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Founding Member, Mass General Brigham

EPILEPSY

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- Clinical Focus: Epilepsy
- Research Focus: Treatments for drug-resistant epilepsy, low intensity focused ultrasound

Disclosures

Advising:
International Transcranial Ultrasound Safety & Standards (ITRUSST), Member
ITRUSST Clinical Research Group, Chair

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Brigham Research Institute
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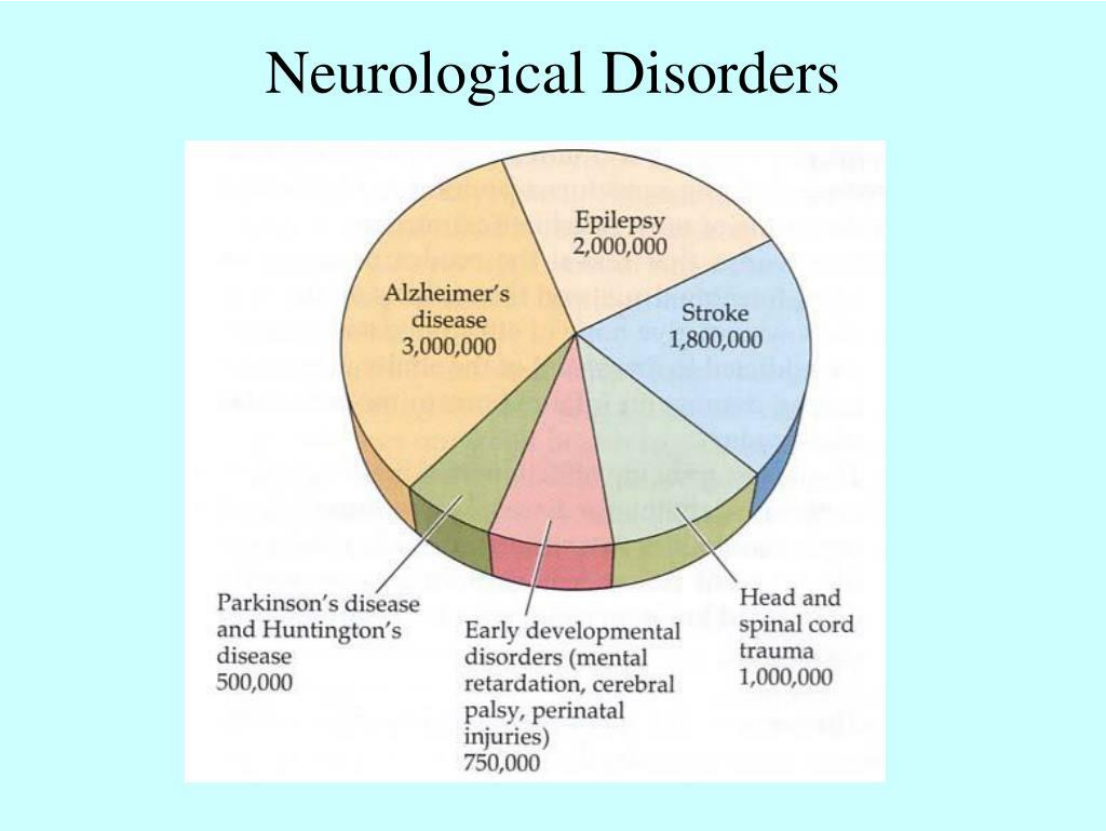
NaviFUS

Industry: uniQure, Scientific Advisory Board/Speaker

Objectives

- Review definitions and epidemiology of epilepsy
- Highlight classification of seizure types and epilepsy syndromes
- Identify key components to successful diagnosis
- Review epilepsy treatment options
- Discuss special situations

Epilepsy Demographics



- Epilepsy affects people of all ages, races, and ethnic backgrounds
- Affects 65 million people worldwide
  - US: 300,000 diagnosed each year
  - >570,000 adults over 65 in the US
- Epilepsy can develop at any time of life, but it is more common in young children and in people older than 60 years

Diagnosis	US Prevalence	US New Cases/yr
Epilepsy	3.5 million	300,000
Parkinson's disease	500,000	50,000
Multiple sclerosis	400,000	10,000

Definitions

Seizure: the clinical manifestation of an abnormal and excessive excitation of a population of cortical neurons

Acute symptomatic seizure: seizure resulting directly from a systemic or neurologic insult

Epilepsy: a tendency toward recurrent seizures unprovoked by systemic or neurologic insults

Epilepsy

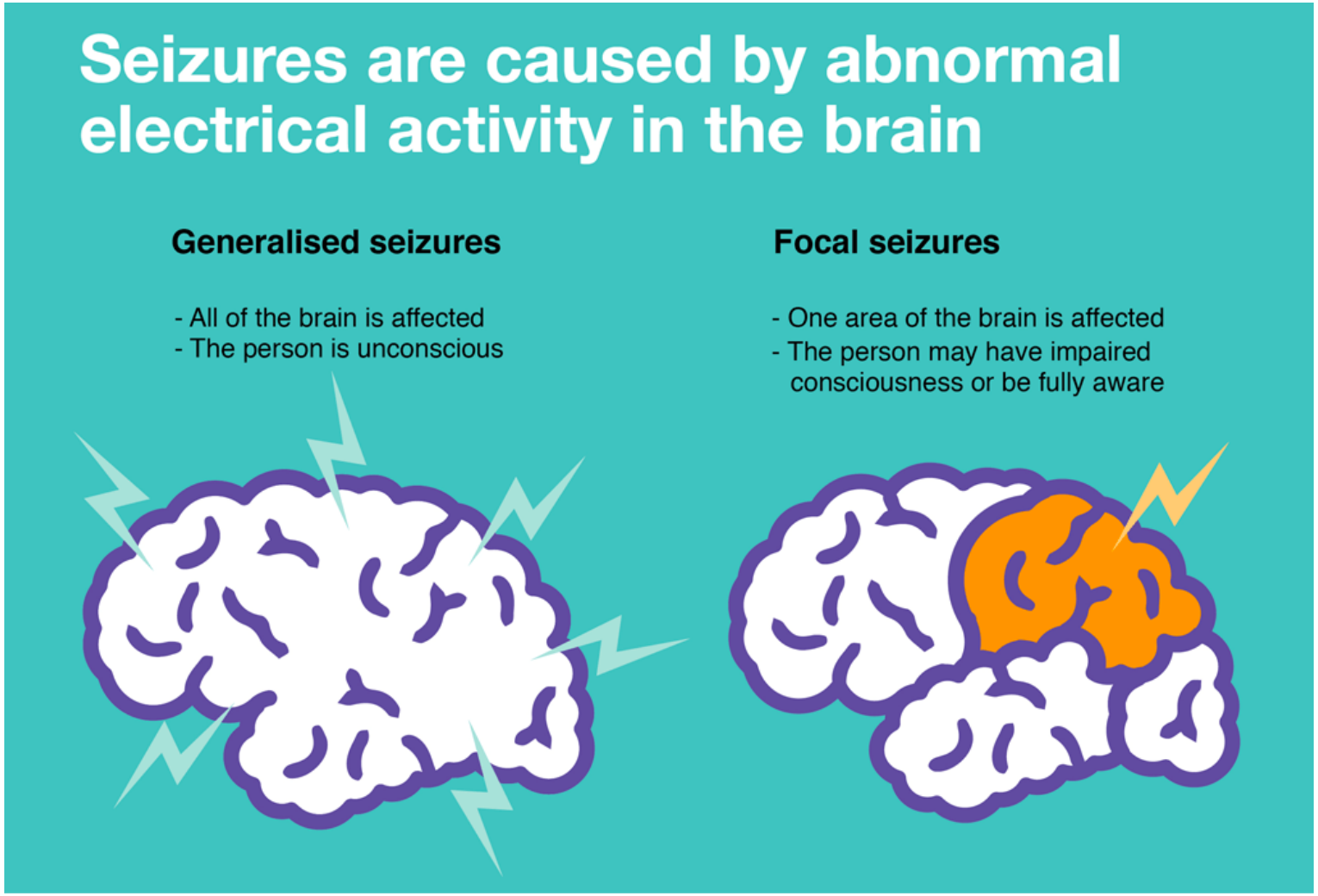
Epilepsy is not a single disease

- Epilepsy is a group of related disorders characterized by recurrent spontaneous seizures
- ~~Two or more~~ unprovoked seizures

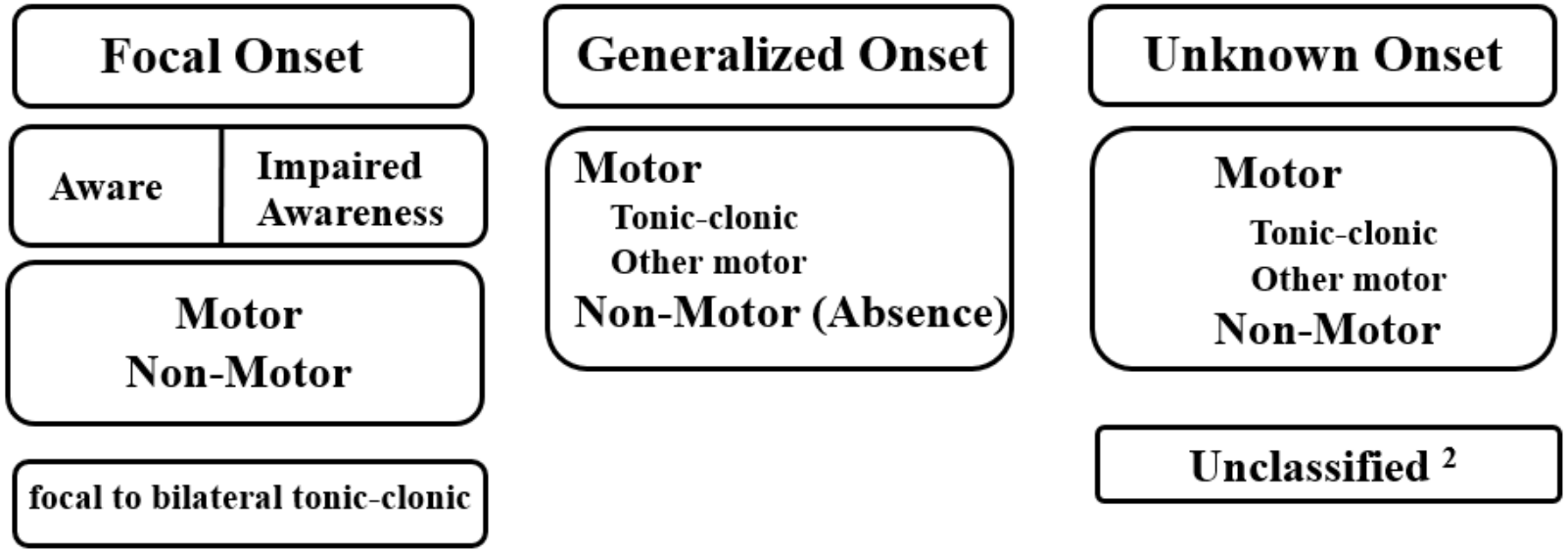
ILAE diagnosis : Disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of **at least one** epileptic seizure (Fisher 2005).

