EPILEPSI

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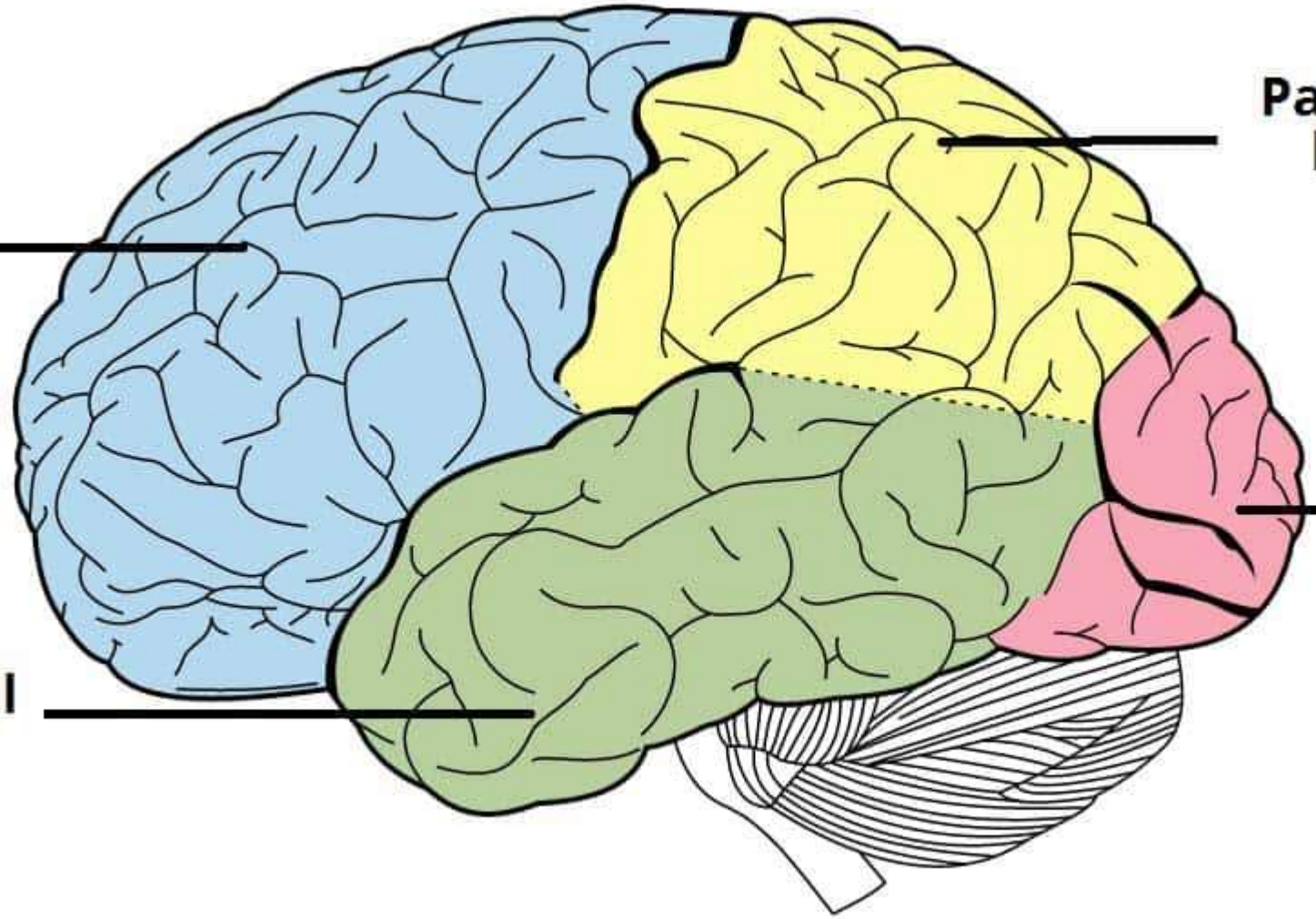
Istilah Penting

- Epilepsi/ epilepsy
- Acute symptomatic seizure
- Kejang
- Bangkitan epileptik
- Seizure
- Iktal
- Convulsive/ non convulsive
- Interiktal
- Focal onset
- General onset
- Aura
- Motorik
- Non Motorik
- Psychogenic non epileptic seizure
- Tonic
- Clonic
- Atonic
- Myoclonic
- Abscence
- Status Epilepticus
- Syncope

Ingat Kembali lobus utama otak dan fungsinya

Fungsi luhur eksekutif
Pusat gerakan mata
Pusat menulis
Pusat ekspresi bicara
Pusat motorik

Frontal lobe



Parietal lobe

Pusat sensoris
Lapang pandang ¼ inferior

Occipital lobe

Pusat visual

Temporal lobe

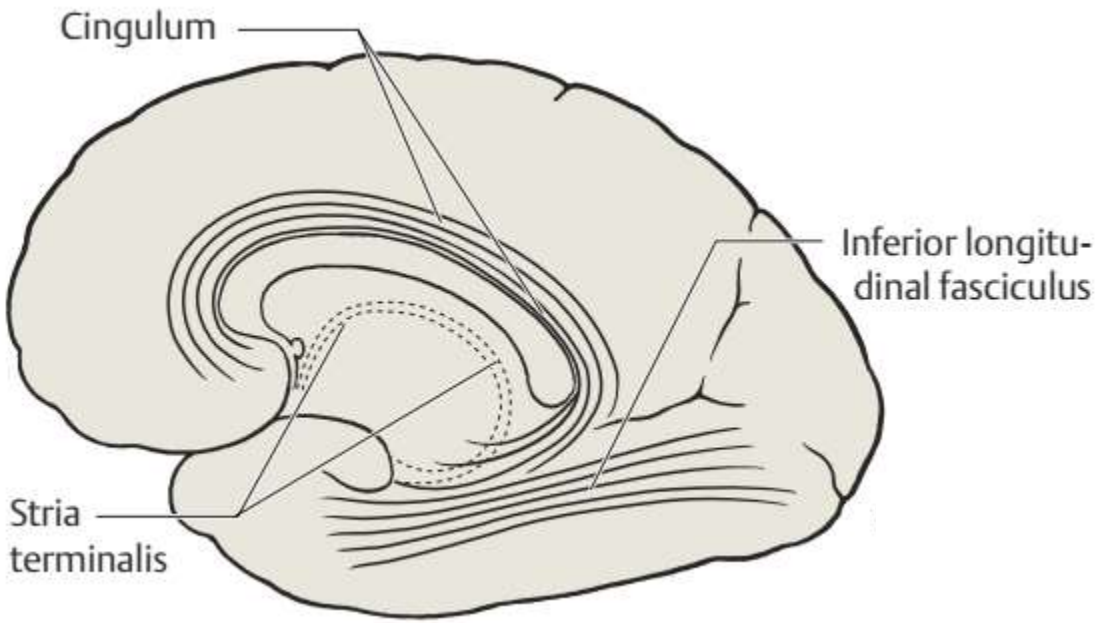
Pusat auditoris
Pusat memori
Pusat emosi (sistem limbik)
Pusat pemahaman bahasa
Lapang pandang ¼ superior

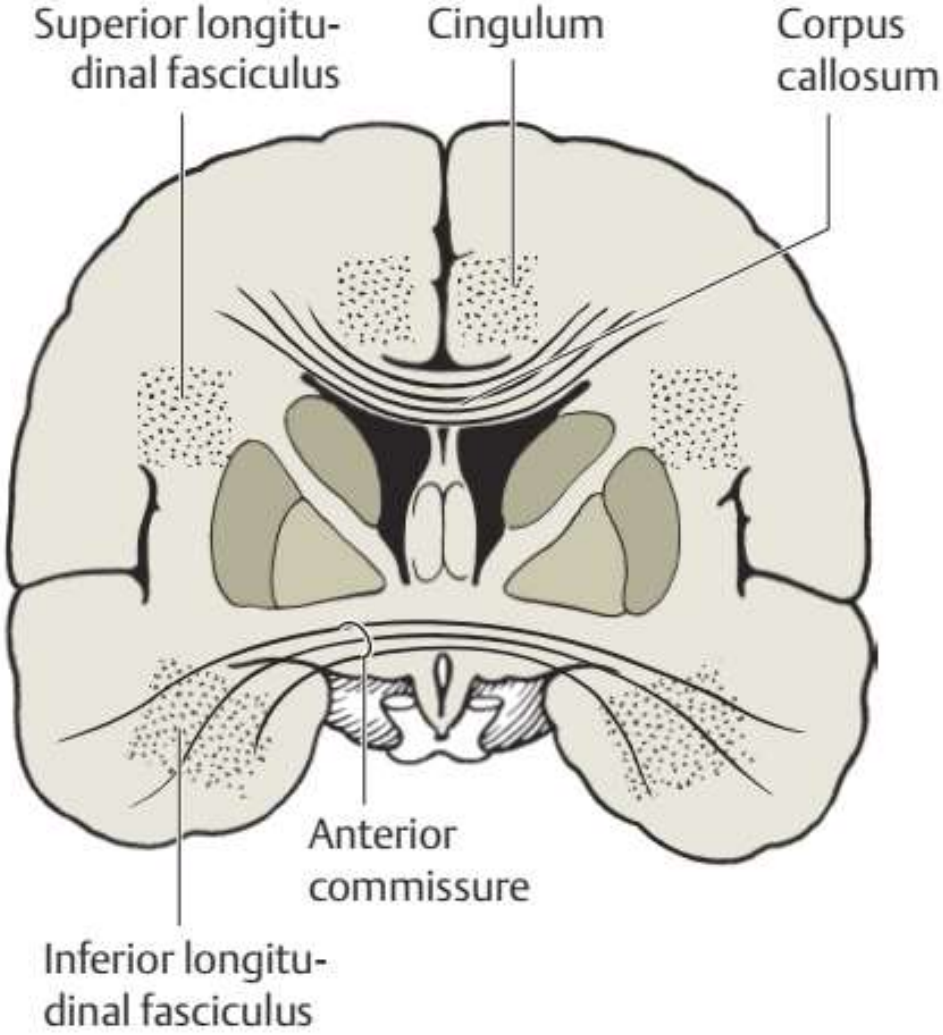
Pasien mengeluhkan kesemutan pada ujung mulut →
kelemahan wajah kiri, sehingga liur mengalir dari sudut mulut sebelah kiri →
pasien dapat menuruti perintah dan menjawab pertanyaan tetapi pelo →
Mata berkedip-kedip saat serangan dan kelopak mata kiri lebih menyipit

Dimana asal area otak yang mengalami kejang ?

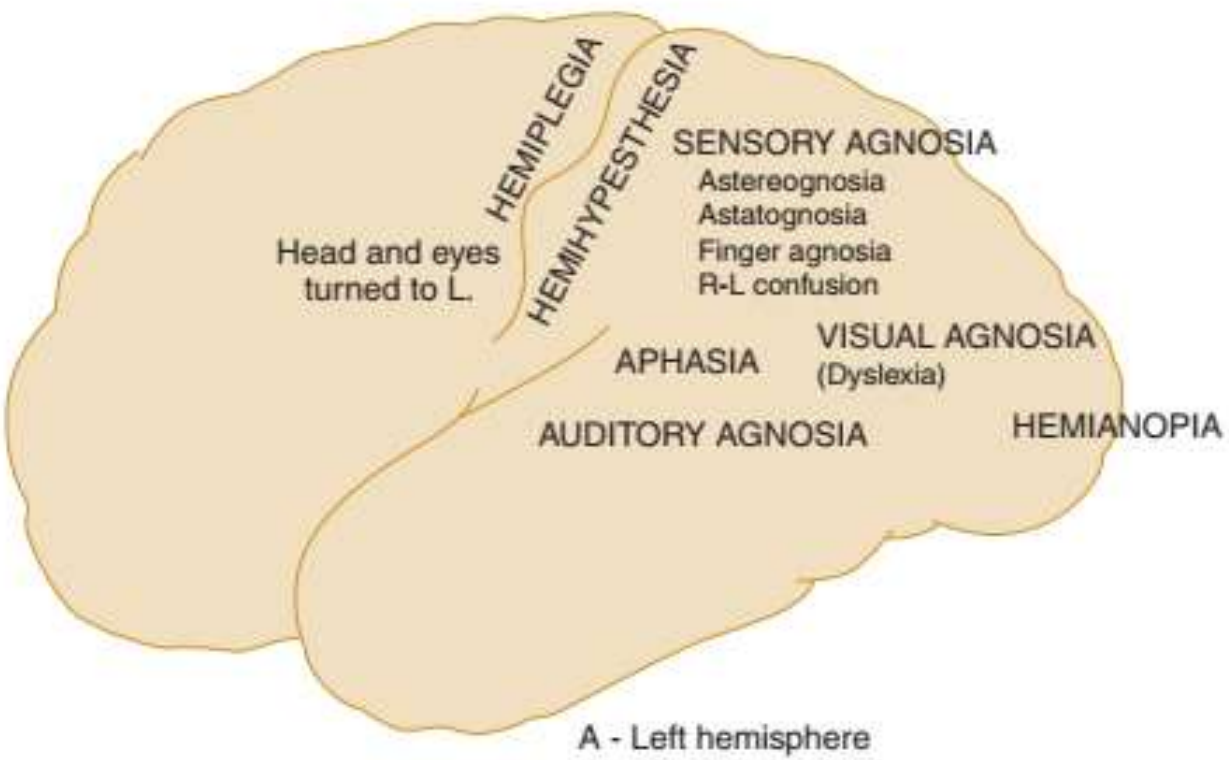
Area otak satu dengan yang lain dihubungkan dengan *network*

