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Evaluating Drug Resistance, Surgical Timing, and Post-operative Medications

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Pretest 1.

Which of the following resective epilepsy surgery gives the best seizure-free outcome?

A. Vagus nerve stimulation

B. Anterior temporal lobectomy

C. Lesionectomy for focal cortical dysplasia

D. Corpus callosotomy

E. Multiple subpial resection

Pretest 2.

How many drugs should be tried before epilepsy surgery?

A. 2

B. 3

C. 4

D. 5

E. 6

Epilepsy Care

Seizure

Epilepsy diagnosis

Medication trials

Imaging for pathology

Medical intractability

Surgical Consideration

Surgical workup

Surgery

Not surgery

Pathway of epilepsy management

Paroxysmal events

Dx of SZ/Epilepsy

Initial Monotherapy

Remission (50%)

2nd Drug Rx
(mono- vs add-on)

Additional Remission
(15-20%)

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Treatment Response with AEDs

Drug #	% Seizure free
1st mono	**47.2**
2nd mono	**60.2**
3rd mono or combination	**64**

+13%

+4%

36% (~1/3) of patients have resistant to medication

Kwan & Brodie. NEJM 2000;342:314-9

3rd gen AEDs

Old	Newer (2nd gen)	Newest (3rd gen)
Phenobarbital 1919	Felbamate 1993	**Pregabalin 2005**
Phenytoin 1938	**Gabapentin 1993**	Rufinamide 2009
Primidone 1954	**Lamotrigine 1994**	**Lacosamide 2009**
Ethosuximide 1960	**Topiramate 1996**	Vigabatrin 2009
Carbamazepine 1974	Tiagabine 1997	**Clobazam 2011**
Valproic acid 1978	**Levetiracetam 1999**	Ezogabine 2011
	Oxcarbazepine 2000	**Perampanel 2012**
	Zonisamide 2000	Eslicarbazepine 2014

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Pattern of treatment response

Table 1 Seizure-free rates with successive antiepileptic drug regimens

Drug regimens	No. of patients	Seizure-free on monotherapy	Seizure-free on combination	Total no. seizure-free	% of cohort seizure-free	% Seizure-free on regimen
First	1,098	543	0	543	49.5	49.5
Second	398	101	45	146	13.3	36.7
Third	168	26	15	41	3.7	24.4
Fourth	68	6	5	11	1.0	16.2
Fifth	32	1	3	4	0.4	12.5
Sixth	16	1	1	2	0.2	12.5
Seventh	9	1	1	2	0.2	22.2
Eighth	3	0	0	0	0.0	0.0
Ninth	2	0	0	0	0.0	0.0

SZ freedom does not differ substantially whether an established or a new-generation AED is used.

Brodie MJ, et al. Neurology 2012;78:1548–54

Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

"Drug-resistant or Medically intractable epilepsy"

- "a failure of adequate trials of **2 tolerated, appropriately chosen** and used anticonvulsant
  drug schedules (whether as **monotherapy or in combination**) to achieve sustained seizure freedom."

Kwan P, et al. Epilepsia 2010

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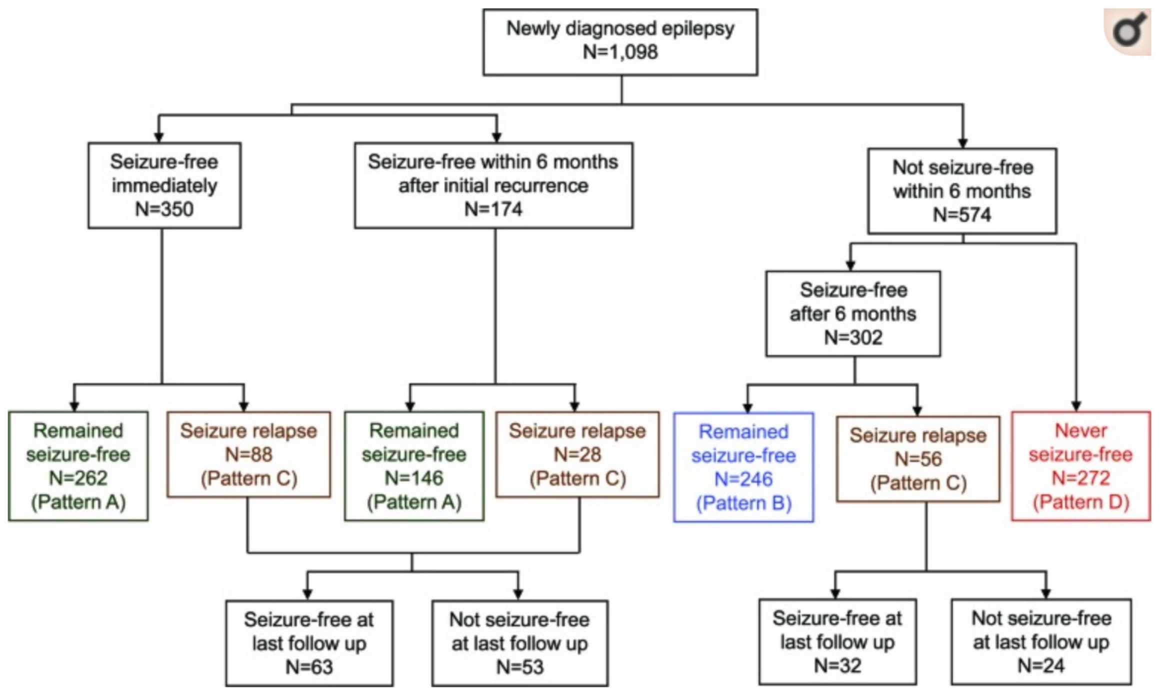
Exclude pseudoresistance

Table 1. Some Reasons for Pseudoresistance to Antiepileptic Drug Therapy.

Reason	Examples
Wrong diagnosis	Syncope, cardiac arrhythmia, or other conditions; psychogenic nonepileptic seizures
Wrong drug (or drugs)	Inappropriate for seizure type; pharmacokinetic or pharmacodynamic interactions
Wrong dose	Too low (overreliance on "therapeutic" blood levels); side effects preventing drug increase
Lifestyle issues	Poor compliance with medication; alcohol or drug abuse

Kwan P, et al. N Engl J Med 2011;365:919-26.

Pattern of treatment response

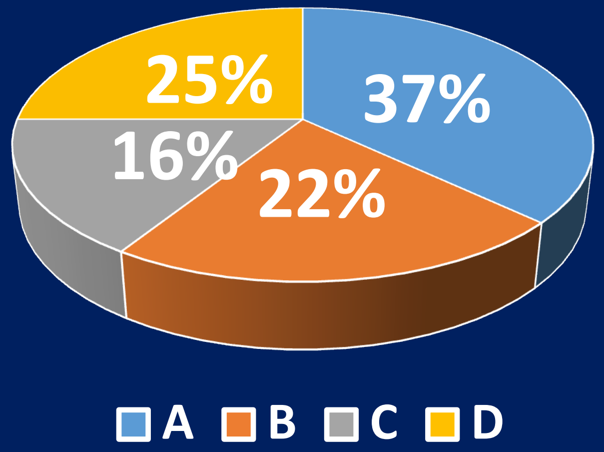


Pattern A: Early and sustained

Pattern B: Delayed and sustained

Pattern C: Fluctuating course

Pattern D: Never SZ-free



Neurology. 2012 May 15; 78(20): 1548–1554.

