NEW TREATMENTS FOR REFRACTORY EPILEPSY

Zeenat Jaisani, MD
Assistant Professor
UAB Neurology/Epilepsy

DISCLOSURE

- Nothing to disclose, no conflict of interest

OVERVIEW

- Epilepsy: classification, types, etiology
- Response to AEDs
- Epilepsy surgery; when to consider
- Minimally invasive surgery LITT (Laser Interstitial Thermal Therapy)
- Palliative approach to TRE: RNS, VNS, DBS

SEIZURE AND EPILEPSY

- A seizure is a transient disruption of brain function due to abnormal and excessive electrical discharges in brain cells.
- Epilepsy: when two or more unprovoked seizures have occurred (24 hour apart).

EPILEPSY EPIDEMIOLOGY

- People who live a normal lifespan have a 5% to 10% risk of experiencing at least one seizure, and one-third of these will develop epilepsy.
- Incidence 30-60 per 100,000 per year
- US about 3.4 million people have epilepsy
- 40% of people with epilepsy will continue to have seizures despite adequate treatment with antiseizure drugs, and they are responsible for 80% of the cost of epilepsy.

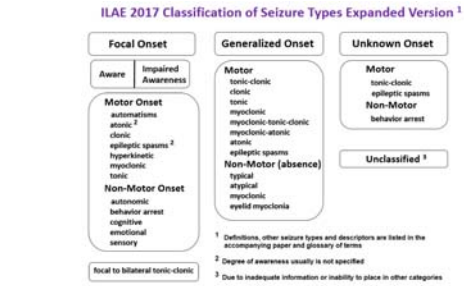
Hauser WA, Hesdorffer DC. *Epilepsy: frequency, causes and consequences.* New York: Demos;1990 :1–51
So EL. **Classifications and epidemiologic considerations of epileptic seizures and epilepsy.** *Neuroimaging Clin N Am* 1995;5:513–26

CAUSES OF EPILEPSY

- Four most common are head trauma, stroke, brain tumor, and brain infection.
- Other -drug effects or intoxication, genetics, metabolic disturbances.
- The causes may vary by age with
  - -young children: genetic, congenital malformations or metabolic disturbances
  - -young adults: trauma and tumors
  - -older adults: stroke

The cause is "unknown" in 60 to 70% of cases (i.e. idiopathic / cryptogenic).

ILAE – NEW SEIZURE CLASSIFICATION



FOCAL EPILEPSY

- Temporal- most common (66%)
- Frontal- second most common (24%)
- Parietal
- Occipital
- Multi-lobar

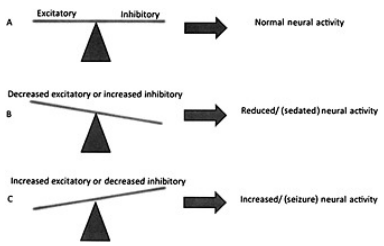
Semah, M. C. Picot, C. Adam et al., "Is the underlying cause of epilepsy a major prognostic factor for recurrence?" Neurology, vol. 51, no. 5, pp. 1256–1262, 1998.

DIAGNOSIS OF EPILEPSY

- Clinical history with clinical seizure semiology
- EEG
- Video EEG (scalp)
- Imaging

PROVOKED SEIZURE

- Metabolic derangements (hypoglycemia, hyponatremia)
- Drug related: cocaine, methamphetamine, LSD
- Alcohol withdrawal seizure
- Benzodiazepine withdrawal
- Certain medication: bupropion (Wellbutrin), TCA, neuroleptics as phenothiazine, clozapine, amphetamine, Tramadol +/- antidepressant , diphenhydramine, antibiotics as imipenem, metronidazole, isoniazid.



Treatment of drug-induced seizures Br J Clin Pharmacol. 2016 Mar; 81(3): 412–419 Hsien-Yi Chen, Timothy E. Albertson, and Kent R. Olson

TREATING EPILEPSY

- Anti-epileptic drug (AED) is the primary treatment to control seizures
- Epilepsy surgery should be considered when 2 or more medications fail to satisfactorily control seizures and the seizure origin in the brain can be well localized and safely removed- treatment resistant epilepsy (TRE)
- When curative epilepsy surgery is not an option palliative procedures may be:
  - -Vagal Nerve Stimulation (VNS; LivaNova)
  - -Responsive neurostimulation (RNS; Neuropace)
  - -Investigational drug trials
  - -Deep Brain Stimulation (DBS; Medtronic)
  - -Dietary therapies

Not considered curative at this point.

NEWER AED'S

- Despite the introduction of over 20 new antiseizure drugs over the past several decades, the proportion of patients with TRE has not changed appreciably.
- This indicates that the new drugs are treating the same population of patients as the old ones, albeit with different side effect profiles, which make them useful.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

TREATMENT OUTCOMES IN PATIENTS WITH NEWLY DIAGNOSED EPILEPSY TREATED WITH ESTABLISHED AND NEW ANTIEPILEPTIC DRUGS: A 30-YEAR LONGITUDINAL COHORT STUDY.

- 63.7% of patients were seizure free for the previous year or longer at the end of the study period;
- Approximately half (50.5%) of all subjects were seizure free for 1 year or longer with their initial AED.
- If the initial AED was ineffective, the second and third regimens resulted respectively in 11.6% and 4.4% chances of seizure freedom

Chen Z, Brodie MJ, Liew D, Kwan P. *JAMA Neurol* 2018;75:279–286.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

DRUG-RESISTANT EPILEPSY (DRE)

- Failure of 2 appropriate trials of antiseizure drugs due to inefficacy and not intolerance
- ILAE definition- "drug-resistant epilepsy is defined as a failure of adequate drug trials of 2 tolerated appropriately chosen and used antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure freedom."
- This definition results from prospective evidence that only 11% of patients eventually become seizure-free after failure of the first antiseizure drug trial, and only 3% after failure of the second, due to inefficacy and not intolerance.

