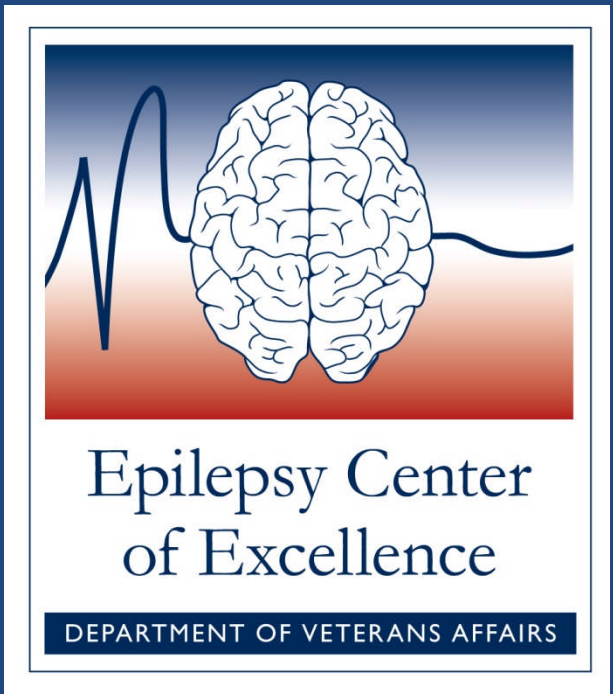
Seizures and Epilepsy Diagnosis and Treatment



Karen L. Parko, M.D.
National Director
VA Epilepsy Centers of Excellence
San Francisco VA Medical Center

Objectives

- Define seizures and epilepsy
- Classification of seizures and epilepsy
- Evaluation/diagnosis of seizures
- Treatment of epilepsy
  - Anticonvulsant medication
  - Medical Devices and surgery
- Referral to epilepsy center
- Organization of VA Epilepsy Centers of Excellence

SEIZURE

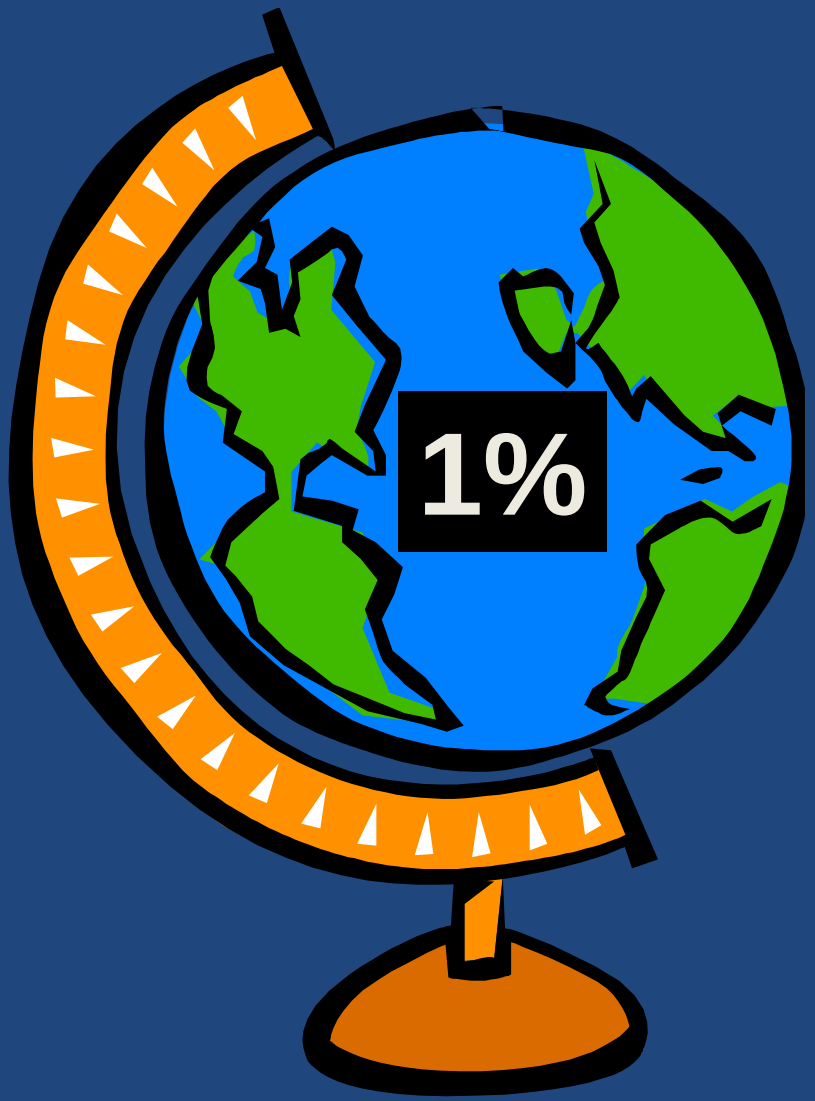
- result of sudden, usually brief, excessive electrical discharges in a group of brain cells (neurons)
- can occur in different parts of the brain
- depending on where in the brain this occurs, the person will experience different symptoms