Classification System

- Designed to provide greater diagnostic specificity for treatment and research
- Change in terminology used to describe seizure type and to describe etiology



ILAE 2017 Classification of Seizure Types Basic Version [1]



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

[2] Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

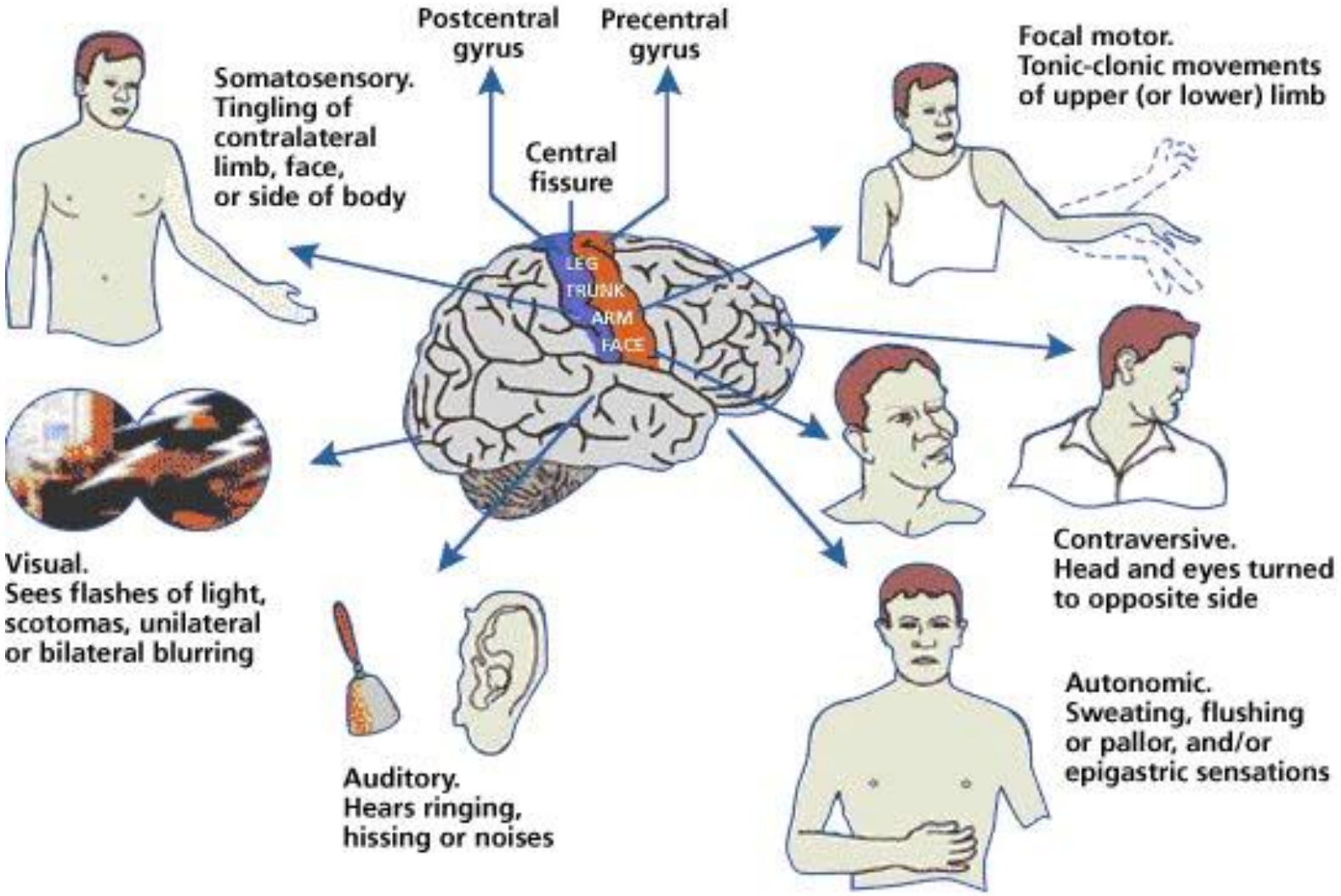
Focal seizures

- "Simple partial" FOCAL AWARE -> Without impairment of consciousness or awareness; Motor component (e.g., focal clonic)
  – Subjective sensory or psychic features ->aura

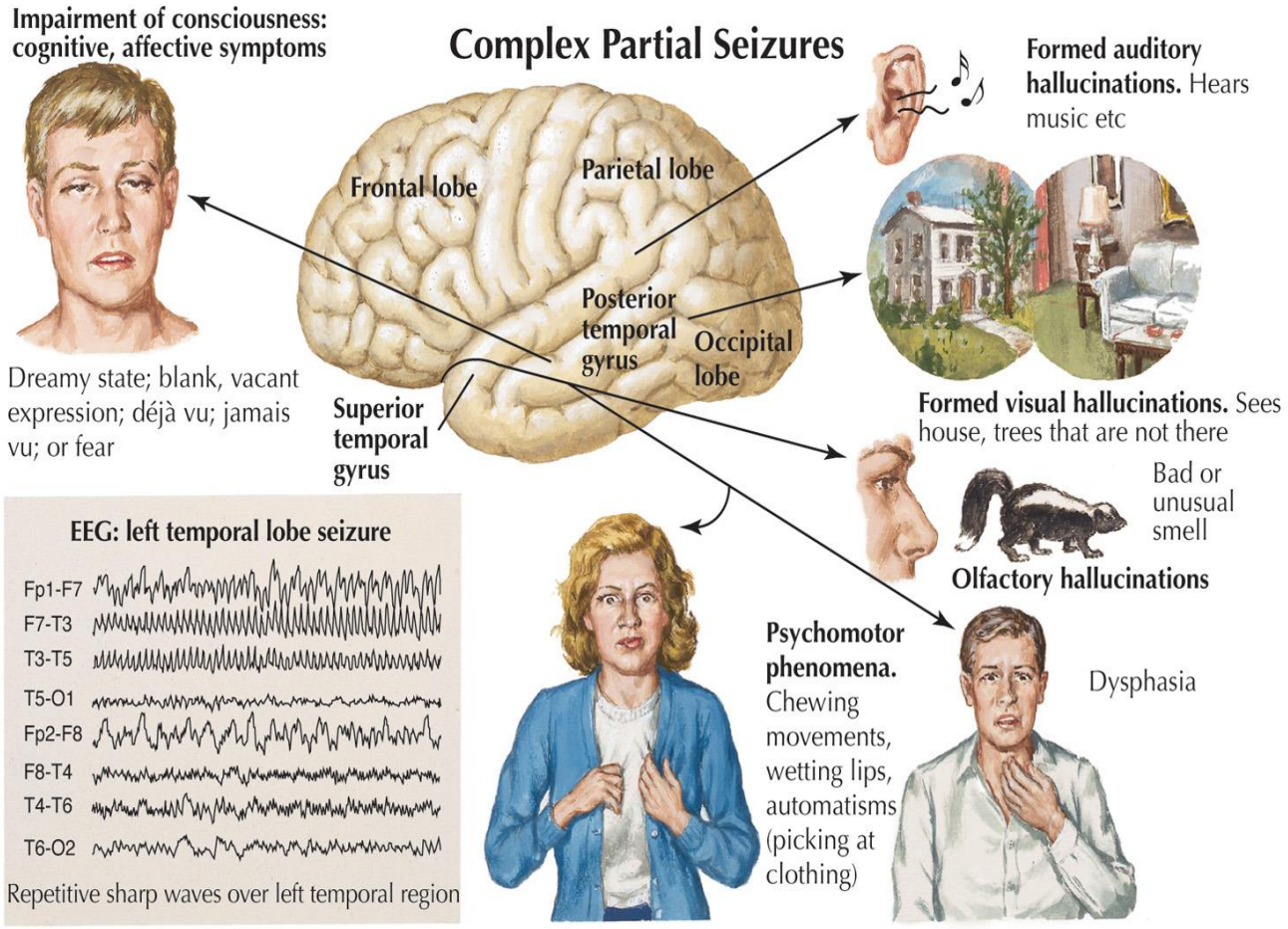
- "Complex partial" FOCAL IMPAIRED AWARENESS
- -> Where alteration of awareness is major feature (dyscogntive);

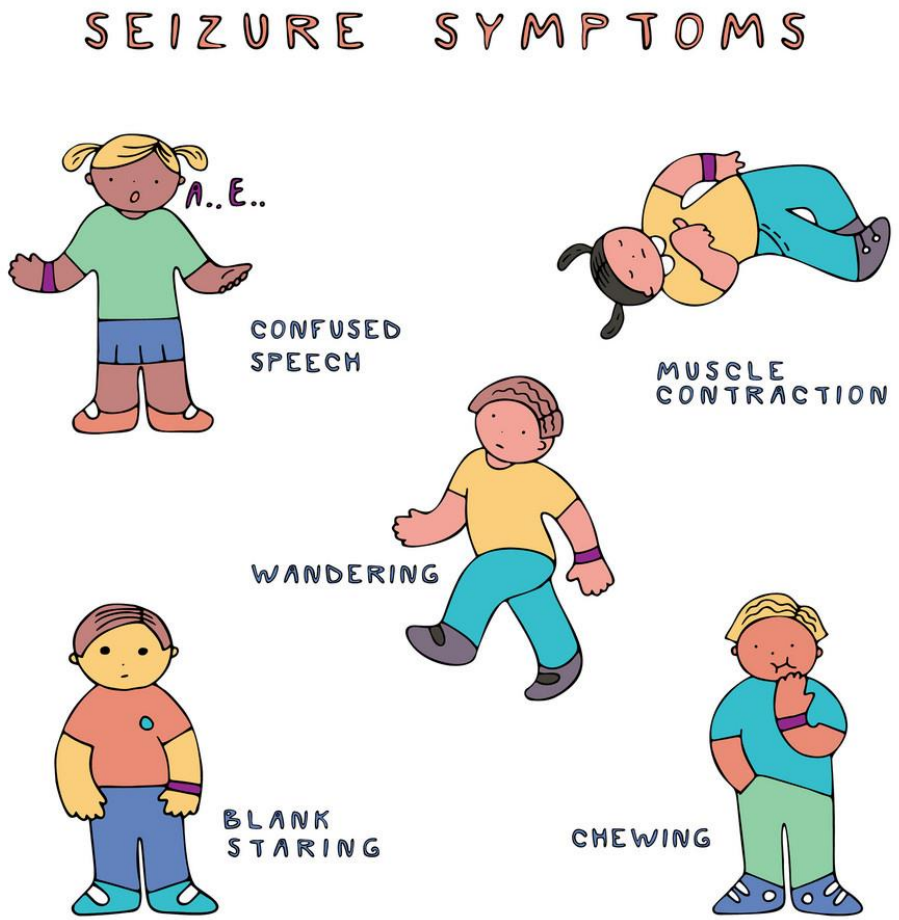
- "Secondarily generalized" FOCAL to BILATERAL TONIC CLONIC-> Evolving to a convulsive seizure

