

Surgical Treatment of Epilepsy

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DEFINITION OF PHARMACORESISTANCE

Drug-resistant \neq Treatment-resistant

N.B. pharmacoresistance is diagnosed by history taking!

Medical intractability (pharmacoresistant epilepsy)

A. Failed 2 medications

2 trials of AEDs at optimal doses with appropriate medications are sufficient to consider referral of patients with focal seizure disorder for presurgical evaluation

- Commission on Therapeutic Strategies of the International League Against Epilepsy (ILAE) definition (officially adopted at the ILAE's 2009 meeting in Budapest, Hungary):
"DRUG-RESISTANT EPILEPSY - failure of adequate trials of **two** tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve **sustained seizure freedom**." – i.e. complete epilepsy control!

B. Failed 3 medications – obsolete!!!

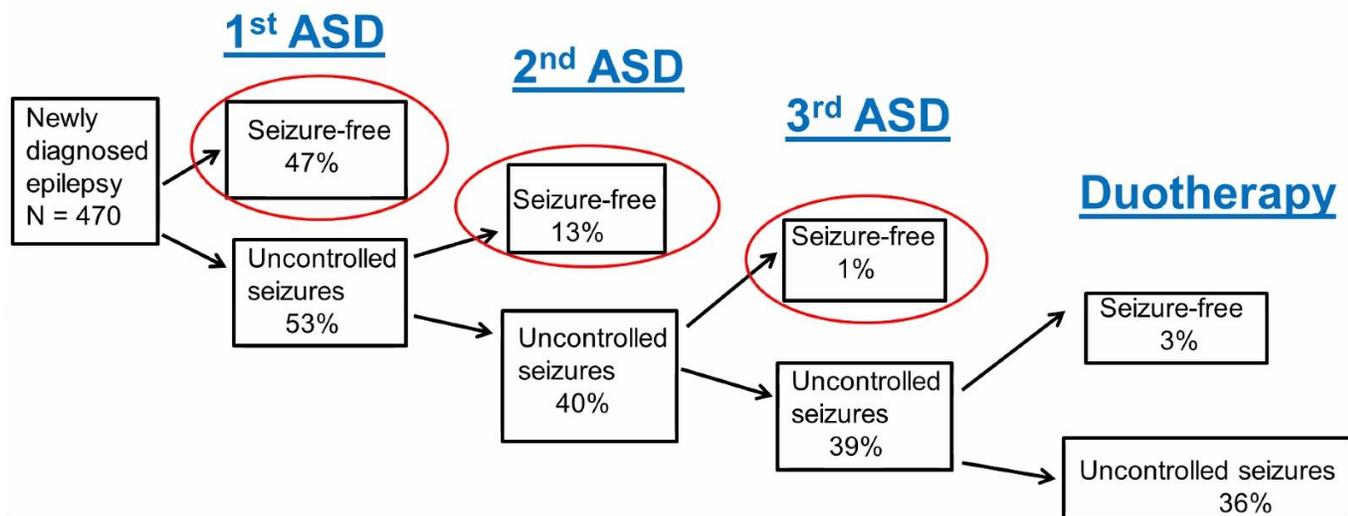
- some advocate at least 3 regimens, including *2 trials of high-dose monotherapy + 1 trial of 2-drug therapy*.
- these therapeutic trials can be accomplished within *6-12 months* - depending on frequency of seizures at baseline (i.e. how quickly can see treatment results).
- no rationale to try different medications with the same mechanism of action.

EPIDEMIOLOGY OF PHARMACORESISTANCE

20-30% patients are not controlled adequately with AED!
(\approx 1/2 of them are potential surgery candidates)

Prevalence of pharmacoresistance: 17% (if count > 1 sz / month) or 26% if count > 1 sz / year)

- among **all patients with epilepsy**, 60-70% are expected to become seizure-free with AEDs:
 - 47% of patients respond to first AED
 - additional 14% respond to second AED
 - additional 3% respond to third AED
 - 36% of patients are refractory**



Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med.* 2000;342(5):314–319

N.B. development of new medications did not change these figures! (same numbers in 2008 Kwan and Brodie study)

Response to first AED is most important predictor of drug-resistant epilepsy!

CHALLENGING THE ABOVE FIGURES

It is true that in Kwan and Brodie's seminal 2000 study, only 4% of the entire study cohort achieved seizure freedom after 2 failed medications. And in the 2018 follow-up by Chen et al, only 4.4% of the study cohort became seizure-free on a third medication regimen.

N.B. *most people in the 2000 and 2018 studies didn't try a third medication regimen* - so they cannot be included when calculating a success rate (i.e. seizure freedom rate for any given medication regimen must include only the patients who tried that regimen, and exclude those who have not)

2018 Kwan and Brodie study: among people who tried a 3rd medication, 23.6% achieved seizure freedom. (15% - 4th, 14.1% - 5th, 14% - 6th medication):

Rates of 1-year seizure freedom with successive anti-epilepsy drug regimens

Regimen	Number of people attempting regimen	Of those who attempted, number achieving seizure freedom	Seizure freedom rate	Number eligible to try next regimen*
First	1,795	820	45.7%	975
Second	742	208	28.0%	534
Third	330	78	23.6%	252
Fourth	140	21	15.0%	119
Fifth	71	10	14.1%	61
Sixth	43	6	14.0%	37
Seventh	15	1	6.7%	14
Eighth	9	0	0%	9
Ninth	5	0	0%	5
Tenth	2	0	0%	2
Eleventh	1	0	0%	1

* This group includes all patients not achieving 1-year seizure freedom, including those who stopped taking medication due to adverse effects, pregnancy, or other concerns. Not all eligible patients go on to try subsequent regimens.

Data from Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol.* 2018;75(3):279-286. doi:10.1001/jamaneurol.2017.3949

- another study showed slightly more optimistic results: 18.5% and 16.5% were made seizure free with a third and fourth AED, respectively, and decreased to 0% after 5 or 6 previous AED failures.
Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology 2008;70(1):54-65
- CRT (16 U.S. centers) of 38 patients with mesial temporal lobe epilepsy of < 2 years duration who failed 2 brand-name AEDs: 0 of 23 patients assigned to continued medical optimization achieved seizure freedom with drug adjustments alone during 2 years of follow up (vs. 11 of 15 in the surgical group became seizure free).
Engel J Jr, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012 Mar 7;307(9):922-30.
- positive therapeutic expectations of AEDs vary according to epileptic syndrome:
 - 80-90% of patients with **idiopathic generalized seizures** are expected to become seizure-free;
 - only 50% of patients with focal seizure disorders are expected to become seizure-free (seizure-freedom may decrease to 30% in cases of temporal lobe epilepsy secondary to **mesial temporal sclerosis** or be as high as 95% in cases of **benign rolandic epilepsy of childhood**).

MECHANISM OF PHARMACORESISTANCE

- remains incompletely understood.

Target hypothesis - changes in the AED targets, such as ion channels, lead to decreased drug efficacy.

Transporter hypothesis - efflux pumps are thought to restrict AED movement into cells and to be overexpressed in patients resistant to AEDs; P-glycoprotein (Pgp) is one such multidrug transporter that has been implicated in drug-resistant epilepsy.

INDICATIONS

Seizures refractory to appropriate medical management

+ seizures seriously **limit** patient's **activities***

+ **well-defined** epileptogenic **focus** not involving eloquent cortex – obsolete condition**.

*patients' **quality of life** must be included (e.g. even as few as 2-3 seizures year may be disabling to individual whose occupation requires transportation with motor vehicle; vs. homebound patients who are not physically harmed by their seizures).

**cortical resection must not intentionally produce significant neurologic deficit such as aphasia or hemiparesis; this is obsolete – RNS / DBS / VNS can treat those patients!

N.B. pharmacoresistance per se is not an indication for surgery!

DRUG-RESISTANT ≠ TREATMENT-RESISTANT

Make sure it is epilepsy and not something else (once a while a mistake is made when cardiac arrhythmias mimic epilepsy)

Complex partial seizures or **partial seizures with secondary generalization** are seizure types most amenable to surgical resection

Today, most “ideal” pathology for surgery is **right-sided temporal lobe epilepsy**.

- N.B. temporal lobe epilepsy is *most medically refractory* but surgical results are the best!
 – studies show that surgical results for frontal lobe epilepsy are also good.

Canadian Appropriateness of Epilepsy Surgery (CASES) tool - a highly sensitive guide for determining candidacy for epilepsy surgery

Jette N, Quan H, Tellez-Zenteno JF, et al. Development of an online tool to determine appropriateness for an epilepsy surgery evaluation. Neurology. 2012;79:1084–93

Online: www.epilepsycases.com

REFERRAL TO EPILEPSY CENTER

- **individuals who have continued seizures after treatment with ≥ 2 AEDs has failed** are very unlikely to achieve seizure freedom with medical treatment alone → guidelines recommend that these patients be **referred to a comprehensive epilepsy center**.

Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology. 2003;60(4):538–547.

Labiner DM, Bagic AI, Herman ST, et al. Essential services, personnel, and facilities in specialized epilepsy centers-revised 2010 guidelines. Epilepsia. 2010;51(11):2322–2333.

Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommittee for Pediatric Epilepsy Surgery. *Epilepsia*. 2006;47(6):952–959.

Patients in whom ≥ 2 AEDs (appropriately chosen and tolerated) have failed to completely control epilepsy (sustained seizure freedom) should be considered drug resistant and referred to a comprehensive epilepsy center for surgical evaluation

National Association of Epilepsy Centers >>

- if you see a **family doctor**, and you are continuing to have seizures, you should ask for **another opinion after 3 months**.
- if you are seeing a **neurologist**, and the seizures have not been brought under control **after 9 to 12 months**, then you should ask for a referral to a **specialized epilepsy center**.

N.B. only one-third of cases general neurologists aligned with epileptologists' opinions.

Erba G, Moja L, Beghi E, et al. Barriers toward epilepsy surgery. A survey among practicing neurologists. Epilepsia. 2012;53:35–43.

- NAEC recommends that patients whose seizures are not fully controlled after treatment for **one year** be referred to a level 3 or 4 specialized epilepsy center.
N.B. patients benefit from the advanced care provided by epilepsy centers if they continue to have seizures despite treatment with **two medications**, experience **unacceptable side effects**, are / want to become **pregnant**.

LEVEL OF CARE AND MORTALITY

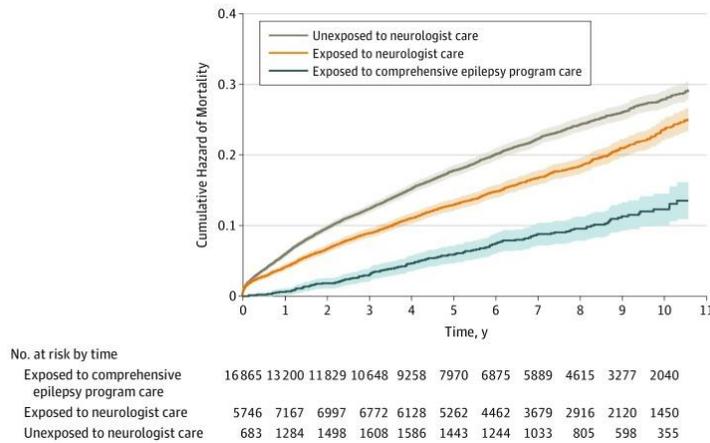
- patients with epilepsy are at an elevated risk of premature mortality.

Canadian study – all-cause premature mortality in epilepsy vs level of care

Lowerison MW, Josephson CB, Jetté N, et al. Association of Levels of Specialized Care With Risk of Premature Mortality in Patients With Epilepsy. JAMA Neurol. 2019;76:1352-1358.

- retrospective study of 23 653 adults (2002-2016).
- carefully control for age, sex, sociodemographic factors, disease severity, and comorbidities.
- 60% were not exposed to specialist neurological care, 40% received care by a neurologist, and 9% received care in the comprehensive epilepsy program.
- standardized mortality rate was 7.2% for the entire cohort; by level of care:
 - **9.4%** - for those receiving nonspecialist care;
 - **5.6%** - for those seen by a neurologist (HR 0.85; 95% CI 0.77-0.93);
 - **2.8%** - for those seen in the comprehensive epilepsy program (HR 0.49; 95% CI 0.38-0.62).
- **exposure to specialist care** (non-neurologist vs. neurologist vs. comprehensive epilepsy program) is associated with an incremental reduction in the risk of premature mortality from all-causes. Those referred to a comprehensive epilepsy program received the greatest benefit.
N.B. importance of early referral!
- possible causes of the observed benefit:
 - 1) expediting an accurate initial diagnosis
 - 2) selecting the right antiepileptic drug at the first opportunity
 - 3) experience in using rational polytherapy
 - 4) greater chances of receiving a new drug with fewer adverse effects
 - 5) access to epilepsy surgery

Mortality Over Time



BARRIERS FOR TIMELY REFERRALS

- epilepsy surgery results in significantly:

- 1) reduced mortality

Sperling MR, Barshow S, Nei M, Asadi-Pooya AA. A reappraisal of mortality after epilepsy surgery. Neurology. 2016;86:1938–44

- 2) increased quality of life

Choi H, Sell RL, Lenert L, et al. Epilepsy surgery for pharmacoresistant temporal lobe epilepsy: a decision analysis. JAMA. 2008;300:2497–505

- referral rates from physicians and approval rates by patients for presurgical assessment remain constantly low.
- neurologists from several countries defined medically refractory epilepsy as a failure of 3-5 AED monotherapy trials = delaying referral to epilepsy surgery

Hakimi AS, Spanaki MV, Schuh LA, Smith BJ, Schultz L. A survey of neurologists' views on epilepsy surgery and medically refractory epilepsy. Epilepsy Behav. 2008;13:96–101.

Erba G, Moja L, Beghi E, et al. Barriers toward epilepsy surgery. A survey among practicing neurologists. Epilepsia. 2012;53:35–43.
- in two recent surveys from Canada and Italy, > 50% of affected patients stated that they considered epilepsy surgery to be very dangerous and > 60% saw it as a last resort treatment only.

Erba G, Messina P, Pupillo E, Beghi E; OPTEFF Group. Acceptance of epilepsy surgery among adults with epilepsy—what do patients think? Epilepsy Behav. 2012;24:352–8

Hrazdil C, Roberts JJ, Wiebe S, et al. Patient perceptions and barriers to epilepsy surgery: evaluation in a large health region. Epilepsy Behav. 2013;28:52–65.

Study of 185 German patients in tertiary epilepsy care center (Charité University Hospital) - how many patients with intractable focal epilepsy were recommended by their epileptologists to undergo presurgical evaluation with noninvasive v EEG and how many patients followed this recommendation.

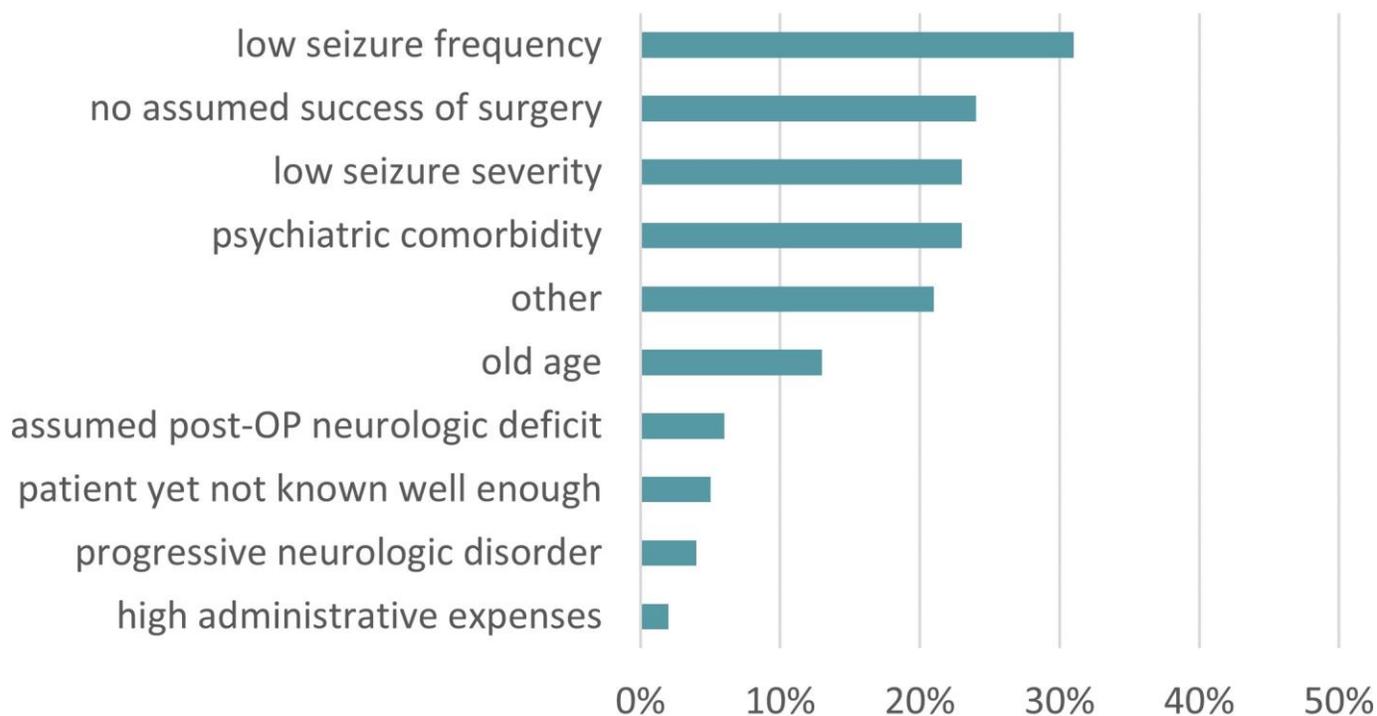
Mirja Steinbrenner et al. Referral to evaluation for epilepsy surgery: Reluctance by epileptologists and patients. Epilepsia. 17 January 2019

- high decision rates against presurgical assessment:
 - 43% were recommended presurgical evaluation by their epileptologists, and only 30% of these patients consented (79% of these had vEEG).
 - 10% of all patients actually underwent noninvasive presurgical assessment, and 5% of these eventually proceeded to resection.

Epileptologists

- the most frequent reason for nonreferral by epileptologists - low seizure frequency (31%):

Epileptologists' reasons for non-referral



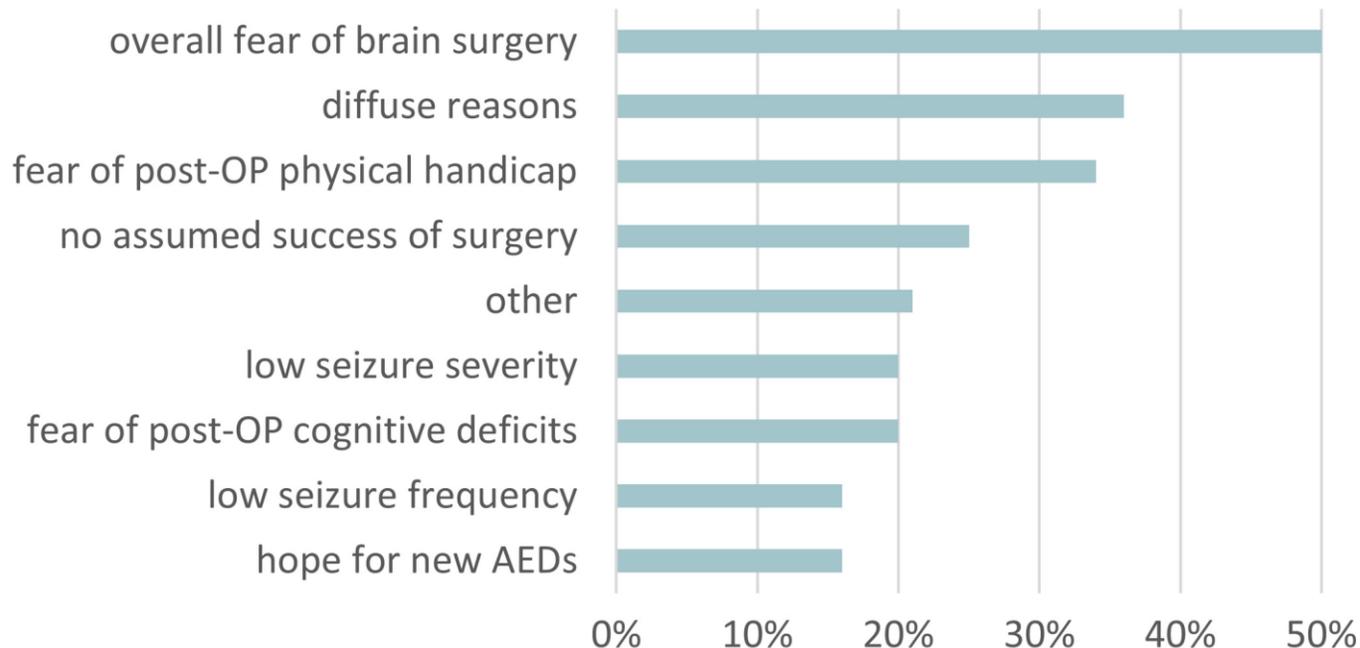
Comments:

- low seizure frequency and severity may be reasonable in some cases (e.g., patients who have one or two focal seizures with impaired awareness per year or who have focal aware seizures exclusively) ;
- severe intellectual disability - even patients with an IQ of 50-69 have been reported to become seizure-free in 37% of cases.
- age > 60 years is not associated with a more unfavorable outcome after seizure focus resection, and patients of this age group should also be offered surgery if eligible
- variables independently associated with nonreferral by epileptologists:
 - 1) older age of patients (odds ratio [OR] = 1.03)
 - 2) no previous evaluation for epilepsy surgery (OR = 4.04)
 - 3) presence of legal guardianship (OR = 4.29)
 - 4) ≥ 11 years of professional experience (OR = 4.62) - reflects higher vigilance of younger generation of epileptologists due to an update in training on the benefits of epilepsy surgery.

Patients

- patients declined most often due to overall fear of brain low surgery (50%):

Patients' reasons for rejecting referral



Other reasons:

- wanting to wait for the evaluation until their children were older in case something “bad” happened to them.
- being content with the current seizure situation and not wanting any change (e.g. seizure freedom may result in reduction or loss of disability pension).
- independent predictors for patients’ rejection of presurgical evaluation:
 - 1) older age (OR = 1.08)
 - 2) lifetime number of antiepileptic drugs ≥ 5 (OR = 4.47)
 - 3) focal aware seizures (OR = 4.37)
 - 4) absence of focal seizures with impaired awareness (OR = 11.24).

TIMING OF SURGERY

Surgery should be performed as early as possible!!! (surgery is no longer therapy of last resort)

Epilepsy is progressive disease! (kindling, new foci, network damage)

- intractable seizures, the longer they persist, portend poorer prognosis for seizure remission and psychosocial outcome (e.g. “mirror” foci can become established as independent foci).
- strategy of *trying all combinations of drugs* is **not acceptable** in syndromes known to have excellent chances of benefiting from surgery.
- it is especially important in **children**, when epileptogenic discharges interfere with normal development! (language can shift to opposite hemisphere if surgery is performed while patient is < 6 years).

N.B. even patients only few months of age are treated surgically if surgery is treatment of choice!

Despite reported success, surgery for pharmacoresistant seizures is often seen as a last resort. Patients are typically referred for surgery after 20 years of seizures, often too late to avoid significant disability and premature death.

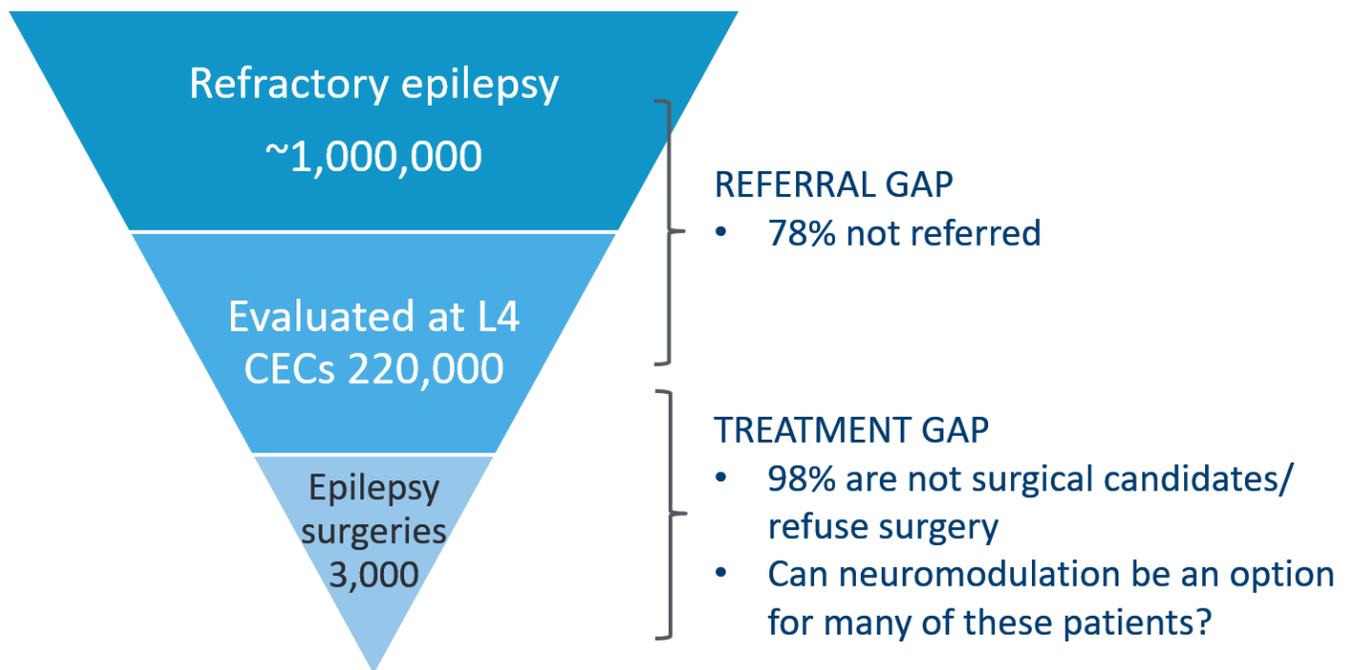
- neurosurgery in patients’ minds is notorious for poor outcomes and mortality in severe TBI, malignant tumors, vascular pathology.

- patients don't know that neurosurgery for epilepsy is very safe (made possible by technological advances and multidisciplinary team work).

Tell patients about the risk of SUDEP in uncontrolled epilepsy! It is not to scare your patient; it is your obligation (“I am obligated to tell you about SUDEP, the same as I tell my patients about diagnosis of cancer and life expectancy”)

Given results of Brodie (2000) and Schiller (2008) studies, timing of surgery should be individualized:

- for **MTS** in which the seizure-free rate is high and the risk low after both ablative and resective surgery, surgery may be considered *earlier, that is, after 2 drug failures*.
- when the chance of seizure freedom after surgery is possibly lower, such as in the **absence of MTS**, and risk is correspondingly higher in the setting of preserved neurocognitive functions, ablative surgical treatment might be delayed until *after a more exhaustive regimen of AEDs or neuromodulation have been attempted*.



Do not delay neuromodulation – involved networks may get damaged as time goes.

STRATEGIES TO IMPROVE PATIENT AGREEMENT

- we work in strong **multidisciplinary team**.
- reassure - we **do not remove normal brain tissue**.
- when counseling patient, **talk about complications at the last step** (cf. car sales people – do not start with “with the car you can get into accident and die”)

CONTRAINDICATIONS

- 1) benign partial childhood epilepsy

- 2) significant noncompliance
- 3) progressive neurologic diseases
- 4) severe concurrent medical illness

Relative contraindications:

- 1) generalized epilepsy (indication for corpus callosotomy or VNS or DBS)
- 2) mental retardation / low IQ (< 70)
- 3) psychiatric disease (psychosis or other serious psychiatric disorder)
- 4) multiple seizure types arising from different brain regions (unless one seizure type is most frequent and disabling)
- 5) coexistence of epileptic and nonepileptic seizures.

Not contraindications:

- 1) epileptogenic focus in *dominant hemisphere*
- 2) epileptogenic focus in *eloquent cortex*
- 3) *bilateral* or *multifocal* epileptogenic foci
- 4) *neurological deficits* on examination

DEFINITIONS OF SURGICAL ZONES

Epileptogenic lesion s. Seizure Onset Zone (SOZ) – lesion / area able to *produce seizures*; needs to be included in resection.

Epileptogenic zone (EZ) (**ictal onset zone + ictal forming zone**) for topography see p. E1 >> – cortical area that *needs to be resected / disconnected / thermo-coagulated / thermo-ablated / desynchronized by multiple transections* in order to make patient seizure free.

- it *cannot be determined directly* (unless surgery is done and patient became seizure free) but it is deduced by outlining related cortical areas, including the irritative zone, the seizure onset zone, the epileptogenic lesion, the symptomatogenic zone, and the functional deficit zone.
- may be *larger than lesion* visible on MRI (includes lesion and surrounding margin, sometimes extends beyond brain lobe boundaries; e.g. cavernoma itself is not epileptogenic but adjacent hemosiderin-lade cortex is) – role of **intracranial EEG**.

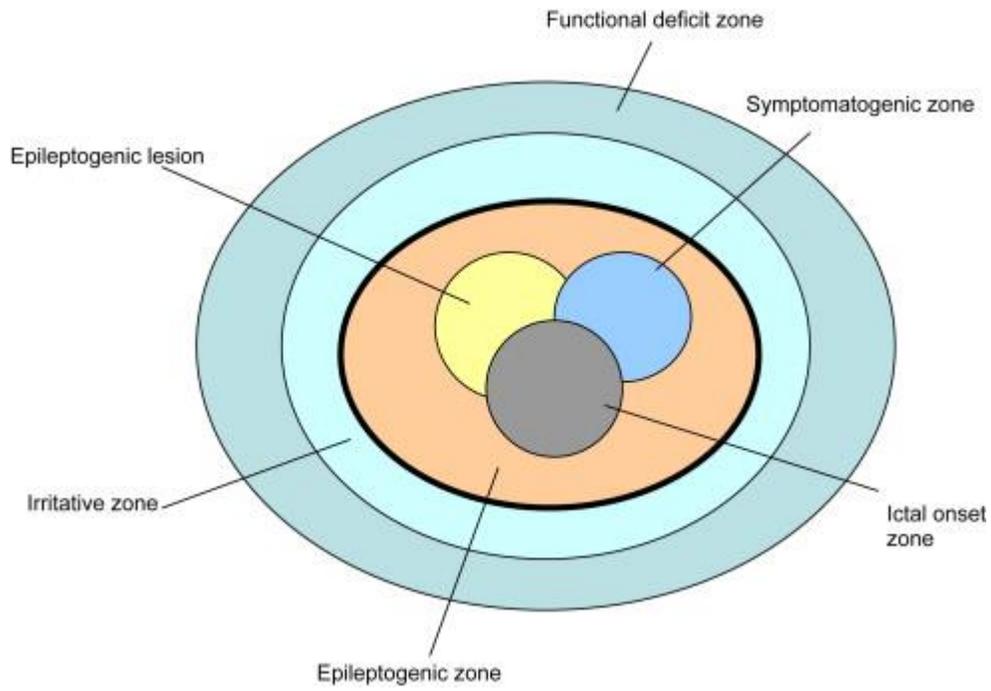
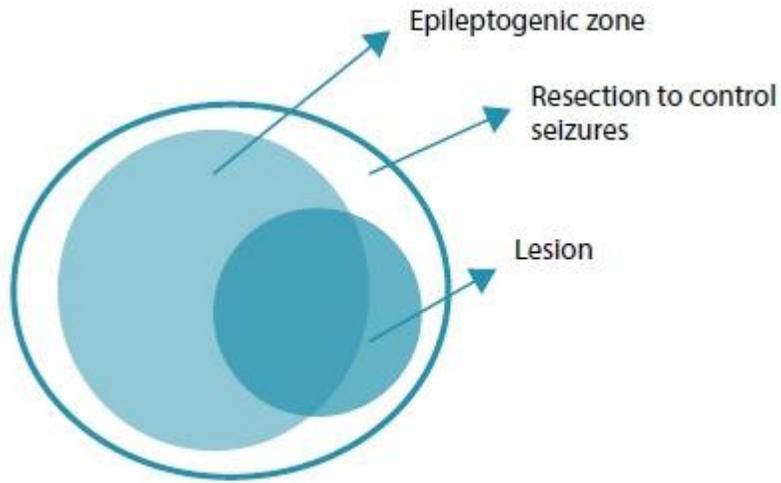
N.B. it is essential to resect EZ and not just SOZ

Irritative zone – cortical area generating epileptiform discharges but whose *resection is not necessary**; usually *larger than epileptogenic zone*.

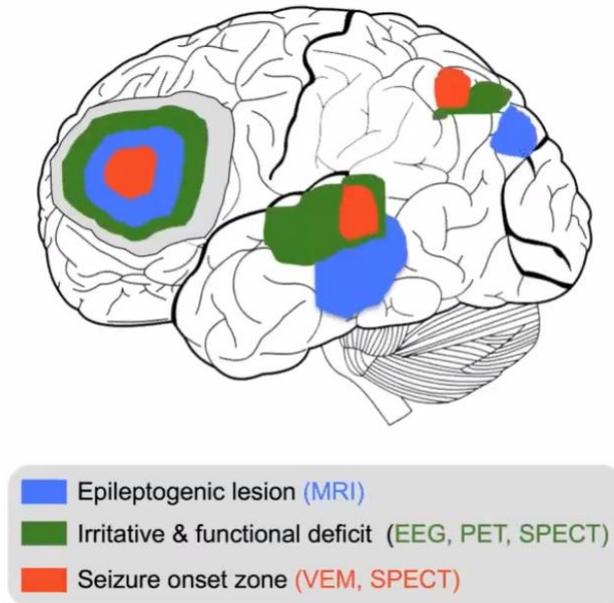
*irritative spikes cease after surgical resection of epileptogenic zone!

Symptomatogenic zone – cortical area that *produces clinical symptoms* but whose removal is not necessary (e.g. seizures may begin silently in frontal lobe and produce typical temporal lobe complex partial seizure when discharge has spread there); cortical stimulation studies have shown that often region producing auras is *much larger than epileptogenic zone*.

Functional deficit zone – cortical area showing *hypometabolism* on **FDG-PET**; *much larger than epileptogenic zone* (e.g. in medial TLE, hypometabolism involves both medial and lateral temporal lobe cortex ± subtle regions of hypometabolism in frontal lobe).



Zones may or may not overlap:



NODE VS. NETWORK DISEASE

There were/are proponent experts in each theory:

In the 1950s, Penfield and Jasper established **surface electrocorticography** as the mainstay for defining an “**epileptogenic focus**,” and Bailey and Gibbs wrote that “surgical eradication of focal seizure activity was comparable to eradicating a tumor.”

vs.

SEEG philosophy (originated by Talairach and Bancaud) focuses on determining the regions of cortex generating clinical manifestation of the seizure whereby the chronologic occurrence of ictal clinical signs (semiology) is crucial for elucidating “**anatomo-electro-clinical**” **organization of seizures**.

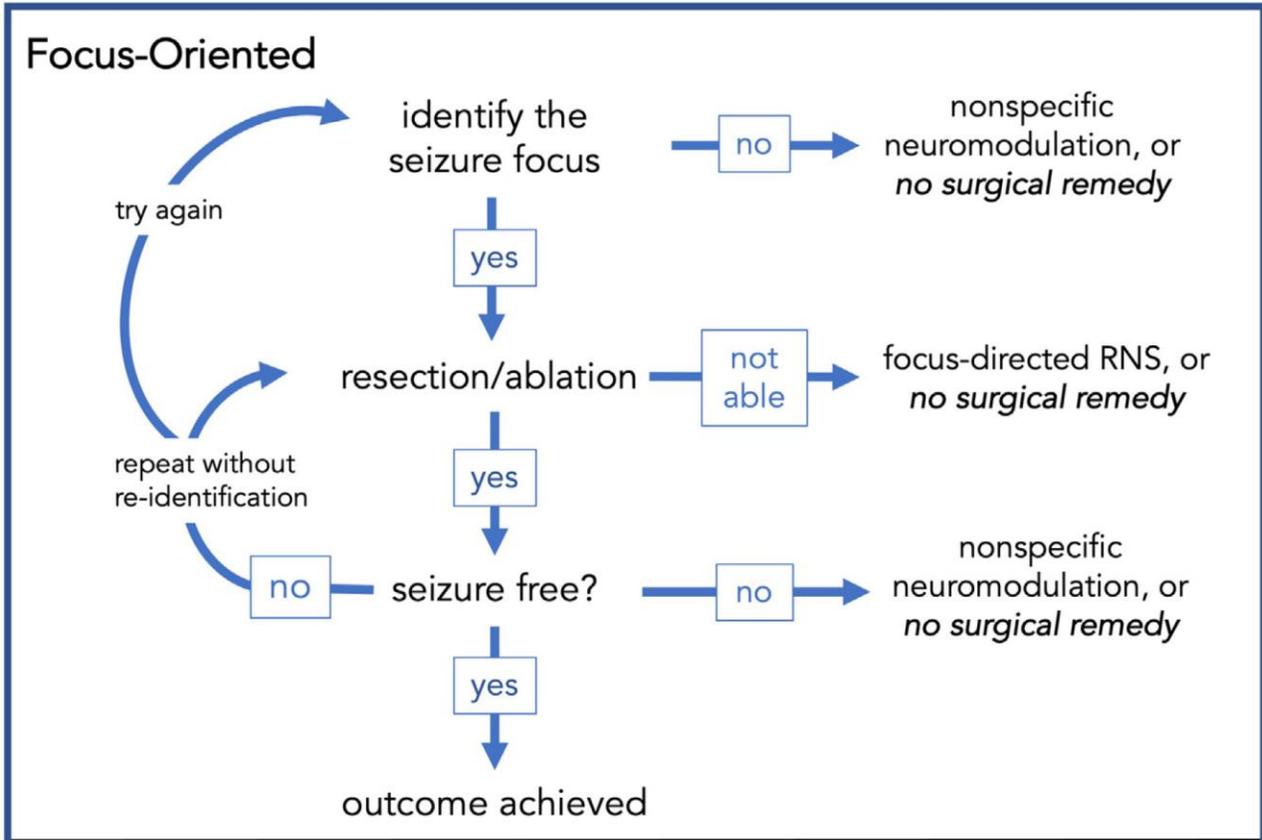
Paradigm shift in 2020s: EPILEPSY SURGERY AS NETWORK SURGERY!

- **generalized epilepsy** – EZ (node) is entire brain (**meganode**)
- why some patients become **seizure free after callosotomy** if it is node disease - two nodes across corpus callosum **can no longer synchronize** oscillations.
- **focal epilepsy** – small local network (**mininetwork**).

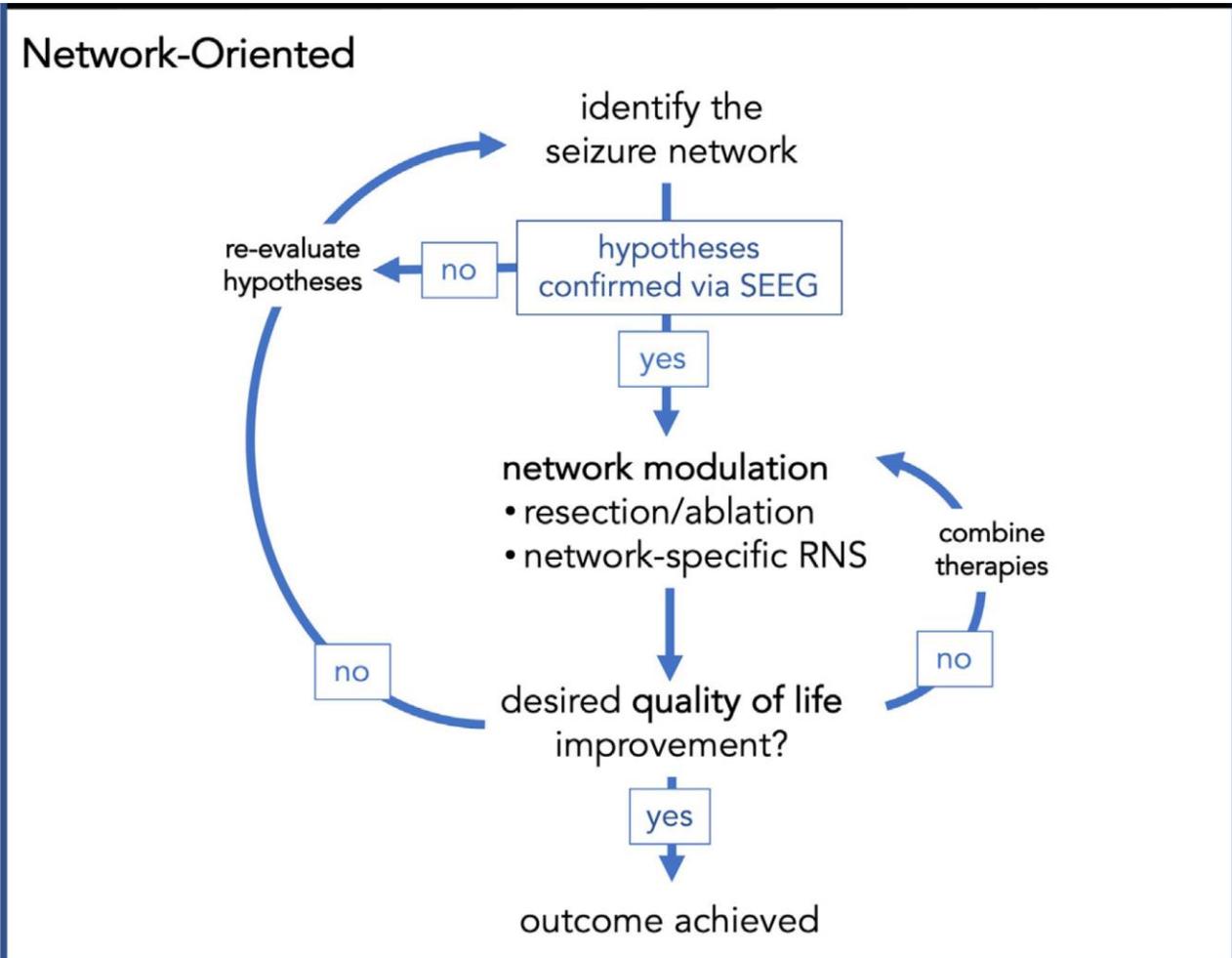
Definition for focal epilepsy: seizure onset at ≤ 4 contiguous contacts

- **treatment goal** – resect / ablate **primary source** and neuromodulate **network nodes** (“take seizure network offline” – role of SEEG exploration).

In 2020s emphasis is shifted from **resection and seizure freedom** to **modulation and improved quality of life**, with the ultimate goal of arresting seizures indefinitely.



Richardson 2022



- downfall of approaching epilepsy surgery solely from the perspective of focus hunting: if a resection is performed and the patient is not seizure free, the interpretation is that one “didn’t get enough” or did not find “the right focus.”

