Epilepsy and seizure

Definitions

- 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

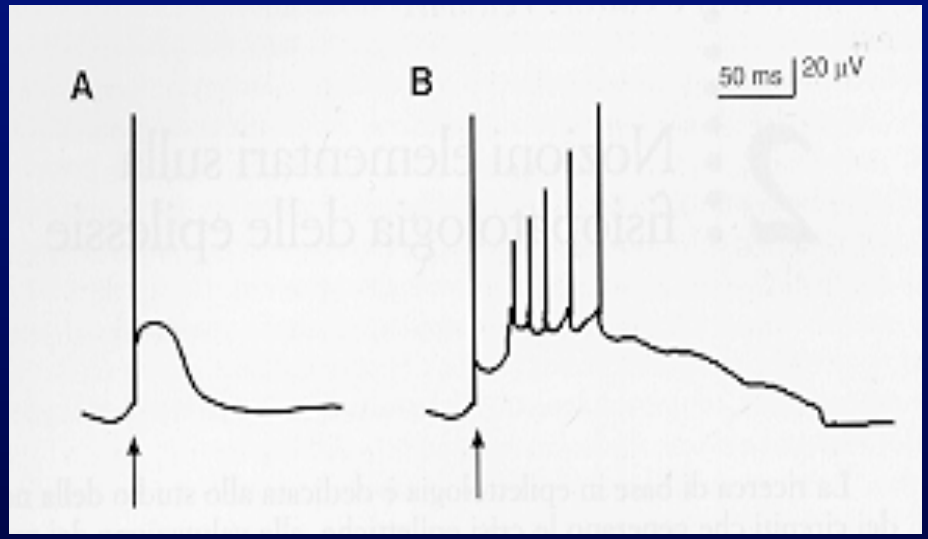
- Seizures
  - Incidence: approximately 80/100,000 per year
  - Lifetime prevalence: 9%
    (1/3 benign febrile convulsions)
- Epilepsy
  - Incidence: approximately 45/100,000 per year
  - Point prevalence: 0.5-1%

Pathophysiology

Seizure results from imbalance in neuronal excitability

Factors characterizing neuronal activity f=during seizure:

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

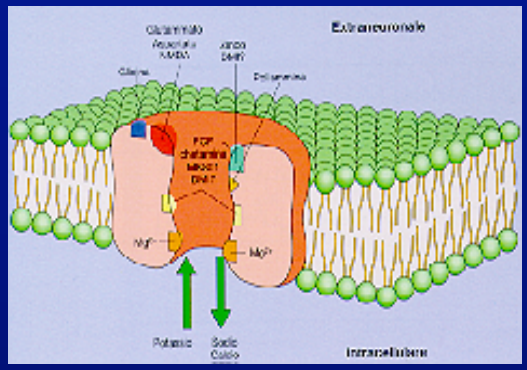


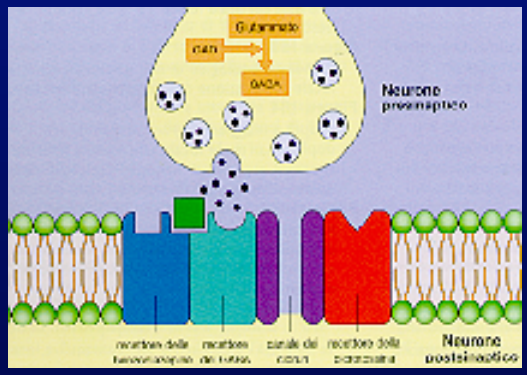
A. Neuron with one action potential

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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medical animation

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

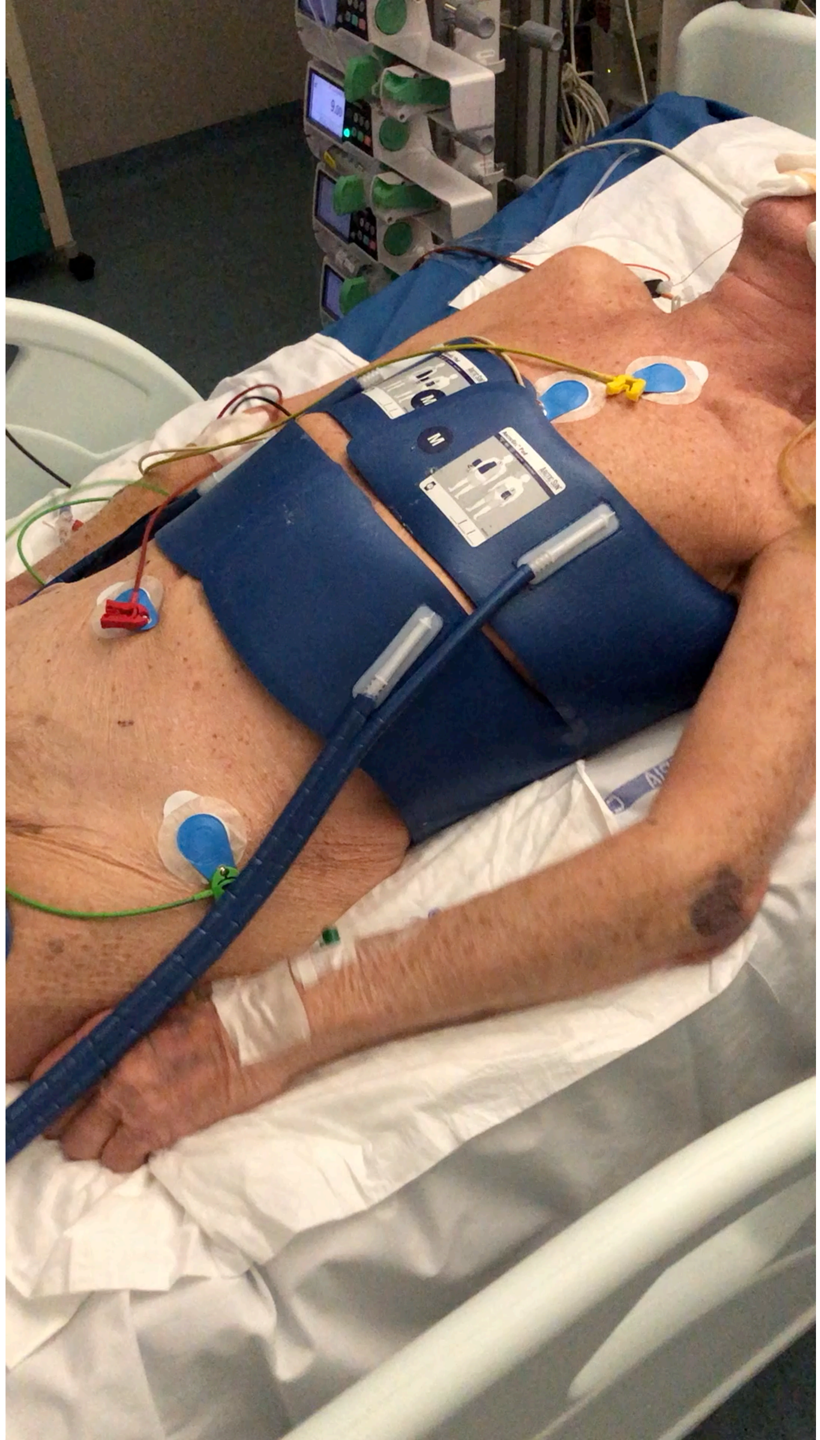
I. Generalized seizures

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

ILAE Commission on Classification and Terminology, 2010

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.
- <u>Pathophysiology</u>:
  - 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 (jacksonnian) 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.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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 (≥ 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)