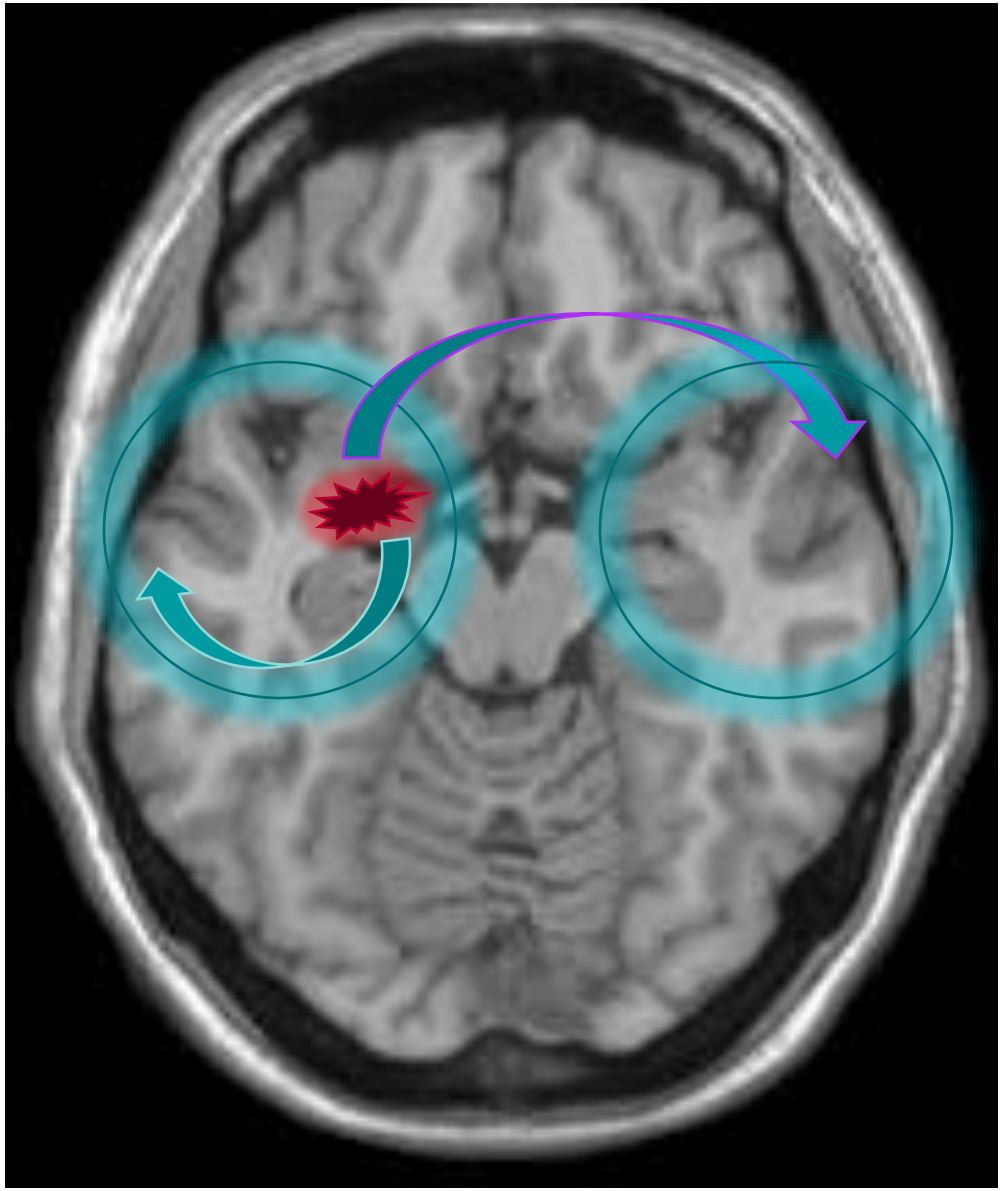
Focal Aware/Aura



Focal Impaired Awareness

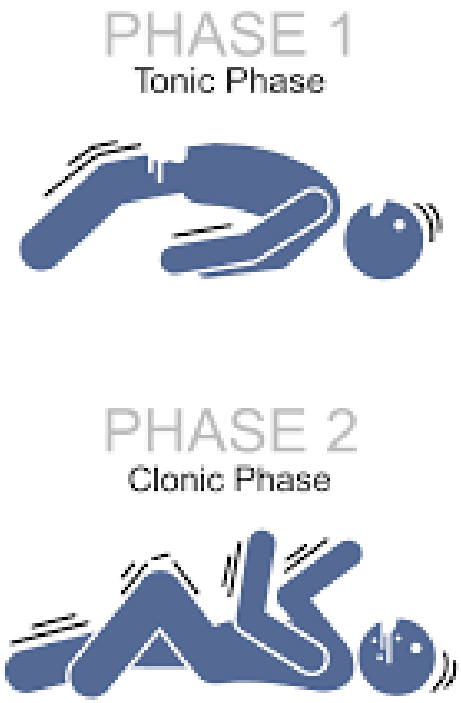


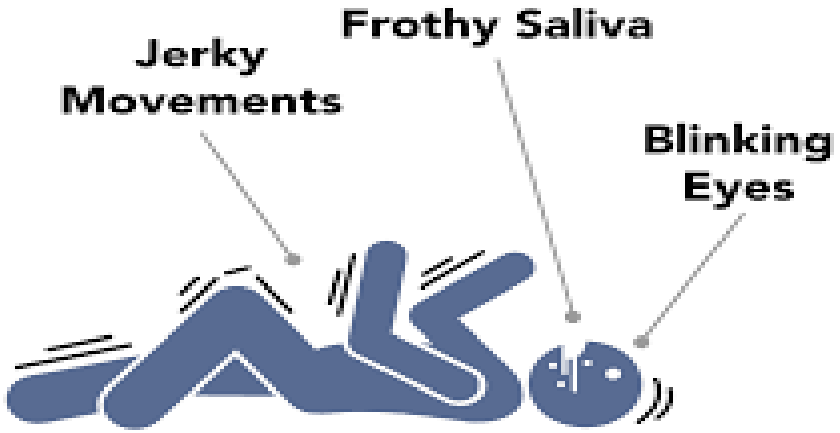




Bilateral Tonic-Clonic (“convlusive”) Seizures

- Occurs in all age groups
- Involves complete loss of consciousness
- Previously referred to as a “grand mal” seizure
- Can be due to generalized epilepsy or secondary generalization of a focal seizure

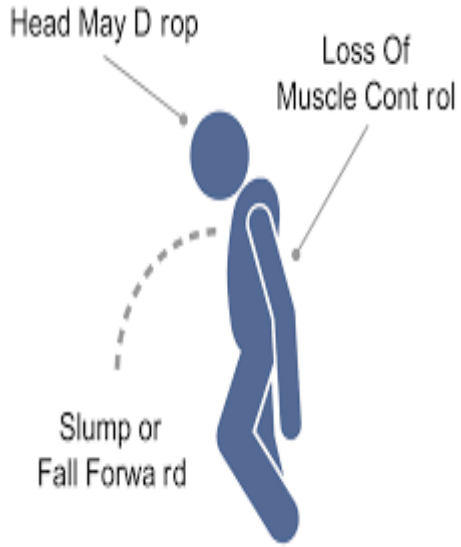




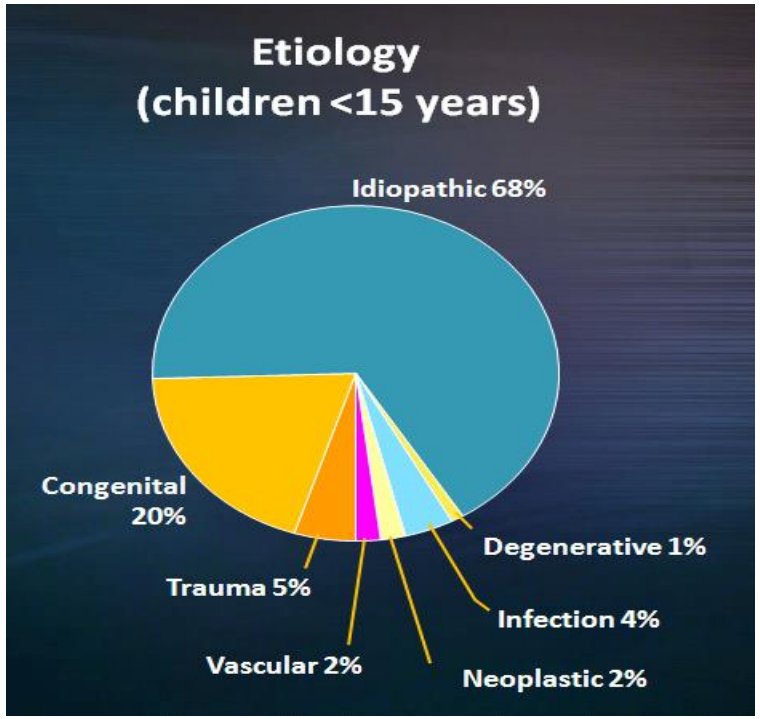
Generalized Seizures

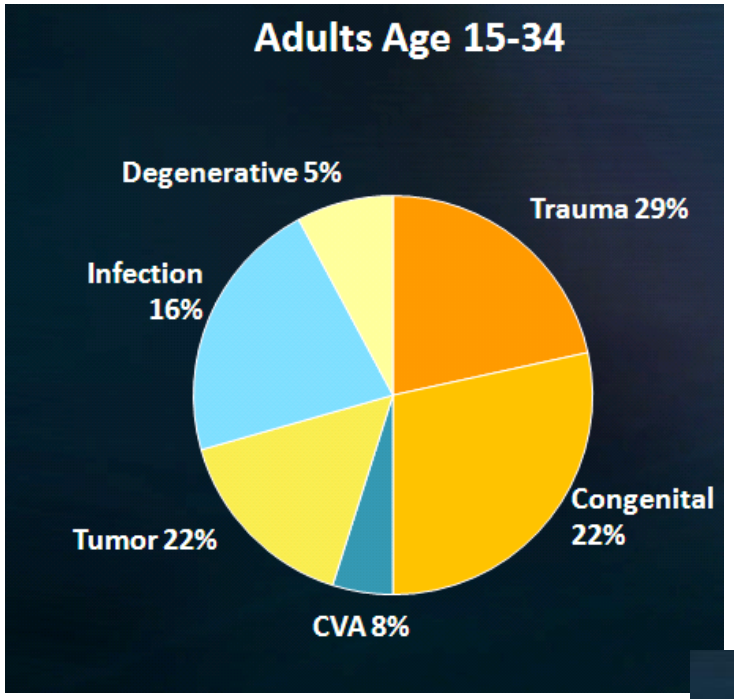
- Tonic-clonic (in any combination)
- Absence
  - Typical
  - Atypical
  - Absence with special features
- Myoclonic absence
- Eyelid myoclonia

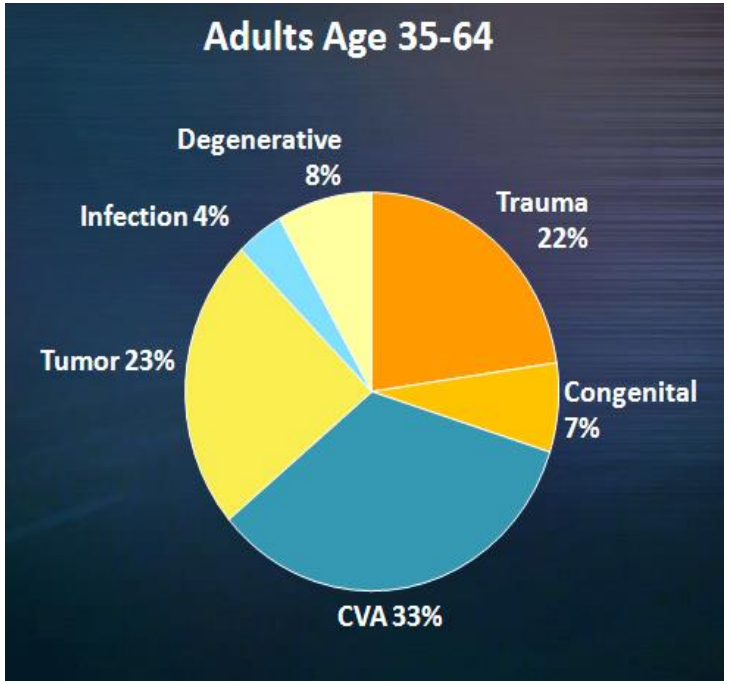
- Myoclonic
  - Myoclonic atonic
  - Myoclonic tonic
- Clonic
- Tonic
- Atonic

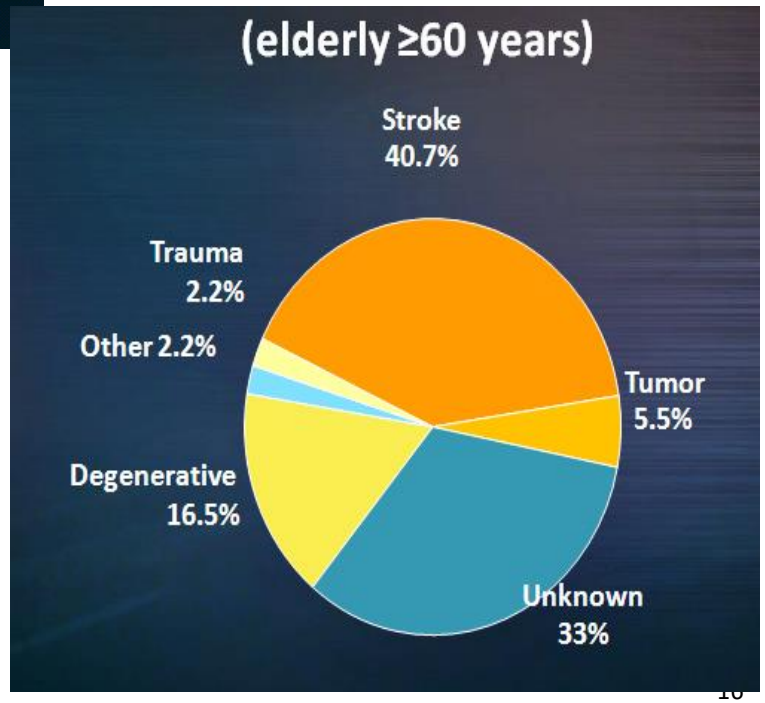


Seizure types thought to occur within and result from rapid engagement of bilaterally distributed systems









Adapted from Hauser WA. *Epilepsia*. 1992;33(suppl 4):S6-S14.

