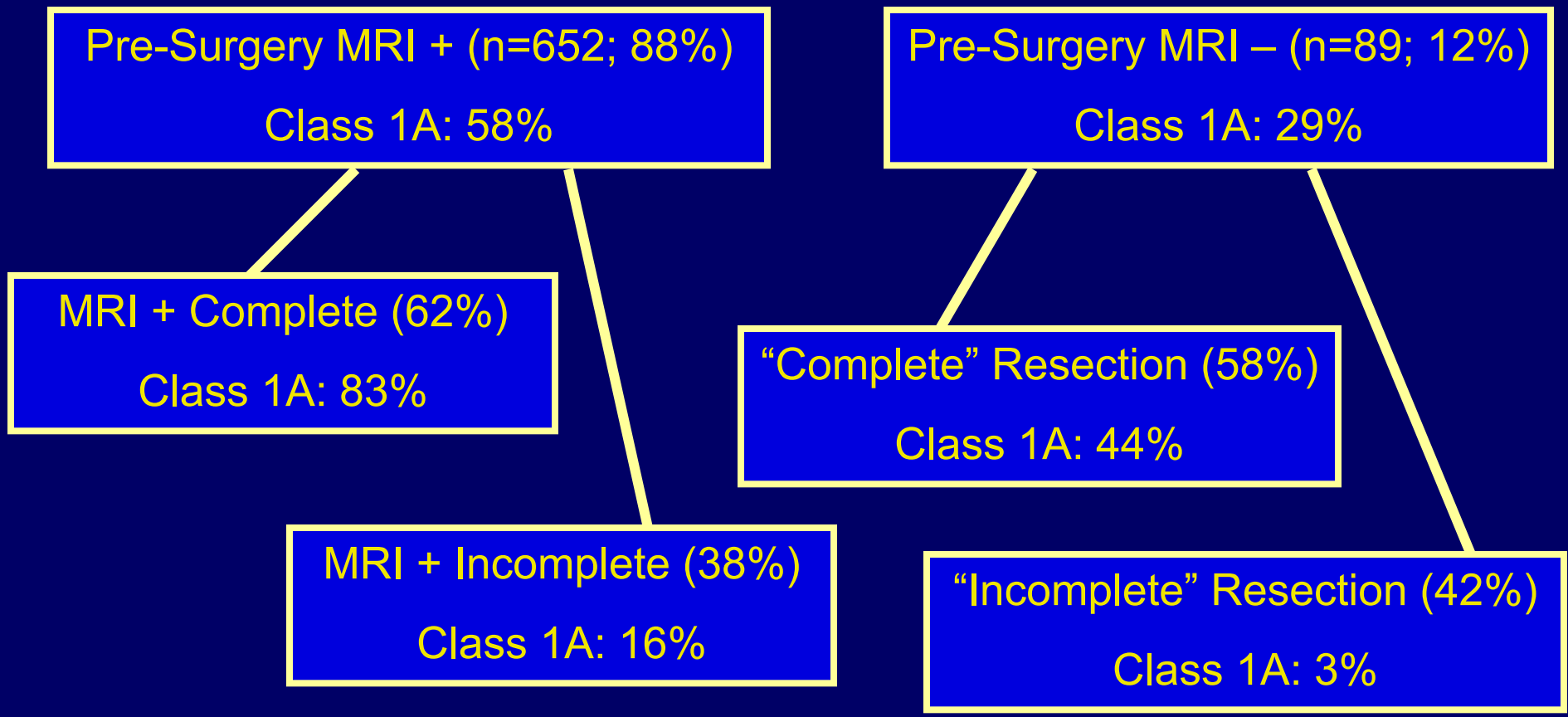
Epilepsy & Functional Imaging

- Direct treatment of Surgical Planning
- Confirmation of focus (critical for epilepsy surgery)
- Identify areas to be spared during epilepsy surgery (cortical and white matter)

Imaging

- PET
- SPECT
- Functional MRI for brain mapping
- DWI for white matter tract identification
- MR Spectroscopy (MRS)

Class 1A Seizure Outcome
2004 ILAE Pediatric Outcome Survey



*PET/SPECT/MEG+ 40-60% EI; Image - <20%

Courtesy G Mathern

Question 2

- Which ligand is most common clinically used for PET
- 1. Cyclofoxy
- 2. Flumazanil
- 3. FDG
- 4. O-15 Water

PET Methods

- Radio tracers tagged to compounds designed to target a physiologic process
  - Blood flow, metabolism, neurotransmitter precursor, receptor binding (agonist/antagonist)
- Information gained limited by tracer half life
  - ^{18}F 90 minutes FDG PET Decrease
  - ^{11}C 20 minutes Flumazenil Decrease
    - ά Methyl Trypotphan Increase
- Requires image acquisition shortly after injection

PET (& SPECT) Methods

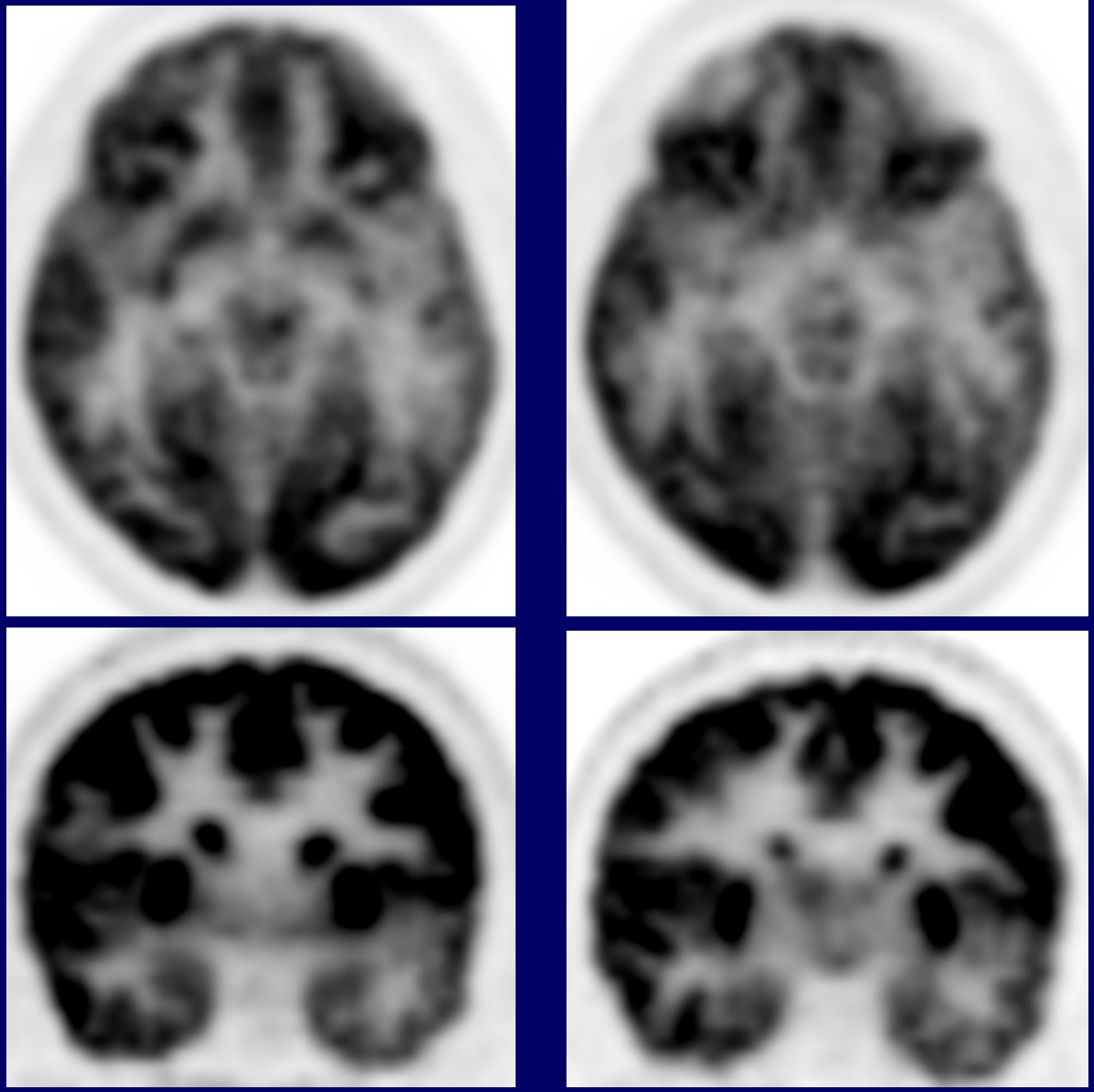
- PET patient studies require EEG
  - Ictal vs. interictal
- Analysis
  - Visual
  - Region of interest (superior to visual analysis adult data, Theodore et al. Ann Neurol 1992) with laterality index
  - Voxel based (e.g. SPM) (beyond 2-3SD mean signal voxle based on Normal (“normal”) data

Imaging: FDG-PET

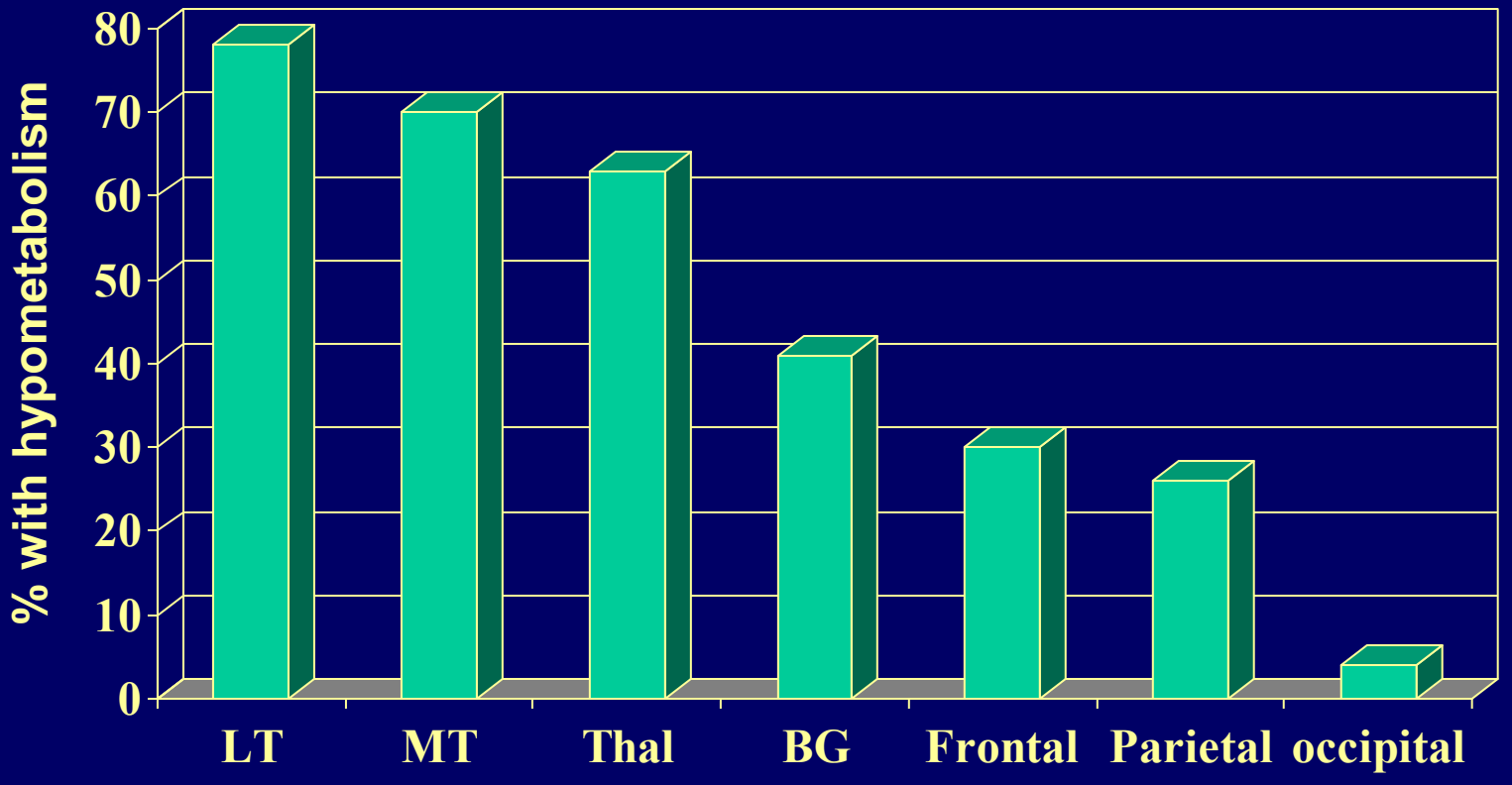
- Measure of metabolic rate: Glucose uptake and consumption
- Ictal FDG-PET uncommon and unreliable
- Interictal: Regional hypometabolism 90% adults with temporal lobe epilepsy (most childhood onset)
- Regional hypometabolism more widespread than epileptogenic zone
- Regional hypometabolism: Good surgical outcome adults with childhood onset epilepsy (class 2)
- Reduces need for invasive (less extensive) recording
- FDG-PET less helpful in neocortical epilepsy (50-60%)

FDG-PET

- Correctly lateralize focus in 60% children with intractable partial epilepsy (including those with normal MRI)
- May be helpful in young, < 2 years, when MRI less sensitive to identifying dysplasia (Class 4)
- Evaluate integrity good hemisphere when considering hemispherectomy (Class 4)

