Refractory Epilepsy:
Clinical Semiology, Neuropsychological, and Neurobehavioral Profiles

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Overview

I. Epilepsy:
   - Definition and differential diagnosis
   - Classification of seizures

II. Localization-related epilepsies
   - Clinical semiology
   - Neuropsychological /neurobehavioral findings
     - Temporal Lobe Epilepsy
     - Frontal Lobe Epilepsy
     - Non-epileptic seizures

III. Case example/Patient Interview (M.L.)

Seizures vs. Epilepsy?

Seizures

- Definition: the clinical manifestation of an abnormal and excessive excitation of a population of cortical neurons
- Incidence: approximately 1-2% of population
- Lifetime prevalence: 10-15% (1/3 benign febrile convulsions)

Epilepsy

- Definition**:** a tendency toward recurrent seizures **unprovoked** by systemic or neurologic insults
- Prevalence: 1% of population
- 20-30% of cases are medically refractory

Seizure vs Epilepsy

Seizures

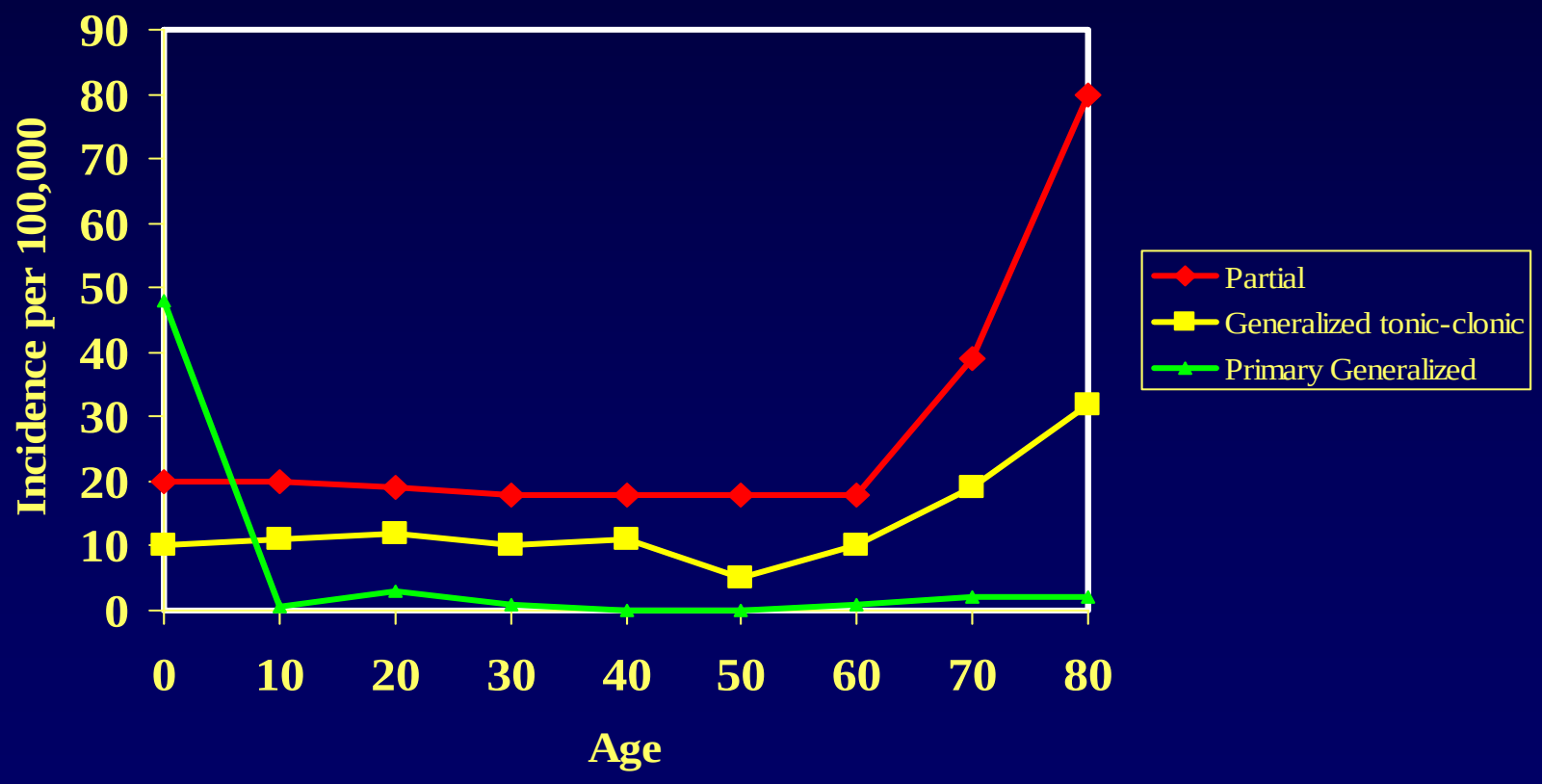
- Nonepileptic
  - Cardiovascular
  - Drug related
  - Syncopal
  - Metabolic (glucose, Na, Ca, Mg)
  - Toxic (drugs, poisons)
  - Poison
  - Infectious
  - Febrile convulsions
  - Pseudoseizures
  - Alcohol/drug withdrawal
  - Substance abuse
  - Psychiatric disorders
  - Sleep disorders (cataplexy)
- Epilepsy (recurrent seizures)
  - Idiopathic (primary)
  - Symptomatic