SZ freedom rate after newly added ASM

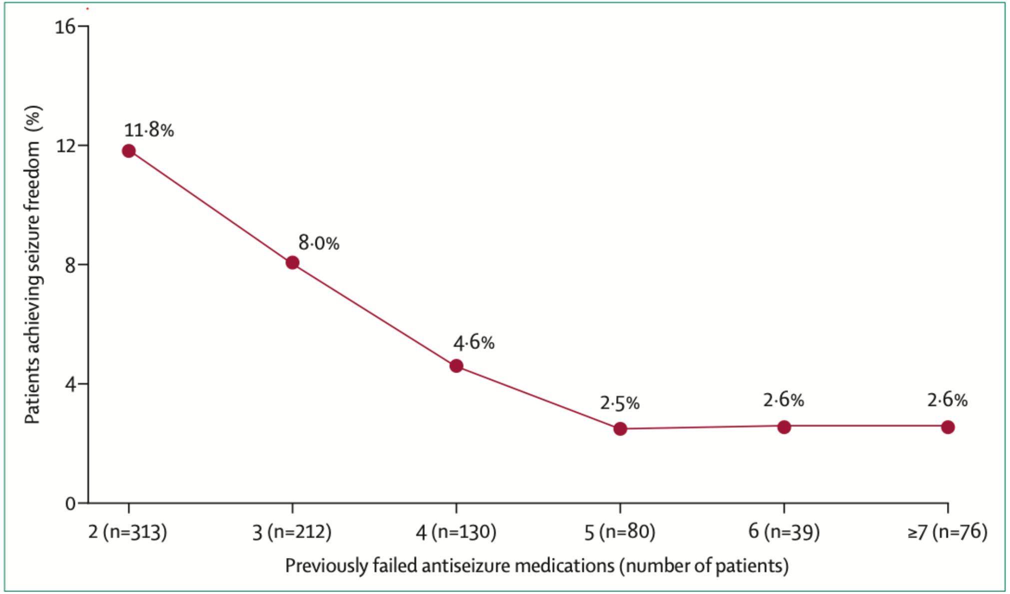
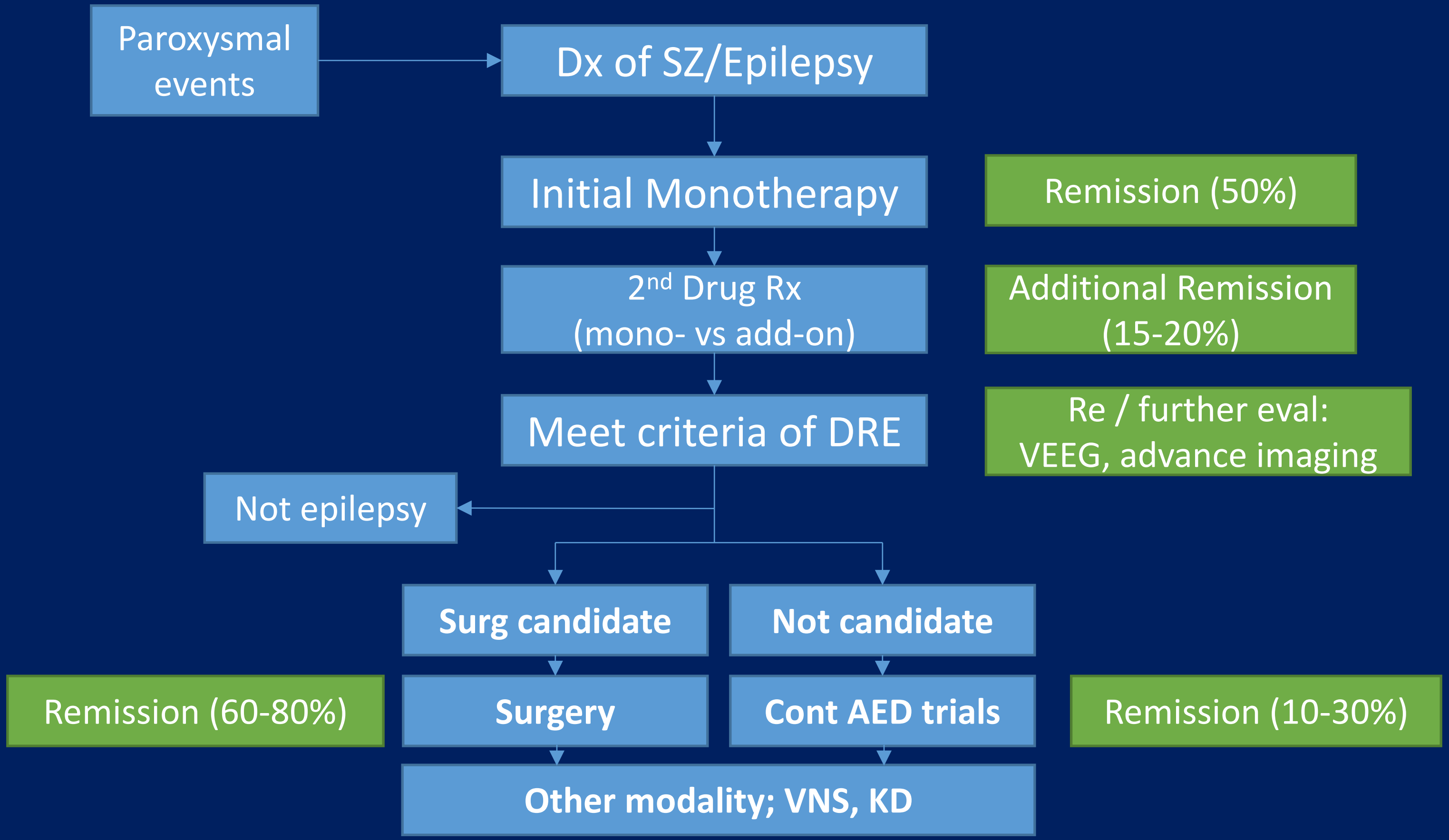


***Figure* 1: Seizure freedom rates after a newly added antiseizure medication, by number of previously tried antiseizure medications**

- 850 DRE focal epilepsy
- Study participants were followed up prospectively over 18 months (max 34 months) after the introduction of another ASM into their regimen.

Perucca E, et al. Lancet Neurol 2023; 22: 723–34
Mula M, et al. Epilepsia 2019; 60: 1114–23