Common Epileptic Pathologies

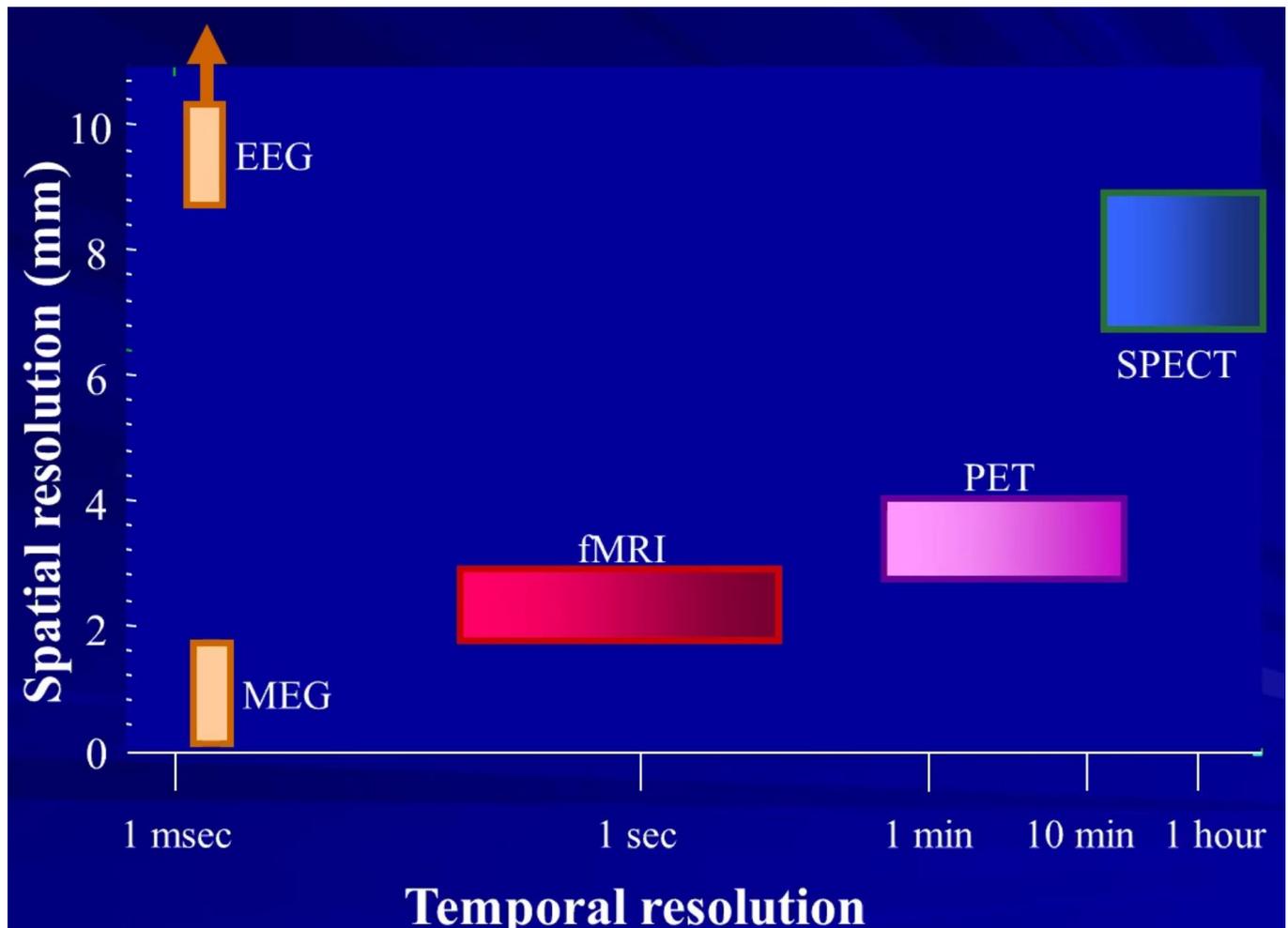
- **hippocampal sclerosis** is #1 among adults (44.5% surgical specimens; only 15% in children)
- **malformations of cortical development** are #1 among children (39.3% surgical specimens with focal cortical dysplasia occupying 70.6%).
- **tumors** (mainly ganglioglioma) are #2 in all age groups.
- **vascular malformations** (mainly cavernomas) - found in 6.1% of specimens.
- TBI, intracranial infections, neurosurgical procedures may leave **glial scars (gliosis)** - found in 4.9% of specimens - hyperintense on T2 and often associated with cortical atrophy.
- **infections** - Rasmussen's encephalitis, herpes simplex encephalitis, neurocysticercosis (most common cause of infection-related epilepsy worldwide).

Presurgical Evaluation (Non-Invasive, Phase I)

- goal is to define **EPILEPTOGENIC ZONE**.

Surgical treatment is presently limited by our *inability to localize epileptogenic focus*.

Comparison of phase I methods:



- all methods can be done for patients of all age groups.

SCALP (SURFACE) EEG

All surgical candidates should begin presurgical evaluation with **EEG-audio-video monitoring** to record actual seizures (*weaning from anticonvulsants* may be necessary) – so called PHASE I MONITORING.

N.B. *seizures* may begin in areas distant from (or even contralateral to) location of *interictal* epileptiform activity - *ictal discharges* are most reliable means of localization!

- interictal EEG is normal in 30% cases; remaining of cases often have nonspecific findings.
- since it is impossible to record from all cortical & subcortical structures from which seizures may arise, exact onset may not involve recording electrodes until spread of discharge has occurred (i.e. early ictal changes are often not identified in scalp recordings).
- foci in *mesial* or *basal* cortical areas are particularly apt to escape detection; *extratemporal seizures* are more difficult to localize (e.g. epilepsy of occipital or frontal lobe origin may have interictal activity at temporal region).
- **modified electrode placements, dense array, and semi-invasive techniques** increase yield.

NEUROIMAGING (ROUTINE)

see also p. E1 >>, p. E9 >> (temporal lobe epilepsy, diagnosis)

CT

- it is now replaced by MRI (only need for high-resolution CT is for intraoperative neuronavigation planning)

- seizure focus may enhance with IV contrast shortly following a seizure.
- small cortical lesions, particularly in orbitofrontal and medial temporal regions, are not detectable on CT.

MRI

All patients with **focal** epilepsy should undergo MRI without and with IV contrast.

MRI is usually not indicated for genetic and self-limited epilepsy syndromes (such as benign childhood epilepsy with centrotemporal spikes).

Lesional MRI = less chances for medication success, more chances for surgical success

- desirable ≥ 3 Tesla
N.B. higher field strength – more geometrical distortion, motion and susceptibility artifacts (caused by air-filled cavities such as nasal cavities)
- there is software (e.g. FreeSurfer) for automated cortical thickness analysis – esp. useful for focal cortical dysplasia (FCD) detection

N.B. MRI and ictal EEG can be discordant or negative in up to 40% of potentially preoperative cases!

ILAE members can take hands-on practice sessions to review major neuroanatomical landmarks:

<https://www.epilepsy-imaging.org/#/>

ILAE PROTOCOL

HARNESS-MRI PROTOCOL

- mandatory and optional sequences for epilepsy.

Bernasconi et al., 2019

Mandatory sequences

1. **3D magnetization-prepared rapid gradient-echo** (MPRAGE, Siemens), Spoiled gradient-echo (SPGR, GE), Turbo field echo (TFE, Phillips)
2. **3D fluid attenuation inversion recovery** (FLAIR) - very useful for evaluation of epileptogenic lesions; sagittal FLAIR provides a complete antero-posterior view of signal distribution along the length of the hippocampus and parahippocampus.
N.B. FLAIR images are not sensitive to epilepsy-associated pathology in **neonates and infants < 2 yo**, as the myelination process is not yet complete.
3. **2D coronal turbo spin echo (TSE)** with acquisition plane perpendicular to the hippocampus long axis) – T2 high in-plane resolution for optimal visualization of hippocampal volume, shape, and internal structure on coronal cuts.

Optional sequences

1. **3D gadolinium-enhanced T1** – to rule out tumor-like lesions, vascular malformations, or infectious processes.
2. **3D susceptibility weighted imaging** – T2 sensitive to iron deposits, blood products and calcifications.

Surgery planning sequences

1. **3D gadolinium-enhanced T1** – to plan trajectories avoiding vasculature.
2. **3D FGATIR** – to plan ANT DBS.

MRI-NEGATIVE CASES

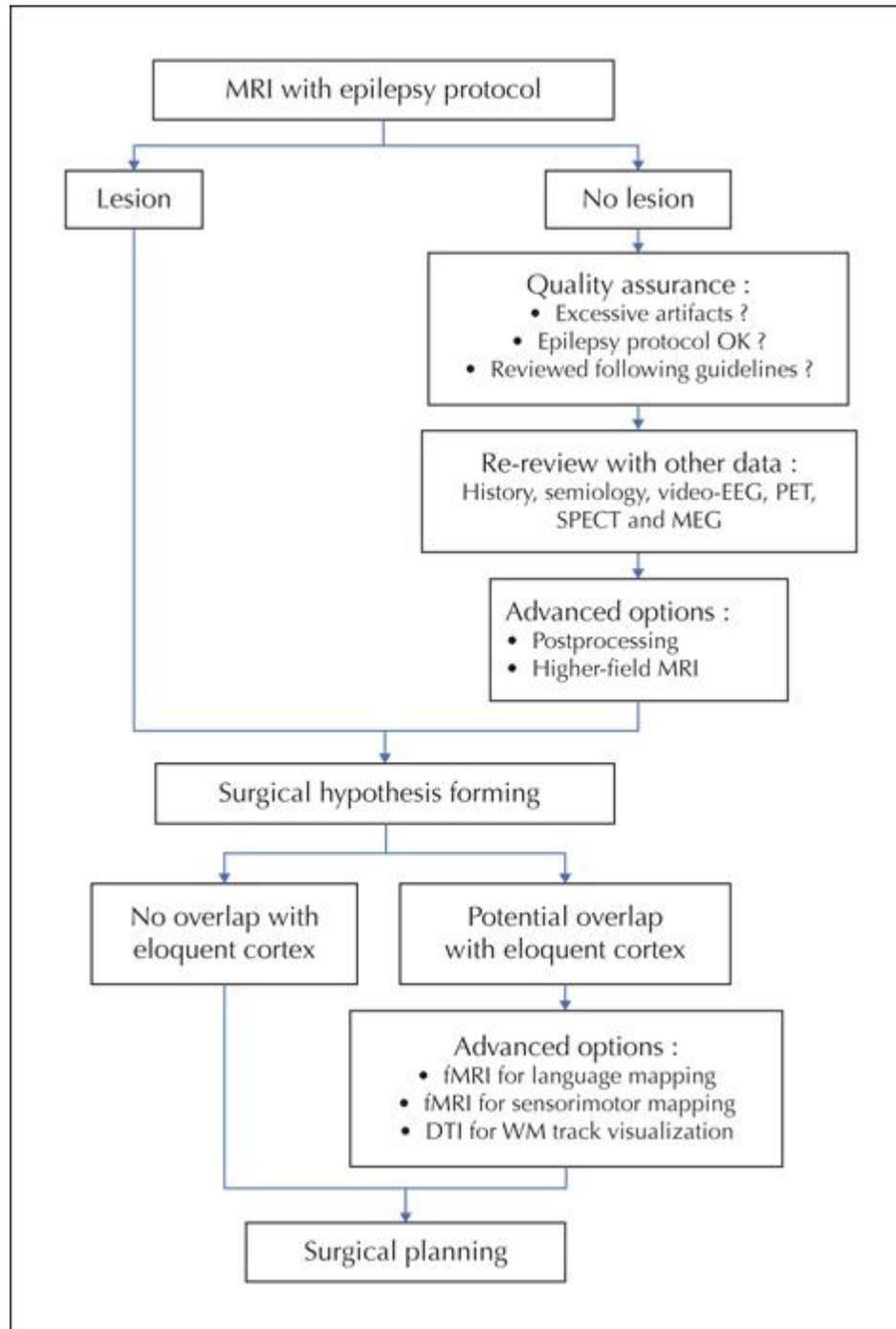
- even experienced observers may miss small and subtle lesions - preferably, an *observer with expertise in epilepsy imaging* should review the scans.
- it is often necessary to **repeatedly review the MRI**, in the context of new information such as PET, EEG, MEG.
- most commonly missed etiology – FCD (esp. bottom of sulcus); then temporal pole encephalocles, hypothalamic hamartomas and subtle double cortex.
- if truly MRI-negative, proceed with advanced outpatient imaging: **MEG, PET** (if nonrevealing → **ictal SPECT**).

Positive result from advanced imaging often requires *verification by depth electrode SEEG recordings*.

Methods to increase MRI sensitivity

7 Tesla scanners

NEUROIMAGING (ADVANCED)



Special MRI postprocessing

TRACTOGRAPHY (DTI)

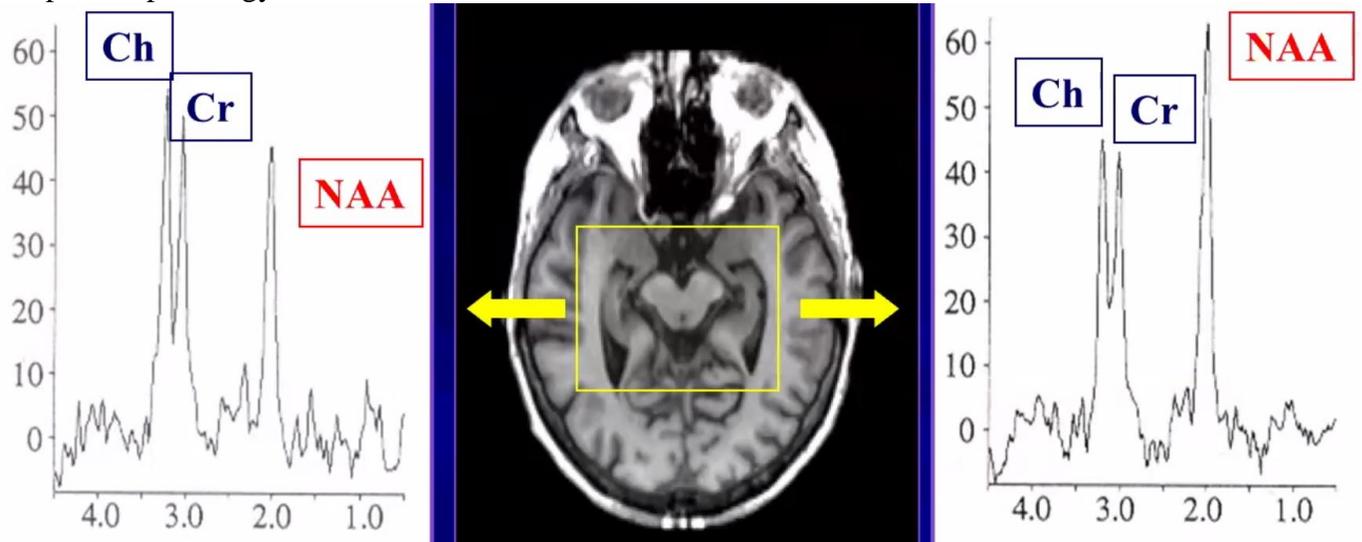
- displays of optic radiations and pyramidal tracts are the most relevant for epilepsy surgery.

HIPPOCAMPAL VOLUMETRY

CORTICAL UNFOLDING

¹HMR (Proton) Spectroscopy

Helps with pathology lateralization:



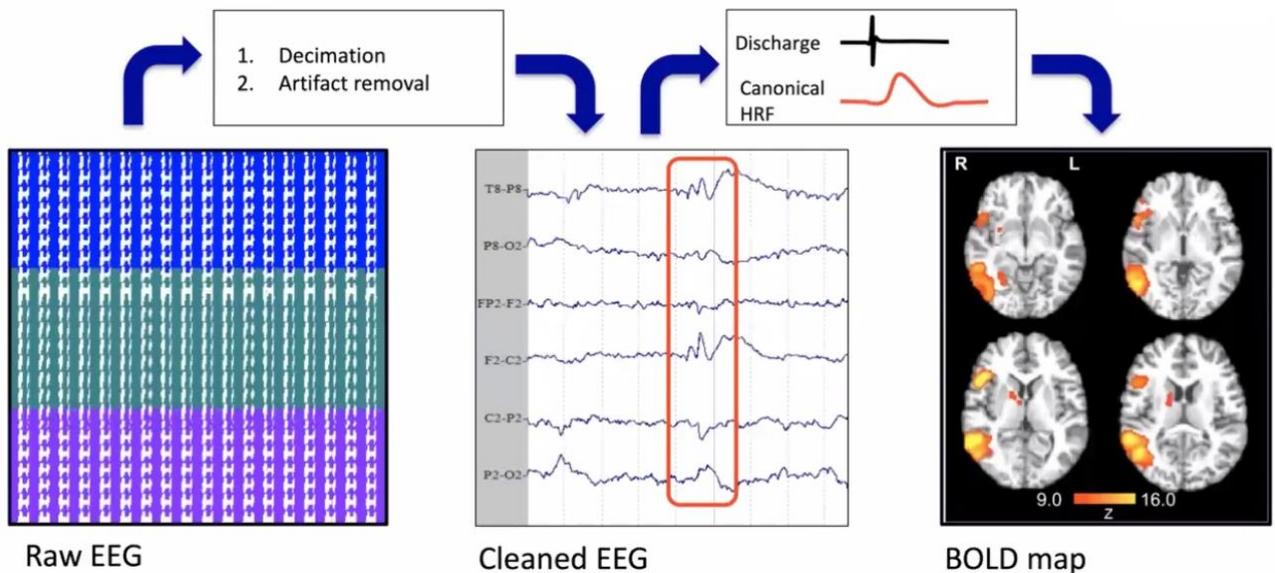
fMRI

- used to determine language dominant side; less commonly – relation of eloquent cortex to EZ

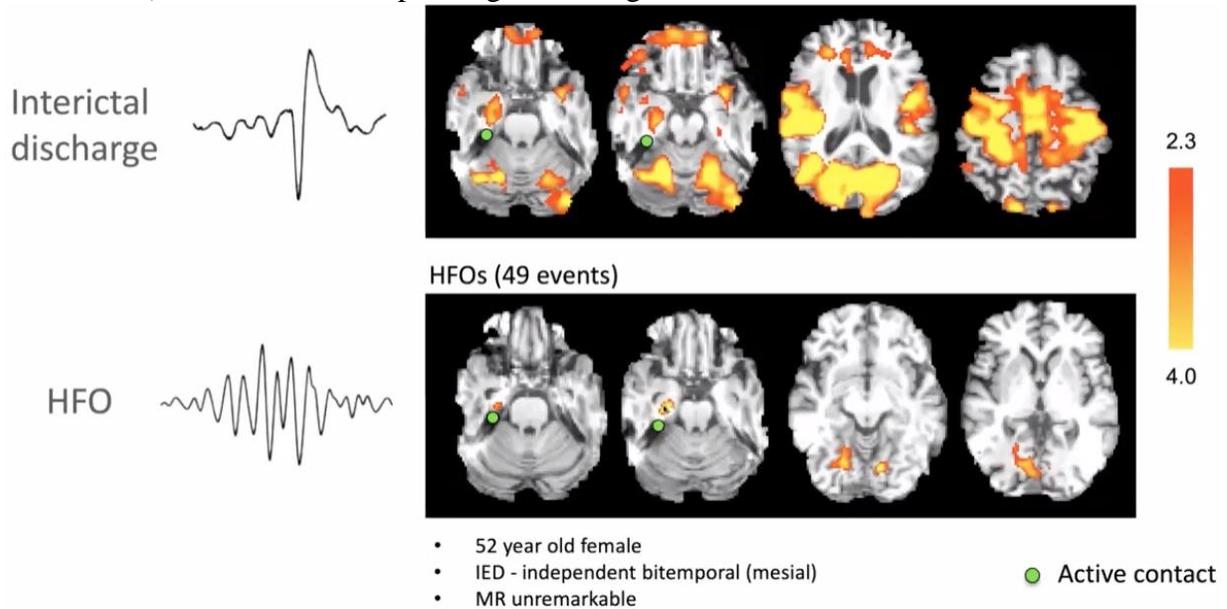
RESTING STATE FMRI

- network analysis; becoming popular for developing surgical strategies and predicting surgery outcomes.
- TLE patients have different subcortical connectivity seen on rs-fMRI (“recovers” after successful surgery).

EEG-FMRI



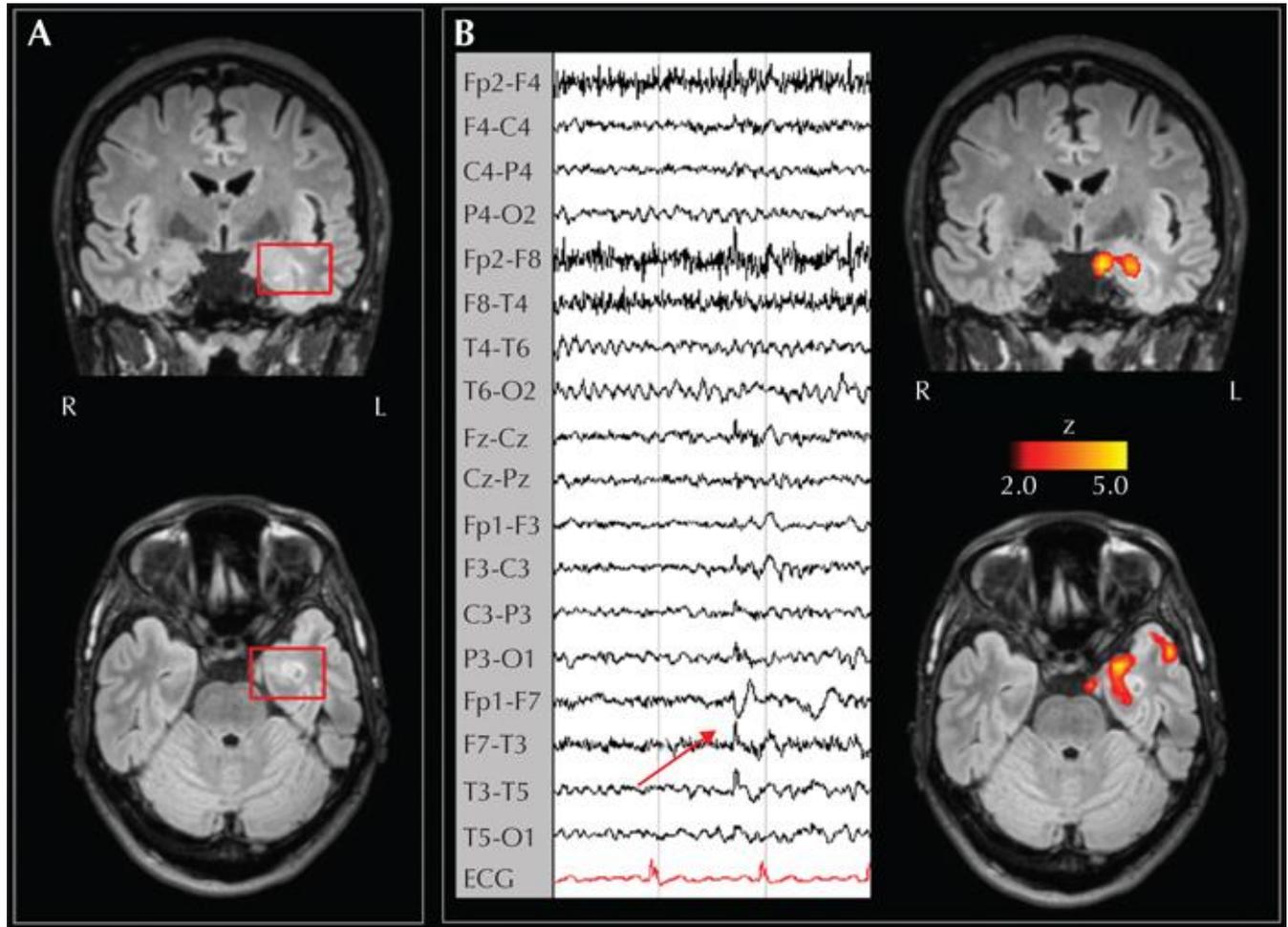
- developed in 1993 by Ives et al.
- indicated for patients that have ≥ 1 epileptiform discharges / min.
- An et al (2013) demonstrated 87.5% sensitivity, 76.9% specificity, 70% PPV, 90.9% NPV – for ILAE class I & II surgery outcomes if resection included BOLD signal areas.
- can be combined with SEEG – resect area around electrode contacts with HFO (high-frequency oscillations) + area with corresponding BOLD signal on fMRI.



Patient with refractory seizures arising from a brain tumor (possibly DNET) in the left mesial temporal region associated with blurring of the grey-white matter interface in the ipsilateral temporal pole:

(A) FLAIR displaying the lesion (red box);

(B) Scalp EEG-fMRI analysis of left frontotemporal discharges (F7-T3) shows a maximum BOLD response on the left amygdala and hippocampus + additional smaller BOLD cluster at the temporal pole (superior temporal gyrus).



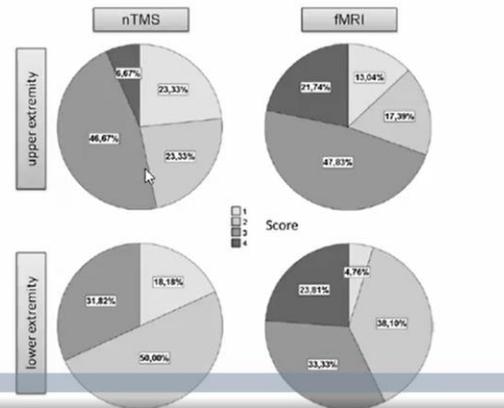
nTMS (navigated transcranial magnetic stimulation)

MAPPING FOR ELOQUENT CORTEX

- FDA approved for “presurgical motor and language mapping”.
- possible for **noncooperative patients** (vs. MEG, fMRI)
- cannot reach **deep parts of brain** (solution – TDCS – transcranial direct current stimulation).
- studies show it may be **more accurate than fMRI** (as compared to gold standard – Direct Cortical Stimulation):

- Several studies have evaluated accuracy of motor mapping with nTMS vs fMRI (with DCS as gold standard)
 - Forster 2011, *Neurosurgery*: 10 pts, mean distance to DCS hotspot 10.5 +/- 5.7 mm for nTMS vs 15.0 +/- 7.6 mm for fMRI
 - Mangraviti 2013, *Neurol Sci*: 7 patients, mean distance to DCS hotspot 8.5 +/- 4.6 mm for nTMS vs 12.9 +/- 5.7 mm for fMRI

Coburger 2013, *Neurosurg Rev*: 30 patients; all 30 completed nTMS, whereas only 23 completed fMRI. Authors binned results into 4 levels, where 1 is most accurate, 4 is least accurate



EPILEPSY PALLIATION

- see below >>

PET (positron-emission tomography)

(FDG-PET, ¹¹C flumazenil-PET)

- determines **functional deficit zone** in focal epilepsy.

- shows **hypometabolism**.
 - N.B. PET often shows hypometabolism in temporal lobes of pediatric patients – ignore it (esp. if symmetric).
 - N.B. temporal lobe is relatively hypometabolic compared to other lobes.
- FDG is made in an expensive medical cyclotron and "hot-lab" (automated chemistry lab for radiopharmaceutical manufacture), and then delivered immediately to scanning sites because of the natural short (110-minute) half-life of Fluorine-18.
- after injection need to scan the patient within 30 minutes (vs. SPECT – have 4 hours).
- PET:
 - has highest accuracy for temporal lobe foci, which are diagnosed most easily with MRI and EEG.
 - is least reliable for extratemporal nonlesional foci, which also are most difficult to define with MRI and standard EEG.
 - PET is superior to interictal SPECT.
- indications:
 - a) discordant MRI and EEG findings
 - b) normal MRI findings.
- cannot do PET if given **insulin** recently (glucose goes into muscle).

- PET can be combined with **simultaneous EEG** – helps to **avoid false lateralizations from hypermetabolism** due to unrecognized ictal / postictal events as well as frequent interictal epileptiform discharges.
- **quantitative PET** – patient's PET subtracted from population-normalized template PET.

SPECT (single-photon emission computerized tomography)

- gamma-emitting tracer used is ^{99m}Tc -HMPAO (hexamethylpropylene amine oxime) - emits gamma rays that can be detected by a gamma camera.
- HMPAO allows ^{99m}Tc to be taken up by brain tissue in a manner proportional to brain blood flow (i.e. SPECT is assessment of regional cerebral blood flow in 3D).
- SPECT is more widely available (than PET), because the radioisotope is longer-lasting and far less expensive.

Interictal SPECT - shows **hypoperfusion**; resolution is inferior to that of PET; useful only for SISCOM.

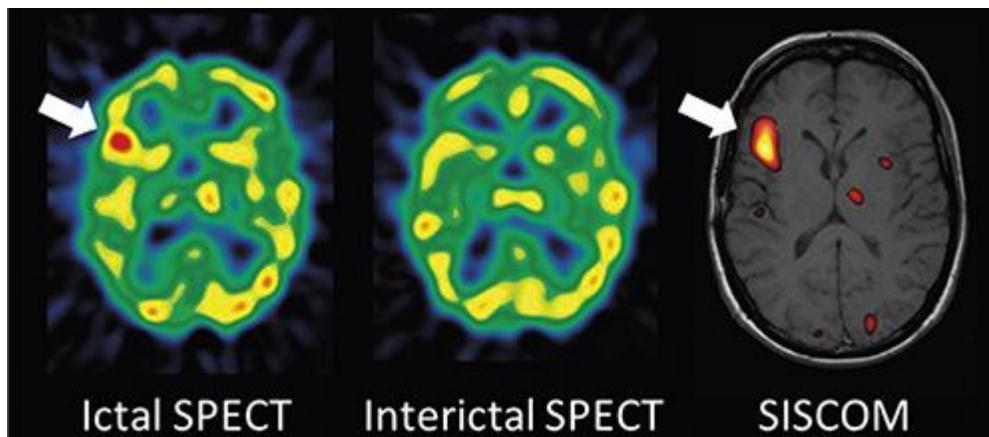
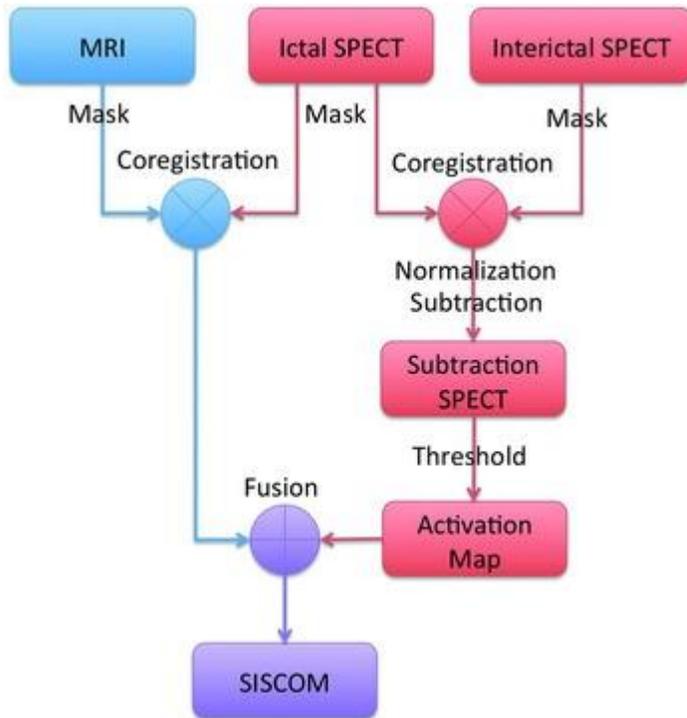
Ictal SPECT - **hyperperfusion** during seizure - high localizing value* (only if ictal injection occurs within 20 seconds of ictal onset - then may scan within next 4 hours**).

*70-100% in temporal epilepsy vs. 33-63% in extra-temporal epilepsy
**vs. PET – within 30 minutes

- may also see hyperperfusion in *ipsilateral basal ganglia, contralateral cerebellum*.

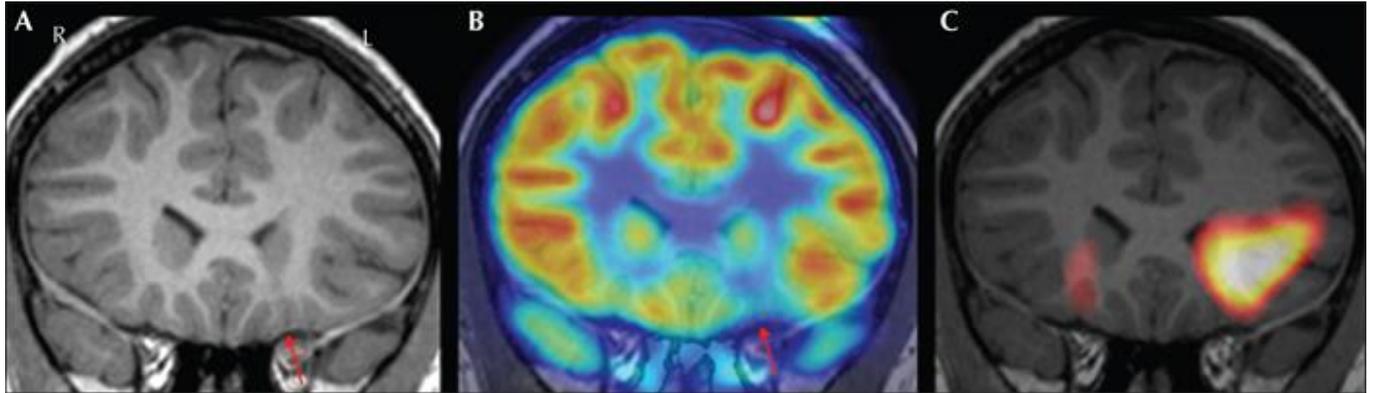
SISCOM (Subtraction Ictal Spect CO-registered to Mri)

- much higher accuracy than either ictal or interictal SPECT! (may provide alternative to depth electrode studies)
 - requires two SPECT scans (separated by ≥ 48 h to accommodate radionuclide washout) - during *interictal* period and *within seconds of seizure onset*.
 - using computer software, these scans are subtracted from each other.
 - subtracted scan then can be co-registered onto MRI to provide support for focus location.



N.B. in *MRI-negative* cases, reliability of functional neuroimaging is much reduced, and positive result from *functional imaging* generally requires verification by *depth electrode recordings*!

Multimodal imaging with interictal FDG-PET (middle) and ictal SPECT (right) which guided focused re-review of MRI (left, T1-weighted MPRAGE sequence) - hypometabolism on interictal PET (arrow) and hyperperfusion on ictal SPECT both pointed to a region in the left orbitofrontal cortex → re-review of the MRI revealed a cortical malformation characterized by gray-white blurring and thickened cortex (arrow). Resection of this region led to postoperative seizure freedom and surgical pathology-confirmed FCD:



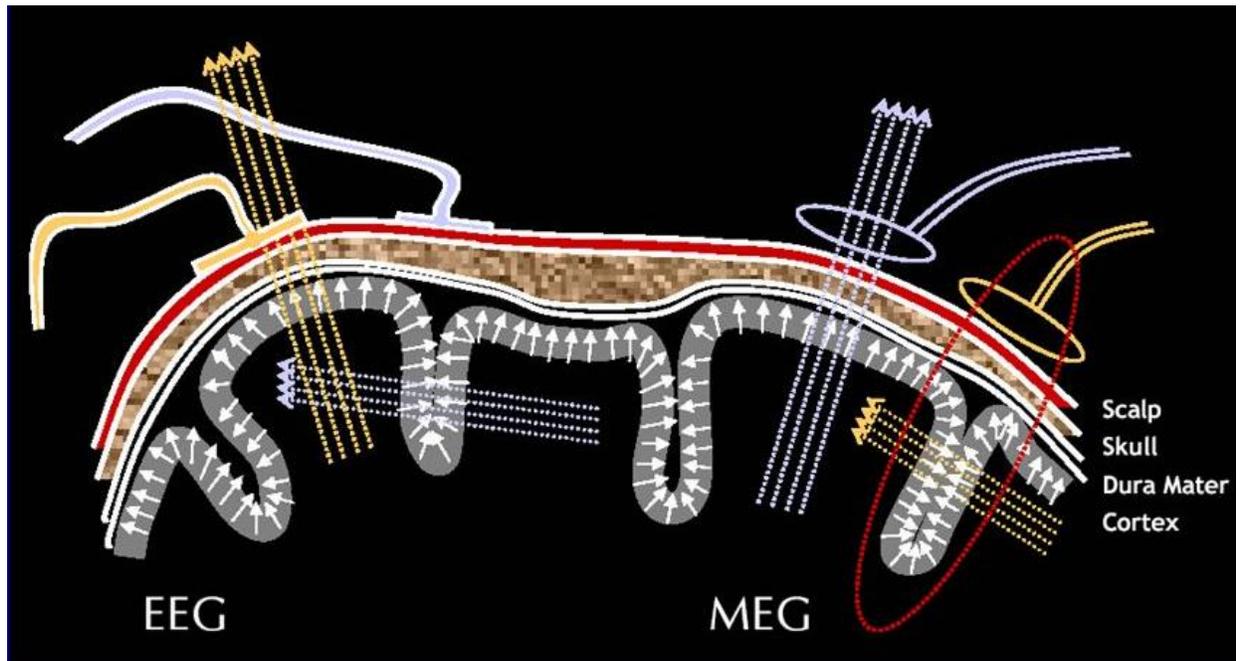
MAGNETOENCEPHALOGRAPHY (MEG)

- method for 3D detection of deep epileptic foci; records magnetic fields produced by brain electrical activity; requires sophisticated expensive suite (well isolated, far from highways).



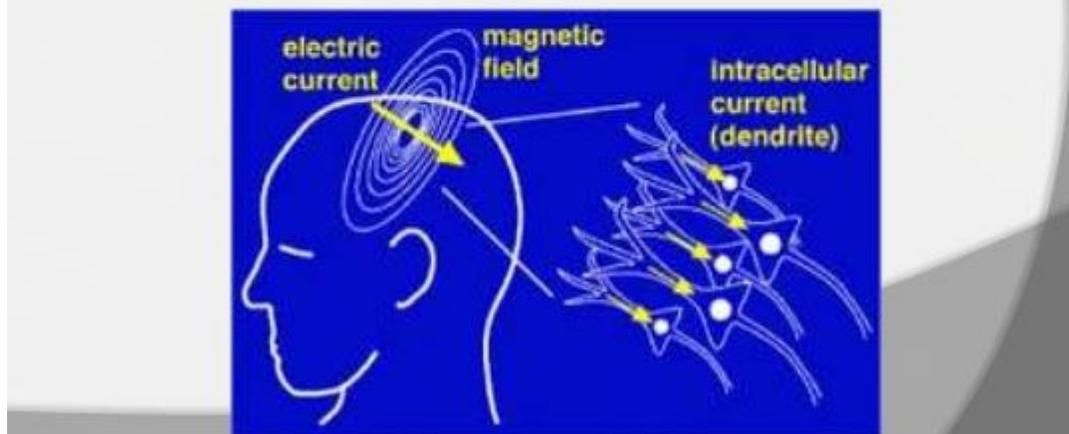
EEG detects **gyri** (radial currents).

MEG detects **sulci** (tangential currents); sulci have larger area than gyri (**MEG detects more spikes**):



50,000 neurons need to fire to generate a Readable signal.

Neurons near the outside of the brain generate the strongest signals.



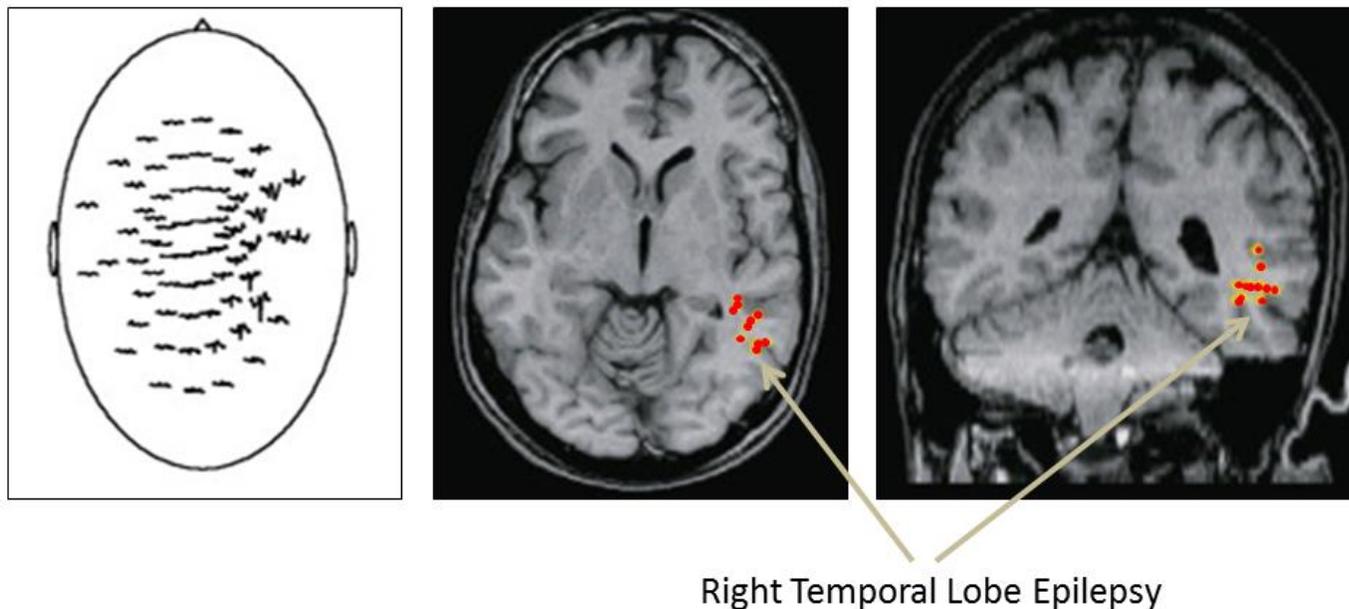
- MEG is closer to pathophysiology (electrical discharge) than PET, SPECT.

MSI

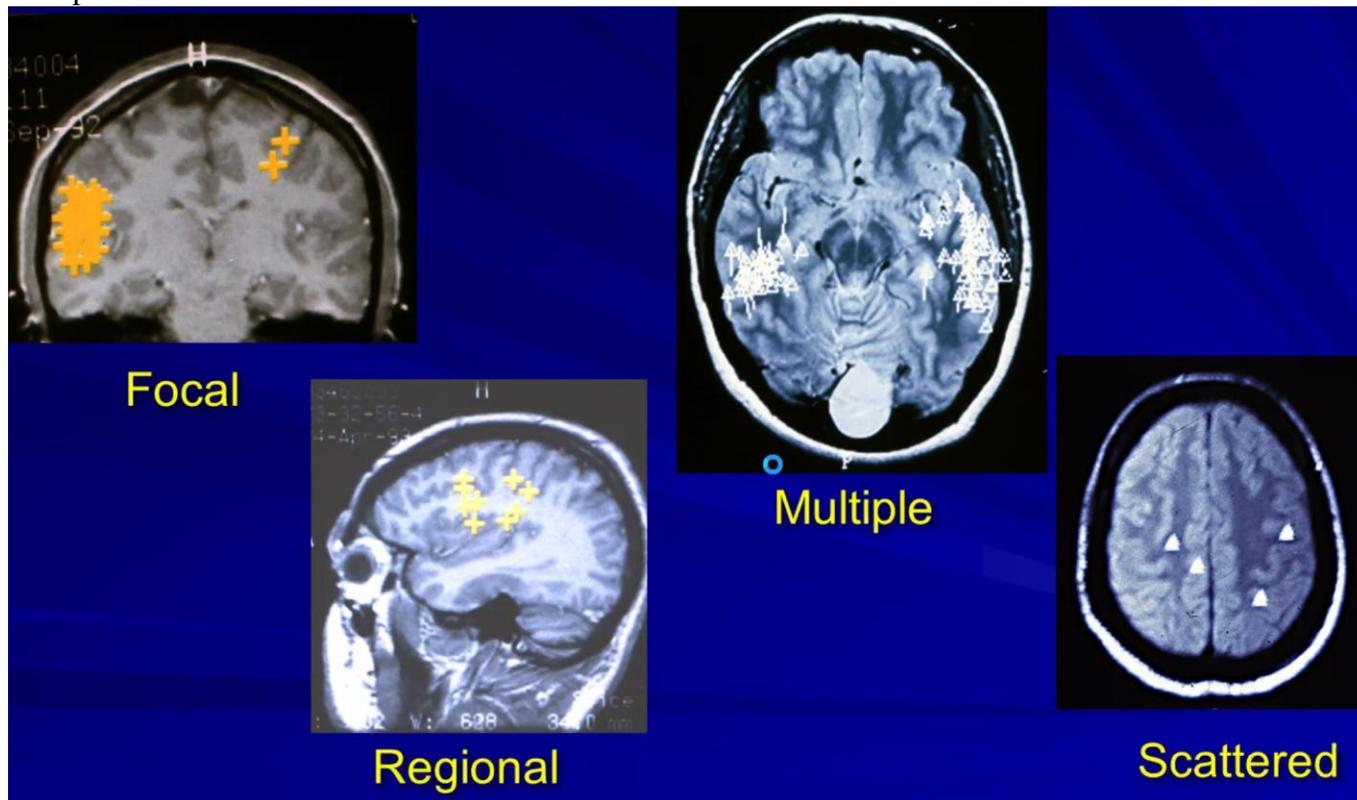
- routine way to export MEG results onto MRI

Identifying Epileptic Spikes

(Merrifield et al., 2007)



MSI patterns:



- diagnostic accuracy 57-70% in temporal cases (44% - extratemporal cases).

NEUROPSYCHOLOGICAL TESTING (NEUROPSYCHOMETRY)

- routinely, *all surgical candidates* undergo extensive neuropsychological testing (possible exception – VNS candidates).
- testing is not standardized between centers.
- test battery contains:
 - 1) **personality** inventory (e.g. Minnesota Multiphasic Personality Inventory)
 - 2) tests of **memory** and **language**
temporal mesial sclerosis in dominant hemisphere – memory↓
 - 3) tests for **interhemispheric transfer** (before callosotomy) - cross-retrieval and naming of objects, cross-replication of hand postures, cross-localization of fingertips.
 - 4) other tests, depending upon interests of neuropsychologist.
- goals of testing:
 - 1) to help **localize epileptogenic focus** (subtle deficits in cognitive functioning might provide additional localization that neurologic examination misses); it is not reliable because very few tests reliably measure frontal and temporal lobe function.
 - 2) identification of **significant cognitive problems** (e.g. memory problems - might not be a candidate for temporal lobectomy).
 - 3) predicting **postoperative cognitive deficits**.
 - 4) formulating **postoperative vocational goals**.
- testing results are valid for max **18 months**.
- patients are instructed to **continue their medications as usual** but **abstain from marijuana for ≥ 72 hours**
 - **AEDs are known to affect processing speed**; many tests are timed so AEDs may have effect on results; there are no tools to differentiate AED side effect from true encephalopathy, thus, neuropsychologist's expertise and insight are needed.
 - **TOPIRAMATE** is has well-researched negative side effect on **verbal** processing and memory.
 - **LEVETIRACETAM** has **mood** effects.

MULTIDISCIPLINARY CONFERENCE

- final results of noninvasive testing (phase I) are presented to **multidisciplinary epilepsy surgery conference** (neurologist specializing in epilepsy, epilepsy neurosurgeon, neuropsychologist, epilepsy nurse, speech pathologist, neuroradiologist, and psychiatrist).

Conference decides on:

- 1) need for WADA test (phase II)
 - 2) need for intracranial EEG (phase III)
 - 3) surgical plan
- in most scenarios, there are several reasonable options, which are not mutually exclusive, and some differences among centers, and even among epileptologists, are expected - this is why all comprehensive epilepsy centers make decisions after discussions at multidisciplinary conferences.

Presurgical Evaluation (Invasive, Phase II)

Two goals:

1. Further define **epileptogenic zone** – intracranial EEG (icEEG) >>
2. Map brain function:
 - 1) fMRI >>
 - 2) MEG >>
 - 3) nTMS >>
 - 4) WADA: chemical (>>), electrical (>>)

CHEMICAL WADA (INTRACAROTID AMOBARBITAL TEST)

- so called PHASE II TESTING
- named after **Japanese epileptologist Juhn Atsushi Wada**, of the University of British Columbia - he developed the test while he was a medical resident in Japan just after World War II, when he was receiving training in neurosurgery. Wada developed the technique of transient hemispheric anesthetization through carotid amytal injection to decrease the cognitive side effects associated with bilateral electroconvulsive therapy.

Wada J (1949). "A new method for the determination of the side of cerebral speech dominance. A preliminary report of the intra-carotid injection of sodium amytal in man". Igaku to Seibutsugaki, Tokyo. 14: 221–222.
- injection of 100 mg SODIUM AMOBARBITAL (AMYTAL®)* / PROPOFOL into carotid artery - to temporarily anesthetize (inactivate) hemisphere in ipsilateral carotid artery distribution (includes amygdala and anterior hippocampus) - allows independent **testing function of contralateral hemisphere**.

*barbiturate derivative that activates GABA_A receptors
- does WADA need to be **bilateral** even if **pathology unilateral**? Wada is the difference score between the two hemispheres as they relate to each other and to baseline (if the second hemisphere couldn't happen due to a seizure, decision can be made after unilateral WADA, it is just not ideal)

INDICATIONS

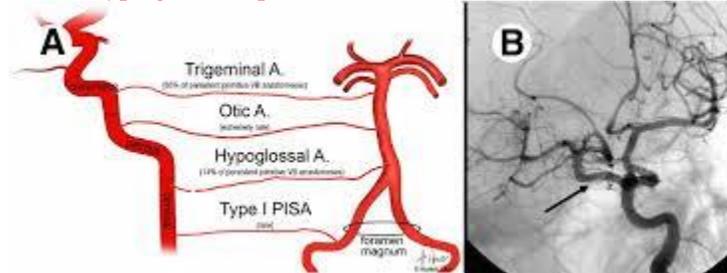
- preparation for ablative surgery (once epileptogenic focus has been identified) - injection ipsilateral to epileptogenic zone:
 1. Which hemisphere contains **LANGUAGE function** (dominant hemisphere inactivation → aphasia; nondominant → dysarthria); fMRI is much less useful here.
 2. Functional adequacy of contralateral hippocampus to **sustain MEMORY** (before anterior temporal lobectomy to avoid permanent amnesia).

N.B. failure of memory function is contraindication to resection of hippocampus and parahippocampal structures on injected side!
Some experts believe that WADA is more important for temporal neocortical resections (and not so much for SAH).
 3. Prognosing **seizure-free OUTCOME**.
 - never has been standardized - there is no such thing as *the* Wada Test - major efforts to establish procedural uniformity across epilepsy centers have been made, but many different *versions* of the test still remain.
 - some centers insist on Wada tests even when clearly right-handed patient is diagnosed with right temporal focus

PROCEDURE DETAILS

- instruct patient as to what is expected.
- catheter is passed into ICA (as for standard carotid arteriograms).
- **4-vessel arteriography** must verify that blood flows to corresponding hemisphere and there is:
 - 5) no **cross flow**

N.B. **significant cross-flow** is relative contraindication to anesthetizing side of dominant supply (patient goes to sleep).
 - 6) no **persistent embryonic communication between anterior and posterior circulation (e.g. trigeminal, otic, hypoglossal, pro-atlantal arteries)** – will cause brainstem failure!



N.B. **fetal PComA** is not contraindication but will cause cortical blindness.

- 7) no significant **vascular abnormalities** - Wada test may be grossly inaccurate with high flow AV fistulas, such as AVM
- start on side of lesion (Wada testing is almost always performed with bilateral carotid amobarbital injections).
 - have patient hold both arms in air and count loudly - inject Amytal rapidly; effect starts almost instantaneously, begins to subside after ≈ 8 minutes.
 - **contralateral hemiparesis** + **ipsilateral EEG slowing** ($> 50\%$) must appear (confirmed adequacy of injection); if not, add 25 mg more of drug.
 - patient is monitored to make certain that **recirculation** has not affected both sides simultaneously during testing.
 - **assess language** by showing patient pictures of objects and ask them to name each one out loud and remember each one.
 - **assess memory** by asking patient to name as many of pictures as they can 15 minutes after test: if they have difficulty, ask them to pick out pictures from a group that contains additional ones not shown to patient.
 - may repeat procedure on other side (use lower Amytal doses with each subsequent injection).

Caveats:

- **portions of hippocampus** may be supplied by **posterior circulation** (not anesthetized by ICA injection).
- despite aphasia, sometimes **ability to sing** is preserved - music and singing uses a different part of the brain than speech and language.

SIDE EFFECTS

1. Drastic **personality changes** are rarely noted, but disinhibition is common.
2. **Shivering** are often seen.
3. Recovery of speech is **dysphasic** (contains errors in speech or comprehension) after a language dominant hemisphere injection.

1% risk of **vessel dissection and stroke!**

INTERPRETATION

Memory scores of > 50-67% have been deemed passing scores.

- operational definition of failure = **corrected score < 5**
- if WADA is failed but ablation is still recommended, amygdalohippocampectomy is preferred over temporal lobectomy, as studies show better verbal outcomes.

N.B. WADA test is still associated with false positives and negatives!

NONINVASIVE ALTERNATIVES TO WADA

Wada test has angiography risks – so check for noninvasive alternatives:

fMRI - can lateralize **language**

Practice Guideline of American Academy of Neurology:

Szaflarski J.P. et al. Practice guideline summary: use of fMRI in the presurgical evaluation of patients with epilepsy: report of the Guideline Development Dissemination and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2017;88:395-402.

- fMRI using **verbal memory or language encoding** **should be** considered for predicting postoperative **verbal memory** outcome (Level B recommendation).
- fMRI using **non-verbal memory encoding** **may be** considered for predicting postoperative **visuospatial memory** outcomes (Level C recommendation).

nTMS

MEG - can lateralize **language**

Near-infrared spectroscopy

H₂¹⁵O-PET

UAMS PROTOCOL

Prerequisites:

Providers-Neurology, Neuropsychology and Interventional Neuroradiology

Location: IR suite

Ancillary: EEG tech with vEEG setup (full montage)

Medication: Amytal (amobarbital sodium preparation) (at least 1 vial for each side)

Team member specific considerations

EEG tech

1. Must be vEEG (live) with patient's face and hand in clear unobstructed view
2. Audio recording should be ON with appropriately placed microphone
3. EEG tech at the machine side annotating the record
 - a. Injection times
 - b. Delta slowing
 - c. 50% delta-theta reduction
 - d. Strength assessment by MD
 - e. EEG return to baseline
4. EEG screen should also be clearly visible to the Epilepsy MD
5. Perform a baseline at least 15 min recording before the start of the procedure (during baseline assessment by Neuropsychology, prepping etc)

Nursing

Amytal (amobarbital sodium preparation)

1. Needed 20 cc of sterile water and 500 mg of amobarbital for EACH side
2. Reconstitute *MAXIMUM* 30 min before use
3. Add 5 cc of sterile water to amobarbital vial.
4. **Do not shake.** Only rotate vial.
5. The dose should also be mixed and allowed to **dissolve for > 5minutes.**
6. Withdraw solution into a 25 cc syringe
7. Wash amobarbital vial with additional 5 cc of sterile water. Withdraw into 25 cc syringe containing first 5 cc of amobarbital solution
8. Add another 10 cc sterile water to 25 cc syringe containing amobarbital solution. Mix
9. **Final concentration: 25 mg/cc**
10. Carefully note and label the syringe with the time the medication was mixed.
11. Discard if not clear in 5 minutes and discard if a precipitate forms.
12. Attach **0.22 micron filter (yellow disc)** to Amytal syringe. **Give 6 ml (150 mg) Amytal to IR MD by pushing** it through the 0.22 micron filter (not pulling up through filter) into 12 ml sterile syringe MD is holding.
13. Amytal once mixed it must be used within 30 minutes. Be prepared to mix a second dose.
 - a. The time gap between two sides injection must be minimum 30 min and preferably 40 min so the previously reconstituted via CANNOT be used for the other side.
14. Usual injection Amount
 - a. First injection (either side); 3 ml (75 mg)
 - b. Repeat injections in 1 ml (25 mg) bolus up to 3 ml (75 mg)
15. Patient's both hands should be out of the sterile field and freely accessible to Epilepsy MD for testing

IR MD

1. Baseline assessment by Neuropsychology before catheter placement
2. Patient's both hands should be out of the sterile field and freely accessible to Epilepsy MD for testing
3. Side planned as the surgical side to be injected first.
4. Pre (amytal)-injection contrast run-through
 - a. Cross-filing?: Yes/ No
 - b. Fetal PCOM?: Yes/ No
5. Pre-injection assessment by Neuropsychology (please see below)
6. Re-explanation of strength testing to the patient by Neurology MD
7. Patient to raise both hands in air and count from 1 to 20 at a paced rate
8. Inject at cue of Epilepsy MD around Count ~ #5-6
16. Inject 3 cc (75 mg) over 3-4seconds
 - a. If flaccid contralateral hemiparesis does not occur after 5 secs, inject additional 1 cc (25 mg – total 100 mg)
 - b. If flaccid contralateral hemiparesis still does not occur after 5 secs, inject additional 1 ccs (25 mg – total 125 mg).
 - c. If flaccid contralateral hemiparesis still does not occur after 5 secs, inject remaining 1 ccs (25 mg – total 150 mgs).
 - d. If flaccid contralateral hemiparesis still does not occur, stop procedure and check catheter position.
 - i. If the lack of hemiparesis was due to inappropriate catheter placement, wait 45 minutes from initiation of injection, then repeat the original injection sequence.
 - ii. If catheter placement is appropriate, wait 45 minutes from initiation of injection.
 1. Draw up 175 mg (7 cc) in 10 ccs sterile water. Hand inject 6 cc (150 mg) over 4 seconds. If flaccid contralateral hemiparesis still does not occur after 5 secs, inject the final 1 cc (25 mg).
- Usual range of Amytal dose 75-125 mg

- Preferred maximum dose: 150 mg
- Absolute maximal dose: 175 mg
- *Time difference between two side injections, minimum 30 min (or complete recovery, whichever is later) preferably 40 min.*

Neurology MD

1. Baseline strength or arm, sensation, vision AND grip
 2. Contralateral hemiparesis achieved? Yes/ No ___/5
 3. Check grip strength
 4. Speech arrest? Yes/ No
 5. Amytal effect on EEG
 - a. Delta/theta slowing (ipsilateral)?
 - b. 50% reduction of EEG delta/theta ipsilateral to injection (or primarily theta background):
for memory item presentation by Neuropsychology
 6. Regularly check strength (may need repeat dose if strength improving fast)
 7. No items presented after strength had recovered to three-fifths in the hand contralateral to injection.
 8. Repeat Neuro exam between side injections
- *Time difference between two side injections, minimum 30 min (or complete recovery, whichever is later) preferably 40 min.*

Neuropsychology

1. Once the patient is arrived and prior to beginning of procedure (catheter placement) approximately 5-10 minutes of baseline testing
 2. Rule out cross-filing and fetal PCOM before Amytal injection
 3. Two minutes prior to injection the first test stimulus is shown
 4. One minute prior to injection the second test stimulus is shown
 5. Re-explanation of strength testing to the patient by Neurology MD
 6. Patient to raise both hands in air and count from 1 to 20 at a paced rate
 7. Inject Amytal at cue to Epilepsy MD ~ at Count #5-6
 - a. Neurology MD to assess and confirm
 - i. Hemiparesis
 - ii. EEG ipsilateral delta slowing
 8. Neuropsychology and neurology run Wada protocol (Neurology monitors strength and EEG; Neuropsychology does language/memory testing per Emory Clinic protocol).
 - 50% reduction of EEG delta/theta ipsilateral to injection (or primarily theta background),
 - Per Neurology MD: Memory item presentation
 9. No items presented after strength had recovered to three-fifths in the hand contralateral to injection.
 10. Assessment of both spontaneous and recognition memory:
 - a. After full motor recovery and return of a 10-s epoch of the patient's usual baseline EEG frequencies.
 - b. At 12 minutes post injection recognition memory testing occurs
- *Time difference between two side injections, minimum 30 min (or complete recovery, whichever is later) preferably 40 min.*

ELECTRICAL WADA

- allows high-precision testing in preparation for highly-selective ablations (esp. when chemical Wada was nonpermissive).
- using depth electrodes.
- simultaneously stimulating across all 8 electrode contacts while patient completes consecutive Wada based memory tests.
- protocol (Dr. Gross): different amplitudes (5, 7.5, 10 mA), pulse frequency 100 Hz, and 500 msec pulse duration.

INTRACRANIAL EEG (icEEG)

(subdural strips and grids, depth electrodes) – so called PHASE III MONITORING – only when noninvasive studies fail to adequately delineate epileptogenic zone. see p. E13 >>

- it may include Stimulation Cortical Mapping - determines **areas of eloquent cortex** that should not be encroached upon at time of operation. see p. E13 >>

ALGORITHM (TREATMENT)

Seizure **semiology** is extremely important in diagnosing ictal zone and seizure propagation network!

Medically refractory disabling focal seizures

↓

Focus can be localized → NO → **VNS** or **DBS**

↓ YES

How many foci → 2 → **RNS**; more than 2 → **VNS** or **DBS**

↓ 1

Safe to resect and cognitive risk is low → NO → **RNS** (or **multiple subpial transections?**)

↓ YES

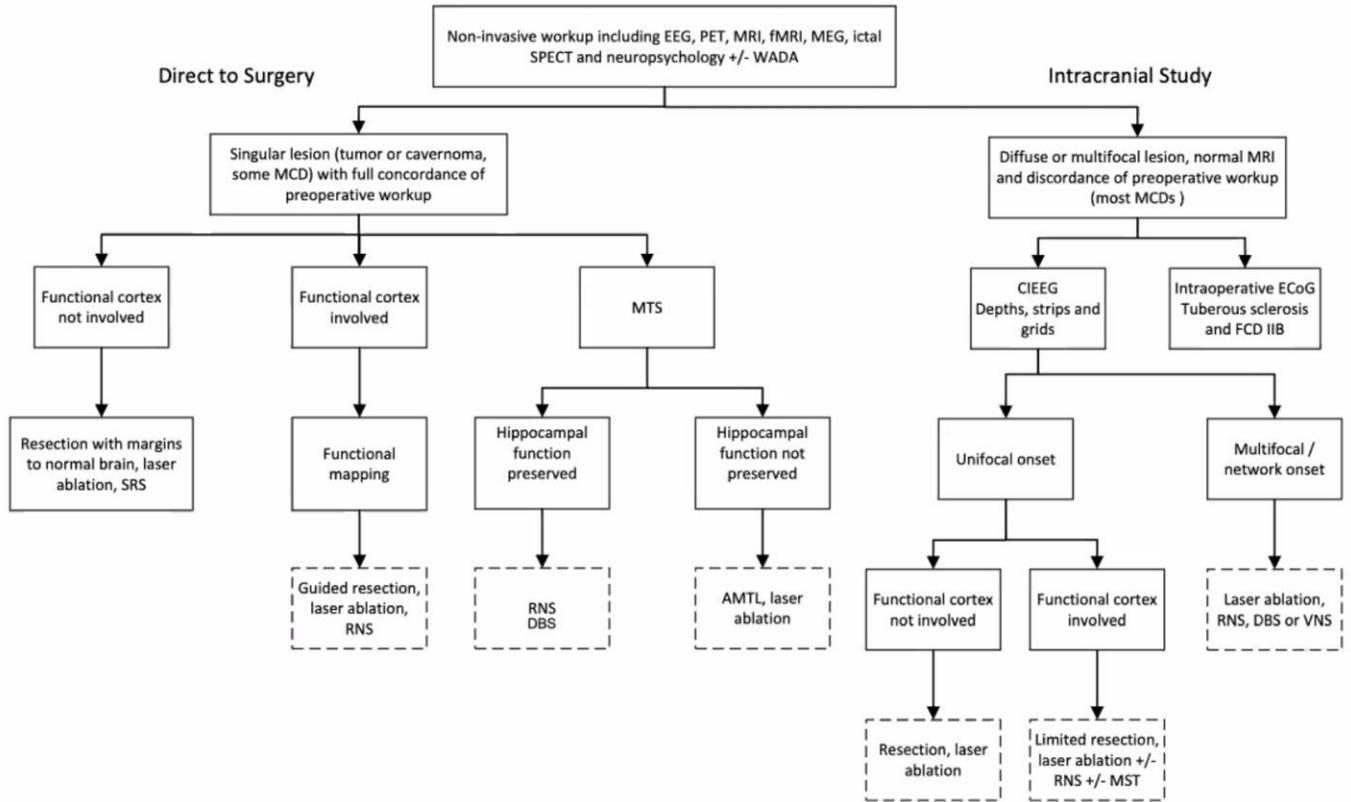
Will it be curative → NO → **RNS**

↓ YES

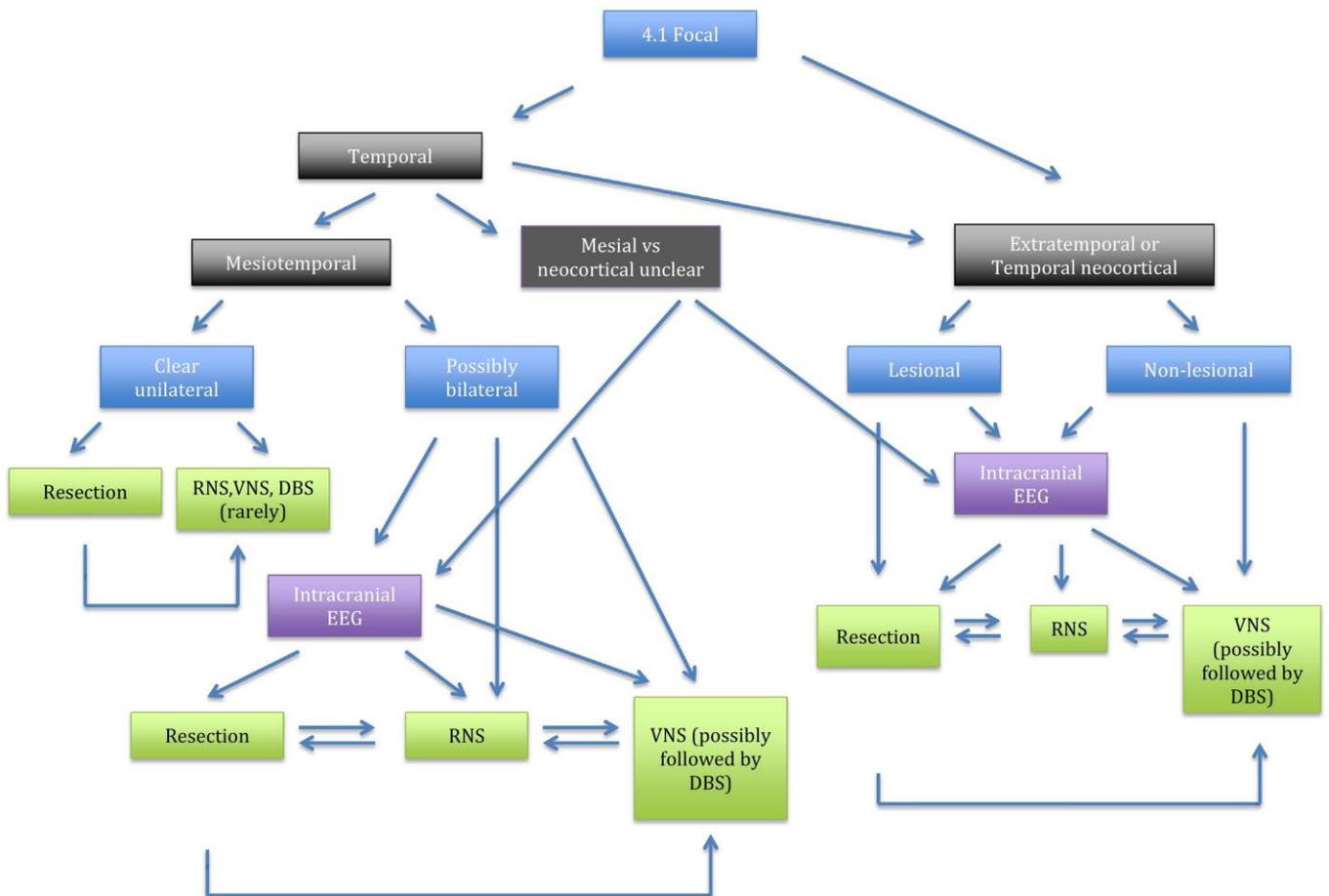
Ablation (resection, laser, SRS, RF, FUS)

N.B. RNS data (in bitemporal epilepsy) may support later resection / laser ablation

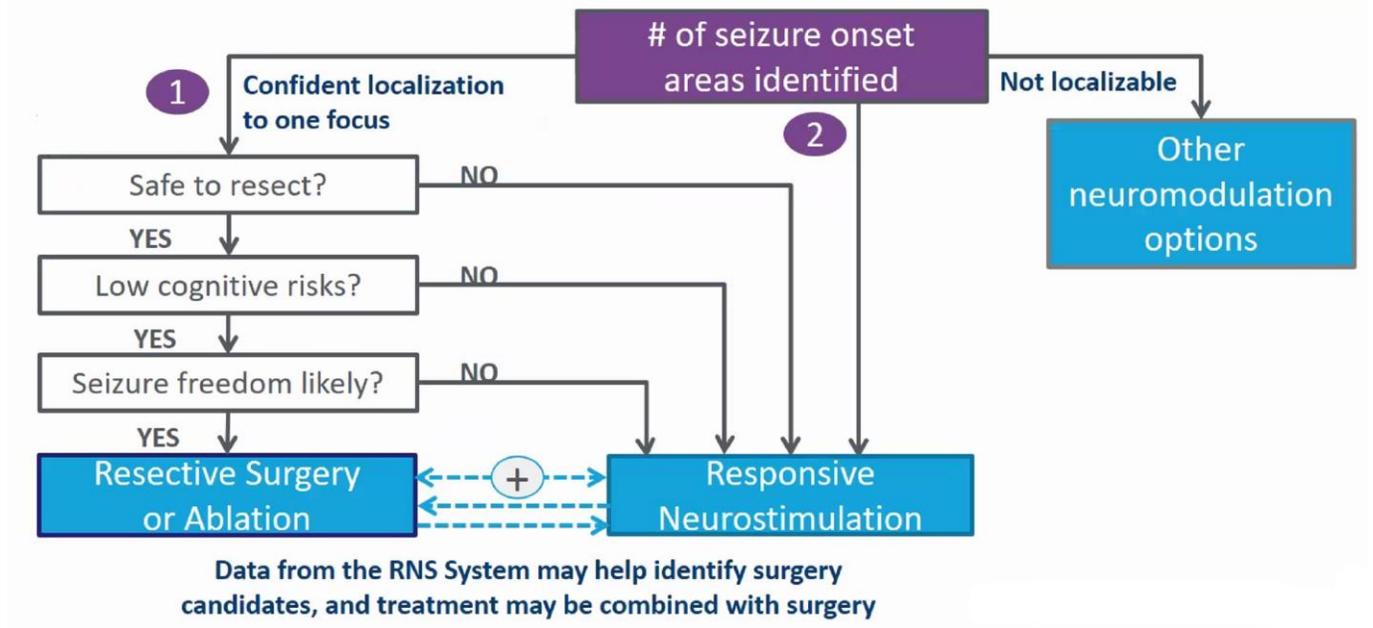
Yale algorithm



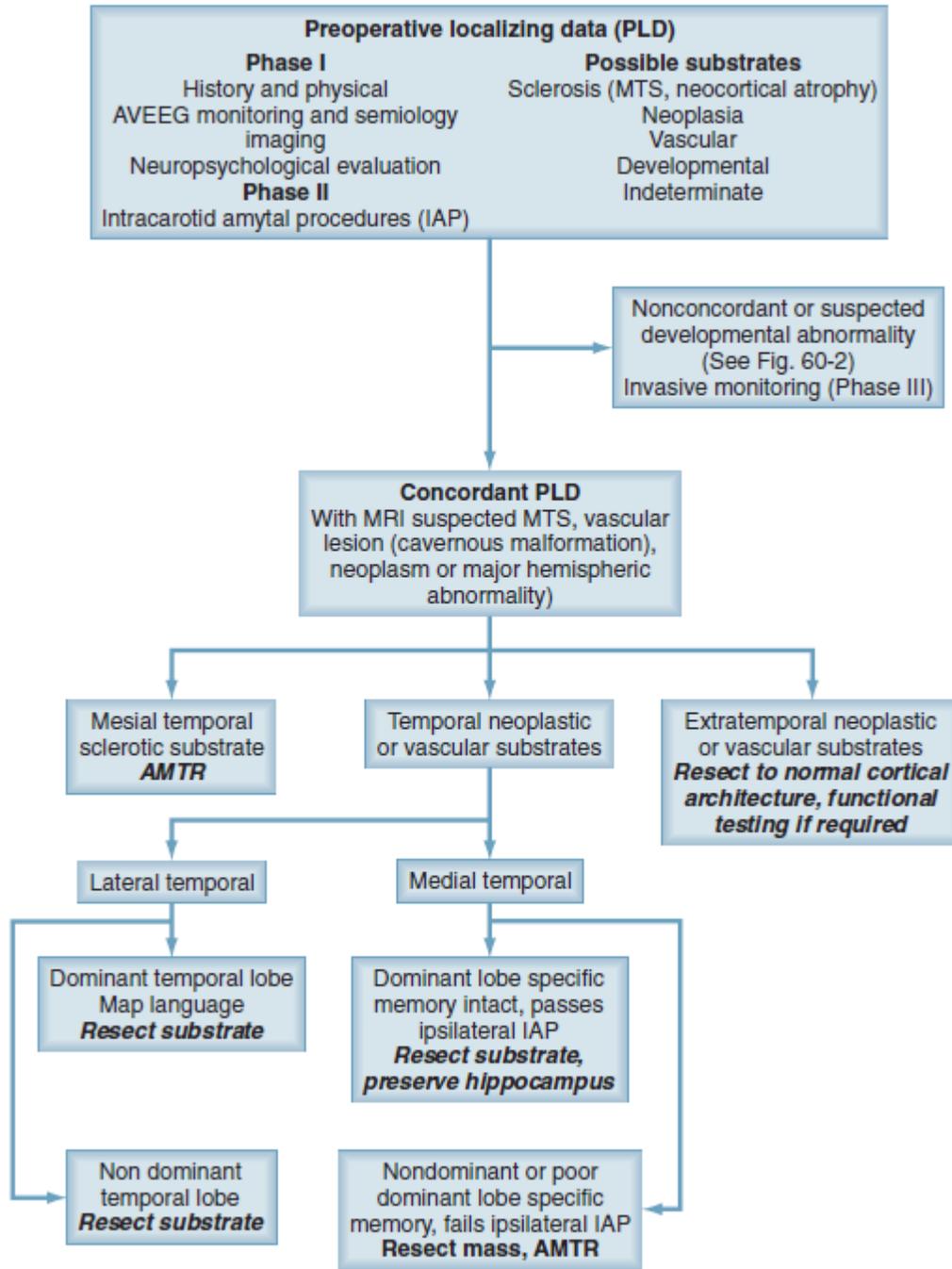
Gerard J et al.



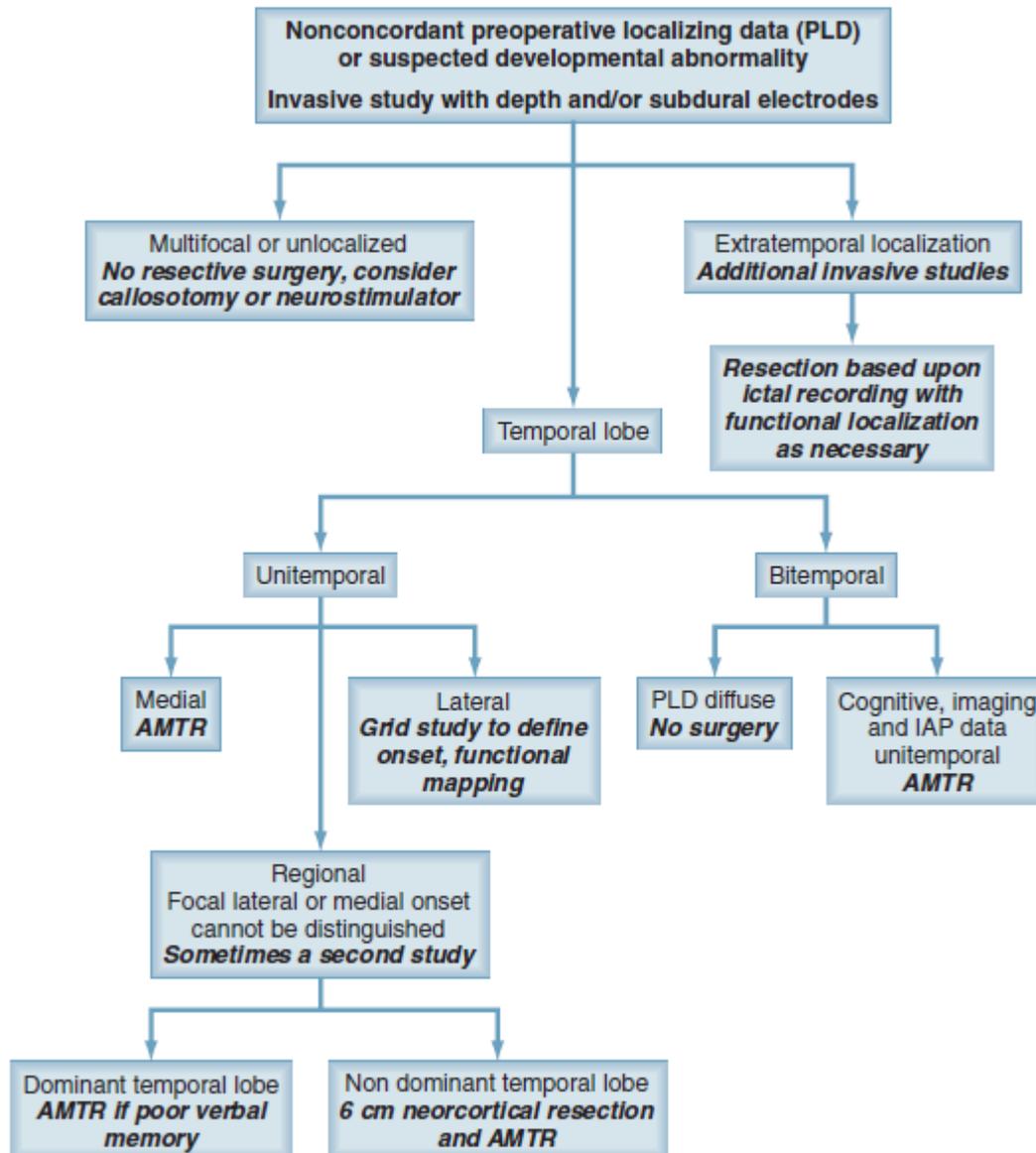
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Alternative algorithm



Alternative algorithm (fig. 60-2)



FOCAL EPILEPSY

- key dichotomies: temporal vs. extratemporal



mesial vs. neocortical

- distinguishing mesial vs neocortical temporal may at times require intracranial EEG, but once that is done, the neocortical temporal group generally follows the same course as extratemporal.

TEMPORAL

Outcomes in bilateral or non-resectable temporal lobe

1. VNS – 60-62.5% response
2. ANT DBS – SANTE trial - 44.2% response
3. RNS - 74 % response in hippocampal epilepsy

4. **Hippocampal DBS** – 25-100% response in hippocampal epilepsy
5. CM DBS – not as effective on focal epilepsy
6. STN DBS – too limited data
7. TMS – probably ineffective for mesial TLE

MESIOTEMPORAL

Unilateral

- resective surgery or ablation is by far the treatment of choice.
- traditionally, **en bloc resection of anterior lateral and mesial temporal lobes structures** has been performed. However, the potential for neuropsychological decline (especially in dominant temporal lobe surgery) has led to the development of **selective amygdalohippocampectomy (LITT of the mesial structures** is an effective option).
- very rarely, **neurostimulation** may be preferable if memory is superior on that side, but this should be exceptional because a minor verbal memory decline is usually offset by seizure freedom.

Bilateral

- the issue is “how bilateral is it?” (continuum from minimal or weak evidence on one side, to definitely and clearly bilateral):
 - a) high concern for bilateral disease (independent seizures on surface EEG, bilateral mesial temporal sclerosis (MTS) on MRI, conflicting lateralizing findings)
 - b) low concern for bilateral disease (very rare interictal spikes on the opposite site)
 - c) most often - anywhere in between high and low concern.
- options:
 - a) straight **unilateral resection**
 - b) bitemporal **intracranial EEG**
 - c) high concern for bilateral disease* → **RNS** (data may allow an eventual resection should there be a strong unilateral predominance).
 - *RNS is preferred over short-term intracranial EEG in order to ascertain lateralization based on a larger sample of seizures (hundreds), rather than on a limited number of seizures obtained in EMU (and usually on reduced doses of AEDs).

NONMESIOTEMPORAL (NEOCORTICAL TEMPORAL, EXTRATEMPORAL)

Lesional

Here, much of the approach depends on the nature of the lesion and, specifically, its suspected nature (tumor, vascular malformation, cortical dysplasia, etc.), size, location (with respect to eloquent cortex), and the degree of certainty (based on semiology and EEG) that the lesion is indeed causing the seizures. If the lesion is a suspected neoplasm, then its potential for evolution into higher grades becomes part of the equation, favoring resection for tumor reasons rather than epilepsy reasons. If the lesion itself is static and not concerning for a neoplasm, then lesionectomy has the highest probability of seizure freedom and will usually be preferred, with neurostimulation being a distant second choice, and probably only appropriate if the resection would involve critical eloquent cortex. Here, a partial resection can be combined with neurostimulation, though RNS can interfere with serial MRI surveillance of lesions. Another complicating factor in lesional focal epilepsy is the potential for dual pathology. Resection can be done with or without intracranial EEG or ECoG. Hemispherectomy represents an extreme example of lesional resection (e.g., hemimegalencephaly, Rasmussen's Syndrome) and also belongs in this category.

Nonlesional

This scenario (neocortical + nonlesional) is the most challenging and a very common scenario at level-4 epilepsy centers.

- A. Strongly lateralized (hemisphere known) Strong lateralization can be based on interictal discharges, ictal EEG, or seizure semiology (e.g., consistent head version prior to secondarily generalized convulsions). This scenario, most commonly frontal, will require intracranial EEG to cover the area in question (frontal, frontotemporal, parietal, occipital, etc.). Since the area is usually extensive, sEEG is increasingly preferred to subdural grids and strips, but both can be used.
- B. Not confidently lateralized (hemisphere unclear) Such cases have often been referred to as “fishing expeditions.” In the past, they could only be pursued with abundant amounts of hardware (bilateral strips and grids), resulting in a higher rate of complications and a relatively poor outcome. For that reason, many centers have tended to not pursue these cases for possible resective surgery. The advent of frameless robot-assisted sEEG, allows better surveying both in space (numerous depth electrodes on both sides) and time (electrodes can remain in place for weeks with little morbidity). Therefore these cases can now be reasonably pursued, “displacing” palliative neurostimulation treatments. One approach here is initially bilateral frontotemporal sEEG, which after the first few seizures can be focused by adding depth electrodes on the confirmed side of seizure onset once clarified [24]. Subdural electrodes and sEEG can also be combined. In this scenario, neurostimulation is also a reasonable option, since it carries less morbidity and the chances of seizure freedom with resective surgery are lower than in temporal or lesional cases.

EXTRATEMPORAL

1. VNS – efficacy in focal epilepsy does not appear to be limited to temporal lobe
 2. RNS – 37% response rate in neocortical epilepsy
 3. CM DBS – not as effective on focal epilepsy
 4. ANT DBS – Sante trial did not demonstrate efficacy in this subgroup
 5. STN DBS – was efficacious in small #'s tested and FLE was main target
 6. TMS – may be effective for MCD
 7. Hippocampal DBS - N/A
- posterior quadrant epilepsies – counsel for hemianopsia risk as often big resections (or disconnection) is needed.

ELOQUENT CORTEX

A. Resections

- need *mapping* - grids are ideal (but preceding sEEG may guide grid implantation)
- resections in eloquent cortex are feasible and safe (as long as preservation of functional areas is observed)
- outcomes are excellent in *lesional* epilepsies.
- in *non-lesional* epilepsies, if intracranial recordings provide convergent data, seizure freedom has high probability
- role of LITT is limited – cannot provide mapping

B. Neuromodulation

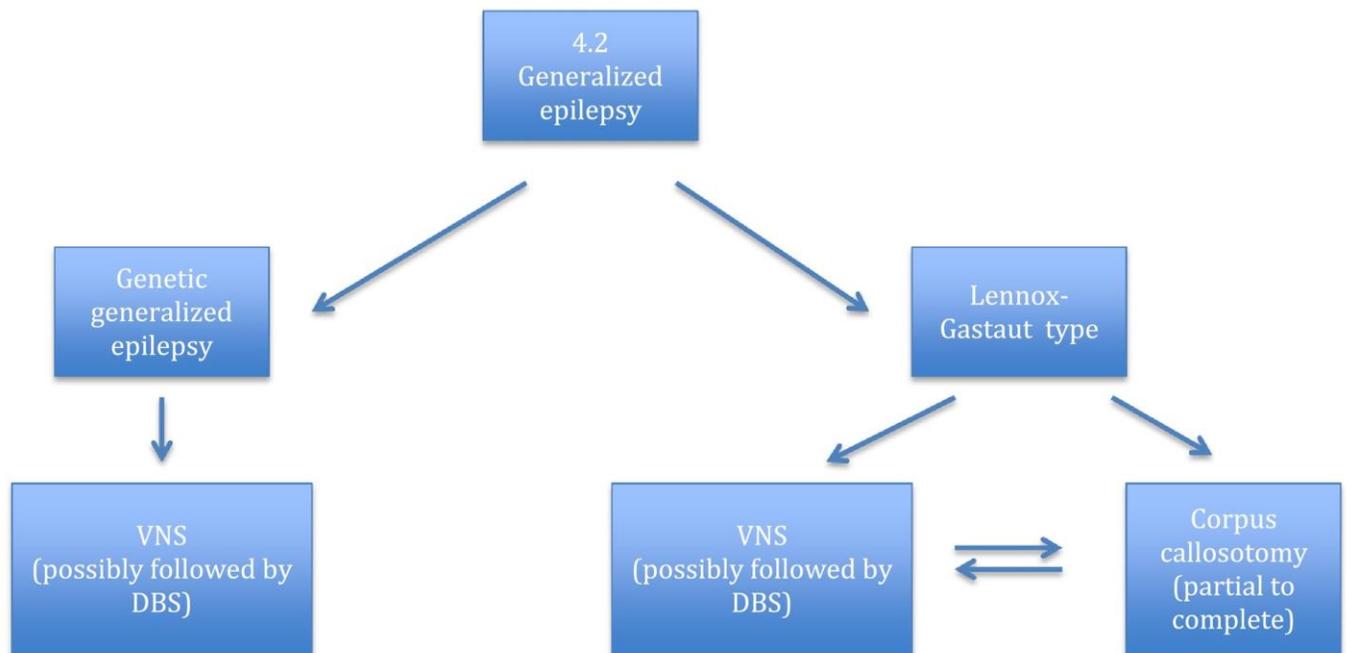
- reserved for nonresectable areas (as determined by direct cortical mapping).

- can be combined with resection (limited topectomy) and mapping (precisely guides RNS electrode placement).

LANGUAGE LOCALIZATION / LATERALIZATION

1. fMRI
2. MEG
3. High-density EEG
4. TMS
5. WADA
6. Cortical stimulation (intraop vs implanted electrodes)

GENERALIZED EPILEPSY



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GENETIC (S. IDIOPATHIC, PRIMARY) GENERALIZED EPILEPSY

- this group is usually not medically intractable, but it can be.
- occasionally, when bifrontal epileptiform discharges mimic generalized spike-wave complexes (“secondary bilateral synchrony”), distinguishing a GGE from a frontal lobe epilepsy can be challenging, and it is generally safer to err on the side of GGE and only pursue surgically if there is strong evidence for a focal onset.

LENNOX-GASTAUT TYPE (S. SYMPTOMATIC, CRYPTOGENIC GENERALIZED EPILEPSY)

- usually with cognitive impairment (developmental intellectual disability), neurologic abnormalities such as cerebral palsy, and characteristic EEG abnormalities.
- cause may be genetic, structural, or metabolic but is often unknown.
- this group can also be considered multifocal rather than “generalized” (epilepsy with ≥ 3 “foci” is equivalent to “generalized”).

Resective surgery and RNS are never options for the generalized epilepsies, but corpus callosotomy, VNS, and DBS can be. Technically, VNS for generalized epilepsy is off label in the US but is nonetheless one of the most common uses of VNS (endorsed by AAN guidelines). Corpus callosotomy is almost never performed in patients with GGE since they are usually mentally and neurologically healthy, but is a viable option for LGS type and while it is most often used in children, it can be performed in adults. Compared with neurostimulation, corpus callosotomy is more invasive, more ambitious, and may have more immediate effects. Neurostimulation is less invasive than callosotomy (VNS less than DBS), and the therapeutic effect is delayed, taking weeks to months. Preferences to use callosotomy or VNS first vary, and both are acceptable strategies that are not mutually exclusive. Additionally, since both are palliative procedures, some patients will benefit from both sequentially. Very rarely, patients with LGS-type of generalized epilepsy with a lesion can benefit from a focal (lesional) resection.

Lastly, patients with true multifocal epilepsy, i.e., related to truly multifocal discrete lesions such as tubers or cavernomas, can be considered for resection if it is confidently proven that one lesion is the source of a majority of the seizures.

Outcomes

1. **VNS** – 44-67% response
2. **ANT DBS** – Sante trial limited to CPE
3. **CM DBS** – 0-100% response
4. **RNS** – by definition excluded
5. **Hippocampal DBS** - by definition excluded
6. **STN DBS**- N/A
7. **TMS** – N/A

PREOPERATIVELY

AED

- **VALPROATE** can cause *bleeding disorders* - routinely check coags and bleeding time - if values are abnormal, decrease or discontinue* valproate and recheck values before surgery!
*at least 3 weeks prior to surgery (replace with another medication).
- on surgery morning, patient receives usual medication dosage with few sips of water.
- some centers taper anticonvulsants, and completely D/C 1 day before surgery (???)

TYPES OF SURGERY

ABLATIONS S. RESECTIONS (curative) - resection of seizure focus (up to entire hemisphere):

- 1) lesionectomy
- 2) neocortical resections

DISCONNECTIONS (palliative) - used when eloquent brain is involved to disconnect seizure focus from other functional parts of brain:

- 1) callosotomy
- 2) hemispherectomy
- 3) multiple subpial transections

STIMULATION S. NEUROMODULATION

- 1) RNS
- 2) DBS
- 3) VNS

Only 10-30% of pharmacoresistant patients are candidates for **resective** surgery (rest of patients – **neuromodulation**)

SURGICAL PHILOSOPHY

Nodes vs. Networks – biggest debate about *pathophysiology of epilepsy* and may affect **surgical philosophy**.

Goals of surgery – **node removal / disruption** (i.e. lesion resection or stimulation with RNS / DBS) vs. **network disconnection** (lesioning) or **neuromodulation** (DBS / VNS).

Analogy with oncology – hope to remove *critical portion of abnormal neurons*, so then local inhibitory mechanisms will take care of the reminder.

1. RESECTION / ABLATION

Temporal Resections

see p. E15 >>

Lesionectomy

– for **structural lesions** delineated by **MRI ± electrocorticography**.

- most often in frontal lobe.
- all larger arteries or veins adjacent to or crossing gyri should be preserved.
- avoid resection of deep fiber pathways in white matter, i.e. stay in cortex (white matter is not epileptogenic).
- most common mistake is to remove only gross tumor and not immediate surrounding tissue (leaving epileptogenic tissue and clinical seizures).
e.g. small vascular abnormalities surrounded by hemosiderin can be extremely epileptogenic.

N.B. lesion in **eloquent cortex** – need **ECoG** to guide resection (else high risk of *postop status epilepticus*)
– if planning awake mapping, tell the patient “if you become noncooperative, we will implant grid and will send you to EMU for extra-operative mapping”.

Lesioning

- a) for **structural lesions** delineated by **MRI ± electrocorticography**.
- b) for **disconnecting** (e.g. callosotomy)

Available modalities:

1. Laser ablation (LITT)

2. RF-ablation (e.g. guided by SEEG)
3. Stereotactic radiosurgery (SRS)
4. Focused ultrasound (FUS)

Tailored Neocortical Resection

– for **nonlesional extratemporal epilepsy** – resection guided by **SEEG** and/or intraoperative **electrocorticography**.

Tailored - no two operations are identical!

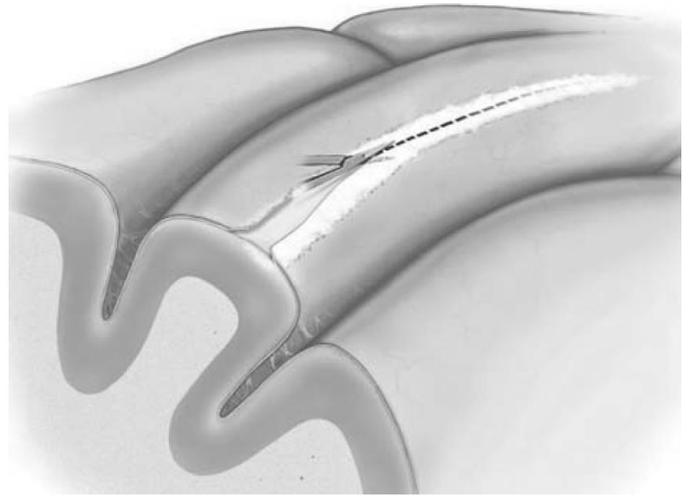
- epileptiform discharges recorded acutely during surgery define boundaries of cortical resection.
N.B. be prepared for larger craniotomy as epileptiform discharges may encompass larger area than expected!
- *eloquent cortical regions* are spared.
*Brazilians call intraop ECoG as an alternative to SEEG in poor countries: ECoG uncovers (interictal spikes) and guides resection of “dormant” EZs that would emerge later if only “active” EZ was removed.

Technique for topectomy:

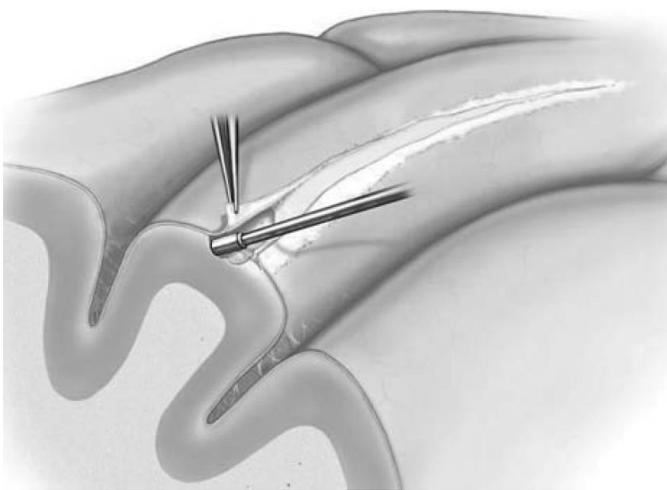
(a) The pia over the center line of the gyrus is coagulated with bipolar electrocautery and (b) divided with microscissors. (c) The pial flap is then elevated and the gray matter evacuated with gentle suction. Bipolar electrocautery is used for small vessel hemostasis, and occasionally to disrupt tissue that is not easily suctioned. (d) The resection is carried down to the bottom of the gray matter of the sulcus. White matter in the gyrus may be resected to this level, but not further.



(a)



(b)



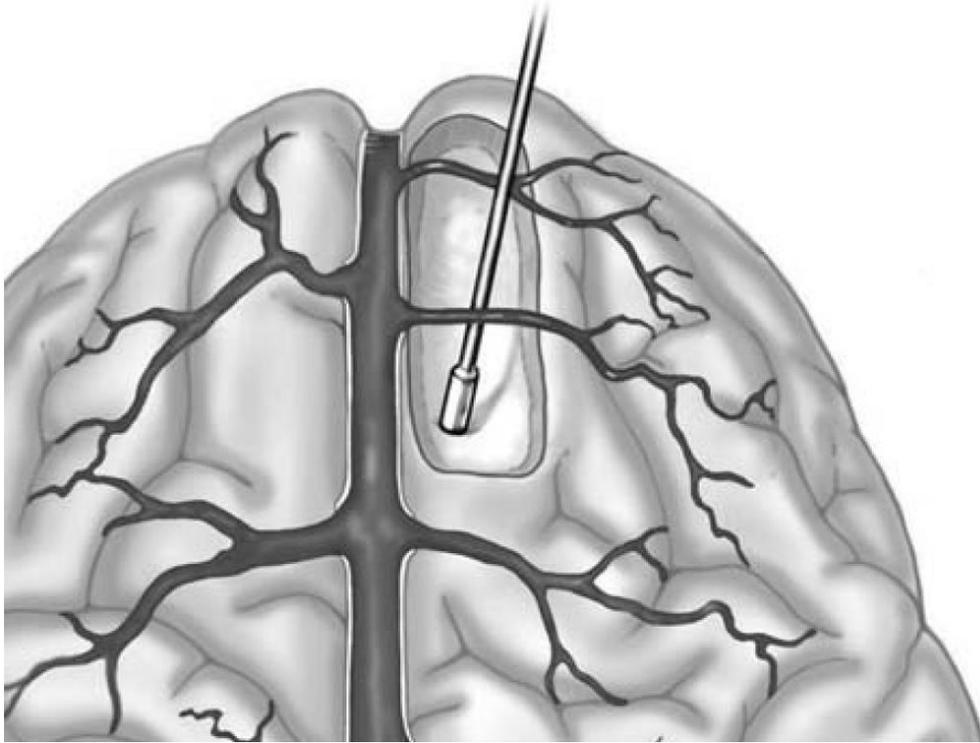
(c)



(d)

Source of picture: Lüders "Textbook Of Epilepsy Surgery" 1st ed. (2008); Publisher: CRC Press; ISBN-10: 1841845760; ISBN-13: 978-1841845760 >>

Preservation of vessels in topography. Respect for the vasculature is of the utmost importance, as sacrifice of en passage arteries or bridging veins may result in infarction of adjacent, functional cortex, leading to loss of function or a new epileptogenic focus:



Source of picture: Lüders "Textbook Of Epilepsy Surgery" 1st ed. (2008); Publisher: CRC Press; ISBN-10: 1841845760; ISBN-13: 978-1841845760 >>

Multilobar Resection

- a) corticectomy (resection of grey matter)
 - b) lobe excision (resection of grey and white matter)
 - c) lobe disconnection
 - d) combination.
- usually involves *frontoparietal*, *parieto-occipito-temporal*, or *parieto-occipital lobes*.
 - indications as for functional hemispherectomy.

2. DISCONNECTIONS

Multiple Subpial Transections (MST)

see p. E17 >>

Hemispherectomies (functional, anatomical)

see p. E19 >>

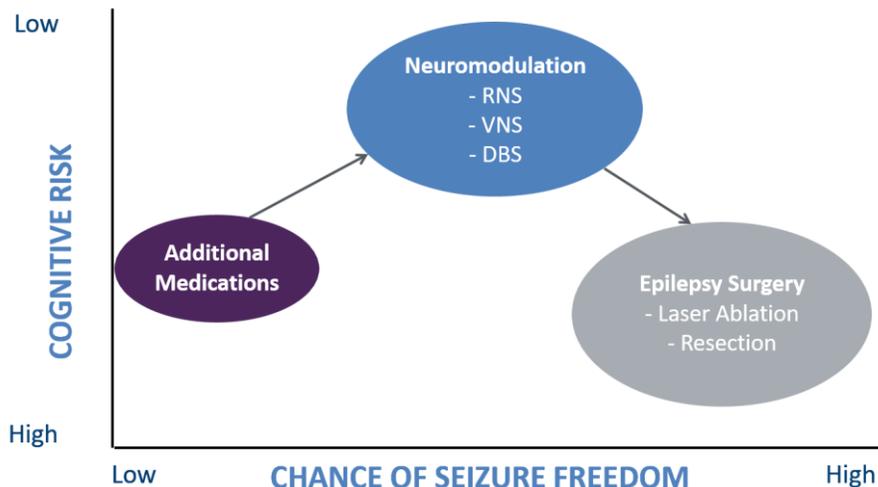
Corpus Callosotomy

see p. E21 >>

3. NEUROMODULATION

- electrical stimulation was first used therapeutically for epilepsy in the 1970s, when the cerebellum became the first therapeutic target for electrical stimulation in human patient epilepsy, with mixed results.

Neuromodulation may help bridge the treatment gap for many refractory patients:



Two theories (mutually nonexclusive and maybe overlapping)

1. **Modulation** of Network / Node
2. **Disruption** of Network / Node abnormal resonance / synchrony

Comparison Of Neuromodulations

Feature	VNS	DBS	RNS
Closed-loop	Partially (newer models may detect tachycardia)	No (newer models record LFPs)	Yes (detects electrographic activity)
Newest model	Sentiva (2017)	Percept PC (2020)	320 (2019)
Generalized or multifocal epilepsy	Yes	Probably (limited evidence)	No
Invasiveness (intracranial)	No	Yes	Yes
Recording capability	No	Low resolution sensing: 6 data points/hr, 5 Hz range	High resolution sensing: 250 data points/sec, 1-125 Hz range
Recording capacity	No	No	Yes (1 MB)
Indication for depression	Yes	No	No
Positive effects on mood & cognition	Yes	Unknown	Probably
Children	Yes	No	No (predicted in 2024)
Patient compliance needed	No	No	Yes

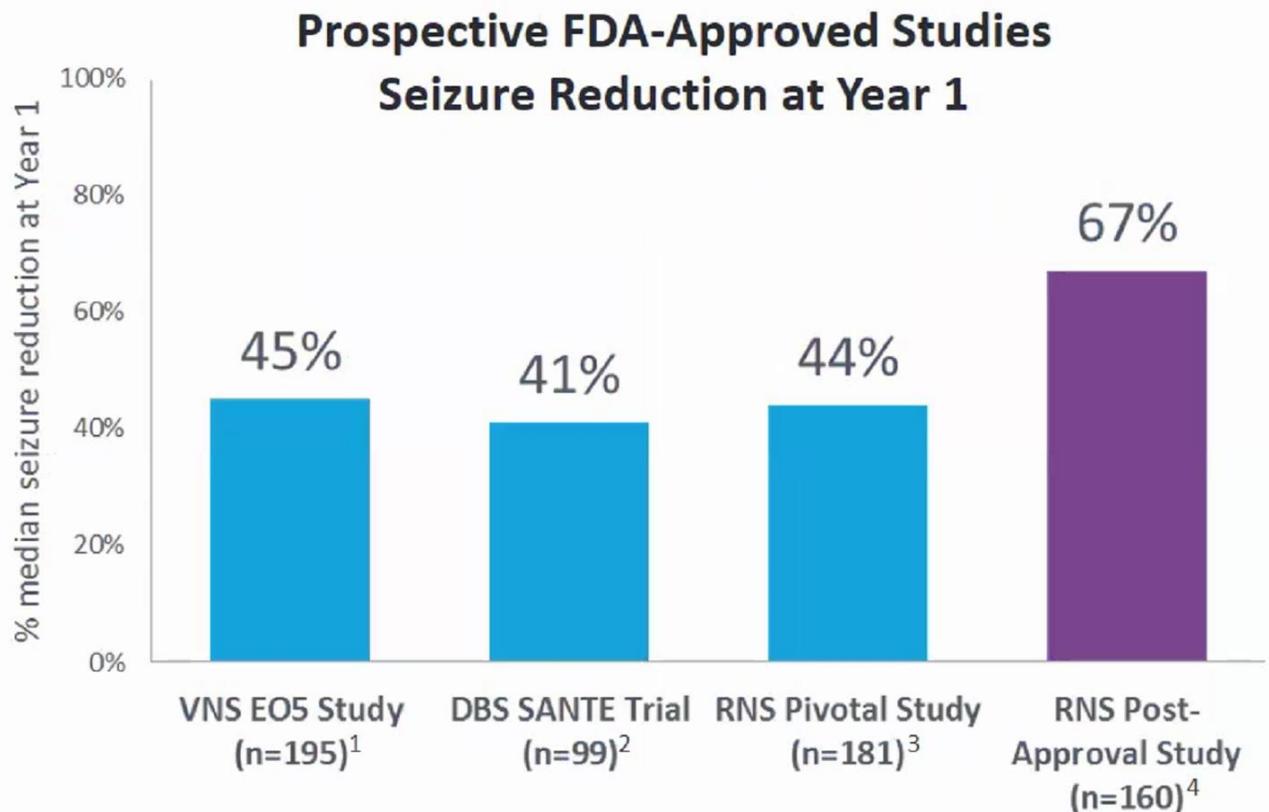
Feedback to the patient	None / swipe magnet to feel stimulation	Yes	Yes
MRI	Yes, exclude C7-T8 region (up to 3 T)	Yes, full body (up to 3T with Percept®)	Yes, full body (up to 1.5 T)
MRI exclusion zones	Yes	No	No
Side effects during stimulation	Yes	No (memory?, depression?)	No
IPG site	Infraclavicular	Infraclavicular	Cranial
Regulatory approval (2018 December)	The whole world (FDA in 1997)	USA (FDA in 2018), Europe (CE mark), Canada, Australia	USA only (FDA in 2013)
Outcomes			
Biomarker predictors of therapeutic response*	Non-lesional epilepsy, generalized seizures	Temporal theta-band desynchronization, hippocampal-evoked potentials, increased functional connectivity between ANT and the default mode network	None
Median seizure reduction at 1 year	45% (EO5)	41% (SANTE)	67% (Post-approval)
Best median seizure reduction**	76% at 10 yrs	75% at 7 yrs	75% at 9 yrs
Seizure remission***	Long term follow up: 8% were seizure free	At 7 yrs: 18% of patients experienced at least one 6-month seizure-free period, 7% were seizure-free for the preceding 2 years	At 7 yrs: at least one seizure-free period lasting: ≥ 3 months - 39% of patients ≥ 6 months - 29% of patients ≥ 1 year - 16% of patients

*reliable predictors of therapeutic response are lacking across neuromodulation options! (also failure of one neuromodulation option does not predict response to another neuromodulation option)

**follow up studies dismissed patients who stopped using devices or were lost for follow up – if to count those as treatment failures, responder rate (50% seizure burden reduction) remains stable over time at ≈ 40% across different devices.

*****medical therapy alone** in drug-resistant epilepsy gives 12-month seizure-remission in 33.4% of patients at 7 years!

Handforth, A et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998;51(1):48-55.



Note: Therapies were studied in different clinical trials. Caution must be exercised when comparing results.

1) DeGiorgio CM, *Epilepsia*, 2000 2) Salanova et al., *Neurology*, 2018 3) Heck et al., *Epilepsia*, 2014 4) Szaflarski et al., Poster AES 2019 5) Morrell MJ. *Neurology*, 2011

6) Ruoff et al., *Epilepsia Open*, 2020 (n=5) *N values are small and caution must be taken when interpreting results. 7) Meador et al., *Epilepsy Behav*, 2015 8) Loring et al., *Epilepsia*, 2015

DBS and VNS may seem similar but DBS gets physically into epilepsy network.

- regardless of neuromodulation modality chosen, the optimal time interval to adjust parameters (if no efficacy) – 3 months.

