UT Southwestern Medical Center

Refractory Epilepsy

Mishu Chandra, MD

Assistant Professor, Division of Epilepsy

Associate Program Director, Neurology

Course Director, Clinician Educator Track

UT Southwestern Medical Center

Conflict of Interest

- I have no conflict of interest

Learning Objectives

- Diagnosing refractory epilepsy
- Recognizing factors associated with higher risk of refractory epilepsy
- Recognizing syndromes and etiologies associated with refractory epilepsy
- **Evaluating appropriate diagnostic tools**
- **Determining appropriate treatment pathways**

Terminology

Refractory Epilepsy

Intractable Epilepsy

Drug-Resistant

Uncontrolled

Incidence and Prevalence

- Prevalence of epilepsy: 5-8 cases per 1,000 per people
- Incidence of epilepsy: 50-100 cases per 100,000 per year

About 30-40% of patients with epilepsy are intractable.

Definition

International League Against Epilepsy proposed a working definition of *refractory seizures:*

"the persistence of seizures after adequate trials of two tolerated and appropriately chosen and used ASM schedules."

Definition

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Epilepsia™

SPECIAL REPORT

Revisiting the concept of drug-resistant epilepsy: A TASK1 report of the ILAE/AES Joint Translational Task Force

Stéphane Auvin[1,2,3] | Aristea S. Galanopoulou[4] | Solomon L. Moshé[4,5] | Heidrun Potschka[6] | Luisa Rocha[7] | Matthew C. Walker[8] | on behalf of the TASK1 workgroup on drug-resistant epilepsy of the ILAE/AES Joint Translational Task Force

[1]Institut Universitaire de France, Paris, France

[2]Paediatric Neurology, Assistance Publique – Hôpitaux de Paris, EpiCARE ERN Member, Robert-Debré Hospital, Paris, France

[3]University Paris-Cité, Paris, France

[4]Saul R. Korey Department of Neurology, Isabelle Rapin Division of Child Neurology, Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, and Montefiore/Einstein Epilepsy Center, Bronx, New York, USA

[5]Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York, USA

[6]Institute of Pharmacology, Toxicology, and Pharmacy, Ludwig-Maximilians-University (LMU), Munich, Germany

[7]Pharmacobiology Department, Center for Research and Advanced Studies (CINVESTAV), Mexico City, Mexico

[8]Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK

Definitions

BOX 1 Definitions

Treatment failure	Treatments have no effect on seizures. This can be due to drug resistance, toxicity, pharmacokinetics/pharmacodynamics, noncompliance. Treatment failure is not necessarily drug resistance.
Resistance to a treatment	Lack or reduction in efficacy of a treatment to control seizures, at treatment schedules that would be expected to have the desired biologic effect. *Limitations*: Effective treatment schedules are usually deduced by population responses and corresponding peripheral blood levels, as target exposure and modification cannot be easily documented in vivo, particularly in humans. Peripheral blood levels do not, however, reflect accurately the presence or effects of a treatment in the targeted brain regions of an individual.
Drug resistant epilepsy (DRE)	"Failure of adequate trials of two tolerated and appropriately chosen and used antiseizure medication (ASM) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[4] It is assumed that DRE mechanisms may be independent of a specific treatment's mechanism of action and extend across various medical treatments. *Limitations*: An individual may still respond to a different treatment, albeit the probability is significantly lower. Partial seizure response may still be a welcome effect for certain individuals or guide the design of more effective treatments.
Tolerance	A subject's diminished response to a treatment after repeated exposure to the treatment, which occurs when the body adapts to the treatment.
Therapeutic levels	Levels of a treatment that can affect the desired biologic effect at the target organ. *Limitations*: Brain levels cannot usually be measured in live subjects. Therapeutic blood levels may not always reflect the levels of a treatment at the target brain region that generates seizures; lack of effect may be also due to inability to reach and modify the function of the target organ or brain region.