Quantifying the response to antiepileptic drugs Effect of past treatment history Yitzhak Schiller, Yussef Najjar January 01, 2008; 70 (1)
Eur J Neurol. 2006 Mar;13(3):277-82.**Diagnosing refractory epilepsy: response to sequential treatment schedules. Mohanraj R, Brodie MJ**

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

TREATMENT RESISTANT EPILEPSY - TRE

- TRE is a serious problem
  - -it constitutes 40% of people with epilepsy
  - -mortality rate 5–10 times that of the general population
- Fewer than 1% of people with TRE are evaluated at a full-service epilepsy center (surgical treatment for epilepsy remains substantially underutilized).
- Early referral provides the best opportunity to avoid irreversible psychological and social problems, a lifetime of disability, and premature death.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Table 3 Common misconceptions about epilepsy surgery

Misconception	Fact
All drugs need to be tried	Seizure freedom is unlikely after 2 drugs have failed
Bilateral EEG spikes are a contraindication to surgery	Patients with unilateral onset seizures usually have bilateral spikes
Normal MRI is a contraindication to surgery	Other techniques often detect a single epileptogenic zone in patients with normal MRIs
Multiple or diffuse lesions on MRI are a contraindication to surgery	The epileptogenic zone may involve only a part of the lesion
Surgery is not possible if primary cortex is involved	Essential functions can be localized and protected
Surgery will make memory worse if there is an existing memory deficit	Poor memory usually will not get worse and could get better
Chronic psychosis is a contraindication to surgery	Patients will still benefit if seizures are eliminated
IQ less than 70 is a contraindication to surgery	Outcome depends on the type of epilepsy and the type of surgery
Patients with focal epilepsy and a focal lesion can have the lesion removed without detailed presurgical evaluation	Focal lesions can be incidental findings unrelated to the epilepsy; epileptogenicity of a lesion always needs to be confirmed

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Engel J., Jr Seizures and Epilepsy, 2nd ed Oxford: Oxford University Press; 2013:607.

HISTORY OF EPILEPSY SURGERY

- Victor Horsely is credited with initiating epilepsy surgery when he successfully localized and removed epileptogenic lesions in three adult patients with partial seizures at London's National Hospital in 1886
- In Germany in the early part of the 20th century Otfrid Foerster applied and standardized the technique of lesion-directed epilepsy surgery.
- In 1928, Wilder Penfield brought these techniques to Montreal, and in collaboration with Herbert Jasper pioneered the techniques of modern day epilepsy surgery and invasive monitoring with depth electrodes, again in adult patients.
- These pioneering techniques led to the gradual acceptance of surgery as a valid and useful therapeutic modality for adults with medically refractory epilepsy.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

WHY TO PURSUE SURGERY

- A randomized controlled trial (RCT) of surgery for temporal lobe epilepsy (TLE) carried out at the University of Western Ontario was published in 2001.
- - Sixty-four percent of patients who had surgery were seizure-free after 1 year, compared to only 8% in the medical arm, and
  - there was 1 death, which occurred in the medical arm.
  - The quality of life was better among the patients in the surgical group than among those in the medical group (P<0.001)
- Pediatric population (Dwivedi et a 2017l)
  - At 12 months, freedom from seizures occurred in 44 patients (77%) the surgery group and in 4 (7%) in the medical-therapy group (P<0.001).
- The AAN, in association with the American Epilepsy Society and the American Association of Neurological Surgeons, subsequently issued a practice parameter, based on this (first RCT) study and 24 Class IV series of 1,952 patients who underwent surgery for TLE. Sixty-seven percent in the Class IV series were seizure-free, compared to a drug trial meta-analysis, where the best result was 54% with a greater than 50% seizure reduction and very few seizure-free.

A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy *Samuel Wiebe, M.D., Warren T. Blume, M.D., John P. Girvin, M.D., Ph.D., and Michael Eliasziw, Ph.D.,*

Surgery for Drug-Resistant Epilepsy in Children *Dwivedi et al. N Engl J Med 2017; 377:1639-1647*

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

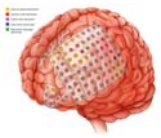
ESTABLISH SURGICAL CANDIDACY

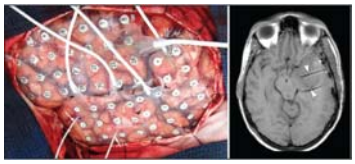
- Comprehensive pre-surgical evaluation
  - -Epilepsy diagnosis: History, scalp video EEG
  - -Neuroimaging: MRI, PET, SPECT, fMRI
  - -MEG
  - -WADA (dominant hemisphere)
  - -Neuropsychological testing
  - -Psychiatric and psychosocial assessments
  - -Counseling to address expectations of surgical outcome and surgical complication
  - -Discussion in Patient Management Conference

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

INVASIVE INTRACRANIAL MONITORING

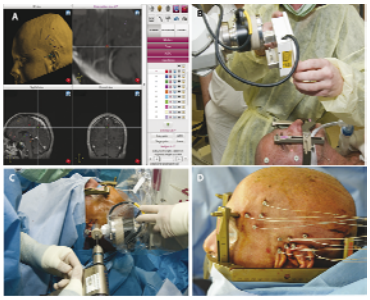
- Grids with depths





THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

STEREO EEG – ROBOT ASSISTED STEREOTACTIC PLACEMENT OF ELECTRODES



Technique, Results, and Complications Related to Robot-Assisted Stereoelectroencephalography Gonzalez-Martinez et al 2016

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

	SEEG	SDE
Age	> 2 years old	All ages
Cortical coverage		
Superficial	Sparse	Dense
Sulci	Good	Only if DE
Deep	Good	Only if DE
Mapping	More difficult—needs extensive pre-op planning	Easily accessible
Craniotomy		
Can perform limited craniotomy for resection	No	Yes
Bilateral	Yes, easily completed	Possible, but requires additional craniotomy

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

| Stereoelectroencephalography Versus Subdural Electrodes for Localization of the Epileptogenic Zone: What Is the Evidence? Neurotherapeutics January 2019, Volume 16,1, pp 59–66 Joel S. Katz, Taylor J. Abel

COMPLICATIONS WITH SEEG VS SDE

	SEEG	SDE
Sample size	2624 patients (30 studies)	2542 patients (21 studies)
Overall complication rate	1.3%	3.6% required additional surgery due to complications
Hemorrhagic occurrence	1.0%	2.4%
Infection	0.8%	2.3% neurologic 3.0% superficial
Mortality	5 patients in series (0.3%)	5 patients in series (0.3%)

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

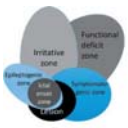
Stereoelectroencephalography Versus Subdural Electrodes for Localization of the Epileptogenic Zone: What Is the Evidence? Neurotherapeutics January 2019, Volume 16,1, pp 59–66 Joel S. Katz, Taylor J. Abel

IDENTIFYING THE AREA OF EPILEPTOGENESIS

"area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures" (Lüders et al. 1993).