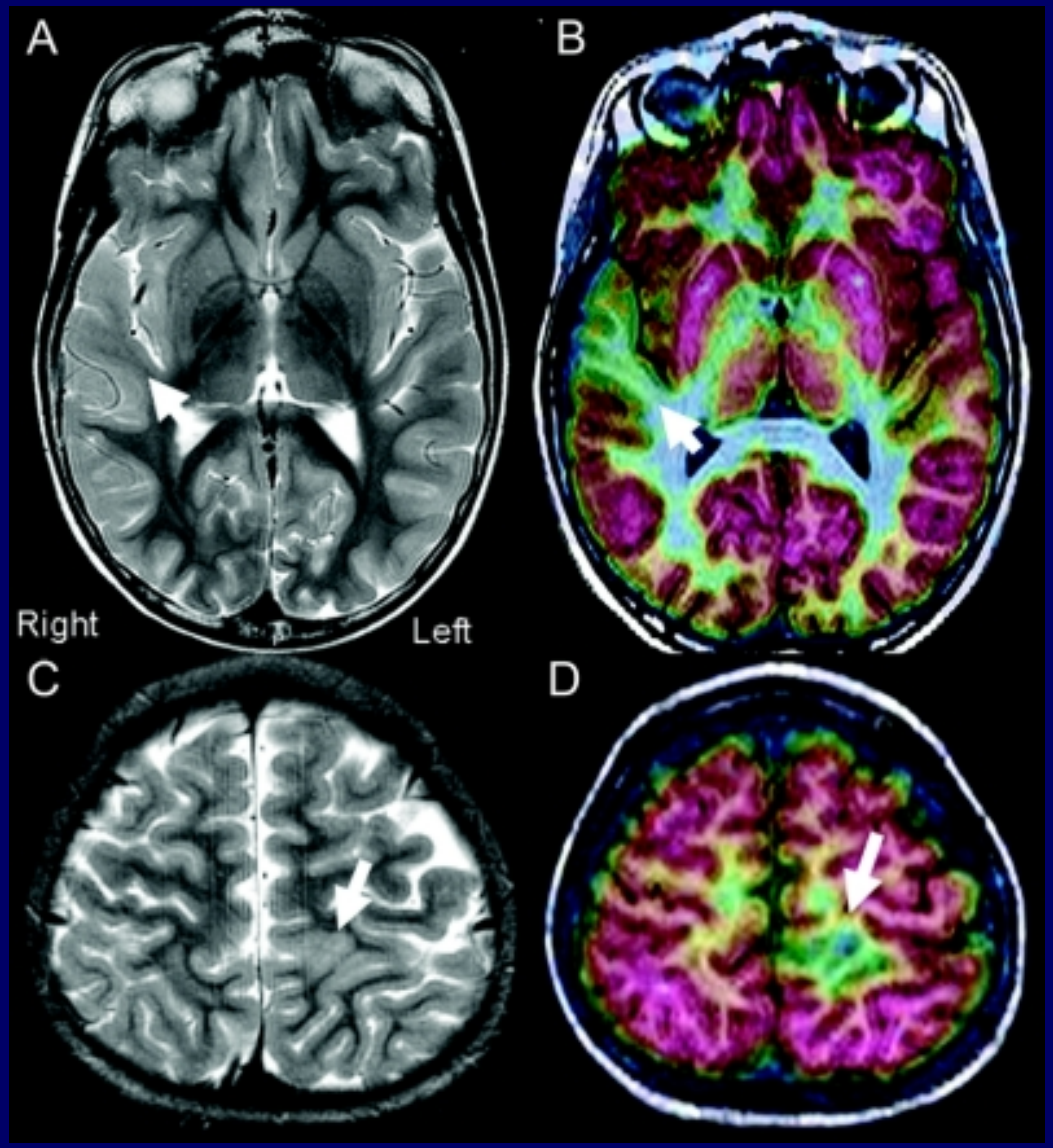


Hypometabolism in TLE



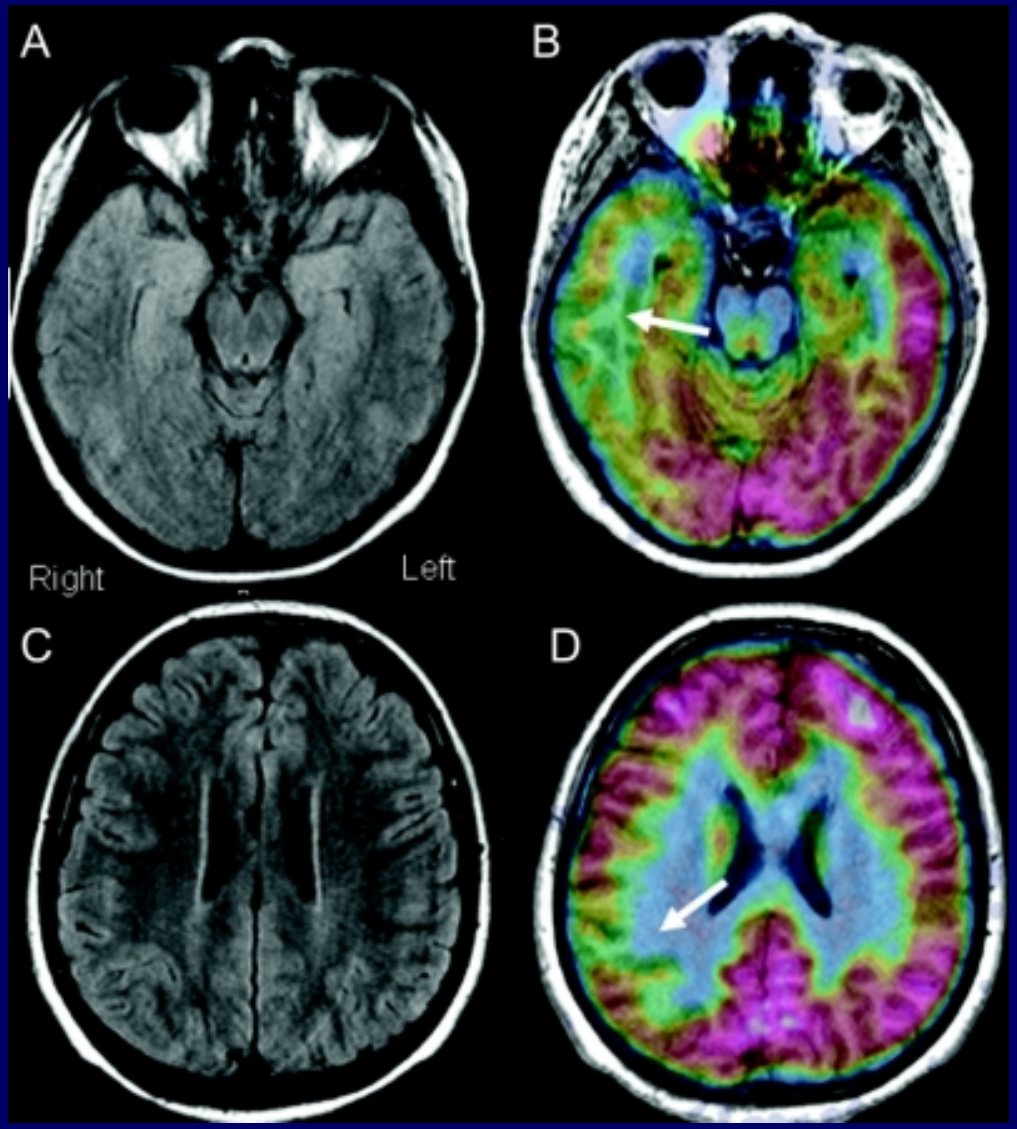
Henry et al, 1993

^{18}FDG-PET Co-Registered with T1 MRI
Type 1 FCD: The second look effect



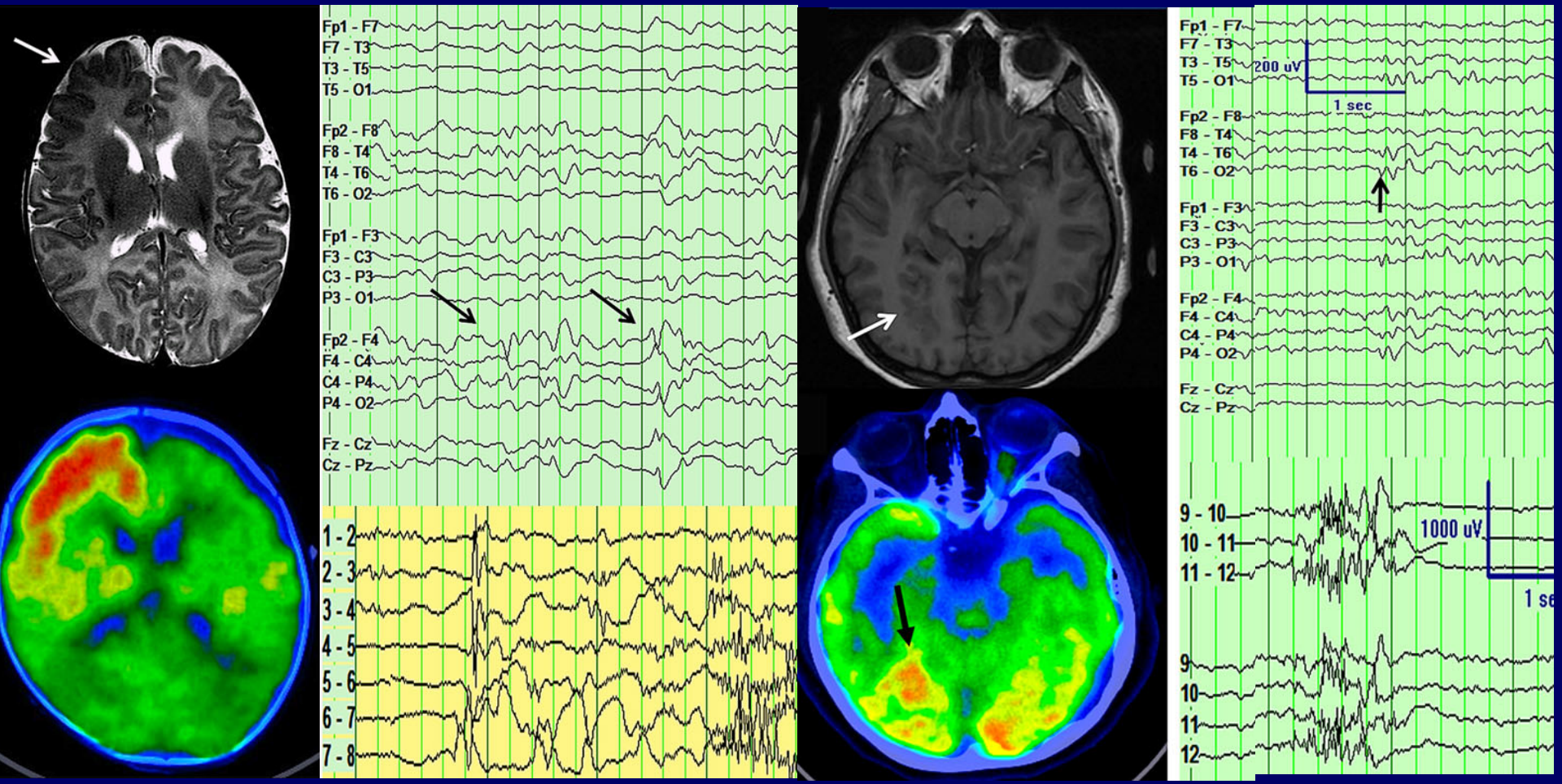
Salamon N, et al *Neurology* 2008

Multilobar FCD I and Normal MRI



Salamon N, et al *Neurology* 2008

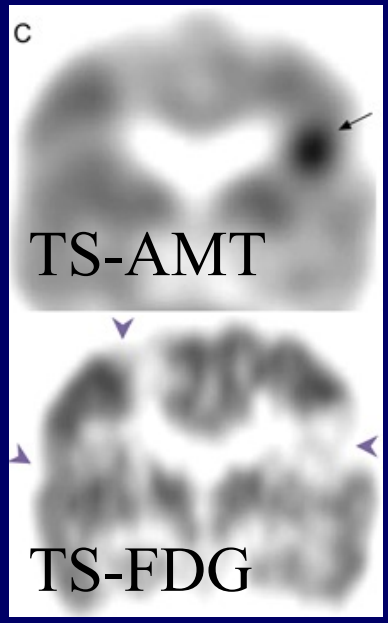
PET Hypermetabolism & FCD
2-6% pediatric series



Bansal L et al, *Epileps*

PET: Other Ligands

- ^{11}C Flumazenil: Not helpful
  - Benzodiazepine/GABA receptor antagonist
- ^{11}C α- Methyl Tryptophan: For TS
  - Precursor to 5HT/amino acid transmitters
- ^{18}FC WAY: Experimental
  - $5HT_{1A}$ Antagonist
- ^{11}C-PBR28 PET: Experimental
  - Peripheral Benzodiazepine Receptor Ligand-microglia



SPECT

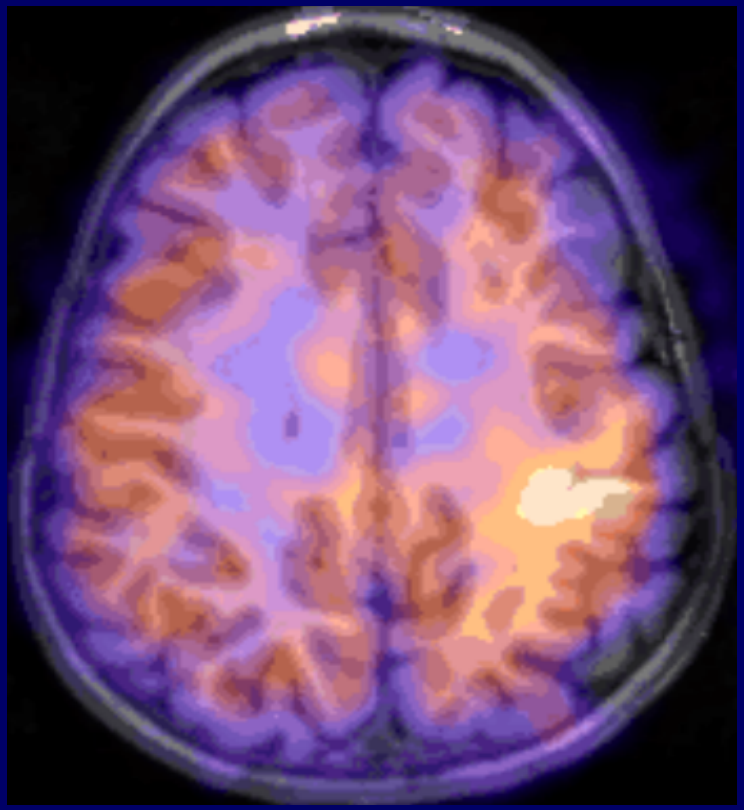
- HMPAO, ECD (99-Technetium)
- Markers of CBF
- Long half life (6 hours)
- Can scan several hours after injection
- Can not quantify
- Always perform with EEG
- Timing of injection in relation to seizure critical

SPECT

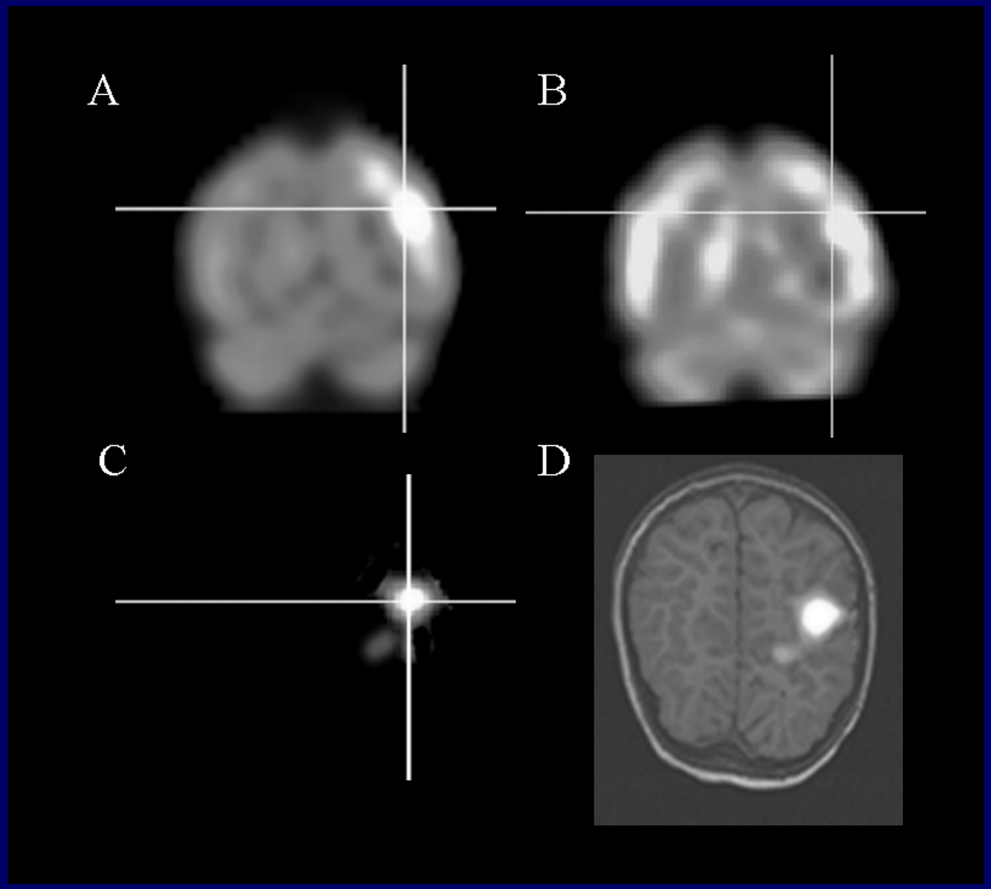
- Interictal, SuSPECT: False lateralizing 10%
- Ictal Superior
- Subtraction Inter-Ictal from Ictal (or SPM)
  - Co-registration with structural MRI
  - Increases inter and intra rater agreement from 70 to 85% & localization value 31-74% to 74-93%
  - 80-90% when lesion present (Class 3 adults)
  - 59-76% non lesional (Class 4)
- Reliability depends on timing/delay injection in relation to seizure onset (later injection increases false localization/lateralization)
- Propagation effects