EPILEPSY

A tendency to have recurrent seizures

1% by age 20

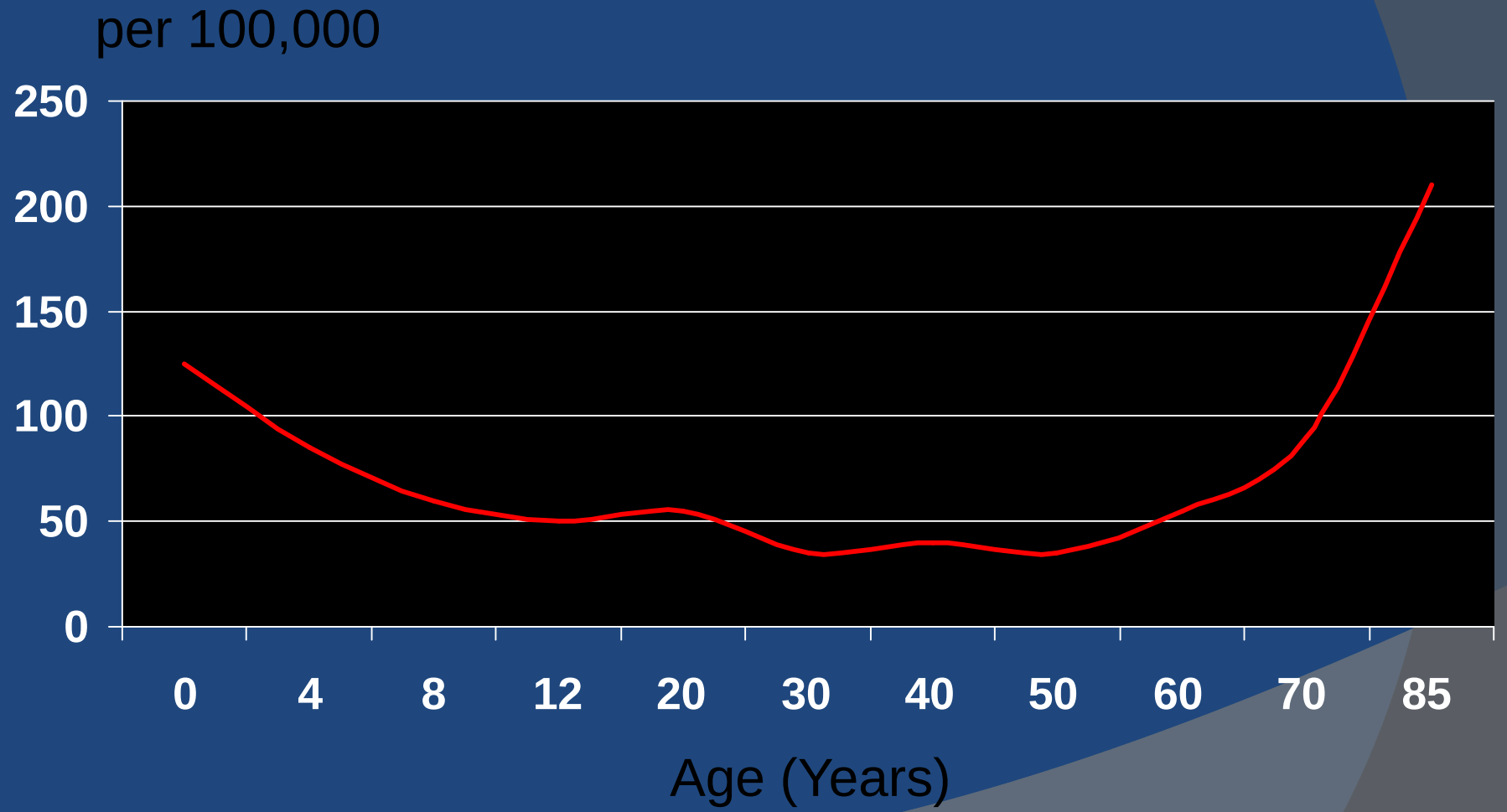
3% by age 75



Epilepsy

Disorder characterized by recurrent, unprovoked seizures

Incidence of Epilepsy



Hauser et al., 1993

International League Against Epilepsy (ILAE)

- The ILAE Classifications of Seizures and the Epilepsies have been used since 1981
- Although imperfect, they have provided invaluable means of communication
- Efforts continue to refine and upgrade the current classifications
- Based on review of video recorded seizures of clinical and electroencephalographic events provided from epilepsy centers worldwide.

- *Epilepsia*, 51(4):676–685, 2010

Terminology

Old	Recent Past	Current (April 2010)
Focal Motor	Simple Partial	Focal
Psychomotor Temporal Lobe	Complex Partial	Focal with impaired consciousness
Grand Mal	Tonic Clonic	Generalized
Petit Mal	Absence	Generalized

Classification of Seizures

Focal seizures

- **Without** impaired consciousness or responsiveness
  - With motor or autonomic components
  - Involving subjective sensory or psychic phenomena (aura)
- **With** impaired consciousness or responsiveness
- Evolving to a bilateral convulsive seizure

Generalized seizures

- Absence seizures
  - Typical vs Atypical
- Tonic-clonic seizures
- Myoclonic seizures
- Tonic seizures
- Clonic seizures
- Atonic seizures

Epilepsy Types (past classification)

Idiopathic (Primary)

- Onset in childhood or young adult
- Probably genetic
- Good AED response
- Favorable prognosis
- “Normal” brain

Symptomatic (Secondary)

- Onset any age
- Multiple etiologies
- Variable response
- Variable prognosis
- Brain pathology

Classification of Epilepsy by Etiology

- Electroclinical syndromes (idiopathic)
  - i.e. Childhood absence, West syndrome, Familial temporal lobe epilepsy, Juvenile Myoclonic Epilepsy
- Distinctive Constellations
  - i.e. Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE with HS)
- Secondary to specific metabolic or structural lesions or conditions (symptomatic)
  - i.e. Tumor, Infection, Trauma, Stroke, Cortical Malformations
- Unknown cause (cryptogenic)

Epilepsia 2010; 51: 676-685.

Post-Traumatic Epilepsy

- Epilepsy is a sequela of head trauma
- Seizures may begin hours to years after injury
- Report of the Vietnam Head Injury Study: 15 years after penetrating brain injury, 53% had epilepsy
- Animal data suggest blast injury may be more injurious to neurons than blunt trauma
- Despite reduced penetrating brain injury, epilepsy incidence in OEF/OIF Veterans may be higher than expected

Salazar, et al., 1985
Garga & Lowenstein, 2006

Epilepsy in the elderly

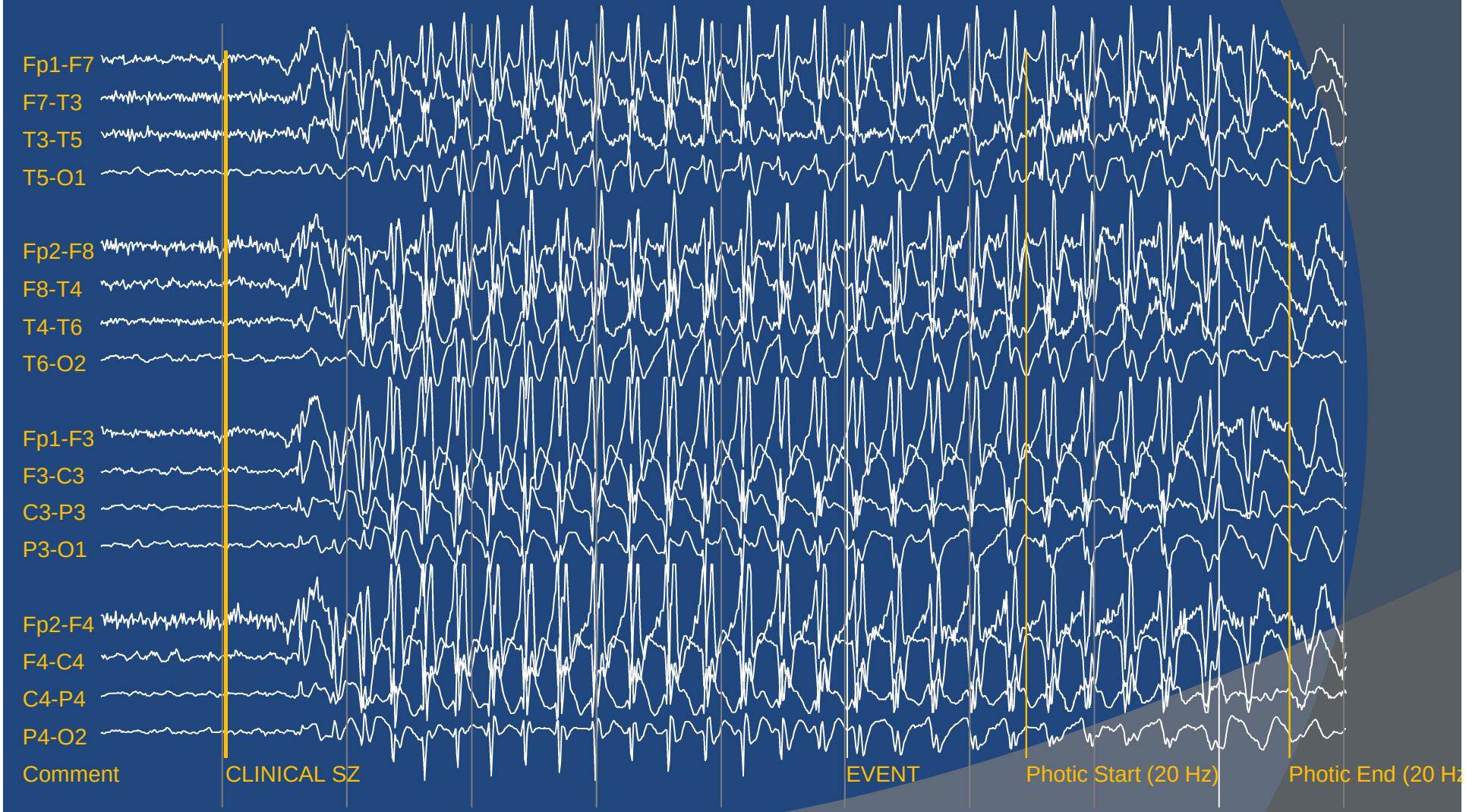
- Under diagnosed and misdiagnosed
- Clinical Manifestations in Elderly may be different
  - Aura-less frequent or is non-specific (Dizziness)
  - Automatisms-less frequent
  - Post-ictal confusion may be prolonged
  - May present with altered mental status, confusion, or memory disturbance