Straight forward

Complex



Implications:
1)- No single zone is equivalent to the EZ
2)- No single TEST allows measurement of the EZ
3)- Specifically, defining the IOZ is not the same as defining the EZ.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Jehi 2018 Epilepsy Curr.2018 Jan-Feb; 18(1): 12–16.

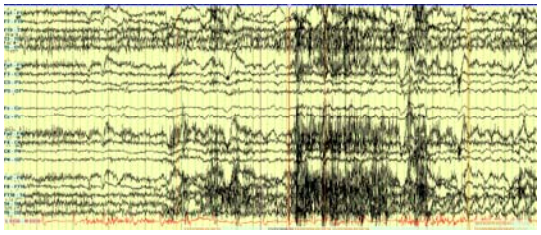
CASE 1

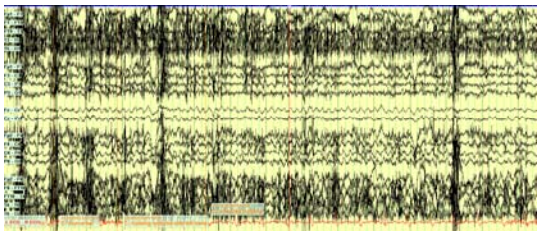
- SM-55 LHWF year old with established PTSD, CHF, Atrial fibrillation and seizures that started at age 51
- Aura: rising feeling of warmness "flushing" in her stomach and progressing up.
- Ictal Semiology: blank stare, chewing lip smacking, hand automatisms, can usually hear surroundings but unable to respond
- Frequency: 4-5 per week
- Current AEDs: LEV 1500mg BID, Vimpat 200-300, Oxcarbazepine 600mg BID

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

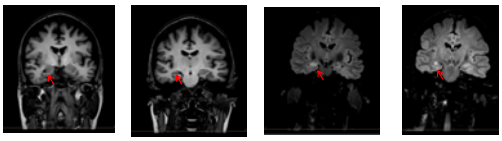
- Scalp video EEG:
- 7 seizures recorded: all stereotypical with aura and then oral automatism and hand automatism.
- Ictal: right temporal onset with later left temporal spread.
- Interictal: Right temporal discharges (FT10 max), rare left temporal discharges.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

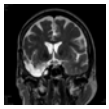




- MRI: Right MTS
- PET: **Right (prominent) and subtle Left temporal lobe hypometabolism**
- MEG: anterior aspect (polar region) of the right temporal lobe.
- fMRI: left hemisphere dominance



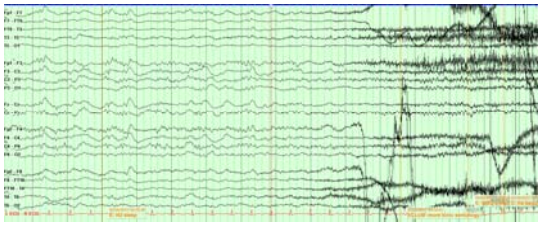
- Discussed in PMC
- Offer Right ATL for better chances of seizure freedom
- Follow up: Seizure (and aura) free 27 months (Surgery: May 19th 2017). Engel Ia
- Pathology: Severe hippocampal sclerosis (ILAE Type I).
  - Severe neuronal losses, CA1, CA3 and CA4 of Ammon's horn.
  - Marked astrogliosis, including diffuse increase in corpora amylacea.
- AEDs: off oxcarbazepine. On LEV 1500 mg BID and reduced (half) dose of lacosamide 100mg BID

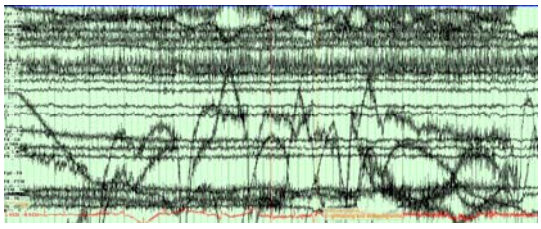


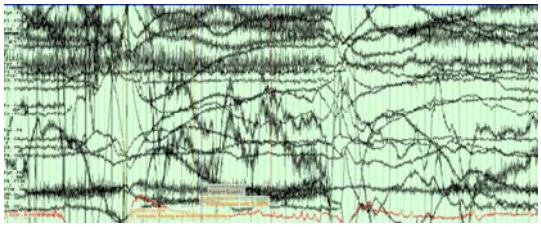
CASE 2

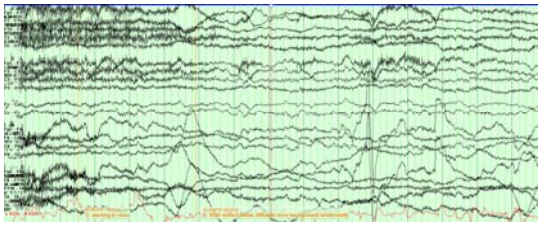
- 48 year old right handed African-american male with history of seizures since age 20
- History of a closed head injury with several minutes of LOC in 1990s and a positive FH for epilepsy/seizures in a 1st degree relative (his son)
- Seizure: Aura: Out of sleep, reports a "funny taste" of water in mouth, abnormal eye mvts , facial grimacing, w/ eyes wide open; gasping for air → both arms thrashing asynchronously and independently and kicking mvts of both legs ("as if patient is in a bad nightmare") – no clear lateralizing pattern; frequently falls out of bed
- Duration: 10-30 seconds to 1 min max; postictal: coughing and throat clearing; triggers: stress, (non-REM) sleep; startle response;
- Frequency: daily, multiple times a night
- Has been evaluated at the level 4 epilepsy center at Emory University in Atlanta, GA