Jaras penghubung antar area otak

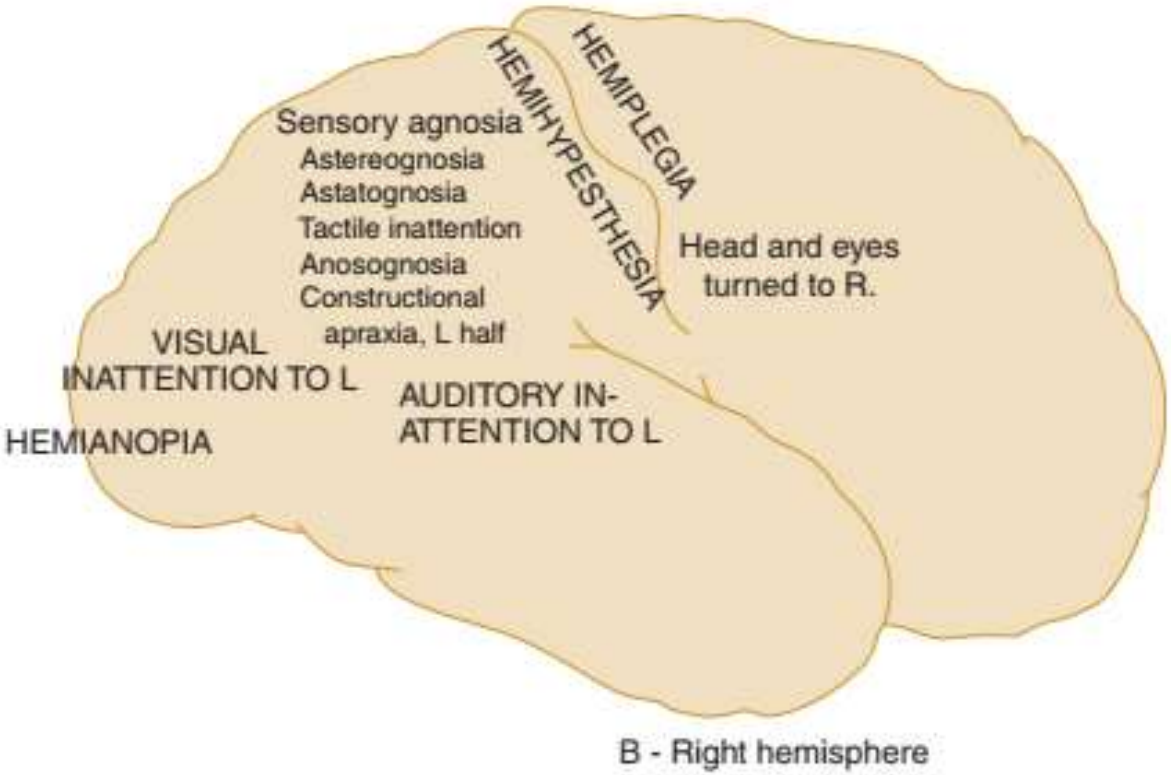




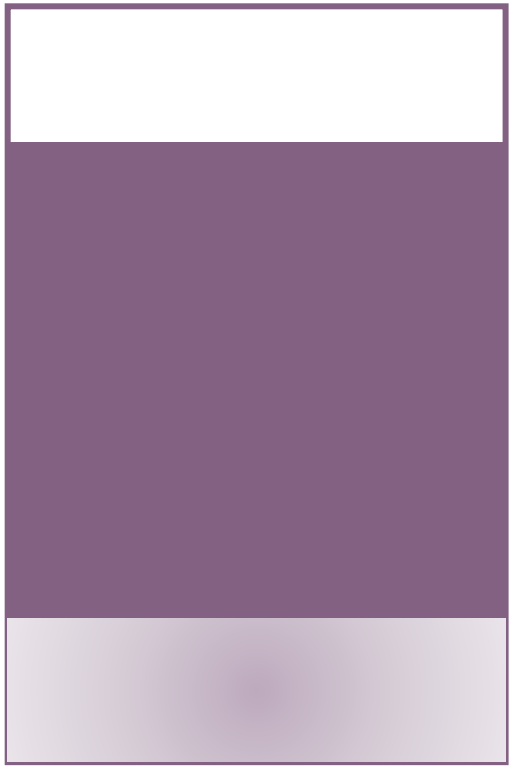
Buka Kembali tentang fungsi otak korteks, termasuk fungsi luhur



A - Left hemisphere

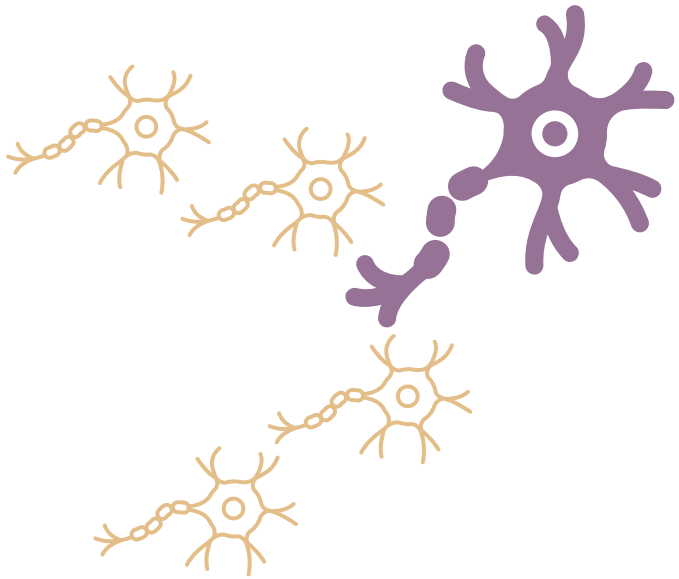


B - Right hemisphere



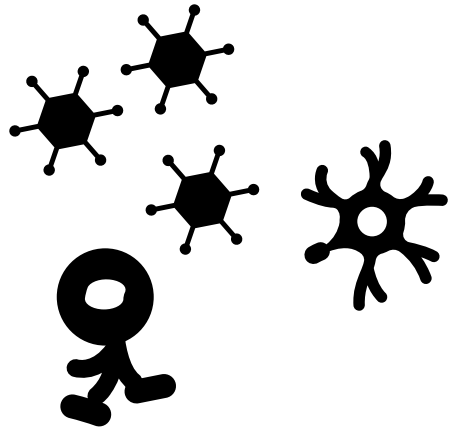
massa otak

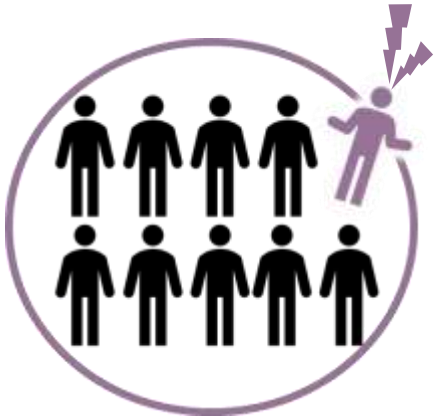
82% adalah
korteks cerebri



19% adalah NEURON

81% adalah GLIA
- Astrosit
- Oligodendrosit
- Mikroglia





11% Populasi pernah kejang dalam hidupnya

97% acute symptomatic seizure

3% epilepsi

Epilepsi

People with Epilepsi sering hidup dalam stigma

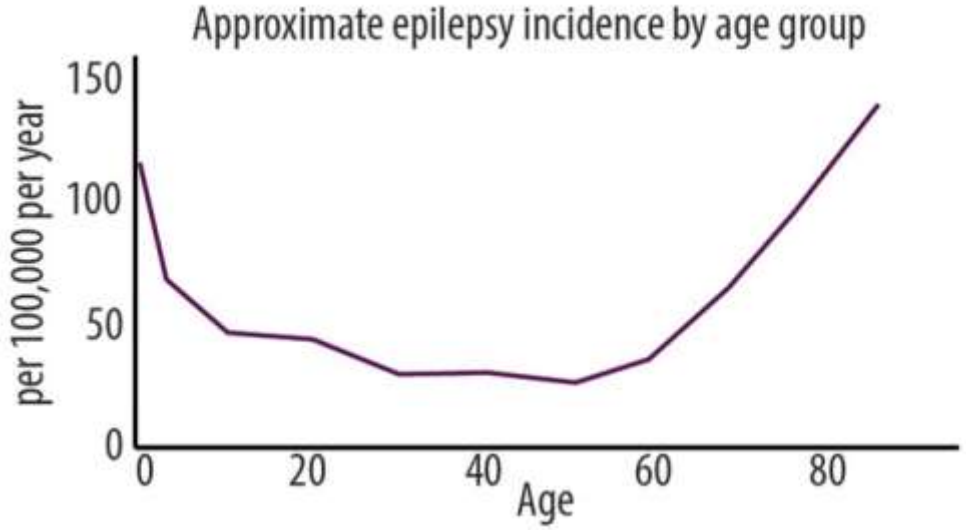
20% pasien epilepsi memiliki komorbid gangguan kognitif

Penyakit neurologis dengan beban tertinggi dan disabilitas terbesar seumur hidup

Mengenai segala usia

Pengobatan dengan ASM

Hanya 44% bebas kejang
Atau seizure on remission



ASM = antiseizure medication

Diagnosis dari dokter

Mengkonsumsi ASM*

Memiliki ≥1 bangkitan/ tahun

Prevalensi per tahun 1.1%

Active Epilepsi

ASM = antiseizure medication

INSIDER

Newsletters

Disney star Cameron Boyce died from epilepsy. A neurologist explains why the disease can be deadly.

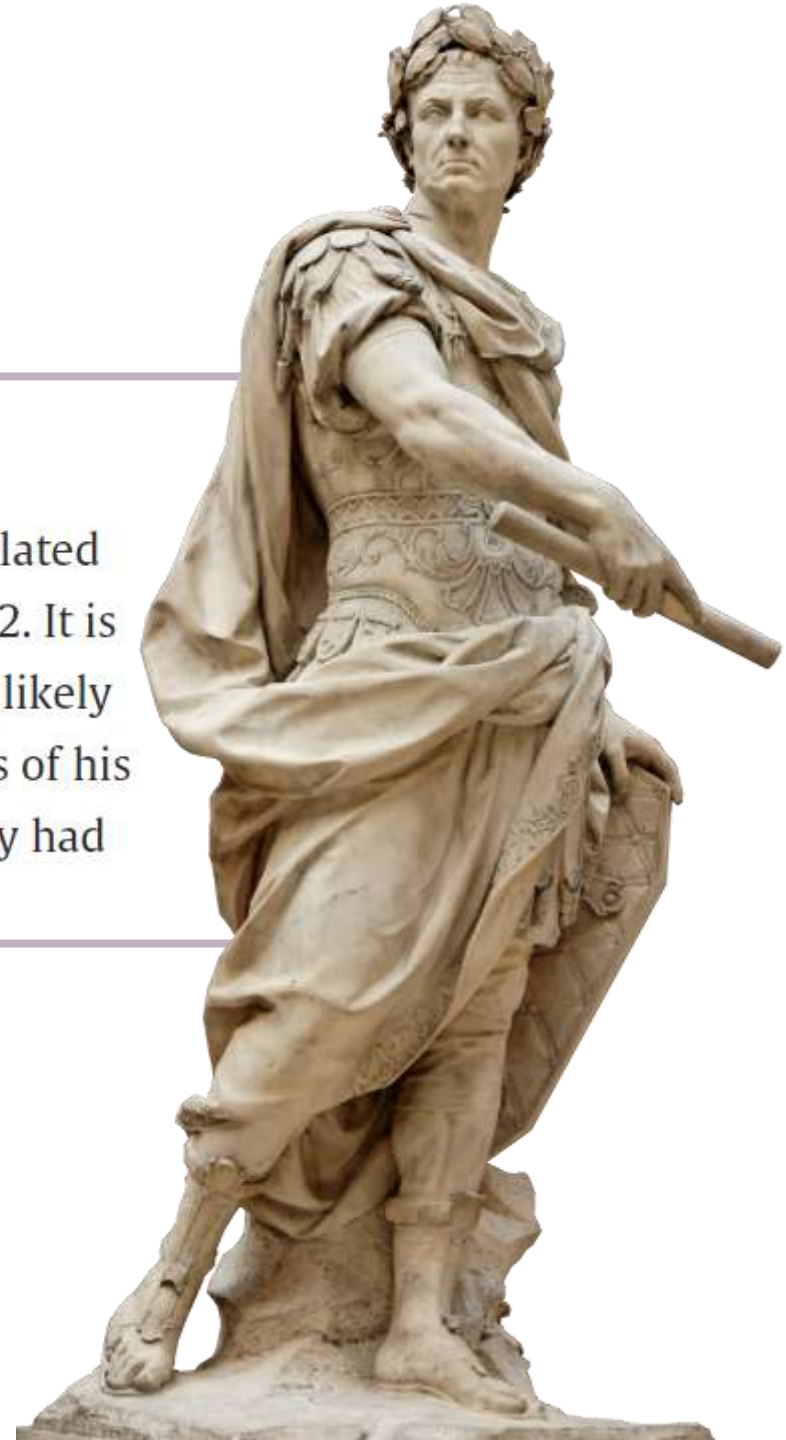
Anna Medaris Updated Nov 13, 2019, 9:52 PM

- Actor Cameron Boyce, best known for his role as Luke in Disney Channel's "Jessie," died suddenly on July 6 at 20 years old.
- His parents recently spoke publicly for the first time on Good Morning America in an effort to raise awareness for the condition that killed him, epilepsy.
- Cases of epilepsy, a chronic brain disease marked by recurrent, unprovoked seizures, can range from mild to severe.
- Epilepsy can be well-managed, but it comes with the risk of sudden unexpected death in epilepsy, or SUDEP, which may be due to seizures causing breathing or heart issues.