Diagnosis of Epilepsy

Failure to diagnose

- Risk of injury or death
- Reduced quality of life due to recurrent events

Misdiagnosed

- Unnecessary use of potentially toxic medications
- Failure to treat correct dx may lead to fatality
- Stigma
- Financial burden

Differential Diagnosis of Paroxysmal Behavioral Events

- Seizure
- Syncope (esp. convulsive)
- Migraine
- Cerebral ischemia (TIA)
- Movement disorder
- Sleep disorder
- Toxic-metabolic disturbance
- Psychiatric disturbance
- Spontaneous or precipitated fluctuations in existing deficits

CASE 1

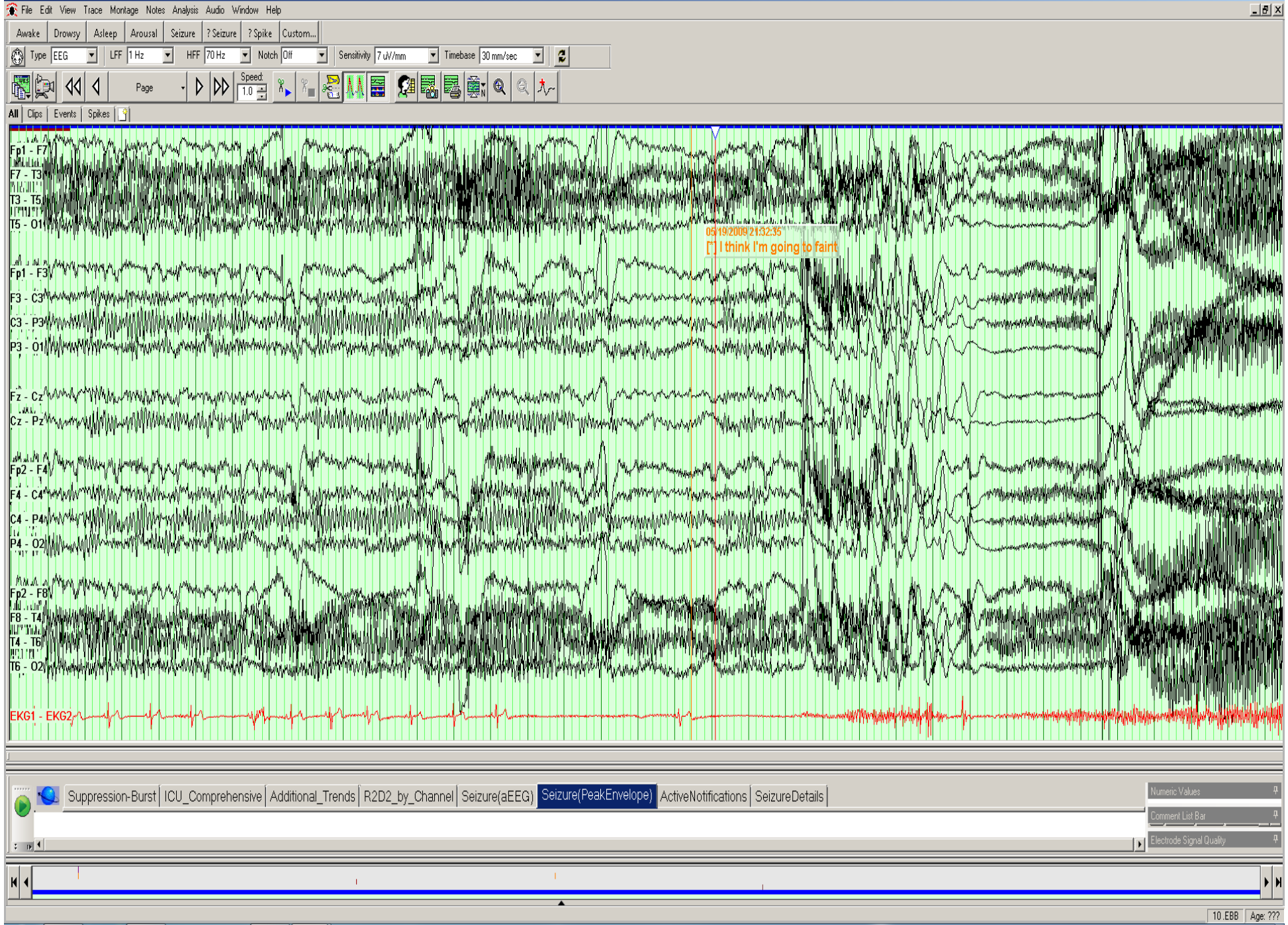
- 19yo woman with history of spells since age 4 involving loss of consciousness, often precipitated by an emotional trigger.
- One time she “passed out" once while standing on a toilet watching father shave, another time after suddenly feeling hot in church.
- As a young teenager it occurred after watching surgery on a dog, and again after cutting her finger.
- This would occur up to 10x/year during some years, other years only 2-3x/yr.
- ? Abnormal EEG due to 3 sec burst of “generalized spike activity”
- She has 2 relatives with epilepsy

CASE 1

- In June '07, the spells recurred, and she has had 3 events over a few weeks. With these she reports a similar onset of lightheadedness, abdominal discomfort, general feeling of being unwell, then she collapses. She had one event last year in Italy, which her mother reports was worse than the previous events. She had been in a hot shower, suddenly felt nauseated, lightheaded, blurry vision. She went to lie down in bed, then lost consciousness. Her mother describes that her arms were extended out and her whole body stiffened. Her eyes were wide open, seemed to be staring straight ahead, was unresponsive. The event lasted about one minute, they estimate, which is longer than usual for her. After the event, she doesn't know what happened, but does recall having had the prodrome prior to losing consciousness. She has never lost consciousness without a warning.

- She had an EEG and a brain MRI at an outside hospital which were both normal. Local neurologist started her on Lamotrigine.