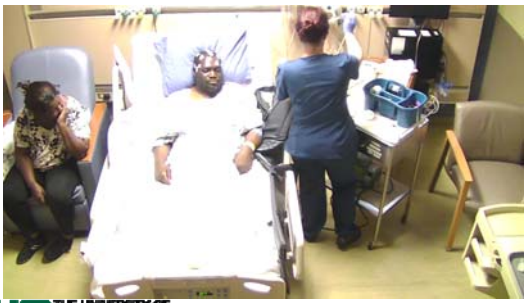
- Scalp veeg monitoring
- Interictal- none
- Ictal-not helpful, no definite ictal pattern
- PET-negative
- MRI- no abnormality to explain seizure
- Ictal SPECT- non diagnostic
- Neuropsych: global cognitive deficits
- MEG: none



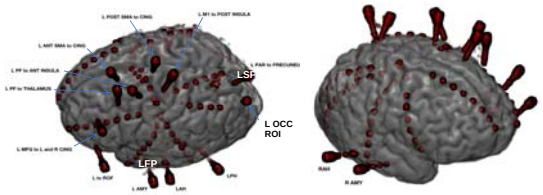








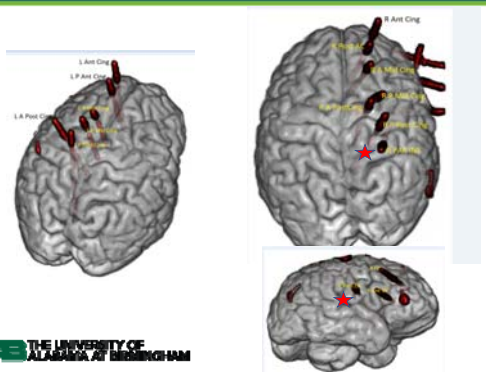
ICEEG IMPLANTATION 3D RECON L AND R HEMISPHERE

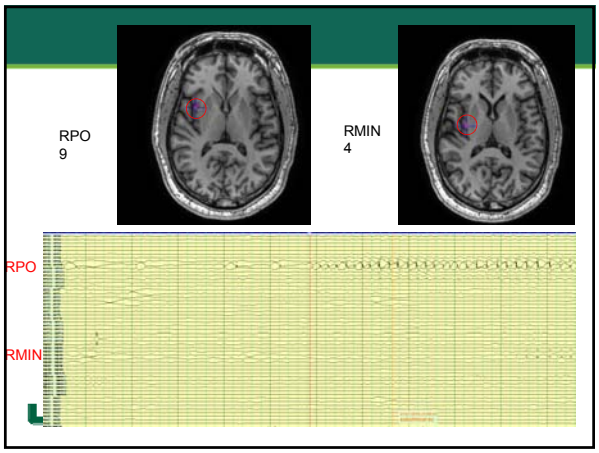


CASE 2

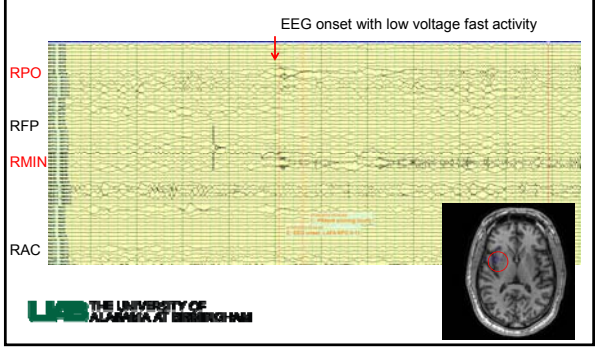
- Straight forward
- Complex

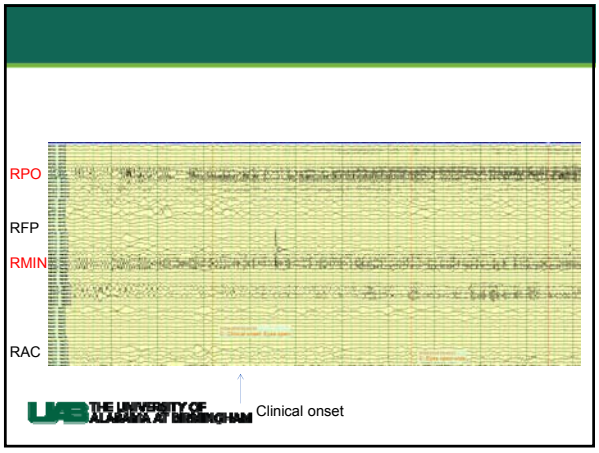
CASE 2

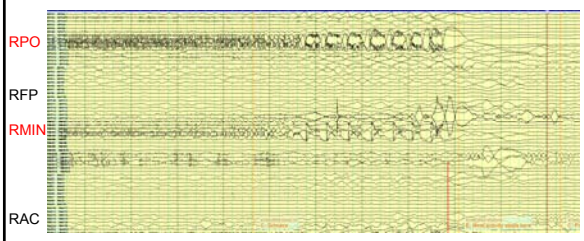




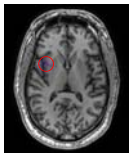
SZ 1- RPO (8-13), RMIN (1-5)
RIGHT INSULAR REGION

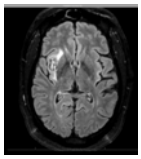






- s/p Right stereotactic placement of cranial bolt for MRI guided laser interstitial therapy on 12/5/2018
- 4 week follow up- Engel III (worthwhile improvement)
- Prior to LITT: 5-10 seizures per day (35-70 per week)
- After the LITT procedure: 2 seizures every 2-3 days (4-6 per week)





- Epilepsy surgery outcome is highly governed by presence of lesion on MRI and its complete resection
- The odds of seizure freedom after surgery are two to three times higher in the presence of a lesion on histopathology or MRI.

Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis.Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S Epilepsy Res. 2010 May; 89(2-3):310-8.

