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A Comprehensive Overview of Epilepsy

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Learning Objectives

1) Describe the difference between provoked and unprovoked seizures and the associated risk for epilepsy
2) Thoroughly evaluate patients who present with a first seizure
3) Recognize status epilepticus
4) Learn different antiseizure medications and how to choose the right one for a patient
5) Identify refractory epilepsy and surgical treatment options

Definitions

- What is a seizure?
- What is epilepsy?

Episodic Events

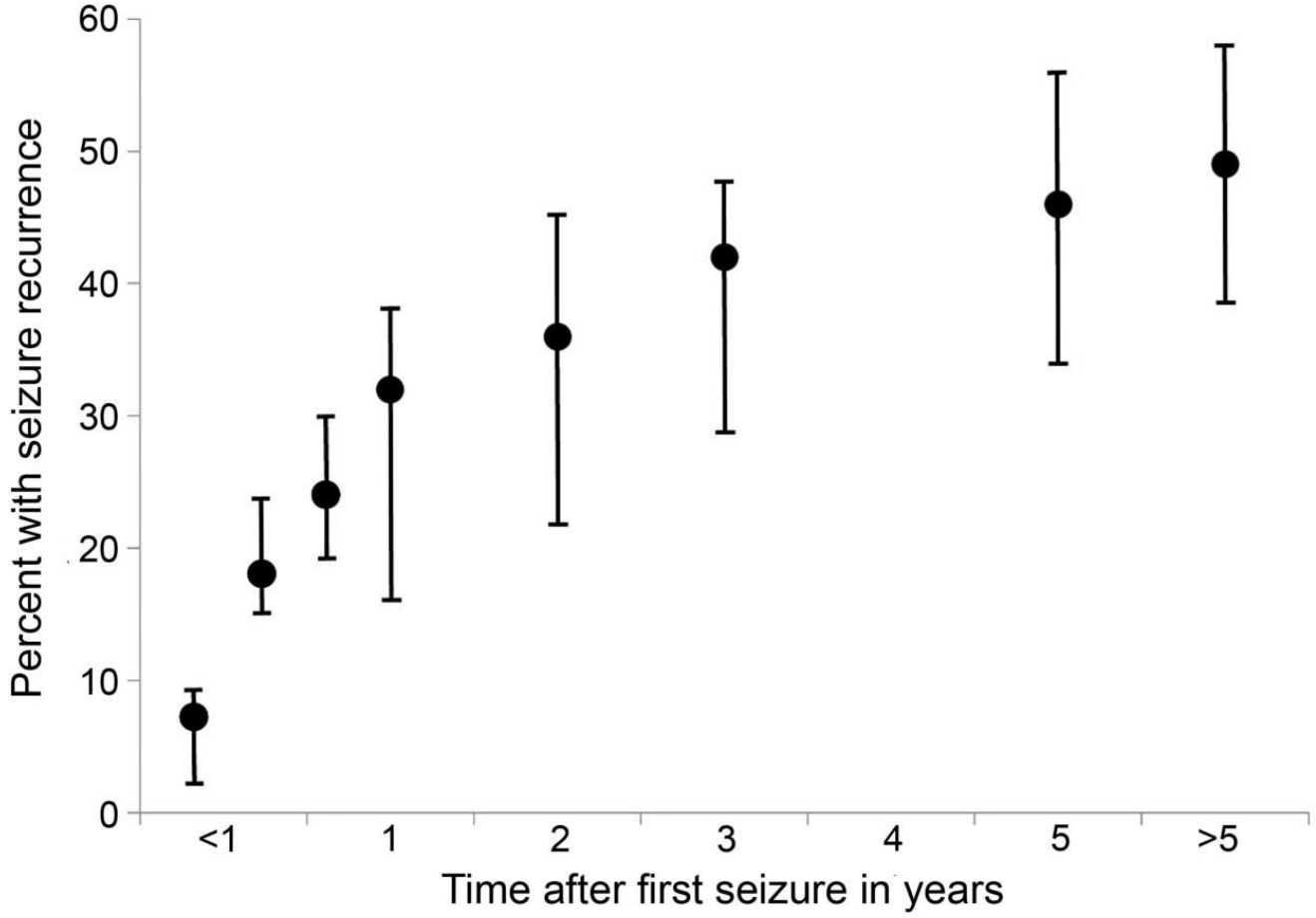
Yearly Incidence of Episodic Events

Episodic Events	Number/100,000
Syncope	3000
Dizziness	2600
Migraine	730
Epilepsy	50
TIA	23
TGA	3

First Seizure

- 150,000 adults will present with 1st seizure each year in the US
- About 33-50% will go on to develop epilepsy
- Lifetime risk for developing epilepsy is 1.4-3.3%
- Risk is highest in the first 1 to 2 years
  - 32% recurrence at 1 year; 46% by 5 years

Percentages of patients with first seizure experiencing a recurrent seizure over time



Evidence-based guideline: Management of an unprovoked first seizure in adults. *Neurology 2015; 84:1705-1713.*

First Steps

- Careful history
  - Any prior, smaller episodes?
- Consider differential diagnosis
  - Physiologic vs psychogenic
  - Provoking factors
    - Alcohol, drug use, hyponatremia, hypo/hyperglycemia, etc.
    - Only 3-10% recurrence risk for provoked seizures

Differential Diagnosis

- Physiologic Events
  - Syncope (orthostatic, arrhythmias, etc.)
  - Migraine (complex)
  - TIA
  - TGA
  - Dizziness/vertigo
  - Sleep disorders (RBD, cataplexy, etc.)
  - Waxing and waning delirium
  - Intermittent movement disorders
- Psychiatric-based Events
  - Panic/anxiety attacks
  - Conversion, PNES
  - Dissociative states
  - Hyperventilation syndrome
  - Acute psychosis
  - Malingering

Differential Diagnosis

- Favors Epilepsy
  - Aura
  - Brief duration
  - Abnormal posturing
  - Events arising from sleep
  - Self-injury (broken bones particularly face, lateral tongue biting)
  - Eyes open at onset of event

- Favors PNES
  - Specific non-traditional triggers (smells, getting upset/angry)
  - Event occurs in waiting room or exam room
  - Histrionic behavior during exam
  - Rapid postictal recovery
  - Ability to induce a seizure
  - Presence of fibromyalgia, chronic pain, chronic fatigue syndrome

**exceptions occur to both categories

History

- Clinical features associated with partial epilepsy
  - Temporal lobe
    - Déjà vu, epigastric sensation, exaggerated emotions: fear/fright, automatisms, speech arrest/disturbances (dominant hemisphere)
  - Frontal lobe
    - Hypermotor activity, forced eye deviation, forced head deviation
  - Parietal lobe
    - Paresthesias/sensory phenomena
  - Occipital lobe
    - Positive basic visual phenomena (flashes, colors), formed visual images (dominant hemisphere, association cortex)

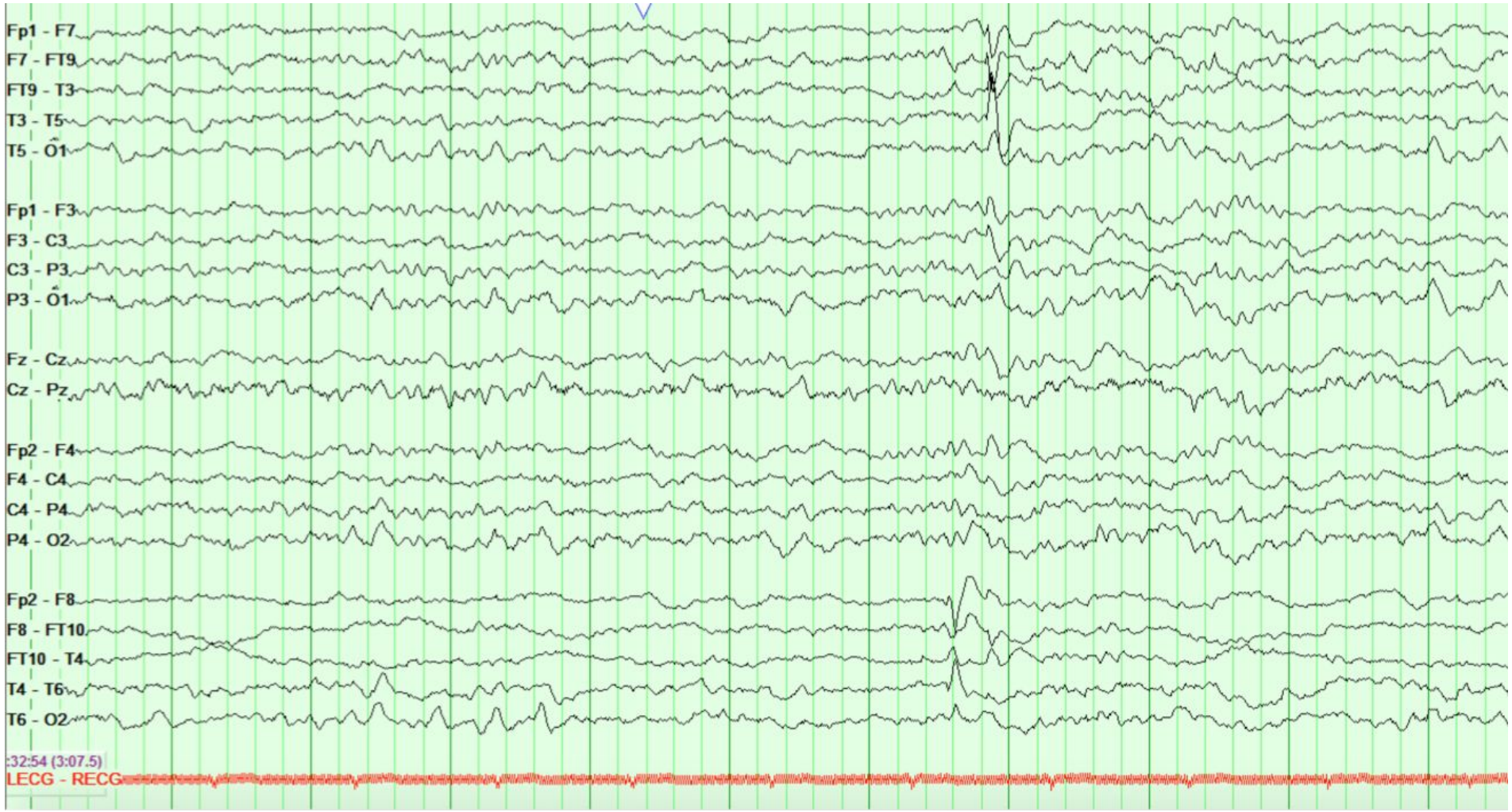
Initial Evaluation

- Careful neurologic examination
- Diagnostic testing
  - Laboratory testing
    - CMP, CBC w/diff, TFTs, UDS
  - MRI
    - Stroke, tumor, MTS, remote trauma, cortical dysplasia, developmental abnormalities
  - EEG
    - Routine, sleep-deprived, ambulatory, EMU
  - LP
    - May be considered in select patients

EEG

- In predicting seizure recurrence, EEG has
  - sensitivity 48-61% and specificity 71-91%
    - IEDs seen in ~ 2% general population
- Initial EEG detected IEDs in 29-55% of patients
  - Mixed adult/peds population
  - IEDs associated with 2-fold risk of recurrence
- Increase diagnostic value by
  - Within 24 hours of seizure episode
    - Inceased sensitivity by 15%
  - Sleep obtained
    - Increases sensitivity by 25%
  - Repeated testing
    - Increases IEDs seen by 15-20% up to 90% by 4th EEG

Interictal Epileptiform Discharge



Seizure Recurrence

- Workup is to assess risk of seizure recurrence
  - 33 – 50% will have recurrence after 1st seizure
    - Majority of recurrence is within the first 2 years
- Increased Risk of Recurrence
  - Prior brain insult had an increased relative rate of recurrence of 2.55
  - EEG with epileptiform abnormalities had an increased relative rate of recurrence of 2.16
  - Abnormal brain imaging had an increased hazard ratio of 2.44
  - Nocturnal seizure had an increased recurrence risk odds ratio of 2.1

Treatment

- When to treat:
  - Single, provoked seizure? NO
  - Initial seizure as status epilepticus? YES
  - Single unprovoked seizure? MAYBE

Epilepsy Case 1

- 24yo right-handed woman with no significant PMH has a seizure like event
  - What else do you want to know?
  - What do you do next?
  - Do you treat?
  - How do you counsel family on risk of recurrence?