Types of Seizures

- Primary Generalized Seizures
  - Absence
  - Myoclonic (brief, symmetric jerks)
  - Atonic (“drop attack”; sudden loss of tone)
  - Clonic
  - Tonic-Clonic (“grand mal”)
- Partial Seizures
  - Simple partial (“focal motor or sensory”)
  - Complex partial
  - Secondary generalized seizures

Epidemiology of Seizures and Epilepsy

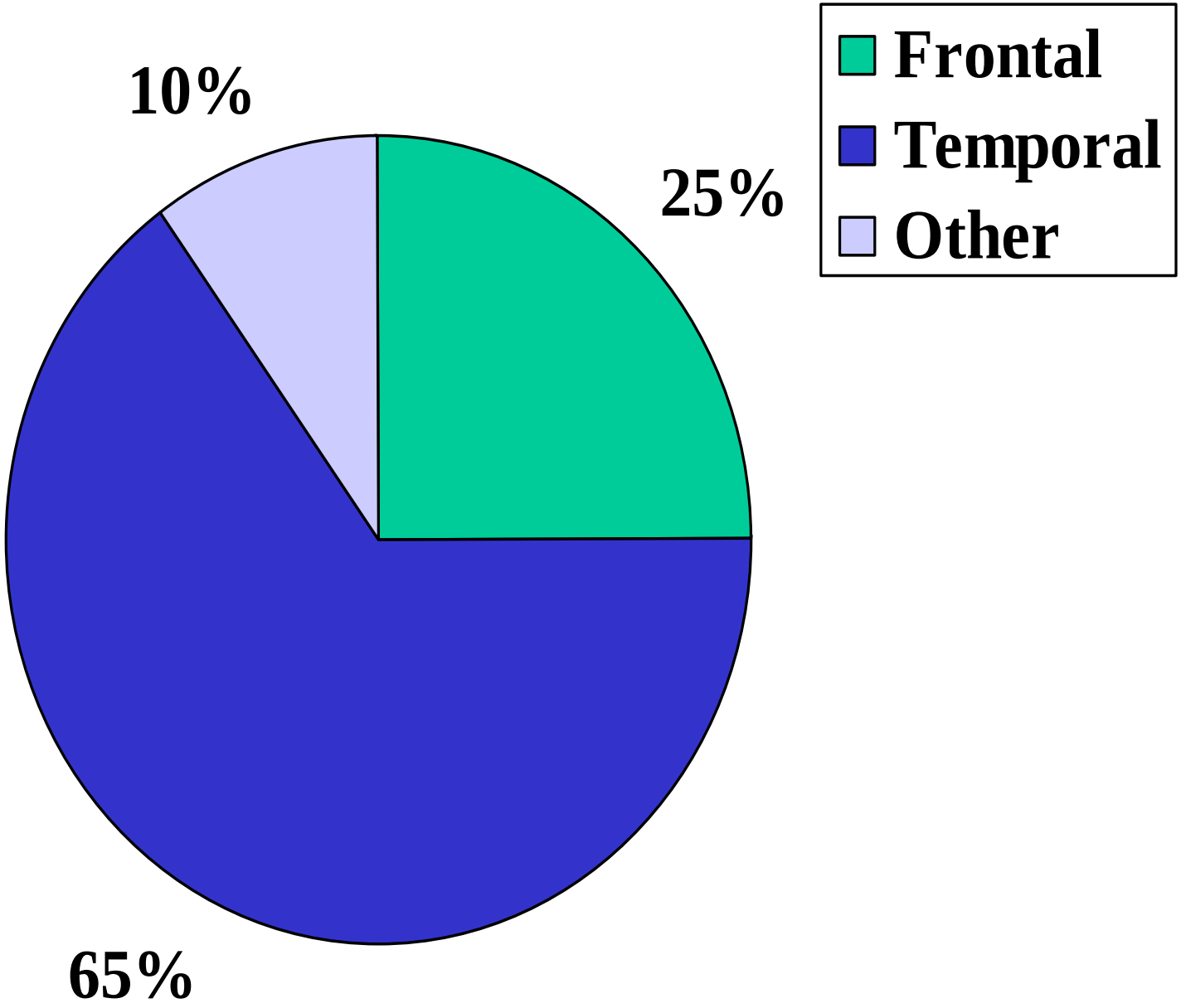
Epilepsy: Incidence Rates by Seizure Type*



