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Epilepsy Essentials

Bridging Basics and Breakthroughs

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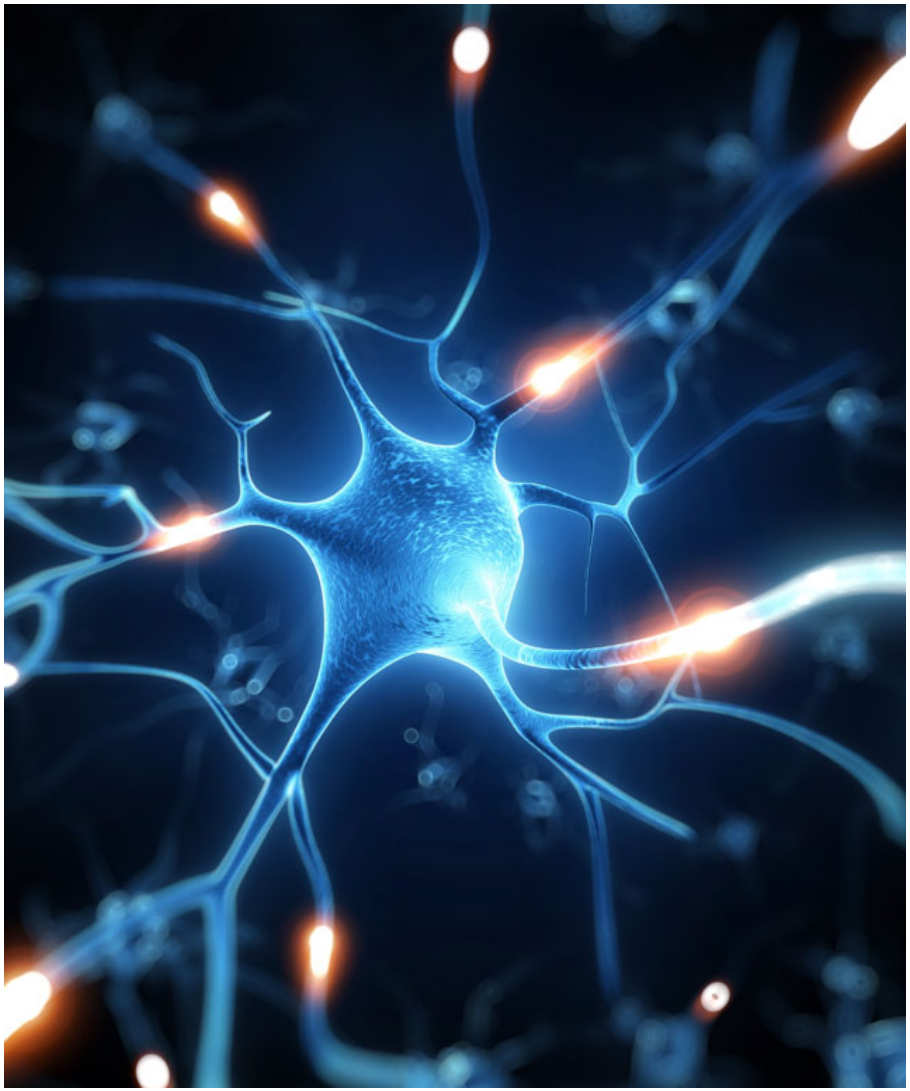

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Disclosures

- None

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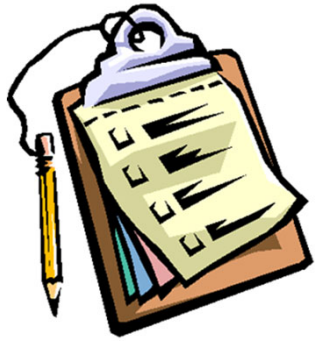
Objectives



- Overview of the current definition, classification of epilepsy and seizure semiology.
- Outline the causes for seizures and epilepsy mimics.
- Review the diagnostic approach to epilepsy, including role of EEG and neuroimaging including pre-surgical work up.
- Describe management options for epilepsy- from anti-seizure medications to epilepsy surgery.
- Highlight the management of epilepsy in women and the elderly, as well as associated comorbidities.

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Historical Background

- Epilepsy is derived from the Greek word- Epilambanei- which means to possess, grab hold of or to seize
- The oldest known document on epilepsy is a clay tablet written in the Sumerian language (dated 1067-1046 B.C)
- Tablet is called *antashubba* which is Sumerian for "falling disease"
- Possession by demons/ evil spirits/ curse

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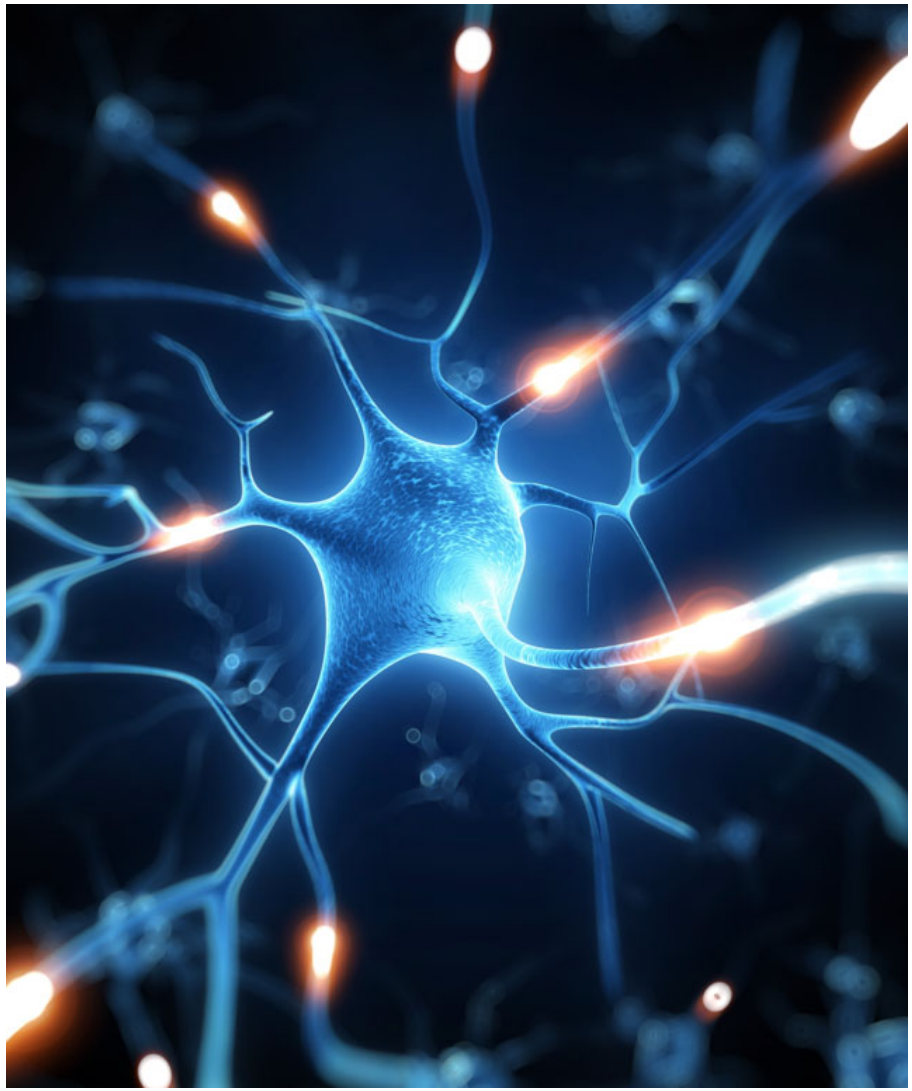
Epilepsy in the 19th/20th century

- 1857 - ASM, Bromide by Sir Charles Locock
- 1873 - John Hughlings Jackson described the electrical theory for seizures
- 1912 - Phenobarbital is discovered
- 1924 - Hans Berger invented the EEG
- 1940 - Penfield develops modern epilepsy surgery
- Last 3 decades: Sophisticated imaging techniques, new medications, evidence-based treatment

DEFINITION



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Conceptual Definition

- Seizure: Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

- Epilepsy: Disease characterized by an enduring predisposition to generate epileptic seizures.

Epilepsia. 2005 Apr;46(4):470-2.

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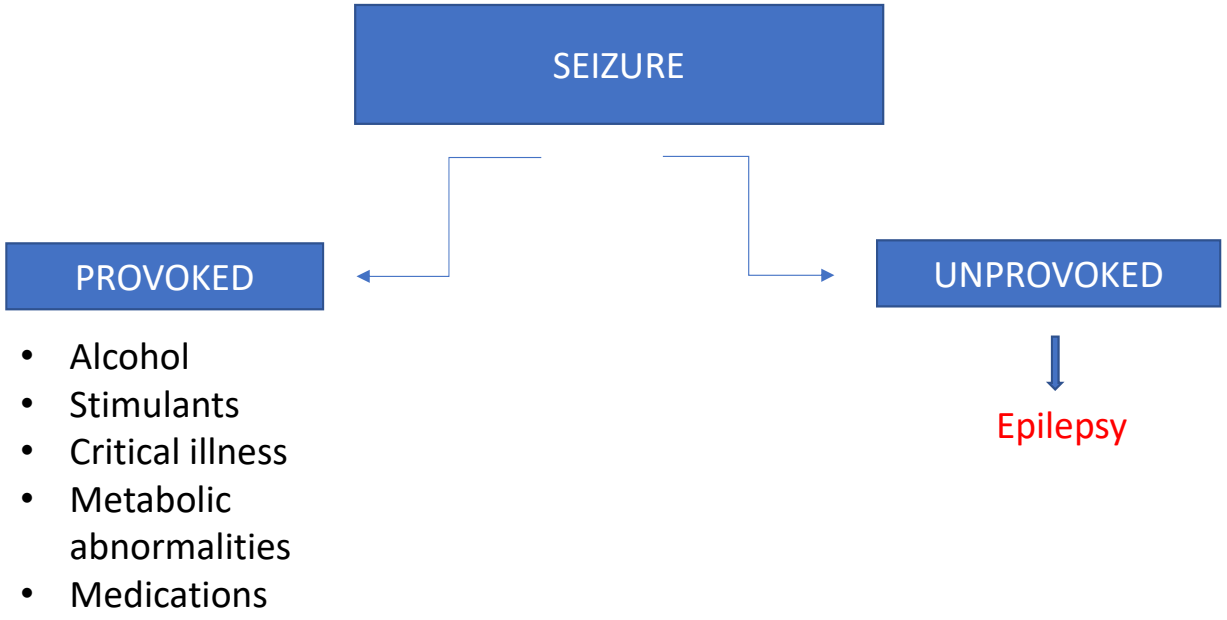
Seizure

- Seizures are very common
- 1 in 10 people can have a seizure



- Alcohol
- Stimulants
- Critical illness
- Metabolic abnormalities
- Medications

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Practical Definition - 2014

- At least two unprovoked (or reflex) seizures occurring >24 hours apart
- One unprovoked seizure and a probability of further seizures of at least 60% over the next 10 years
- Diagnosis of an epilepsy syndrome

ILAE, Fisher et al, Epilepsia 2014, 55(4):475–482

Which of the following describes epilepsy?