- She had no further events until Feb ’08, when one of the loss of consciousness events occurred after a night of very little sleep (woke up at 3am to get on a plane).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P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
EKG1 - EKG2
05/19/2009 21:32:35
[*] I think I'm going to faint
Suppression-Burst ICU_Comprehensive Additional_Trends R2D2_by_Channel Seizure(aEEG) Seizure(PeakEnvelope) ActiveNotifications SeizureDetails
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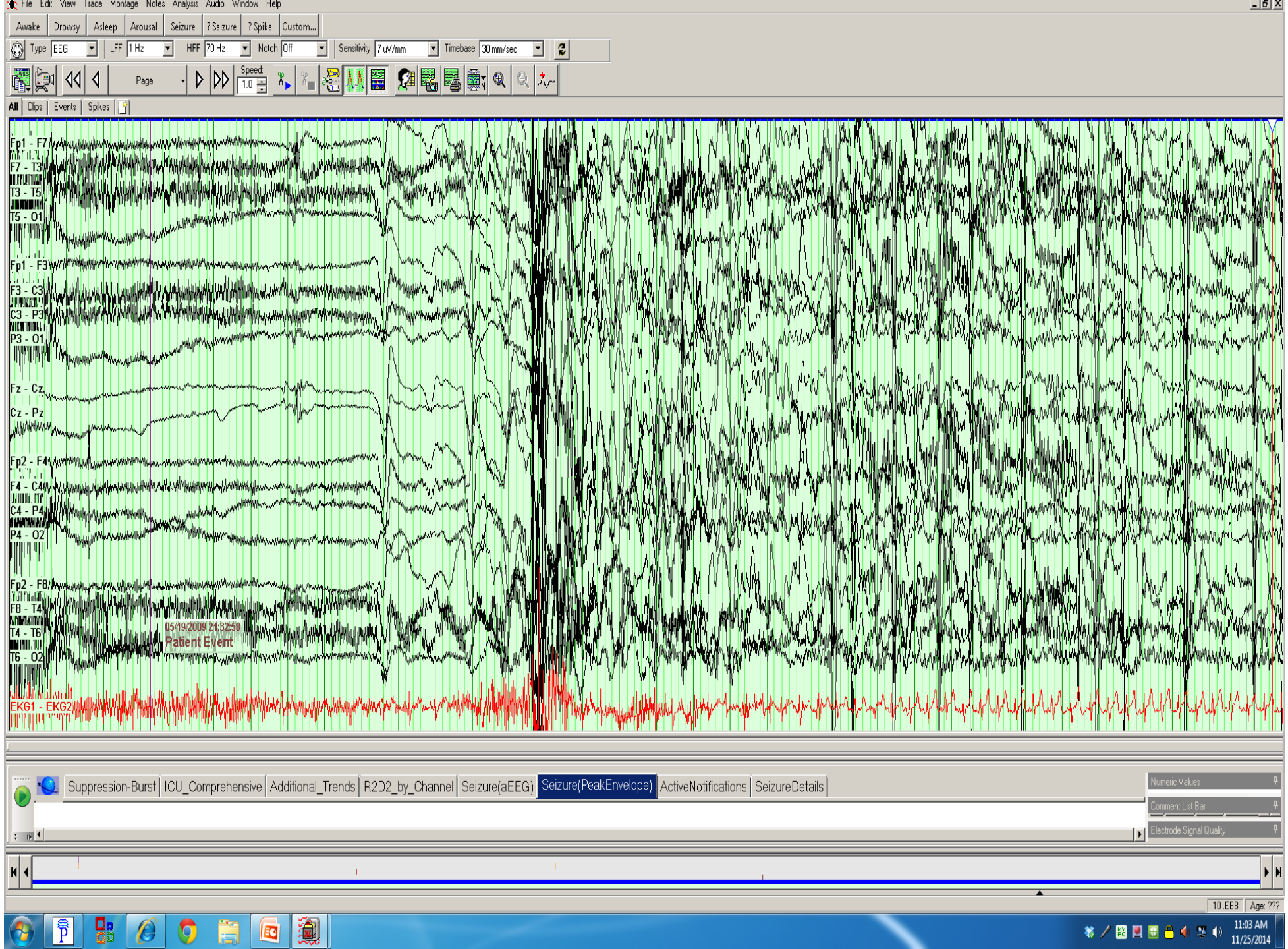
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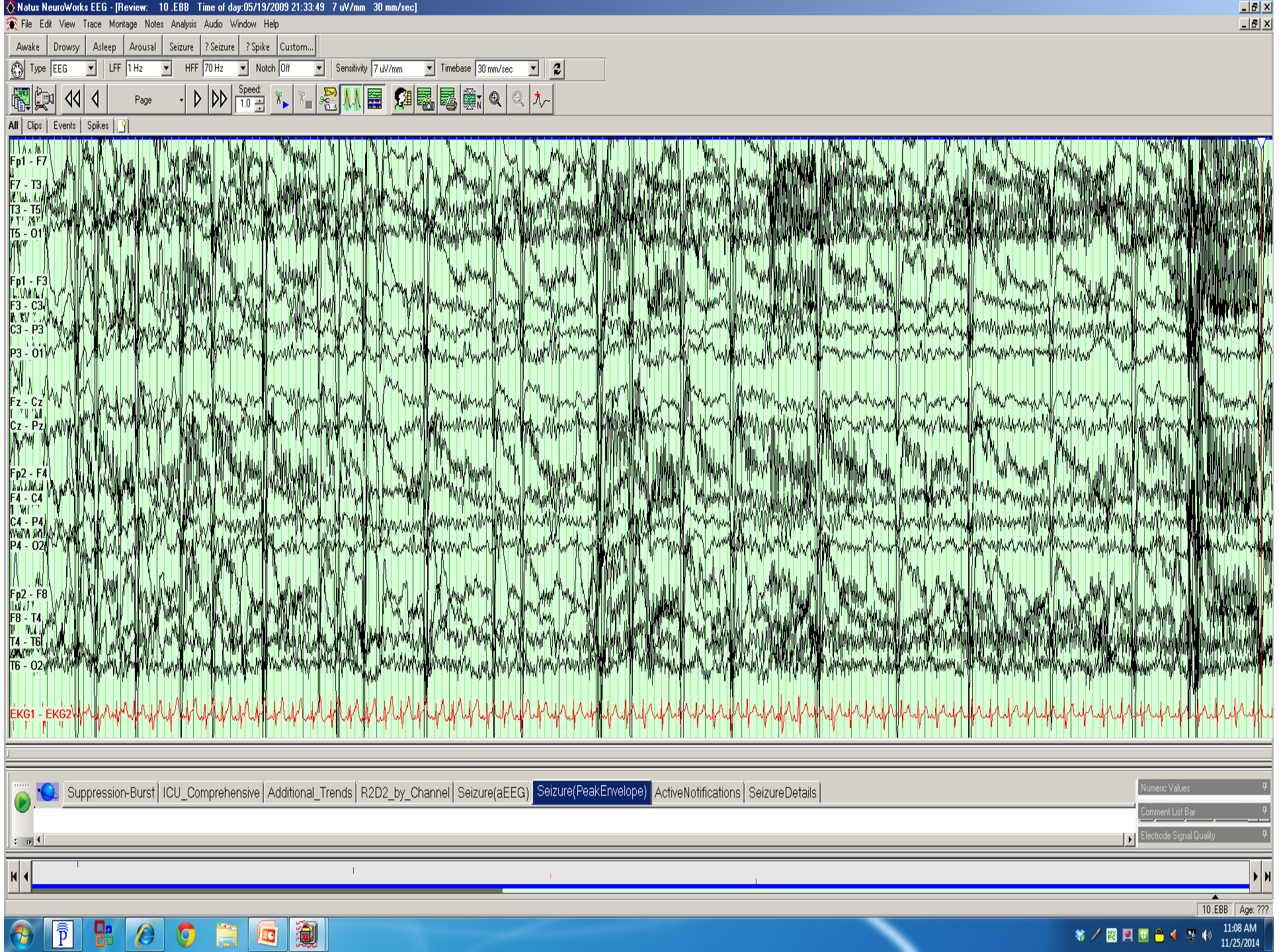
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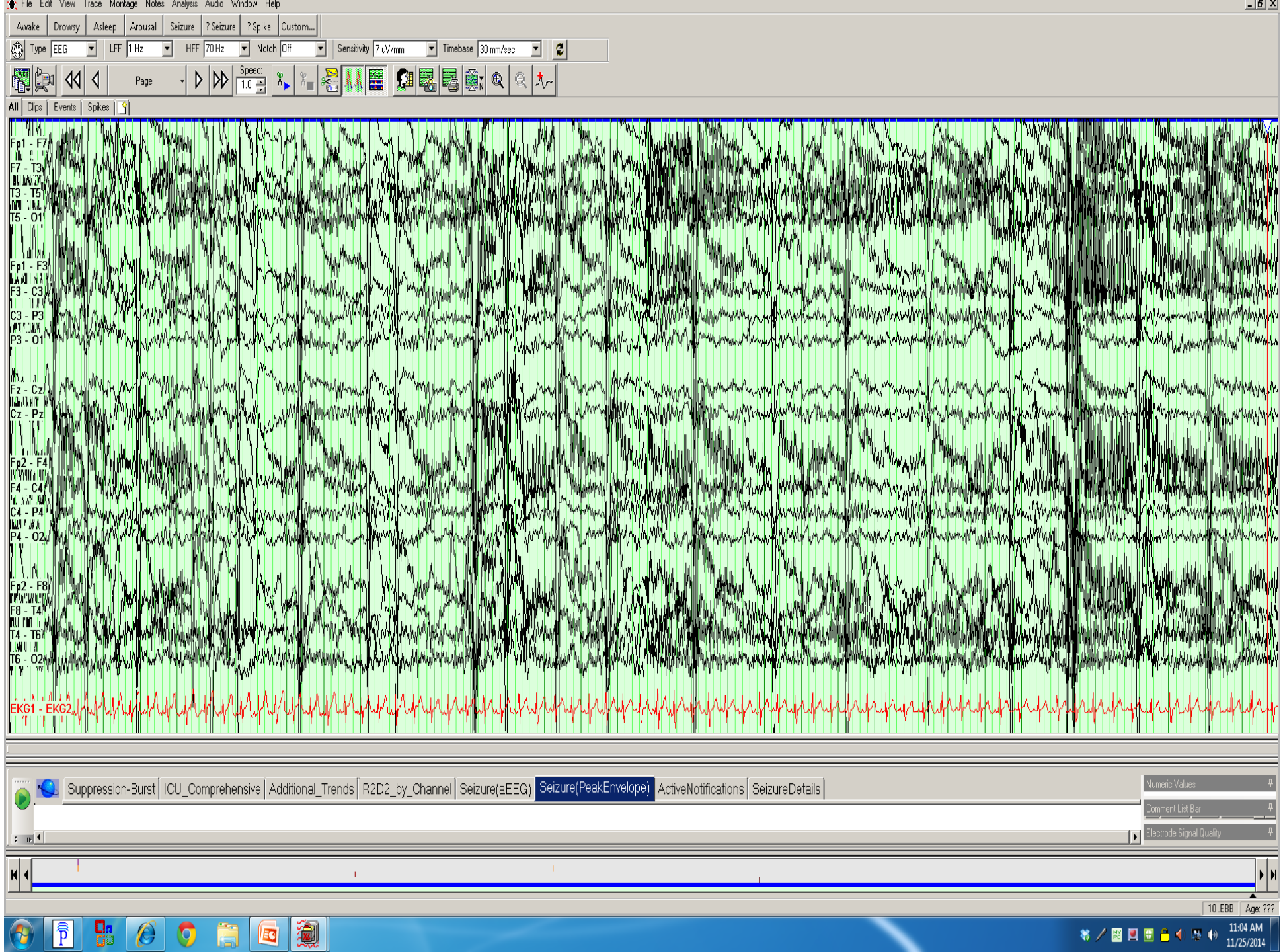
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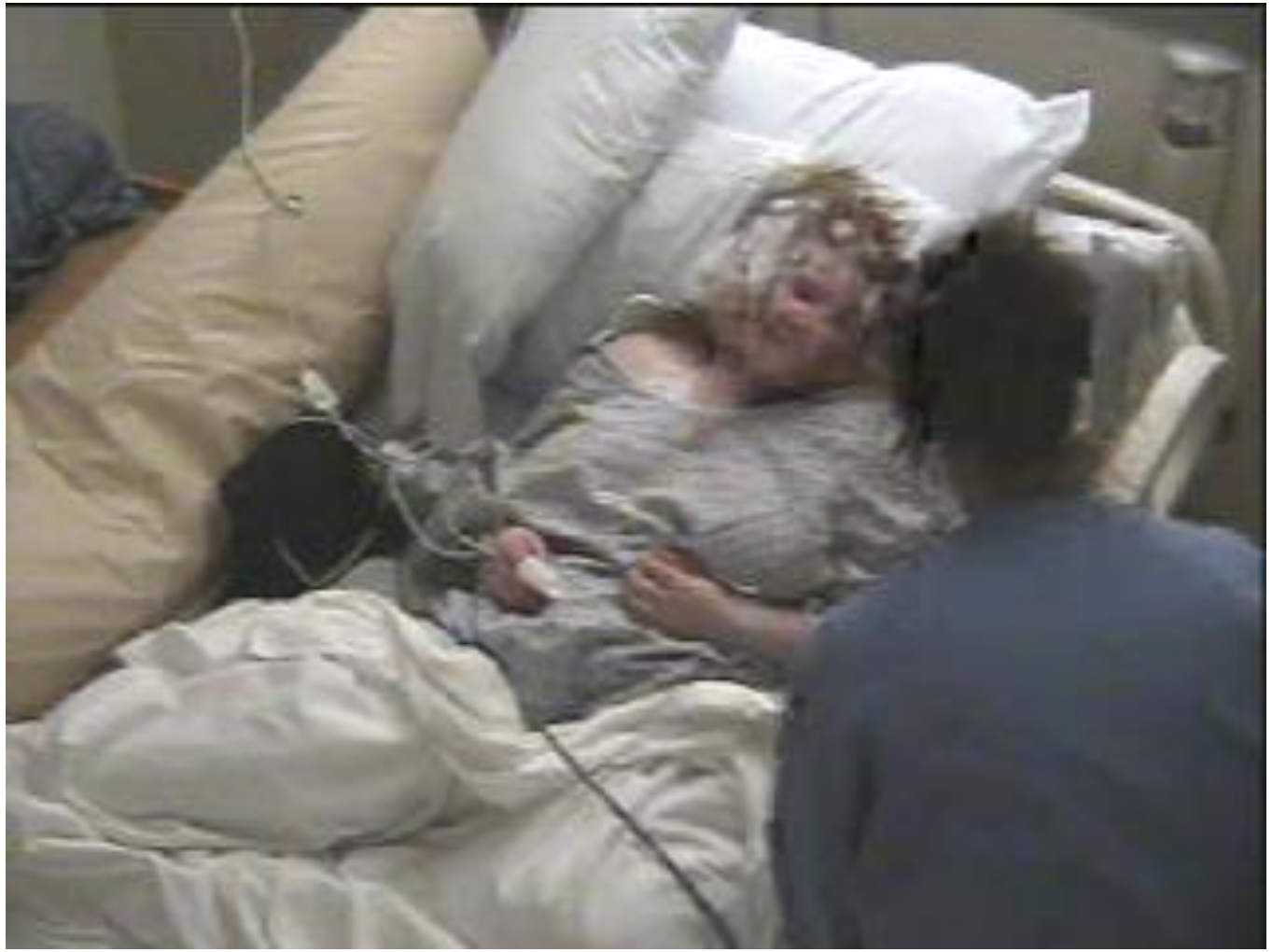
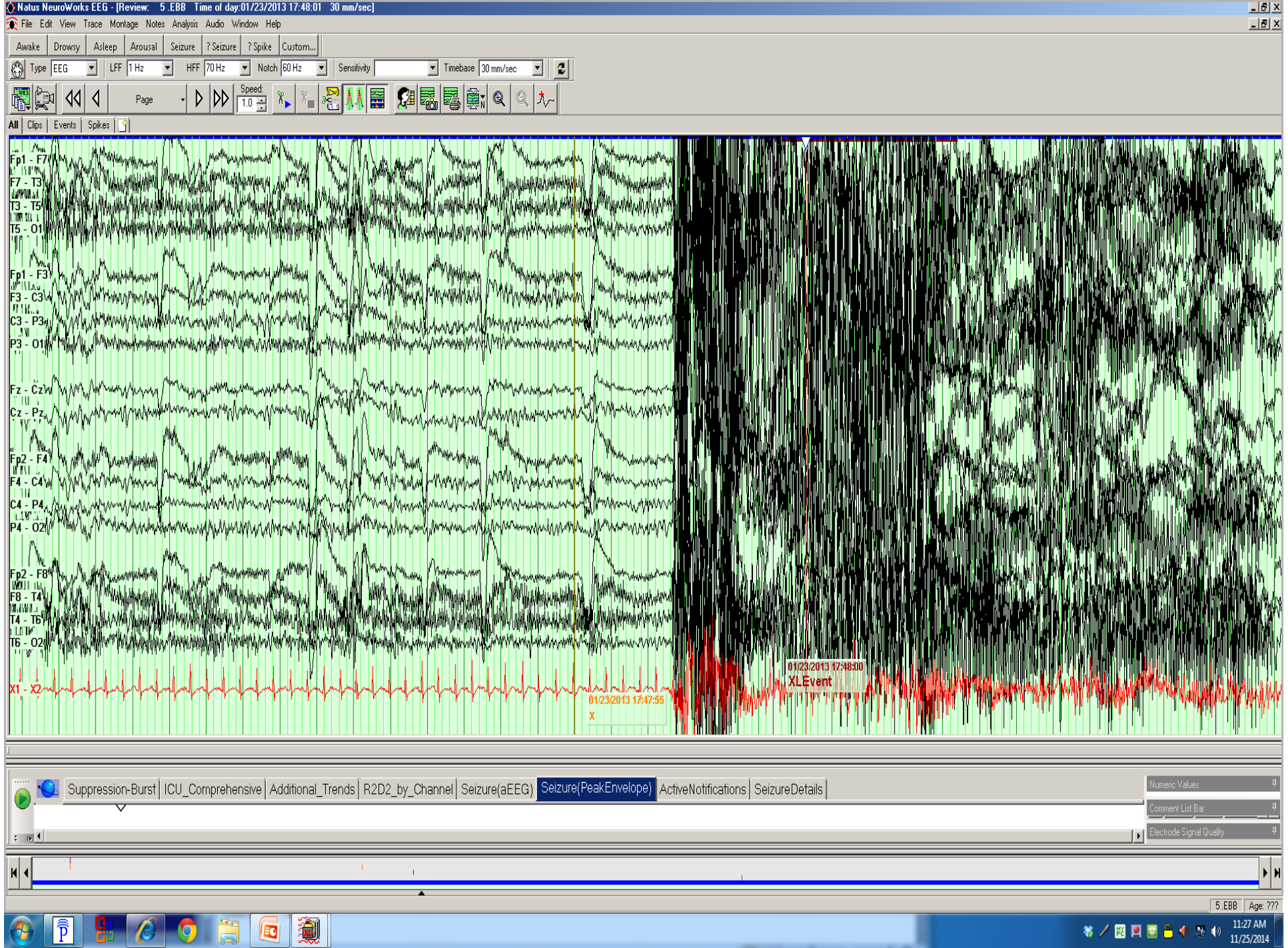
Syncope vs. Seizure: Take Away

Clinical Feature	Syncope	Seizure
Loss of consciousness	Typical	Common
Episode duration	Seconds	Minutes
Involuntary movements	Common	Typical
Triggers	Frequent	Rare
Preceding Symptoms	**Prodrome**: nausea, blurred/tunnel vision, feeling hot, tinnitus, palpitations	sensory, motor, psychic auras
Post-Ictal	+/-Amnesia for event, quick recovery, headache	Amnesia for event plus **confusion**, somnolence, headache
EEG	Slow waves, flattening	Focal or generalized spike-wave

CASE 2

- 30yo woman with history of spells for the past couple of years.
- Spells are preceded by what she terms a bad smell in her nose which she can not elaborate on further, a visual aura, followed by a headache and then generalized shaking.
- No urinary incontinence, does report tongue bites. Triggers for these spells include anxiety, coffee, drinking a lot of red bull, skipping meals.
- Intubated several times after presenting to ER with ongoing convulsions.