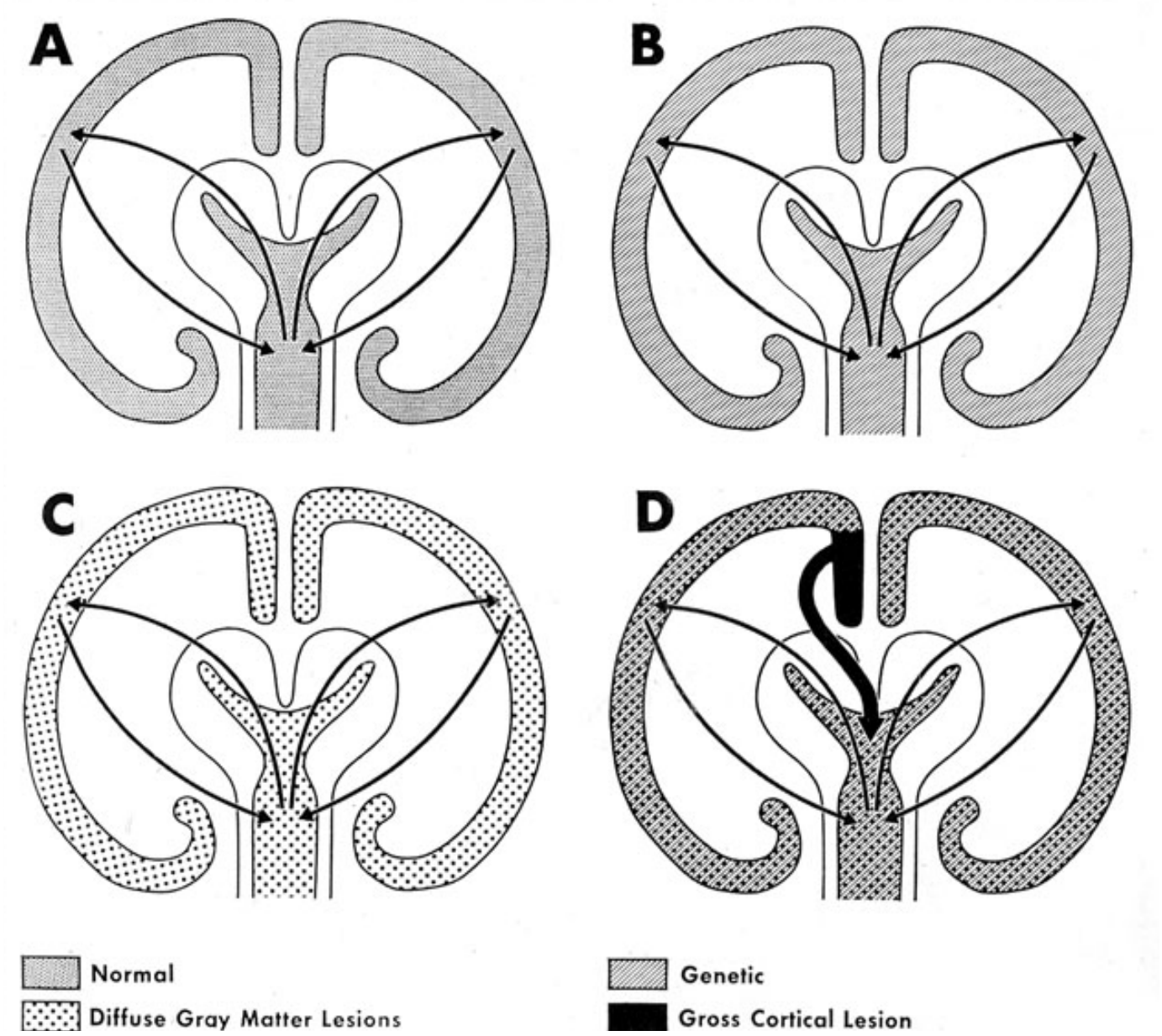
- Epileptic falls (loss of erect posture) due to atonic, myoclonic or tonic seizure mechanism.
- Pathophysiology:
  - depends on the underlying seizure type, and usually result from a generalized seizure disorder.

Absence seizure

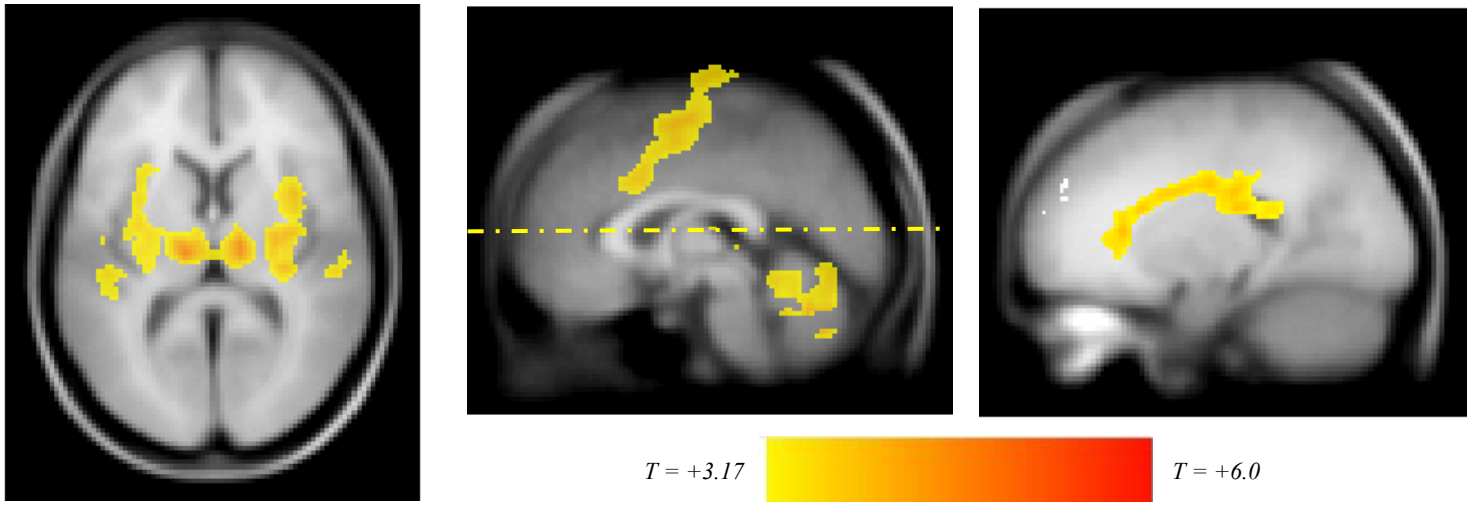
- Episodes of unresponsiveness or decreased responsiveness not explained by motor or speech alterations.
- A manifestation of generalized epilepsies and typically associated with generalized 3 Hz SW complexes in typical absences (sudden onset and ceased abruptly, precipitated by HV); atypical absences (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

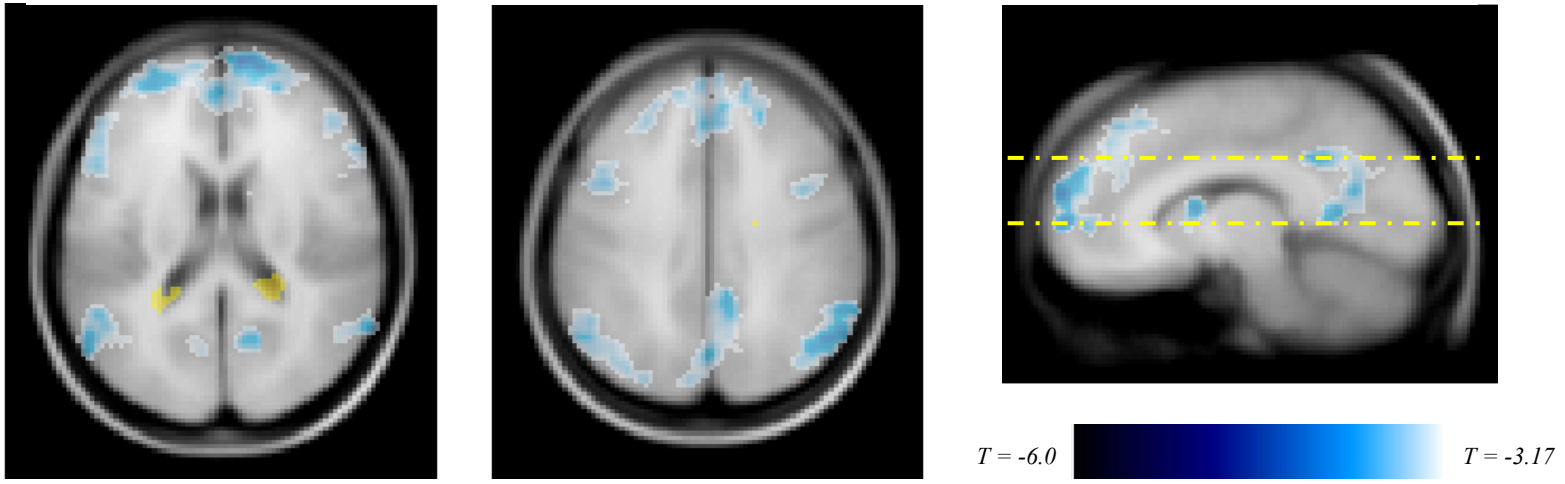
Generalized cortico-reticular epilepsies (Gloor, 1969)



