

Surgical Treatment of Epilepsy

Updated: April 25, 2010

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

DEFINITIONS

Epileptogenic lesion – lesion able to *produce seizures*; needs to be included in resection.

Epileptogenic zone – cortical area that *needs to be resected* (in order to make patient seizure free); may be *larger than lesion* (includes lesion and surrounding margin) - epileptogenic zone may be larger than lesions visible on MRI (H: **intracranial EEG**).

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

***irritative spikes** cease after surgical resection of epileptogenic zone!

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

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

INDICATION

- **seizures refractory to appropriate medical management** + seizures seriously **limit** patient's **activities*** + **well-defined** epileptogenic **focus** not involving eloquent cortex**.

*homebound patients who are not physically harmed by their seizures are not considered for surgical intervention.

**cortical resection must not intentionally produce significant neurologic deficit such as aphasia or hemiparesis.

Medical intractability - seizures that are not controlled after adequate trial with 2-3 first-line* AEDs.
*carbamazepine, valproate, phenytoin

- some advocate at least 3 regimens, including *2 trials of high-dose monotherapy + 1 trial of 2-drug therapy*.
- if *3 trials of monotherapy with first-line drugs* are not successful, chance to respond to fourth drug as monotherapy or polytherapy is only 5%.
- these therapeutic trials can be accomplished within *1-2 years*.
- patients' **quality of life** must be included (e.g. even as few as 2-3 seizures year may be disabling to individual whose occupation requires transportation with motor vehicle).

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

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

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

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

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

CONTRAINDICATIONS

- 1) generalized epilepsy (indication for corpus callosotomy)
- 2) benign partial childhood epilepsy
- 3) significant noncompliance
- 4) progressive neurologic diseases
- 5) severe concurrent medical illness

Relative contraindications:

- 1) mental retardation / low IQ (< 70)
- 2) psychiatric disease (psychosis or other serious psychiatric disorder)
- 3) multiple seizure types arising from different brain regions (unless one seizure type is most frequent and disabling)
- 4) coexistence of epileptic and nonepileptic seizures.
- 5) age > 50 yrs.

Not contraindications:

- 1) epileptogenic focus in *dominant hemisphere*
- 2) *bilateral* or *multifocal* epileptogenic foci (surgery is rarely considered for seizures arising from > 1 epileptogenic focus)
- 3) *neurological deficits* on examination

PRESURGICAL EVALUATION

- goal is to define **epileptogenic zone**.