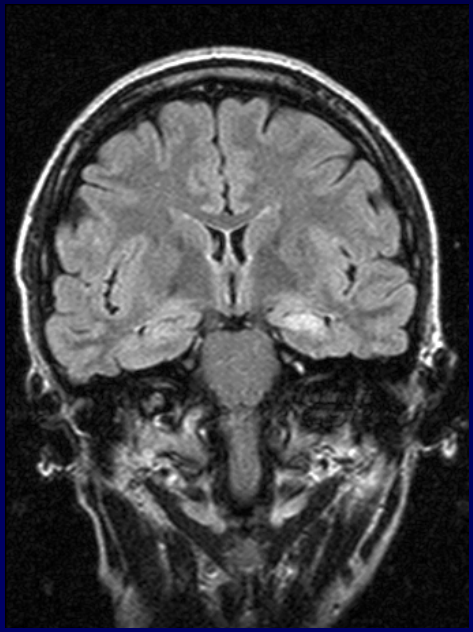
*Data from Rochester, Minn (1935-1979). Adapted with permission from Annegers JF.

In: *The Treatment of Epilepsy: Principles and Practice.* 2nd ed. Baltimore, Md: Williams & Wilkins; 1997:165-172.

Localization of seizure onset (percentage)



Temporal Lobe Epilepsy



Mesial temporal sclerosis

Temporal Lobe Epilepsy : clinical semiology

- Most common type/location (@60-70 ref. cases)
- Arise from hippocampus and other medial temporal structures
- Classic presentation
  - Auras (déjà vu, epigastric sensation, fear)
    - Thought to arise from amygdala and insular cortex
  - Unilateral automatisms / head version
  - Contralateral posturing
  - Brief ictal event (1-2 minutes) or secondary generalization
  - Impaired consciousness/ long postictal period (amnesia, aphasia, disorientation, fatigue, etc.)