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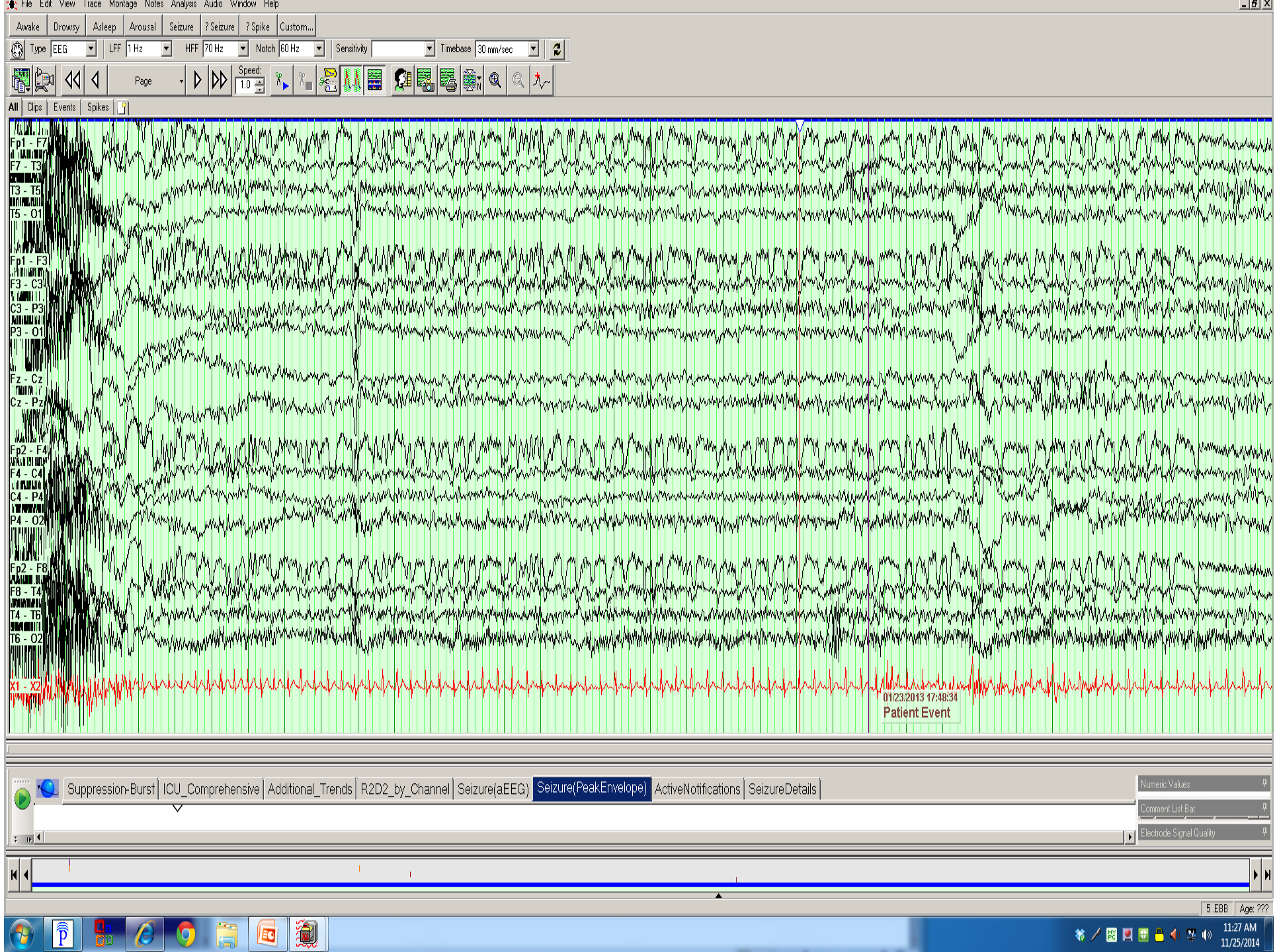
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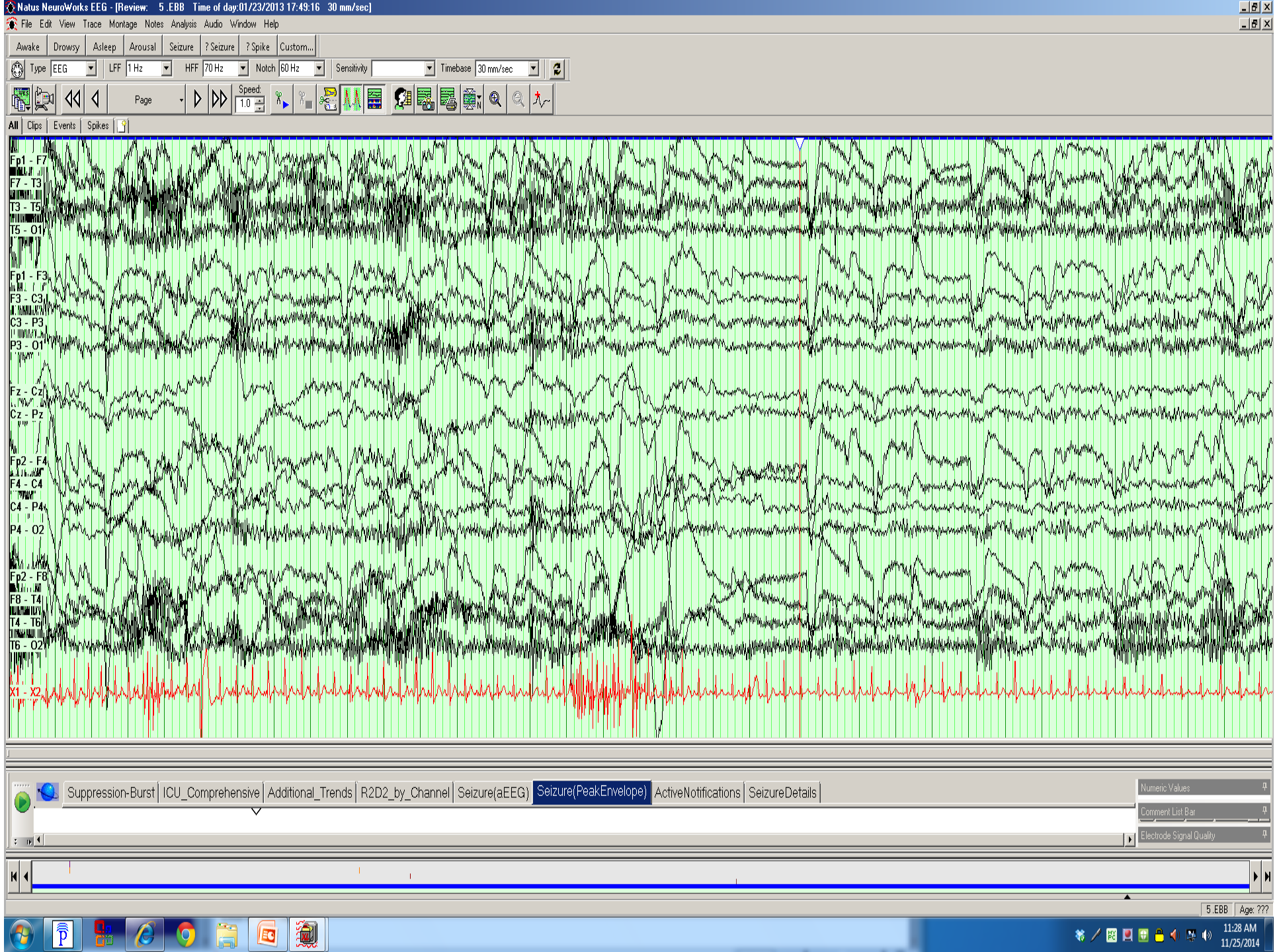
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Functional Seizures (FND)

- Definition: paroxysmal episodes of movement, sensation or experience resembling epileptic seizures, but not associated with epileptiform or ictal changes on electroencephalography (EEG), of psychogenic origin. (conversion)
- Epidemiology:
  - Incidence: 1.4-4/100,000 (incidence of epilepsy: 45/100,000)
  - Prevalence: 33/100,000
  - 5-25% of the 2.5 million people with epilepsy have NES (mixed disorder)
  - ~35-30% of EMU admissions have NES (misdiagnosis of epilepsy)
- Neurologist: To prevent spells from being treated as epilepsy if they are not (do no harm)
- Psychiatrist: To recognize the psychiatric pathology underlying the disorder, and to provide appropriate treatment.
- Diagnosis: VideoEEG is gold standard
- Treatment: Multidisciplinary Team approach
  - Neurologist and Psychiatrist present the information to the patient together in an objective, nonjudgmental, unequivocal manner. Good news/bad news.
  - Transition care to psychiatrist

Functional Seizures: Clinical Features

Observed motor movements:

- Motor activity out of phase
- Thrashing, flailing limbs, wild movements
- Pelvic thrusting
- Back arching
- Side-to-side rolling
- Eyes closed
- Little or no facial involvement
- Clonic activity abruptly ends

Observed behaviors:

- Crying during or after event
- Apparent unresponsiveness (normal waking background on EEG)
- Apparent amnesia to the event
- Preserved conscious with bilateral jerking
- No neurological exam changes
- Urinary incontinence
- Avoidance of injuries (Burn injury w/ epileptic sz)

Other characteristics:

- Gradual, prolonged onset and end
- Longer and wider range of duration
- Waxing/waning movements, start-stop phenomenon
- Rapid recovery
- Situational triggers
- Multiple seizure types, lack of stereotypy

CASE 3

- 30 yo man, presents with increasing spells
- Onset – age 12 yo; felt ill after eating a piece of chicken, sat up, threw his head back, and siblings reported “acted like he was possessed”
- Anxiety attacks in college; when he felt tired and stressed from school, would feel mind racing, heart racing, and could thrash about and scream
- Current spells are 1-2 per day
    - Described as thrashing about, possessed-like behavior, often screams, may go looks for meds, may follow some commands
    - As he comes to, feels thoughts are racing, remembers parts of dreams, feels anxious and weird “like in the movie ‘*The Matrix’*, as if aliens are communicating through me”
    - Can have visual hallucinations. No incontinence or postictal confusion

CASE 3

- Medications: Tried Phenytoin, Phenobarbital and others in the past.
- Currently on CBZ XR 800 mg BID
- Social History: dropped out of college right before obtaining degree; married, children ages 6yo and 2mo; works with library databases, denies tobacco, alcohol, drugs
- Family History: Positive for bipolar disorder in mother, sister, maternal uncle, and maternal GM
- Exam: Normal

