Surgery for Temporal Lobe Epilepsy

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Classification

- Mesial temporal lobe epilepsy
- Lateral (neocortical) temporal lobe epilepsy

* Familial temporal lobe epilepsy

Mesial versus lateral temporal lobe epilepsy

	Mesial TLE	Lateral TLE
Epigastric auras, fears and early oroalimentary automatisms	Predominate	Rare
Non-specific auras, early focal motor, somatosensory, visual or auditory symptoms	Rare	Predominate
Contralateral hand dystonia	Common	Rarer
Early clonic activity following automatisms	Rare	Common
GTCS	Infrequent	Frequent
History of febrile seizures	Predominate	Rare
Interictal EEG	Anterior temporal spikes	Middle and posterior temporal spikes
MRI	Hippocampal sclerosis	Neocortical lesions such as Malformations of cortical development

Panayiotopoulos, 2005

MRI or Pathology

- TLE associated with HS
- Lesional TLE
- TLE with dual pathology (in addition to HS), including abnormality only on pathology
- TLE without structural abnormalities on MRI (nonlesional in general) / Normal or abnormal on pathology

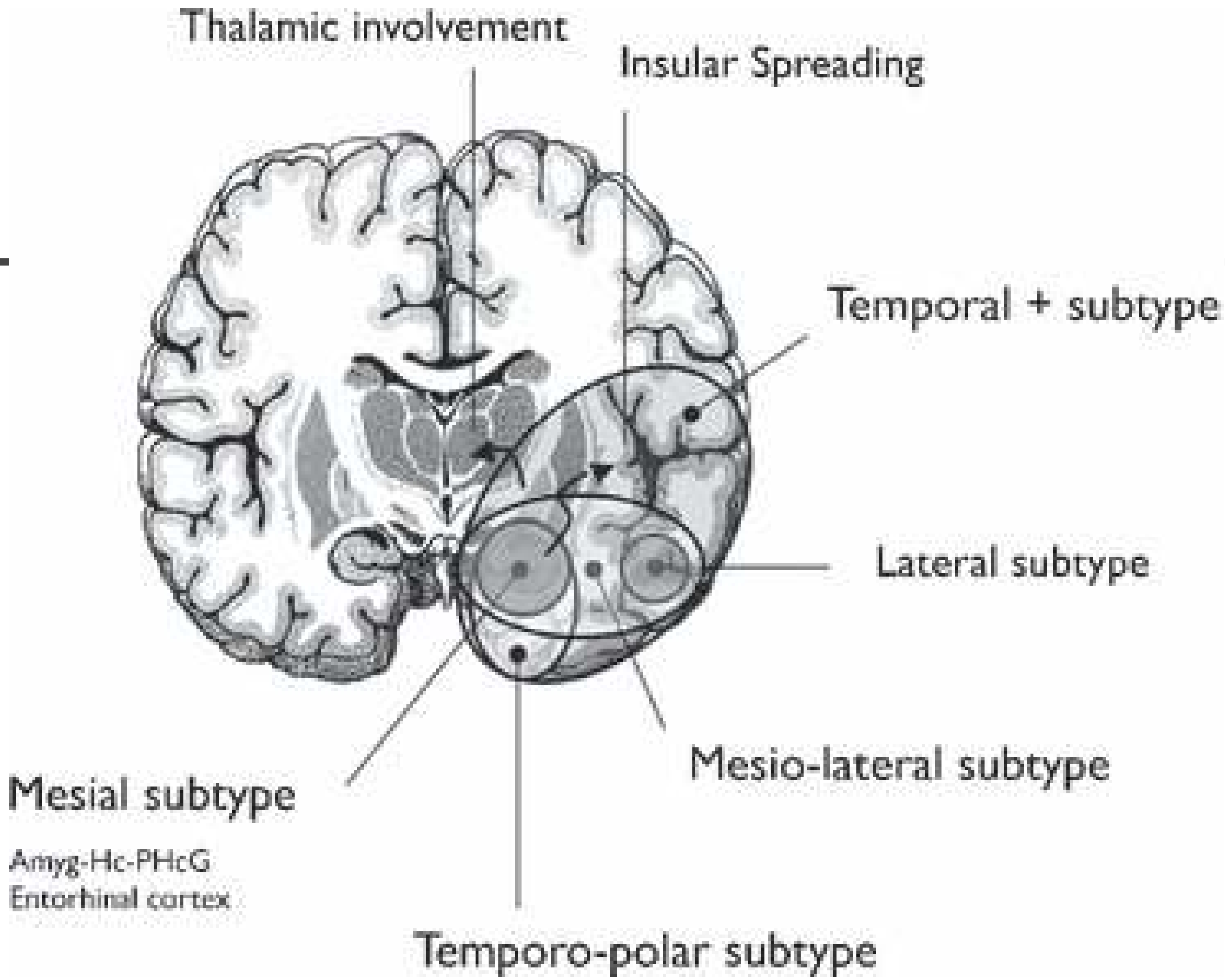
Electrophysiology

- Mesial TLE
- Lateral TLE
- Interplay (simultaneous or independent onset)

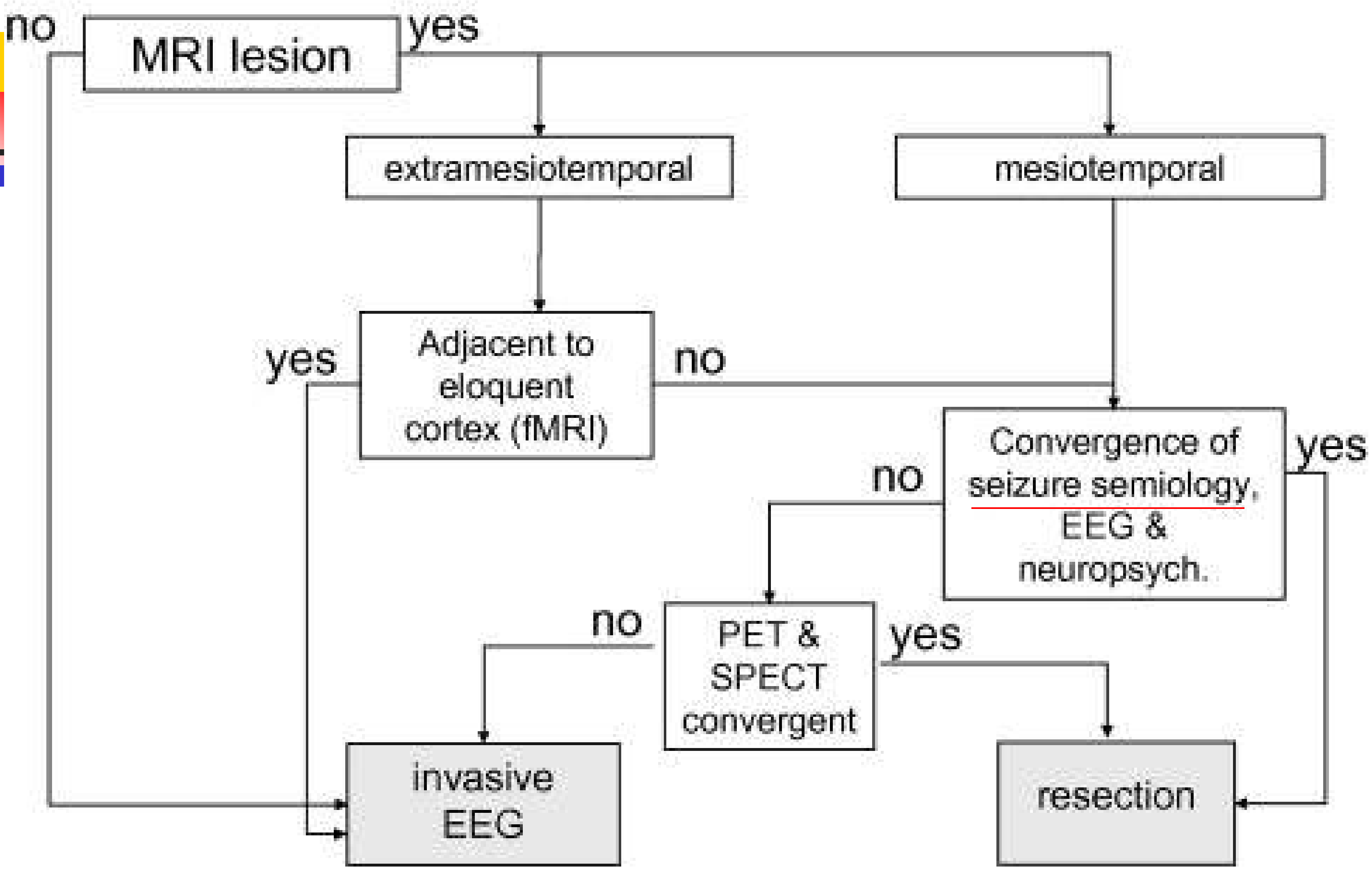
Pathological category of HS

- In terms of the extent (in addition to HS), pathology in adjacent mesial temporal lobe structures (MTS), occult or overt second (dual) pathology, and bilateral hippocampal damage
- (1) classical HS with neuronal loss in cornu ammonis 1 (CA1) and the hilar region; (2) end folium sclerosis (EFS) with neuronal loss primarily in the hilar region; and (3) loss restricted to CA1 only
- Nonclassical or atypical patterns of HS, which overall account for 4% to 10% of cases: less readily identified by preoperative imaging and associated with poorer surgical outcomes
- *Pure amygdalar sclerosis, no hippocampal neuronal loss in MTLE*

- TLE may comprise one-third of all epilepsies.
- Two-thirds of TLE originate from the mesial and the other third from the lateral temporal regions.
- Two-thirds of MTLE have HS: about 50% are intractable cases that require neurosurgical intervention and account two-thirds of surgical cases; This disorder is the most common refractory partial epilepsy which has been well characterized, and can usually be identified with noninvasive studies including scalp EEG and video monitoring with ictal recording, MRI, single-photon-emission computed tomography (SPECT), positron emission tomography (PET), neuropsychological assessment, and historical and clinical data.
- Recent observations from the histopathology of resected tissue, preoperative neuroimaging, and the basic science laboratory suggest that MTLE with HS is not always a uniform entity.

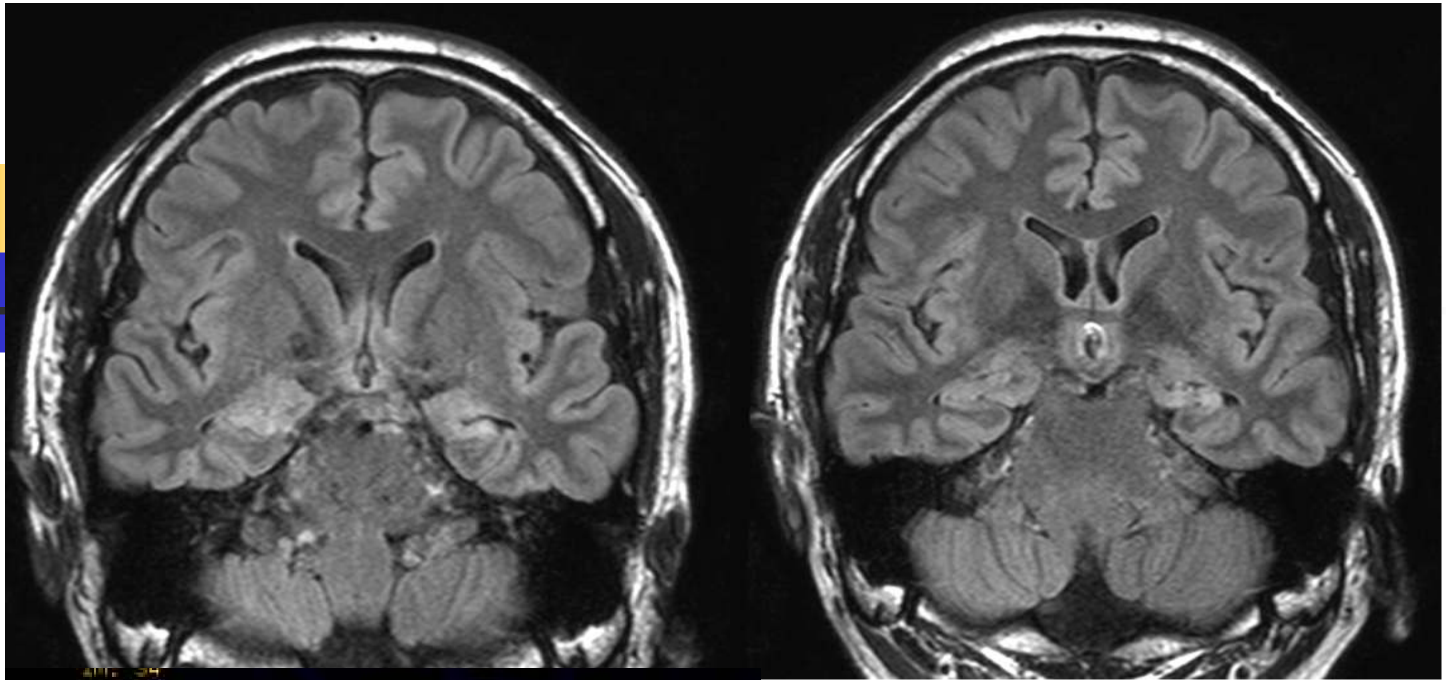


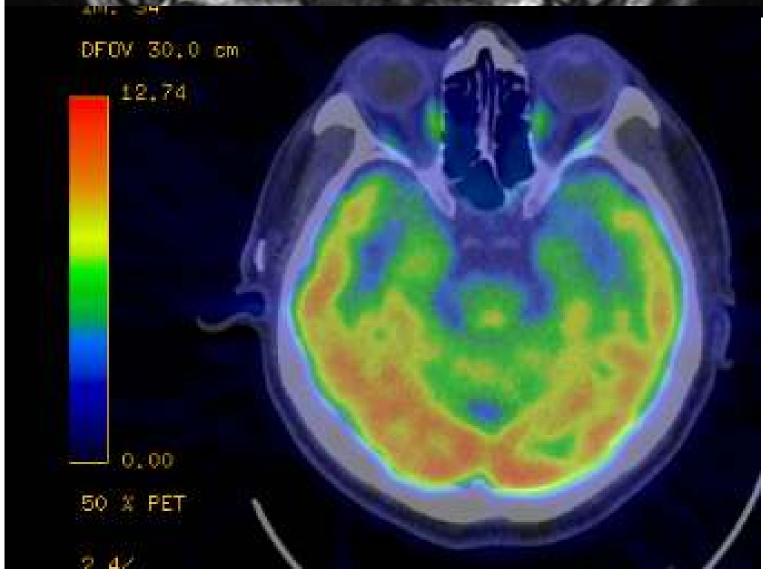
The spectrum of temporal lobe epilepsy associated with hippocampal sclerosis. There might be a continuum from a focal network centered over mesiotemporal lobe structures to a widely extended network that goes beyond the limit of the temporal lobe. Kahane & Bartolomei, 2010



Flowchart of diagnostic evaluation in epilepsy surgery

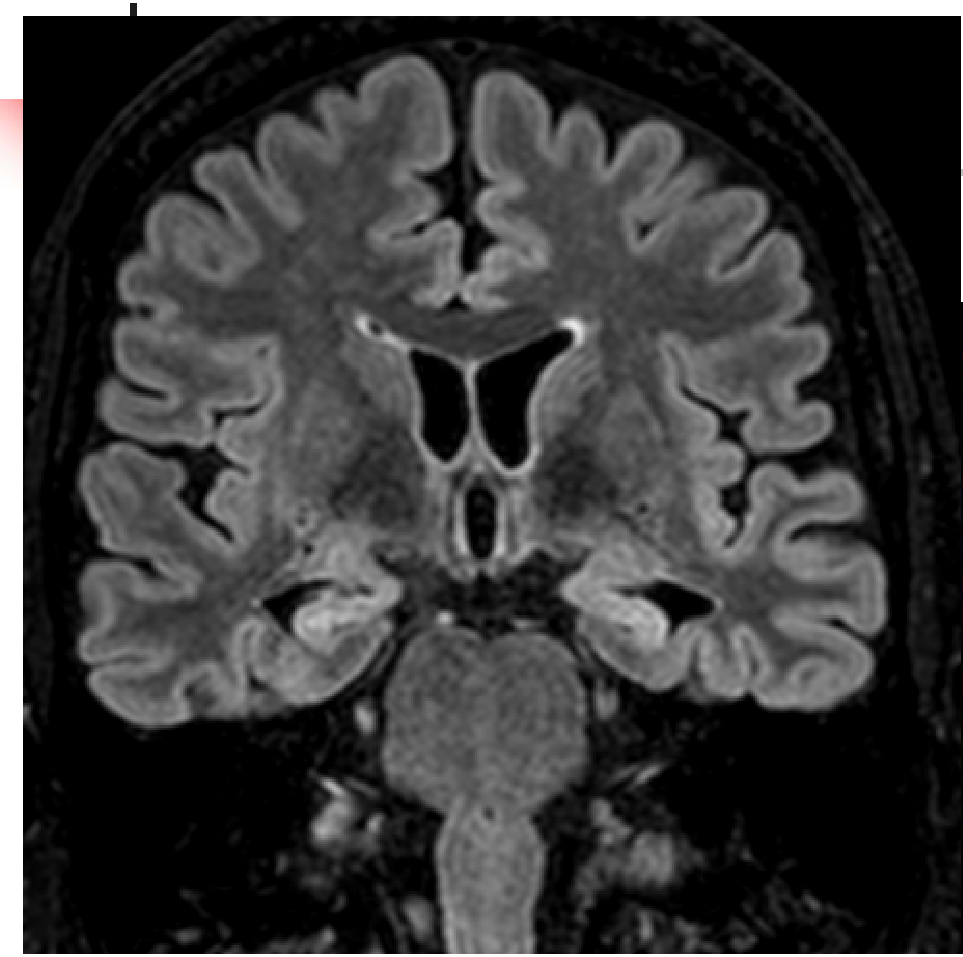
Noachtar & Borggraefe, 2009



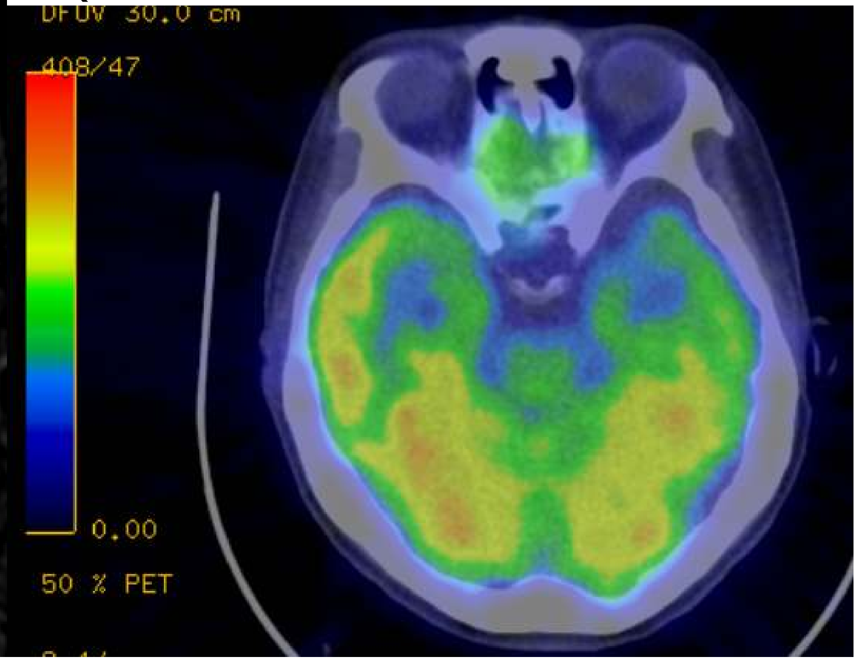


Left temporal IEDs (maximum on sphenoidal electrode) and ictal activity beginning in the left temporal region on scalp EEG
Left temporal hypometabolism on FDG-PET

TLE with HS

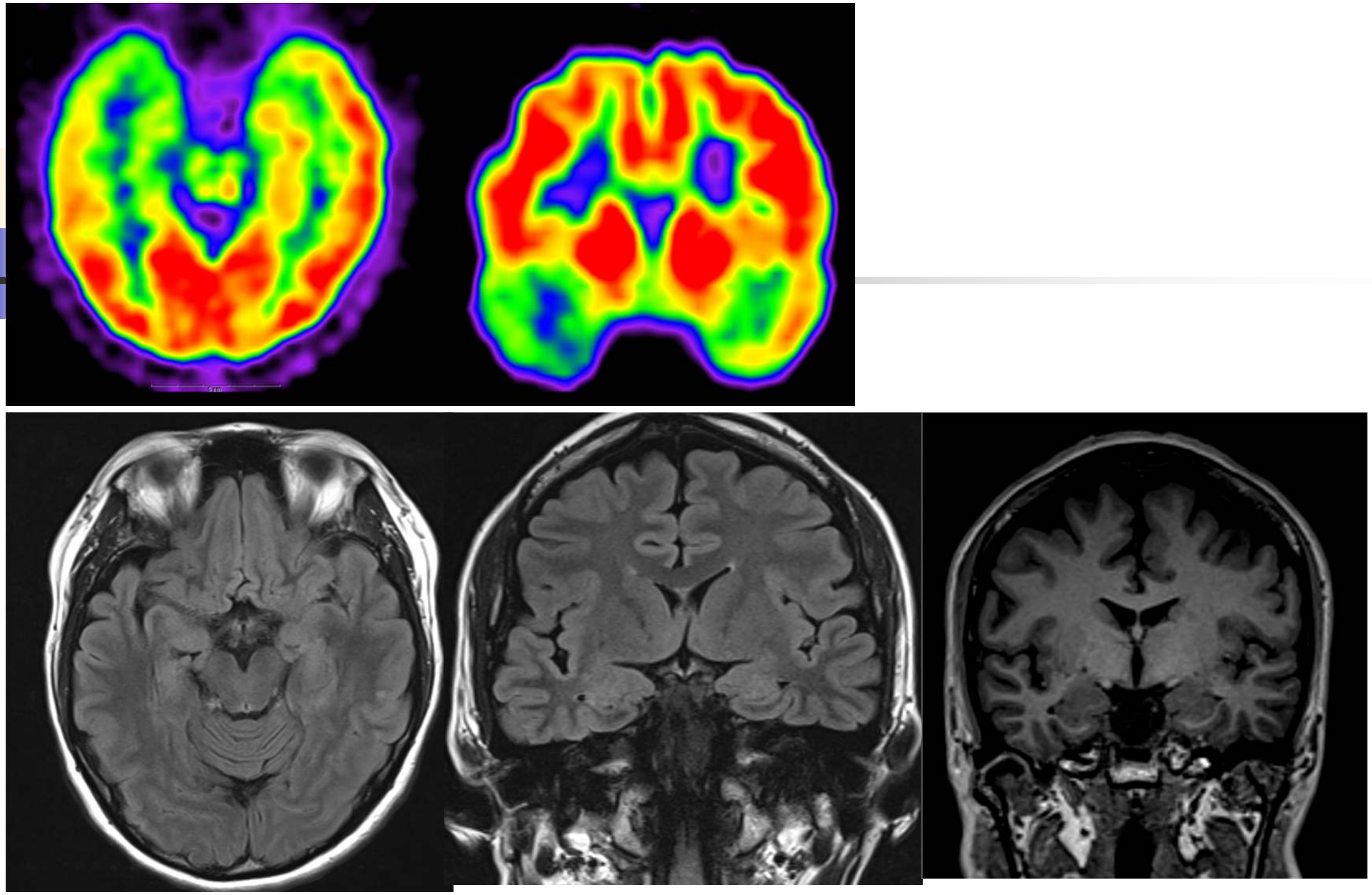


Independent bitemporal IEDs
Independent bitemporal ictal onset on scalp EEG
Left temporal hypometabolism on PET
(at least more involved in the left side)



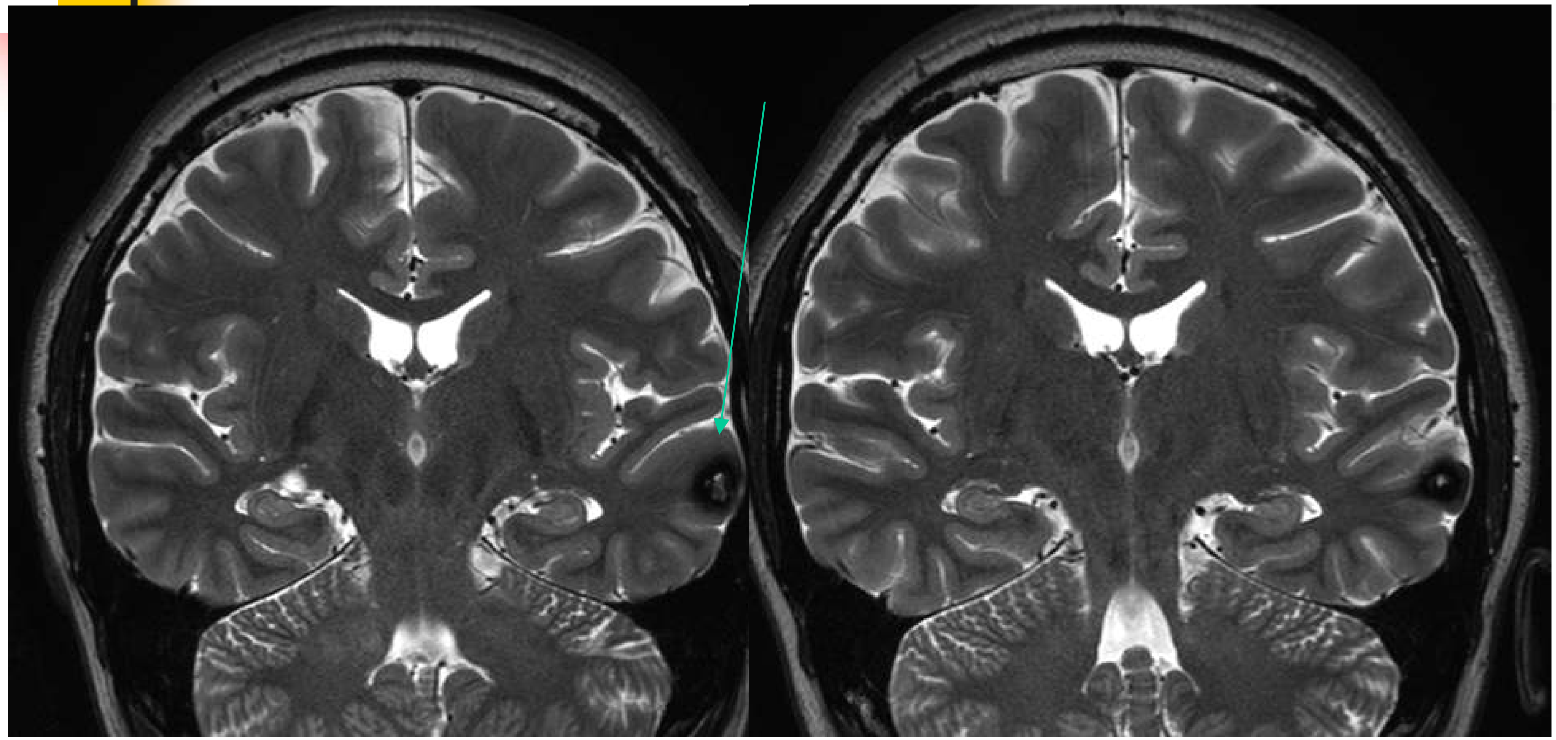
TLE with bilateral HS

Intracranial EEG with depth electrodes showed seizure onset in left hippocampus.

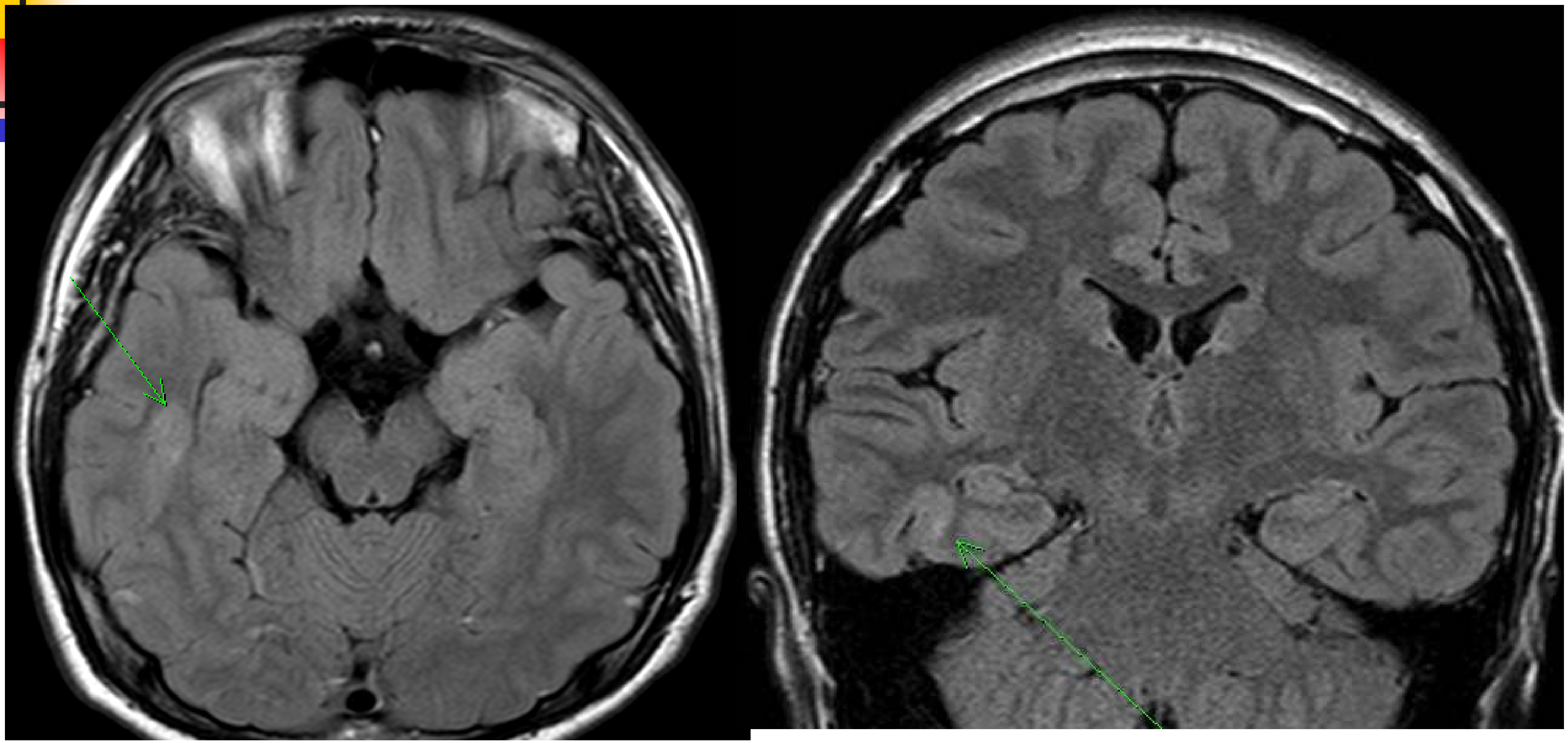


TLE with lesion

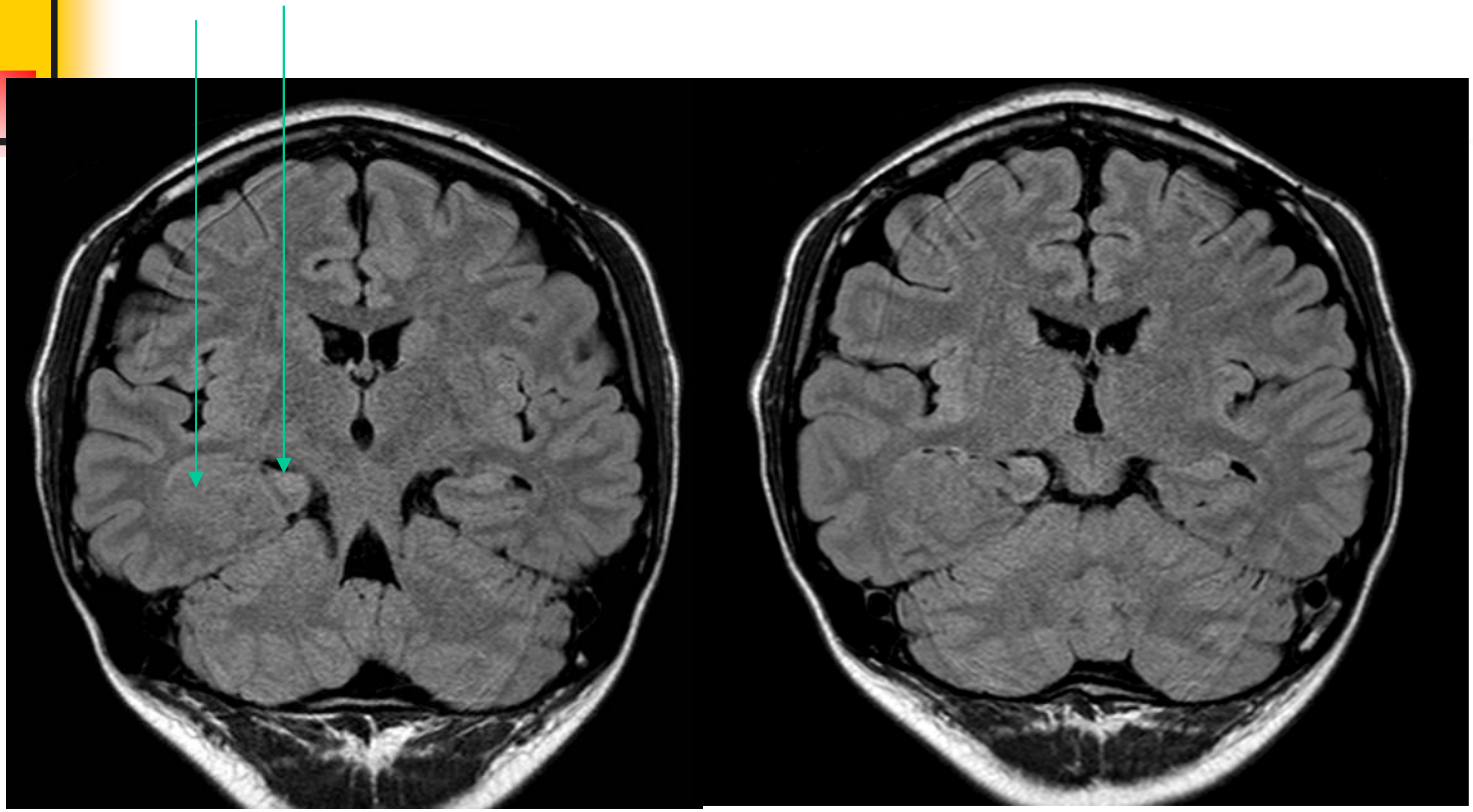
PET and MRI shows
right temporal hypometabolism and amygdalar enlargement, respectively
(pathologically cortical dysplasia)



TLE with lesion (cavernous malformation)

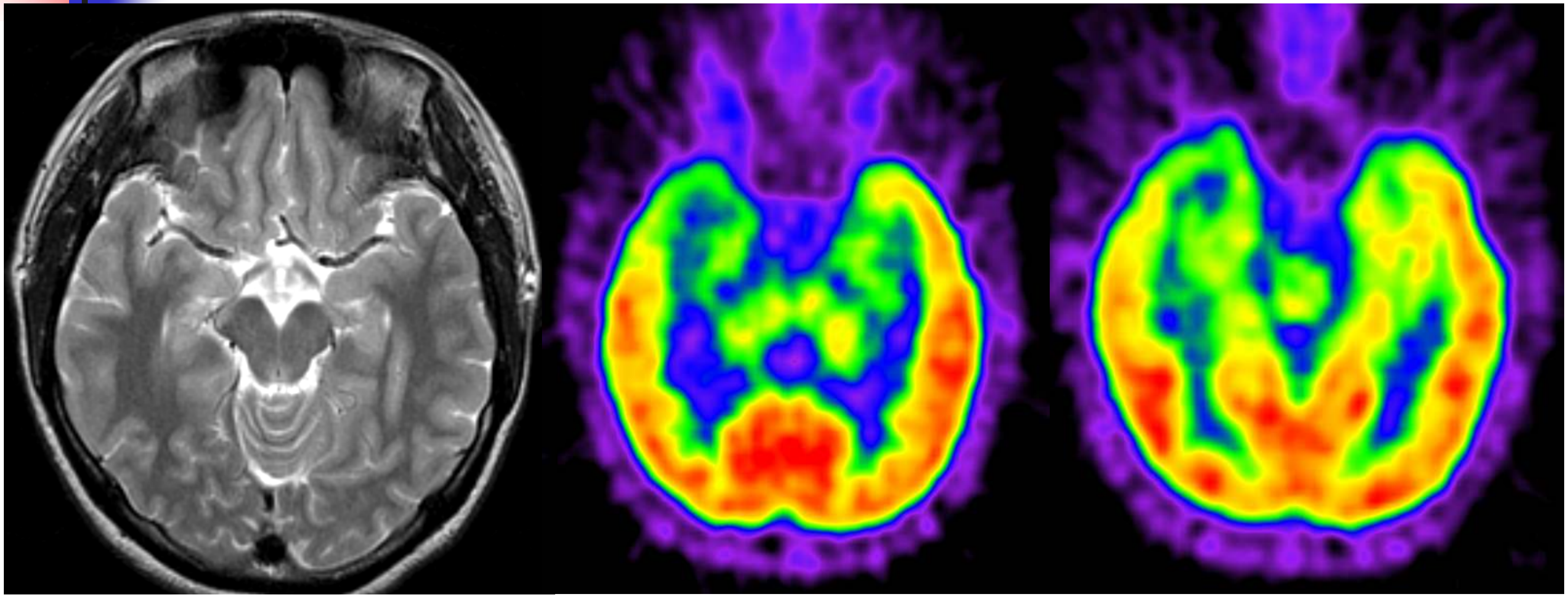


TLE with lesion (ganglioglioma)



Dual pathology (HS plus): HS + cortical dysplasia

- Dual pathology: Some MTLE patients have another lesion together with HS, such as a tumor, cortical dysplasia, or a cavernous malformation; is HS a "secondary" process induced by the lesion?; however, no evidence for secondary hippocampal neuronal loss from seizures generated by extralimbic abnormalities (in addition, a number of studies which suggest that the majority of the neuronal loss likely precedes the onset of seizures). Mild dysplasias or cortical malformations (MRI-invisible) in the temporal lobe associated with HS have been observed, but the role of these abnormalities (epiphenomenon or active participant) is uncertain.
- In the presence of a well-circumscribed lesion, such as tumor or vascular malformation, lesionectomy might suffice unless there is associated hippocampal atrophy. Generally, resection of both lesions of dual patholgy can provide seizure-free outcome; complete seizure freedom after a mean follow-up of 37 months was lowered from 73% with lesionectomy plus mesial temporal resection to 20% with mesial temporal resection alone and 12.5% with lesionectomy alone (Jehi, 2008).



TLE with normal MRI

Nonlesional TLE

- The surgical approach to nonlesional temporal lobe epilepsy presents a more significant challenge due to uncertainties regarding the localization of epileptogenic focus and the extent of resection necessary to result in a seizure-free state.
- Usually, more preoperative evaluations (FDG-PET, ictal SPECT, MEG, MRS…) and intracranial EEG monitoring
- PET-positive, MRI-negative TLE patients may had excellent surgical outcomes after anterior temporal lobectomy, similar to those in patients with MTS (Carne et al., 2004; Kuba et al., 2011; LoPinto-Khoury et al., 2012).

Cases

- 30-year-old man

Seizure-free (including aura) without AED treatment after temporal lobectomy (right HS) at the age of 17 years.

Seizure relapse at the age of 26 years; currently monthly SGTCS on sleep and aura only with AED treatment

- 35-year-old man

Seizure-free for 6 months after temporal lobectomy (right HS) at the age of 27 years.

Seizure relapse (CPS twice per month, aura only) for the next 26 months.

Seizure-free with AED treatment for 6 years (except for one episode of aura occurring 4 year before)

Prognosis after epilepsy surgery

- Seizure outcome

  * Early or late seizure-free (early or late relapse)

  Postoperative seizure outcome is a dynamic state with chances of ongoing seizure freedom dropping steadily after surgery (although after longer postsurgical seizure freedom, the risk for seizure recurrence is lower).

  Conversely, up to 20% to 30% of TL patients have intermittent seizures within the few months following surgery only to become seizure free later.

  * Disabling seizure (CPS) free or completely SF

  * With or without AED therapy

- Neurocognitive, social, psychiatric, and functional implications of surgery, as well as its potential complications

- Only two controlled trials for temporal lobectomy versus AED treatment
- Using cross-sectional methods of analysis which, by definition, are inaccurate in analyzing longitudinal dynamic time-dependent outcomes like postoperative seizure freedom; many surgical studies do not provide the proportion of patients free of any seizures including auras or simple partial seizures for a defined duration and thus can inflate provide an inflated seizure outcome after surgery: different seizure outcome methods.
- Heterogenous causes or pathologic substrates in TLE
- The limited number of studies with long-term follow-ups

Seizure outcome after temporal lobectomy

- 66–70% of patients seizure-free at short-term (<5 years) follow-up (Spencer et al.'s review, 2008)
- Up to 50% to 55% of patients seizure-free as late as a decade after surgery
- The only two randomized, controlled studies to date (for patients with MTLE); 58% of 40 patients assigned to the surgical arm were free of seizures impairing consciousness at 1 year after surgery, compared with 8% of those who were medically managed (Wiebe et al., 2001); Zero of 23 participants in the medical group and 11 of 15 in the surgical group were seizure free during year 2 of follow-up (Engel et al., 2012).

Longer postsurgical seizure freedom, the risk for seizure recurrence is lower

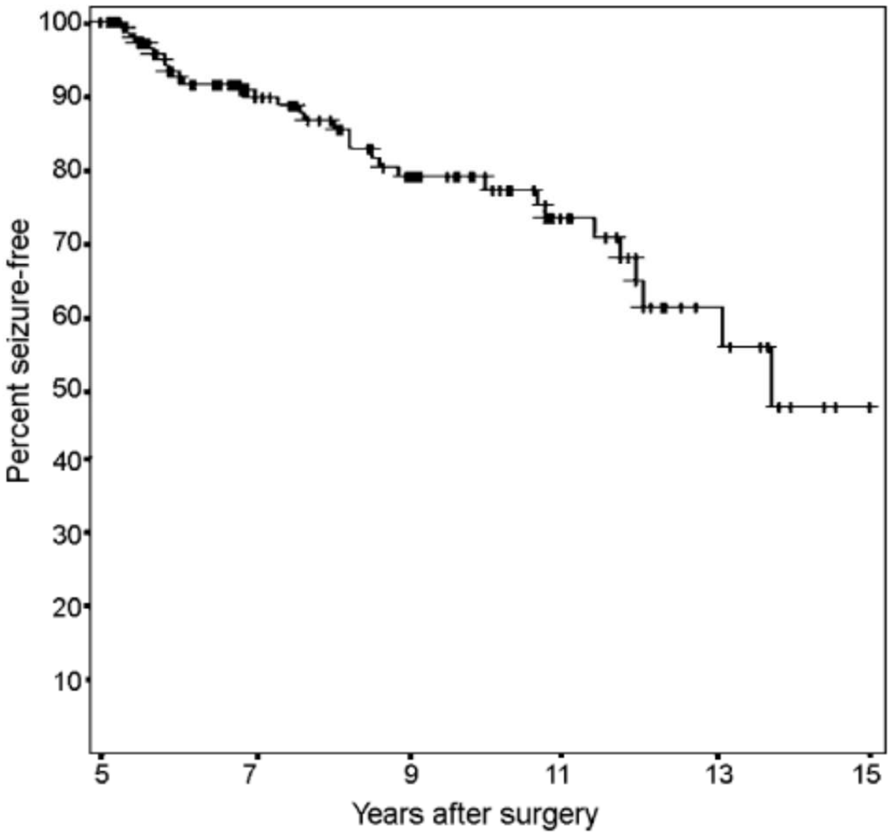
- If a patient is SF at 1 year postoperatively, the likelihood of remaining SF is 87% to 90% at 2 years, 74% to 82% at 5 years, and 67% to 71% at 10 years (Yoon et al., 2003; McIntosh et al., 2004; Kelley & Theodore, 2005; Schwartz et al., 2006). If a patient is SF for 2 years postoperatively, chances of SF increase up to 95% at 5 years, 82% at 10 years, and 68% at 15 years (McIntosh et al., 2004; Sperling et al., 1999)

* In surgical failures, more than half of seizure recurrences start within 6 postoperative months, and more than 95% recur within 2 to 5 postoperative years (Sperling et al., 1996; Jeha et al., 2006); an initial phase of steep recurrence, followed by a relapse rate of 2% to 5% per year for 5 years with subsequent more stable seizure freedom

“Running-down phenomenon”

- A significant portion of patients achieves SF outcome after TL after a period of recurrent seizures or auras after surgery (late remissions and relapses may occur but were usually rare extratemporal lobe epilepsy surgery): 11 to 14% (Berkovic et al., 1995; Salanova et al., 1999; Wieser et al., 2003).
- The mechanism: still unclear but may represent the resolving process of a secondary epileptogenesis (intermediate stage) resolved after a period of months to years following removal of the primary lesion (Morrell, 1959/60).
- Increasing cumulative probability of 2-year remission (with or without isolated aura) at 2, 3, 4, and 5 years after surgery was 0.46, 0.60, 0.66, and 0.69 (Spencer et al., 2005: the multicenter study).
- After TL in 88 patients for longer follow-up than 3 years, 66 (75%) patients achieved complete seizure freedom for ≥1 year; 28 patients were SF immediately after surgery (immediate success); and 38 patients became SF after some period of recurrent seizures (delayed success, 43.2% of all patients) (Kim et all, 2005).

Sperling et al., 2008



159 patients who were SF (allowing for simple partial seizures) for the first 5 years after resective epilepsy surgery, mostly TLEs.
32 had at least one recurrent seizure.
Time to event analysis showed an annual relapse rate of 4% between years 5 and 10 after surgery. At study termination, 143 of 159 patients (89.9%) were in terminal remission (for 30 patients with late relapse and at least 1-year follow-up thereafter, 53% were in terminal remission and 30% had experienced only rare or nocturnal Seizures).

The proportion of SF patients decreased to approximately 50% at 15 years after surgery

Long-term seizure outcome?

Temporal lobe surgery: seizure free rates by prognostic variable (40 studies involving 3895 patients ≥5 years of follow-up), *Téllez-Zenteno et al, 2005*

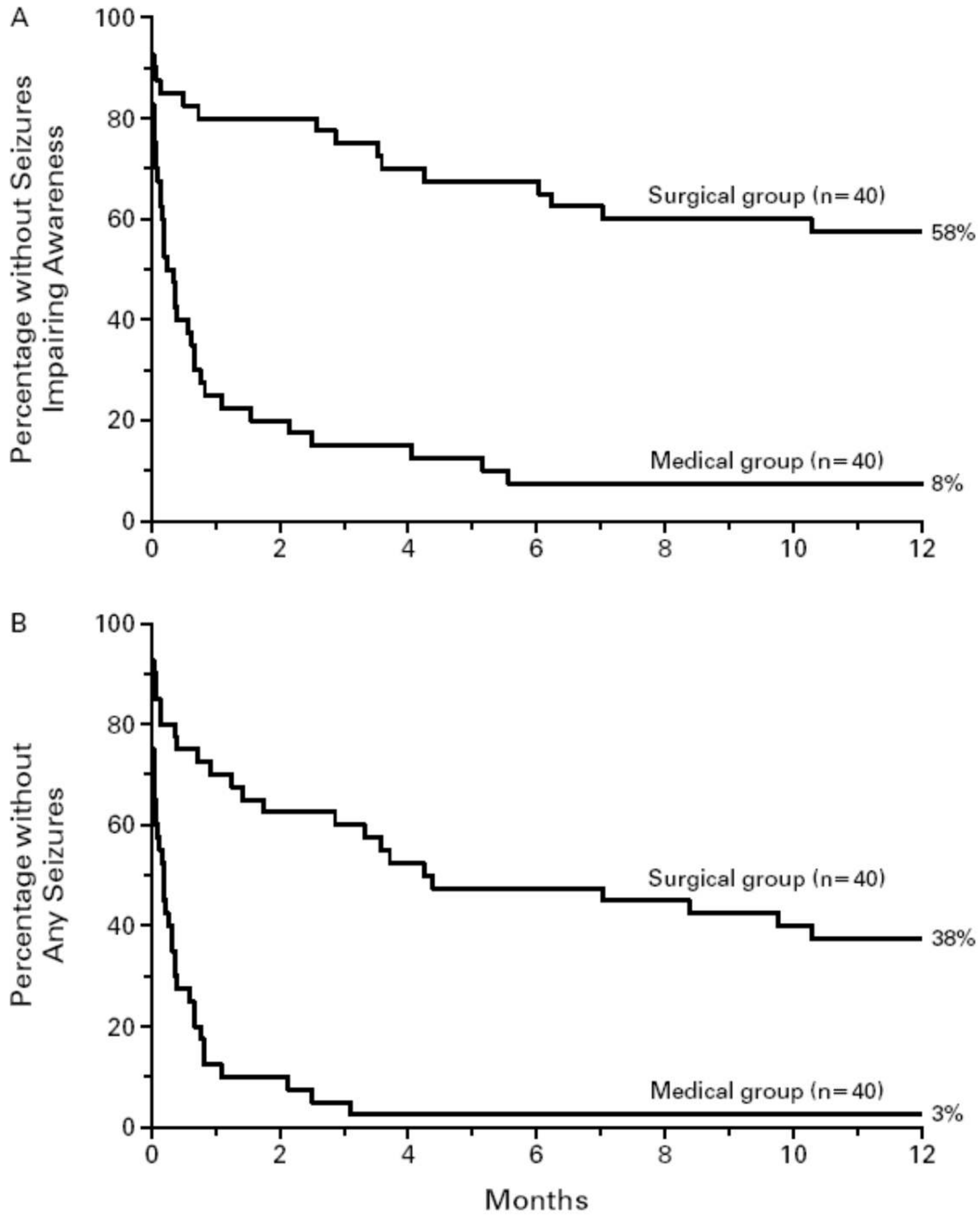
Group of studies	Number of patients	Pooled (%)	95% CI	Risk ratio†	95% CI
Studies with patients operated after 1980 ($n = 35$)	3512	64	61, 67	1.1	0.9, 1.5
Studies with patients operated before 1980 ($n = 5$)	383	54	48, 60		
Studies with five to ten years of follow-up ($n = 35$)	3407	61	59, 63	1.3	1.0, 1.7
Studies with more than ten years of follow-up ($n = 5$)	488	45	41, 49		
Studies in adults ($n = 30$)*	2947	63	61, 65	1.0	0.7, 1.3
Studies in children ($n = 9$)*	444	62	57, 67		
Studies using Engel's outcome classification ($n = 19$)	1803	66	64, 69	1.0	0.8, 1.4
Studies using other classification systems ($n = 21$)	2092	61	59, 64		
Other groups					
Studies including patients older than 50 years ($n = 2$)**	50	41	29, 53	0.6	0.4, 0.8
Studies including patients with tumours ($n = 3$)**	269	76	73, 79	1.1	0.9, 1.4

*One out of 40 studies did not specify the age group. **Ratio of probability of being seizure free in these studies relative to all other studies of temporal lobe epilepsy. †Ratio of probability of being seizure free in one group relative to its comparison; <1 denotes lower and >1 higher chance of being seizure free.

Slightly higher and less heterogeneous in studies using Engel's classification (66%) than in those using other classifications (61%); in univariate analyses, long-term seizure freedom was highest in patients with tumoral epilepsy (76%), and lowest in studies of patients older than 50 years at time of surgery (41%), in older studies (54%), and in those with follow-up >10 years (45%)

How many patients become seizure-free because of surgery?

- The long-term prognosis of surgery vs. continued AED treatment
- Effect of regression of seizure activity and improved medical care (rational AED treatment and introduction of new AEDs) which can change natural history (intractability) (?)



In a per protocol analysis, 23 of 36 patients (64%) who actually underwent surgery were free of seizures with impaired awareness and 15 of 36 patients (42%) were free of all seizures.

Wiebe et al., 2001

Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of AAN, in association with AES and AANS, 2003

- A single Class I study and 24 Class IV studies indicate that the benefits of anteromesial temporal lobe resection for disabling complex partial seizures is greater than continued treatment with AEDs, and the risks are at least comparable. For patients who are compromised by such seizures, referral to an epilepsy surgery center should be strongly considered. Further studies are needed to determine if neocortical seizures benefit from surgery, and whether early surgical intervention should be the treatment of choice for certain surgically remediable epileptic syndromes.

Epilepsy Surgery for Pharmacoresistant Temporal Lobe Epilepsy

A Decision Analysis

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Context Patients with pharmacoresistant epilepsy have increased mortality compared with the general population, but patients with pharmacoresistant temporal lobe epilepsy who meet criteria for surgery and who become seizure-free after anterior temporal lobe resection have reduced excess mortality vs those with persistent seizures.

Objective To quantify the potential survival benefit of anterior temporal lobe resection for patients with pharmacoresistant temporal lobe epilepsy vs continued medical management.

Design Monte Carlo simulation model that incorporates possible surgical complications and seizure status, with 10000 runs. The model was populated with health-related quality-of-life data obtained directly from patients and data from the medical literature. Insufficient data were available to assess gamma-knife radiosurgery or vagal nerve stimulation.

Main Outcome Measures Life expectancy and quality-adjusted life expectancy.

Results Compared with medical management, anterior temporal lobe resection for a 35-year-old patient with an epileptogenic zone identified in the anterior temporal lobe would increase survival by 5.0 years (95% CI, 2.1-9.2) with surgery preferred in 100% of the simulations. Anterior temporal lobe resection would increase quality-adjusted life expectancy by 7.5 quality-adjusted life-years (95%, CI, –0.8 to 17.4) with surgery preferred in 96.5% of the simulations, primarily due to increased years spent without disabling seizures, thereby reducing seizure-related excess mortality and improving quality of life. The results were robust to sensitivity analyses.

Conclusion The decision analysis model suggests that on average anterior temporal lobe resection should provide substantial gains in life expectancy and quality-adjusted life expectancy for surgically eligible patients with pharmacoresistant temporal lobe epilepsy compared with medical management.

JAMA. 2008;300(21):2497-2505 www.jama.com

EPILEPSY ACCOUNTS FOR 1% OF THE global burden of disease due to disability, affecting 0.5% to 1% of the world's population.[1] Despite currently available antiepileptic drugs, 20% to 40% of all patients with epilepsy remain refractory to medical management.[2-5] For such patients, epilepsy surgery still remains underused worldwide.[6-8] Few patients are referred for epilepsy surgery evaluation, and these referrals commonly occur late in the course of their disease, after 20 years of seizures.[9-11] Temporal lobe epilepsy is the most common form of epilepsy[12] and the most likely to be medically refractory.[13]

Epilepsia, 50(6):1301–1309, 2009
doi: 10.1111/j.1528-1167.2008.01997.x

CRITICAL REVIEW AND INVITED COMMENTARY

Long-term seizure outcome of surgery versus no surgery for drug-resistant partial epilepsy: A review of controlled studies

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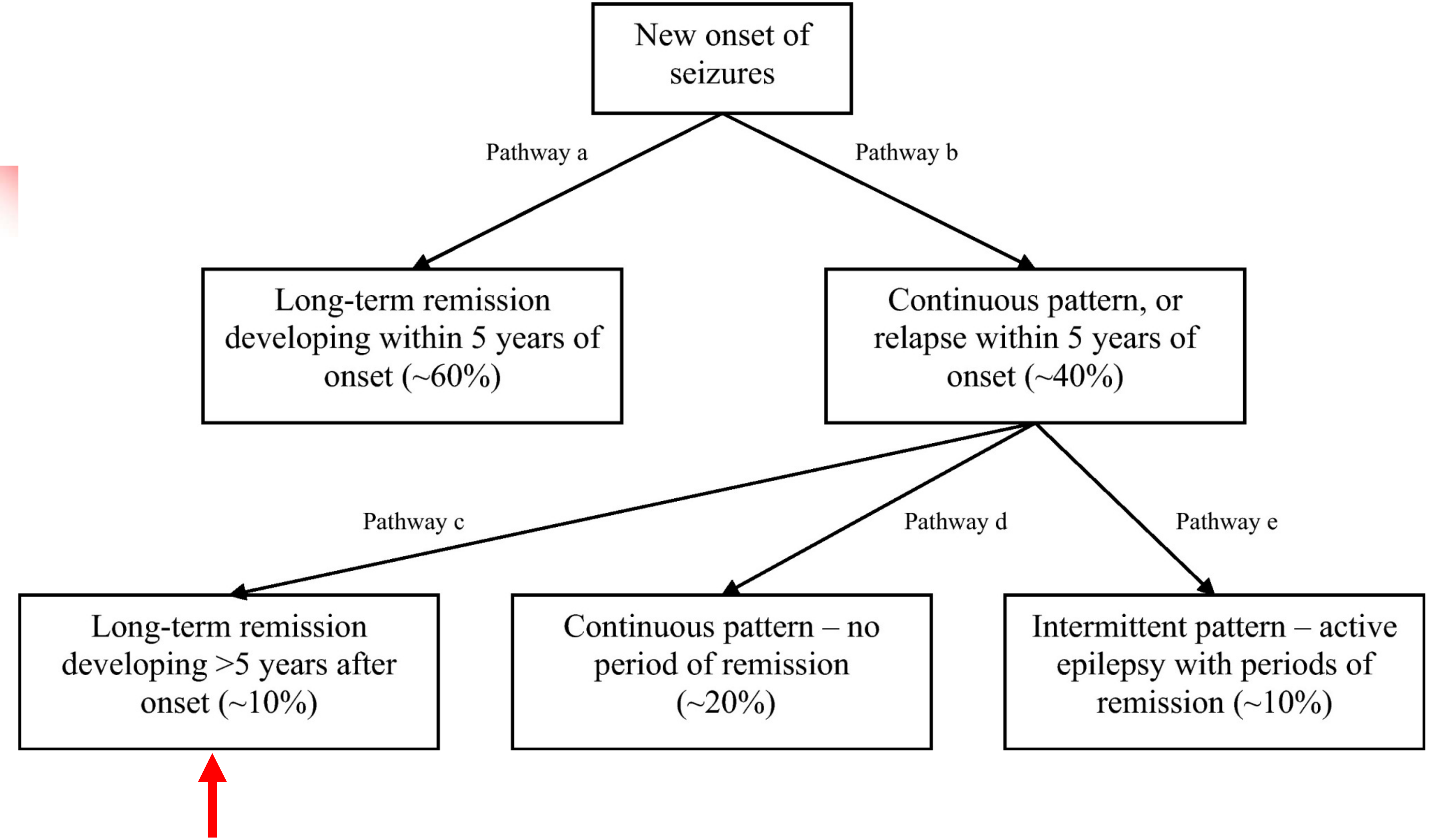
Summary

A majority of patients with formerly drug-resistant temporal lobe epilepsy become seizure-free after surgery. However, apart from one 12-month randomized trial, it is unclear how many become seizure-free because of surgery. To determine the net benefit of surgery, we performed a systematic review and meta-analysis of the published evidence of how many patients in similar studies become seizure-free without surgery. Of 155 potentially eligible articles reviewed in full text, 29 (19%) fulfilled eligibility criteria. After excluding 9 publications, 20 studies form the base of evidence. Overall, 719 of 1,621 (44%) of patients with mostly temporal lobe surgery were seizure-free compared to 139 of 1113 (12%) of nonoperated controls [pooled random effects relative risk (RR) 4.26, 95% confidence interval (CI) 3.03–5.98]. The pooled risk difference in favor of surgery was 42% (95% CI 32–51%). We found no comparative outcome data in patients with extratemporal lobe epilepsy only. The available evidence from mostly nonrandomized observational studies indicates that in appropriately selected patients with drug-resistant temporal lobe epilepsy, the combination of surgery with medical treatment is 4 times as likely as medical treatment alone to achieve freedom from seizures.

KEY WORDS: Epilepsy surgery, Long-term outcome, Chronic epilepsy, Antiepileptic drugs, Seizure prognosis.

- Recent open, long-term, add-on trials performed in single centers might achieve 6 months or more of terminal seizure remission in 11–25% of patients who do not respond to at least two AEDs. (Luciano & Shorvon, 2007; Callaghan et al., 2007; Liimatainen et al., 2007; Schiller & Najjar., 2008; Choi et al., 2008); no control group, how about prognosis of patients with SF? (relapse in patients with seizure remission?), too short follow-up to suggest long-term prognosis
- **Intractability is inevitable if seizure control is not obtained within a few years of the onset of therapy: incorrect**



Remission and relapse model of the temporal aspects of prognosis of epilepsy
Neligan et al., 2011

Can early surgical treatment for MTLE be recommended?

- Risks associated with continued seizures: increased mortality, more load of AEDs, progressive cognitive decline (?), expansion of epileptogenic network or formation of secondary epileptogenesis (?)
- Vocational and social rehabilitation may be more difficult once a patient has settled into a disabled lifestyle (?).
- Greater functional recovery after TLE surgery in children (Gleissner et al., 2005); Adults and children with left resections showed expected mean declines in verbal memory at 3 months. By 1 year, the mean scores for children were no longer different from presurgical scores, but adult scores remained below.

Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy
A Randomized Trial

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Context 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.

Objective We sought to determine whether surgery soon after failure of 2 antiepileptic drug (AED) trials is superior to continued medical management in controlling seizures and improving quality of life (QOL).

Design, Setting, and Participants The Early Randomized Surgical Epilepsy Trial (ERSET) is a multicenter, controlled, parallel-group clinical trial performed at 16 US epilepsy surgery centers. The 38 participants (18 men and 20 women; aged ≥12 years) had mesial temporal lobe epilepsy (MTLE) and disabling seizues for no more than 2 consecutive years following adequate trials of 2 brand-name AEDs. Eligibility for anteromesial temporal resection (AMTR) was based on a standardized presurgical evaluation protocol. Participants were randomized to continued AED treatment or AMTR 2003-2007, and observed for 2 years. Planned enrollment was 200, but the trial was halted prematurely due to slow accrual.

Intervention Receipt of continued AED treatment (n=23) or a standardized AMTR plus AED treatment (n=15). In the medical group, 7 participants underwent AMTR prior to the end of follow-up and 1 participant in the surgical group never received surgery.

Main Outcome Measures The primary outcome variable was freedom from disabling seizures during year 2 of follow-up. Secondary outcome variables were health-related QOL (measured primarily by the 2-year change in the Quality of Life in Epilepsy 89 [QOLIE-89] overall T-score), cognitive function, and social adaptation.

Results Zero of 23 participants in the medical group and 11 of 15 in the surgical group were seizure free during year 2 of follow-up (odds ratio=∞; 95% CI, 11.8 to ∞; $P<.001$). In an intention-to-treat analysis, the mean improvement in QOLIE-89 overall T-score was higher in the surgical group than in the medical group but this difference was not statistically significant (12.6 vs 4.0 points; treatment effect=8.5; 95% CI, −1.0 to 18.1; $P=.08$). When data obtained after surgery from participants in the medical group were excluded, the effect of surgery on QOL was significant (12.8 vs 2.8 points; treatment effect=9.9; 95% CI, 2.2 to 17.7; $P=.01$). Memory decline (assessed using the Rey Auditory Verbal Learning Test) occurred in 4 participants (36%) after surgery, consistent with rates seen in the literature; but the sample was too small to permit definitive conclusions about treatment group differences in cognitive outcomes. Adverse events included a transient neurologic deficit attributed to a magnetic resonance imaging–identified postoperative stroke in a participant who had surgery and 3 cases of status epilepticus in the medical group.

Conclusions Among patients with newly intractable disabling MTLE, resective surgery plus AED treatment resulted in a lower probability of seizures during year 2 of follow-up than continued AED treatment alone. Given the premature termination of the trial, the results should be interpreted with appropriate caution.

Trial Registration clinicaltrials.gov Identifier: NCT 00040326

JAMA. 2012;307(9):922-930

EPILEPSY IS A WORLDWIDE SERIOUS health concern, accounting for 1% of the global burden of disease, equivalent to lung cancer in men and breast cancer in women.[1] The 20% to 40% of patients who have medically intractable[2] epilepsy account for 80% of the cost of epilepsy.[3] Temporal lobe epilepsy (TLE) is the most common cause of drug-resistant seizures,[4-7] but it can be treated surgically.[8-10] The American Academy of Neurology practice parameter recommends surgery as the treatment of choice for medically intractable TLE,[9] based in part on a single-center Canadian randomized controlled trial (RCT) that demonstrated the efficacy of sur-

Presurgical Predictors of Seizure Control for MTLE

- Controversial predictors: duration of epilepsy history
- Positive predictors: circumscribed hippocampal sclerosis, circumscribed low grade tumors, greater volume resected, atrophy ipsilateral to EEG abnormality, only hippocampal atrophy on MRI, concordant memory asymmetry on Wada test
- Negative predictors: no histopathology in surgical specimen, lesion outside of resection, decreased hippocampal asymmetry, history of secondary generalization, bilateral atrophy on quantitative MRI, greater diffuse ipsilateral atrophy on MRI surface modeling, incomplete mesial resection including parahippocampal region, wider FDG PET abnormality, atypical ictal SPECT changes outside resection mesial temporal lobe, amygdala and hippocampal atrophy on MRI

- *Preoperative neuroimaging in MTLE is used to lateralize the abnormality to the right or left temporal lobe. At present, neuroimaging is not considered sufficiently accurate to define the seizure focus well enough to determine the site and extent of a resection and reliably predict those unlikely to be SF following standard anterior temporal lobe resection. FDG-PET, ictal SPECT, T2 relaxometry, MR spectroscopic imaging, voxel-based morphometry, anatomic surface modeling, DTI tractography, PET with MRI fusion, EEG-fMRI, resting connectivity fMRI … can provide contralateral involvement and the extent of abnormalities and can be somewhat predictive of surgical outcomes. However, to be useful for presurgical evaluation, characteristic abnormalities must be clearly defined as applicable to individual patients and the abnormalities must mean epileptogenicity.*
- Hippocampal sclerosis (atrophy) (by qualitative visual review) ipsilateral to EEG abnormalities is the most reliable predictor of seizure control following surgery, with high specificity and sensitivity.

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CRITICAL REVIEW AND INVITED COMMENTARY

Temporal lobe epilepsy surgery and the quest for optimal extent of resection: A review

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SUMMARY

The efficacy of surgery to treat drug-resistant temporal lobe epilepsy (TLE) has been demonstrated in a prospective randomized trial. It remains controversial which resection method gives best results for seizure freedom and neuropsychological function. This review of 53 studies addressing extent of resection in surgery for TLE identified seven prospective studies of which four were randomized. There is considerable variability between the intended resection and the volumetrically assessed end result. Even leaving hippocampus or amygdalum behind can result in seizure freedom rates around 50%. Most authors found seizure outcome in selective amygdalohippocampectomy (SAH) to be similar to that of lobectomy and there is considerable evidence for better neuropsychological outcome in SAH. Studies varied in the relationship between extent of mesial resection and seizure freedom, most authors finding no positive correlation to larger mesial resection. Electrophysiological tailoring saw no benefit from larger resection in 6 of 10 studies. It must be concluded that class I evidence concerning seizure outcome related to type and extent of resection of mesial temporal lobe structures is rare. Many studies are only retrospective and do not use MRI volumetry. SAH appears to have similar seizure outcome and a better cognitive outcome than TLR. It remains unclear whether a larger mesial resection extent leads to better seizure outcome.

KEY WORDS: Temporal lobe epilepsy, Resection extent, Temporal lobectomy, Epilepsy, Amygdalohippocampectomy.

- Most studies have also found that a larger, nonspecific temporal lobe resection is not associated with better outcome (Jack et al., 1988; Bonilha et al., 2007). However, the size of the resection of specific structures, which may be responsible for generating seizures independently, such as the hippocampus (Wyler et al., 1995; Bonilha et al., 2004), the parahippocampal gyrus (Siegel et al., 1990), and the entorhinal cortex (Bonilha et al., 2007), are directly related to seizure control.
- It appears that a larger temporal lobe resection is not always associated with better outcome, but a complete resection of the epileptogenic structures may be the key to surgical success (it remains unclear, however, how to predict before surgery which patients are more likely to benefit from a larger medial cortical resection).

Why early vs. late relapse?

- Early recurrences” occurring within 1 to 2 years of surgery may be due to incomplete removal of the initial epileptogenic zone, whereas later relapses may reflect an underlying continued changes in neuronal and synaptic function leading to a new epileptogenic zone, progression of an “age-dependent” etiology such as mesial temporal sclerosis, or surgical scar.

Why not seizure free in a significant number of patients?: Clinical aspect

- Previously unidentified bitemporal seizures
- Erroneous identification of the epileptogenic zone (pseudotemporal) and/or underestimation of the epileptogenic zone: temporal plus epilepsy
- Insufficient extent of the mesial temporal resection
- Insular origin

The Role of the Insular Cortex in Temporal Lobe Epilepsy

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The role of the insular cortex in the genesis of temporal lobe epileptic (TLE) seizures has been investigated in 21 patients with drug-refractory TLE using chronic depth stereotactic recordings of the insular cortex activity and video recordings of ictal symptoms during 81 spontaneous electroclinical seizures. All of the recorded seizures were found to invade the insula, most often after a relay in the ipsilateral hippocampus (19/21 patients). However, 2 patients had seizures that originated in the insular cortex itself. Ictal symptoms associated with the insular discharges were similar to those usually attributed to mesial temporal lobe seizures, so that scalp video-electroencephalographic monitoring does not permit making any difference between ictal symptoms of temporo-mesial and insular discharges. A favorable outcome was obtained after a temporal cortectomy sparing the insular cortex in 15 of 17 operated patients. Seizures propagating to the insular cortex were found to be fully controlled by surgery, whereas those originating in the insular cortex persisted after temporal cortectomy. The fact that seizures originating in the insular cortex are not influenced by temporal lobectomy is likely to explain some of the failures of this surgical procedure in TLE.

Isnard J, Guénot M, Ostrowsky K, Sindou M, Mauguière F. The role of the insular cortex in temporal lobe epilepsy. Ann Neurol 2000;48:614–623

Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal 'plus' epilepsies

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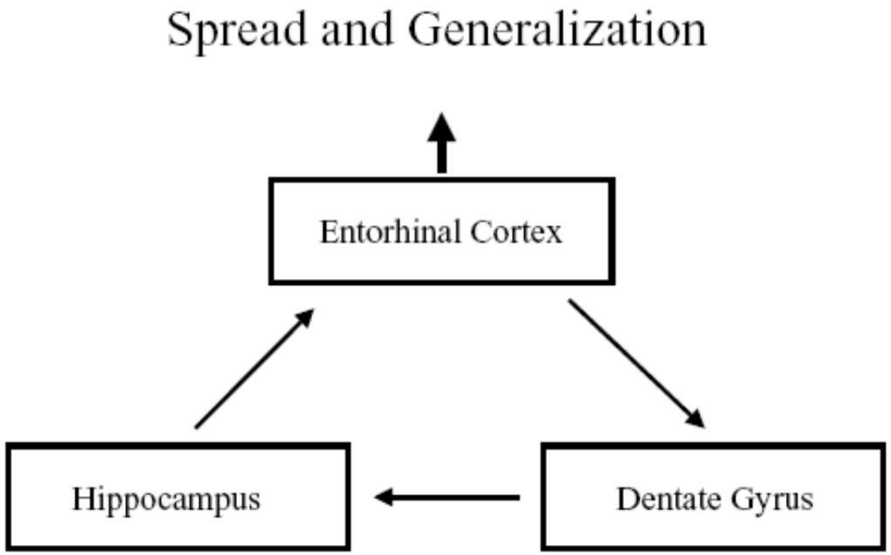
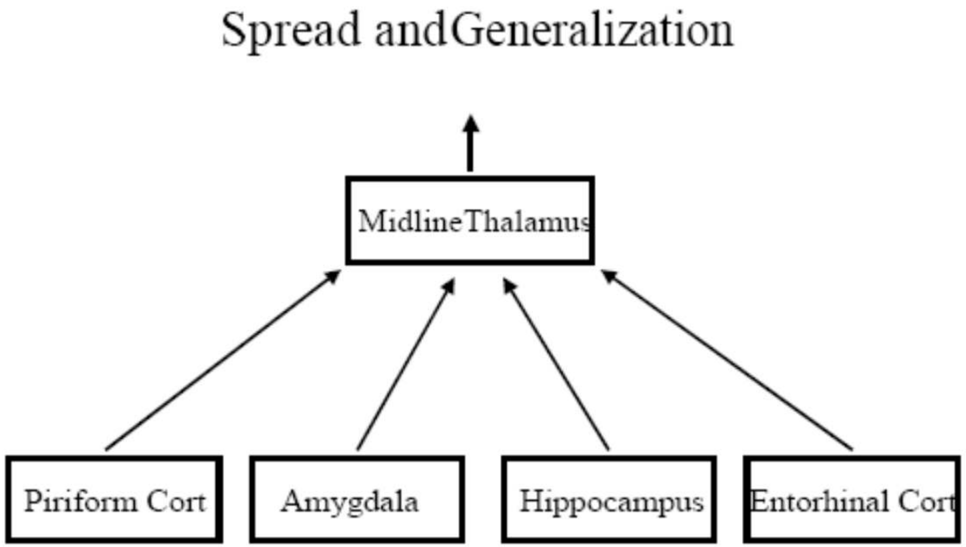
Temporal 'plus' epilepsies are characterized by seizures involving a complex epileptogenic network including the temporal lobe and the closed neighboured structures such as the orbito-frontal cortex, the insula, the frontal and parietal operculum and the temporo–parieto–occipital junction. Temporal 'plus' epilepsies are currently identified by means of intracerebral electrodes but whether their diagnosis can be suspected non-invasively has not been evaluated yet. The aim of this retrospective study was to address this issue in 80 consecutive patients who were thought to suffer from non-lesional temporal lobe seizures which finally proved, on the basis of stereotactic intracerebral EEG (SEEG) recordings, to be 'purely' temporal (TL group, $n = 58$) or temporal 'plus' (T+ group, $n = 22$). Our results showed that the two groups of patients were difficult to differentiate on the basis of general clinical features or MRI data. Even the presence of hippocampal sclerosis did not distinguish the two groups. Conversely, both ictal clinical symptoms and scalp-EEG findings significantly differentiated TL from T+ patients. Patients with TL epilepsies more frequently presented an ability to warn at seizure onset ($P = 0.003$), an abdominal aura ($P = 0.05$), gestural automatisms ($P = 0.04$) and a post-ictal amnesia ($P = 0.02$). Patients suffering from T+ epilepsies more frequently had gustatory hallucinations ($P = 0.02$), rotatory vertigo ($P = 0.02$) and auditory illusions ($P = 0.02$) at seizure onset; they exhibited more frequently contraversive manifestations of the eyes and/or head ($P = 0.001$), piloerection ($P = 0.03$) and ipsilateral tonic motor signs ($P = 0.05$), and they were more often dysphoric in the post-ictal phase ($P = 0.0001$). Cluster analysis mainly indicated that some associations of symptoms were relevant for differentiating TL cases from T+ cases. Interictal EEG of T+ patients more frequently exhibited bilateral or precentral abnormalities, while ictal EEG more frequently pointed over the anterior frontal, temporo-parietal and precentral regions. Neither TL interictal spikes, nor TL ictal EEG onset, allowed us definitely to rule out the possibility of T+ epilepsies. Our findings may be useful for identifying, among patients suffering from 'atypical' non-lesional TL epilepsies, those who should undergo invasive recordings before surgery.

Brain (2007), **130**, 1957–1967

Why not seizure free in a significant number of patients?: Pathophysiologic aspect

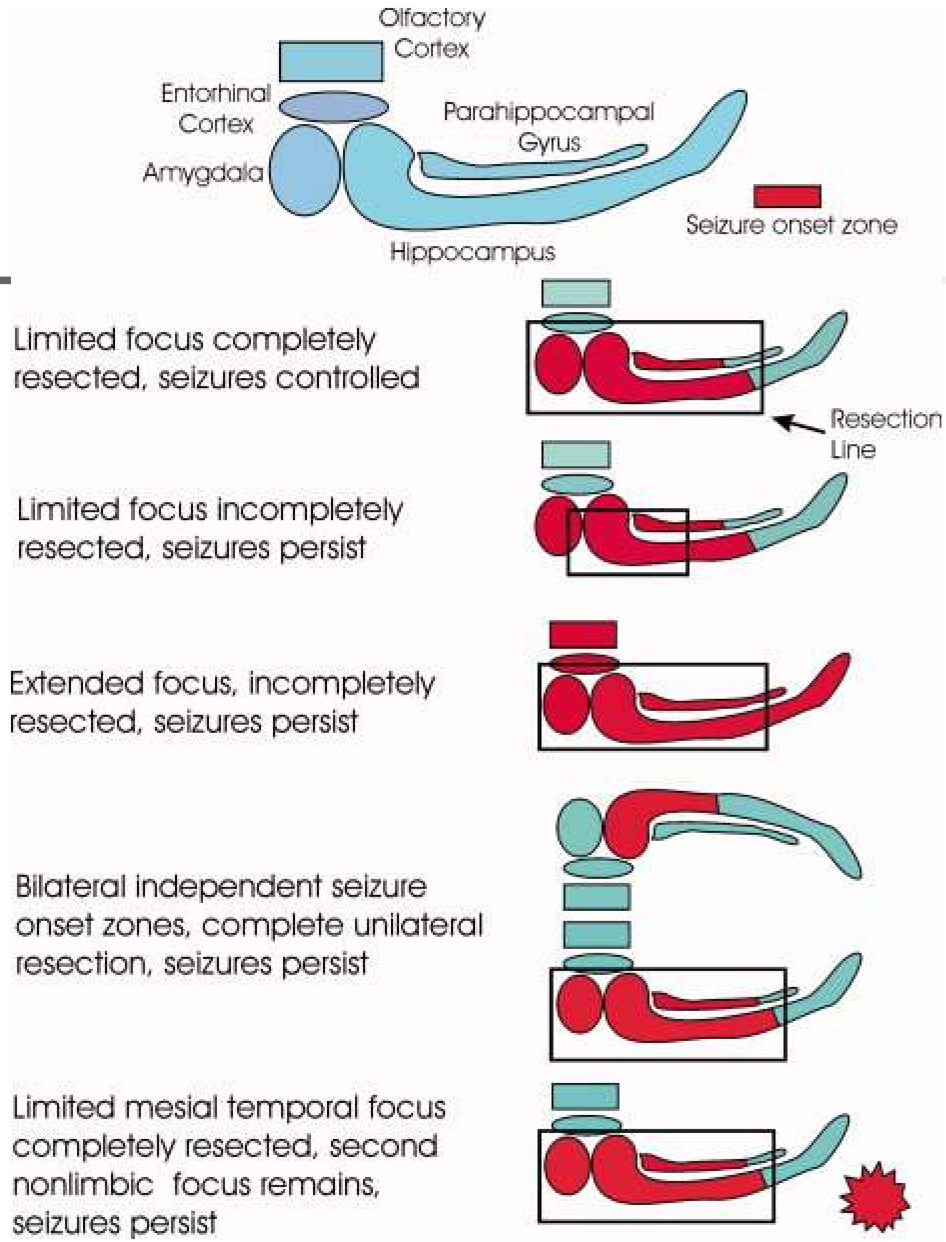
- The pathology associated with mesial TLE is widely distributed throughout the limbic system and involves not only the hippocampus but also the amygdala, entorhinal cortex, the piriform cortex and the thalamus (from human studies) with frequent bilateral involvement as well.
- Different sites might play in seizure initiation: observation of a regional rather than focal onset (i.e within a single structure) across animals and during human depth electrode studies (So., 1991; Spencer et al., 1992).
- These findings suggest that this particular epilepsy syndrome is a disorder of the limbic system as a whole and not just of a single structure such as the hippocampus. In addition, the observations of distributed and variable pathology raise the possibility that in any one individual, one structure may be more likely to drive seizures than another.





Seizures arise in a "trisynaptic loop" that involves the entorhinal cortex, the dentate gyrus and the hippocampus (Lothman et al., 1991).
Multiple limbic sites are independent seizure generators (Bertram et al., 1998)

Variation from one individual to another in the relative contribution of a particular region.
Any removal of "loop" can result in seizure freedom (even leaving hippocampus or amygdala behind).
A second focus that was relatively inactive which is capable of generating seizures (particularly, when the medications are not present).



Thom et al., 2010

Risks associated with epilepsy surgery

- Surgical complications:

Neurological deficits such as dysphasia (3%), hemiparesis (2%), and field defects greater than a quadrantanopia (2%) occurred in 34 of 556 patients, and only half (3%) were permanent. Two deaths (0.4%) occurred perioperatively and were unrelated to surgery (Engel et al., 2003 from 7 surgical centers).

Memory outcome

(surgical outcome beyond seizure control)

- Declines in verbal memory and word finding are the most common cognitive side effects, occurring in up to 40% of patients (Chelune et al., 1993; Seidenberg et al., 1998); often predictable from presurgical information, allowing for a more informed risk–benefit analysis presurgically (resection in the dominant hemisphere, MRI findings other than exclusively unilateral MTS, intact preoperative immediate and delayed verbal memory function, and intact IAP memory performance following injection contralateral to the seizure focus) (Stroup et al., 2003).
- Surgery can accelerate the memory decline seen with medical treatment (particularly in left TL and if seizures do not stop). However, memory decline may be stopped and even reversed if seizures are fully controlled (Helmstaedter et al., 2003).
- Memory decline was associated with declines in quality of life, but only when seizures persist (Langfitt et al., 2007). Fortunately, this disappointing outcome occurred in only 8% of patients.

Psychiatric outcome

- The impact on psychotic disorders is less clearly defined (varied from unchanged in most cases to improved psychotic status); epilepsy surgery especially when successful, appears to reduce the prevalence of psychiatric comorbidities of epilepsy; exacerbation of an underlying psychopathology or de-novo psychopathology after surgery in some patients
- The psychiatric outcome were significantly worse in the temporal resections group (vs. extratemporal resections) during 3-month follow-up; by the 3-month follow-up, 13% of ATL patients had developed a de-novo depression as opposed to none in the ETL group, not related to SF (Wrench et al., 2004).

Psychosocial outcome

- Driving, regaining or improving employment, and overall independence intimately may be linked to the absence of any "functional" worsening (memory, language….); the impact on functional status has not been adequately studied.
- Improvements in self-reported QOL have consistently been associated with improved postsurgical seizure control, but not when seizures persist (Spencer et al., 2007); also, associated with higher presurgical IQ score, younger age at surgery, and more stable mood at baseline (Sperling et al., 1996; So & Dodrill, 2008)
- Improvements in employment and marital status are less common; better seizure outcome was associated with gaining employment at 2 years among those unemployed before surgery, but in the entire sample, employment status was unchanged in 75%, improved in 16% and worse in 8% (Chin et al., 2007) (modest employment gain).

Can antiepileptic drug treatment discontinue after successful epilepsy surgery?

Type of surgery (number of studies)	N	Pooled (%)	CI_{95}	Mean follow-up (range)
All types of surgery (n = 15) not specifying seizure outcome*				
AED free (n = 11)	904	20	18–23	6.0 (4.5–10)
Monotherapy (n = 7)	566	41	37–45	5.8 (5.0–7.5)
Polytherapy (n = 7)	566	31	27–35	5.8 (5.0–7.5)
Specifying seizure outcome (n = 9)*				
Seizure-free and AED free	936	22	20–25	6.9 (5.0–10.3)
Temporal lobe surgery only (n = 10)* not specifying seizure outcome				
AED free (n = 5)	482	14	11–17	5.7 (5.0–7.5)
Monotherapy (n = 4)	397	50	45–55	5.9 (5.0–7.5)
Polytherapy (n = 4)	397	33	29–38	5.9 (5.0–7.5)
Specifying seizure outcome (n = 8)*				
Seizure-free and AED free	831	20	17–23	6.9 (5.0–10.3)
Other types of surgery (n = 5),*,† not specifying seizure outcome				
AED free (n = 5)	387	36	31–41	5.7 (5–7)
Monotherapy (n = 3)	169	24	18–31	5.5 (4.5–7)
Polytherapy (n = 3)	169	27	20–33	5.5 (4.5–7)
Specifying the seizure outcome (n = 2)*				
Seizure-free and AED free	151	39	31–46	5.1 (4.8–5.1)
Medical group (n = 2) not specifying seizure outcome*				
AED free (n = 2)	227	0	0	8.9 (4.8–17)
Monotherapy (n = 1)	102	24§	15–32§	5 (2–10)
Polytherapy (n = 1)	102	75§	66–83§	5 (2–10)
Children (n = 6) not specifying seizure outcome*				
AED free (n = 5)	275	38	33–43	6.3 (4.5–10)
Monotherapy (n = 3)	169	24	18–31	5.5 (4.5–7)
Polytherapy (n = 3)	169	27	20–33	5.5 (4.5–7)
Specifying seizure outcome*				
Seizure-free and AED free (n = 2)	430	27	23–31	7 (4.5–9.6)
Adults (n = 9) not specifying seizure outcome*				
AED free (n = 6)	629	15	13–18	5.9 (5–7.5)
Monotherapy (n = 5)	397	50	45–55	5.9 (5–7.5)
Polytherapy (n = 5)	397	33	29–38	5.9 (5–7.5)
Specifying seizure outcome*				
Seizure-free and AED free (n = 9)	506	19	16–22	6.5 (5–10)

*Categories are not mutually exclusive. Not all studies reported all outcomes.
†Two studies focused on hemispherectomy, which had the best outcomes in this group; three combined patients with temporal and extratemporal resections.
§Data from one study only (not pooled) (Helmstaedter *et al.*, 2003).

Téllez-Zenteno et al, 2007

- Analyses including all types of surgery (n = 15 studies) showed that 20% of patients were free of medication without specifying seizure outcome. For all types of surgery, the pooled proportion of patients who were SF and off AEDs (n = 9) was 22%.
- **In 10 studies of TL surgery, 14% of patients were free of AEDs without specifying seizure outcome. The pooled proportion of patients who were SF and off AEDs was 20%.**
- AED outcomes seemed superior in studies that did not focus on TL surgery (n = 5), the proportion of patients who were SF and off AEDs was 36% (including two studies on hemispherectomy, which reported better outcomes (Kossoff et al., 2003; Pulsifer et al., 2004). Studies focusing on children (n = 6) had overall better AED outcomes than adults (n = 9) and 27% of children were SF and off AEDs, as compared to 19% of adults.

- 37 patients (42.0%) discontinued AEDs and did not experience seizure recurrence for more than 1 years (in 88 patients with TLE) (Kim et al, 2005).
- AEDs were discontinued in 41 patients (24.8%) (165 patients with MTLE related to HS); all remained SF for at least 2 years that could be accepted as "cure." (Özkara et al., 2008).
- 59 (34.5%) patients discontinued AEDs and did not experience seizure recurrence for more than 2 years (in 171 patients with MTLE related to lesion including HS) (Lee et al., 2008).

Seizure relapse after AED discontinuation

- The recurrence rate for patients with seizure- and aura-free state for≥1 year was highly dependent on the status of AED therapy; 7% with no AED change (n=30), 14% with AED reduction (n=96), and 36% with AED discontinuation (n=84), as estimated at the 5-year follow-up (Schiller et al., 2000).
- Reduction of AEDs in 38 SF patients led to a higher recurrence rate of 61% compared with a seizure recurrence of 34% in 39 patients who discontinued AEDs completely (Murro et al., 1991).
- 114 (39%) patients relapsed: 73 (45%) of 162 in the nonreduction group and 41 (32%) of 129 in the reduction group ($p = 0.02$) (in 301 subjects who attained a 1-year seizure remission after surgery) (Berg et al., 2006).
- AED discontinuation was attempted in 60 patients. In 13 (22%) patients, seizure relapse developed during AED reduction, and in 7 (12%) patients after discontinuation of AEDs (Kim et al., 2005).
- AEDs were tapered in 124 and discontinued in 79 seizure- and aura-free patients. 50 of these 124 (40.3%) patients experienced seizure recurrence. After AED discontinuation, seizures recurred in 15 of the 79 (19.0%) patients (Lee et al., 2008).

- In a review of literature (Schmidt, 2004), AED discontinuation is associated with seizure recurrence in one-third of the patients rendered SF by epilepsy surgery; Seizure recurrence was unaffected by the duration of postoperative AED treatment. The occurrence of rare seizures or auras after surgery did not eliminate the possibility of eventual successful AED discontinuation.
- *Complete discontinuation of AEDs after two postoperative years was not associated with an increased risk of recurrence (McIntosh et al., 2004).*
- *Medication use was not associated either with likelihood of relapse or entering remission after relapse in patients who are SF for the first 5 years after epilepsy surgery (Sperling et al., 2008).*

- Neither study was designed to answer the question as to how long to prescribe AEDs after surgery and whether AED therapy lowers relapse risk over many years after surgery.
- Selection of patients for AED discontinuation may be biased towards those individuals perceived as 'low risk'.

The subsequent control of seizures after relapse related to AED withdrawal, or later relapse: Good!

- Reinstitution of AED treatment resulted in seizure control for ≥1 year in 20 of 22 patients who had recurrent seizures after AED discontinuation (Schiller et al., 2000).
- Among 20 patients with seizure relapse related to AED tapering, 9 (45%) regained SF after reinstitution of AED treatment, and AEDs were eventually discontinued in 6 of them (Kim et al., 2005).
- 26 (63%) of 41 who had relapsed after reduction of an AED and 37 (51%) of 73 whose relapses occurred despite maintaining all AEDs experienced a subsequent remission for≥1 year (Berg et al., 2006).
- After AED discontinuation, seizures recurred in 15 (19%) of 79 patients; 1 patient later achieved SF state after re-discontinuing AEDs and 6 achieved SF outcome after reintroducing AEDs (Lee et al., 2008).
- 22 (25.3%) of 87 SF patients had seizure recurrence associated to AEDs discontinuation and 12 became SF with dose arrangements (Özkara et al., 2008).
- For 30 patients with late relapse and at least 1-year follow-up thereafter, 53% were in terminal remission and 30% had experienced only rare or nocturnal seizures (Sperling et al., 2008).

Potential Approaches to Improve Outcome for MTLE Surgery (Thom et al., 2010)

- Define extent of seizure-associated histopathology through enhanced imaging.
- Preoperative identification of type of underlying MTS or dual pathology to identify subtypes.
- More exact correlation of type of MTS histopathology and extent of seizure onset zone.
- Identification of interictal biomarkers that differentiate seizure onset zone from surrounding tissue.
- Determine basis for failed surgeries and surgeries that do not achieve a cure.
- More extensive use of intracranial monitoring or other noninvasive technologies to define limits of seizure onset zone.

Conclusions

- Two-thirds of patients undergoing ATL become seizure-free (aura only) for long-term period with continued AED treatment and seizure recurrence occurs in one-third of patients when AEDs are withdrawn; *ATL may restore the AED response or reverse drug resistance to similar degree to that of AED treatment in new-onset epilepsy.*
- Accordingly, even MTLE with HS may be not a single disorder but group of closely-related syndromes with variable type and extent of histopathology.
- Further studies should be required for determination of the potential seizure onset zone or clinically relevant network of epileptogenic activity for identifying the appropriate subgroups which will require different diagnostic and surgical approaches to improve surgical outcomes, especially in nonlesional TLE.
- To address the question of timing of surgery, future studies are required: natural history, timing and determinants of sustained intractability of patients with surgically treatable epilepsies