EPILEPSY

Reactive seizure – mainly neonates and adults!

Neonatal seizures are ***only rarely idiopathic***!

Epilepsy - **≥ 2 unprovoked* seizures** > 24 hours apart; generally apparent by age 18

*no underlying CNS / systemic disorder

N.B. many persons who experience *first unprovoked seizure* never have second, so do not need treatment!; *second unprovoked seizure* is reliable marker of epilepsy (risk for further recurrence after second unprovoked seizure is > 80%).

N.B. almost all seizures that begin in **ADULTHOOD** (after age 20) are focal (whether or not this is apparent clinically) - caused by focal brain disease!

New partial seizure represents structural lesion until proven otherwise

SEIZURE - ***CLINICAL MANIFESTATION*** reflecting sudden, brief* physiologic dysfunction characterized by abnormal paroxysmal excessive hypersynchronous** discharge*** of cortical neurons:

*i.e. usually self-limited activity except for status epilepticus
**normal neuronal activity occurs in nonsynchronized manner
***high-frequency bursts of action potentials

Seizure:

generalized seizures - loss of consciousness, no focal features

N.B. generalized TCS are not observed in neonatal period!

tonic-clonic seizure (s. grand mal) - < 90 sec duration

tonic seizure

atonic seizure
clonic seizure
myoclonic seizure
absence seizures (s. petit mal) - sudden attack of impaired consciousness (behavioral arrest with motionless staring and unresponsiveness); onset in childhood (diagnosis of new-onset absence seizures in *adulthood* is incorrect); EEG - generalized **3 Hz spike-rounded wave complexes** provoked by *hyperventilation*; H: ETHOSUXIMIDE, VALPROIC ACID;

GABA agonists (e.g. GABAPENTIN, TIAGABINE, VIGABATRIN), PHENYTOIN, CARBAMAZEPINE exacerbate absence seizures!

Differentiating staring due to absence from that of complex partial seizures:

FEATURES	ABSENCE	COMPLEX PARTIAL
Sleep activation	None	Common
Hyperventilation	Induces the seizures	No activating effect
Seizure frequency	Frequent, many per day	Less frequent
Seizure onset	Abrupt	Slow
Aura	None	If preceded by a simple partial seizure
Automatism	Rare	Common
Progression	Minimal	Evolution of features
Cyanosis	None	Common
Motor signs	Rare, or minimal	Common
Seizure duration	Brief (usually <30 sec)	Minutes
Postictal confusion or sleep	None	Common
Postictal dysphasia	None	Common in seizures originating from dominant hemisphere

partial – focal features

Focal seizures with RETAINED awareness, s. without dyscognitive features (formerly - **simple partial seizures**) - *consciousness is preserved*; all sensory / motor symptoms remain ipsilateral!!!!

Focal seizures with LOSS of awareness, s. with dyscognitive features (formerly - **complex partial seizures**) – *aura* (simple partial seizure – sensory or psychic) → *impaired consciousness (awareness)*

temporal lobe epilepsy, s. ***psychomotor epilepsy***, ***limbic epilepsy*** - AURA (epigastric rising sensation) → activity arrest and motionless stare → unilateral or bilateral automatisms (stereotypic episodes of repetitive bizarre or atypical behavior), often with dystonic arm / hand posturing *contralateral* to seizure discharge (± head turning *ipsilateral** or *contralateral*** to seizure discharge,)

*most temporal seizures (i.e. if the turns to the right, seizure onset is in the right temporal lobe)

**mostly temporal seizures with secondary generalization

N.B. aura is not "warning" (as was once considered)! aura is seizure!

Aura is SPS preceding CPS

Secondarily generalized seizures
Todd's paralysis - postictal focal neurologic deficit – indicates focal epileptogenic site

breath holding spell - first attack at 6-18 months of age; initiated by *emotional angry / frightening episode that leads to crying*!!! do not reinforce child's behavior! anticonvulsants are not helpful!
catamenial epilepsy - seizure frequency↑↑↑ around time of MENSES (H: ACETAZOLAMIDE as adjunctive therapy)

Dyscognitive seizures: aphasic, akinetic, amnestic, dialeptic (= alteration of consciousness – synonyms: absence, petit mal)

DIAGNOSIS

Patients who experience first seizure should have:
1. **MRI** (except children with generalized seizures, e.g. absences)

   N.B. routine imaging is not necessary for children with idiopathic epilepsy!
2. On individual basis – **blood** (CBC, electrolytes, Ca, Mg, glycemia), **ECG** (incl. Holter monitoring), **echocardiography**; blood / urine **for substance abuse, serum prolactin** - elevated within 30–60 minutes after generalized seizure (compare to baseline, typically elevate ≥ 3-4-fold (esp. in GTC) - considerable variability precludes routine clinical use)
3. Fever → add **lumbar puncture**.
   N.B. if seizure was focal or if mass lesion is suspected, be sure there is no ***papilledema*** or ***midline shift*** before doing LP!
4. If above are negative then **EEG**
   EPILEPTIFORM DISCHARGES (INTERICTAL HALLMARK OF EPILEPSY!) - abnormal paroxysmal events containing **sharp waves** or **spikes**

   Absence of epileptiform discharges does not rule out epilepsy diagnosis!
   - present in only < 50% of epilepsy patients
   Epileptiform discharges do not establish epilepsy diagnosis –
   - found in 2-5% normal people!

Epilepsy can be definitively established only by recording **characteristic ictal discharge during representative clinical attack**.

N.B. slowed background is "normal" during postictal state!

Monitoring known epileptic:
1. CBC
2. LFT
3. Serum level of **anticonvulsant**

if problem is **TOXICITY**, *peak serum level* is desirable;
if problem is **EFFICACY/COMPLIANCE** - use *trough serum level* (just before next dose)

Known epileptic patient who has had single, typical seizure and whose mental status has returned to baseline need not be transported to ED (vs. **first seizure** → transport to ED).

Advise to ***continue taking AED even if drinking***

EEG

N.B. EEG reflects summated cortical ***local potentials*** (inhibitory / excitatory postsynaptic potentials of vertically oriented pyramidal cells, passive spread of electrical activity into dendrites), not ***action potentials***! (action potentials are of too brief duration to have effect on EEG)

- EEG is measure of **gray matter** neuronal function.

N.B. EEG is usually not abnormal in **white matter** disease!

- psychiatric diseases have no effect on EEG.
- ***locked-in syndrome*** simulating unconsciousness - EEG is normal
- ***herpes simplex encephalitis*** - periodic lateralizing epileptiform discharges (PLEDs) in temporal lobe

DELTA WAVES

- large, slow (< 4 Hz) waves during *deep sleep*.

THETA RHYTHM

- large-amplitude, regular 4-7 Hz waves in *children* or in *moderately deep sleep*.

- theta and delta waves are known collectively as slow waves.

ALPHA RHYTHM

- 8-12 Hz in *awake state at rest* (with mind wandering and eyes closed).

- **alpha coma** (e.g. in hypoxic-ischemic encephalopathy, pontine hemorrhage) - alpha waves are distributed uniformly both anteriorly and posteriorly in patients who are unresponsive to stimuli.

BETA RHYTHM

– present to variable extent *in addition to alpha rhythm*; 13-30 Hz

- enhanced by benzodiazepines, barbiturates.

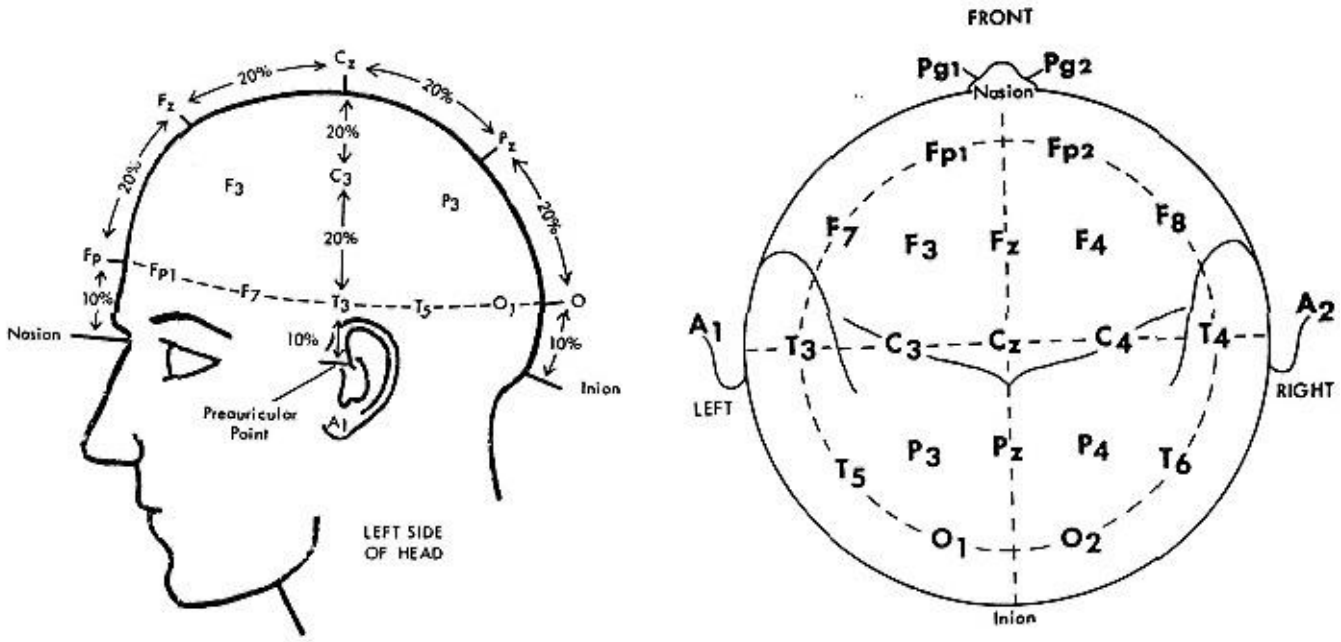
N.B. ***high-voltage beta activity*** suggests presence of sedative-hypnotic medications!

GAMMA OSCILLATIONS

– 30-80 Hz somewhat irregular low-voltage activity when individual *focuses attention* on something.

specific sensory systems → **midbrain** → enters **RAS** via collaterals → interlaminar **thalamic** nuclei → nonspecific thalamic projection to **cortex**

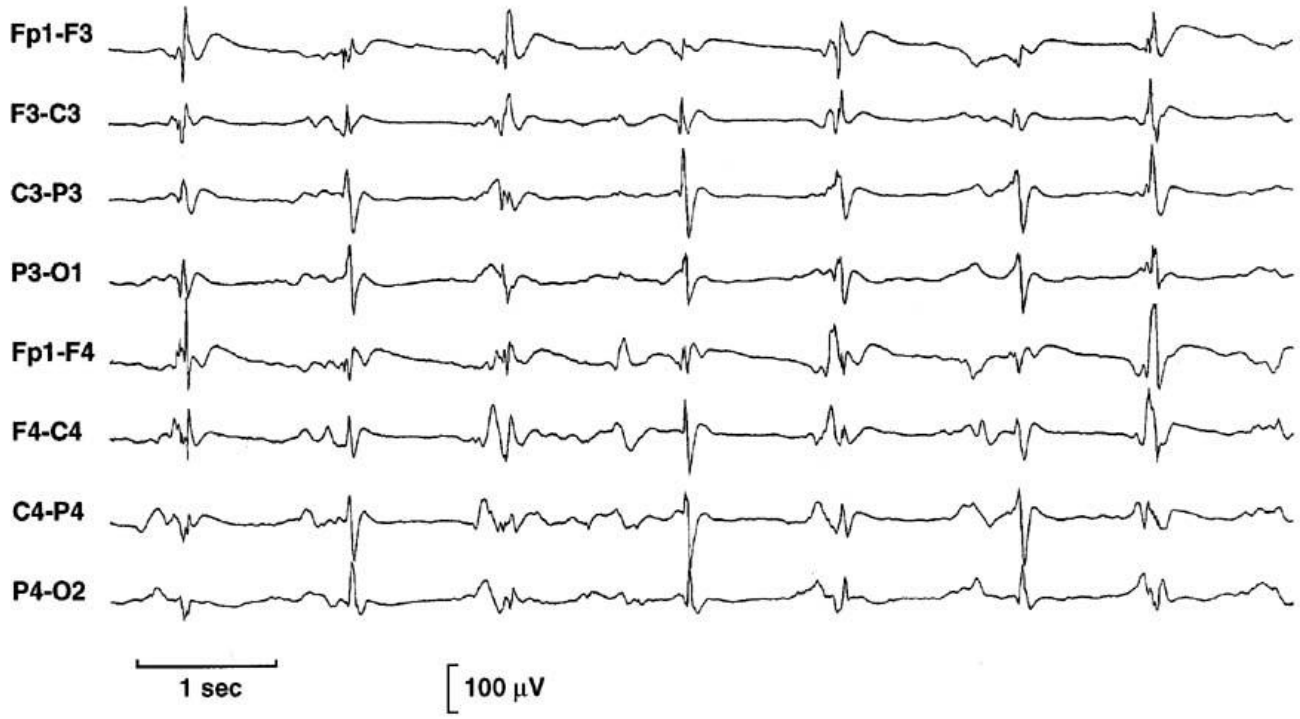
- **10-20 system** - internationally agreed locations that use standardized percentages of head circumference (i.e. "10/20" refers to interelectrode distances expressed as percentages of *anterior-posterior*, *transverse*, and *circumferential* head measurements):



Right-sided placements - **even numbers**, *left-sided placements* - **odd numbers**, *midline placements* - **Z**.

N.B. spikes and sharp waves are EPILEPTIFORM DISCHARGES and are associated with epilepsy!
Burst-suppression pattern (bursts of mixed-frequency activity separated by intervals of relative cerebral inactivity) - ***any severe encephalopathy***

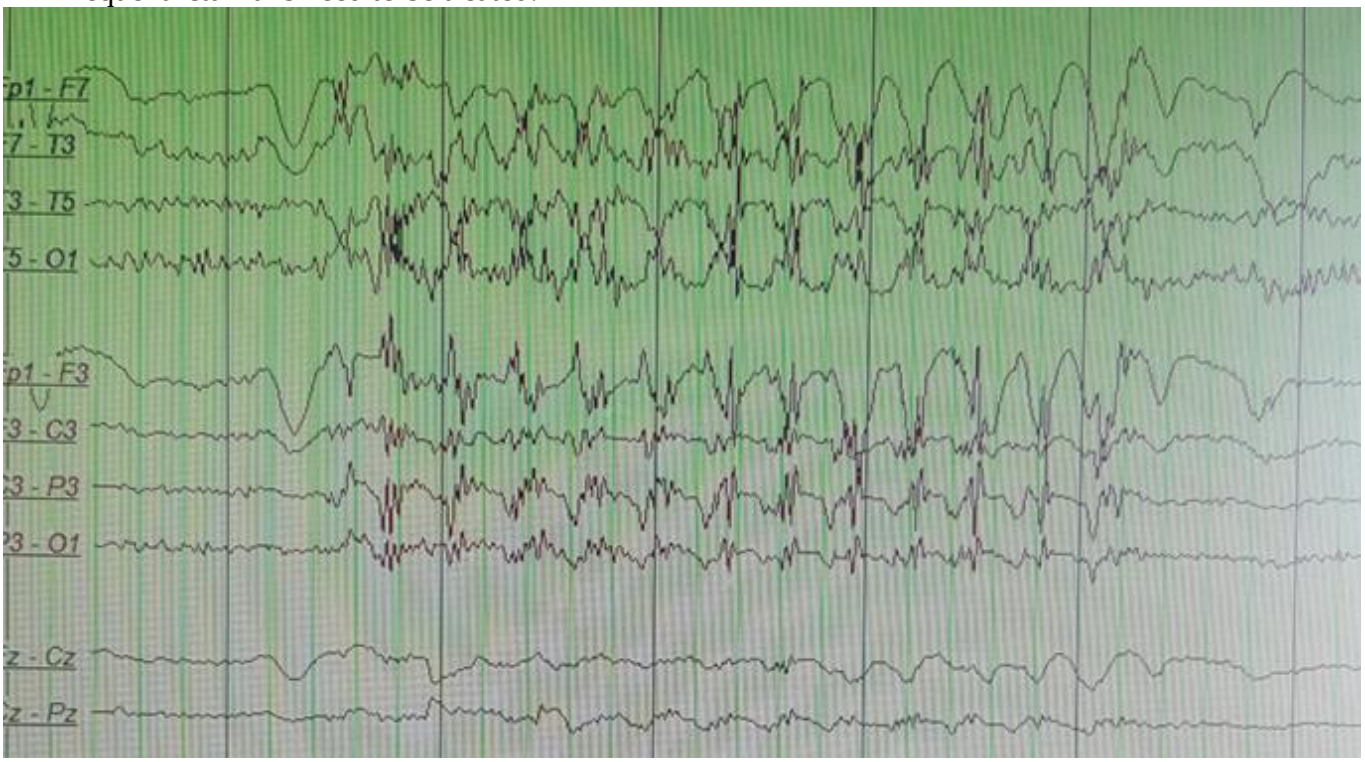
Spike - wave with sharp contour and < 80 msec duration; amplitude significantly greater than background.
Sharp wave - potential with sharp contour and > 80 (i.e. 80-200) msec duration; may occur ***without any clinical significance vs*** generalized periodic sharp waves in ***cerebral anoxia, Creutzfeldt-Jakob disease:***



ICTAL RUN

- cluster of ***epileptiform discharges*** with duration < 6 seconds.

- frequent ictal runs need to be treated.



SEIZURE

- cluster of ***epileptiform discharges*** with duration > 6 seconds; has evolution stage* (when amplitude steadily increases) and termination stage.

*exception – drop attacks in infantile spasms: large wave → silence.

ACTIVATING PROCEDURES (to precipitate seizure discharges):

a) **hyperventilation** for 3-4 minutes (reduces arterial CO_2 → cerebral vasoconstriction):
   normal patients → bilateral rhythmic EEG slowing.
   patients with absence seizures → paroxysmal rhythmic spike and wave discharges.

b) **photic flash stimulation** at 20 Hz:
   normal patients → rhythmic synchronous posterior activity (*PHOTIC DRIVING RESPONSE*).
   some patients → synchronous myoclonic jerks (*PHOTOMYOCLONIC RESPONSE*).
   patients with generalized epilepsy → seizure activity (*PHOTOCONVULSIVE RESPONSE*).

c) **sleep deprivation** (on night before examination) - increases diagnostic EEG sensitivity for epilepsy (in some patients, it will induce seizures).

d) hydration, alcohol, caffeine, Metrazol, Amytal, Brevital

BREACH PHENOMENON

- high amplitudes at craniectomy site

PERIODIC LATERALIZING EPILEPTIFORM DISCHARGES (PLEDS)

- *lateralized* (confined to single hemisphere) discharges that occur with *regular periodicity* (e.g. at 1-2 Hz) in setting of *focally slow or attenuated background* – continuum between interictal and true ictal discharges.

- suggest presence of ***acute destructive hemispheric insult***.
- very high association with clinical and electrographic seizures; 17% progress to epilepsy.

Suprachiasmatic Nucleus (SCN)

- internal circadian rhythm generator (pacemaker)!!!

MEG

- *EEG is handicapped by high impedance of tissues* through which signal must pass before being recorded.

Magnetic signals are *not significantly affected* by medium conductivity through which they pass!

- MEG is insensitive to conductivity variations (e.g. skull defects, vascular malformations).
- *magnetic dipoles* are at right angles to their *electrical dipoles* (electrical dipoles are oriented radially, perpendicular to cortical surface; magnetic dipoles – tangentially).
- MEG is particularly useful in "MRI-negative" cases – re-evaluation of MRI near MEG dipole clusters may allow finding of subtle cortical abnormalities.

- 40% of patients without spikes on EEG have positive MEG!
- strongly consider MEG ***before every SEEG case***:
  Philosophically: SEEG electrode is never in the right place vs. MEG dipole always shows the true location of spike!
  MEG provides nonredundant info for 1/3 of surgical candidates.
  Not doing MEG is "not a benign neglect"!
- wait a few days after MRI before MEG (MRI magnetizes tissues).
- at present, MEG role is complementary to EEG.
- negative MEG → admit to EMU, wean AEDs, and repeat MEG.

CONTRAINDICATIONS

- programmable VPS valves.
- pacemakers, VNS, RNS* are OK (software can filter those artefacts).
  *except if RNS is on the same side as epileptogenic zone – difficulty analyzing dipoles.
- metal implants are OK

TREATMENT

All antiepileptics increase risk of **suicidality**!

VALPROIC ACID and PHENYTOIN interfere with **platelet** function!

Enzyme-inducing AEDs (CMZ, PRM, PHT) cause **lipids↑** (even if on statins) – nobody should be prescribed inducing AEDs

1. **Na^+ channel blockers**:
   N.B. Na-channel blockers (esp. carbamazepine) increase sudden cardiac death risk!
   1) CARBAMAZEPINE, OXCARBAZEPINE - **LFT** *potential for serious liver toxicity* **& CBC** *aplastic anemia* monthly for 3-4 mos!!!
   2) PHENYTOIN – only AED metabolized through nonlinear, zero-order kinetics; negative inotrope and can cause hypotension
   3) FOSPHENYTOIN (IV) safer and clearly better tolerated than PHT - can be infused 3 times faster than intravenous PHT - indicated for **status epilepticus**
   4) LAMOTRIGINE - very effective, broad spectrum and well-tolerated!; preferred during pregnancy!!! Not sedating! (preferred in elderly)
   5) "-AMIDES" (ZONISAMIDE, LACOSAMIDE, RUFINAMIDE)
2. **Ca^{2+} channel inhibitors**: ETHOSUXIMIDE – just for **absences**
3. **GABA enhancers**
   Benzodiazepines, **barbiturates**

"-GAB-" (TIAGABINE, VIGABATRIN, GABAPENTIN)

VALPROATE - very potent AED effective against all types (generalized and partial) of seizures!; idiosyncratic, genetically determined ***hepatic toxicity;*** **thrombocytopenia** and inhibition of platelet aggregation – important for surgical patients!!!

4. **Glutamate receptor blockers**: "-AMATE" (FELBAMATE, TOPIRAMATE)
5. **Unknown mechanisms of action**

   LEVETIRACETAM linear pharmacokinetics - ***no level monitoring needed***; ***no drug interactions***

   BRIVARACETAM - psychiatric side effect profile is better than with LEV

   PREGABALIN

   KETOGENIC DIET - strict high-fat, low-protein, very low-carbohydrate diet (i.e. most calories provided as fat) - for **refractory generalized** seizures.

   CANNABIDIOL (CBD) (Epidiolex®) - nonpsychoactive ingredient in marijuana.

   - mechanism of action – unknown.
   - FDA-approved indications:
     1) tuberous sclerosis complex (TSC)
     2) Lennox-Gastaut syndrome (LGS)
     3) Dravet syndrome (DS)

Seizure Type	First-line Agents	Adjunctive Agents
Tonic-clonic	VALPROATE - esp. generalized seizures when several seizure types coexist LAMOTRIGINE CARBAMAZEPINE PHENYTOIN	PHENOBARBITAL PRIMIDONE TOPIRAMATE
Absence	ETHOSUXIMIDE VALPROATE*	**LAMOTRIGINE** TOPIRAMATE BENZODIAZEPINES ACETAZOLAMIDE PHENOBARBITAL
Myoclonic	VALPROATE BENZODIAZEPINES	**LAMOTRIGINE** TOPIRAMATE FELBAMATE ZONISAMIDE ACETAZOLAMIDE KETOGENIC DIET
Tonic/atonic	VALPROATE BENZODIAZEPINES	**LAMOTRIGINE** TOPIRAMATE FELBAMATE
Focal (partial) onset	LEVETIRACETAM LAMOTRIGINE - first-choice in elderly, pregnancy CARBAMAZEPINE	GABAPENTIN OXCARBAZEPINE TOPIRAMATE PHENOBARBITAL / PRIMIDONE

	PHENYTOIN VALPROATE	PREGABALIN ZONISAMIDE TIAGABINE

N.B. visais atvejais tinka VALPROATE and LAMOTRIGINE

- VALPROATE can cause ***bleeding disorders*** - routinely check coags and bleeding time - if values are abnormal, decrease or discontinue* valproate and recheck values before surgery!

*at least 3 weeks prior to surgery (replace with another medication).

many persons who experience ***first unprovoked seizure*** never have second, so do not need treatment!; after ***second unprovoked seizure*** (reliable marker of epilepsy) risk for further recurrence is > 80% → start AED therapy.

risk of recurrence after first seizure:
normal EEG + normal MRI + no evidence of focal onset → risk 15% → do not treat.
abnormal EEG + abnormal MRI + focal onset → risk 80% → start treatment.

If ***provoking factor cannot be promptly corrected*** → start AED therapy.

N.B. diagnosis of epilepsy refers to recurrent seizures and cannot be made on basis of single episode, even if anticonvulsant treatment is administered!

- ***slowly increase (titrate) dosage*** until seizures are controlled* or toxic signs occur (do not rely solely on therapeutic levels, which is only range in which most patients have seizure control without side effects)

*AED efficacy can only be evaluated in STEADY STATE (not earlier!)

"start low, go slow"

N.B. steady state is reached after time interval equal to $5 \times T_{1/2}$

patient's *individual clinical response* should prevail over *laboratory reading*

PREGNANCY

It is currently recommended that pregnant women be maintained on effective drug therapy!

AEDs are **teratogenic** + may precipitate *failure of oral contraceptives*!
vs.
Frequent convulsions can lead to **miscarriage** or **malformations**!

LAMOTRIGINE - one of preferred treatments during pregnancy (low incidence of congenital malformations!!!)
VALPROATE - highest risk for major congenital malformations of all antiepileptics

- most critical period is first 5 weeks of gestation.

TREATMENT TERMINATION

Discontinuing AED therapy is reasonable if been **seizure free for at least 2 years**.

Therapy should never be terminated abruptly - seizures may result.

N.B. normal / abnormal EEG is only guide (not criterion) for treatment termination!

- most recurrences occur in **first 6 months** (50% in first 3 months) after discontinuing therapy - patients should be advised to avoid potentially dangerous situations.
- relapse is rare **after 2 years**!

CONDITIONS

Generalized Tonic–Clonic Seizure (s. **bilateral tonic–clonic seizure**) (formerly **"Grand Mal" seizure**) - bilateral symmetric tonic contraction and then bilateral clonic contractions of somatic muscles, usually associated with autonomic phenomena.

AURA

- subjective ictal phenomenon that, in a given patient, may ***precede*** observable seizure; if alone, constitutes ***sensory seizure***.

FEBRILE SEIZURE

- GENERALIZED CONVULSIONS during sudden temperature rise (37.9°C may be enough) in children < 7 yrs; neither life-threatening nor damaging to brain.

Rx ir profilaktikos nereikia (geriausiai **PHENOBARBITAL**; arba – rectal **DIAZEPAM** at onset of febrile illness)

Simple febrile seizures (80-97%) - single, generalized tonic-clonic convulsions < 15 min duration, with brief postictal period.

Complex (s. complicated) febrile seizures (perform MRI, EEG, LP):

a) **focal** seizure (± secondary generalization)
b) **> 15 min** duration.
c) occur **more than once in 24-hour period**.
d) incomplete or **slow return to normal** neurologic status (e.g. Todd paralysis)

WEST syndrome (INFANTILE SPASMS)

- **age-dependent** generalized epilepsy consisting of TRIAD:

1. **Infantile spasms** - sudden, brief (few seconds), bilaterally symmetrical simultaneous **flexions** of neck, trunk, and limbs ("salaam" or "jackknife")
2. **Psychomotor retardation** – moderate ÷ severe
3. **Hypsarrhythmia** (characteristic interictal EEG - ***chaotic high-amplitude slow waves*** with interspersed random ***multifocal epileptiform discharges*** and poor interhemispheric synchrony (no organized background rhythm)

- mechanism - increased synthesis and activity of **CRH**
- most common treatment – **ACTH,** VIGABATRIN

Epileptic Spasm (formerly **Infantile Spasm**) - sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles.

- usually more sustained than a myoclonic movement but not so sustained as a tonic seizure (i.e. duration ~1 s).

LENNOX-GASTAUT syndrome

- heterogeneous group of early childhood epileptic encephalopathies (i.e. nonspecific brain response to diffuse neural injury): **MULTIPLE SEIZURE TYPES + DIFFUSE COGNITIVE DYSFUNCTION**

- seizures respond very poorly to AED - *polytherapy is usually required*! CANNABIDIOL
    - treatment of choice for atonic seizures (drop attacks) is corpus callosotomy (VNS is bad choice).
    - treatment of choice for other refractory seizures – DBS (centromedian nucleus) is probably better than VNS.

INSULAR EPILEPSY

- insula has ***broad reciprocal connections*** with frontal, temporal, and posterior cortical structures → heterogeneous mix of semiologies ("the great mimicker").
- according to electrocortical stimulation studies - 4 qualitatively and spatially distinct areas in the human insular cortex – **all sensory**:
    1. General somatosensory
    2. Thermal and pain perception
    3. Viscerosensation (interoception)
    4. Gustation.
- seizures tend to feature preserved awareness – sensory and motor features (long latency from electrical onset and hypermotor manifestations)
- scalp EEG changes can be variable or misleading
- for *nonlesional* insula - RNS (laser heat may spread to white matter).
- unilateral ***insular*** resection – no deficits to anticipate.
- Dr. Gonzalez-Martinez: avoid posterior insula resections - very high (13%) risk of permanent hemiparesis.

MESIAL TEMPORAL (S. HIPPOCAMPAL) SCLEROSIS (MTS)

- most common (60-80%) pathological substrate of TLE:

> 30% pyramidal cell loss in CA1 and / or CA4, with relative sparing of CA2 + severe astrogliosis

- many cases begin several years after complicated febrile seizures (!), TBI, or CNS infection.

1. **COMPLEX PARTIAL SEIZURES** (50% secondarily generalized):
    - most have aura:

aura in **mesial TLE** – visceral (esp. epigastric) sensations, olfactory / psychic phenomena (fear, anxiety) → synonyms ***psychomotor epilepsy***, ***limbic epilepsy***.
aura in **neocortical TLE** – auditory hallucinations, complex visual phenomena.

- CPS begin with arrest & stare; oroalimentary & complex automatisms are common.
- **posturing** of ***contralateral arm*** may occur; **nose wiping** with ***ipsilateral arm*** is specific for MTS.
- seizure usually lasts 1-2 mins.
- postictal disorientation, recent-memory deficit, amnesia of ictus and (in dominant hemisphere) aphasia usually last several mins.

2. Most patients have *material-specific* **MEMORY *impairment*** that lateralizes to side of seizure onset - either *verbal* or *visuospatial skills* – only finding on physical exam!

3. May have **FRONTAL LOBE *dysfunction*** on neuropsychological testing.

N.B. *EXTRATEMPORAL SEIZURES* may propagate to medial temporal lobe and produce seizure semiology indistinguishable from medial temporal lobe onset seizures; most commonly from:
(1) cingulate gyrus via cingulum
(2) orbitofrontal cortex via uncinate fasciculus
(3) occipital lobe via inferior longitudinal fasciculus.

Interictal EEG

N.B. **unilateral** mesial temporal lobe epilepsy often gives bitemporal spikes (if seizures are unilateral, then bitemporal spikes are not contraindication for surgery, although surgery outcomes are worse)

- usually maximal at anterior temporal (F7 and F8) and mid temporal regions (T3 and T4 electrodes).

Ictal EEG: *attenuation* (regionalized or generalized) → gradual buildup of rhythmical *theta or alpha frequencies* intermixed with *epileptic discharges*.

- EEG manifestations are maximal:
  mesial TLE – in anterior or mesial temporal region.
  neocortical TLE – in lateral or posterior temporal area.

High-resolution MRI

N.B. radiologic findings may be extremely subtle!

FDG-PET - focal **hypometabolic areas** *much larger than epileptogenic zone* (e.g. in medial TLE, hypometabolism involves both medial and lateral temporal lobe cortex ± subtle hypometabolism in frontal lobe, thalamus, basal ganglia).

- drugs usually suppress ***secondarily generalized seizures***, but 30-40% patients continue to have ***partial seizures***

FRONTAL SEIZURES

- seizures tend to be short but frequent, EEG difficult to localize.
  Some frontal lobe seizures are *considered pseudoseizures for many years* until appropriate diagnosis is made by video-EEG!
- unique characteristics: rapid seizure spread, bifrontal synchrony.
- tendency for seizures to cluster and to occur **at night or in morning**
- **SECONDARILY GENERALIZED** tonic-clonic seizures are common.
- treatment - ***lesionectomy*** (for structural lesions) or ***tailored (EEG-guided) cortical resection*** (for nonlesional extratemporal epilepsy)

FEATURES	FRONTAL LOBE	TEMPORAL LOBE
Seizure frequency	Frequent, often daily	Less frequent
Sleep activation	Characteristic	Less common
Seizure onset	Abrupt, explosive	Slower
Progression	Rapid	Slower
Initial motionless staring	Less common	Common
Automatisms	Less common	More common and longer
Bipedal automatism	Characteristic	Rare
Complex postures	Early, frequent, and prominent	Late, less frequent and less prominent
Hyperkinetic motor signs	Common	Rare
Somatosensory symptoms	Common	Rare
Speech	Loud vocalization (grunting, screaming, moaning)	Verbalization speech in non-dominant seizures
Seizure duration	Brief	Longer
Secondary generalization	Common	Less common
Postictal confusion	Less prominent or short	More prominent and longer
Postictal dysphasia	Rare, unless it spreads to dominant temporal lobe	Common in dominant temporal lobe seizures

RASMUSSEN SYNDROME (S. KOZHEVNIKOV EPILEPSY)

- rare childhood epilepsy syndrome with EPC.

CHRONIC FOCAL ENCEPHALITIS - stimulating **autoantibodies** against **GLUTAMATE receptors**

- ***inevitable slow neurologic deterioration*** - mental impairment, HEMIPARESIS, HEMIANOPIA, APHASIA (if affected dominant hemisphere).
- **MRI**: early unilateral ***cortical swelling*** FLAIR hyperintensity → progressive ***cortical atrophy*** with ***gliosis***.
- **rituximab, RNS**

PSEUDOSEIZURE (PSYCHOGENIC SEIZURE)

N.B. most distinguishing feature of true epileptic seizures is stereotypy!

- 75% children with pseudoseizures also have epilepsy!
- behaviors such as pelvic thrusting, head turning from side to side, bizarre vocalizations usually are not seen in epileptic seizures (exception - frontal lobe seizures).

SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

- **sudden**, **unexpected**, witnessed or unwitnessed, **nontraumatic** and **nondrowning** death in patient with epilepsy, with or without evidence of seizure and ***excluding documented status epilepticus***, in which postmortem examination ***does not reveal toxicological or anatomical cause*** of death.

ANNUAL INCIDENCE: 2017 AAN/AES SUDEP practice guideline summary describes the risk of SUDEP for adults with epilepsy as small

1:1000 in ***general epileptic population*** ***(much lower in children)***

4:1000 in ***patients in EMU*** – patient must be warned that the goal of staying in EMU is to provoke seizures but that may lead to death!

Risk factors:

1) generalized tonic-clonic seizures; ≥ 3 convulsive seizures per year - 15-fold increased risk of SUDEP (18:1000)
2) drug-resistant epilepsy
3) not escalating treatment in medically refractory epilepsy
4) seizures during sleep
5) other factors:
    a. prior status epilepticus (odds ratio [OR] of 7.83 for SUDEP)
    b. prior epilepsy surgery (OR, 4.23)
    c. taking several antiepileptic drugs (OR, 4.7).

Prophylaxis:

1) **seizure freedom** (esp. eliminating grand mal)
2) **nocturnal supervision** (e.g. seizure-alerting systems, presence in the bedroom of another individual at least 10 years of age and of normal intelligence)
3) implantation of **cardiac pacemaker-defibrillator device**.

ASYSTOLE

Ictal – self-limited, no deaths reported (actually, ictal asystole with no brain perfusion stops the seizure)

- ictal asystole recurs in 40% cases – implant pacemaker
- ictal asystole only happens in focal seizures – not a risk factor for SUDEP (vs. postictal asystole in generalized seizures)

Postictal – much more ominous.

STATUS EPILEPTICUS

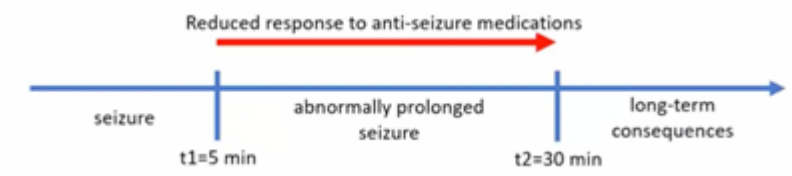
- failure of inhibitory mechanisms!

a) **continuous** seizure activity (clinical or electrical) ≥ 30 min.
b) **repetitive** seizures with incomplete neurological recovery interictally for ≥ 30 min (vs **seizure cluster** – patient fully recovers)

If seizure lasts > **2 minutes**, place *intravenous line* and *draw blood* for tests, because most seizures must terminate spontaneously within 1-2 minutes.

If seizure continues **beyond 5 minutes**, begin treatment as status epilepticus with *benzodiazepine*

- *> 30 minutes (status epilepticus) is associated with brain damage*.



t1 – time when seizure will likely be prolonged (time to initiate treatment)
t2 – time when seizures likely will leave long-term consequences (i.e. brief seizures probably are not harmful) - "Time is brain"

2015 ILAE task force definition (t1 and t2 are different for different seizure types):

a) seizure lasting **> 5 min** for generalized tonic-clonic seizures (t2 = 30 mins)
b) seizure lasting **> 10 min** for focal seizures (t2 = 30-60 mins)
c) seizure lasting **> 15 min** for absence seizures (t2 unknown)

REFRACTORY SE

– if seizures continue beyond t2 despite two AEDs after 30 minutes (for generalized seizures) or 60 minutes (for focal seizures) - mortality 17-39%.

SUPER-REFRACTORY SE

– if SE continues or recurs 24 hours after onset of anesthetic therapy or at withdrawal.

TREATMENT

Neuroimaging has no impact on immediate management until seizures are controlled.

MRI-DWI shows diffusion restriction (up to 3 days after status)

N.B. *use of neuromuscular blockers is inappropriate* (unless needed for intubation – use short acting agent) because they do not stop seizure activity in brain (which is cause of brain damage!).

Treatment should be continued until ***electrographic seizure activity**** has resolved completely!

*CNS injury can occur even when patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures.

STEP 1 (0-5 minutes of seizure) – **ABC + Coma**

1. ***ABC*** - secure oral airway (e.g. nasopharyngeal airway), prevent aspiration (turn head to side, suction secretions), administer 100% O_2 (via properly fitting face mask); intubate if respirations compromised or if seizure persists > 30 min.
    - ***monitor*** - ECG, SaO_2, vital signs.

2. **Establish IV line**.
    - ***blood tests*** – glucose, CBC, BMP (***hyponatremia***), LFT, tox screens, AEDs levels (if indicated)
3. THIAMINE 50 mg IV → DEXTROSE 50% 50 ml IV.
4. Search for probable cause of SE (tests should not impede rapid and aggressive treatment!):
    1) some feel that ***vEEG*** should be routine part; others use EEG only selectively.
        In general, EEG has no role in management of GCSE!
    2) ***neuroimaging*** - CT is sufficient to exclude acute brain lesion; MRI obtained later.
    3) ***LP*** in any febrile patient; if ICP↑ / mass lesion are suspected, antibiotics should be given immediately and CT obtained first.
        WBC pleocytosis (up to 80) can occur following SE (**benign postictal pleocytosis**)

- ***acidosis*** should not be treated (acidosis is anticonvulsant).
- ***hyperthermia*** should be treated aggressively - fans and antipyretics.

STEP 2 (5-20 minutes of seizure) – intravenous **ANTICONVULSANTS**

2016 American Epilepsy Society (AES) guidelines:

Seizure > 5 minutes: IV bolus of *rapid-acting* anticonvulsant:

a) LORAZEPAM 0.1 mg/kg (e.g. patient > 40 kg → 4 mg; if seizures continue after 1 minute wait → given additional doses up to max 9 mg) – **preferred agent**!

b) DIAZEPAM 0.1 mg/kg (q5min, up to 10 mg)

c) PHENOBARBITAL 20 mg/kg (max 1000 mg) - slower rate of administration, so it is a second choice to benzos

d) IM MIDAZOLAM 10 mg - first choice **if patient has no IV line**

Seizure > 20 minutes (practically, start at the same time as benzos): → loading dose of *long-acting* anticonvulsant (all equally effective at stopping SE):

a) LEV 60 mg/kg (max 4500 mg)

b) VPA 40 mg/kg (max 3000 mg) – platelet risk, esp. in neurosurgery!

c) FOSPHENYTOIN 20 mg PE/kg (max 1500 mg – i.e. 75 kg dose) – proconvulsant if overdosed!

If SE does not stop – it is RSE

*

N.B. **give full dose at once** (do not break down in small doses to check for response)! – "time is brain and SE is not a benign condition"

– benzos IV in normal person risks respiratory depression; vs. in patient with status - benzos IV decrease the risk of needing intubation.

N.B. DIAZEPAM enters CNS slightly faster than LORAZEPAM but affords only 30 minute protection - drug redistributes to other fatty tissues (vs. 12 hrs by LORAZEPAM).

STEP 3 – pharmacological COMA:

1. Elective **intubation** using rapid sequence technique (all patients are considered full stomach).

2. Place **arterial line** + draw **arterial blood gases**.
3. Start **IVI** (be ready for induced hypotension):
    a) **PENTOBARBITAL** 0.5-5 mg/kg/hr (titrated to *burst-suppression*).
    b) PROPOFOL 2-10 mg/kg/h
    c) MIDAZOLAM IVI

STEP 4 – general anesthesia using inhaled anesthetic (ISOFLURANE).

STEP 5 – emergency surgery (seizure focus resection with ECoG guidance, VNS at high stimulation parameters, etc).

See N5 case >>

MEDICAL INTRACTABILITY (DRUG-RESISTANT EPILEPSY)

A. 2 medications

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

– Commission on Therapeutic Strategies of the International League Against Epilepsy (ILAE) definition (officially adopted at the ILAE's 2009 meeting in Budapest, Hungary):
"DRUG-RESISTANT EPILEPSY - failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."
– these therapeutic trials can be accomplished within *6-12 months*.

B. 3 medications

– 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%.

Kwan P, Brodie MJ Early identification of refractory epilepsy. N Engl J Med. 2000;3;342:314-319.

- first monotherapy trial can achieve freedom from seizures in 47% of patients;
- switch-over to second AED trial in monotherapy yields freedom from seizures in only 13% of patients
- third trial increases total number of seizure-free patients by only 4%.

- among all patients with epilepsy, 60-70% are expected to become seizure-free with AEDs:

47% of patients respond to first AED
additional 14% respond to second AED
additional 3% respond to third AED
36% of patients are refractory

Surgery should be *performed as early as possible*!!!

– 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).

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

N.B. temporal lobe epilepsy is *most medical refractory* but surgical results are the best!

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

1) lesionectomy
2) neocortical resections

DISCONNECTIONS (palliative) - to disconnect seizure focus from other functional parts of brain:

1) callosotomy
2) hemispherectomy
3) multiple subpial transections

STIMULATION:

1) RNS
2) DBS
3) VNS

Feature	VNS	DBS	RNS
Closed-loop	Partially (newer models may detect tachycardia)	No	Yes (detects electrographic activity)
Newest model	Sentiva (2017)	Percept PC (2020)	320 (2019)
Generalized or multifocal epilepsy	Yes	Probably (limited evidence)	No
Invasiveness (intracranial)	No	Yes	Yes
Recording capability	No	Low resolution sensing: 6 data points/hr, 5 Hz range	High resolution sensing: 250 data points/sec, 1-125 Hz range
Recording capacity	No	No	Yes (1 MB)
Indication for depression	Yes	No	No
Positive effects on mood & cognition	Yes	Unknown	Probably
Children	Yes	No	No (predicted in 2024)
Patient compliance needed	No	No	Yes
MRI	Yes, exclude C7-T8 region (up to 3 T)	Yes, full body (up to 3T with Percept®)	Yes, full body (up to 1.5 T)
Side effects during stimulation	Yes	No (memory?, depression?)	No

IPG site	Infraclavicular	Infraclavicular	Cranial
Regulatory approval (2018 December)	The whole world (FDA in 1997)	USA (FDA in 2018), Europe (CE mark), Canada, Australia	USA only (FDA in 2013)
Outcomes			
Median seizure reduction at 1 year	45% (EO5)	41% (SANTE)	67% (Post-approval)
Best median seizure reduction	76% at 10 yrs	75% at 7 yrs	75% at 9 yrs

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

Drug-resistant ≠ Treatment-resistant

Seizures **refractory** to appropriate **medical** management + seizures seriously **limit** patient's **QOL**
N.B. pharmacoresistance per se is not an indication for surgery!

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

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

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

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

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!

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

- if truly MRI-negative, proceed with advanced imaging – however, positive result from advanced imaging often requires ***verification by SEEG***.

COMMON EPILEPTIC PATHOLOGIES

- hippocampal sclerosis is #1 among adults (44.5% surgical specimens; only 15% in children)
- malformations of cortical development are #1 among children (39.3% surgical specimens with focal cortical dysplasia occupying 70.6%).
- tumors (mainly gangliоglioma) are #2 in all age groups.
- vascular malformations (mainly cavernomas) - found in 6.1% of specimens.
- TBI, intracranial infections, neurosurgical procedures may leave glial scars (gliosis) - found in 4.9% of specimens - hyperintense on T2 and often associated with cortical atrophy.

- infections - Rasmussen's encephalitis, herpes simplex encephalitis, neurocysticercosis (most common cause of infection-related epilepsy worldwide).

PET

N.B. PET often shows hypometabolism in temporal lobes of pediatric patients – ignore it (esp. if symmetric)
N.B. temporal lobe is relatively hypometabolic compared to other lobes.

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

SPECT

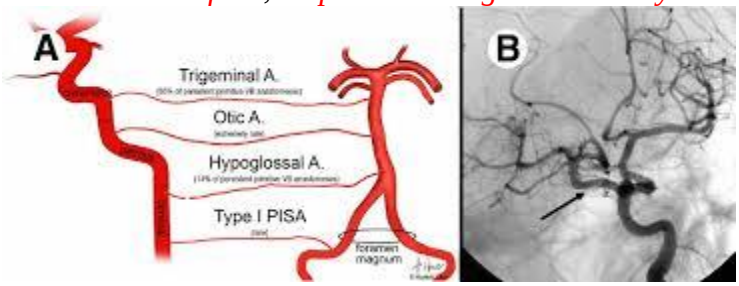
Interictal SPECT - shows hypoperfusion; resolution is inferior to that of PET.

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

WADA

– so called PHASE II TESTING
– injection of 100-150 mg SODIUM AMOBARBITAL (AMYTAL®) / PROPOFOL into *carotid artery* - to temporarily anesthetize (inactivate) hemisphere (includes amygdala and anterior hippocampus) → independent testing **function of contralateral hemisphere**.

- **4-vessel arteriography** must verify that blood flows to corresponding hemisphere (not to brainstem or contralateral side – i.e. no *cross flow*, no *persistent trigeminal artery* – will cause brainstem failure)



N.B. fetal PComA is not contraindication but will cause cortical blindness.
N.B. significant cross-flow is relative contraindication to anesthetizing side of dominant supply (patient goes to sleep).

- start on side of lesion (Wada testing is almost always performed with bilateral injections).
- have patient hold both arms in air and count loudly - ***contralateral hemiparesis*** and ***ipsilateral EEG slowing*** (> 50%) must appear (confirmed adequacy of injection); if not add 25 mg more of drug.
- caveats:
  - Wada test may be grossly inaccurate with high flow AVM.
  - portions of hippocampus may be supplied by posterior circulation (not anesthetized by ICA injection).

POSTOP

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

60% of patients are able to stop all AEDs (22% remain seizure-free and medication-free after > 5 years)

- 90% of seizures that recur do so within 2 years; per Dr. R. Gross – if seizures recur, they do it within 6 months (therefore, outcomes are measured earliest at 12 months).
- neuromodulation antiseizure effect keeps improving over time.

"It takes time for epilepsy to develop, it takes time to undevelop"

Jerome ENGEL'S classification of postoperative outcome:
Class I: Free of disabling seizures (***residual auras*** are OK)
Class II: Rare disabling seizures ("almost seizure free")
Class III: Worthwhile improvement (> 90% reduction)
Class IV: No worthwhile improvement (< 90% reduction)

INTRACRANIAL ELECTRODES (icEEG)

- ***SEEG may access any cortical area*** (incl. mesial, depth of sulci, insula, postoperative, multilobar, bilateral) but spatial coverage may be incomplete (i.e., unexplored gray matter areas).

vs. 2/3-3/4 of cortex is inaccessible to subdural electrodes.

One 8x8-grid covers 4% of one hemispheric cortex
One 10-contact depth electrode samples 5 mL, so ten electrodes sample 50 mL ≈ 8% of one hemispheric volume

	SEEG	Subdural grids
Superficial cortex	Fair (limited coverage)	Excellent
Deep structures, sulci	Good	Poor
MRI-negative cases	Preferred	Less optimal
Anatomic relationships	Can be challenging	Straightforward
Cortical mapping	Fair (requires careful planning, good at exploring cortical depths, e.g. perisylvian opercula); if need to resect near language areas, better do awake crani	Good (regular contiguous pattern, surface well covered)
Extensive unilateral EZ		Preferred
Bilateral	Straightforward	Challenging (can use burholes for strips)
Stereotaxy	Good	Poor (displacement, distortion)
Data	3D	2D

Seizure capture	Earlier	May capture only late cortical projection of deep EZ
Complications	1-5%	5-30%
Cortical violation	Penetrates	No violation
Brain distortion	None	Common
Pneumocephalus	None	Common
CSF leak	Less common	More common
Children, thin skull	Need at least 2 mm bone	Preferred
Previous craniotomy*	Straightforward (must avoid hardware)	Difficult (subdural adhesions)
Adding additional electrodes (during EMU stay)	Possible	Not practical
Electrode removal	At bedside (but better in OR)	Requires OR
Subsequent resection	Challenging (performed after removal, must use stereotaxy) but also gives more time for planning**	Straightforward but needs to happen at the same procedure with grid removal (reopen same craniotomy, use electrodes to guide)
Historic preference***	France, Italy, Brazil	North America, the United Kingdom, Germany
Implantation procedure time: total OR time / surgical time	322 / 121 minutes	429 / 308 minutes
Blood product transfusion rate, postop narcotic use	Lower	Higher

*alternative – **epidural peg electrodes** can be used; another alternative – subdural electrode can be placed in the epidural space, but unless the dura has been denervated, these electrodes cannot be used for stimulation-based mapping.
**there is no min or max time when to perform surgery after SEEG is done; SEEG does not obligate to surgery (SEEG is more like presurgical evaluation tool – it is the whole advantage as intracranial EEG should be diagnostic tool and not to push to have surgery at the end (vs. grids lead to resection almost 100% - it is not fair for diagnostic tool to be so pushy!)
***advent of stereotactic robots made SEEG adopted worldwide

<u>Cases where SEEG is better</u>

1) widely extensive or multiple lesions where only a small portion may be epileptogenic (e.g. nodular heterotopia, tuberous sclerosis)
2) cases of temporal lobe epilepsy (unclear laterality, potentially neocortical, “temporal plus”, etc).
3) insular epilepsy
4) deep lesions
5) after previous craniotomy

<u>Cases where Subdural Grid is better</u>

1) near / in eloquent area

2) discrete cortical lesion with unclear extent of epileptogenic zone (e.g. ganglioglioma, cavernous angioma, cortical dysplasia)
3) questionable lesion not clearly distinguishable from normal tissue
4) young children, whose skull is too thin to hold SEEG bolts

Combination (grid + SEEG) cases – implant SEEG first then do craniotomy.

Unilateral **temporal** seizures with red flags - suspected to extend to extratemporal areas* (so called "temporal plus" epilepsies):

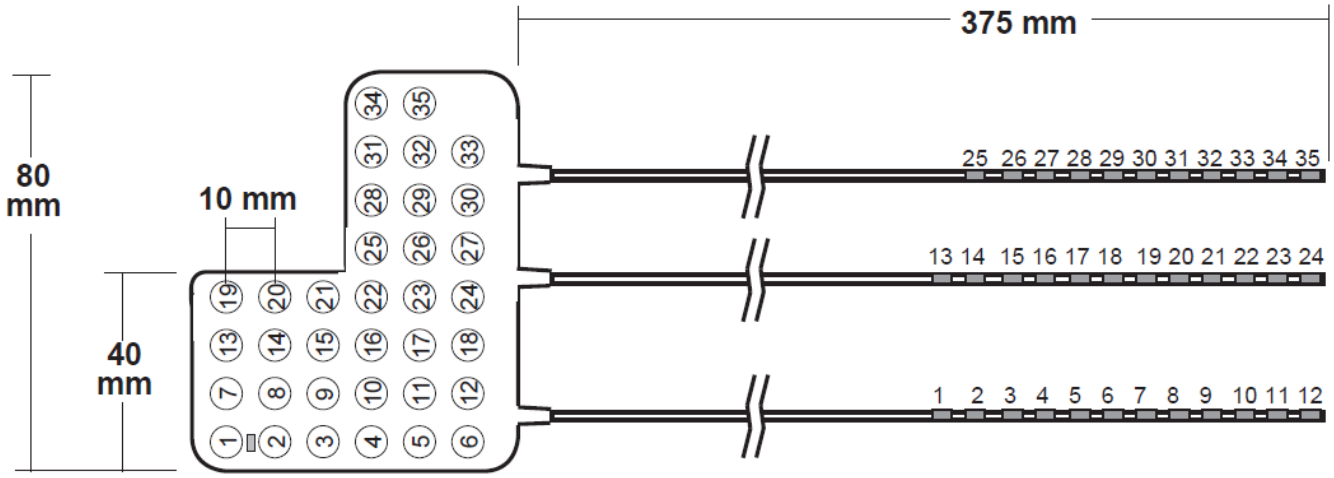
a) absence of febrile seizures, atypical history
b) secondary generalized GCTS
c) atypical EEG
d) head trauma, encephalitis
e) subtle MRI abnormalities outside mesial temporal lobe

— otherwise, cases of temporal lobe epilepsy with consistent anatomo-electro-clinical findings are usually operated on after noninvasive investigations.

*insulo-opercular complex, temporo-parieto-occipital junction, anterior frontal cortex

There special **temporal lobe grids**

- designed for the temporal and sub-temporal cortex.



- consider Dermabond and BioPatch around wires at exit sites.
- *strip ground **epidural** electrode* is placed inversely, i.e. contacts facing bone.
- head is wrapped in a bulky dressing with a chin strap to prevent dislodgement during seizures.

CONTRAINDICATIONS

- mental retardation or uncooperative patient – will pull leads in EMU.
- skull thickness is a consideration for kids (there are SEEG cases done on 2 yo).

- previous craniotomy might be a contraindication for electrodes over the eloquent cortex due to the risk of damage while dissecting adhesions; H: SEEG.

PREOPERATIVE, PERIOPERATIVE

- continue home AEDs perioperatively; once in EMU, epileptologists will discontinue AEDs (for seizure activation).
- no dexamethasone – risk of infections.
- no NSAIDs – risk of bleeding.
- check platelet function if patient is on VALPROIC ACID.
- Dr. Jerome Engel does WADA after SEEG – to make sure damage was not done with SEEG

- ***regional venous anatomy*** may dictate the use of custom-cut grids or subdural strips to avoid sacrificing a critical vein (e.g. location of the vein of Labbé may make grid placement difficult).

COMPLICATIONS

- primarily is **infection**
  Dr. Spencer switched to placing titanium mesh instead of putting native bone back after subdural electrode implantation (if patient comes for resection, replace the bone or leave titanium mesh)
- **mass effect** from cerebral edema (most common in children, where subdural space is minimal) - grid should be removed immediately.
- **subdural hematoma** from damage to bridging vein during implantation (EEG shows attenuation and becomes useless).

SEEG

For sole electrodes, may use **other implantation methods** (than **bolt**) - electrodes may enter through the holes / slits in grid electrode (if one is placed).

a) use ***navigation of electrode itself*** (e.g. AxiEM – stylet goes through the lumen of electrode
b) use ***slotted cannula***

Cleveland Clinic group concluded: **MRI T1w + CTA**

— SEEG sensitivity distance is ≤ 5 mm (electrodes practically need to be inside lesion, esp. if electrical activity is very low amplitude as in PVNH)

SEEG should sample - most common **deep nodes** (insula, cingulate) and **major "highways"** (fronto-parietal, cingulo-opercular) – seizures maybe originating and / or propagating there.

- implantations of > 15 depth electrodes are rare and should be avoided (complication rate starts increasing exponentially).

Temporal

French school for temporal SEEG

– use orthogonal (not oblique) trajectories for temporal explorations.
– always add **insula** and vertical trajectory for **orbitofrontal cortex**.

In suspected TLE, SEEG often includes extratemporal structures to rule out TLE mimickers:

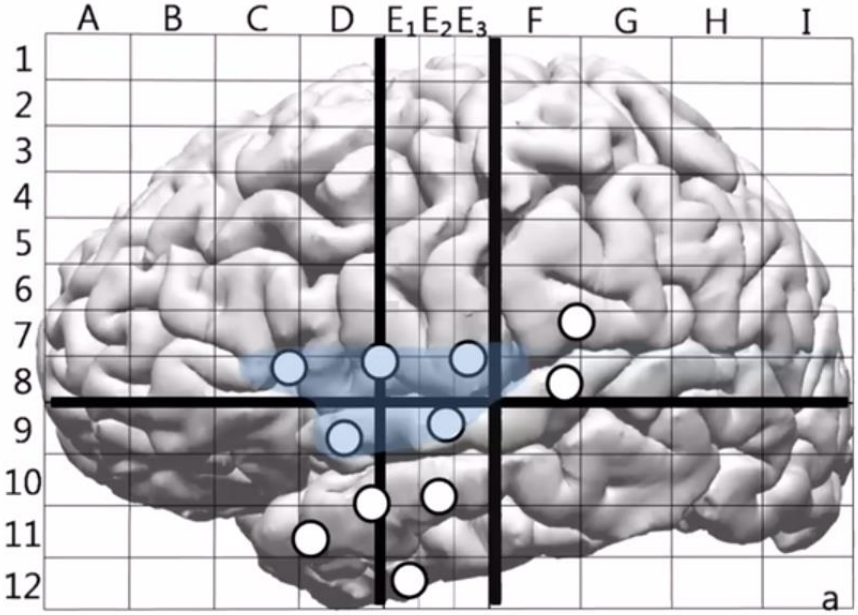
- ***insular operculum*** region
- ***orbitofrontal*** region
- ***parietal*** region
- ***cingulate*** region
- some suggest adding exploration of ***limbic pathways*** - thalamic nuclei (ANT, medial group)

- rapid seizure propagation (< 10 sec, esp. < 5 sec) out of temporal lobe is a good predictor of ATL failure (may chose RNS instead).
  N.B. intraventricular electrode position is OK.

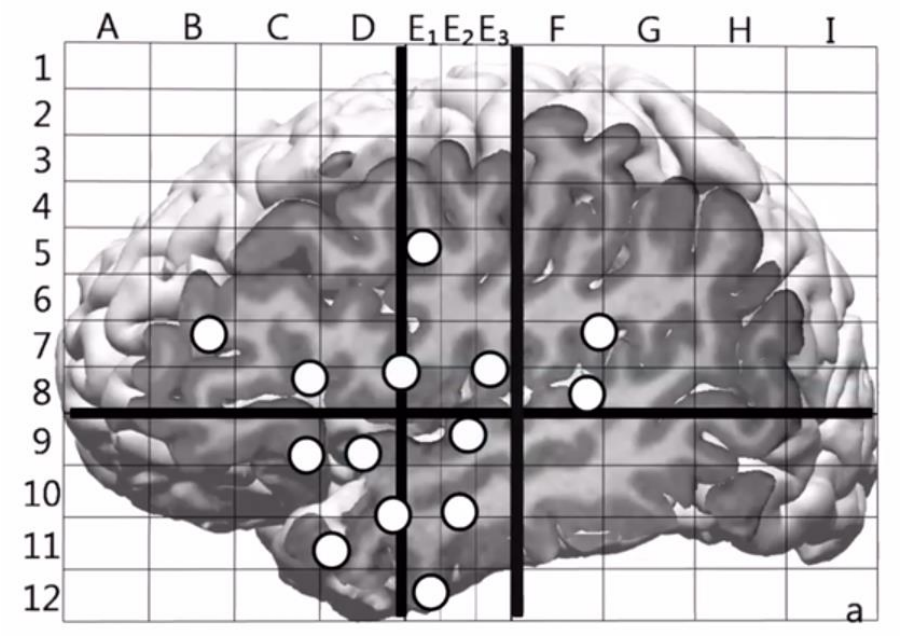
<u>Insular</u>

- insula sometimes requires ***very dense SEEG coverage***; however, high vascular risk results in an incomplete exploration of the insular cortex.
- Dr. Spencer: to cover insula need **at least 3 electrodes** – 2 orthogonal and 1 parasagittal.
- Dr. Gonzalez-Martinez: often need **bilateral** insula implantation due to high-speed connectivity between sides.
- also implant whole cingulate (if posterior cingulate shows early propagation, avoid surgery – i.e. SEEG is here not to guide surgery but to tell when to avoid surgery).

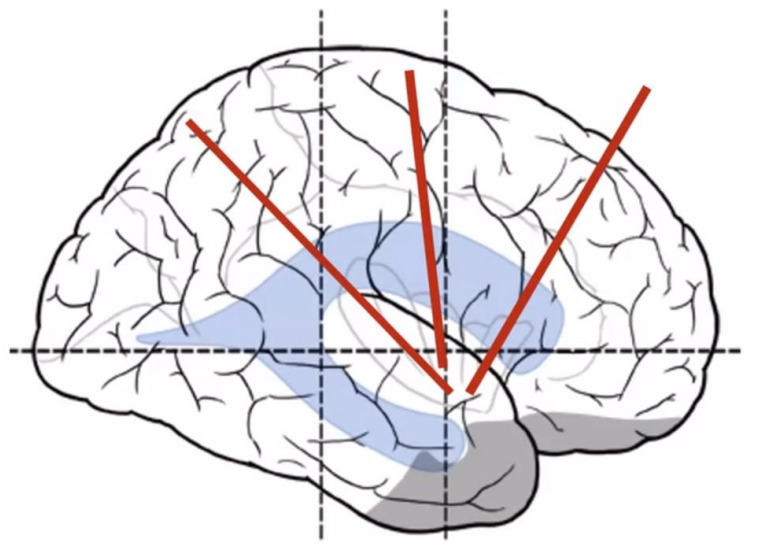
A. **orthogonal (transopercular)** - through the supra- or infra-sylvian opercula – only point sampling of insula but also includes opercula (important!); supplement with temporal and posterior perisylvian implantations:



plus anterior cingulate:



B. **parasagittal (oblique)** - by a *retro-insular trajectory* with a fronto-polar entry point just lateral to SSS – better exploration of the whole insular cortex:



Orbito-frontal epilepsy – investigate:

1) gyrus rectus
2) frontal pole
3) anterior cingulate gyrus
4) temporal pole.

EMU STAGES

1. Recording interictal activity
2. Recording ictal activity, s. **spontaneous seizures (SS)** and make sure seizures are *habitual**

first record without stopping AEDs – may give enough information; if not, after 1-2 days consider activation - sleep deprivation, gradual AED withdrawal, dialing down VNS output

3. Stimulation for **brain mapping** - after enough seizures are captured in EMU because cortical mapping stimulation causes suppression (↓ chances of seizures), i.e. mapping stimulation works as AED (principle of RNS)!
4. Stimulation to induce seizures s. **direct cortical stimulation induced seizures (DCS-S)** – may shorten EMU stay (if not enough spontaneous seizures were captured and DCS-Ss are *habitual*)
   - bipolar (vs. monopolar) stimulation requires lower currents but both (bipolar and monopolar) are safe procedures and give similar eloquent cortex mapping
   - 1 and 50 Hz (with low frequency need higher mA), delivered for 2-5 sec (most experts say 2 sec is enough)
     – 1 Hz is less effective to induce seizure but more specific prognostically for favorable surgery outcomes.
   - start at 1 mA and increase in 1 mA steps (up to 14 mA) until clinical subjective or objective responses or afterdischarges were obtained.
     – if using SEEG, stimulation **current** is much less (than if using grids): 0.2-5 mA.
     It is all about safe charge density!
     – in tumor surgery (as opposed to epilepsy surgery), intraoperative stimulation uses lower current so to maximize tumor resection (but risk of false negative responses).

     Afterdischarge may lead to false* positive response or even may lead to seizure!
     *i.e. while stimulating, monitor adjacent EEG activity to ensure that disruption of neurologic function is directly correlative to stimulation and not to focal afterdischarge.
     Afterdischarge is "all or none" phenomenon and is produced once a critical number of neurons are depolarized.
   - if mapping stimulus *induces seizures*, stimulate again (often aborts seizure, but have Ativan 2 mg IV ready at bedside).

Goal - constructing a composite 'drawing' of the brain area to be removed ('what-to-remove area').

ictal onset zone - the first clear ictal electrical change that: (1) occurs prior to the clinical onset of the seizure, and (2) manifests by a fast synchronizing discharge (low-voltage fast activity or recruiting fast discharge of spikes).

N.B. lack of one of these two criteria implies an incorrect SEEG investigation (**"missing electrode" phenomenon** – electrodes are recording arriving seizure activity but are not at ictal onset zone)!

N.B. there are practically no absolute "100%" results

TEMPORAL LOBECTOMY

Dominant side – always do WADA testing!

Measurements are made along MIDDLE TEMPORAL GYRUS:

dominant temporal lobe: up to 4-5 cm may be removed (over-resection may injure *speech centers*, which cannot be reliably localized visually)

non-dominant temporal lobe: 6-7 cm may be resected (slight over-resection → *partial contralateral upper quadrant homonymous hemianopsia* "pie-in-the-sky"; resection of 8-9 cm → complete *quadrantanopsia*)

N.B. only (intraoperative) mapping can reliably determine location of language centers.

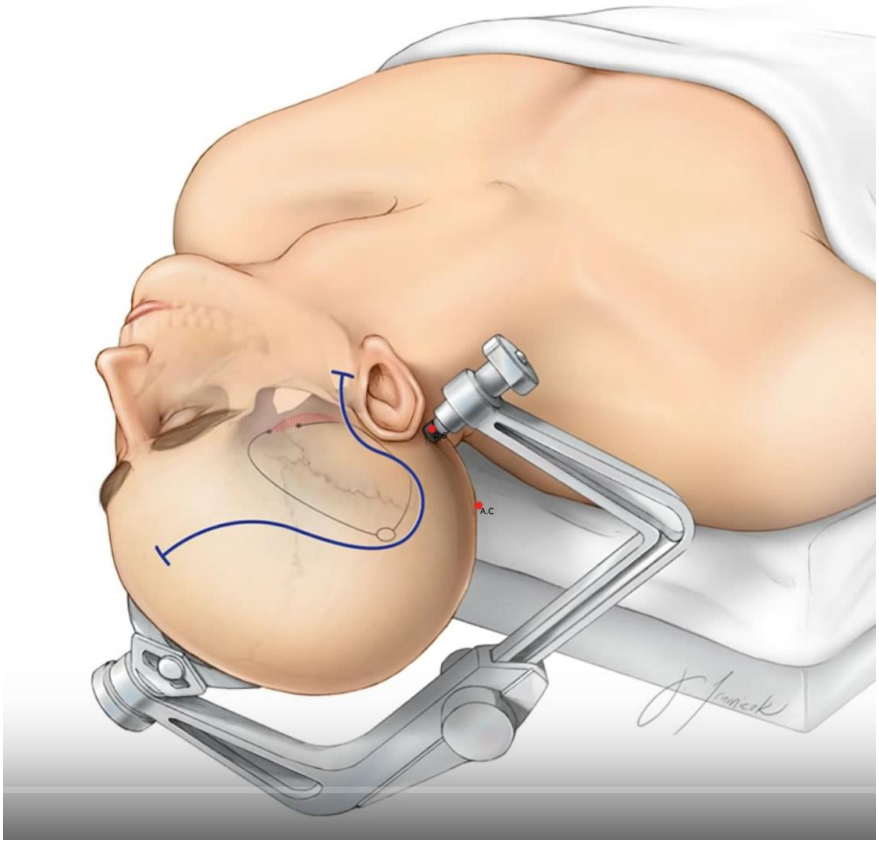
N.B. representation of language as far anterior as **2.5 cm from temporal tip** has been documented!

- **Lüders area** (s. basal temporal language area) at inferior temporal gyrus – if damaged during surgery, transient (up to 6 weeks) dysnomia for kids; no deficits for adults.

1. **Standard en bloc anterior temporal lobectomy (ATL)** - initially described by Penfield and Baldwin, in 1952.
   1) *superior temporal gyrus* resected 2 cm from temporal tip.
   2) *middle* and *inferior temporal gyrus* resected 4-5 cm from tip of nondominant side and 3-4 cm of dominant side.
   3) *amygdala* resected totally.
   4) *hippocampus* resected to level of colliculus (3.5-4 cm of hippocampus).

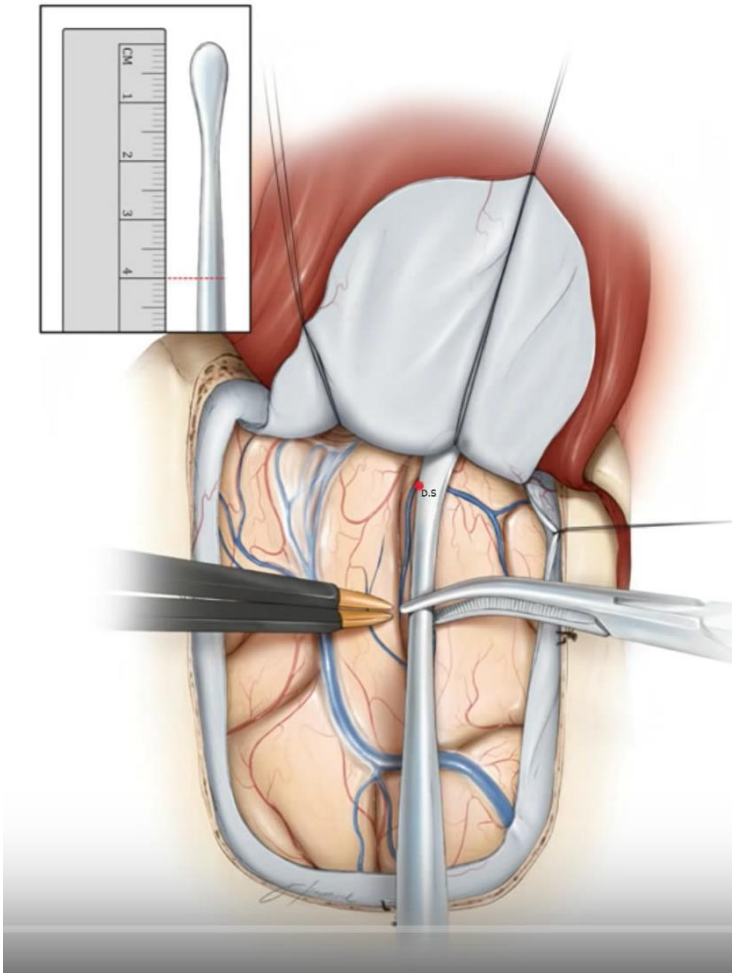
2. **SPENCER anteromedial temporal lobectomy (AMTL)** - *superior temporal gyrus* is spared (important in dominant side).

- **supine** ± with foam wedge or shoulder roll ipsilateral to side of surgery.
- head held in **Mayfield 3-pin holder**
- **navigation** should be used.
- **microscope** for hippocampectomy part.
  head turned to contralateral side and extended* 50 degrees with vertex lowered 10 degrees
  *extension allows surgeon to view long axis of hippocampus with microscope
- positioned properly, *zygoma will be the highest point* of head.



- Dr. Spencer – posteriorly incision is up to **mastoid-vertex line** - allows for retraction of superior temporal gyrus and frontal lobe without compressing brain against skull edge.
- ***cuff of temporalis muscle*** is preserved
- bone flap should be based low in middle fossa, extending just above sphenoid wing but within confines of temporalis muscle fan (use rongeur / high-speed drill to enlarge bone opening towards middle fossa floor and anteriorly into sphenoid wing for several centimeters).

  Maximal exposure of temporal tip!!!
- protect vein of Labbé
- resection is performed in ***subpial plane*** - to prevent injury to MCA branches.
- to plan **posterior margin of lateral cortical resection** of middle and inferior temporal gyri, No. 4 Penfield and mosquito clamp are used to measure from temporal tip along middle temporal gyrus approximately 3-4 cm - posterior limit of proposed lobectomy:

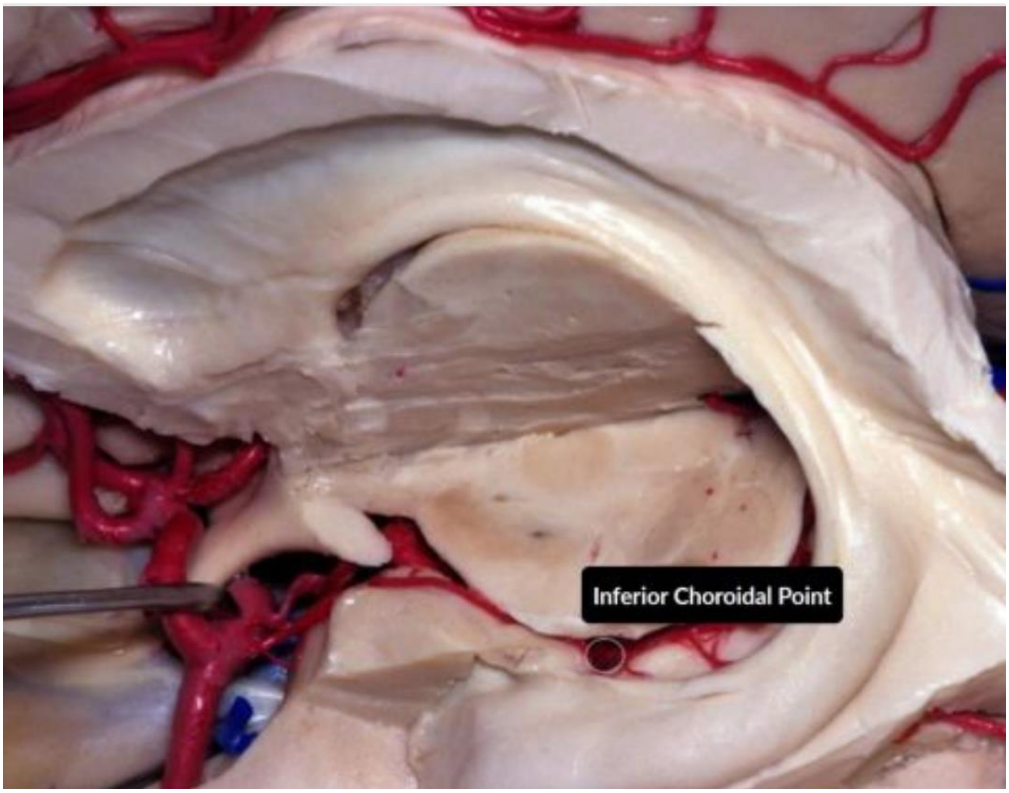


N.B. identify temporal horn early – guides anatomy! – *do not resect above TH*, i.e. care is taken not to dissect superiorly into temporal stem.

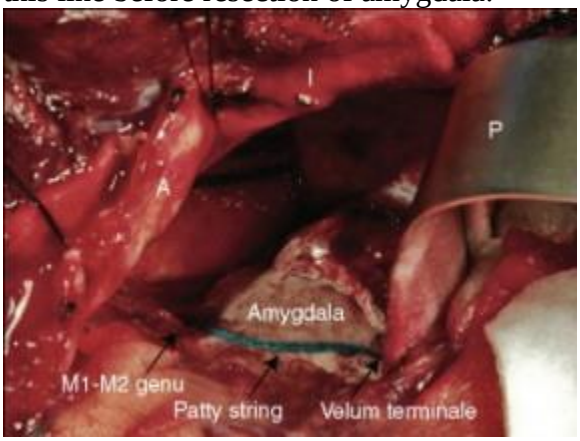
- while searching for temporal horn, if one misses it and dissects too far superiorly, temporal stem, basal ganglia/amygdala complex, and then crus cerebri may be entered;

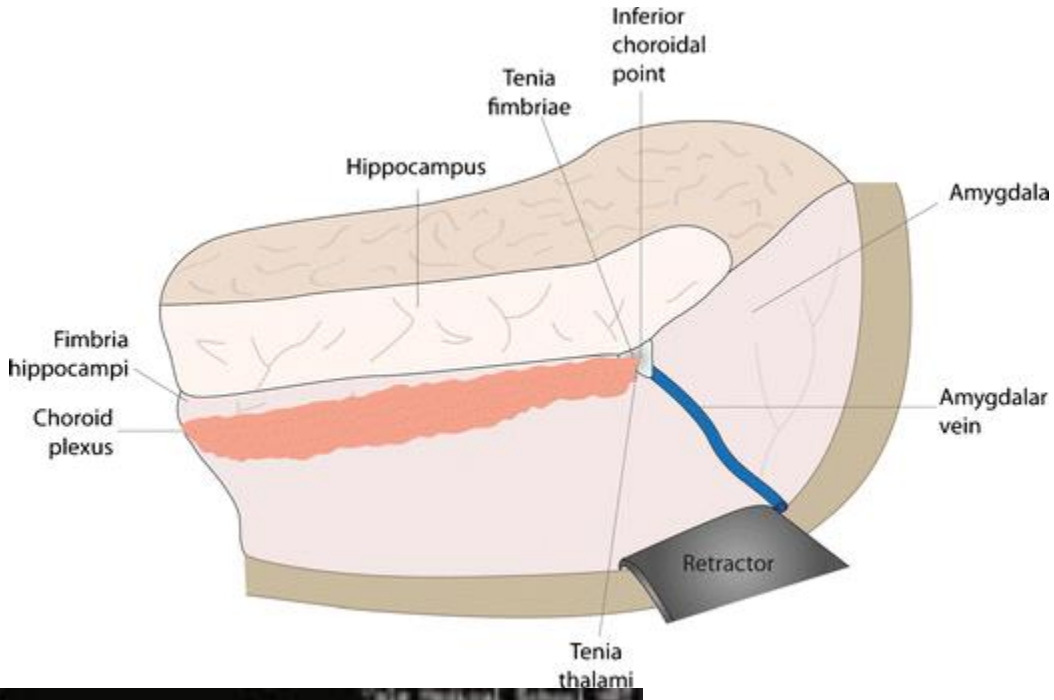
- using irrigating bipolar and sucker, ***middle and inferior temporal gyri*** are removed as single surgical specimen.
- ***medial temporal pole*** is resected subpially from its anterior aspect until **middle cerebral artery (MCA)** is exposed, then remainder of amygdala is resected inferior to line between velum terminale (inferior choroidal point) and genu of MCA at junction between the M1 and M2 segments.

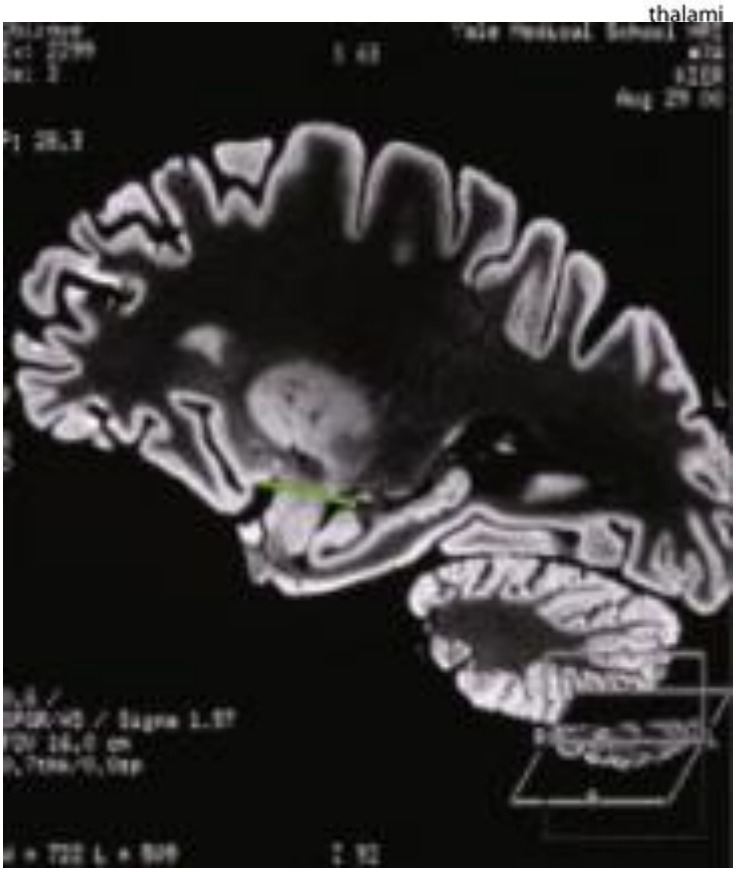
The inferior choroidal point communicates the ambient cistern with the temporal horn and is the point of entry of the anterior choroidal artery, which supplies the choroid plexus of the temporal horn, among other structures.



– **velum terminale** is union of taeniae of fimbria fornicis and stria terminalis at origin of choroid plexus; resecting inferior to this line prevents injuring basal ganglia and crus cerebri.
N.B. if surgeon resects tissue above *line between M1 and velum terminale*, temporal stem, basal ganglia/amygdala complex, and crus cerebri also may be injured - patty string has been laid along this line before resection of amygdala:





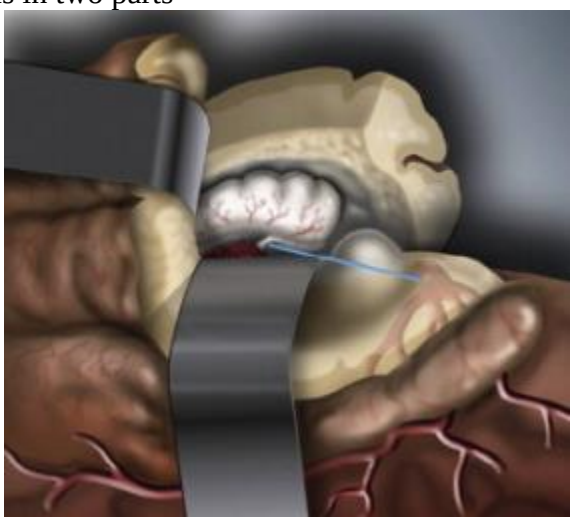


How much hippocampus needs to be removed – more than 2 cm (some say at least 3 cm);

Class I evidence: removing more hippocampus does not adversely affect memory but improves seizure outcomes!

neuronal loss in CA1 has gradient from anterior to posterior (if marked cellular loss is found at most posterior extent of hippocampal resection - high correlation with persistent seizures).

- use Greenberg 3/8 retractor blades.
- use microscope.
- resect hippocampus in two parts



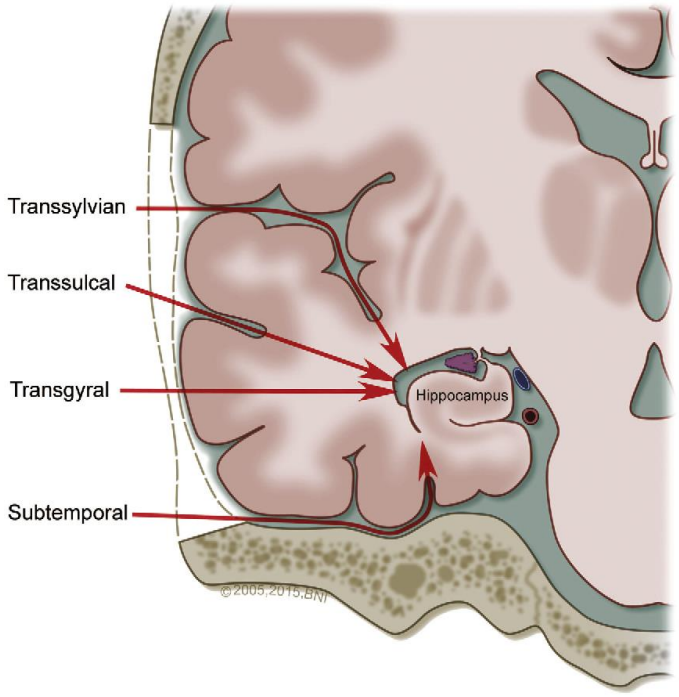
- choroid plexus is protected underneath patty and retracted medially toward thalamus (*choroid plexus should not be coagulated* because this may lead to injury of anterior choroidal artery → ischemia of internal capsule and lateral thalamus; manipulation of choroid plexus should be minimized to prevent it from bleeding).

  N.B. never retract above choroid plexus!

  "Choroid plexus is your friend – guides anatomy!"
- care is taken to avoid dividing any vessels that are not clearly going into hippocampus because occasionally thalamic perforators can be seen in this area
- at choroid fissure there is arcade of 1-4 small feeding arteries passing through pia to hippocampus - these must be isolated, coagulated, and then divided (avulsion of these branches from parent vessels in incisura may result in infarction of posterior limb of internal capsule, with attendant hemiparesis).
- subpial dissection and endopial aspiration of the hippocampal formation is accomplished with the ultrasonic dissector (CUSA) set at very low parameters of vibration and suction

Structures at risk: CN3, optic tract, PCA and PComA, cerebral peduncle, anterior choroidal artery

SELECTIVE AMYGDALO-HIPPOCAMPECTOMY (SAH)



Semiology: dyscognitive seizures consistent with mesial temporal onset, ± aura (typically smell, epigastric sensation, fear, déjà vu)
MRI: mesial temporal sclerosis positive (MTS+) or negative (MTS-)
PET: temporal lobe hypometabolism lateralized or greater on the same side as EEG
VideoEEG: localization to anterior temporal region (e.g., F7/T1 or F8/T2)
Neuropsychological testing (assume normally organized memory function):

- domain-specific memory decline present on side of anticipated ablation - SAH acceptable
- in absence of domain-specific memory decline referable to side of ablation:

MTS+: SAH acceptable (but if there is domain-specific memory loss on contralateral side, Wada test is considered)
MTS-:
nondominant side - SAH is acceptable (i.e. absence of visuospatial memory decline is acceptable for nondominant SAH)
dominant side – consider RNS (i.e. normal verbal memory is incompatible with dominant-side SAH)

Rephrasing:
damaged hippocampus (either MTS+ or ipsilateral [domain-specific] memory decline*) is acceptable for ablation.
*if ipsilateral memory is normal but contralateral memory is declined, do WADA (if fails WADA, do RNS instead of SAH); if ipsilateral and contralateral memories are normal, assume that contralateral hippocampus took over (WADA test may give reassurance before proceeding with SAH)
intact (visuospatial memory, MRI-) nondominant hippocampus is acceptable for ablation.
intact (verbal memory, MRI-) dominant hippocampus – do RNS (or VNS) instead of SAH.

N.B. electroclinically typical temporal lobe epilepsy but intact (verbal memory, MRI-) hippocampus – be careful it is not a mimicker (epilepsy and normal lobe function are hardly compatible) – consider SEEG!

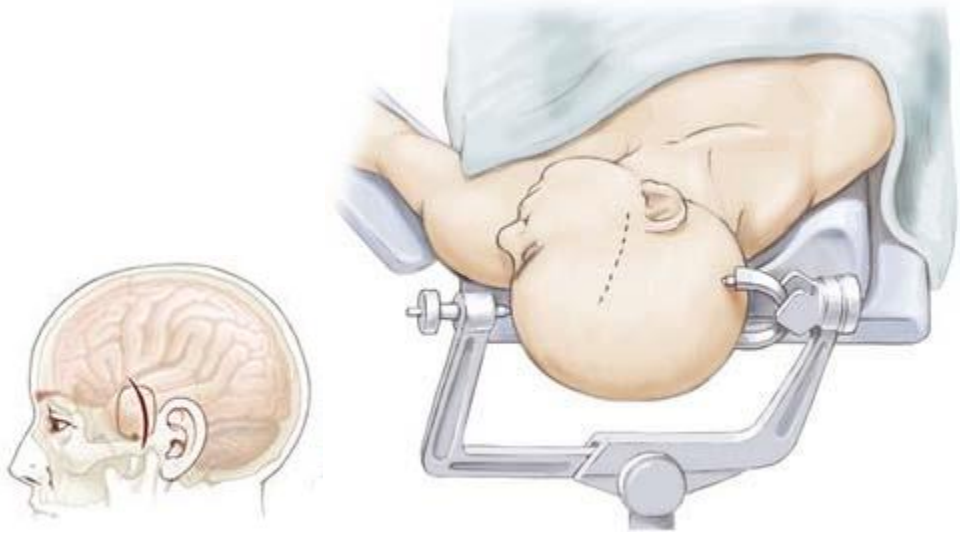
Intracranial EEG (indicated only in setting of ambiguity as to seizure onset zone from noninvasive studies): onsets referable to ipsilateral mesial temporal lobe + absence of contralateral onsets.

- in MTS- (nondominant side), if positive PET is concordant with videoEEG, may proceed directly to SAH without icEEG, however, *maintain a low threshold for iEEG in MTS- cases*
- if icEEG is needed, use depth electrodes with orthogonal trajectory to provide lateral and mesial temporal coverage.
- if minimally invasive procedure (such as LITT or RNS) is anticipated, try to avoid macro invasive diagnostic approach (such as grids or even strips).

RNS does not preclude later LITT/SAH.

TRANSCORTICAL- TRANSVENTRICULAR APPROACH

- linear incision starting at the zygoma and curving slightly backwards



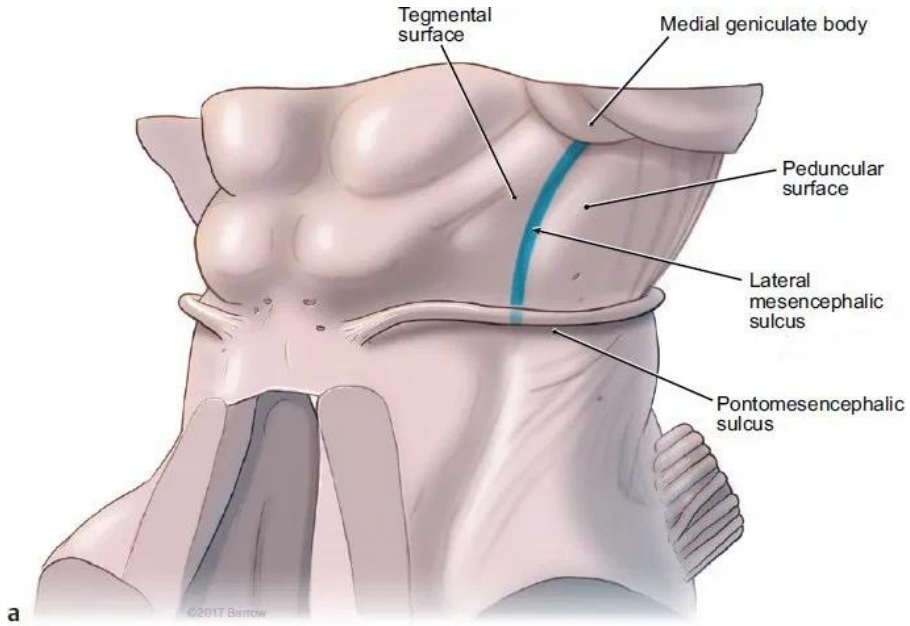
- temporal muscle is split along its fibers and held with a self-retaining retractor. A burr hole and craniectomy is made through the temporalis muscle and centered over the second temporal gyrus.
- keyhole 2-3 cm longitudinal cortical incision through *middle temporal gyrus* centered at a point ≈ 3-4 cm posterior to temporal tip.

LITT

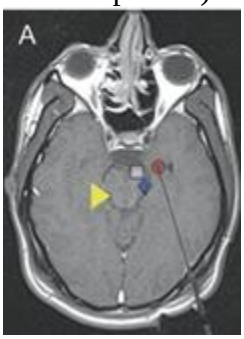
- LITT largely preserves naming / object recognition following language dominant ablations, functions that commonly decline following ATL or SAH.

Ablations must prioritize amygdala and also include hippocampal head, parahippocampal gyrus, and rhinal (entorhinal, perirhinal) cortices to maximize chances of seizure freedom.

Ablations posterior to the lateral mesencephalic sulcus yields diminishing returns + increased damage to optic radiations



- safety points (to automatically terminate laser delivery if these structures exceeded 45°C or even 43°C):
    1) lateral thalamus
    2) basal ganglia
    3) optic tract
    4) lateral mesencephalon (white square in anterior mesencephalon, and blue diamond in lateral mesencephalon):



Complications:

1) **visual field defects (VFD)** - due to optic radiation damage (either at Meyer's loop by laser heating or occipitally by laser passing through optic fibers).
    - prophylaxis - optic radiation mapping through DTI, avoid ablating hippocampus tail.
    - incidence is much lower than after ATLs (37% vs. 64%)
2) CN3-4-5 palsy – due to heat and/or inflammatory injury; tend to resolve in 12 mos

RNS

Implantation strategies for unilateral MTS:

a) depth along hippo axis + anterior subtemporal strip

b) depth along hippo axis + depth in parahippocampal gyrus

OUTCOMES

Seizure freedom (at 1 year)
ATL – 75% (< 50% in long term)
SAH – 67%
LITT – 58% Engel I (77% Engel I or II)*
*60-89% seizure freedom in patients with radiographic evidence of hippocampal sclerosis

Causes of "failure"

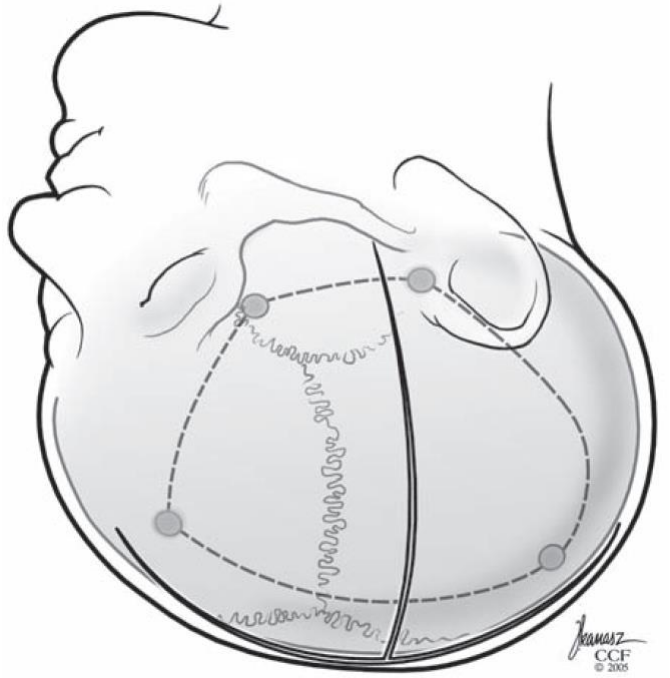
1. **Incomplete resection** of epileptogenic zone
2. **Incorrectly diagnosed** epileptogenic zone
3. **Dual pathology** – discrete lesions in same temporal lobe (e.g. MTS and FCD)
4. **Temporal +** epilepsy
5. **Bitemporal** epilepsy
6. **New** epileptogenesis

See Case F2 >>

ANATOMICAL HEMISPHERECTOMY

- entire hemisphere, excluding *basal ganglia*, anatomically removed from cranium → potentially lethal **hydrocephalus** and progressive potentially lethal **superficial cerebral hemosiderosis**.

- ideal candidate has a contralateral hemiparesis and hemianopsia without fine finger movements.
- **WADA test** may be of use in older patients before dominant hemispherectomy.



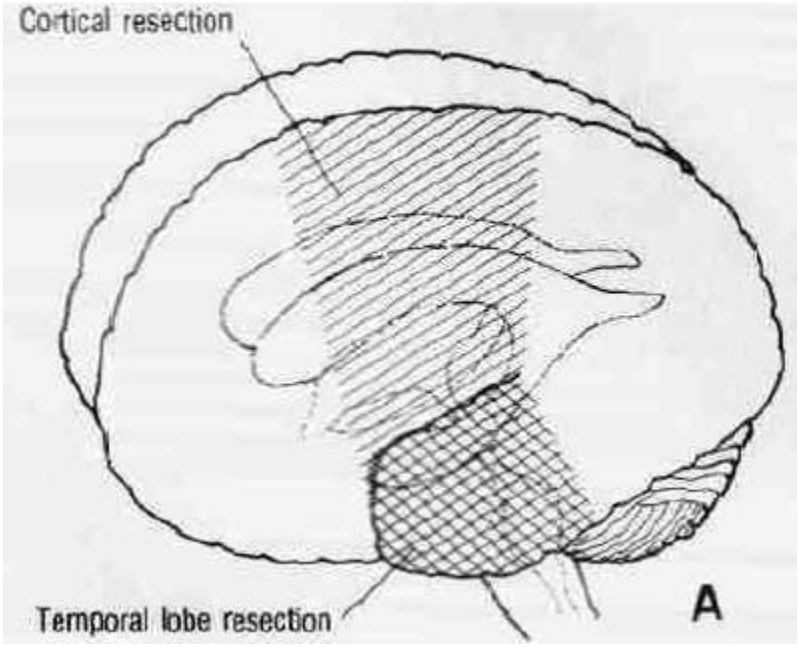
FUNCTIONAL HEMISPHERECTOMY

- combination of ablation and disconnection:
    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).

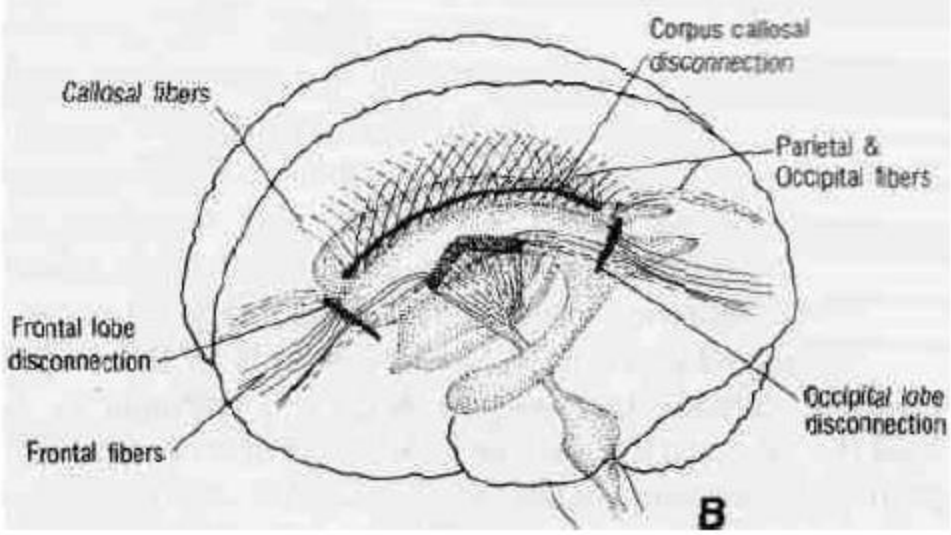
Indication

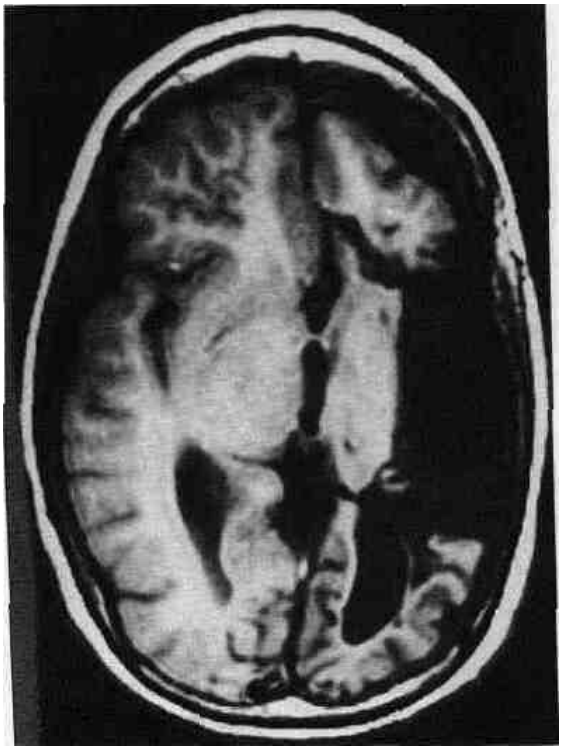
- severely incapacitating unilateral seizures (when foci cannot be isolated) associated with permanent hemiplegia (with useless hand), hemisensory loss, hemianopia, hemiatrophy; i.e. when entire hemisphere is considered epileptogenic with little or no remaining functional cortex.

A. Shaded area - cortical resection in central region, cross-hatched area - temporal lobe resection.



B. Incisions in corpus callosum and deep projection fibers in white matter disconnecting remaining frontal and occipital lobes.





CORPUS CALLOSOTOMY

Disconnection syndrome **(split brain)** – transient: lethargy, mutism, apathy, confusion, bilateral frontal lobe reflexes, ideomotor apraxia of nondominant hand (usually left), incontinence.

- best seizure results come from complete callosal section.

80-90% section sparing *splenium* seems to be optimal.

- advisable to perform in two stages (anterior-posterior) - avoids acute prolonged apathy and confusion seen after complete division in single stage
    1. First stage resects **anterior 2/3** of corpus callosum.
    2. If necessary, **complete** callosotomy is performed at second stage (↑risk of disconnection syndrome)

INDICATIONS

- rarely performed today (replaced by **VNS**; in the past, Corpus Callosotomy was the only applicable surgery for **GENERALIZED seizures**).
- indications - primarily and secondarily GENERALIZED seizures (esp. Lennox-Gastaut syndrome*).
  *treatment of choice for Lennox-Gastaut syndrome is VNS
- **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
  Drop seizures – 60-100% responder rate (> 50% seizure reduction)

PREOPERATIVE

1) **Wada testing** – for R-handed person with right-hemisphere language dominance or L-handed person - if WADA shows ***mixed cerebral dominance*** for handedness and language ("crossed dominance") - risk for *postcallosotomy persistent severe aphasia*.
2) coronal **MRI** – may find *singular (s. simian) pericallosal artery*.

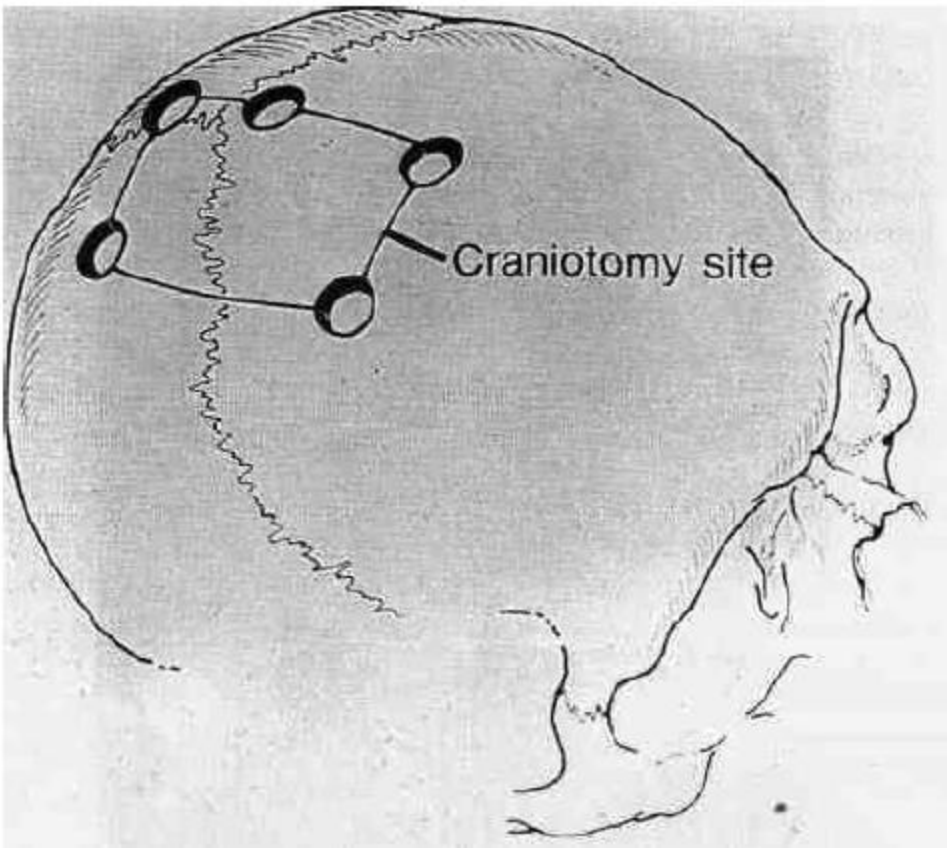
- routine extensive neuropsychological testing is not required.

ANESTHESIA

- most dangerous complication - **air embolism** (tear in superior sagittal sinus).
- **bleeding** from sagittal sinus can be extensive – do not to start surgery without transfusable blood in operating room for pediatric cases.

Better LITT! - need 3 laser trajectories - on one (nondominant) side and ablate full thickness of CC

SURGERY



- problem where falx ends – sometimes cingulate gyri are adherent – dissect meticulously (esp. vessels) – ***lysis of midline adhesions*** between arachnoid and dura is performed using bipolar cautery.
- attempt to preserve *bridging veins*, but 1 or 2 veins (anterior to coronal suture) can be sacrificed.
- need clear visualization of both *pericallosal arteries* (without this verification, inexperienced surgeon may mistake cingulate gyrus for callosum) – separate them
- incision is carried into CC until cavum septum pellucidum is entered.
- stay within cavum septum pellucidum and avoid entry into ventricle (→ chemical meningitis that might be fatal)
- entire rostrum, genu, and body are divided → dissection is carried posteriorly until ***only splenium remains intact***;
- if second stage is required, craniotomy is performed using more posterior bone flap.

VNS

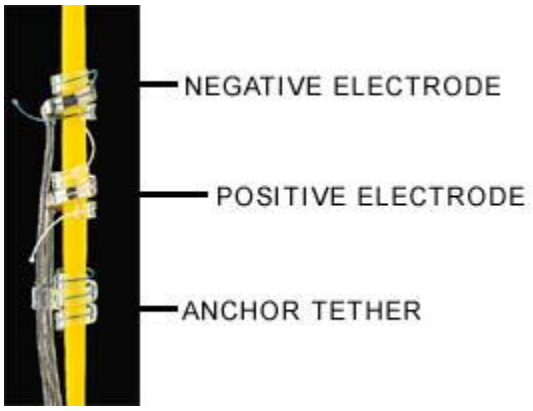
- FDA approved in 1997: *adjunctive therapy for reducing the frequency of seizures in patients > 4 years with partial-onset seizures refractory to antiepileptic medications*" in patients > 12 years
- effectiveness in **generalized** epilepsy (VNS is treatment of choice for Lennox-Gastaut syndrome)

  N.B. *on label* is only for **partial** epilepsy! (*off label* can use for **generalized** epilepsy – VNS works very well!!!)

- FDA approved (2007) as adjunctive long-term treatment of chronic / recurrent depression in patients > 18 years with a major depressive episode not adequately relieved by ≥ 4 antidepressant treatments

- **ECG** – look for AV node or bundle branch blocks – high risk of cardiac side effects during VNS stimulation.

Minus goes cranial:



sleep apnea (in adults, esp. if 500 msec pulse width is used).

- 50% reduction in seizure frequency in 60% of patients after 2 years of therapy (76% at 8 years)
- up to 8% patients become seizure free.

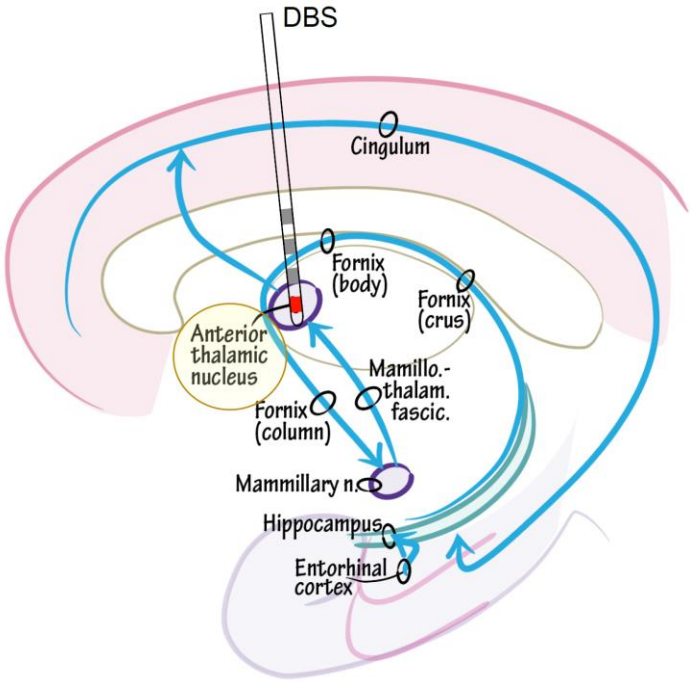
DBS of ANT

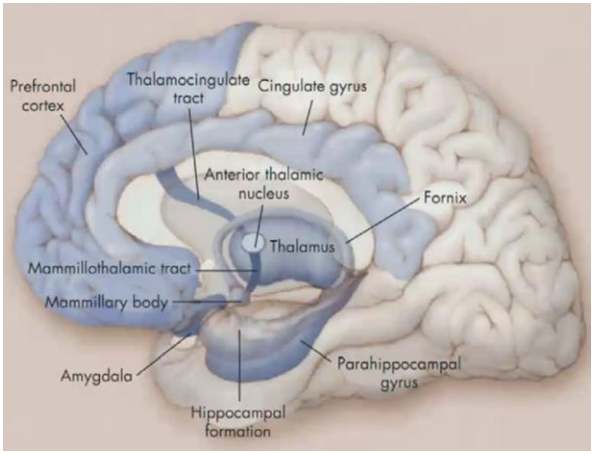
May 1, 2018 FDA has granted premarket approval for Medtronic's DBS therapy:

- adjunctive therapy for reducing the frequency of seizures
- bilateral anterior thalamic nucleus stimulation
- 18 years of age or older
- **partial-onset** seizures, with or without secondary generalization
- refractory to **≥ 3** antiepileptic medications.
- ≥ 6 seizures per month over the 3 most recent months (with no more than 30 days between seizures).

vs. Centromedian nucleus - majority of data support CMT DBS for generalized epilepsy

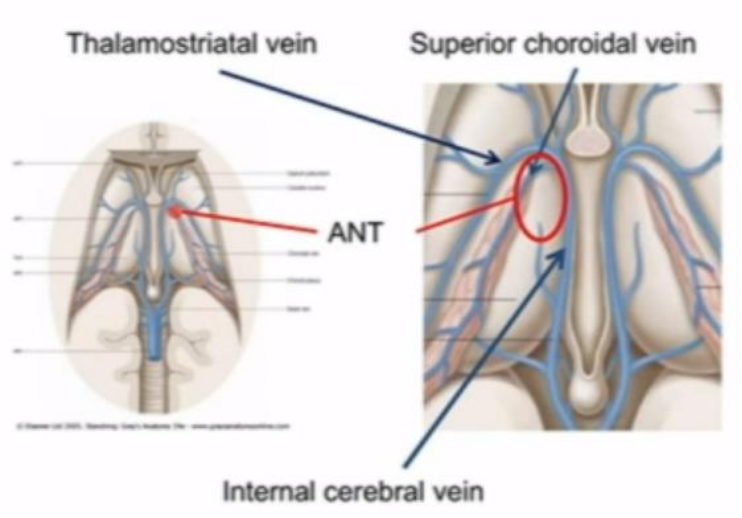
Central node of **Papez circuit**

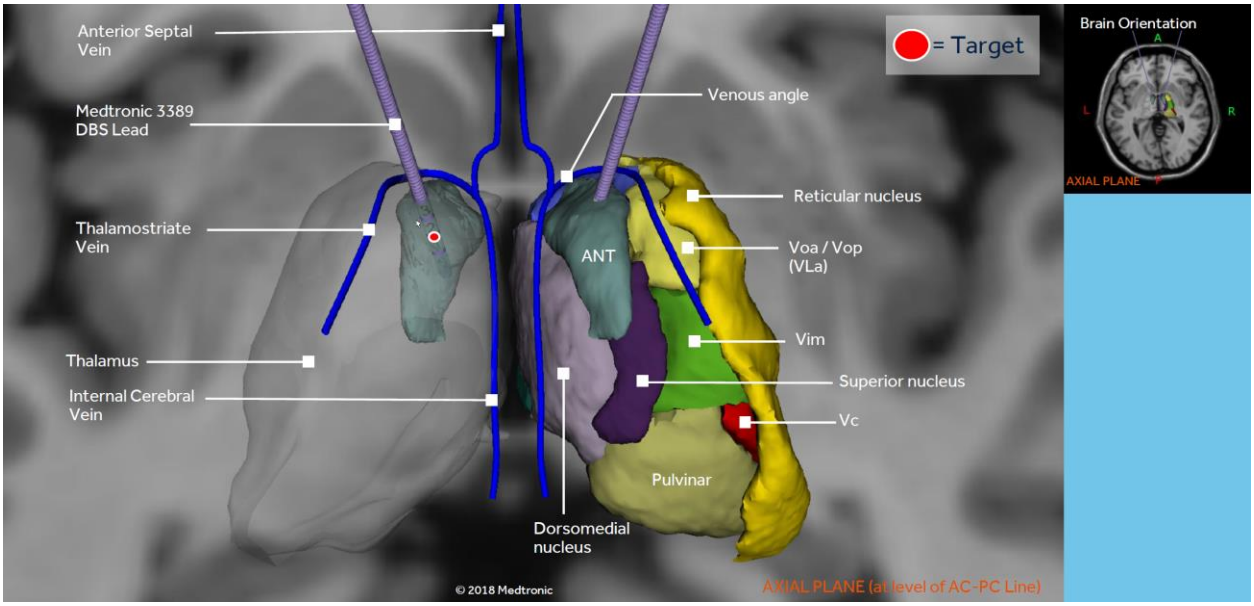




Fronto-temporal epilepsies may respond best (as opposed to parieto-occipital epilepsies).

- partially enveloped (isolated from the rest of thalamus) by a myelin-rich sheath belonging to the ***mammillothalamic tract (MTT)*** and the ***internal medullary lamina***
- surrounded by plexus choroideus (superior choroidal vein), thalamostriate vein, and internal cerebral vein:





Nucleus (antero)principalis

- superior, anterior part of ANT
- best stim contacts – 2-3 mm above where mammillothalamic tract terminates.

High anatomical variability (more variable coordinates than any other stereotactic target) – direct targeting is preferable!
MRI FGATIR on 3T scanner
Best in transventricular trajectory as in SANTE trial

BrainSense™ technology - captures **local field potentials (LFP)** using the implanted DBS lead simultaneously while delivering therapeutic stimulation
SenSight (Medtronic) – directional 1-3-3-1 lead
or older **lead 3389**
Use "at target" cannula;

1. **Psychiatric** side effects

- SANTE: depression 37.3% (vs 1.8% in controls) – patients need to be watched closely! + slow titration
- changing stim contacts almost always helps.

2. **Cognitive** side effects

- SANTE: ***subjective*** memory impairment 27.3% (vs 1.8% in controls); all resolved with no group differences on ***objective*** neuropsychological testing.

  At 7 years: no significant cognitive declines or worsening of depression scores were observed through the blinded phase or at year 7.

Phase I (start 2-3 weeks postop) – **increasing output**
Amplitude – start at 0.5 mA (old way - 1.5-2.0 V) and increase q2-4 weeks by 0.5 mA (0.5 V) (or even longer intervals – analogy with adjusting AEDs) up to 4 mA (4.5-5.0 V, up to 9.0 V); most patients need 2-3 mA.

- gradual amplitude increase helps to minimize occurrence of psychiatric side effects
- keep symmetrical between sides.
- corresponds to 4-7 mA (some experts recommend current-based programming to mitigate impedance effects that maybe very asymmetric)

Pulse width 90 msec (this is invariable*)
Frequency 145 Hz (this is invariable*)
*hardware allows to change it but in studies it did not make any difference
Duty cycle: 1 min on, 5 mins off.
Monopolar

- usually most centrally located contact
- do not use contacts with low impedances – electrical current will shunt into CSF (not into parenchyma).
- contacts in thalamus but outside ANT cannot stimulate ANT as white matter capsule creates barrier.
- alternative – wide bipolar stim (anode most distal).
  N.B. bipolar stimulation is used to limit current spread into surrounding structures.

Phase II – **changing cycling**
Decreasing off time from 5 to 3 min.

OUTCOMES

- it takes time for efficacy to build up (vs. DBS in movement disorders).
- seizures may intensify upon initiation of stimulation.
- patients with ≥ 50% reduction in seizures (median seizure reduction numbers are very close):
  7 years - 74% (18% experienced at least one 6-month seizure-free period)

RNS

FDA APPROVED (2013)

- *adjunctive* therapy in **reducing frequency of seizures** in individuals ≥ 18 years**** with **partial onset** seizures who have undergone diagnostic testing that localized **no more than 2* epileptogenic foci**, are **refractory** to ≥ 2 antiepileptic medications, and currently have ***frequent**** ***and disabling***** ***seizures***.

*Neuropace has receptacle only for two leads.
** ≥ 3 disabling seizures per month over three most recent months (with no month with fewer than two seizures); RNS® System has not been evaluated in patients with less frequent seizures.
***motor partial seizures, complex partial seizures and / or secondarily generalized seizures
****FDA indication for RNS is age > 18 years, but it likely has efficacy in children (limitation - skull thickness before it reaches adult size).

Summary

a) ≥ 2 foci

b) eloquent areas
c) mesial temporal lobe (uni- or bilateral)
d) difficult to resect (e.g. insula, large regional onsets, interhemispheric)
e) failed previous surgery or VNS (24% RNS patients have VNS)

VNS, RNS, and DBS are all palliative and comparable in efficacy, both in pivotal trials and over longer-term trials. VNS is sometimes a first choice as it is extracranial. A specific scenario where RNS may have an advantage is ***bilateral mesiotemporal epilepsy*** – RNS allows for long-term ECoG recording, which may in turn (occasionally) allow for eventual resection (of seizure-dominant hippocampus or prove that "bilateral" disease is de facto unilateral).

- at 9 years:
  75% median seizure reduction.
  73% responder rate (≥ 50% seizure reduction)
  at least one seizure-free period lasting:
  ≥ 6 months - 28% of patients

LITT

- based on Arrhenius equation:
  Temperature ≤ 43º - tissue damage never occurs, no matter how long exposed.
  Temperature ≥ 60º - instantaneous tissue damage (protein denaturation).

- high safety points set at 90°C (automatic laser turn off) if temperature **at any voxel** reaches 90º (don't want to reach 100º where gas bubbles and eschar form).
- low safety points, set at 43°C
- LITT is not good for:
  1) extra-axial tumors; exception – separation surgery for spinal epidural tumors (gives margin for SRS to spare cord) but respirations are problematic for MRI monitoring.
  2) calcified lesions
  3) hypervascular
  4) cystic
  5) diffuse and large
- previous craniotomy - resist urge to go through resection cavity – may bleed into it.
- target size: creates 25-35 mm **diameter** lesion.
- thermography lag 5-8 sec H: slow heating.
- if skull is too thin (< 3-4 mm) to use bolt, may use skull-mounted AXiiiS mini-frame.
- **FLAIR** is best to confirm position of laser probe (i.e. first MRI sequence to obtain)
- **Gradient Recalled Echo (GRE)** pulse sequence for ablation thermography.
- ablation volume plateaus at 200 sec (3.5 mins) – so turn power up → bigger and faster ablation, but MRI more inaccurate.
- Blue line – treatment area (equivalent of 43°C for 10 minutes duration)
- Yellow line – time-dependent thermal damage area – equivalent of 43°C for 2 minutes - *keep 1-3 mm away from eloquent brain*

Immediate postoperative MRI - T1w gadolinium (MPRAGE) or GRE

Home with DEX 4q6 for 7 days then rapid taper.

UMN & LMN DISORDERS

LOWER MOTONEURON (LMN) = α-motoneuron – neuron directly innervating **striated skeletal muscles**.

UPPER MOTONEURON (UMN) – term used in two senses:

a) ***senso stricto*** – cortical neurons forming **tractus pyramidalis**.
b) ***senso lato*** – all neurons forming descending tracts that **ultimately play on LMN** (tr. pyramidalis, tr. reticulospinalis, tr. rubrospinalis, tr. vestibulospinalis, etc).

muscle tone = resistance to passive muscle stretch

TONUS↓ - A(HYPO)TONIA (S. FLACCIDITY) - *LMN disease*, *cerebellar disease*, *sensory nerve damage*.

TONUS↑:

a) SPASTICITY - *UMN disease*

Modified Ashworth scale (MAS) measures spasticity:

0: No increase in muscle tone

1: Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension.

1+: Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM.

2: More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.

3: Considerable increase in muscle tone, passive movement difficult.

4: Affected part(s) rigid in flexion or extension.

b) RIGIDITY - *extrapyramidal UMN disease*.
c) PARATONIA / GEGENHALTEN (German "hold against") – *diffuse forebrain dysfunction* (*dementia*, *frontal lobe* or *thalamic disorders*).

TREATMENT OF SPASTICITY

Spasticity may be helpful in compensating for weakness

1. **Stretching exercises** (to maintain joint mobility).
2. **Local injections** of BOTULINUM TOXIN (effect for 3-6 months).
3. **Drugs with systemic effects**

$GABA_B$ agonist - **BACLOFEN** (20-240 mg/d in divided doses q8hrs*) - most effective drug available!
*i.e. single oral max dose is 70-80 mg

Baclofen withdrawal – "itchy, twitchy, bitchy" (severe itching, excessive sweating, spasticity↑ → severe rigidity, fever, irritability/insomnia/confusion/agitation/hallucinations, labile blood pressure, seizures; potentially lethal - rhabdomyolysis, DIC, organ failure - can look like autonomic dysreflexia, malignant hyperthermia (vs. opioid withdrawal), septic shock.

Treatment - options:

1) ORAL BACLOFEN – titrate up to max 240 mg/d – balance spasms vs CNS depression
2) IV DIAZEPAM, 2-10 mg q 6-8 hours PRN
3) CYPROHEPTADINE 6 mg q 6 hours
4) DANTROLENE 2.5 mg/kg IV daily.
5) if due to IT system failure and unable to replace full dose orally → insert temporary IT catheter and post for surgery;
6) if for IT system infection, start antibiotics and, as long as patient is not septic / meningitic, ***titrate IT rate down*** to where oral replacement becomes feasible (target 240 mcg/d)

Baclofen overdose - somnolence, respiratory depression, hypothermia, seizures, rostral progression of hypotonia, coma.

Treatment: no antidote

- if no heart conduction defects, PHYSOSTIGMINE 0.5-2 mg reverses central effects.
- **aspirate drug** from pump reservoir + **aspirate CSF** 30-40 mL.
- central effects of overdose clear in 24-48 hours.

$GABA_A$ agonist - DIAZEPAM
direct muscle inhibitor - DANTROLENE

4. **SURGICAL MEASURES – NEUROSURGICAL**
    1) **intrathecal baclofen delivery system**.
    2) **selective posterior rhizotomy** (procedure of choice for *spasticity due to cerebral palsy*) - can be done **percutaneously** at any segment
    3) **spinal cord stimulation (SCS)** caudal to injured level

LMN lesion
"Three **A**":

1. **A(hypo)reflexia**

2. **A(hypo)tonia**
3. **Atrophy** of *denervation* (early & severe)
4. **Paralysis of individual muscles**
5. **Fasciculations**, **Fibrillations**

EMG - ***recruitment*** of motor units is delayed / reduced

Bulbar Paralysis – peripheral (LMN) palsy of CN 9, 10, 12:

1. **3D**: **d**ysphagia, **d**ysphonia, **d**ysarthria
2. **Absent swallowing & gag reflexes** (vs. in pseudobulbar paralysis!)
3. Tongue atrophy and fasciculations

Pseudobulbar palsy – bilateral supranuclear palsy of CN 7, 9, 10, 12:

1) *spastic* 3D (dysarthria, dysphonia, dysphagia)
2) *bifacial* paresis
3) *hyperactive* reflexes (gag, facial, jaw jerks)
4) *oral automatisms* (snout, suck, etc)
5) *emotional incontinence* (reflexive *crying* and spasmodic, mirthless *laughing* with minimal provocation)

"Locked in" Syndrome (s. Pseudocoma)

- bilateral *basis pontis* lesion, i.e. damage to corticospinal-corticopontine-corticobulbar tracts *below reticular formation* (therefore sparing consciousness – normal EEG) but *above ventilatory nuclei of medulla* (therefore, precluding death).

- most commonly due to ***basilar artery infarction***; other causes - *central pontine myelinolysis*.
- almost complete de-efferentation:
    1) **quadriplegia** – due to corticospinal tracts damage.
    2) paralysis of **horizontal eye movements** (horizontal ophthalmoplegia) – due to PPRF and CN6 nuclei, corticopontine tracts damage.
    3) paralysis of **jaw-face-bulbar muscles** (facial & bulbar diplegia; no volitional vocalization!) – due to CN7 nuclei, corticobulbar tracts damage.
- very resembles coma, but:
    1) fully ***conscious*** and ***mentally intact***
    2) ***can feel, see, hear***
    3) preserved ***vertical eye movements*** – the only way to communicate!; when patient is not actively moving eyes, spontaneous ***ocular bobbing*** may occur.
    4) eyes are open and partially ***blink*** (via inhibition of levator palpebrae) – another way to communicate!
- if lesion also affects *dorsal pontine tegmentum* → sudden coma, pinpoint pupils, ophthalmoplegia, hyperthermia, progression to death.
- survival in locked-in state has lasted as long as 18 years.

Similar state may occur in Guillain-Barré syndrome, but *vertical eye movements are not selectively spared*.

Paraparesis

- lesion location is bilateral (!):

Lesion Location	Pattern of Signs
Medial hemispheres	Spastic leg paraparesis with no sensory level
Thoracic spinal cord	Spastic leg paraparesis, thoracic sensory level
Lumbar spinal cord	Flaccid paraparesis, double incontinence (flaccid bladder and sphincters)

Cerebellar disorders

In cerebellar disorders vision has no effect on clinical signs! N.B. exceptions exist!
vs. vestibular, proprioceptive disorders

Romberg sign might be present or absent, depending on site of cerebellar lesion!

MOVEMENT DISORDERS

BASAL NUCLEI, MOVEMENT DISORDERS

Term "EXTRAPYRAMIDAL DISORDERS" is now replaced by more descriptive and accurate term "MOVEMENT DISORDERS"!

For all hyperkinesias / dyskinesias – antidopaminergics! (vs. hypokinesia / parkinsonism – dopamine agonists)

All (!) motor disorders fall into TWO CLASSES OF DEFICITS:

A. **PRIMARY FUNCTIONAL DEFICITS (negative signs)** – loss of function of damaged neurons.

B. **SECONDARY DEFICITS (positive signs / release phenomena)** – abnormal patterns of action when controlling input (usually inhibitory) is destroyed.

HYPERKINESIAS = DYSKINESIAS – ***involuntary*** movements

N.B. excessive ***voluntary*** movements (e.g. in attention deficit disorders, mania) are not hyperkinesias!

HYPOKINESIAS (***supplementary motor cortex, corpus striatum, subst. nigra***) – decreased ***amplitude/speed/amount*** of movement without paralysis

Fatigue is particularly prominent in hypokinesias.

"hypokinetic syndrome" = "parkinsonism".

COGNITIVE dysfunctions (***nucl. caudatus***), **AFFECTIVE (LIMBIC)** dysfunctions (***nucl. accumbens***).

HYPOKINESIA (dopamine↓, Acch↑, serotonin↑, GABA↑, prolactin↑) H: dopamine agonists, anticholinergics.

HYPERKINESIA (dopamine↑, Acch↑, serotonin↓, GABA↓) H: dopamine antagonists, anticholinergics.

Basal nuclei → contralateral signs
Disorders of basal ganglia *do not cause weakness or reflex changes*!!!

Cerebellar hemisphere → ipsilateral signs

Tics (brief, stereotypic, repetitive but nonrhythmic!, suppressible by patient!; can persist during sleep); treatment – **dopamine antagonists** (PIMOZIDE, FLUPHENAZINE, HALOPERIDOL)

Gilles de la Tourette syndrome - motor AND vocal tics for > 1 year (e.g. coprolalia); starts at age < 18 yrs; various prognosis; may develop ***obsessive-compulsive disorder, ADHD***

a) ***neuroleptics (dopamine receptor blockers)*** - PIMOZIDE, FLUPHENAZINE, HALOPERIDOL.
b) ***dopamine depleters*** (TETRABENAZINE).
c) DBS of thalamus (centromedian nucleus)

transient tic disorder of childhood - motor OR vocal tics with duration < 1 year.
chronic tic disorder - motor OR vocal tics (but not both!) for > 1 year.

Athetosis (**slow**, twisting-writhing, large amplitude movements of ***distal limb muscles***)

Chorea (involuntary **rapid, jerky, multiple, unpredictable** movements that flow from one body part to another – generally ***distal limb & facial muscles*** – primena "nenustygimą vietoje"); treatment – **dopamine antagonists**

Huntington disease = prototypic chorea

Ballismus ("violent chorea, involving ***proximal limb muscles***") – contralateral ***nucl. subthalamicus*** lesion; treatment – **dopamine antagonists**

N.B. **most severe hyperkinesis**! (death may result from exhaustion)

Myoclonus (**unpredictable** jerks of ***limbs or trunk***; persist during sleep); H: CLONAZEPAM!!! – drug of choice.

Asterixis - *most common form of negative myoclonus*

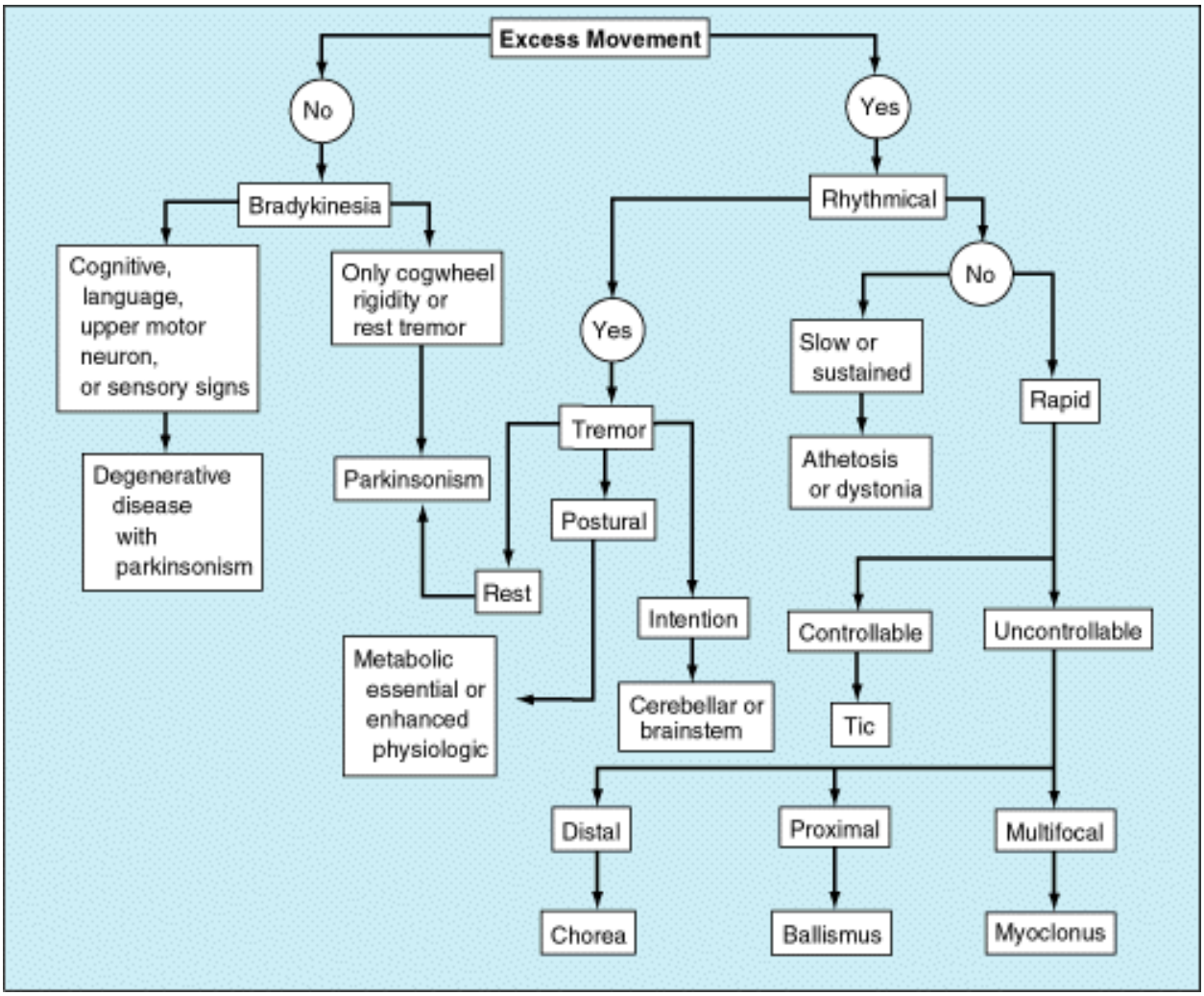
Dystonia (long sustained twisting movements of ***axial muscles***)

- treatment: ***anticholinergics***, ***dopamine-depleting drugs***, BOTULINUM A TOXIN.

Akathisia - compulsion to stereotypically move ***extremities*** (usually legs)

Tremor – **regular (rhythmic) oscillatory** movements!:

a) rest – PD - ***substantia nigra (pars compacta)***
b) postural / action – ET - ***no specific structural abnormality***
c) intention – ***cerebellar/brainstem***



Ataxia:

Friedreich ataxia (trinucleotide repeat) (***pyramidal*** tracts, ***spinocerebellar*** tracts, ***posterior columns*** + AXONAL sensory ***neuropathies***) - in lower limbs: proprioreceptive ataxia (vibration & position sense↓) + areflexia + cerebellar dysarthria + hypertrophic obstructive cardiomyopathy; Dx: MRI (severe atrophy of cervical spinal cord) + DNA diagnosis

ataxia-telangiectasia - ATAXIA + TELANGIECTASIAS + IMMUNODEFICIENCY

spinocerebellar ataxias – AD with onset in adults (***olivopontocerebellar atrophy*** + degeneration of ***ascending spinal pathways***)

acute cerebellar ataxia - Acute viral cerebellitis, Postinfection immunologic syndrome

- *no specific treatment*!

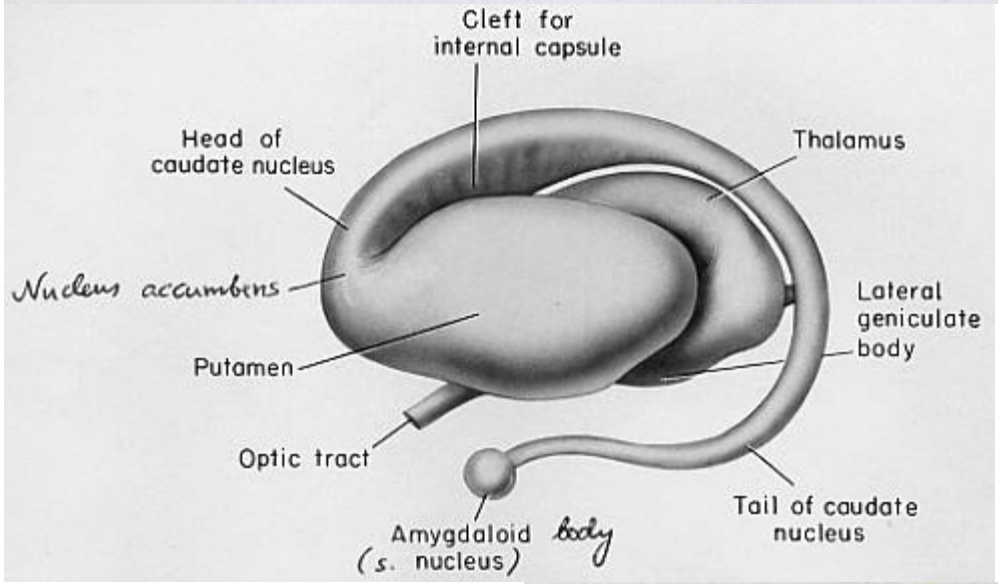
NORMA

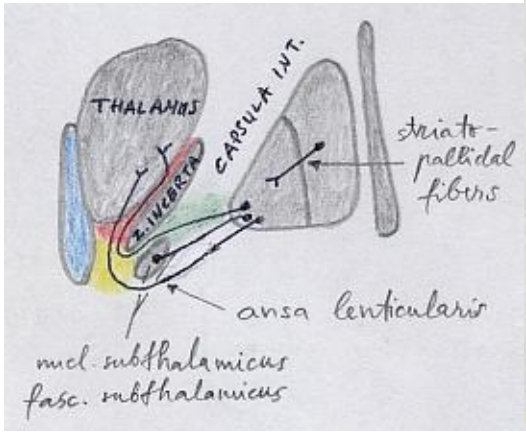
Archistriatum = amygdaloid body

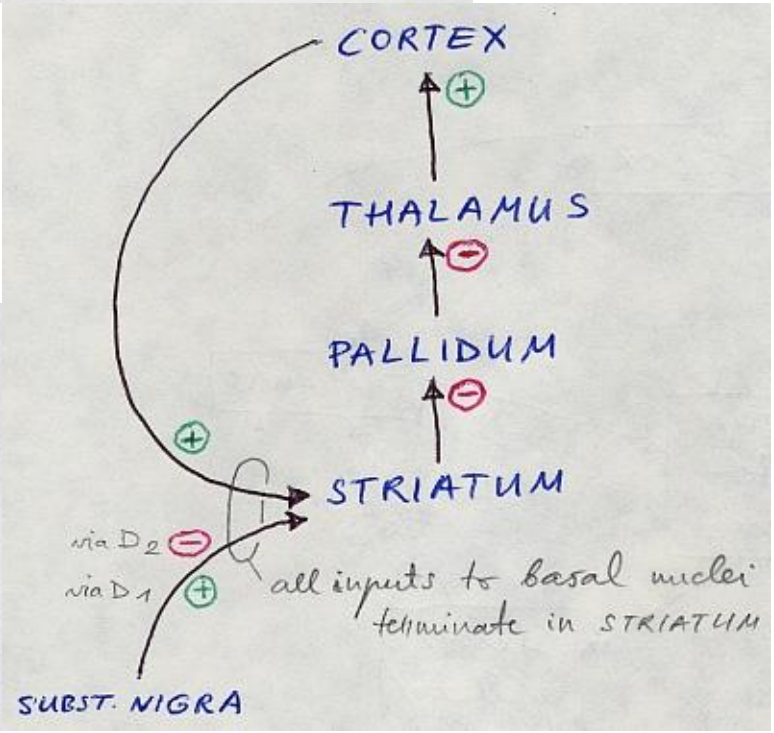
Paleostriatum = globus pallidus
↳ diencefalinės kilmės

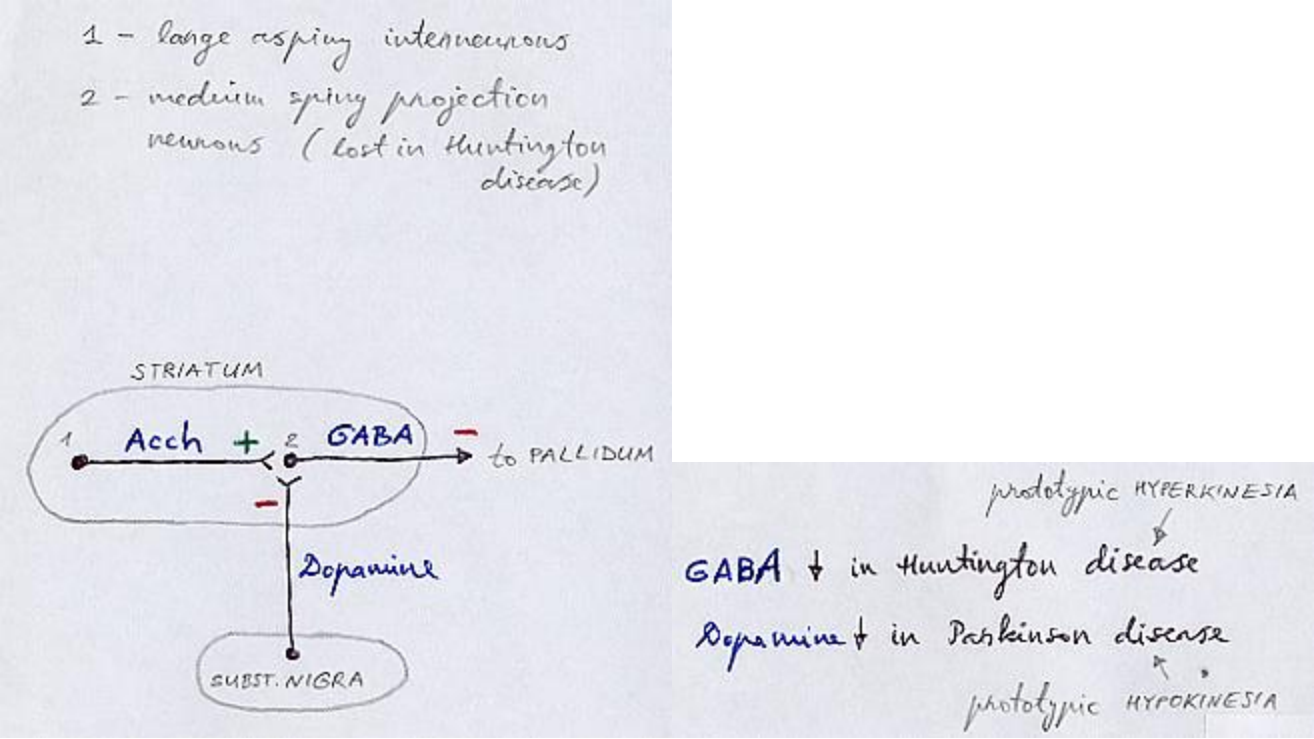
Neostriatum = putamen + caudate nucleus = striatum

corpus striatum









Normoje esti balansas tarp sistemų:

CHOLINERGIC (***excitatory***) – **INTRASTRIATAL.**

GLUTAMATERGIC (***excitatory***) – **everywhere excitation** is needed, except intrastriatal.

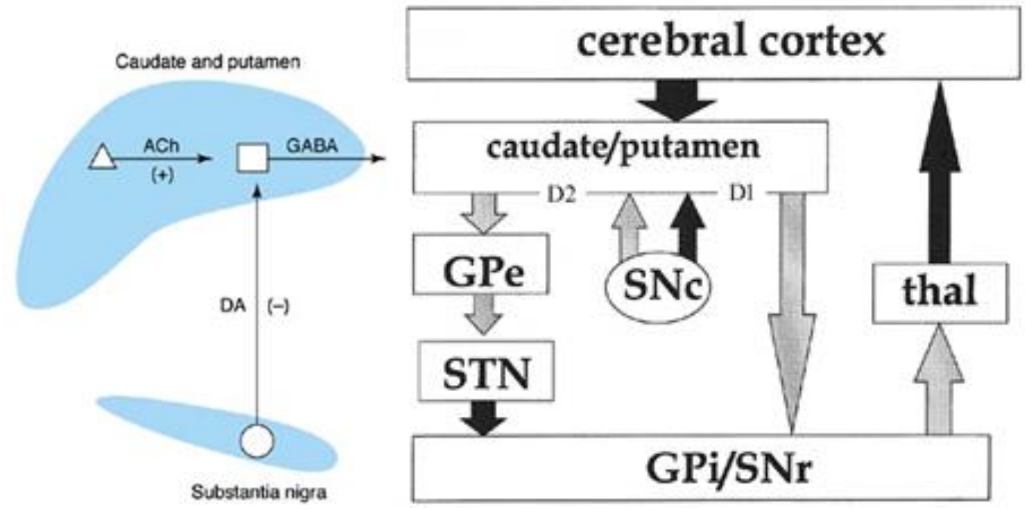
DOPAMINERGIC (***inhibitory*** via D_2 receptors; ***excitatory*** via D_1 receptors) – **NIGROSTRIATAL.**

GABAERGIC (***inhibitory***) – **everywhere inhibition** is needed (e.g. striatonigral, striatopallidal), except nigrostriatal.

Striatum acts via 2 pathways:

direct pathway inhibits GP_i / SNr;
indirect pathway stimulates GP_i / SNr.

- normally, dopaminergic input *activates* **direct pathway** neurons that express **D_1 receptors** and *inhibits* **indirect pathway** neurons that express **D_2 receptors** – net effect is decreased stimulation of GP_i / SNr.

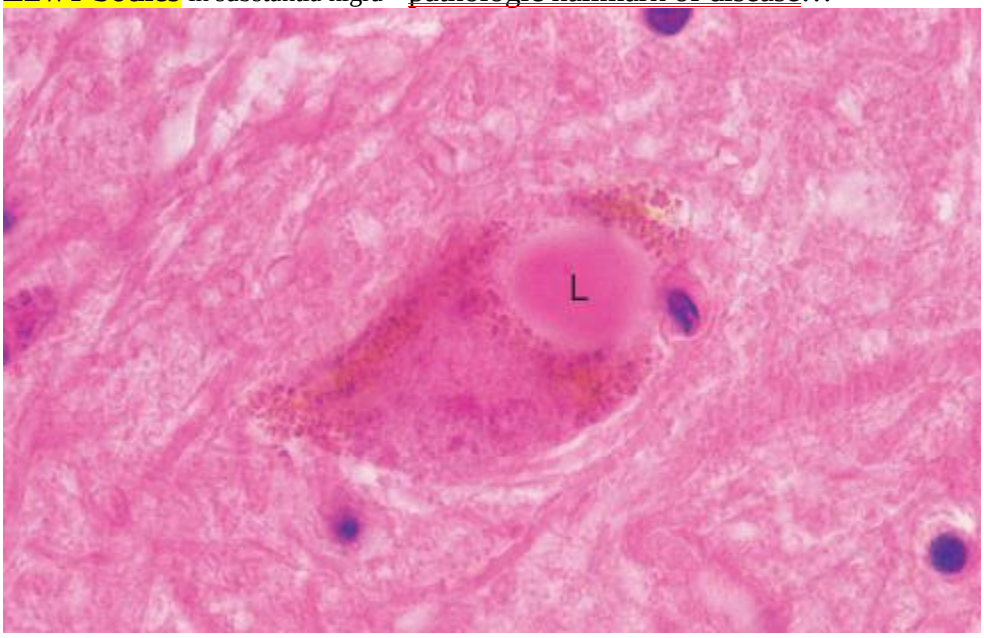


black arrows – ***excitation***;
speckled arrows - ***inhibition***.

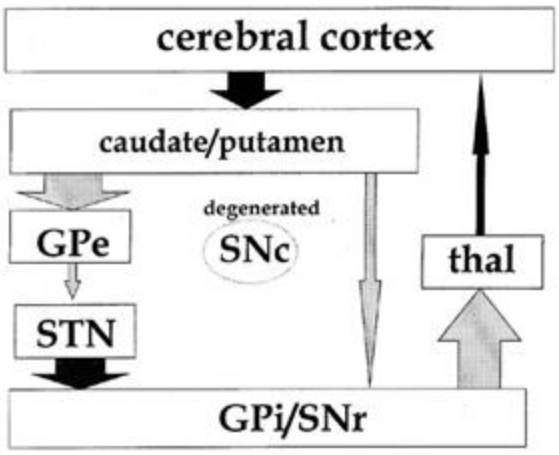
PARKINSONISM

PATHOPHYSIOLOGY

Area first affected is **pars compacta in substantia nigra** - **depigmentation & neuronal loss.**
LEWY bodies in substantia nigra - pathologic hallmark of disease!!!



DOPAMINERGIC UNDERACTIVITY → relative **cholinergic** overactivity* → increased **GABAergic output** to indirect pathway:



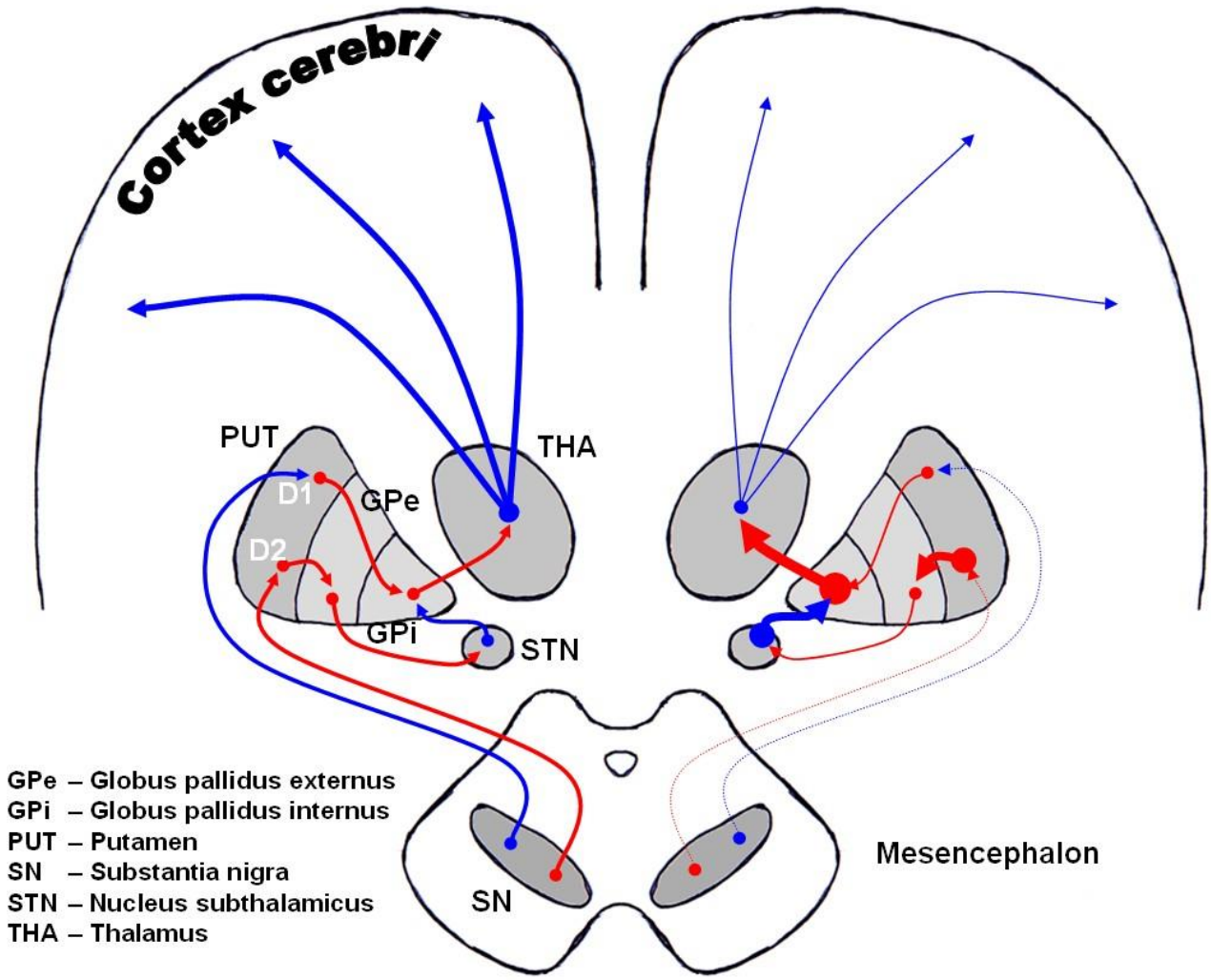
Įsisiautėję stimuliacinis STN → inhibicinis GPi → nebestimuliuojamas cortex

Net effect – hyperactivity of GPi → thalamic inhibition → less cortical activation → HYPOKINESIA

N.B. D_2 receptors are more important in mediating parkinsonian symptoms!

*but concurrent cholinergic deficit in nucleus basalis of Meynert → cognitive decline

Dopaminergic pathways in **normal condition** (left) and **Parkinson's Disease** (right).



Red arrows indicate suppression of the target, blue arrows indicate stimulation of target.

CLINICAL

- both HYPOKINETIC and HYPERKINETIC features ("paralysis agitans", "shaking palsy"):

1. **RESTING TREMOR**
   - occurs in 80% patients with idiopathic PD.
   - rarely is seen in Parkinson-plus syndromes or secondary parkinsonism (except in drug-induced and MPTP-induced parkinsonism).
     N.B. resting tremor helps distinguish idiopathic PD from other causes of parkinsonism!
2. **RIGIDITY**
3. **BRADYKINESIA, AKINESIA**

Term "hypokinetic syndrome" is synonymous with "parkinsonism"

N.B. hypokinesia is not caused by rigidity!

4. **POSTURAL INSTABILITY**: PRO-, LATERO-, RETROPULSION → **festinating gait, falls**.

Tremor, **rigidity**, **flexed posture** are POSITIVE PHENOMENA (S. RELEASE PHENOMENA);
In general, positive phenomena are *amenable to surgery*!
Bradykinesia, **loss of postural reflexes**, **freezing** are NEGATIVE PHENOMENA.
In general, *negative phenomena are more disabling*!

- patients with axial (akinetic-rigid, no-tremor) disease are more resistant to both medical treatment and DBS; they are more likely to be on complex medication regimens and are considered to have more severe disease (incl. cognitive decline).

Parkinsonian patient gaits:
Shuffling gait – slow small steps
Festinating gait – walks faster and faster, then falls
Dyskinetic gait – wobbly (H: amantadine)
Freezing – main cause of falls (H: may or may not respond to L-dopa; PPN DBS; modafinil)
Dystonic gait – leg posturing (H: L-dopa*, Botox)
*dystonic gait may also be a side effect of L-dopa

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

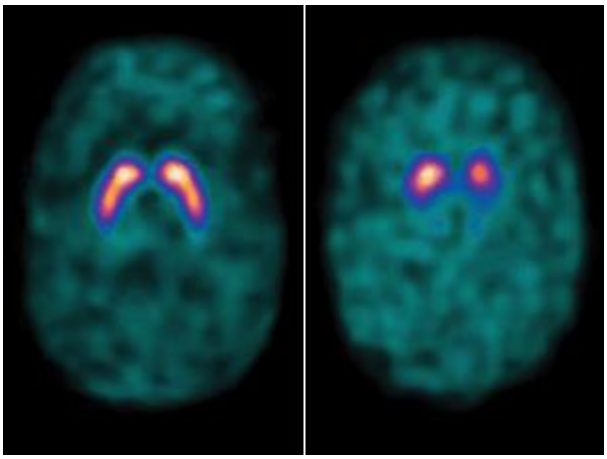
- made up of following sections:
  UPDRS I (mentation, behavior, and mood)
  UPDRS II (ADL): self-evaluation of the activities of daily life (ADLs) - speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, cutting food;
  UPDRS III (motor): clinician-scored monitored motor evaluation in off-state* and on-state;
  UPDRS IV (complications of therapy): **Hoehn and Yahr scale**.
  UPDRS V: **Schwab and England Activities of Daily Living scale**.
  *PD medications withheld for > 12 hours (so typically, patient needs special clinic visit; for some medications or for patients with ↓GI motility, medications may need to be withheld for ≥ 48 hours).
- score 0 means normal.

DIAGNOSIS

- **no diagnostic test** to confirm diagnosis! Diagnosis is clinical!

Parkinson's disease = all four cardinal signs + brisk response to LEVODOPA!!!

DaTscan
IOFLUPANE IODINE-123 SPECT – FDA approved in suspected parkinsonian syndromes: abnormal distribution of **dopamine transporters (DaT) in striatum** in *parkinsonian syndromes*
Normal (*left*) and abnormal (*right*) DaTscan:



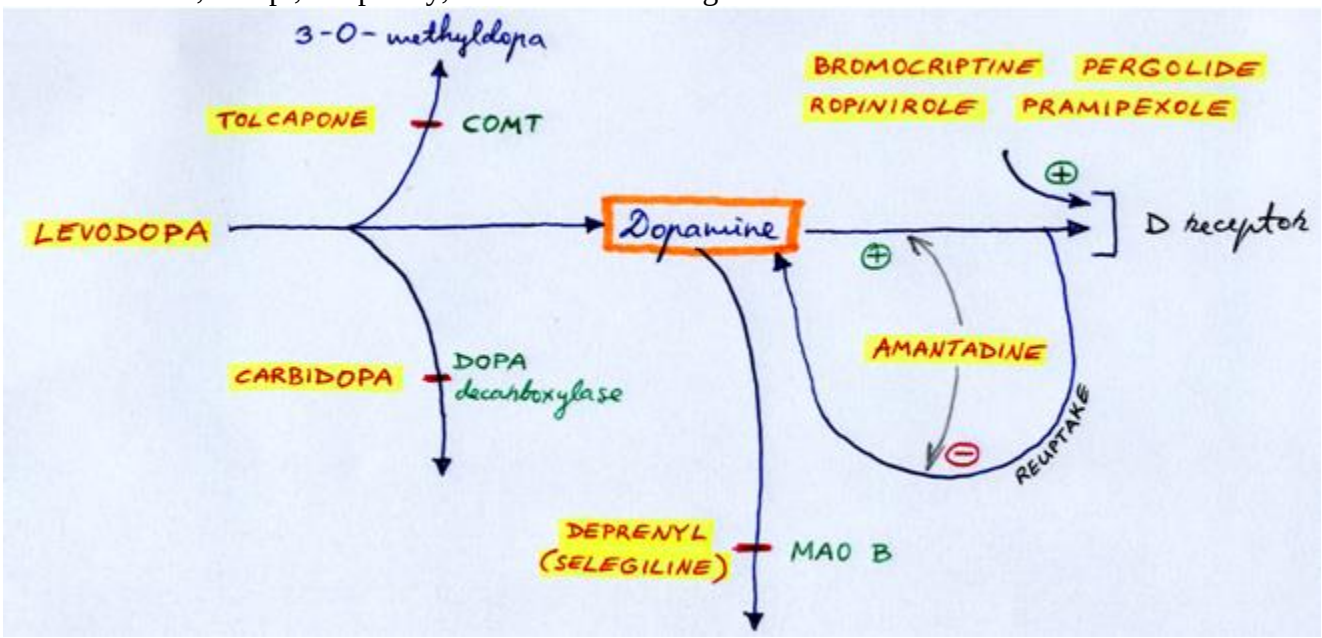
TREATMENT

LEVODOPA - natural immediate precursor of dopamine that can cross BBB.

– if response is nil or minor, disorder probably is not PD;
adequate response, however, does not assure diagnosis of PD!

Side effects: **nausea & vomiting** + **dyskinesias** (choreic, sometimes dystonic) + **visual hallucinations**
N.B. 75% patients have serious complications after 5 years of LEVODOPA therapy! - **fluctuations** (irregular and unpredictable responses to medications – **"on-off" phenomenon**), **dyskinesias**, **lack of efficacy**.

Chronic LEVODOPA therapy - **MOTOR FLUCTUATIONS** become ***less predictable*** - **"on-off"** – random, abrupt, temporary, not related to timing of LEVODOPA intake – time for DBS



CARBIDOPA, BENSERAZIDE – peripheral (does not cross BBB) inhibitors of *DOPA decarboxylase*
TOLCAPONE, ENTACAPONE (better), **OPICAPONE** – selective COMT inhibitors
MAO-B inhibitors: **DEPRENYL** (s. **SELEGILINE**), **RASAGILINE**

D agonists: **BROMOCRIPTINE,** PERGOLIDE (off market due to cases of serious heart valve damage)**,**
PRAMIPEXOLE, ROPINIROLE, CABERGOLINE, LISURIDE, APOMORPHINE, ROTIGOTINE
APOMORPHINE s/c - FDA approved for "off" periods!

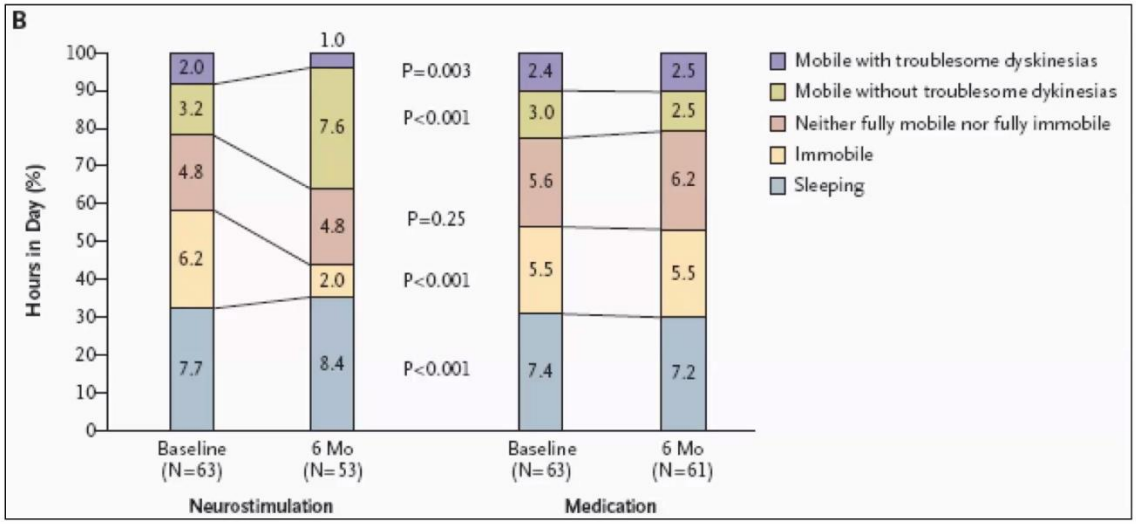
AMANTADINE - mostly used to abolish ***dyskinesias***

For resistant tremor - antimuscarinics (**BENZTROPINE**, **TRIHEXYPHENIDYL**, **BIPERIDEN**)

- anti-dementia cholinergic treatment worsens parkinsonism.

DBS

Patients enjoy ~5 additional hours of best on time



PARKINSONISM-PLUS SYNDROMES (MULTIPLE SYSTEM DEGENERATIONS)

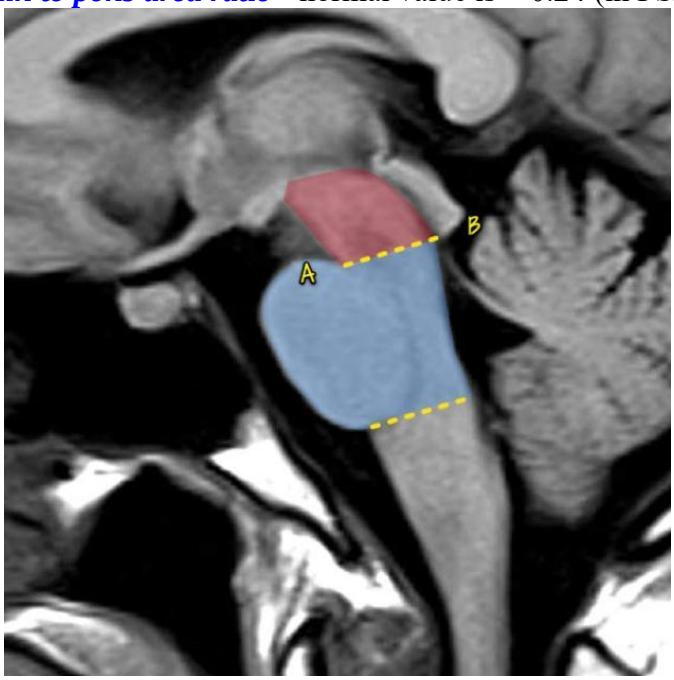
- primary neurodegenerative conditions:
  - ***parkinsonism*** is one of major clinical features (10-15% of all parkinsonism cases) but usually no tremor!!!
  - ***additional features*** not typical of Parkinson's disease.
  - *poorer response* to antiparkinsonian therapy (destroyed postsynaptic D receptors).
  - pharmacological therapies remain disappointing!
  - overall *worse prognosis* – most patients are dead at 5 years after diagnosis.
    N.B. first 5 years after PD diagnosis have greatest risk of misdiagnosis; after 5-10 years only true PD patients survive

Shy-Drager syndrome – degeneration of ***central autonomic nuclei*** - severe autonomic failure!

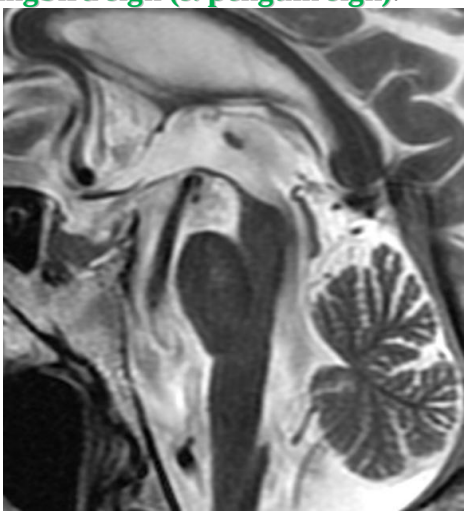
Progressive Supranuclear Palsy

atrophy of midbrain (AP diameter of midbrain < 15 mm):

- ***Midbrain to pons area ratio*** - normal value is ≈ 0.24 (in PSP, it is significantly reduced to 0.12)



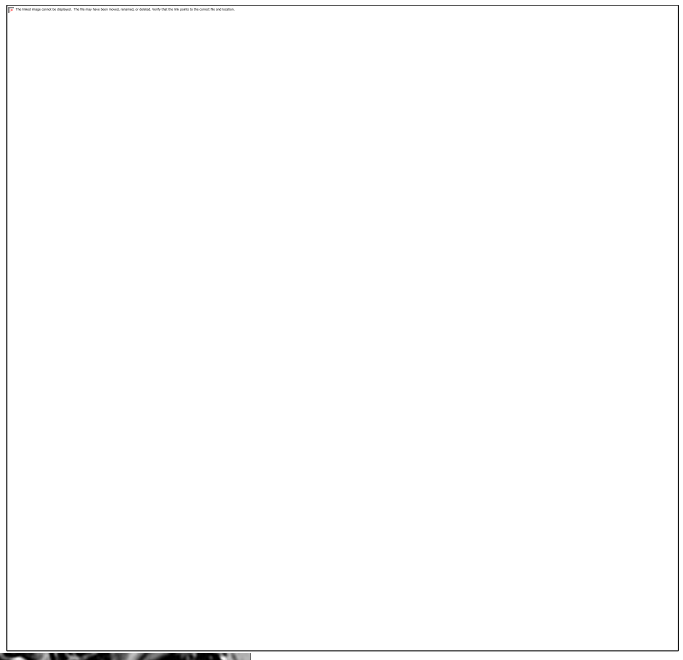
hummingbird sign (s. penguin sign):

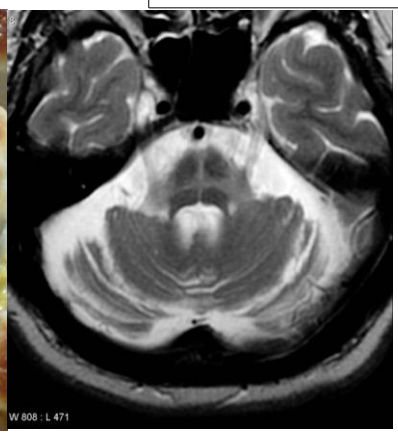


Olivo-ponto-cerebellar Atrophy

- **MRI** - marked atrophy of ventral pons and of "pontine nuclei" and their axons.

A. Sagittal T1-MRI
B. Axial T2-MRI - **"hot-cross bun" appearance**





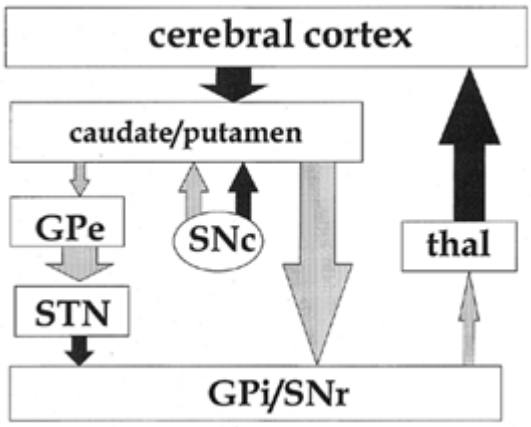
ESSENTIAL TREMOR

postural / action – ET - ***no specific structural abnormality***
steadily progressive with age
H: **PROPRANOLOL** (drug of choice), **PRIMIDONE**
GABAPENTIN, ALPRAZOLAM, small ALCOHOL doses.

HUNTINGTON DISEASE

– AD inheritance (*triplet repeats* - unstable expansion of **CAG repeats**) - generalized brain atrophy (particularly caudate nucleus - **GABAergic projection neurons**); gradual onset of **chorea** + **dementia** + **personality disorder** ± FAMILY HISTORY in young / middle-aged adult.
Prototypic chorea!

GABAergic UNDERACTIVITY + **cholinergic** underactivity → decreased **GABAergic output** to indirect pathway → thalamus no longer inhibited → cortex overexcitation → **chorea**!



Gradual onset of chorea + dementia + psychiatric abnormalities in young / middle-aged **adult**

Dx: **MRI** (generalized brain atrophy, esp. caudate!) + **DNA testing**
Rx: **ANTIDOPAMINERGIC drugs**: **HALOPERIDOL** (dopamine receptor blocker)**, TETRABENAZINE** (dopamine-depleter)
death within 12-15 years of onset

SYDENHAM CHOREA

– in rheumatic fever; child with **chorea**, **hypotonia**, and **emotional lability**.
Rx – as Huntington + **steroids**
– spontaneous full recovery

PRIMARY DYSTONIA (S. DYSTONIA MUSCULORUM DEFORMANS)

autosomal dominant DYTl gene
- **long sustained twisting** movements of ***axial muscles***
- begins as focal condition (*writer's cramp, torticollis, blepharospasm*) and may sequentially progress to segmental → generalized; interferes with function = makes *voluntary activity extremely difficult*.
progression: **task-specific dystonia → action dystonia → overflow dystonia → continual dystonia (dystonia at rest) → fixed postures**

Rx: ANTICHOLINERGICS (BENZTROPINE, TRIHEXYPHENIDYL, BIPERIDEN), BACLOFEN (IT for generalized), BOTULINUM TOXIN (for focal, segmental), trial of LEVODOPA
BILATERAL PALLIDAL DBS (FDA approved!) – good results (vs. secondary dystonias)

CERVICAL DYSTONIA (S. SPASMODIC TORTICOLLIS)

DBS (BILATERAL GPI) – for botulinum toxin refractory cases.

MICROVASCULAR DECOMPRESSION (MVD) of CN11 at cervicomedullary junction – for local vascular compression – manifests as *horizontal rotary torticollis* during upright or recumbent position.

DRUG-INDUCED MOVEMENT DISORDERS

D_2 receptor-blocking agents can cause **extrapyramidal side effects**

- esp. ***high-potency*** agents that exhibit *weak anticholinergic activity* (HALOPERIDOL, FLUPHENAZINE)
- less common with:
    a) drugs that exhibit *strong anticholinergic activity* (THIORIDAZINE).
    b) ***newer "atypical" agents*** (CLOZAPINE, RISPERIDONE)!!!!! - predominantly block D_4 receptors; almost free of motor side effects.

NEUROLEPTIC MALIGNANT SYNDROME

due to blockade of D_2 receptors
TRIAD:

1) **HYPERTHERMIA** (> 40°C) → chronic cerebellar syndrome.
2) **AUTONOMIC dysfunction** (e.g. pallor, diaphoresis, blood pressure instability, tachycardia, pulmonary congestion).
3) **MOVEMENT disorder** (e.g. **akinesia**, "lead pipe" **rigidity**, **dystonia**) → CK↑, myoglobinuria → renal failure.
   + **altered mental status** resembling **catatonia** (eventually leading to **stupor** or **coma**) - **mortality** 5-30%!

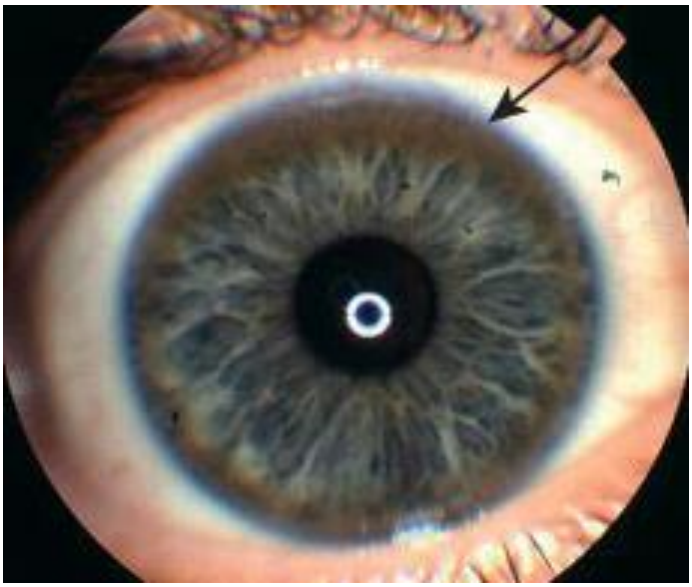
Rx: **BROMOCRIPTINE** or another dopamine agonist, **DANTROLENE,** ***nondepolarizing muscle relaxants***
N.B. rigidity can be blocked with muscle relaxants (vs. malignant hyperthermia)!

TARDIVE DYSKINESIAS

- repetitive stereotypic rapid bizarre choreoathetoid movements of ***lower facial muscles & tongue*** chronic [6 months may be enough!] blockade of *dopamine receptors (→ hypersensitivity)* by **neuroleptics** – ***late (tardive)*** side effect! often permanent
Rx: dopamine-depleting drugs (**RESERPINE**, **TETRABENAZINE**, **VALBENAZINE** – FDA approved for tardive dyskinesia.
N.B. TD may worsen following neuroleptic withdrawal

WILSON'S DISEASE

KAYSER-FLEISCHER RING - in Wilson's disease:



DBS

- stimulate subcortical structures with electrical current.
  - DBS stimulates axons (not cell bodies).

Low (< 40 Hz) frequencies *stimulate*, high (> 100 Hz) frequencies *inhibit*

DBS INDICATIONS

1. **Movement disorders**:
   1) **PD** (if PD is nonresponsive to medications, patient is poor candidate for DBS; exception - tremor)
      - FDA approved in 2002.
      - "positive" symptoms (tremor, rigidity, and bradykinesia) improve substantially; "negative" symptoms (balance) are typically refractory; gait has a variable response (freezings that respond to levodopa, tend to respond to DBS)
      - ideal patient – classical L-dopa-responsive Parkinson's disease with worsening unpredictable wide **motor fluctuations** (offs) in medication response and / or drug-induced **dyskinesias**
      - beware *"Parkinson's plus" syndromes* - unlikely to benefit from DBS.
      - good candidates for surgery typically have > 30% improvement in **UPDRS motor score** with levodopa challenge.
        - there are no insurance requirements of how severe UPDRS has to be and how much it has to respond to medications.
        - 5-point difference in UPDRS represents ***minimum difference for clinical significance***

Dr. Holloway: DBS improves **tremor** 80%, **other PD symptoms** 40-60%** (but only if responsive to medications)

**parkinsonian dystonia and dyskinesias respond better than 40-60%

Freezing: if gait freezing is responsive to medications, DBS may help.
Postural stability – DBS helps.
Falls – may increase after DBS as patients become more mobile.

2) **ET**
   - target – **VIM**
   - FDA approved in 1997.
   - tremor control is best for arms and tends to be better for distal tremors than for proximal ones.
   - head or vocal tremors are typically refractory (they may be improved with ***bilateral implantation***, but this cannot be accurately predicted).

3) **dystonias** (improvement is not observed during intraop - several months of stimulation and programming may be required before significant improvements are detected)
   - FDA approved in 2003.
   - primary generalized dystonias respond best! DYT1-positive dystonia has 80-95% response rate.
   - segmental dystonias also respond well.
   - secondary dystonias (e.g. TBI, cerebral palsy) – DBS is off-label use; outcomes are less predictable and usually more limited.
   - target - **GPi** – target is slightly different than for PD. Implantation is always **bilateral**!

2. **Epilepsy**
3. **Psychiatric disorders**:
   1) OCD
   2) depression
   3) Gilles de la Tourette's syndrome
   4) addiction – nucl. accumbens, ALIC (anterior limb of internal capsule)
4. Chronic **pain disorders**
5. Minimally conscious and vegetative states
6. Obesity
7. Alzheimer's disease

DBS EFFICACY

DBS improves **tremor** 80% in 80% of patients, **other PD symptoms** 40-60% (but only if responsive to medications)

Goal of DBS – achieve the best score patient had on meds preop and smoothen fluctuations!

- DBS effects are:
    a) **immediate** (e.g. tremor control)
    b) **accrue over weeks to months** (e.g. dystonia)

DBS CONTRAINDICATIONS

1) **parkinsonism-plus syndromes / parkinsonism unresponsiveness to levodopa**

2) ≥ **moderate cognitive dysfunction**

3) **anxiety** – difficulty postop DBS programming

4) **depression** – risk of postop suicide

5) **general surgical contraindications** (anticoagulants, terminal cancer, infectious disease, immunodeficiency, poorly controlled HTN, and so on)

PREOPERATIVE WORK UP

OFF/ON TESTING

- detect other PD features - will require GPi in otherwise "only tremor" patient, i.e. in patients with seemingly only resting tremor (VIM would suffice).
- to establish which features respond to medications.

NEUROPSYCHOLOGICAL EVALUATION

- to detect contraindications:
    1) cognitive decline
    2) anxiety
    3) depression

PREOP MEDS

- no PD meds after 21:00 – to have good tremor to work with (caution: some patients experience significant hypertension due to this).
    modern trend is to give meds (in worse case, do image-guided under general anesthesia and EMG) – still can do MER but cannot do clinical testing
- for ET, avoid beta-blockers; if tachycardia in OR, then give short acting IV

VTA (VOLUME OF TISSUE ACTIVATED)

With stimulation configuration of: pulse width= 90 microsecond:

-1V: Horizontal spread = 1.97 mm; vertical spread = 1.81 mm; VTA = 29 mm cube.
-2V: Horizontal spread ~ 2.25 mm; vertical spread ~ 2.4 mm; VTA ~ 57 mm cube.
-3V: Horizontal spread = 3.32 mm; vertical spread = 3.21 mm; VTA = 148 mm cube.

i.e. roughly **2 mm radius ball** (center is center of electrode)

"MICROELECTRODE" EFFECT

- symptoms improve when electrode enters target
  - makes it impossible to do stimulation "on" testing because patient already improved!
  - spontaneously abates in 2 weeks

GPi vs. STN vs. VIM

Feature	GPi	STN	VIM
Speech	Less affects but also does not help	More problems	Dysarthria is common
Tremor	Helps only tremor responsive to medications	Helps with tremor responsive and unresponsive to medications	Helps with tremor responsive and unresponsive to medications
Dystonia	GPi helps for both medication-responsive and –nonresponsive (GPi better for "*on*-meds" dystonia)	STN helps for both medication-responsive and –nonresponsive (STN better helps "*off*-meds" dystonia)	
Bradykinesia		STN is better than GPi	
Dyskinesia	GPi helps for both medication-*on* and –*off* dyskinesias	STN helps by decreasing levodopa dose (GPi is better for *off* dyskinesia) N.B. STN DBS may induce dyskinesias!	
Falls, gait disturbance		Significant worsening with STN DBS (vs. best medical management)	
Levodopa usage reduction	3%	Up to 3-fold (38%)	
Neurocognitive measures*	Better than STN	Slight but significant worsening** with STN DBS (vs. best medical management)	
Depression	Better than STN	Slight worsening with STN DBS (vs. best medical management)	

*working memory, processing speed, delayed recall, phonemic fluency (esp. for elderly people)
**selectively of frontal cognitive functions

N.B. STN and GPi have similar efficacy in tremor control but *STN causes longterm cognitive problems*.

- STN does job of both VIM and GPi but worse *cognitive & mood outcomes, increased risk of falls.*

- with current MRI, **GPi** and **STN** are ***visualized directly***, but **VIM** is derived from Schaltenbrand and Wahren ***atlas*** coordinates – benefits from intraop testing.
  N.B. if patient cannot get MRI, it is easier to target VIM (than STN) from CT.
- average AC-PC distance is 23-27 mm; greater than 30 mm should raise accuracy concerns.

STN

INDICATIONS, SIDE EFFECTS

1) **tremor** unresponsive to medications (vs. GPi – tremor needs to be responsive to medications)
2) rigidity, bradykinesia.

COORDINATES

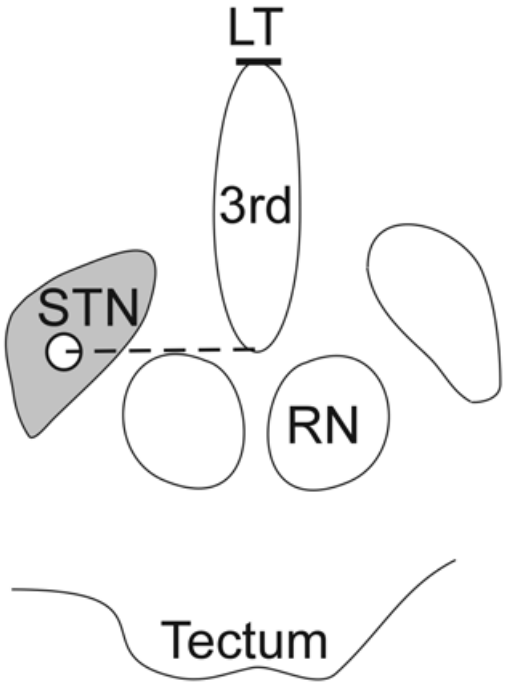
Relative to midcommissural point: -4 / -4 / 12 ← very reliable

- 4 (1-5) mm posterior
- 4 (3-6) mm inferior
- 12 (11-14) mm lateral

Anatomically: **motor (dorsolateral) STN**.

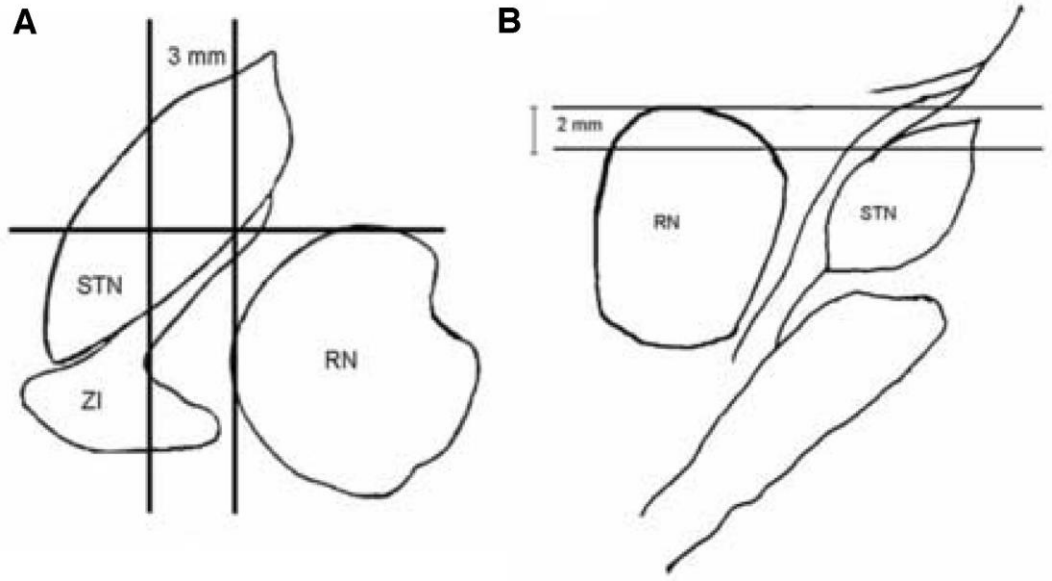
- 3-3.5 mm posterior to the anterior border
- 2.5-3 mm medial to internal capsule boundary with deepest electrode contact placed at STN/SNr boundary.

Target relative to red nucleus (**T2 MRI**):
In axial plane, line is drawn perpendicular to midline, tangent to anterior border of red nucleus, extending 2 mm lateral to medial border of STN:



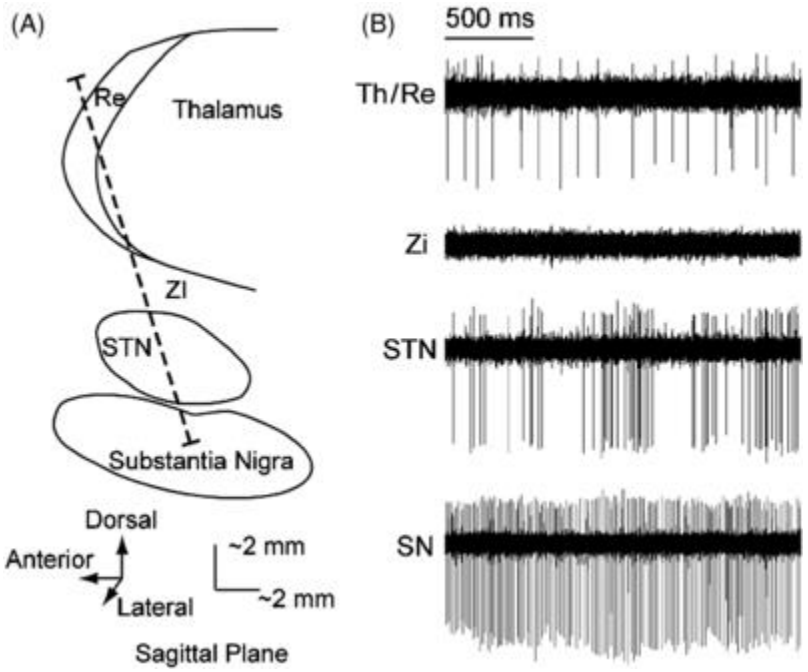
A, axial projection; B, coronal projection:

x - 3 mm lateral to the lateral border of red nucleus
y – anterior border of red nucleus
z - 2 mm inferior to the superior border of red nucleus



ELECTROPHYSIOLOGY

STN - large asymmetrical spikes at rather high frequency (30-40 Hz) and biphasic spikes at 10-13 Hz responsive to passive movement and tremor;



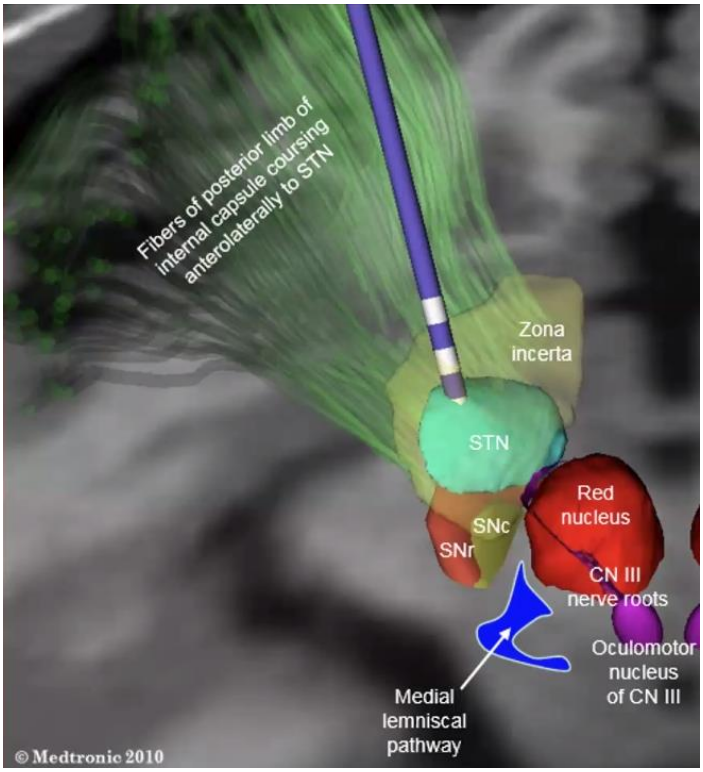
N.B. just recording cells from STN is not sufficient to delineate sensorimotor STN as one cannot electrophysiologically recognize a sensorimotor cell from a non-sensorimotor cell; thus, looking for **kinesthetic cells** is necessary!

STIMULATION

- stimulation of STN normally induces dyskinesias (sign of electrode location at target)

MALPOSITIONED ELECTRODE

1) **anterolateral** - muscular contraction (face and upper limb primarily) - corticospinal tract; stimulation of corticonuclear fibers induces conjugated binocular deviation toward contralateral side.
2) **medial** – CN3 – monocular deviation toward midline or either upward or downward.
   N.B. eye deviation with stimulation:
   a) one eye only – too medial (CN3)
   b) both eyes (conjugate) – too lateral (corticonuclear fibers from frontal eye field)
3) **posterior** - lemniscus medialis - paresthesias.
4) **deep** – SNr - profound depression.
5) **anterior** – risk of permanent hypophonia



VENTRALIS INTERMEDIUS (VIM) nucleus of thalamus

- afferents:
  1. Contralateral **cerebellum**: VIM is cerebellar relay nucleus to motor cortex (i.e. VIM is terminus of cerebellar afferents – dentatorubrothalamic tract via superior cerebellar peduncle).
  2. Ipsilateral **globus pallidus**
- efferentes: ipsilateral **motor cortex**.

INDICATIONS

- tremor (parkinsonian*, intention, essential) refractory to medication (vs. GPi – tremor needs to be responsive to medications)

VIM is target of choice for treatment of all types of tremor!
Distal upper extremity tremor responds best!

*if tremor is main PD symptom and cognition severely↓

SIDE EFFECTS

- bilateral surgery is too often associated with neurocognitive deficits + dysarthria (patients are taught to increase voltage when they need fine motorics in hands and decrease when they need to speak)

  Don't do bilateral thalamotomy! (for DBS - space implantations apart by several months)
- better tolerated in demented patient than STN.

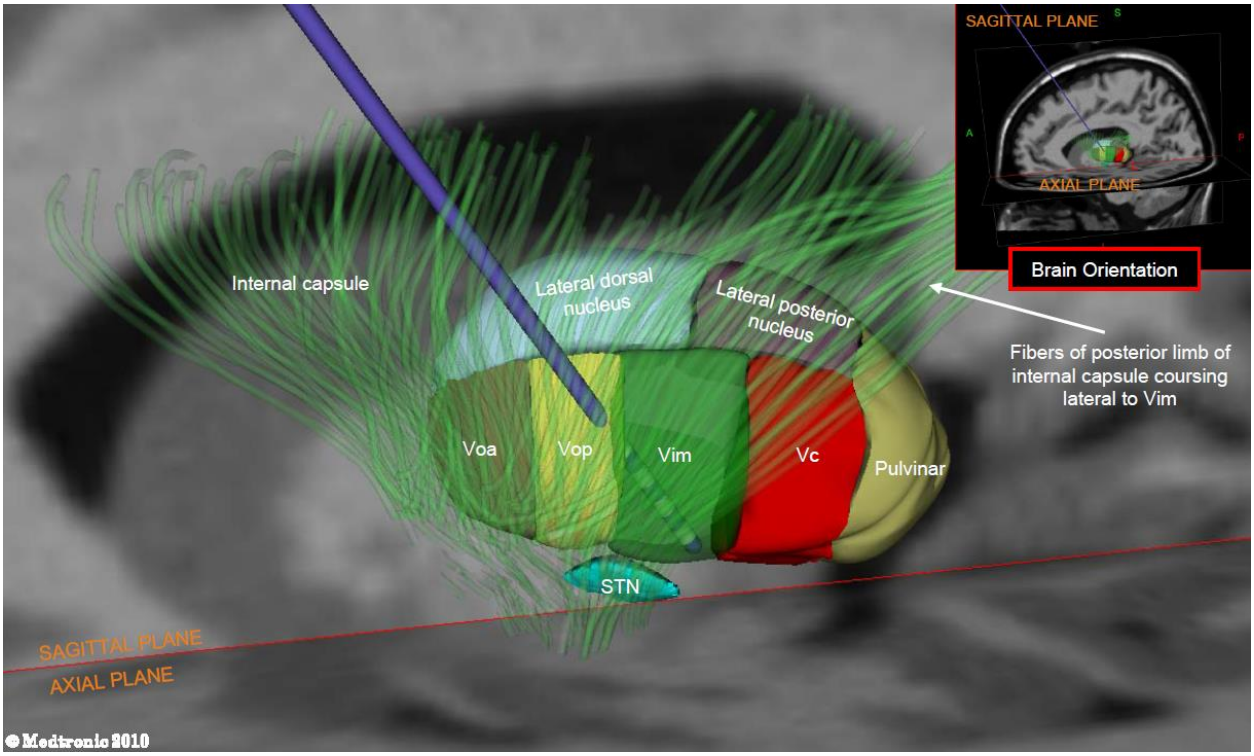
COORDINATES

Relative to midcommissural point (T1 MRI)

- 6 mm posterior (anterior to PC by 20% of AC-PC length)
- 0 mm (i.e. AC-PC plane)
- 10-11.5 mm lateral + ½ width of 3rd ventricle

Anatomically: Cannot see VIM on MRI!

- target - middle of nucleus, 1-2 mm anterior to VC border (hand region of VC), contact 0 at base of VIM
- VIM is somatotopically organized along medial-lateral axis - face/tongue representation is medial, foot is lateral.



ELECTROPHYSIOLOGY

- typically not done.

- high concentration of tremor cells (rhythmic bursting activity close to frequency of tremor).
- kinesthetic cells present.

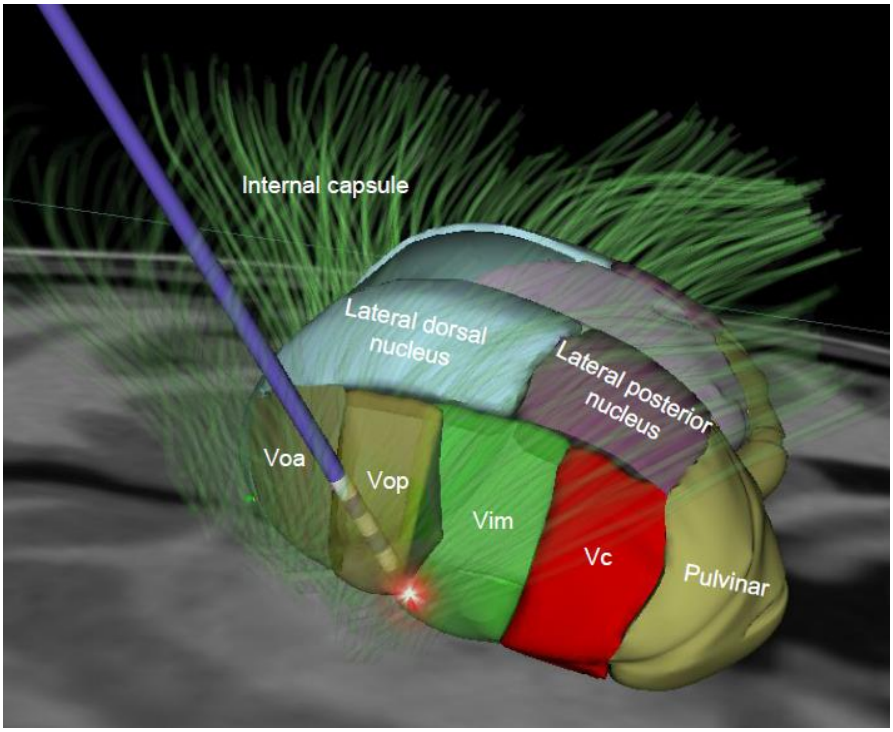
STIMULATION

- tremor arrest.

- expect transient (!) paresthesias – sign of correct position!
- if overshoot with voltage for tremor control, then start seeing dysmetria.

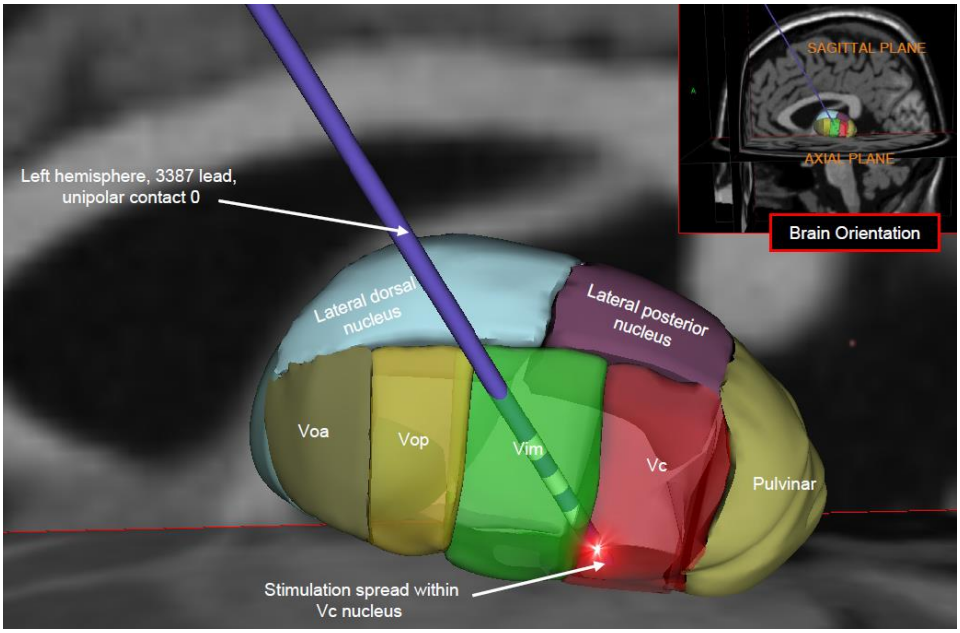
MALPOSITIONED ELECTRODE

Location relative to VIM	Nucleus	Observed Effect If Stimulated
Anterior	Vop	Reduction in tremor at voltages higher than typical
Anterior to Vop	Voa	No effect

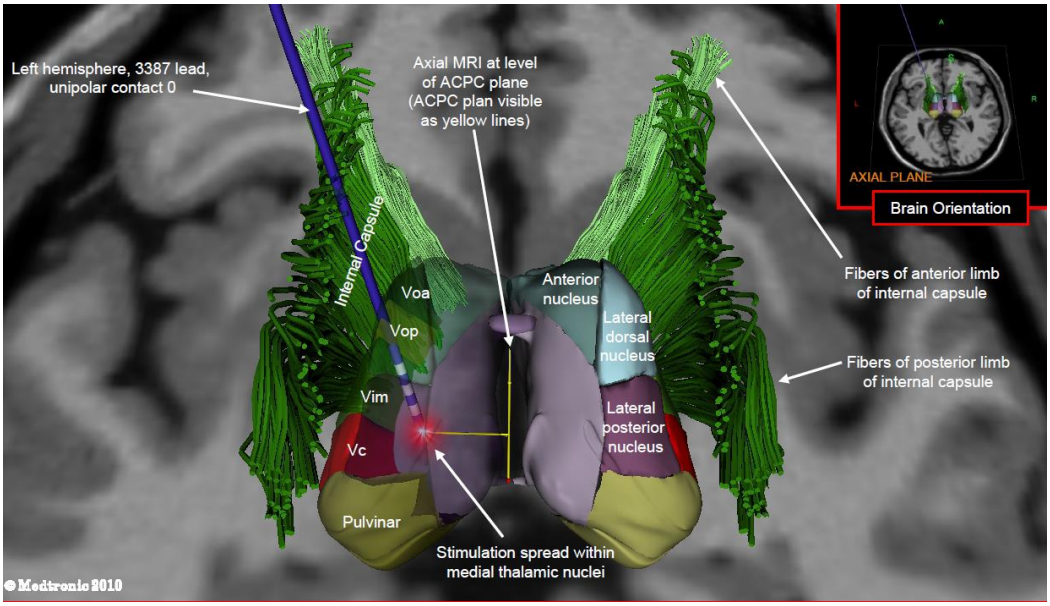


Location relative to VIM	Nucleus	Observed Effect If Stimulated
Posterior	VC	Paresthesias (long lasting) that increase in severity with increasing voltage

N.B. VC is somatotopically organized along medial-lateral axis - face/tongue representation is medial, foot is lateral.
Transient paresthesias do not necessarily indicate a lead that is too posterior.

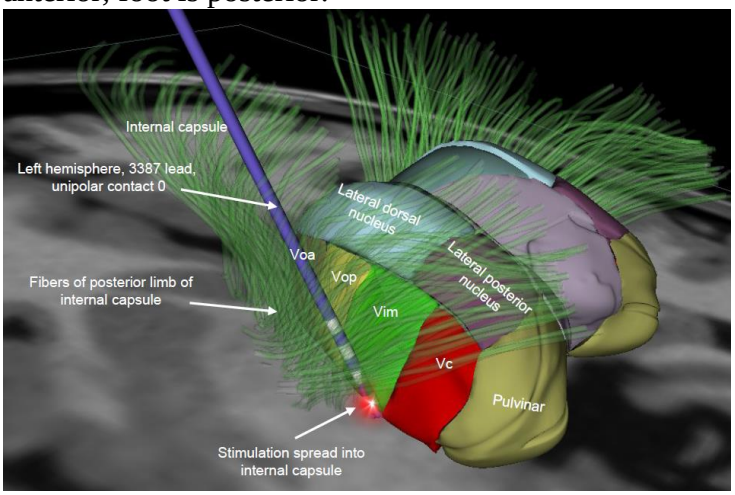


Location relative to VIM	Structure	Observed Effect If Stimulated
Medial	Medial aspect of VIM	Dysarthria, dysphagia in addition to tremor control
	Centromedian/Parafascicular Complex	No effect

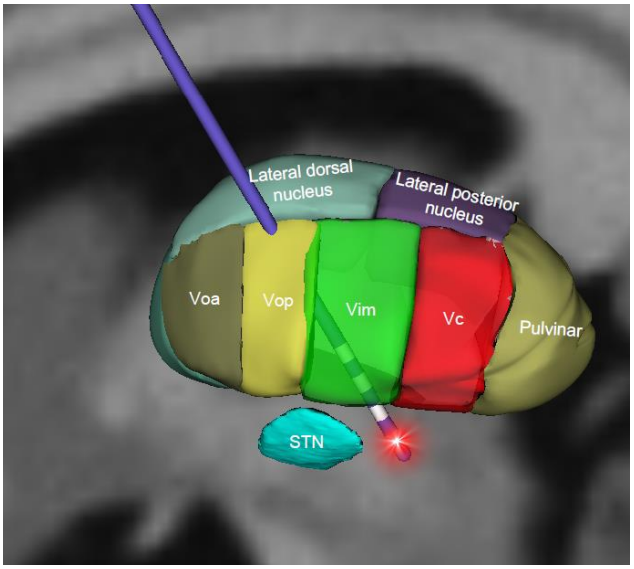


Location relative to VIM	Structure	Observed Effect If Stimulated
Lateral	Posterior limb of internal capsule	Dysarthria, facial pulling, muscle contractions

N.B. Internal capsule is somatotopically organized along anterior-posterior axis - face representation is anterior, foot is posterior.



Location relative to VIM	Structure	Observed Effect If Stimulated
Ventral and medial	Brachium conjunctivum (cerebellar fibers)	Ataxia
Ventral	Zona incerta	No effect on tremor
Ventral and posterior	Medial lemniscus	Paresthesias
Ventral and lateral	Internal capsule	Dysarthria, muscle contractions



GPi

INDICATIONS, SIDE EFFCETS

- tremor and other parkinsonian symptoms
  N.B. do not put DBS into GPi if tremor is not responsive to levodopa (vs. VIM and STN).

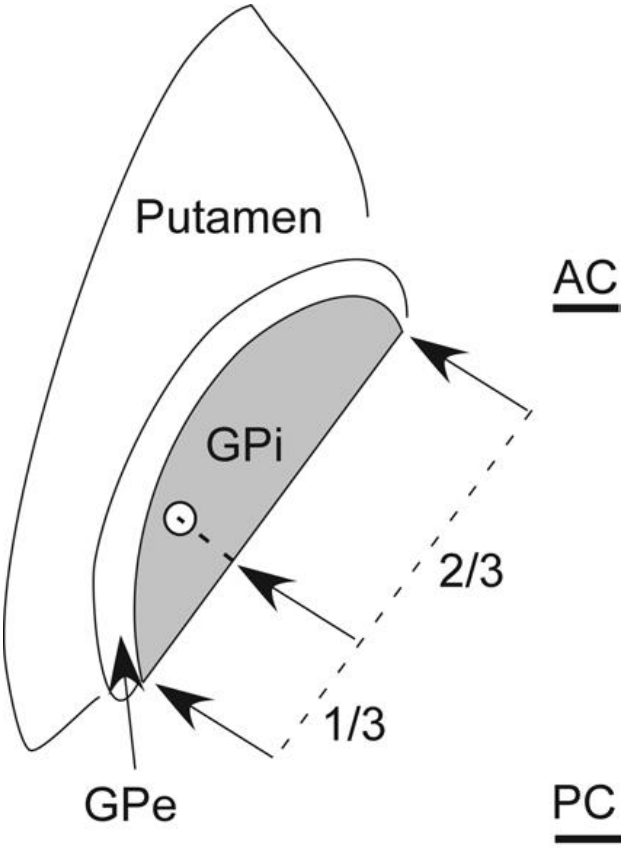
COORDINATES

Relative to midcommissural point (classic Leksell's pallidotomy target): +2 / -4 / 21 (FGATIR, FLAIR)

- 2-3 (2) mm anterior
- 2-6 (-4) mm inferior
- 18-23 (21) mm lateral

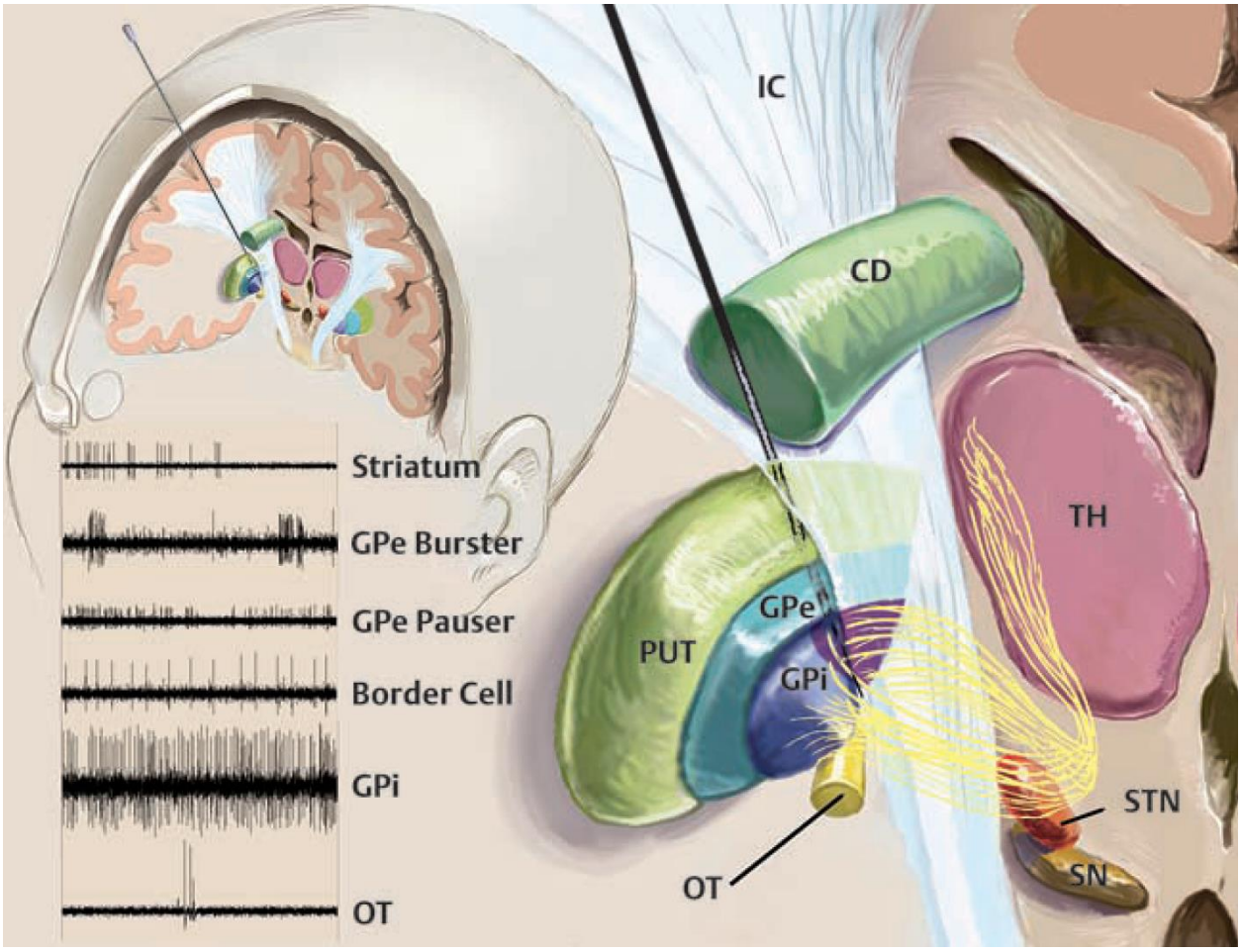
Anatomically: **motor (posterolateral) GPi**

- ***rule of thirds***: axial plane of commissures → dividing pallidocapsular border into thirds → drawing 3-4 mm line perpendicular to the pallidocapsular border at the junction of its posterior one-third and anterior two-thirds:



- the deepest electrode contact is immediately superior to optic tract.

ELECTROPHYSIOLOGY



- the most common <u>side effect</u> of stimulation – too medial – internal capsule - increased tone in the arm or facial contraction.
- stimulation **inferior** to the GPi – optic tract – phosphenes.

DBS CURRENT STEERING (DIRECTIONAL DBS)

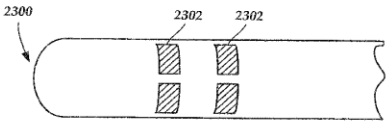


FIG. 23

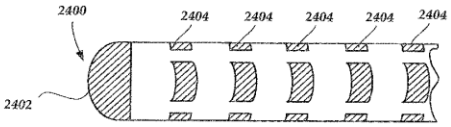


FIG. 24

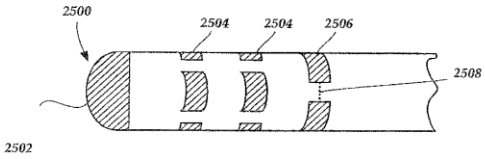


FIG. 25

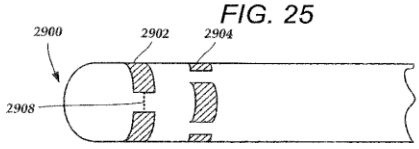


FIG. 29

TECHNICAL ASPECTS

- if patient cannot have MRI (e.g. pacemaker), **intraop ventriculogram** can be used: EVD is passed through right frontal burr hole into lateral ventricle → Omnipaque 3 mL is injected → immediate O-arm.
- often leads end up posteromedially – due to friction forces (when inserting cannula) pushing brain in opposite direction.

N.B. only remaining indications for awake DBS:

1. MRI-invisible targets (e.g. VIM)
2. DBS revisions for lack of effect
3. bilateral DBS (target shift)

MER

Only for GPi, STN (not for VIM)
N.B. MER does not improve outcomes! (still considered if patient cannot get MRI)

MER records single units (single cell, extracellular recordings) – resolution 0.2 mm (vs. local field potentials – 1 mm; ECoG – 1 cm; EEG – 3 cm).

MRI gets you near target, but physiology proves that you have exact spot!

- MERs can be done using PROPOFOL or DEXMEDETOMIDINE for sedation.

COMPLICATIONS

IPG infection → explant IPG and extensions (leave DBS lead in situ)

LESIONING SURGERY

Drawbacks

1) when lesion is well placed but too small, effects may not last - reoperation is required.
2) when lesion is too large and involves nearby structures (particularly internal capsule), side effects could occur, such as motor deficits (not always reversible).

RF allows awake stimulation before lesioning (vs. SRS – no ways to stimulate; LITT – patient under anesthesia)

SRS

Not safe pallidotomy – GPi has different radiosusceptibility.
Thalamotomy – 130 Gy through 4 mm collimator – takes 5-6 months for tremor reduction