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

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

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

EEG

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

Surface EEG

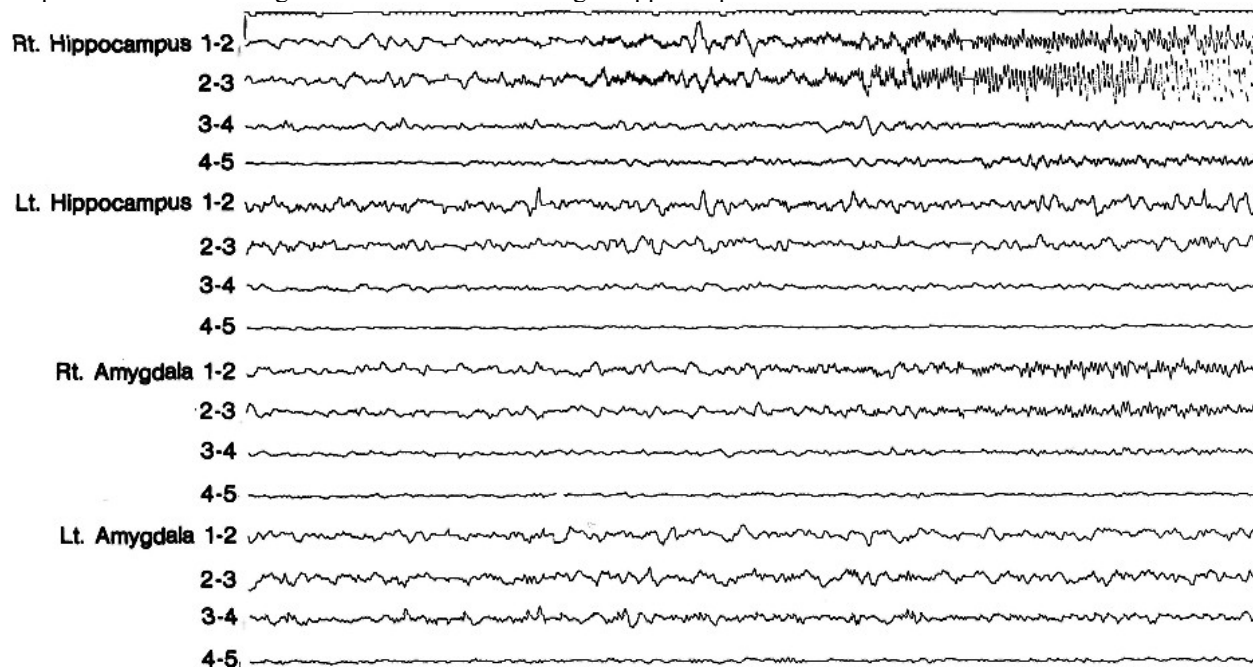
N.B. *seizures* may begin in areas distant from (or even contralateral to) location of *interictal* epileptiform activity - *ictal discharges* are most reliable means of localization!

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

Intracranial EEG - only when noninvasive studies fail to adequately delineate epileptogenic zone.

1. **Subdural electrodes** - embedded in thin Silastic plates arranged in STRIPS or GRIDS (strip electrodes and grid electrodes differ only in shape); see p. E13 >>
 - placed through burr holes (strips) or craniotomy (grids).
 - contact **cortical surface** directly.
 - some surgeons implant in *epidural space* (esp. in patient with prior craniotomy - scarring may obliterate subdural space).
 - allows recording of multiple regions and cortical mapping.
 - cortical gyri within depth of sulcus are not sampled adequately!
 2. **Depth electrodes** - multiple-contact wires placed stereotactically; see p. E13 >>
 - sample **deep structures** (such as hippocampus and amygdala).
 - primary indication – to record from hippocampus (esp. bitemporal abnormalities on surface EEG / MRI).
 - electrodes may be implanted:
 - a) orthogonal to temporal lobe (sample temporal lobe from medial to lateral).
 - b) along AP axis of hippocampus (most anterior contact in amygdala, most posterior - in posterior temporo-occipital lobe).
 - technically also feasible for other deep lesions (e.g. hypothalamic hamartoma, periventricular heterotopia, cortical dysplasia).
- *sensitive*, but provides **limited view** (records only from electrode area) – prior noninvasive studies must provide enough information to ensure appropriate electrode placement.
N.B. intracranial EEG is most helpful when hypothesis about location of epileptogenic zone is clearly defined on basis of noninvasive data!
 - with advent of newer imaging techniques, only 10-20% surgical candidates require invasive EEG (vs. 50-60% 10 years ago).
cortical resections based on invasive EEG data without MRI abnormality → seizure-free outcome in only 20% patients
 - indications for intracranial EEG:
 1. **Discordant** EEG localization and MRI findings!!!
 2. Epileptogenic zone in or near **eloquent cortex** – indication for cortical mapping (intraoperative or preoperative).
 3. Localization to particular lobe when **imaging has no abnormalities**
 4. **Temporal lobe seizures**:
 - a) bilaterally independent
 - b) with normal MRI and FDG-PET findings
 - c) to distinguish neocortical from medial TLE
 - d) extratemporal lobe-onset seizures with rapid propagation to medial temporal lobe
 - *no established number of seizures* must be recorded – rely on clinical judgment.
 - due to potential for infection, duration of recording period is limited to 7-10 days (rarely, up to 2 weeks).
 - most important are **ictal data** (esp. during **ictal onset**); seizures within seconds to minutes after another seizure are disregarded as potentially misleading.
 - three most common patterns that signal seizure onset:
 - (1) voltage **attenuation**
 - (2) **high-frequency** rhythmic activity
 - (3) **high-amplitude** spike and wave (or sharp and slow-wave) discharge followed by attenuation or high-frequency rhythmic discharges.
 - discharge confined to 1-2 contacts suggests focal onset precisely localizing origin of seizure; vs. involvement of multiple contacts indicates regional onset (secondary activation of recording sites).