O'Brien et al, 98, 99; Vera et al, 99

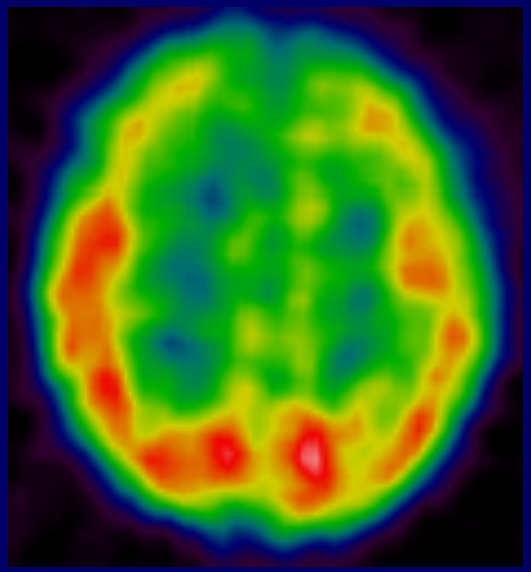
Ictal SPECT
Co-registered with MRI



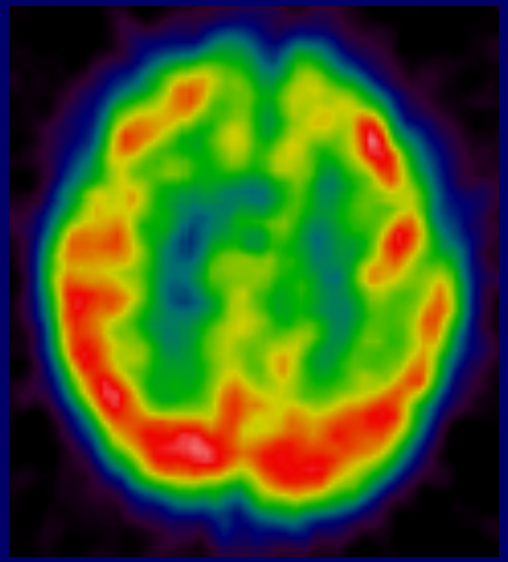
Courtesy P Jayakar MCH



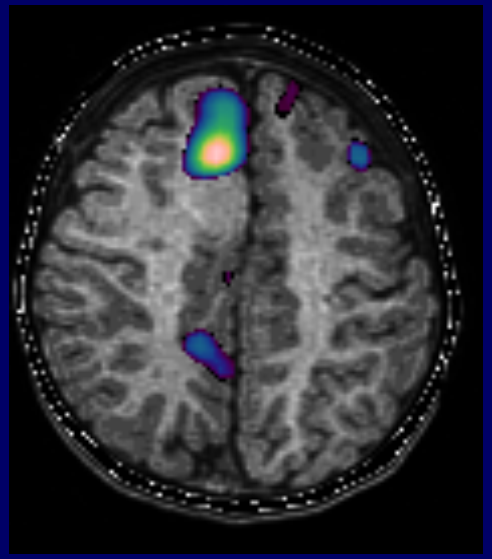
Courtesy G Cascino. In Wyllie E Principles and Practice of Epilepsy



interictal



ictal

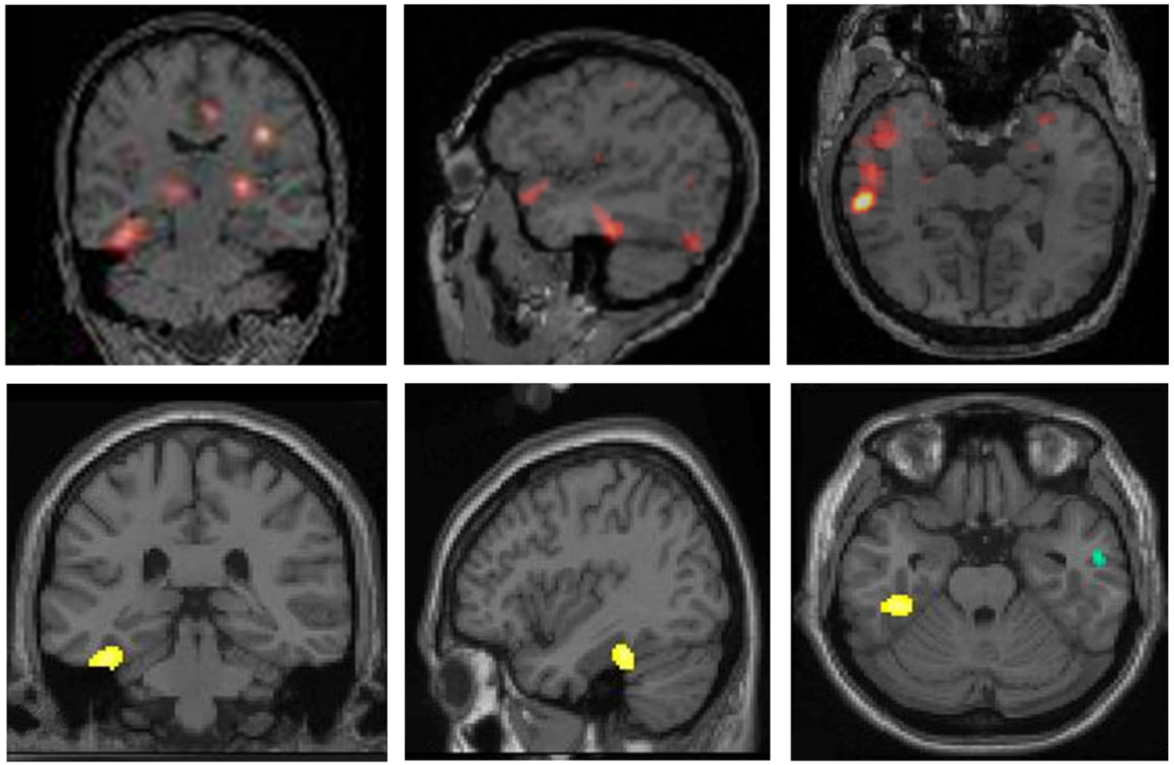


« SISCOM »

Courtesy C Chiron

SISCOM
κ=0.36
66% all
24% TLE subtype
47% normal MRI

STATISCOM
κ=0.81
84% all
68% TLE subtype
80% normal MRI
Outcomes better



Statistical Ictal SPECT Voxel-Wise Statistical Threshold Difference
N=87; controls =11

Kazemi et al *Neurology* 2009

N=160; 77 iEEG; 72 Seizures; 62 resection; 38 (61%) Engle I
MRI negative (43%), unclear, small FCD NB 1.5T MRI

n		MEG	PET	iSPECT
62	Sensitivity	55		
	Specificity	75		
51	Sensitivity	56	59	
	Specificity	79	79	
34	Sensitivity	38		50
	Specificity	72		72
27	Sensitivity	31	54	62
	Specificity	79	86	86

Knowlton R et al, *Ann Neurol*, 2008

Question 3

- Under what conditions is SPECT (ECD or HMPAO) most reliable
- 1. Inter-Ictal
- 2. Peri-ictal
- 3. Icta-ictal
- 4. Post- ictal

Summary

- Lesional (MRI) studies: PET and SPECT add little
  - Unless wish to localize within large lesion
- FDG-PET: Non-lesional MRI helpful 30-60% (>TLE)
- Ictal (subtraction) SPECT when PET negative or unavailable
- 2nd look effect; re-review MRI based on new data
- Discordant Results → Invasive monitoring
- Negative MRI: think genetic or inflammatory causes

Functional MRI (fMRI)

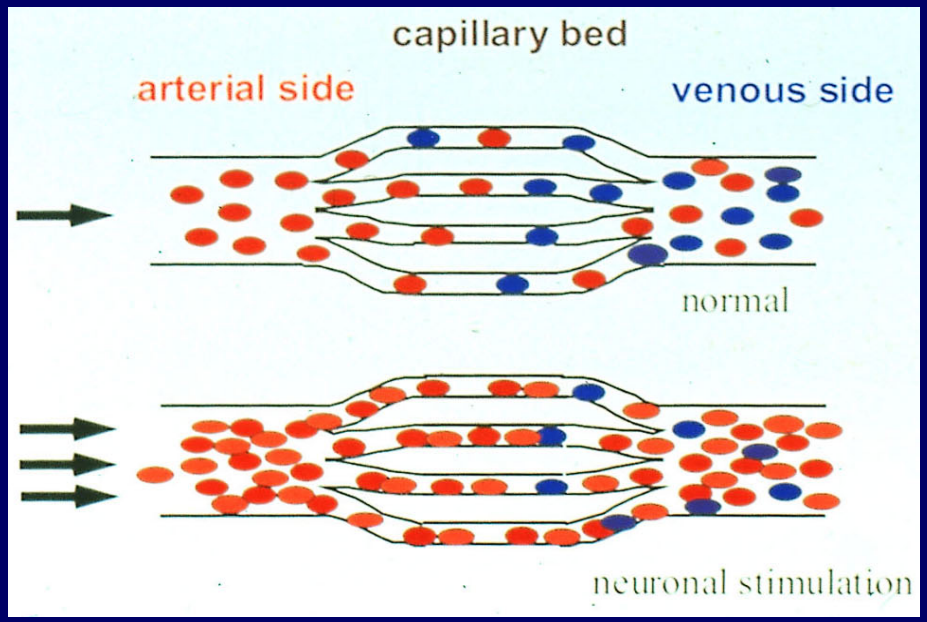
- Identify Epileptogenic Cortex
  - Interictal
  - Ictal
- Identify what to spare during epilepsy surgery
  - Motor
  - Sensory
  - Language
  - Memory

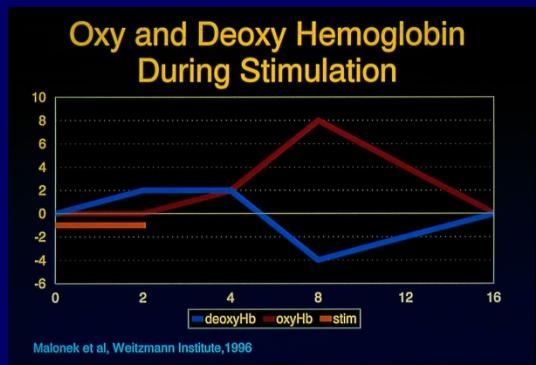
Blood Oxygen Level Dependent signal

↑neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal

BASAL STATE
Normal CBF
Basal level [Hbr]
Basal CBV
Normal MRI signal

ACTIVATED STATE
Increased CBF
Decreased Hbr
Increased CBV
Increased MRI signal





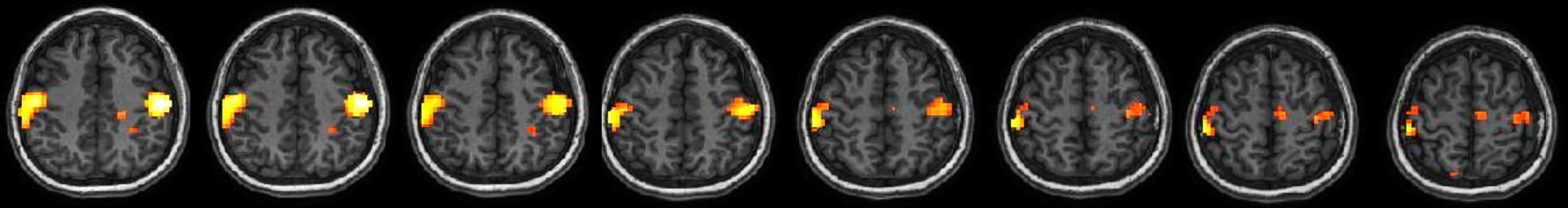
Source: fMRIB Brief Introduction to fMRI

Motor & Sensory Mapping

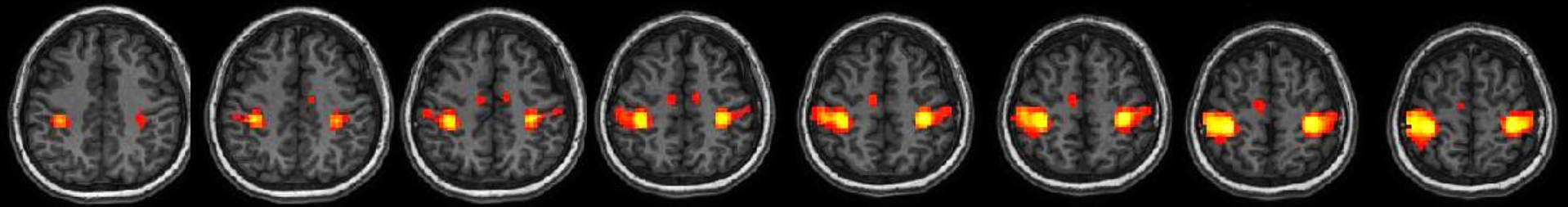
- Extra-temporal lobe epilepsy
- Lesion (Tumor/AVM)
- Identification of Motor/Sensory strip
- Agreement with Evoked potential & electro-cortical stimulation (<5 mm)

MOTOR	SENSORY
Finger Tapping	Visual Flash (primary visual)
Tongue Wiggling	Tones (primary auditory)
Foot Tapping	Brush (Sensory strip)
	Face, Hand, Foot

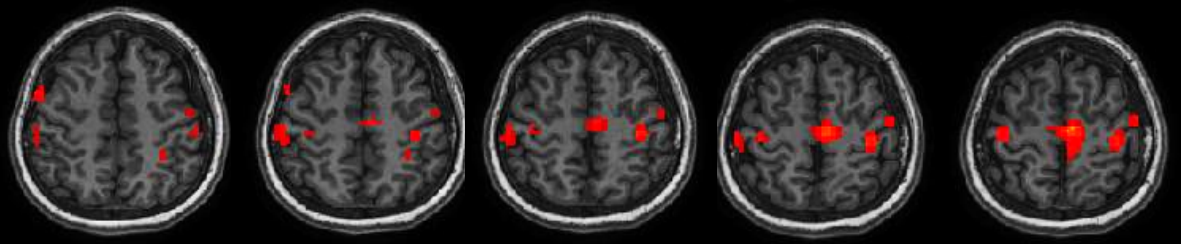
Motor Mapping



Tongue Wiggling



Finger Tapping



L Foot Tapping

R

Language Mapping

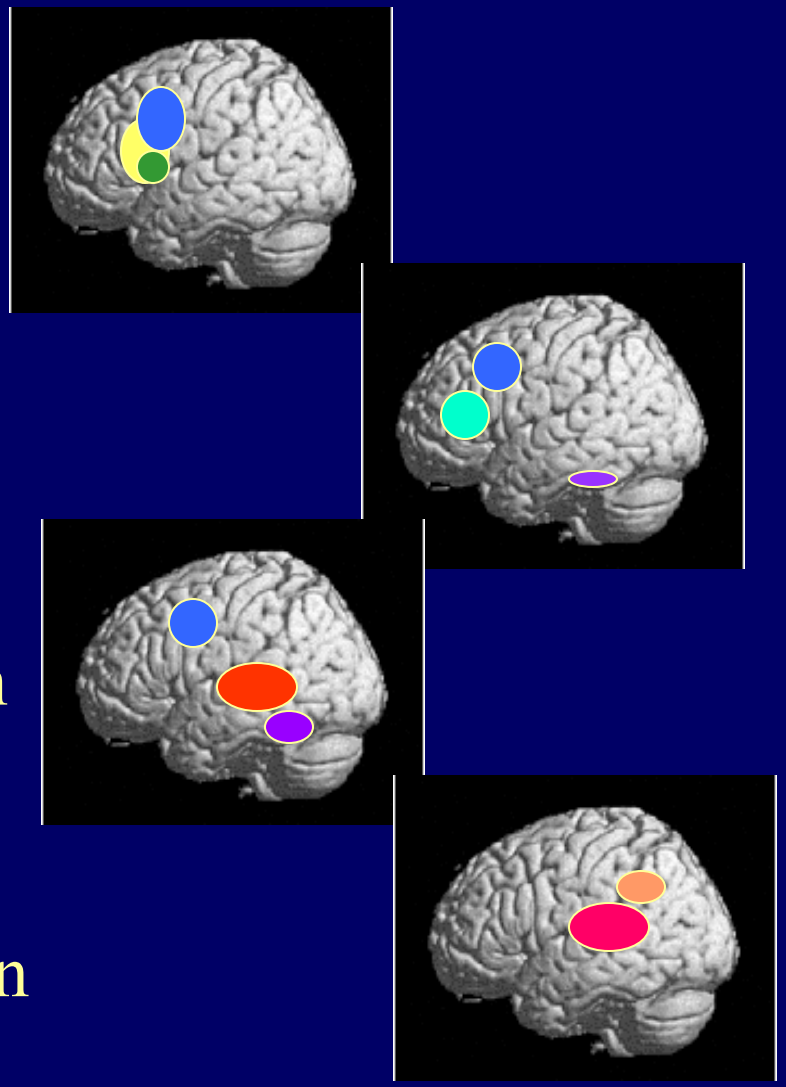
- 30% patients atypical language (75% acquired L handedness)
  - vs 5% R handed controls and 22% L handed controls
- Selection of Tasks
- Determination of Language Dominance
- Location of Language Function
- Multiple Tasks
- Individual Analysis
- Correlation with Electro-cortical stimulation
- Correlation with Wada
- Resection fMRI negative safe
- Resection fMRI positive some peril