CASE 3

Brain MRI: Normal

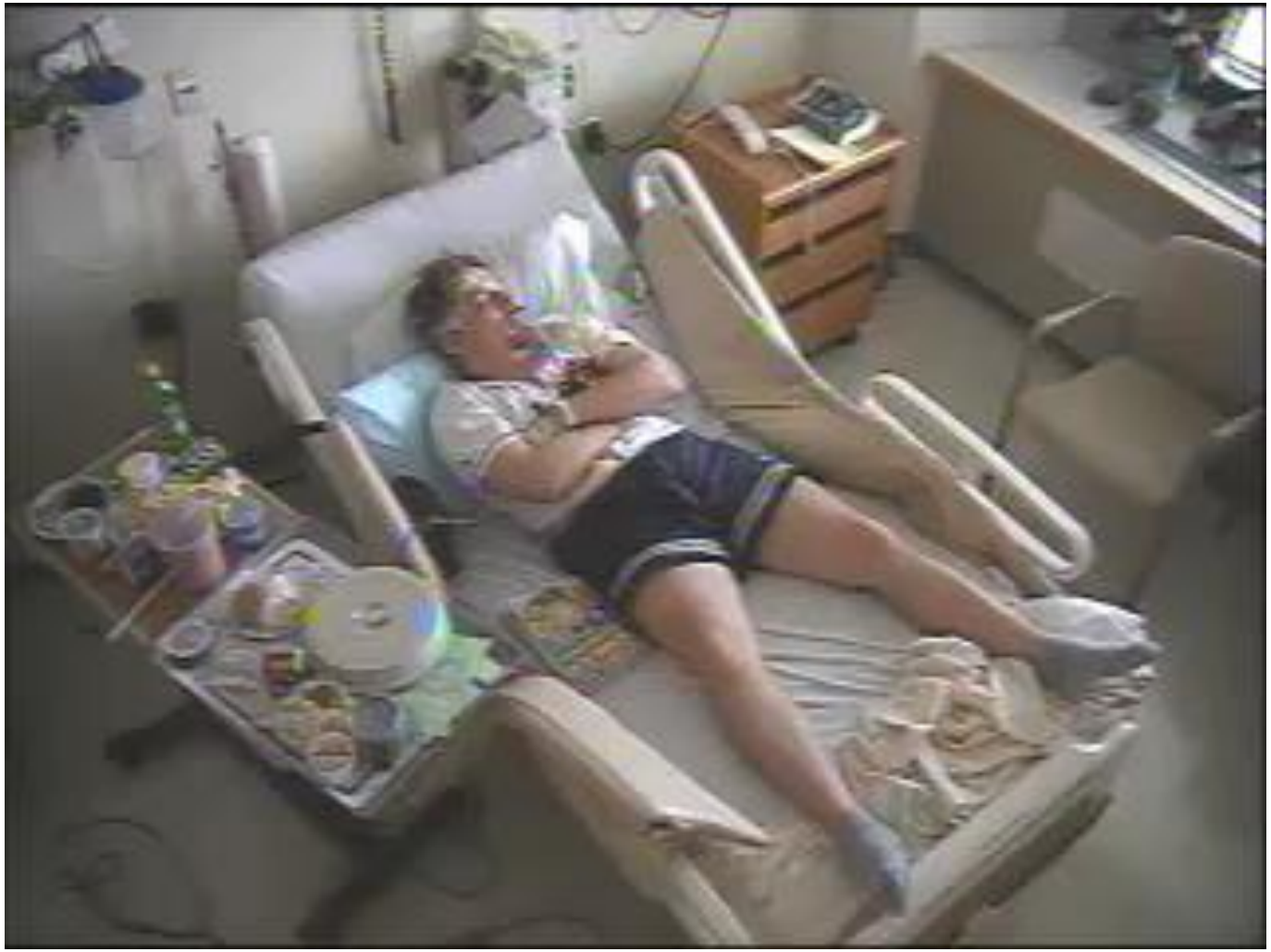
Psychiatry consult

Neuropsychological evaluation

Social Work consult

Video-EEG LTM

- 6 spells captured



Pseudo-pseudoseizure (Frontal Lobe Epilepsy): Take Away

- When it might be a seizure, but sounds bizarre, think frontal lobe epilepsy
- Complex behaviors with motor agitation, strong emotional feelings, repetitive motor activity involving pelvic thrusting, pedaling, thrashing
- Often accompanied by vocalizations or laughter/crying
- Often bizarre and misdiagnosed as psychogenic
- Tend to be frequent and brief, with less post-ictal confusion
- Ictal EEG often not reliable (big surface area, hidden in deep cortex/sulci)
  - Unilateral but non-focal rhythmic activity over a broad field
  - Bilateral rhythmic activity
  - No clear ictal activity
- Clues: stereotyped semiology, occurrence during sleep, brief in duration, abnormal MRI

HISTORY and Examination

- Details of event and witness' account
  - Aura
  - Duration
  - Post-ictal
- Prior events
- Substance use
- Sleep history
- Other medical problems
- Other provoking factors
- Risk factors for epilepsy: family history, TBI, other brain injuries, birth trauma, febrile seizures
- Full neurologic and general physical examination: focal neurologic signs, cognitive or developmental disorder, unrecognized medical disease

Seizure Triggers in Epilepsy

- Missing a dose of medication
- Poor sleep
- Illness, infection
- Increased stress level
- Excessive use of alcohol
- Drugs such as cocaine and other stimulants
- A small number of people may be sensitive to flickering lights
- Many people with epilepsy cannot pinpoint specific triggers for their seizures

Key Questions Guiding the History:
Take Aways

- Was it a seizure? Open ended questions and guidance with the patient and an eye-witness. What was your first clue something was happening? Did you have any warning at all?
  - BEFORE event
  - DURING event
  - AFTER event
- Anything weird thinking back? Anything like this every happen before?
- Was it a provoked seizure? A common cause of seizures is alcohol or drugs and these seizures are treated very differently.
- Was it the first seizure? (myoclonus, CPS, photosensitive)
- Localization/Type of seizure
- Cause of seizure
- Epilepsy syndrome

What I Listen For: Take aways

- Trouble describing aura
- Description of aura that I can translate into an epilepsy aura
  - Hallucinations, illusions
  - Deja-vu
  - Automatisms
- Unresponsiveness and lost time
- Epileptic cry
- Cyanosis, tonic-clonic, foaming at the mouth, bleeding from the mouth
- Post-ictal breathing and agitation

Evaluation of a first unprovoked seizure: Practice guidelines- Take Away

- **EEG** - after a first seizure an EEG should be considered as part of the routine neurodiagnostic evaluation because it has substantial yield and has value in determining risk of seizure recurrence (Level B).

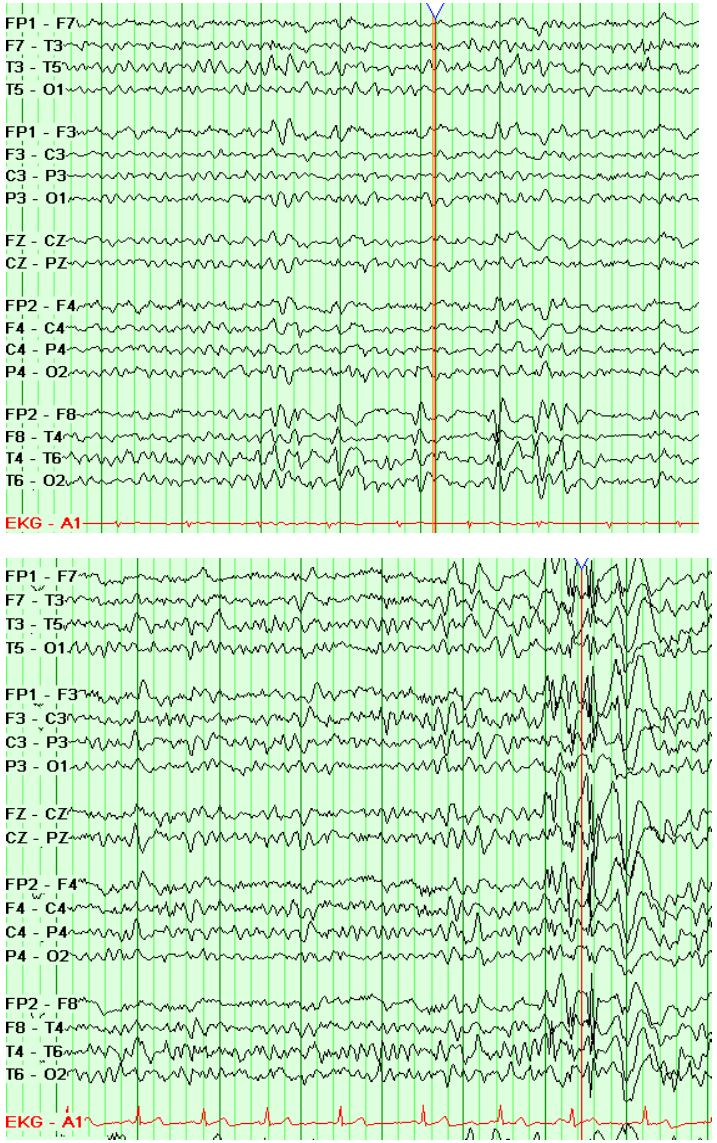
- **Neuroimaging** - brain imaging using CT or **MRI** should be considered as part of the neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B).

- Lab tests**:** In the adult initially presenting with an apparent unprovoked first seizure, blood glucose, blood counts, and electrolyte panels (particularly sodium) may be helpful in specific clinical circumstances, but there are insufficient data to support or refute routine recommendation of any of these laboratory tests (**Level U**).

- Lumbar puncture - may be helpful in patients with immunosuppression or fever (Level U).

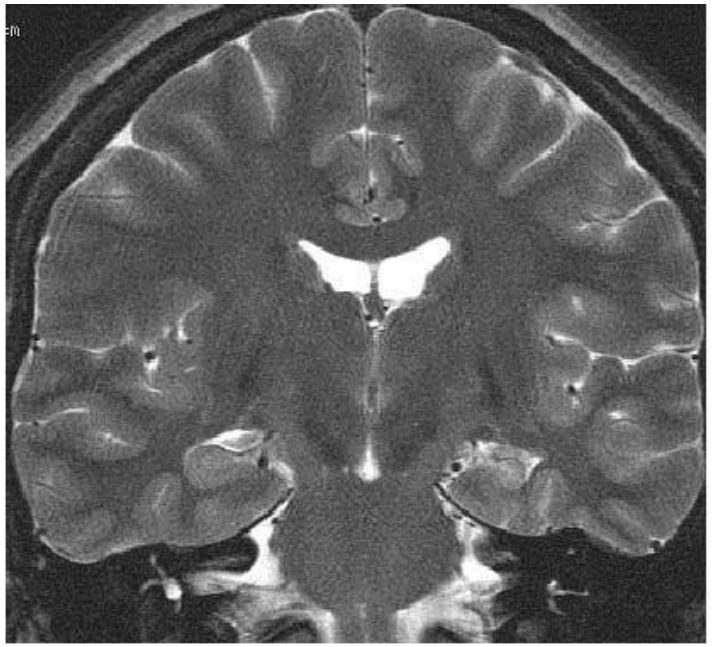
EEG

- Assess for epileptiform discharges (30%, increases to 80-90% with 3 EEGs)
- Help diagnose presence, type, and location of epilepsy
- Negative EEG does not rule out epilepsy
- Sleep deprived EEG more sensitive (increase yield by 30%)
- EEG after spell or seizure is more sensitive (51% vs 30%)
- Extended monitoring: video EEG or ambulatory EEG



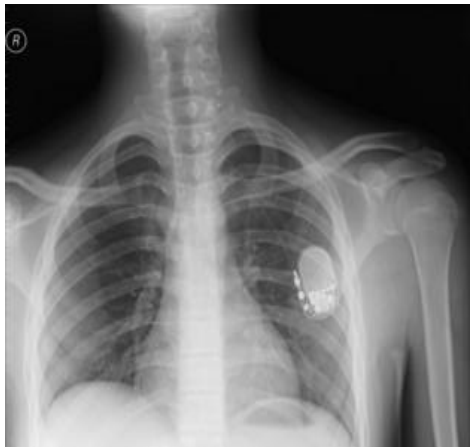
Imaging

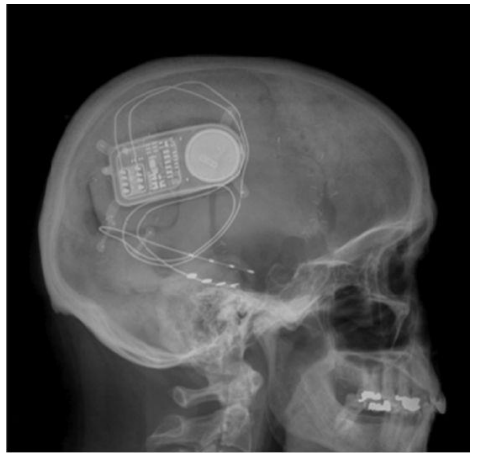
- After 1st seizure → MRI is indicated
- Yield of about 10% leading to diagnosis of brain tumor, stroke, cystircercosis or other structural lesions
- May help determine risk of seizure recurrence