SUDEP | Sudden unexpected death in epilepsy

Julius Caesar and His Epileptic Seizures

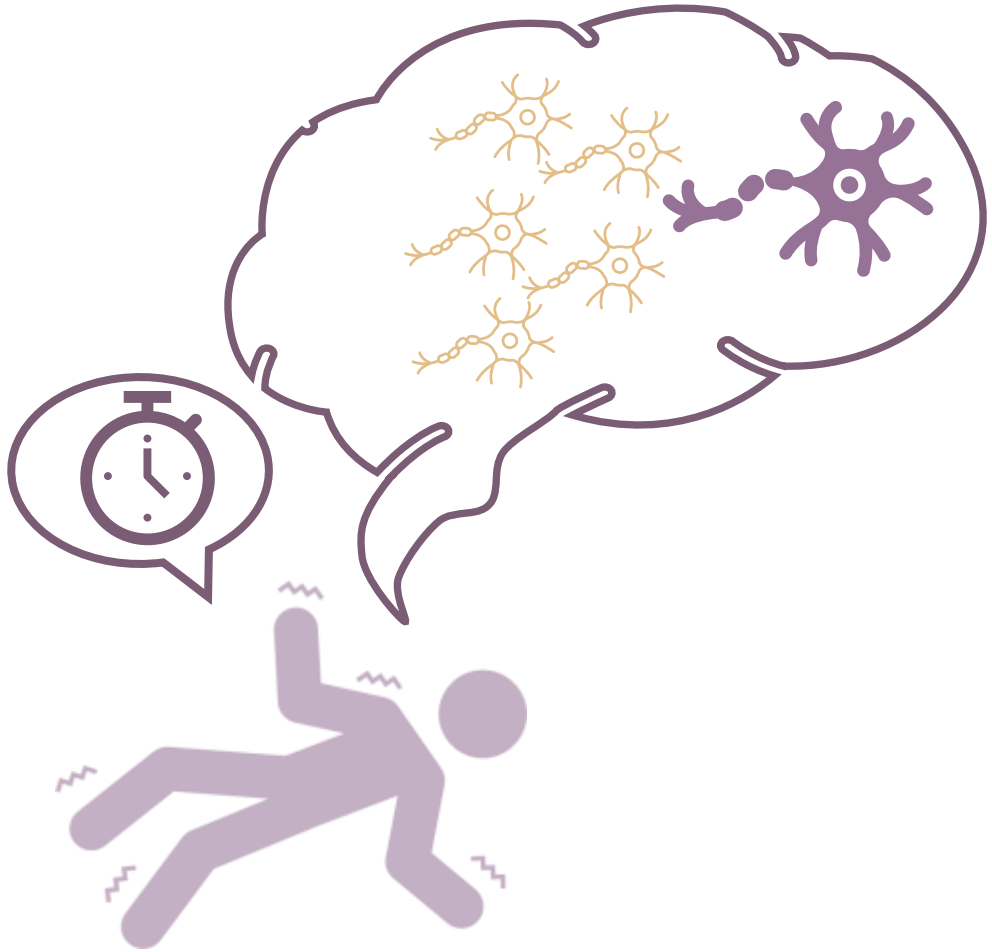
Historical sources reported that Julius Caesar suffered from seizures related to epilepsy or, as it was known at that time, “the falling sickness” 26, 32. It is difficult to obtain reliable information about his disease, as it is highly likely that Augustus censored most of all documents talking about the illness of his illustrious uncle after his death. Hughes (14) reported that Caesar likely had 4 attacks of epilepsy, which were probably complex partial seizures.



Kejang = seizure
= bangkitan epileptik

DEFINISI

Suatu kejadian tanda dan gejala yang berlansung *transient* akibat aktivitas neuron di otak yang berlebihan abnormal atau tersinkronisasi



Definisi konseptual oleh ILAE 2005

The clinical manifestation :
a sudden and transitory abnormal phenomena:

- alterations of consciousness
- Motor
- Sensory
- Autonomic
- psychic events

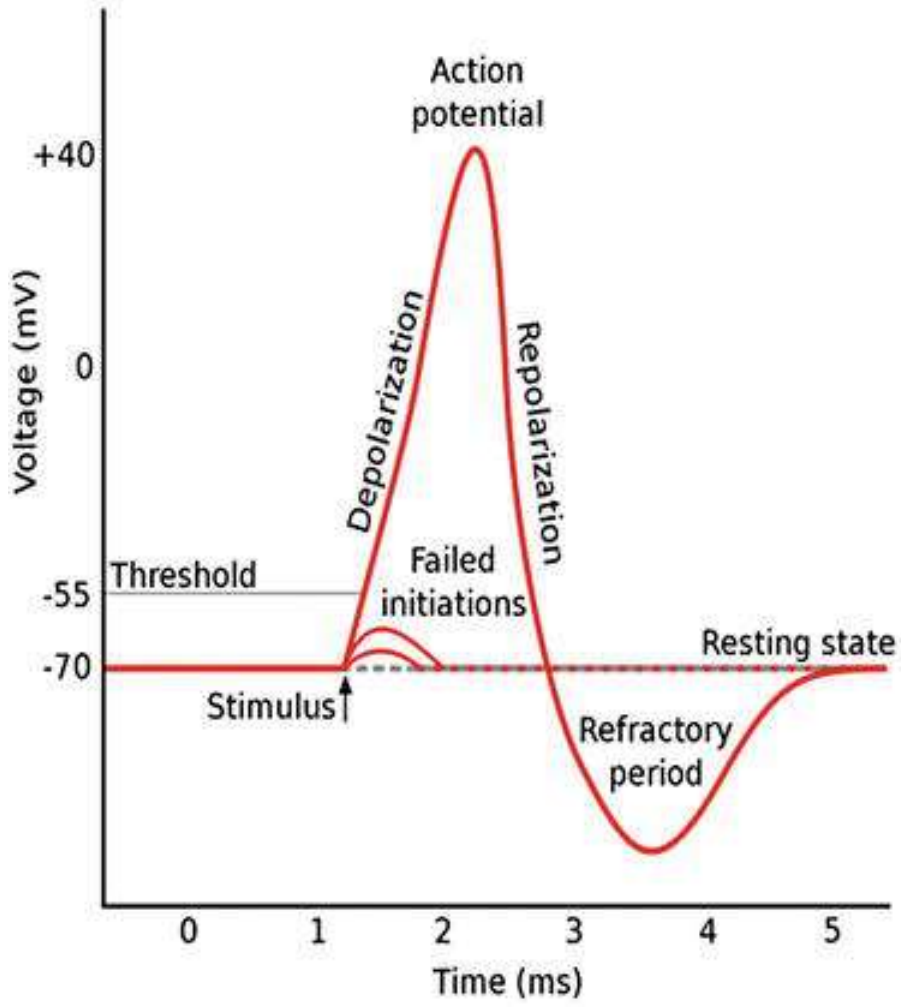
perceived by the patient or an observer

Bangkitan Epileptik

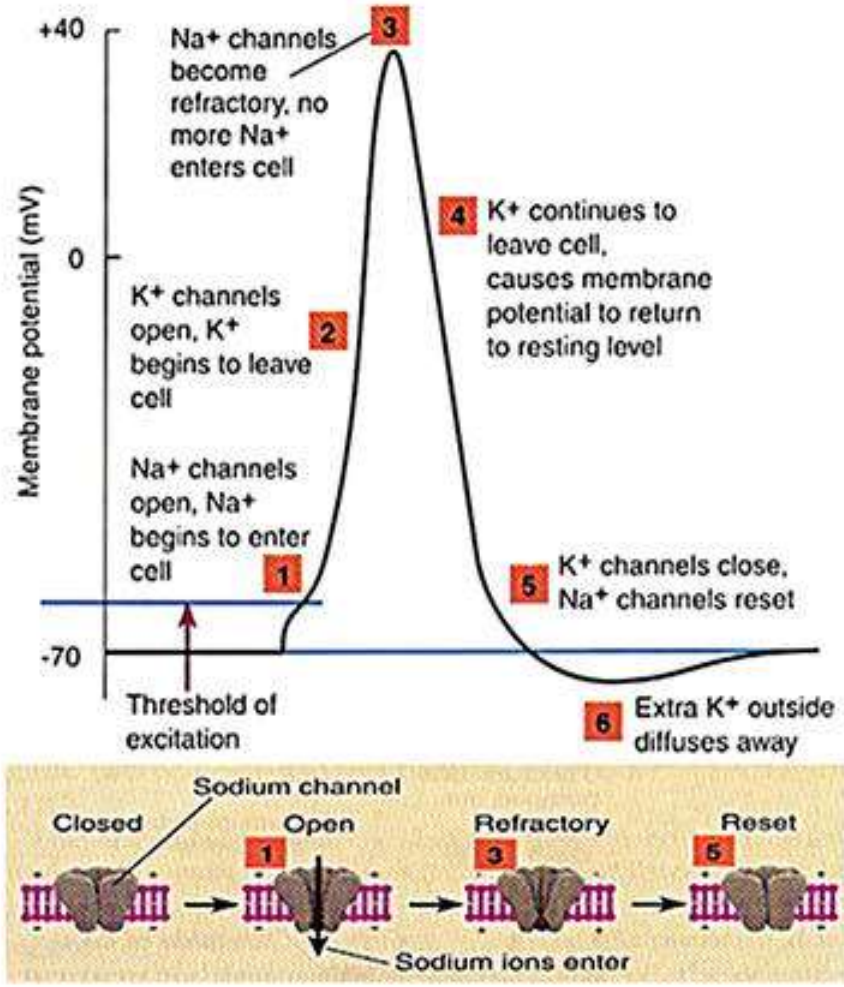
=

Transient

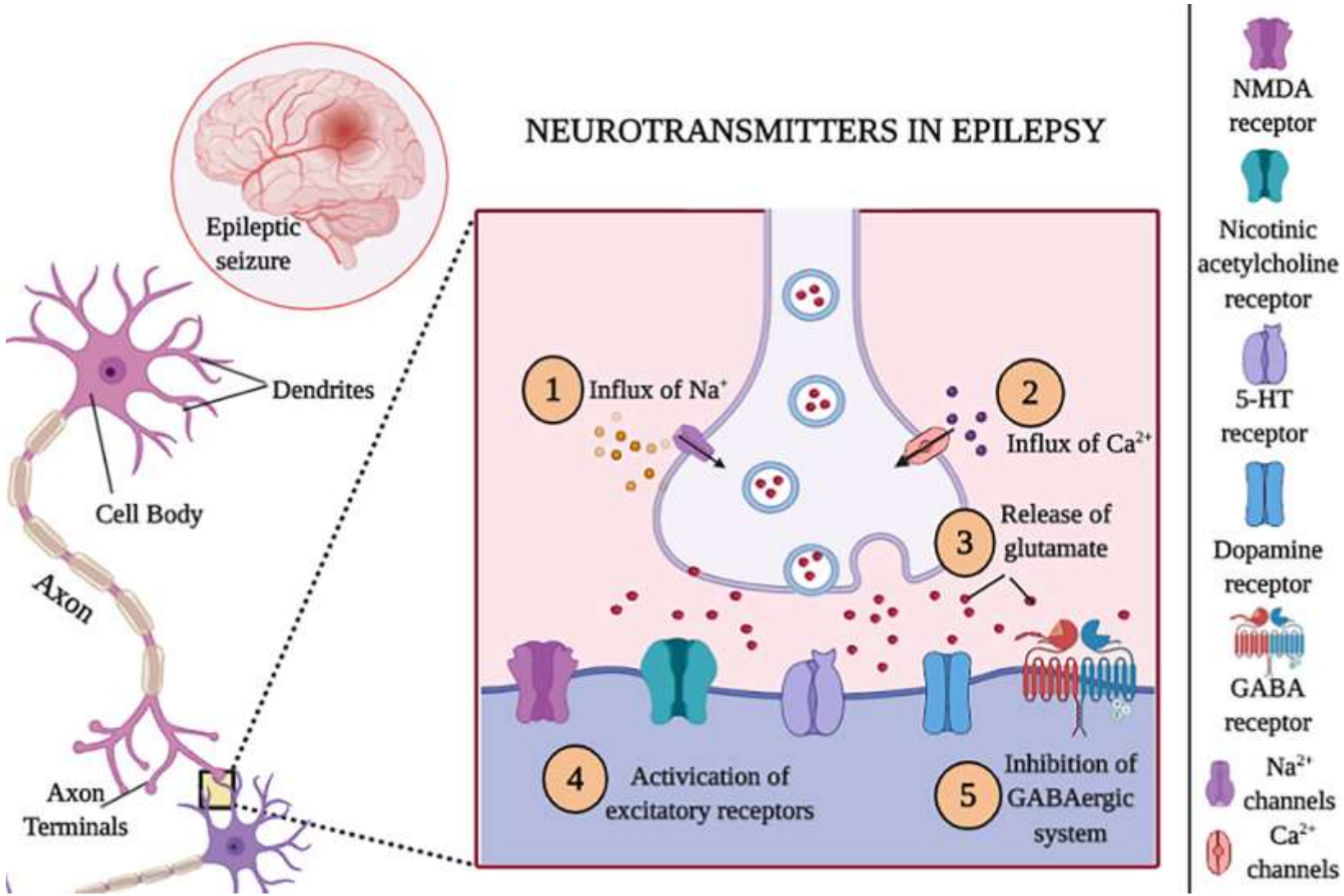
Bila tidak singkat, bisa jadi merupakan diagnosis banding lainnya


Action potential
+40
0
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed initiations
Resting state
Stimulus
Refractory period
0
1
2
3
4
5
Time (ms)

(a)

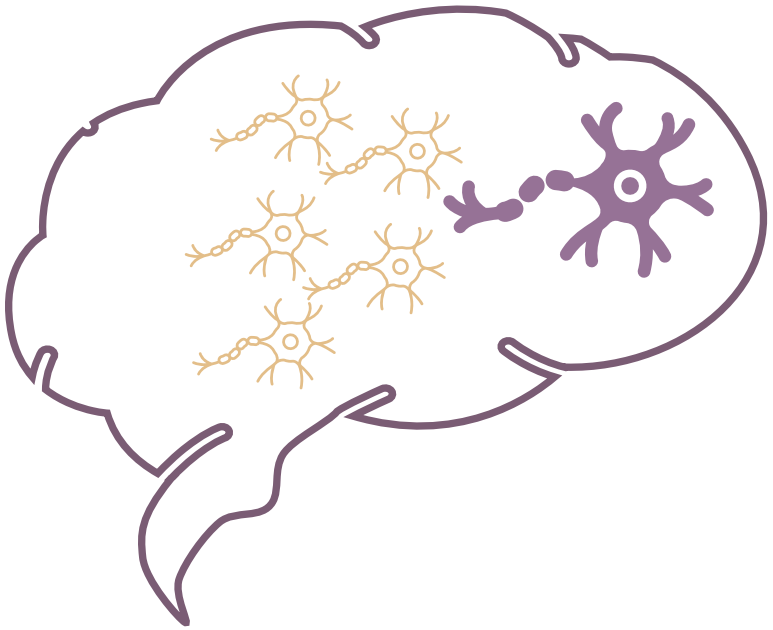

+40
0
-70
Membrane potential (mV)
Na+ channels become refractory, no more Na+ enters cell
3
4 K+ continues to leave cell, causes membrane potential to return to resting level
K+ channels open, K+ begins to leave cell
2
Na+ channels open, Na+ begins to enter cell
1
5 K+ channels close, Na+ channels reset
Threshold of excitation
6 Extra K+ outside diffuses away
Sodium channel
Closed
Open
Refractory
Reset
1
3
5
Sodium ions enter

(b)


NEUROTRANSMITTERS IN EPILEPSY
Epileptic seizure
Dendrites
Cell Body
Axon
Axon Terminals
1 Influx of Na+
2 Influx of Ca2+
3 Release of glutamate
4 Activication of excitatory receptors
5 Inhibition of GABAergic system
NMDA receptor
Nicotinic acetylcholine receptor
5-HT receptor
Dopamine receptor
GABA receptor
Na2+ channels
Ca2+ channels

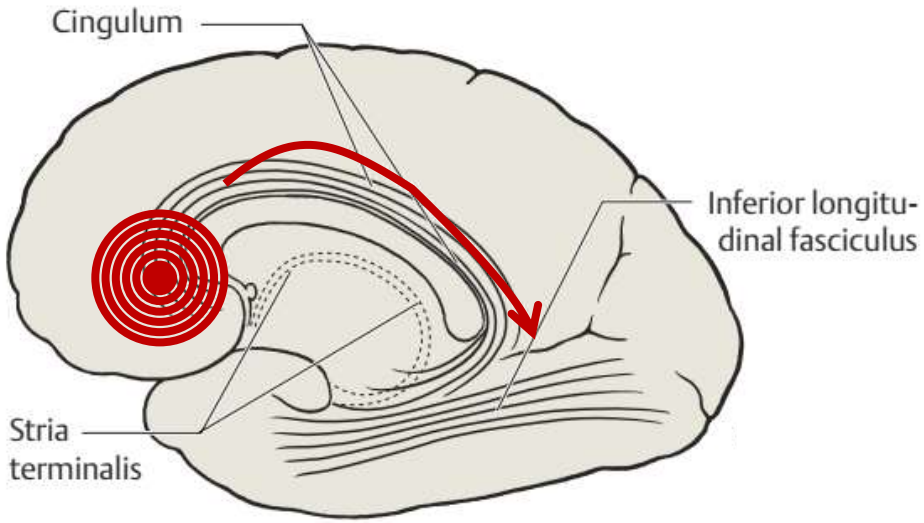
Inisiasi seizure

1. high-frequency bursts of action potentials
2. hypersynchronization of a neuronal population



propagasi seizure

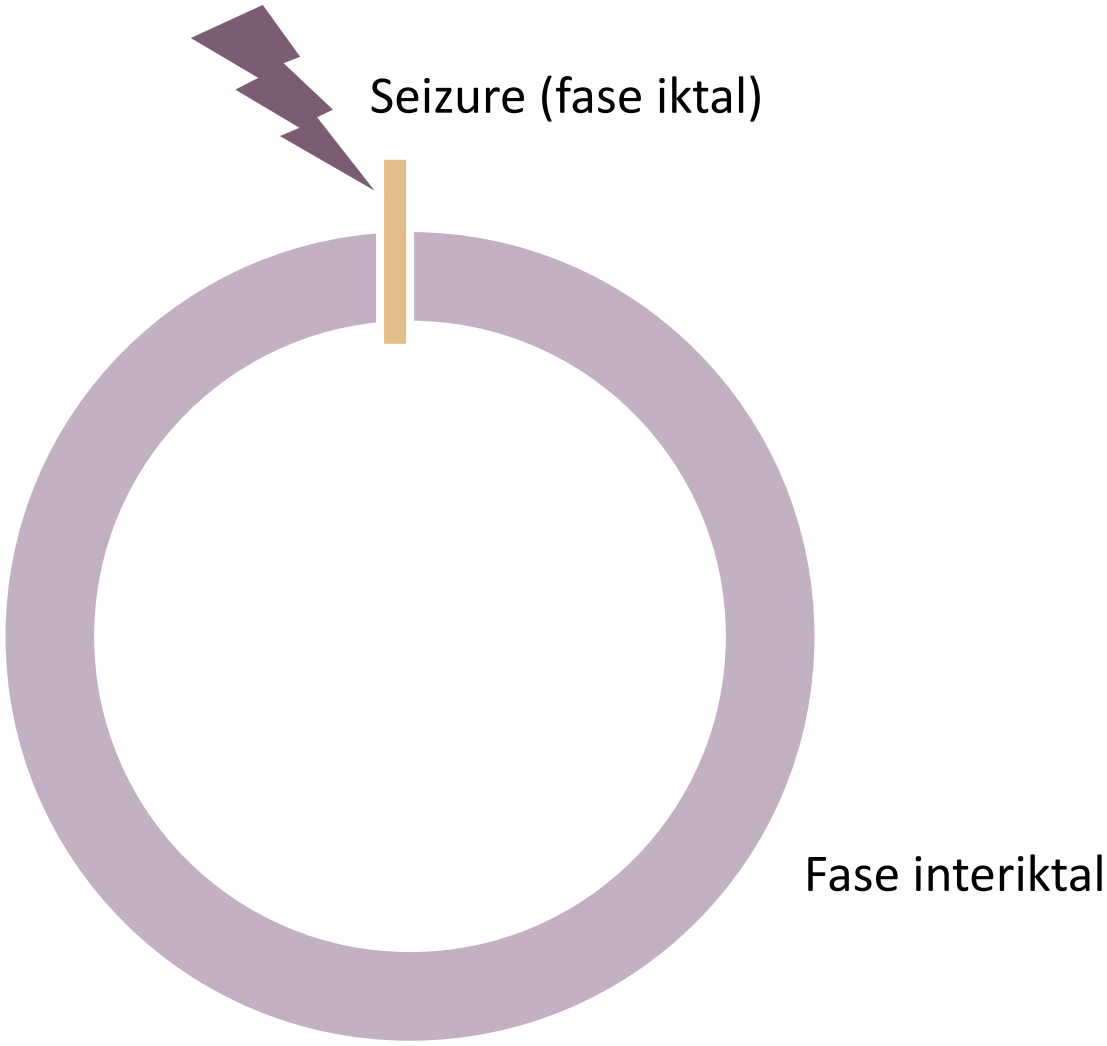
seizure spreads within the brain. occurs when there is sufficient activation to recruit surrounding neurons.



terminasi seizure

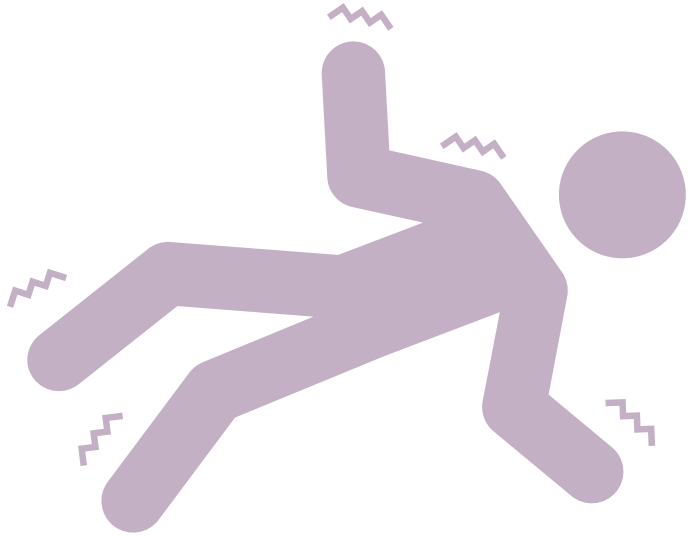
GABAergic synaptic inhibition mediated by local interneurons

Failed:
Status epilepticus


Seizure (fase iktal)
Fase interiktal

Definisi epilepsi

Definisi konseptual oleh ILAE 2005



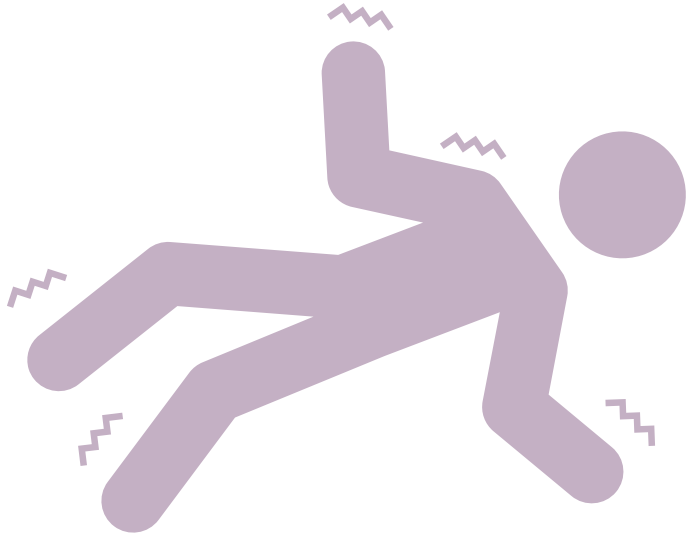
Epilepsi merupakan **penyakit otak**

1. Berpredisposisi mengalami bangkitan epileptik
2. Kondisi ini berkonsekuensi secara neurobiologis, kognitif, psikologis, dan sosial
3. Terjadi minimal 1 bangkitan epileptik

ILAE, 2014

Definisi epilepsi

Definisi operasional *(practical)* oleh ILAE 2014



Epilepsy is a **disease of the brain**
defined by any of the following conditions:

1. At least **two unprovoked (or reflex) seizures** occurring >24 h apart
2. **One unprovoked (or reflex) seizure and a probability** of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

ILAE, 2014

EPILEPSI

=

Unprovoked

Bila bangkitannya “terprovokasi” : *acute symptomatic seizure*

What is unprovoked seizure?

- Unknown etiology
- Related to preexisting brain lesion or progressive brain disorder

EPILEPSI

What is provoked seizure?