Epilepsy Case 2

- 24yo right-handed woman with no significant PMH has a seizure like event
- She has a second seizure-like event 3 months later
  - How does this change things?
  - What do you do now?

Summary

- Not all episodic events are seizures
- Thorough history and proper evaluation of risk recurrence is crucial for determining who would benefit from immediate treatment with ASMs
- Risk of seizure recurrence after a first unprovoked seizure is highest in the first 2 years
- Immediate treatment with ASMs reduces risk of recurrence in the subsequent 2 years, but over the long-term is unlikely to improve prognosis for sustained seizure remission

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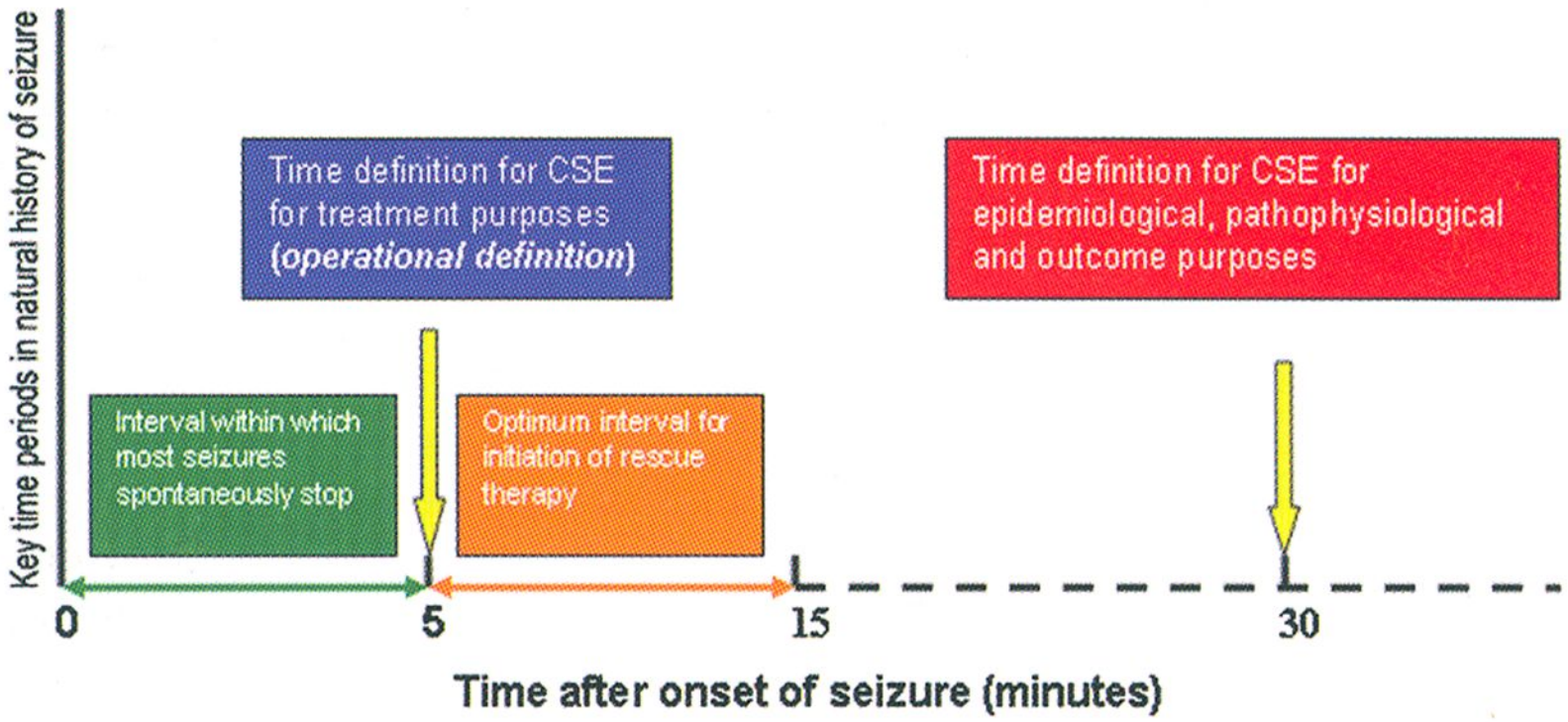
Status Epilepticus

Status Epilepticus (SE)

- Continuous seizure activity > 5 minutes or recurrent seizures without return to baseline between seizures
- SE can damage brain even if convulsive activity is controlled (e.g., paralytic) and adequate oxygenation, energy supplies, and circulation are maintained!
- Longer the duration, the more difficult to stop
- Mortality is ~20%
- TIME IS BRAIN

Timeline of Status Epilepticus

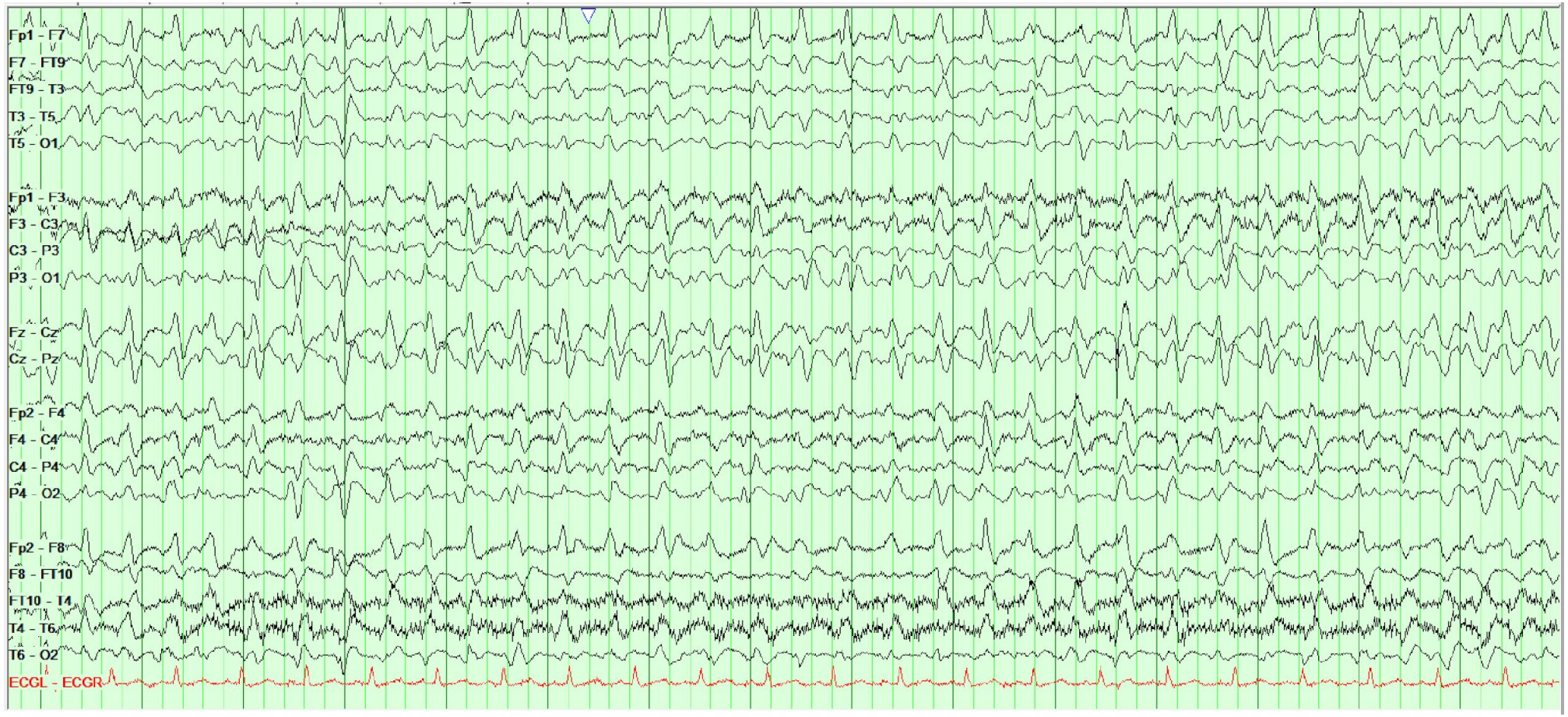


1. Duration of seizure activity against key time periods in the natural history of a prolonged seizure.

Types of Status Epilepticus

- Generalized Convulsive
- Focal Motor (Epilepsia Partialis Continua)
- Myoclonic
- Nonconvulsive
  - Subtle generalized “convulsive”
  - Complex partial (altered consciousness)
  - Absence

Status Epilepticus



Treatment of SE

0–5 minutes:

- Diagnose; give O2; ABCs; obtain IV access; begin ECG monitoring;
- Bloodwork including Chem-7, magnesium, calcium, phosphate, CBC, LFTs, ASM levels, ABG, troponin; toxicology screen (urine and blood)

6–10 minutes:

- Thiamine 100 mg IV, 50 mL of D50 IV unless adequate glucose known
- Lorazepam 2 mg IV every 2 minutes to a maximum dose of 0.1 mg/kg
- Alternatively, midazolam 10 mg IM, fosphenytoin (not phenytoin) IM, or diazepam 20 mg PR

10–20 minutes:

- Fosphenytoin** 20 PE mg/kg IV at a maximum rate of 150 mg/min, with blood pressure and ECG monitoring

Treatment of SE

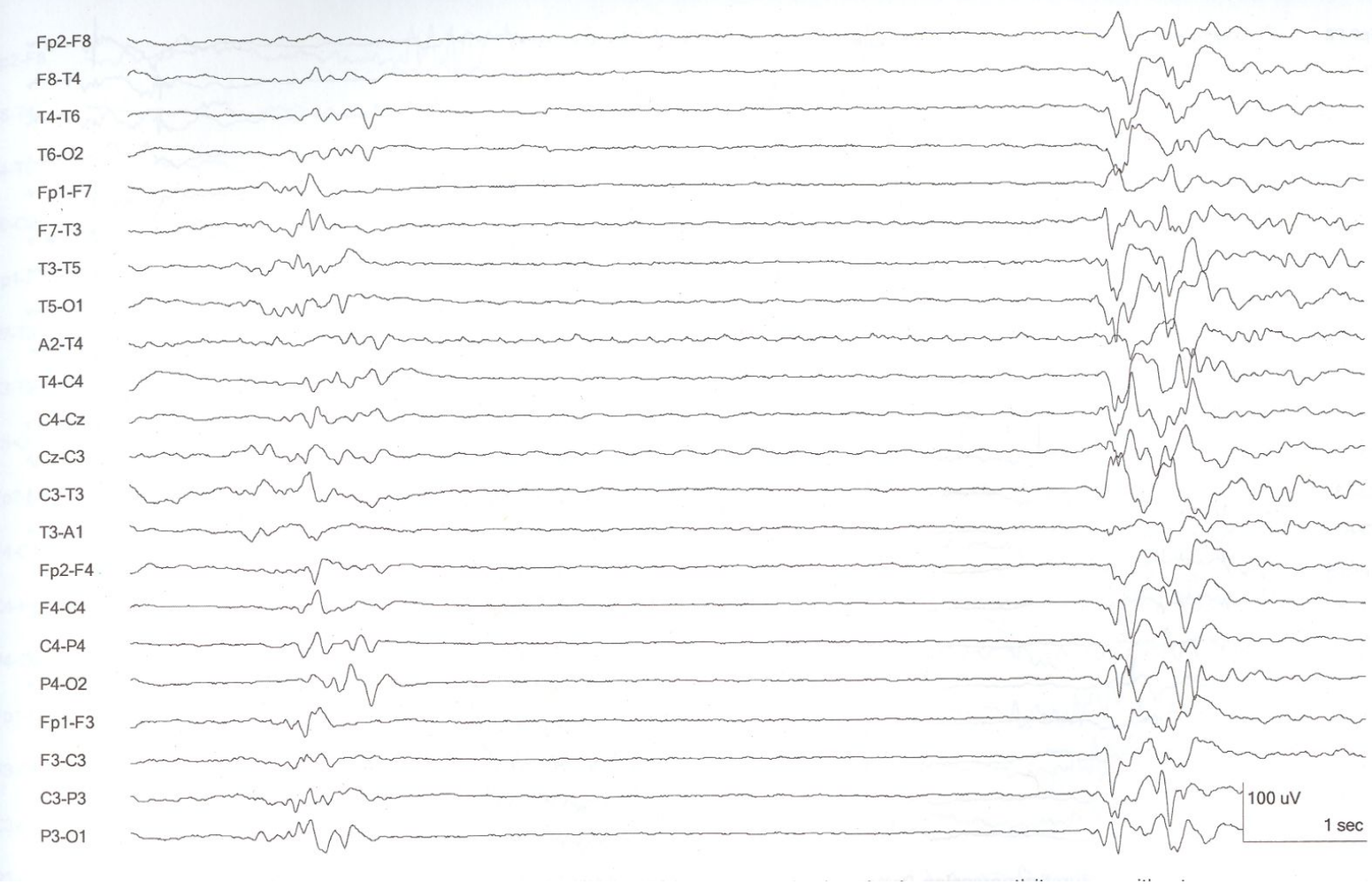
10–60 minutes:

- Start one of the following continuous IV (CIV) medications: midazolam, pentobarbital, or propofol
  - Intubation, arterial and central venous access will be necessary
  - Monitor closely for hypotension and cardiac arrhythmias
- Consider CIV ketamine (consider only if others don't work)

Treatment of SE

- EEG recommendation:
  - When starting any CIV medication, order continuous EEG
  - CIV infusions should be titrated to EEG burst suppression
    - A general rule is to have approximately >50% of the EEG as suppression (i.e., 1 – 2 seconds of 'burst' activity separated by 3 – 8 seconds of suppression) but there is no data to support this.
- If you cannot get seizures to stop, or have the patient in burst suppression within 2-3 hours, then the urgency of care needs to increase rather than diminish

Burst Suppression



Treatment of SE

- Supplemental seizure control:
  - If the patient requires a CIV medication, then supplemental anti-convulsants need to be added to fosphenytoin / phenytoin to aid in long-term seizure control
  - The options available are many, but medications with IV formulations should be initiated first to address any concerns regarding absorption while patient is heavily sedated
    - Consider levetiracetam, phenobarbital, valproate, lacosamide

Summary

- Status epilepticus is a neurologic emergency
  - Mortality is ~ 20%
- SE should be identified and appropriately treated as soon as possible to improve patient outcomes

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Antiseizure Medications

Epilepsy Case 2

- 37 yo right-handed man who reports having seizures for the past 2 years. He describes his seizures as beginning with a sense of déjà vu, followed by fumbling with his right hand, repetitive lip smacking, and unresponsiveness. Finally, he will be staring off into space with loss of awareness. Seizures will last for approximately 2 minutes and have been occurring 2-3 times per week. The patient reports he is completely unaware of his seizures. Occasionally, he will have generalized convulsive activity.

- Next steps?
- Treatment?

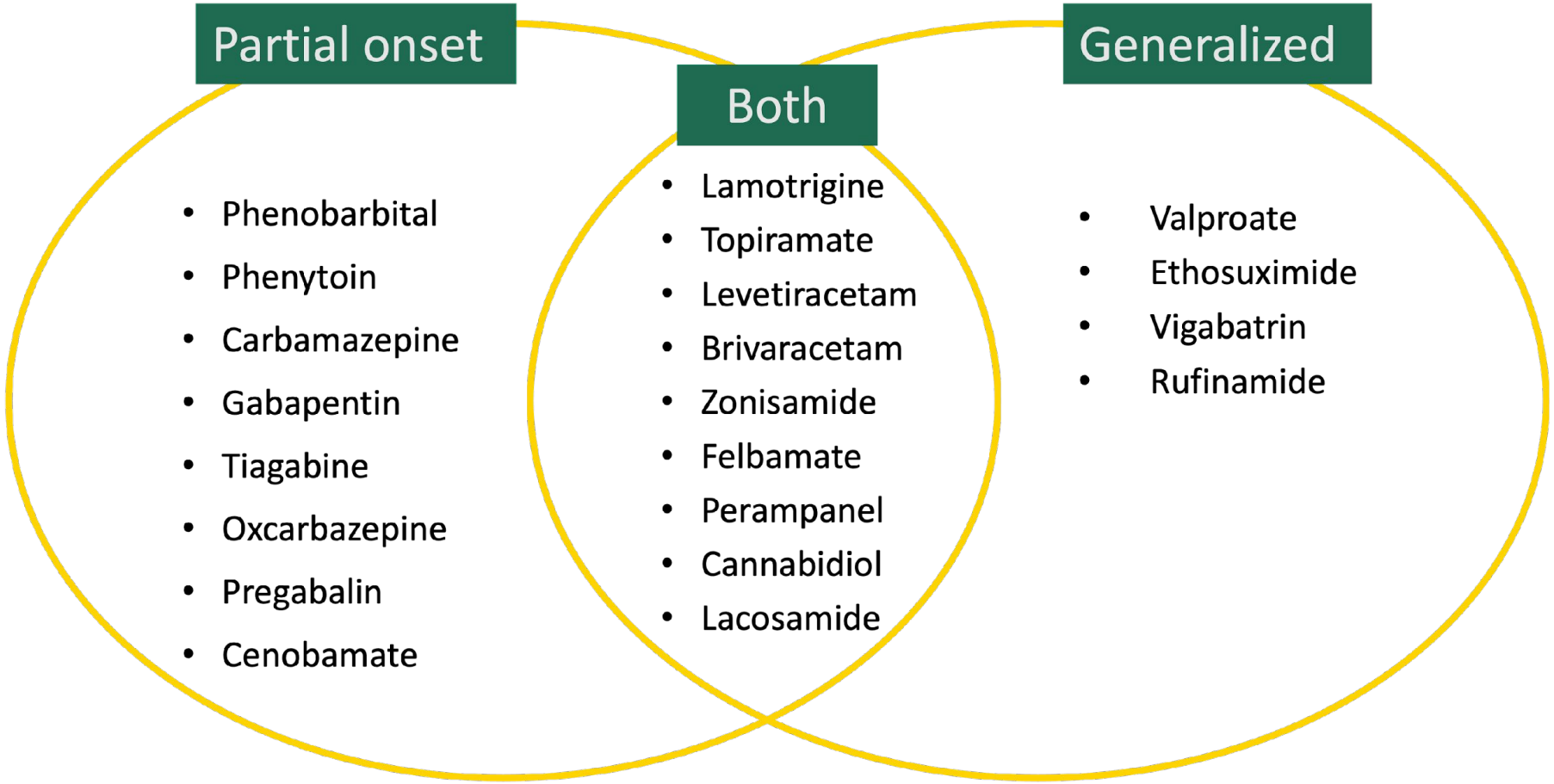
Treatment

- When to start ASMs?
  - Acute symptomatic seizure vs onset of epilepsy
  - High risk vs low risk patients
    - Abnormal EEG
    - Abnormal MRI
    - Underlying neurologic disease
- Which medication to choose?
  - Approx 2/3 will become seizure free on the first or second ASM used
  - AEs occur in 7-30% of patients and are usually mild and reversible
  - Choose most tolerable and lowest potential for harm

Selection of ASMs

- Epilepsy classification
  - Partial onset vs generalized epilepsy
- Side effects
  - Dose-related: usually central nervous system; often predictable
    - Somnolence, dizziness, diplopia, mental slowing
  - Idiosyncratic: reactions specific to each medication; unpredictable
    - Rash, organ toxicity, blood dyscrasias
  - Beneficial: often desirable; somewhat predictable
    - Weight loss, mood stabilization, neuropathic pain improvement, headache relief
- Medication interactions
  - Effect on ASM or by ASM
- Dosing issues
  - Formulation (tablet/capsule, IV, elixir)
  - Frequency of dosing (daily, twice daily, etc.)

Medication choice by epilepsy type



Efficacy and ASMs

- Some medications are good for partial onset sz, some for generalized onset sz, some for both, but within each of those classes statistical efficacy is relatively similar across medications and other factors become more important.
- Effectiveness of a given medication will vary dramatically from patient to patient, and effectiveness for a given patient will vary dramatically from medication to medication.

Mechanism of Action and Selection of ASMs

- Many medications work through multiple mechanisms
- IMPORTANT: Mechanism of action does NOT have a predictable impact on effectiveness or similarity of response with other medication with same mechanism
  - Just because one Na^+ channel medication works doesn't mean another Na^+ channel medication will work in a given individual patient
- It is not clear whether or not *combinations* of medications with the same MOA are redundant or just as effective as combinations with different MOA

Epilepsy Case 2

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- Treatment options for our patient?

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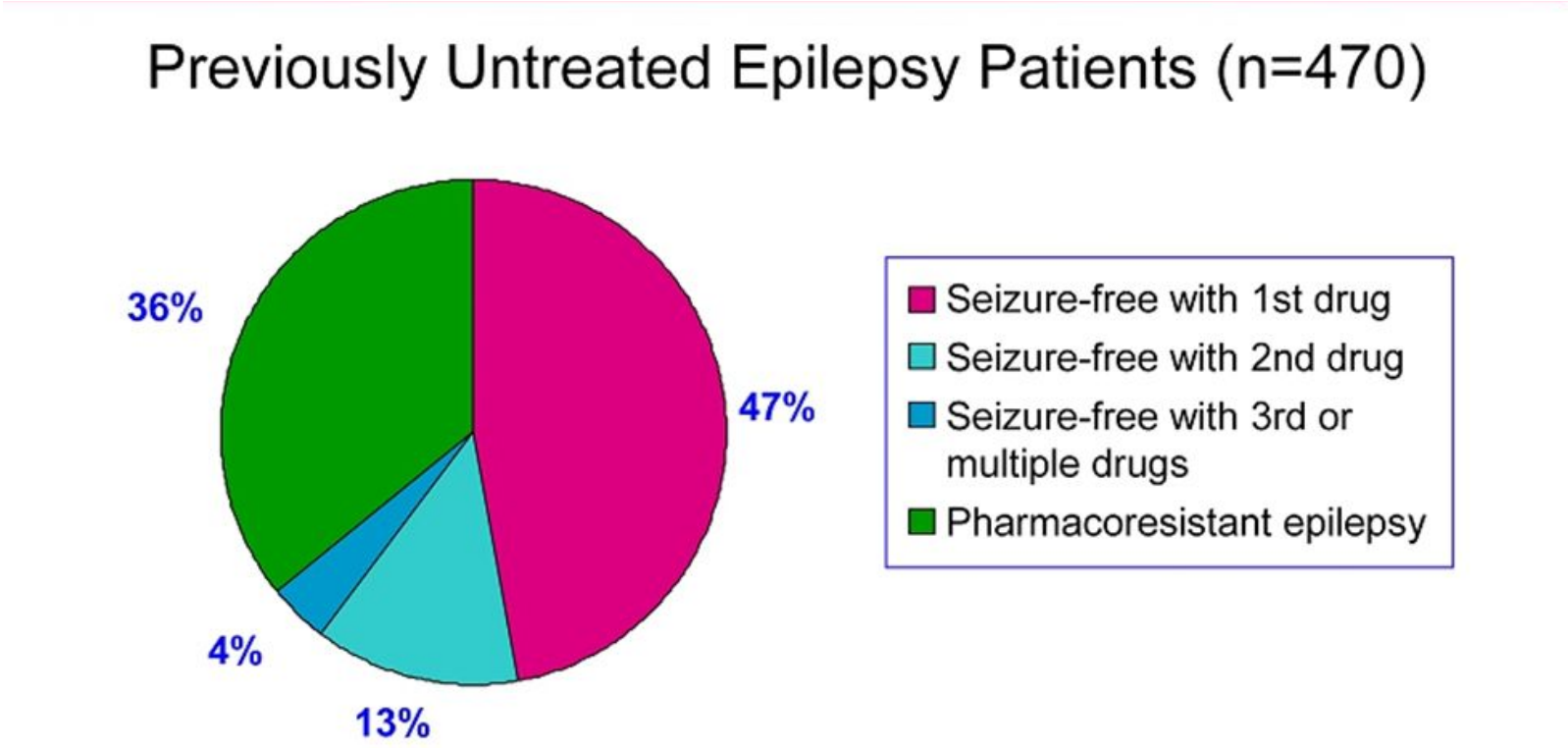
Refractory Epilepsy

Epilepsy Prognosis



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342:314-319.

