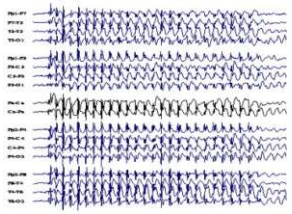
UCL School of Pharmacy

Epilepsy: Terminology, seizure classification, causes and treatment 2025

Introduction and definitions

- **Epilepsy (from the Greek word *epilepsia* - to take hold of or to seize) -** the "sacred" or "divine" disease – "falling sickness" - recorded in early Egyptian, Chinese and Indian writings.

- **A chronic neurological condition** affecting ~0.5-1% of the general population.



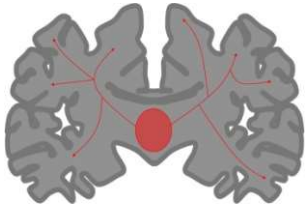
- **Characterized by abnormal cortical seizure discharges,** causing abnormal motor movements, sensory perceptions, altered behaviour/emotions, or transient loss of consciousness, depending on **affected cortical area** and **degree of spread.**

Epileptic seizure classification

- **A seizure (ictus)** -sudden explosive electrical over-activity of a set of cortical neurones.

- **Partial-onset (focal) seizures:-** develop at particular cortical focus - involve a convulsion of only a part of the body.

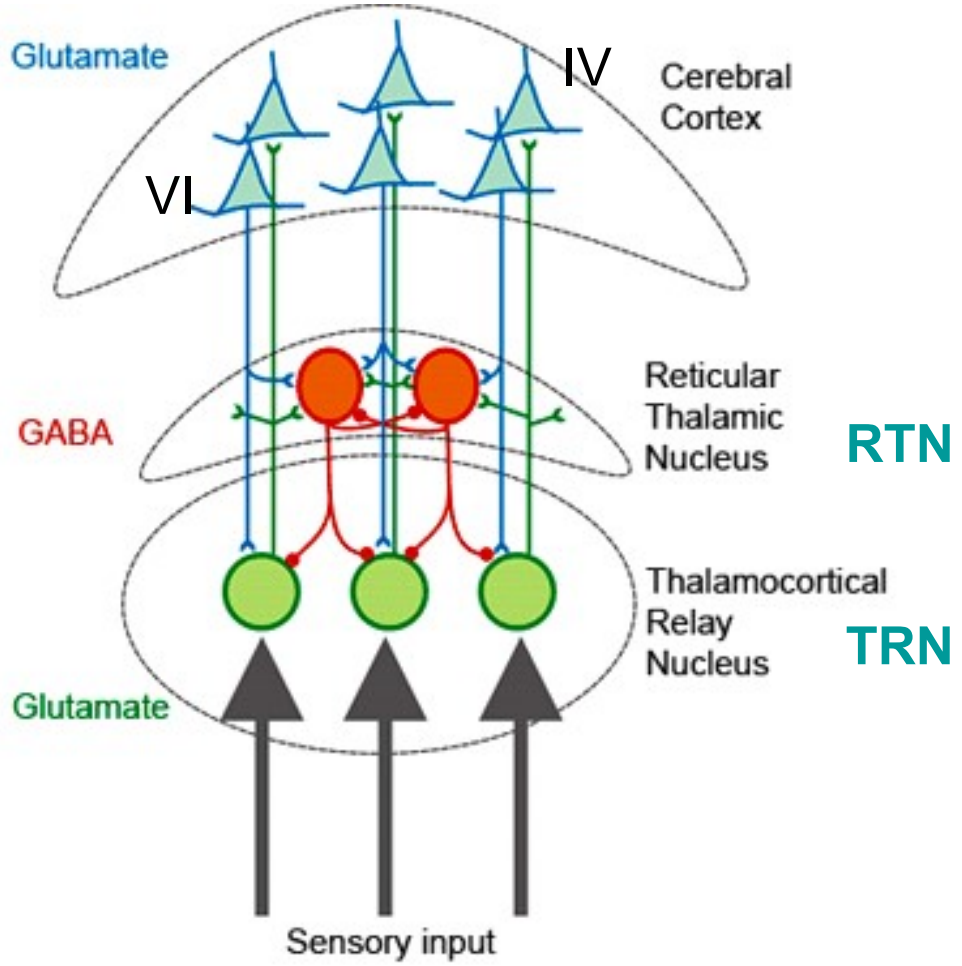
- **Grand Mal seizures:-** involving both hemispheres of the brain simultaneously - 'whole body' convulsion - loss of consciousness.



- **Absence (Petit Mal) seizures:-** **non-convulsive** - subject becomes transiently unresponsive. They mainly affect children, but can happen at any age.

Thalamocortical circuit involved in absence epilepsy

Perturbation of these neuronal networks may lead to abnormal neuronal oscillatory rhythms within thalamocortical circuitry, resulting in generation of bilaterally synchronous spike wave discharges (SWDs) that characterize absence seizures.



Primary sensory afferents form excitatory synapses on TRN relay cells. Relay cell axons pass through the RTN and project to layer 4 of the cortex. Layer 6 cells, from the same cortical area, send axons back to the thalamus, also passing through the RTN. Reticular cells, receiving both feedforward and feedback excitation, send inhibition back into the thalamic nucleus.

Epileptic seizure classification

PARTIAL-ONSET

- **Simple partial:** lasting a few seconds-minutes – ***no loss of consciousness***; manifestation - depends on region of cortex activated - motor, sensory, autonomic, psychic symptoms - scalp EEG normal.

- **Complex partial:** lasting 60-90s- behavioural arrest, staring -***impairment of consciousness;*** from **temporal lobe** (affecting visual-auditory and speech perception, personality, memory, fear/panic) or **frontal lobe** (affecting motor function and emotional control); manifestation - lip smacking, chewing, hand wringing, fumbling **(*automatisms*)**, mumbling - post seizure confusion – no memory of the event.

Epileptic seizure classification

PARTIAL-ONSET

- **Partial (simple or complex), with secondary Tonic-Clonic generalization:**

– often preceded by a **warning 'aura'** indicative of the part of the brain where the seizure focus is located – a subjective sensation (fear, *déjà vu*)– a sound, smell, taste or visual disturbance – can be useful to allow person to prepare for the seizure (*e.g.* lie down) and therefore avoid injury.

Epileptic seizure classification

GENERALIZED-ONSET

- **Involve both cerebral hemispheres from the outset**
- **Consciousness impaired**
- **Absence (typical and atypical)** –brief episodes of impaired consciousness - involves reciprocal firing of thalamus and cortex; mainly affects children but also occurs in adults.

- **Tonic** – sudden extension of arms/legs -sustained contractions of muscles throughout body– rigid extensor spasm); patient may fall over – risk of injury.

- **Clonic** – continuous rhythmic jerking; repetitive eye closures; loss of consciousness may also occur.

Epileptic seizure classification

GENERALIZED-ONSET

- **Myoclonic** – very brief muscle jerks – immediate recovery.

- **Tonic-Clonic –** periodic tonic limb extensions [tonic] followed by clonic jerks - loss of consciousness - no aura.

- **Atonic – 'drop' attacks** (+ other neurologic abnormalities) – all muscles suddenly relax, so patient may fall to the ground – risk of injury.

- **Unclassifiable** - (mixture of several seizure types that do not fit the above categories).

Epileptic seizure classification

Status epilepticus

- is a life-threatening **medical emergency** - when a patient remains in tonic-clonic for >5 mins (30 mins by definition), or when onset of additional seizures occurs following recovery from previous seizure (of any type) – in an endless cycle, without regaining consciousness. Risk factors include <5 years of age, elderly age, genetic predisposition, or structural brain pathology. Can also be induced by drug withdrawal, metabolic disturbance (*e.g.* hypoglycaemia), or alcohol intoxication or withdrawal.

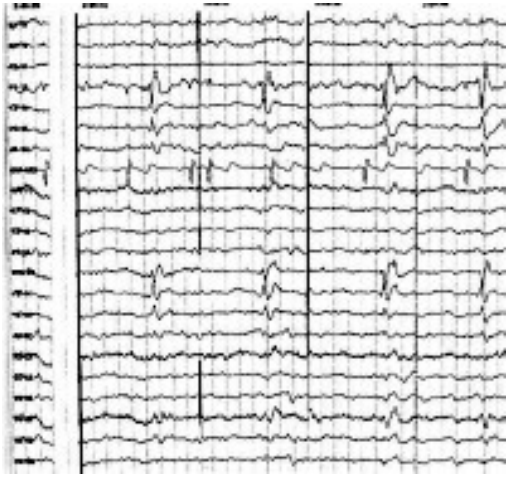
Can cause possible brain damage –O_2 deprivation.