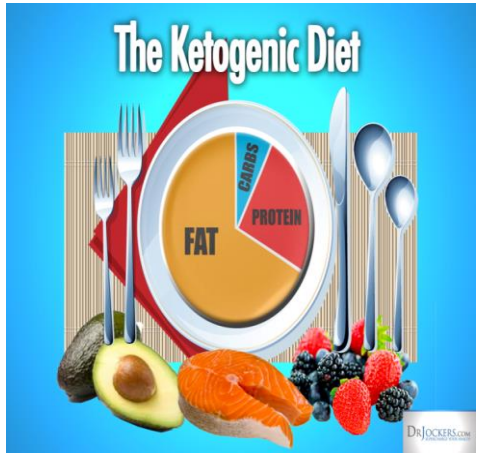


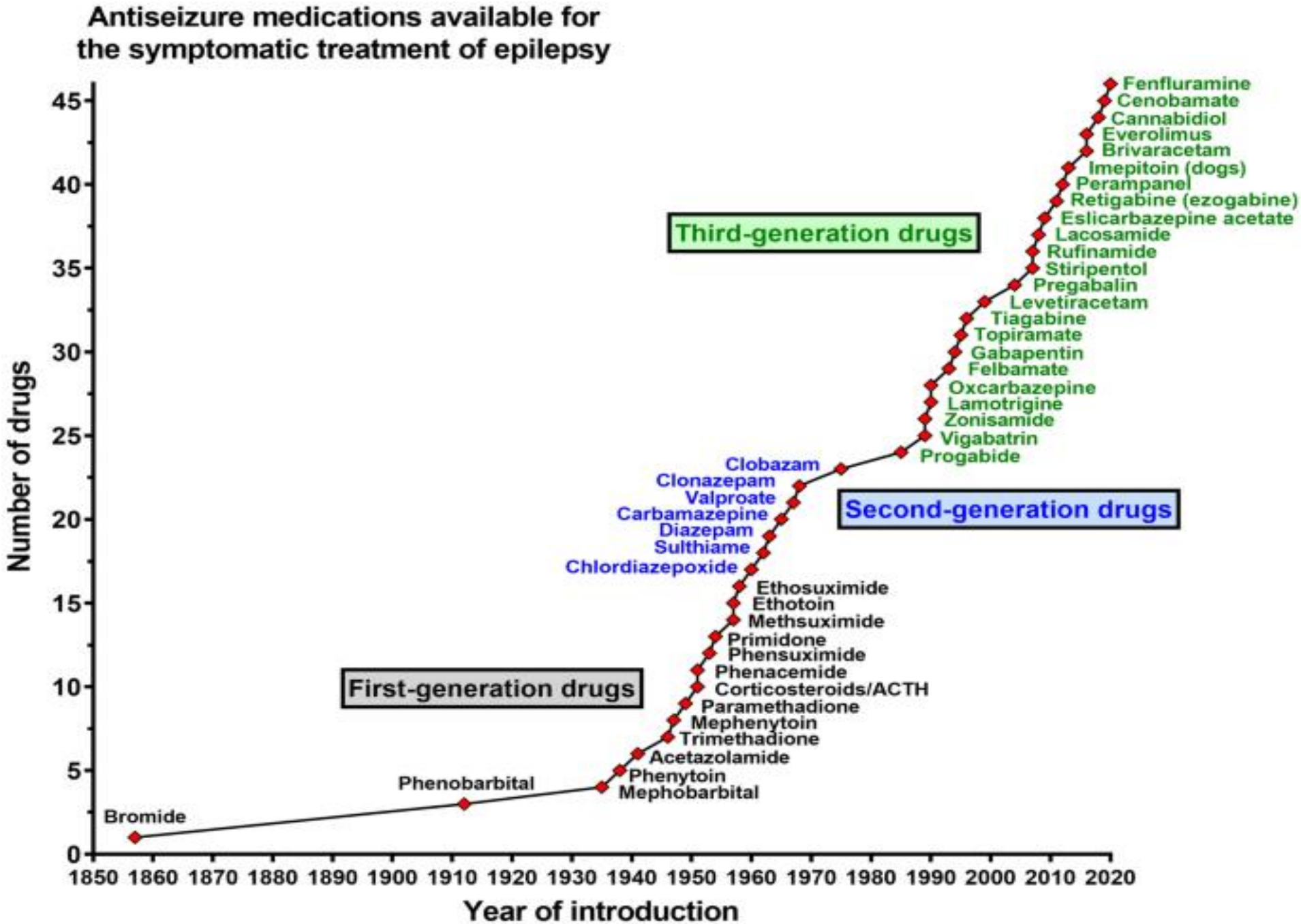
Treatment Options in Epilepsy

- Antiseizure medications (ASMs)
  - 1st generation
  - 2nd generation
  - Extended release
- Epilepsy surgery
- Devices
  - Responsive neurostimulation (RNS)
  - Deep brain stimulation
  - Vagus nerve stimulation (VNS®)
- Diets
- Alternative therapies





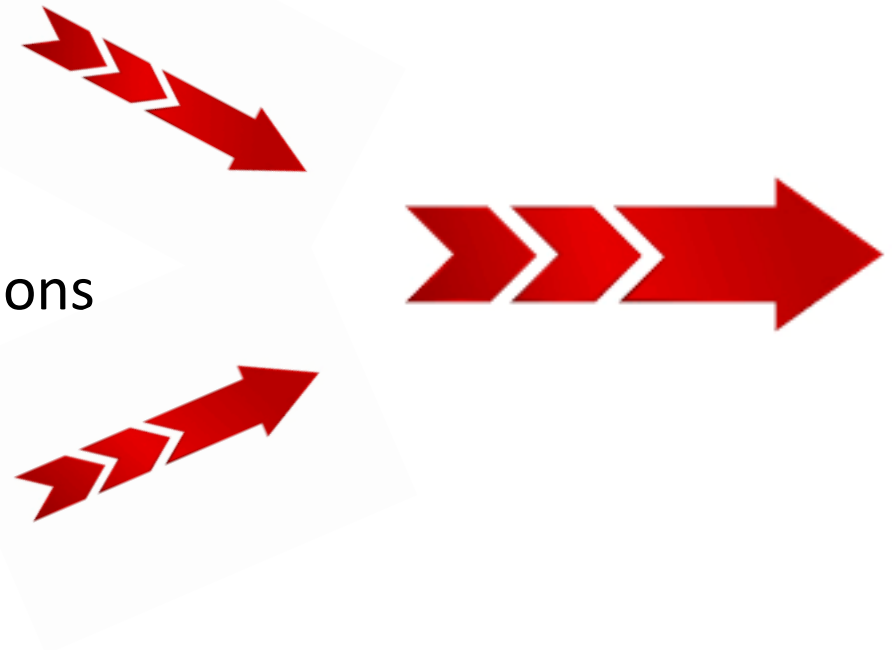




Löscher, W., Klein, P. The Pharmacology and Clinical Efficacy of Antiseizure Medications: From Bromide Salts to Cenobamate and Beyond. *CNS Drugs* **35**, 935–963 (2021).

Considerations in choosing an Antiseizure Medication (ASM):

1. Efficacy
2. Safety
3. Tolerability
4. Co-Morbid Conditions
5. Cost
6. Ease of use
7. Birth control



EPILEPSY TYPE

Anti-Seizure Medication (ASM) Considerations: Take Away

- GENERALIZED EPILEPSIES

  Spectrum of action: Broad
  - Valproic acid
  - Lamotrigine
  - Levetiracetam
  - Topiramate
  - Zonisamide
  - Lacosamide
  - Felbamate
  - Perampanel
  - (Ethosuximide)

  - (Clobazam)
  - (Cenobamate)
  - (Epidiolex- LGS)
  - (Fenfluramine- LGS, DS)

- FOCAL EPILEPSIES

  Spectrum of action: Narrow
  - Carbamazepine
  - Oxcarbazepine
  - Eslicarbazepine
  - Gabapentin
  - Pregabalin
  - Phenytoin
  - Phenobarbital
  - Cenobamate
  - Lacosamide
  - Perampanel
  - Valproic acid
  - Lamotrigine
  - Levetiracetam
  - Topiramate
  - Zonisamide

ASMs: Adverse Effects

Idiosyncratic: usually systemic/allergic

- Rashes
- Organ toxicity

Dose-related: **usually CNS**

- Dizziness, drowsiness, ataxia
- Cognitive slowing, depression (may also be idiosyncratic)

Chronic: drug-induced diseases

- Osteoporosis

Definition of Drug Resistant Epilepsy

In ‘10, The International League Against Epilepsy’s ad hoc Task Force of the ILAE Commission on Therapeutic Strategies published a consensus paper including a formal definition

*“Drug resistant epilepsy may be defined as failure of **two tolerated, appropriately chosen and used AED** schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”*

Kwan P et al. Epilepsia 51(6):1069-77, 2010

Key words: Tolerated, Appropriate, Used

The Burden of Uncontrolled Epilepsy

- Ongoing seizures can be very debilitating, often associated with morbidity and mortality.
- High rates of depression/anxiety, seizure-related injuries (burns, falls), accidental deaths and suicide (SUDEP 1:100 in surgical candidates).
- Very important to identify if a patient is drug resistant as early as possible, best chance for ***CURE*** may be epilepsy **surgery.**
- Increasing evidence suggesting referral for surgery earlier in the course.
- Possible that continued seizures may result in progressive neurologic damage over time→ surgery is "neuroprotective" as opposed to AED polypharmacy.
  - cortical atrophy (Bernhardt et al, '09), lower IQ over time
  - Becoming seizure-free at a younger age may lessen the cognitive, behavioral, and psychosocial problems experienced by epilepsy patients, potentially improving societal integration.
  - Even **one seizure** per year ~ **lower QOL** (Jacoby et al, '92)
- Despite this…… epilepsy surgery remains largely underutilized.

Special Considerations

In women of childbearing age:

- Periodically readdress ASM therapy and birth control; be aware of drug-drug interactions between ASMs and oral contraceptives
- Remove VPA if possible
- Folic acid

All patients on inducing agents or VPA:

- Bone health (CBZ, OXC, ESL, VPA, PhB, PHT), bone density scan 3-5yrs

In women considering pregnancy:

- Most pregnancies in mothers with epilepsy produce normal children.
- Increased volume of distribution, Lower serum albumin, Faster metabolism
- Seizure control may worsen, especially if doses are not increased, check levels regularly.
- Most pregnancies in mothers with epilepsy produce neuro-typical children.
- Some ASMs are teratogenic; 4-9% monotherapy, higher with VPA and polytherapy.
- Higher dose, but probably less than predicted by total level (measure free level)
- Consider more frequent dosing

- Return to pre-pregnancy conditions rapidly (within 2 weeks) after delivery

Driving

- Epilepsy likely accounts for a small percentage of reported car crashes
- Required seizure-free intervals vary greatly among jurisdictions (typically 3 to 12 months)
- Mandatory physician reporting: CA, OR, PA, DE, NV, NJ
- State driver licensing laws available at http://www.epilepsyfoundation.org
- Discuss driving with patient and document in medical record

Epilepsy Quality Measures

2014 Epilepsy Update Quality Measurement Set
1A. Seizure frequency specified at each encounter (paired measure) (2009 measure revised)
1B. Seizure intervention specified at each encounter (paired measure) (2009 measure revised)
2. Etiology, seizure type, and epilepsy syndrome specified at each encounter (2009 measure revised)
3. Querying and intervention for side effects of antiseizure therapy specified at each encounter (2009 measure revised)
4. Personalized epilepsy safety issue and education provided yearly (2009 measure revised)
5. Screening for psychiatric or behavioral health disorders specified at each encounter (new measure)
6. Counseling for women of childbearing potential with epilepsy yearly (2009 measure affirmed with updated specifications)
7. Referral of treatment-resistant epilepsy to comprehensive epilepsy center every 2 years (new measure)

https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/3.Practice_Management/2.Quality_Improvement/15%20Quality%20Measurement_Cli%20v102.pdf

Discontinuing ASMs: Take away

- No seizure for 2-5 yrs >60% success
- Favorable factors
  - control on one drug at low dose
  - no unsuccessful attempts at withdrawal
  - Normal neurologic exam, EEG, MRI,
  - "benign syndrome"
- Consider risks/benefits (e.g. driving, pregnancy, job issues)
- Always taper

Summary of Key Points: Take aways

- Epilepsy is a common disease with different causes and manifestations
- Other disorders can mimic seizures, including convulsive syncope and functional seizures
- History is key to accurate diagnosis
- Diagnostic studies for all patients: MRI, EEG
- There are many therapeutic options
- Education and safety issues are important considerations

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https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/3.Practice_Management/2.Quality_Improvement/15%20Quality%20Measurement_Cli%20v102.pdf

Question 1

An adult who presents after a first seizure should have which of the following diagnostic tests:

a) Brain MRI
b) EEG
c) LFTs
d) Genetic testing
e) A & B

Question 1

An adult who presents after a first seizure should have which of the following diagnostic tests:

a) Brain MRI
b) EEG
c) LFTs
d) Genetic testing
e) A & B CORRECT ANSWER

Question 2

To meet criteria for drug-resistant epilepsy, a patient must have tried but had persisting seizures on how many antiseizure medications:

a) 5
b) 3
c) 2
d) 0

Question 2

To meet criteria for drug-resistant epilepsy, a patient must have tried but had persisting seizures on how many antiseizure medications:

a) 5
b) 3
c) B CORRECT ANSWER
d) 0