Pathway of epilepsy management



Epilepsy Care

Seizure

Epilepsy diagnosis

Medication trials

Imaging for pathology

Medical intractability

Surgical Consideration

↓

Surgical workup

↓ Surgery

↘ Not surgery

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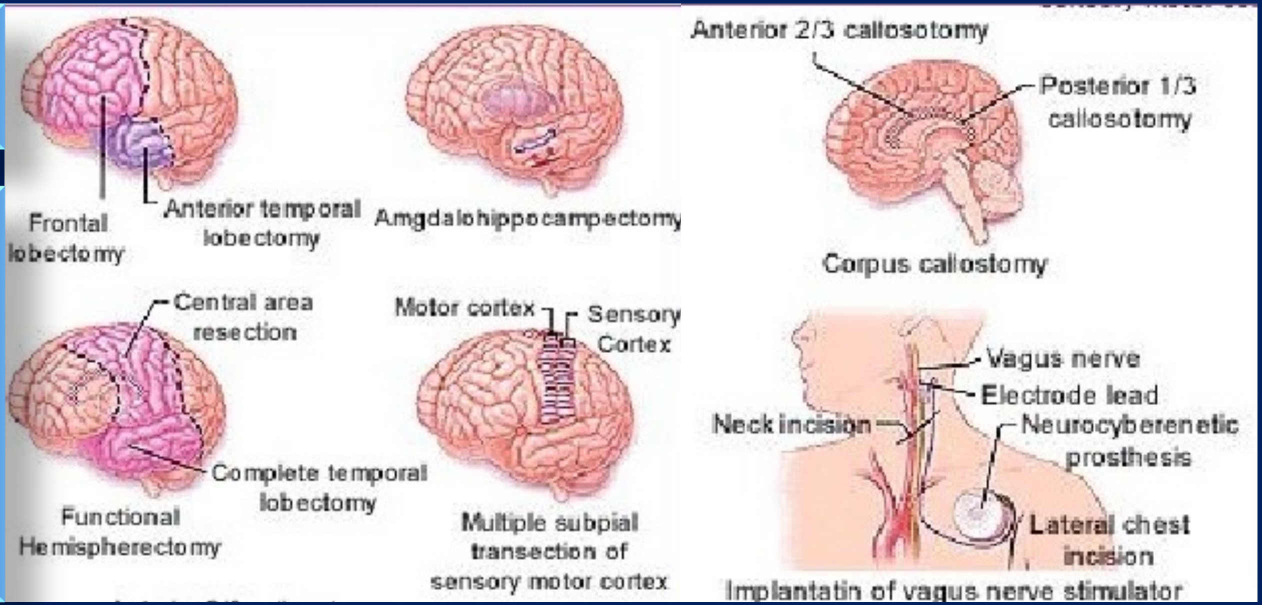
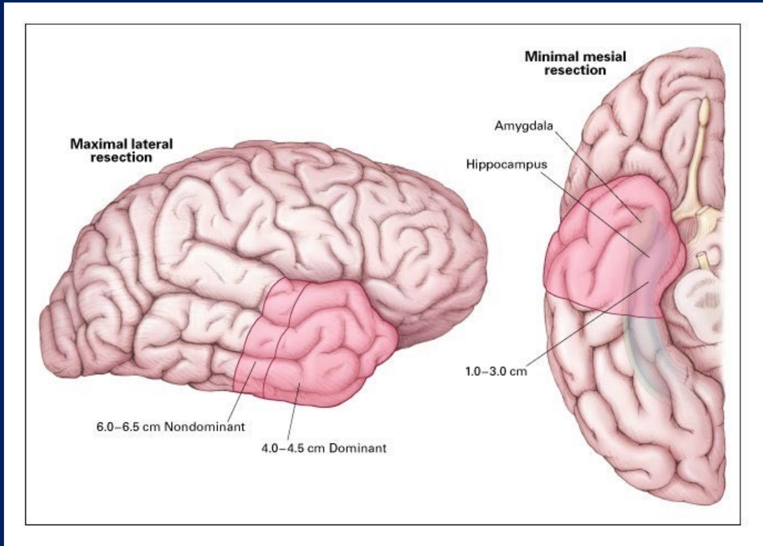
Type of surgical procedure

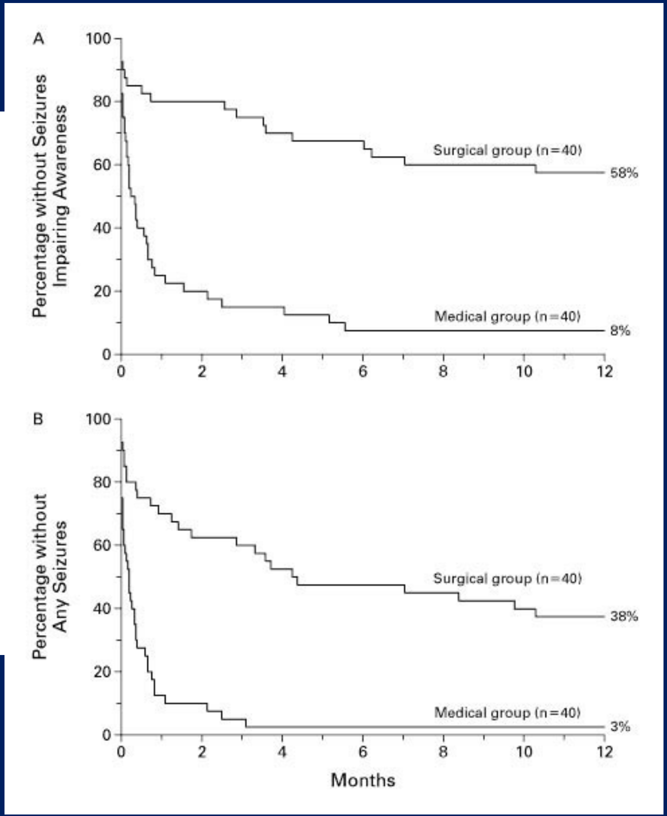
Surgery

- Resective surgery
- Palliative surgery
- Non-resective technique



Anterior temporal lobectomy outcome





Wiebe S. N Engl J Med 2001; 345:311-318

Results of epilepsy surgery

Procedure	SZ free%
Surgically treatable syndromes	
Mesial TLE -> amygdalohippocampectomy w/ or w/o ATL	70-80%
Neocortical epilepsy with single circumscribed lesion -> lesionectomy - Temporal - Extratemporal	 70-80% 60-70%
Poorer outcomes	
Neocortical epilepsy with single poorly-circumscribed lesion: - Temporal - Frontal - Parietal - Occipital	 66% 27-34% 46% 46%
Non-lesional epilepsy - Temporal - Extratemporal	 60% 35%

Neurología. 2015;30 (7):439-446

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DOI: 10.1111/epi.17944

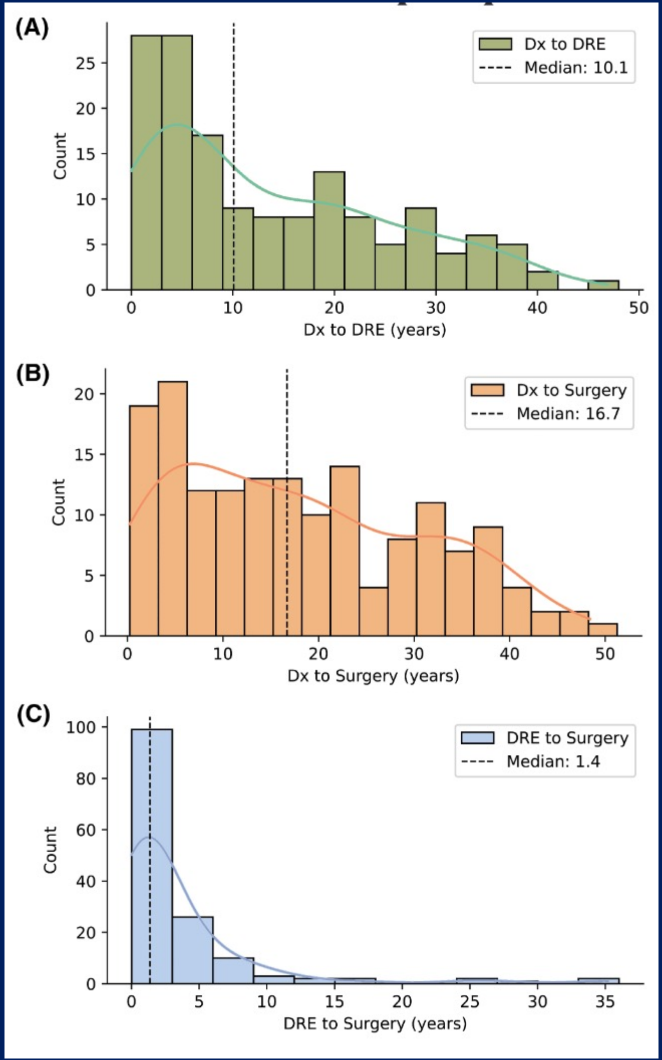
Epilepsia®

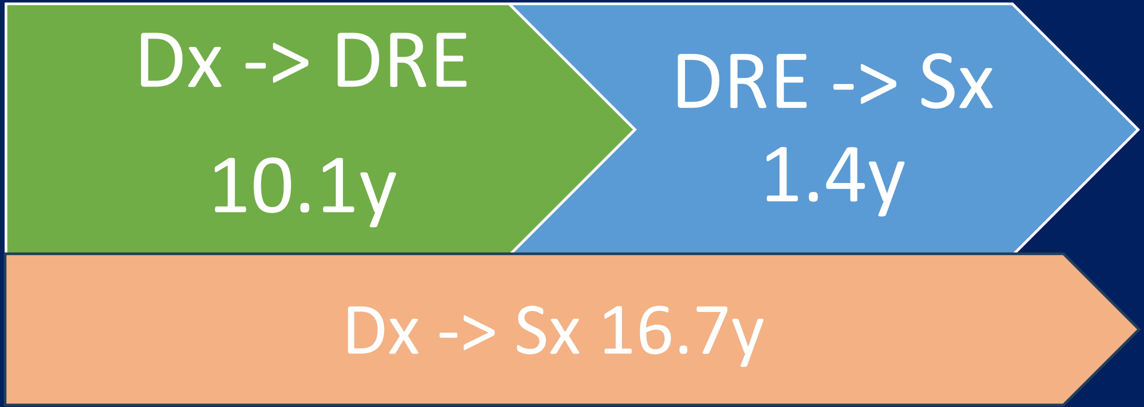
RESEARCH ARTICLE

Delays in the diagnosis and surgical treatment of drug-resistant epilepsy: A cohort study