Treatment: Secure airway, give O_2; i/v lorazepam or diazepam.

Diagnosis of epilepsy

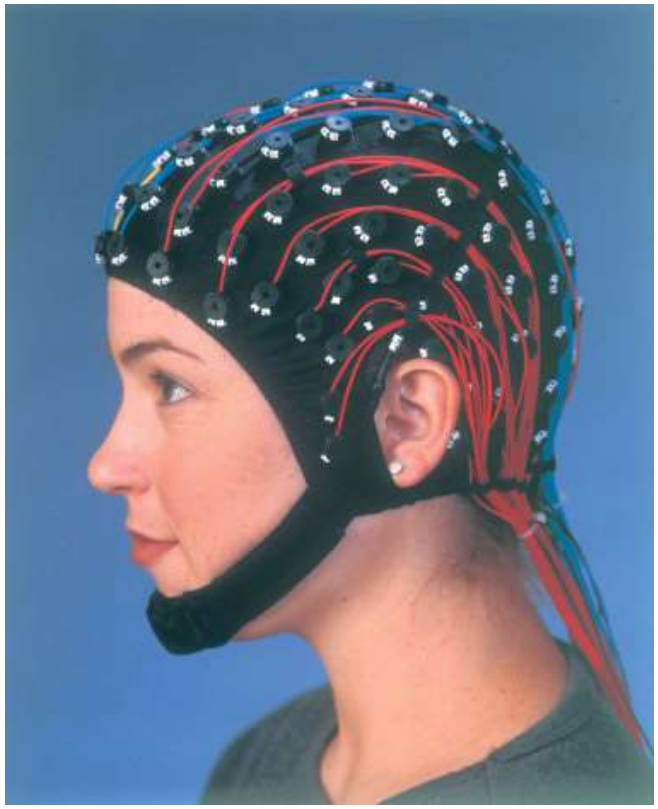
- **Diagnosis of epilepsy** is difficult - normally based on taking an accurate patient medical history, **+ scalp EEG** – indicates mass firing of many thousands of underlying cortical neurones.

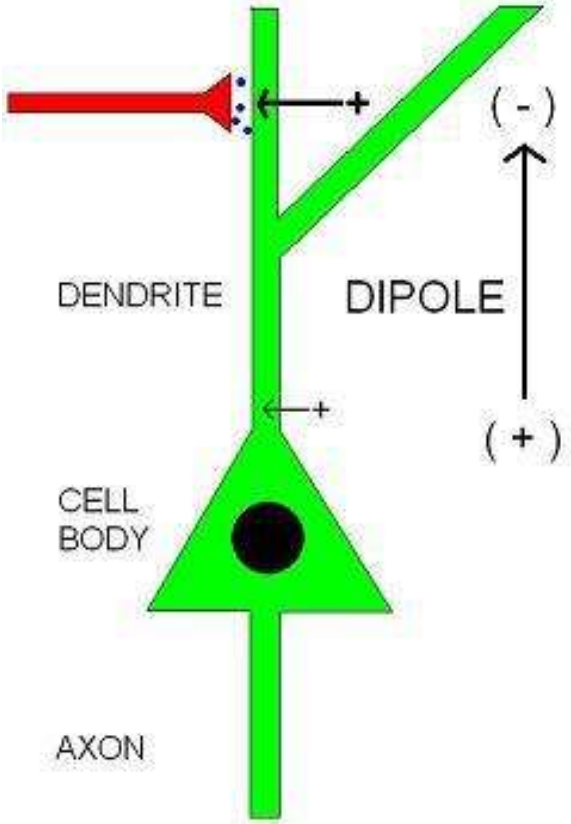
- **The EEG applied to epilepsy patients** can reveal electrical burst activity corresponding to a single seizure event **(ictus)** as well as intermediate **(interictal)** activity.

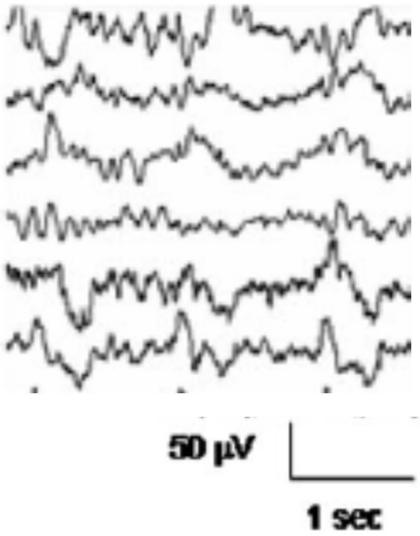


Interictal epileptiform discharges (IEDs)

Brain EEG recording



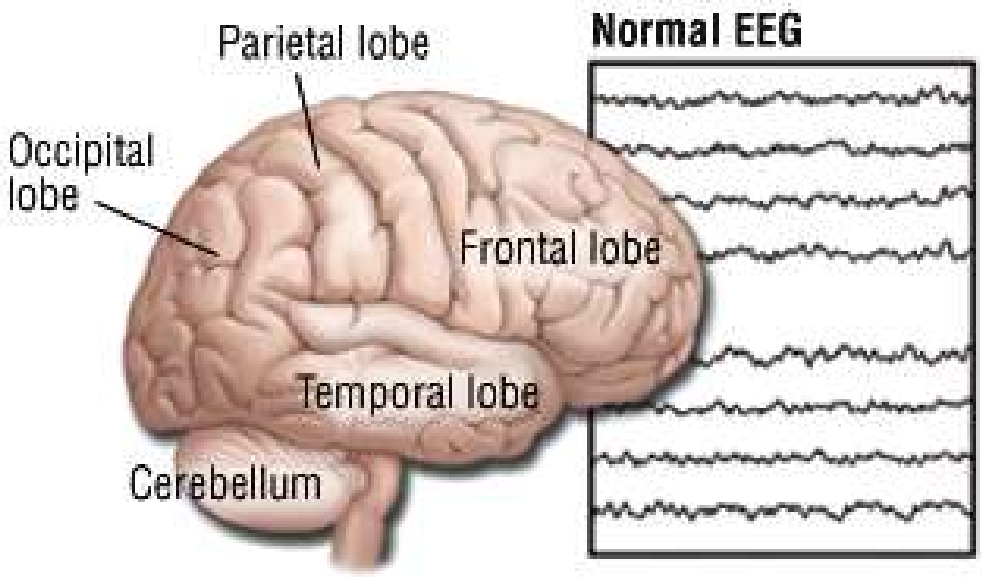


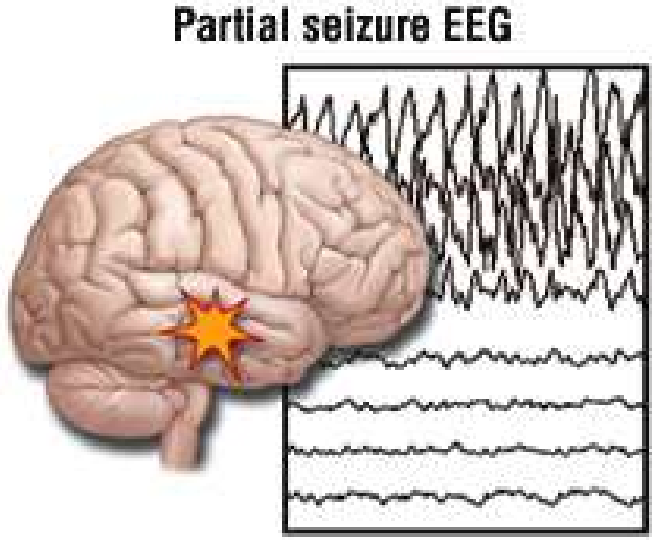


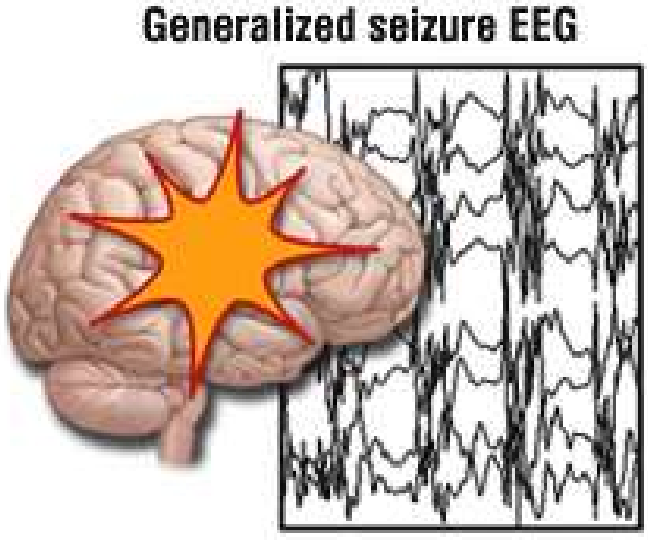
EEG tracing

Dendritic activation of a neurone causes net depletion of positive ions outside the synapse, creating a dipole along the axis of the neurone. When thousands of neurones with similar orientation receive similar synaptic inputs, the dipoles sum together to yield strong voltage signals at the scalp, detectable with EEG.