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



Gotman et al., *PNSA* 2005



Axis 2 – seizure types

self-limited epileptic seizures

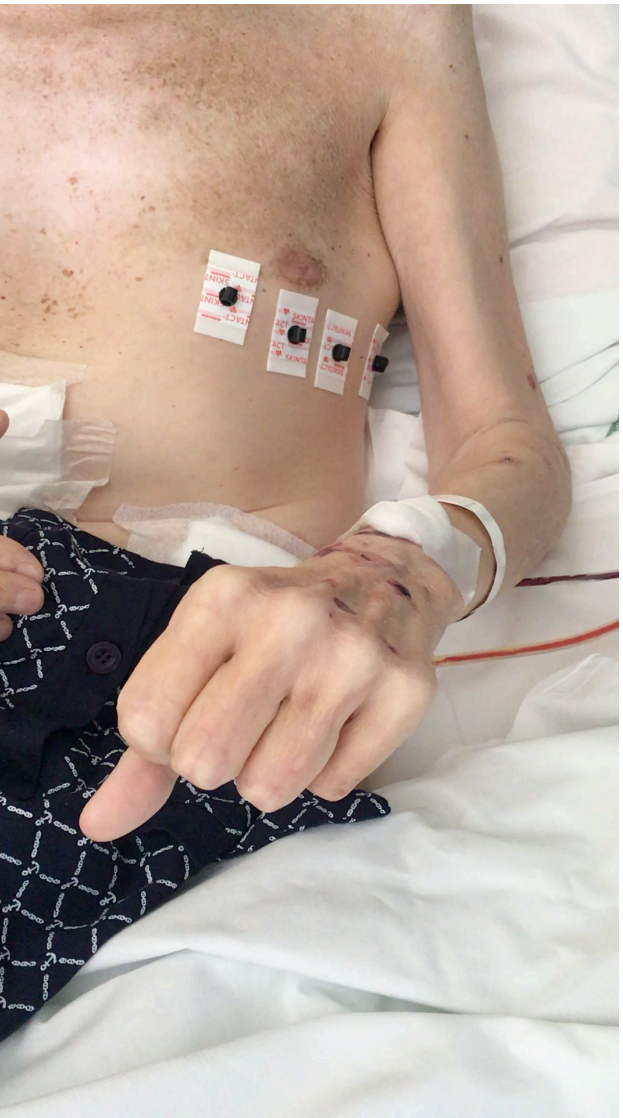
II. Focal seizures

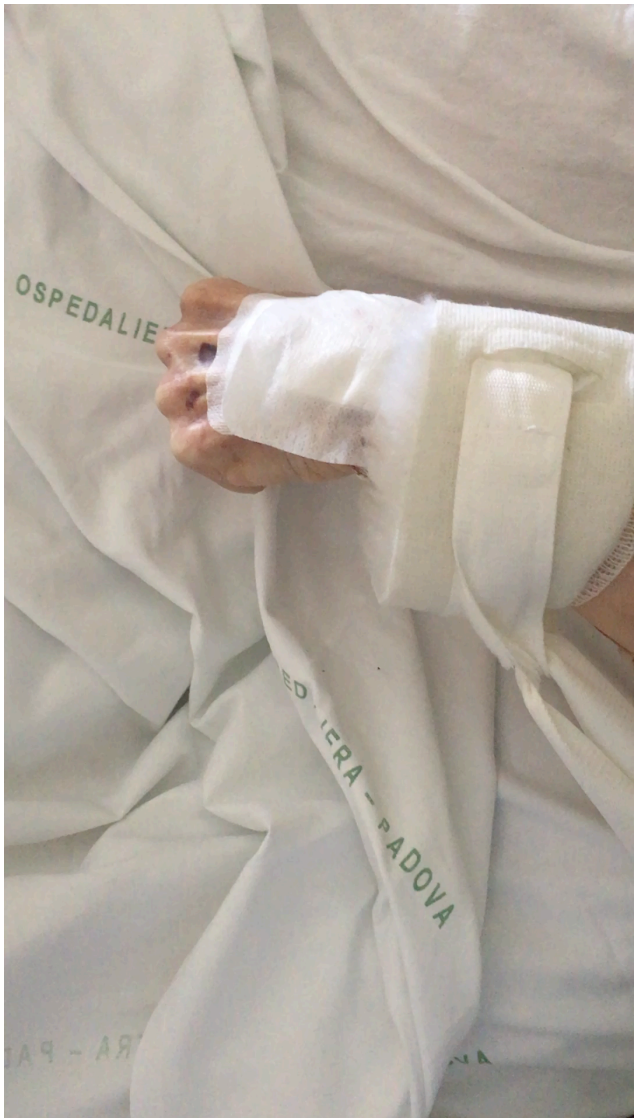
- Without impairment of consciouness or awareness
  with observable motor or autonomic components
  involving subjective sensory or psychic phenomena
- With impairment of consciousness or awareness
- Evolving to a bilateral convulsive seizure

* Glossary of descriptive terminology for ictal semiology

ILAE Commission on Classification and Terminology, 2010

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))

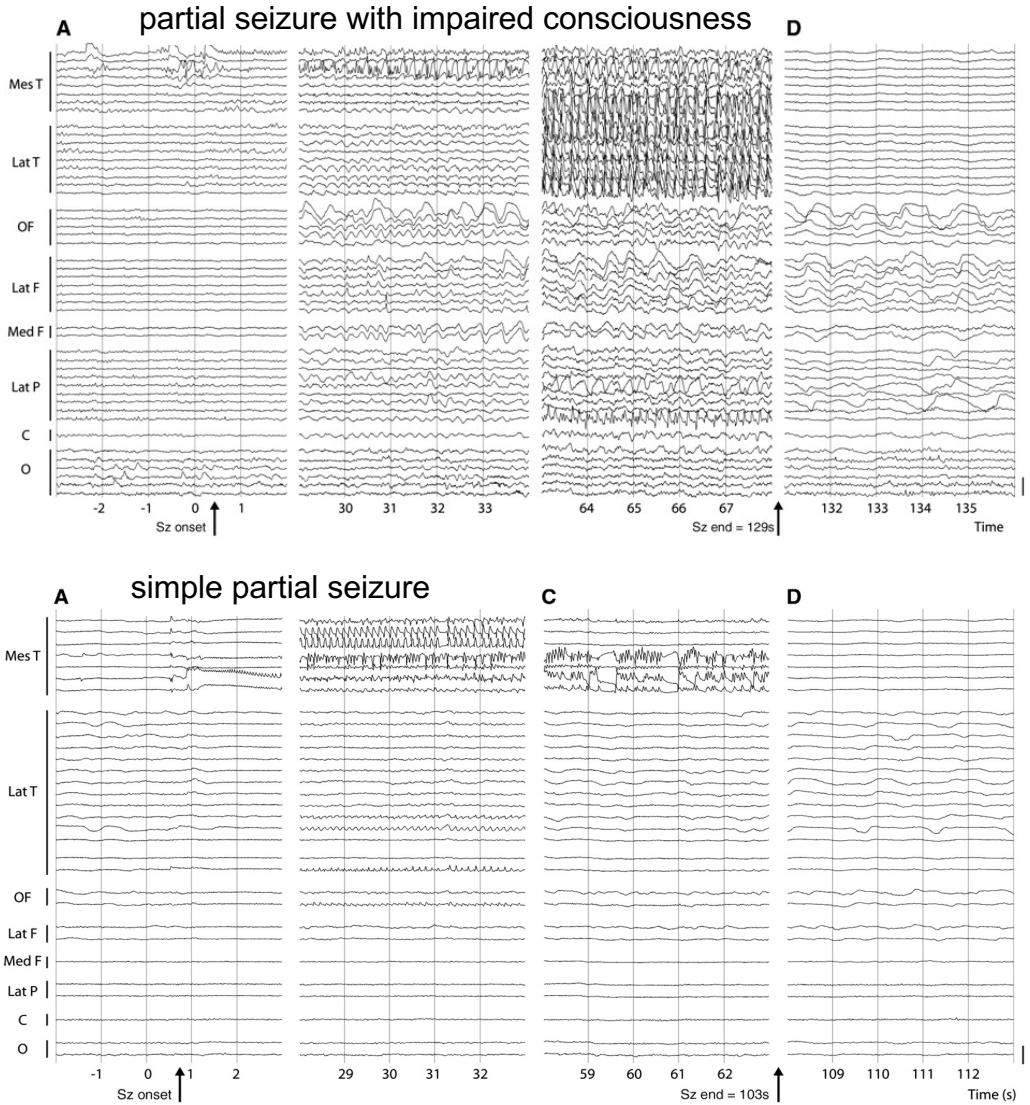
  Gustatory (S2 and rolandic operculum, insula)