- MRI-negative (MRI–) pharmacoresistant focal epilepsy (PFE) patients constitute one of the most challenging and cost-intensive groups for epilepsy surgical
- Focal cortical dysplasia's (FCD) represent the most common pathological substrate of neocortical DRE and are often difficult to delineate by conventional MR imaging.
- The most common pathologies found in this MRI-negative (n=95) cohort included: focal cortical dysplasia (n=43, 45%), gliosis (n=21, 22%), hamartia+gliosis (n=12, 13%), and hippocampal sclerosis (n=9, 9%).
- Up to 25%-30% of pathologically verified FCD is not visible on preoperative MRI (Tassi et al 2002, Krsek et al 2008)

The pathology of magnetic-resonanceimaging-negative epilepsy
Z Irene Wang1, Andreas V Alexopoulos1, Stephen E Jones2, Zeenat Jaisani3, Imad M Najm1 and Richard A Prayson4 Modern Pathology (2013), 1–8

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

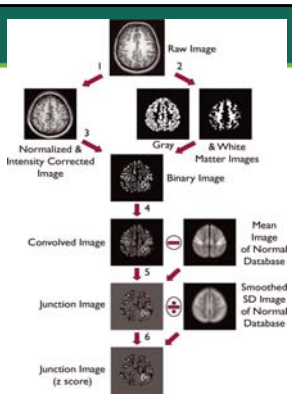
VOXEL-BASED MORPHOMETRIC (VBM) MRI POST-PROCESSING

- MRI post-processing algorithm is based on basic principles of VBM but customized to be used on an individual patient basis
- Currently the processing is performed in Matlab-based SPM software
- It can detect FCD related abnormalities such as blurring of gray-white matter junction and abnormal gyral pattern

-Huppertz et al 2005:Huppertz et al Enhanced visualization of blurred gray-white matter junctions in focal cortical dysplasia by voxel-based 3D MRI analysis. Epilepsy Res.2005 Oct-Nov;67(1-2):35-50. Epub 2005 Sep 19.

-Ashburner et al 2000 Voxel based morphometry-the methods Neuroimage 11, 805-821

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM



Huppertz et al 2005

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

- Retrospective study in MRI negative epilepsy
- 150 MRI-surgical patients.
- **Results**
- MAP showed a 43% positive rate
- Overall, patients with MAP+ region completely resected had the best seizure outcomes, followed by the MAP− patients, and patients who had no/partial resection of the MAP+ region had the worst outcome ($p<0.001$).
- Subgroup analysis revealed that visually identified subtle findings are more likely correct if also MAP+.
- False-positive rate in 52 normal controls was 2%.
- Surgical pathology of the resected MAP+ areas contained mainly non-balloon-cell FCD.
- Multiple MAP+ regions were present in 7% of patients

Voxel-based Morphometric MRI Post-processing in MRI-negative Epilepsies
Zi Wang, SE Jones, Z Jaisani, IM Najm, RA Prayson, RC Burgess, B Krishnan, A Ristic, CH Wong, W Bingaman, JA Gonzalez-Martinez, AV Alexopoulos Ann Neurol. 2015 Jun; 77(6): 1060-1075

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

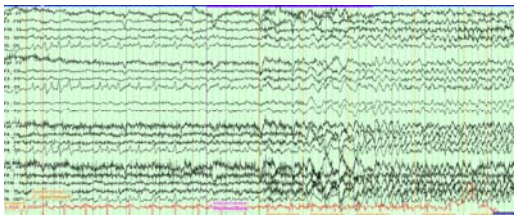
- SW 50 year old with d/o MS and seizures since age 40
- Semiology: Abrupt numbness/tingling paresthesia's over neck radiating over occiput into forehead and tongue + "weird taste" à spread into LUE/LLE (more recently) à LOA + unresponsiveness with blank stare w/o any particular automatisms

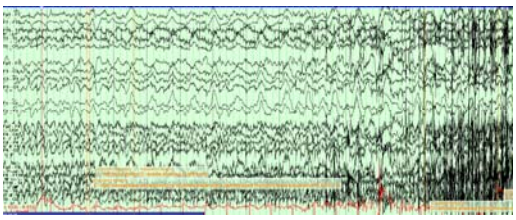
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

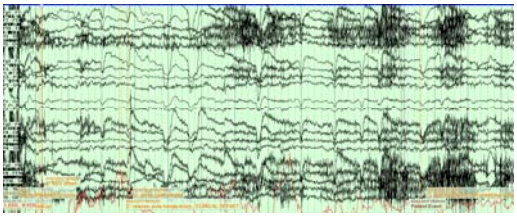
SCALP EEG

- Interictal: Multifocal R hemispheric discharges: very frequent, complex appearing polyspike discharges over R anterior temp region (max at F8, FT10, T4) and broader spike/sharp wave discharges over R mid-temporal region (max at T4 with field extending into C4 and T6); rare spikes over R frontal region (max at FP2, F8); very rare L temporal/frontotemporal spikes (potential spread from R-sided spikes)
- Ictal: Right hemispheric onset

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM



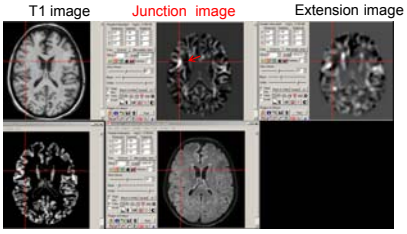




- Sz protocol MRI (3/3/2017) Multiple hyperintensities consistent with chronic microvascular changes
- PET at UAB (3/21/2017) Probable focal hypometabolism in the R inferior frontal lobe/frontal operculum
- fMRI (4/7/2017) L language dominance
- MEG (3/21/2017) Spike cluster in R mid-insula, frontal opercular region and to less extent parietal operculum. Some of the repetitive spikes on EEG did not have clear MEG correlates, possibly radial source in the same region
- MAP (5/5/2017) Two (2) distinct lesions in the R lateral inferior frontal gyrus close to R frontal opercular region and R superior frontal gyrus close to the more prominent R hemispheric juxta-cortical white matter lesion