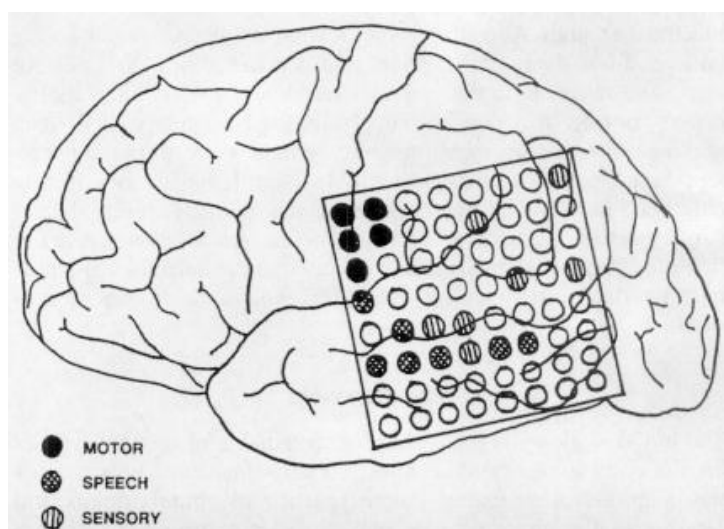
Depth electrode recording of focal seizure onset in right hippocampus:



Stimulation Cortical Mapping

- determines **areas of eloquent cortex** that should not be encroached upon at time of operation. see p. E13 >>

- technique requires **testing protocol** (appropriate to cortical region investigated) and **neuropsychologist trained** in cortical testing.
- implanted **grid electrode** is used.
- if surgeon is willing to operate on awake patients, mapping and resection can take place during same craniotomy (**movable dipole electrode** is used on exposed cortex).



- **BIPOLAR METHOD** - current passes between two electrodes and stimulates cortex. see p. E13 >>
- **motor responses** are contractions of muscle groups, and **sensory responses** are perceived as tingling, vibration, light flashes, buzzing or ringing.
- at the same time stimulated cortex is so completely occupied with electrical intrusion that it is not available for normal function ("**BUSY LINE EFFECT**"):
 - if patient attempts to use extremity involved in motor stimulation sequence, patient will be unable to do so.
 - functional speech areas are inactivated; e.g.:
 - if current blocks language* (positive result) - underlying cortex is eloquent for language and spared at time of resection;
 - if language is not blocked* (negative result) → current strength is progressively increased to, if possible, threshold for afterdischarges.
- stimulation of **association areas** does not produce activated response; in epileptogenic zones, however, stimulation may activate circuits habituated by epileptic discharge (responses may be of perceptual illusions, "déjà vu", memory of previous events).
- when performing **depth electrode** stimulation:
 - **threshold** is established **for after-discharge** (highest threshold is found at site of major pathology).
 - attempt is made to **reproduce** component of patient's typical **seizure** (typical seizure may be produced in many patients).

NEUROIMAGING

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

All patients with partial epilepsy should undergo **MRI**.

FDG-PET - determines **functional deficit zone** in some patients with partial epilepsy.

- **not necessary** in most surgical workups, because PET:
 - has highest accuracy for temporal lobe foci, which are diagnosed most easily with MRI and EEG.
 - is least reliable for extratemporal nonlesional foci, which also are most difficult to define with MRI and standard EEG.
- **indications:**
 - a) discordant MRI and EEG findings
 - b) normal MRI findings.