Justin M. Campbell[1,2] | Samantha Yost[2] | Diwas Gautam[2] | Alysha Herich[2,†] | David Botros[3] | Mason Slaughter[3] | Michael Chodakiewitz[4,5,6] | Amir Arain[7] | Angela Peters[7] | Sindhu Richards[7] | Blake Newman[7] | Brian Johnson[7] | Shervin Rahimpour[3] | Ben Shofty[3]

Campbell JM, et al. Epilepsia. 2024;65:1314–1321





Campbell JM, et al. Epilepsia. 2024;65:1314–1321

Received: 1 March 2022 | Revised: 25 June 2022 | Accepted: 27 June 2022

DOI: 10.1111/epi.17350

Epilepsia

SPECIAL REPORT

Timing of referral to evaluate for epilepsy surgery: Expert Consensus Recommendations from the Surgical Therapies Commission of the International League Against Epilepsy

Lara Jehi[1] | Nathalie Jette[2] | Churl-Su Kwon[3] | Colin B. Josephson[4] | Jorge G. Burneo[5] | Fernando Cendes[6] | Michael R. Sperling[7] | Sallie Baxendale[8] | Robyn M. Busch[1] | Chahnez Charfi Triki[9] | J. Helen Cross[10] | Dana Ekstein[11] | Dario J. Englot[12] | Guoming Luan[13,14,15] | Andre Palmini[16] | Loreto Rios[17] | Xiongfei Wang[13,14,15] | Karl Roessler[18] | Bertil Rydenhag[19] | Georgia Ramantani[20] | Stephan Schuele[21] | Jo M. Wilmshurst[22,23] | Sarah Wilson[24] | Samuel Wiebe[4]

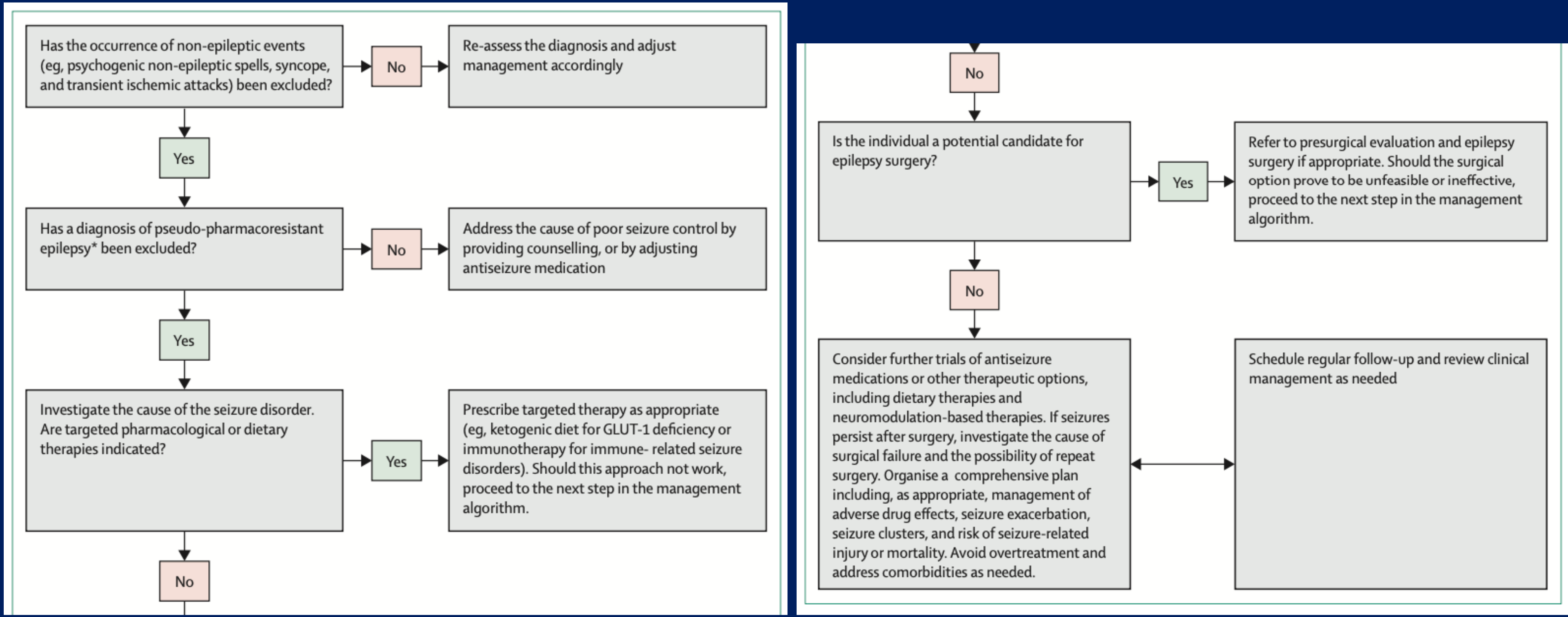
Jehi L, et al. Epilepsia. 2022;63:2491–2506

Recommendation

1. Referral for a surgical evaluation **should** be offered to every patient with DRE (up to 70 years of age), as soon as DRE is ascertained,
2. A surgical referral **should** be considered for
   - older patients with DRE who have no surgical C/I
   - patients who are seizure-free on 1–2 ASMs but have a brain lesion in non-eloquent cortex
3. Referral for surgery **should not** be offered to patients with active substance abuse who are non-cooperative with management

Jehi L, et al. Epilepsia. 2022;63:2491–2506

Guideline for suspected or confirmed DRE



Perucca E, et al. Lancet Neurol 2023; 22: 723–34

Misconception re; epilepsy surgery

Misconception	Fact
Many drugs need to be tried.	After failing two AEDs, the chance of seizure remission is very low.
Multiple or diffuse lesions on MRI contraindicate surgery.	The epileptogenic zone may involve only one lesion, or part of a lesion.
Bilateral EEG spikes contraindicate surgery.	Bilateral interictal spikes are common in people with unilateral seizure onset.
Surgery is not possible if eloquent cortex is involved.	Risks and benefits can be evaluated on a case-by-case basis.
If there is an existing memory deficit, surgery will worsen it.	Poor memory usually will not get worse after surgery, and may improve.
Chronic psychosis contraindicates surgery.	These individuals may benefit from eliminating or reducing seizures.
IQ<70 contraindicates surgery.	These individuals may benefit from eliminating or reducing seizures.

(Adapted from Vakharia et al. Ann Neurol 2018;83:676–690.)