Temporal Lobe Epilepsy : history

- Occurrence of febrile convulsions or injury

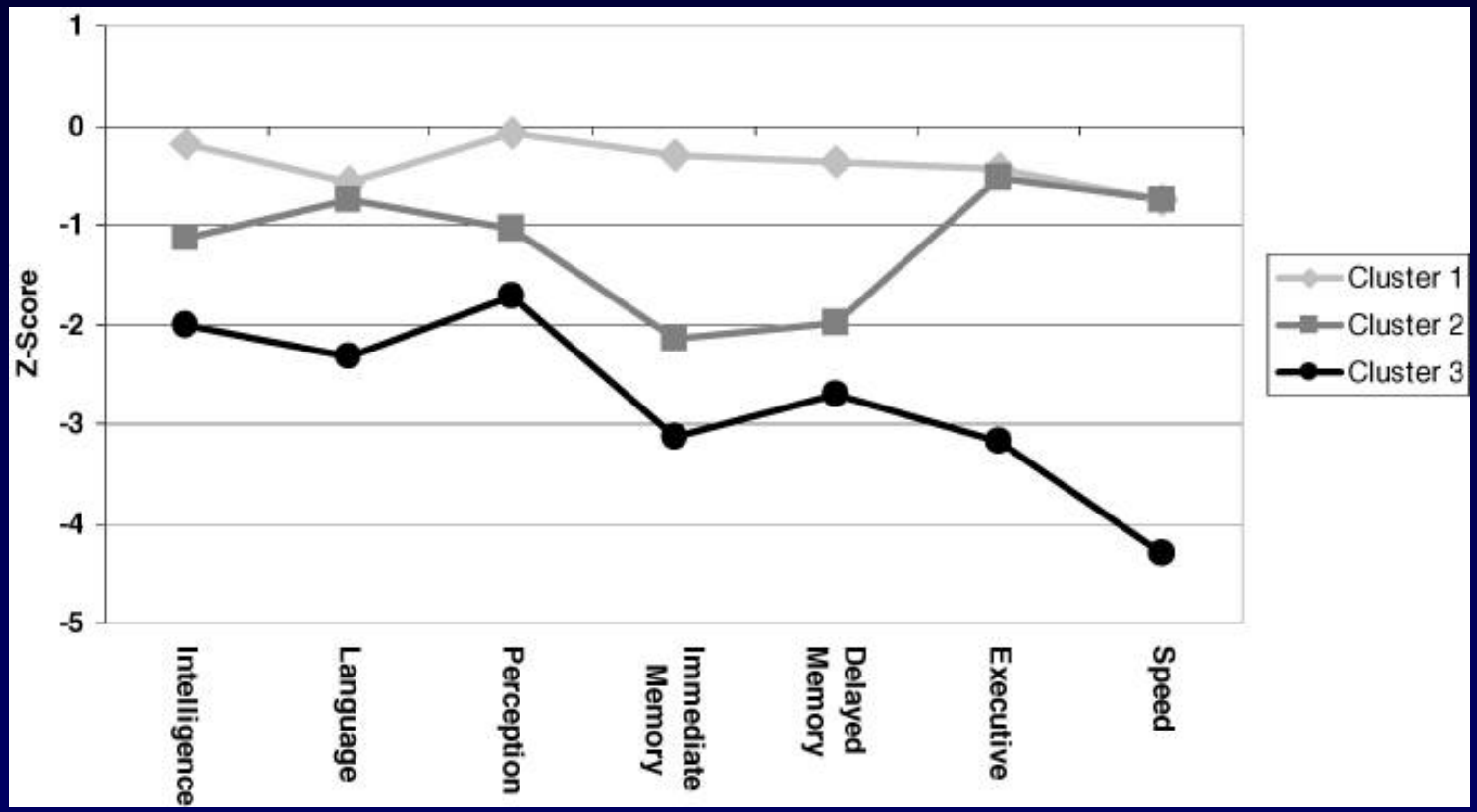
< 5 years of age

- Family history of seizure disorder
- Seizure disorder begins in first decade or adolescence
- Highly refractory to medications
- Interictal behavioral disturbance (depression)

Temporal Lobe Epilepsy: cognition

- Memory impairment
  - Verbal impaired with left TLE
  - Visual impaired with right TLE
  - **depends on the degree of MTS
- Language impairment
  - naming, word finding, comprehension
  - Related to extra-hippocampal pathology?
- Executive dysfunction
  - Propagation of seizures to frontal areas
  - Lack of specificity of neuropsych measures
  - Chronic TLE more impaired overall/developmental abnormalities

TLE subtypes?

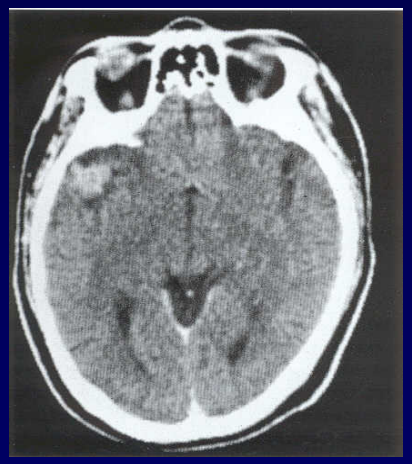


Cluster 1: **Minimally impaired (47%)** -- mildly impaired language, memory and executive skills
Cluster 2: **Predominantly memory impaired (27%):** marked memory impairment; mild otherwise
Cluster 3: **Generalized impairment (29%):** global impairment; especially in speed and executive dys.

Temporal Lobe Epilepsy: behavior

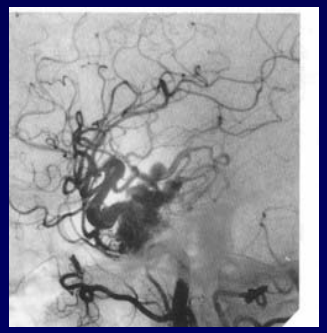
- Depression & Anxiety
  - Reactive or endogenous?
- Psychosis?
  - Careful attention to symptoms!
  - Medication-induced?
- “TLE personality”
  - Obsessionalism
  - Religious and philosophical interests; circumstantial thought
  - Interpersonal “viscosity”
  - Impulsivity
  - Hypergraphia
  - Hyposexuality and/or sexual deviations
  - **Highly controversial**

Frontal Lobe Epilepsy



Ganglioglioma

Cortical dysplasia



Venous angioma

AVM

Frontal Lobe Epilepsy: clinical semiology

- 2nd most common location of seizures (25-30%)
- Often misdiagnosed as pseudoseizures
  - Normal/inconclusive EEGs
  - Motor/psychiatric manifestations of seizures
    - Hypermotor activity, brief in duration
    - Only mildly impaired consciousness / rapid recovery
    - Often nocturnal / fencer's posture
- Poorer seizure and cognitive outcome after surgery relative to temporal lobe epilepsy (TLE)

Frontal Lobe Epilepsy: cognition

- Executive Dysfunction
  - Poor cognitive flexibility, verbal and nonverbal fluency, planning, concept formation, abstract reasoning, cognitive inhibition
- Working memory impairment
- Word retrieval/naming problems
- Poor organization and retrieval of information
- Some material-specificity, but not as striking as TLE

Location of FLE and ictal features

• Motor area	-1:1 manifestation with motor homonculus
• SMA	-tonic posturing
• Premotor	-contraversive head and eye movements
• Prefrontal	-explosive and complex motor automatisms -bizarre and hysterical behavior (screaming) -mood change -mesial region: negative behaviors, loss of consciousness

Frontal Lobe Epilepsy: behavior

- Behavioral disinhibition
- dys-executive syndrome
- “organic personality change”
  - Offends others, perseverative, misunderstands information, irritates others, apathetic
- Helmsteadter (2001)
  - Hyperactivity, conscientiousness, tendency toward obsessions and addictions