Interictal SPECT - resolution is inferior to that of PET.

Ictal SPECT - high localizing value* (only if ictal injection occurs within 20 seconds of ictal onset).

* accuracy is not sufficient to justify routine use

Subtraction SPECT co-registered to MRI

- much higher accuracy than either ictal or interictal SPECT! (may provide alternative to depth electrode studies)

- requires two scans (separated by ≥ 48 h to accommodate radionuclide washout) - during **interictal** period and **within seconds of seizure onset**.
- using computer software, these scans are subtracted from each other.
- subtracted scan then can be co-registered onto MRI to provide support for focus location.

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

Magnetoencephalography is emerging method for 3D detection of deep epileptic foci.

Intracarotid Amobarbital (Wada) test

- injection of 100-150 mg SODIUM AMOBARBITAL into carotid artery - to temporarily anesthetize (inactivate) hemisphere in ipsilateral carotid artery distribution (includes amygdala and anterior hippocampus) - allows independent **testing function of contralateral hemisphere**.

Clinical uses (once epileptogenic focus has been identified):

1. Determining which hemisphere contains **LANGUAGE function** (dominant hemisphere inactivation → aphasia; nondominant → dysarthria).
 2. Injection ipsilateral to epileptogenic zone assesses functional adequacy of contralateral hippocampus to **sustain MEMORY** (before anterior temporal lobectomy to avoid permanent amnesia).
 - N.B. failure of memory function is contraindication to resection of hippocampus and parahippocampal structures on injected side!
 3. Prognosing **seizure-free OUTCOME**.
- catheter is passed from femoral artery (as for standard carotid arteriograms).
 - **arteriography** must verify that blood flows to corresponding hemisphere (not to brainstem or contralateral side).
 - **contralateral hemiparesis** and **ipsilateral EEG slowing** must appear (confirm adequacy of injection).
 - patient is monitored to make certain that **recirculation** has not affected both sides simultaneously during testing.
 - never has been standardized, but many centers insist on Wada tests even when clearly right-handed patient is diagnosed with right temporal focus.
 - possible future alternatives to Wada test – fMRI, magnetoencephalography, $H_2^{15}O$ -PET.

NEUROPSYCHOLOGICAL TESTING

- routinely, **all surgical candidates** undergo extensive neuropsychological testing.
- testing is not standardized between centers.
- test battery contains:
 - 1) **personality** inventory (e.g. Minnesota Multiphasic Personality Inventory)
 - 2) tests of **memory** and **language**

- 3) tests for **interhemispheric transfer** (before callosotomy) - cross-retrieval and naming of objects, cross-replication of hand postures, cross-localization of fingertips.
 - 4) other tests, depending upon interests of neuropsychologist.
- goals of testing:
 - 1) to help **localize epileptogenic focus** (subtle deficits in cognitive functioning might provide additional localization that neurologic examination misses); it is not reliable because very few tests reliably measure frontal and temporal lobe function.
 - 2) identification of **significant memory problems** (might not be candidate for temporal lobectomy).
 - 3) formulating **postoperative vocational goals**.

PREOPERATIVELY

- **VALPROATE** can cause **bleeding disorders** - discontinue at least 3 weeks prior to surgery (replace with another medication).
- on surgery morning, patient receives usual medication dosage with few sips of water.
- 1 g **cephalosporin** can be administered intravenously 1 hour before incision; no further antibiotics are administered.
- 10 mg **DEXAMETHASONE** IV 1 hour before surgery (pediatric dose is adjusted appropriately); continued postoperatively at 4 mg q6h for first 48-72 hours, then convert to Medrol Dosepak.

TYPES OF SURGERY

ABLATIVE PROCEDURES (curative) - resection of seizure focus (up to entire hemisphere).