(A) Two seizures 12 hours apart, toxicology screen: Cocaine +ve

0%

(B) Two unprovoked seizures > 24 hours apart

0%

(C) One unprovoked seizure and MRI brain indicative of a low grade glioma

0%

(D) b and c

0%

(E) a, b and c

0%

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Epidemiology

- 3.5 million Americans (1.2% of population)
- 1 in 26 patients will be diagnosed with epilepsy in their lifetime

- Highest incidence occurs at the extremes of life

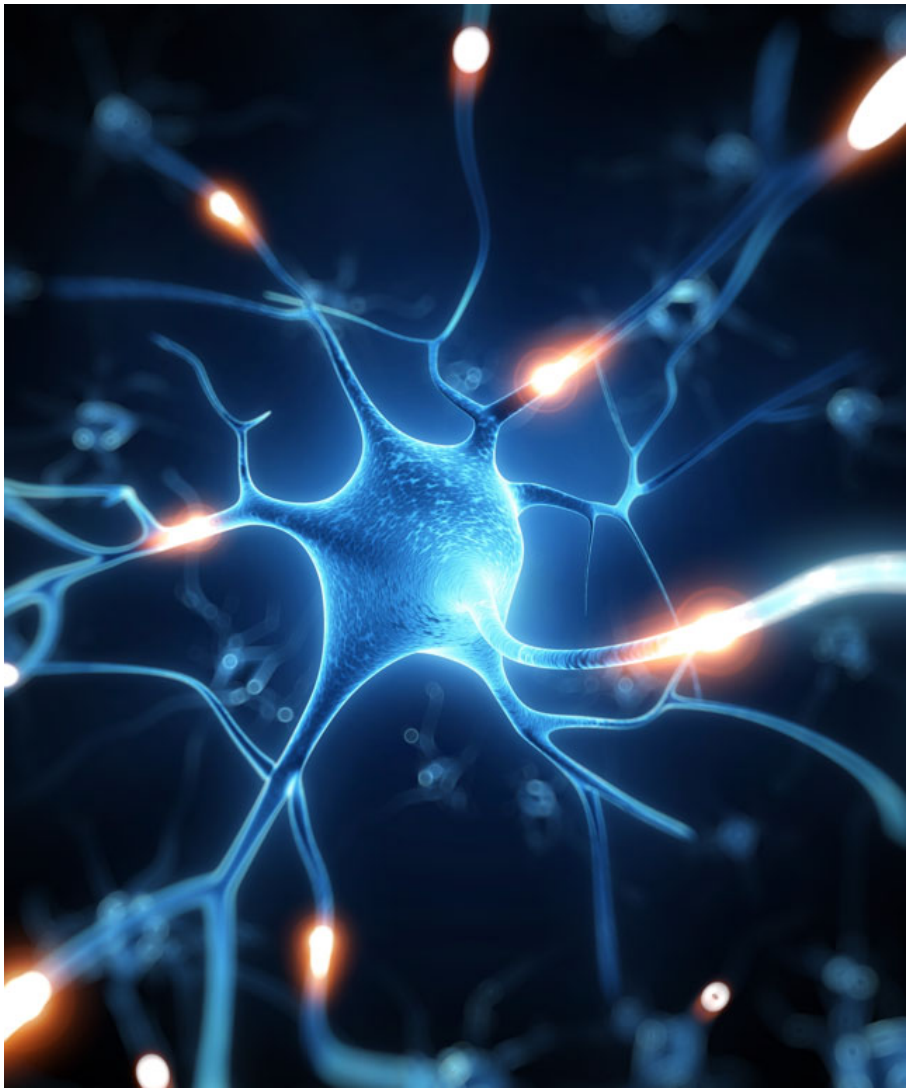
- Nearly 70% of treated epilepsy patients enter remission
- Mortality is 2-3 times higher in epilepsy patients

- Negatively effects quality of life

CDC 2017

Hauser et al; Epilepsia 2008;49(suppl 1): 8–12.

CLASSIFICATION



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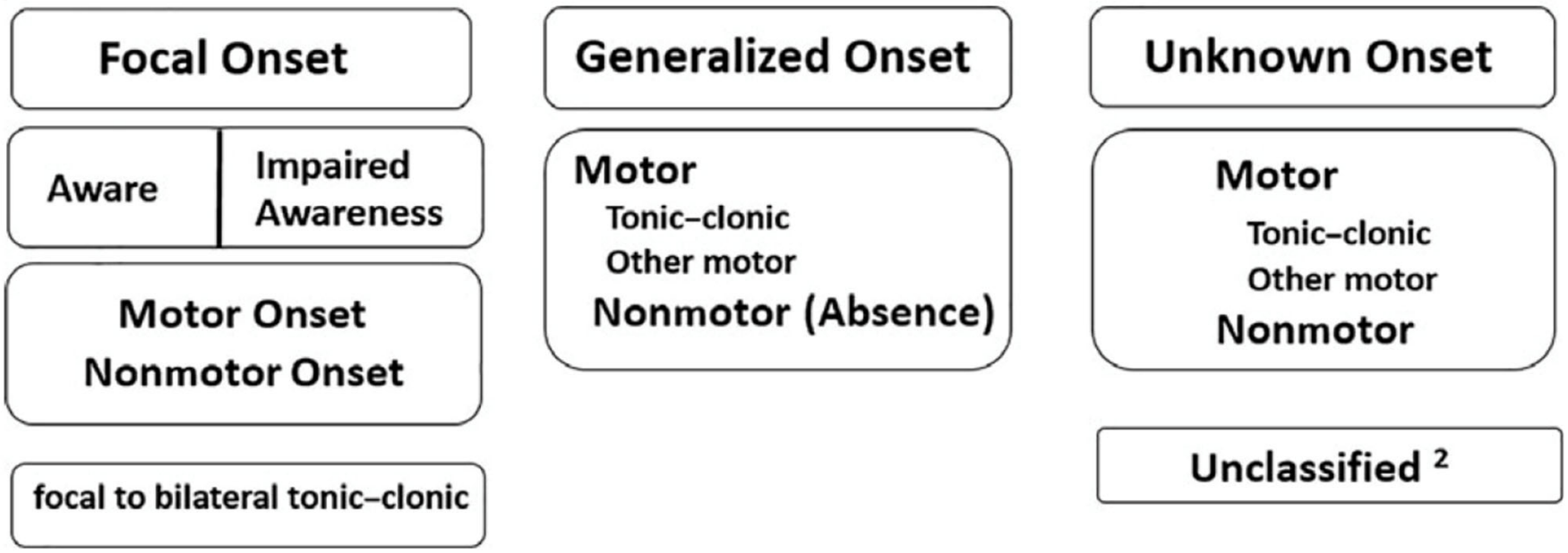
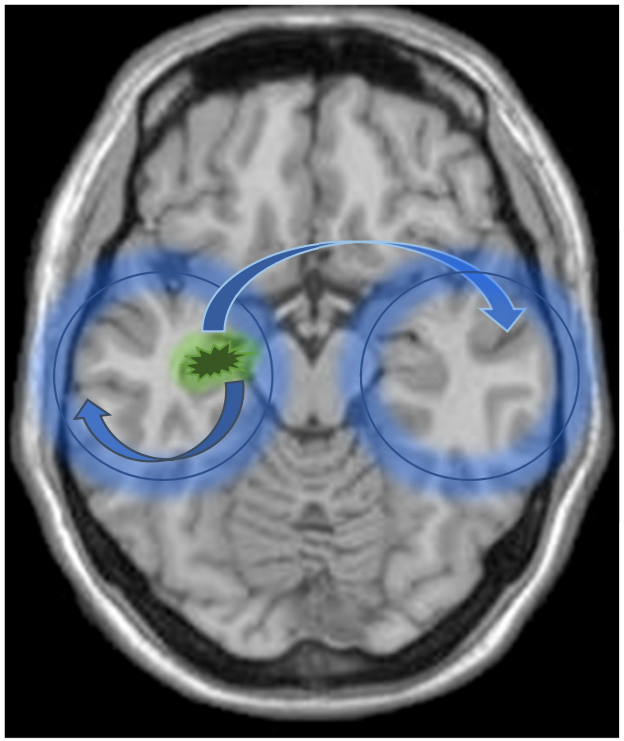
ILAE 2017 Classification of Seizure Types Basic Version [1]



Focal seizures

- Originate within networks limited to one hemisphere

- May be discretely localized
  or more widely distributed



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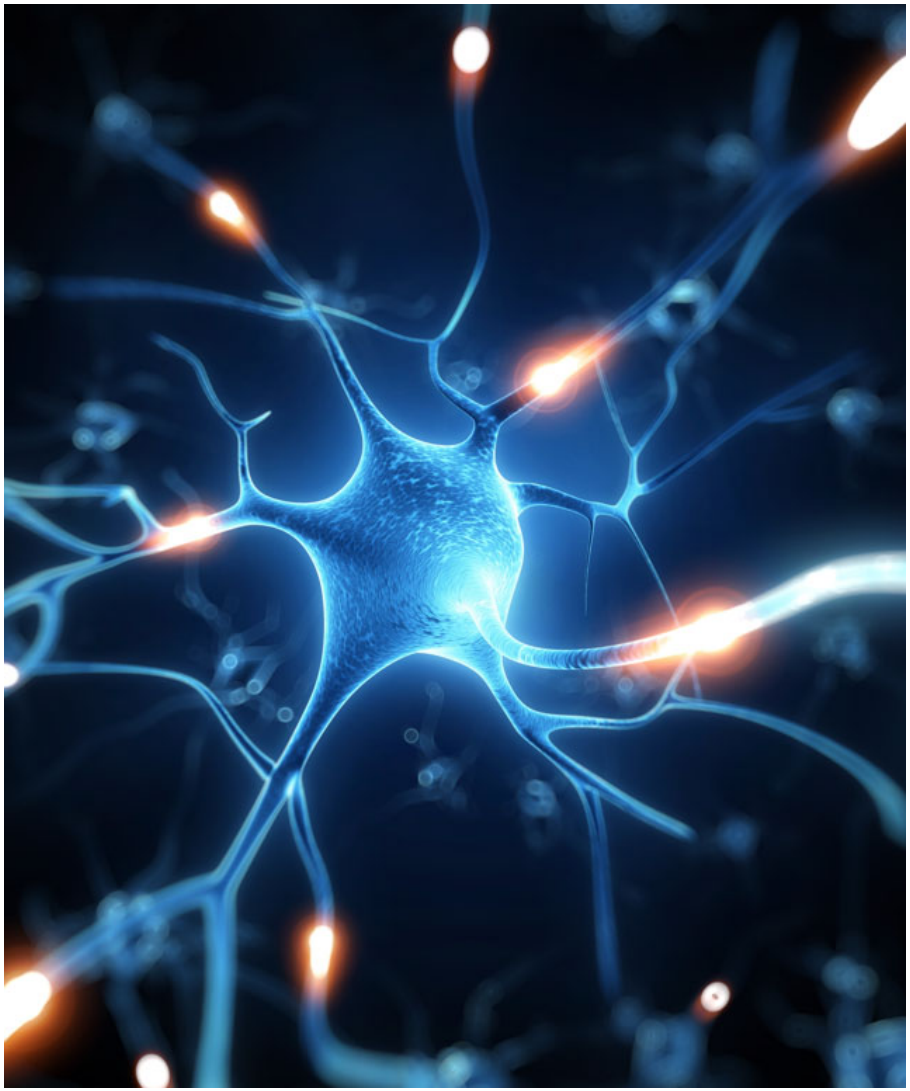
Generalized Seizures

- Originate at some point within and rapidly engage bilaterally distributed networks
- Can include cortical and subcortical structures but not necessarily

CLINICAL DESCRIPTION OF SEIZURES

(SEIZURE SEMIOLOGY)



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Focal Aware Seizures
(Simple Partial Seizures)

- Aura: Subjective sensation preceding the seizure; by itself is a focal seizure
- Usually reflective of the region of seizure origin
- Temporal lobe epilepsy: 80% have auras- Déjà vu, epigastric rising sensation, distortions of time, sudden fear, metallic taste, tinnitus
- Parietal lobe: contralateral sensory symptoms
- Occipital lobe: contralateral visual symptoms

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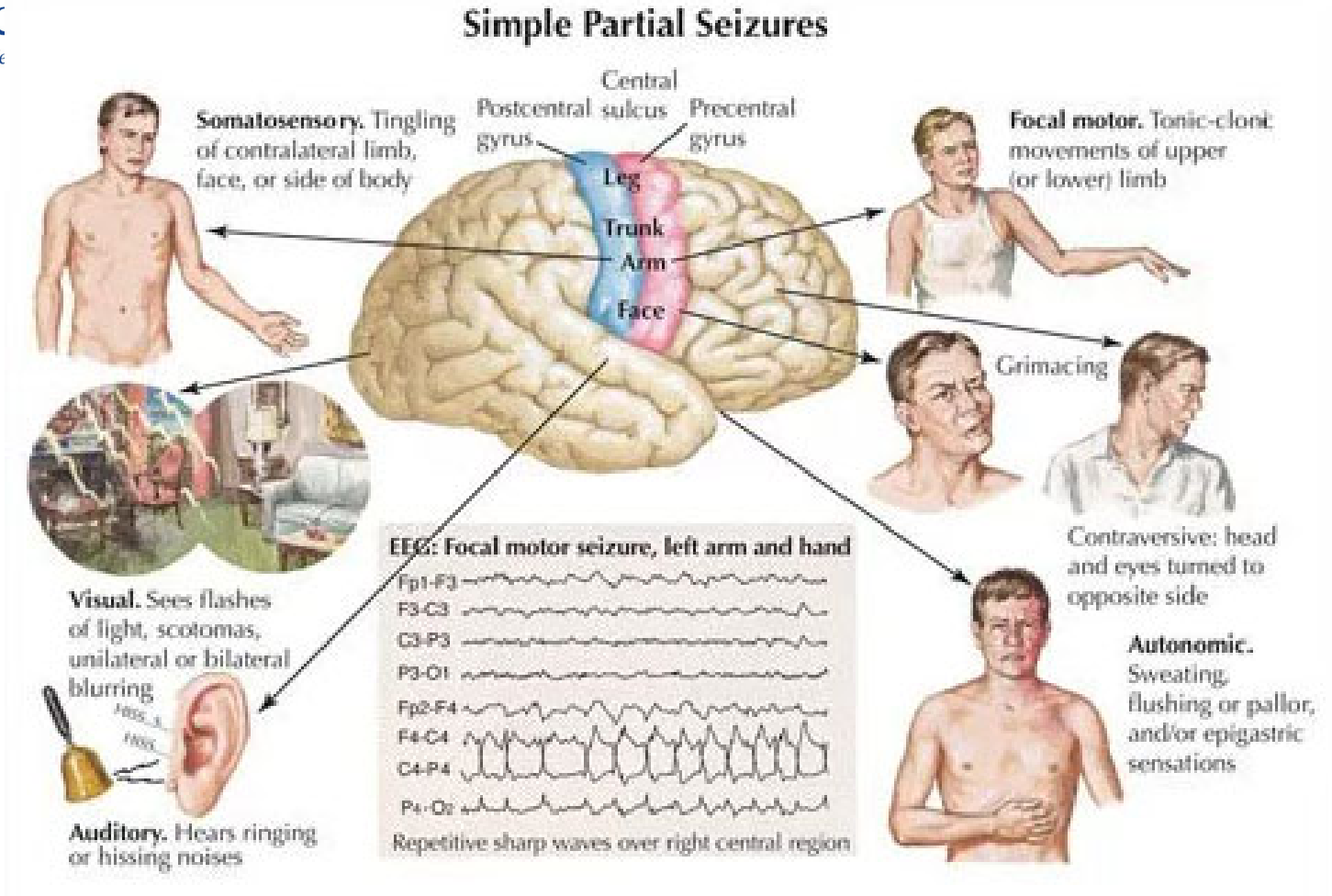