LESION 1: RIGHT INFERIOR FRONTAL GYRUS

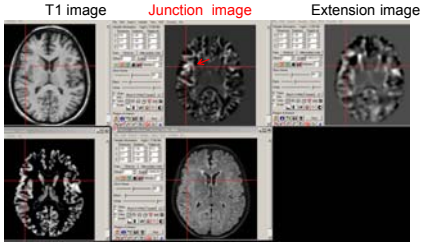
T1 image Junction image Extension image



Thickness image FLAIR image

LESION 1: RIGHT INFERIOR FRONTAL GYRUS TO SHOW EXTENT- CLOSE TO FRONTAL OPERCULAR REGION

T1 image Junction image Extension image

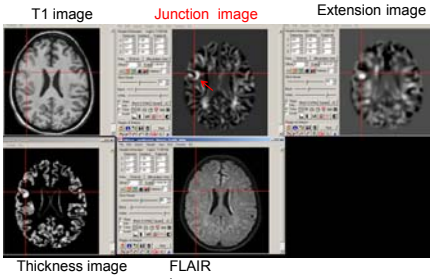


Thickness image FLAIR image

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

LESION 1 TO SHOW EXTENT

T1 image Junction image Extension image

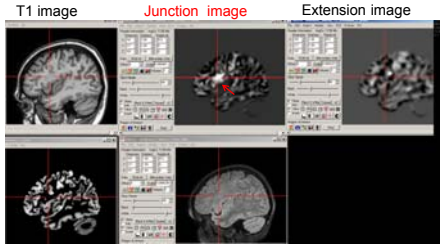


Thickness image FLAIR image

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

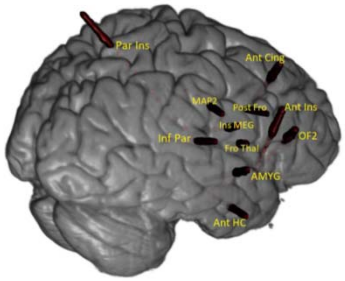
LESION LESION 1: RIGHT INFERIOR FRONTAL GYRUS (SAGITTAL VIEW)

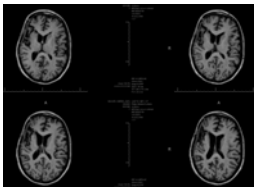
T1 image Junction image Extension image

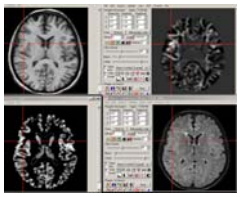


Thickness image FLAIR image

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM





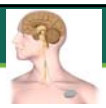


Path: FCD type 1b
Seizure (and aura) free 20 month : Engle IA (DOS 12/8/2017)

MINIMALLY INVASIVE NON-RESECTIVE PALLIATIVE APPROACHES

- VNS- FDA approved 1997
- RNS- FDA approved February 2013
- DBS- FDA approved 2018

VNS DATA

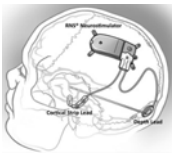


- The efficacy of VNS for intractable seizures has been evaluated by 3 blinded, randomized controlled trials.
- In the first trial, Ben-Menachem and colleagues randomized 114 patients with focal epilepsy to receive therapeutic or sham stimulation after VNS implantation, and reported a significantly greater reduction in seizure frequency with therapeutic stimulation after 3 months of treatment (25% versus 6%) .
- Similar results were reported in 2 subsequent blinded randomized, controlled trials and 2 nonblinded controlled studies
- In a large meta-analysis including 3321 patients treated with VNS from 77 reports,
- 51% of patients treated with VNS achieved ≥50% reduction in seizure frequency from baseline, after a mean follow-up of 10 months.
- Longer duration of therapy had a significant positive influence on seizure control rates, although few (5–10%) patients achieved complete seizure freedom, and one-quarter of individuals reported no measurable benefit from stimulation.
- Similar outcomes have been found with analysis of the device manufacturer's patient database. Interestingly, patients with a history of posttraumatic epilepsy or Lennox–Gastaut syndrome may have improved response to treatment .
- Adverse events associated with treatment include hoarseness (37–62%), cough (7–21%), pain (6–17%), and infection (4–6%), and rare incidences of asystole have been reported].

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

RNS

- RNS uses a closed-loop stimulation system.
- Implanted subdural and depth electrodes continuously record and analyze regional electrocorticographic signals, and stimulation is triggered by electrographic activity concerning for seizure initiation, with the hope of terminating the discharge before it becomes clinically apparent
- Bifocal/multifocal/bitemporal epilepsy
- Focal epilepsy within eloquent cortex/ preserved memory



THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

- Responsive neurostimulation was evaluated in a multicenter, double-blind, randomized, controlled trial termed the RNS System Pivotal Trial (Morrell et al).
- In the study, 191 adults with pharmacoresistant partial epilepsy were implanted with the RNS system and randomized to receive responsive stimulation or seizure detection alone during a 12-week blinded period.
- Patients receiving stimulation reported a decrease in seizure frequency of 38% versus 17% in the sham-treated group, and 29% of stimulated patients reported ≥50% reduction in seizures, though this outcome was also reported in 27% of control subjects.
- After 3 months, patients in both groups were assigned to receive therapeutic stimulation during the open-label period. The median percent reduction in seizures during the open-label period was 44% at 1 year and 53% at 2 years, representing a progressive improvement with time . (Heck et al)
- Overall adverse events included device site infection (5.2%), headache (10.5%), dysesthesia (6.3%), increase in complex-partial (5.8%) or generalized (4.7%) seizures, and other less common complications .