Treatment Alternatives for DRE:

Surgery	Non-Surgery
- Resective surgery - Palliative surgery - Non-resective technique	Diet - Ketogenic diet

Resective surgery

Resect **epileptogenic zone** to eliminate or reduce SZ

Without causing deficits

Indication

DRE with SZs that interfere daily living

The progression timeline should reach > 2 years, except in patients with life-threatening SZs or in children

Epilepsies that can be treated with surgery

Contraindication

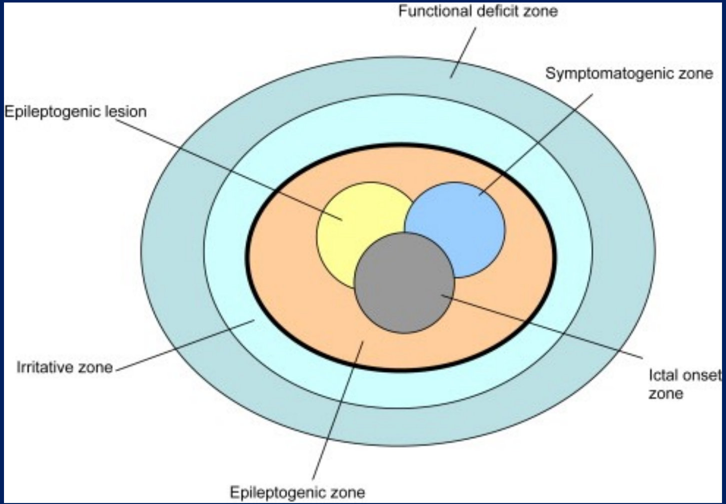
No absolute C/I

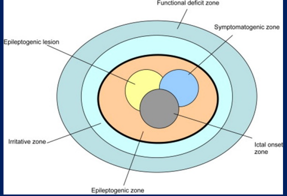
1. Age; in elderly should be carefully assessed
2. Etiology; progressive neurological disease, except Rasmussen encep
3. Concerning comorbidity that high risk for surgery
4. Concomitant psychiatric disorder: if it may compromise the result
5. IQ < 70 shows poorer prognosis; but not absolute C/I

Epileptogenic zone (EZ)

- EZ cannot be directly defined by any test but can be estimated by a number of other zones.

1. Symptomatogenic zone
2. Irritative zone
3. Ictal onset zone
4. Epileptogenic lesion
5. Functional deficit zone



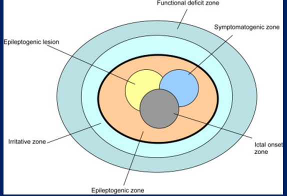


Symptomatogenic zone

- Cortex or regions produce the seizure manifestations.
- Tools: History taking and Video EEG monitoring
- Lateralization >> Localization

- **Caveat**
  - Not focus only motor signs, but also focus on AURA

- **Limitation**
  - Not all the cortex leading to ictal semiology
  - The earliest detected sign may consider as spreading

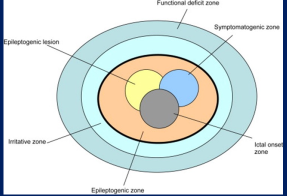


Irritative zone

- Zone that generates interictal epileptiform d/c.
- Tools: EEG, MEG
- Usually localized within the epileptogenic zone.

Limitation

- in some cases → multiple irritative zones, but might be only 1 of corresponding to the epileptogenic zone.

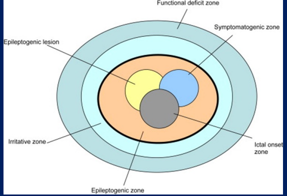


Ictal onset zone

- Area of cortex that is generating seizures.
- Tools: EEG; noninvasive, invasive
- This zone, if accurately defined, is contained within the epileptogenic zone.

Limitation

- The earliest detected ictal activity may have already undergone considerable spread.
- Even with Intracranial EEG recording, the ictal onset zone may be missed unless the electrodes placed directly over that zone.

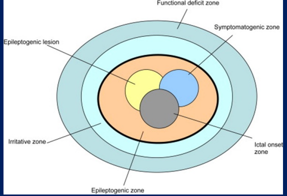


Epileptogenic lesion

- Structural brain on CT or MRI → (presumed) to be the cause of the epilepsy.
- Epileptogenic lesion vs EZ
- EZ - within the lesion
    - cortical dysplasia or hypothalamic hamartoma.
- EZ - from brain surrounding
    - cavernous malformations and benign tumors.

Limitation

- Certain lesions may be accidental findings and not related to the epilepsy. eg. Arachnoid cysts and venous malformations.
- Multifocal lesions, Huge lesion
- Non-lesional MRI



Functional Deficit Zone

- Responsible for functional deficits.
- Tools:
  - Neurological examination
  - Neuropsychological testing
  - Interictal EEG focal slow activity
  - Local glucose uptake by PET
  - Local cerebral blood flow by interictal SPECT.
- While the functional deficit zone may include the epileptogenic zone, it is often considerably larger.

Zones	Tools
Symptomatogenic zones	History taking Video EEG monitoring
Irritative zones	EEG MEG
Ictal onset zones	EEG MEG Ictal SPECT
Epileptogenic lesion	CT or MRI
Functional deficit	Neurological examination Neuropsychological testing Interictal EEG focal slow activity PET, SPECT

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Presurgical Evaluation

- History and Physical Exam
- Video EEG monitoring
  - Noninvasive, invasive
- Imaging
  - MRI
  - Functional MRI: PET , SPECT
- Neuropsychology Evaluation
- Comprehensive Patient Care Conference

- Presurgical work-up is time and labor-intensive and has cost implications.

HISTORY

- Aura and other early SZ semiology help with the lateralize/localization of symptomatogenic zone.
- Ask from patient and witness.
- Neurological examination can identify focal neurological deficits – define the functional deficit zone.

HISTORY

- Specific risk factors can help predict epileptogenic lesion.
- Febrile status epilepticus in infancy has a strong == hippocampal sclerosis.
- Meningitis and encephalitis
  - <age 5 == hippocampal sclerosis
  - >age 5 == neocortical epileptogenic zones.
- Earlier head trauma == hippocampal sclerosis.

EEG & VIDEO-EEG MONITORING

- The interictal focal attenuation and focal slow activity - Functional deficit zone
- Interictal epileptiform discharges – Irritative zones
- EEG localization of seizure onset - ictal onset zone
- Seizure semiology – symptomatogenic zone: lateralizing and localization

Common semiology

- Head turning
  - Early – I/L TLE
  - Late forceful head turning preceding secondary generalization tends to be C/L.
- Oroalimentary automatisms → temporal lobe
- Dystonic posturing is a strong C/L basal ganglia
- Postictal aphasia - dominant hemisphere
- Well-formed ictal speech – nondominant hemisphere
- Ictal vomiting, ictal spitting, ictal drinking - nondominant hemisphere

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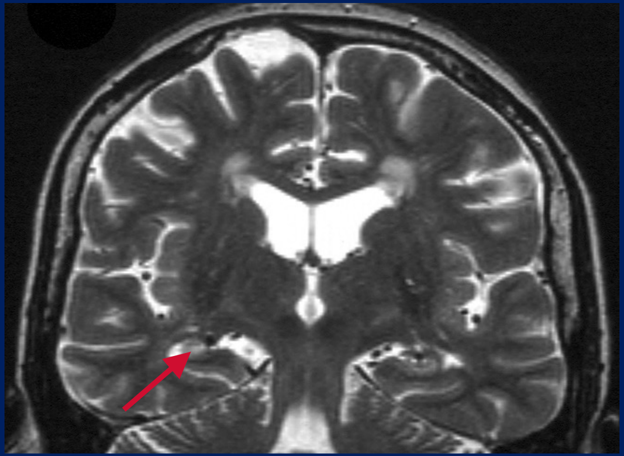
MRI

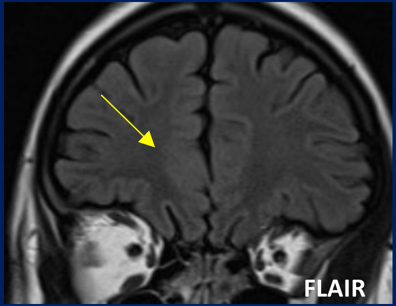
Lesion – epileptogenic lesion

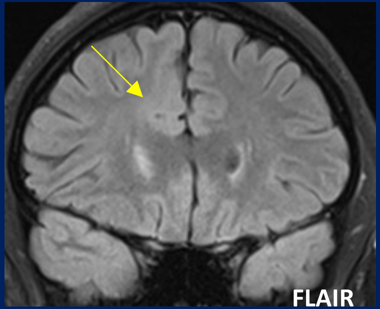
For MTS, MRI should include oblique coronal images perpendicular to the axis of the hippocampus,
including T1-W, T2-W and FLAIR

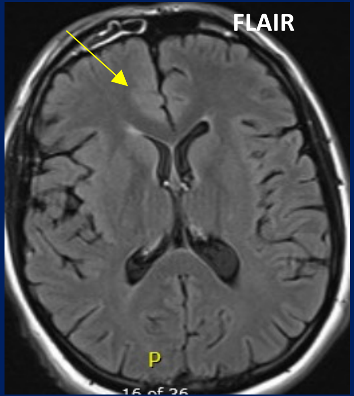


Right hippocampal sclerosis (arrow)

Focal cortical dysplasia



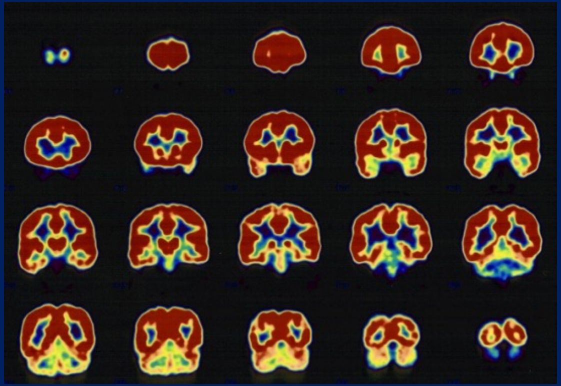


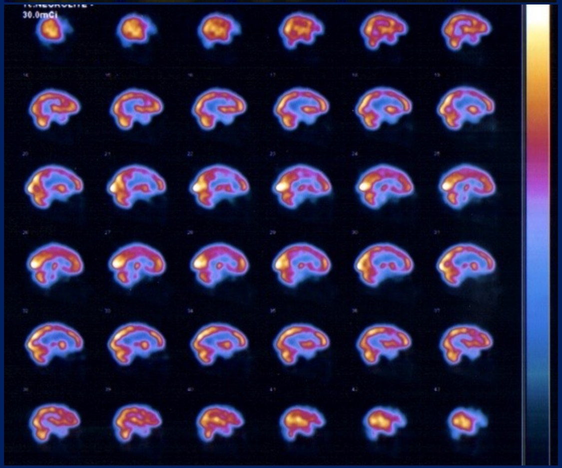


Cortical thickening and hyperintense FLAIR lesion at the right anterior cingulate region.

Functional Imaging

- **PET**
  - hypometabolism interictally
  - Functional deficit zone
- **SPECT**
  - hypoperfusion interictally
  - hyperperfusion ictally – ictal onset zone
- PET and/or SPECT may be coregistered with MRI





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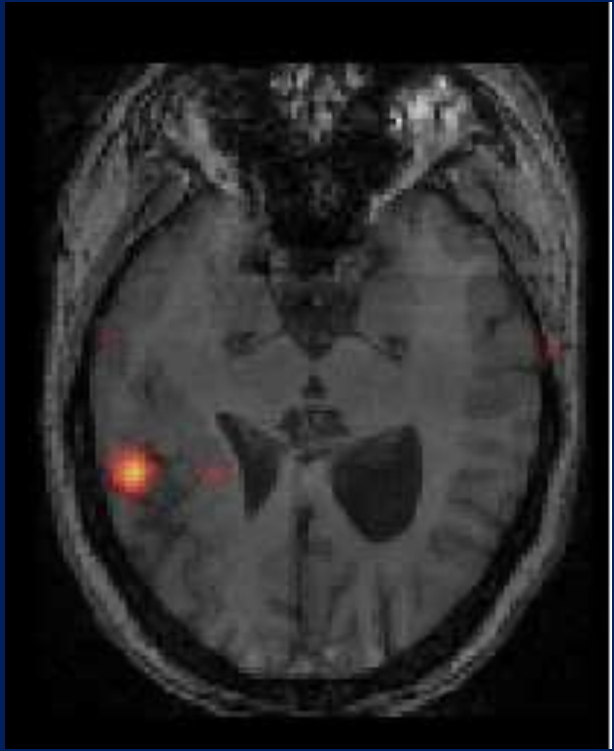
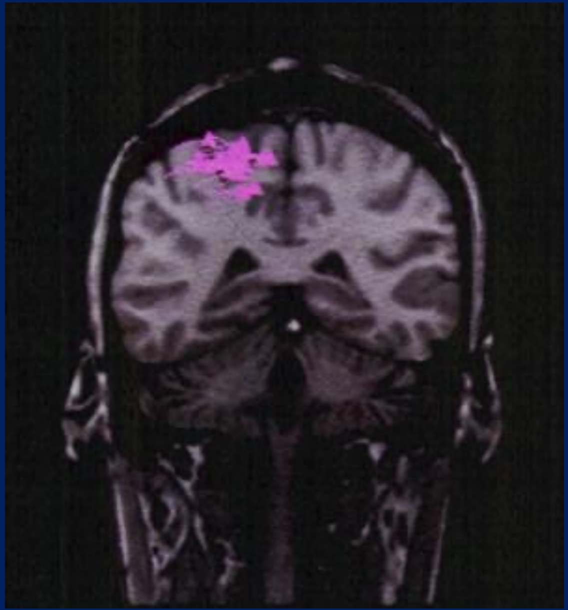
Presurgical Evaluation- SISCOM



SISCOM
(SPECT with MRI coregistration)
in a patient with extratemporal epilepsy

Presurgical Evaluation- MEG

- Magnetoencephalography (MEG)
  - Magnetic source localization of interictal epileptiform discharges
  - Functional mapping



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Testing for Surgical Candidates

Visual fields

- Formal testing if resection will endanger vision

Intracarotid Amobarbital Procedure (Wada)

- Language dominance
- Verbal memory
- Prediction of postoperative decline

NPI Testing includes:

  - IQ battery of tests
  - Language localization
  - Memory- verbal and visual localization
  - Visuospatial function
  - Attention/Executive
  - Motor- coordination and speed

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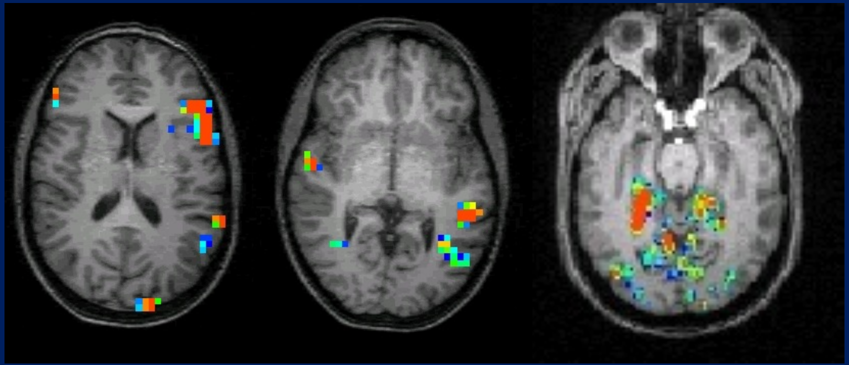
Presurgical evaluation - fMRI

fMRI- language lateralization, hippocampus function, epileptogenic focus assessment

Patient with left TLE

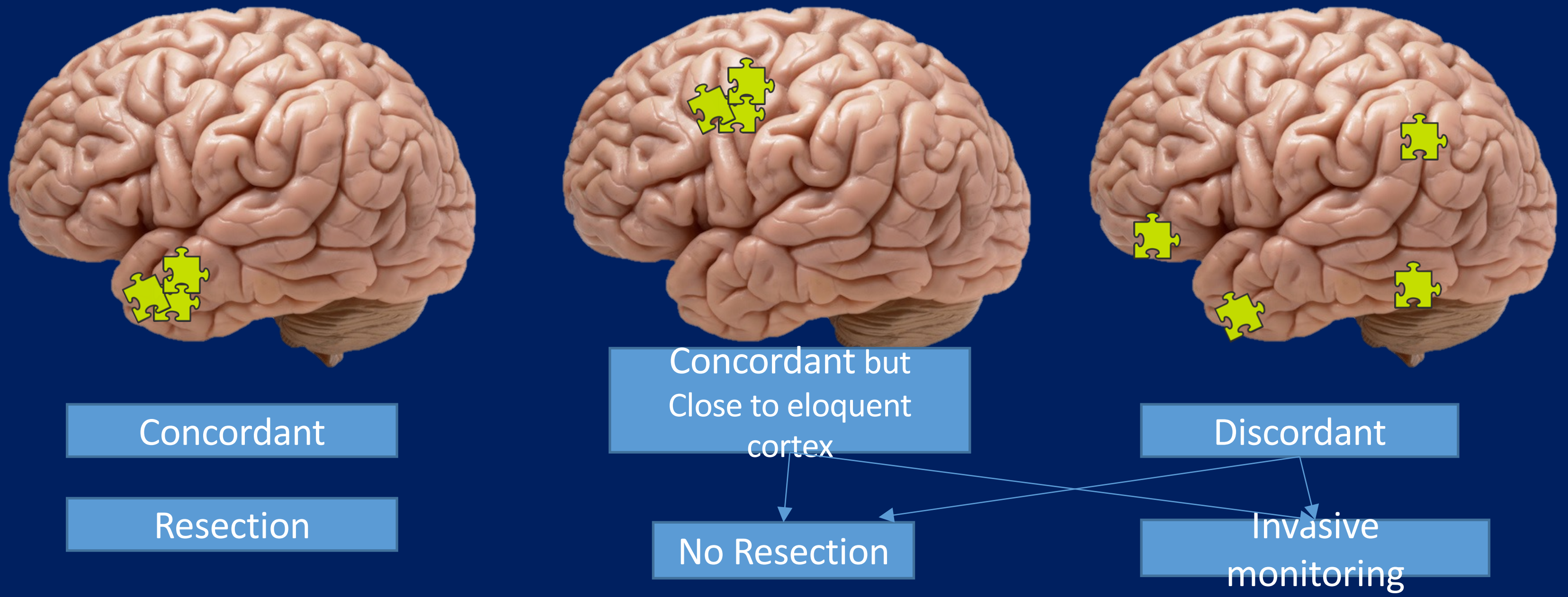
Left: Language mapping with verb generation task - activation in Broca's and Wernicke's areas.

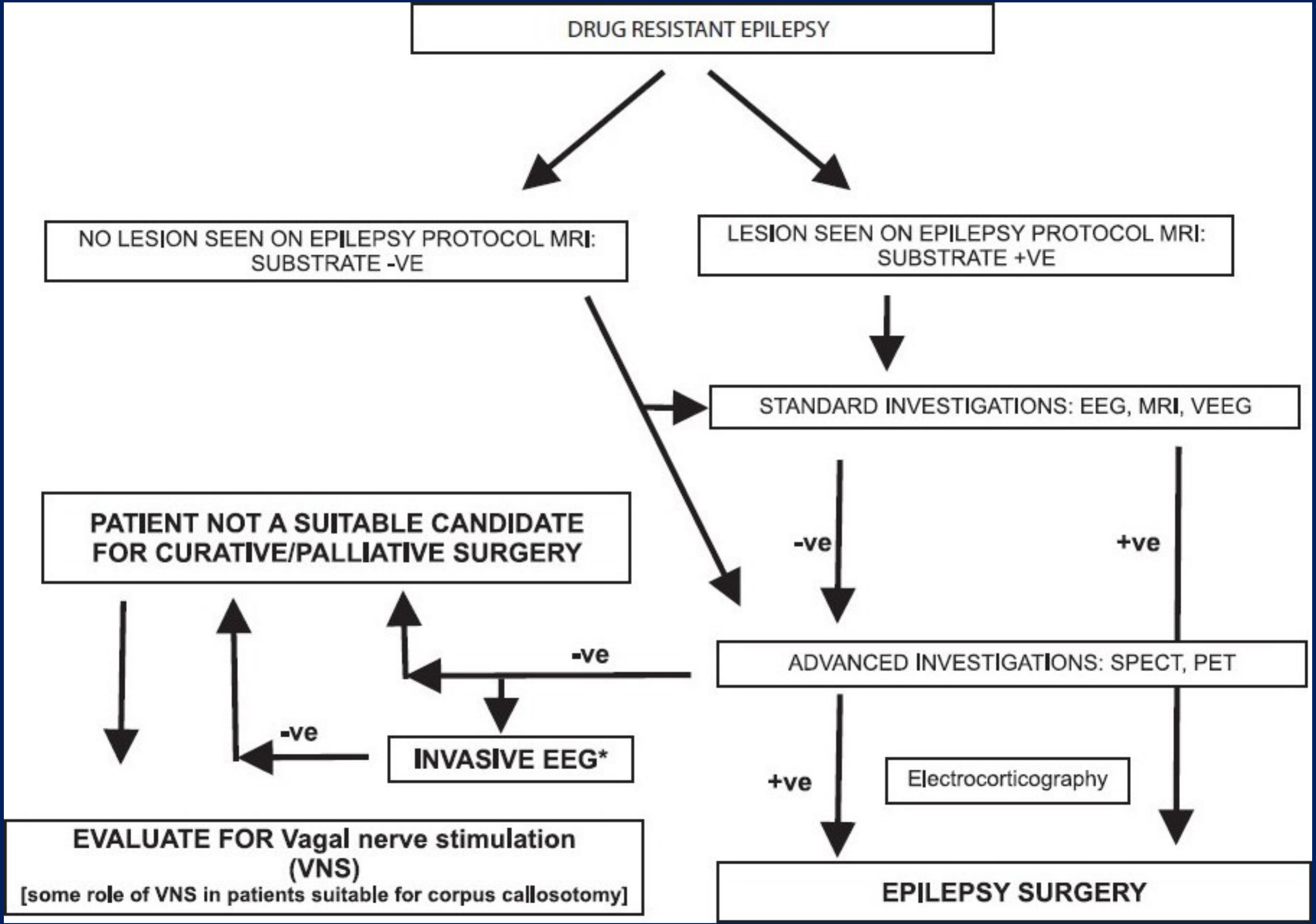
Right: Memory localization with picture encoding task - decreased activation in the left hippocampus.