Refractory Epilepsy

- Not seizure-free despite adequate trials of at least 2 ASMs
- Significant impact on quality of life:
  - Psychosocial interactions, vocation and driving
- Significant adverse impact on the patient's cognition and development
  - Related to recurrent seizures and ASM use
- Five-fold increased risk of death due to Sudden Unexpected Death in Epilepsy (SUDEP)
- Requires additional treatment considerations

Epilepsy Case 2

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- Patient continues to have frequent seizures despite current use of levetiracetam and lamotrigine.
- He has tried phenytoin in the past.
- Next steps?

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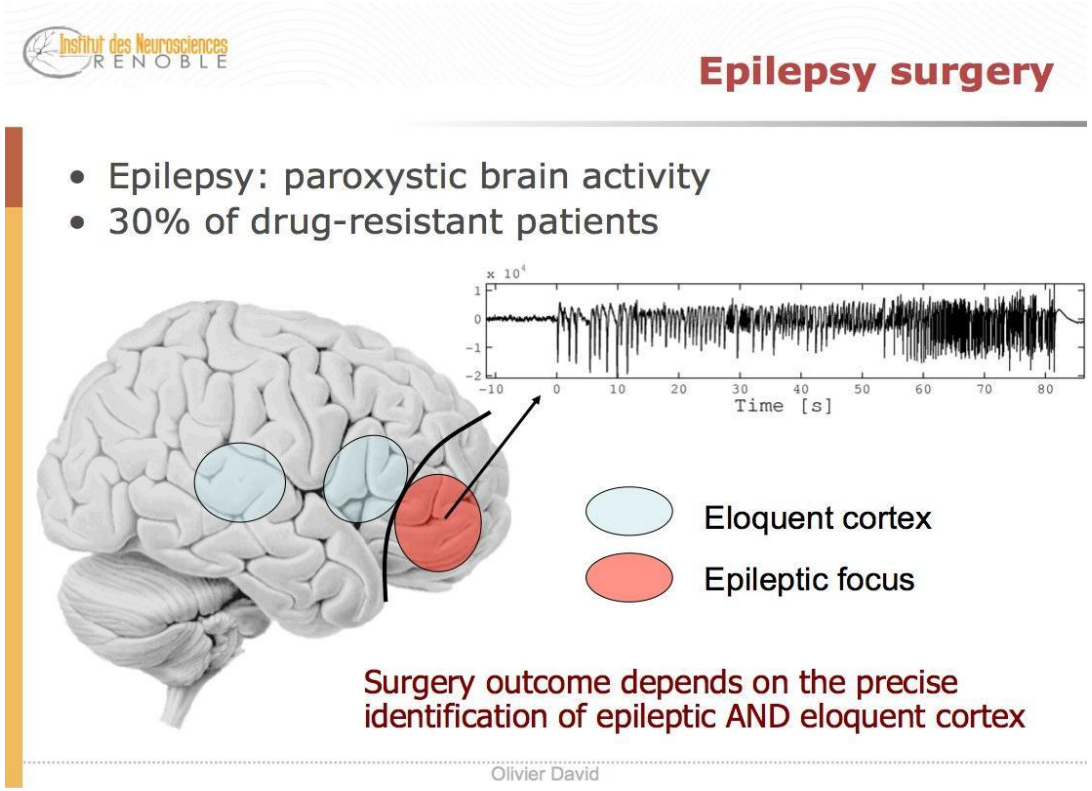
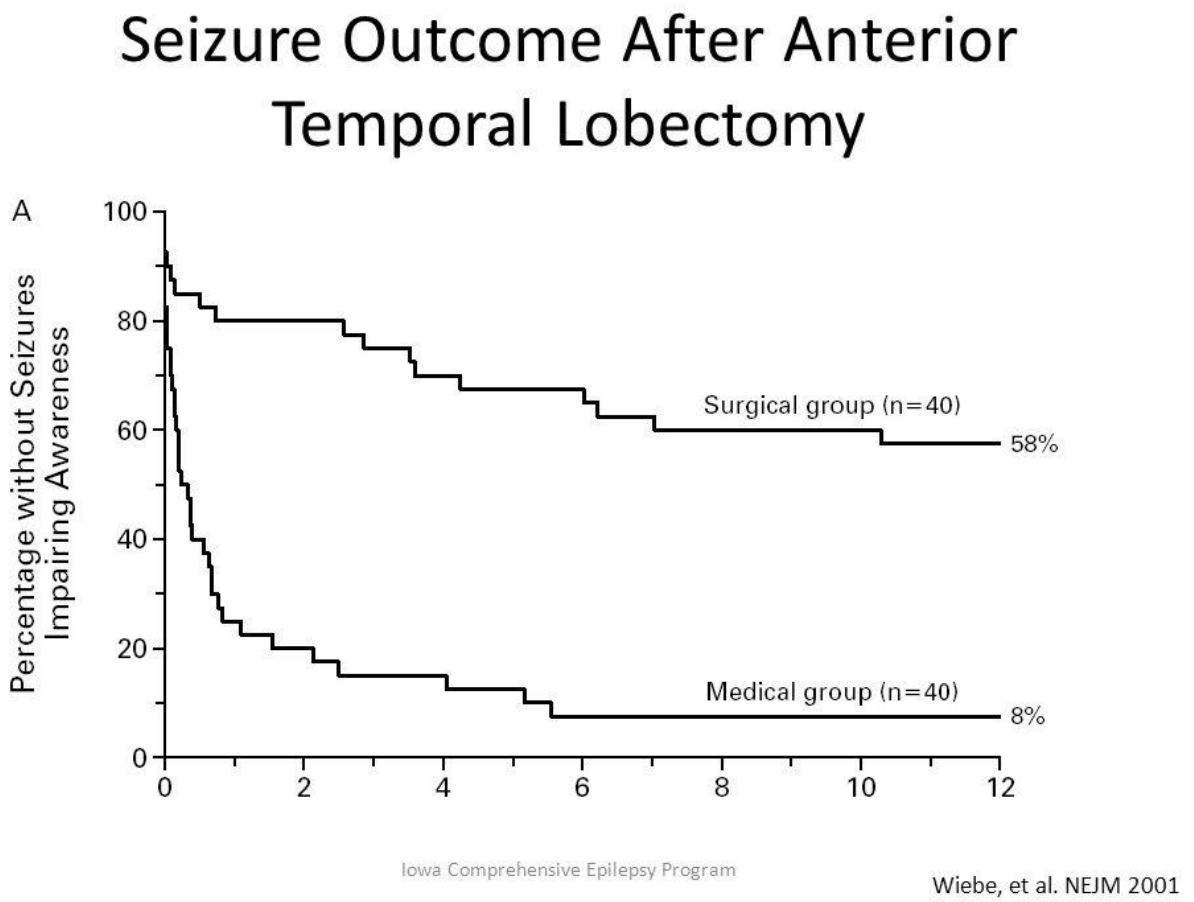
Epilepsy Surgery

Foundations of surgical resection for epilepsy

Spontaneous seizures arises from a focus and removing this focus provides seizure freedom without any additional functional deficit



Why do we offer surgery?



**Seizure outcome with surgery is superior to medication.

Epilepsy Surgery

- Resection
  - Open resection
  - Laser interstitial thermal therapy (LITT)
- Neuromodulation
  - Responsive neurostimulation (RNS)
  - Deep brain stimulation (DBS)
  - Vagus nerve stimulation (VNS)
- Disconnection
  - Corpus callosotomy
  - Multiple subpial transections (MST)

Patient Selection

- Refractory epilepsy
  - Continued seizures despite trial of 2 ASMs
- Frequent, disabling seizures
- High risk for SUDEP

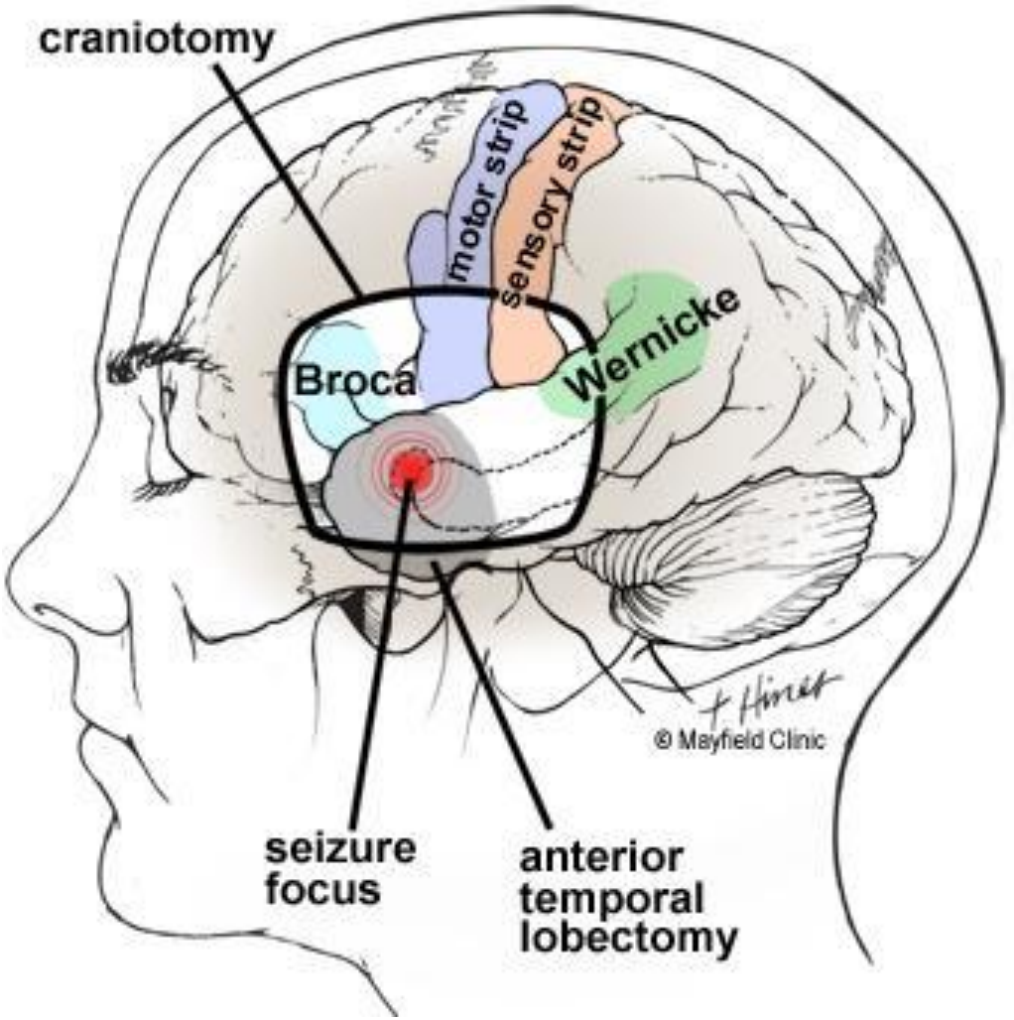
- Single seizure focus (not eloquent cortex) **only for resection surgeries

* Patient selection is key for successful epilepsy surgery

Pre-surgical evaluation

Goals of evaluation are to

- Localize the epileptogenic focus
- Determine if that focus is in eloquent cortex
  - Will resection of that focus provide additional functional deficit?



Pre-surgical evaluation

- Scalp video EEG (EMU) – Phase 1
- Structural imaging (MRI)
- Functional imaging (PET, ictal SPECT, fMRI)
- Magnetoencephalography (MEG)
- WADA test

Epilepsy Case 2

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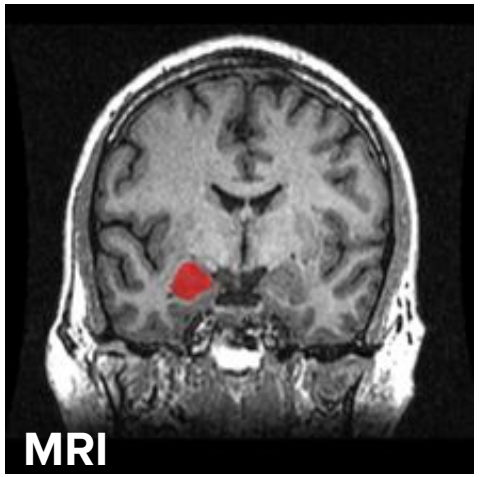
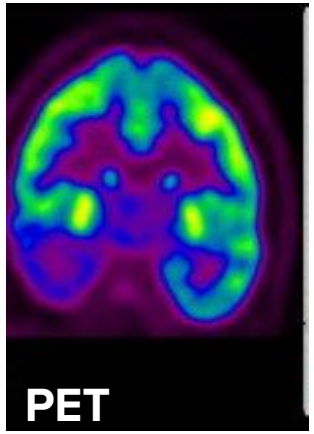
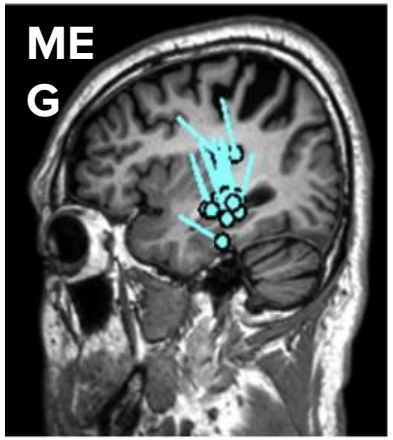
- Localization
  - Based on semiology and EEG findings

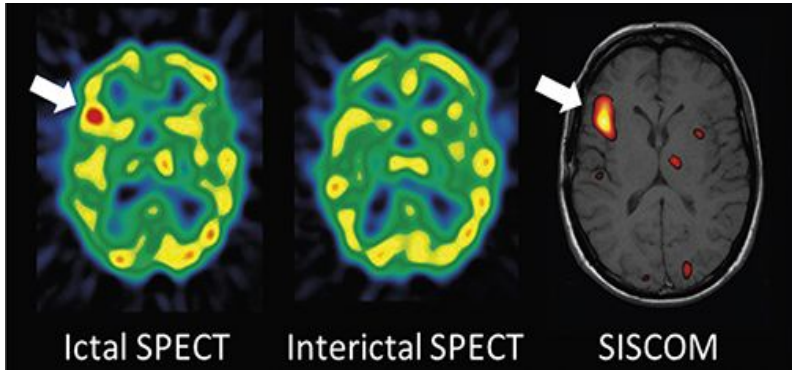
Temporal lobe epilepsy

- Déjà vu
- Out of body experiences
- Rising epigastric discomfort, nausea
- Anxiety
- Fear





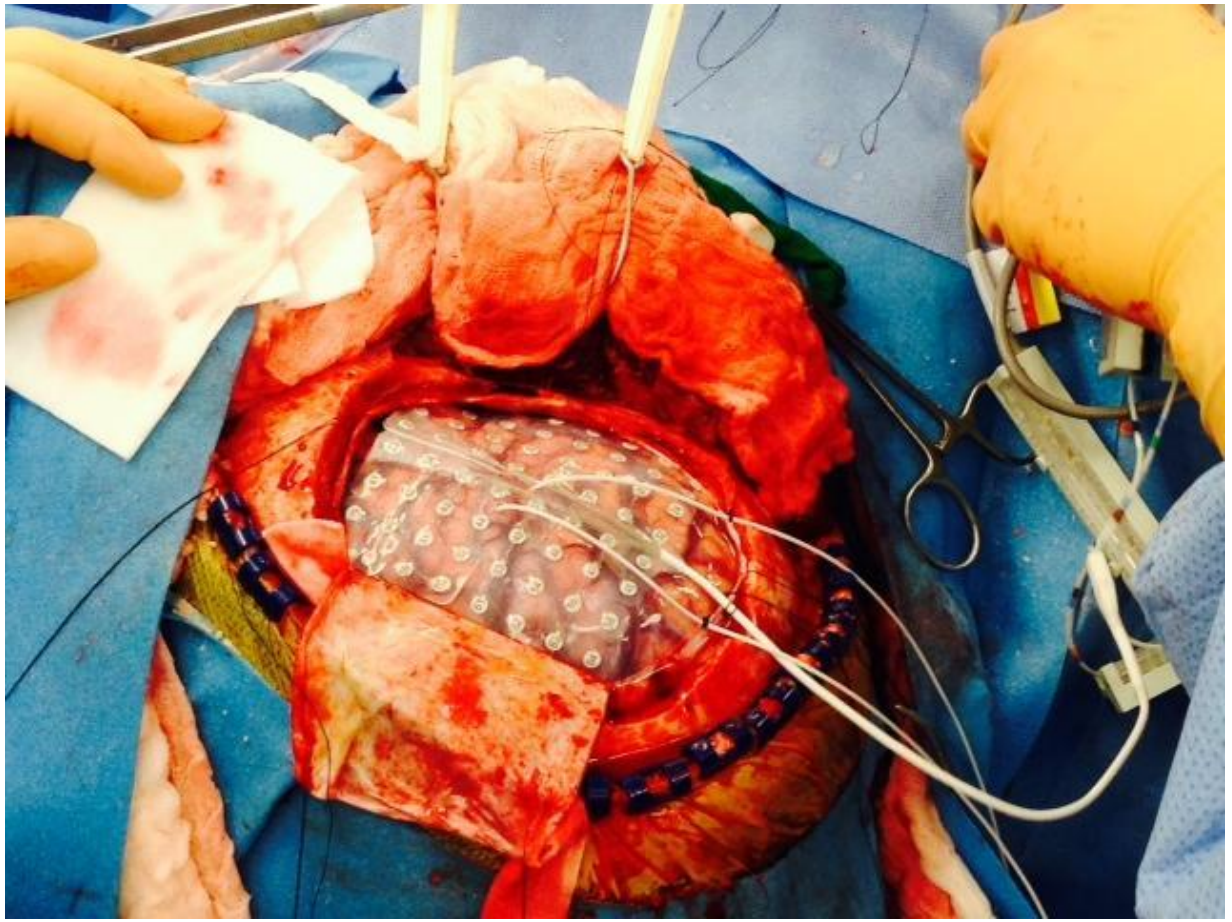


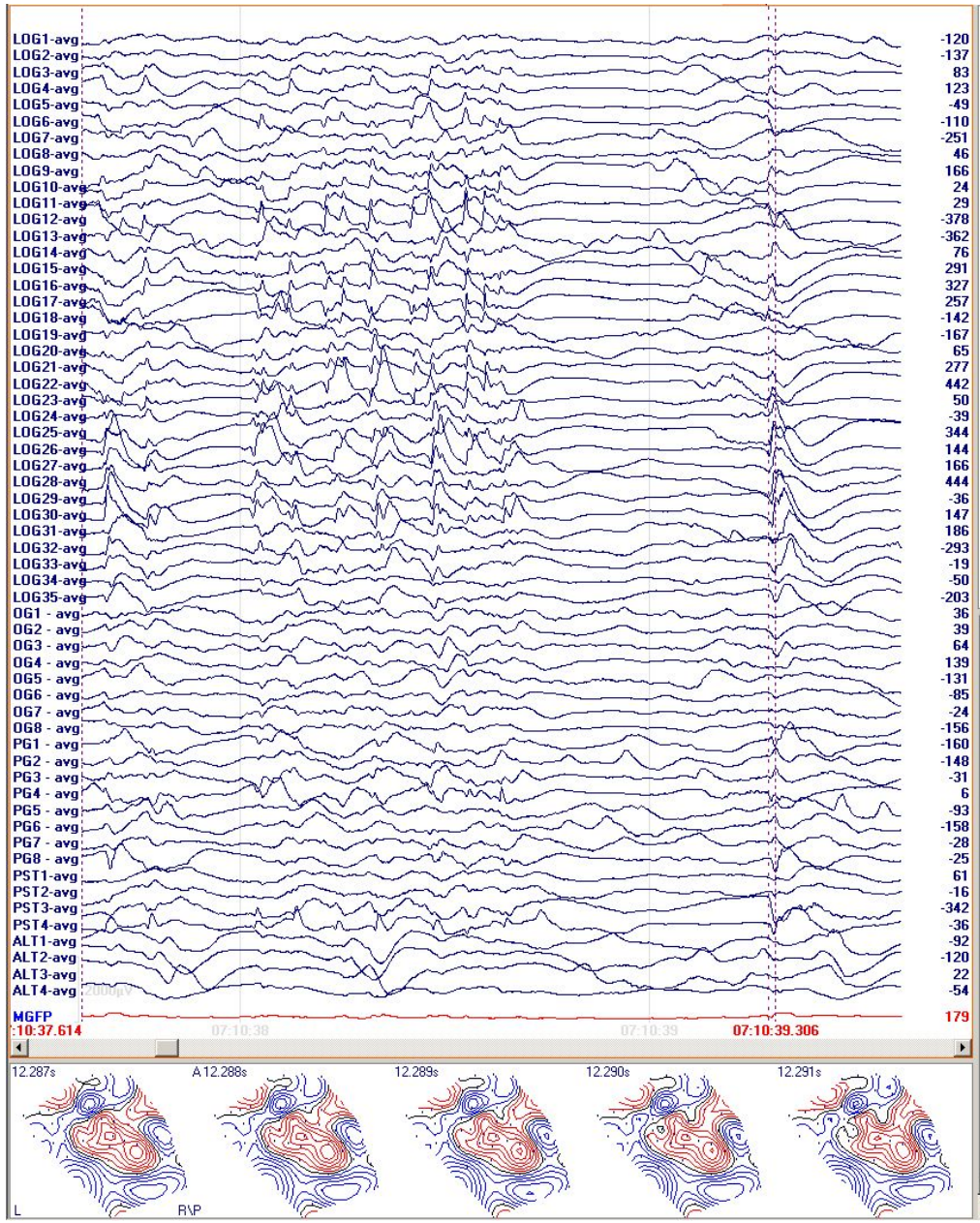


Invasive Monitoring (Phase II)

- Non-concordant noninvasive workup
  - More data needed prior to irreversible intervention
- Multiple ways to acquire
  - Grids, strips, depth electrodes, SEEG techniques
- Requires surgery to place or remove

Subdural Grid Electrodes

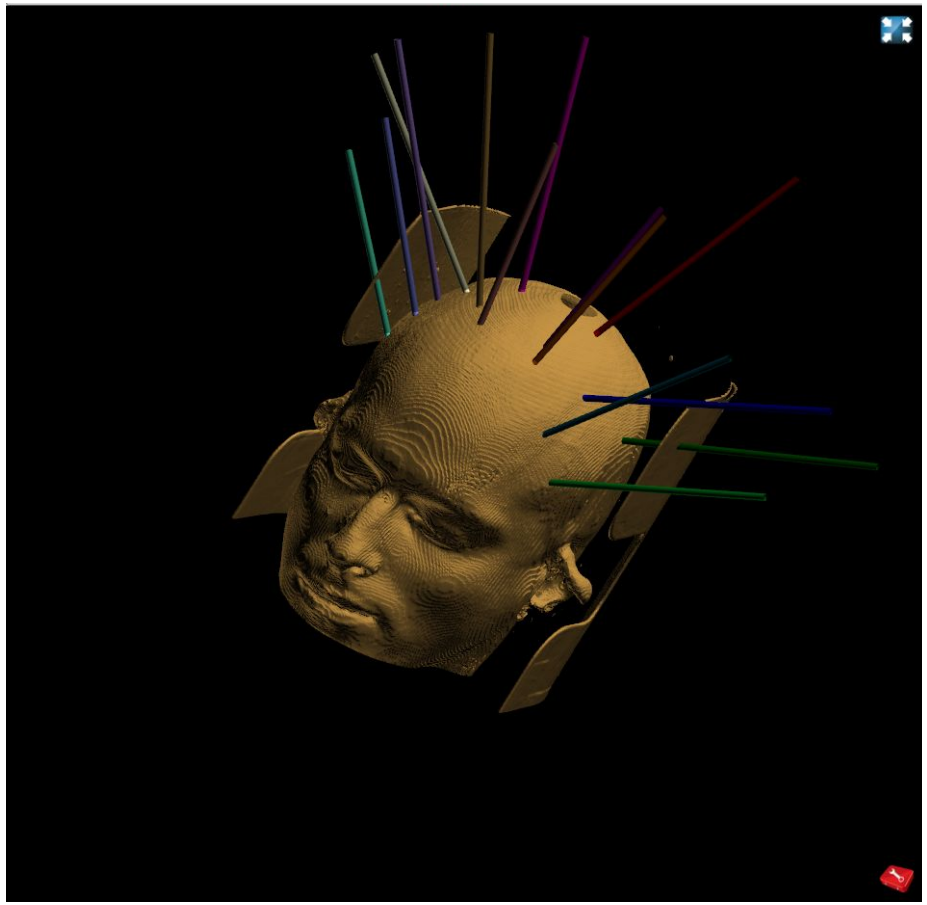


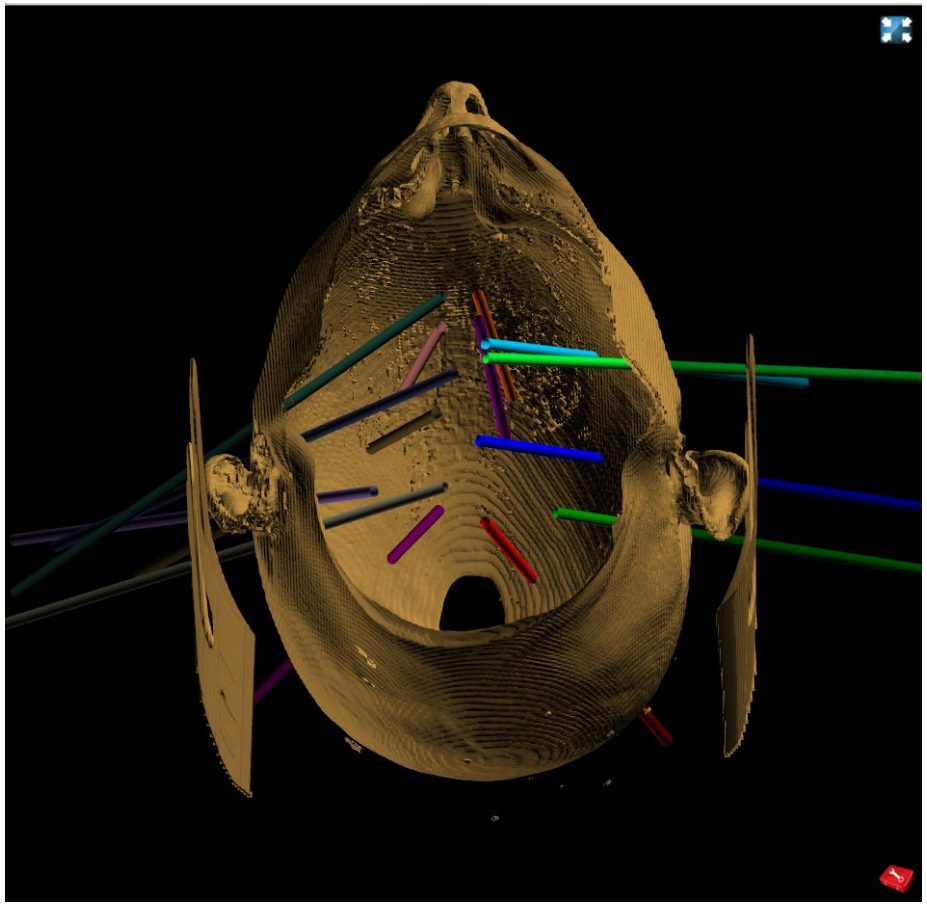


Stereo EEG (SEEG) Electrodes

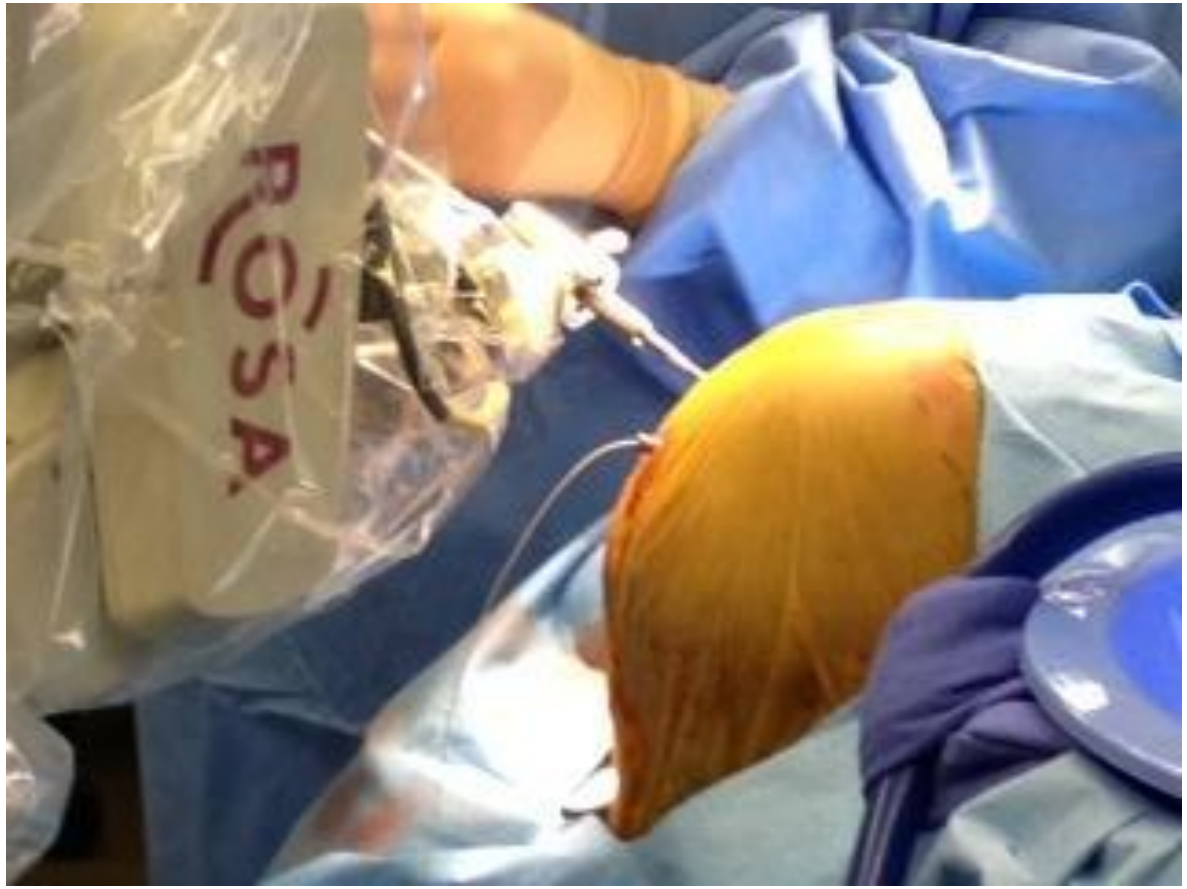
- Invasive monitoring based on placement of numerous needle-like intracranial electrodes
- Different philosophy of investigation than surface (grid) recording
- Can sample from both hemispheres, multiple lobes, deep structures