Morrell MJ, Group RNSSiES Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77:1295–304

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

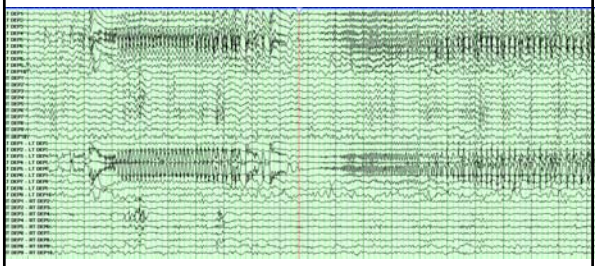
- 33 years old RH with NF-1 and epilepsy
- Seizures for several years; failed LEV, VPA, LCM, OXC, TPM, LTG (rash)
- AEDs at the time of initial evaluation:
  - OXC 600-900
  - TPM 100-100
  - KLO 1mg hs
- Semiology – lip smacking and zoning out occurring 1-2 times per week but could have up to 4 seizures in one day

CASE #2 – INDEPENDENT HIPPOCAMPAL ONSET

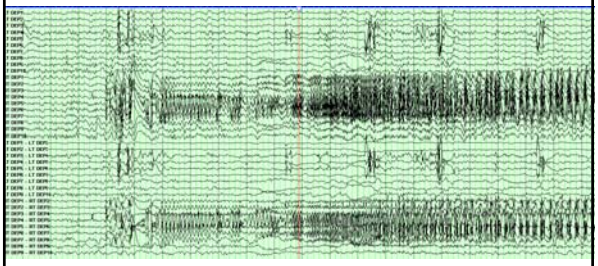
- MRI – 3T normal (questionable paracentral cortical abnormality felt to be meningioangiomatosis)
- PET – bi-T decreased signal L=R
- IAP:
  - Memory performance better L than R (25% vs. 13%)
  - Language Left 12/12 correct; Right 0/12 correct
- NPT – substantial decline when compared to 2012
  - IQ scores in low normal range (79-86)
  - Bi-T deficits with superimposed depression and possibly TPM effects
- EMU: L medial temporal lobe seizures but independent L and R ATL EDs with 50:50 distribution

CASE #2 - DEPTH ELECTRODES PLACEMENT

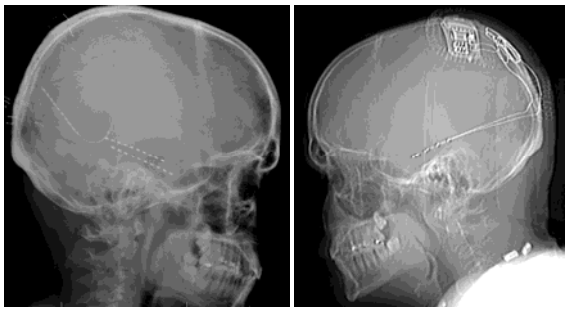
CASE #2 - PHASE II – LH SEIZURE



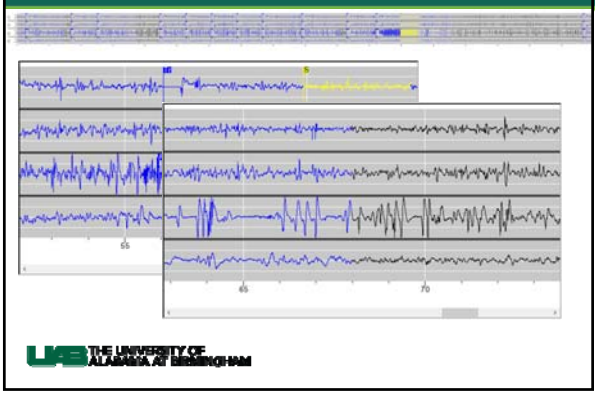
CASE #2 - PHASE II – RH SEIZURE



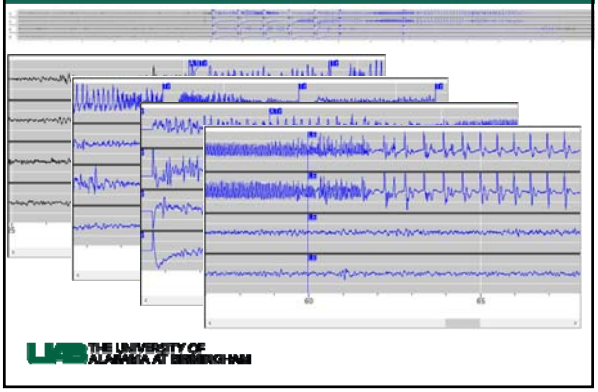
CASE #2 - RNS ELECTRODE PLACEMENT



CASE #2 – RNS SEIZURES



CASE #2 – RNS SEIZURE

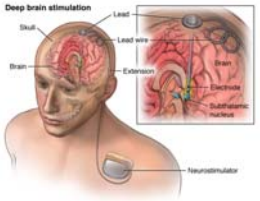


CASE #2 - AT THE LAST F/U (2/2017)

- No seizures in 6+ months – all detections aborted by ECoG data
- Current AEDs
  - PGB 100-100 (started after Phase II evaluation but prior to RNS; dose decreased after RNS)
  - OXC 600-600 (higher SE)
  - TPM 100-100 (higher NE + SE)
  - KLO 1 mg hs

DBS

- Stimulation of anterior nucleus of the thalamus, a structure intimately involved in limbic circuitry and with widespread neocortical projections.
- Thalamic stimulation has received approval as an adjunctive treatment for pharmacoresistant epilepsy by the FDA.



THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

- In 2010, the effectiveness of thalamic DBS was studied in 100 adults with pharmacoresistant partial epilepsy in the double-blinded, randomized Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial (Fisher et al)
- In the initial 3-month blinded phase of the SANTE trial, patients receiving stimulation had a significantly larger decrease in seizure frequency (40%) than those in the control group (14.5%).
- After patients were unblinded and all were treated with stimulation for 2 years, median seizure frequency was reduced by 56%, with 54% of individuals achieving seizure reduction of ≥50%.
- There was a trend towards better seizure control with longer periods of stimulation, resembling a similar relationship between treatment duration and efficacy observed with VNS.
- Adverse events in the first year of thalamic DBS included paresthesias in 18% of patients, surgical site pain in 11%, site infections in 9%, and lead replacement in 8%, though these rates declined in the second treatment year
- There were no differences in cognition or mood between treated and untreated patients, but depression was more commonly reported with stimulation.

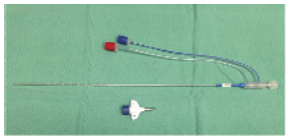
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

LASER INTERSTITIAL THERMAL THERAPY (LITT)

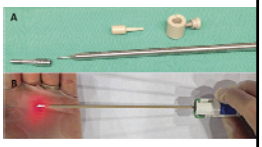
- Lasers (light amplification by stimulated emission of radiation) were developed in the late 1950s
- 1966- First report of laser treatment of a brain tumor
- 1970s and 1980s-the application of lasers in neurosurgery remained limited to use as a handheld tool
- 1980- Bown first proposed the use of laser interstitial thermal therapy (LITT) for thermal ablation of tumors
- 1994, Kahn et al reported intraoperative magnetic resonance imaging monitoring of laser ablation (MR-guided LITT).