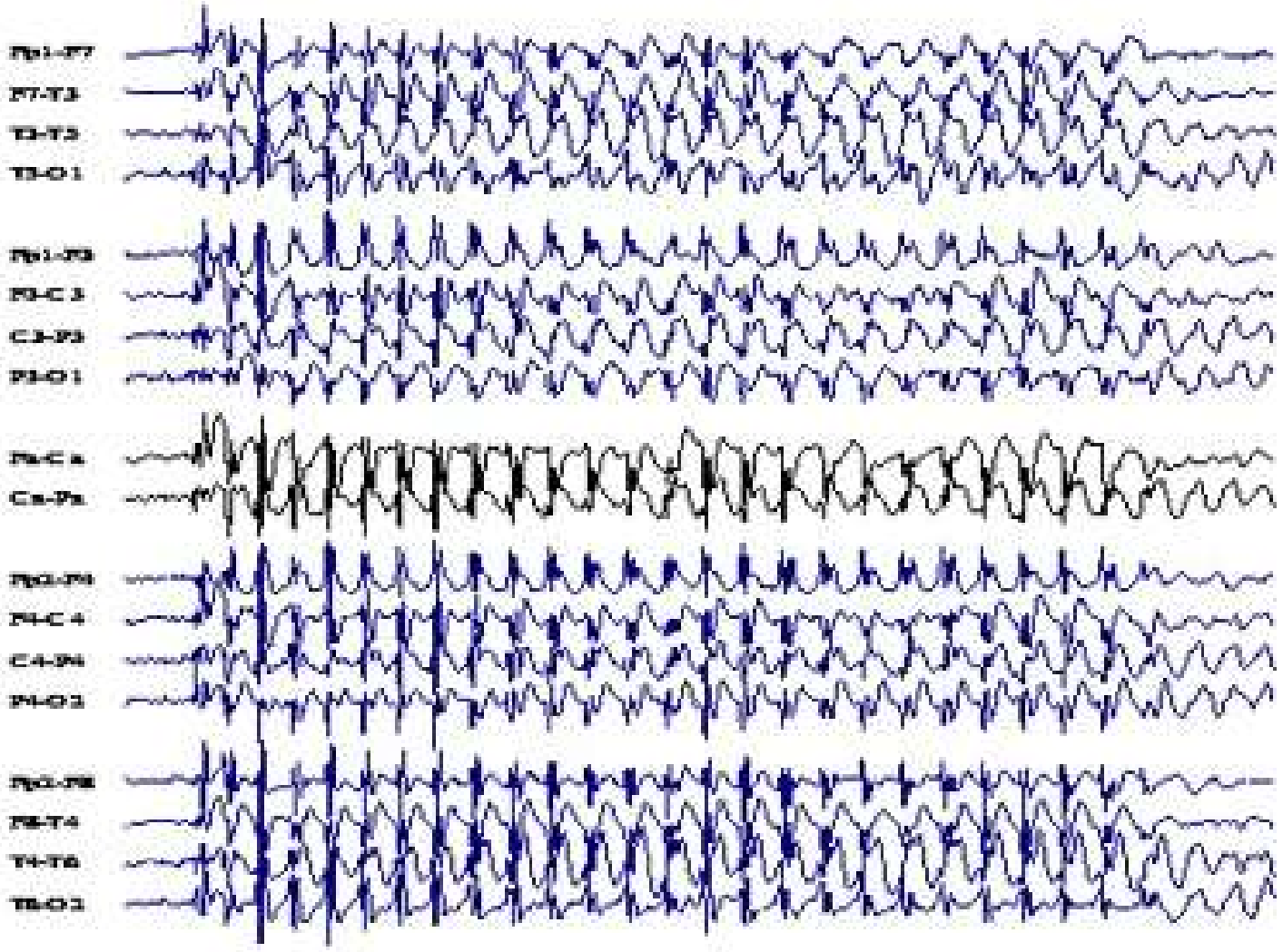
Diagnosis of epilepsy





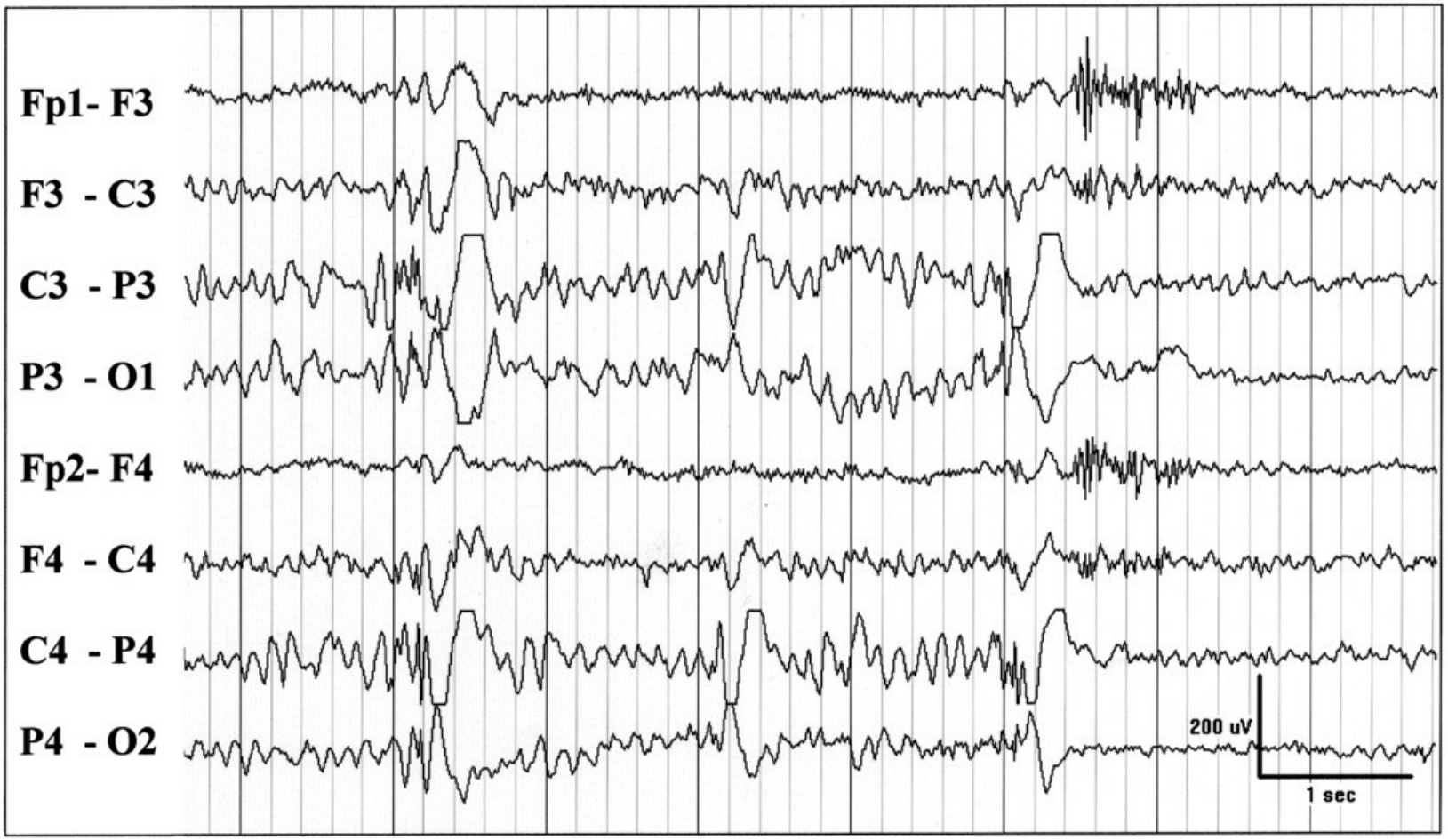


Diagnosis of epilepsy



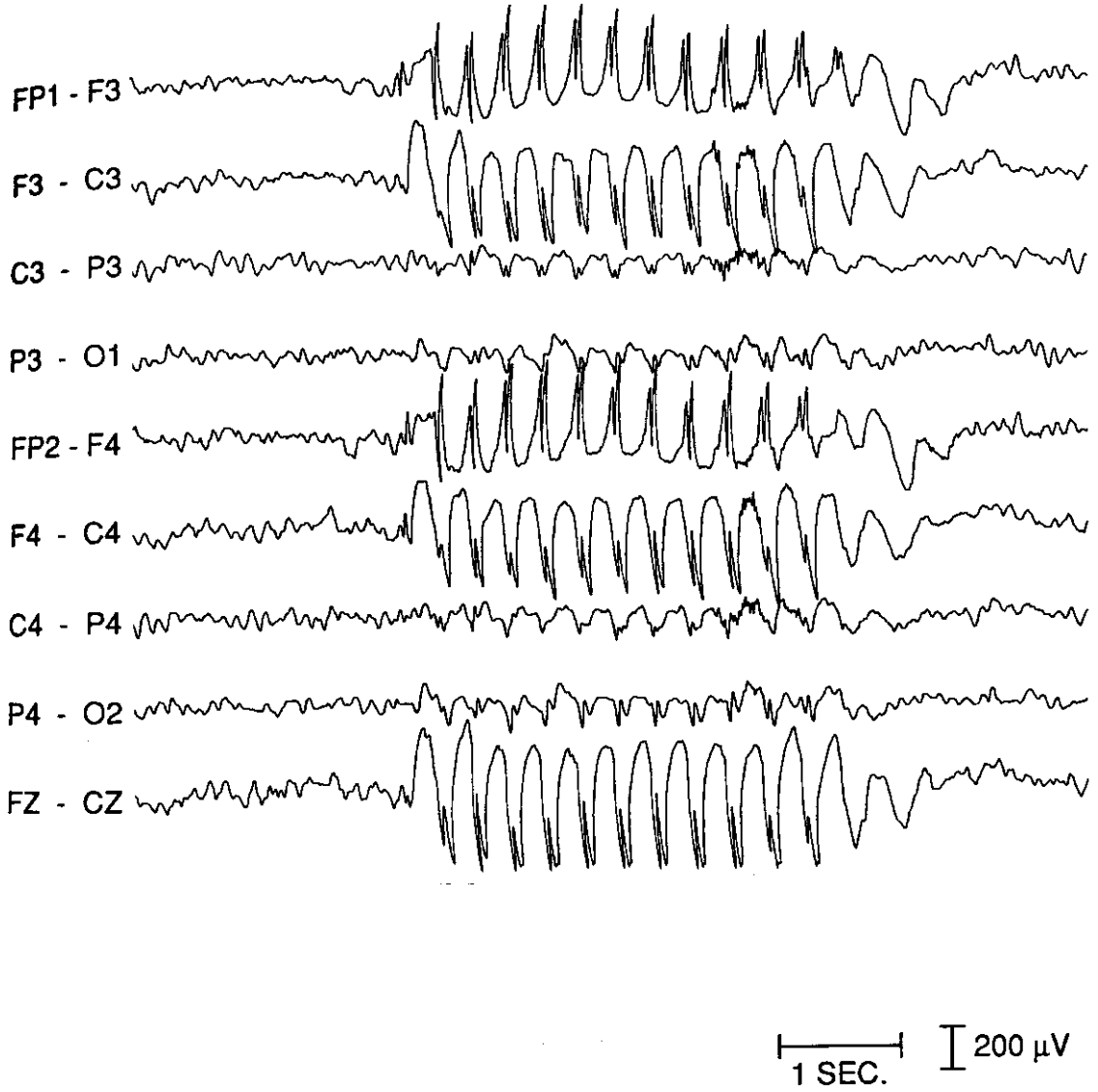
EEG traces of generalized epilepsy

Diagnosis of epilepsy