Acute symptomatic condition

metabolic or toxic disturbance, cerebral trauma, stroke

BUKAN EPILEPSI

EPILEPSI

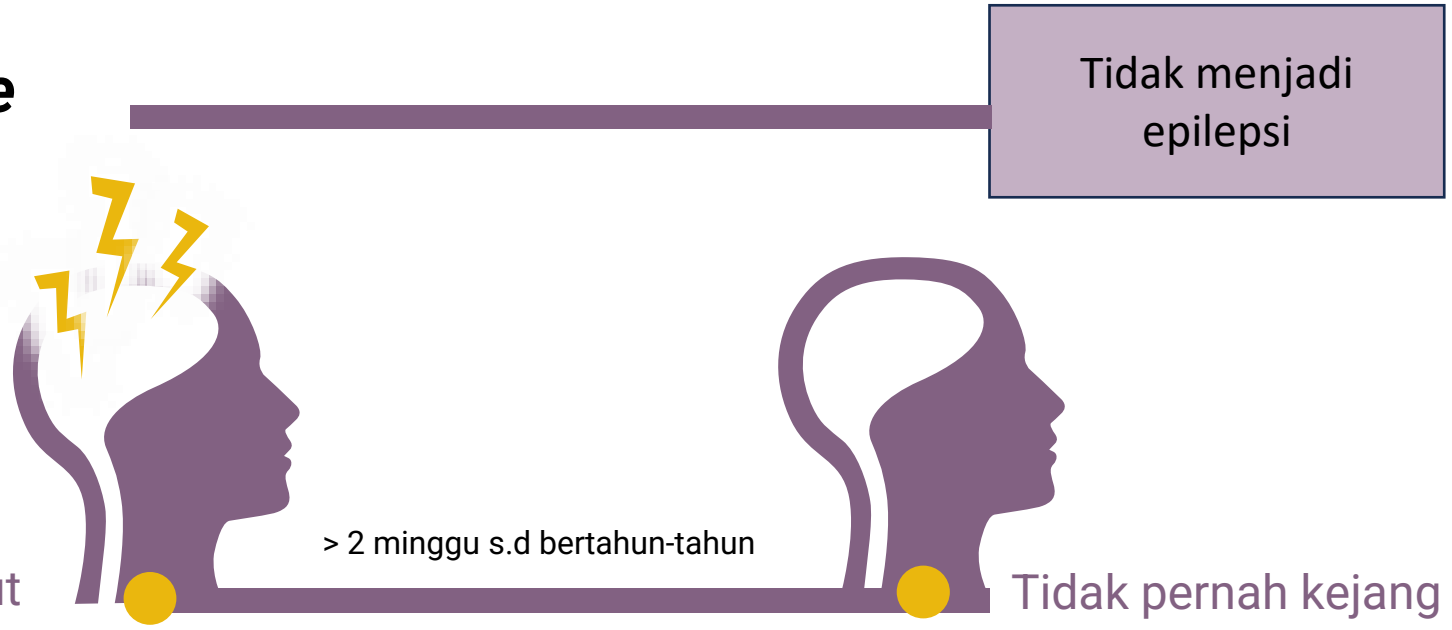
Terjadi kelainan KRONIS di otak sehingga pasien rentan mengalami kejang berulang

KEJANG

Terdapat provokasi yang menyebabkan glutamate meningkat dan GABA berkurang

Misalnya:
TIK meningkat
Demam
Infeksi otak

Acute symptomatic seizure
Provoked seizure

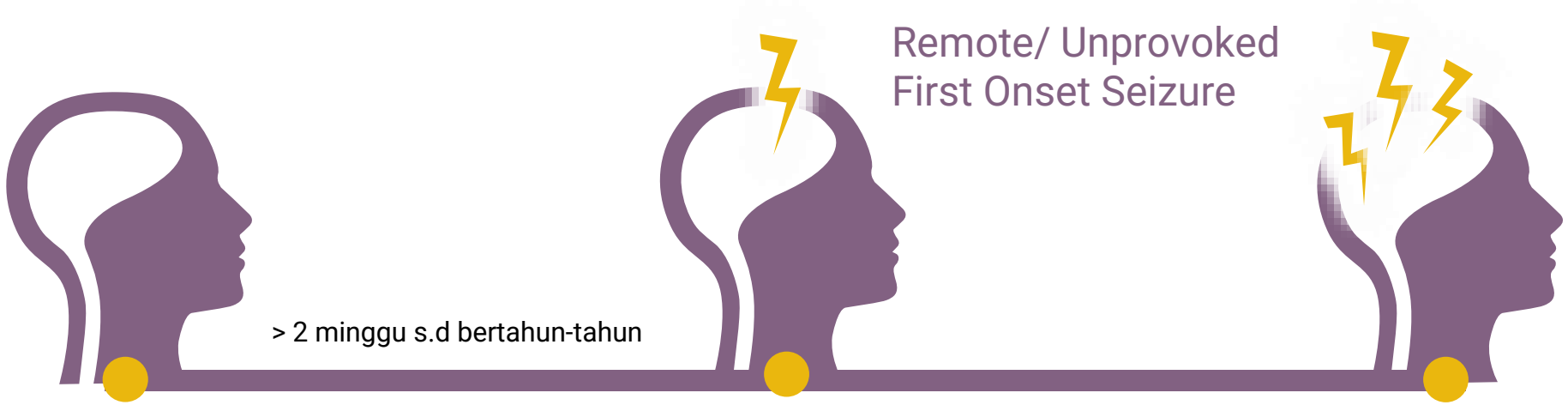


Pasien dengan penyakit akut

- Stroke fase akut
- Trauma kepala fase akut
- Meningitis
- Meningoensefalitis
- Hiperglikemia
- Hiponatremia
- Hipoglikemia
- Hipoksia

Tidak pernah kejang kembali

Krumholz et al. 2015. Neurology®



Jejas kepala

- Infeksi otak
- Tumor otak
- Trauma kepala
- Stroke

Initial insult

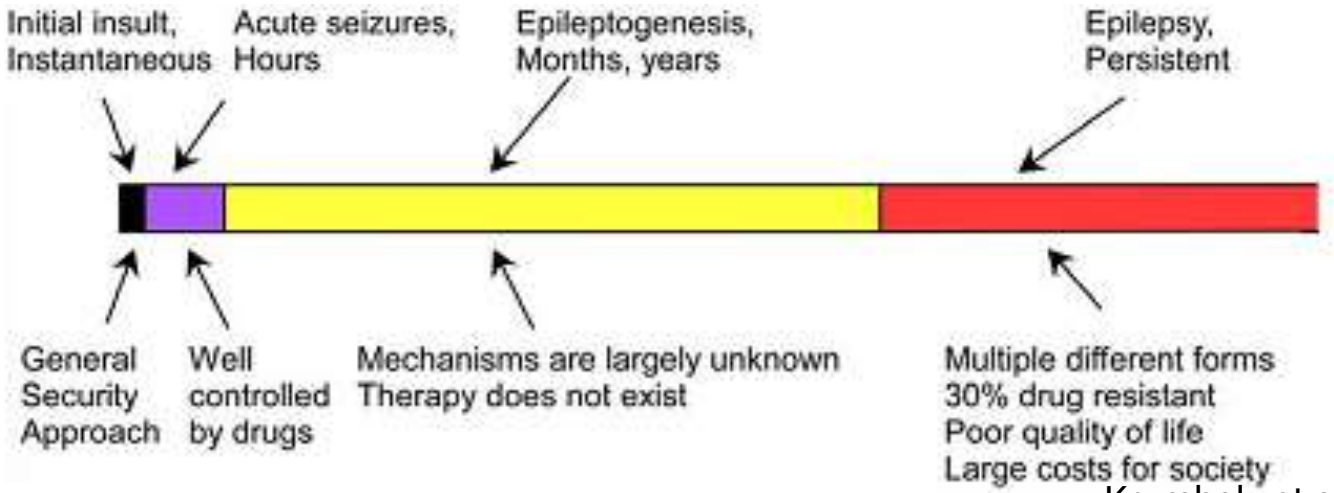
- tidak diketahui kapan
- Genetik
- Dalam kandungan

1st Seizure

Recurrent Seizure

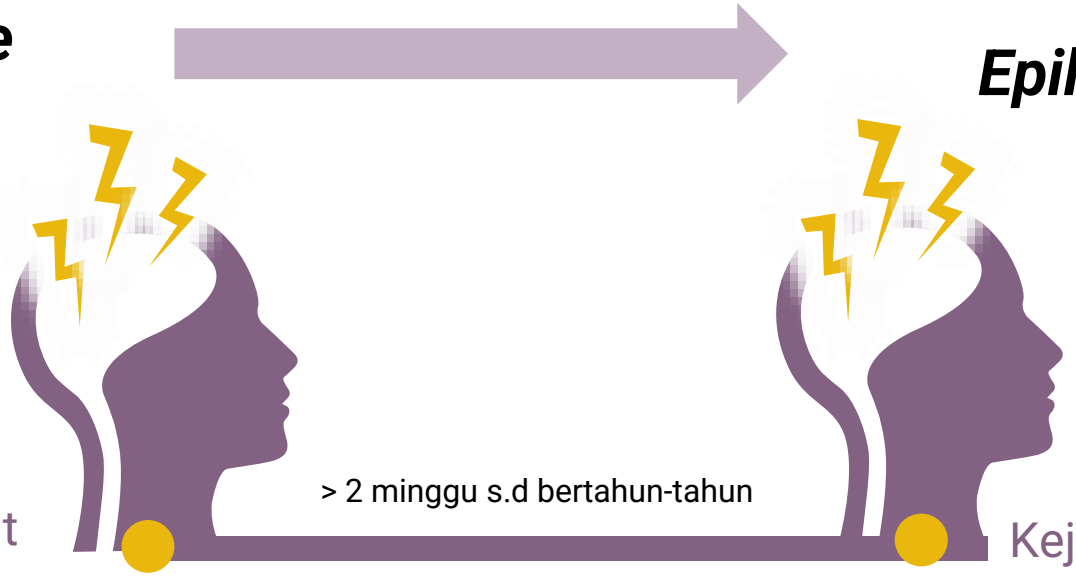
DIAGNOSIS EPILEPSI

> 24 jam



Krumholz et al. 2015. Neurology®

Acute symptomatic seizure
Provoked seizure



Pasien dengan penyakit akut

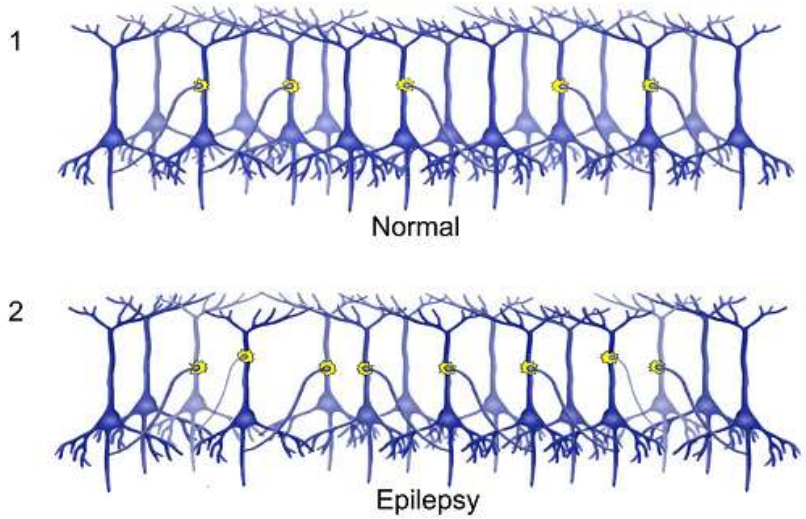
Meningoensefalitis

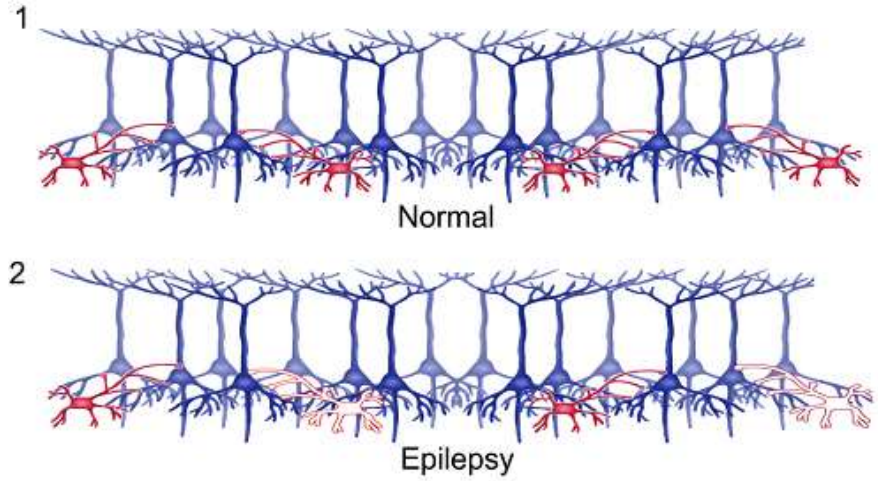
- Akut hemiparese sinistra
- Penurunan kesadaran
- Kaku kuduk positif
- Febris 3 hari
- Status epilepticus et causa acute symptomatic seizure