BownSGPhototherapy in tumors. World J Surg.1983;7(6):700–709
KahnT, BettagM, UlrichF , et al. MRI-guided laser-induced interstitial thermotherapy of cerebral neoplasms J Comput Assist Tomogr.1994;18(4):519–532

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

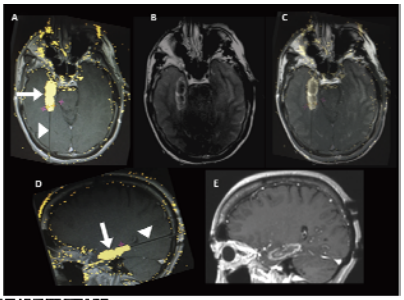


Visualase
FDA 2007



NeuroBlate
FDA 2009

LITT IN EPILEPSY



THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

LITT DATA FOR SEIZURE FREE RATE

TABLE. Studies to Date of Laser Interstitial Thermal Therapy for Temporal Lobe Epilepsy[a]

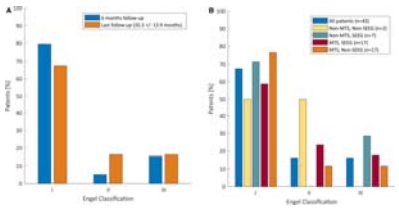
Study	Study Type	No. Patients	Age Range, y	System Used	MRI Modality	Complications	Follow-up, mo	Outcomes[b]
Curry et al[41]	Retrospective review	1	16	Visualase	1.5 T	None	12	Engel 1D
Willie et al[42]	Prospective case series	13	16-64	Visualase	1.5 T	1/13; visual field deficit	14 (median)	MTS = 67% Engel I
						1/13; acute SDH (without neurologic deficit)		All = 54% Engel I
Drane et al[43]	Prospective case series	19 (including the 13 patients reported in Willie et al[42])	——	Visualase	Not specified	——	——	11 Engel I; 1 Engel II; 4 Engel III; 3 Engel IV
Lewis et al[44]	Retrospective review	1	12	Visualase	Not specified	Inaccurate laser fiber placement	——	Treatment not pursued
Waseem et al[45]	Prospective case series	7	54-67	Visualase	1.5 T and 3 T (varied per case)	2 patients with partial visual field deficit; 1 patient with early postoperative seizure requiring readmission	12 (mean)	Engel I = 4 of 5; Engel II = 1 of 5

[a]MRI, magnetic resonance imaging; MTS, mesial temporal sclerosis; SDH, subdural hematoma.
[b]In Waseem et al[45] outcomes were presented at 12 months. Two patients had not completed their 12-month follow-up appointment at the time of publication.
Kang et al[27] is included in the text but not in the table because it was published during revision of the manuscript.

Mean seizure-free rate of 55% (12 of 22).
The number of patients with nonlesional MTLE who underwent MRg-LITT is too small to be meaningful.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

LITT RECENT DATA FOR TLE



At 6 month follow up: 79% Engel I
At 20 month follow up : **67 % Engel I (compared to prior studies that showed 55%)**

In patients undergoing LITT in the dominant hemisphere, a decline in verbal and narrative memory, but not in naming function was noted.

Laser ablation for mesial temporal lobe epilepsy: Surgical and cognitive outcomes with and without mesial temporal sclerosis
Cristian Donos, Joshua Breier, Elliott Friedman, Patrick Rollo,Jessica Johnson, | Lauren Moss, Stephen Thompson Melissa Thomas,Omotola Hope, Jeremy Slater, Nitin Tandon Epilepsia 2018

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

LITT FOR EPILEPSY

- Advantage
  - Minimally invasive
  - Shorter hospital stay
  - Naming and face recognition is better preserved
- Disadvantage
  - Need more studies with longer follow up to assess for seizure freedom rates (recent study noted a decline by 8% from 6 to 20 month follow up) (55-67%)
  - No pathology

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

- Standard ATL remains the gold standard in the treatment of medically refractory TLE, with seizure freedom resulting in 60–80% of patients.
- It is currently the only resective epilepsy surgery supported by randomized controlled trials and offers the best protection against lateral temporal neocortical seizure onset.
- Stereotactic laser thermo-ablation allows destruction of the mesial temporal structures with low complication rates and minimal recovery time, but seizure freedom rates appear lower compared with open resection, and long-term outcomes remain under investigation.
- Neuromodulatory devices such as RNS, VNS, and DBS have an important role in the treatment of certain patients, these remain palliative procedures for individuals who are not candidates for resection or ablation, as complete seizure freedom rates are low

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

SUMMARY

- Medically refractory epilepsy: Failure of 2 appropriate trials of antiseizure drugs due to inefficacy and not intolerance
- Early referral for epilepsy surgery is recommended

  -Resective surgery

  -LITT

  -RNS,DBS,VNS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

EPILEPSY TEAM

- Phone number (205) 934-6418 (Sharra)
- Fax number (205) 975-6360

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

UAB LEVEL 4 EPILEPSY CENTER

Division Director: Jerzy Szaflarski, MD, PhD
EMU director: Jennifer DeWolfe, DO

Faculty: Gaston, Tyler, MD
Grayson, Leslie, MD
Houston, James T, MD
Jaisani, Zeenat, MD
Muhlhofer, Wolfgang, MD
Pati, Sandipan, MD
Thomas, Ashley, MD
Ver Hoef, Larry, MD
Allendorfer, Jane, PhD
Goodman, Adam, PhD

APPs:
Hayley A. French, PA
Itia Dowdell, PA
Elizabeth Ritchie, NP

Neuropsychologist: Roy Martin, PhD
Psychologist: Christopher Litton PsyD
Neurosurgeon: Kristen Riley, MD
Nicole Bentley, MD

Contact info for vEEG

- Phone number (205) 934-6418 (Sharra)
- Fax number (205) 975-6360

Division admin: Toni Clayton toniclayton@uabmc.edu

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM