# Epilepsy and Epilepsy Surgery

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**Abstract:** Epilepsy affects approximately 50 million people throughout the world, making it one of the most common neurological disorders. Around 60–70% of epilepsy patients react to treatment, whereas 30–40% become resistant to anti-epileptic drugs. Patients not responding to medical treatment are supposed to undergo evaluation for surgical intervention. Not all cases of drug-resistant epilepsy (DRE) are remediable by surgery. Worldwide, 10.1 million persons with active epilepsy could benefit from surgery every year. Methodical, careful, and skillful presurgical evaluation to select appropriate candidates for surgical intervention and choosing an appropriate procedure are the most critical parts of epilepsy surgery. A short synopsis of epilepsy, including definitions, diagnostic criteria, etiology, classification, and differentials of epilepsy, is given in first part of the chapter. Epilepsy surgery is discussed in the later part of the chapter and includes principles of presurgical evaluation, tools for presurgical evaluation, epileptic conditions remediable by epilepsy surgery, and common surgical procedures for epilepsy.

**Abbreviations**

| | | | |
|---|---|---|---|
| AEDs | anti-epileptic drugs | AKA | also known as |
| AMTL | anteromedial temporal lobectomy | CNS | central nervous system |
| CT | computed tomography | DNET | dysembryoplastic neuroepithelial tumor |
| DRE | drug-resistant epilepsy | ECoG | electrocorticogram |
| ECS | electrical cortical stimulation | EEG | electroencephalogram |
| EZ | epileptogenic zone | FCD | focal cortical dysplasia |
| FDA | food and drug administration | FDG-PET | flurodeoxyglucose PET |
| fMRI | functional MRI | HME | hemimegaencephaly |
| ILAE | international league against epilepsy | IEEG | intracranial EEG |
| IVIG | intravenous immunoglobin | LGS | Lennex–Gastaut syndrome |
| LKS | Landau–Kleffner syndrome | MEG | magnetic encephalography |
| MTLE | mesial temporal lobe epilepsy | MRI | magnetic resonance imaging |
| MTS | mesial temporal sclerosis | PET | positron emission tomography |
| RNS | responsive neurostimulation | SAH | selective amygdalohippocampectomy |
| SEEG | scalp EEG | SPE CT | single photon emission CT |
| SRT | stereotactic radiofrequency thermocoagulation | TIA | transient ischemic attack |
| TLE | temporal lobe epilepsy | VEM | video EEG monitoring |
| VNS | vagus nerve stimulation | | |

## 1. Introduction

Epilepsy affects approximately 51.7 million people worldwide, making it one of the most common neurological disorders. Every year, 4.6 million people are diagnosed with epilepsy for the first time. Epilepsy is more common in LMICs (low- and middle-income countries), with 104 per 100,000 person-years in low-income countries and 78 per 100,000 in middle-income countries, compared to 51 per 100,000 person-years in HICs (High-income income countries). According to various studies, 60–70% of epilepsy patients react to treatment, whereas 30–40% become resistant to anti-epileptic medicines (AEDs) (Kalilani et al. 2018; Kwan and Brodie 2000). Patients not responding to medical treatment are supposed to undergo evaluation for surgical intervention. Not all cases of drug resistance epilepsy (DRE) are suitable for remediation by surgery. Worldwide, 10.1 million persons with active epilepsy could benefit from surgery, and 1.4 million new surgically treatable epilepsy patients are diagnosed each year, potentially increasing the number of surgical candidates (Vaughan et al. 2019). Methodical presurgical evaluation to select appropriate candidates for surgical intervention and choosing an appropriate procedure are the most critical parts of epilepsy surgery.

Definition of epilepsy (ILAE n.d.): Epilepsy is a brain disorder characterized by one or more of the following criteria:

- At least two spontaneous (or reflex) seizures that occur within 24 h.

- One spontaneous (or reflex) seizure, with a danger of subsequent seizures analogous to the overall recurrence risk (at least 60%), following two unprovoked seizures over the next 10 years.
- An epilepsy syndrome is diagnosed.

Individuals who have stayed seizure-free for the last 10 years with no anti-epileptic drug for the last 5 years are regarded as having resolved epilepsy if they had age-based, self-limited epilepsy syndrome but have now past the applicable age.

Definition of Seizure (ILAE n.d.): A seizure is a brief episode of symptoms and/or indications in the brain caused by abnormally high or synchronized neuronal activity. Unless the criteria for epilepsy diagnosis are met, a seizure event does not essentially suggest the presence of epilepsy.

The following are the different forms of epileptic seizures:

- Unknown-onset seizures;
- Focal (localized)-onset seizures;
- Generalized-onset seizures.

### *1.1. ILAE (International League against Epilepsy) Classification of Seizure Types, Expanded Version*

ILAE Classification of Seizure Types is shown in Figure 1.

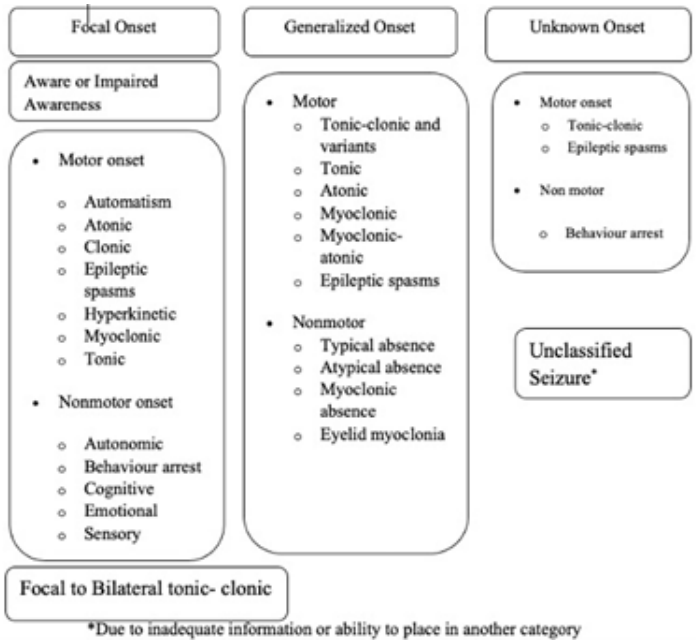


**Figure 1.** ILAE (International League against Epilepsy) Classification of Seizure Types, Expanded Version. Source: Authors' compilation based on data from Fisher et al. (2017).

#### 1.1.1. Generalized Onset Seizure

A generalized seizure is thought to start somewhere within bilaterally dispersed networks and spread very quickly. Cortical and subcortical structures can be included in bilateral networks, but they do not always contain the entire cerebral cortex. Individual seizure onsets may appear isolated, yet their lateralization and location vary from one seizure to the next.

#### 1.1.2. Focal Onset Seizure

Focal seizures are thought to originate in networks that are restricted to one hemisphere. They could be concentrated in one area or widely spread. Focal seizures could be caused by subcortical structures. Ictal initiation is uniform from one seizure to the next one for each seizure type, with ipsilateral and/or opposite hemispheres showing preferred propagation patterns. During a seizure, semiology (symptoms/signs) can be utilized to determine the specific brain region, lobe, or hemisphere that is engaged in seizure onset and propagation.

#### 1.1.3. Unknown Onset Seizure

Unknown onset seizures are those that cannot be characterized as either generalized or focal in onset seizures. Seizures with uncertain initiation can be characterized as motor (tonic–clonic and epileptic spasm) and nonmotor (behavioral arrest, for example).

### *1.2. Classification of Epilepsy*

Epilepsies are categorized as follows:

- Focal epilepsy;
- Generalized epilepsy;
- Combined generalized and focal epilepsy;
- Unknown epilepsy (ILAE n.d.).

#### 1.2.1. Generalized Epilepsy

Generalized epilepsy patients have a generalized type of seizure, which might involve ictal and/or interictal EEG irregularities (such as generalized spike and wave). A family history of epilepsy or generalized seizures is beneficial.

#### 1.2.2. Focal Epilepsy

Focal epilepsy patients have specific seizure types, which may include ictal and/or interictal EEG abnormalities (for example, focal sharp waves or focal interictal slowing). Patients with hereditary causes and normal imaging can have localized epilepsy; however, imaging that reveals a focal structural brain anomaly may be useful. Unifocal, multifocal, and hemispheric epilepsies are the three types of focal epilepsies.

#### 1.2.3. Combined Generalized and Focal Epilepsy

Patients may have both focal and generalized seizures, as well as interictal and/or ictal EEG irregularities. Patients with Dravet syndrome and Lennox–Gastaut syndrome can experience both generalized and localized seizures.

#### 1.2.4. Unknown Epilepsy

The term "unknown" is utilized when it is impossible to tell whether a patient has focal, generalized, or a combination of focal and generalized epilepsy. This can happen when there is not enough information to define epilepsy, such as when the EEG is normal/uninformative.

### *1.3. Epilepsy Syndrome*

An epileptic syndrome is a collection of signs and symptoms that makes up a distinct epilepsy condition with varied causes (Daroff et al. 2015). A typical age at which seizures begin, distinct seizure types with EEG features, and other criteria, when combined, allow the detection of a specific epileptic conditions. The detection of an epilepsy syndrome is beneficial since it indicates which underlying causes should be explored as well as which antiseizure medication(s) may be most effective (ILAE n.d.). Some epilepsy syndromes are inherently intractable and long trials with medication before considering surgical evaluation seem unwise. Some other syndromes, i.e., Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS), may have poor control of seizures with medication but will ultimately remit and do not need surgery. Surgically remediable epilepsy syndromes will be discussed later.

## 2. Etiology of Epilepsy

Advances in contemporary neuroimaging (Figure 2) and genetic testing have contributed to a major increase in explaining the underlying causes of epilepsies in recent years (ILAE n.d.). As a result, terms like "idiopathic," "cryptogenic," and "symptomatic" are no longer employed.

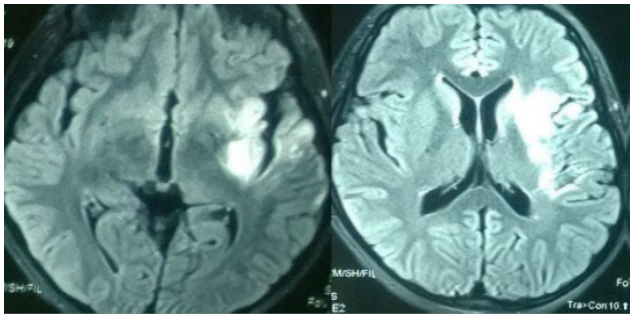

**Figure 2.** MRI of brain axial views showing insular cortical dysplasia (CD). Source: Figure by authors.

*2.1. Etiology Genetic*

4p–syndrome, Angelman syndrome, inversion duplication 15 syndrome, Miller–Dieker syndrome, ring chromosomes 14 and 20, terminal deletions of chromosome 1q and 1p, and ring chromosomes 14 and 20 are chromosomal abnormalities with a high association with seizures.

*2.2. Structural Etiology*

Common structural brain abnormalities associated with epilepsy, including cavernoma-causing, drug-resistant TLE:

- Developmental malformation of the cortex (Figure 2);
- Malformations of blood vessels (Figure 3);
- Sclerosis of hippocampus (Figures 4 and 5);
- Structural abnormalities from hypoxia +/ischemia (Figure 6);
- Head injury (Figure 7);
- Neoplasms (Figures 8 and 9) and porencephalic cysts;
- Cerebral gliosis (Figure 10).

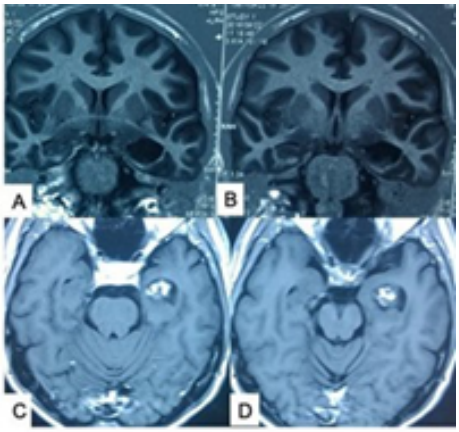


**Figure 3.** MRI of brain: (**A**,**B**) coronal views and (**C**,**D**) axial views showing hippocampal head. Source: Figure by authors.

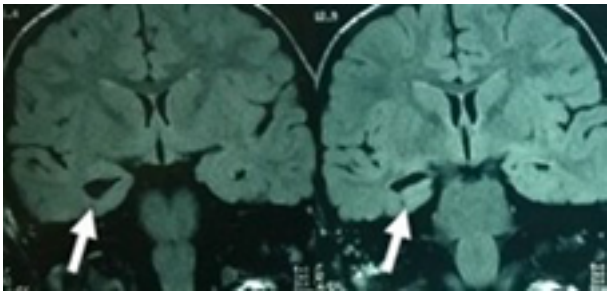

**Figure 4.** MRI of brain coronal views showing right-sided (arrow indicated) MTS (mesial temporal sclerosis). Source: Figure by authors.

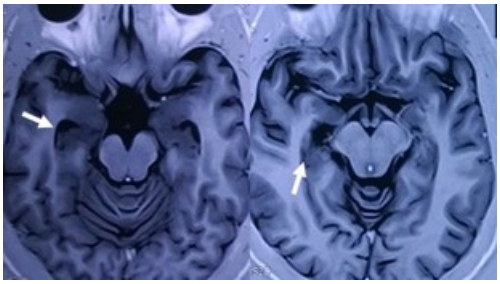

**Figure 5.** MRI of brain axial views showing right hippocampal head sclerosis (arrow indicated). Source: Figure by authors.