Other factors affecting cognition/behavior

- Age of seizure onset
- Seizure frequency and duration
- Degree of MTS and/or dual pathology
- Number of AEDs
- History of status epilepticus
- History of GTC seizures
- Comorbid mood/psychotic disorder

Mood/Behavior in Epilepsy

- Depression, Anxiety, psychosis, ADHD
  - Incidence of depression – 4-5x that of general population
  - Depression contributes more to reduced quality of life than ongoing seizure activity
  - Strong biologic basis for depression, especially with left-sided foci
  - *Self-reported cognitive complaints are more strongly correlated with mood than with actual cognitive dysfunction
- Treatments for mood disturbance?
  - Standard treatments (i.e., therapy, antidepressants—tricyclics and SSRIs)
  - Gabapentin (improved mood + mild cognitive profile)
  - Lamotrigine (especially if comorbid bipolar disorder)
  - Leviteracetam ??
  - Vagus nerve stimulation

Non-epileptic seizures
“Pseudoseizures”
“Psychogenic seizures”

Psychogenic Nonepileptic Seizures

- Represent genuine psychiatric disease
- 10-45% of refractory epilepsy at tertiary referral centers
- Females > males
- Psychiatric basis: dissociation, conversion, unconscious
- Epileptic and nonepileptic seizures often co-exist
- Video-EEG monitoring often helps clarify the diagnosis
  - Seizures that are unusually long and violent, but without injury
  - Brief post-ictal period with partial or total recollection of event
  - Usually occur in the presence of others
  - Nonresponsive to AEDs
  - Unusual posturing of muscles; pelvic thrusting
- 50% respond well to specific psychiatric treatment

