



# Epilepsy and seizure

# *Definitions*

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- ♦ Seizure: the clinical manifestation of an abnormal and excessive excitation and synchronization of a population of cortical neurons
- ♦ Epilepsy: two or more recurrent seizures unprovoked by systemic or acute neurologic insults
- ♦ Name originates from ancient Greek meaning to seize, possess or afflict



# *Epidemiology of Seizures and Epilepsy*

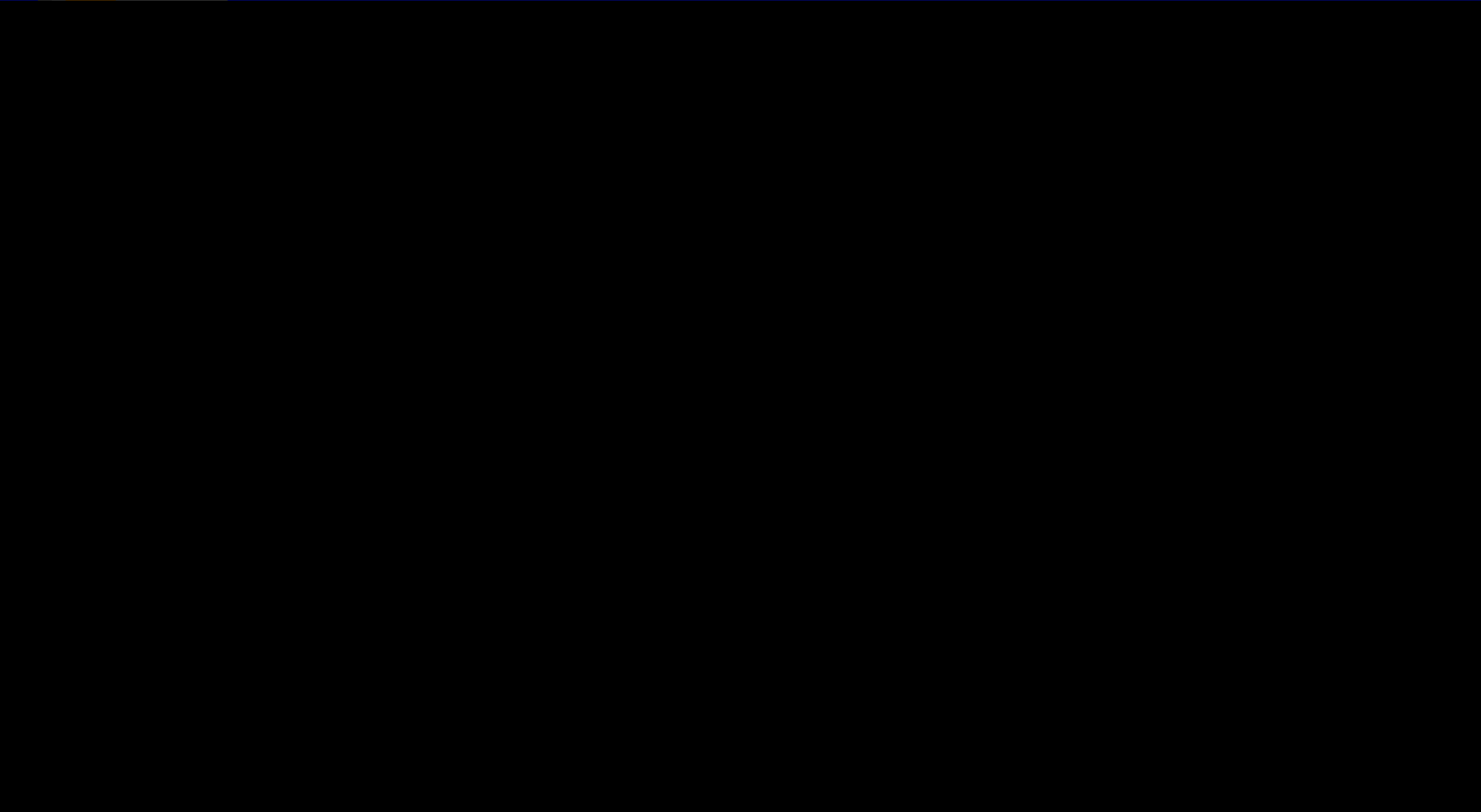
## ♦ Seizures

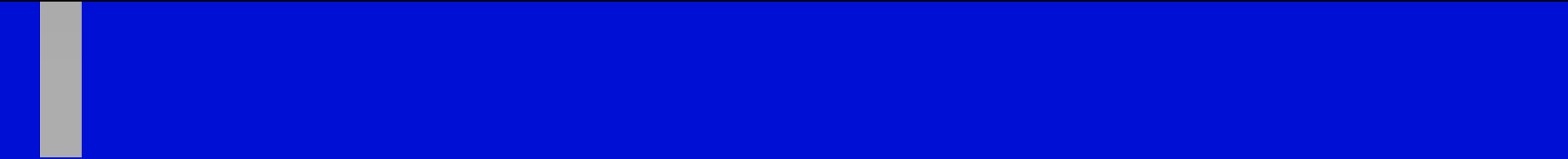
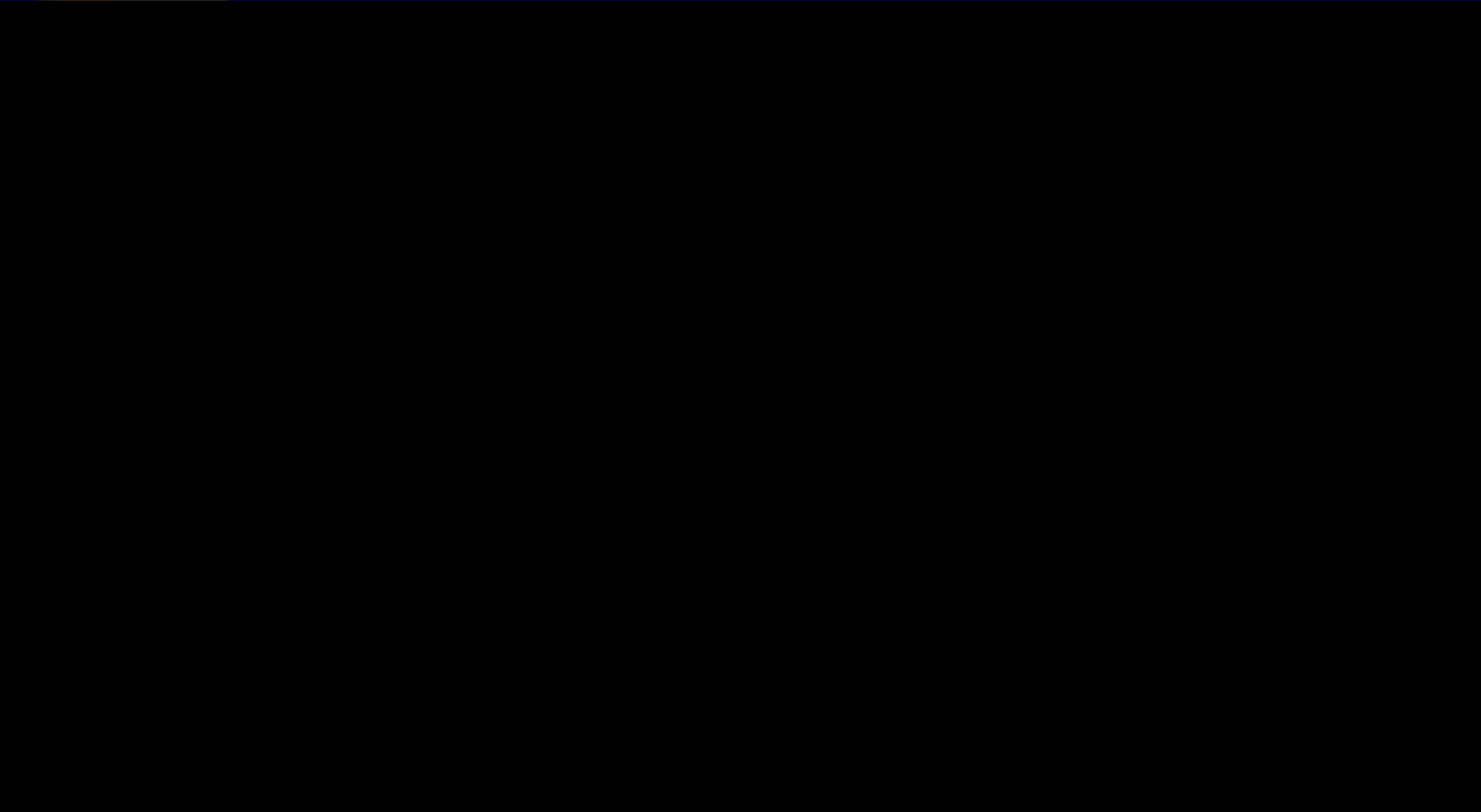
- Incidence: approximately 80/100,000 per year
- Lifetime prevalence: 9%  
(1/3 benign febrile convulsions)

## ♦ Epilepsy

- Incidence: approximately 45/100,000 per year
- Point prevalence: 0.5-1%





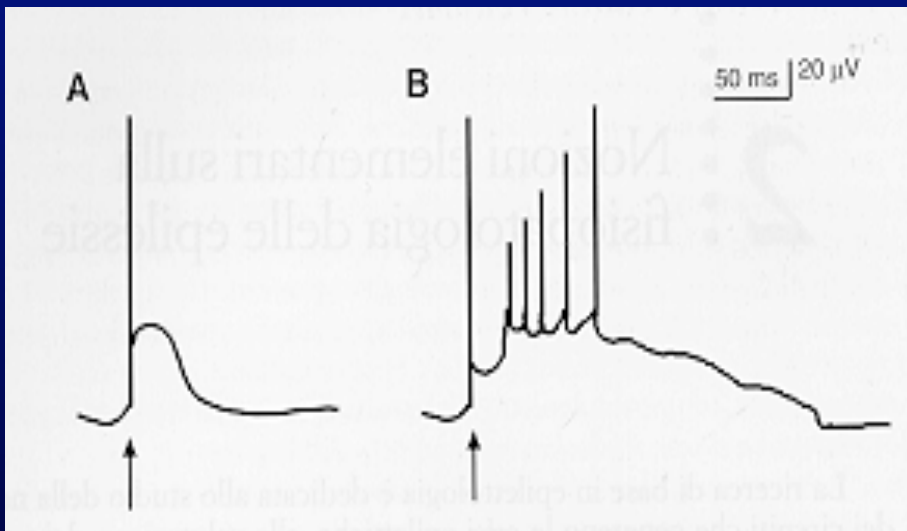


# Pathophysiology

## Seizure results from imbalance in neuronal excitability

Factors characterizing neuronal activity during seizure:

- hyperexcitability – Tendency to generate repeated discharges in response to a stimulus
- hyposynchrony – Capacity of single neurons to generate a series of action potentials

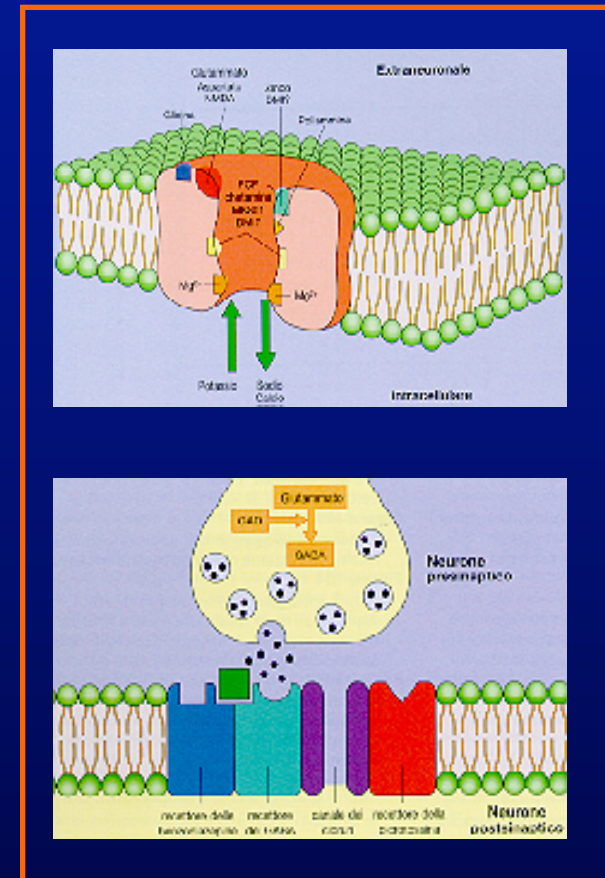


A. Neuron with one action potential

B. Epileptic neuronal firing with «trains» of action potentials

# Pathophysiology (2)

- Abnormal ion-gated channels in the membrane
- Imbalance between excitory and inhibitory transmission:
  - ↓ GABA
  - ↑ Glutammate



# definitions of key terms

## ▪ **what is an epileptic seizure?**

- the result of a sudden disruption of the electrical activity of the brain. There is an abnormal, usually self-limited, excessive and hypersynchronous activity (a discharge) of a population of neurons in the brain (cerebral cortex, thalamo-cortical systems and brainstem);
- the semiology reflecting the cerebral structures and circuits involved during this seizure;
- assuming normal anatomy, circuitry and metabolism, at a given age (maturity of the brain and then senescence) and under the modulatory effects of endogenous (e.g. sleep-wake cycle) and exogenous factors (e.g. medication).



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# definitions of key terms

- **what is an epileptic seizure?** Cont'd
  - Seizures can affect:
    - sensory, motor and autonomic function
    - consciousness
    - cognition, emotional state and behavior.

Phases of a seizure



**Pre-Ictal (prodroma)** →

includes the precipitating factors (fever, lack of sleep etc.) and prodromal symptoms (change in behavior, headache etc.);

**Ictal (aura and progression)** →

includes the ictal onset (aura, warning) and the ictal phase, which in case of focal seizures may have localizing characteristics;

**Post-Ictal**

end of seizure usually more difficult to define than onset; may also demonstrate in focal seizures, localizing characteristics.