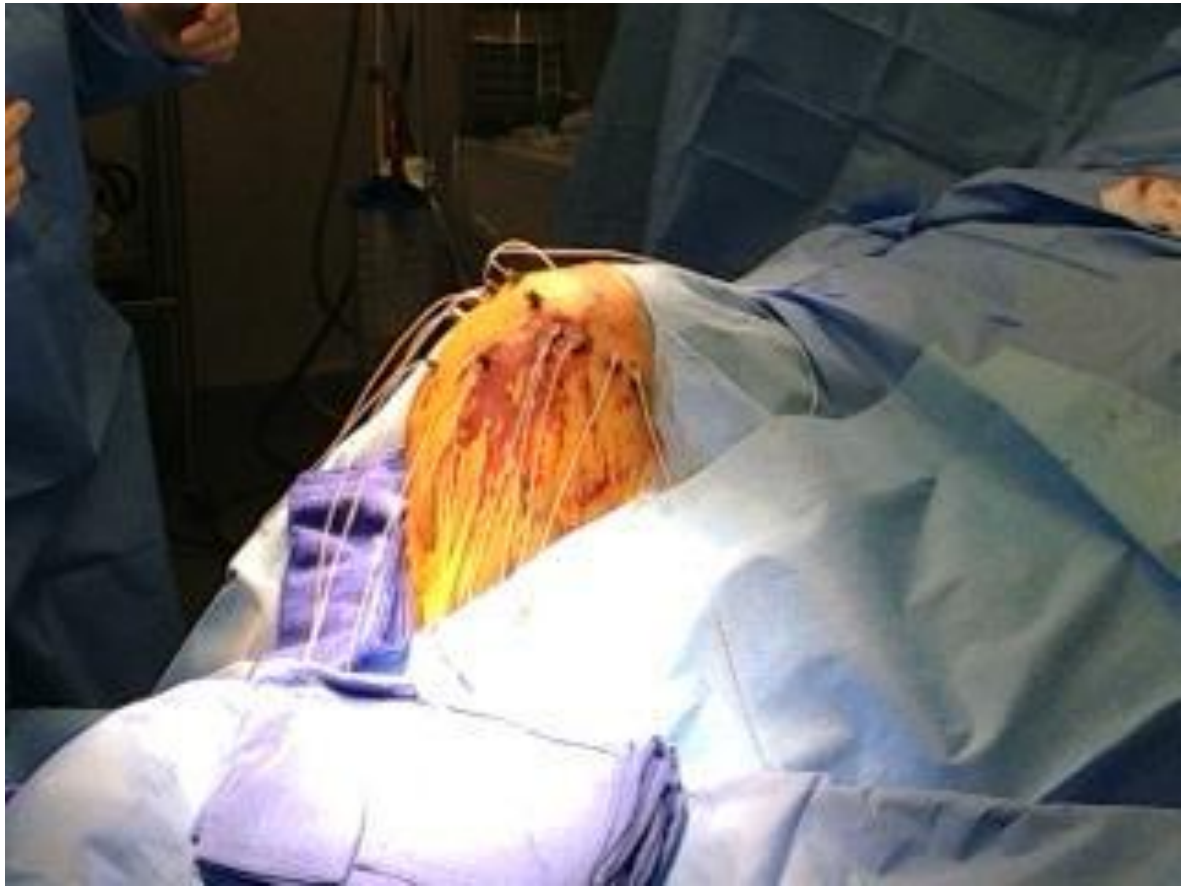
SEEG Electrodes





SEEG Electrodes

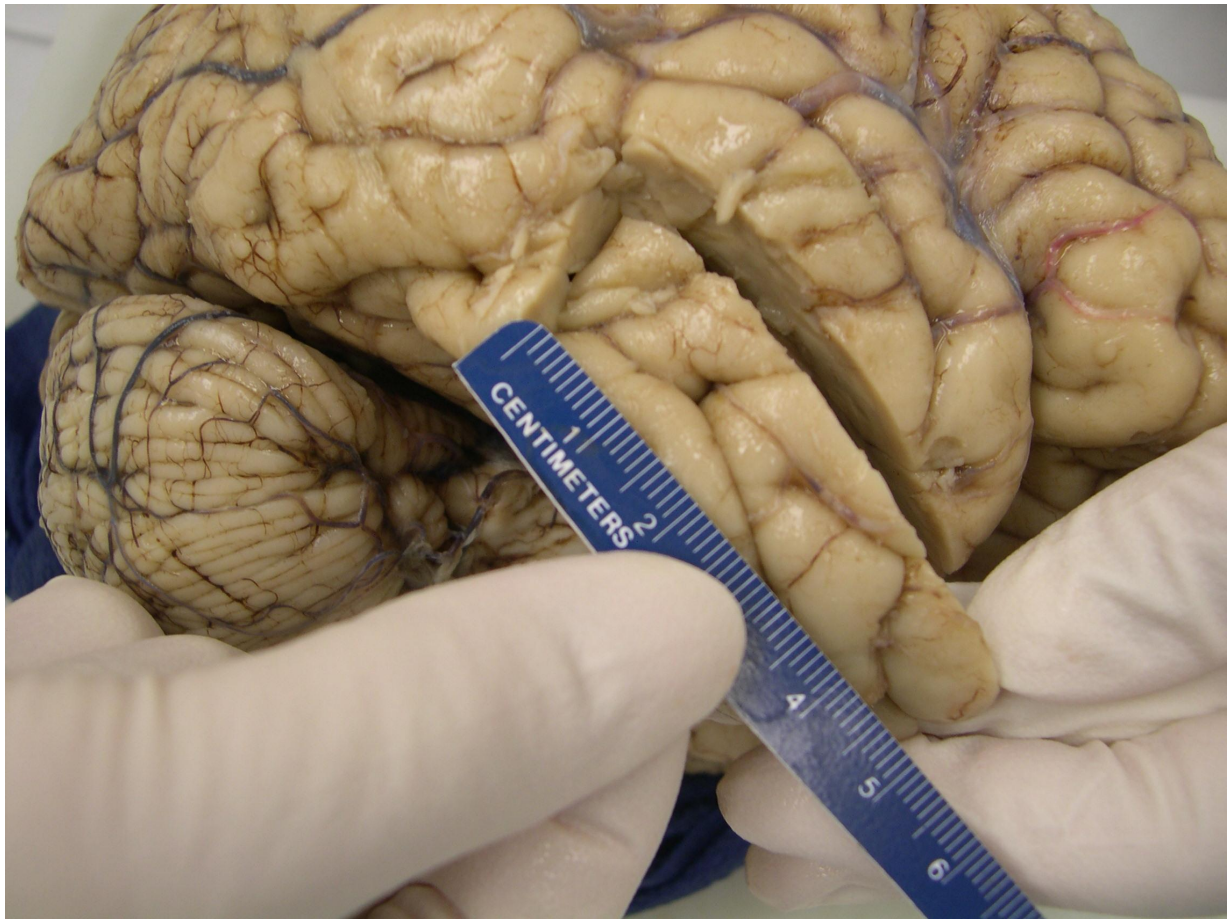




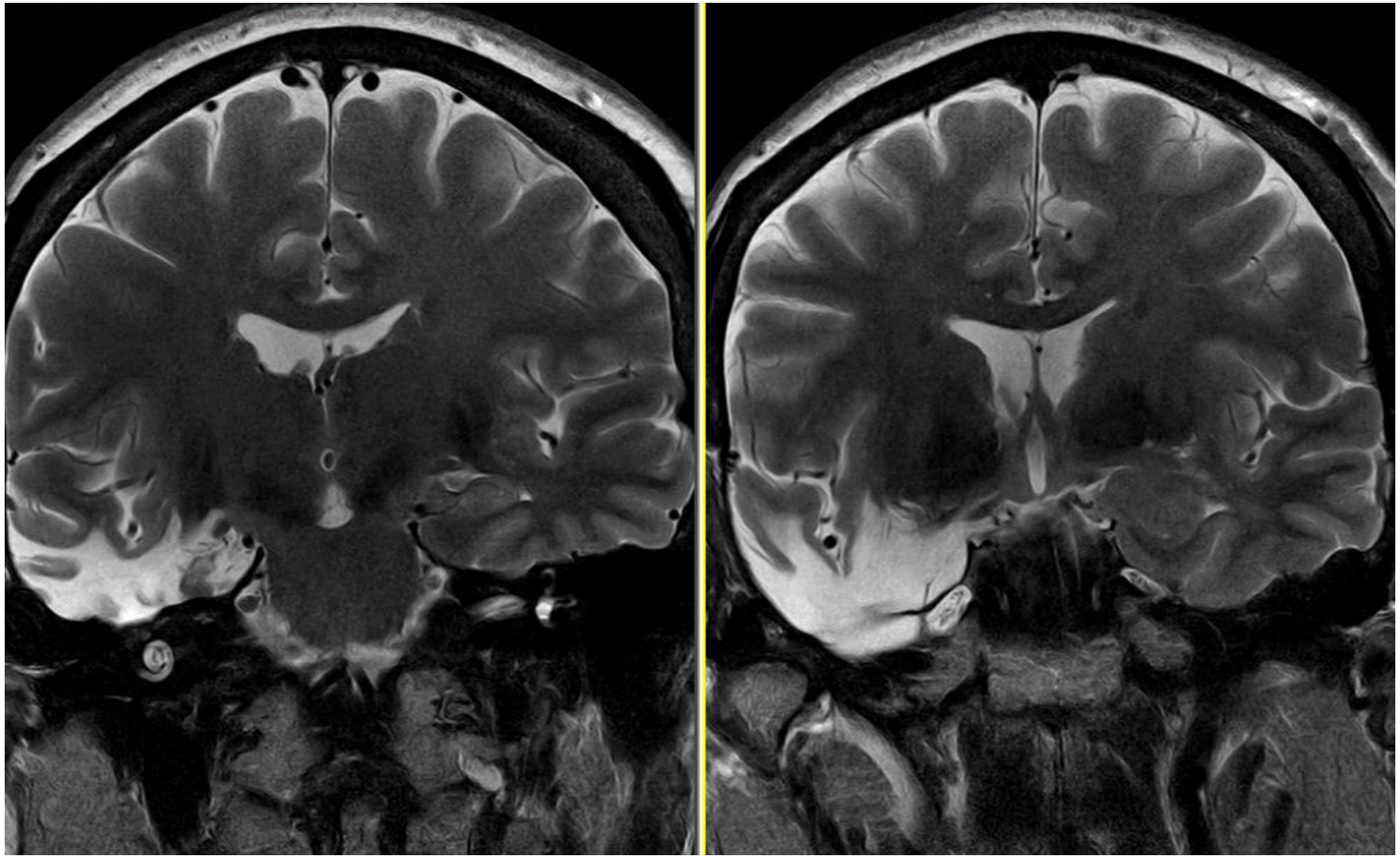
Epilepsy Multidisciplinary Conference

- Review all noninvasive and invasive tests
- Determine which type of surgical intervention is appropriate or if patient remains on medical therapy
  - Resection
    - Open resection
    - Laser interstitial thermal therapy (LITT)
  - Neuromodulation
    - Responsive neurostimulation (RNS)
    - Deep brain stimulation (DBS)
    - Vagus nerve stimulation (VNS)
  - Disconnection
    - Corpus callosotomy
    - Multiple subpial transections (MST)

Surgical open resection



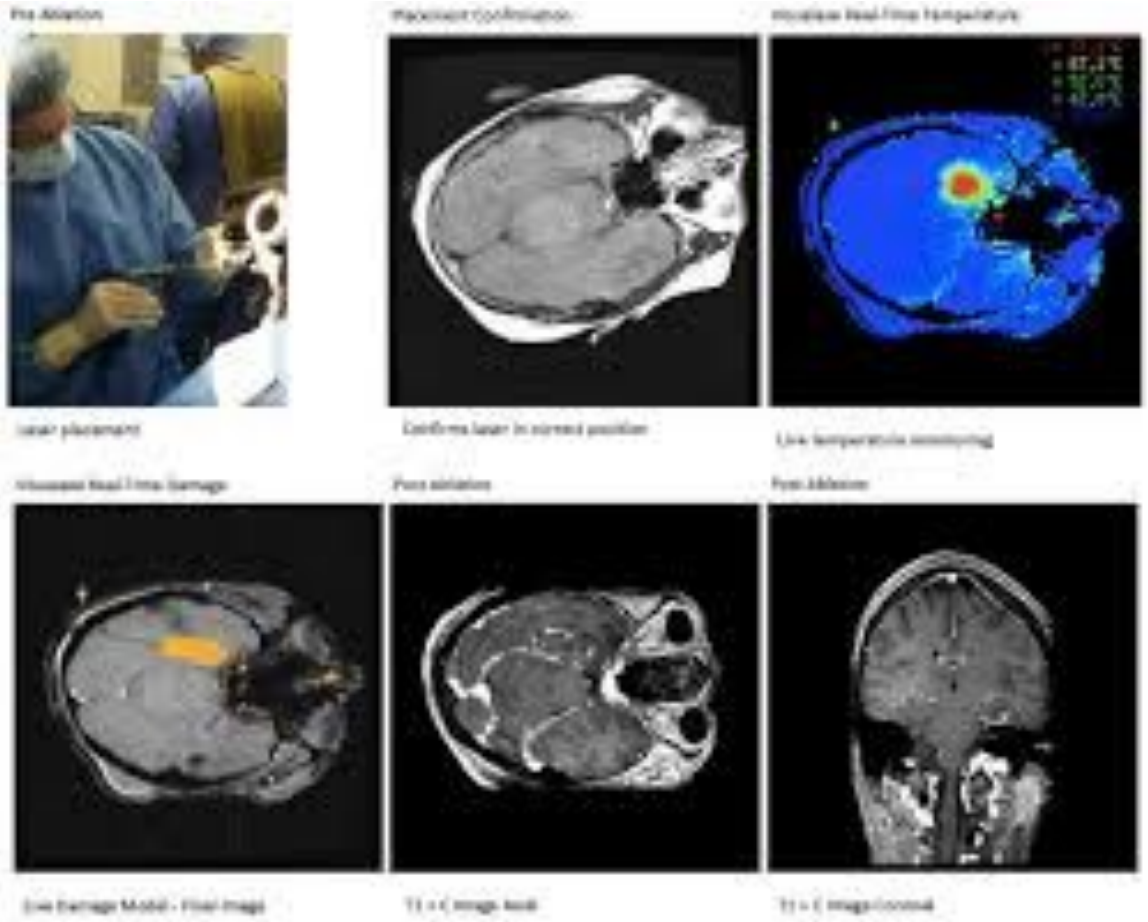
Surgical open resection



Laser ablation

- Laser interstitial thermal therapy (1980's)
- Laser energy delivered via implanted optical fibers. Photons thru tissue lead to local heating and thermocoagulative necrosis and devascularization
- Advances: MRI thermal imaging to monitor real time tissue heating, better control of heating and delivery
- Requires stereotaxy, OR and MRI suite usage
- Seizure responses seen immediately

Laser ablation

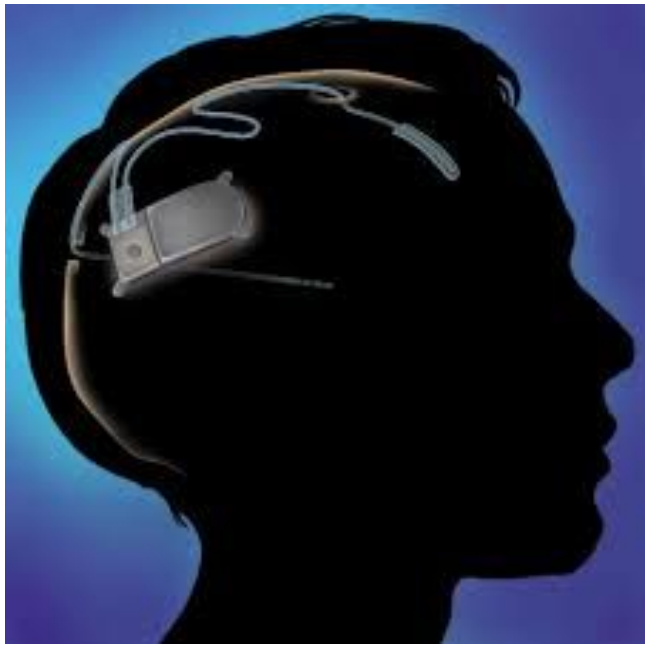


Neuromodulation

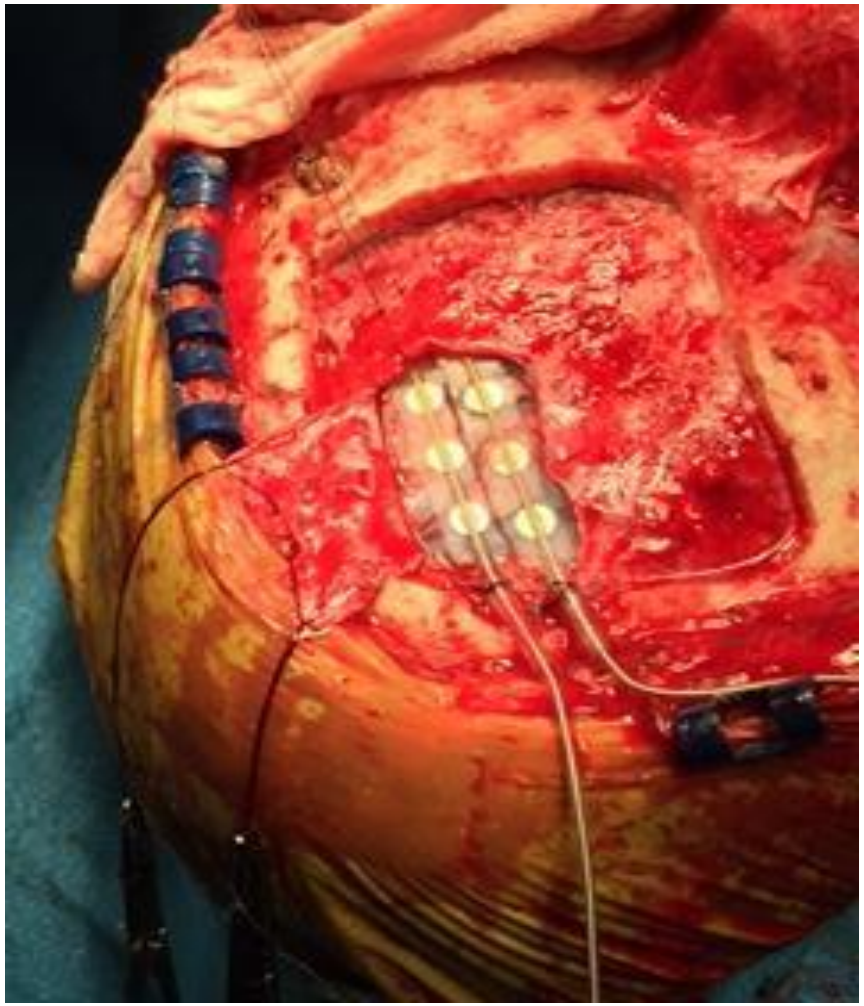
- Responsive neurostimulation (RNS)
- Deep brain stimulation (DBS)
- Vagus nerve stimulation (VNS)