Predictors for Intractable Epilepsy

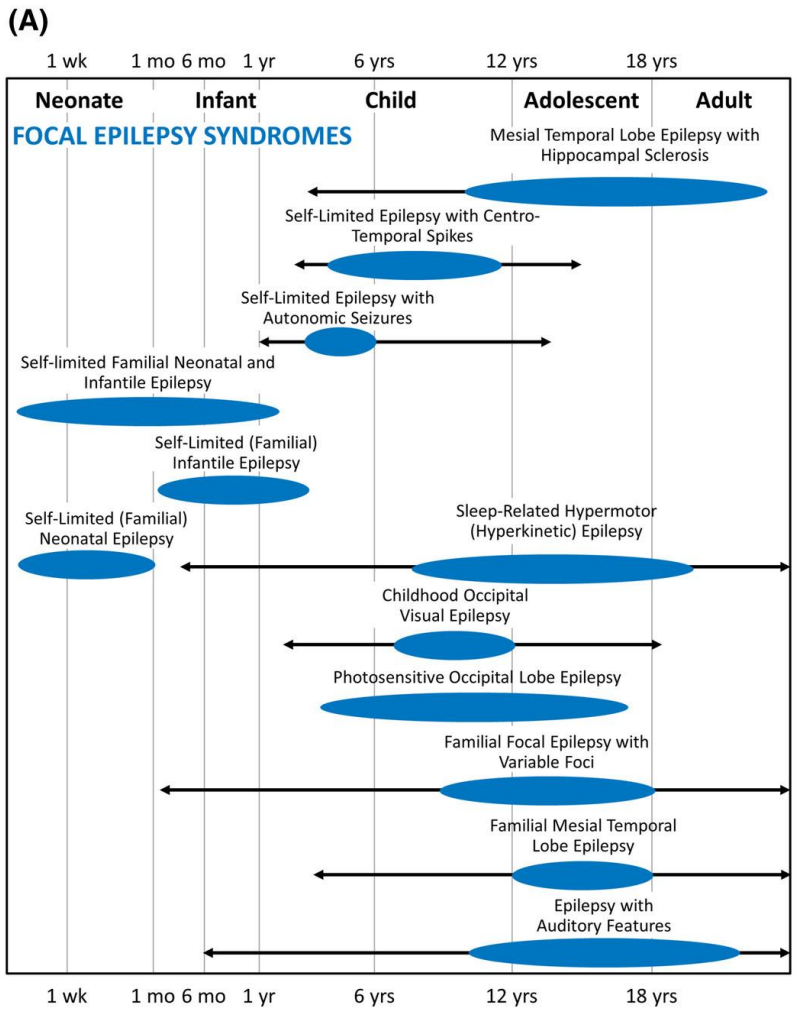
TABLE 1 Factors proposed in the literature to increase risk for DRE in certain human epilepsies.