# ILAE Task Force on Classification and Terminology, 2001

- Dichotomy focal/generalized does not define the continuum existing between these two ends. A variety of conditions include diffuse, or widespread, or multifocal or bilateral abnormalities
- A diagnostic scheme for use in describing individual patients. The scheme consists of 5 Axis:
  - **Axis 1. description of ictal semiology**
  - **Axis 2. seizure type as a diagnostic entity**
  - Axis 3. syndrome diagnosis
  - Axis 4. etiology
  - Axis 5. impairment

# Axis 1 – description of ictal semiology

- Glossary of Descriptive Ictal Terminology can be used to describe ictal events with any degree of detail needed

Blume et al., *Epilepsia* 2001;42:1212-1218

# Axis 2 – seizure types

## self-limited epileptic seizures

### I. Generalized seizures

- Tonic-clonic (in any combination)
- Absence (typical, atypical, with special features; myoclonic absence, eyelid myoclonia)
- Myoclonic (myoclonic, myoclonic-atonic, myoclonic-tonic)
- Clonic
- Tonic
- Atonic

# Tonic-clonic seizure

- Typical sequence of a generalized tonic contractions followed by clonic contractions:
  - *Pre-tonic-clonic phase* (few sec): versive mvts of H and E and vocalisations → *tonic phase* (10-20 sec): tonic posturing → adduction and extension of all 4 limbs and flexion of the wrists and fingers → *clonic phase* (30 sec): twitching or tremor-like leading to clonic phase = flexion myoclonic jerks of elbows, hip and knees.
- Consciousness always disturbed from onset, autonomic activation and followed by post-ictal coma and confusion.
- 1-2 min in duration.
- Pathophysiology:
  - Often represents the final step in the evolution of various seizure types;
  - Probably generated in the cortical motor areas, with involvement of diencephalum, brain stem and thalamus.





# Tonic seizure

- Sustained contraction of one or more muscle groups lasting few seconds leading to body posture:
  - In focal seizures, proximal musculature is primarily involved, posture is asymmetric or unilateral and often consciousness is partially preserved at onset;
  - In generalized seizures (LGS), posture is more symmetrical and consciousness is disturbed from onset.
- Usually brief seizures (< 1 min, a few sec to min).
- Pathophysiology:
  - In focal seizures: primary, pre-motor or supplementary motor cortex;
  - In generalized seizures: brain stem (reticular nuclei) and thalamus involved in their generation.

# Clonic seizure

- Repeated, rhythmic, short contractions (at ~2-3 Hz) of one or more muscle groups lasting few seconds leading to body posture:
  - In focal seizures, distal segments (e.g. hand, face) are primarily involved, may show a march (jacksonian) from distal to proximal; consciousness is usually preserved if origin in the FL, but altered if result from a propagation.
- Usually brief seizures.
- Pathophysiology:
  - In focal seizures: primary and pre-motor cortices, rarely the expression of epileptic activation of supplementary motor cortex;
  - Generalized clonic seizures result from intermittent generalized activation of both motor regions.



# Myoclonic seizure

- Sudden muscle jerks of variable topography (distal, proximal, axial): uni- or bilateral, focal, multifocal or generalised, proximal > distal musculature; consciousness likely preserved.
- 100-400 msec in duration
- Pathophysiology:
  - Epileptic (cortical) vs non-epileptic myoclonus (brain stem or spinal);
  - Likely generated in the primary motor or premotor cortex, but usually the expression of a generalised epilepsy (JME, LGS), in which case a participation of thalamic nuclei is likely.

# Epileptic Spasm

- Symmetric tonic and myoclonic event with high variability from one seizure to the other, affecting proximal and axial musculature leading to typical flexion of neck, ABD of both arms, flexion of both legs, or extension, or mixed extension-flexion.
- ~ 1 sec (2-10 sec) in duration, often in clusters (myoclonic mixed with tonic contractions).
- Pathophysiology:
  - Immature CNS is crucial (infantile spasms) or diffuse cerebral dysfunction (children and adults); needs for an epileptogenic cortex; immature or abnormal interhemispheric (cortico-cortical) connections; and of an abnormal interaction between cortical and subcortical nuclei (brainstem).

# Atonic seizure

- Sudden loss or reduction of postural tone resulting in a loss of posture (i.e. head drop, falls, drop-attacks); may be preceded by a myoclonic seizure (with retro- or propulsion); affecting primarily axial muscles.
- Brief ( $\geq 1$  to 2 sec).
- Pathophysiology:
  - generalized seizures (LGS) resulting from a sudden cortically-mediated activation of inhibitory brain stem centers via fast corticoreticulospinal tracts.

# Astatic seizure (drop attack)

- Epileptic falls (loss of erect posture) due to atonic, myoclonic or tonic seizure mechanism.
- Pathophysiology:
  - depends on the underlying seizure type, and usually result from a generalized seizure disorder.

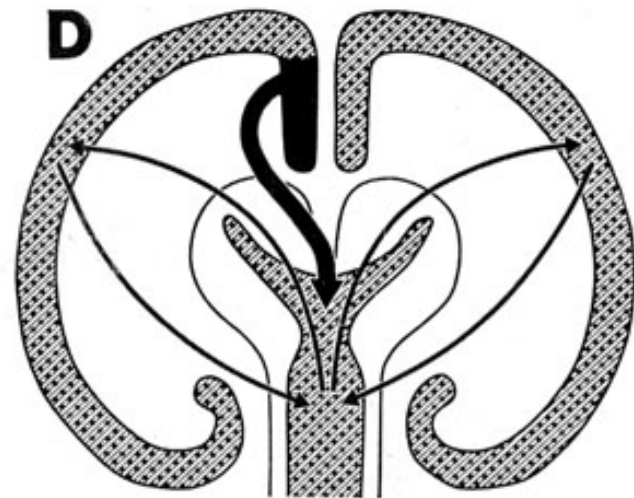
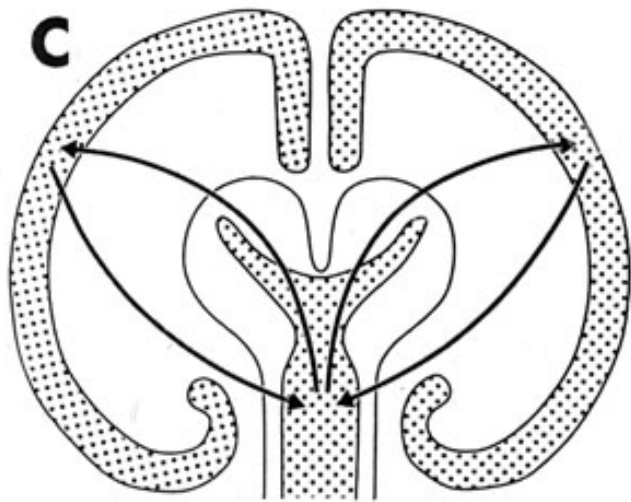
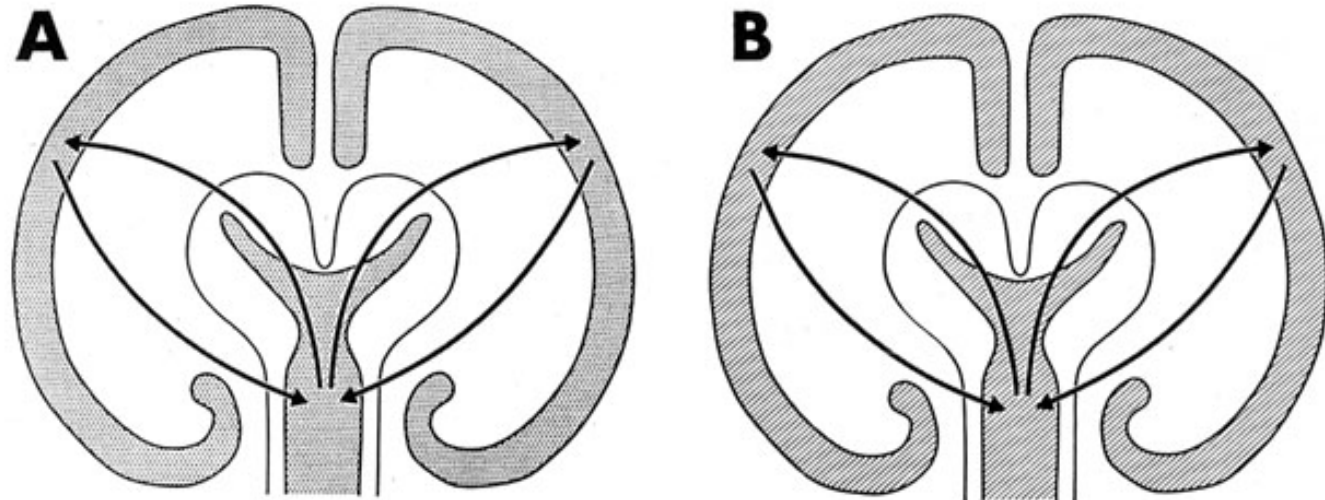
# Absence seizure

- Episodes of unresponsiveness or decreased responsiveness not explained by motor or speech alterations.
- A manifestation of generalized epilepsies and typically associated with generalized 3 Hz SW complexes in typical absences (sudden onset and ceased abruptly, precipitated by HV); atypical absences (in LGS) are longer and show a less acute onset and cessation, and associated with slow 2-2.5 Hz SW complexes.
- Typical absences: 5-20 sec in duration.
- Pathophysiology:
  - In generalized epilepsies, by corticothalamic neuronal mechanisms



# Hailey's Absence Seizures

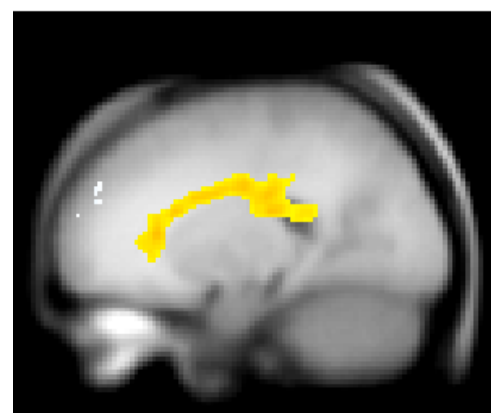
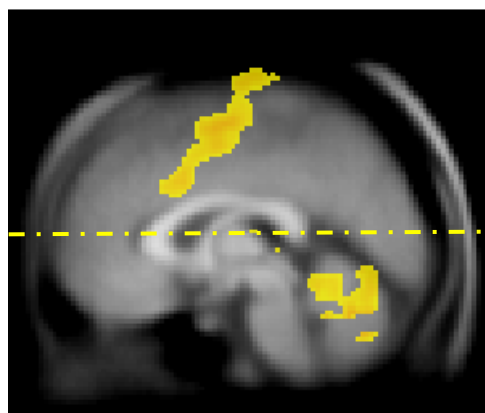
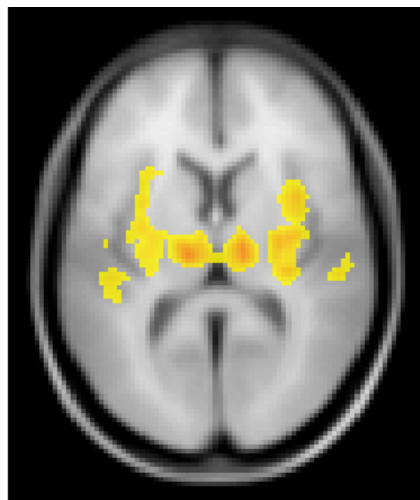
# Generalized cortico-reticular epilepsies (Gloor, 1969)



Normal  
Diffuse Gray Matter Lesions

Genetic  
Gross Cortical Lesion

# Generalized epileptic discharges show thalamocortical activation and suspension of the default-mode state of the brain

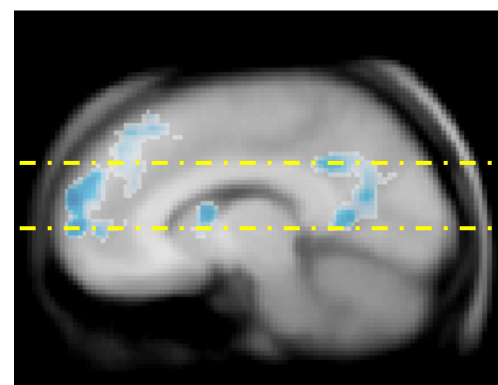
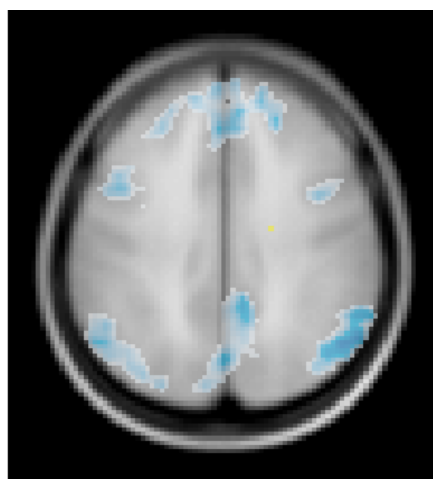
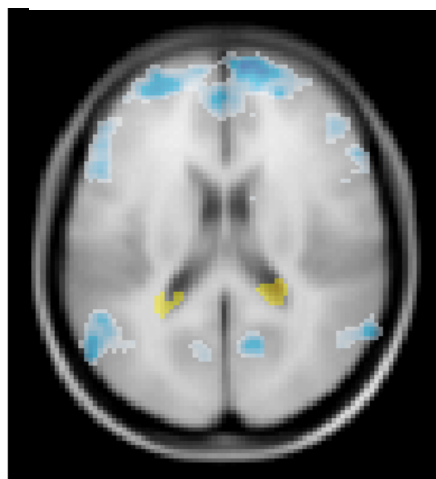


$T = +3.17$



$T = +6.0$

Gotman et al., *PNSA* 2005



$T = -6.0$



$T = -3.17$

# Axis 2 – seizure types

## self-limited epileptic seizures

### II. Focal seizures

- Without impairment of consciousness or awareness with observable motor or autonomic components involving subjective sensory or psychic phenomena
- With impairment of consciousness or awareness
- Evolving to a bilateral convulsive seizure
- \* Glossary of descriptive terminology for ictal semiology



# **Focal motor seizure**

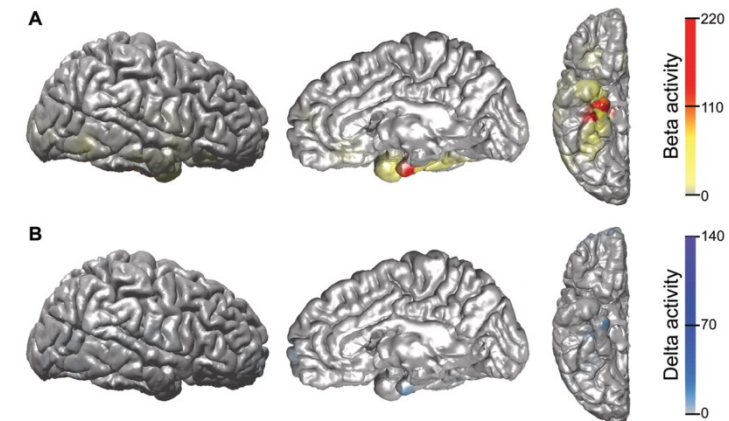
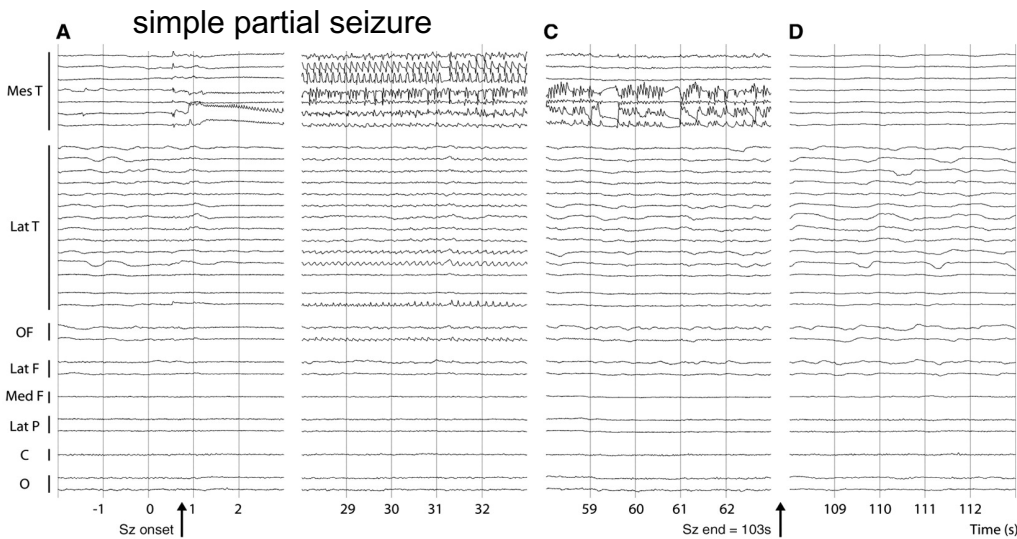
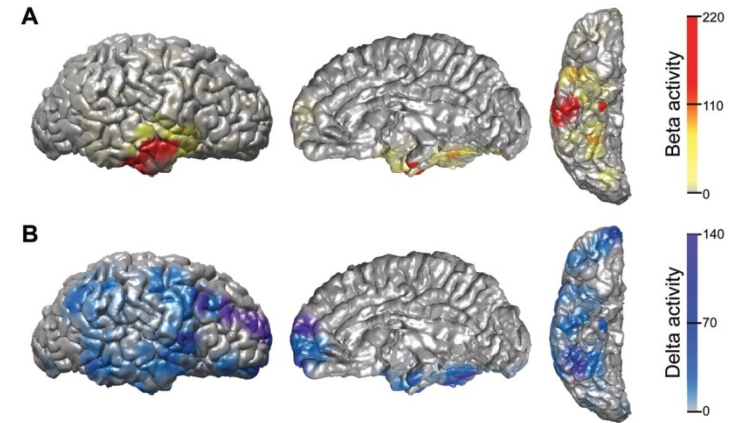
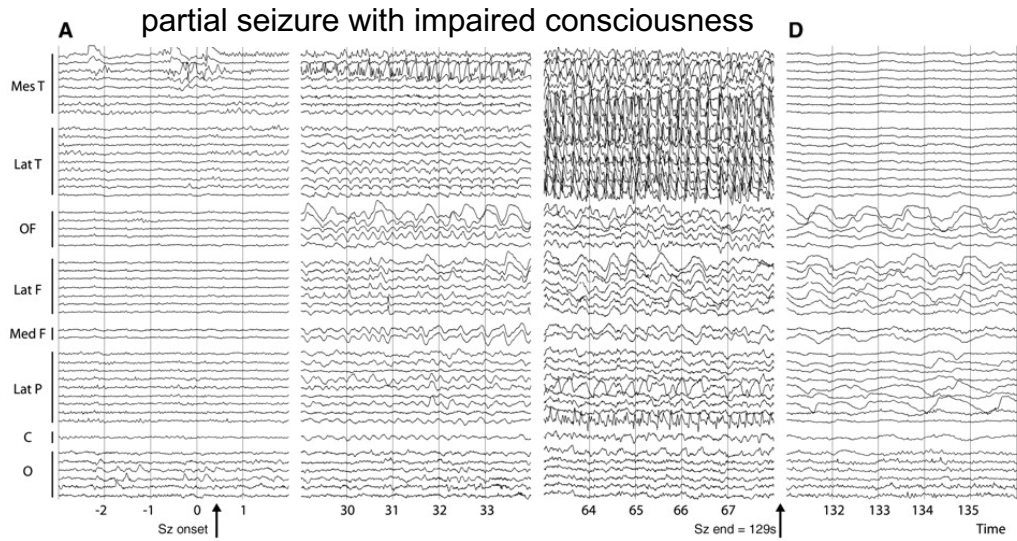


# Auras

- A perceptual (subjective) ictal experience that usually precedes an observable seizure; may occur alone (sensory seizure); often provides high localizing information.
- Types:
  - Somatosensory* (S1, S2, SMA)
  - Visual* (visual cortex, temporal asso. cortex)
  - Auditory* (Heschl's gyrus, temporal asso. cortex)
  - Olfactory* (amygdala, OF cortex (gyrus rectus))
  - Gustatory* (S2 and rolandic operculum, insula)
  - Vestibular* (insular-parietal-temporal)
  - Autonomic* (TL, basal frontal, ant cingulate, insula)
  - Experiential*: affective (Am for fear), mnemonic (basal temporal), hallucinatory or illusory (temporal asso. cortex).



# Ictal neocortical (bil fronto-parietal) slow wave (1-2 Hz) activity is related to impaired consciousness in TLE



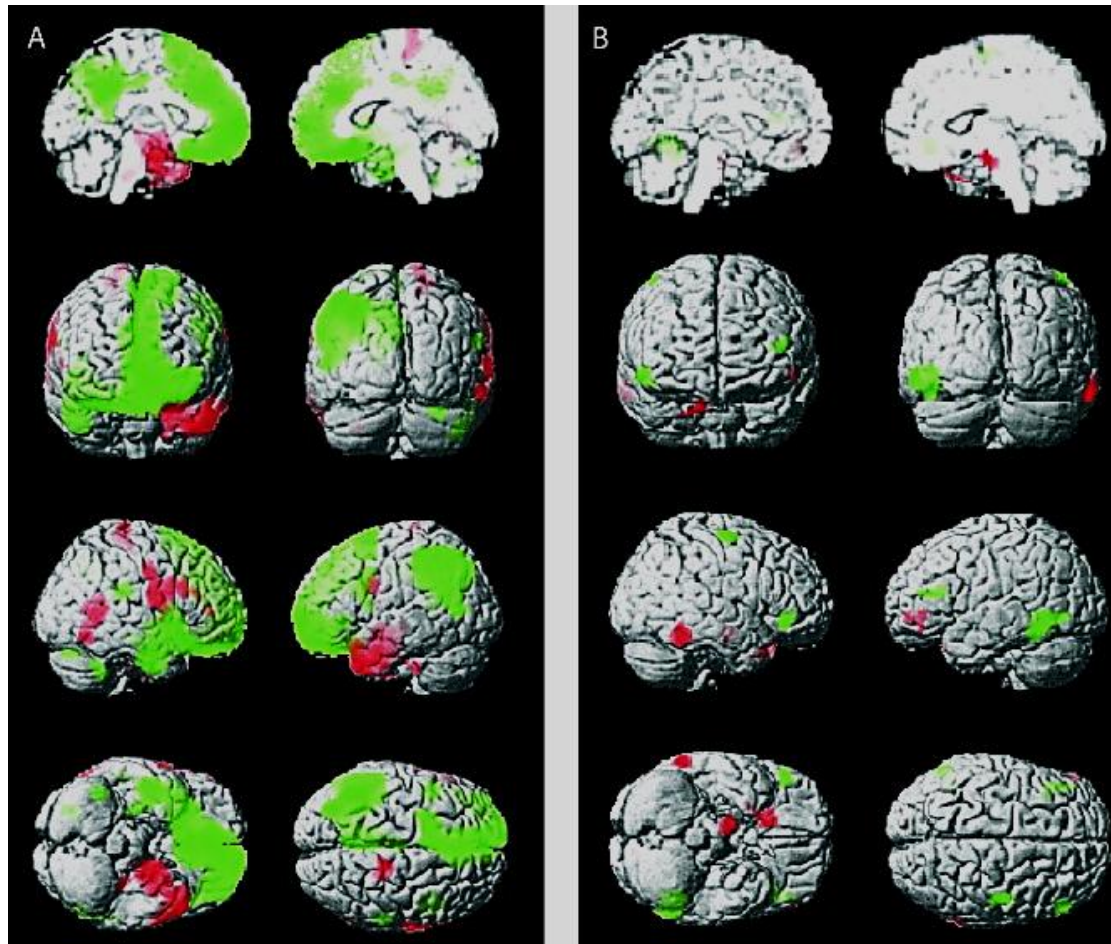
# Focal TL seizures with impaired consciousness are associated with CBF decreases in frontal and parietal association cortex

focal seizures with  
impaired consciousness

n = 8

Simple focal seizures

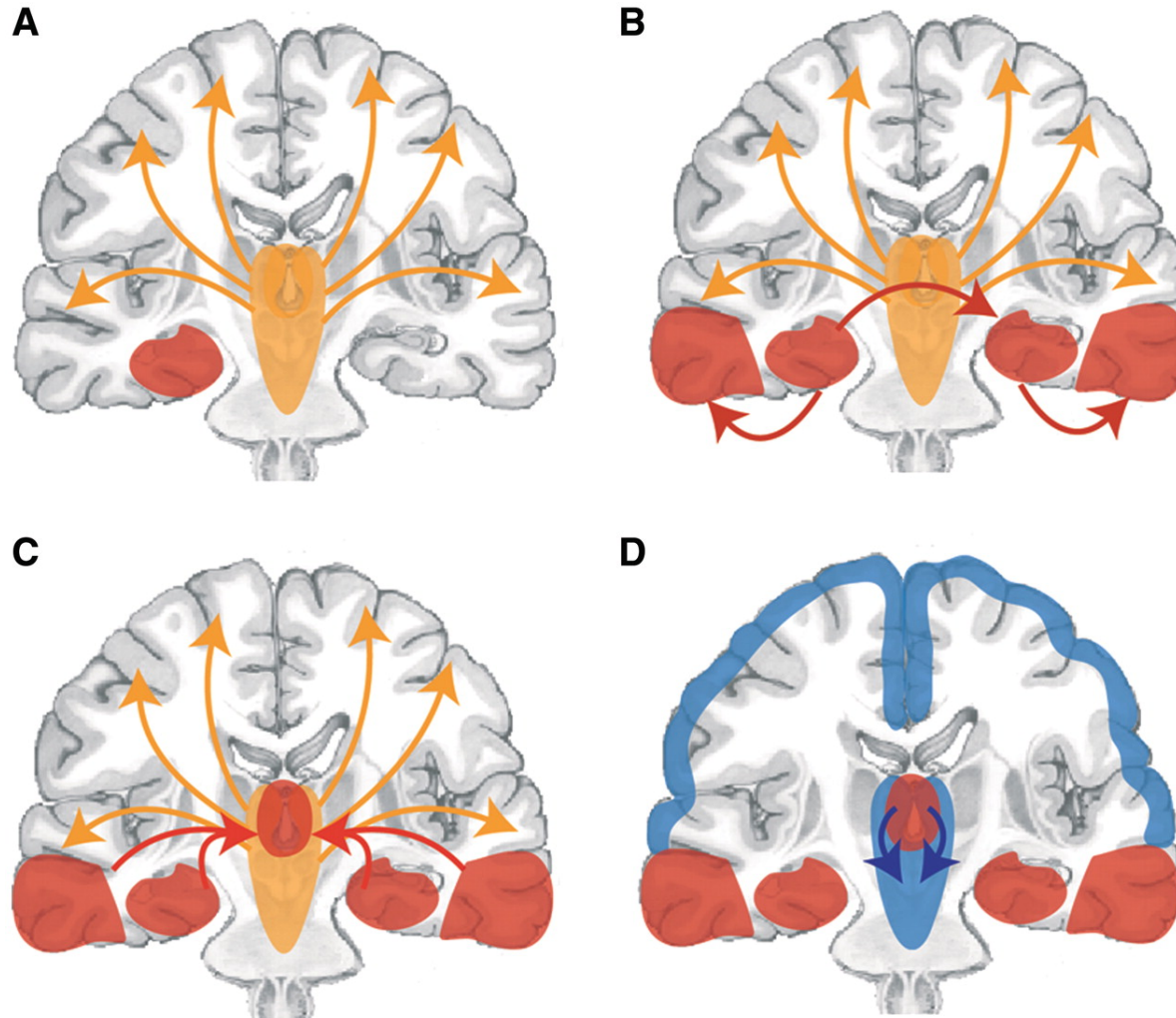
n = 6

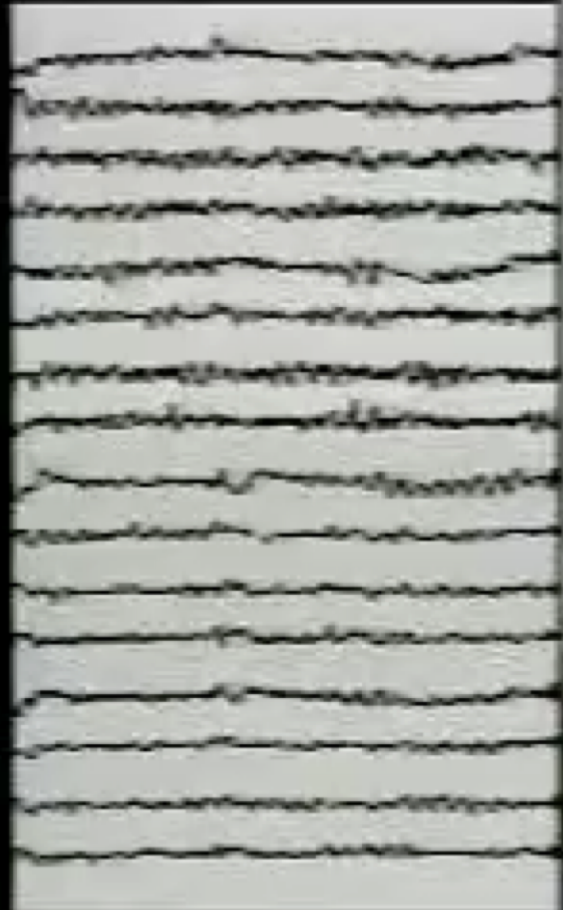


Blumenfeld et al.  
*Cerebral Cortex* 2004



# Network inhibition hypothesis for impaired consciousness during focal seizures.





07-01 10:33:20.7

Georg Thieme Verlag - Neurologische Differenzialdiagnose

# Ictal simple and complex motor phenomena

(head, eye and limb movements)

- Versive seizure (eyes, head or trunk)
- Unilateral clonic or tonic seizures
- Dystonia
- Automatism (oro-alimentary, mimetic, manual, pedal, gestural, hyperkinetic, gyratory, dysphasic, dyspraxic, gelastic, dacrystic, vocal and verbal)
- Autonomic (urinary, spitting, water drinking, piloerection, and vomiting)
- Eye blinking
- Nystagmus
- Akinetic seizures (immobile limb)
- Negative myoclonic seizures

# Versive seizure

(forced version, head turning etc.)

- *Versive*: forced, sustained, unnatural head and eyes turning with neck extension and head tilting, often with clonic component (eyes, face), with or without LOC;  
*Nonversive turning*: more natural, head turning.
- Pathophysiology:
  - Brain regions involved in voluntary eye mvts: FEF, SEF, DLPFC, parietal eye field, sup colliculus, striate cortex, basal ganglia;
  - Early versive seizure are the expression of an earlier activation of FEF (usually consciousness is preserved); late (or later) versive seizure may be associated with activation of disparate, cortical regions (usually consciousness is impaired, if version results from a propagation to FEF);
  - Nonversive head turning often associated with ipsilateral TL focus, and explained by relative inhibition of the attention systems (e.g. ipsilateral parietal lobe).

# Voluntary eye movements are supported by a distributed network of cortical and subcortical regions

Sharma et al. Arch Neurol 2011

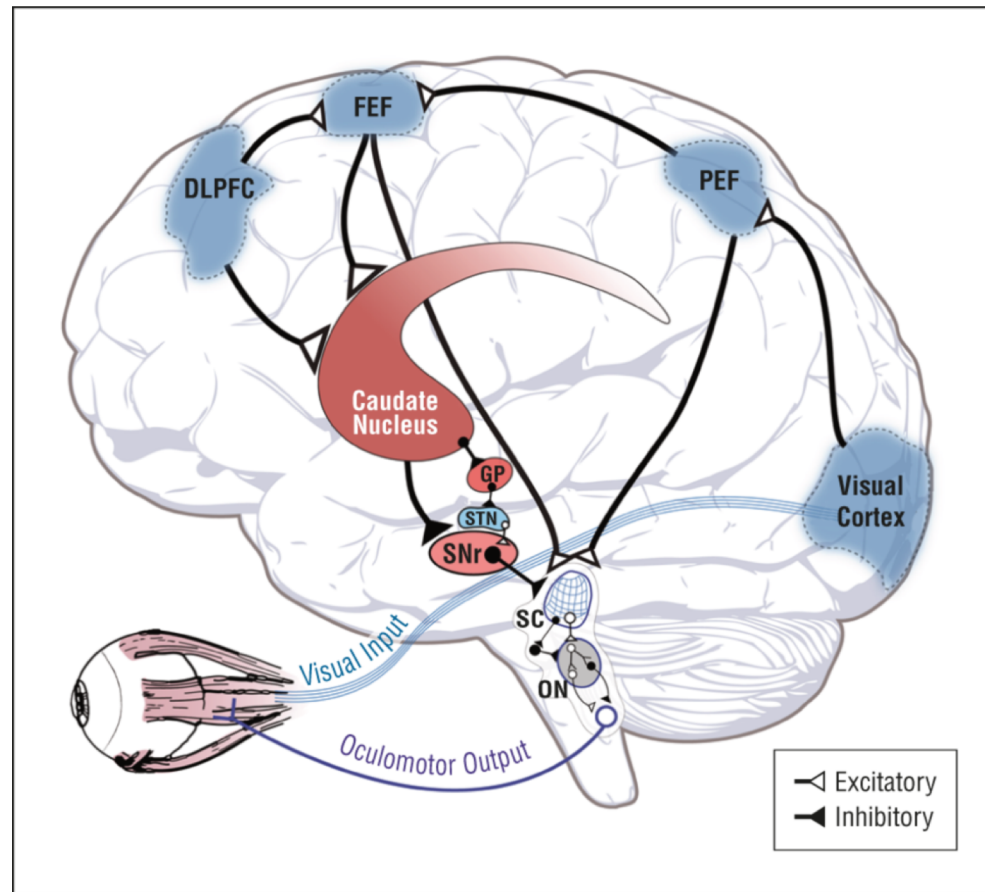


Figure. Saccadic eye movements are supported by a distributed network of cortical and subcortical regions. Saccades are initiated by direct signals sent from the frontal or parietal eye fields (FEFs or PEFs) to the superior colliculus (SC), which drives the oculomotor network (ON) in the brainstem. An indirect “gating” circuit arising from the FEFs and dorsolateral prefrontal cortex (DLPFC) projects via the basal ganglia (caudate nucleus, globus pallidus [GP], and subthalamic nucleus [STN]) to the substantia nigra pars reticulata (SNr). The SNr inhibits the SC, preventing saccade generation. To switch off this inhibition, when the FEFs and other frontal structures are activated before a saccade, the caudate nucleus is activated, which, in turn, inhibits the SNr via an inhibitory pathway.

# Oro-alimentary and manual automatisms

- Chewing, swallowing and lip smacking, and hand (distal, exploratory) automatisms often fumbling, usually with impaired consciousness (consciousness may be preserved in non-dominant TL seizures).
- Pathophysiology:
  - Expression of TL seizures > OF;
  - Masticatory mvts are the expression of an activation of the AM or peri-Am region; distal automatisms may be explained by an epileptic activation of the anterior cingulate gyrus, septal region and pallidum.









# Hyperkinetic seizure

- Complex sequences of movement affecting primarily the proximal body segments: gesticulation, agitation, bizarre or violent mvts, stereotypies, vocalisations etc.; short events with or without LOC; with or without psychic (fear), autonomic or tonic motor manifestations.
- Pathophysiology:
  - Primarily an expression of the epileptic activation of mesial frontal lobe structures (ventral mesial vs dorsal parasagittal), but may also be the result of a propagation from other structures (TL, insula).

# Ictal lateralizing phenomena - motor

Clinical feature	Origin	Lateralization	Reliability
Nonversive head turn	T	ipsi	++
Versive head turn	F, T	contra	+ / +++ / +++++
Isolated eye deviation (rare)		none	
Nystagmus	FEF, P-T, O	contra (fast)	+++
Ictal eye closure	none-epil.	none	++
Unilat. eye blinking	T, extra-T	ipsi	+ / +++
Unilat. (focal) clonic, tonic activity	M1	contra	+++
Unilat. limb (hand-arm) dystonia	T, F, basal ganglia	contra	+++
Complex postures (fencing, fig 4)	F (SMA), T	contra	+ / +++
Asymmetric clonic ending	T, F	ipsi (last cloni)	+++
Ictal paresis (immobile limb)	T, extra-T	contra	+ / +++
Negative myoclonus	M1, premotor, S1	contra	+ / +++
Speech arrest	T, F	dom. hem.	++

# Ictal lateralizing phenomena - automatisms

Clinical feature	Origin	Lateralization	Reliability
Oral (oroalimentary)	T, F	none	++
Unilat. manual limb (distal)	T, F	ipsi	++
Bipedal	F	none	++
Complex gestural (proximal)	mesial F	none	++
Spitting (rare)	T	non-dom. hem	+
Drinking (rare)	T	non-dom. hem	+
Gelastic (laugh, mirth, giggling)	Hypothalamus, cing., F operculum, mesial T	none	+/>++
Smiling	TPO	non-dom. hem.	+
Vocal (sounds, grunts, screams)	F, T	none	+/>++
Verbal (ictal speech)	T	Non-dom. hem	+++

# Ictal lateralizing phenomena - autonomic

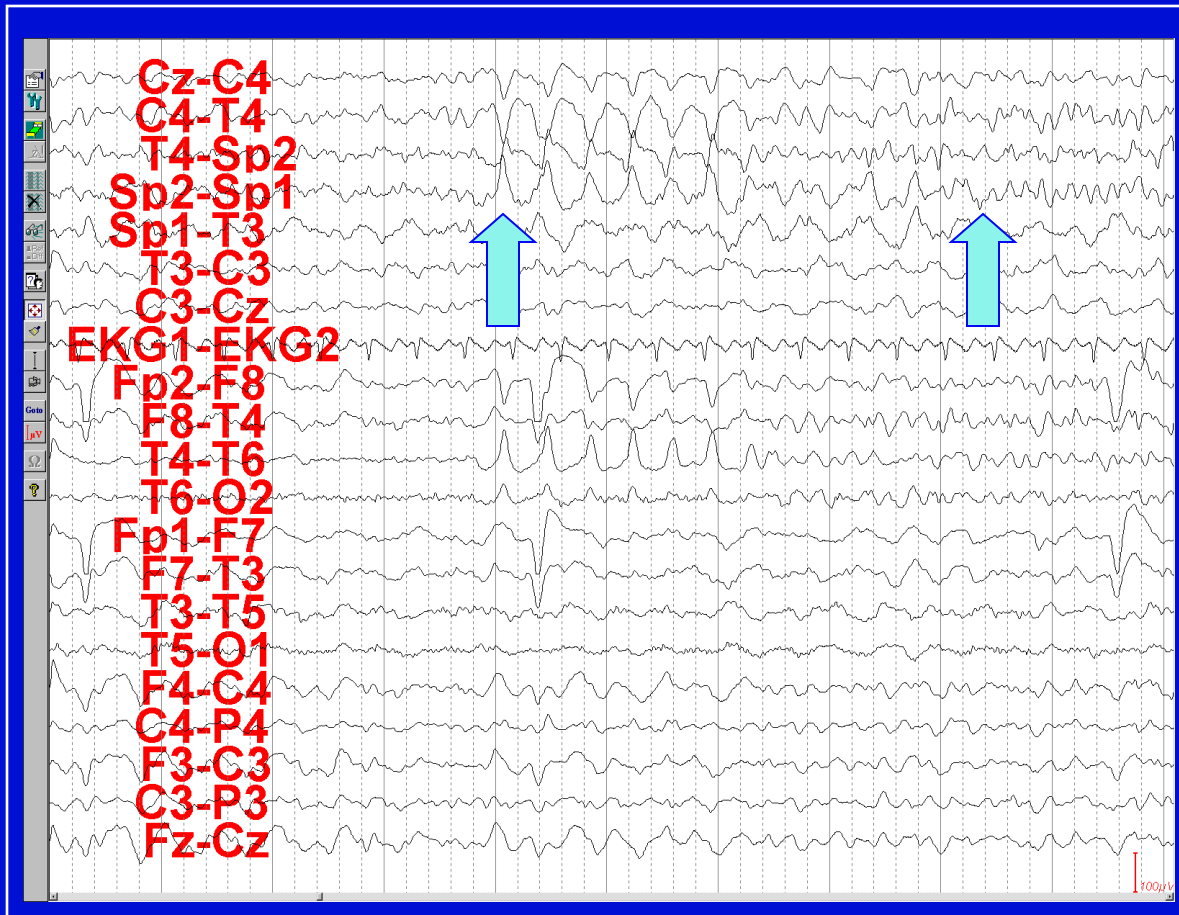
Clinical feature	Origin	Lateralization	Reliability
Piloerection	Am, insula, post hypothalamus	ipsi if unilateral	+
Vomiting	T, ant . insula	non dom. hem	+
Spitting	T	non dom. Hem	+
Urinary urge	T, mesial F	non dom. hem	+
Ascending visceral feelings	mesial T, insula, SMA	none	+ / ++
Cardio-vascular (tachycardia)	T	none	+
Cephalic	F, T, post.	none	



# Post-Ictal lateralizing phenomena

Clinical feature	Origin	Lateralization	Reliability
Amnesia	T, F	none	+ / +++
Aphasia/dysphasia/dysnomia	F, T, P	dom hem.	+++
Paresis	F (M1), T	contra	+++
Nose wiping/rubbing	T, F	ipsi	+++
Coughing	T	non-dom. hem	+ / +++
Headache	T (F)	ipsi (none)	++
Visual field defect	O (striate, peri-striate)	contra	++
Asymmetric ending	T	ipsi	++

# EEG: Simple Partial Seizure



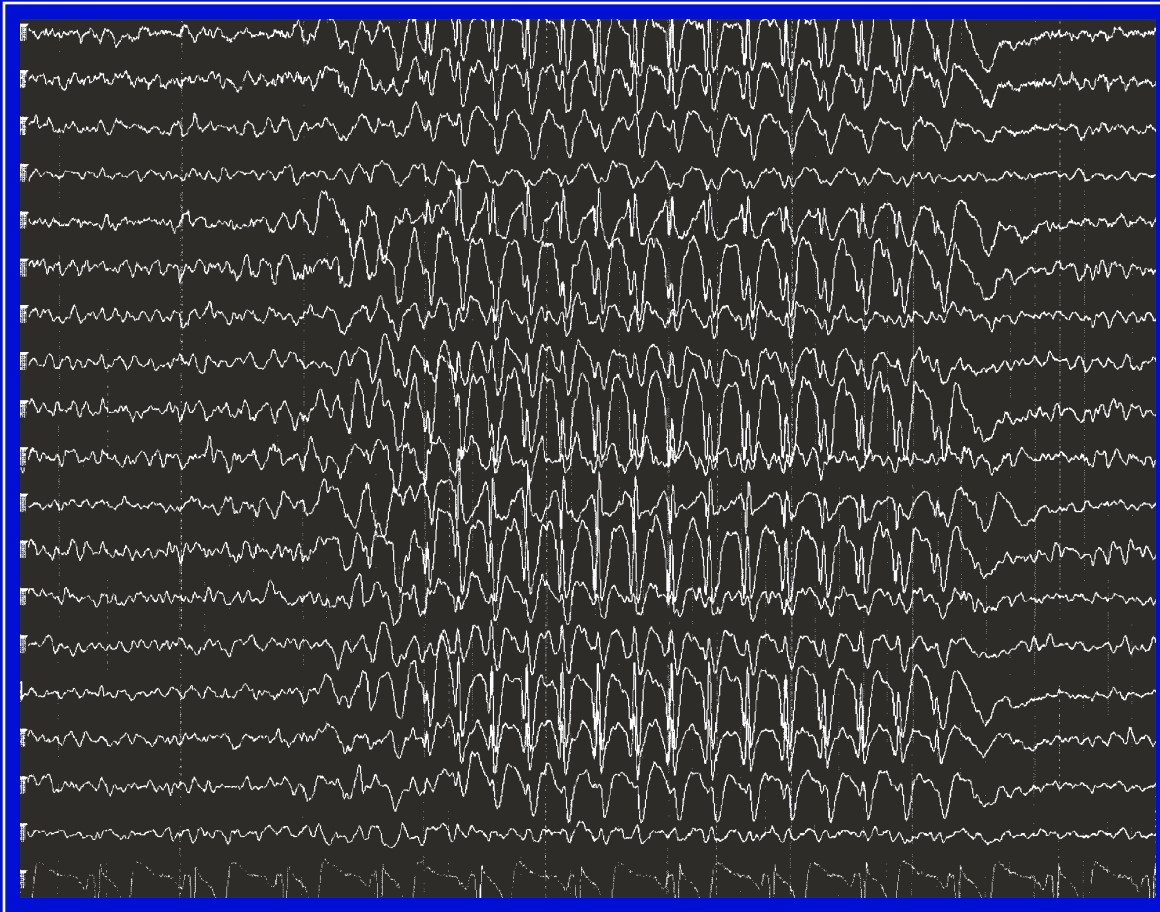
Right temporal seizures with maximal phase reversal in the right sphenoidal electrodes

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# *EEG: Absence Seizure*



# *Etiology of Seizures and Epilepsy*

- ◆ **Infancy and childhood**
  - Prenatal or birth injury
  - Inborn error of metabolism
  - Congenital malformation
- ◆ **Childhood and adolescence**
  - Idiopathic/genetic syndrome
  - CNS infection
  - Trauma

# *Etiology of Seizures and Epilepsy (cont.)*

- ◆ **Adolescence and young adult**
  - Head trauma
  - Drug intoxication and withdrawal\*
- ◆ **Older adult**
  - Stroke
  - Brain tumor
  - Acute metabolic disturbances\*
  - Neurodegenerative

\*causes of acute symptomatic seizures, not epilepsy

# *Questions Raised by a First Seizure*

- ◆ Seizure or not?
- ◆ Focal onset?
- ◆ Evidence of interictal CNS dysfunction?
- ◆ Metabolic precipitant?
- ◆ Seizure type? Syndrome type?
- ◆ Studies?
- ◆ Start AED?

# *Seizure Precipitants*

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- ◆ Metabolic and Electrolyte Imbalance
- ◆ Stimulant/other proconvulsant intoxication
- ◆ Sedative or ethanol withdrawal
- ◆ Sleep deprivation
- ◆ Antiepileptic medication reduction or inadequate AED treatment
- ◆ Hormonal variations
- ◆ Stress
- ◆ Fever or systemic infection
- ◆ Concussion and/or closed head injury

# *Seizure Precipitants, con't*

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## Metabolic and Electrolyte Imbalance

- ♦ Low (less often, high) blood glucose
- ♦ Low sodium
- ♦ Low calcium
- ♦ Low magnesium

# *Seizure Precipitants, con't*

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## Stimulation/Other Pro-convulsant Intoxication

- ◆ IV drug use
- ◆ Cocaine
- ◆ Ephedrine
- ◆ Other herbal remedies
- ◆ Medication reduction

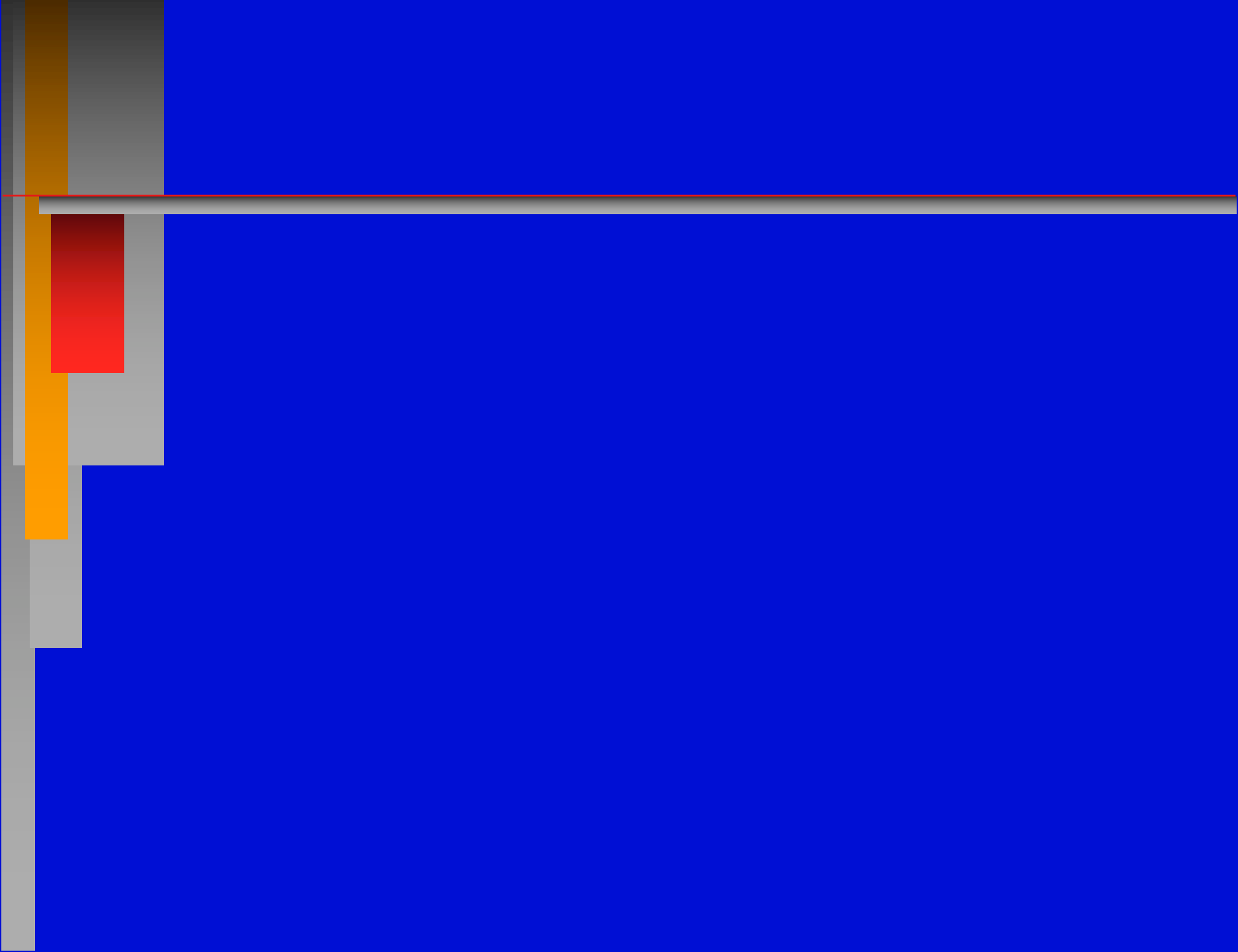
# *Evaluation of a First Seizure*

- ◆ History, physical
- ◆ Blood tests: CBC, electrolytes, glucose, Calcium, Magnesium, phosphate, hepatic and renal function
- ◆ Lumbar puncture only if meningitis or encephalitis suspected and potential for brain herniation is ruled out
- ◆ Blood or urine screen for drugs
- ◆ Electroencephalogram
- ◆ CT or MR brain scan



# *EEG Abnormalities*

- ◆ Background abnormalities: significant asymmetries and/or degree of slowing inappropriate for clinical state or age
- ◆ Interictal abnormalities associated with seizures and epilepsy
  - Spikes
  - Sharp waves
  - Spike-wave complexes
- ◆ May be focal, lateralized, generalized



# *Medical Treatment of First Seizure*

Whether to treat first seizure is controversial

- ◆ 16-62% will recur within 5 years
- ◆ Relapse rate might be reduced by antiepileptic drug treatment
- ◆ Abnormal imaging, abnormal neurological exam, abnormal EEG or family history increase relapse risk
- ◆ Quality of life issues are important

Reference: First Seizure Trial Group. Randomized Clinical Trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. *Neurology* 1993; 43 (3, part1): 478-483.

Reference: Camfield P, Camfield C, Dooley J, Smith E, Garner B. A randomized study of carbamazepine versus no medication after a first unprovoked seizure in childhood. *Neurology* 1989; 39: 851-852.

# *Choosing Antiepileptic Drugs*

- ♦ Seizure type
- ♦ Epilepsy syndrome
- ♦ Pharmacokinetic profile
- ♦ Interactions/other medical conditions
- ♦ Efficacy
- ♦ Expected adverse effects
- ♦ Cost

# *Choosing Antiepileptic Drugs (cont.)*

## Partial onset seizures

carbamazepine

phenytoin

felbamate

primidone

gabapentin

tiagabine

lamotrigine

topiramate

levetiracetam

valproate

oxcarbazepine

zonisamide

phenobarbital



# *Antiepileptic Drug Monotherapy*

- ◆ Simplifies treatment, reduces adverse effects
- ◆ Conversion to monotherapy from polytherapy
  - Eliminate sedative drugs first
  - Withdraw antiepileptic drugs slowly over several months

# *Antiepileptic Drug Interactions*

- ♦ Drugs that induce metabolism of other drugs: carbamazepine, phenytoin, phenobarbital
- ♦ Drugs that inhibit metabolism of other drugs: valproate, felbamate
- ♦ Drugs that are highly protein bound: valproate, phenytoin, tiagabine, carbamazepine
- ♦ Other drugs may alter metabolism or protein binding of antiepileptic drugs



# *AED Serum Concentrations*

- ♦ AED serum concentrations are simply to be used as a guide.
- ♦ Serum concentrations are useful when optimizing AED therapy, assessing compliance, pregnancy, or teasing out drug-drug interactions.

# *AED Serum Concentrations*

- ◆ AED serum concentrations can be useful for documenting compliance and steady-state serum level.
- ◆ Individual patients define their own “therapeutic” and “toxic” ranges.

# *Dose Initiation and Monitoring*

- ◆ Discuss likely and unlikely but important adverse effects
- ◆ Discuss likelihood of success
- ◆ Discuss recording/reporting seizures, adverse effects, potential precipitants

# *Evaluation After Seizure Recurrence*

- ◆ Progressive pathology?
- ◆ Avoidable precipitant?
- ◆ If on AED
  - Problem with compliance or pharmacokinetic factor?
  - Increase dose?
  - Change medication?
- ◆ If not on AED
  - Start therapy?

# *Discontinuing AEDs*

- ♦ Seizure freedom for  $\geq 2$  years implies overall  $>60\%$  chance of successful withdrawal in some epilepsy syndromes
- ♦ Favorable factors
  - Control achieved easily on one drug at low dose
  - No previous unsuccessful attempts at withdrawal
  - Normal neurologic exam and EEG
  - Primary generalized seizures except JME
  - “Benign” syndrome
- ♦ Consider relative risks/benefits (e.g., driving, pregnancy)

# *Non-Drug Treatment/ Lifestyle Modifications*

- ◆ Adequate sleep
- ◆ Avoidance of alcohol, stimulants, etc.
- ◆ Avoidance of known precipitants
- ◆ Stress reduction — specific techniques

# *Ketogenic Diet*

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- ◆ Main experience with children, especially with multiple seizure types
- ◆ Anti-seizure effect of ketosis (beta hydroxybutyrate)
- ◆ Low carbohydrate, low protein, high fat after fasting to initiate ketosis
- ◆ Long-term adverse effects unknown

# *Ketogenic Diet for Treatment of Intractable Epilepsy*

- **First used in the 1920' s**
- **Increasing frequency of use past 10 years**
- **High fat, very low carbohydrate, moderate protein diet that produces ketones from the breakdown of fat**
- **Mechanism of benefit is unknown but it appears to change brain chemistry**
- **Usually started in the hospital; MCT oil may be used as a fat source**



# *Guidelines for the Modified Ketogenic Diet*

- **Over 90% of calories come from fat (by weight, 80% of food eaten is fat)**
- **Oil, heavy cream and margarine are used as fat sources to supplement foods**
  - **Examples: One tablespoon of margarine for each Saltine cracker, 5 tablespoons of cream for 2 ounces of oatmeal, 3 teaspoons of oil in an ounce of apple sauce**

<http://www.ketogenic.org>

# *Ketogenic Diets: Results*

- **Over 100 uncontrolled studies published and extensive research in animals**
- **Overall effectiveness in children with intractable epilepsy:**
  - **16% become seizure-free**
  - **16% more become almost seizure-free**
  - **24% more have a greater than 50% reduction in seizure frequency**

**56% response overall**

**Similar results occur in adults**

**Benefits maintained over a 3 to 6 year period.  
At Johns Hopkins, about 20-30% of children maintaining the diet become drug-free**

# *Ketogenic Diets: Side Effects*

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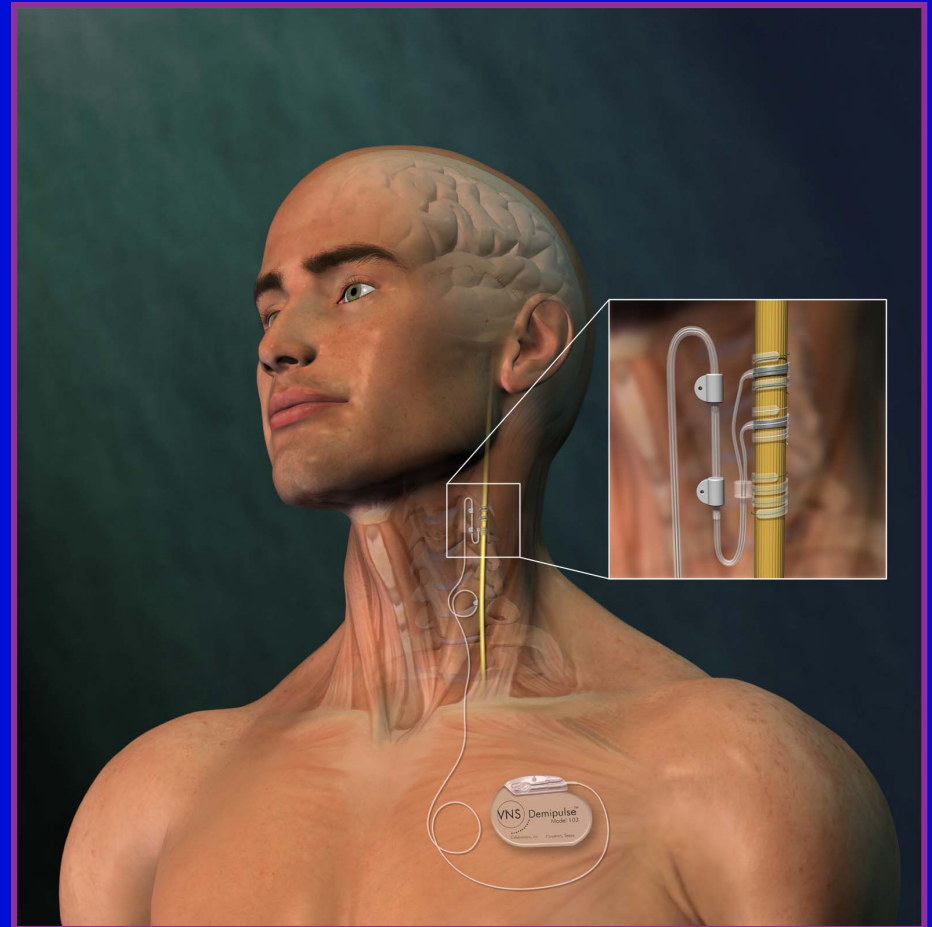
- **Increase in cholesterol (total and LDL) and triglycerides, decrease in HDL-cholesterol**
- **Decrease in blood levels of L-carnitine, may be temporary**
- **Loss of calcium in urine**
- **Abnormal electrocardiograms (rare)**
- **Kidney stones occur in 5-8%**

# *Vagus Nerve Stimulator*

- ◆ Intermittent programmed electrical stimulation of left vagus nerve
- ◆ Option of magnet activated stimulation
- ◆ Adverse effects local, related to stimulus (hoarseness, throat discomfort, dyspnea)
- ◆ Mechanism unknown
- ◆ Clinical trials show 26% effective and <10% seizure free
- ◆ May improve mood and allow AED reduction
- ◆ FDA approved for partial onset seizure

# *What is VNS Therapy?*

*The VNS Therapy System consists of an implanted pacemaker-like generator and nerve stimulation electrodes, which deliver intermittent stimulation to the patient's left vagus nerve that sends signals to the brain.*



# *On-demand magnet stimulation is a unique benefit of VNS Therapy*

- **Offers more control for patients and their families<sup>1,2</sup>**
- **Initiates on demand stimulation**
  - May abort or decrease severity of seizures<sup>1-3</sup>
  - May improve postictal period<sup>2</sup>
- **Stops stimulation**
  - Acutely manage side effects<sup>3</sup>



## *VNS Therapy has a unique side effect profile*

- **Most side effects associated with VNS Therapy**
  - **Occur only during stimulation<sup>1,2</sup>**
  - **Generally diminish over time<sup>2</sup>**
  - **May be diminished or eliminated by the adjustment of parameter settings<sup>2</sup>**
  - **May be controlled by use of the magnet<sup>3</sup>**
  - **Similar across age groups<sup>4,5</sup>**

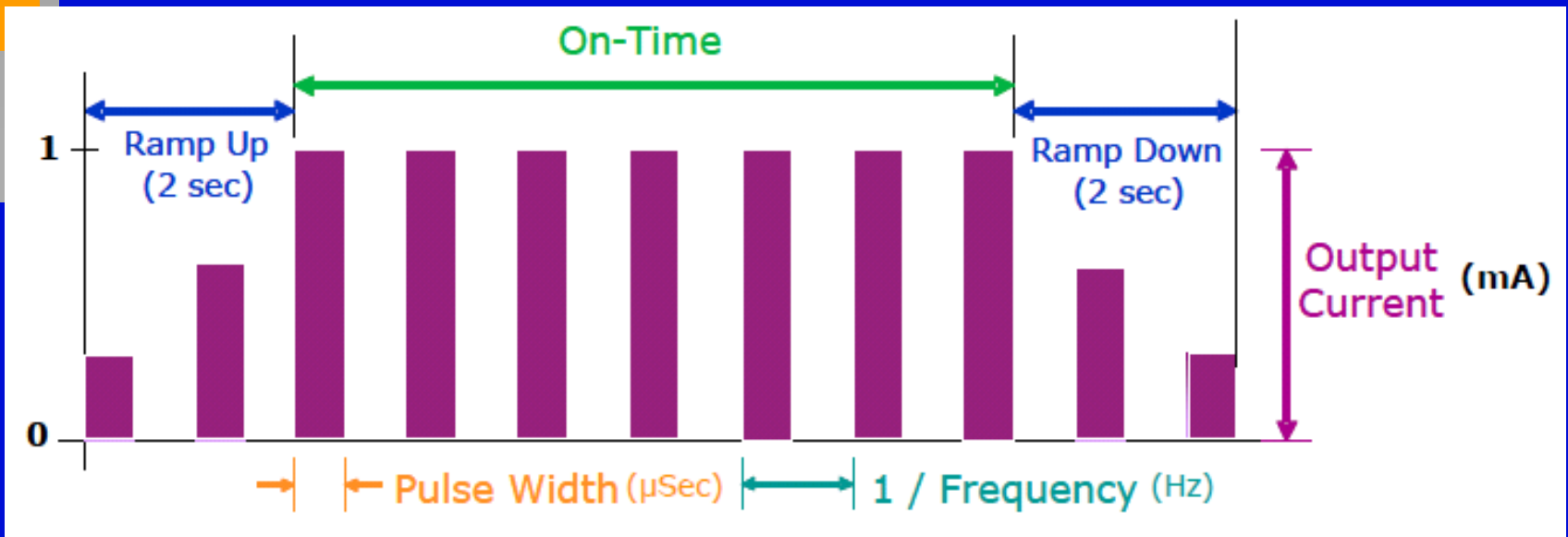
# *VNS Therapy is a proven treatment with a unique safety profile*

- **More than 60,000 patients worldwide have been implanted with VNS Therapy**
- **No known interactions with medications**
- **No reported systemic neurotoxic effects, rash, renal impairment, or bone marrow suppression**
- **No increase in sudden, unexpected death in epilepsy (SUDEP)<sup>1</sup>**
- **Gestational outcomes**
  - **Animal study has shown no evidence of impaired fertility or harm to the fetus due to VNS Therapy<sup>2,3</sup>**
  - **Pregnancies have gone to term with VNS<sup>4,5</sup>**



# *Several parameters can be adjusted to individualize treatment<sup>1</sup>*

- Each parameter can be independently programmed, thereby offering multiple setting combinations from which optimal stimulation for the patient can be selected<sup>1</sup>
- Safe and effective VNS Therapy is dependent primarily on output current, signal frequency, pulse width, ON/OFF time<sup>2</sup>



# *Patient Selection for Surgery: Criteria*

- ◆ Epilepsy syndrome not responsive to medical management
  - Unacceptable seizure control despite maximum tolerated doses of 2-3 appropriate drugs as monotherapy
- ◆ Epilepsy syndrome amenable to surgical treatment

# *Evaluation for Surgery*

- ◆ History and Exam: consistency, localization of seizure onset and progression
- ◆ MRI: 1.5 mm coronal cuts with sequences sensitive to gray-white differentiation and to gliosis
- ◆ Other neuroimaging options: PET, ictal SPECT
- ◆ EEG: ictal and interictal, special electrodes
- ◆ Neuropsychological battery
- ◆ Psychosocial evaluation
- ◆ Intracarotid amobarbital test (Wada)

# *Surgical Treatment*

- ◆ **Potentially curative**
  - Resection of epileptogenic region (“focus”) avoiding significant new neurologic deficit
- ◆ **Palliative**
  - Partial resection of epileptogenic region
  - Disconnection procedure to prevent seizure spread — corpus callosotomy
  - Multiple subpial transection

# *Epilepsy Surgery Outcomes*

	Temporal	Extra Temporal	Lesional	Hemispheric	Callosotomy
Seizure Free	68%	45%	66%	45%	8%
Improved	23%	35%	22%	35%	61%
Not improved	9%	20%	12%	20%	31%
Total	100%	100%	100%	100%	100%

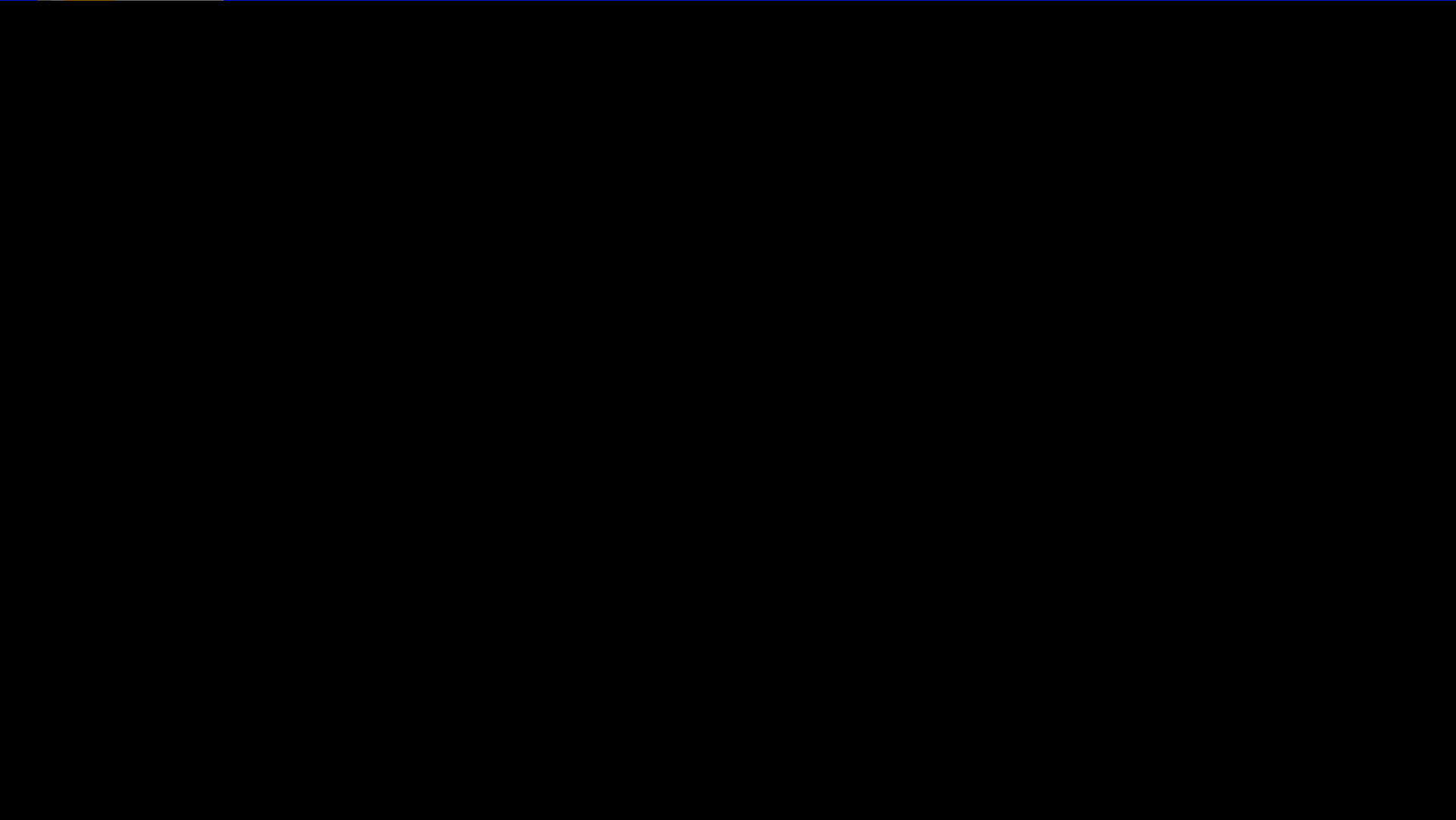
# *Status Epilepticus*

## ◆ Definition

- More than 30 minutes of continuous seizure activity  
or
- Two or more sequential seizures spanning this period without full recovery between seizures