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Focal seizures with Impaired Awareness (Complex Partial Seizures)

- Automatisms: Repetitive involuntary semi purposeful movements
- Most common: Lip smacking, chewing, fumbling, patting, picking
- Objective signs help in lateralization and localization of seizure focus
- Speech arrest- dominant temporal lobe
- Eye deviation- contralateral frontal lobe

In this picture- seizure focus is contralateral to the extended forearm
(left frontal lobe- specifically SSMA area)

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Generalized seizures

- Generalized Tonic-Clonic (GTC) seizure (AKA grand-mal seizure): Impairment of awareness and bilateral, often symmetric motor manifestations
- Dramatic, more chance for physical injuries
- Tonic-Clonic, Tonic, Atonic, Clonic, Myoclonic, Absence

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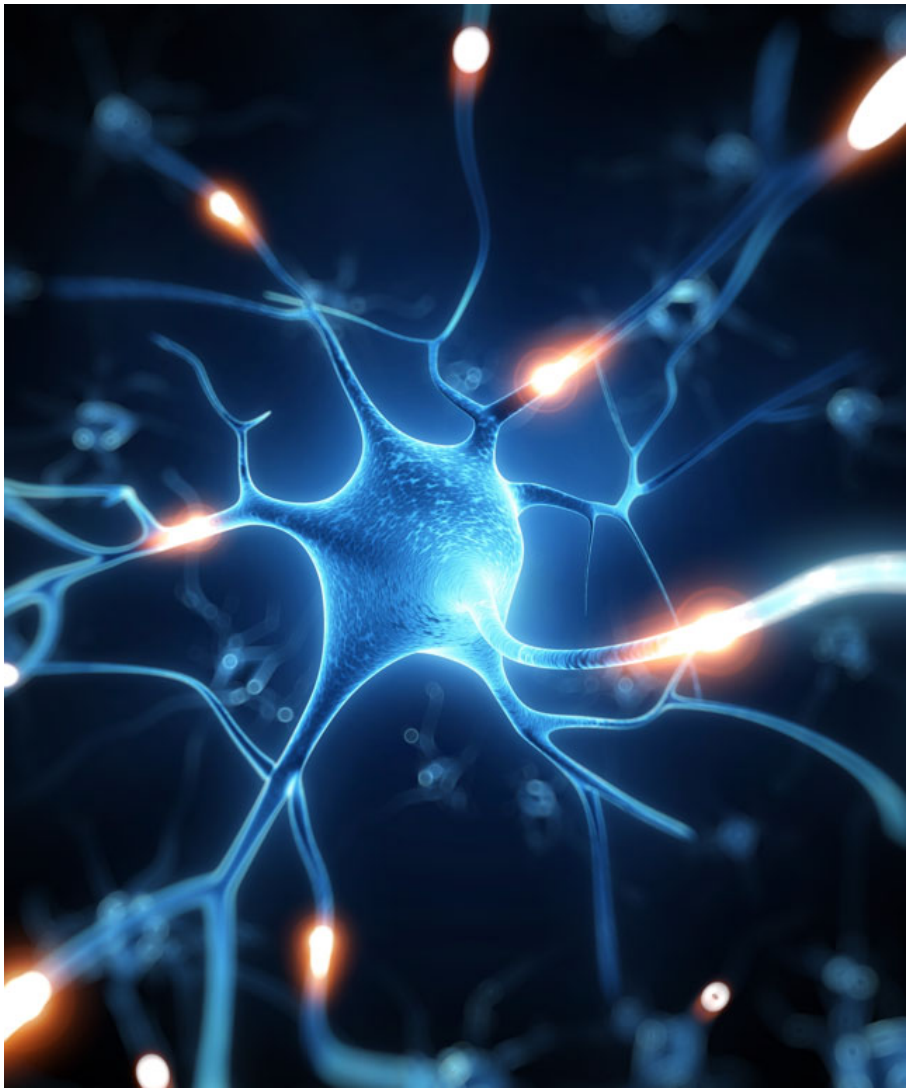
Summary of Classification/ Semiology

Focal/ Partial Seizures	Focal Aware No loss of awareness	- Motor: focal muscle movements - Sensory: sensation/ smell/ taste change - Autonomic- sweating/ chills/ epigastric sensation
	Focal Unaware Loss of Awareness	- Automatisms - Objective signs- dystonic arm posture, speech problems
Generalized Seizures	Generalized Tonic Clonic seizure	Whole-body stiffening and then rhythmic shaking
	Absence Seizures	Staring and not responding
	Tonic	Brief whole-body stiffening
	Atonic	Brief whole-body going limp
	Clonic	Whole-body rhythmic shaking
	Myoclonic	Sudden muscle jerk of body/ limbs- no loss of awareness

Two common epilepsy syndromes



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Childhood Absence Epilepsy (CAE)
Absence seizures

- Onset: age 4-10 (peak 5-6), can extend up to adulthood
- Girls > boys

- Typical absence seizure: No aura, sudden onset/offset, momentary loss of awareness (staring), eyelid flutter, oral automatisms, 3-15 second duration

- Positive family history
- EEG: 3 Hz spike-and-wave discharges
- Treatment of choice: Ethosuximide
- Outgrown 50% of the time

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Epilepsy Syndrome Question

This is a 28 y/o gentleman with twitching of extremities since age 16, mostly in the mornings.

Worsened with sleep deprivation and consuming “bit too much” alcohol. He has had a few ‘grand mal’ seizures since this began, mostly when he drinks those extra beers.

See the video for description!

EEG shows ‘polyspike-and-wave’ activity.

Normal MRI Brain

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What is the diagnosis?

Childhood absence epilepsy 0%

Juvenile absence epilepsy 0%

Juvenile myoclonic epilepsy 0%

Alcohol withdrawal seizures 0%

Focal epilepsy 0%

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Juvenile Myoclonic Epilepsy

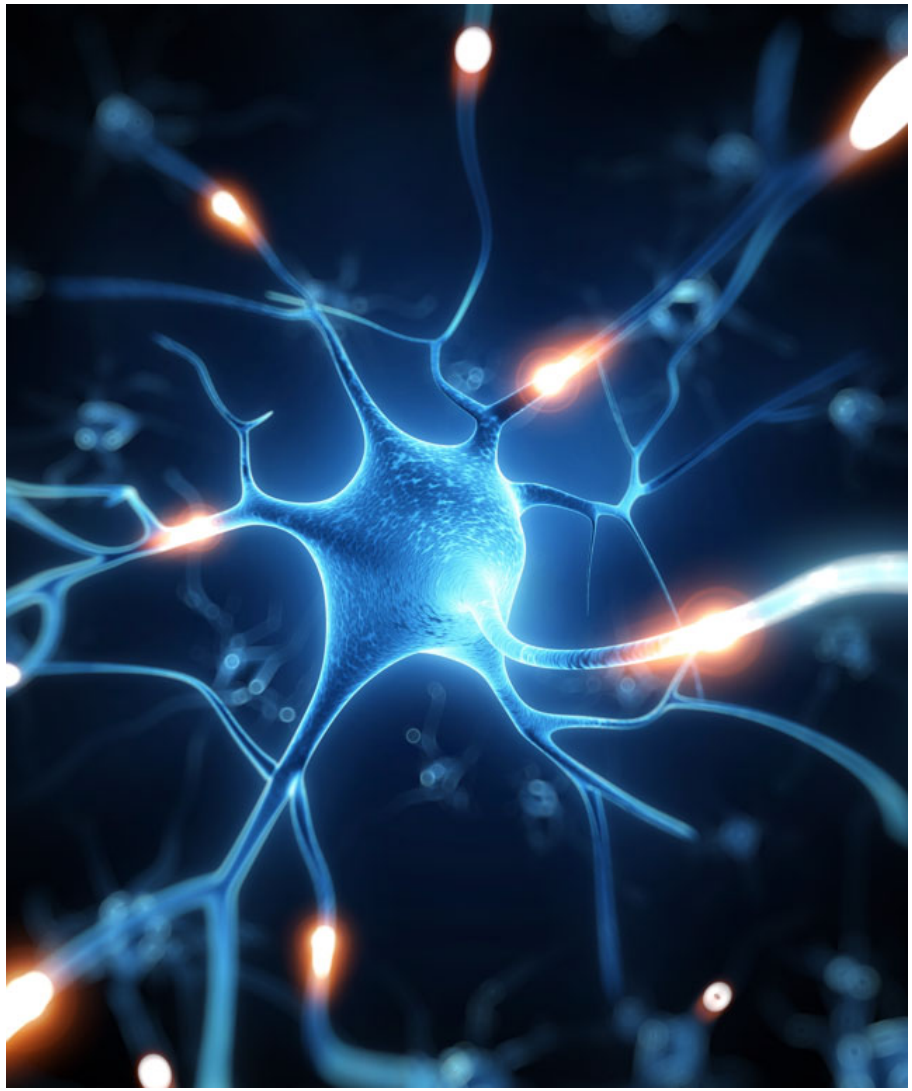
- Most common genetic generalized epilepsy, 5-10%
- Onset: 12-18 years
- Females > males

- Myoclonic jerks in the morning, generalized tonic-clonic seizures
- Provoked by sleep deprivation, alcohol, exposure to flashing lights, stress

- EEG: 4-6 Hz polyspike-and-wave discharges, 50% photoparoxysmal response
- Treatment: Valproic acid, levetiracetam, lamotrigine

- Prognosis: Lifelong therapy, remission is rare

ETIOLOGY



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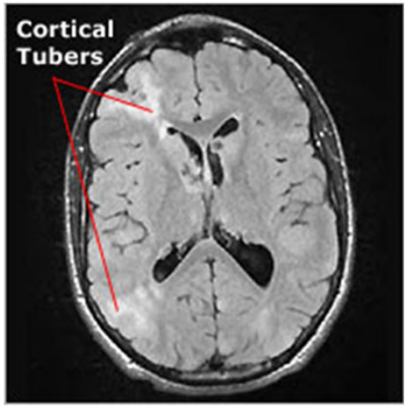


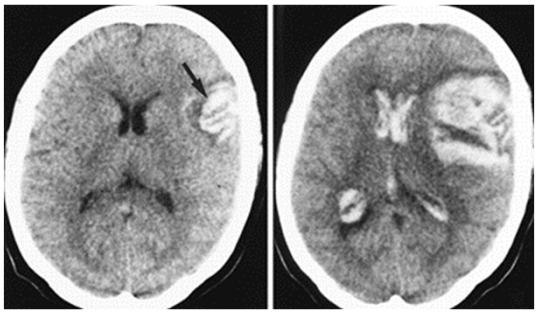
STRUCTURAL

CONGENITAL:

- Developmental Malformations- cortical dysplasia, heterotopia
- Neurocutaneous Syndromes- Tuberous Sclerosis, Neurofibromatosis

ACQUIRED:

- Stroke: Hemorrhagic > Ischemic
- Antenatal/ Perinatal insults
- Tumor, Trauma, Infections