Ramsey, Rowen & Pryor, 2004

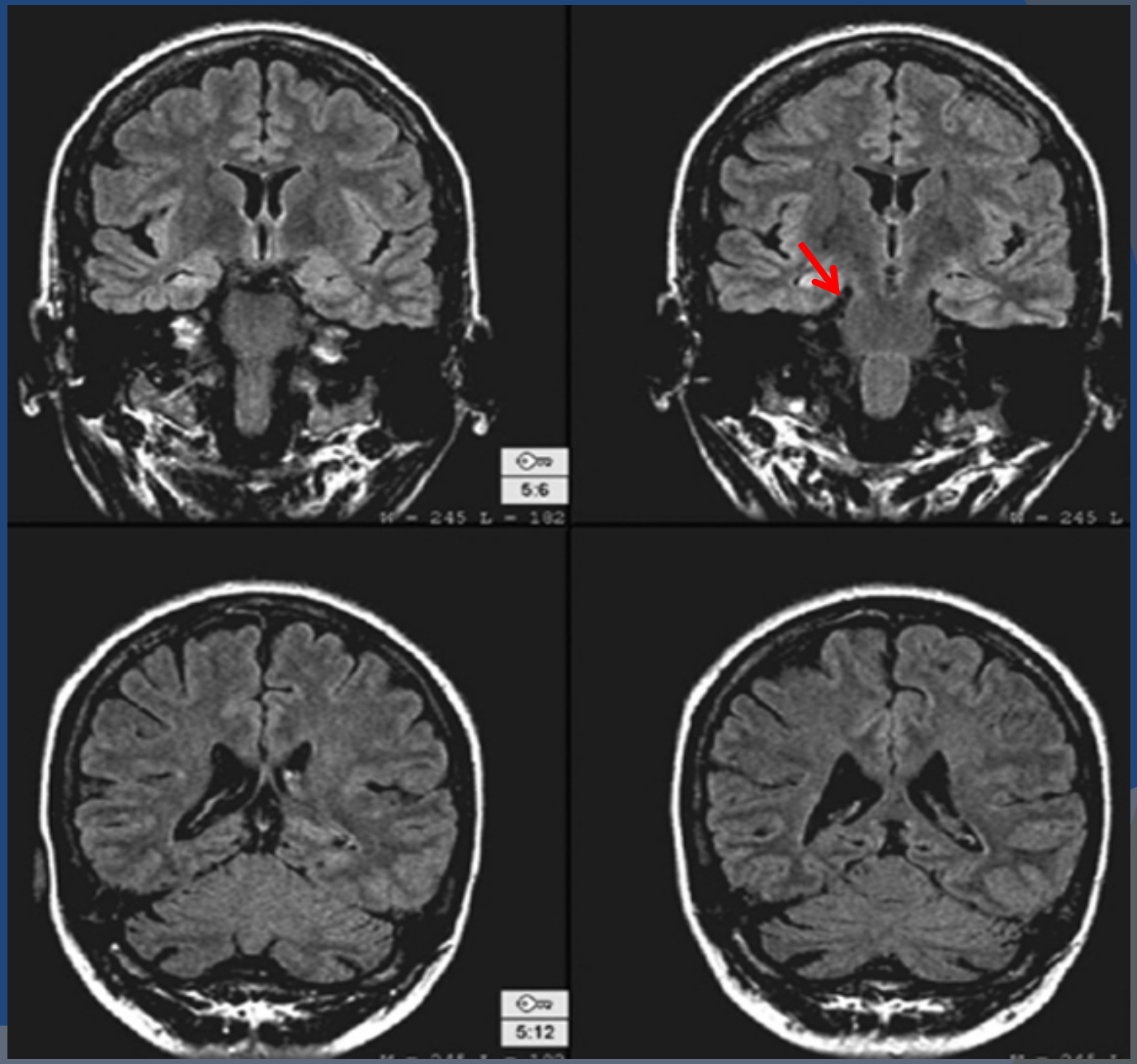
Diagnostic Work-Up for Seizure

- History & Physical
  - Was it seizure or other LOC?
  - Identify risk factors: Brain Infection or lesion, metabolic disturbance, drug or alcohol related, FHx, trauma
- Labs
  - Chemistry Panel, Consider Lumbar Puncture
- Electroencephalography
  - Stat if patient not returning to baseline
- Imaging
  - MRI with gad (usually not urgent)

Routine EEG Findings in Childhood Absence Epilepsy: Generalized 3Hz Spike and Wave Discharges



MRI in Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis



Epilepsy Treatment in 2011

- FDA-Licensed Antiepileptic Drugs
- Epilepsy Surgery
- Vagus Nerve Stimulation
- Ketogenic Diet
- Investigational Therapies
  - Deep brain stimulation
  - Responsive neurostimulation

Goals of Therapy

Pharmacotherapy

- Up to 70% of newly diagnosed children and adults can be successfully treated
- Ascend monotherapy to maximum tolerated dose (*regardless of serum levels!)*