EEG traces of partial epilepsy

Diagnosis of epilepsy

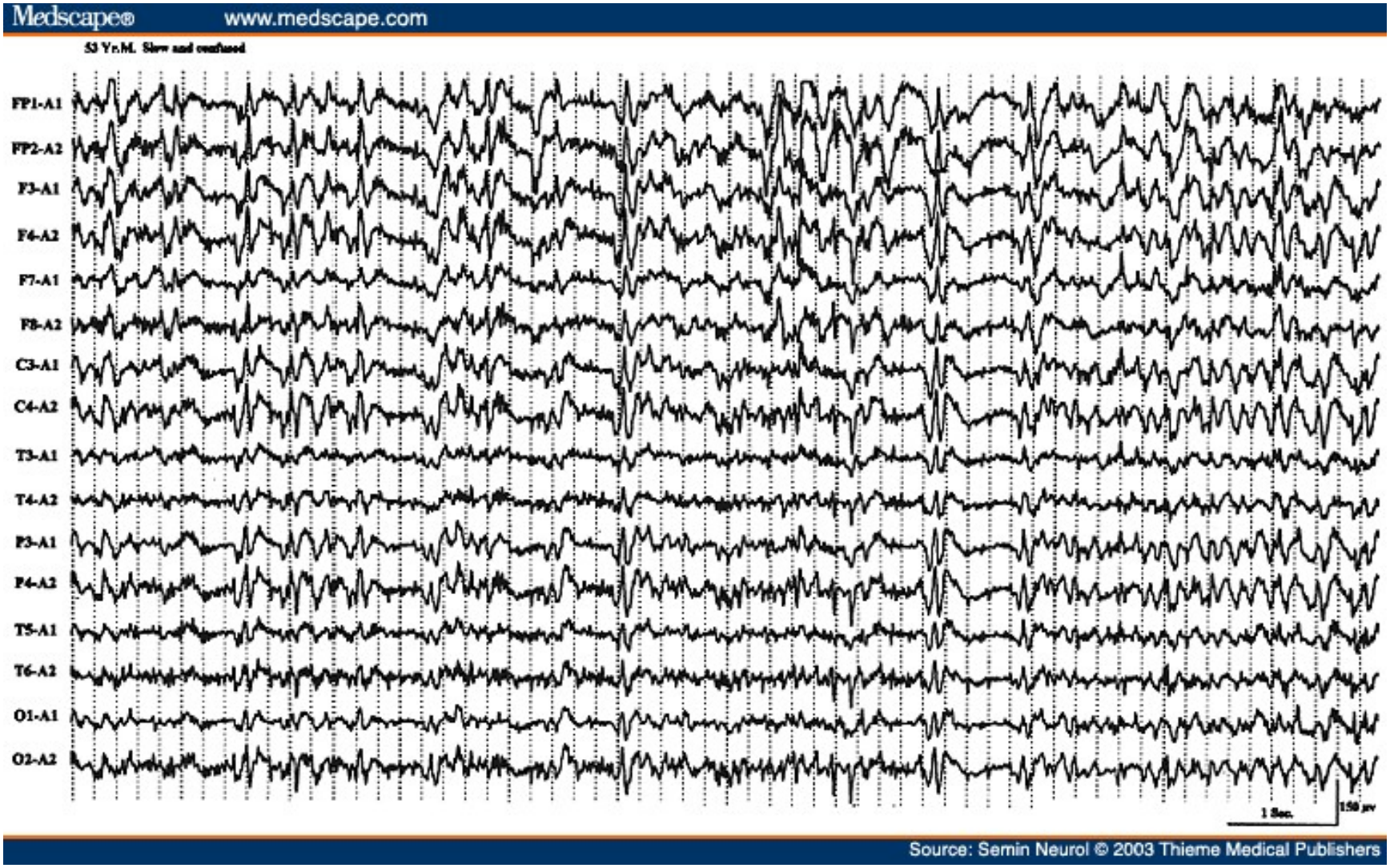


EEG recording of absence epileptic seizure. Paroxysmal 3 Hz spike and wave pattern emerges abruptly out of normal background activity and ceases after a few seconds.

EEG traces of absence epilepsy

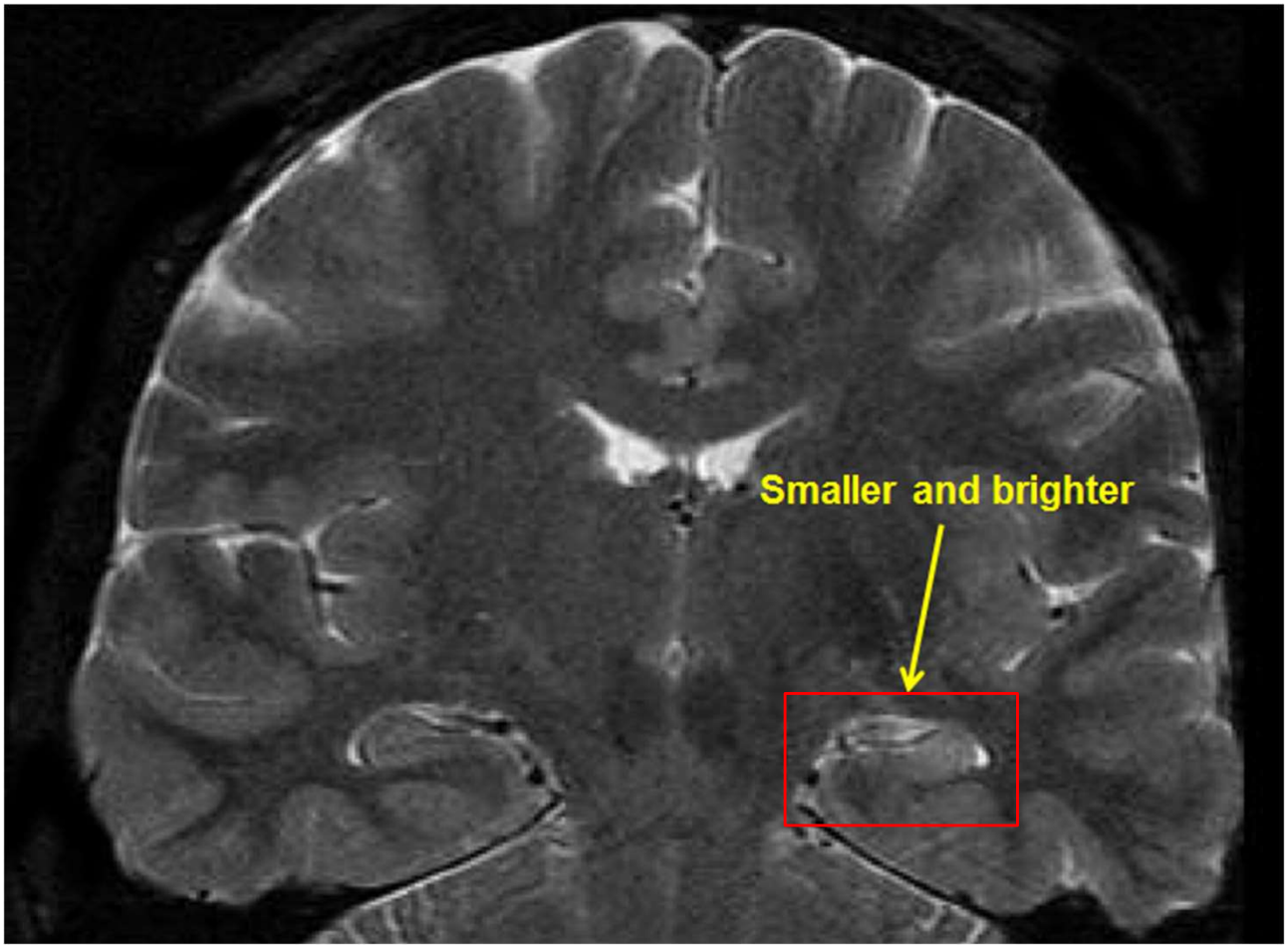
Diagnosis of epilepsy

Status epilepticus



Diagnosis of epilepsy

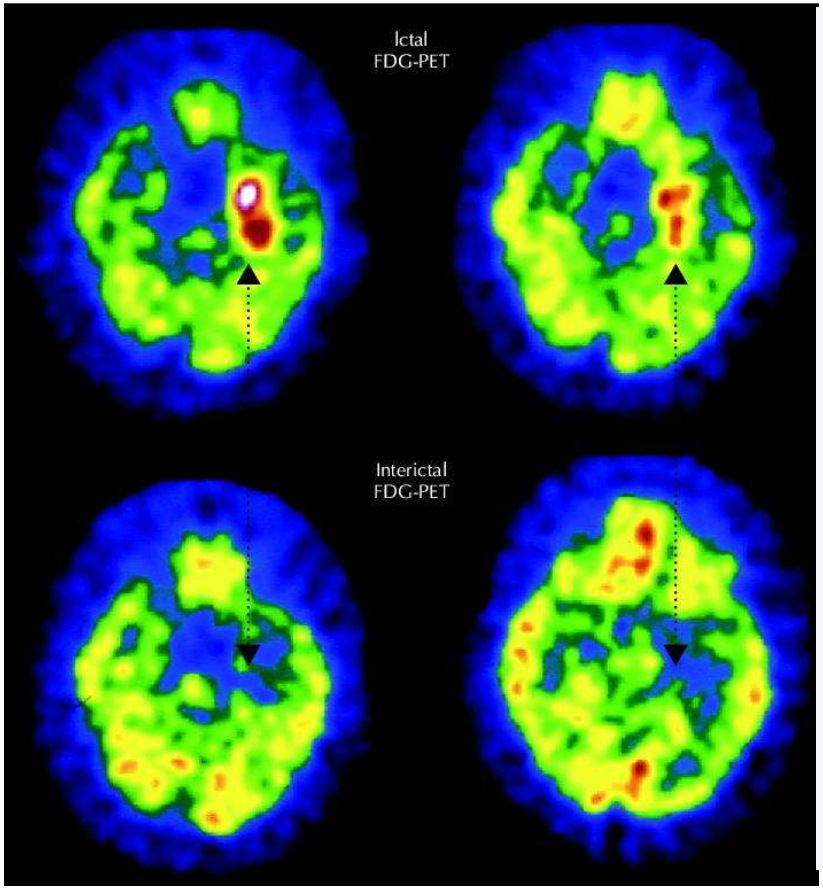
Whole brain imaging methods

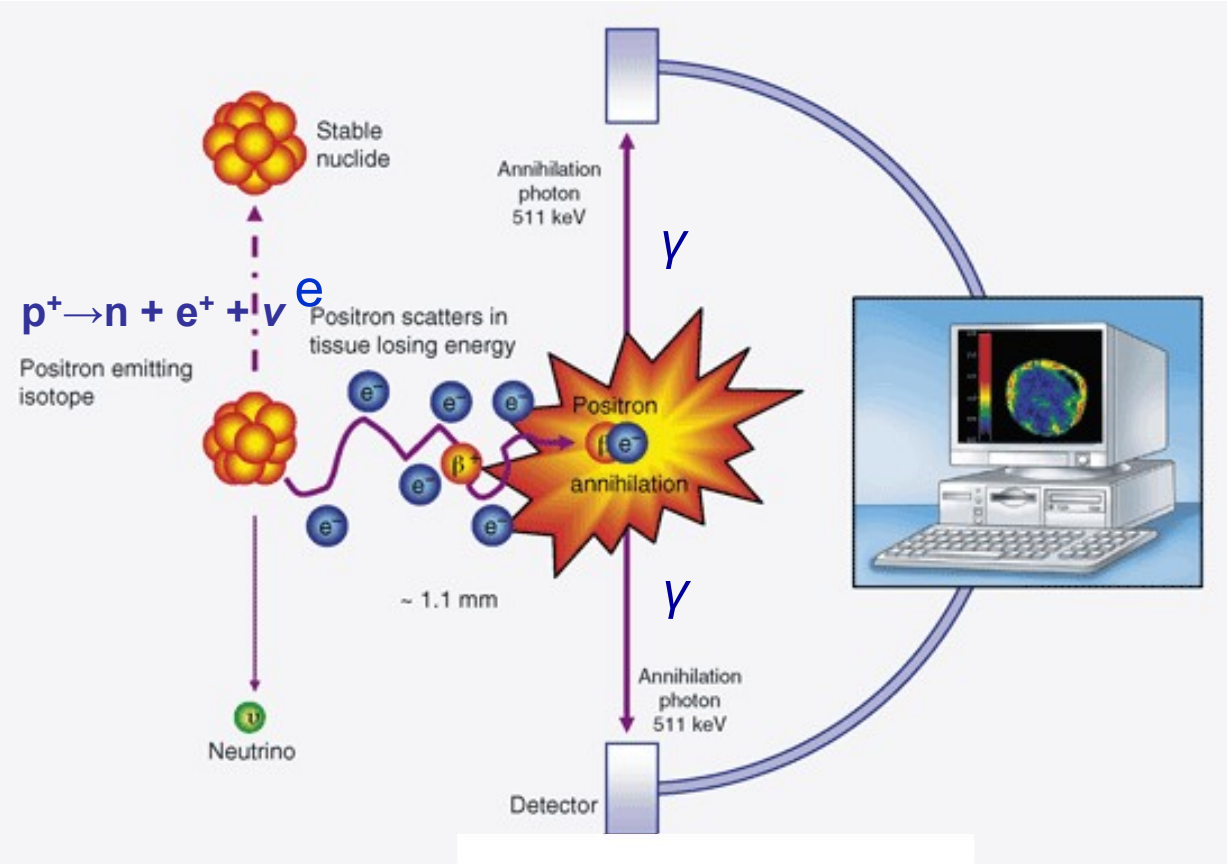


Coronal MRI brain scan shows hippocampal sclerosis associated with TLE

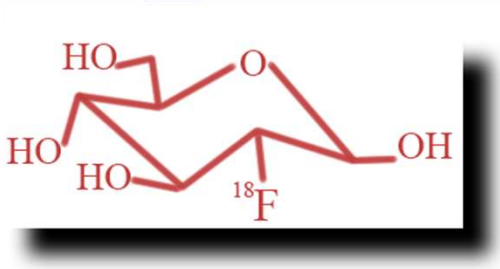
Diagnosis of epilepsy

Whole brain imaging methods





Brain scan using F-18 FDG-PET



F-18 FDG

FDG= Fluorodeoxyglucose

Diagnosis of epilepsy

Whole brain imaging methods

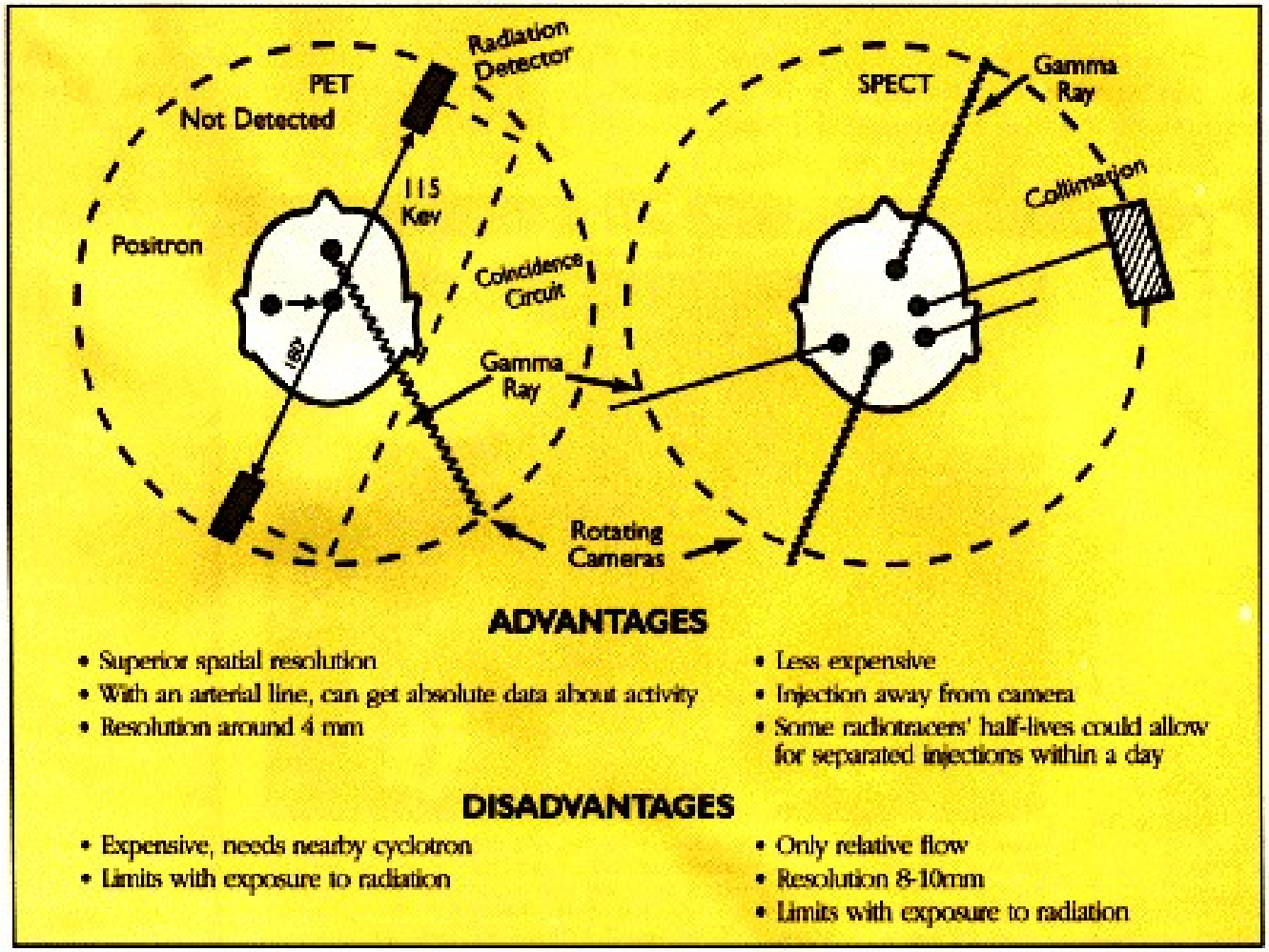
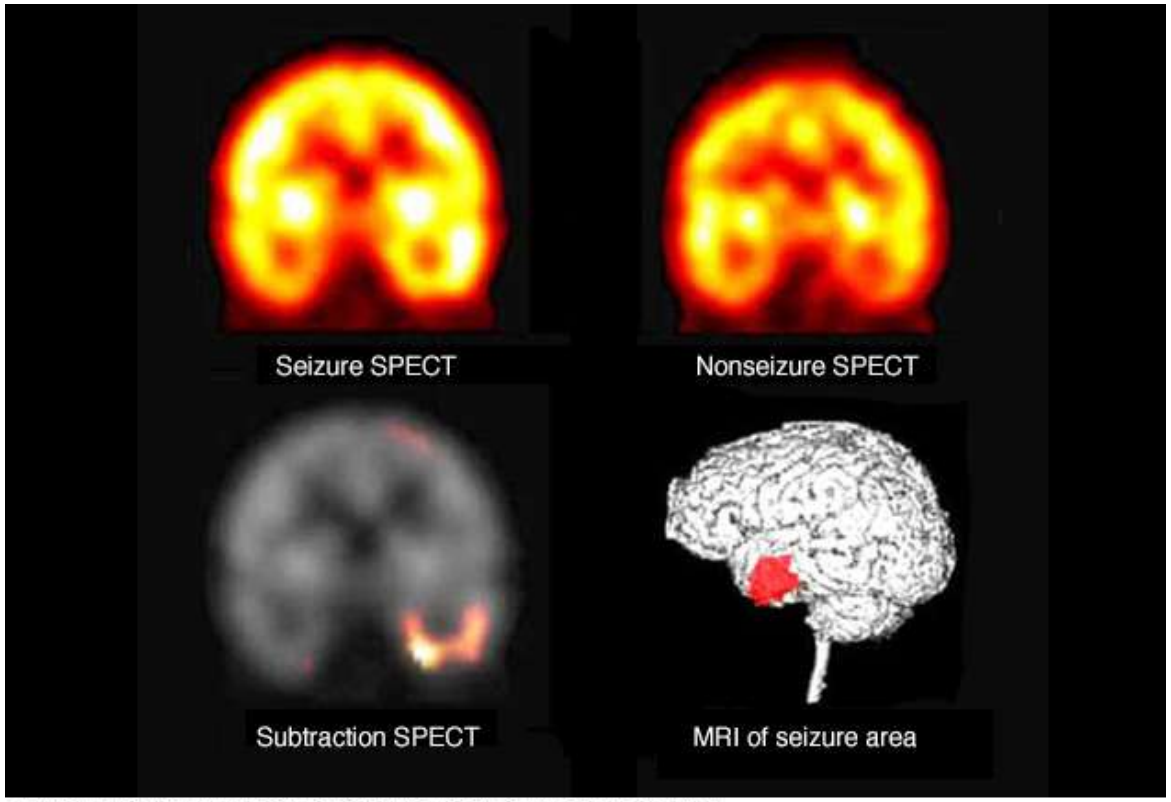


Figure 1 - This is a diagram of the imaging technique behind SPECT (right of image) and PET (left of image).

SPECT (single photon emission computed tomography) tracers emit a single gamma ray

Diagnosis of epilepsy

Whole brain imaging methods



Brain scan using SPECT in an epilepsy patient – **measures cerebral blood flow** – using **^{99m}Tc-based radioactive tracers.** During seizures, metabolic demand of the brain increases therefore CBF increases.

Diagnosis of epilepsy

Whole brain imaging methods

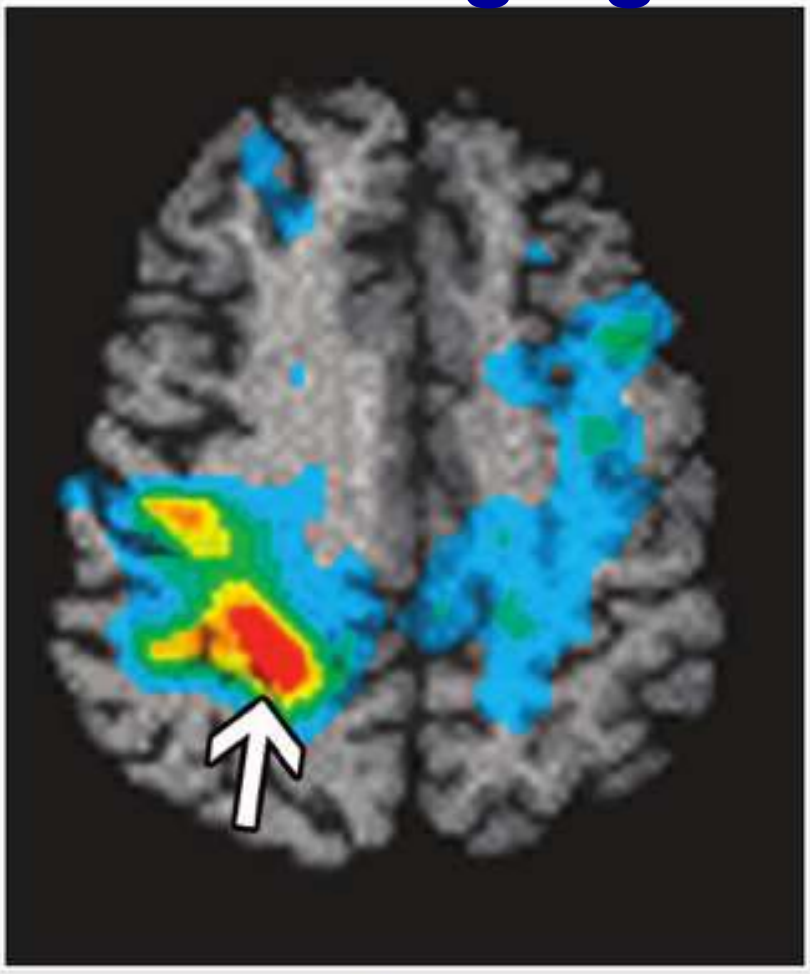
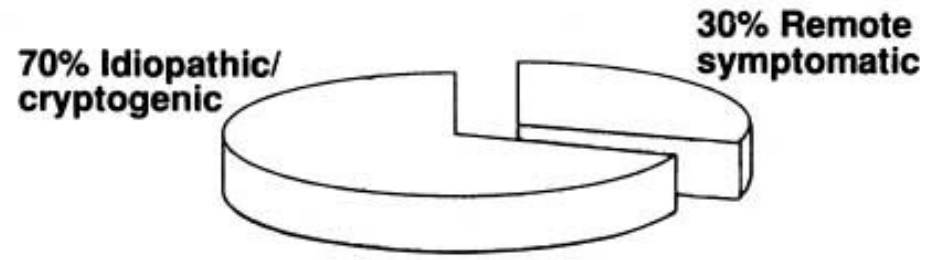


FIGURE 9-5 Subtraction ictal SPECT coregistered to MRI (SISCOM) study. The study shows blood flow changes (*arrow*) over the coregistered MRI. Localization of epileptic focus is highly reliable.

Causes of epilepsy

The epilepsies can be further classified into those that arise from a known or suspected CNS disorder **[Symptomatic]** and can occur at any time of life -

and those which have no underlying cause apart from a hereditary predisposition or a genetic-neurochemical or ion channel defect **[Idiopathic].**



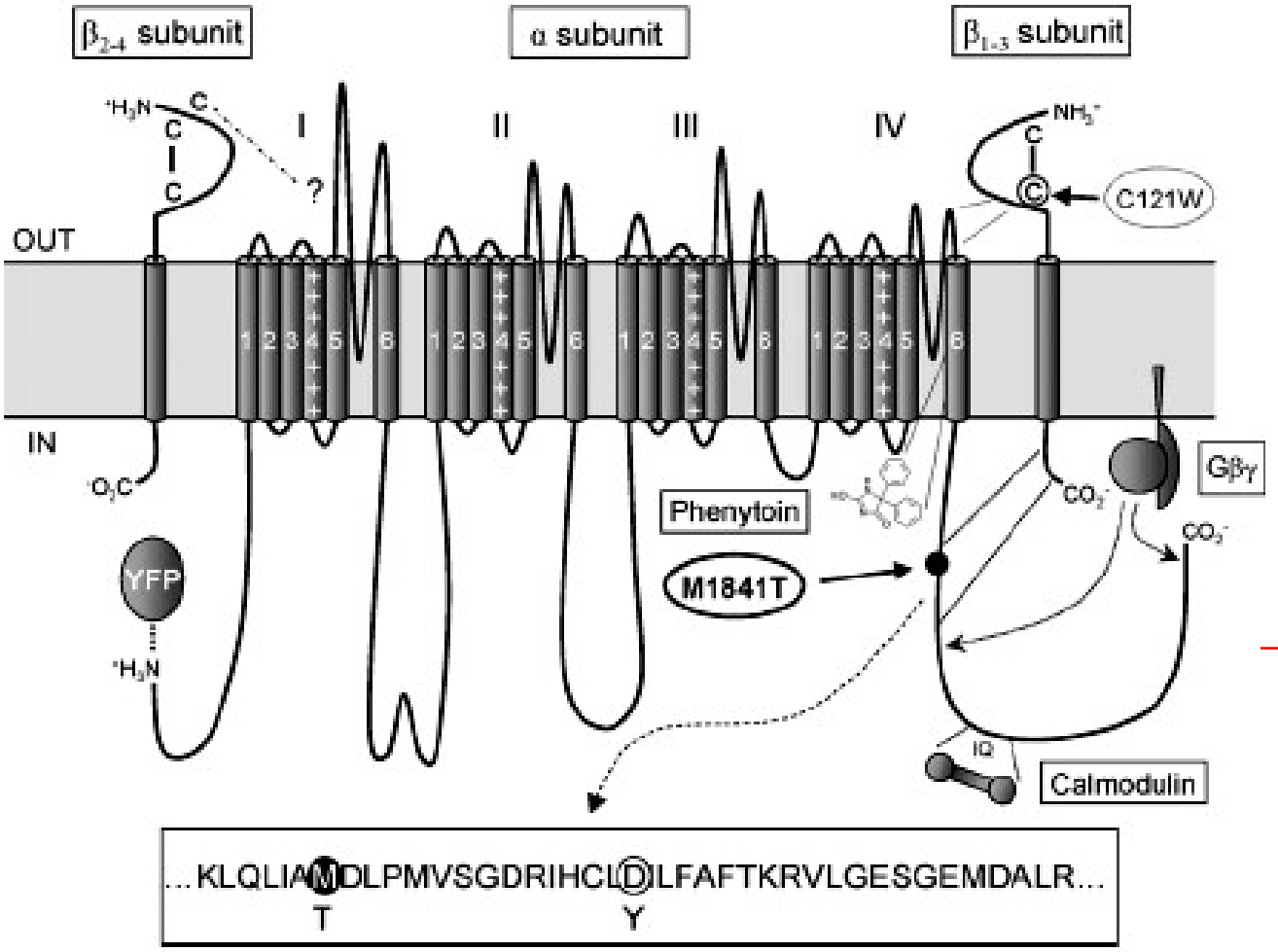
Causes of newly diagnosed cases of epilepsy. Despite growing knowledge of causes, 70% of cases are of unknown cause. *(From Hauser, 1990)*

Causes of epilepsy

- **Symptomatic (provoked)** – from acute head injuries; trauma; excessive alcohol/drug toxicity; CNS infections (meningitis, viral encephalitis); brain tumours, cerebrovascular disease (stroke); neurodegenerative diseases, or long-standing systemic, metabolic or toxic insults.

- **Idiopathic (unknown cause)** – presumed genetic – *e.g.* Na^+, K^+ or Ca^{2+} channel mutations; $GABA_A$ or ACh nicotinic receptor subunit mutations.

Causes of epilepsy



Methionine →Threonine

A single misense mutation [M1841T] of the brain $Na_v1.1$ Na^+ channel α-subunit causes **Generalized Epilepsy with Febrile Seizures+ (GEFS+).**

Treatment of epilepsy

- **Epilepsy is treated** with available **anticonvulsant** medications.

- **The aim of therapy** is to achieve a long-term seizure-free status, with minimal adverse side effects.

- **Monotherapy** is preferred - ↓incidence of side-effects and risk of drug interactions.

- **Polytherapy** is considered when a patient's seizures cannot be adequately controlled by a single drug.

Treatment of epilepsy

Vagus Nerve Stimulator

The VNS device is implanted under the skin in the chest: electrical stimulation of the left vagus nerve in the neck can stop seizures in some patients with **refractory partial epilspsy.**

Treatment of epilepsy

Currently used anticonvulsants

1. **Na^+ channel blockers** - Phenytoin, Carbamazepine, Oxcarbazepine, Eslicarbazepine, Valproate, Primidone.
2. **$GABA_A$ enhancers** - Phenobarbital, Diazepam, Clonazepam, Clobazam, Lorazepam, Primidone.
3. **Glutamate receptor blockers** - Topiramate, Perampanel.
4. **T-type Ca^{2+} channel blockers** - Ethosuximide, Valproate.
5. **N- and L-type Ca^{2+} channel blockers** - Lamotrigine, Topiramate, Zonisamide, Valproate
6. **Blockers of unique binding sites** – Gabapentin, Pregabalin (Ca^{2+} channel $\alpha_2\delta$ subunit), Levetiracetam (synaptic vesicle protein 2A [SV2A]), Perampanel (AMPA receptor), Tiagabine (GABA transporter 1 [GAT-1]).

Treatment of epilepsy

Currently used anticonvulsants

7. **Enhancers of slow inactivation of the Na^+ channel**- Lacosamide, Rufinamide
8. **Carbonic anhydrase inhibitors** – Acetazolamide, Topiramate, Zonisamide
9. **Neuronal potassium channel (KCNQ [Kv7]) openers** - Retigabine, Ezogabine (USA) – **now withdrawn (2017).**
10. **H-current modulators** – Gabapentin, Lamotrigine.
11. **GABA transaminase (GABA-T) inhibitor** – Vigabatrin.

Treatment of seizure types

Partial onset – Carbamazepine (first line) or Lamotrigine, Oxcarbazepine, Phenytoin, Topiramate.

Absence – Ethosuximide.

Tonic or atonic – broad–spectrum drugs – Valproate, Lamotrigine, Topiramate.

Myoclonic – Valproate, Lamotrigine, Topiramate.

Generalized onset tonic-clonic – Valproate (first line), Phenytoin, Lamotrigine, Topiramate.

Status epilepticus – Lorazepam, Diazepam, Midazolam, Phenytoin, Valproate, Phenobarbital.

Treatment of seizure types

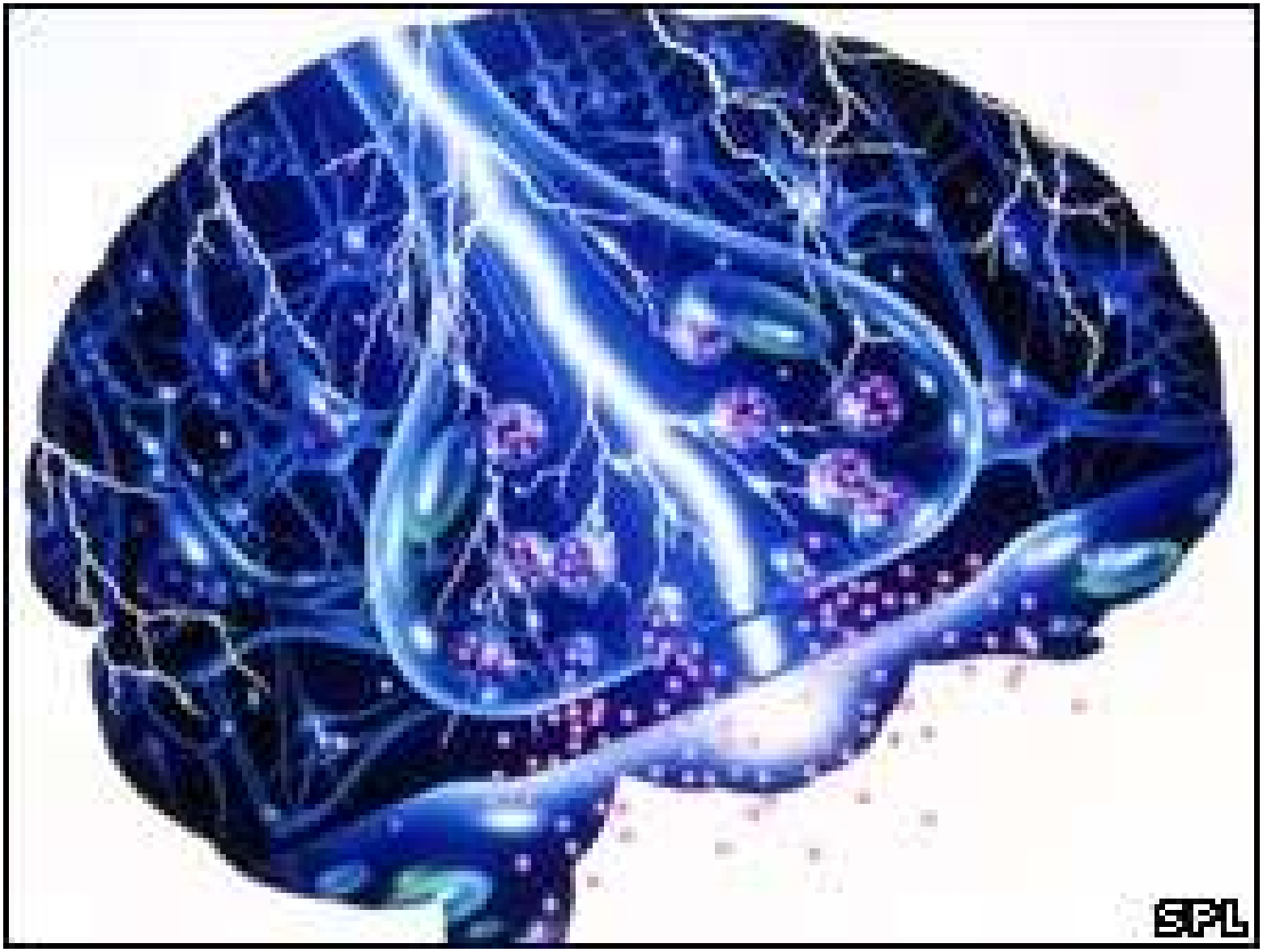
Valproate Use in Women and Girls of Childbearing Years– Valproate is licensed for use in epilepsy and bipolar disorder. It is also used off-label for depression, neuropathic pain, dementia and migraine.

Children born to women who take valproate during pregnancy are at significant risk of birth defects and persistent developmental disorders. If valproate is taken during pregnancy, up to 4 in 10 babies are at risk of developmental disorders, and approximately 1 in 10 are at risk of birth defects. Valproate must not therefore be used in women and girls of childbearing potential.

Epilepsy surgery

Surgery can be considered for ~1% of epilepsy patients – poorly controlled with available medication, and who have an identifiable **epilepsy focus** in a part of the brain where removal would not significantly influence brain function.

In such patients, resection of the focal area can be curative (*e.g.* patients with **temporal lobe epilepsy** or **children** are good candidates for surgery).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