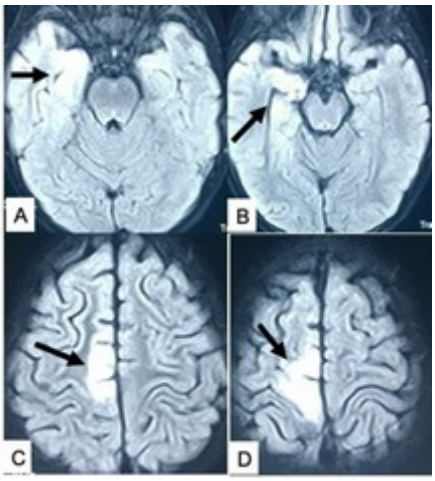


**Figure 6.** MRI of brain axial views in a 7-year-old girl with a history of birth asphyxia with intractable focal seizures: (**A**,**B**) showing right MTS (arrow indicated) and (**C**,**D**) showing right superior frontal focal CD (arrow indicated). Source: Figure by authors.

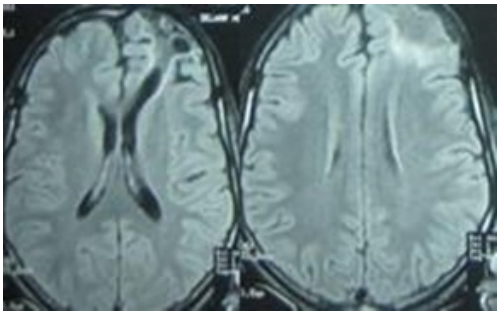

**Figure 7.** MRI of brain axial views showing post-traumatic left fronto-polar gliosis causing drug-resistant focal seizures. Source: Figure by authors.

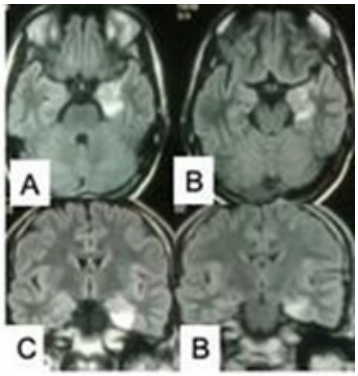


**Figure 8.** MRI of brain: (**A**,**B**) axial and (**C**,**D**) coronal views showing left amygdalo-hippocampal DNET causing TLE. Source: Figure by authors.

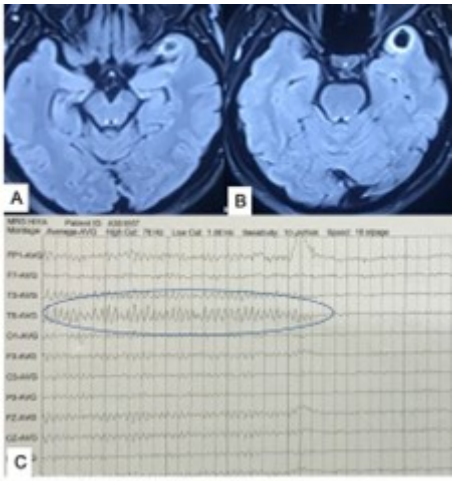


**Figure 9.** (**A**,**B**) MRI of brain axial views showing left temporal polar cystic lesion causing complex partial seizures. (**C**) Scalp EEG tracing showing left temporal focal discharges. Source: Figure by authors.

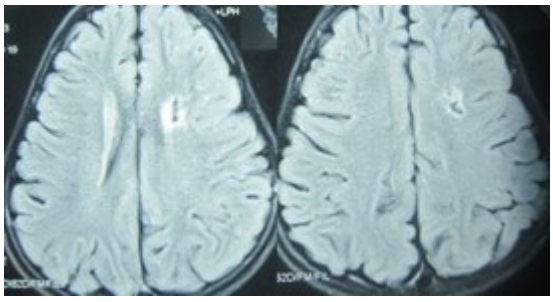

**Figure 10.** MRI of brain FLAIR axial views showing left frontal subcortical gliosis causing focal seizures. Source: Figure by authors.

*2.3. Metabolic Etiology*

- Creatine problems;
- Deficiency in cerebral folate;
- Deficiency in biotinidase and holocarboxylase synthase;
- Glucose transporter 1 (GLUT1) deficiency;
- Pyridoxine-dependent epilepsy/PNPO deficiency;
- Mitochondrial disorders;
- Folinic acid responsive seizures;
- Peroxisomal disorders.

*2.4. Immune Etiology*

- Antibody mediated etiologies;
- Rasmussen syndrome.

*2.5. Infectious Etiology*

Infectious disease is the most common etiology of epilepsy throughout the world, particularly in developing nations. Infections of the CNS may result in both acute symptomatic epilepsy and seizures (both are linked to the time of the initial infection). HIV, Tuberculosis, cerebral malaria, cerebral toxoplasmosis, subacute sclerosing panencephalitis, and neurocysticercosis are all infectious etiologies.

*2.6. Unknown Etiology*

The term "unknown" is meant to be taken in a neutral manner and used to indicate a type of the underlying etiology of epilepsy which is still unclear; it could be a basic genetic abnormality or a distinct, undiagnosed condition.

## 3. Epilepsy Imitators

There are a number of disorders linked to recurring paroxysmal occurrences that can mimic epilepsies and lead to misdiagnosis. Epilepsy misdiagnosis rates are high all throughout the world. Video recordings are quite important in determining a precise diagnosis. Epileptic and non-epileptic episodes can coexist under certain circumstances. Common epilepsy imitators are reflex anoxic seizures, syncopal attack, breath-holding attacks, psychogenic non-epileptic seizures, parasomnias, narcolepsy–cataplexy, stereotypies, paroxysmal kinesigenic dyskinesia, paroxysmal nonkinesigenic dyskinesia, hyperekplexia, migraine, shuddering attacks, and TIA (ILAE n.d.).

## 4. Drug-Resistant Epilepsy

Drug-resistant epilepsy, also called refractory epilepsy or intractable epilepsy, may be defined as "the failure of 02 tolerated and correctly designed and utilized AED regimens (whether as mono or combination therapy) to get persistent seizure independence" (Kwan et al. 2010). Seizure freedom lasting at least three times the longest seizure-free period previous to a new therapeutic intervention is defined as a treatment response in these criteria.

Factors associated with the risk of DRE include early-onset epilepsy, symptomatic generalized epilepsy, the presence of neuropsychiatric disorders, abnormal neuroimaging test results, abnormal EEG, focal EEG slowing, high initial seizure frequency, and a history of febrile seizures (Kalilani et al. 2018; Ko and Holmes 1999).

## 5. Epilepsy Surgery

### *5.1. Introduction*

Despite much improvement in understanding the pathophysiology of epilepsy, improved imaging facilities, and the availability of newer-generation AEDs, the prevalence of DRE (0.30%) has been somewhat similar over decades. Surgical intervention could assist 10.1 million people with active epilepsy worldwide, and 1.4 million new epilepsy patients per annum could potentially be surgical candidates (Vaughan et al. 2019). Methodical presurgical evaluation to select appropriate candidates for surgical intervention and choosing appropriate procedures are the most important part of epilepsy surgery.

### *5.2. Principle of Presurgical Evaluation*

Presurgical evaluation aims to detect and define the epileptogenic zone, its function, and spatial relation with eloquent brain, as well as to determine the best surgical procedure for that particular case. The following questions should be addressed:

1. Does the person truly have epilepsy? It is quite common that epilepsy imitators are misdiagnosed as epilepsy and treated with AED with ultimate failure and referral to a comprehensive epilepsy management program.
2. Is the epilepsy truly refractory? The selection of an appropriate AED and treatment with the maximum tolerable dose is needed before considering surgery.
3. What is the underlying etiology? Surgery has little effect in a patient with epilepsy secondary to an underlying progressive metabolic or degenerative condition.
4. Is remission still a possibility? Benign rolandic epilepsy patients may have difficult-to-control seizures but ultimately will recover.

#### 5.2.1. Definition of Cortical Zones

The epileptogenic zone (EZ) is an area of the brain that is essential for epileptic seizures to begin. It may contain a "potential epileptogenic zone," which is a region of cerebral cortex that may induce seizures once the presurgical seizure onset zone has been removed, as well as an actual EZ, which is the cortical region producing seizures prior to surgery.

When stimulated by an epileptiform discharge, the symptomatogenic zone of the cortex generates ictal symptoms. It is defined by a thorough examination of seizure semiology, which includes either a detailed history or an examination of ictal video records.

Interictal electrographic spikes are generated in the irritative zone, which is characterized as a region of cortical parenchyma. Interictal spikes trigger EEG (invasive or scalp), functional MRI (fMRI), or

magnetoencephalography (MEG) to quantify the irritative zone. This irritative zone, which is frequently greater than the EZ, encompasses all regions where the epileptic focus could potentially be found.

In contrast to the EZ, which is required for the development of epileptic seizures, the seizure start zone is the region of the cerebral cortex from which clinical seizures are (actually) produced. Either calp EEG or invasive EEG techniques are often utilized to locate the seizure onset zone.

A radiographic lesion that causes epileptic episodes is called an epileptogenic lesion. High-resolution MRI is the best way to define this now. However, not all lesions detected in epileptic seizure patients are epileptogenic. It is possible that some radiographic abnormalities have nothing to do with the clinical seizures.

In the interictal stage, the functional deficit zone is mentioned as the area of cortex that is functionally unusual. This dysfunction could be a direct outcome of the lesion's destructive effect, or it could be functionally mediated, i.e., aberrant neuronal transmission affecting cerebral function either locally or far away from the epileptogenic tissue. The functional deficiency zone can be measured using a variety of techniques; some examples include a neurological exam, cognitive testing, EEG evaluation, [$^{18}$F]fluorodeoxyglucose-PET (FDG-PET) scan, and interictal SPECT.

The eloquent cerebral cortex is the part of the brain that has a specific critical clinical role. The eloquent cortex refers to primary sensory, primary motor, memory, or language skills in the context of epilepsy surgery (Rosenow and Luders 2001).

5.2.2. Modalities/Tools in Presurgical Evaluation

1. History and clinical examination;
2. Neurophysiological assessment;
3. Structural neuroimaging;
4. Functional neuroimaging;
5. Neuropsychological assessment;
6. Intracarotid amobarbital procedure (Wada test);
7. Electrical cortical stimulation.

History and Clinical Examination

Presurgical evaluation starts with detailed clinical history and general and neurological examination. History details include the age of onset of seizures and frequency. The sequence of incidents at the time of a seizure should be obtained from the patient and also from one or more witnesses and compared with videotaped seizures recorded at home and in an epilepsy monitoring unit. The past medical history should include birth history, history of febrile seizures, significant head trauma, and CNS infections. Medication trials and their adverse effects should be noted. Family history of febrile/afebrile seizures and other neurological illness should be taken. Most patient's neurological examinations reveal no findings. In children, the skin should be examined for signs of neurocutaneous disorders. Any focal weaknesses or asymmetric reflexes might have a lateralizing value.

The semiology of seizures is an important aspect of the epilepsy surgery examination. Clinicians can benefit from a thorough examination of seizure semiology. In three-quarters of patients, semiology locates and lateralizes seizures (Elwan et al. 2018).

The following are characteristics that indicate lateralization of the seizure. These characteristics support the idea of lateralization (ILAE n.d.):

- Ictal dystonia or unilateral ictal clonic activity indicate lateralization of the seizure to the opposite hemisphere. The initial forced-head version alludes lateralization to the cerebral hemisphere opposite the head version direction, i.e., if the head rotates to the right side, the seizure initiation is in the left hemisphere.
- Ictal speech does lateralize to the cerebral hemisphere—it is not dominant.
- The dominant hemisphere is affected by ictal aphasia.
- The dominant hemisphere is affected by postictal dysphasia.
- During ictal automatisms, awareness is preserved and lateralized to the non-dominant cerebral hemisphere.
- After ictal nose-wiping, the hemisphere ipsilateral to the nose-wiping hand lateralizes.
- Unilateral eye-blinking does lateralize to the hemisphere on the opposite side.
- The non-dominant hemisphere is affected by ictal vomiting.

However ictal semiology is also an area fraught with pitfalls. Seizures may arise from a "silent" or non-eloquent cortex and then spread to a functional area and express its manifestation. Thus, semiology would

indicate the site of seizure propagation instead of the site of seizure onset. Generally, the late features of seizure semiology reflect ictal spread and have less localizing value.

Neurophysiological Assessment

Electroencephalography (EEG): EEGs record the electrical activity of the brain in real time. An interictal scalp EEG (also known as a routine EEG) is used as the initial investigation for seizure disorders. It is a simple, noninvasive procedure where EEG electrodes are put on the scalp according to a standard, international 10/20 system. Recording is conducted for 30 to 60 min. Digital EEG recordings allow reformatting of EEG montages with judicious utilization of filters to improve reporting, hence it is adopted by most epilepsy centers. Routine EEGs very rarely record actual seizures, except generalized absence seizures. The main positive findings of routine EEGs are interictal epileptiform activity, which includes spikes and sharp waves and focal slowing. Both spikes (duration < 70 ms) and sharp waves (duration 70–200 ms) have pointed peaks of negative polarity, in most cases. Epileptiform discharges tend to have aftercoming slow waves. Sharp and spiked waves and focal slowing on the interictal EEG indicate the irritative zone and the functional deficit zone, respectively (Figure 11). Even without an epileptogenic lesion, subtle background asymmetries may be significant for localization and lateralization.

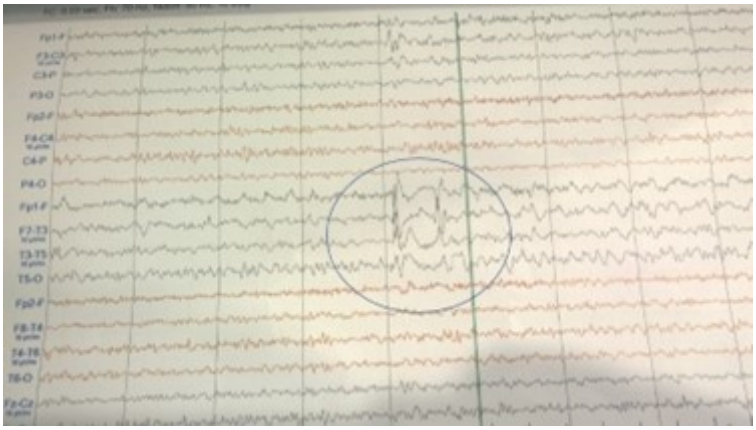

**Figure 11.** Interictal scalp EEG tracing showing focal electrical discharge from left frontotemporal regions. Source: Figure by authors.

However routine EEGs have important limitations. The electrical activity detected by a scalp EEG is attenuated by the impedance of intervening tissue. Epileptiform discharges are detected only if more than a 6 $cm^2$ area of cortical surfaces is involved in synchronized activity (Cooper et al. 1965). Interictal activity originating from the midline or deep area do not show up in scalp recordings. Therefore, the yield of the first routine EEG is normal in 50% of patients. With multiple recordings, epileptiform EEGs detected abnormality in more than 90% of epilepsy patients (Salinsky et al. 1987).

Prolonged video EEG monitoring (VEM) is considered a cornerstone of presurgical evaluation. Anti-epileptic drugs are tapered or withdrawn to capture 4–10 habitual seizures. The ictal onset zone is detected by electrographic discharge and clinical manifestations that reflect the symptomatic zone. Placement of additional electrodes increases the precision of localization of the ictal onset zone. Ictal EEG activity should be analyzed in the background of time-locked symptoms and signs. Most video recordings at home miss the initial events, which are more important. VEM provides better opportunities for analysis of seizure semiology. The interpretations are more accurate when ictal events are analyzed in conjunction with simultaneously recorded EEGs. VEM is a sensitive tool to exclude pseudoseizures.

The scalp EEG recorded at the start of the seizure can take at least five different forms (Fisher et al. 2014):

1. Rhythmically evolving frequencies in the theta, delta, or alpha bands;
2. Rhythmic spiking;
3. Spike–wave patterns;
4. Electrodecremental patterns;
5. No change in the scalp EEG.

Similar to routine EEGs, ictal recording of scalp EEGs comes with limitations in detecting deep foci and very focal small partial seizures, which explain the fifth pattern of ictal EEGs mentioned above. Furthermore, signals are obscured by muscle and movement artifacts in tonic–clonic seizures. In the presence of substantial

atrophy on the side of the epileptogenic focus, false lateralization of the ictal EEG might occur. The reliability of scalp ictal EEG recordings appears to be contingent on the presence of enough brain in the epileptogenic focus area to provide an amplitude signal that can be distinguished from the surface. Furthermore, the amplitude of the ictal EEG signal from the non-diseased hemisphere surpasses that of the atrophic side during bilateral ictal propagation, resulting in a falsely lateralized image (Chang et al. 2007). Invasive intracranial monitoring is frequently required when MRI and EEG data are inconsistent. Intracranial electroencephalography (IEEG) is an invasive procedure and is utilized only when noninvasive tools fail to define EZ adequately. ILAE-recommended general indications for IEEG are as follows (Jayakar et al. 2016):

1. To properly identify the EZ when noninvasive data are equivocal;
2. To reconcile noninvasive data divergence pointing to two or more areas;
3. To correctly map eloquent cerebral cortical functions;
4. Secondary indications: to confirm the EZ or offer prognostic information by targeted ablation of active areas with thermocoagulation.

There are subdural grid and strip electrodes and depth electrodes of multiple configurations for IEEG. Intracranial EEGs may be recorded intraoperatively or extraoperatively. Craniotomy and placement of subdural and depth electrodes and recording of electrical activity intraoperatively is known as electrocorticography (ECoG) (Figure 12). ECoG records interictal epileptiform discharge and background abnormalities, thus defining the irritative zone. In lesional epilepsy, ECoG-based stepwise resections of tumors and the peritumoral irritative zone improve outcomes significantly (Mikuni et al. 2006). ECoG is unlikely to capture ictal events. Thus, for more complex cases, after the placement of electrodes, IEEGs are recorded extraoperatively.

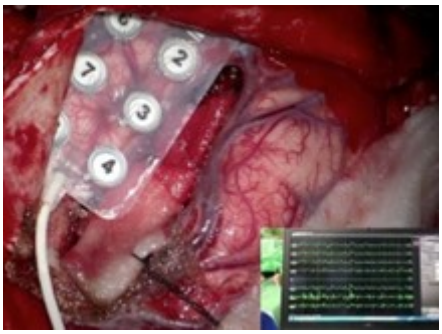

**Figure 12.** Peroperative electrocorticogram (ECoG). Source: Figure by authors.

Strips can be inserted through burr holes. Craniotomy is needed for grid placement. Depth electrodes could be placed through the burr, via craniotomy, or under neuronavigation guidance but are more commonly placed using the stereotactic method. Some centers practice only stereotactically placed, bilateral multiple electrodes for chronic invasive recording, known as an SEEG. Based on noninvasive evaluations, a hypothesis was to made of a presumptive EZ. Electrodes are placed to cover the EZ and irritative zone and adjacent EC. Cortical stimulation mapping could be conducted through IEEG electrodes after EEG recording is completed. AEDs should be restarted before ECS.

Magnetoencephalography is a promising noninvasive tool for defining the epileptogenic cortex and to delineate the eloquent cortex as well. The MEG signal is generated using the same neurophysiological process as the EEG signal (Barth 1993). Extracranial magnetic fields created by intracellular neuronal currents are detected using an MEG recording device made up of highly sensitive bio-magnetometers. MEG signals, unlike EEG signals, are unaffected by inhomogeneous tissue conductivity. Magnetic source imaging is the co-registration of MEG-determined source localization of epileptic spikes and evoked responses with MRI (MSI). As a result, in extratemporal localization epilepsy, presurgical assessment of MEG spike sources (MEGSS) and evoked responses on MSI is very reliable (Çataltepe and Jallo 2019). MEGSS in temporal lobe epilepsy is not precise enough to locate the source of interictal epileptiform discharges (Ebersole 1997).

Magnetoencephalography is also useful in the localization of the sensory motor cortex, primary auditory cortex, and language area. However, the establishment of an MEG recording system is very expensive and it has a very large running cost. Hence, despite encouraging results in clinical trials, its use in routine clinical set-ups is limited to a few centers. For a minority of patients with intractable localization-related epilepsy, improved clinical application of MEG has the potential to replace invasive subdural and depth electrode recordings.

Structural Neuroimaging

MRI is the mainstay investigation for epilepsy. The ILAE recommends MRI evaluation for all patients who have experienced their first seizure, except patients with genetic generalized epilepsy. Radiologically detected epileptogenic lesions help in syndromic classification and are a predictor of poor seizure freedom with medication and better outcomes following surgery. However, the presence of a lesion does not necessarily mean that it is responsible for seizures. Moreover, multiple lesions do not confirm that the epilepsy is multifocal. The concordance of a radiological lesion with seizure semiology and/or an EEG is to be established. Common pathological indications for DRE include hippocampal sclerosis, malformation of cortical development, epilepsy-associated tumors, Rasmussen encephalitis, hypothalamic hamartoma, arteriovenous malformation, and cavernoma.

The neuroimaging task force of the ILAE recommend the "Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) protocol" for the evaluation of seizures (Bernasconi et al. 2019). Key features of the HARNESS–MRI protocol are as follows:

1. High-resolution, 3D, T1-weighted MRI in gradient echo sequence with isotropic millimetric voxel resolution; slice thickness of 1.5 mm or less; and no interslice gap.
2. Acquisition of a high-resolution, 3D, fluid-attenuated inversion recovery (FLAIR) sequence in the turbo spin with isotropic millimetric voxel resolution and no interslice gap.
3. High in-plane resolution, 2D, coronal, T2-weighted MRI with sub-millimetric voxel resolution and no interslice gap obtained perpendicular to the long axis of the hippocampus.
4. Available in 1.5 T and 3 T scanners.

In children with FCD, MRI conducted at one year of age is more sensitive as subsequent myelination may hide the features of dysplasia on later scans. MRI should be repeated for patients with DRE if the available scan is not optimized or normal.

Computed tomography (CT) scanning has low sensitivity for identifying small cortical lesions and basal lesions and, therefore, is not a primary imaging modality in epilepsy. However, CT scans should be considered in new-onset seizure patients presenting in the emergency room to rule out intracerebral hemorrhage, subarachnoid hemorrhage, or brain abscess. Furthermore, CT scans may be followed to identify any area of focal calcification, when MRI shows tuberous sclerosis, Sturge–Weber syndrome, or an epilepsy-associated tumor.

Functional Neuroimaging

Blood flow and metabolism in the epileptic zone and eloquent cortex are different from adjacent brain tissue. The epileptic region shows hypometabolism and hypoperfusion in the interictal period and the reverse in the ictal period. During a particular task, blood flow and oxygenation levels increase in the corresponding functional cortex. Functional neuroimaging was developed based on these physiological phenomena (So and Ryvlin 2018).

Functional MRI (fMRI) is a noninvasive and widely available tool for presurgical evaluation of cognitive function and the motor cortex. Functional mapping in fMRI is performed by calculating the blood-oxygen-level-dependent (BOLD) signal change in T2-weighted images while patients engage in functional tasks. fMRI is comparable with IAT for determining hemispheric dominance for language and speech. But, fMRI detects both essential and nonessential language regions. fMRI-based motor cortex mapping is performed when the presumed EZ is adjacent to the motor cortex.

During seizures, blood flow in the epileptic zone (EZ) increases up to three times. For ictal SPECT, patients remain admitted in the video EEG monitoring unit. At the onset of a seizure, ethylene cysteine dimer (ECD) or hexamethyl propylene amine oxime (HMPAO) labeled with 99 mTc is injected. HMPAO/ECD crosses the BBB and is trapped within the neuron in proportion to regional cerebral perfusion during a seizure. Trapped radiotracers emit gamma rays, which are then detected by a rotating camera. The exact timing of the radiotracer is crucial and ictal SPECT is less feasible in very-short-lasting seizures such as myoclonic epilepsy. In SPECT, the EZ displays hyperperfusion. Interictal SPECT depicts normal perfusion or hypoperfusion in the epileptic region and is compared with the ictal image. Interictal SPECT is subtracted from ictal SPECT and the resulting image is co-registered to an MRI (SISCOM). SISCOM improves ictal SPECT's specificity and sensitivity.

In positron emission tomography (PET), various biological substrates leveled with a radioisotope such as $^{18}$F, $^{11}$C, or $^{15}$O are injected intravenously. $^{18}$Flurodeoxyglucose (FDG) is the most commonly used radiotracer. FDG is taken up by brain tissue and phosphorylated to FDG-6-phosphate and becomes trapped within the cell. FDG-6-phosphate trapped in the body emits gamma rays, which are identified by a PET camera and used to

rebuild quantified tomographic pictures, which are then combined with CT images. As metabolism is low in the epileptic region in the interictal period, FDG PET shows reduced radiotracer uptake in the EZ. The area of hypometabolism detected by PET extends far beyond the EZ; thus, it is less precise for defining EZ. However, PET reliably lateralizes the EZ and, thus, a hypothesis could be made of a presumed EZ for subsequent placement of IEEG electrodes. The FDG-PET findings may guide reviews of MRI images retrospectively and reveal the pathology. Moreover, concordant findings on PET increase confidence in subtle MRI findings (So and Ryvlin 2018).

### Neuropsychological Testing

It is standard practice that all epilepsy surgery candidates should receive a presurgical outpatient neuropsychological evaluation. It provides a baseline neurocognitive profile for comparison after surgery. The domains of neuropsychological testing include verbal memory and nonverbal memory, expressive and receptive language skills, verbal fluency, semantic fluency, visuospatial function, general cognitive ability, and higher executive functions. The location of the epileptic focus, the age at which the seizures began, the epilepsy syndrome, and the brain's plasticity all influence the pattern of cognitive deficits. For example, a person with dominant temporal lobe epilepsy would have remarkable language and verbal memory problems.

An identical type of seizure arising on the right (non-language-dominant) side, on the other hand, would usually result in visual memory problems (Bell and Davies 1998). Thus, neuropsychological test findings have lateralizing and localizing value, especially useful in MRI-negative epilepsy to further confirm—or argue against—the assumed epileptogenic zone. Patients with a similar cognitive profile have a better seizure result, while those with a lower baseline intellectual profile have worse postoperative seizure control. Memory and language tests help determine the ipsilateral lobe's functional capacity and the contralateral lobe's functional reserve.

Memory deficit is a common complication of anteromedial temporal lobectomy. Patients with better preoperative memory and language function (i.e., suggesting better functional integrity of the parenchyma to be removed) have a higher risk of postsurgical memory and language deterioration than those with lower scores in this category.

### Intracarotid Amobarbital Injection Procedure (IAP, Wada Test)

Dr. John Atsushi Wada developed the procedure in 1949 and it has since been further modified by others. It is the gold standard for determining language and speech hemisphere dominance. The Wada test's more delicate function is to assess memory function in each hemisphere as well as the functional adequacy of the contralateral hippocampus in supporting memory following ipsilateral mesial temporal lobe resection. Additionally, the Wada test aids to predict seizure freedom following surgery.

Anterior circulation feeds the anterior two-thirds of the cerebrum. Short-acting barbiturate introduced into the ICA (internal carotid artery), thus, will induce temporary disruption in the function of the anterior two-thirds the of cerebrum, including the temporal lobe. Prior to the procedure, an angiogram is performed to assess anatomical variation and the extent of cross flow. Then 100–150 mg of sodium amobarbital is injected into one ICA at a time and cognitive ability and language function for each hemisphere are assessed in isolation.

However, the Wada test is an invasive procedure and has potential minor and major complications (Loddenkemper et al. 2008). More importantly, this technique is not standardized and there are reports of false positive and false negative results. At present, in most centers, the Wada test is replaced by noninvasive fMRI (Binder 2011).

### Electrical Cortical Stimulation (ECS)

The encroachment of the epileptic zone on the eloquent cortex necessitate precise mapping using cortical stimulation to ensure adequate removal of potential epileptogenic tissue without creating new functional deficits. Extraoperative ECS is performed at the end of IEEG by stimulating subdural and depth electrodes. Intraoperative ECS is performed after ECoG. During stimulation, clinical responses and electrocorticographic changes are monitored. Cortical stimulation at primary and supplementary motor areas produce tonic or clonic movements. Sensory responses are elicited at sensory cortex stimulation. Stimulation of motor or sensory speech areas causes

speech arrest (Çataltepe and Jallo 2019). With the availability and increasing accuracy of noninvasive tools such as fMRI, ECS is reserved for MRI-negative epilepsy and complex cases of malformation near eloquent cortex.

#### 5.2.3. Epilepsy Remediable by Epilepsy Surgery

##### Malformations of Cortical Development

Cortical malformations occur when neuronal proliferation, migration, or cortical structures are disrupted during the development of the cortex (Jamuar and Walsh 2015; Barkovich et al. 2012). The disruption of any of these processes can raise the risk of seizures and neurodevelopmental delays in children (Jamuar and Walsh 2015). Malformations may be focal or multifocal such as focal cortical dysplasia, polymicrogyria, schizencephaly, and hypothalamic hamartomas, which require focal, lobar, or multilobar resection. Malformation may involve most or all of one hemisphere (e.g., hemimegalencephaly), making these patients ideal candidates for some form of hemispherectomy. Less commonly, malformation may be widespread and bilateral, e.g., lissencephaly and subcortical band heterotopia, and not amenable to surgery.

##### Hemimegalencephaly (HME)

This is a spontaneous congenital brain deformity that is extremely rare. It can be found on its own or in conjunction with a neurocutaneous syndrome. The abnormal growth of a significant piece of one hemisphere, a whole hemisphere, or a hemisphere and part of the opposite side characterizes HME. There may be ipsilateral cerebellar and brainstem hypertrophy, as well as cranial expansion.

Mental retardation, contralateral hemiparesis, intractable epilepsy, macrocephaly, and hemi-anopsia are common clinical characteristics. Motor function and linguistic impairment are typically worse in persons with localized cortical dysplasia. Partial-onset seizures, epilepsia partialis continua, infantile spasms, and drop attacks are all examples of seizures (Terra-Bustamante et al. 2006).

An enlarged cerebrum (proportion or entirety) with a broad gyrus, thicker cortex, neuronal heterotopia, aberrant gray–white matter differentiation, ventricular asymmetry, and internal capsule and basal ganglia abnormalities are all seen on post-natal MRI. The damaged hemisphere may shrink as the disease progresses, and it may not be greater than the contralateral, unaffected hemisphere during imaging. Cortical tubers may or may not exist in the non-HME hemisphere (Terra-Bustamante et al. 2006).

Slow, rhythmic, or rapid activity, as well as multifocal bilateral or unilateral high-amplitude spikes and spike–wave complexes, are all examples of interictal EEG abnormalities. Generalized or independent bilateral discharges are possible. Ictal abnormalities might be made up of a build-up of unilateral or widespread fast rhythmic activity or bilateral independent activity (Terra-Bustamante et al. 2006).

Histopathologic changes include abnormal gyrification, dyslamination, neuronal heterotopia, marked gliosis, and balloon cells (Terra-Bustamante et al. 2006).

For intractable epilepsy, hemispherotomy or functional hemispherectomy is the technique of choice. Following hemispherectomy, patients with HME had a dramatically improved seizure load and quality of life, although less than patients with Rasmussen's encephalitis or congenital vascular anomalies (Ikeda and Mirsattari 2017).

##### Focal Cortical Dysplasia

Localized patches of cortical lamination disruption characterize focal cortical dysplasias (FCDs), which are frequently linked to epilepsy in both adults and children (Figure 2). In children receiving epilepsy surgery, FCD is the most frequent pathogenic condition (Wyllie et al. 1998). The ILAE Task Force recommends a three-tiered clinicopathological classification system for FCD. Isolated lesions of the neocortex that show as radial (FCD Type Ia) or tangential (FCD Type Ib) dyslamination, microscopically diagnosed in one or more lobes, are referred to as FCD Type I. Cortical dyslamination as well as dysmorphic neurons without (Type IIa) or with balloon cells describe FCD Type II (Type IIb). Cortical dysplasia develops in FCD Type III in conjunction with hippocampal sclerosis (FCD Type IIIa) or epilepsy-related malignancies (FCD Type IIIb) (Blümcke et al. 2011).

MRI characteristics of FCD include cortical thickening, blurring of the gray matter–white matter junction, an enhanced signal on T2-weighted imaging, a radially oriented linear or conical T2 hyperintensity stripe, cortical thinning, and regional brain atrophy. Unfortunately, none of these indicators are dependable or constant (Blümcke et al. 2011).

On MRI, FCD can sometimes go undetected, especially in type I. Furthermore, possible epileptogenic zones are often bigger than lesions shown by MRI, necessitating the use of additional technologies for precise surgical resection planning (Kabat and Król 2012). Extratemporal FCDs are more prevalent, and they have a tendency to encroach on the eloquent cortex. IEEG improves the accuracy of both ictal and interictal data, making it easier to distinguish the EZ. Electrical stimulation using the implanted electrodes can also be used to perform functional mapping.

A discrete epileptogenic focus is removed via focused resection. When the ictal area is big, lobectomy or multilobar resections are considered. When a lesion encroaches into the functional cortex, partial resection combined with multiple subpial resection for the rest of the EZ is the safest surgical strategy.

### Rasmussen's Encephalitis

Rasmussen's encephalitis is an uncommon neurological illness marked by inflammation of one cerebral hemisphere, persistent epilepsy, progressive hemiparesis and hemianopia, and cognitive decline. Rasmussen's encephalitis is most likely caused by a T-cell response to one or more antigenic epitopes, with autoantibodies playing a role as well. The inflammatory process in the brain is seen with MRI as T2/FLAIR hyperintensity in the cortical or subcortical region with ipsilateral caudate atrophy. The evolution of signal alteration and atrophy is usually visible on serial MRIs (Chiapparini et al. 2003; Yamazaki et al. 2011). In Rasmussen's encephalitis, seizures are localized and around half of the patients develop epilepsia partialis continuous. Electroencephalography shows continuous high-amplitude delta activity over the injured hemisphere within months of the seizure starting, but epilepsy partialis continua is not always associated with visually evident ictal surface EEG activity (So and Gloor 1991). Interictal aberrations in the non-affected hemisphere can indicate cognitive decline, but they do not appear to be suggestive of bilateral disease (Longaretti et al. 2012).

Choosing the correct time to transition from medical care to surgery is a significant therapeutic challenge for many patients, families, and clinicians, especially when the neurological damage is partial. The sole solution for seizures is anatomical or functional hemispherectomy, which comes at the cost of some functional constraints. Immunomodulatory therapy appears to reduce rather than stop the progression of Rasmussen's encephalitis, with no effect on the final result.

Corticosteroid and intravenous immunoglobulin are used as immunomodulators in Rasmussen's encephalitis, while AED is used to lessen seizure intensity and frequency. However, interventions have thus far merely addressed the symptoms rather than the underlying causes. Total disconnection of the afflicted hemisphere (hemidisconnection), either via hemispherotomy or functional hemispherectomy (Figures 13 and 14), is the only treatment for the convulsions due to Rasmussen's encephalitis (Varadkar et al. 2014).

### Temporal Lobe Epilepsy

The commonest epilepsy surgically treated is temporal lobe epilepsy (TLE), which impacts the majority of patients with localization-related epilepsy observed in tertiary epilepsy centers (Téllez-Zenteno and Hernández-Ronquillo 2012).

Based on the anatomical area of seizure onset, TLE can be categorized into two categories. Lateral or neocortical epilepsy occurs when the epileptogenic zone is lateral to the collateral sulcus, while mesial temporal TLE occurs when the epileptogenic zone is medial to the collateral sulcus (MTLE).

The limbic regions that make up the temporal lobe's mesial part are strongly epileptogenic. The fornix connects the anteromesial frontal lobe to the anterior nucleus of the thalamus, and the uncinate fasciculus connects the mesial temporal lobe to the orbitomesial frontal lobe (Duvernoy et al. 2013). The mesial temporal structures are closely linked to the anterolateral neocortical temporal lobe. The two TLE groups frequently share seizure semiology due to the substantial linkages between the mesial temporal structures and the anterior and lateral temporal lobes, as well as other limbic regions (O'Brien et al. 1996; Burgerman et al. 1995).

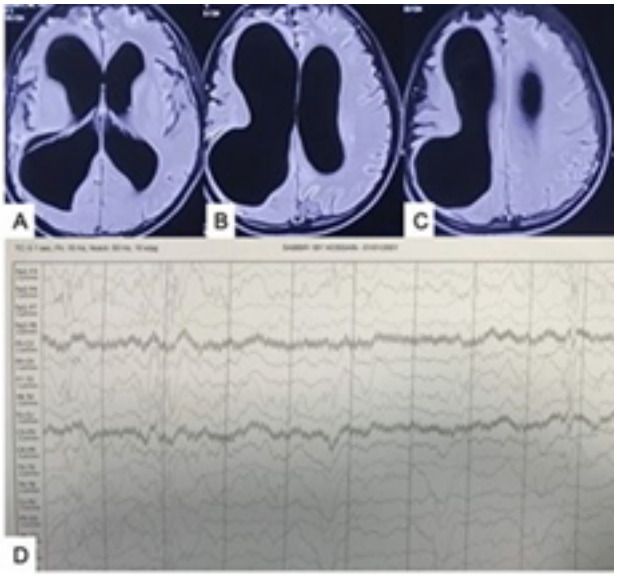


**Figure 13.** (**A**–**C**) MRI of brain axial views showing right hemispheric atrophy (with intractable left-sided focal convulsion to generalization). (**D**) Scalp EEG tracing showing multifocal electrical discharges mainly from right-sided leads. (But, left-sided lead spikes and sharps are more pronounced due to more parenchymal tissue-paradoxical affects.) Source: Figure by authors.

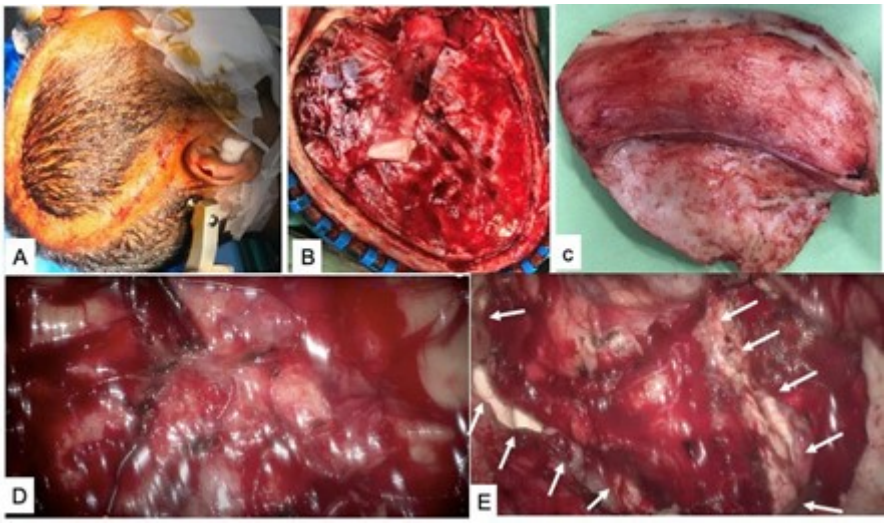


**Figure 14.** Peroperative pictures of right-sided functional hemispherotomy: (**A**) incision mark, (**B**) after craniotomy, (**C**) craniotomy bone flap, (**D**) right hemisphere before hemispherotomy, and (**E**) right hemisphere after hemispherotomy (arrows marked). Source: Figure by authors.

Behavioral arrest and reduced awareness are common symptoms of temporal lobe seizures. Automatisms, such as oral and/or manual automatisms, are common during seizures. There may be sensory (auditory), cognitive (déjà vu), emotional (terror), or autonomic (tachycardia, epigastric sensation, and color change) characteristics before the onset of diminished consciousness. Postictal confusion is very common.

Ictal speaking, spitting, the urge to urinate, vomiting, drinking, and automatisms with maintained consciousness reflect non-dominant temporal lobe seizure onset. A dominant temporal lobe seizure is indicated by postictal speech difficulties. Upper limb dystonia is a good lateralizing trait since it shifts the seizure to the other hemisphere. On the other hand, manual automatisms frequently occur on the ipsilateral side.

The most prevalent substrate for MTLE is mesial temporal sclerosis, which manifests in MRI as hippocampal atrophy and sclerosis, as well as elevated T2 and FLAIR signal intensity (Berkovic et al. 1991). FCD, cavernoma, epilepsy-associated tumors, and post-traumatic gliosis are some of the other indications for mesial or neocortical TLE.

Despite significant semiological overlap between the two types of TLE, noninvasive testing can usually pinpoint the seizure focus. In a limited number of people, intracranial electrode monitoring may be needed to

analyze the lateralization of seizure onset to a temporal lobe (So et al. 1989) or to verify temporal lobar localization in one hemisphere (Olivier et al. 2012).

The standard temporal resection accomplished at most epilepsy facilities is anteromedial temporal lobectomy (AMTL). It mainly entails removing temporal mesial tissues after anterior temporal neocortical resection.

Selective amygdalohippocampectomy (SAH) for MTLE has sparked a lot of attention since Yasargil et al. published their findings (Yasargil et al. 1985). SAH may have the advantage of selectively removing the seizure focus, preserving temporal lobe areas that are not actually epileptogenic.

The outcome on seizure independence is the same as for anteromedial temporal lobectomy at centers with experience in SAH (AMTL) (Little et al. 2009). SAH appears to have better cognitive outcomes than typical temporal resections (Kessels et al. 2004; Gleissner et al. 2004).

Epilepsy Associated Tumors

A neoplasm is the second most prevalent etiology of focal epilepsy (Englot and Chang 2014) among individuals considered for epilepsy surgery, and it is found in roughly 30% of cases intervened in for focal epilepsy (Tassi et al. 2009).

The risk of focal seizures differs based on the tumor's location and histological type. Low-grade neoplasms are, thus, frequently more epileptogenic compared to high-grade tumors (van Breemen et al. 2007).

The biologic activity of epileptogenic tumors is normally benign, yet certain tumors may recur or develop into cancer (Luyken et al. 2003). Gangliogliomas (Figure 15), dysembryoplastic neuroepithelial tumors (DNET), pleomorphic xanthoastrocytoma, diffuse astrocytoma, papillary glioneuronal tumor, oligodendroglioma, pilocytic astrocytoma, and angiocentric gliomas are all examples of epileptogenic tumors.

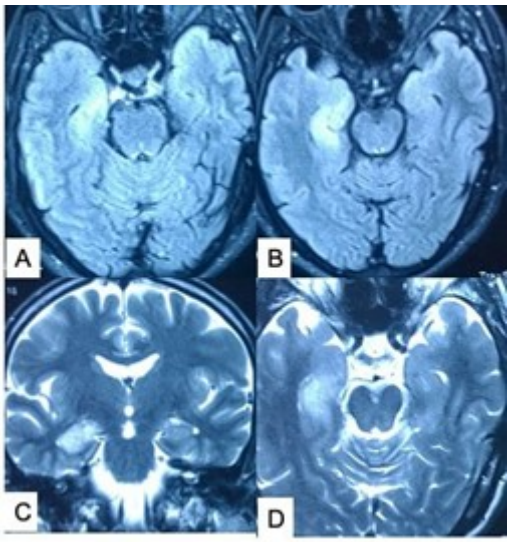


**Figure 15.** MRI of brain: (**A**,**B**) axial sections and (**C**,**D**) coronal sections showing right-sided medial temporal (hippocampal) ganglioglioma. Source: Figure by authors.

The most common and often only sign of malignant tumors that develops in young adulthood and adolescence is focal seizure.

As a result of the presence of a mixture of solid, calcified, and cystic elements, the MR signal of ganglioglioma is inhomogeneous and variable, with no contrast enhancement; an axial CT scan reveals the calcified element.

DNETs are multinodular, wedge-shaped, "bubbly" intracortical tumors that are usually mistaken for other LGGs. DNETs are more likely than GGs to have a multi-cystic shape and to stay the same size throughout time.

In around 30% of cases, contrast enhancement was discovered. The tumor presents on CT scana as a hypoattenuating cortical–subcortical mass with occasional calcifications. The surrounding inner table of the cranium may also have scalloping. On MRI, DNETs are most commonly seen as multinodular, pseudocystic cerebral cortical lesions that are hypointense on T1W images but hyperintense on T2W images, with or without circumferential vasogenic edema.

Anti-epileptic medicines are frequently ineffective in controlling epilepsy-related tumors, although surgery can provide great benefits (Clusmann et al. 2004). Lesionectomy, extended lesionectomy, and customized resection

are among the surgical strategies used. When a tumor is found in the mesial or neocortical temporal lobe, some authors recommend anterior temporal lobectomy.

When the tumor is extratemporal or in the temporal neocortex, most of the authors concur that lesionectomy alone delivers the best seizure reduction result (Cataltepe et al. 2005). However, the effects of temporomesial lesionectomy are debatable (Cataltepe et al. 2005). The involvement of temporomesial areas, according to some writers, may extend and complicate the epileptogenic zone.

### Hypothalamic Hamartoma

A hypothalamic hamartoma (HH) is an uncommon, developing, disordered tissue mass that arises from the tuber cinereum and the bottom of the third ventricle and is found in the hypothalamus. Precocious puberty is associated with infraventricular HHs linked to the tuber cinereum. Intraventricular HHs are connected to the third ventricle's floor and cause seizures. Gelastic seizures (GSs) are the commonest type of seizure in pediatric patients; however, patients can also have dacrystic seizures, complicated partial seizures, or other types of seizures. Epilepsy linked to HH is pharmacoresistant and results in severe epileptic encephalopathy and infantile catastrophic epilepsy (Harvey and Freeman 2007).

Scalp electroencephalograms do not exhibit epileptiform discharge in gelastic seizures caused by HH, whereas depth electrodes implanted into the hamartoma clearly indicate epileptiform activity.

The suprasellar cistern and anterior third ventricle are obliterated on non-enhanced CT scans, and the nodule is iso- or hypodense compared to the grey matter. On high-dose, contrast-enhanced CT, HHs do not enhance. On T1WI, signal intensity is frequently isointense to normal gray matter, and on T2/FLAIR, signal intensity is usually isointense to slightly hyperintense. Following contrast injection, HHs do not improve (Saleem et al. 2007).

Surgery appears to be the best technique for acquiring seizure independence and preventing the steady loss of neurocognitive function in HHS patients who were resistant to AED. Surgical options include the transcallosal interhemispheric approach, endoscopic removal, stereotactic radiosurgery (Rosenfeld et al. 2004), and stereotactic radiofrequency thermocoagulation (SRT) (Wang et al. 2009).

### The Lennox–Gastaut Syndrome

Lennox–Gastaut syndrome (LGS) is one of the most severe epileptic syndromes. It generally develops between the ages of 3 and 5, but it can also occur later in life, even into adulthood (Camfield 2011; Arzimanoglou et al. 2009). LGS is a clinical diagnosis marked by polymorphous epileptic seizures, primarily axial tonic, atypical absences, and atonic seizures; permanent psychological disturbances; and an electroencephalogram (EEG) that frequently shows either paroxysmal fast activity or slow spike–waves brought on by sleep when superimposed on a slow background (Camfield 2011; Arzimanoglou et al. 2009).

LGS is still difficult to treat and seizures are extremely pharmacoresistant. Patients with LGS who have not responded to pharmacological treatment may be candidates for surgery.

Neuroimaging studies in patients with LGS may have two patterns of findings. MRI may reveal a well-circumscribed lesion, the removal of which will lead to seizure freedom. More usual is that MRI reveals no epileptogenic lesion or lesions that are extensive, bilateral, diffuse, or not well defined and, thus, not removable. In the second situation, it is possible to perform a palliative operation such as corpus callosotomy or vagus nerve stimulation.

### The Landau–Kleffner Syndrome

This is an epileptic encephalopathy with the EEG characteristic of continuous spikes and waves during slow sleep (CSWS). During a vital phase of language development, an epileptogenic lesion in the speech area (or that influences the speech cortex) causes the disease.

Neurocysticercosis, subpial gliosis, encephalitis, vasculitis, and neuronal migration disorder have all been recognized as pathologic entities in children with LKS (Cole et al. 1988). In most patients with LKS, however, standard neuroimaging reveals no structural abnormalities.

The onset of language disturbances is temporally linked to the onset of seizures. Seizures are typically low in severity, infrequent, and nocturnal. AEDs, steroids, high-dose benzodiazepines, and IV immunoglobulin have all been used to treat LKS (IVIG). Clinical seizures can be effectively treated with AEDs and other medical treatments; however, cognitive impairments and epileptiform discharge are treated differently.

Surgical options for LKS include lesionectomy, when appropriate, and multiple subpial transection (MST), when there is no identifiable lesion in MRI.

The target of epilepsy surgery for LKS is to obtain seizure freedom and remission of the language problems. AEDs can usually achieve the latter goal in most patients. As a result, the most common reason for considering surgery is to eliminate epileptiform discharge and thereby improve language function. There are reports of excellent outcomes following lesionectomy (Nass et al. 1993).

Morell and colleagues introduced MST for selected children with LKS who failed medical therapy, and the outcome of their series was encouraging (Morrell et al. 1995). A similar outcome was also published by Grote et al. (1999) and Irwin et al. (2001). However, Downes et al. found reason to recommend MST over medical therapy (Downes et al. 2015).

#### 5.2.4. Classification of Epilepsy Surgery

The surgical approach and method in a case with refractory epilepsy is determined by the seizure type, location of epileptic focus, presence or absence of an identifiable pathology on MRI, and its proximity to eloquent brain and the patient's functional baseline. Epilepsy surgery is divided into two types: curative and palliative. Without the use of AEDs, the goal of curative surgery is to fully eliminate seizures and create long-term remission. When "curative" surgery is not an option, palliative surgery is considered. Resection of the epileptic zone, disconnection at the level of white fibers, and neurostimulation are the three basic techniques in epilepsy surgery.

##### Resective Surgery for Epilepsy

Anteromedial temporal lobectomy (AMTL) and its modifications are the most commonly accomplished surgeries for the management of refractory epilepsy.

In conventional resection (AMTL), the neocortical resection in the non-dominant and dominant temporal lobes is roughly 5 cm and 3.5 cm, respectively. The amygdala and the first 3 cm of the hippocampus are removed (Figure 16). A more extensive hippocampus resection was not linked to a higher risk of seizure freedom after surgery (Schramm et al. 2011). Selective amygdalohippocampectomy (SAH) was created for people with obvious hippocampal sclerosis to prevent the removal of lateral (neocortical) temporal tissue and has been demonstrated to be as effective in controlling seizures (Figure 17) (Tanriverdi et al. 2009). Yasargil advocated for a trans-sylvian route (Siegel et al. 1990), but the same surgery might be performed using an inferior temporal approach or a transcortical method through the middle temporal gyrus.

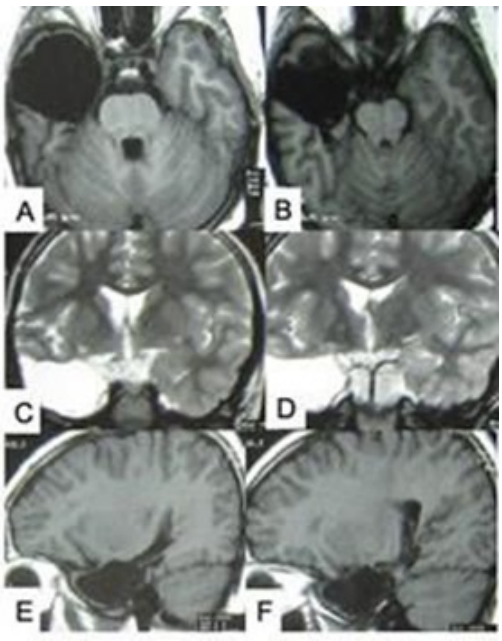


**Figure 16.** MRI of brain; (**A**,**B**) T1W axial, (**C**,**D**) T2W coronal and (**E**,**F**) T1W sagital postoperative images after right amygdalohippocampectomy plus standard anterior temporal lobectomy in a case of MTS. Source: Figure by authors.

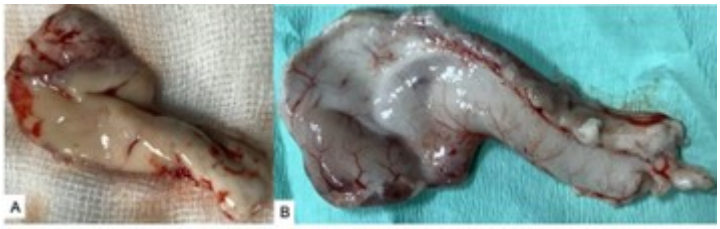


**Figure 17.** Resected specimens (**A**,**B**) of amygdala and hippocampus after selective amygdalohippocampectomy. Source: Figure by authors.

Approximately 70% of correctly selected patients achieve seizure-free status after ATL, and the majority of those who remain, benefit greatly from seizure reduction and increased quality of life (Engel 1996; Spencer et al. 1984).

When there is a well-demarcated structural lesion, such as a benign tumor, FCD (Figures 18–20), gliosis (Figures 21 and 22), or cavernous malformation, lesionectomy is a viable surgical option if seizure semiology and EEGs are in agreement. In general, removing the epileptogenic brain area completely increases the likelihood of seizure freedom. Overlap with the eloquent cortex makes adequate resection difficult. As a result, the extent of resection should be assessed against these risks and tailored to each individual instance.

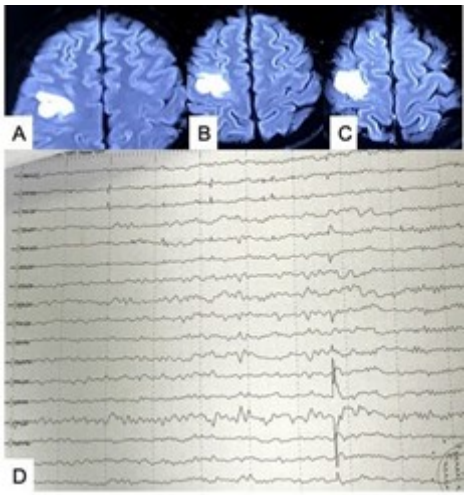


**Figure 18.** (**A**–**C**) MRI of brain axial sections showing right middle frontal gyrus FCD. (**D**) EEG showing right frontal focal discharge. Source: Figure by authors.

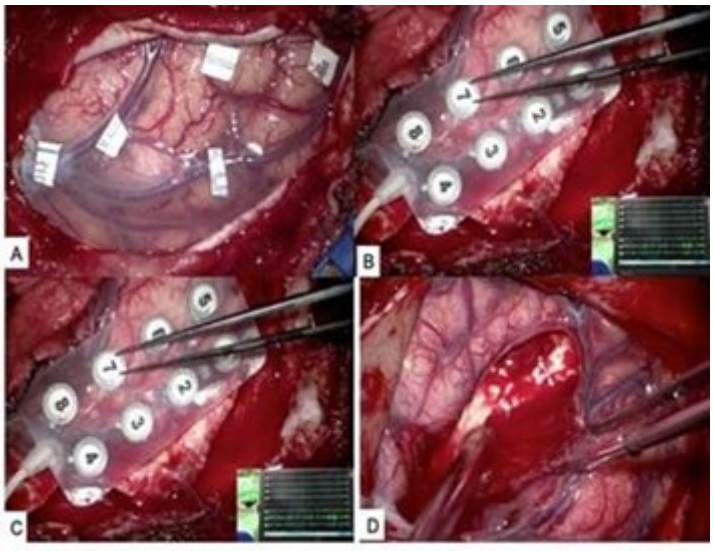


**Figure 19.** Peroperative (ECoG- and neuronavigation-guided excision) pictures: (**A**) before excision, (**B**,**C**) ECoG-guided excision, and (**D**) after excision. Source: Figure by authors.

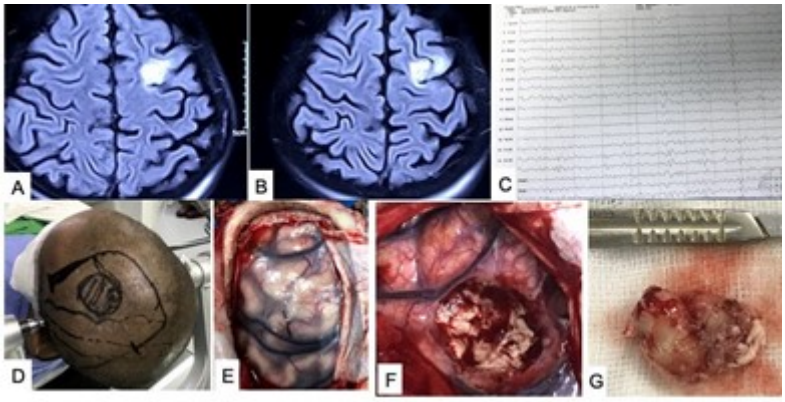


**Figure 20.** (**A**,**B**) MRI of brain axial sections showing left frontal FCD. (**C**) EEG showing abnormal electrical discharge concordant with lesion. (**D**–**F**) Peroperative pictures of focal excision of lesion. (**G**) Specimen after resection of lesion. Source: Figure by authors.

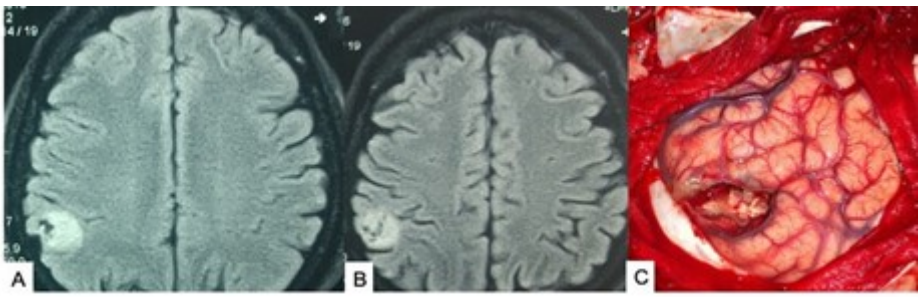


**Figure 21.** (**A**,**B**) MRI of brain showing right-sided parietal post-neurocysticercosis gliosis. (**C**) Peroperative picture of excision of lesion. Source: Figure by authors.

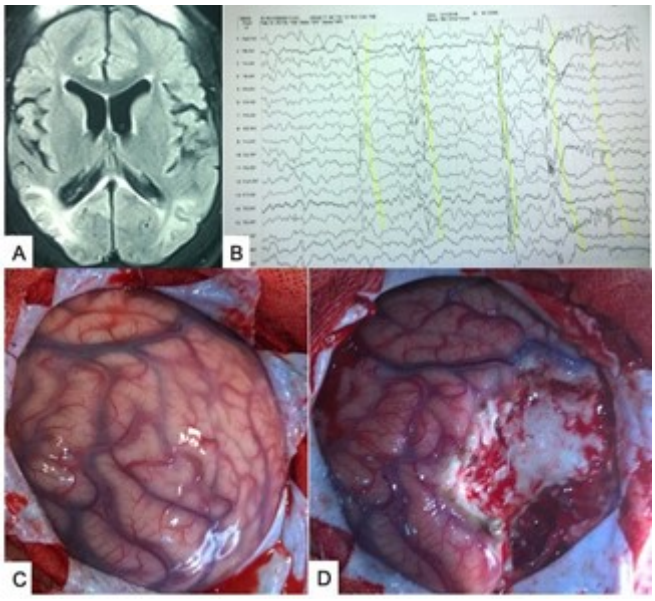


**Figure 22.** (**A**) MRI of brain axial view showing post-viral-infection occipital gliosis and atrophy (right > left) with resistance epilepsy with a history of repeated severe head injury due to falls. (**B**) EEG showing abnormal electrical discharges predominantly from the right occipital area. (**C**,**D**) Peroperative pictures of right occipital focal excision (patient was hemianopic). Surgical excision eased seizure control with drugs. Source: Figure by authors.

Removal of hemosiderin-stained tissue around the malformation is required in cavernoma. The use of intraoperative cortical mapping and intraoperative electrocorticography (ECoG) (Figure 19) (Van Gompel et al. 2009) and awake craniotomy with neuronavigation-guided (Figure 23) resection improves outcomes and reduces postoperative neurological deficits.

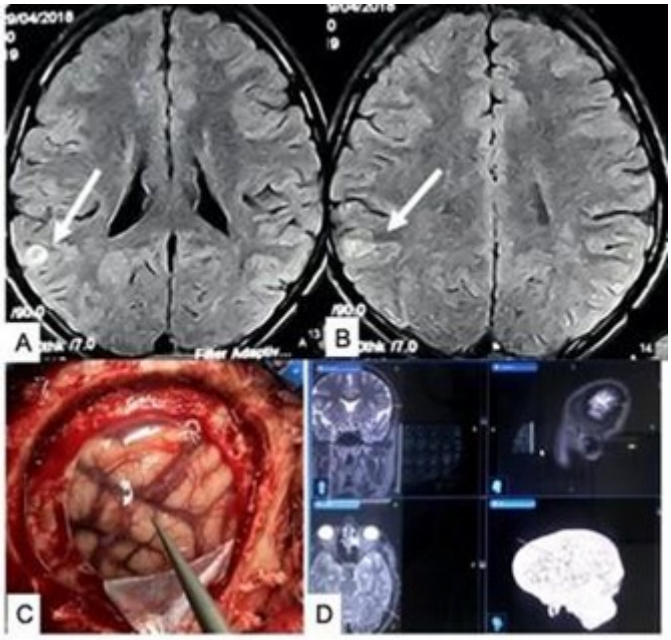


**Figure 23.** (**A**,**B**) MRI of brain axial sections showing right parietal small FCD. (**C**,**D**) Peroperative identification of lesion with neuronavigation guide. Source: Figure by authors.

After the ictal onset zone and cortical functions have been established using intracranial recordings, most typically utilizing subdural grids or SEEGs, MRI-negative epilepsy usually requires a customized resection.

While open brain resection has traditionally been the basis of surgical treatment, recent advancements have enabled less-invasive ablative treatments such as MRI-guided laser interstitial thermotherapy (LITT). Following is a brief rundown of the many technological approaches and procedures.

Recently, laser ablation under real-time MR thermographic guidance has been shown as an alternative to open resection in patients with hippocampal sclerosis (Willie et al. 2014). Its main advantages are decreased surgical morbidity and better cognitive outcomes (Drane et al. 2015). This approach can also be used for other small, deep epileptogenic lesions.

### Laser Ablation Surgery

In both extratemporal and temporal lobe epilepsy, laser ablation surgery has recently been found to be successful in both non-lesional and lesional instances. MTS, FCD, unsuccessful prior open surgery, and deeper lesions relatively inaccessible to open surgery are all examples (Gonzalez-Martinez et al. 2014).

This approach has the advantage of precisely targeting seizure-causing lesions without the need for a craniotomy, leading to less pain as well as a shorter hospital stay. The goal of an MRIgLITT (MRI-guided laser interstitial thermal therapy) system is to use interstitial irradiation or thermal therapy to necrotize soft tissues while employing MRI guidance. This method has been used to treat MTS, cavernous angioma, hypothalamic hamartoma, cortical development abnormalities, and tuberous sclerotic lesions (Gross et al. 2016). MRIgLITT can also be used to treat mesial temporal epilepsy. It has been compared to open surgery in terms of safety, accuracy, and efficacy but provides reduced morbidity (Kang et al. 2016), especially in elderly patients (Waseem et al. 2015).

### Corpus Callosotomy

Corpus callosotomy (CC) is a palliative surgical treatment that involves severance of the corpus callosum in the anterior two-thirds or its entirety. The treatment is most commonly utilized for drop attacks, with roughly three-quarters of patients benefiting and more than a third being free of drop attacks (Tanriverdi et al. 2009). Detaching the corpus callosum is thought to stop rapid bilateral seizure spread, which causes loss of consciousness or posture, and so lessens the intensity and frequency of secondary generalized seizures in people who are not surgical candidates. In seizure types that require bi-hemispheric synchrony for seizure expression, CC has the potential to eliminate clinical seizure symptoms. Patients with very refractory, generalized tonic–clonic seizures may benefit from CC in the case of IGE (Cukiert et al. 2009; Jenssen et al. 2006).

Multiple Subpial Transection Procedure

This approach, developed by Morrell in 1989, is largely used to treat refractory epilepsies in which resection is impossible due to the epileptogenic zone being close to, or overlapping, the eloquent cortex (Morrell et al. 1989). Ictal discharges frequently spread along horizontal fibers, whereas cortical activities tend to be organized vertically. Multiple vertical subpial transections are performed in 5 mm intervals of the cortex based on this principle, severing horizontal intracortical fibers but maintaining vertical connections. In an awake patient, MST on the eloquent cortex is frequently combined with the excision of neighboring nonessential cortex. Excision surgery has been found to be more successful than this method (Morrell et al. 1989).

Hemispherectomy

The most favored surgical strategy in the care of children with unilateral hemispheric epilepsy and hemisphere functions that are compromised or projected to become impaired is hemispherectomy (Figures 13 and 14) (Limbrick et al. 2009). Indications for hemispherectomy include Rasmussen syndrome, hemimegalencephaly, Sturge–Weber syndrome, infantile spasms, hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome, multilobar cortical dysplasia, and congenital hemiplegia. In anatomical hemispherectomy, the entire abnormal hemisphere is resected, giving excellent seizure freedom. But, patients develop serious late postoperative complications including superficial cerebral hemosiderosis and hydrocephalus. With subsequent modifications, anatomical hemispherectomy has been almost completely abandoned and replaced by functional hemispherectomy and hemispherotomy. Current functional hemispherectomy surgery removes the temporal and centroparietal portions of the brain, keeping the frontal and occipital poles alive but isolated from the rest of the brain. Around three-quarters of patients have total seizure control after hemispherectomy, with the majority of the remaining patients having better seizure control (Limbrick et al. 2009). Seizure independence generally improves the function of the remaining hemisphere, resulting in enhanced cognitive function and behavior during follow-up.

Non-Resective Surgical Treatments: Neurostimulation

i. Vagus Nerve Stimulation (VNS)—The US Food and Drug Administration (FDA) approved VNS for refractory focal onset epilepsies with or without secondary generalization in cases aged 4 years and up. A battery generator is inserted in the left upper chest wall and tunneled beneath the skin to the vagus nerve in the VNS system. The device is set to send electrical stimulation to the brain via the left vagus nerve. The mean seizure frequency dropped by 26% after one year, 30% after five years, and 52% after 12 years, according to a retrospective assessment assessing the efficacy of VNS in 48 patients with intractable partial epilepsy (Uthman et al. 2004).

ii. Responsive Neurostimulation (RNS)—The FDA authorized RNS in 2013 for medically resistant focal epilepsy. In reaction to ictal discharges recorded by the RNS device, it gives cortical stimuli. This programmable neurostimulator is implanted in the brain and coupled to one or two depth and/or subdural cortical strip electrodes over seizure foci. In the final months of the two-year trial, the randomized investigation of 191 patients found a progressive decrease in the frequency of debilitating seizures in the treatment group (41.5%) compared to the control group (9.4%) (Heck et al. 2014).

iii. Deep Brain Stimulation (DBS)—DBS of the anterior nucleus of the thalamus has been licensed in the European Union as an adjunctive treatment for drug-resistant focal epilepsy in adults since 2010. It is also FDA-approved. In a multicenter trial, the treatment group experienced a 29% reduction in seizures in the first month, analogous to the control group, and at least a 50% seizure decrease in 54% of patients after two years (Fisher et al. 2010).

## 6. Conclusions

Drug-resistant epilepsy has a remarkable impact on cognitive development and life quality. Many of them can be addressed successfully with surgery. In managing patients with DRE, appropriate utilization of diagnostic tools to identify a patient's suitability for surgical management as well as to determine what type of surgical technique would be safer and most useful to the particular case is critical. Both presurgical examination and surgical approaches will improve as diagnostic and treatment technologies advance.

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## References

Arzimanoglou, Alexis, Jacqueline French, Warren. T. Blume, J. Helen Cross, Jan-Peter Ernst, Martha Feucht, Pierre Genton, Renzo Guerrini, Gerhard Kluger, John M. Pellock, and et al. 2009. Lennox-Gastaut syndrome: A consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurology* 8: 82–93. [CrossRef] [PubMed]

Barkovich, A. James, Renzo Guerrini, Ruben I. Kuzniecky, Graeme D. Jackson, and William B. Dobyns. 2012. A developmental and geneticclassification for malformations of cortical development: Update 2012. *Brain* 5: 1348–69. [CrossRef]

Barth, Daniel S. 1993. The neurophysiological basis of epileptiform magnetic fields and localization of neocorticalsources. *Journal of Clinical Neurophysiology* 10: 99–107. [CrossRef] [PubMed]

Bell, Brian D., and Keith G. Davies. 1998. Anterior temporal lobectomy, hippocampal sclerosis, and memory: Recentneuropsychological findings. *Neuropsychology Review* 8: 25–41. [CrossRef]

Berkovic, Samuel F., Frederick Andermann, André Olivier, Roméo Ethier, Denis Melanson, Yvon Robitaille, Ruben Kuzniecky, Terence Peters, and William Feindel. 1991. Hippocampal sclerosis in temporal lobe epilepsy demonstrated by magnetic resonanceimaging. *Annals of Neurology* 29: 175–82. [CrossRef]

Bernasconi, Andrea, Fernando Cendes, William H. Theodore, Ravnoor S. Gill, Matthias J. Koepp, Robert Edward Hogan, Graeme D. Jackson, Paolo Federico, Angelo Labate, Anna Elisabetta Vaudano, and et al. 2019. Recommendations for the use of structural magnetic resonance imaging inthe care of patients with epilepsy: A consensus report from the International League Against Epilepsy Neuroimaging Task Force. *Epilepsia* 60: 1054–68. [CrossRef]

Binder, Jeffrey R. 2011. Functional MRI is a valid noninvasive alternative to Wada testing. *Epilepsy & Behavior* 20: 214–22. [CrossRef]

Blümcke, Ingmar, Maria Thom, Eleonora Aronica, Dawna D. Armstrong, Harry V. Vinters, Andre Palmini, Thomas S. Jacques, Giuliano Avanzini, A. James Barkovich, Giorgio Battaglia, and et al. 2011. The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 52: 158–74. [CrossRef]

Burgerman, Robert S., Michael R. Sperling, Jacqueline A. French, Andrew J. Saykin, and Michael J. O'Connor. 1995. Comparison of mesial versusneocortical onset temporal lobe seizures: Neurodiagnostic findings and surgical outcome. *Epilepsia* 36: 662–70. [CrossRef]

Camfield, Peter R. 2011. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia* 52: 3–9. [CrossRef]

Çataltepe, Oguz, and George I. Jallo. 2019. *Pediatric Epilepsy Surgery: Preoperative Assessment and Surgical Intervention*. New York: Thieme Medical Publishers.

Cataltepe, Oguz, Güzide Turanli, Dilek Yalnizoglu, Meral Topçu, and Nejat Akalan. 2005. Surgical management of temporal lobetumor-related epilepsy in children. *Journal of Neurosurgery: Pediatrics* 102: 280–87. [CrossRef] [PubMed]

Chang, Victor, Jonathan Edwards, and Oren Sagher. 2007. False Lateralization of Electrographic Onset in the Setting of CerebralAtrophy. *Journal of Clinical Neurophysiology* 24: 438–43. [CrossRef] [PubMed]

Chiapparini, L., T. Granata, L. Farina, E. Ciceri, A. Erbetta, F. Ragona, E. Freri, L. Fusco, G. Gobbi, G. Capovilla, and et al. 2003. Diagnostic imaging in 13 cases of Rasmussen's encephalitis: Can early MRI suggest thediagnosis? *Neuroradiology* 45: 171–83. [CrossRef] [PubMed]

Clusmann, Hans, Thomas Kral, Ulrike Gleissner, Robert Sassen, Horst Urbach, Ingmar Blümcke, Jacek Bogucki, and Johannes Schramm. 2004. Analysis ofdifferent types of resection for pediatric patients with temporal lobe epilepsy. *Neurosurgery* 54: 847–59. [CrossRef]

Cole, A. J., F. Andermann, L. Taylor, A. Olivier, T. Rasmussen, Y. Robitaille, and J. P. Spire. 1988. The Landau-Kleffnersyndrome of acquired epileptic aphasia: Unusual clinical outcome, surgical experience, and absence ofencephalitis. *Neurology* 38: 31–38. [CrossRef]

Cooper, Ray, A. L. Winter, H. J. Crow, and W. Grey Walter. 1965. Comparison of subcortical, cortical, and scalp activityusing chronically indwelling electrodes in man. *Electroencephalography and Clinical Neurophysiology* 18: 217–28. [CrossRef]

Cukiert, Arthur, Jose Augusto Burattini, Pedro Paulo Mariani, Cristine Mella Cukiert, Meire Argentoni-Baldochi, Carla Baise-Zung, Cássio Roberto Forster, and Valeria Antakli Mello. 2009. Outcome after extended callosal section in patients with primary idiopathic generalizedepilepsy. *Epilepsia* 50: 1377–80. [CrossRef]

Daroff, Robert B., Joseph Jankovic, John C. Mazziotta, and Scott L. Pomeroy. 2015. *Bradley's Neurology in Clinical Practice*. Amsterdam: Elsevier, p. 1571.

Downes, Michelle, Rebecca Greenaway, Maria Clark, J. Helen Cross, Nicola Jolleff, William Harkness, Marios Kaliakatsos, Stewart Boyd, Steve White, and Brian G. R. Neville. 2015. Outcome following multiple subpial transection in Landau-Kleffner syndrome andrelated regression. *Epilepsia* 56: 1760–66. [CrossRef]

Drane, Daniel L., David W. Loring, Natalie L. Voets, Michele Price, Jeffrey G. Ojemann, Jon T. Willie, Amit M. Saindane, Vaishali Phatak, Mirjana Ivanisevic, Scott Millis, and et al. 2015. Better object recognition and naming outcome with MRI-guided stereotactic laser Amygdalohippocampotomy for temporal lobe epilepsy. *Epilepsia* 56: 101–13. [CrossRef]

Duvernoy, Henri M., Françoise Cattin, and Pierre-Yves Risold. 2013. *The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI*. New York: Springer.

Ebersole, John S. 1997. Defining epileptogenic foci: Past, present, future. *Journal of clinical neurophysiology* 14: 470–83. [CrossRef]

Elwan, Sherif, Andreas Alexopoulos, Diosely C. Silveira, and Prakash Kotagal. 2018. Lateralizing and localizing value of seizure semiology:comparison with Scalp EEG, MRI and PET in patients successfully treated with respective epilepsy surgery. *Seizure* 61: 203–8. [CrossRef] [PubMed]

Engel, Jerome, Jr. 1996. Surgery for seizures. *New England Journal of Medicine* 334: 647–57. [CrossRef] [PubMed]

Englot, Dario J., and Edward F. Chang. 2014. Rates and predictors of seizure freedom in resective epilepsy surgery: Anupdate. *Neurosurgical Review* 37: 389–404. [CrossRef]

Fisher, Robert S., Helen E. Scharfman, and Marco DeCurtis. 2014. How Can We Identify Ictal and Interictal Abnormal Activity? In *Issues in Clinical Epileptology: A View from the Bench*. Edited by Helen E. Scharfman and Paul S. Buckmaster. Dordrecht: Springer, pp. 3–23. [CrossRef]

Fisher, Robert S., J. Helen Cross, Jacqueline A. French, Norimichi Higurashi, Edouard Hirsch, Floor E. Jansen, Lieven Lagae, Solomon L. Moshé, Jukka Peltola, Eliane Roulet Perez, and et al. 2017. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58: 522–30. [CrossRef]

Fisher, Robert, Vicenta Salanova, Thomas Witt, Robert Worth, Thomas Henry, Robert Gross, Kalarickal Oommen, Ivan Osorio, Jules Nazzaro, Douglas Labar, and et al. 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51: 899–908. [CrossRef] [PubMed]

Gleissner, Ulrike, Christoph Helmstaedter, Johannes Schramm, and Christian E. Elger. 2004. Memory outcome after selectiveamygdalohippocampectomy in patients with temporal lobe epilepsy: One-year follow-up. *Epilepsia* 45: 960–62. [CrossRef]

Gonzalez-Martinez, Jorge, Sumeet Vadera, Jeffrey Mullin, Rei Enatsu, Andreas V. Alexopoulos, Ravish Patwardhan, William Bingaman, and Imad Najm. 2014. Robot-Assisted Stereotactic Laser Ablation in Medically Intractable Epilepsy: Operative Technique. *Neurosurgery* 10: 167–72. [CrossRef]

Gross, Robert E., Jon T. Willie, and Daniel L. Drane. 2016. The Role of Stereotactic Laser Amygdalohippocampotomy in Mesial Temporal Lobe Epilepsy. *Neurosurgery Clinics of North America* 27: 37–50. [CrossRef]

Grote, Christopher L., Patricia Van Slyke, and Jo-Ann B. Hoeppner. 1999. Language outcome following multiple subpial transections forLandau-Kleffner syndrome. *Brain* 3: 561–66. [CrossRef]

Harvey, A. Simon, and Jeremy L. Freeman. 2007. Epilepsy in hypothalamic hamartoma: Clinical features. *Seminars in Pediatric Neurology* 14: 60–64. [CrossRef]

Heck, Christianne N., David King-Stephens, Andrew D. Massey, Dileep R. Nair, Barbara C. Jobst, Gregory L. Barkley, Vicenta Salanova, Andrew J. Cole, Michael C. Smith, Ryder P. Gwinn, and et al. 2014. Two-year seizure reduction in adults with medically intractable partialonsetepilepsy treated with responsive neurostimulation: Final results of the RNS System Pivotal trial. *Epilepsia* 55: 432–41. [CrossRef] [PubMed]

Ikeda, Kristin M., and Seyed M. Mirsattari. 2017. Evolution of epilepsy in hemimegalencephaly from infancy to adulthood: Case report and review of the literature. *Epilepsy & Behavior Case Reports* 7: 47–48. [CrossRef]

ILAE. n.d. *EpilepsyDiagnosis.org*. Available online: https://www.epilepsydiagnosis.org/ (accessed on 31 July 2021).

Irwin, Kate, Victoria Birch, Janet Lees, Charles Polkey, Gonzalo Alarcon, Colin Binnie, Martin Smedley, Gillian Baird, and Richard O. Robinson. 2001. Multiplesubpial transection in Landau-Kleffner syndrome. *Developmental Medicine and Child Neurology* 43: 248–52. [CrossRef] [PubMed]

Jamuar, Saumya S., and Christopher A. Walsh. 2015. Genomic variants and variations in malformations of cortical development. *Pediatric Clinics of North America* 13: 571–85. [CrossRef] [PubMed]

Jayakar, Prasanna, Jean Gotman, A. Simon Harvey, André Palmini, Laura Tassi, Donald Schomer, Francois Dubeau, Fabrice Bartolomei, Alice Yu, Pavel Kršek, and et al. 2016. Diagnostic utility of invasive EEG for epilepsy surgery: Indications, modalities, and techniques. *Epilepsia* 57: 1735–47. [CrossRef]

Jenssen, Sigmund, Michael R. Sperling, Joseph I. Tracy, Maromi Nei, Liporace Joyce, Glosser David, and Michael O'Connor. 2006. Corpus callosotomy inrefractory idiopathic generalized epilepsy. *Seizure* 15: 621–29. [CrossRef]

Kabat, Joanna, and Przemysław Król. 2012. Focal Cortical Dysplasia—Review. *Polish journal of radiology* 77: 35–43. [CrossRef]

Kalilani, Linda, Xuezheng Sun, Barbara Pelgrims, Matthias Noack-Rink, and Vicente Villanueva. 2018. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. *Epilepsia* 59: 2179–93. [CrossRef]

Kang, Joon Y., Chengyuan Wu, Joseph Tracy, Matthew Lorenzo, James Evans, Maromi Nei, Christopher Skidmore, Scott Mintzer, Ashwini D. Sharan, and Michael R. Sperling. 2016. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia* 57: 325–34. [CrossRef]

Kessels, Roy PC, Marc PH Hendriks, Jacob Schouten, Marieke Van Asselen, and Albert Postma. 2004. Spatial memory deficits in patientsafter unilateral selective amygdalohippocampectomy. *Journal of the International Neuropsychological Society* 10: 907–12. [CrossRef]

Ko, Tae-Sung, and Gregory L. Holmes. 1999. EEG and clinical predictors of medically intractable childhood epilepsy. *Clinical Neurophysiology* 110: 1245–51. [CrossRef] [PubMed]

Kwan, Patrick, Alexis Arzimanoglou, Anne T. Berg, Martin J. Brodie, W. Allen Hauser, Gary Mathern, Solomon L. Moshé, Emilio Perucca, Samuel Wiebe, and Jacqueline French. 2010. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force ofthe ILAE Commission on Therapeutic Strategies. *Epilepsia* 51: 1069–77. [CrossRef]

Kwan, Patrick, and Martin J. Brodie. 2000. Early identification of refractory epilepsy. *New England Journal of Medicine* 342: 314–19. [CrossRef] [PubMed]

Limbrick, David D., Prithvi Narayan, Alexander K. Powers, Jeffrey G. Ojemann, Tae Sung Park, Mary Bertrand, and Matthew D. Smyth. 2009. Hemispherot-omy: Efficacy and analysis of seizure recurrence. *Journal of Neurosurgery: Pediatrics* 4: 323–32. [CrossRef] [PubMed]

Little, Andrew S., Kris A. Smith, Kristin Kirlin, Leslie C. Baxter, Steve Chung, Rama Maganti, and David M. Treiman. 2009. Modifications to thesubtemporal selective amygdalohippocampectomy using a minimal-access technique: Seizure and neuropsychological outcomes. *Journal of Neurosurgery* 111: 1263–74. [CrossRef]

Loddenkemper, Tobias, Harold H. Morris, and Gabriel Möddel. 2008. Complications during the Wada test. *Epilepsy & Behavior* 13: 551–53. [CrossRef]

Longaretti, Francesca, Colin Dunkley, Sophia Varadkar, Faraneh Vargha-Khadem, Stewart G. Boyd, and J. Helen Cross. 2012. Evolution of the EEG inchildren with Rasmussen's syndrome. *Epilepsia* 53: 1539–45. [CrossRef]

Luyken, Cordelia, Ingmar Blümcke, Rolf Fimmers, Horst Urbach, Christian E. Elger, Otmar D. Wiestler, and Johannes Schramm. 2003. The spectrum oflong-term epilepsy-associated tumors: Long-term seizure and tumor outcome and neurosurgicalaspects. *Epilepsia* 44: 822–30. [CrossRef] [PubMed]

Mikuni, Nobuhiro, Akio Ikeda, Jun A. Takahashi, Kazuhiko Nozaki, Susumu Miyamoto, Waro Taki, and Nobuo Hashimoto. 2006. A step-by-stepresection guided by electrocorticography for nonmalignant brain tumors associated with long-termintractable epilepsy. *Epilepsy & Behavior* 8: 560–64. [CrossRef]

Morrell, Frank, Walter W. Whisler, and Thomas P. Bleck. 1989. Multiple subpial transection: A new approach to thesurgical treatment of focal epilepsy. *Journal of neurosurgery* 70: 231–39. [CrossRef]

Morrell, Frank, Walter W. Whisler, Michael C. Smith, Thomas J. Hoeppner, Leyla de Toledo-Morrell, Serge J. C. Pierre-Louis, Andres M. Kanner, Janice M. Buclow, Ruzica Ristanovic, Donna Bergen, and et al. 1995. Landau-Kleffner syndrome. Treatment with subpialintracortical transection. *Brain* 118: 1529–46. [CrossRef] [PubMed]

Nass, Ruth, Linda Heier, and Russell Walker. 1993. Landau Kleffner Syndrome: Temporal lobe tumor resection results in goodoutcome. *Pediatric Neurology* 9: 303–5. [CrossRef] [PubMed]

O'Brien, Terence J., Christine Kilpatrick, Vanessa Murrie, Simon Vogrin, Kevin Morris, and Mark J. Cook. 1996. Temporal lobe epilepsy caused bymesial temporal sclerosis and temporal neocortical lesions. A clinical and electroencephalographicstudy of 46 pathologically proven cases. *Brain* 119: 2133–41. [CrossRef]

Olivier, André, Warren W. Boling, and Taner Tanriverdi. 2012. *Techniques in Epilepsy Surgery: The MNI Approach*. New York: Cambridge University Press.

Rosenfeld, Jeffrey V., Jeremy L. Freeman, and A. Simon Harvey. 2004. Operative technique: The anterior transcallosal transseptal inter forniceal approach to the third ventricle andresection of hypothalamic hamartomas. *Journal of Clinical Neuroscience* 11: 738–44. [CrossRef] [PubMed]

Rosenow, Felix, and Hans Luders. 2001. Presurgical evaluation of Epilepsy. *Brain* 124: 1683–700. [CrossRef]

Saleem, Sahar N., Ahmed-Hesham M. Said, and Donald H. Lee. 2007. Lesions of the hypothalamus: MR imaging diagnostic features. *Radiographics* 27: 1087–108. [CrossRef]

Salinsky, Martin, Roy Kanter, and Richard M. Dasheiff. 1987. Effectiveness of multiple EEGs in supporting the diagnosis ofepilepsy: An operational curve. *Epilepsia* 28: 331–34. [CrossRef]

Schramm, Johannes, T. N. Lehmann, J. Zentner, C. A. Mueller, J. Scorzin, R. Fimmers, H. J. Meencke, A. Schulze-Bonhage, and C. E. Elger. 2011. Randomized controlled trial of 2.5-cm versus 3.5-cm mesial temporal resection intemporal lobe epilepsy—Part 1: Intent-to-treat analysis. *Acta Neurochirurgica* 153: 209–19. [CrossRef]

Siegel, Adrian M., Heinz G. Wieser, Werner Wichmann, and Gazi M. Yasargil. 1990. Relationships between MR-imaged total amountof tissue removed, resection scores of specific mediobasal limbic subcompartments and clinicaloutcome following selective amygdalohippocampectomy. *Epilepsy Research* 6: 56–65. [CrossRef]

So, Elson L., and Philippe Ryvlin. 2018. *MRI Negative Epilepsy: Evaluation and Surgical Management*. Cambridge: Cambridge University Press.

So, Norman, and Pierre Gloor. 1991. Electroencephalographic and electrocorticographic findings in chronic encephalitis of the Rasmussen type. In *Chronic Encephalitis and Epilepsy: Rasmussen's Syndrome*. Edited by Frederick Andermann. Boston: Butterworth-Heinemann, pp. 37–45.

So, Norman, Pierre Gloor, L. Felipe Quesney, Marilyn Jones-Gotman, André Olivier, and Frederick Andermann. 1989. Depth electrode investigationsin patients with bitemporal epileptiform abnormalities. *Annals of Neurology* 25: 423–31. [CrossRef]

Spencer, Dennis D., Susan S. Spencer, Richard H. Mattson, Peter D. Williamson, and Robert A. Novelly. 1984. Access to the posterior medialtemporal lobe structure in surgical treatment of temporal lobe epilepsy. *Neurosurgery* 15: 667–71. [CrossRef] [PubMed]

Tanriverdi, Taner, André Olivier, Nicole Poulin, Frederick Andermann, and François Dubeau. 2009. Long-term seizure outcome after corpuscallosotomy: A retrospective analysis of 95 patients. *Journal of Neurosurgery* 110: 332–42. [CrossRef] [PubMed]

Tassi, Laura, Alessandra Meroni, Francesco Deleo, Flavio Villani, Roberto Mai, Giorgio Lo Russo, Nadia Colombo, Giuliano Avanzini, Chiara Falcone, Manuela Bramerio, and et al. 2009. Temporal lobe epilepsy: Neuropathological and clinical correlations in 243 surgicallytreated patients. *Epileptic Disorders* 11: 281–92. [CrossRef] [PubMed]

Téllez-Zenteno, Jose F., and Lizbeth Hernández-Ronquillo. 2012. A Review of the Epidemiology of Temporal Lobe Epilepsy. *Epilepsy Research and Treatment* 2012: 630853. [CrossRef]

Terra-Bustamante, Vera C., Hélio R. Machado, and Américo C. Sakamoto. 2006. Hemimegalencephaly and epilepsy:an overview. *Journal of Epilepsy and Clinical Neurophysiology* 12: 99–105. [CrossRef]

Uthman, B. M., A. M. Reichl, J. C. Dean, S. Eisenschenk, R. Gilmore, S. Reid, S. N. Roper, and B. J. Wilder. 2004. Effectiveness of vagus nerve stimulation in epilepsy patients: A 12-year observation. *Neurology* 63: 1124–26. [CrossRef]

van Breemen, Melanie S. M., Erik B. Wilms, and Charles J. Vecht. 2007. Epilepsy in patients with brain tumours: Epidemiology, mechanisms, and management. *The Lancet Neurology* 6: 421–30. [CrossRef]

Van Gompel, Jamie J., Jesus Rubio, Gregory D. Cascino, Gregory A. Worrell, and Fredric B. Meyer. 2009. Electrocorticography-guided resectionof temporal cavernoma: Is electrocorticography warranted and does it alter the surgical approach? *Journal of Neurosurgery* 110: 1179–85. [CrossRef]

Varadkar, Sophia, Christian G. Bien, Carol A. Kruse, Frances E. Jensen, Jan Bauer, Carlos A. Pardo, Angela Vincent, Gary W. Mathern, and J. Helen Cross. 2014. Rasmussen's encephalitis: Clinical features, pathobiology, and treatment advance. *The Lancet Neurology* 13: 195–205. [CrossRef]

Vaughan, Kerry A., Christian Lopez Ramos, Vivek P. Buch, Rania A. Mekary, Julia R. Amundson, Meghal Shah, Abbas Rattani, Michael C. Dewan, and Kee B. Park. 2019. An estimation of global volume of surgically treatable epilepsy based on a systematic review and meta-analysis of epilepsy. *Journal of Neurosurgery* 130: 1127–41. [CrossRef]

Wang, Wei, Weimin Wang, Xiaofei Guo, Yanjun Zeng, and Xiaodan Jiang. 2009. Hypothalamic hamartoma causing gelastic seizures treated with stereotactic rad iofrequency thermocoagulation. *Epileptic Disorders* 11: 333–38. [CrossRef] [PubMed]

Waseem, Hena, Katie E. Osborn, Mike R. Schoenberg, Valerie Kelley, Ali Bozorg, Daniel Cabello, Selim R. Benbadis, and Fernando L. Vale. 2015. Laser ablation therapy: An alternative treatment for medically resistant mesial temporal lobe epilepsy after age 50. *Epilepsy & Behavior* 51: 152–57. [CrossRef]

Willie, Jon T., Nealen G. Laxpati, Daniel L. Drane, Ashok Gowda, Christina Appin, Chunhai Hao, Daniel J. Brat, Sandra L. Helmers, Amit Saindane, Sherif G. Nour, and et al. 2014. Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Neurosurgery* 74: 569–84. [CrossRef] [PubMed]

Wyllie, Elaine, Youssef G. Comair, Prakash Kotagal, Juan Bulacio, William Bingaman, and Paul Ruggieri. 1998. Seizure outcome after epilepsy surgery in children and adolescents. *Annals of Neurology* 44: 740–48. [CrossRef]

Yamazaki, Etsuko, Yukitoshi Takahashi, Noriyuki Akasaka, Tateki Fujiwara, and Yushi Inoue. 2011. Temporal changes in brain MRI findings in Rasmussen syndrome. *Epileptic Disorders* 13: 229–39. [CrossRef]

Yasargil, M. G., P. J. Teddy, and P. Roth. 1985. Selective amygdalo-hippocampectomy: Operative anatomy and surgical technique. In *Advances and Technical Standards in Neurosurgery*. Edited by L. Symon. New York: Springler-Wien.