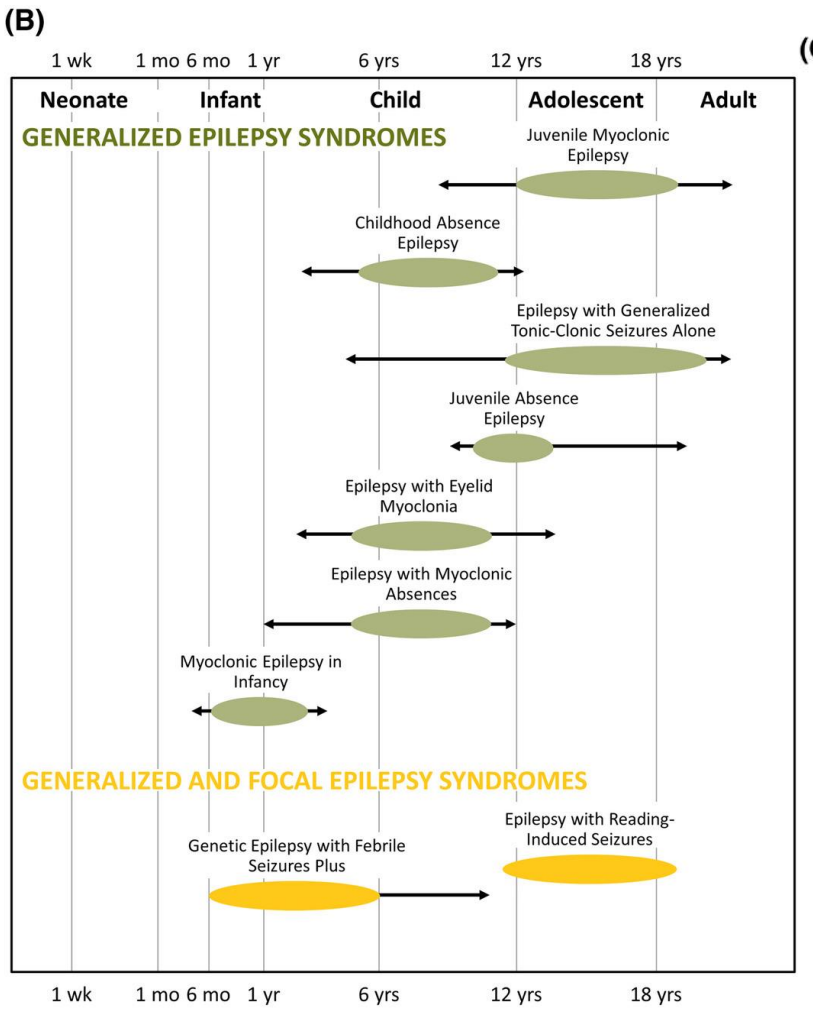
DRE predictors	References
Clinical	
Younger age at epilepsy onset	1,5–11
Short latency to epilepsy development (i.e., after stroke)	12
Neurodevelopmental abnormalities	1,5,7
Neuropsychiatric comorbidities	1,6,7,13–15
Recreational drug use	13
Focal seizure related comorbidities, e.g., migraine	1
History of febrile seizures or complex febrile seizures	1,5–7,13
Seizure types, e.g., focal, infantile and epileptic spasms, initial myoclonic seizures	5,8,15
Focal or mixed (vs generalized)	1,11
Multiple seizure types	1,5,6,16,17
Status epilepticus at epilepsy onset	18
Status epilepticus	5–7,10,11
Photoparoxysmal response, seizure triggers	1
Seizure clusters	1
History of CAE progressing to JME	6
High seizure frequencies	5,8
High baseline seizure frequency	1
Poor response to first ASM	1,5,8
Number of previous ASMs	1
Number of seizures prior to starting ASM	13,17
Ethnicity, socioeconomic factors	1,6,19
History of catamenial epilepsy (JME, GGE)	1,6,15
Family history of epilepsy	6,13

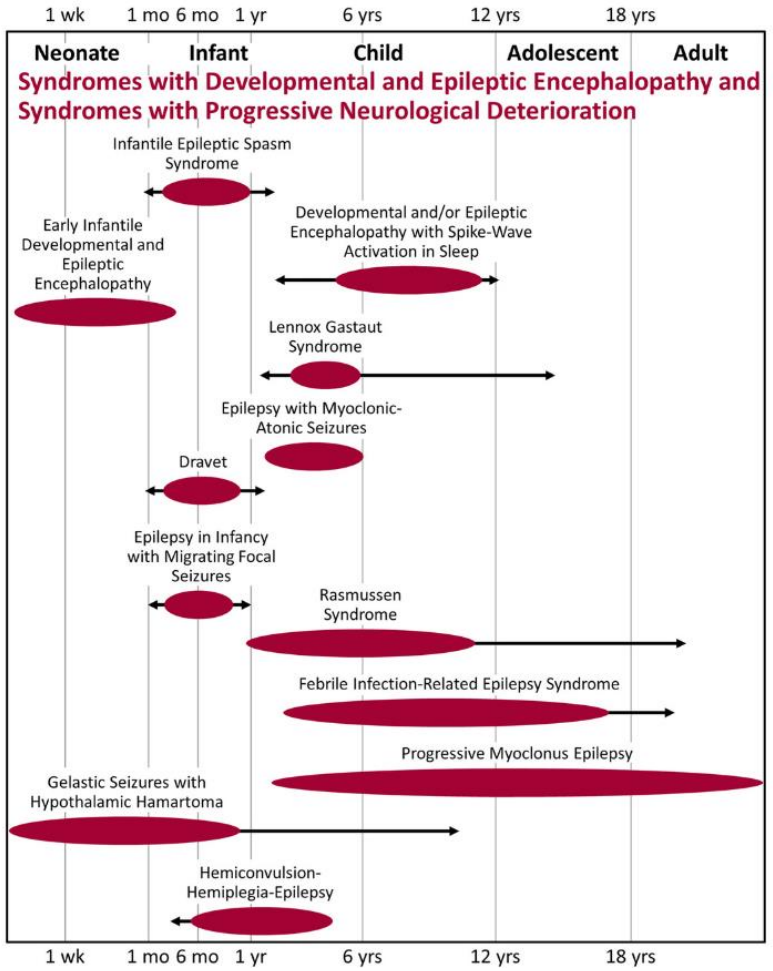
TABLE 1 (Continued)