Case Presentation/Videos

Temporal Lobe Epilepsy

vs

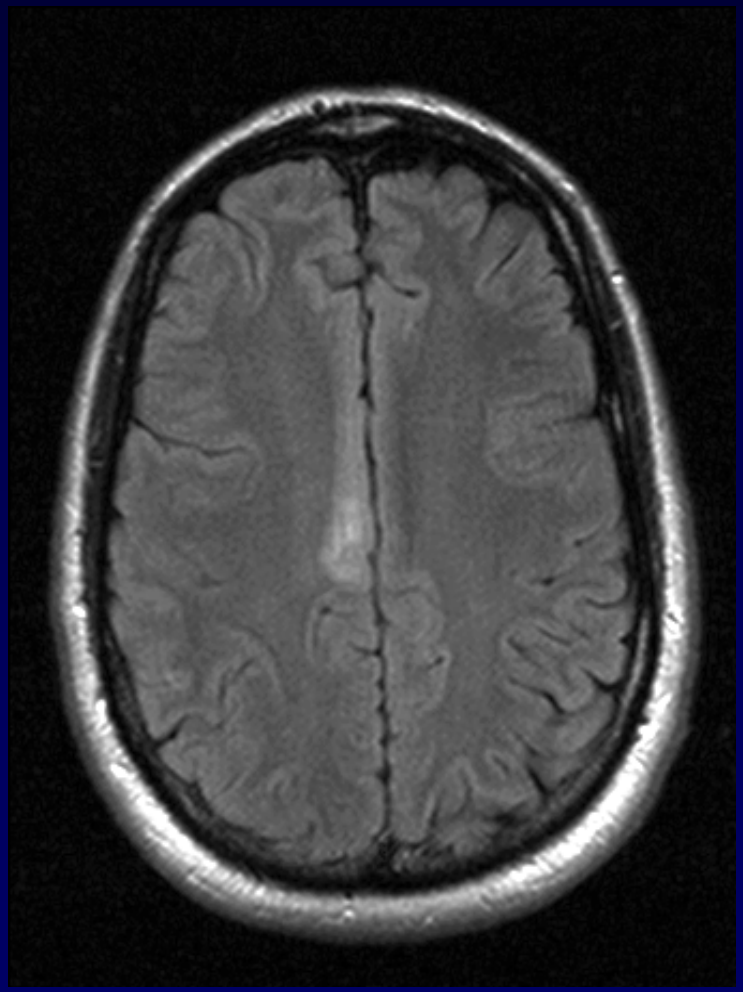
Frontal Lobe Epilepsy

vs

Nonepileptic seizures

CASE EXAMPLE 1

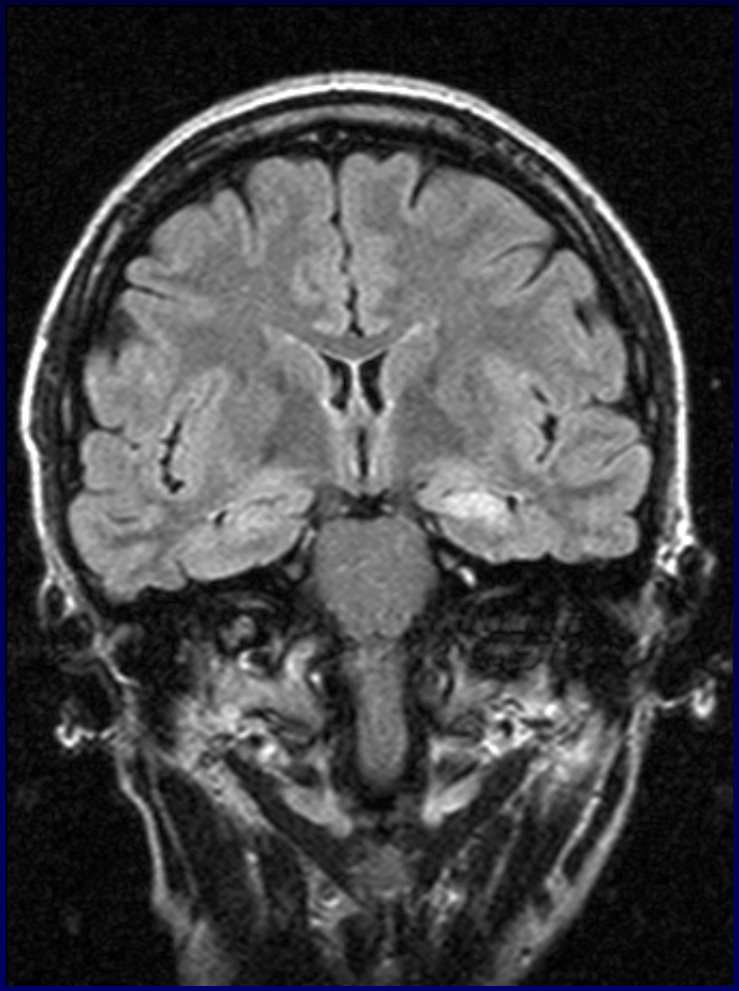
- 47-year old male
- 16 years education
- Environmental engineer
- Seizures 3 years
- Nocturnal only
- Violent, screaming attacks and thrashing
- No history of neurological illness



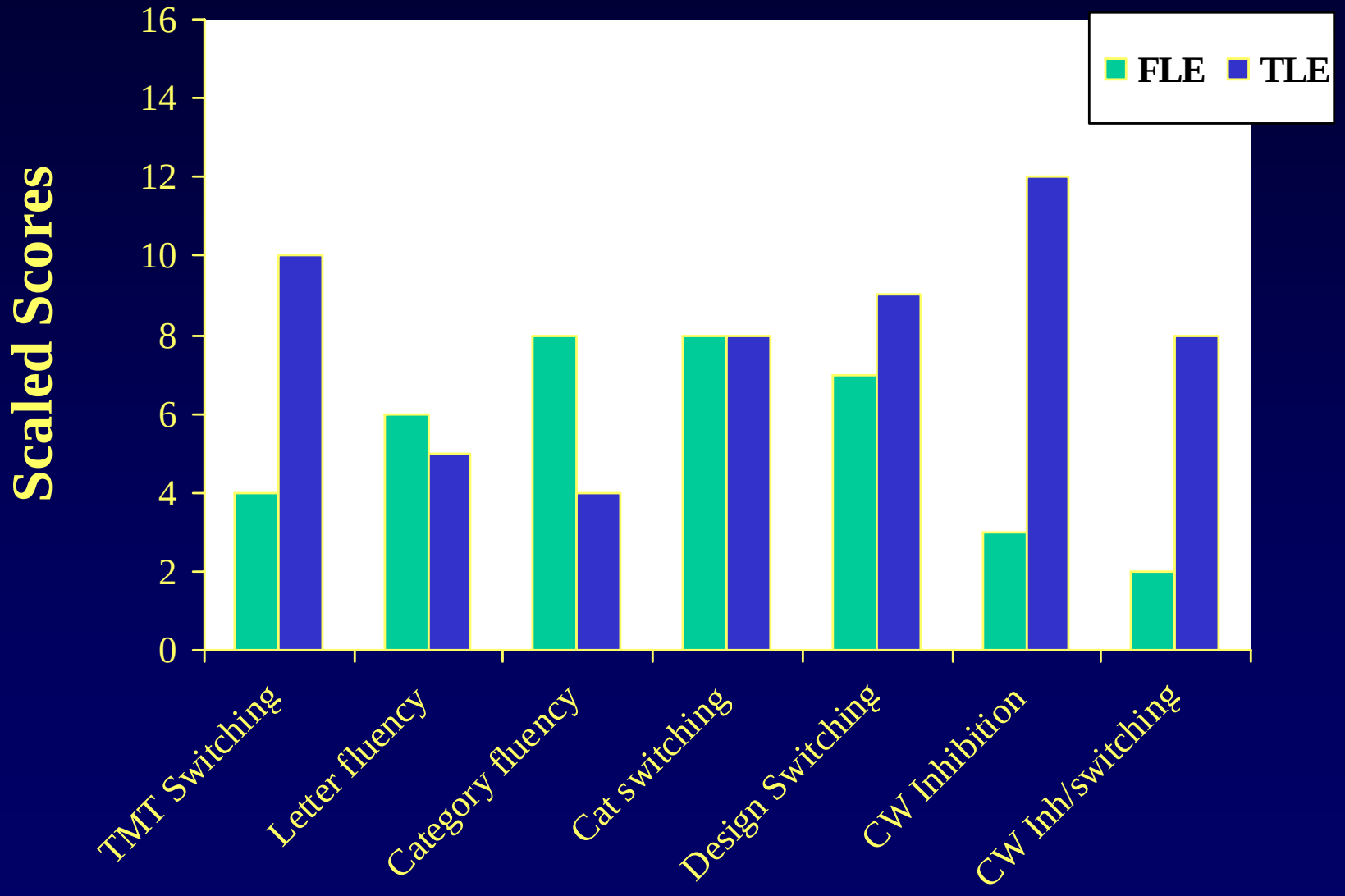
Low grade glioma in right cingulate gyrus