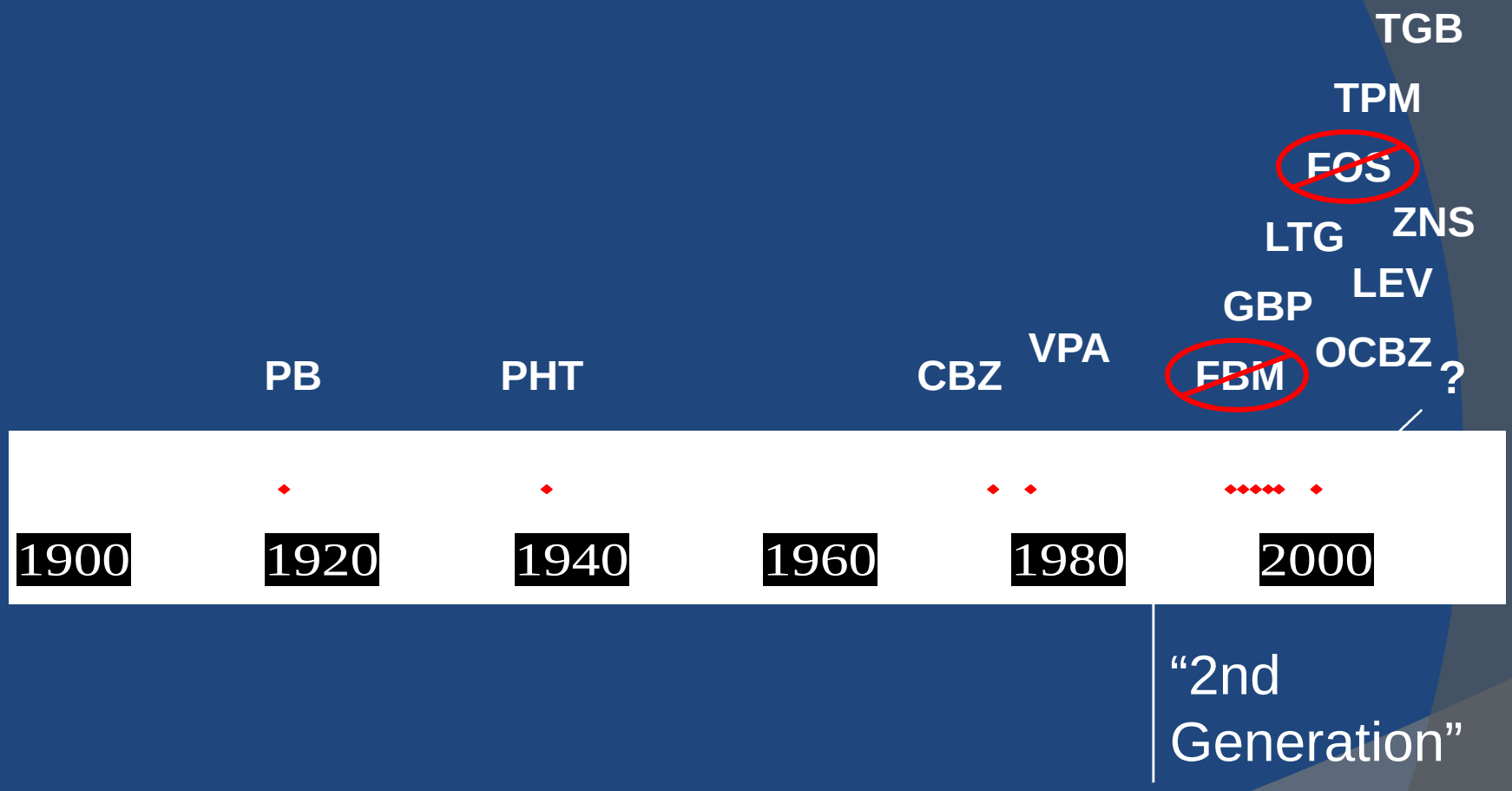
AEDs: Alphabet Soup

Generic name	3-letter abbreviation	Brand names
Phenobarbital	PHB	Luminal
Phenytoin	PHT	Dilantin, Phenytek, Mylan Phenytoin
Primidone	PMD	Mysoline
Ethosuximide	ESX	Zarontin
Carbamazepine	CBZ	Tegretol, Tegretol XR, Carbatrol
Valproate	VPA	Depakote, Depakote ER, Depacon
Felbamate	FBM	Felbatol
Gabapentin	GBP	Neurontin
Lamotrigine	LTG	Lamictal
Tiagabine	TGB	Gabatril
Topiramate	TPM	Topamax
Levetiracetam	LEV	Keppra, Keppra XR
Oxcarbazepine	OXC	Trileptal
Zonisamide	ZNS	Zonegran
Pregabalin	PGB	Lyrica
Lacosamide	LCM	Vimpat
Vigabitrin	VGB	Sabril

Historical Perspective:

	Tablet/ Capsule	IV	IM	Sprinkle Capsule	Chewable	Suspension/ Syrup/Elixir	Extended-Release
Phenobarbital	+	1912	+			+	
Phenytoin	1938				1995	1995	1995
Primidone	1954						
Ethosuximide	1960					2000	
Carbamazepine	1974				2000	2000	1997
Valproate	1978	1997		1996		1978	2002
Felbamate	1993					1993	
Gabapentin	1993					1993	
Lamotrigine	1994				1998		
Fosphenytoin		1996	1996				
Topiramate	1996			1999			
Levetiracetam	1999	2008					2009
Oxcarbazepine	2000					2000	
Zonisamide	2000						
Pregabalin	2004						
Lacosamide	2009						
Vigabitrin	2009					2009	

Antiepileptic Drug (AED) Therapy



1st Generation AEDs

- Vast Clinical Experience
- Use in Both Partial and Primary Generalized Epilepsies
  - exception: CBZ-Absence
  - Incomplete Efficacy
  - Unfavorable Kinetics
  - Narrow Therapeutic Range
  - Adverse CNS Effects
  - Drug Interactions

Hepatic Metabolism-1st Generation AEDs

- Inducers
  - Phenobarbital
  - Phenytoin
  - Carbamazepine
- Inhibitor
  - Valproate
- Clinical Significance (statins, OCPs, ABX, coumadin)

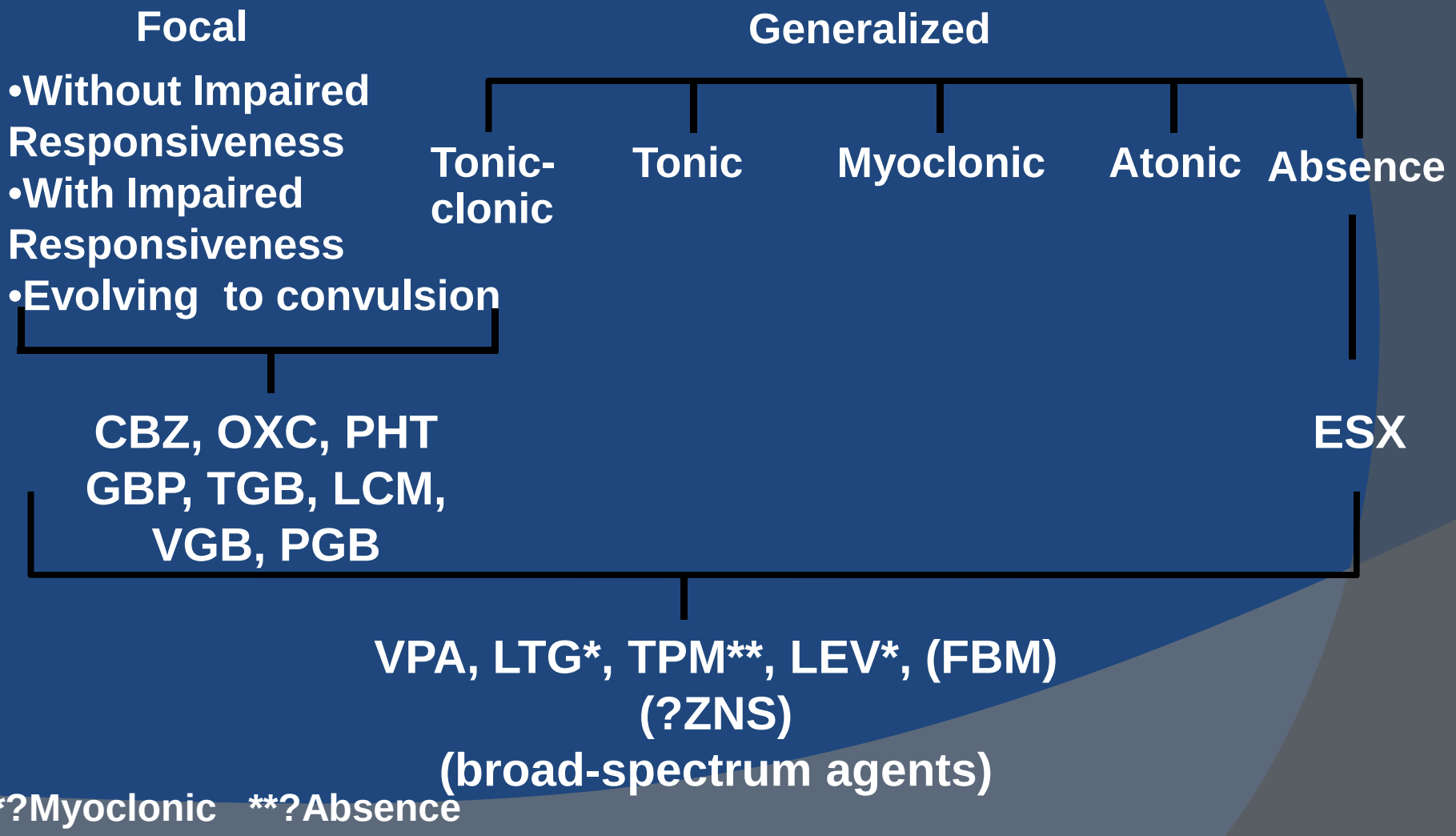
2nd Generation AEDs

- Safer
- More expensive (not as expensive as admission)
- Specific MOA
- Simple Pharmacokinetics
- Better Tolerability
- No therapeutic monitoring
- Lower Drug Interactions
- NO generics (bioavailability issues)
- Not profoundly more potent