- mortality for ablative surgery varies 0-1.7%.

DISCONNECTION PROCEDURES (palliative) - disconnection of seizure focus from other functional parts of brain.

SPENCER Anteromedial Temporal Lobectomy (AMTL)

- **superior temporal gyrus** is spared.
 - **middle** and **inferior temporal gyrus** are resected 4-5 cm from tip of nondominant side and 3-4 cm of dominant side.
 - **amygdala** is resected totally; **hippocampus** is resected to level of colliculus.
- psychiatric effects of temporal lobectomy → see p. Psy5 >>

Standard en bloc Anterior Temporal Lobectomy (ATL)

- as AMTL + **superior temporal gyrus** is also resected 2 cm from temporal tip. see p. E15 >>

Amygdalo-Hippocampectomy

- spares **lateral temporal neocortex**.

Lesionectomy (focal cortical resection)

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

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

Tailored Neocortical Resection

- for **nonlesional extratemporal epilepsy** - resection guided by intraoperative **electrocorticography** (under local anesthesia).

Tailored - no two operations are identical!

- epileptiform discharges recorded acutely during surgery define boundaries of cortical resection.
- **eloquent cortical regions** are spared.

Multiple Subpial Transections (MST)

- indicated if **epileptogenic zone involves eloquent cortex!**

- nonresective surgical technique - **horizontal association fibers** (important for intracortical seizure propagation) are interrupted at 5-mm intervals; **vertically oriented projection fibers** (important for function) and pial nutrient vessels remain intact - ideal for treating epileptogenesis while preserving intrinsic cortical function! see p. E17 >>
- **special indication** - **Landau-Kleffner syndrome**.

Functional Hemispherectomy

- combination of ablation and disconnection: see p. E19 >>

- 1) removal of **sensorimotor cortex** and **temporal lobe**.
 - 2) **frontal lobe** and **parieto-occipital lobes** are left intact but are disconnected from cortical and subcortical structures (interhemispheric commissures are divided).
- **indication** - severely incapacitating unilateral seizures (when foci cannot be isolated) associated with permanent hemiplegia (with useless hand), hemisensory loss, hemianopia, hemiatrophy; i.e. intractable partial and secondarily generalized seizures when entire hemisphere is considered epileptogenic with **little or no remaining functional cortex**.
 - **special indications** - infantile hemiplegia syndromes, Rasmussen's encephalitis, Sturge-Weber syndrome, hemimegalencephaly, large hemispheric infarctions.
 - results in seizure control are comparable to anatomic hemispherectomy.
 - function also improves (seizures may have caused functional impairment).

Anatomical hemispherectomy (entire hemisphere, excluding **basal ganglia**, anatomically removed from cranium) → potentially lethal hydrocephalus and progressive cerebral hemosiderosis.

see p. E19 >>

Corpus Callosotomy

- only applicable surgery for **GENERALIZED seizures!**

- resects **anterior 2/3** of corpus callosum. see p. E21 >>
- sometimes, **complete** callosotomy is performed at second stage (↑risk of disconnection syndrome)

Callosotomy performed in two stages (anterior-posterior) avoids acute prolonged apathy and confusion seen after complete division in single stage.