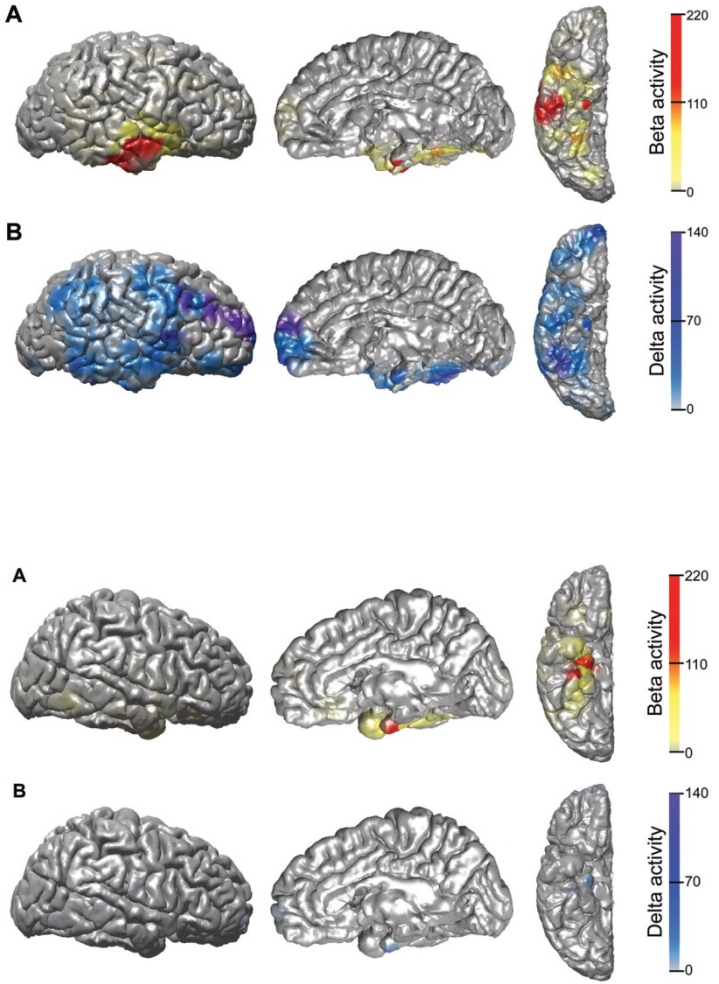
  Vestibular (insular-parietal-temporal)

  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





Englot et al. *Brain* 2010

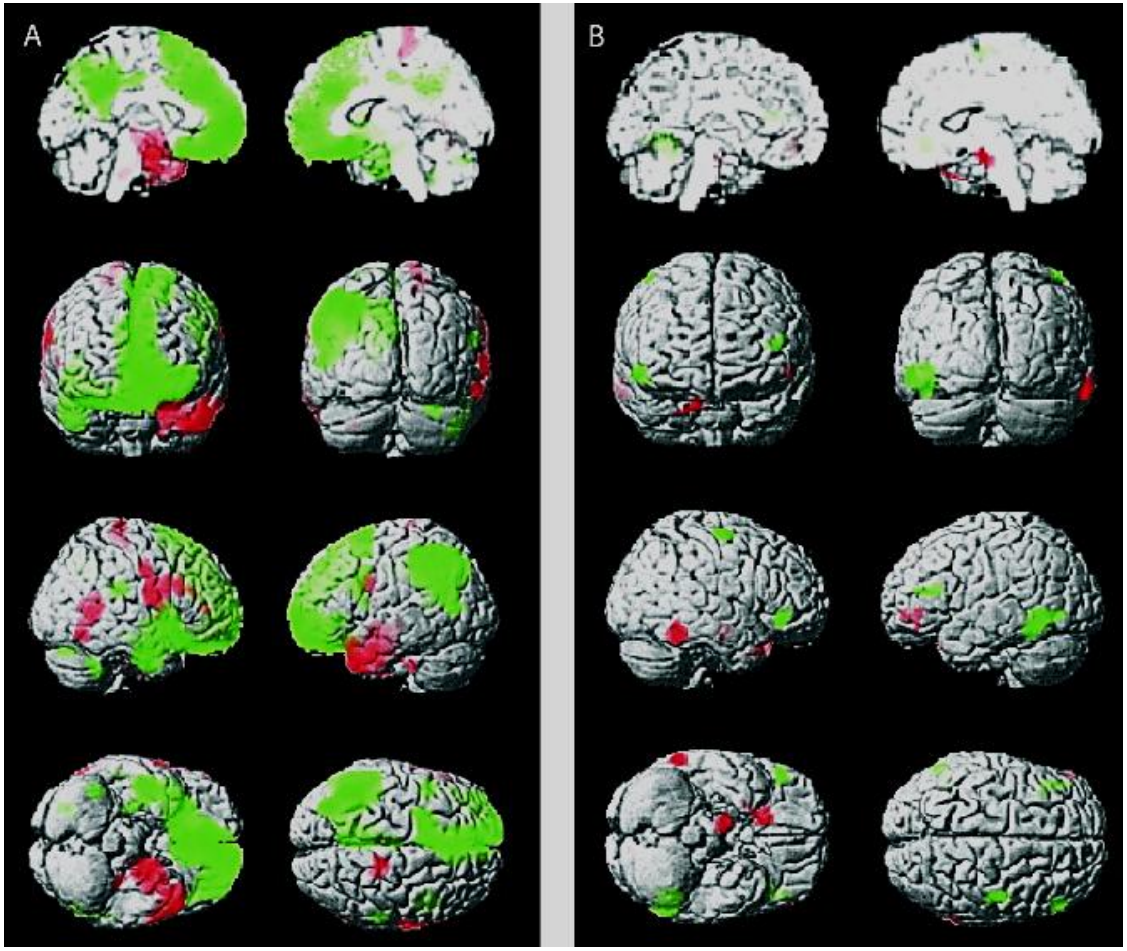
Focal TL seizures with impaired consciousness are associated with CBF decreases in frontal and parietal association cortex