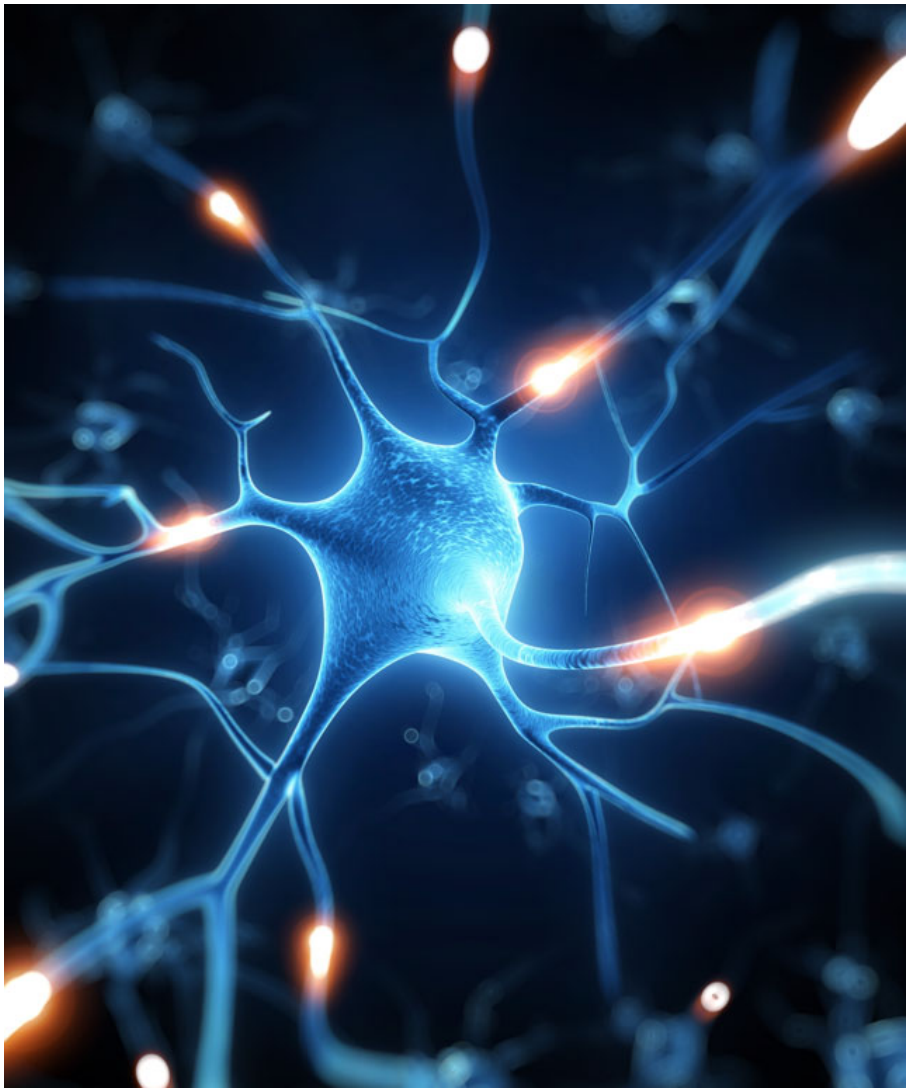
GENETIC

- Direct result of a known or presumed genetic defect (runs in families)
- Childhood Absence Epilepsy, or Juvenile Myoclonic Epilepsy (JME)

UNKNOWN

- About 1/3rd of the cases
- Autoimmune

EPILEPSY IMITATORS



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40 y/o woman had this event in the EMU

Tell me what you think this is:

Generalized tonic clonic seizure 0%

Focal clonic seizure 0%

Psychogenic seizure 0%

Convulsive syncope 0%

Tripped on something and fell 0%

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Physiologic

- Syncope/ Fainting
- Transient Ischemic Attack (TIA)
- Transient Global Amnesia(TGA)
- Complex migraine
- Parasomnias
- Movement Disorders (Tremors, non-epileptic myoclonus, hemifacial spasm)

Psychogenic

- Psychogenic Non-Epileptic Seizures (PNES)

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Syncope

- Closest imitator of epilepsy
- Sudden, unpredictable, may have a prodrome
- Brief loss of consciousness
- Can be stereotypic
- “Convulsive myoclonus”
- Prompt recovery
- No confusion/ disorientation afterwards

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Psychogenic Non-Epileptic Seizures(PNES)

- Female > Males; younger age group
- Events- longer duration, asynchronous body movements, eyes closed, crying or able to respond during events, stuttering
- Mean time to diagnosis: 7-9 years
- Prior sexual abuse in 20-50%, especially females
- Gold standard test for diagnosis is Video-EEG monitoring
- ~40% of Epilepsy Monitoring Unit (EMU) admissions

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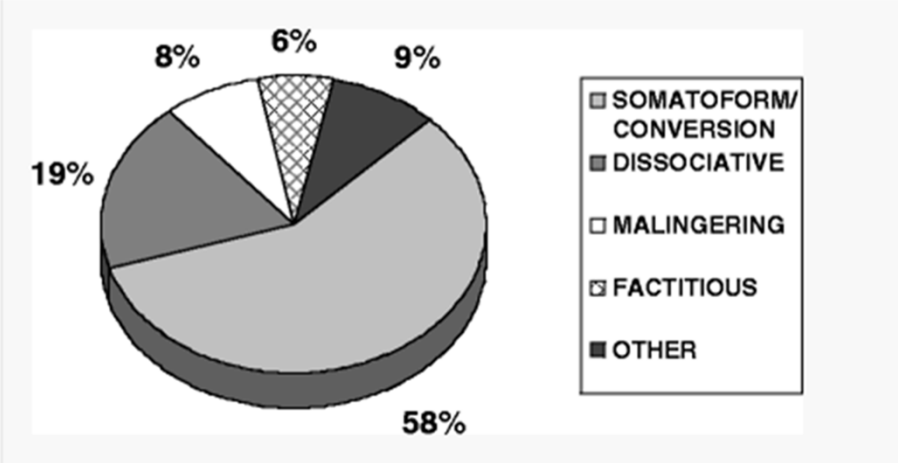
Diagnoses in PNES

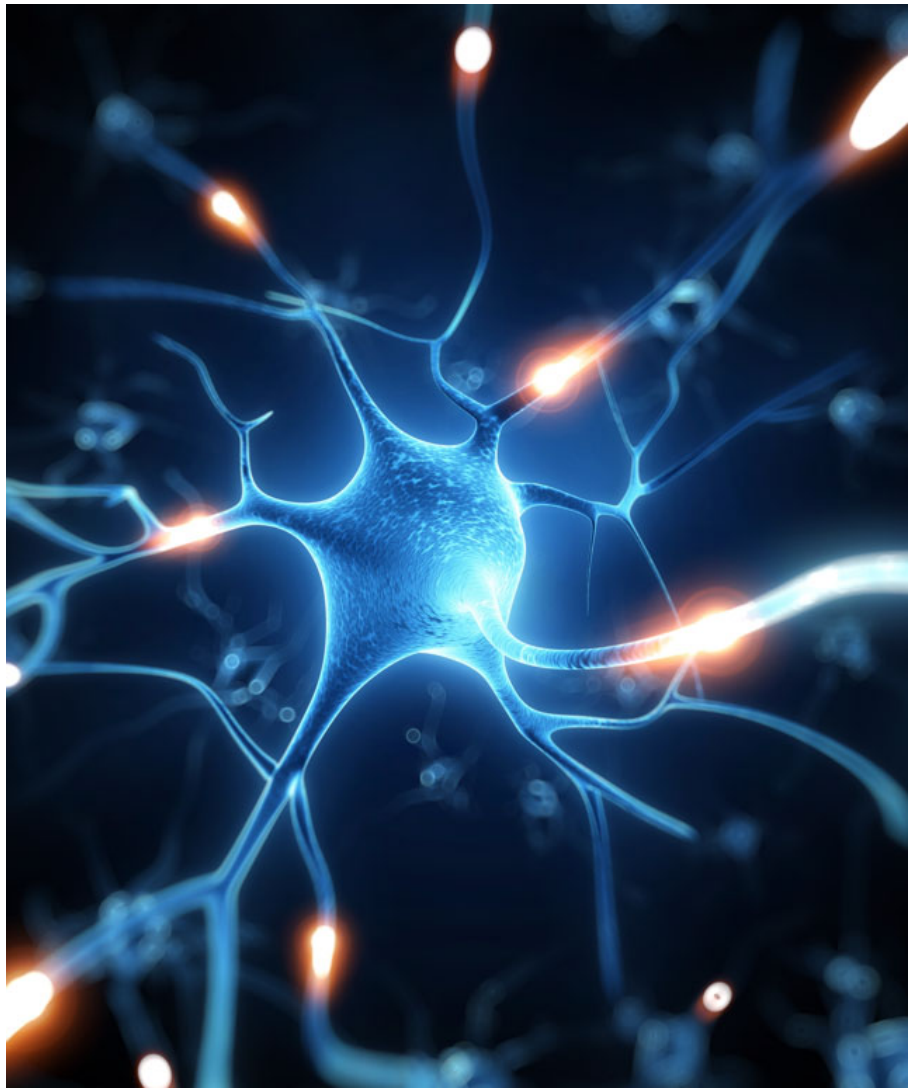


- Treatment: Cognitive and Behavior Therapy (form of psychotherapy)
- 12-22% of PNES patients have epilepsy
- Avoid being judgmental
- Refer to a psychotherapist
- Provide support during follow-up
- Encourage psychotherapy follow-up

Binder et al, Neuropsychol Rev (2007) 17: 405
Martin et al, Neurology 2003;61:1791-2

SEIZURE/ EPILEPSY WORK UP

- Detailed History
- Electroencephalogram (EEG)
- MRI Brain epilepsy protocol



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Detailed History

- GTC seizure gets the most attention
- Ask for other events - auras, staring spells, myoclonus
- Nocturnal seizure

- Triggers- sleep deprivation/ alcohol/ lights/ sounds

- Epilepsy risk factors- pre-maturity, hypoxia during birth, febrile seizures, stroke/ TBI/ intracranial infections
- Family history of epilepsy

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EEG

- Routine EEG (20 minutes- 4 hours):
- Sensitivity of a single EEG: 50%
- Three or more serial EEG's, Specificity increases to 80-90%

- Home Based Ambulatory EEG (24-72 hours)

- Gold Standard- Continuous video-EEG monitoring
- Preferably in the Epilepsy Monitoring Unit (EMU)
- >80% will have interictal epileptiform discharges during 3 days of vEEG

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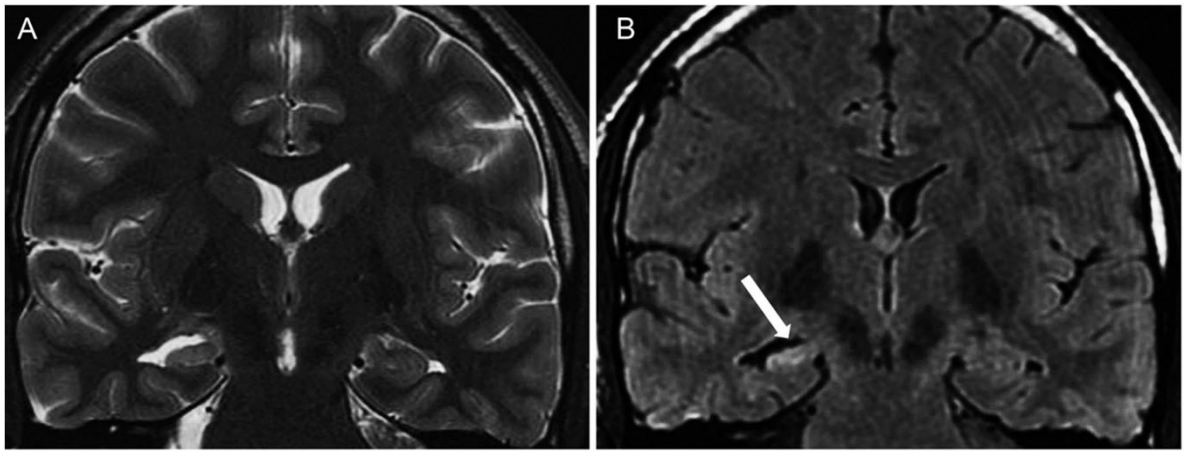
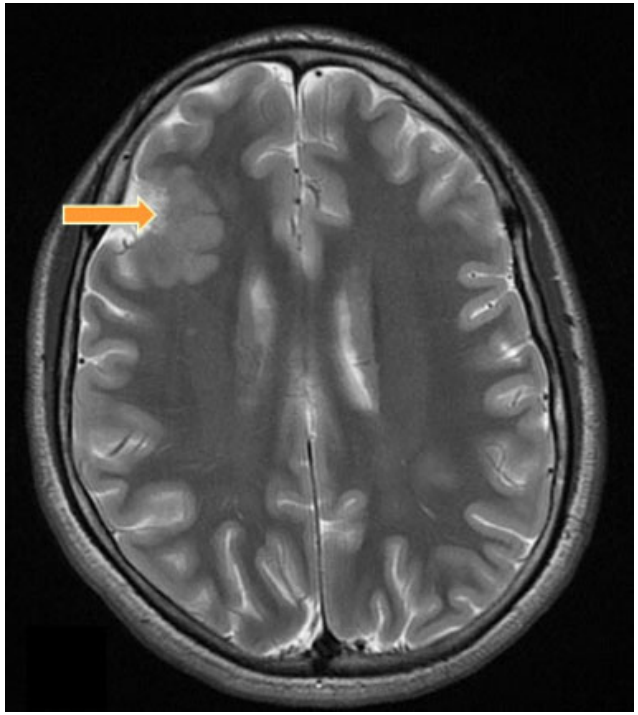
Neuroimaging