CASE EXAMPLE 2

- 28-year old female
- 10 years education
- receptionist
- Seizures 26 years
- catamenial seizures
- lip-smacking, humming,
- Anoxia at birth



Executive Dysfunction (D-KEFS)



M.L.

- 35 yr old Vietnamese female
- Absence seizures in childhood
- First GTC seizure in 1990; 2nd in 2001
- 16 years education; valedictorian of H.S. class; B.S. in chemical engineering from UCSD
- Works as a senior processing engineer for past 12 years
- Video-EEG telemetry, MRI, MRS, and PET revealed left medial temporal focus

Evaluation for Surgery

1.)Video EEG Localization

2.) Neuroimaging

3.) Neuropsychological battery*

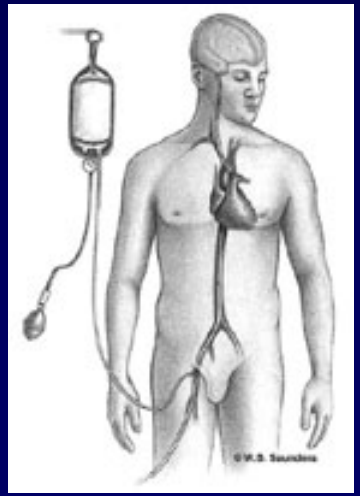
4.) Wada test (Intracarotid amobarbitol test)*

Neuropsychological Evaluation

- Clinical interview
  - Awareness of seizures, injuries, expectation for surgery, understanding of procedures, subjective cognitive /mood symptoms
- Neuropsychological testing
  - IQ and achievement (reading)
  - Verbal Memory: California Verbal Learning Test / Logical Memory (WMS-III)
  - Visual Memory: Rey-O, WMS-III figures,
  - Language: BNT, Verbal Fluency, Category Fluency, comprehension
  - Executive Functions: Trail Making Test, WCST
  - Attention: Digit Vigilance
  - Visuospatial: block design (WAIS-III), matrix reasoning, Rey-O copy
- Mood
  - Beck Depression Inventory, Beck Anxiety Inventory, MMPI (if you suspect psychosis or severe psychopathology)

Wada Procedure (IAP)

- Intracarotid Amobarbitol procedure
- Sodium amytal (internal carotid artery)
- Anesthetizes medial temporal lobe (anterior hippocampus, amygdala, uncus, surrounding cortex)
- Memory and language testing
- Scoring?
  - "functional reserve"
    - Predictive of **LEVEL** of post-op functioning
  - "hippocampal adequacy"
    - Predictive of **Decline** in functioning
  - Most use cut-off point and asymmetry score



Wada (IAP) protocols

- Medical College Georgia (Loring et al., 1992)
  - Pulsed amobarbitol injections until contralateral hemiparesis is achieved
  - Language testing
    - Repetition
    - Response to auditory commands
    - Naming of objects and line drawings
    - [Total Score Right – Total Score Left / Total Score Right + Total Score Left]
  - Memory testing (10 minutes after item presentation)
    - Spontaneous recall
    - Yes/no recognition testing w/distractors
    - Total score = .05 [hits – (false positives x .05)]

Cognitive Effects of Epilepsy Surgery

Naming

- most common post-operative change following language-dominant resection
  - More common/severe if seizures developed > 5 years or if there was no significant seizure risk factor (i.e., febrile seizures)
  - More common if there was no MTS on MRI

Memory

- Memory *decline* is greatest in patients who had normal ipsilateral hippocampal functioning (i.e., no MTS)
- Memory *functioning* is poorest in patients who have bilateral disease (lack of "functional reserve")

**These often do not surface until patient returns to work or other demanding roles

Cognitive Profile – M.L.

I.Q.