focal seizures with impaired consciousness

n = 8

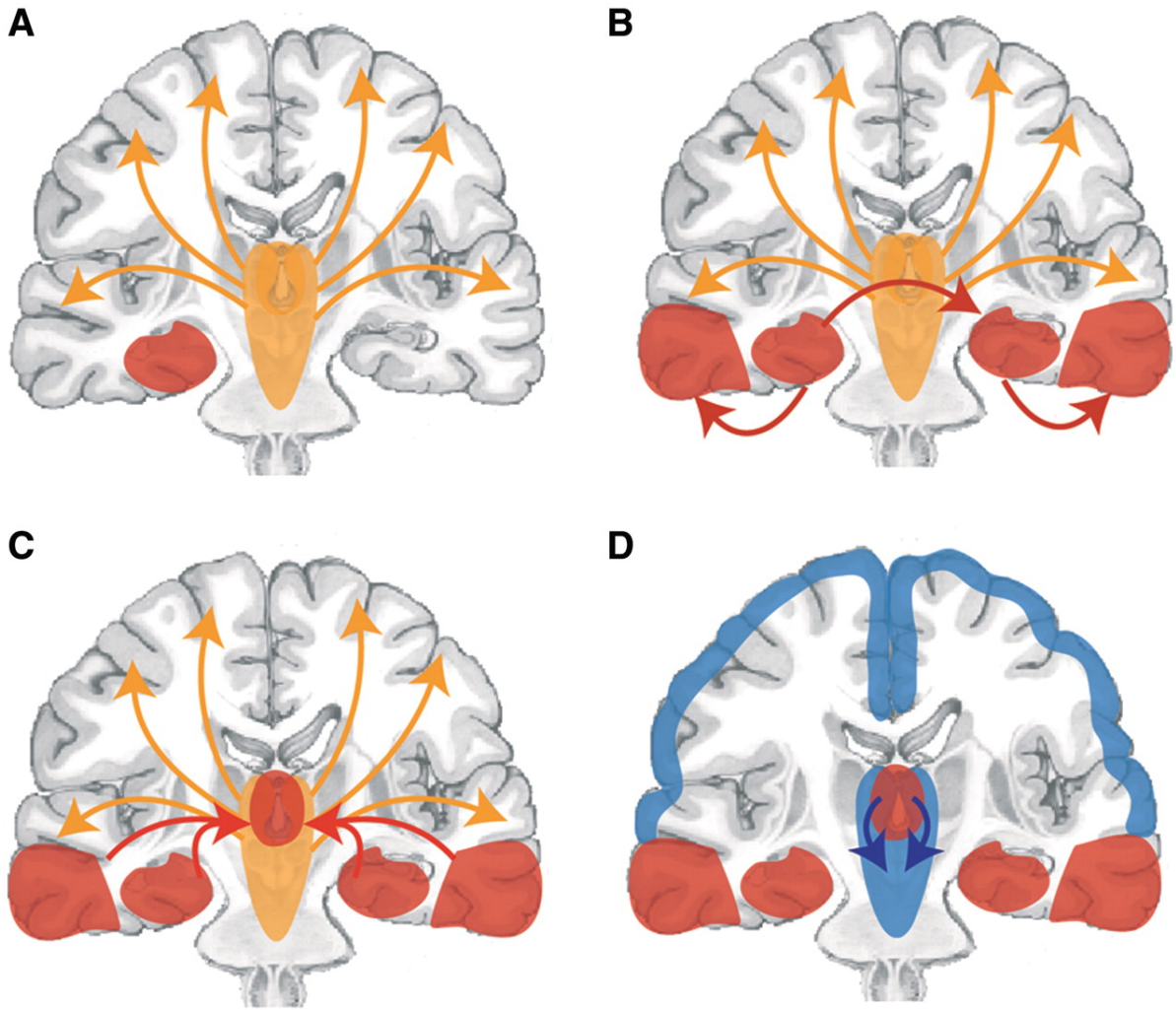
Simple focal seizures

n = 6



Blumenfeld et al.
Cerebral Cortex 2004

Network inhibition hypothesis for impaired consciousness during focal seizures.



Englot D J et al. *Brain* 2010

Ictal simple and complex motor phenomena
(head, eye and limb movements)

- Versive seizure (eyes, head or trunk)
- Unilateral clonic or tonic seizures
- Dystonia
- Automatisms (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


Georg Thieme Verlag - Neurologische Differenzialdiagnose

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

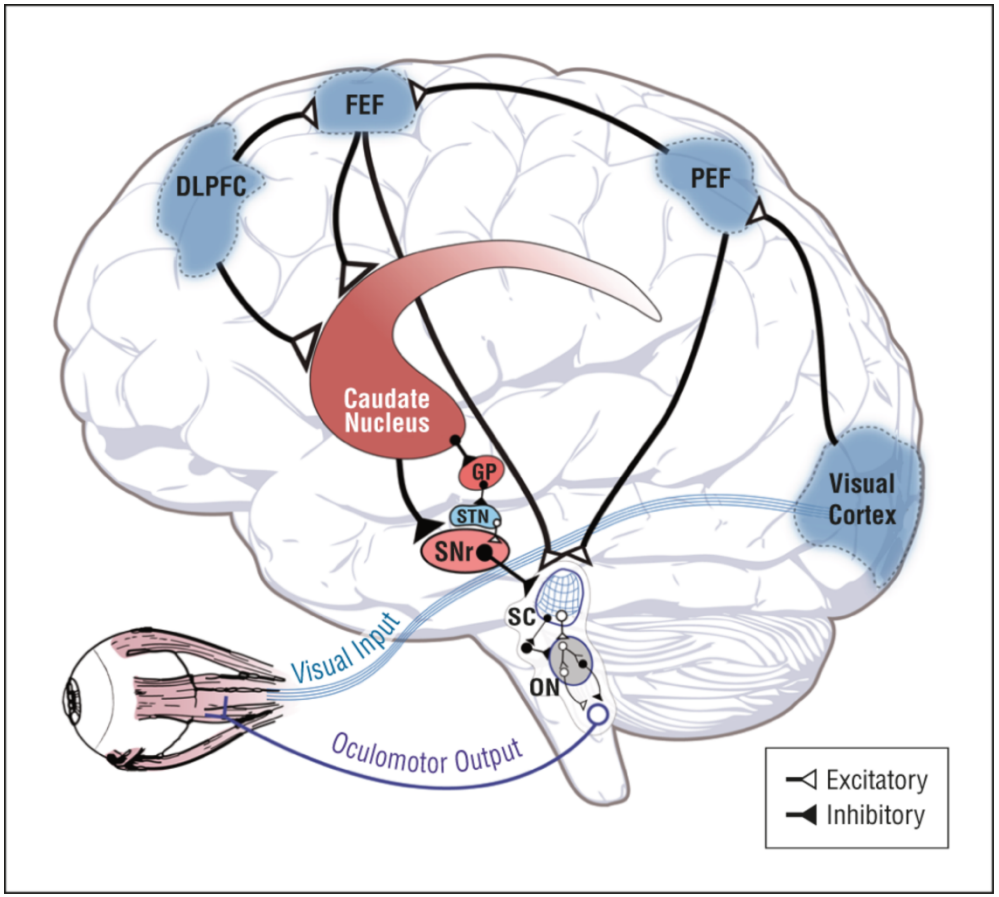
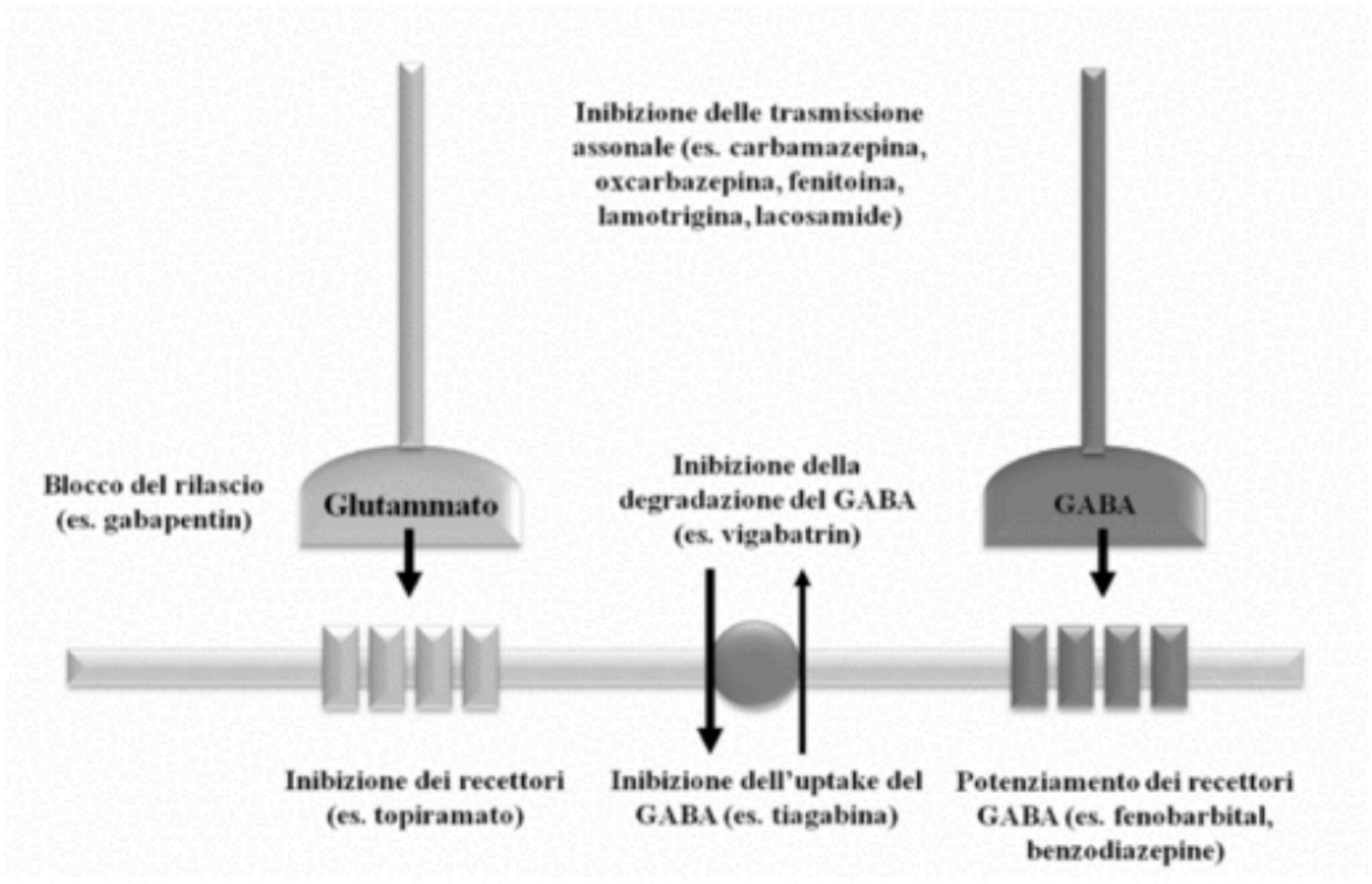


Figure. Saccadic eye movements are supported by a distributed network of cortical and subcortical regions. Saccades are initiated by direct signals sent from the frontal or parietal eye fields (FEFs or PEFs) to the superior colliculus (SC), which drives the oculomotor network (ON) in the brainstem. An 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.