DRE predictors	References
Genetic	
Gene variants etiologically associated with DREs (multiple, e.g., *SCN1A* variants)	20–23
Gene variants associated with drug resistance	
ABCB1, *ABCC2*, *CCL2* variants	8
$GABA_A$ receptor subunit variants conferring resistance to benzodiazepines	24
Biomarkers (protein, miRNAs)	
Plasma, serum or CSF biomarkers: multiple, validation needed	Reviewed in 8
Epilepsy etiology	
Structural, metabolic, infectious	1,5,7,8,17
Traumatic brain injury	13
Intracerebral hemorrhage	18
Severe stroke	18
Neuroimaging (brain)	
MRI brain abnormalities	1,5,7
Electrophysiological	
Slow background, multifocal epileptiform EEG	5,10
Epileptiform EEG	1,11
Epileptiform focality (JME)	6
Abnormal EEG	1,7,8,10
Increased generalized spike wave discharges in sleep, generalized polyspikes (IGEs)	16

Epilepsy Syndromes







Etiology-Specific Syndromes

Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

Other Etiologies

Structural

- Malformations of cortical development
- Vascular Malformations
- Hippocampal Sclerosis
- Hypoxic-Ischemic
- Traumatic Brain Injury
- Tumors
- Porencephalic Cyst

Immune

- Anti-NMDA Receptor Encephalitis
- Voltage-Gated Potassium Channel Antibody
- GAD65 Receptor Antibody
- Steroid-Responsive Encephalopathy Associated with Thyroid Disease
- Celiac Diseases and Cerebral Calcification Syndrome

Infectious

- Meningitis
- Cerebral Malaria
- Cerebral Toxoplasmosis
- CMV
- HIV
- Neurocystericosis
- Tuberculosis
- Viral Encephalitis

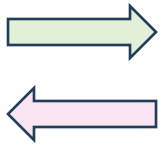
Diagnostic Pathway: Initial Steps

Initial Workup

Seizure Type, Syndromic Classification, Intractability?

- History
- Exam
- MRI Brain
- Video-EEG

Other:
EMU Evaluations
Genetic Testing
Autoimmune
Metabolic Testing



Treatment

Anti-seizure Medications:

- **Brivaracetam**
- Carbamazepine
- **Cannabidiol- LGS, Dravet, TSC**
- **Clobazam - LGS**
- Clonazepam
- **Cenobamate- focal seizures**
- Diazepam
- Ethosuximide
- Felbamate
- **Fenfluramine- LGS, Dravet**
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- **Perampanel**
- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- **Rufinamide- LGS**
- **Retigabine**
- Valproic Acid
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

Etiology-Specific Treatment:

- Pryridoxine- PD-EE, PNPO-DEE
- **Everolimus- TSC**
- **Stripentol- Dravet**
- **CDKL5- ganaxalone**

Immune Therapies:

- IVIG, Steroids, PLEX
- Anankinra, Tocilizumab, Rituximab

Dietary Considerations:

- Ketogenic Diet (GLUT- DS)
- Modified Atkins Diet
- Low Glycemic Index

Genetic Counseling

Pre-Surgical Evaluation

- **What is the average delay in referral for seizure in the U.S.?**

22 years!