How to Choose the Right AED

- Spectrum: Broad or Narrow
- Adverse and Side Effect Profiles
  - Long term and Short term
- Interactions with Other Medications
- Dosing Frequency and Compliance
- Comorbid Indications
  - TPX for weight loss or headache
  - VPA for migraine
  - LTG for mood disorders
- Refer to Neurology or Epilepsy Center for Expertise

AED Treatment Options by Seizure Type



*?Myoclonic **?Absence

CNS Adverse Effects of Antiepileptic Drugs

- Most frequent side effects of AEDs are similar
  - Drowsiness
  - Incoordination
  - Dizziness
  - Cognitive impairment
- Toxicities are additive

Drug Specific AEs

- Pedal Edema – GPN & VPA
- Weight Gain – CBZ, GPN & VPA
- Weight Loss – FBM, TPM & ZNA
- Word Finding Difficulty - TPM
- Peripheral Paresthesia – TPM and ZON
- Renal calculi –TPM, ZNG
- Concentric visual field restriction –VGB
- Osteoporosis – CYP450 Inducers + VPA
- Hyponatremia – CBZ and OXC
- Rash – LTG, CBZ, PHB, DPH
- Hyperammonemia –VPA
- Encephalopathy – TGB and VPA
- Peripheral Neuropathy – PB, PHT and CBZ
- Closed angle glaucoma – TPM, ZNG

Serum AED Levels are...

- Only a rough guide to efficacy & toxicity
- Of little value when performed on a “routine” basis
- Not predictors of serious adverse reactions (unlike levels for other drugs, e.g., digoxin, lithium, theophylline)
- Of little help if not trough
- Potentially dangerous to patients!!!
- Over-used!!!

Response to AED Treatment: Complete Seizure Control

First Drug	→	**~40%**
Second Drug	→	**~20%**
Third Drug	→	**<10%**
Add'l Drugs	→	**<5%**

→ **>20% Refractory!**

Medically Refractory Epilepsy

- Definition: Persistent disabling seizures despite adequate trials of 2 AEDs that are appropriate for seizure type
- 30-40% of patients with partial seizures
- Increased overall mortality rate
- Increased cognitive morbidities
- 200,000 patients in US with MR epilepsy are candidates for surgical treatment but only 2-3,000 epilepsy surgeries are performed annually

Uncontrolled seizures need evaluation in an Epilepsy Center

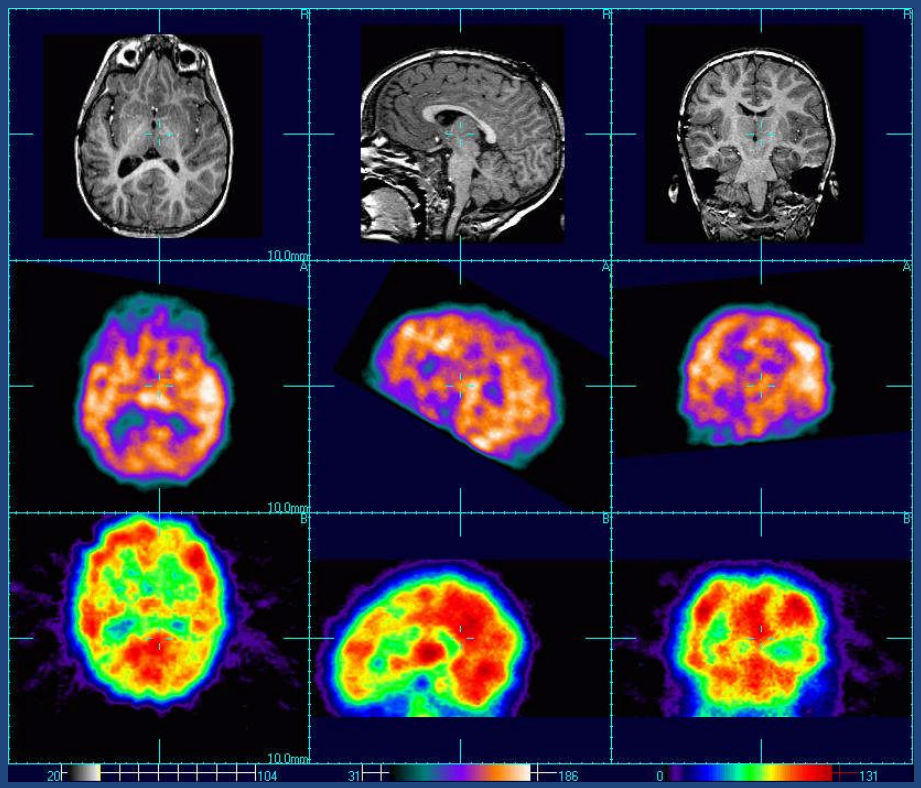
- Video EEG Telemetry
  - Are the events seizures?
  - What type of seizures? Are AEDs appropriate?
  - Does the seizure onset allow for surgical options?

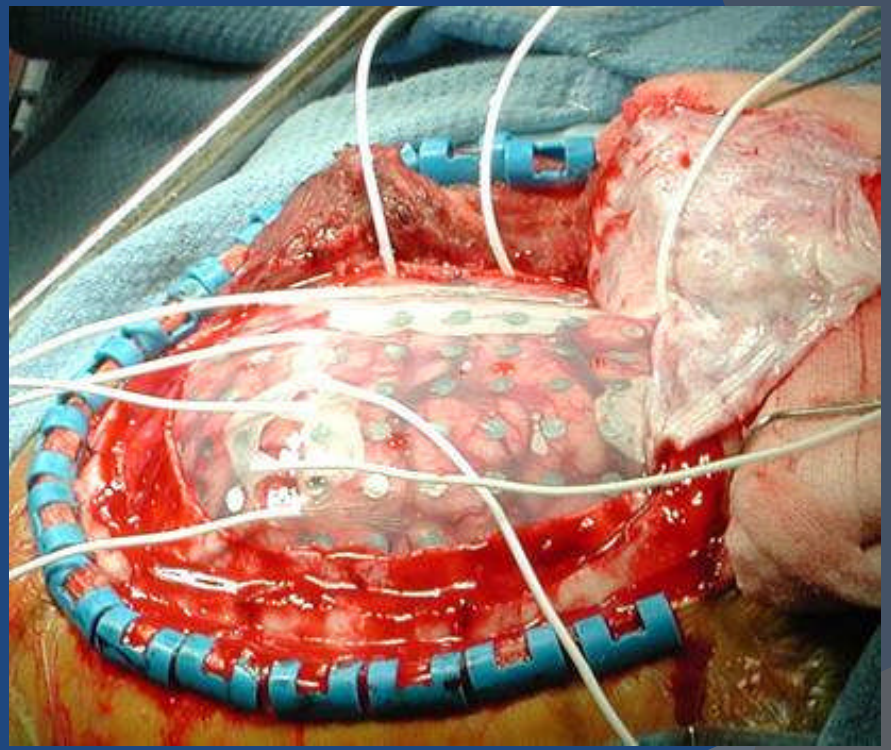
Epilepsy Monitoring Unit
Video/EEG telemetry