- CT head- r/o bleed, or large structural changes

- MRI brain w/wo contrast- epilepsy protocol:
- Most valuable for localizing the lesion

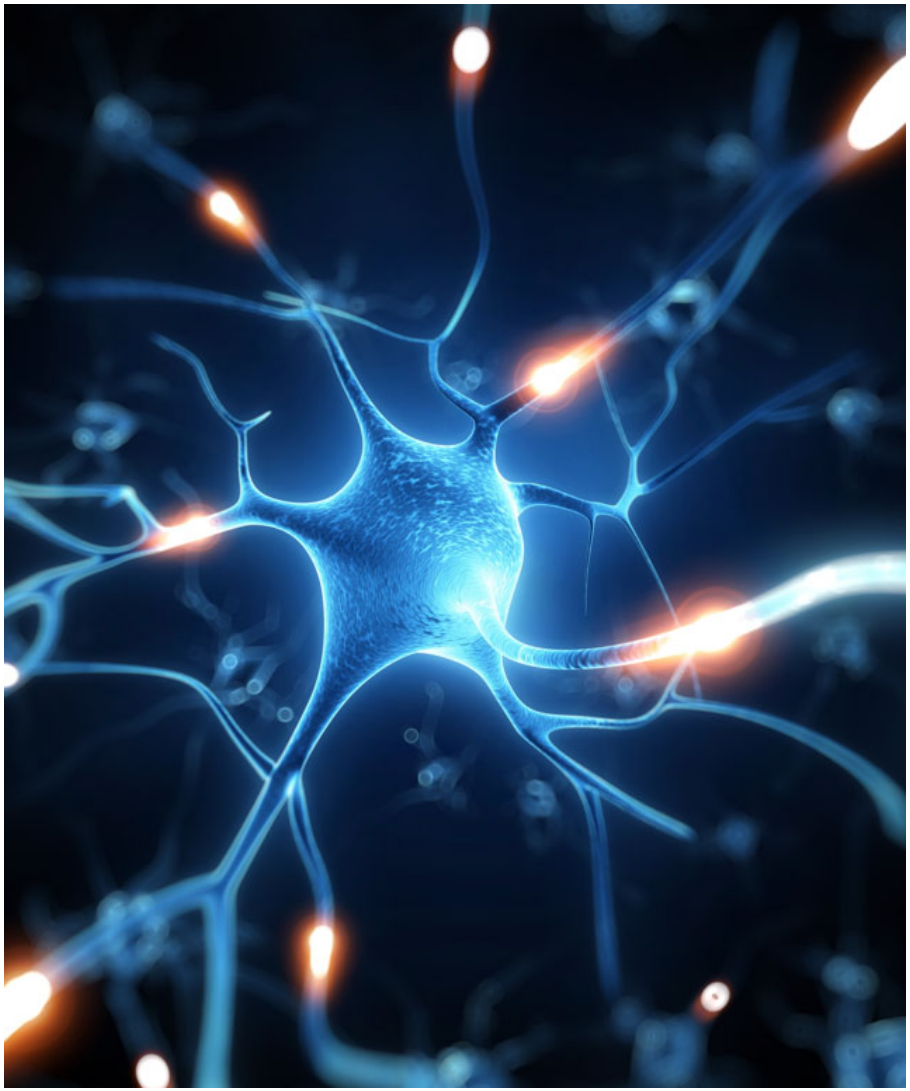


Arrow- Right hippocampus is atrophied and bright on FLAIR sequence
Mesial Temporal Sclerosis



Focal Cortical Dysplasia Right frontal region

APPROACH TO FIRST SEIZURE



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Classification of a First Seizure

- Provoked seizure (toxin, medication, or metabolic factors)
- Acute symptomatic seizure (stroke, TBI, encephalitis/meningitis)
- Remote symptomatic seizure (preexisting brain injury)
- Epileptic syndrome (JME)
- Other unidentified

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Why all this fuss?

Recurrence Risk

&

Need for treatment

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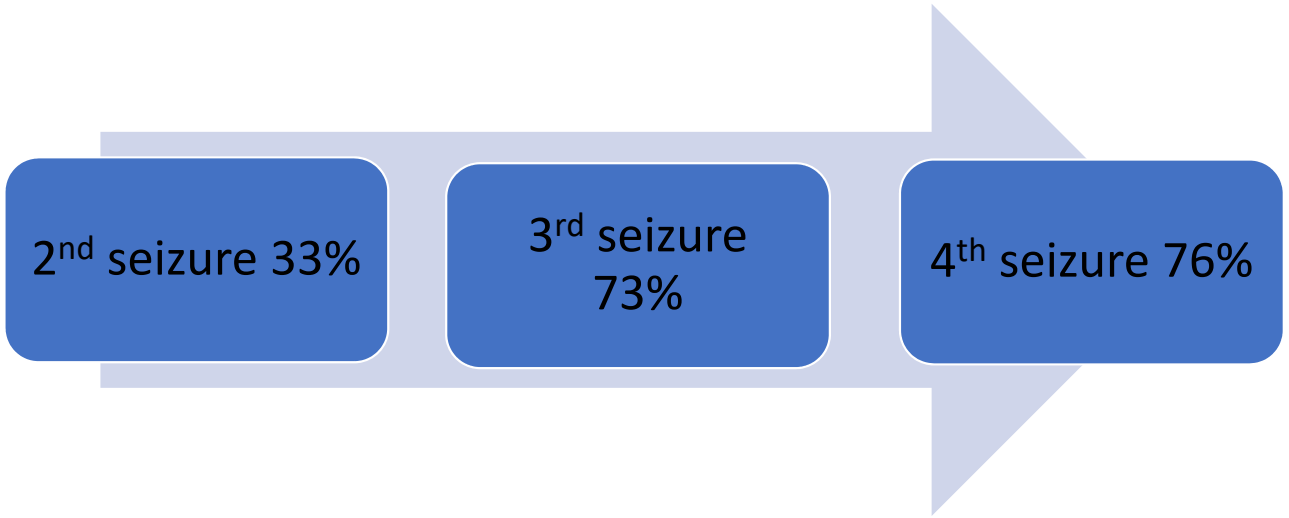
Recurrence risk after first unprovoked seizure

- Hauser et al, 1998 - prospective study
- n= 204



Hauser et al. Risk of recurrent seizures after two unprovoked seizures. NEJM 1998;338:429.

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Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

A. Krumholz, MD[1,2]; S. Wiebe, MD[3]; G. S. Gronseth, MD[4]; D. S. Gloss, MD[5]; A. M. Sanchez, MD[1]; A. A. Kabir, MD[1]; A. T. Liferidge, MD[6]; J. P. Martello, MD[1]; A. M. Kanner, MD[7]; S. Shinnar, MD, PhD[8]; J. L. Hopp, MD[1]; J. A. French, MD[9]
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[6]Department of Emergency Medicine, George Washington University School of Medicine, Washington, DC
[7]Department of Neurology, International Center for Epilepsy, University of Miami Miller School of Medicine, FL
[8]Departments of Neurology, Pediatrics, and Epidemiology & Population Health, Albert Einstein College of Medicine, Yeshiva University, Bronx
[9]New York University Comprehensive Epilepsy Center, New York, NY

Level A – Strong Evidence
Level B – Moderate Evidence
Level C – Weak Evidence

Conclusion:

- Adults with an unprovoked first seizure should be informed that seizure recurrence risk is greatest early within the first 2 years (21%–45%) (Level A), and **clinical variables associated with increased risk may include:**
  - a prior brain insult (Level A),
  - an epileptiform EEG (Level A),
  - an abnormal CT/MRI(Level B)
  - a nocturnal seizure (Level B)