Comprehensive Patient Care Conference for Surgical Candidates

- Epileptologist presents the patient
- Video-EEG studies are reviewed
  - Semiology
  - Interictal EEG morphology
  - Ictal EEG morphology
- Neuroradiologist discusses imaging studies
- Neuropsychology results are examined
- Neurosurgeon delineates surgical options
- Discussion of risks/benefits/outcomes
- Group consensus


Concordant
Resection
Concordant but Close to eloquent cortex
No Resection
Discordant
Invasive monitoring

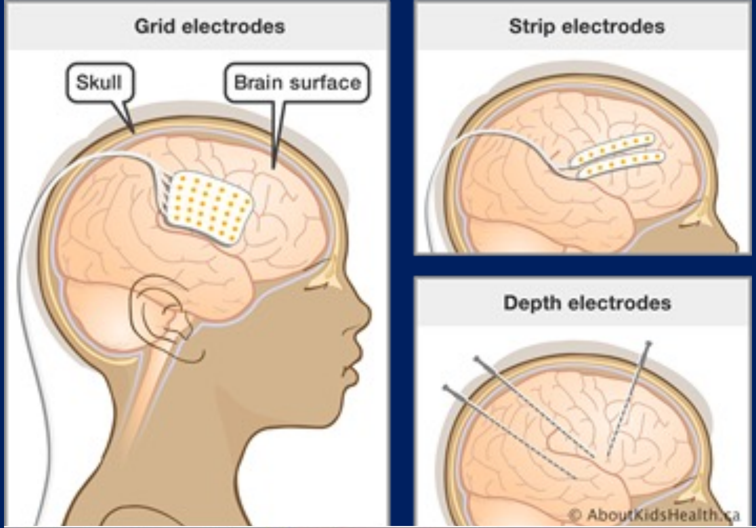


Annals of Indian Academy of Neurology 2010 13(2):87-93

Invasive intracranial monitoring

- Conditions require Invasive intracranial monitoring

1. SZs are lateralized but not localized. Seizures are localized but not lateralized.
2. SZ are neither localized nor lateralized.
3. SZ localization is discordant with other data.
4. SZ onset to functional tissue must be determined: close to eloquent cortex.


Grid electrodes
Skull
Brain surface
Strip electrodes
Depth electrodes
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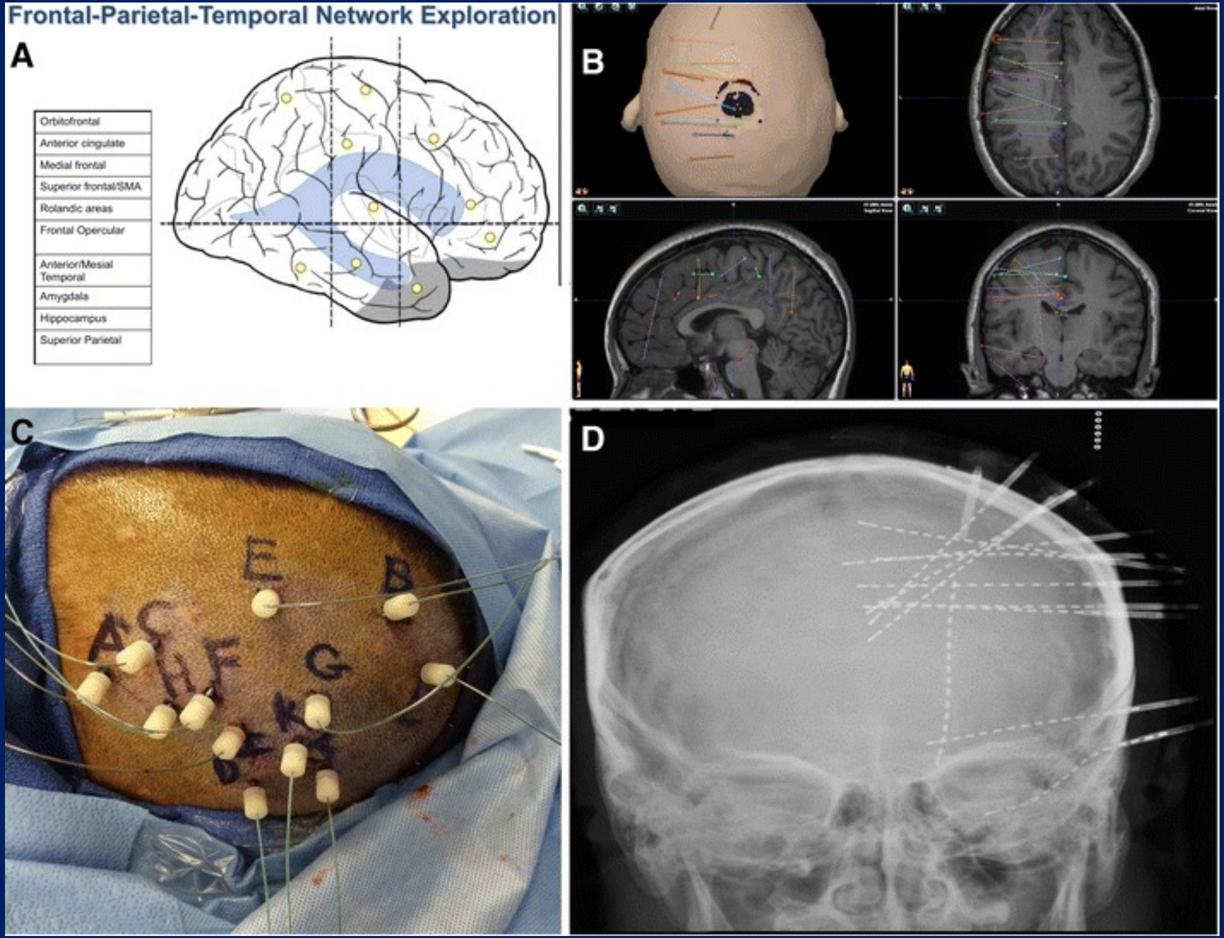
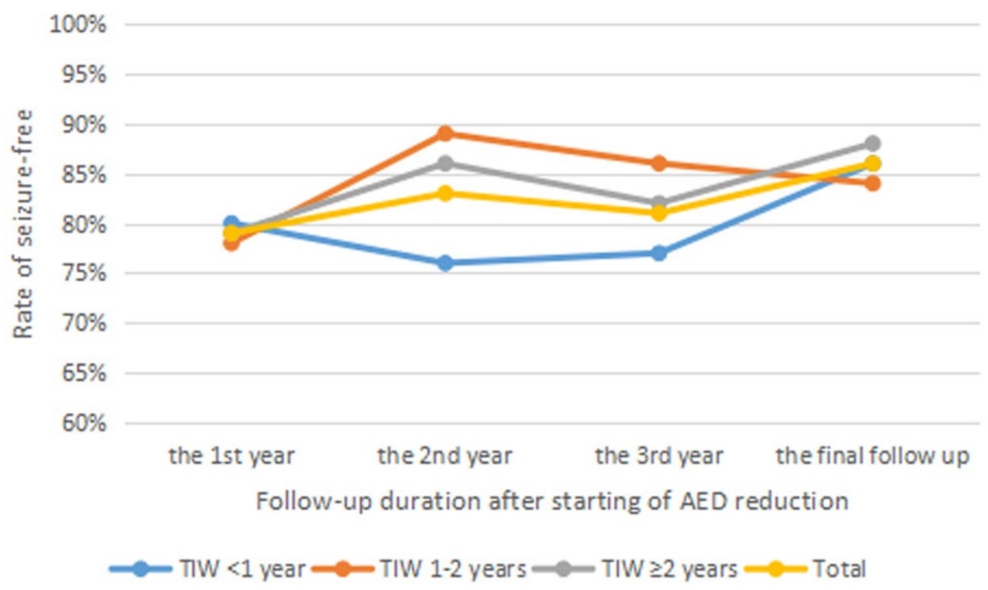
Stereotactic EEG (SEEG)



Postoperative ASM withdrawal

- Early withdrawal (at 6 or 9 months)
- Late withdrawal (after 1 or 2 years)
- What to concern? – side effects of ASMs vs recurrent SZ
- Overall studies; SZ after surgery easier to control than pre-op



TIW; time interval to start ASM withdrawal

- No significant Different
- 50% SZ recurrent
- 62% SZ free at final f/u
- Favorable factor at 1 year; Temporal lobe surgery
- Unfavorable; post-op GTC

Zhang L, et al. Scientific REPORTS (2018) 8:13782
DOI:10.1038/s41598-018-31092-3

Summary

- DRE takes 1/3 of all epilepsy patients
- Surgical treatment should be considered if possible; lesion, temporal.
- Delay epilepsy surgery showed poorer outcome, so referal to epilepsy center should be offered in DRE patients.