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
Fp2-F8
F8-A2
T6-O2
T5-O1
20:44:35


Inibizione delle trasmissione assonale (es. carbamazepina, oxcarbazepina, fenitoina, lamotrigina, lacosamide)
Blocco del rilascio (es. gabapentin)
Glutammato
Inibizione della degradazione del GABA (es. vigabatrin)
GABA
Inibizione dei recettori (es. topiramato)
Inibizione dell'uptake del GABA (es. tiagabina)
Potenziamento dei recettori GABA (es. fenobarbital, benzodiazepine)

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	+++

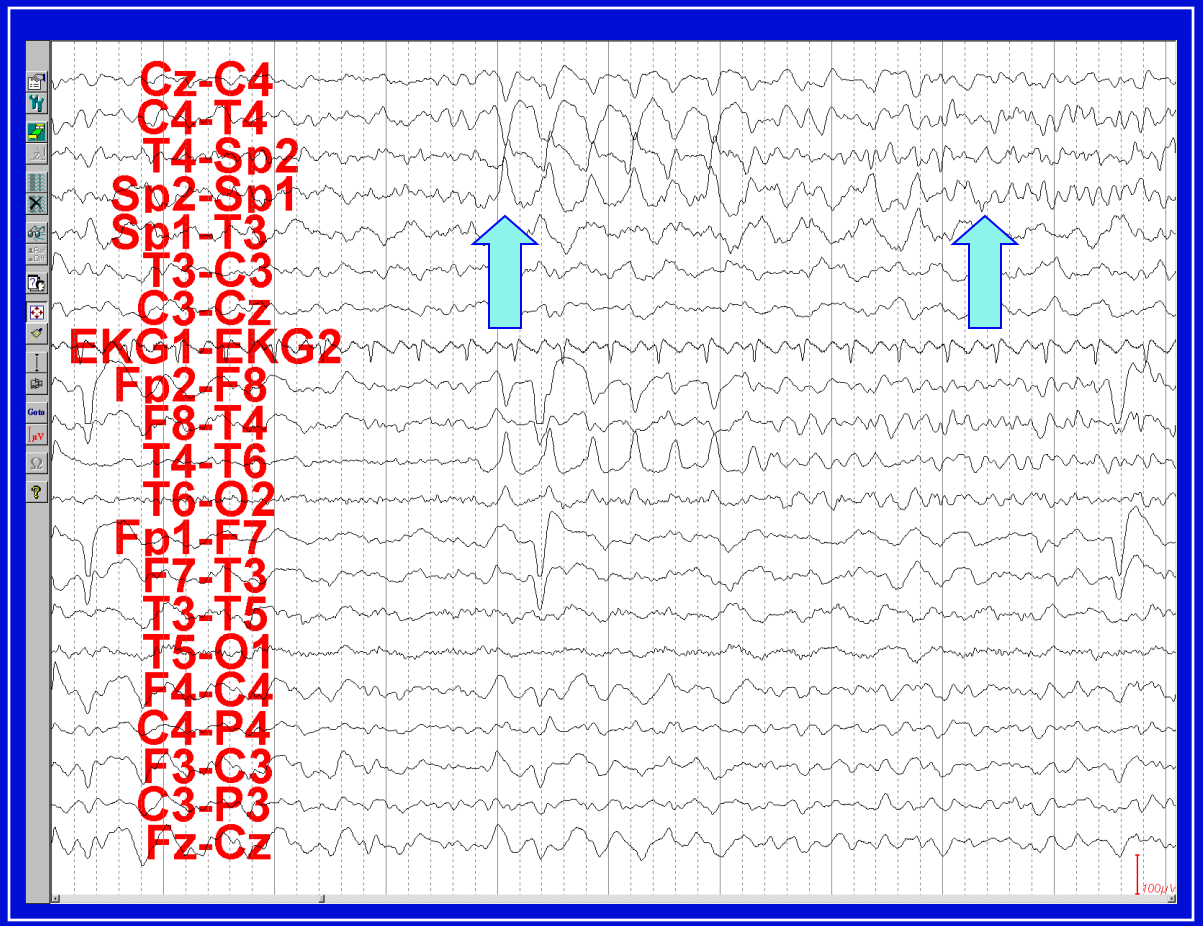
Ictal lateralizing phenomena - autonomic