Presurgical Evaluation done at Epilepsy Centers

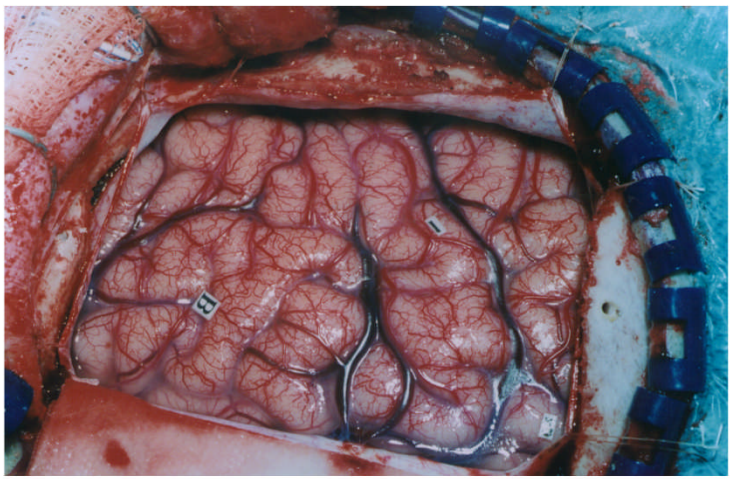
- MRI Seizure protocol
  - Sensitive for specific lesions of interest
- Magnetoencephalography (MEG)
- PET
- Wada
- Neuropsychological testing

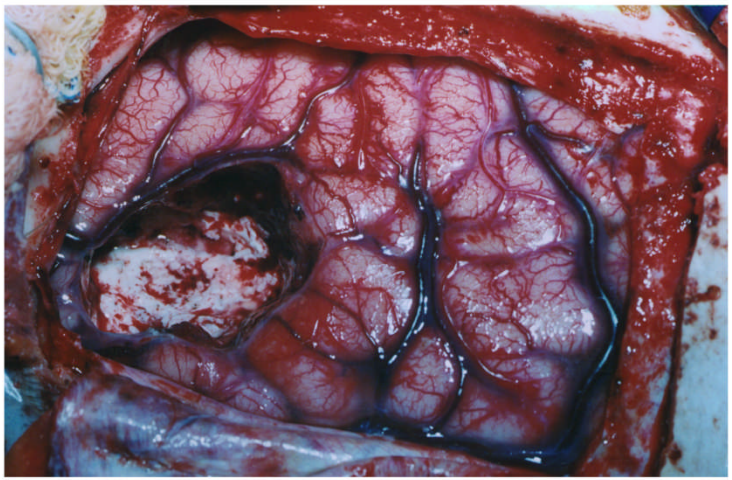
Multi-Modality Evaluation



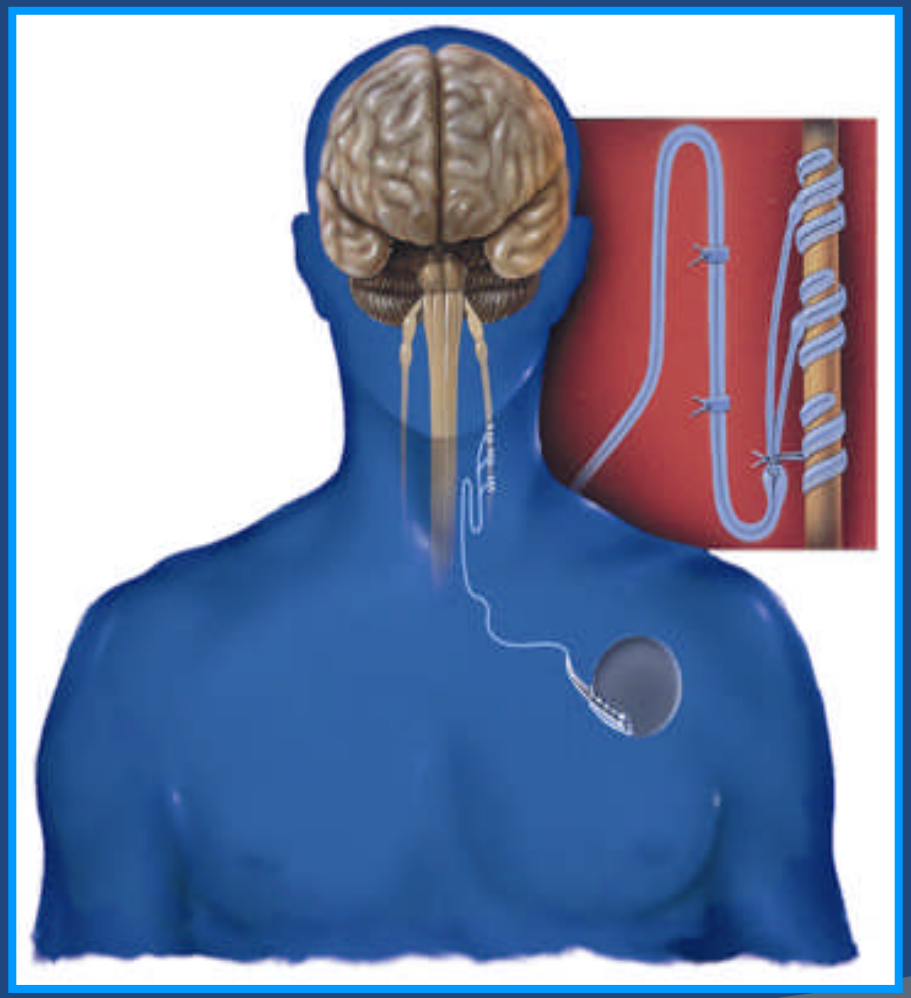


Epilepsy Surgery





Vagus Nerve Stimulation



- FDA approved to treat epilepsy not controlled by medication
- Often reduces, but usually does not completely control, seizures
- Offered at SFVA since 1998

Emerging Treatments

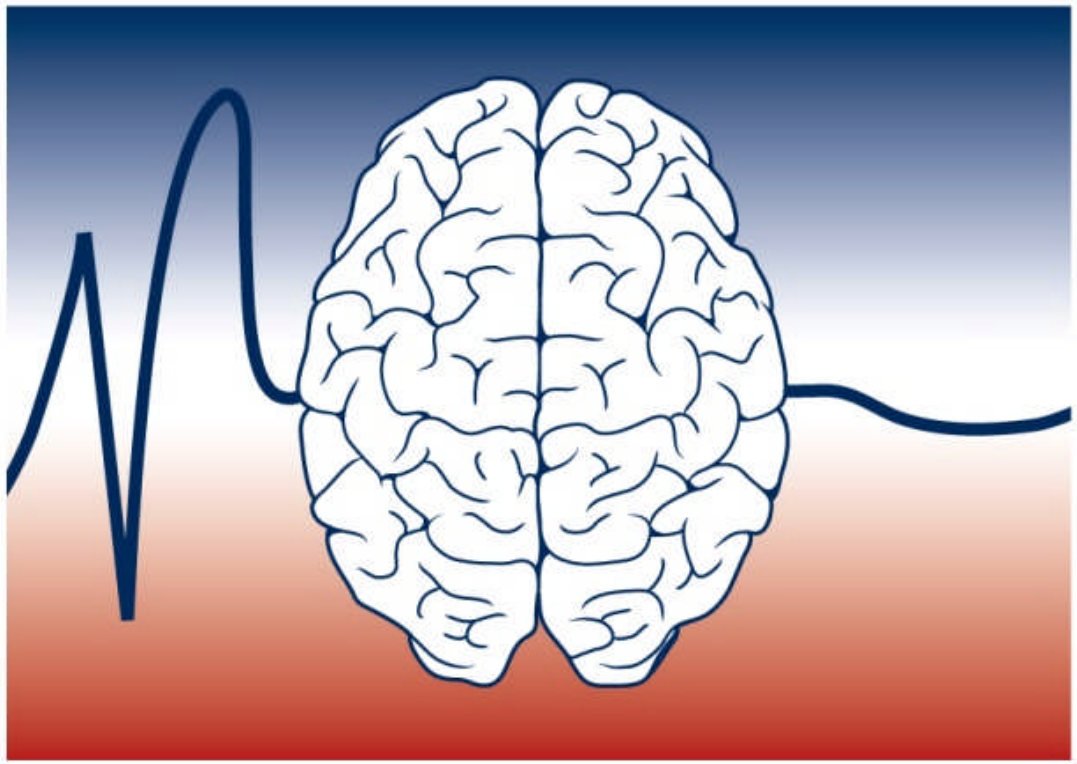
- Deep Brain Stimulation: SANTE
  - Bilateral stimulation of the anterior nuclei of the thalamus (ANT)
  - Continuous cyclic stimulation similar to VNS
  - Did not receive FDA approval in US
- Responsive Neurostimulation
  - Implanted device detects electrical seizure activity in the brain
  - Delivers electrical stimulation to suppress the propagation