Test parameter	Standard score	Classification
Full Scale IQ	118	High average
Performance IQ	117	High average
Verbal IQ	116	High average

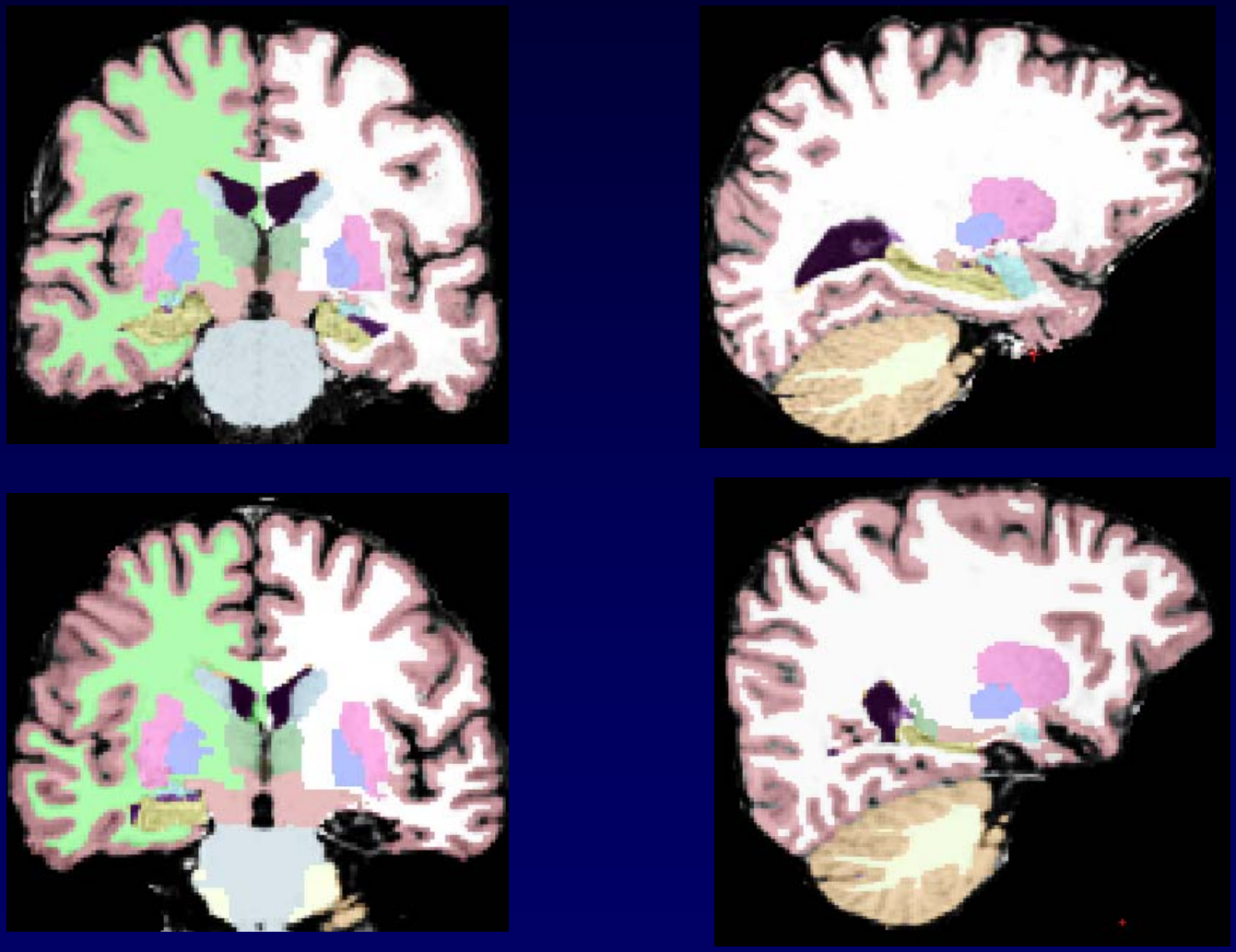
NP

Language	Verbal fluency Naming	Average Moderately impaired
Executive Functioning	Cognitive flexibility Verbal abstract reasoning Nonverbal abstract reasoning	Average High average High average
Verbal Memory	Learning Delayed free recall Story Memory (immediate) Story Memory (delayed)	High average High average Average High average (retention 76%)
Visual Memory	Immediate Delayed	Superior High average (retention 88%)

Wada

Behavioral characteristics	Left injection (95mg)	Right injection (95mg)
Speech	Speech arrest	Dysarthria
Pronator drift / arm drop	Yes	Yes
Aphasia	Yes	No
Correctly identified	16/21	20/23
False positives	8	3
Discriminability index	69%	88%
Results	**19% favoring memory in left**	

Pre- and Post-op MRI for M.L.



Post-operative volumes: Right HC = 4118 mm^3 Left HC = 1339 mm^3
Right AMG =1662 mm^3 Left AMG = 348 mm^3