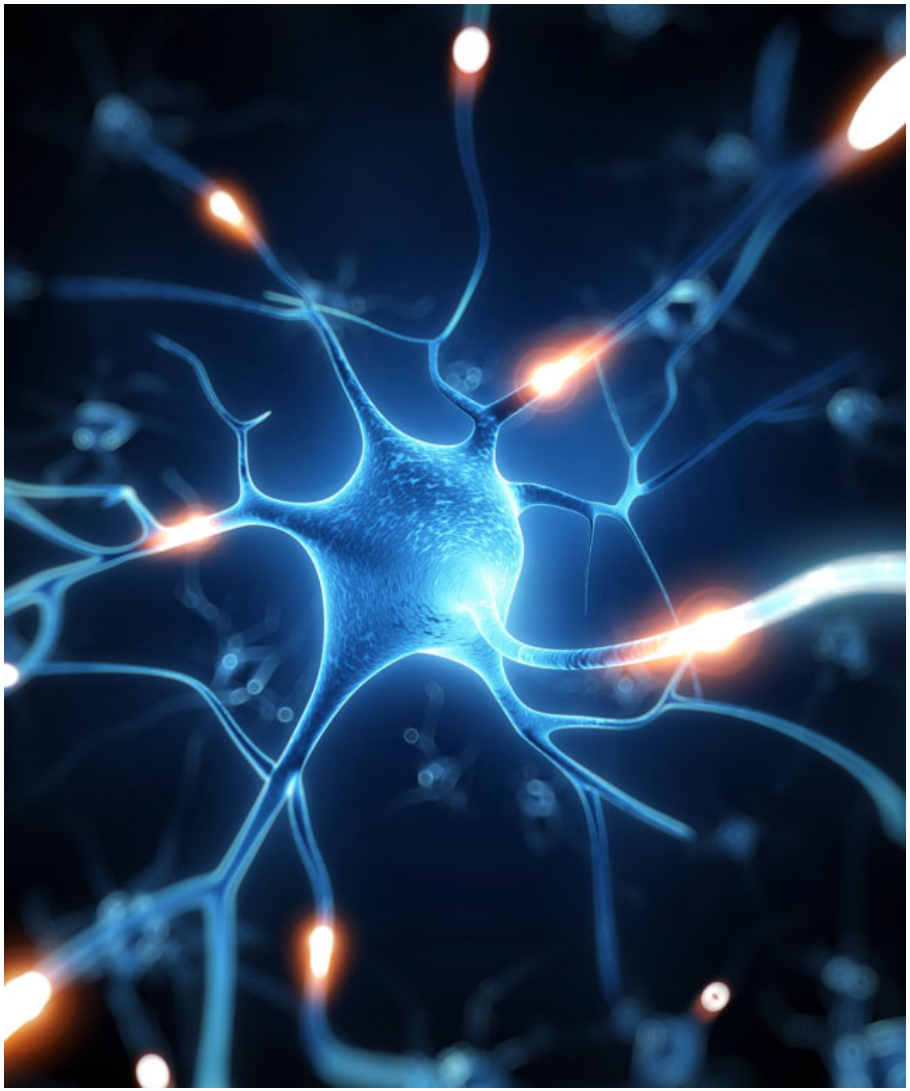
TREATMENT OPTIONS

1. MEDICATIONS

2. NEUROMODULATION

3. SURGERY

4. DIET



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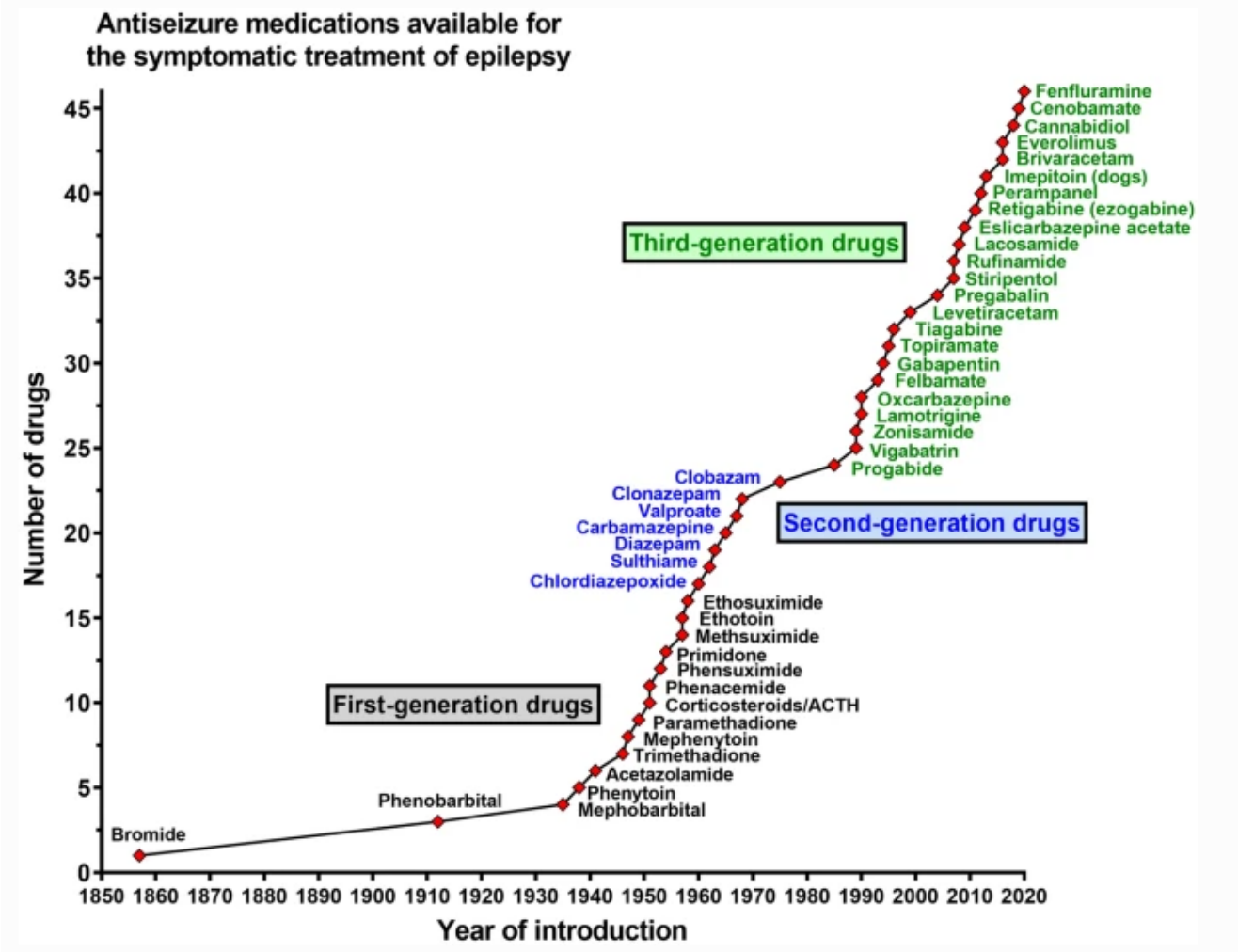

Löscher, W., Klein, P. *CNS Drugs* 35, 935–963 (2021)

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Older ASM's - Important adverse effects/ Lab monitoring

ASM	Adverse effects
Phenytoin	Side Effects: Hirsutism, Gingival hypertrophy, Neuropathy, Vitamin D Deficiency, Osteoporosis, Cerebellar Degeneration Labs: CBC, CMP, yearly DEXA Remember: CYP enzyme inducer, non-linear kinetics, not an ideal ASM
Carbamazepine	Side Effects: Aplastic Anemia, Hyponatremia, Osteoporosis Labs: CBC, CMP (hyponatremia), yearly DEXA Remember: CYP enzyme inducer, autoinduction, not an ideal ASM
Valproic Acid	Side Effects: Weight gain, tremor, hepatotoxicity, alopecia, PCOS Labs: CBC (thrombocytopenia), LFT's Remember: CYP enzyme inhibitor, Avoid in women age 12-45

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Newer ASM's
Important adverse effects/ Lab monitoring

ASM	Adverse effects
Lamotrigine	Skin rash/SJS, Insomnia No specific labs needed, safe and effective ASM, needs slow titration
Levetiracetam Brivaracetam	Depression, irritability No specific labs needed, safe and effective ASM ALWAYS SCREEN FOR DEPRESSION/ ANXIETY
Oxcarbazepine / Eslicarbazepine	Hyponatremia (highest with OXC), Dizziness, Diplopia Labs: CBC, BMP (Na levels)
Topiramate Zonisamide	Renal stones, word finding difficulty, cognitive changes, paresthesia's, closed angle glaucoma, metabolic acidosis, anhidrosis No specific labs, Avoid TPM in young women
Lacosamide	Dizziness; no specific labs needed
Perampanel	Psychosis, Homicidal ideation (Screen for anxiety)

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Newer FDA approved ASM's

1. Cannabidiol

- Treatment for refractory epilepsy as seen in Lennox-Gastaut syndrome or Dravet syndrome; or for refractory focal epilepsy not controlled by several medications/ surgical treatment

2. Stiripentol: Dravet syndrome

3. Fenfluramine: Dravet & Lennox-Gastaut Syndrome; will need echocardiogram

4. Cenobamate: For focal seizures

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Rescue ASM's for seizure clusters/ status epilepticus

- Rectal diazepam (old) → Intranasal midazolam or diazepam
- Pre-measured dose, 5-20 mg

- Clonazepam ODT

- Rapid onset, prevents ER visits
- Patients love the rescue option

Gidal et al, Epilepsia 2022;63(Suppl. 1):S34–S44

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Suggested Approach to Management of New Onset Seizures

- If just one seizure, order routine EEG, MRI brain w/wo contrast and refer to neurology
- If more than 1 seizure (includes simple partial seizures), order work up as above, and start an ASM

- Broad Spectrum ASM is the best to start

- LEV 500 mg BID is the safest as long patient does not have SI, or extreme anxiety
- Zonisamide 100 – 200 mg QHS is another safe alternative
- Lamotrigine- be careful of titration, a very safe ASM

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What's in the Pipeline

Drug	Company	Mechanism of action	Indication	Development phase
Focal epilepsy				
XEN1101/XEN496	Xenon pharmaceuticals	KCNQ channel opener	Focal epilepsy	Phase III
CVL-865	Cerevel Therapeutics	GABA-A modulator	Focal seizures	Phase II
CX-8998	Jazz Pharmaceuticals	T-type calcium channels	Focal seizures	Phase II
Generalized epilepsy				
CX-8998	Jazz Pharmaceuticals	T-type calcium channels	Absence	Phase II
Soticlestat	Ovid & Takeda pharmaceuticals	Inhibitor of CH24H	DS and LGS	Phase III
Status epilepticus (SE)				
Ganaxolone	Marinus pharmaceuticals	Neurosteroid	Refractory SE	Phase III
Ketamine	-	NMDAR antagonist	Established SE	?Phase III
ARS/prolonged seizures				
Staccato alprazolam	UCB Pharma	GABA-A activation	Prolonged seizures	Phase III

French et al., 2019. Epilepsia
Loscher and Klein, 2021. CNS Drugs
Vaitkevicius et al., 2022. Epilepsia
Coles et al., 2023. Epilepsy Behav

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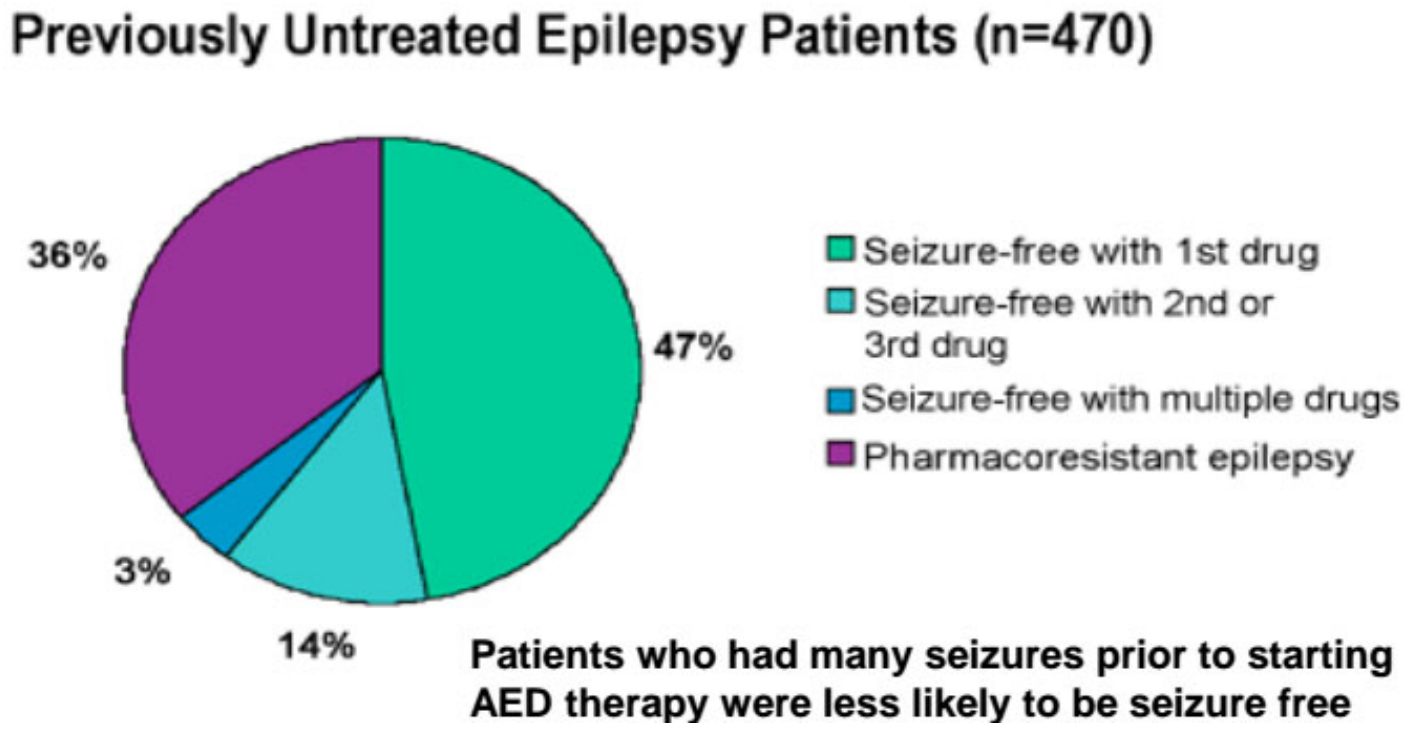
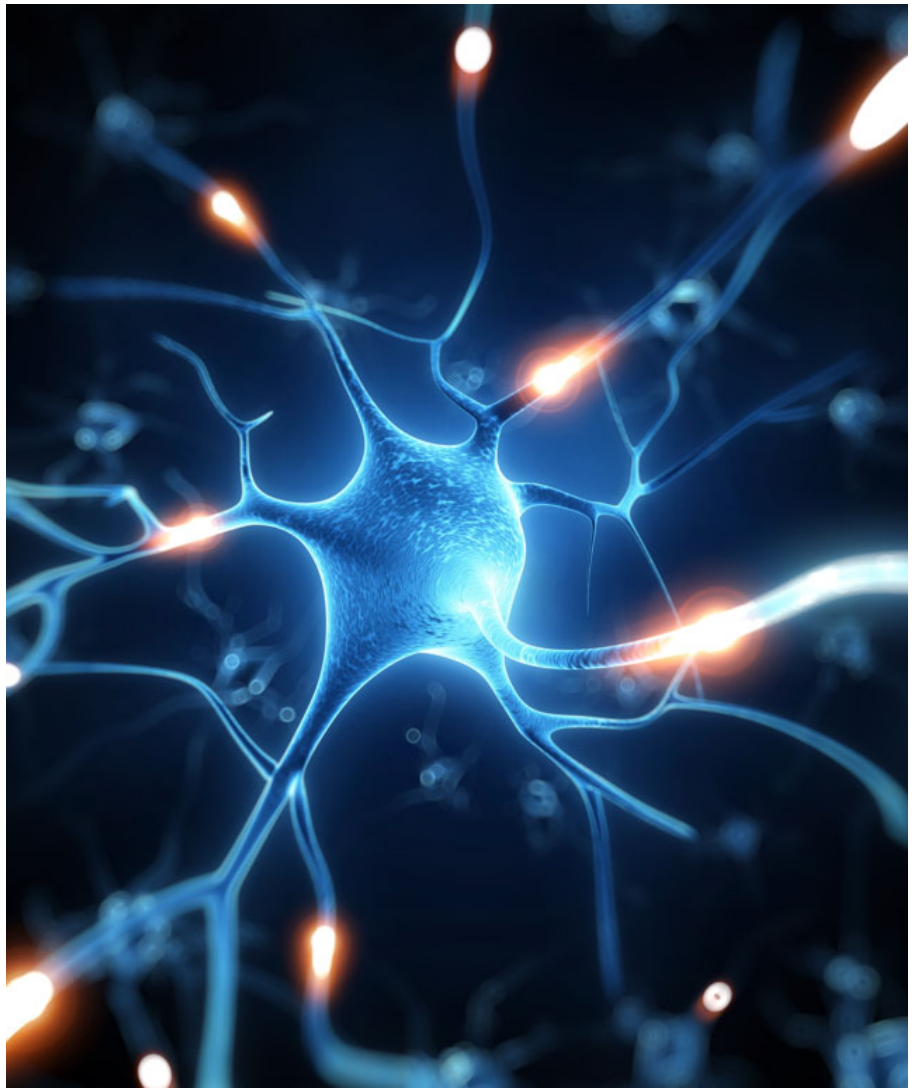
Success of ASM's in newly diagnosed epilepsy



Kwan P, Brodie MJ, N Engl J Med 342:314, 2000

WHEN MEDICATIONS DON’T WORK

CONSIDER EPILEPSY SURGERY



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Why do surgeries?