When to Refer a Patient

- Newly diagnosed epilepsy or 1st unprovoked seizure:
  - AEDs: start? which one(s)?
  - Counseling: driving, psychosocial issues
- Patients with established epilepsy
  - AEDs: continue? change? tailor…
  - Special populations: women, elderly, medically refractory
  - New concerns: drug interactions, side effects
- Patients with indeterminate spells

If seizure control is not promptly achieved…

Refer the patient to an epilepsy specialist



Epilepsy Center of Excellence

DEPARTMENT OF VETERANS AFFAIRS

Establishment of VA Epilepsy Centers of Excellence

Response in 2008 to Section 404 (Epilepsy Centers) of Veterans Mental Health and Other Care Improvements Act of 2008 (PL110-387)

Requirements of PL110-387

- VHA is to establish 4-6 epilepsy centers and appoint an overall director
- Centers must:
  - link to existing polytrauma centers
  - link to academic centers and conduct research
  - be established by a Peer Review Panel
  - be geographically dispersed
  - be involved with education and fellowship training
- Funding level of $6 million per year 2009-14

Facilities Specific Strengths

ECOE	Linked Polytrauma Site	Sites of Epilepsy Strength	States Covered (note that these may need to change for balance)
Northwest	Minneapolis	Madison, Portland, Seattle	AK, WA, OR, ID, MT, WY, ND, SD, MN, IA, IL, IN,MI, WI
Southwest	Palo Alto (San Antonio in future)	San Francisco, West Los Angeles, Albuquerque, Houston	CA, UT, CO KS, NE, NV, HI, AZ, NM, TX, OK,
Southeast	Tampa	Miami, Gainesville, Durham	FL, AL, GA, MS, TN, KY, SC, PR, AR, LA, NC, MO
Northeast (Atlantic)	Richmond	Baltimore, New Haven	VA, WV, OH, IN, PA, DE, NJ, NY, VT, MA, CT, RI, NH, ME, DC

ECoE Site

ECoE & Polytrauma

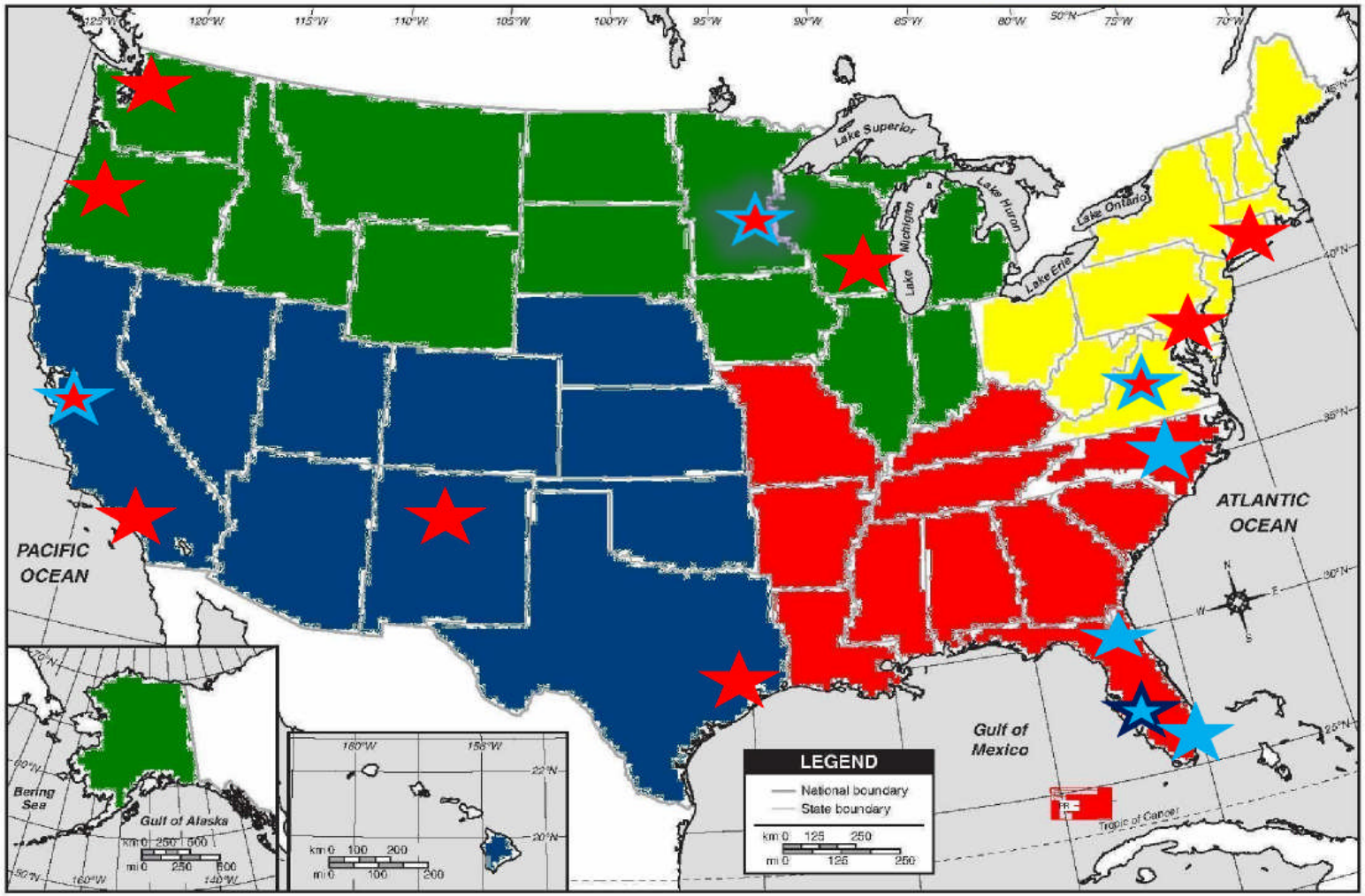
Territories of the Epilepsy Centers of Excellence

Northwest

Southwest

Southeast

Atlantic



NORTHEAST REGIONAL CENTERS

Epilepsy Center of Excellence
NORTHEAST

Maryland Health Care System

Regional and Site Director: **Alan Krumholz**

10 North Greene Street Baltimore, MD 21201

West Haven VA CT Healthcare System

Site Director: **Huned Patwa**

950 Campbell Avenue, West Haven, CT 06516

Richmond VAMC

Site Director: **Alan Towne**

1201 Broad Rock Boulevard Richmond, VA 23249

NORTHWEST REGIONAL CENTERS

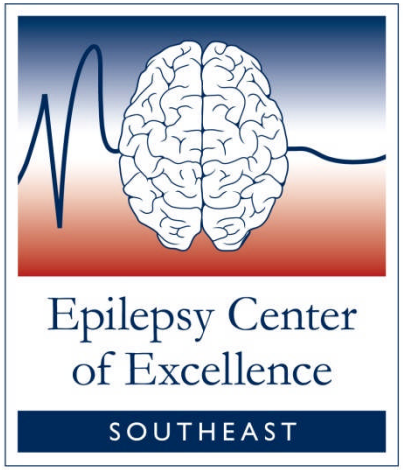
Epilepsy Center of Excellence
NORTHWEST

William S. Middleton Memorial VA Hospital
Regional and Site Director: **Paul Rutecki**
2500 Overlook Tr. Madison, WI, 53705