Kejang unprovoked berulang

Krumholz et al. 2015. Neurology®

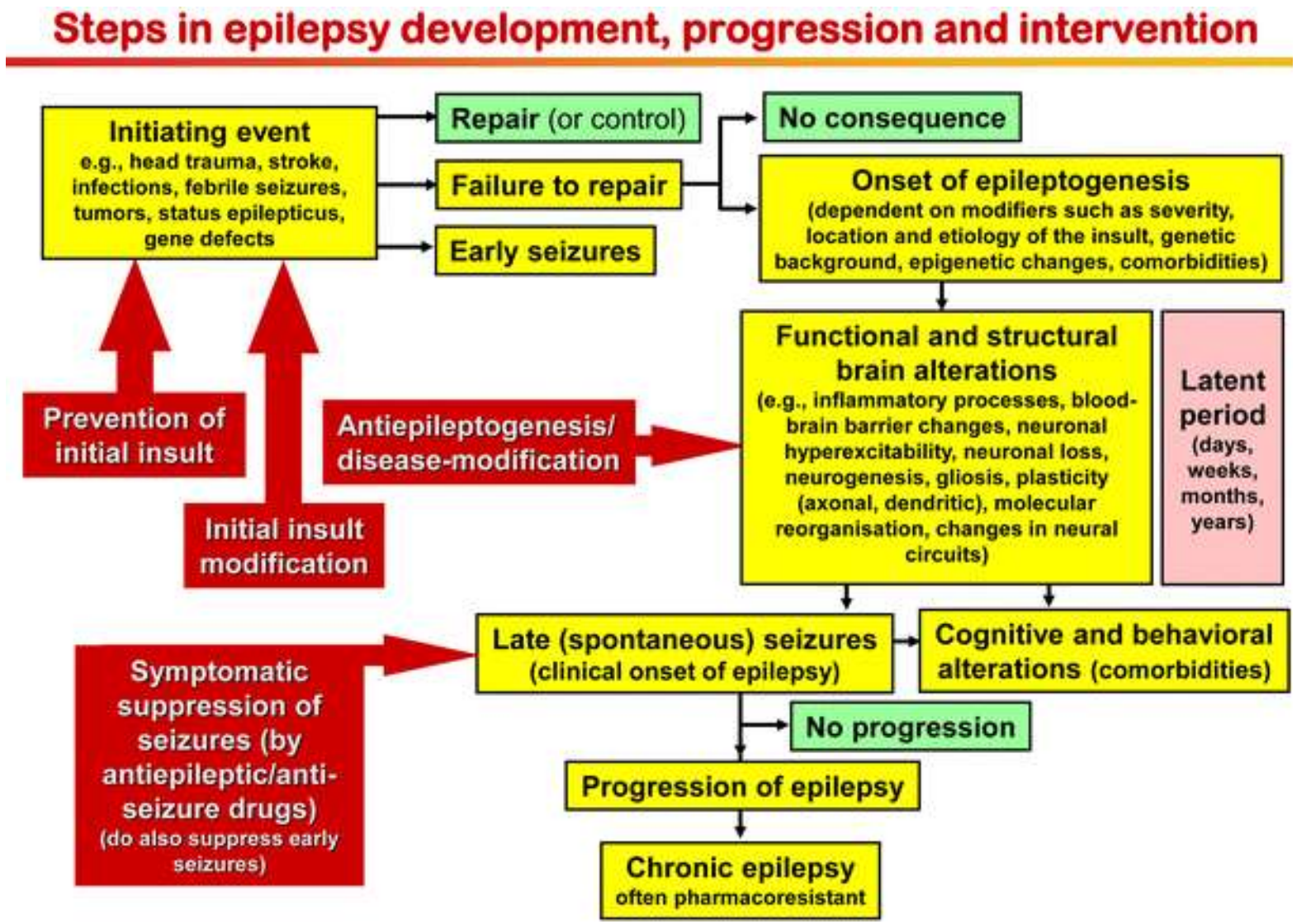
Epileptic brain vs normal brain



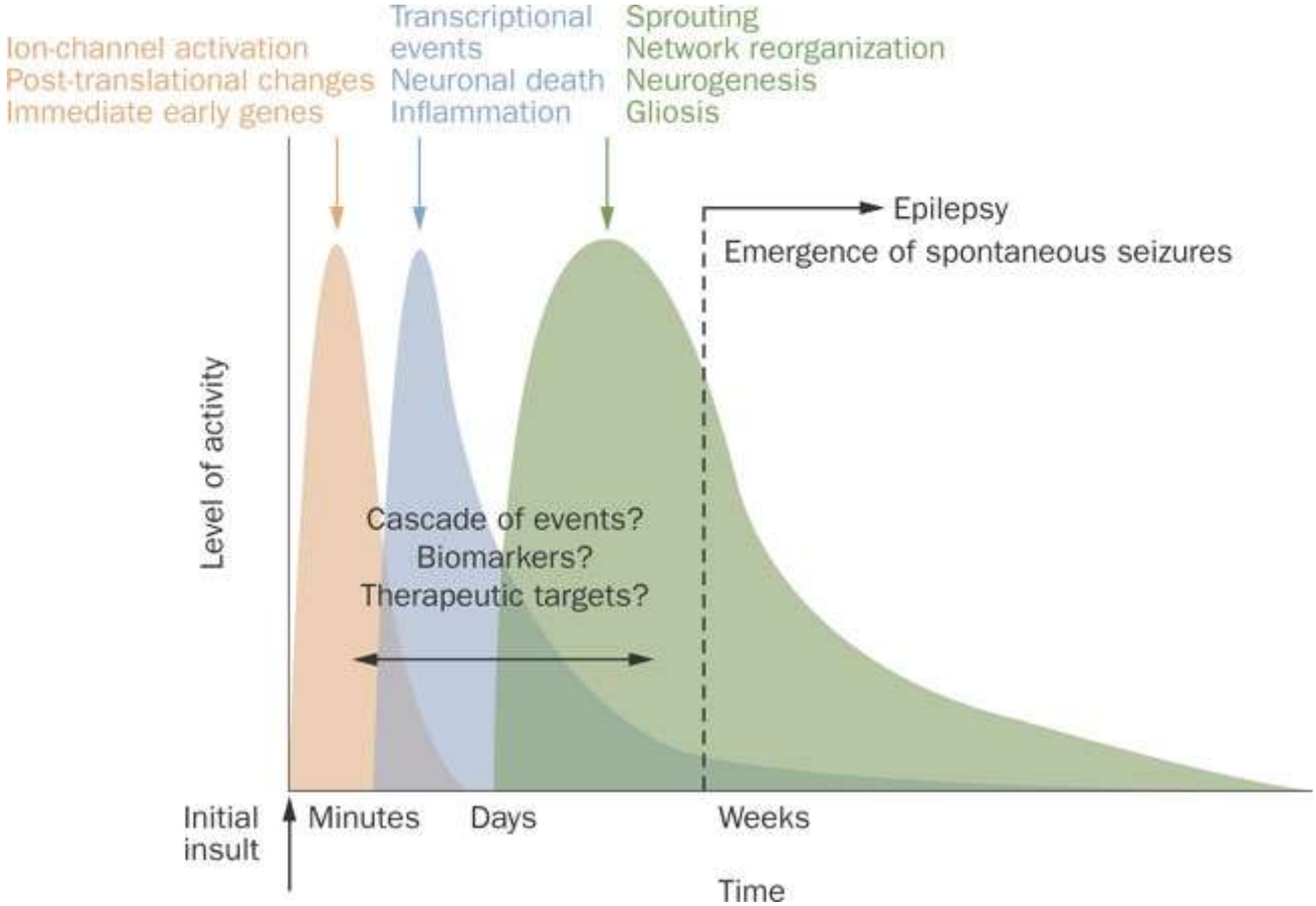


sinaps eksitasi meningkat

Berkurangnya neuron inhibisi



Vezzani. 2016. *Acta Neuropathologica* 131(2)


Ion-channel activation
Post-translational changes
Immediate early genes
Transcriptional events
Neuronal death
Inflammation
Sprouting
Network reorganization
Neurogenesis
Gliosis
Epilepsy
Emergence of spontaneous seizures
Level of activity
Cascade of events?
Biomarkers?
Therapeutic targets?
Initial insult
Minutes
Days
Weeks
Time

Langkah Diagnosis Epilepsi

Menentukan tipe onset kejang

☐ Focal onset

Bila bangkitan fokal, tentukan kesadaran.
(*Kosongi bila tidak diketahui)*

- ☐ Aware
- ☐ Impaired awareness

Bila bangkitan fokal, tentukan bentuk kejang.
(*Kosongi bila tidak diketahui)*

- ☐ Motor onset
- ☐ Non motor onset
- ☐ Focal to bilateral tonic clonic

☐ Generalized onset

Bila bangkitan general, tentukan bentuk kejang.
Kosongi bila tidak diketahui

- ☐ Motor
- ☐ Non motor (absence)

☐ Unknown onset

Bila bangkitan onset tidak diketahui, tentukan bentuk kejang. *Kosongi bila tidak diketahui*

- ☐ Motor
- ☐ Non motor

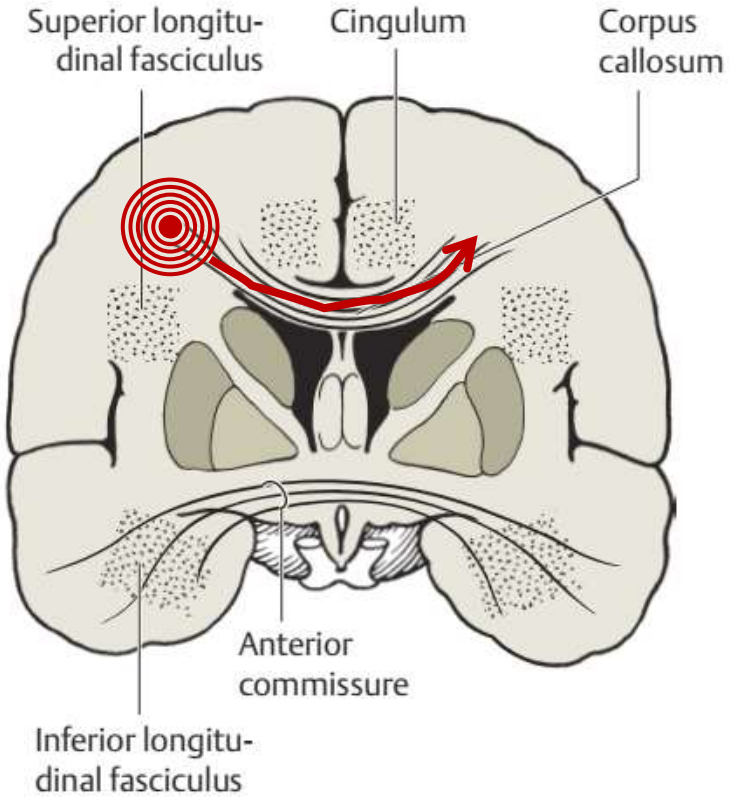
Menentukan tipe kejang

From Fisher RS, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia, 58(4):531–542, 2017.

Focal onset seizure

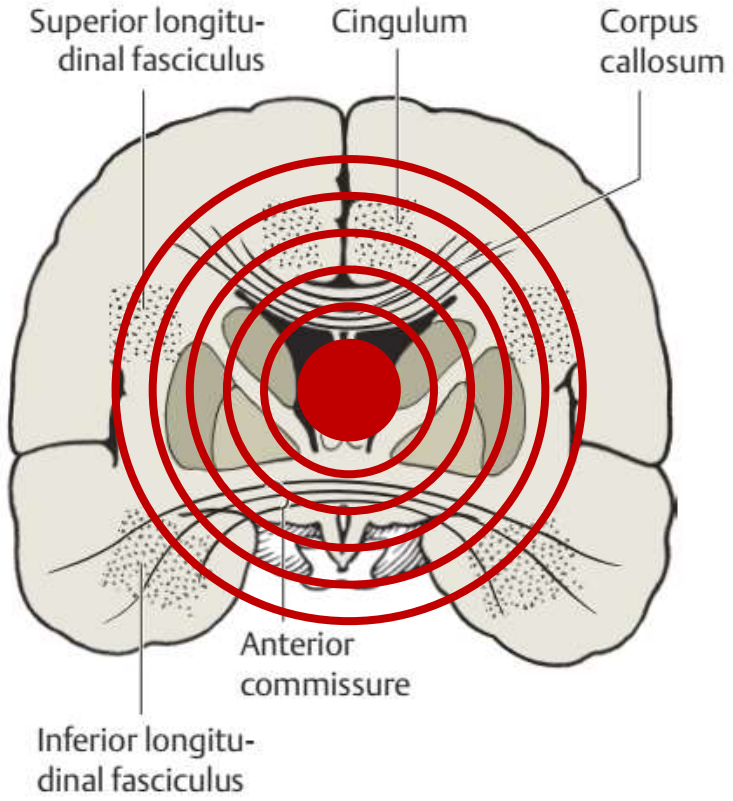
Dimulai dari 1 sisi hemisfer

- Dapat tetap pada sirkuit 1 hemisfer
- Dapat menyebar bilateral



general onset seizure

Dimulai dari 1 titik, dan menyebar dengan cepat ke sirkuit (network) bilateral



Theories of the generation of generalised discharges associated with absence seizures and GTCSs