Pre-Surgical Evaluation

Phase 1 Evaluation

- Phase 1 EMU Admission
- Outpatient Testing:
  - **Positron Emission Tomography (PET)**
  - **Single- Photon Emission Computed Tomography (SPECT)**
  - Magnetoencephalography (MEG)
  - Functional Magnetic Resonance Imaging (fMRI)
  - Wada
  - Neuropsychology Testing
  - Genetics
  - Automimmune Testing

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Pre-Surgical Conference

Do we need more information?

Yes

- Intracranial EEG/Stereoelectroenecphalography (SEEG)
- Subdural Grid
- Additional Diagnostics

No

Destructive Surgery:

- Lobectomy (temporal lobectomy → 70-80% Seizure Freedom)
- Lesionectomy
- Laser Interstitial Thermal Therapy (LITT)
- Corpus Callosotomy
- [Functional] Hemispherectomy
- Multiple Subpial Transections

Neuromodulation:

- Vasal Nerve Stimulation
- Responsive Neurostimulation (RNS)
- Deep Brain Stimulation (DBS)

Case Study:

35 yr old right-handed woman with seizure onset at 18 years of age

Etiology & Risk Factors:
Premature Birth at 24 weeks
Prolonged NICU Stay (10 weeks)

Semiology & Frequency:
•FAS (focal aware seizures): deja vu, occurs several times per month
•FIAS (focal impaired awareness seizures): starts with FAS, progresses to staring and unresponsiveness.
Occurs 3-4 times per week
•FTBTCS (focal to bilateral tonic clonic seizures): FIAS can rarely progress to full body convulsions.
Occurs about once per year

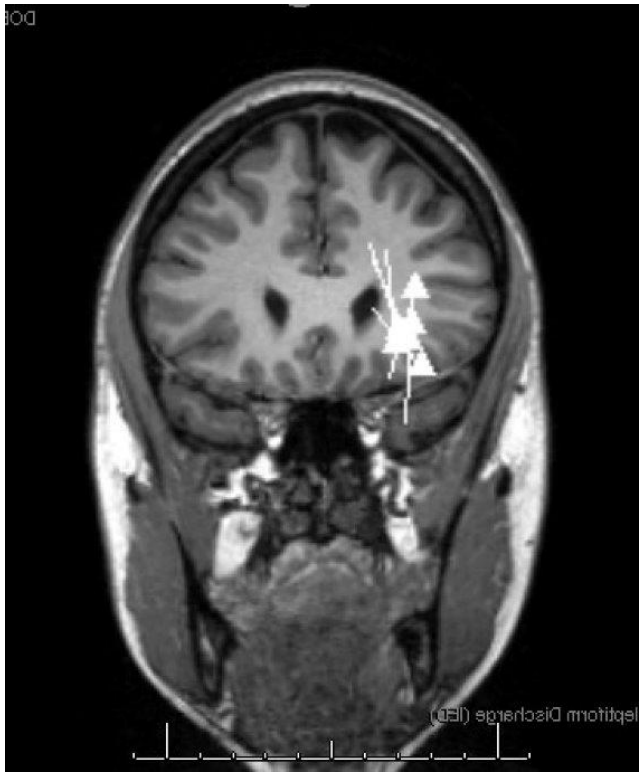
•Past Medication Trials: Levetiracetam, Lamotrigine, Lacosamide
•Works at a financial executive