# *Status Epilepticus*

- ◆ **A medical emergency**
  - Adverse consequences can include hypoxia, hypotension, acidosis and hyperthermia
  - Know the recommended sequential protocol for treatment with benzodiazepines, phenytoin, and barbiturates.
  - Goal: stop seizures as soon as possible





# *Status Epilepticus Treatment*

<u>Time post onset</u>	<u>Treatment</u>
Onset	Ensure adequate ventilation/O <sub>2</sub>
2-3 min.	IV line with NS, rapid assessment, blood draw
4-5 min.	Lorazepam 4 mg (0.1 mg/kg) or diazepam 10 mg (0.2 mg/kg) over 2 minutes via second IV line or rectal diazepam
7-8 min.	Thiamine 100 mg, 50% glucose 25 mg IV Phenytoin or fosphenytoin 20 mg/kg IV (phenytoin PE) at $\leq 50$ mg/per minute phenytoin or 150 mg per minute fosphenytoin ( $\leq 0.75$ mg/kg/min) Pyridoxine 100-200 mg IV in children under 18 mo.

# *Status Epilepticus Treatment (cont.)*

<u>Time post onset</u>	<u>Treatment</u>
10 min.	Can repeat lorazepam or diazepam if seizures ongoing
30-60 min.	EEG monitoring unless status ended and patient waking up
40 min.	Phenobarbital 20 mg/kg at $\leq 5$ mg per minute (0.75 mg/kg per minute)

continued

# *Status Epilepticus Treatment (cont.)*

Time post  
onset

Treatment

70 min.

Pentobarbital 3-5 mg/kg load, 1 mg/kg per hour infusion, increase to burst-suppression OR

Propofol 3-5 mg/kg load, 5-10 mg/kg/hr initial infusion then 103 mg/kg/hr OR

Midazolam 0.2 mg/kg load, .25-2 mg/kg infusion

# *Neonatal Seizures*

- ◆ Incidence: 1.6 – 3.5 per 1000 live births
- ◆ Major risk factors are prematurity, low-birth weight, HIE
- ◆ Association with increased morbidity and mortality
- ◆ May be symptomatic of treatable, serious condition (hypoglycemia, meningitis)
- ◆ Diagnosis: observation with vs. without EEG

References: Ronen, J Pediatr, 1999; Lanska, Neurology, 1995; Saliba, Am J Epidemiol, 1999.

# *Recognition of Neonatal Seizures*

- ♦ Observation of abnormal, repetitive attacks of movements, postures or behaviors
- ♦ Classification
  - subtle
  - tonic
  - clonic
  - myoclonic
  - autonomic
- ♦ Evaluation for cause(s) of seizures
- ♦ Confirmation/support by EEG

# *Examples of Acquired Conditions That May Provoke Neonatal Seizures*

- ◆ Hypoxia-ischemia
- ◆ Physical trauma
- ◆ Toxic-metabolic
- ◆ Inborn errors of metabolism
- ◆ Systemic or CNS infections
- ◆ Intracranial hemorrhage

# *Acute Treatment of Neonatal Seizures*

- ◆ Phenobarbital  
loading dose: 20 mg/kg
- ◆ Fosphenytoin  
loading dose: 20 mg/kg PE@ 1
- ◆ Diazepam  
first dose about 0.25 mg/kg
- ◆ Lorazepam  
first dose about 0.05 to 0.1 mg/kg

# *Selected Pediatric Epilepsy Syndromes*

## ◆ **Epileptic Encephalopathies**

- West Syndrome — infantile onset, hypsarrhythmic EEG, tonic/myoclonic seizures; idiopathic vs. symptomatic
- Lennox-Gastaut Syndrome — childhood onset, slow spike-wave EEG, tonic, atypical absence, atonic and other seizure types
- Myoclonic epilepsies of infancy and early childhood — heterogeneous



# *Selected Pediatric Epilepsy Syndromes (cont.)*

- ◆ **Febrile convulsions — 6 mo.-5 yrs.**
  - Simple: Duration less than 15 minutes, generalized, and do not recur within 24 hours
  - Complex: Duration longer than 15 minutes, focal in nature or recur within 24 hours
- ◆ **Febrile convulsions: Risk Factors for development of epilepsy:**
  - Complex febrile seizures
  - Neurodevelopmental abnormalities
  - Afebrile seizures in first-degree relatives
  - Recurrent febrile seizures
  - Febrile seizures following brief and low grade fever
  - Febrile seizure onset in first year

# *Selected Pediatric Epilepsy Syndromes (cont.)*

- ◆ Benign epilepsy with centrotemporal spikes — nocturnal oropharyngeal simple partial, rare secondarily generalized seizures
- ◆ Childhood epilepsy with occipital paroxysms — visual phenomena, at times with secondary generalization

# *Selected Pediatric Epilepsy Syndromes (cont.)*

- ◆ Idiopathic generalized epilepsies
  - Childhood absence epilepsy — absence, occasionally with tonic-clonic seizures
  - Juvenile myoclonic epilepsy — myoclonic, tonic-clonic, at times absence

# *AEDs in Pediatrics*

- ◆ Extrapolation of efficacy data from adult studies
- ◆ Importance of adverse effects relative to efficacy
- ◆ Susceptibility to specific adverse effects (valproate hepatotoxicity, lamotrigine rash)
- ◆ Age-related pharmacokinetic factors
- ◆ Neonate: low protein binding, low metabolic rate, possible decreased absorption if given with milk/formula
- ◆ Children: faster metabolism

# *Differential Diagnosis of Non-epileptic Events*

- ◆ Syncope
- ◆ Migraine
- ◆ Cerebral ischemia
- ◆ Movement disorder
- ◆ Sleep disorder
- ◆ Metabolic disturbance
- ◆ Psychiatric disturbance
- ◆ Breath-holding spells

# *Psychogenic Nonepileptic Seizures*

- ◆ 10-45% of patients referred for intractable spells
- ◆ Females > males
- ◆ Psychiatric mechanism — disassociation, conversion
- ◆ Common association with physical, emotional, and sexual abuse
- ◆ Spells with non-epileptic etiology
- ◆ Non-ictal pattern on EEG

# *Psychogenic Nonepileptic Seizures (cont.)*

- ◆ Represents psychiatric disease
- ◆ Once recognized, approximately 50% respond well to specific psychiatric treatment
- ◆ Epileptic and nonepileptic seizures may co-exist
- ◆ Video-EEG monitoring often required for diagnosis

# *Syncope*

- ♦ Characteristic warning, usually gradual (except with cardiac arrhythmia)
- ♦ Typical precipitants (except with cardiac arrhythmia)
- ♦ Minimal to no postictal confusion/somnolence
- ♦ Convulsive syncope — tonic>clonic manifestations, usually < 30 sec; usually from disinhibited brainstem structures (only rarely from cortical hypersynchronous activity)



# *Pregnancy and Epilepsy*

- ◆ Most pregnancies in mothers with epilepsy produce normal children
- ◆ Fetal anomalies (up to 10% of pregnancies) are multifactorial
  - Drug effects
  - Consequences of the mother's underlying diseases
  - Consequence of maternal seizures during pregnancy
- ◆ All antiepileptic drugs carry teratogenic risks
- ◆ Polytherapy increases risk

Reference: Practice Parameter: Management issues for women with epilepsy (summary statement): Report of the Quality of Standards Subcommittee of the American Academy of Neurology. *Neurology* 1998; 51: 944-948.

# *Pregnancy and Epilepsy Guidelines for Management*

- ♦ All women of child-bearing potential should receive education and carefully considered management before and during pregnancy to optimize the chances of a good outcome for both mother and child.

*Reference: Liporace J, D'Abreu. Epilepsy and Women's Health: Family Planning, Bone Health, Menopause, and Menstrual Related Seizures. Mayo Clinic Proceedings 2003; 78: 497-506.*

# *Pregnancy and Epilepsy Guidelines for Management*

## ♦ Education

- Most women with epilepsy have normal children
- Risk of fetal malformations is increased
- AED teratogenicity is related to exposure in the first trimester of pregnancy
- Prenatal diagnosis of fetal malformations is possible
- Seizures may be deleterious to the fetus
- Compliance with AED treatment is important

# *Pregnancy and Epilepsy Guidelines for Management*

## ◆ Before pregnancy

- Attempt AED monotherapy with lowest effective dose
- Folate supplementation (at least 1 mg/day orally)

## ◆ During pregnancy

- Monitor AED dose requirements to maximize seizure control
- Continue folate supplementation
- Consider prenatal diagnosis of fetal malformations
- Vit K (10 mg/day orally) starting at 36 weeks
- General prenatal care

# *Driving and Epilepsy*

- ◆ Regulation varies state by state regarding:
  - Reporting requirements
  - Required seizure-free period
  - Favorable/unfavorable modifiers
- ◆ Insurance issues
- ◆ Employment issues

Resource: [www.efa.org](http://www.efa.org)

# *First Aid*

## *Tonic-Clonic Seizure*

- ◆ Turn person on side with face turned toward ground to keep airway clear, protect from nearby hazards
- ◆ Transfer to hospital needed for:
  - Multiple seizures or status epilepticus
  - Person is pregnant, injured, diabetic
  - New onset seizures
- ◆ **DO NOT** put any object in mouth or restrain



## *Case Study 5*

- ♦ **Seizure History:** Her birth was unremarkable except that she was born with syndactyly requiring surgical correction.
- ♦ **Early developmental milestones were met at appropriate ages.**
- ♦ **She had her first convulsive episode at age 2 in the setting of a febrile illness.**



## *Case Study 5*

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- ◆ **How would you evaluate and treat a patient with a febrile seizure?**
- ◆ **What clinical features are important in guiding your evaluation?**

## *Case Study 5*

- ♦ **She began to develop a new type of episode in the third grade.**
- ♦ **The attacks consisted of her seeing a pink elephant that was sitting on various objects and waving to her.**
- ♦ **The patient has subsequently found a ceramic model of an elephant that was the same as the elephant that she saw during her seizures.**

## *Case Study 5*

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- ◆ **How are her symptoms different from most patients with schizophrenia?**

## *Case Study 5*

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- ◆ **She was not diagnosed with seizures until the age of 15.**
- ◆ **Initially, the seizures were controlled with medicine.**
- ◆ **After a few years, however, the attacks re-occurred despite treatment with anticonvulsants.**

## *Case Study 5*

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- ♦ **At age 20, the seizures changed in character to the current pattern.**
- ♦ **The seizures begin with an aura of “a chilling sensation starting at the lower back with ascension to the upper back over the course of 10-20 seconds”.**

## *Case Study 5*

- ♦ **Observers then note a behavioral arrest.**
- ♦ **She tends to clench her teeth and breath heavily, such that her breathing sounds “almost as if she were laughing”.**
- ♦ **She is unable to fully respond to people for 5-10 minutes.**
- ♦ **Typically, she experiences 4-5 seizures per month.**

## *Case Study 5*

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- ◆ She has had several EEGs in the past; the most recent available report is from seven years ago, which revealed mild, diffuse slowing of background elements with no abnormalities noted during three minutes of hyperventilation and photic stimulation.
- ◆ She had an MRI 13 years ago with no reported abnormalities.

## *Case Study 5*

- ♦ **She has tried several different medications, but is currently maintained on carbamazepine and lamotrigine. Her carbamazepine dose is 700 mg/day and Lamotrigine 125 mg/day with BID dosing.**
- ♦ **She feels excessively tired on higher doses.**
- ♦ **She has been on carbamazepine 32 years and on lamotrigine for four years.**
- ♦ **She states that she has had some success with the lamotrigine.**



## *Case Study 5*

- ♦ In the past, she has been unsuccessfully tried on phenobarbital, primidone, valproate, gabapentin, phenytoin and ethosuximide.
- ♦ She had marked weight gain while taking valproate.
- ♦ She hated having seizures in public and she “felt like a prisoner in my own home”.
- ♦ Upon hearing of seizure surgery, she requested a referral for evaluation.

## *Case Study 5*

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- ◆ **When are seizures “medically refractory”?**
- ◆ **When should you consider an inpatient video EEG evaluation?**
- ◆ **What might you learn from such an evaluation?**

# *Case Study 5*

## Past Medical History:

- 1) Migraine headaches (with the last one occurring four years ago)
- 2) status-post hysterectomy with removal of one ovary 25 years ago
- 3) history of syndactyly at birth with surgical corrections;
- 4) partial thyroidectomy 32 years ago during pregnancy.