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	++

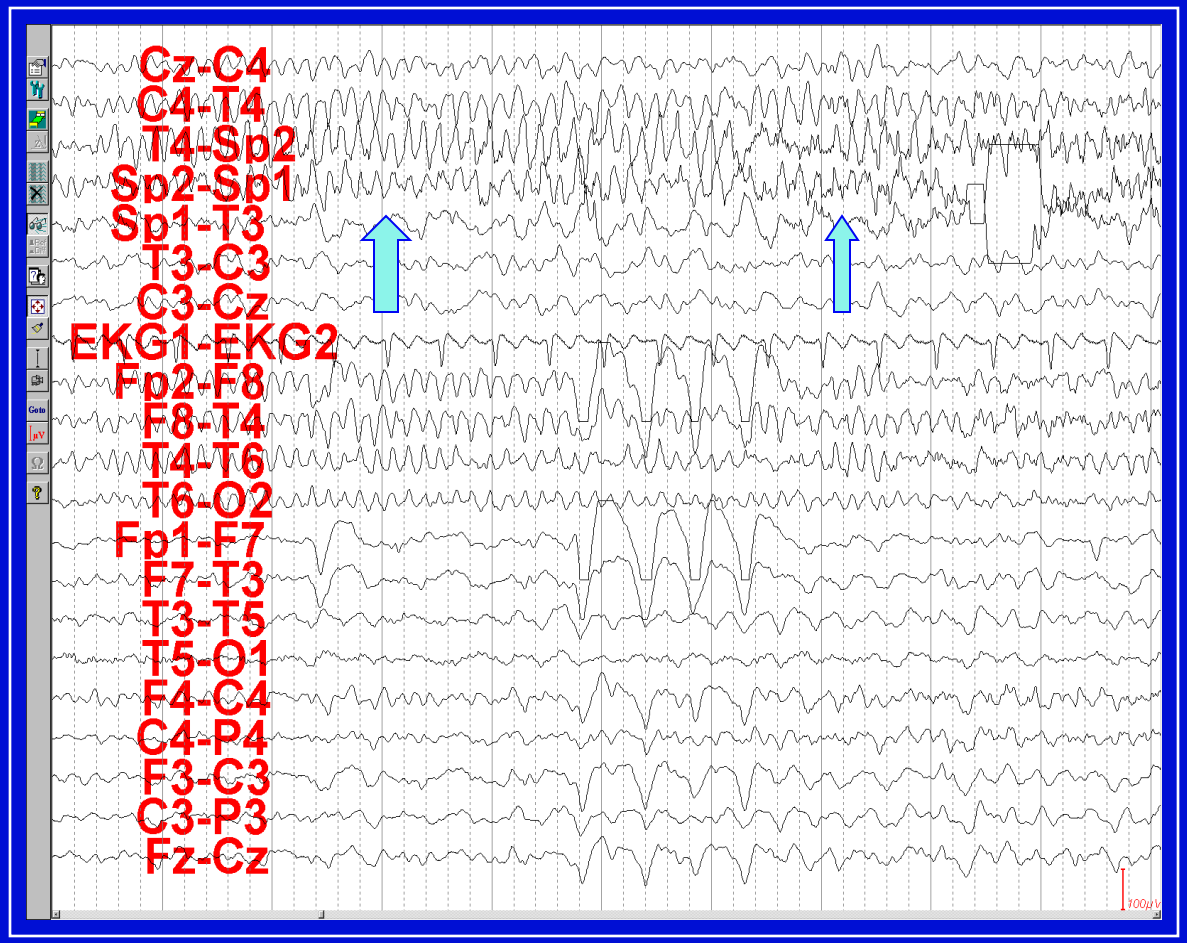
EEG: Simple Partial Seizure



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

Continued on C-Slide9

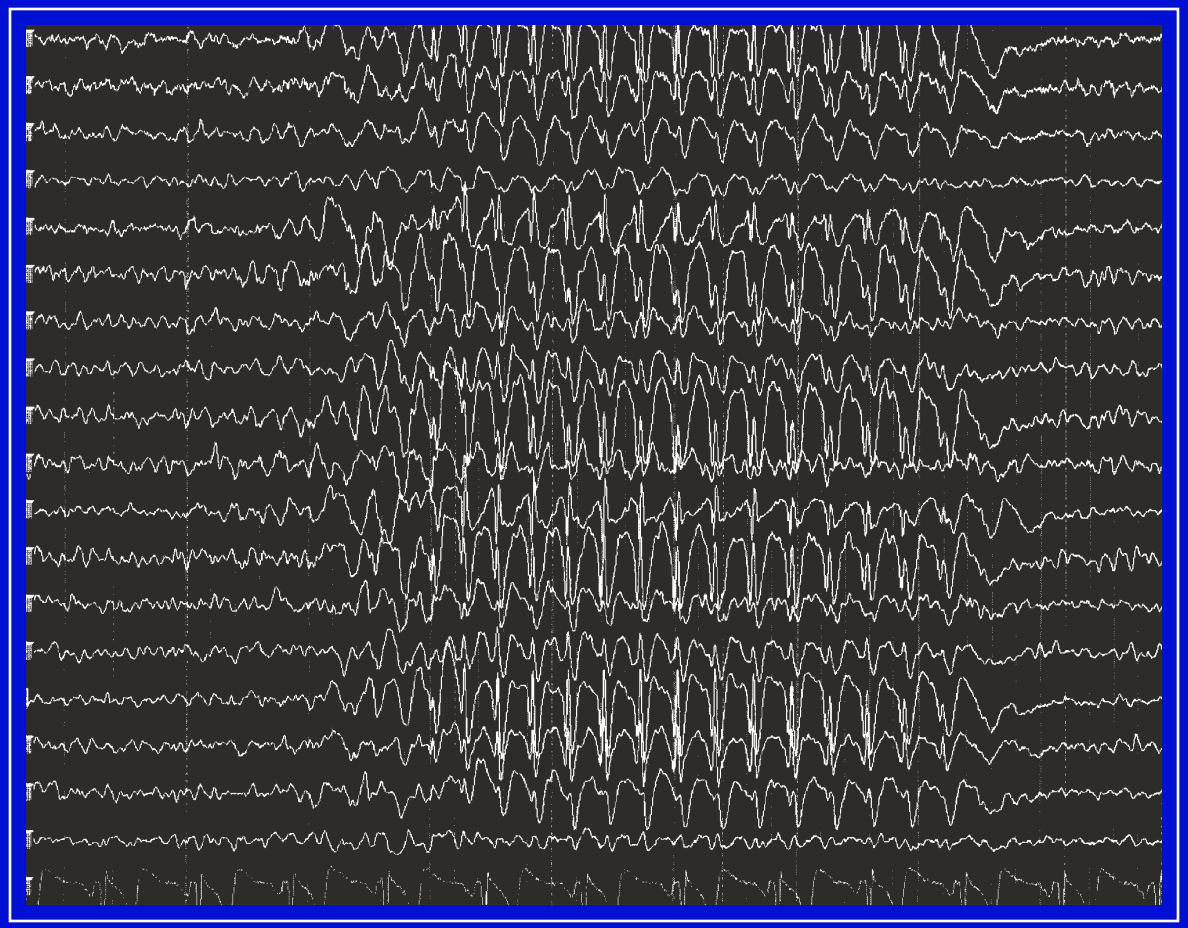
EEG: Simple Partial Seizure



Continuation of same seizure (C-slide-8)

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

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

- 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

Metabolic and Electrolyte Imbalance

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

Seizure Precipitants, con't

Stimulation/Other Pro-convulsant Intoxication

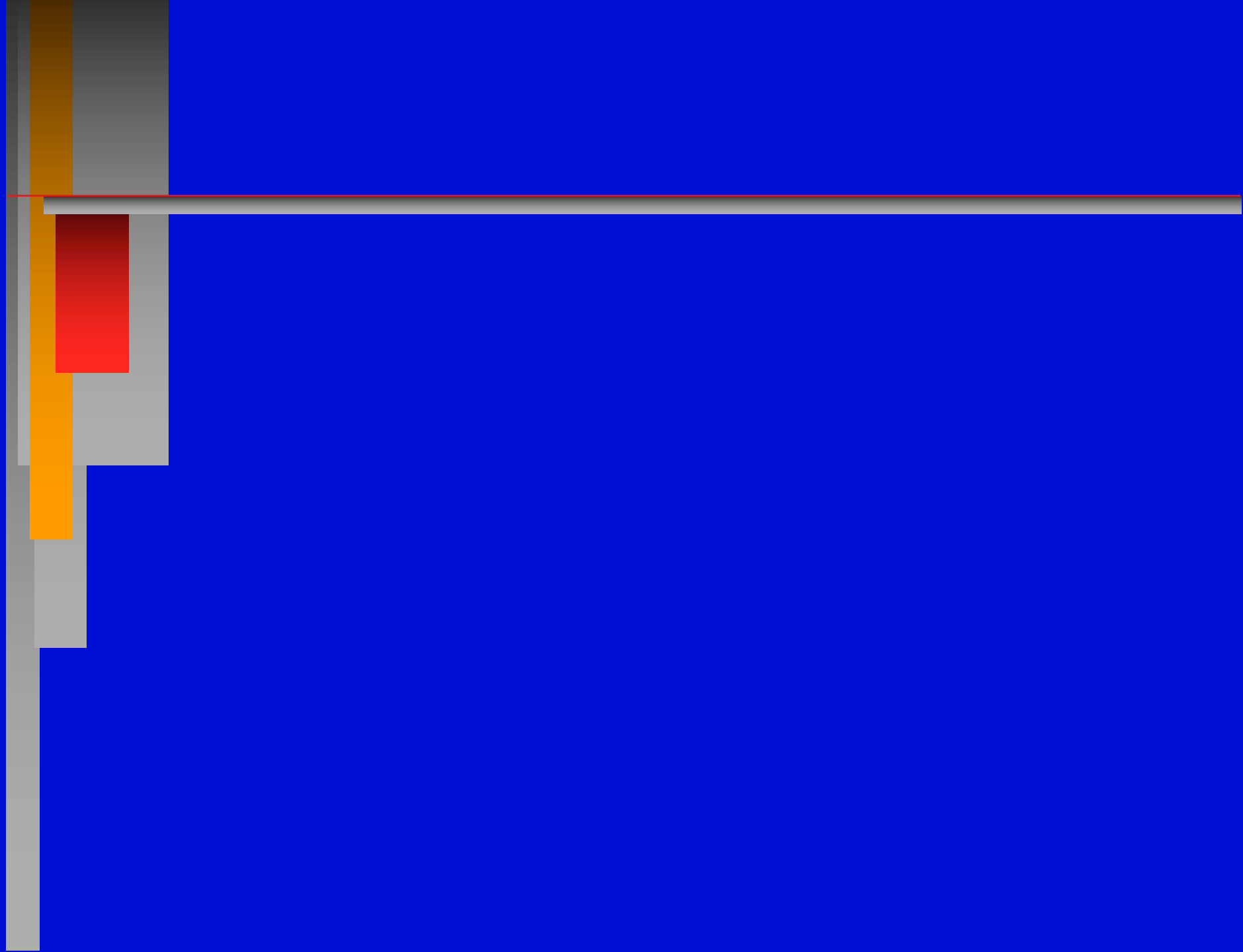
- IV drug use
- Cocaine
- Ephedrine
- Other herbal remedies
- Medication reduction

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
felbamate
gabapentin
lamotrigine
levetiracetam
oxcarbazepine
phenobarbital
phenytoin
primidone
tiagabine
topiramate
valproate
zonisamide

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 ≥ 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