- Seizure freedom, up to 70%
- Prevent complications of long-term epilepsy (cognitive)
- Prevent sudden unexpected death in epilepsy (SUDEP)
- Improvement in Quality of Life (mainly employment and driving)
- Very few surgery related complications

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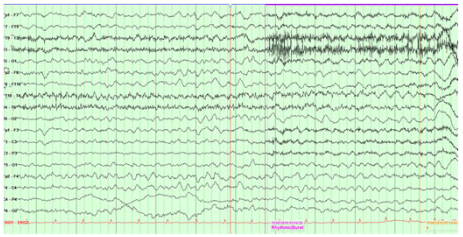
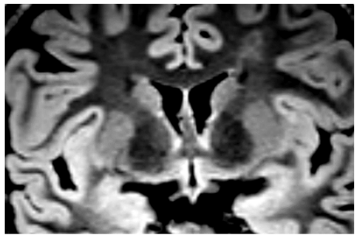
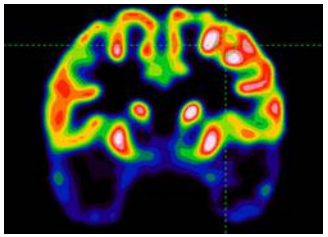
Typical pre-surgical evaluation → focal epilepsy



Scalp EEG



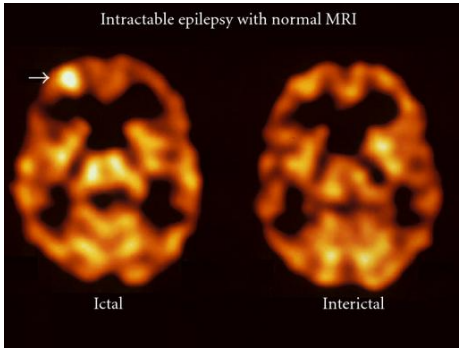
MRI brain 3 T



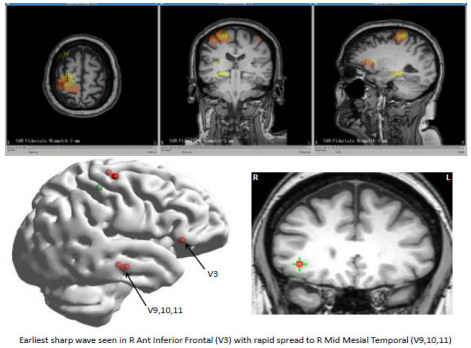
FDG PET

FMRI – language, motor tracts > language

Neuropsychological Assessment for Epilepsy Surgery



SPECT



MEG

WADA

Concordant data
No eloquent cortex

↓

Resection

If not → Invasive EEG

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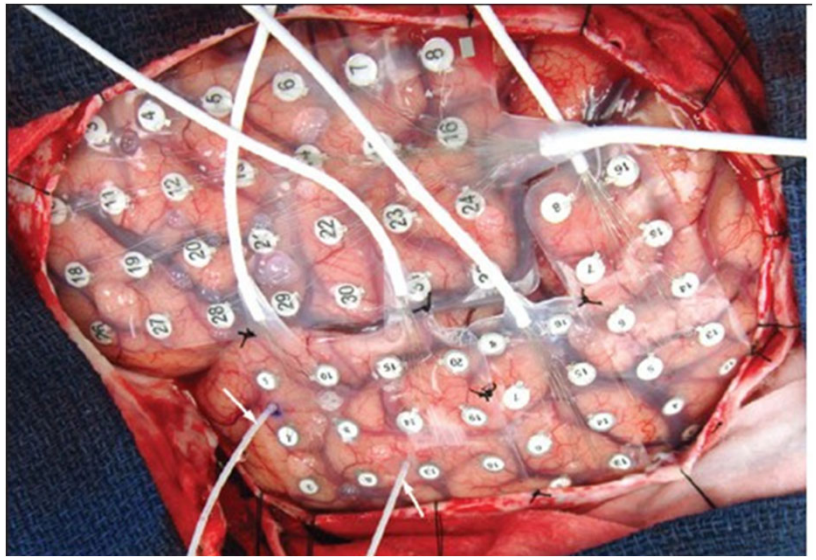
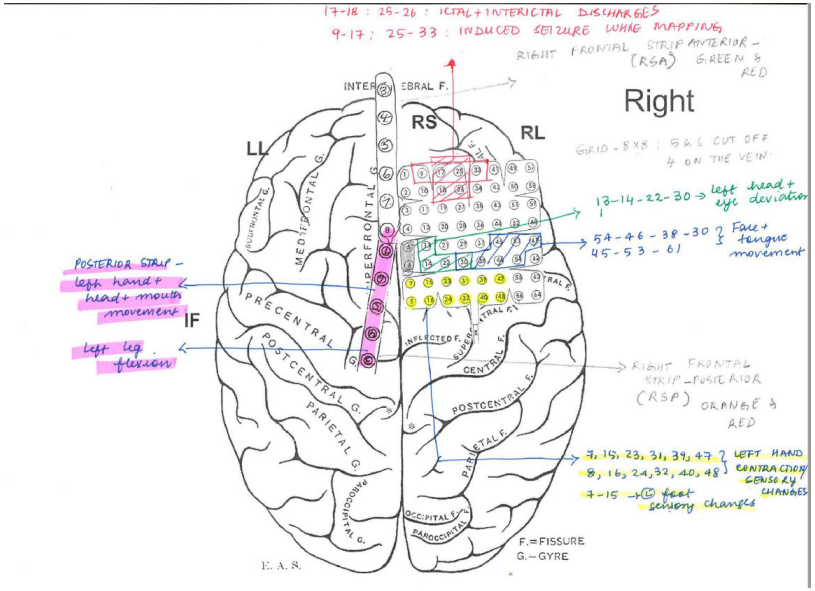
Intracranial EEG Monitoring - Grids

Subdural grid electrodes



Functional Brain mapping



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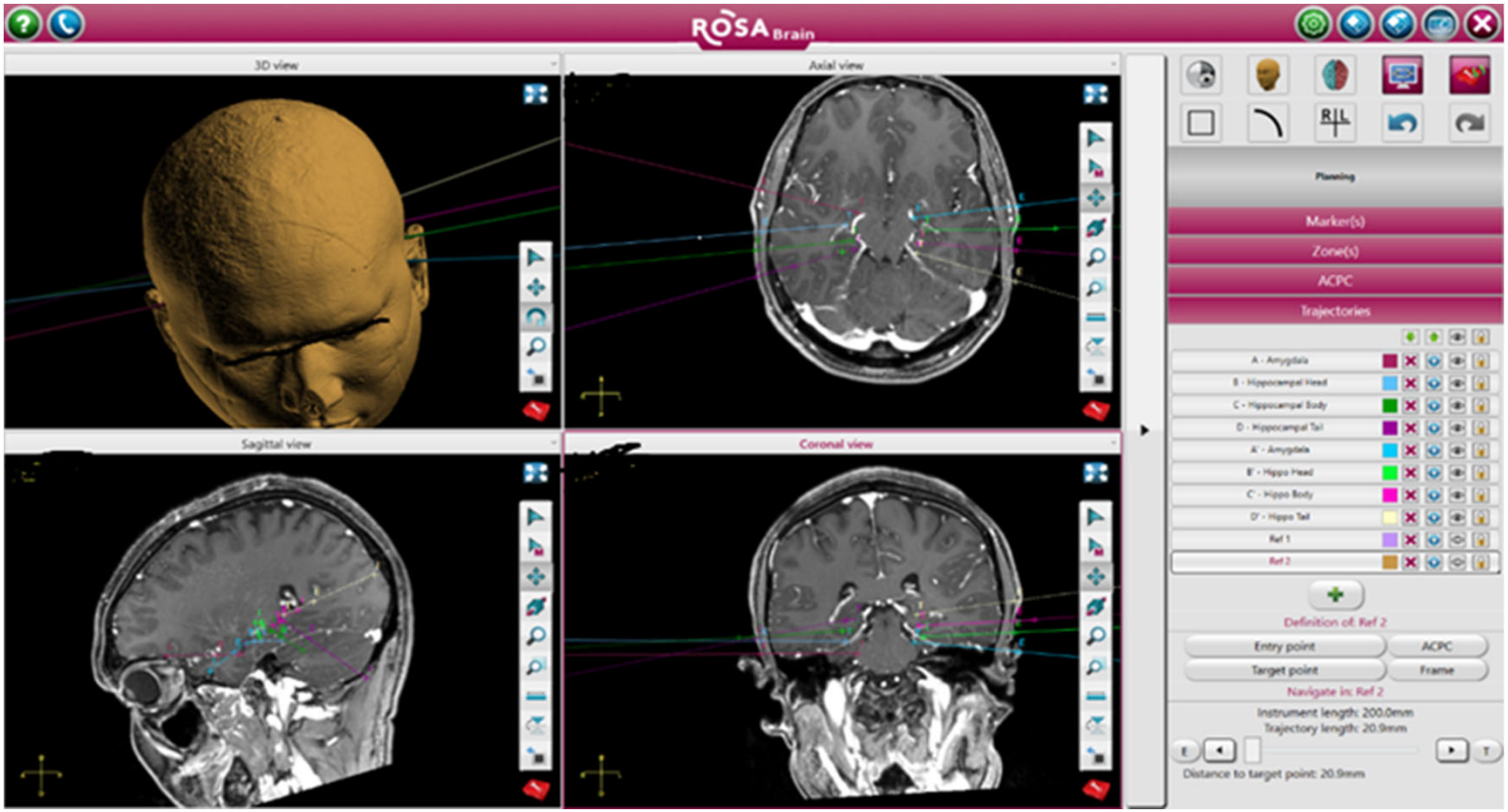
Intracranial EEG Monitoring – SEEG/ Depths

Stereo-EEG using a robot



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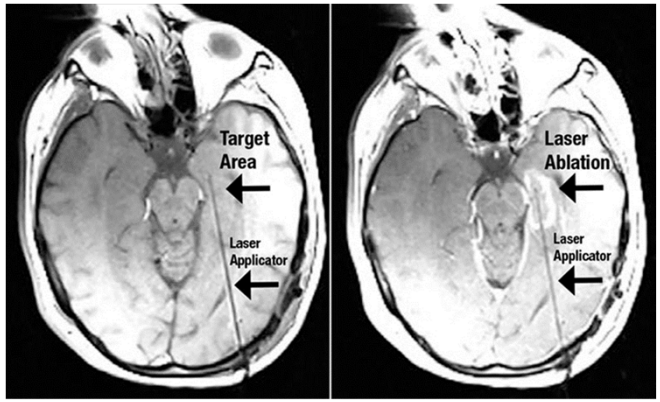
Types of surgeries

- Resection – removal of a lesion or part of the lobe
- Ablation – either laser ablation, stereotactic radiosurgery or thermo-frequency anticoagulation
- Disconnection Procedures – callosotomy, hemispherotomy
- Neuromodulation- VNS, RNS, DBS
- Combination (Resection + Neuromodulation)



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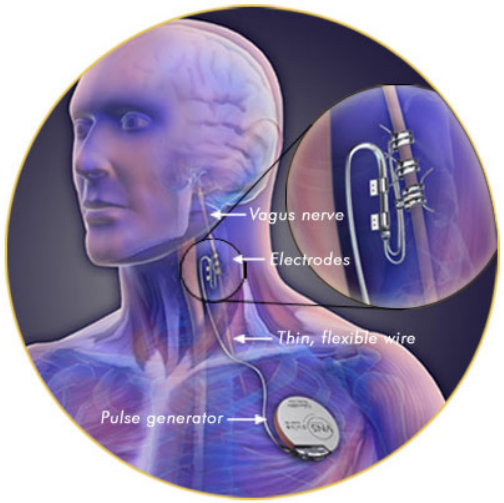
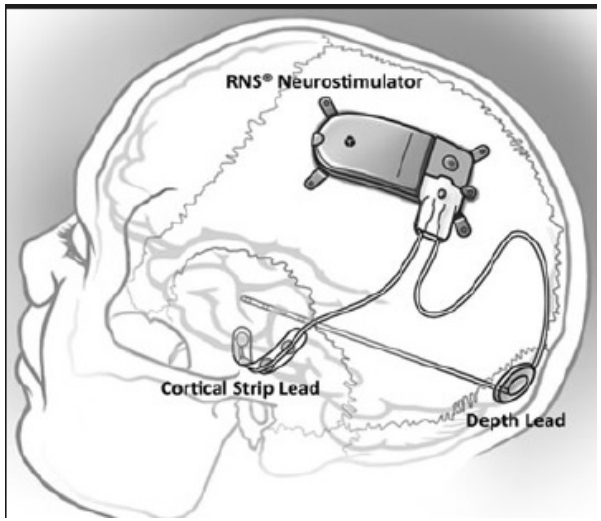
Neuromodulation