DBS vs RNS if either is placed in seizure focus – different opinions (FDA approved only RNS)

SEIZURE OUTCOMES

	VNS (LilaNova)	RNS (NeuroPace)	DBS (Medtronic)
Median Seizure Reduction Versus Baseline (%):	Year 1	• 45% (N=195, E05) • 33% (N=102, E03)	• 44% (N=181)
	Year 2	• 41% (N=51, E03)	• 53% (N=174)
	Year 3	• 40% (N=49, E03)	• 60% (N=214)
	Year 4		• 63% (N=204)
	Year 5		• 65% (N=172)
	Year 6		• 66% (N=115)
	Year 7		• 72% (N=185)
	Year 8		• 73% (N=163)
	Year 9		• 75% (N=147)
Responder Rate > 50% Seizure Reduction:	Year 1	• 35% (N=195, E05)	• 44% (N=181)
	Year 2	• 39% (N=51, E03)	• 55% (N=174)
	Year 3	• 39% (N=49, E03)	• 58% (N=214)
	Year 4		• 61% (N=204)
	Year 5		• 61% (N=172)
	Year 6		• 59% (N=115)
	Year 7		• 66% (N=185)
Seizure Freedom Rate:	≥ 3 Months		• 39%
	≥ 6 Months		• 28%
	≥ 1 Year		• 18%
	≥ 2 Years		• 5.4% (5 years)

STIMULATION TIME

Average time stimulation is delivered in 24 hrs:

- RNS – 6 mins
- VNS – 130 mins
- DBS – 240 mins

PSYCHIATRIC SIDE EFFECTS

Deep brain stimulation-ANT nucleus thalamus

- depression
- psychosis/ anxiety

Modification of settings may reverse effect

Responsive neurostimulation

No psychiatric adverse effects identified

Vagal nerve stimulator

FDA approved to treat depression

Data in epilepsy is limited

Deep Brain Stimulation (DBS)

see p. E27 >>

Vagus Nerve Stimulation (VNS)

see p. E23 >>

Responsive Neurostimulation (RNS)

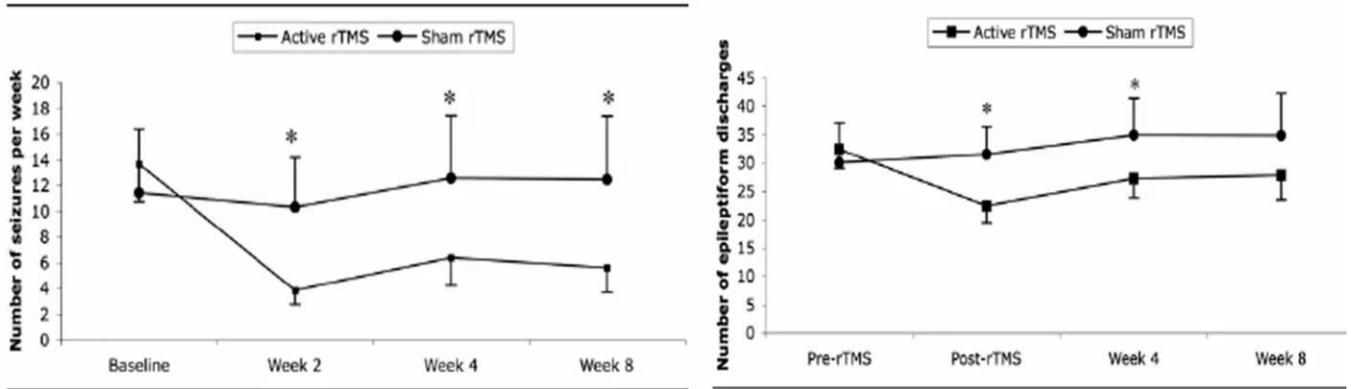
see p. E25 >>

Transcranial Magnetic Stimulation (nTMS)

- cortical stimulation with **low-frequency trains** decrease cortical excitability.
- some studies show ne efficacy.
- Randomized Double Blind Sham Controlled Trials

Study	Theodore (NIH) 2002 Neurology	Fregni (Sao Paulo) 2006 Ann Neurol	Cantello (Multicenter Italy) 2007 Epilepsia
N	24	21	43
Sz Type /Location	Mesial TLE 10 Lateral TLE 10 Frontal 3 Parietal 1	neocortical	mTLE 7 Neocortical 34
MRI	all lesions except MS were excluded	all malformation of cortical development (MCD)	Posttraumatic 6 MTS 5 Hemiatrophy 4 Cortical dysplasia 2 Tuberous Sclerosis 1
Stim Target	EEG identified <i>seizure focus</i>	MRI abnormality in 17, vertex in 4 with diffuse MCD	Vertex
Stim Parameters	1 Hz, 120% MT, 900 stim bid x 7 days	1 Hz, 70% max coil output, 1,200 stim/day x 5 days	0.3Hz, 120% MT, 1,000 stim/day x5 days
Outcome	No sig diff in stim vs sham, trend for better results in neocortical	Stimulated 2 weeks 72% p=0.003 4 weeks 53% p= 0.002 8 weeks 58% p=0.001 Sham – no change	No effect

- Fregni et al. 2006:



- rTMS may be effective in patients with epilepsy
 - In 21 patients with seizures due to malformations of cortical development, rTMS resulted in significant decrease in seizure count and the frequency of epileptiform discharges

- Chinese trial:

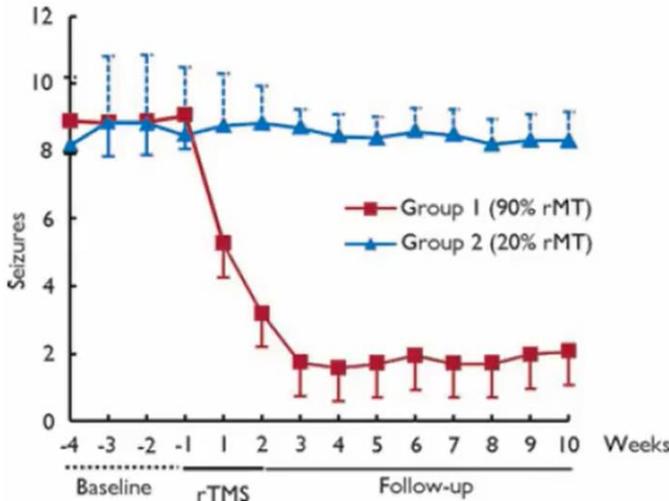


Table 2. Effect of rTMS on seizures (mean ± SD)

	Baseline	Follow-up	SRR (%)
Group 1 (n = 31)	8.9 ± 11.1	1.8 ± 3.7 ^a	79.8
Group 2 (n = 29)	8.6 ± 10.8	8.4 ± 10.1 ^b	2.3

^aSignificantly different from baseline (p < 0.05).
^bSignificantly different from group 1 (p < 0.05).
 SRR, Seizure Reduction Rate = [(Baseline seizures-Follow-up seizures)/Baseline seizures] × 100 (%).

Sun et al, 2012:

60 patients with refractory focal epilepsy randomized to receive 2 weeks of low-frequency rTMS at a moderate or very low intensity

POSTOPERATIVELY

- patient is returned to seizure monitoring room in epilepsy unit (vs. overnight ICU).

AED

Patients generally need to remain on AED therapy (for \approx 2 years); some continue to require AED therapy to remain seizure free (e.g. if pathology showed heterotopia, then other foci of heterotopia likely exist).

N.B. surgery is not indicated if patient expects to be AED-free!

- even if almost seizure free can try to reduce medication.

60% of patients (53% in temporal lobe epilepsy) are able to stop all AEDs (**22% remain seizure-free and medication-free after > 5 years**)

- if patient is taking 2 AEDs, least effective drug is tapered after 1 year.
- if patient is seizure free at 2 years, remaining drug can be tapered.
- one seizure during or after withdrawal → resume single medication therapy.
- negative risk factors: multiple lesions, EEG abnormalities, post operative seizures, longer preoperative seizure duration - but even they deserve a chance to be free of medication if seizure free!
- Can weaning medication make things worse? Probably not (Kerling 2009, Jehi 2012)
 - 70% regain control (Menon et al 2012).
 - those who recur are controlled with less aggressive regimen.
- **postoperative seizures**:
 - seizures *within first 24 hours ("honeymoon seizures")* do not correlate with poor long-term seizure outcome - may be due to irritation and edema of tissues adjacent to resection (neighborhood seizures).

Convulsions in immediate postop phase are common in first 3-5 days, if they are stereotypic of seizures prior to surgery, they may indicate lower chances of success and seizure freedom, but otherwise, they are not of huge concern unless they do not stop.

Acute postoperative seizures (up to 1 week after surgical resection) are not counted as evidence of recurrent epilepsy

- seizures *after 48 hours* (with adequate serum AED levels) do not bode well for eventual outcome.

N.B. many patients may continue to have **components of preoperative auras**;

- some may have *occasional seizures for few years* which then cease (*wind down*);
- others may be *seizure-free for few years*, then have recurrence.

Alternative view – early withdrawal of AEDs - safe and does not affect long-term seizure outcome or cure, might unmask incomplete surgical success sooner (identifying patients who need continuous drug treatment and preventing unnecessary continuation of AEDs in others).

- if seizures recur postop, only minority do recur during AED withdrawal.
- if seizures recur, restarting AED helps regain control.

BEFORE DISCHARGE

- 1) neuropsychiatric evaluation? (usually delayed for 6-12 months)
- 2) serum anticonvulsant levels
- 3) EEG

SURGERY OUTCOMES**SEIZURES**

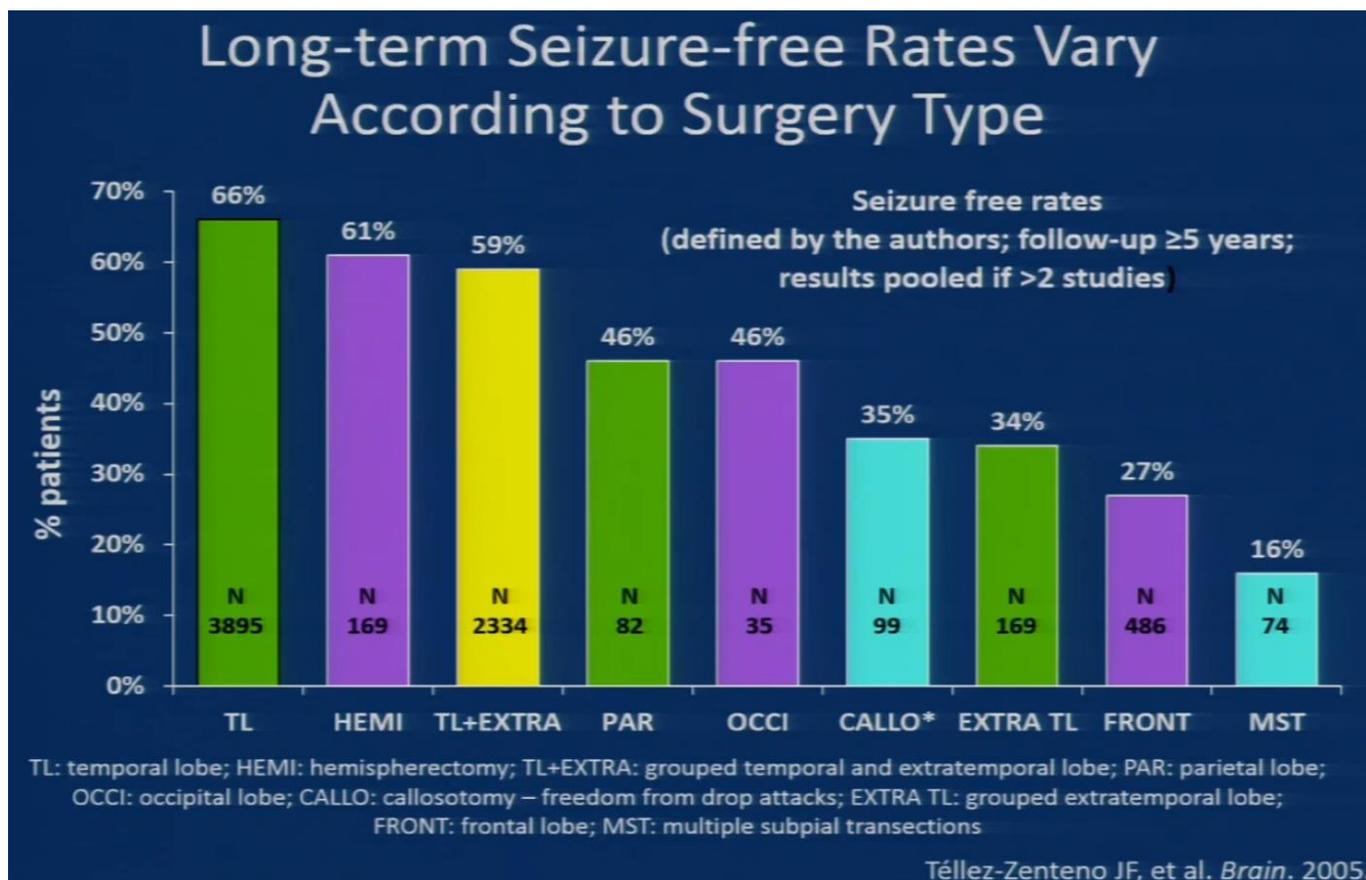
The only reliable predictor of seizure-free outcome – resection of lesional focus! (unclear if laser ablation qualifies for that)

- goal of epilepsy surgery:
 - **palliative** epilepsy surgery - seizure reduction (still can be very desirable for some patients, e.g. getting rid of convulsive seizures)
 - **radical** epilepsy surgery - seizure freedom
- in medical therapy, > 50% reduction in seizures = success
- seizure control is assessed at 1, 3 & 6 most post op, and then annually.
 - 90% of seizures that recur do so within 2 years; per Dr. R. Gross – if seizures recur, they do it within 6 months (therefore, outcomes are measured earliest at 12 months).
 - neuromodulation antiseizure effect keeps improving over time.
 - “It takes time for epilepsy to develop, it takes time to undevelop”

Procedure	Seizure Free (%)	Improved* (%)
Anterior temporal lobectomy	76	24.0-27.2
Amygdala-Hippocampectomy	68.8	22.3
Extratemporal cortical resection	25.0-60	18.2-35.2
Lesionectomy	66.6	21.5
Hemispherectomy	67.4-77.3	18.2-21.1
Corpus callosotomy	7.6-8.0	60.9-80.0

*50% reduction of seizure frequency

Long-term (> 5 years) outcome combining all kinds of epilepsy surgeries – 22% seizure free and no AEDs



- ablative surgery is associated with IMPROVEMENT in *intelligence*, in *psychiatric* and *behavioral* disorders, in *social* and *vocational* function (abnormal brain tissue resection may remove undesirable functional effects which are interfering with function of other cortical areas).
N.B. cognitive function starts to improve after successful surgery but after the lag period.
- parents often wonder whether their child's personality will change or if he / she will become more depressed or anxious after undergoing resection of temporal or frontal lobe surgery – *surgery doesn't appear to have major effect on mood or anxiety in children*, and some kids even do better.
- **RUNNING DOWN phenomenon** - gradual decline of seizures over several months or years until seizure freedom is achieved after surgery.

CLASSIFICATION OF OUTCOMES

Jerome ENGEL'S classification of postoperative outcome:

Class I: Free of disabling seizures

- C. Completely seizure free since surgery
- D. Nondisabling simple partial seizures only since surgery
- E. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
- F. Generalized convulsions with AED discontinuation only

- class 1 includes patients with *residual auras*.
 - 1) auras do not bother patient if they are infrequent.
 - 2) depending on nature of auras (e.g. intense fear), they can affect quality of life.

Class II: Rare disabling seizures (“almost seizure free”)

- A. Initially free of disabling seizures but has rare seizures now

- B. Rare disabling seizures since surgery
- C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
- D. Nocturnal seizures only

Class III: Worthwhile improvement (> 90% reduction)

- A. Worthwhile seizure reduction
- B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not < 2 years

Class IV: No worthwhile improvement (< 90% reduction)

- A. Significant seizure reduction
- B. No appreciable change
- C. Seizures worse

ILAE classification of postoperative outcome:

1. Completely seizure free; no auras
2. Only auras; no other seizures
3. 1-3 seizure days per year; ± auras
4. 4 seizure days per year to 50% reduction of baseline seizure days; ± auras
5. Less than 50% reduction of baseline seizure days; ± auras
6. More than 100% increase of baseline seizure days; ± auras

SEIZURE FREEDOM

Factors predictive of freedom from seizures:

- 1) MRI-detectable *lesion* (unless functional constraints limit extent of resection); better temporal than extratemporal.
- 2) concordant interictal *epileptiform discharges*.
- 3) more extensive *resections*.

SEIZURE WORSENING / DE NOVO SEIZURES

Population-Based Register Study

Johan Bjellvi et al. Risk Factors for Seizure Worsening After Epilepsy Surgery in Children and Adults: A Population-Based Register Study. Neurosurgery, Volume 87, Issue 4, 1 October 2020, Pages 704–711

- 2-year seizure outcome - 1407 procedures.
- increased seizure frequency compared to baseline - 4.0%
- new-onset TCS (grand mal) - 3.9% (6.6% in patients without preoperative TCS).
- risk factors:
 - 1) reoperations compared to first surgeries
 - 2) lower age of onset
 - 3) lower age at surgery
 - 4) shorter epilepsy duration
 - 5) preoperative neurological deficit
 - 6) intellectual disability
 - 7) high preoperative seizure frequency

- 8) extratemporal procedures
- 9) nonresective procedures (for new-onset TCS)

Risk of worsening seizures after epilepsy surgery:

- Overall: 10%
- New onset GTC: 1.4%
- New onset of Status: 2.2%
- SUDEP: 1.4%

Sarkis et al., 2012

SURGICAL REFRACTORINESS

“Widespread, ‘malignant’ epileptogenic network with a tendency to develop new epileptogenic zones upon resection of the prior zone, causing a progressive disease state”

Yardi Ruta et al. Long-term outcomes of reoperations in epilepsy surgery. Epilepsia. Volume 61, Issue 3 p. 465-478.27 February 2020

- 898 patients (one-third were pediatric patients and 68% underwent temporal lobe resection), 110 had reoperations (92 had one resection prior to the index surgery and 18 patients had ≥ 2 prior resective surgeries).
- 2 years after index surgery - Engel I score:
 - 69% of patients with no prior surgeries
 - 42% of patients with 1 prior surgery
 - 33% of patients with ≥ 2 prior resections ($P < .001$).
- odds of seizure freedom diminish with each additional operation.
- risk factors for “surgical refractoriness”: male sex ($P = .011$), history of secondary generalization ($P = .016$), increasing number of prior surgeries ($P = .002$).

QUALITY OF LIFE

Quality of life in pediatric patients (surgery vs. medications):

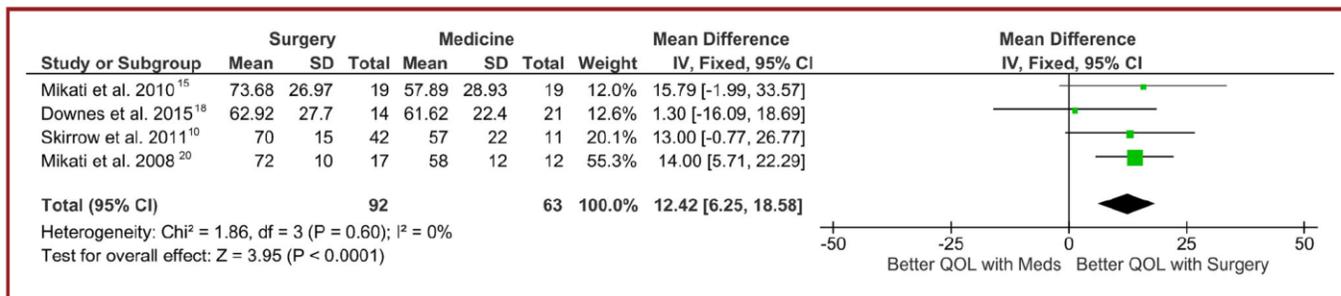
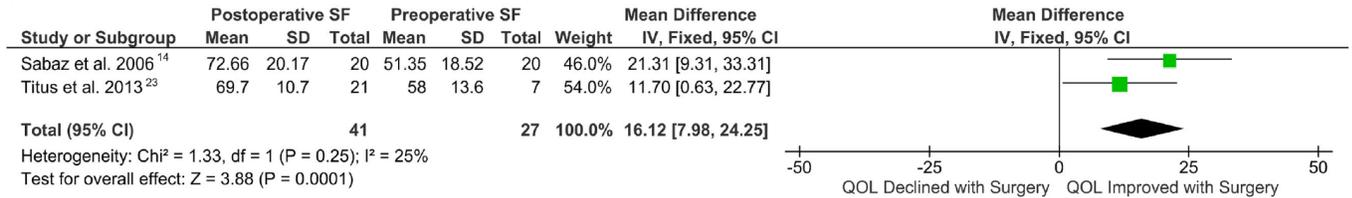
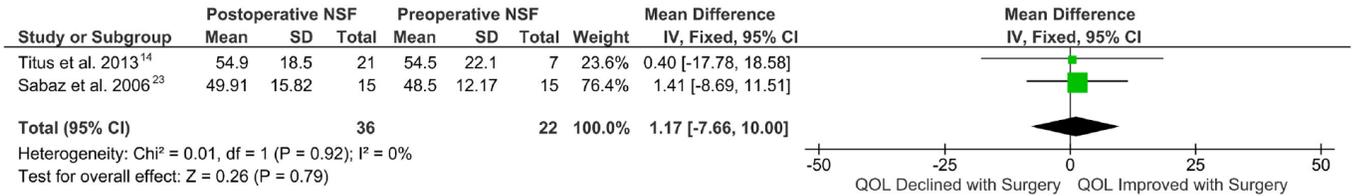


FIGURE 2. Forest plot for the comparison between postoperative QOL and QOL after the same time period on antiepileptic medications. Abbreviations: SD, standard deviation; CI, confidence interval; QOL, quality of life.

Subgroup with seizure freedom:



Subgroup with residual seizures:



Maragkos et al. 2020

- when looking at the secondary outcome of IQ, there was a **significant improvement of about 10 IQ points in patients treated surgically** than matched controls treated medically.

PSYCHIATRIC

De Novo Psychopathology

Novais F et al. Predicting De Novo Psychopathology After Epilepsy Surgery: A 3-Year Cohort Study. Epilepsy Behav. 2019;90:204-208. doi:10.1016/j.yebeh.2018.11.037. PMID: 30573340.

- 106 patients
- psychiatric evaluations were made before surgery and every year, during a 3-year follow-up period.
- resective surgery (93%) and ANT-DBS (7%).
- survival analysis model was used to determine pre- and postsurgical predictors of de novo psychiatric events after surgery.
- **15% developed de novo psychiatric disorders** that were never identified before surgery.
 - significant predictors - **multilobar epileptogenic zone** (P = .001) and **ANT-DBS** (P = .003).
 - hypotheses:
 - a) failure to establish adequate baseline.
 - b) surgery eliminates seizures, which could be an endogenous psychiatric treatment (ECT – a medically monitored generalized seizure - is a particularly effective treatment for depression).

BIBLIOGRAPHY for ch. “Epilepsy and Seizures” → follow this [LINK](#)