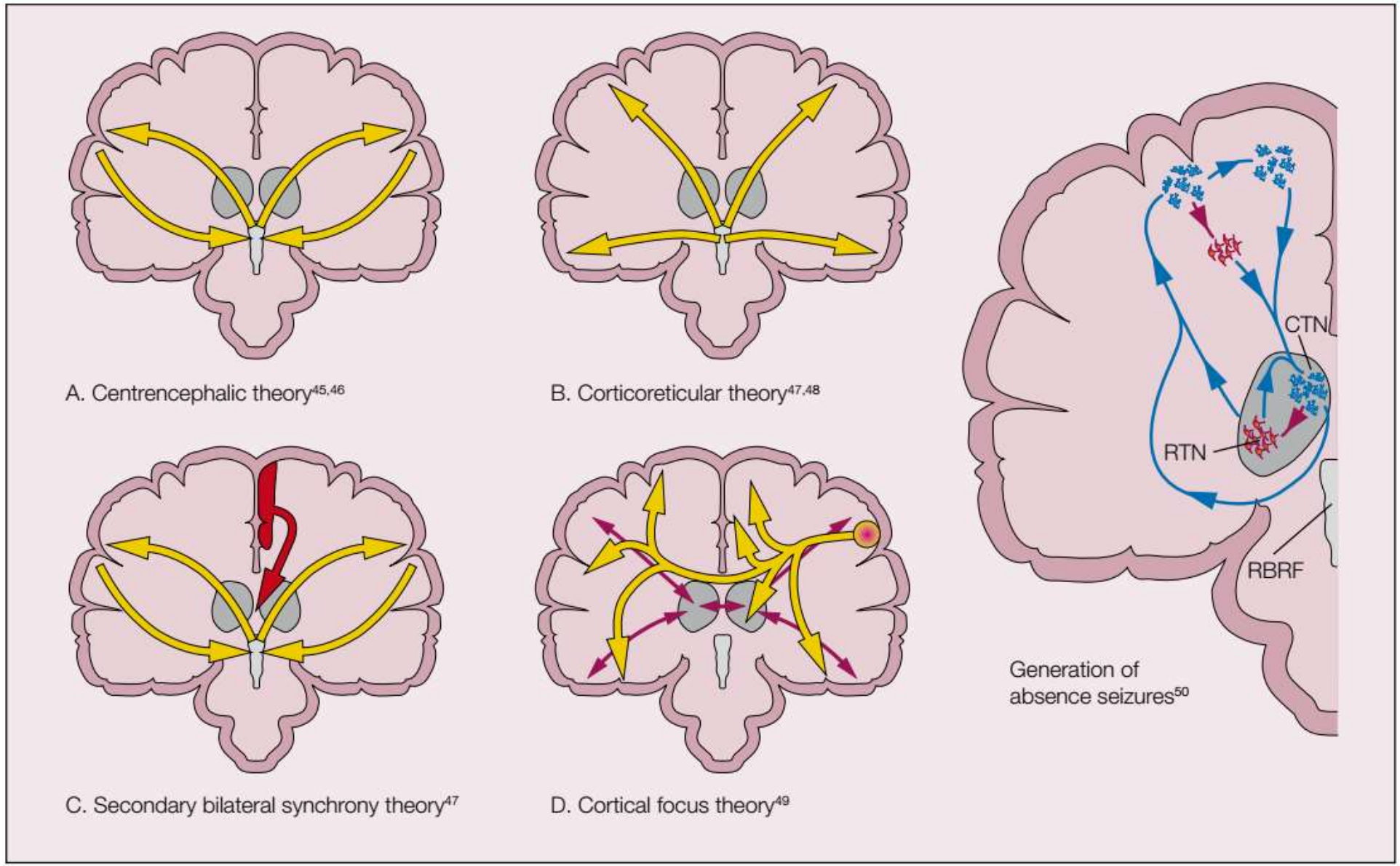
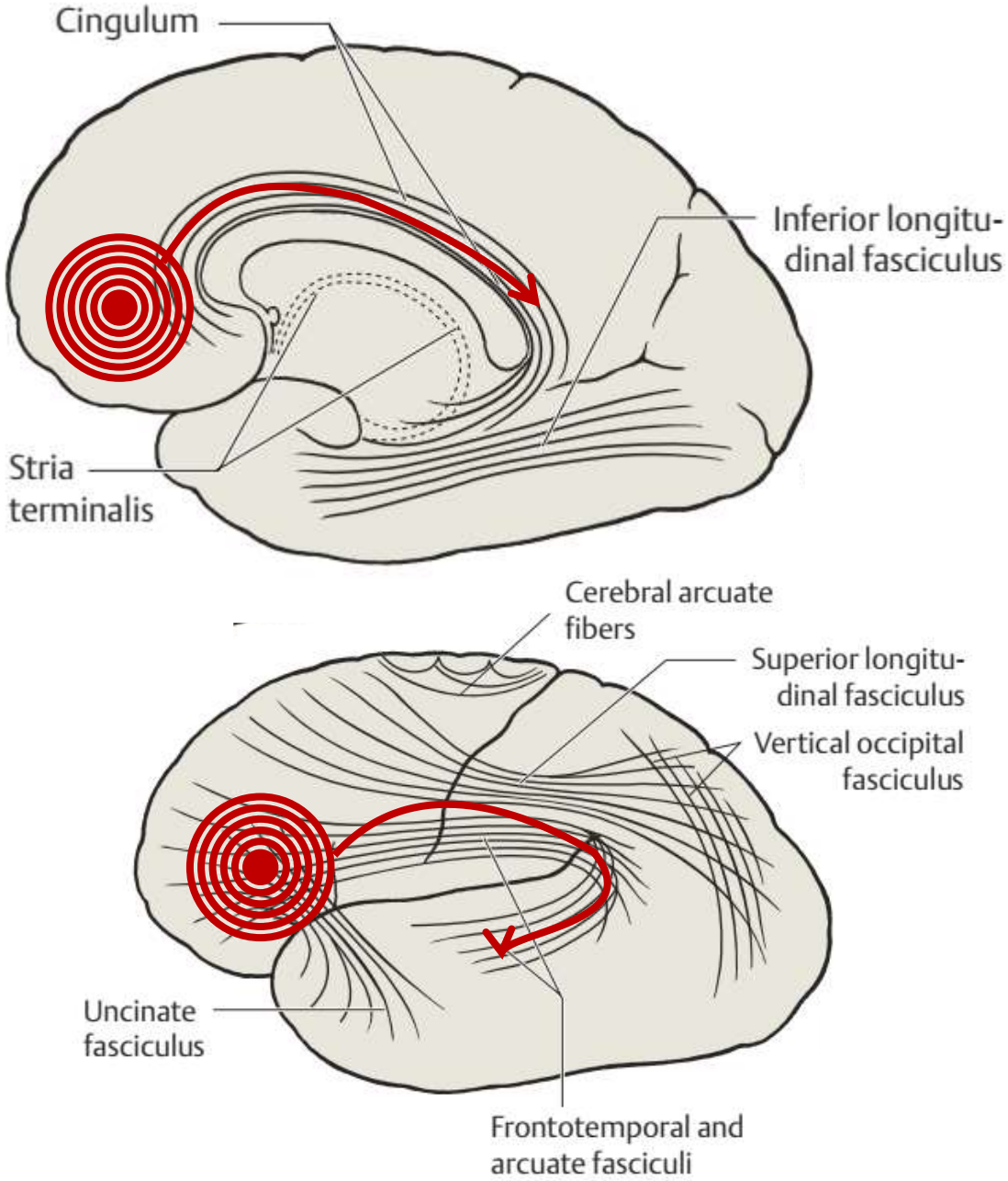
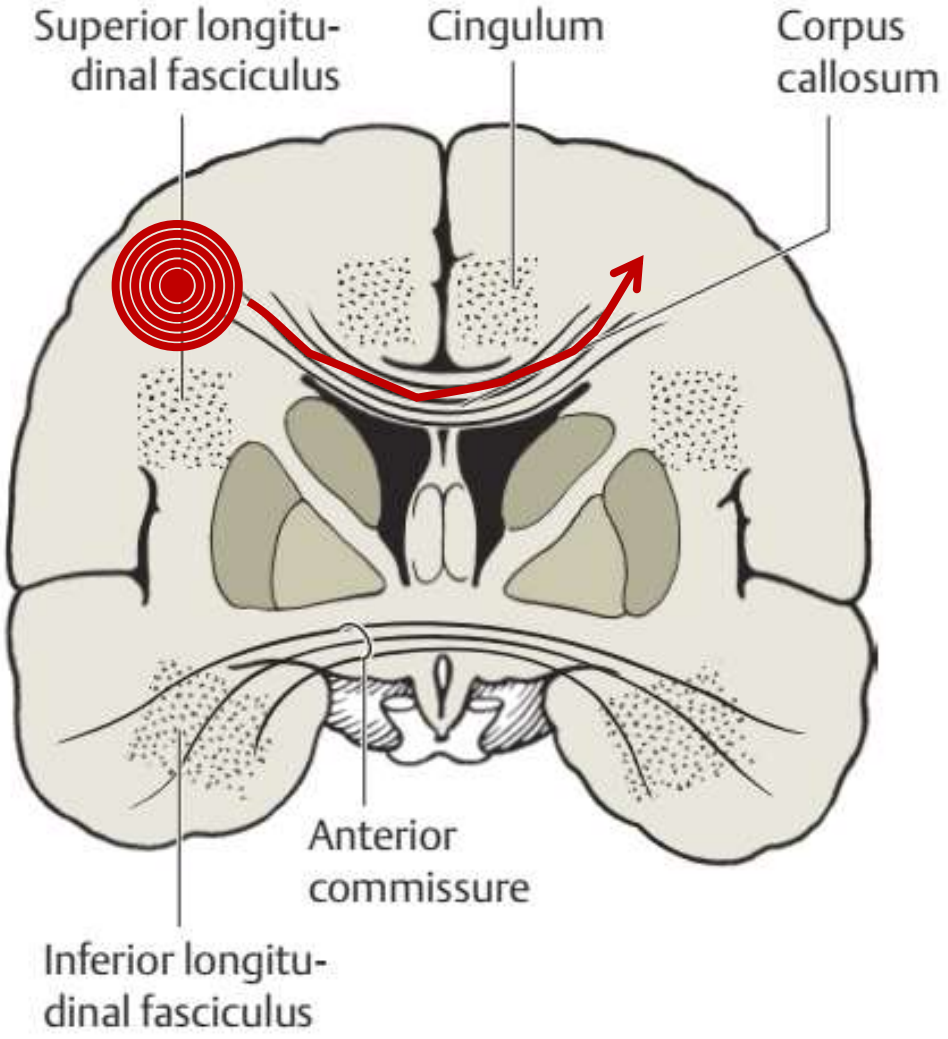


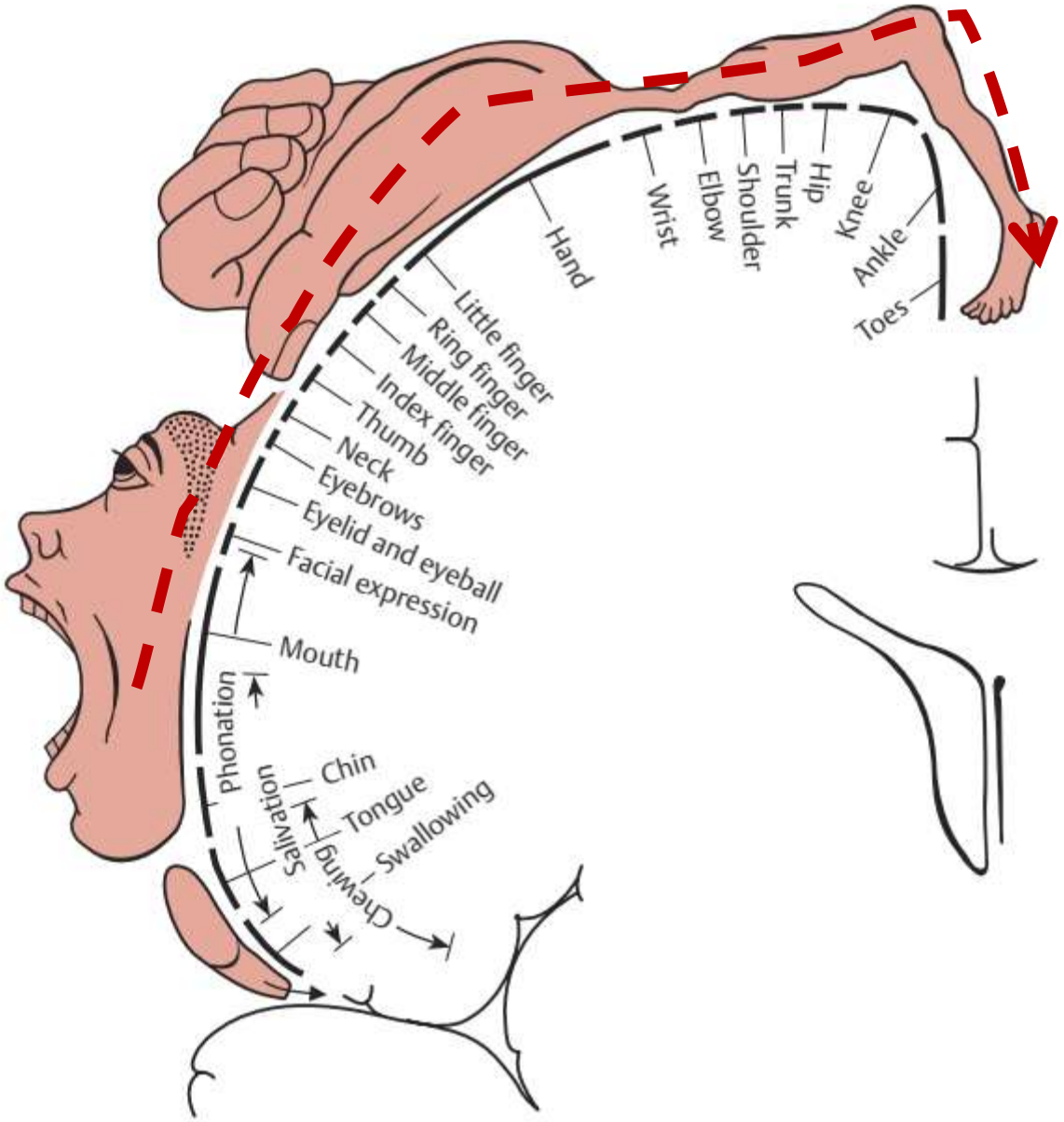
Figure 2.6 CTN, corticothalamic neurones; RTN, reticular thalamic nucleus; RBRF, rostral brain-stem reticular formation.