fMRI & Language Lateralization

- Agreement with Wada
  - Over 20 studies, more than 400 patients
  - 85-90% complete agreement
  - 10-15% partial disparity
  - Rare absolute discordance (1%)
- Excellent but not complete agreement with electro-cortical stimulation (localization)
- Predicts post operative language capacity
- fMRI better predictor of outcome than IAT

fMRI Language Paradigms

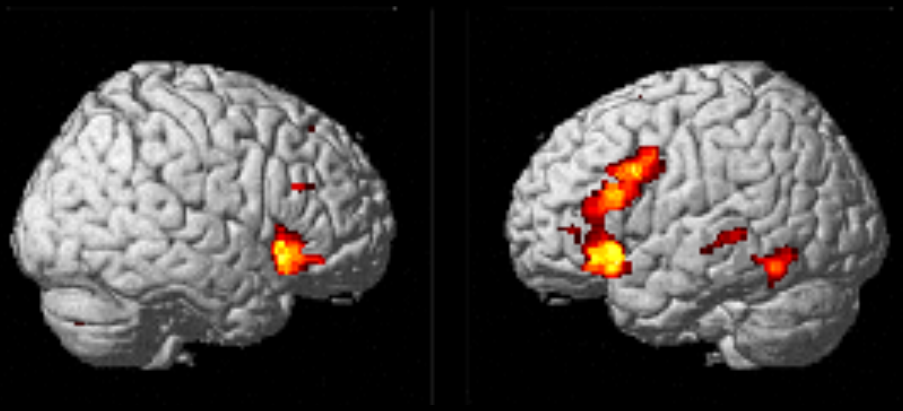
- Verbal Fluency
  - (semantic/ phonologic)
- Semantic Decision
  - (visual/auditory)
- Reading Comprehension
  - (whole language)
- Auditory Comprehension
  - (whole language)



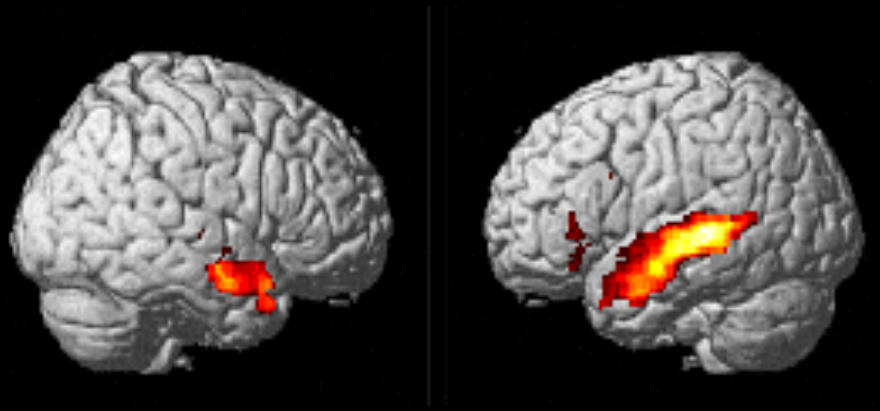
Binder *Neurology* 1996; Benson, *Neurology* 1999; Lehericy *Neurology* 2000; Gaillard *Neurolgy* 2002

fMRI Language Group Maps for Children

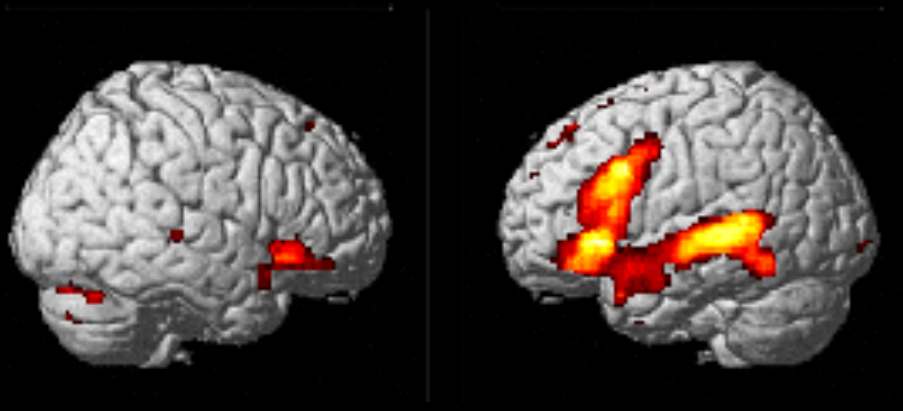
Ages 4-12 years (n=68, p<0.05 corrected)



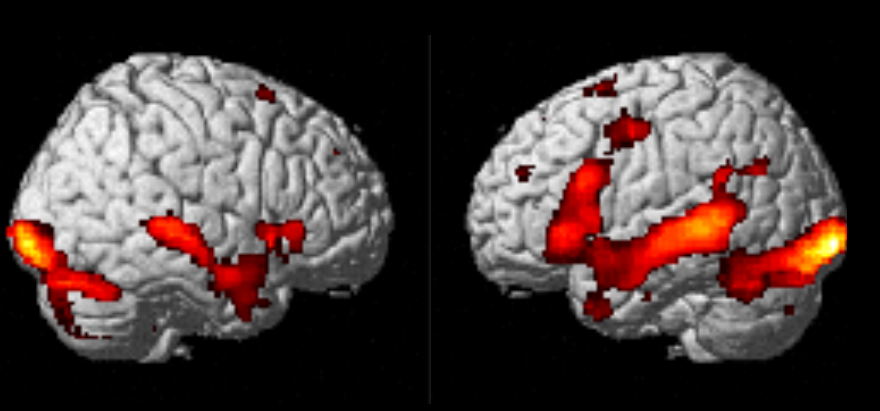
Auditory Category Decision



Listening to Stories

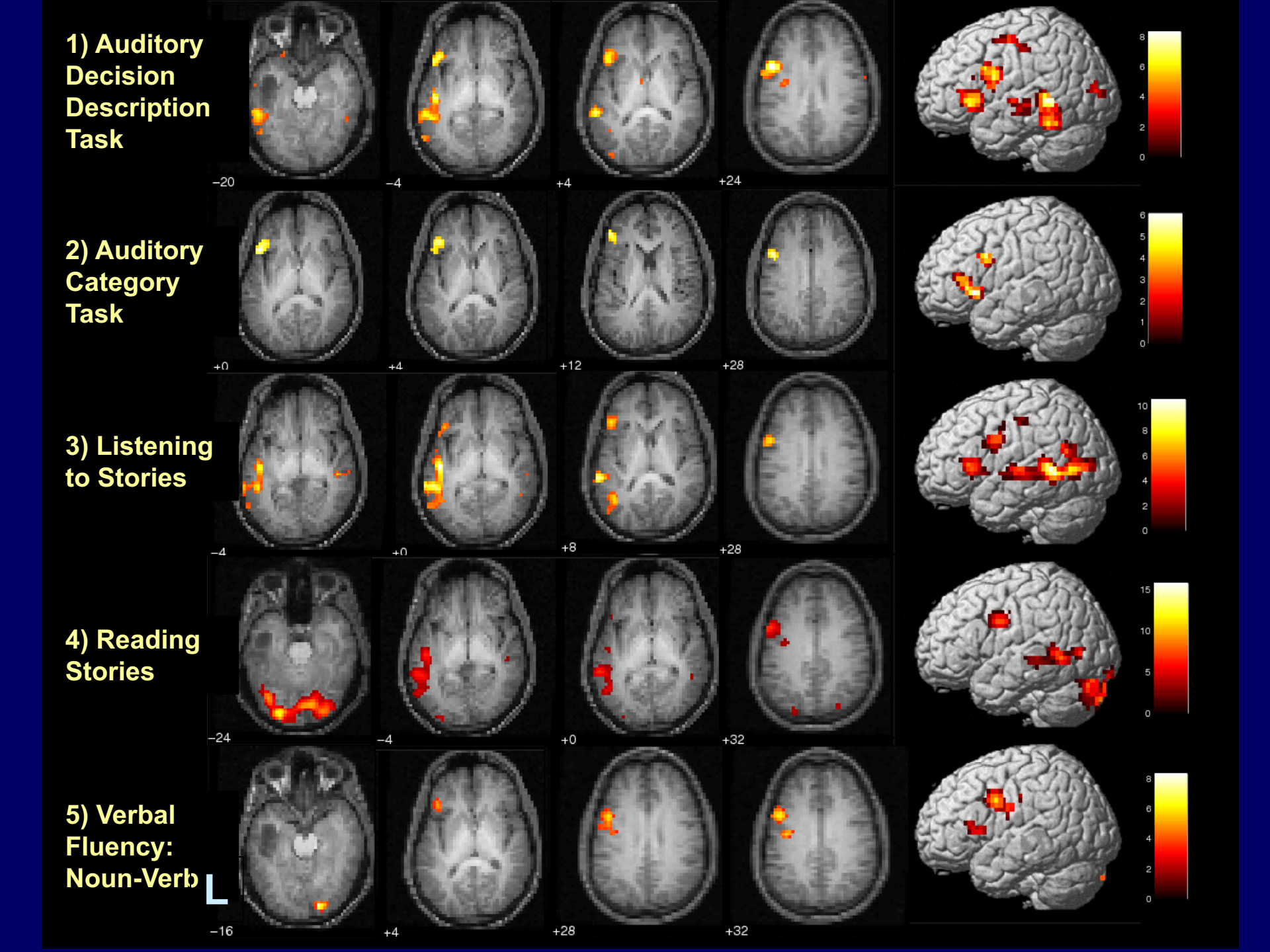


Auditory Description Decision Task

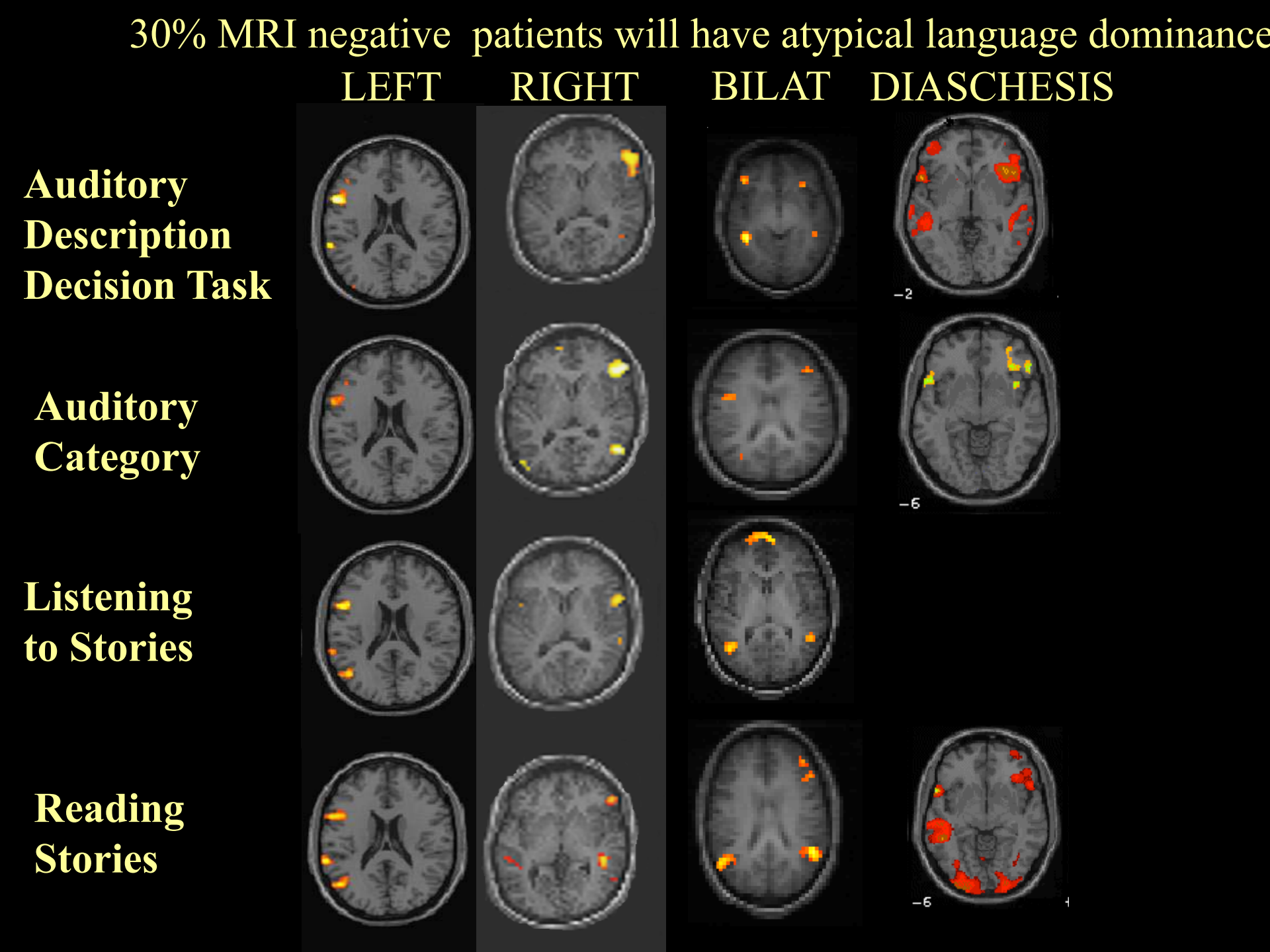


Reading Stories

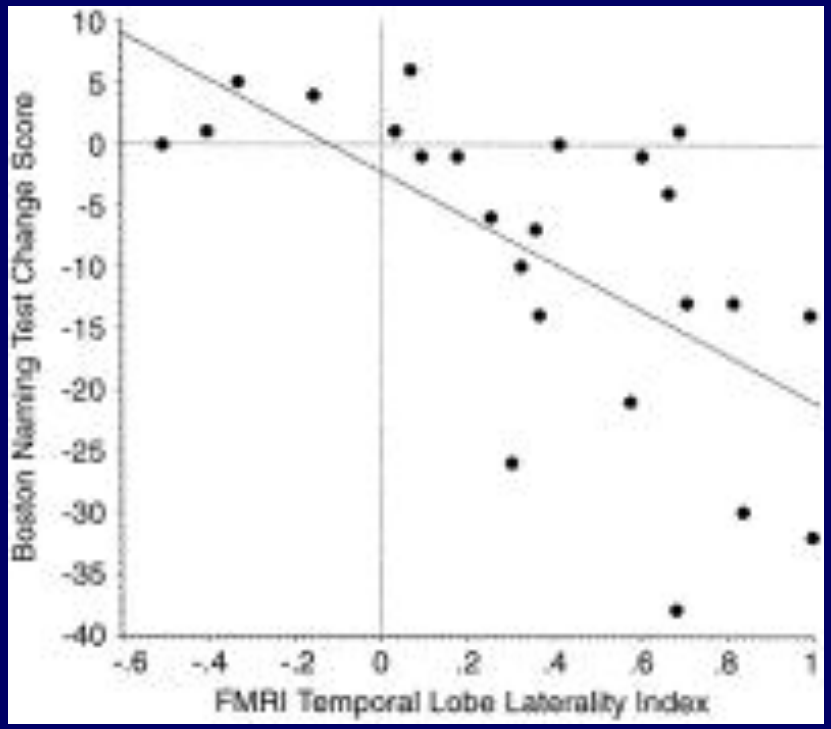
(6-12, n=48)