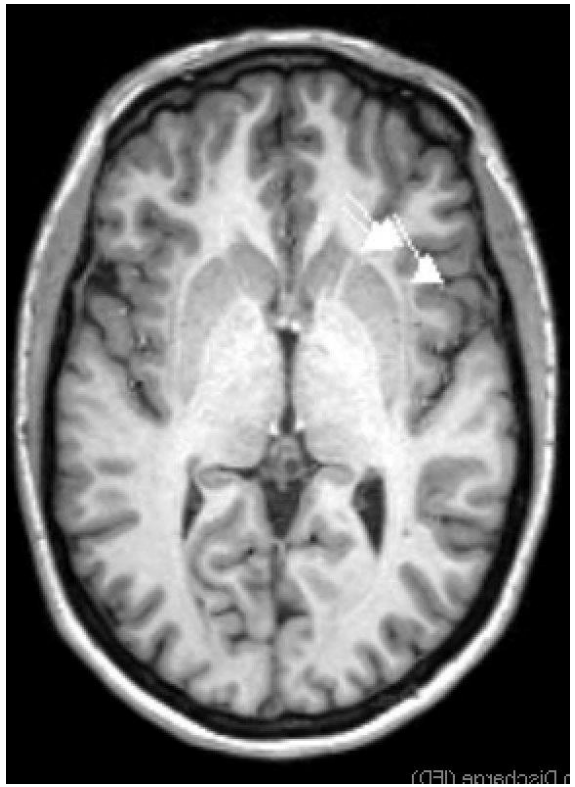
Case Study:

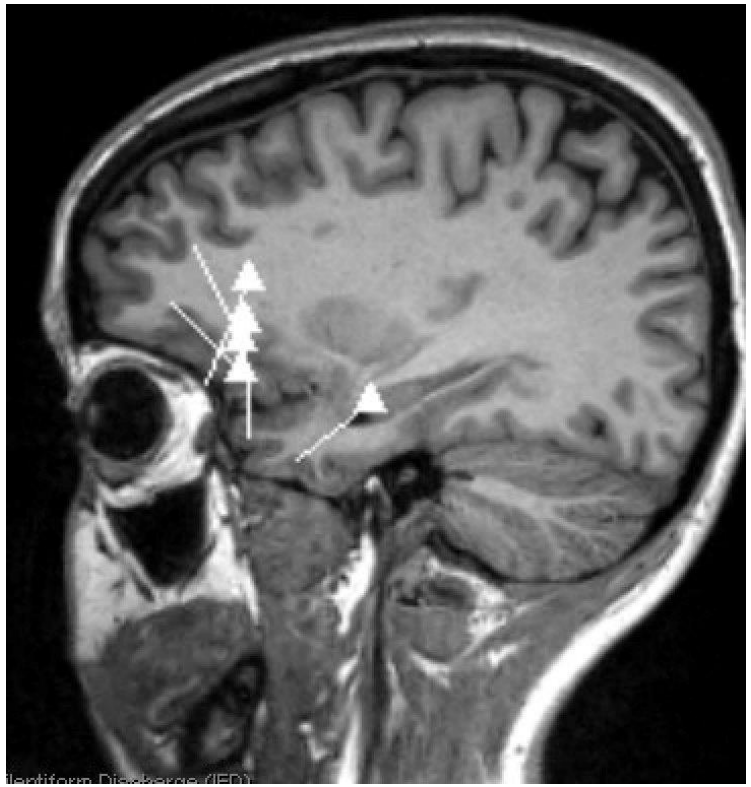
Presurgical Summary

ID: 35 y/o RHF with seizure onset at age 18 yrs
Risk factors: premature birth
Semiology: déjà vu => back out, oral automatisms => +/- FTBTC
Ictal EEG: non-lateralizing onset, organized right temporal after 5-9 seconds of the onset
Interictal EEG: right temporal sharp waves
MRI: right amygdala edema post ictal, non-lesional
PET: bilateral right> left temporal hypometabolism
SPECT: n/a
MEG: tight cluster in the right orbitofrontal and inferior frontal gyrus with stable orientation
fMRI: language is left hemispheric dominant
Neuropsych: non-lateralizing
Wada: n/a
Autoimmune tests: negative
Genetics: n/a
Previous neurosurgery: n/a