Vagal Nerve Stimulator (VNS)



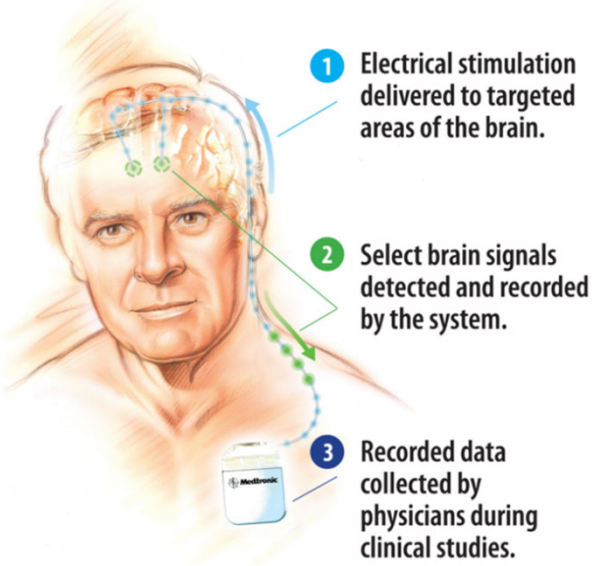
- Voice Alteration
- Needs to be turned off to get MRI

Responsive Neurostimualtion (RNS)



- 1 or 2 epileptogenic foci
- Approved for MRI (needs to be off)
- Patient downloads data on laptop

Deep Brain Stimulator (DBS)



- Anterior nucleus of Thalamus
- Main Indication: Multi-focal epilepsy

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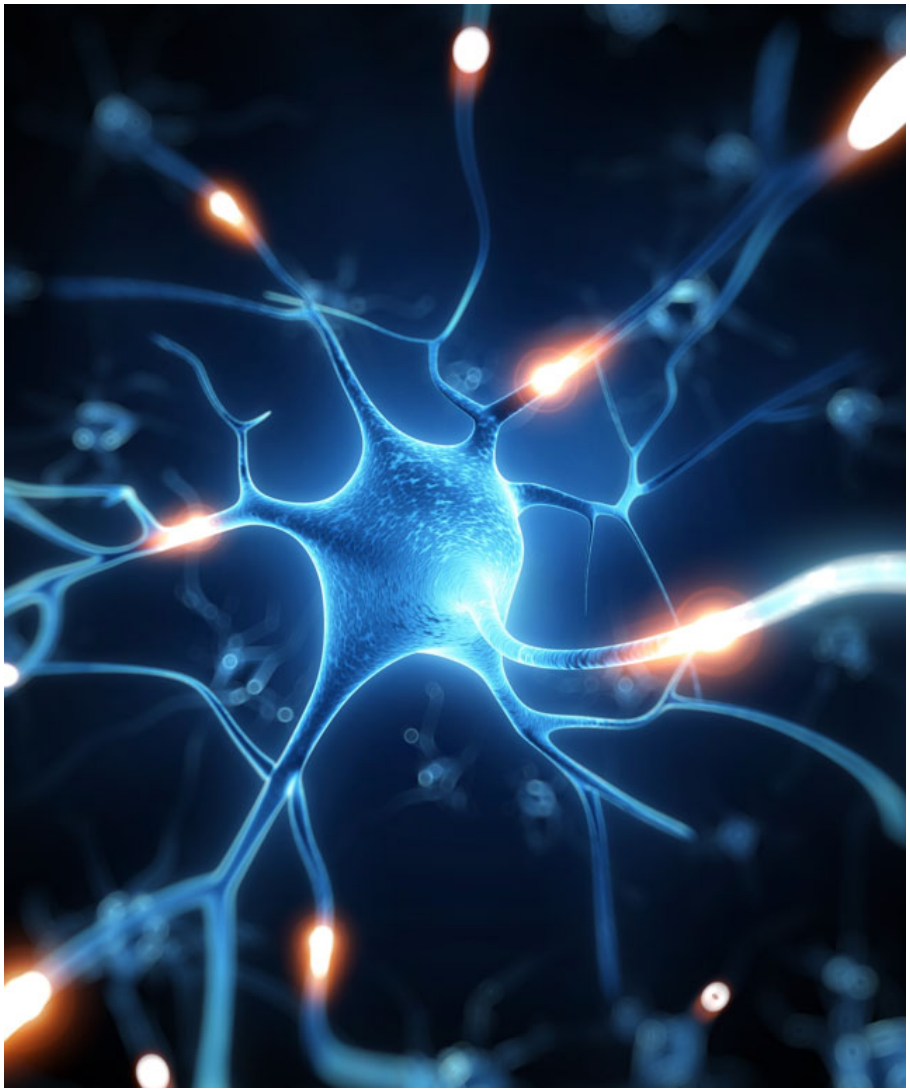
Diets for seizure control

- Ketogenic diet : Oldest anti-epileptic treatment by fasting (starvation ketosis)
- Most appropriate in children, adults least compliant

- Modified Atkins Diet : Less beneficial than ketogenic diet

EPILEPSY IN SPECIFIC POPULATIONS

WOMEN & ELDERLY



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- **Hormones:** Estrogen- proconvulsant, Progesterone- anticonvulsant

- **Fertility:** April 2016- prospective, multi-center observational study – WWE had a comparable likelihood of achieving pregnancy, time to be pregnant and pregnancy outcomes compared to healthy peers.

- **Catamenial Epilepsy:** Cyclic exacerbation of seizures in relation to the menstrual cycle (~1/3 of women with focal epilepsy)

- **Menopause:** Erratic fluctuations in gonadal steroids may worsen seizures, Estrogen replacement can exacerbate seizures in some WWE

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Epilepsy and Pregnancy

- 50-83% have no significant change in seizure frequency during pregnancy
- Seizure freedom for at least 9 months prior to pregnancy is associated with a high likelihood (84–92%) of remaining seizure free during pregnancy
- ASM exposure in utero causes congenital malformations 2-3 % higher than general population
- Folic acid supplementation reduces neural tube defects, improves IQ
- Recommended dose: up to 1 mg daily

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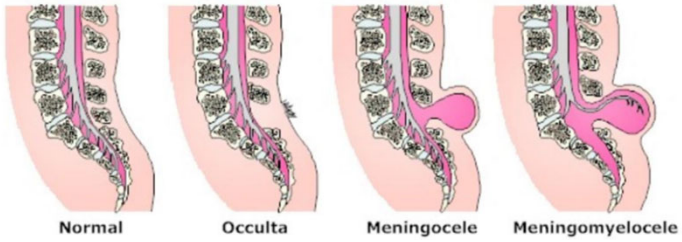
Neural Tube Defects- Valproic Acid (most common medication to cause this)



Child with facial features of FVS: Trigonocephaly which has been surgically repaired, broad forehead, thin arched eyebrows, flat nasal bridge, infraorbital grooves, short anteverted nose, long and smooth philtrum and thin upper lip.

Topiramate
Cleft Lip and Palate

Phenobarbital

Heart defects, craniofacial abnormalities, growth deficiency

Phenytoin Exposure

IUGR with small head circumference, dysmorphic facies, orofacial clefts, cardiac defects, distal digital hypoplasia with small nails

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Epilepsy in the Elderly

- Incidence is 2-3 x higher than general population
- Recurrence rate >90% if untreated
- Most common cause: Stroke
- Other causes: Dementia, TBI, Tumors
- Hypertension is an independent risk factor
- Intermittent confusion may be the presenting symptom
- 80% of treated population achieve seizure control with monotherapy

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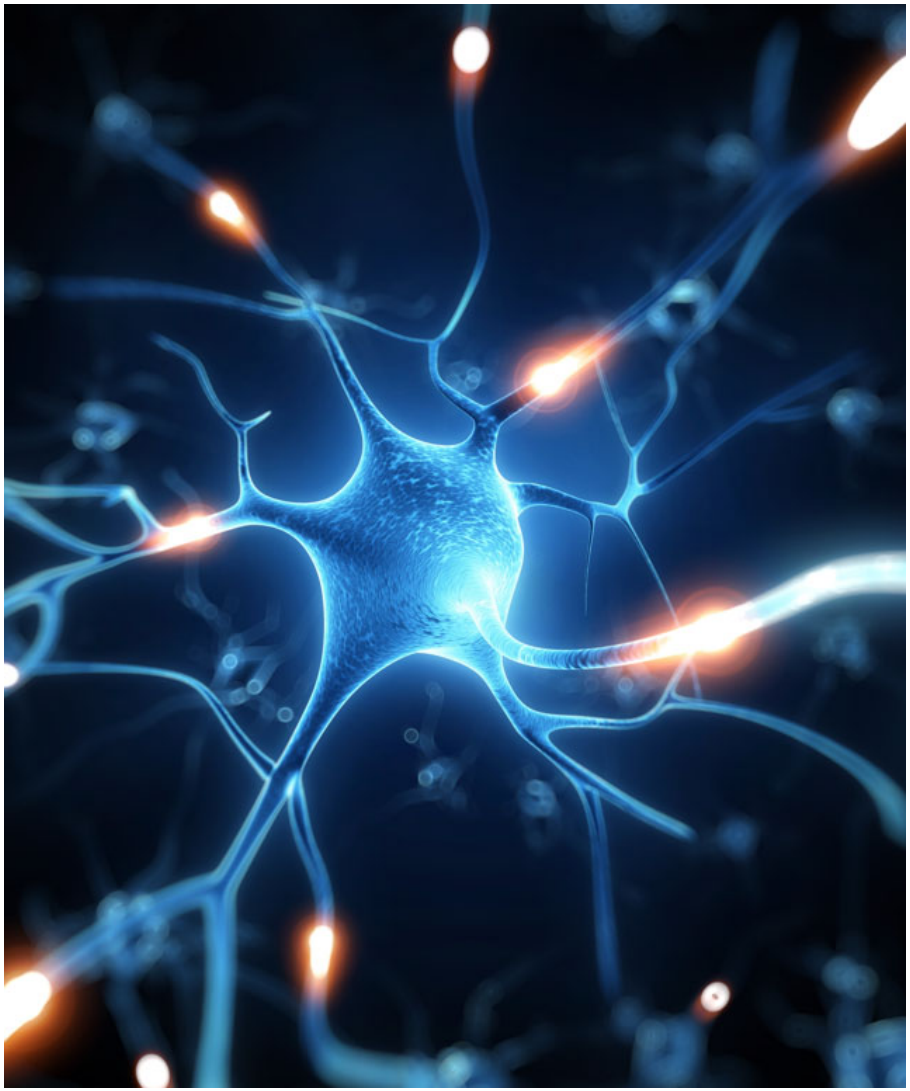
Epilepsy in the Elderly

- Physiologic changes may affect ASM absorption and metabolism
- Start low and go slow, check ASM levels
- Choose appropriate ASM being mindful of other medications, tolerability and safety issues
- Phenytoin is frequently prescribed- not ideal due to many reasons
- Medications causing dizziness, imbalance, diplopia leading to falls
- Concurrent diuretics with CBZ/OXC can lead to hyponatremia

COMORBIDITIES WITH EPILEPSY



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Psychiatric:

- Depression (35%) and anxiety (19%)
- Suicide risk 25 times more than in general population
- Psychosis (7%)
- 2008 meta-analysis found a 1.8-fold increased risk of suicidality associated with ASMs

Cognitive

- Higher prevalence of impaired cognition compared to age-education matched healthy individuals

Mortality

- Risk of Sudden Unexpected Death in Epilepsy (SUDEP)
- 1.2/1000 patient years in adults
- Main risk factor: poorly controlled GTC seizures

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Bone Health

- More than 50% of adults on ASMs have decreased bone density of either the hip or the spine
- Certain ASM's increase the risk of Osteopenia and Osteoporosis- Phenytoin, Phenobarbital, Primidone, Carbamazepine and Valproate
- Yearly DEXA scans
- Adequate nutrition, exercise, avoidance of smoking/alcohol
- Calcium and Vitamin D supplementation

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Functional restrictions that impact Quality of Life (QOL)

Driving:

- Privilege and not a right
- # 1 reason that impacts QOL
- Restrictions vary by state, only 6 states have mandatory physician reporting laws (CA, DE, NV, NJ, OR, PA)

Occupation:

- Airline pilot
- Armed forces
- CDL license- interstate 18-wheeler truck drivers
- Barriers to employment- Heavy machinery, sharp objects, open flames
- Odd work hours

Take Home Points- Management

- Obtain a good history for a proper seizure classification
- Start epilepsy work up- EEG and MRI
- Start ASM if recurrence risk is high
- Be mindful of ASM side effects, ASM levels, pertinent labs, DEXA scan
- Folic acid in all women of reproductive age group taking ASM's
- Assess for depression/ anxiety/ suicide in patients with epilepsy
- Refer to a neurologist/ closest epilepsy center if patient has seizures
- Consider surgical options early and referral of patients with focal epilepsy to nearest comprehensive epilepsy center for possible surgery

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