# *Case Study 5*

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## Social History:

- ♦ She currently lives with her mother.
- ♦ She works as a sales clerk.
- ♦ She completed twelve years of school and finished one semester of college.
- ♦ She has not driven a car after being reported to the DMV by her doctor 23 years ago.

## *Case Study 5*

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- ♦ **She tells you that she still has her driver's license.**
  - 1) **What are your legal and ethical obligations as a physician?**
  - 2) **What are some of the employment issues experienced by people with epilepsy?**

# *Case Study 5*

- ♦ **Family History:** She has a cousin with a history of "grand mal" seizures who died at age 12.
- ♦ **Habits:** She does not use of alcohol, tobacco, or illicit drugs.
- ♦ **Medications:** Carbamazepine 600/400 mg/day BID, Lamotrigine 50/75 mg/day BID, Conjugated estrogens 1.25 mg PO qd, thyroxine 100 mcg PO qd, and sumatriptan PRN.
- ♦ **Neurologic Examination:** Normal

# *Case Study 5*

## ◆ **Impression**

- **Possible Mesial Temporal Lobe Epilepsy**
  - Auras of forced recall and rising autonomic experience
  - Complex Partial Seizure
- **Seizures refractory to multiple antiepileptic medications**

## ◆ **Recommendation**

- **Epilepsy Surgery Evaluation**

## *Case Study 5*

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- ◆ **The patient underwent video-EEG monitoring.**

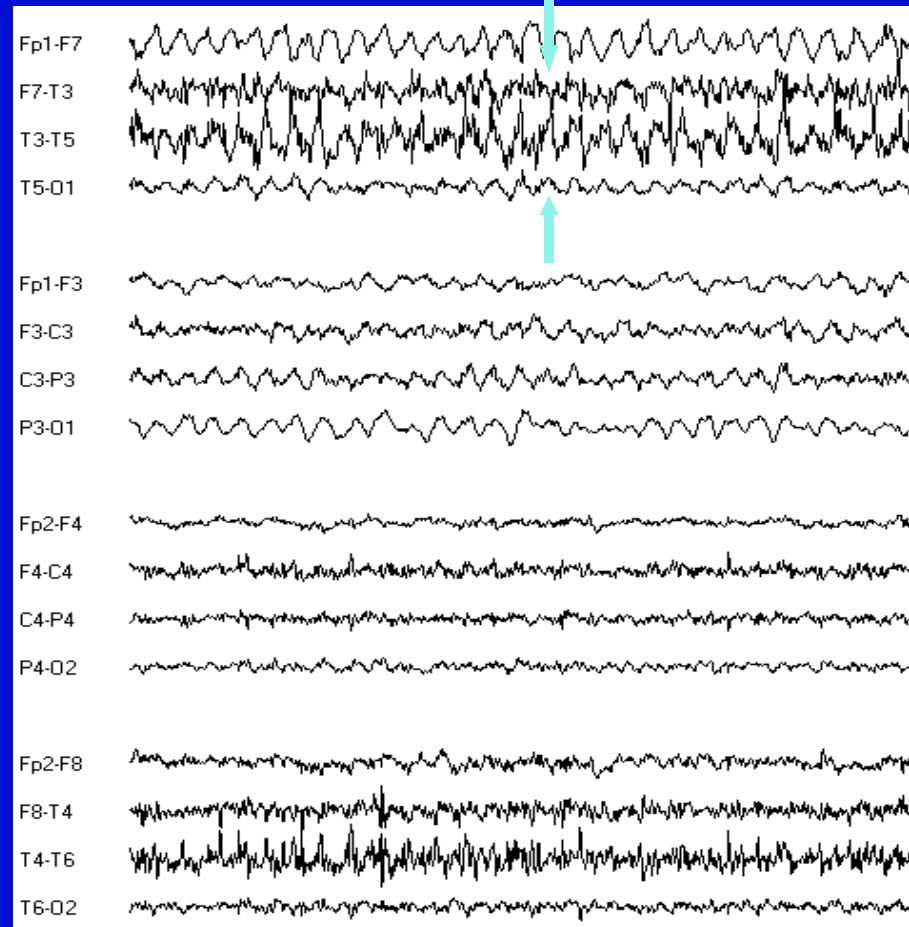


## *Case Study 5*

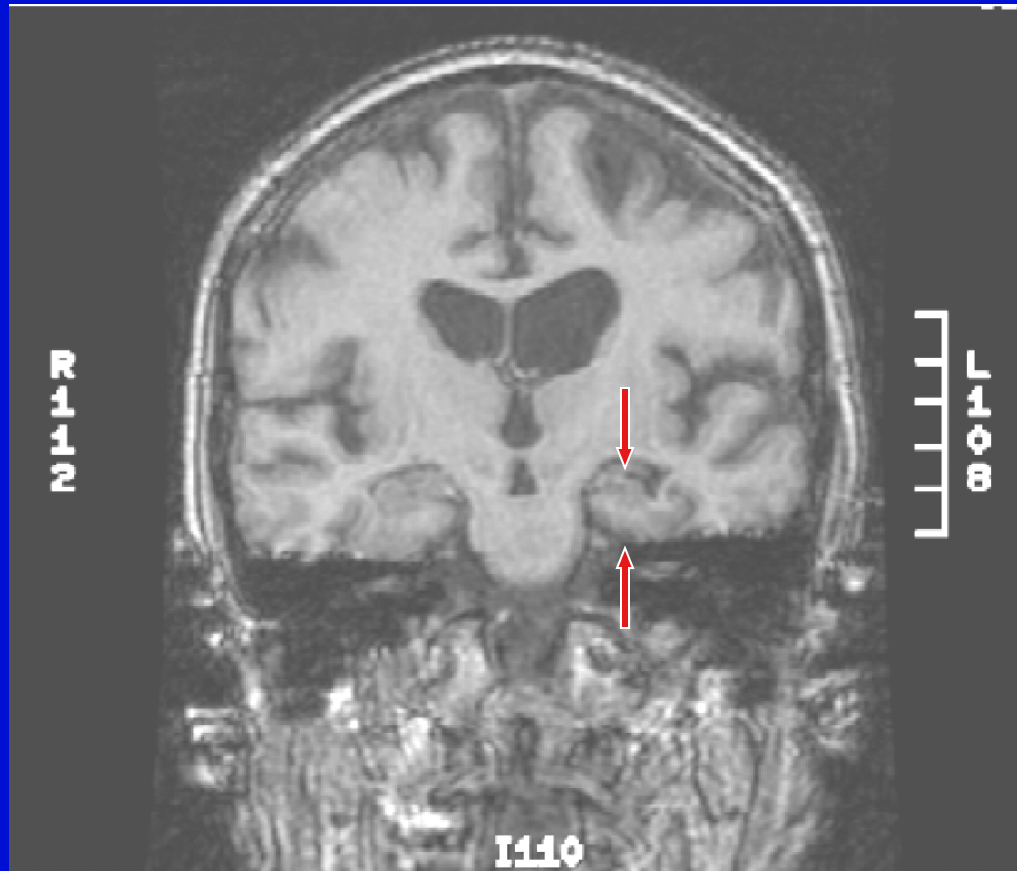
- ◆ **During 5 days of video EEG, she had 3 typical CPS.**
- ◆ **Her seizures began with her typical aura followed by lip smacking and left hand automatisms. Right hand had tonic posture**
- ◆ **She had a brief post-ictal aphasia**

# Case Study 5

EEG onsets consisted of a rapid build up of rhythmic theta frequency activity over the left temporal region (Arrows)



# Case Study 5



- ♦ MRI reveals an atrophic L. Hippocampus

# *Case Study 5*

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## **Pre-surgical Evaluation:**

### **◆ Neuropsychological Testing**

- **Performance and Verbal IQ normal**

### **◆ Wada (Intracarotid amobarbital) test**

- **Language on Left side only**
- **No memory difference with left and right injections**

# *Case Study 5*

## **Pre-surgical Evaluation: Conclusions**

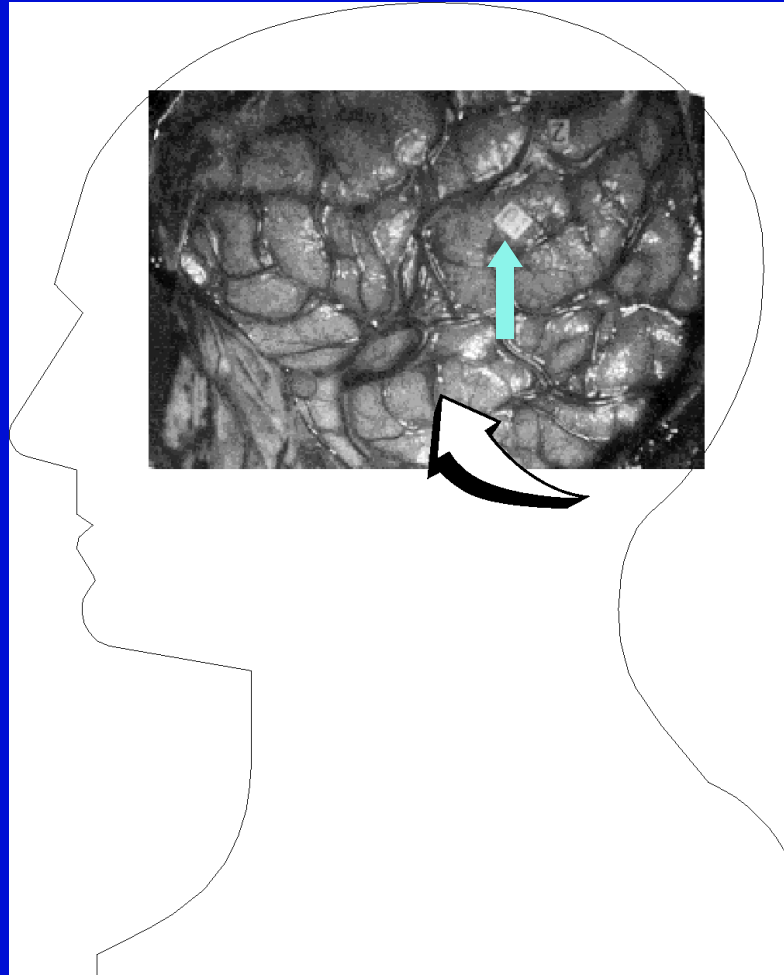
- ◆ **She has complex partial seizures refractory to anticonvulsant treatment**
- ◆ **Clinical and EEG features are compatible with seizure origin from the left, language-dominant temporal lobe**
- ◆ **MRI suggests mesial temporal sclerosis is the underlying pathology**
- ◆ **She has an excellent chance for a seizure-free outcome with a left anterior temporal lobe resection**

# *Case Study 5*

## **Surgery**

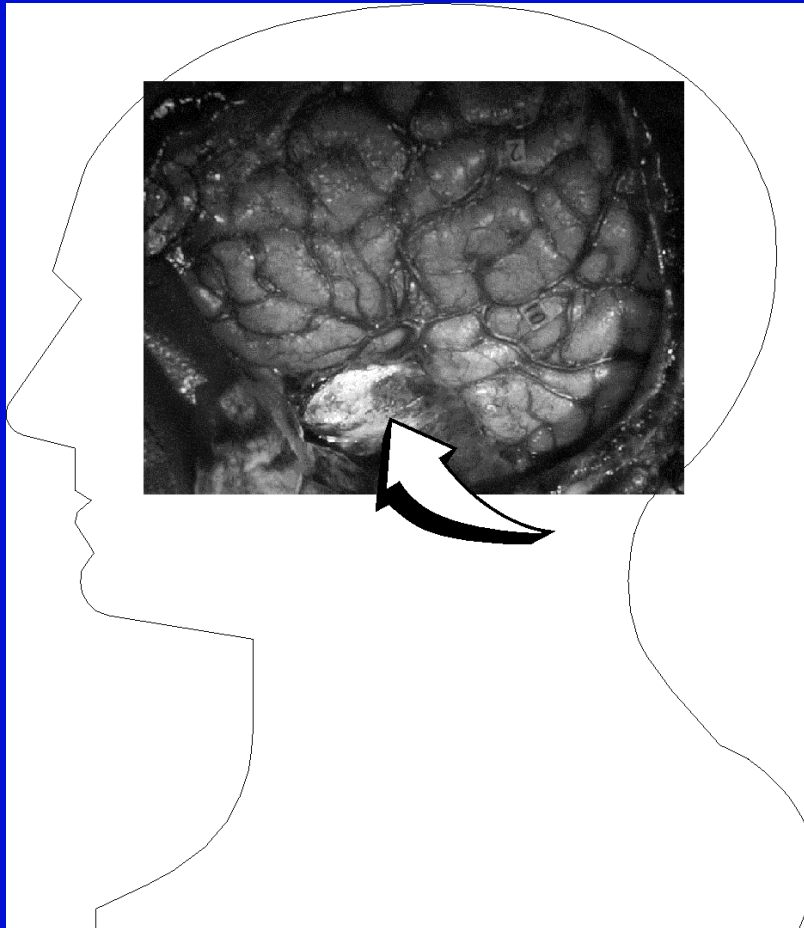
- ♦ **Surgery under local anesthesia**
- ♦ **Language map determined by electrical stimulation**
- ♦ **Language areas (green arrow) and epileptogenic tissue (white arrow) labeled on next slide**

# Case Study 5



- ◆ MRI showing language areas

# Case Study 5



## Surgery

- ♦ Anterior temporal lobe resected (arrow)
- ♦ Amygdala and hippocampus also resected



# *Case Study 5*

## **Follow-up**

- ◆ **Immediately following surgery she had mild dysnomia**
- ◆ **At three months post-op, cognitive testing confirmed no change from pre-op**
- ◆ **She has had no seizures for two years. She declines a trial off of anticonvulsants for fear of recurrent seizures. She drives to her appointment in a new car.**
- ◆ **She writes, “I’ m now having a life I never knew was possible”**