MEG







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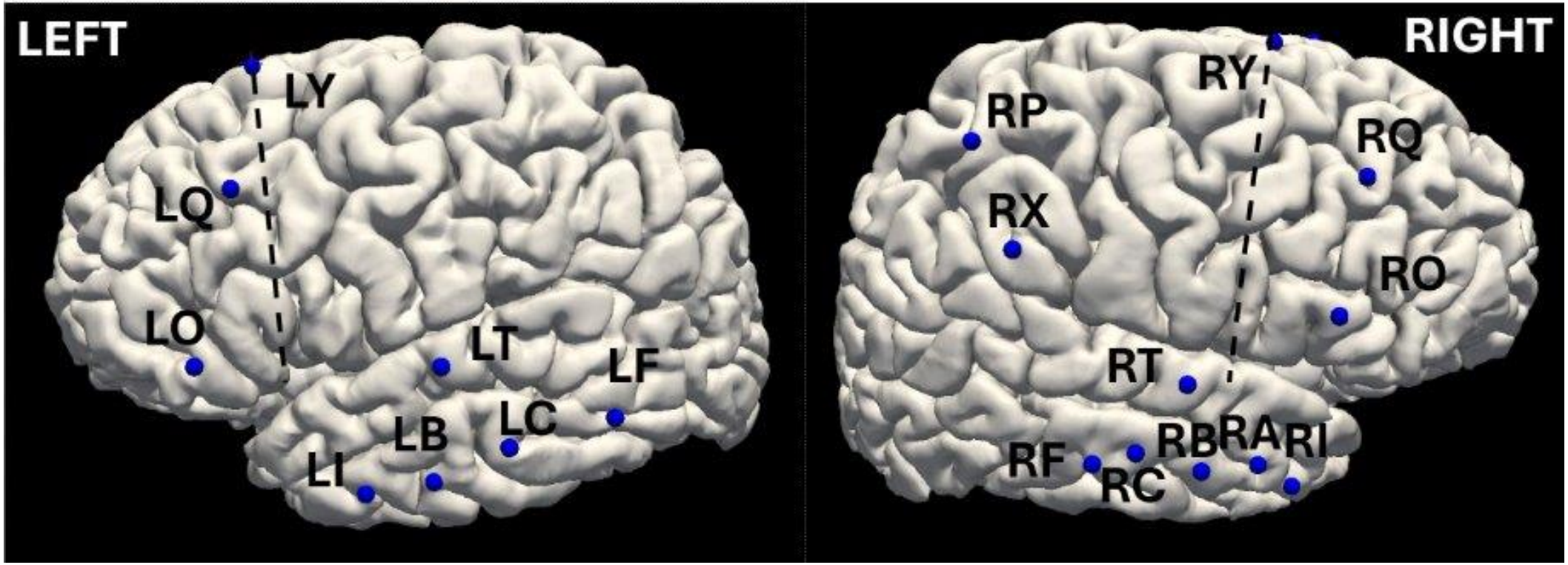
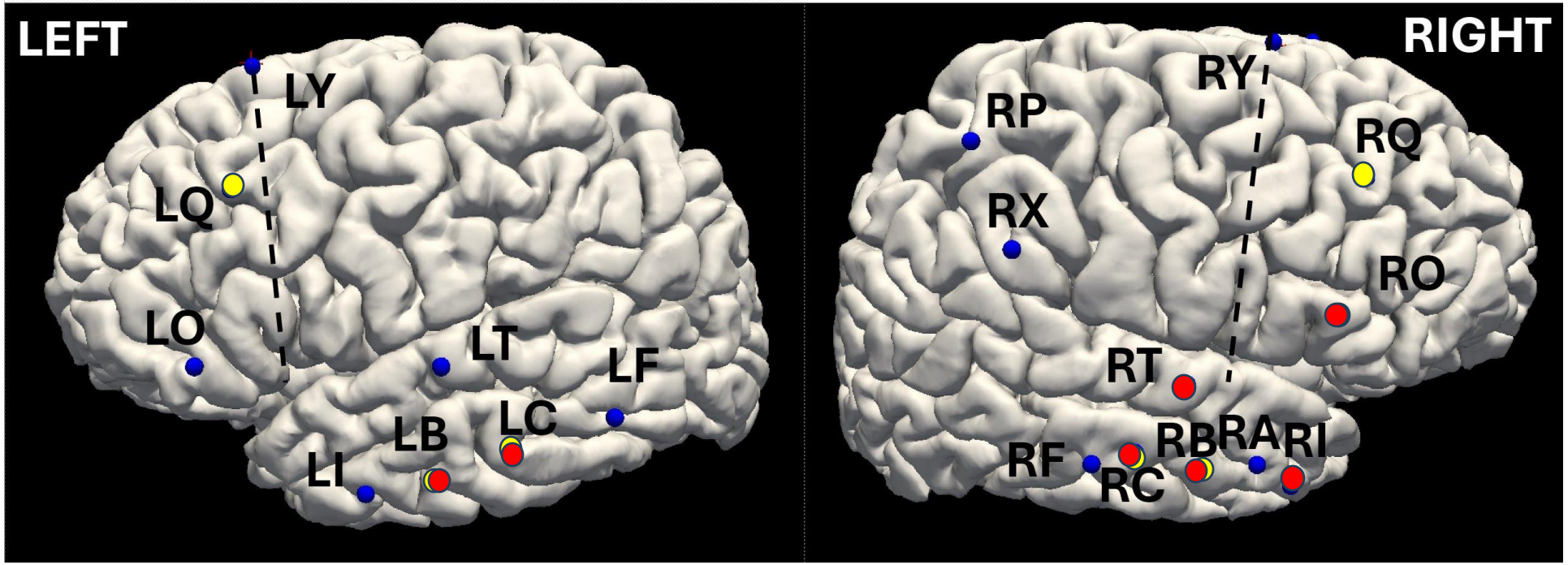