1) Auditory Decision Description Task
2) Auditory Category Task
3) Listening to Stories
4) Reading Stories
5) Verbal Fluency: Noun-Verb
−20
−4
+4
+24
+0
+4
+12
+28
−4
+0
+8
+28
−24
−4
+0
+32
−16
+4
+28
+32
L

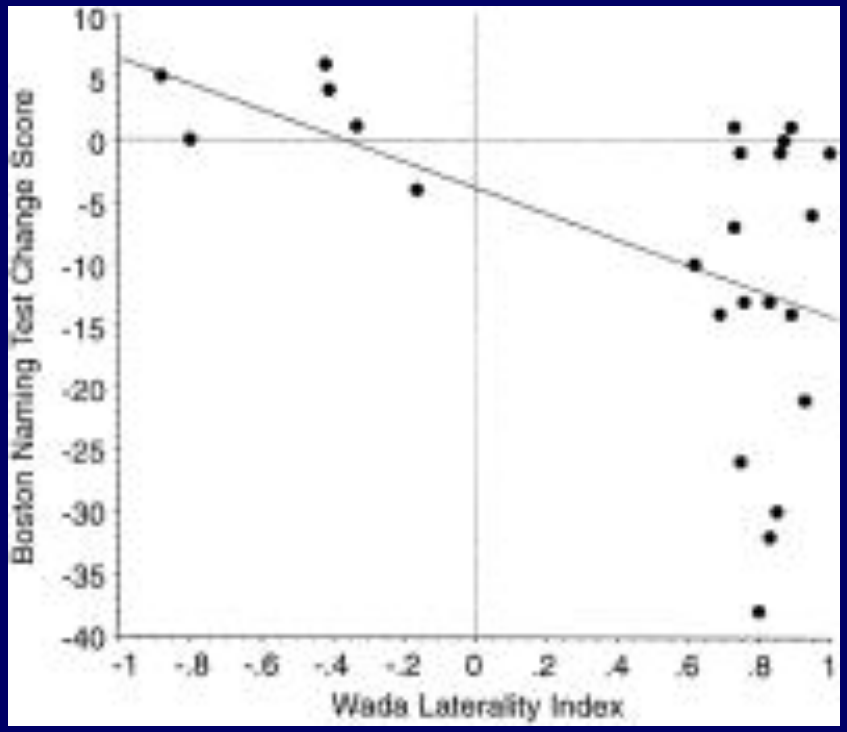
30% MRI negative patients will have atypical language dominance



fMRI Semantic Decision Task Predicts Post-Op Naming



fMRI AI



Wada LI

AI > 0.4 risk of language measure decline

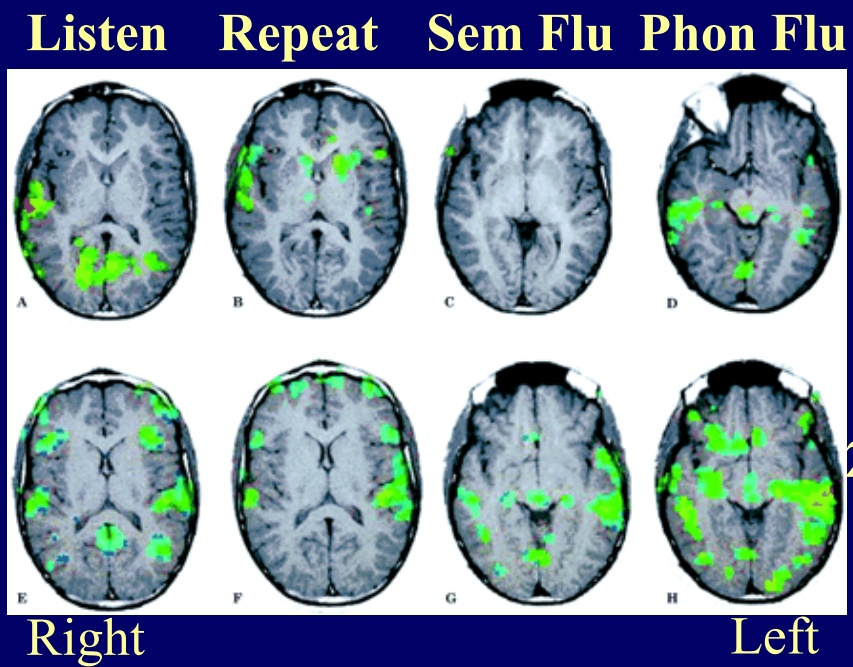
Sabsevitz DS, et al. *Neurology* 2003

fMRI Language

- Activated Areas Involved, **NOT** Critical
- Critical Areas **NOT** always Activated
  - Blood flow response trigger threshold
  - Individual vs. Group analysis
  - Data analysis threshold
- False Lateralization: Homologous non-dominant activation misinterpreted
- Null activation interpreted as no function

Failed fMRI

- Disruption BOLD Signal
  - Glioma, Edema & Mass Effect (Bookheimer et al, 1997)
  - AVM and Vascular Steal (Lehericy et al, 2002)
  - Post-Ictal state (Jayakar et al, 2002)
  - Arterial Stenosis (Rother et al, 2002)



2 Weeks Later

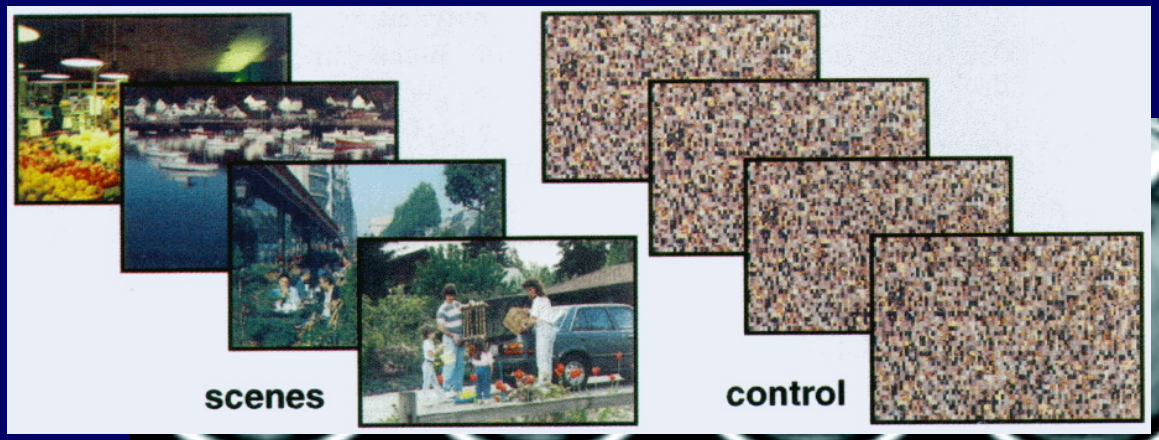
Memory Paradigms: Material Specificity

- Verbal encoding — L>R Activation
- Scene decision or encoding — L=R Activation
- Mental navigation (Roland) — L=R Activation
- Face recognition — R≥L Activation
- Pattern encoding — R>L Activation

- HF and parahippocampal activation
- Functional Adequacy > Functional Reserve

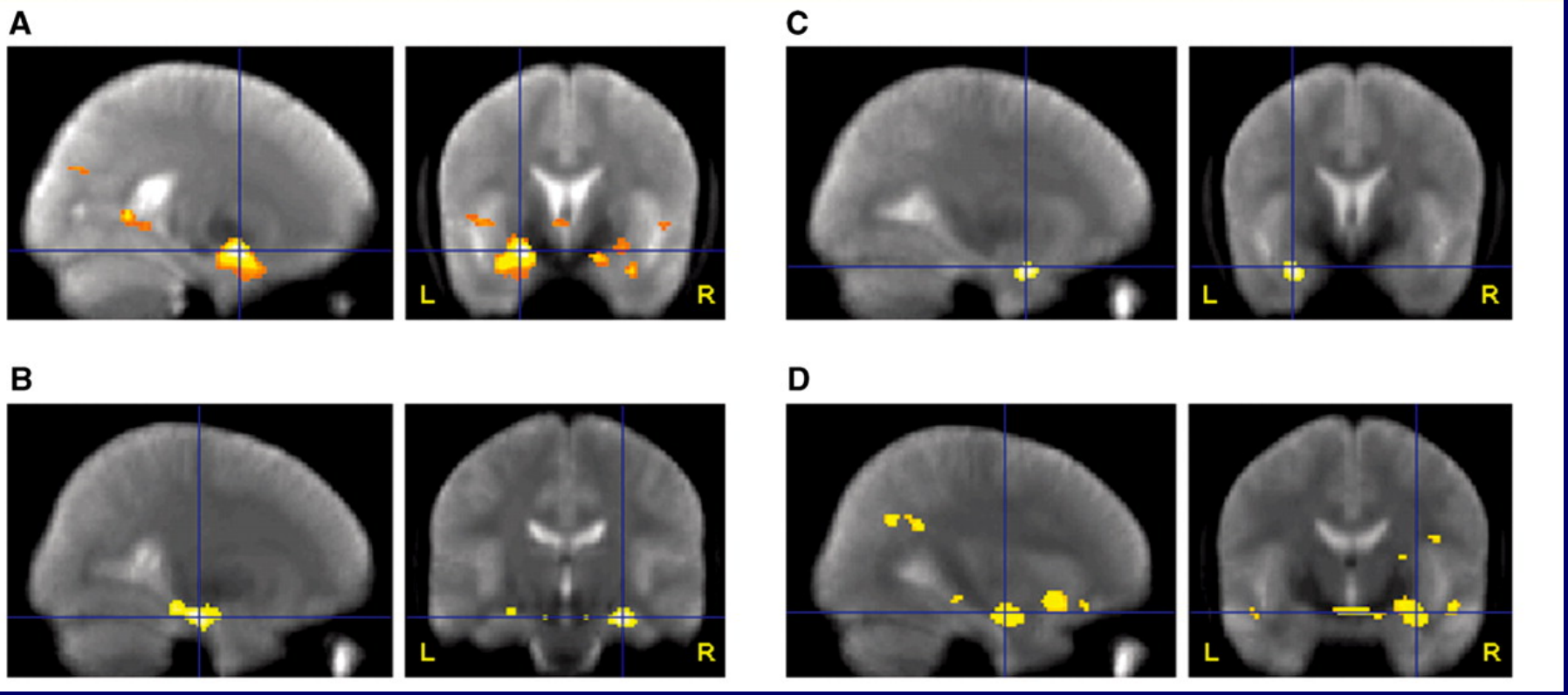
- Activation linked to performance
- Has not predicted risk of amnesia

Picture Encoding



Predicts Post Surgical change in Scene Memory Adequacy not Reserve

Rabin et al *Brain* 2004



Event related, forced encoding, design

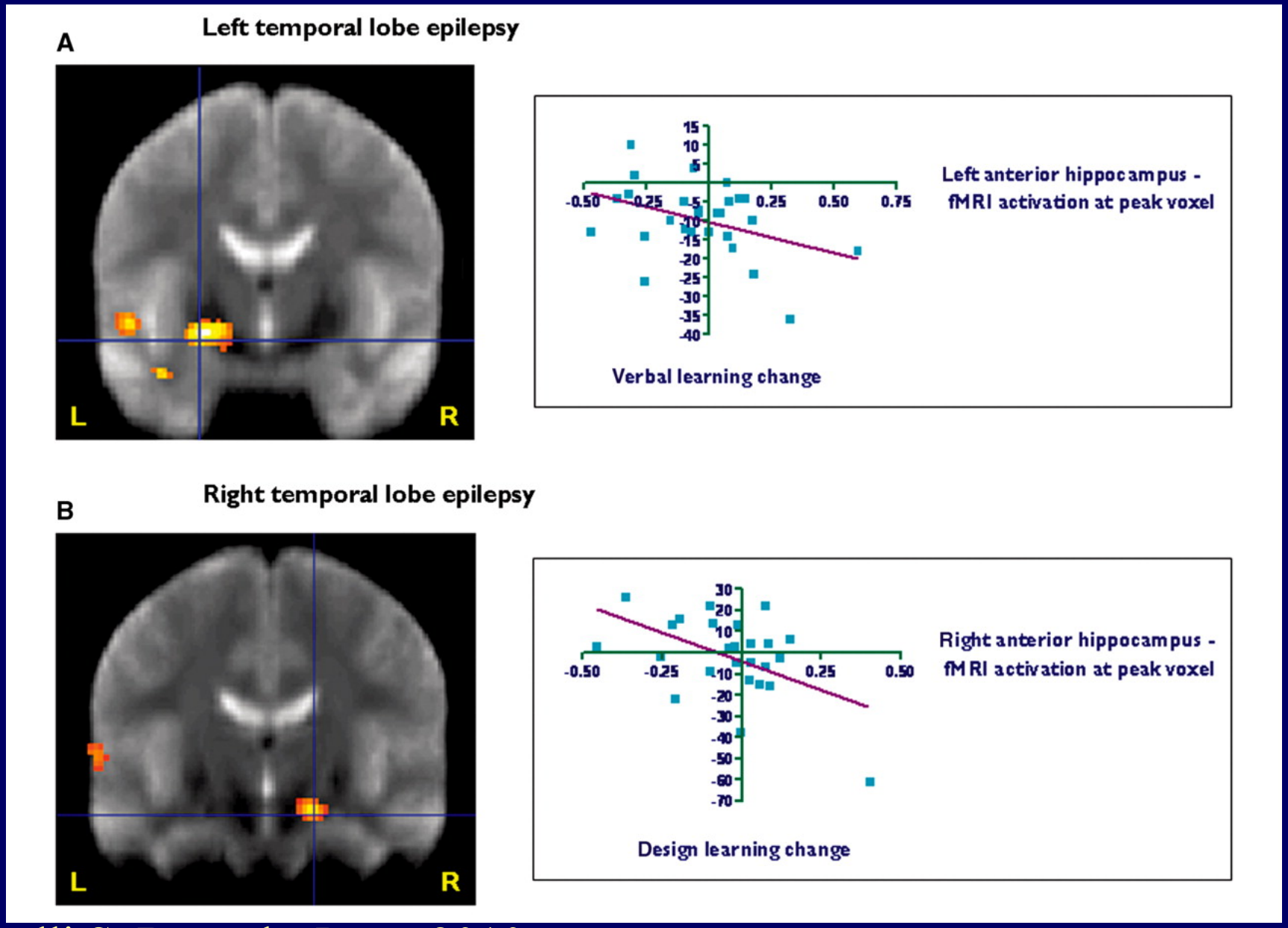
- Verbal encoding
- Face encoding

10 controls; 72 patients (40 left; 68 MTS); 54 resection (29 left)