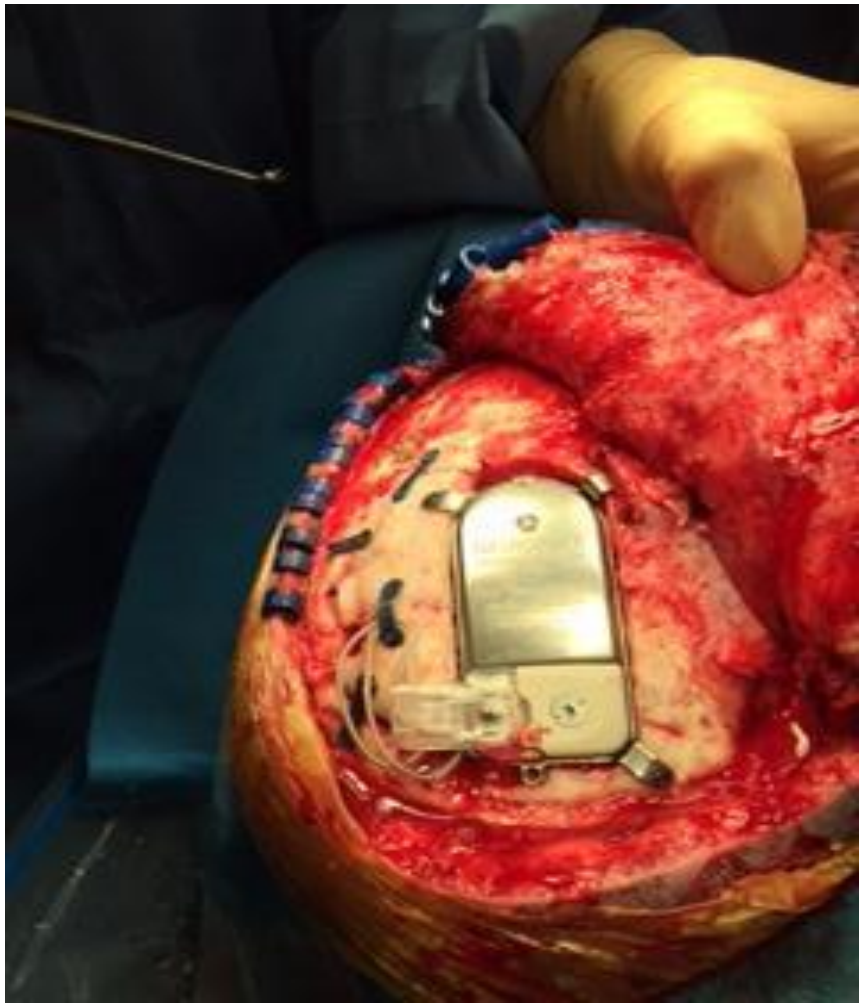
RNS

- Utilizes strip and/or depth electrodes
- Requires localization—helpful when seizure focus is on eloquent cortex
- 40-50% seizure reduction

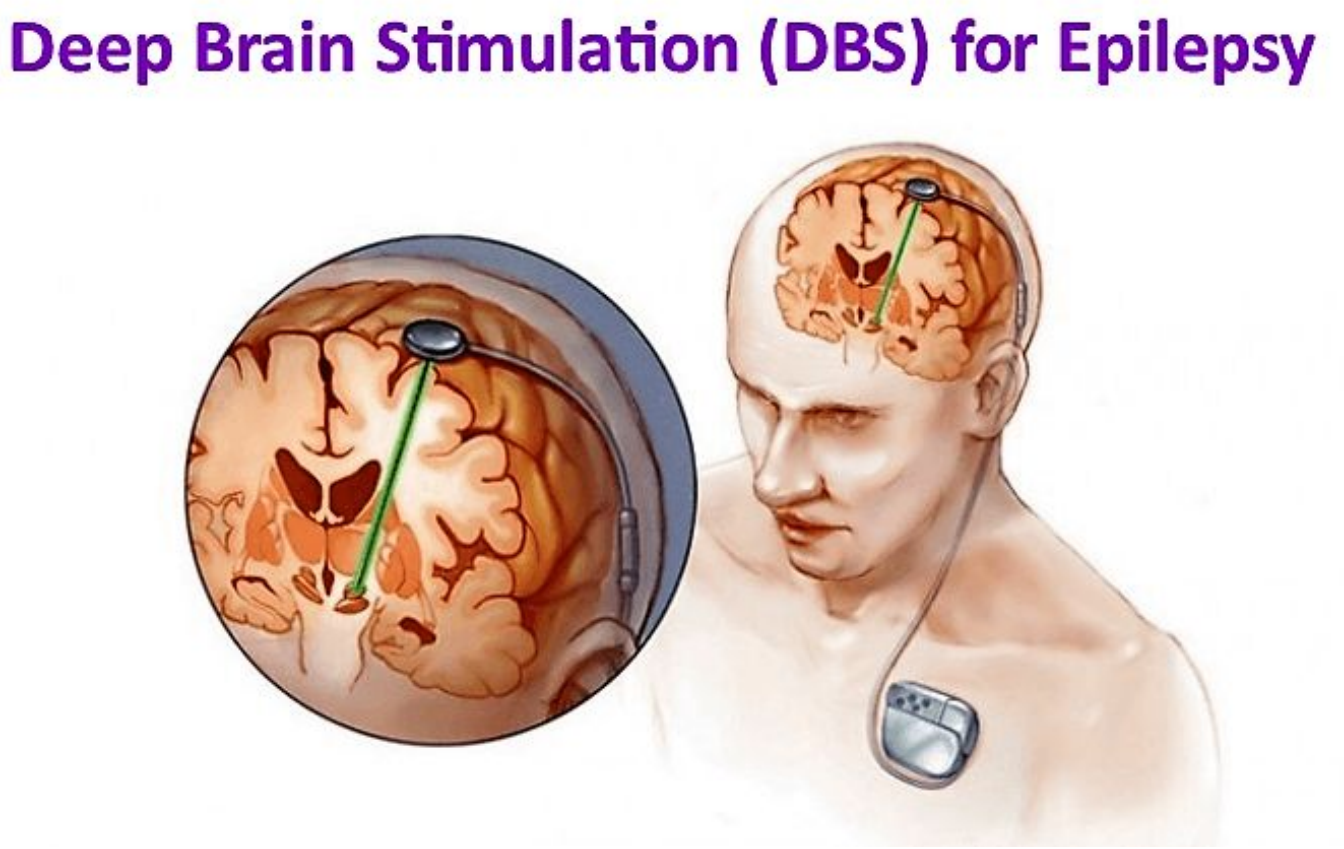


RNS





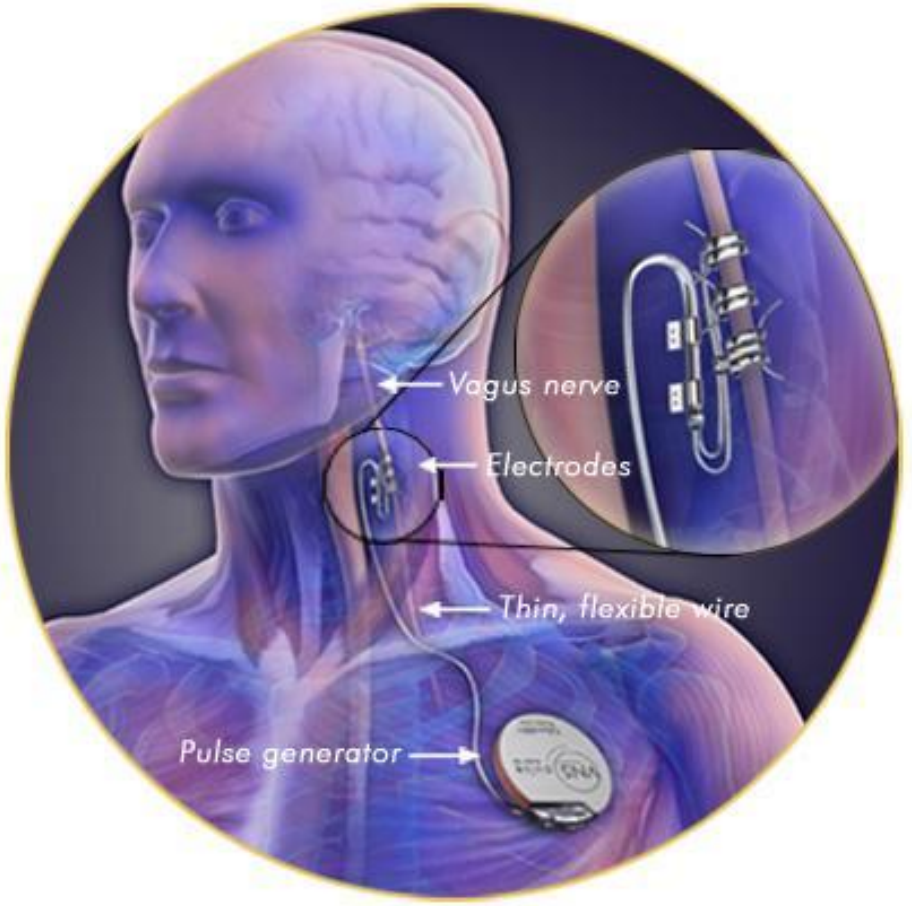
DBS



- Targets anterior nucleus of the thalamus
- 40% reduction in seizures

VNS

- Does not require intracranial surgery
- VNS efficacy becomes optimal around the sixth month of treatment and a 50-100 % seizure frequency reduction is achieved in approximately 45-65 % of the patients.



Disconnection

- Corpus Callosotomy
  - Anterior 2/3, typically reserved for generalized epilepsy and drop attack seizures
- Subpial transection
  - Eloquent cortex

Epilepsy Case 2

- 37 yo right-handed man who reports having seizures for the past 2 years. He describes his seizures as beginning with a sense of déjà vu, followed by fumbling with his right hand, repetitive lip smacking, and unresponsiveness. Finally, he will be staring off into space with loss of awareness. Seizures will last for approximately 2 minutes and have been occurring 2-3 times per week. The patient reports he is completely unaware of his seizures. Occasionally, he will have generalized convulsive activity.

- Which procedure would benefit this patient the most?

Summary

- Over 30% of patients will be refractory to ASMs and require surgical treatments to improve seizure control
- Multiple surgical options are available to improve patients' seizure control
  - Resection surgery can significantly reduce seizure burden and in certain patients can be curative
- Patient selection is the key for optimal outcome
- Neuromodulation strategies can significantly reduce seizure frequency

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Questions?

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Thank you!