Minneapolis VA Healthcare System
Site Director: **Stephen Holloway**
One Veterans Dr Minneapolis, MN 55416

Portland Oregon VA
Site Director: **Martin Salinsky**
3710 SW U.S. Veterans Hospital Road Portland, OR 97239

Puget Sound Health Care System
Site Director: **William Spain**
1660 S. Columbian Way Seattle, WA 98108-1597



SOUTHEAST REGIONAL CENTERS

Durham VA Healthcare System
Regional and Site Director: **Aatif Husain**
508 Fulton Street Durham, NC 27705

Miami VAMC
Site Director: **Enrique Carazanas**
1201 N.W. 16th Street, Miami, FL 33125

Malcolm Randall VAMC
Site Director: **J. Chris Sackellares**
1601 S.W. Archer Road Gainesville, FL 32608

James A Haley Tampa
Site Director: **Alfred Frontera**
13000 Bruce B. Downs Blvd. Tampa, FL 33612

SOUTHWEST REGIONAL CENTERS

Epilepsy Center of Excellence
SOUTHWEST

VA Greater Los Angeles Health Care System
Regional and Site Director: **Claude Wasterlain**
11301 Wilshire Boulevard Los Angeles, CA 90073

San Francisco VA Medical Center
Site Director: **Karen Parko**
4150 Clement Street San Francisco, CA 94121

Michael E. DeBakey VA Medical Center
Site Director: **Richard A. Hrachovy**
2002 Holcombe Blvd. Houston TX, 77030

New Mexico VA Health Care System
Site Director: **Larry E. Davis**
1501 San Pedro Dr. SE Albuquerque, NM 87108

Audie L. Murphy VA Hospital
Site Director: **Jose Cavazos**
7400 Merton Minter
San Antonio, TX 78229

VA Epilepsy Centers Established under PL-110 in 2009

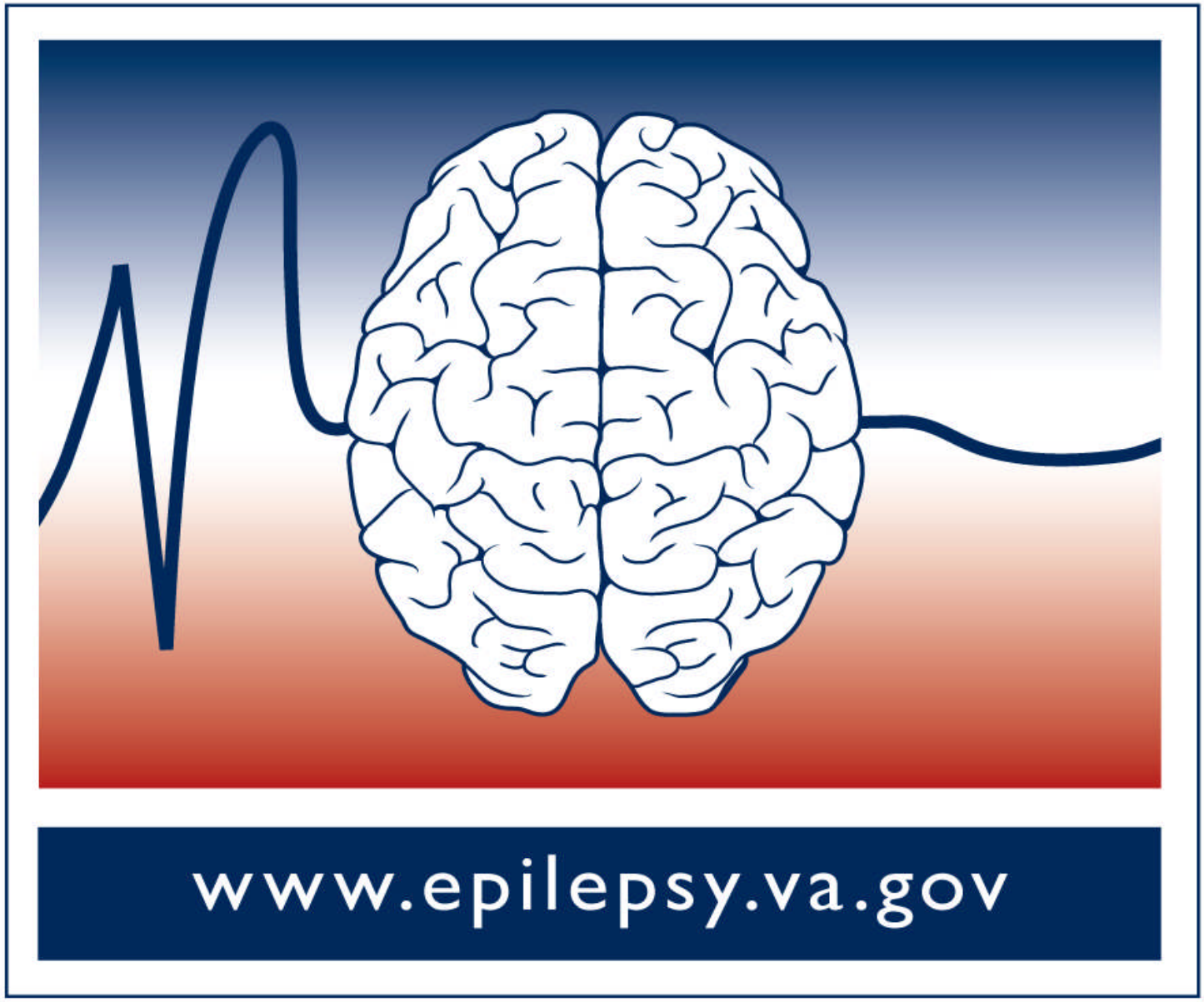
Directors	Regions	Facilities	Station	Contact Information
Southwest Centers				
***Claude Wasterlain**	**West LA VA**	**Greater Los Angeles HCS**	**691**	**(310) 268-3595**
Richard A Hrachovy	Houston	Michael E. DeBakey VAMC	580	(713) 791-1414 x 4007
Karen Parko	San Francisco	San Francisco VAMC	662	(415) 221-4810 x 4702
Larry E. Davis	Albuquerque	New Mexico VAHCS	501	(505) 265-1711 x 2752
Southeast Centers				
*** Aatif Husain**	**Durham**	**Durham VAMC**	**558**	**(919) 286-0411 x2230**
Enrique Carazanas	Miami	Miami VAHCS	546	(305) 324-4455 x 3151
J. Chris Sackellares	Gainesville	Malcolm R	150	(352) 376-1611
Alfred Frontera	Tampa	J. A. Haley	673	(813) 972-2000 x7633
Northwest Centers				
*** Paul Rutecki**	**Madison**	**William S. Middleton Memorial**	**648**	**(608) 256-1901**
Stephen Holloway	Minneapolis	Minneapolis VAMC	607	(612) 725-2000 x 4236
Martin Salinsky	Portland	Portland VAMC	618	(503) 494-5682
William Spain	Seattle	Puget Sound	663	(206) 764-2021
Northeast Centers				
***Alan Krumholz**	**Baltimore**	**VA Maryland HCS**	**512**	**(410) 605-7000**
Huned Patwa	West Haven	VA Connecticut HCS	689	(203) 932-5711 x4724
Alan Towne	Richmond	Hunter Holmes McGuire VAMC	652	(804) 675-5127

ECOE Goals

- Delivery the highest quality care to veterans with epilepsy
- Establish network for regional epilepsy care
- Promote outreach and educational efforts
- Provide an efficient and cost-effective mechanism of care delivery

Resources

- www.epilepsy.va.gov
- www.epilepsyfoundation.org
- www.epilepsy.com
- www.cureepilepsy.org
- www.ninds.nih.gov/disorders/epilepsy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