*Simple Line Picture Encoding little effect

Bonelli S. B. et al., *Brain* 2010

Group Map: HF signal and change in verbal & visual memory

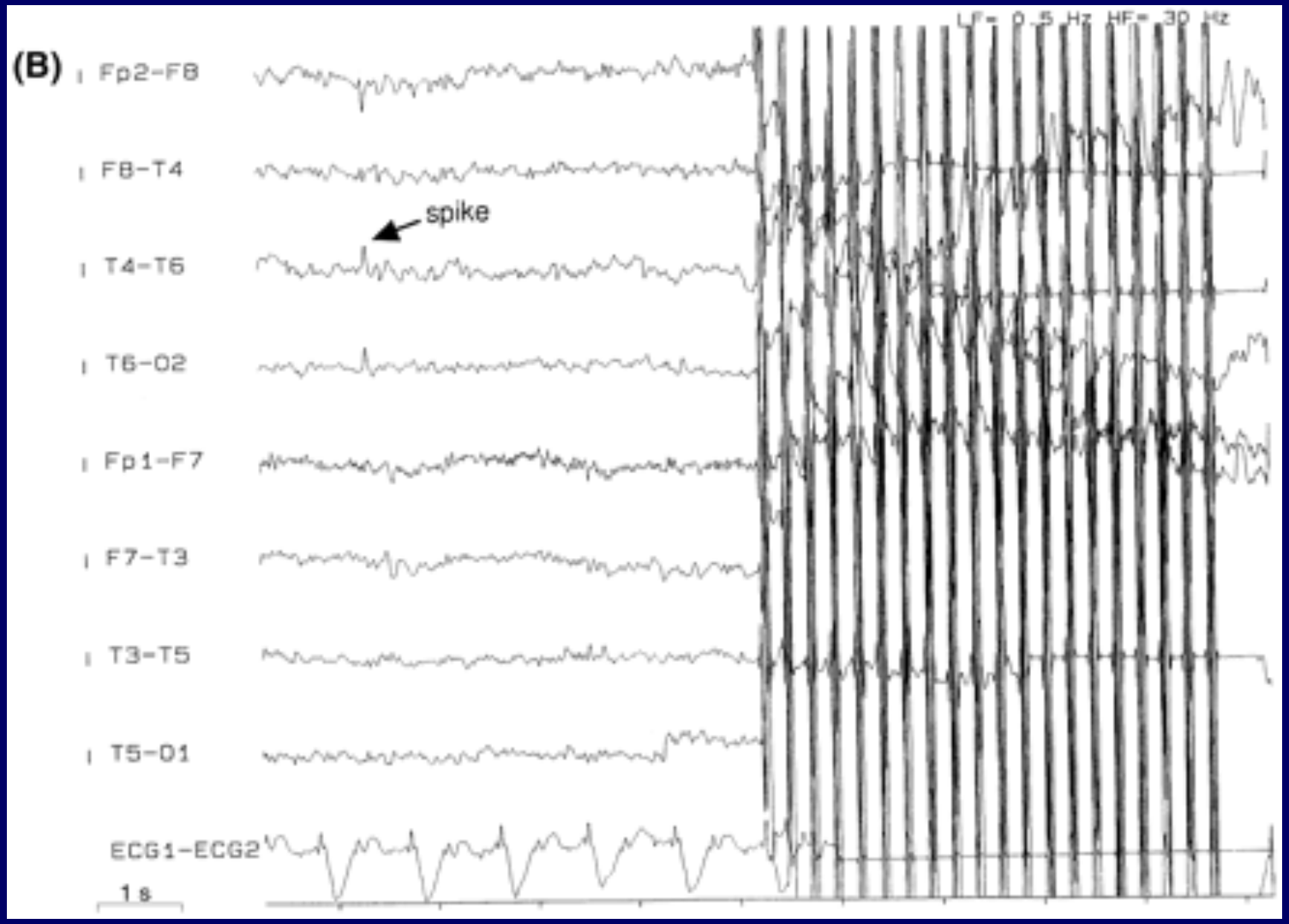


Bonelli S. B. et al., *Brain* 2010

Interictal fMRI

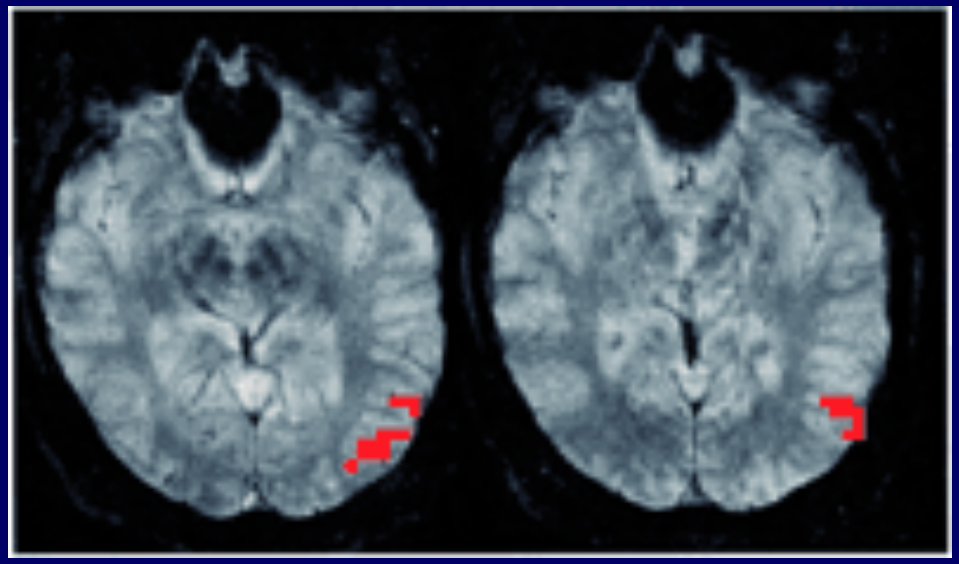
- Event related
  - On line EEG manual fMRI trigger
  - Post hoc analysis with continuous EEG
  - Older literature 50 events (only for patients with frequent spikes)
  - More recent can obtain data from few spikes; may augment by manipulating HDR function to optimize signal
  - ~67 % of patients reliable data
  - Spike or slow wave may be mapped
- Relation to focus uncertain, as in MEG, but good concordance with invasive mapping

EEG Spike Event Related fMRI



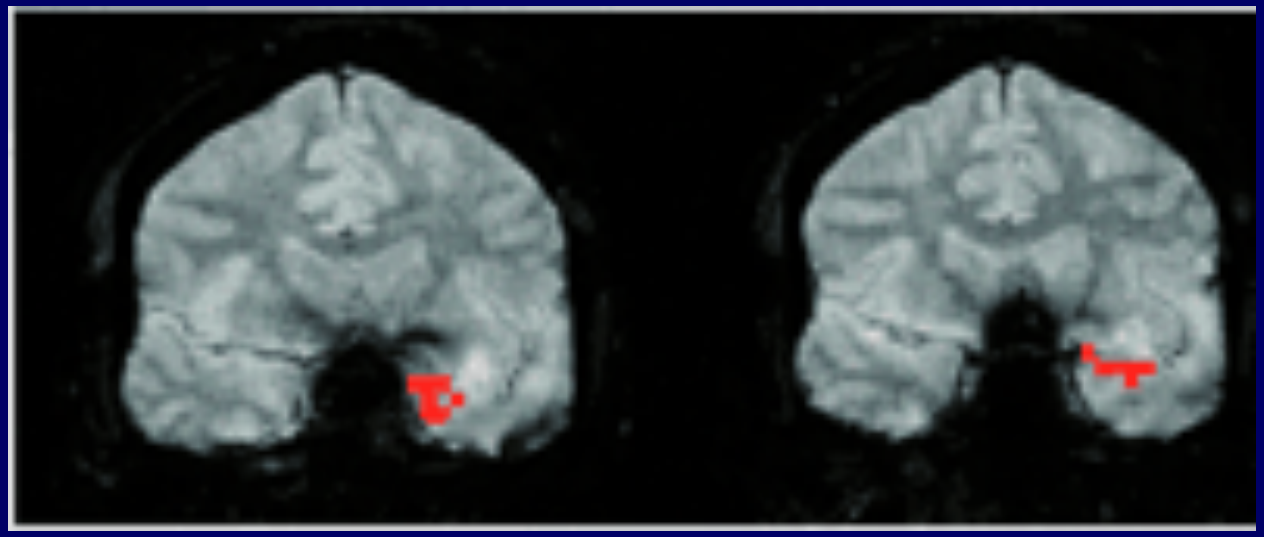
Krakow et al. *Brain* 2000

EEG Spike Event Related fMRI



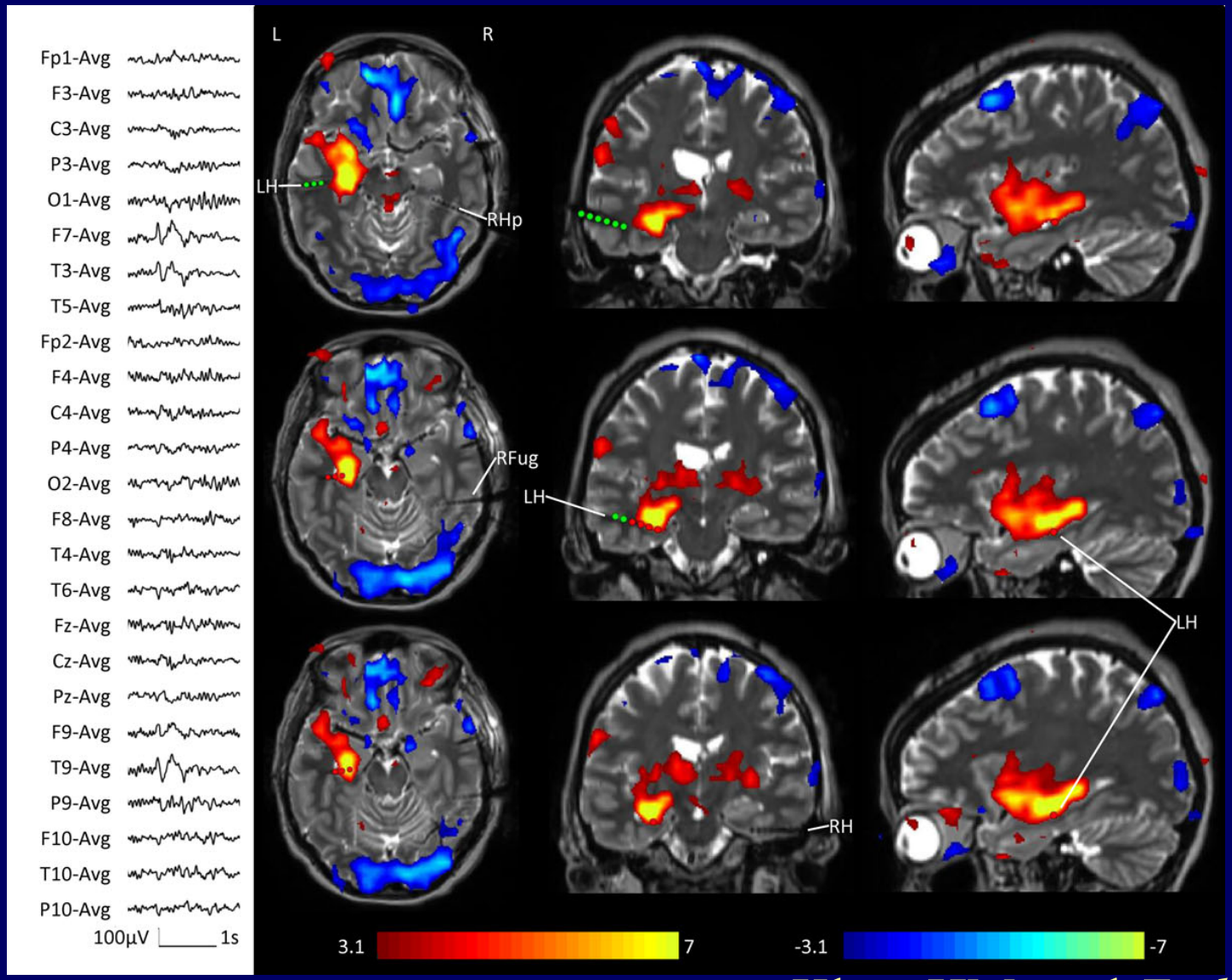
Neocortical focus

Mesial Temporal Focus



Krakow et al. *Brain* 2000

fMRI EEG BOLD response from generator of interictal spike



Khoo HM et al *Epilepsia* 2017

Question 4

- Functional imaging may be used for all of the following except:
- 1. Identifying eloquent cortex
- 2. Source localization
- 3. Identifying co-morbidities
- 4. Predicting outcomes

Functional MRI: Practical Applications for Epilepsy

- Reliable for language lateralization
  - More tasks the beter/ select task to target area of interest
- Agreement w/ invasive methods
- Predicts surgical outcome language and memory

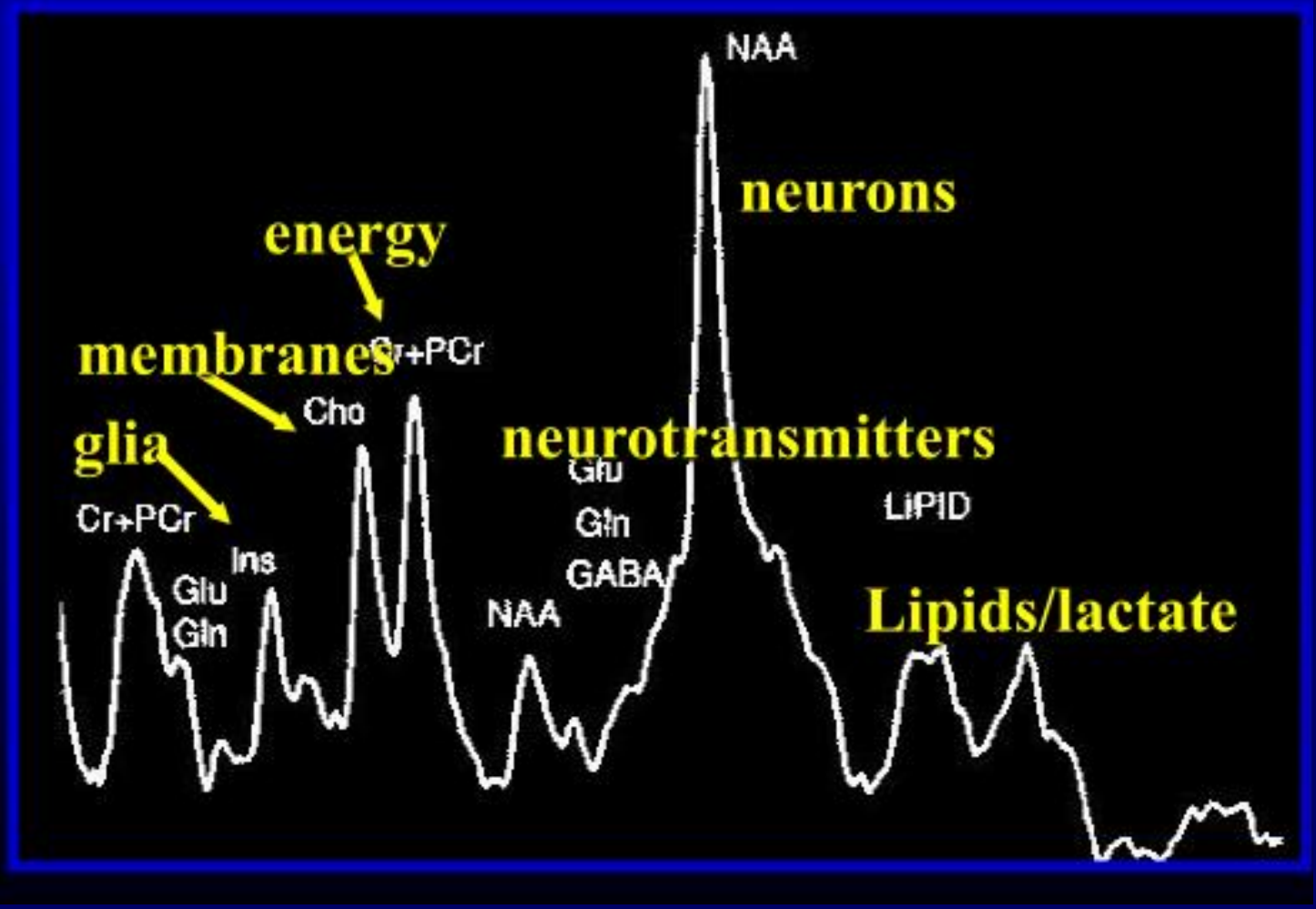
  Guide for motor, sensory, language localization
- Reliable for Hippocampal memory (Untested for predicting amnesia)
- Interictal localization reliable for selected patients
- Ictal localization rare

Functional MRI: Practical Applications in Epilepsy

- Conditions where BOLD disrupted and data falsely lateralizing
- No activation is NON Diagnostic
- Repeat Atypical or Null activation studies: confirm with Wada/Electro-cortical stimulation

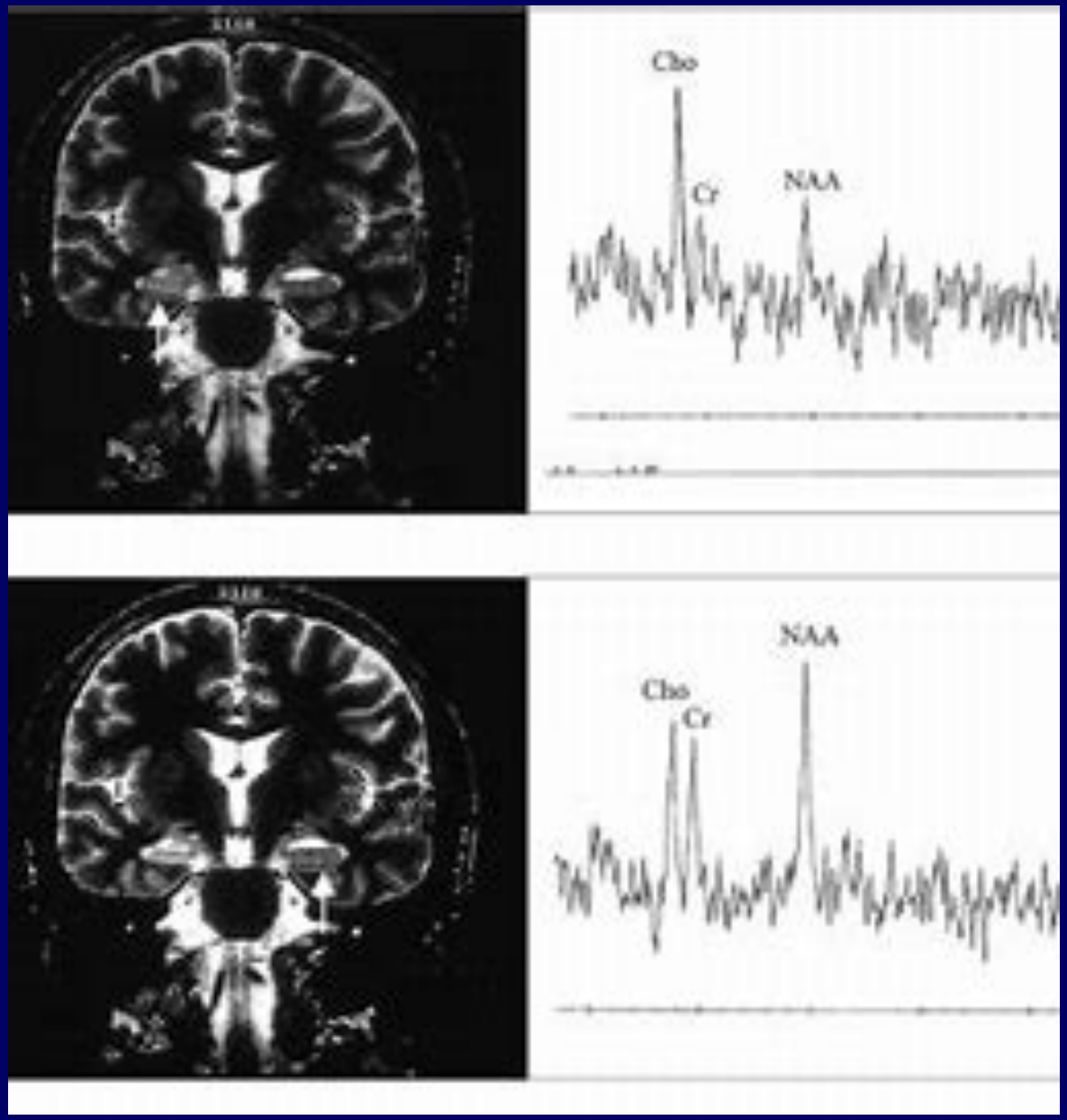
MRS

with water suppression



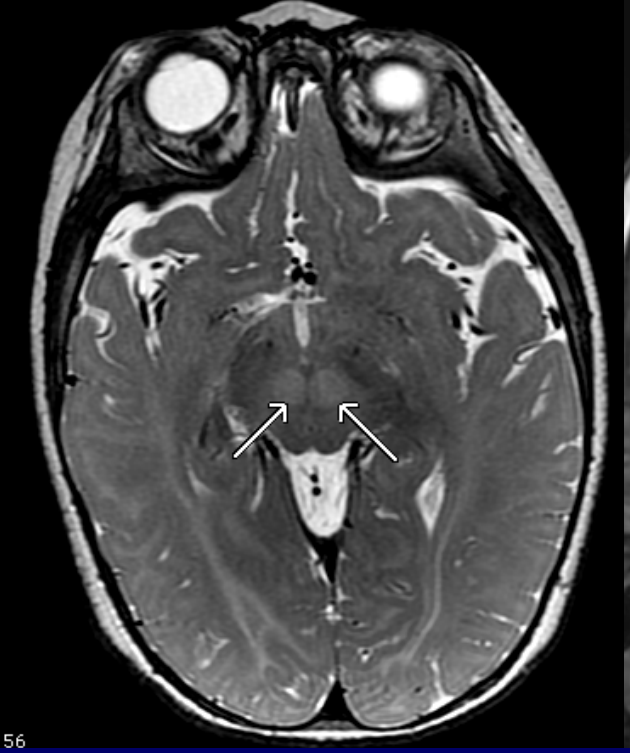
Ratio NAA/Cho: Decreased cell loss/gliosis

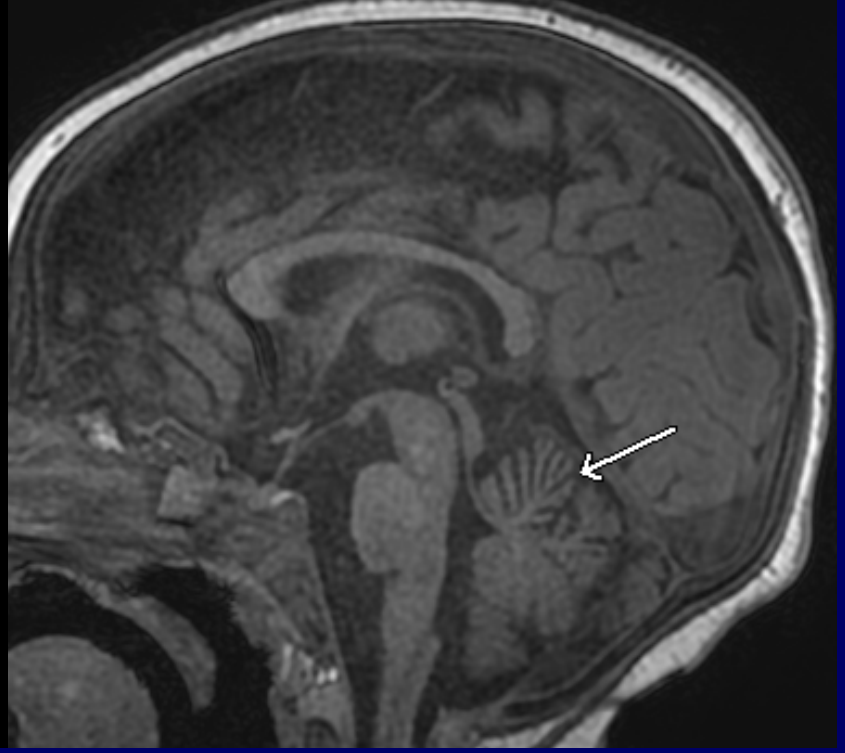
Lactate peak: Anaerobic metabolism (bad)



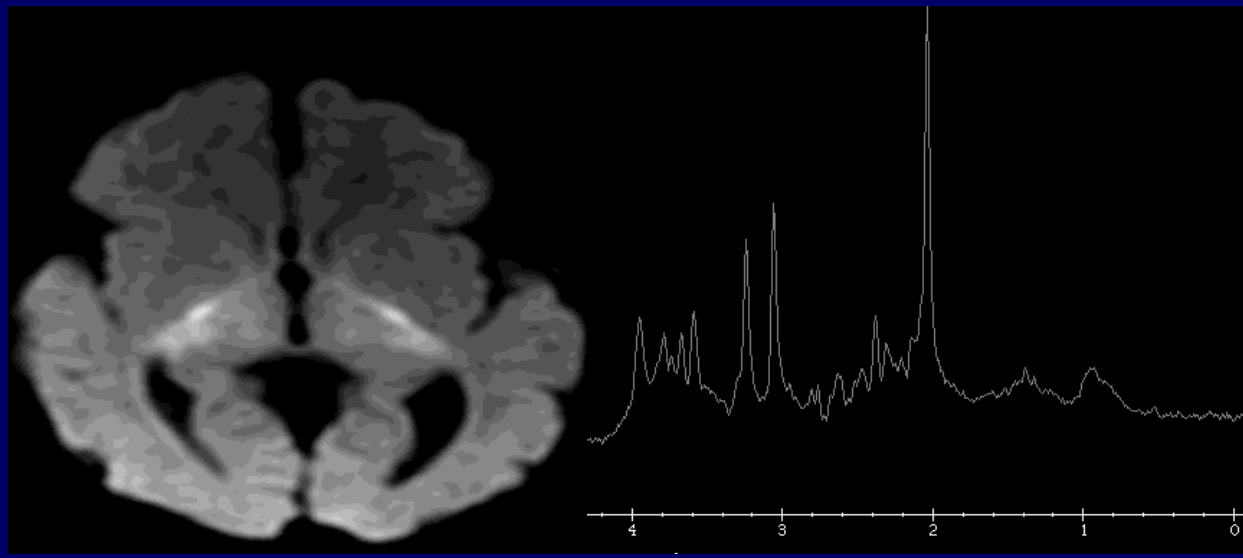
ABnormal
Hippocampus
Mesial Temporal
Sclerosis
Low NAA
High Choline
? Lactate

Normal
Hippocampus



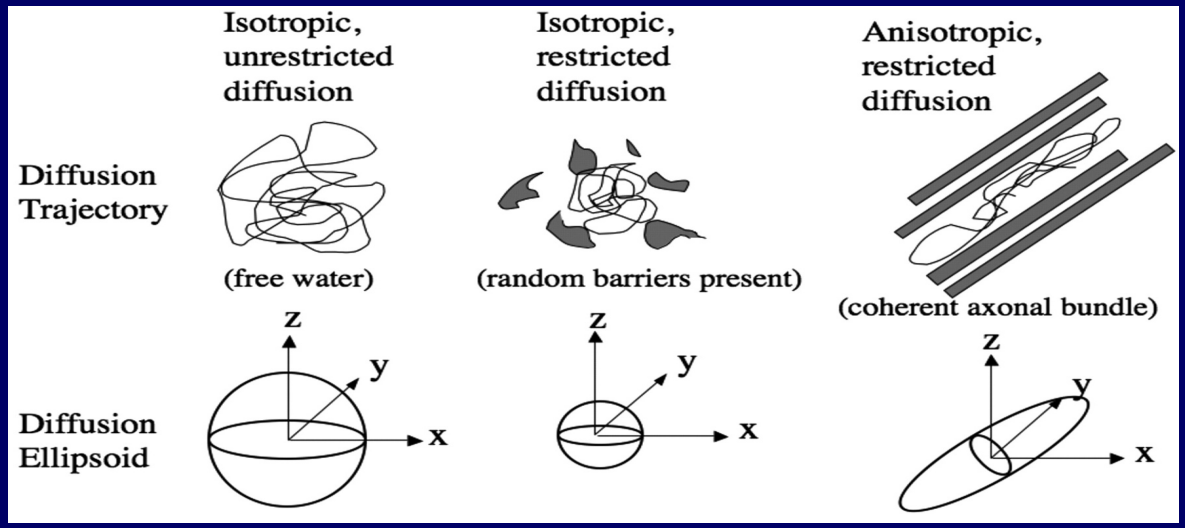


Metabolic Imaging
MRS
Lactate Peak



Diffusion Weighted Imaging

- Diffusability: Distance molecule of water will move
- Fractional Aniosotropy: Directionality of water molecule movement)
  - to identify long white matter tracts that underlie cortical function



CSF

Gray Matter

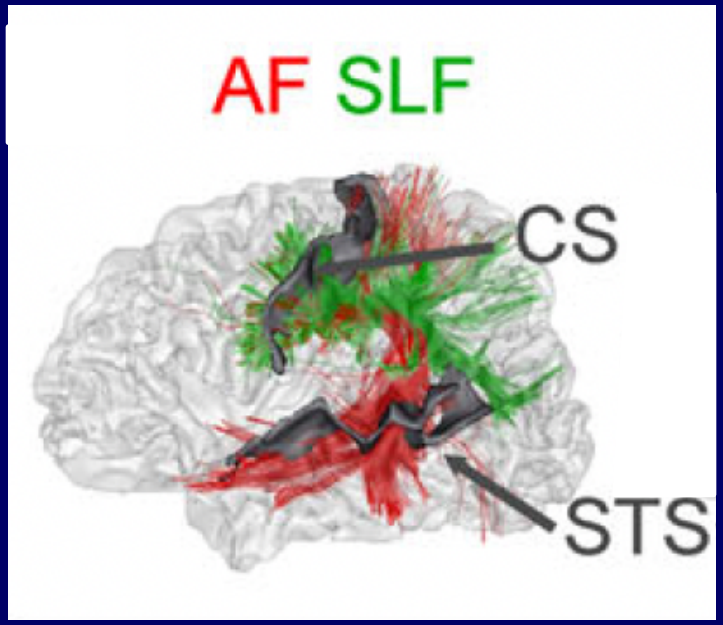
White Matter

Diffusion Weighted Imaging

- To identify perturbations in gray/white matter integrity
  - Fractional Anisotropy (FA) → bundle organization & axonal directionality
  - Mean Diffusivity (MD) → overall density of axonal bundles & brain water content
  - Radial Diffusivity (RD) → myelin content and axonal packing
  - Axial Diffusivity (AD) → axon internal structure and coherence
- To identify long white matter tracts that underlie cortical function
- Seeds
  - fMRI activation
  - Anatomic regions (usually 2)
  - White matter tract strings (mid track)

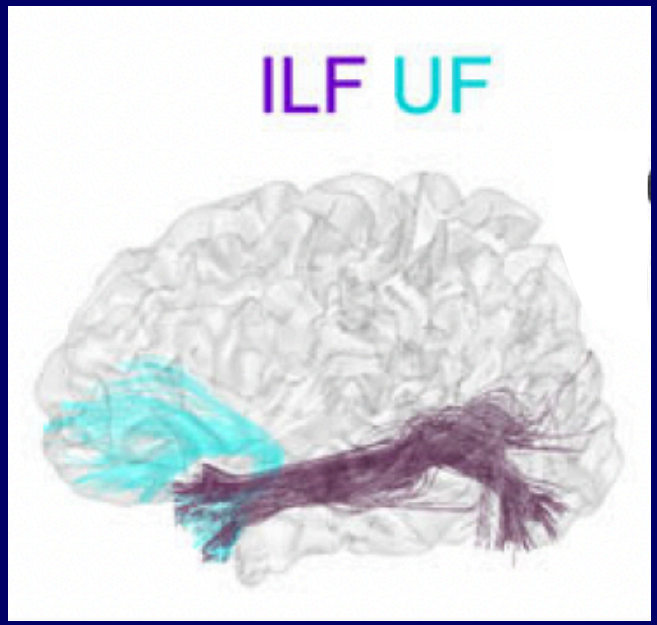
- Motor/Sensory, Language, Visual (Meyer's loop)
- Avoid critical white matter tracts to avoid deficits

White Matter in the Language Network



Dorsal Stream

- Phonological & syntactic processing
- Working Memory
- Auditory-motor integration
- Tracts:
  - Arcuate Fasciculus (AF)
  - Superior Longitudinal Fasciculus (SLF)

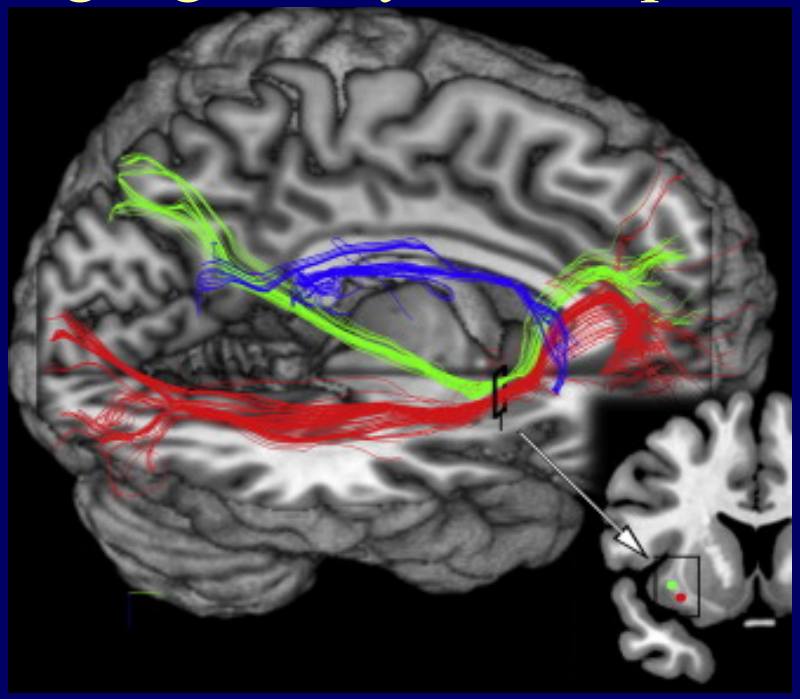


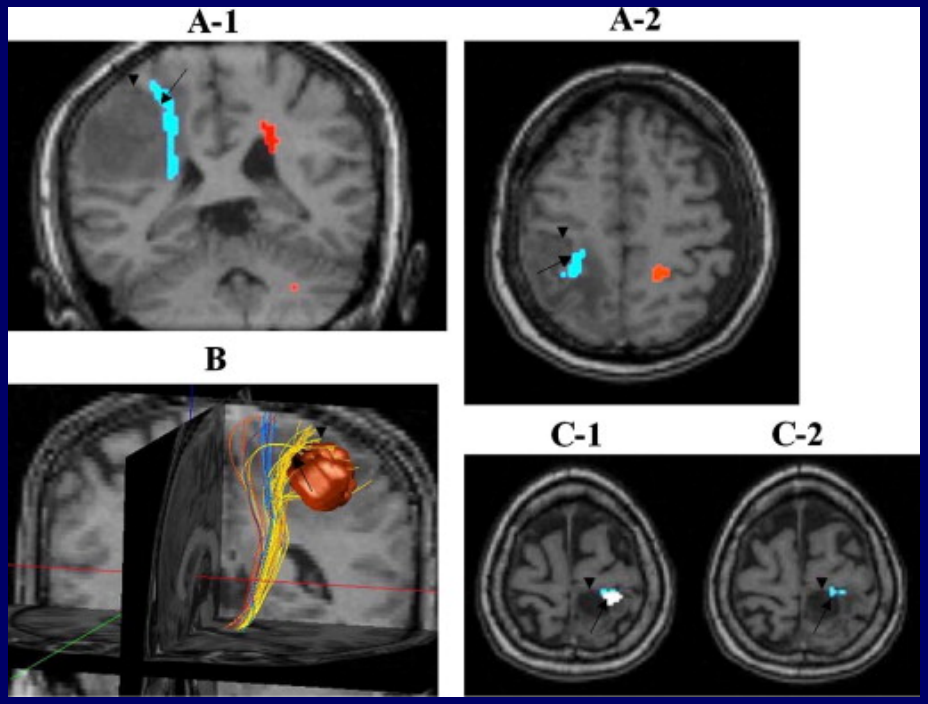
Ventral Stream

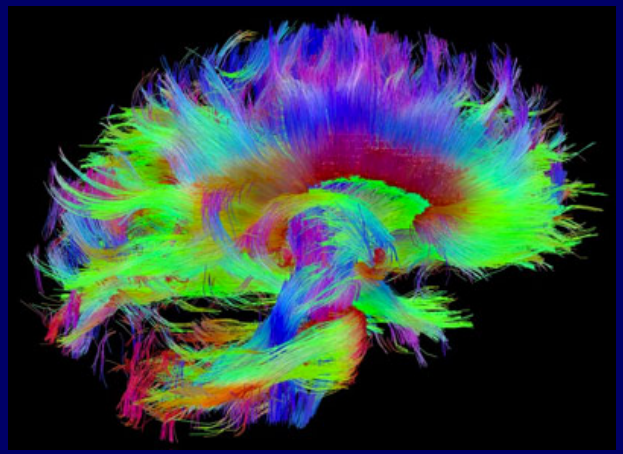
- Lexical-semantic processing
- Mapping auditory speech sounds to meaning
- Tracts:
  - Uncinate Fasciculus (UF)
  - Inferior Frontal Occipital Fasciculus (IFOF)
  - Extreme Capsule (EmC)

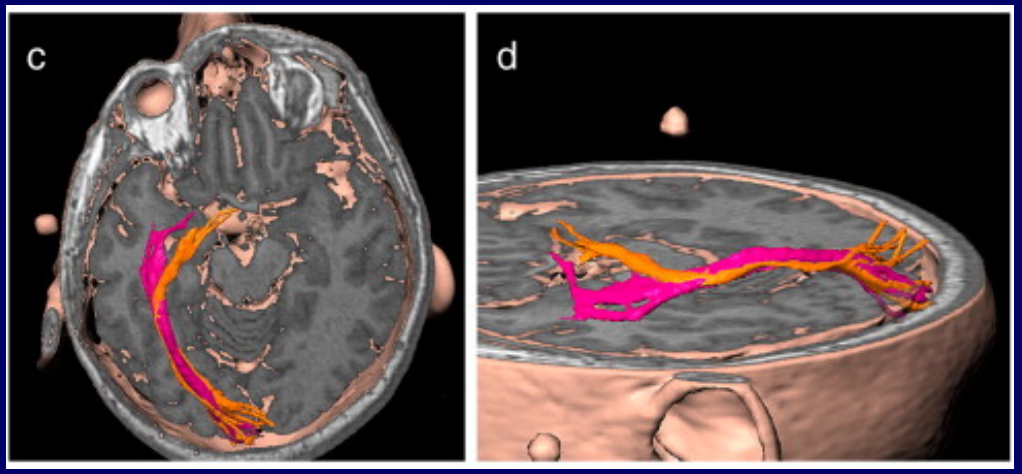
Dubois et al, 2016

DWI Tractography: White Matter, Anatomic, Functional Seed Language, Meyers Loop, Motor Tracks





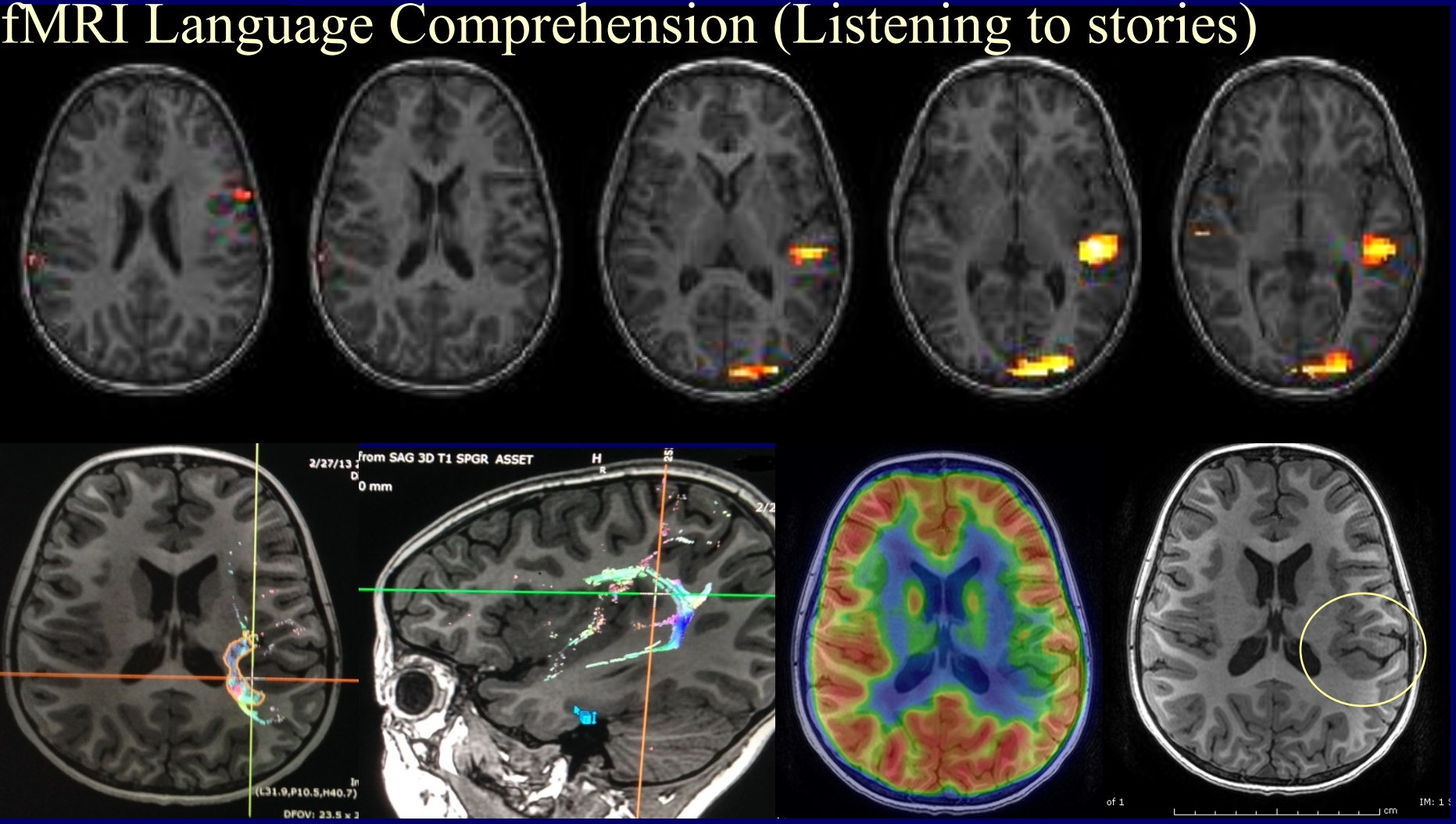




Shinoura, *J Clin Neurosci* 2009; Axer, *Brain & Lang* 2012, Chen, *NeuroImage* 2009

Multi-Modal Imaging

fMRI Language Comprehension (Listening to stories)



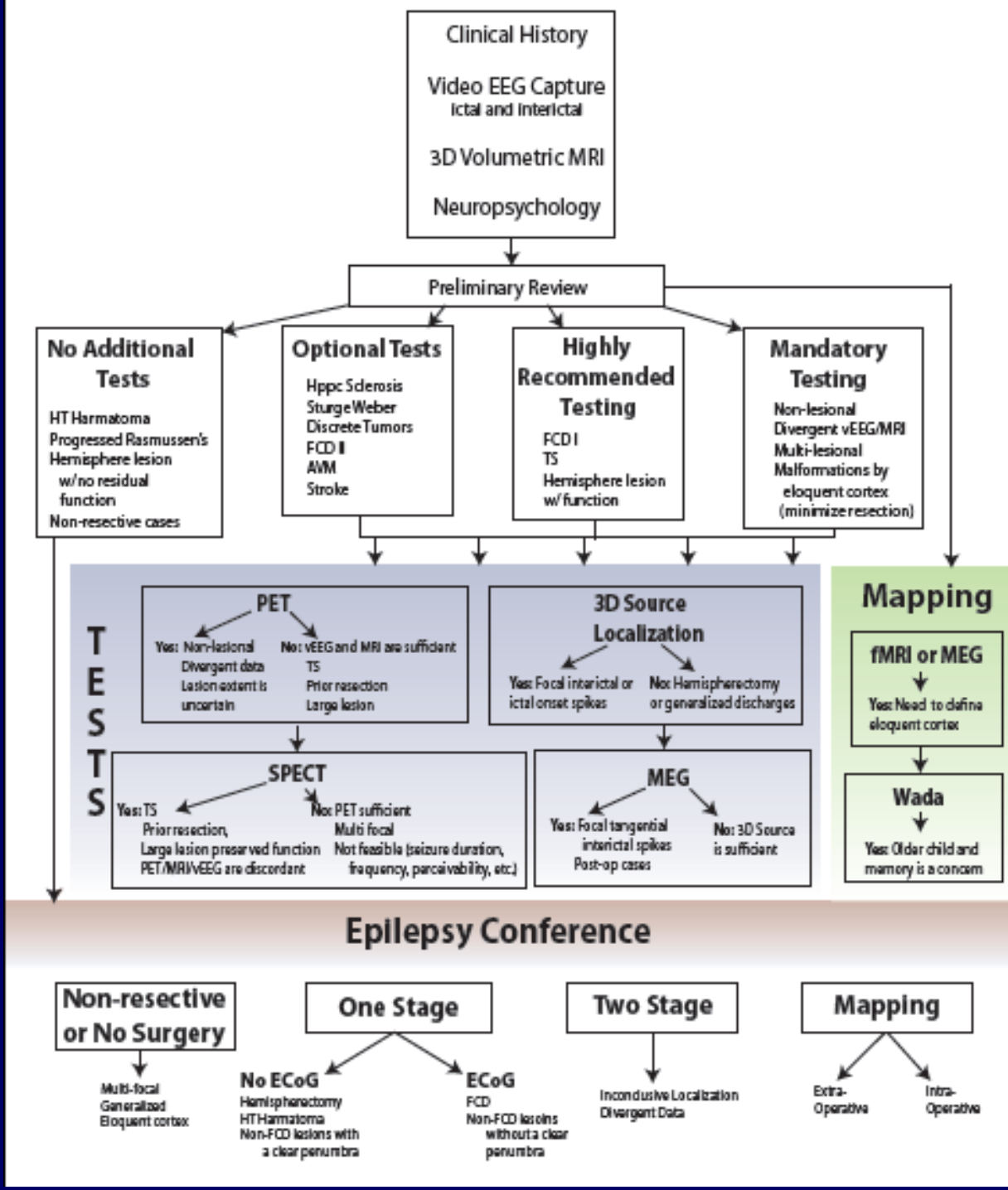
DTI Tractography
Arcuate Fasciculus

FDG-PET

MRI

Epilepsy Surgery Evaluation Protocol

ILAE



Jayakar P. *Epilepsia* 2014

Conclusions: Functional Imaging

- MRI MRI MRI
- PET (interictal) and SPECT (ictal subtraction) to identify the seizure focus when MRI normal; comparable in utility
- fMRI to identify eloquent cortical areas to spare during epilepsy surgery
- fMRI may be used for source localization
- DWI to identify white matter tracts to minimize neurological deficits
- MRS: neuronal integrity/altered metalabomics

Question 5

- A good rule to follow when removing epileptic tissue in normal appearing brain from your hospital CEO family member when electrocaudery is broken, massive bleeding is occurring, & the blood pressure is dropping is
- 1. Always Panic
- 2. Never Panic
- 3. Panic only when safe to do so