- **no clearly defined indications** - medically refractory primarily and secondarily **GENERALIZED seizures** (esp. Lennox-Gastaut syndrome).
- **atonic seizures (drop attacks)*** are helped most significantly, but having atonic seizures does not guarantee benefit from surgery (seizures still occur as partial seizures, but they do not result in falls). *frequent facial and neck injuries due to fall
- **complex partial seizures** can be reduced in $\approx 50\%$ patients, but exacerbated in $\approx 25\%$.
- **mentally handicapped patients** fare less favorably.
- **aim is to REDUCE SEIZURE FREQUENCY** (vs. resective surgery – to achieve SEIZURE-FREE OUTCOME); additional goals of social or vocational rehabilitation are not realistic expectations.
N.B. callosotomy disrupts EEG bilateral synchrony but does not eliminate epileptiform discharges!
- **preoperative tests** must include:
 - 1) **tests for interhemispheric transfer** (incl. cross-retrieval and naming of objects, cross-replication of hand postures, cross-localization of fingertips); routine extensive neuropsychological testing is not required.
 - 2) **Wada testing** - if **mixed cerebral dominance** for handedness and language exists (e.g. right-handed person with right-hemisphere language dominance) - risk for *postcallosotomy language impairments*.
 - 3) selective **visual field testing**.
 - 4) coronal **MRI** – may find *singular (s. simian) pericallosal artery*.
- rarely performed today (replaced by **vagus nerve stimulation**).

Multilobar Resection

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

Vagus Nerve Stimulation

- palliative intermittent electrical stimulation with chest-implanted pacemaker-like device.
- primary **indication** - **partial-onset** epilepsy in adults (even with anatomically defined single foci); mounting evidence suggests effectiveness in **generalized** epilepsy.
- used as adjunct to anticonvulsant.
- vast majority of vagal fibers are afferent - project to many structures in brain (incl. hippocampus, amygdala, thalamus).
- stimulation of either vagus nerve is effective, but **left nerve is always chosen** (less likely to cause cardiac effects), usually **left cervical vagus nerve**.
- after device is programmed, patients can activate it with magnet when they sense seizure is imminent.
- **side effect** – **hoarseness, cough** during stimulation.
- **results:**
 - 30-50% reduction in seizure frequency.
 - only 1% patients become seizure free.
 - long-term stimulation (> 6 months) → greater rather than lesser effect.

POSTOPERATIVELY

- patient is moved to **overnight ICU** (unless he can be returned to seizure monitoring room in epilepsy unit).
- night of surgery, patient **sits at bedside** and **deep breathes** for pulmonary toilet; should fever occur, incentive spirometer is used.
- Foley catheter and arterial line are removed ASAP (usually before leaving recovery room).
- moved to **surgical floor** next morning.
- IV drip is converted to heparin lock as soon as patient is taking oral fluids.
- **ambulation** is encouraged, as is **sitting in chair**.
- **discharged** on 3rd postoperative day.

AED THERAPY

- patients generally need to **remain on AED therapy (for ≈ 2 years)**; some continue to require AED therapy to remain seizure free.
- if patient is taking 2 AEDs, least effective drug is tapered after 1 year.
- if patient is seizure free at 2 years, remaining drug can be tapered.
- one seizure during or after withdrawal → resume single medication therapy.
- **postoperative seizures:**
 - seizures **within first 24 hours** do not correlate with poor long-term seizure outcome - may be due to irritation and edema of tissues adjacent to resection (neighborhood seizures).
 - seizures **after 48 hours** (with adequate serum AED levels) do not bode well for eventual outcome.

N.B. many patients may continue to have **components of preoperative auras**; some may have **occasional seizures for few years** which then cease (**wind down**); others may be **seizure-free for few years**, then have recurrence.

SURGERY OUTCOMES

Procedure	Seizure Free (%)	Improved (%)
Anterior temporal lobectomy	55.5-67.9	24.0-27.2
Amygdala-Hippocampectomy	68.8	22.3
Extratemporal cortical resection	25.0-45.1	18.2-35.2
Lesionectomy	66.6	21.5
Hemispherectomy	67.4-77.3	18.2-21.1
Corpus callosotomy	7.6-8.0	60.9-80.0

- ablative surgery is associated with **IMPROVEMENT** in **intelligence**, in **psychiatric** and **behavioral** disorders, in **social** and **vocational** function (abnormal brain tissue resection may remove undesirable functional effects which are interfering with function of other cortical areas).

ENGEL seizure-based outcome classification system (1987) is most commonly used scale.

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

Factors predictive of freedom from seizures:

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

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