Ictal & Interictal Map



Interictal: ●

Spikes- Right Hippocampus (RB 1-2, RC 1-2)
Spikes & PFA- Right Orbitofrontal (RO 1-3, 3-7)
Spikes- Right Anterior Cingulate (RQ1-2)

Spikes- Left Hippocampus (LB 1-2, LC 1-2)
Spikes- Left Anterior Cingulate (LQ1-2)

Ictal: ●

Left Hippocampus (LB1-2, LC1-2), **Subclinical vs FIAS, 6 recorded**

Right Hippocampus (RB1-2, RC1-2), **FIAS, 1 recorded**

Right Orbitofrontal- Medial Orbital/Gyrus Rectus (RO1-3, 3-7), **FIAS, 1 recorded**

Right Neocortical & Mesial Temporal- (STG/STS/MTG, Temporal Operculum)- RB 1-2, 7-9/RC 1-2, 6-9, RI 1-2, 6-9, RT 2-4, **1 subclinical and 1 FIAS**

Discussion & Recommendations:

Seizures captured from multifocal onsets including the Left Hippocampus, Right Hippocampus, Right Orbitofrontal, and Right Mesial and Neocortical Temporal regions.

Three different options were discussed:

1.) RNS and implant three electrodes (Right Hippocampus, Left Hippocampus, and Right Orbitofrontal), and record over the bilateral hippocampi (first 6 months), then over the Right Orbitofrontal (next 6 months) to assess which foci may be responsible for her clinical seizures.

2.) Resect the Right Orbitofrontal region first, and then implant RNS electrodes to the bilateral temporal region (anterior), given robust MEG dipoles in the former.

3.) DBS (anterior) would also be offered to patient if preferred.

Overall, given large bilateral mesial temporal and extratemporal network, the patient should be counseled on expectations for seizure reduction.

Thank you

- Questions?

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