- 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

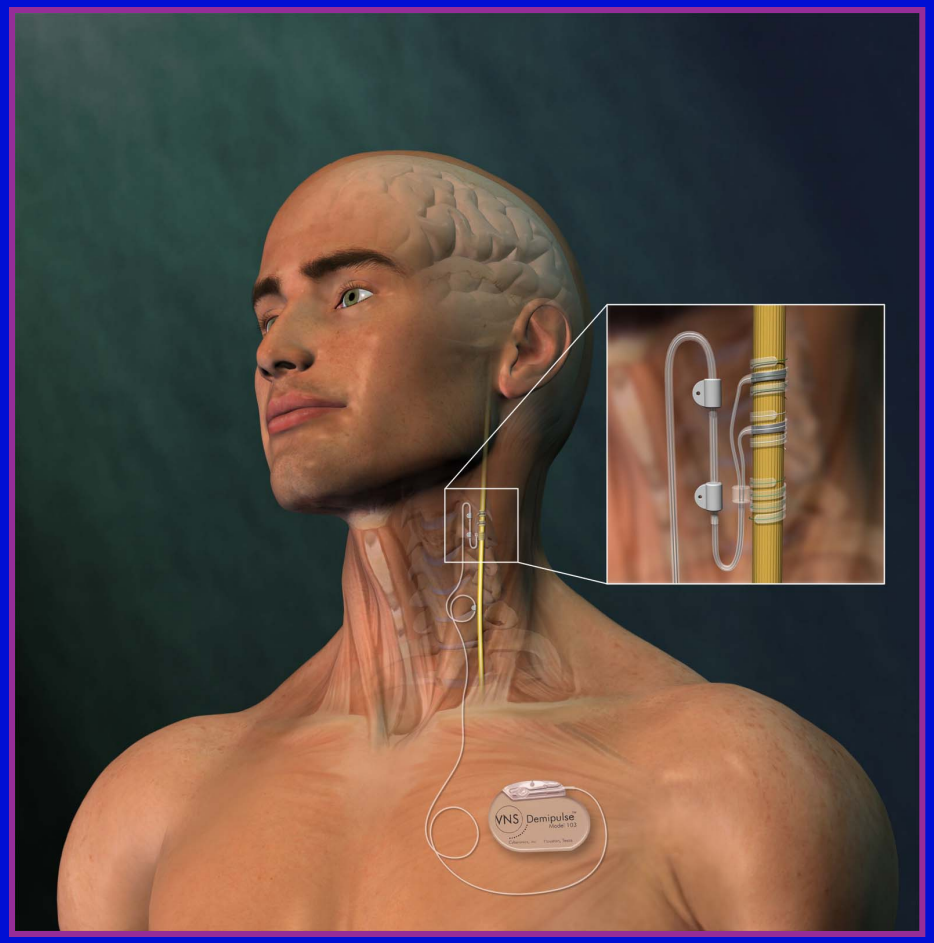
- Increase in cholesterol (total and LDL) and triglycerides, decrease in HDL-cholesterol
- Decrease in blood levels of L-carnitine, may be temporary
- Loss of calcium in urine
- Abnormal electrocardiograms (rare)
- Kidney stones occur in 5-8%

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[1,2]**
- **Initiates on demand stimulation**
  - **May abort or decrease severity of seizures[1-3]**
  - **May improve postictal period[2]**
- **Stops stimulation**
  - **Acutely manage side effects[3]**

1. Boon P, et al. J Clin Neurophys. 2001;18:402-407. 2. Fromes GW, et al. Epilepsia. 2000;41(suppl 7):117. 3. Schachter SC and Saper CB. Epilepsia. 1998;39:677-686.

VNS Therapy has a unique side effect profile

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

1. Ben-Menachem E, et al. Neurology. 1999;52(6):1265-1267. 2. Ben-Menachem E. J Clin Neurophysiol. 2001Sep;18(5):415-418. 3. Schacter SC. Neurology. 2002;59(suppl 4):S15-S20. 4. Alexopoulos AV, et al. Seizure. 2006;15(7):491-503. 5. Sirven JI, et al. Neurology. 2000;54:1179-1182.

VNS Therapy is a proven treatment with a unique safety profile

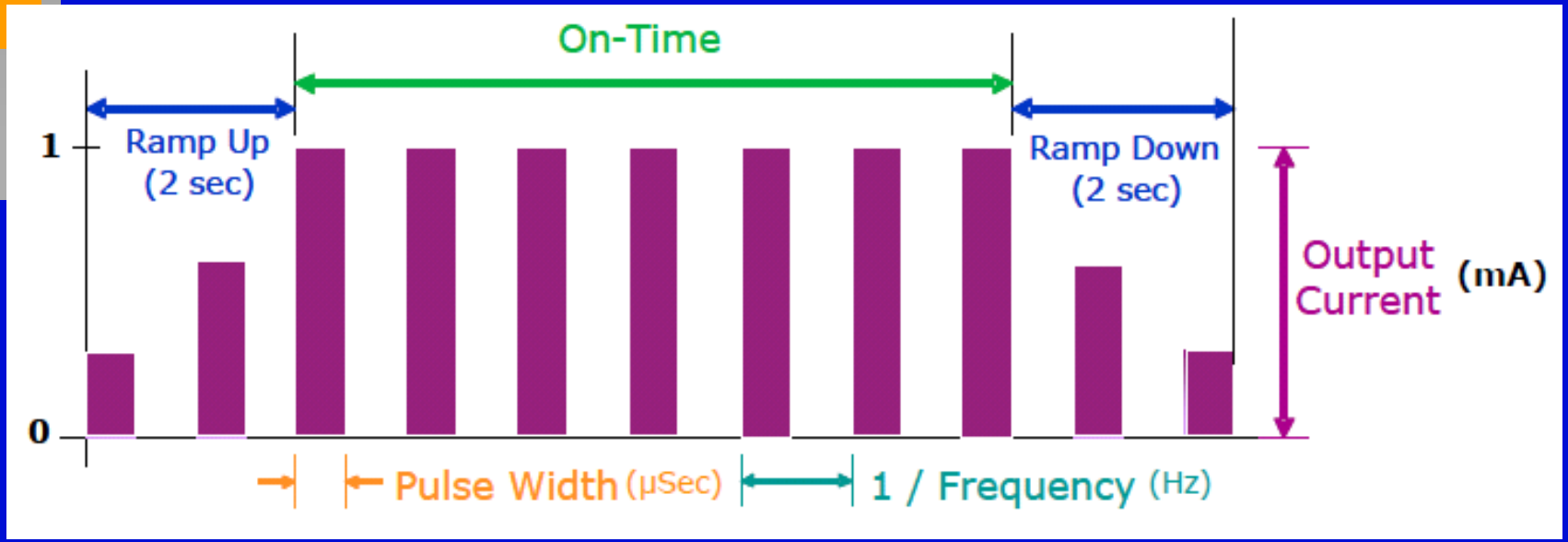
- More than 60,000 patients worldwide have been implanted with VNS Therapy
- No known interactions with medications
- No reported systemic neurotoxic effects, rash, renal impairment, or bone marrow suppression
- No increase in sudden, unexpected death in epilepsy (SUDEP)[1]
- Gestational outcomes
  -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

1. Annegers JF, et al. Epilepsia. 1998;39:206-212. 2. Physician's Manual. Houston, TX: Cyberonics, Inc. 3. Danielsson et al. 4. Ben-Menachem E, et al. Epilepsia. 1998;39(6):180. 5. Husain MM, et al. Ann Gen Psychiatry. 2005;4:16.

Several parameters can be adjusted to individualize treatment[1]

- **Each parameter can be independently programmed, thereby offering multiple setting combinations from which optimal stimulation for the patient can be selected[1]**

- **Safe and effective VNS Therapy is dependent primarily on output current, signal frequency, pulse width, ON/OFF time[2]**



1. Physician's Manual. Houston, TX: Cyberonics, Inc. 2. Heck C, et al. Neurology 2002;59(Suppl 4):S31-S37.

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%

Reference: Engel, J. NEJM, Vol 334 1996, 647-653

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

Time post onset	Treatment
Onset	Ensure adequate ventilation/O2
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 ≤ 50 mg/per minute phenytoin or 150 mg per minute fosphenytoin (≤ 0.75 mg/kg/min) Pyridoxine 100-200 mg IV in children under 18 mo.

Status Epilepticus Treatment (cont.)

Time post onset	Treatment
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 ≤ 5 mg per minute (0.75 mg/kg per minute)

continued

Reference: Lowenstein DH, Alldredge BK, Status Epilepticus. NEJM 1998; 338: 970-976.

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

Reference: Lowenstein DH, Alldredge BK, Status Epilepticus. NEJM 1998; 338: 970-976.

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 patern 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

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