Focal onset seizure





Focal onset motor seizure



Homunculus cortex motoric

Jacksonian's march seizure

Dapat terjadi post ictal paralysis

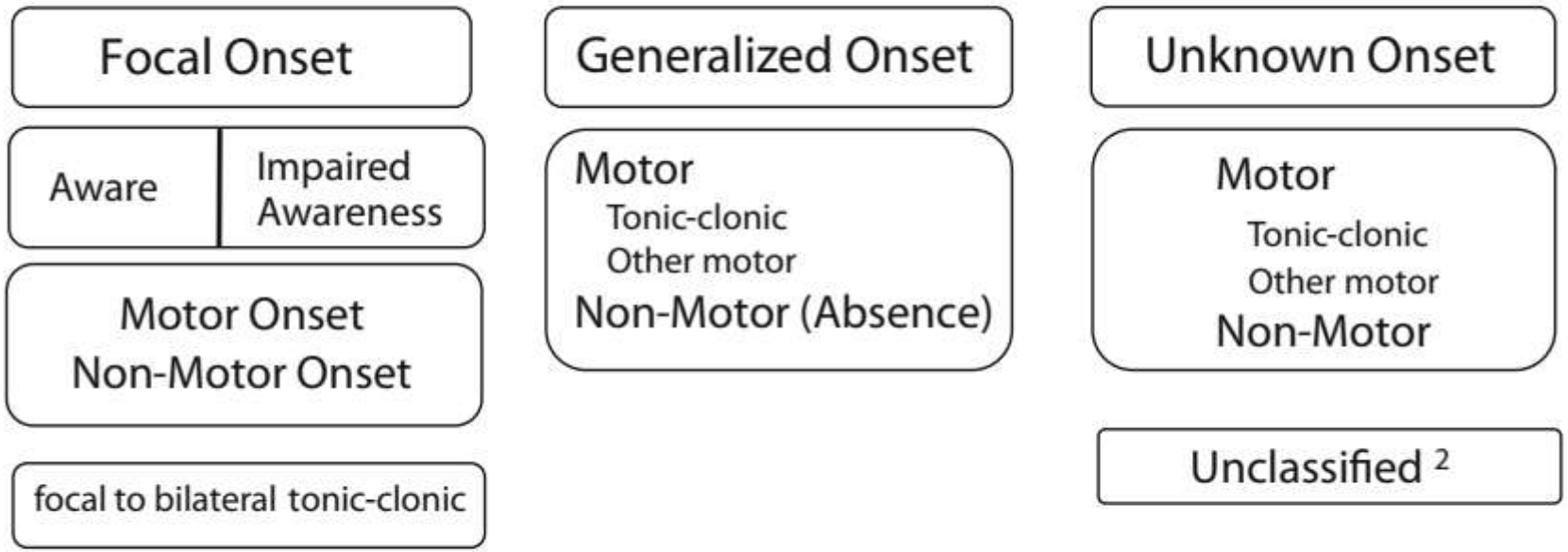
Semiologi bangkitan kejang

Menunjukkan aktivasi, disfungsi, dan area otak dimana suatu bangkitan dimulai dan berevolusi.

Pada **EPILEPSI FOKAL**: semiologi memberikan informasi lokasi seizure onset zone yang penting dalam penilaian sebelum operasi epilepsi

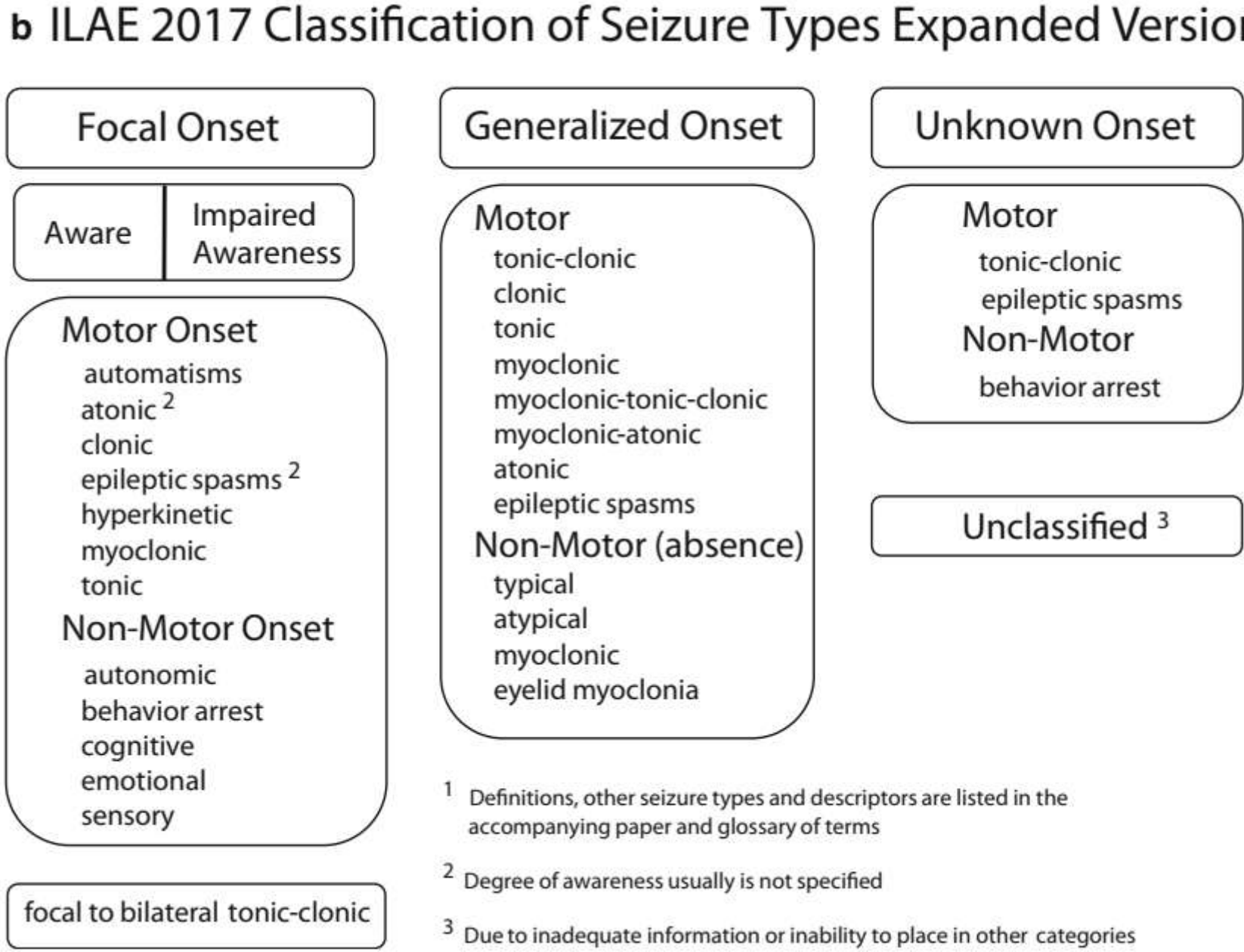
SYMPTOMATOGENIC ZONE: lokasi dimana gejala dan tanda dari kejang berasal. Biasanya berdekatan dengan *epileptogenic zone*

a ILAE 2017 Classification of Seizure Types Basic Version [1]

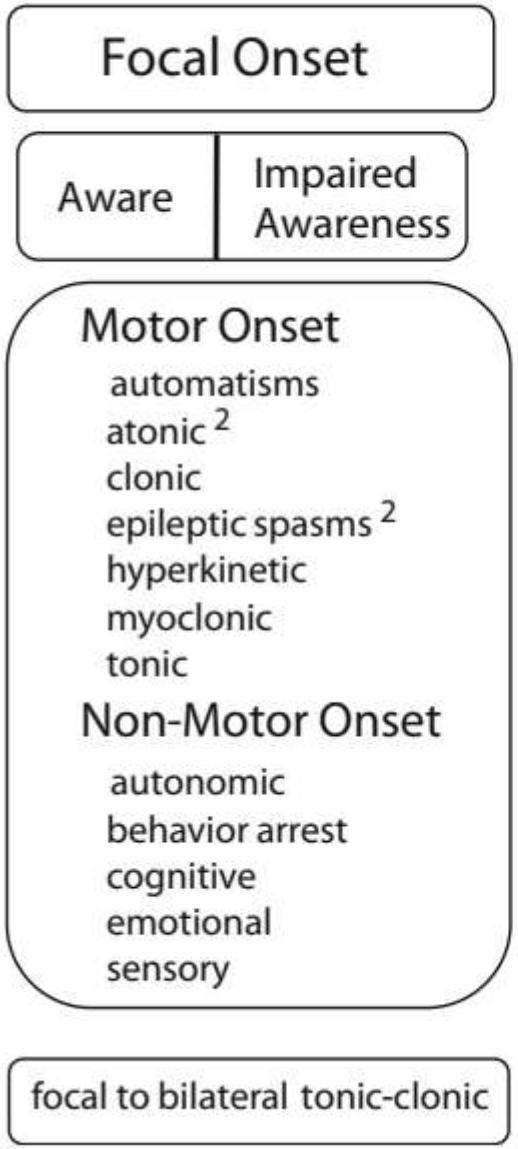


[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

[2] Due to inadequate information or inability to place in other categories


b ILAE 2017 Classification of Seizure Types Expanded Version [1]
Focal Onset
Aware
Impaired Awareness
Motor Onset
automatisms
atonic [2]
clonic
epileptic spasms [2]
hyperkinetic
myoclonic
tonic
Non-Motor Onset
autonomic
behavior arrest
cognitive
emotional
sensory
focal to bilateral tonic-clonic
Generalized Onset
Motor
tonic-clonic
clonic
tonic
myoclonic
myoclonic-tonic-clonic
myoclonic-atonic
atonic
epileptic spasms
Non-Motor (absence)
typical
atypical
myoclonic
eyelid myoclonia
Unknown Onset
Motor
tonic-clonic
epileptic spasms
Non-Motor
behavior arrest
Unclassified [3]
1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms
2 Degree of awareness usually is not specified
3 Due to inadequate information or inability to place in other categories

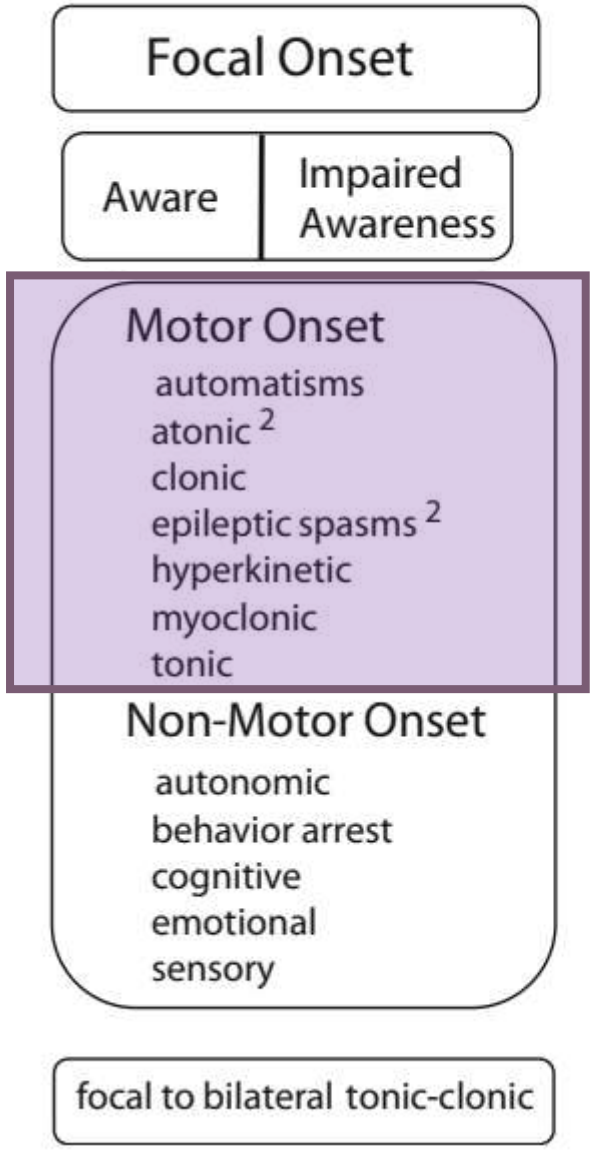
b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Focal onset seizure

https://www.epilepsydiagnosis.org/seizure/

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Otomatisme

Atonik

Klonik

Spasme

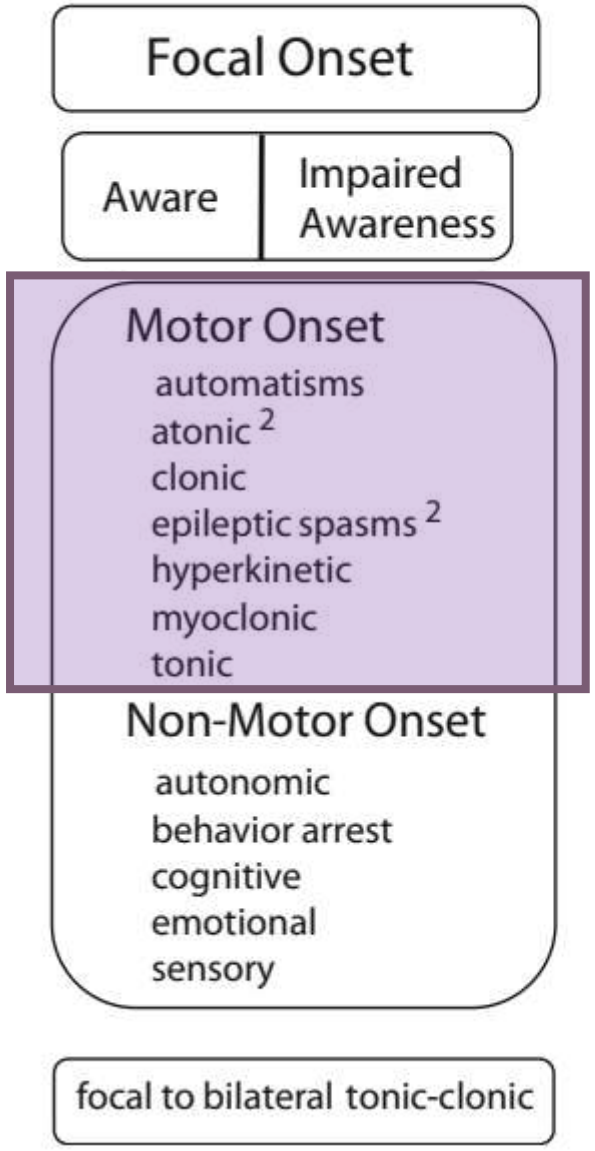
Hiperkinetik

Mioklonik

Tonik

https://www.epilepsydiagnosis.org/seizure/

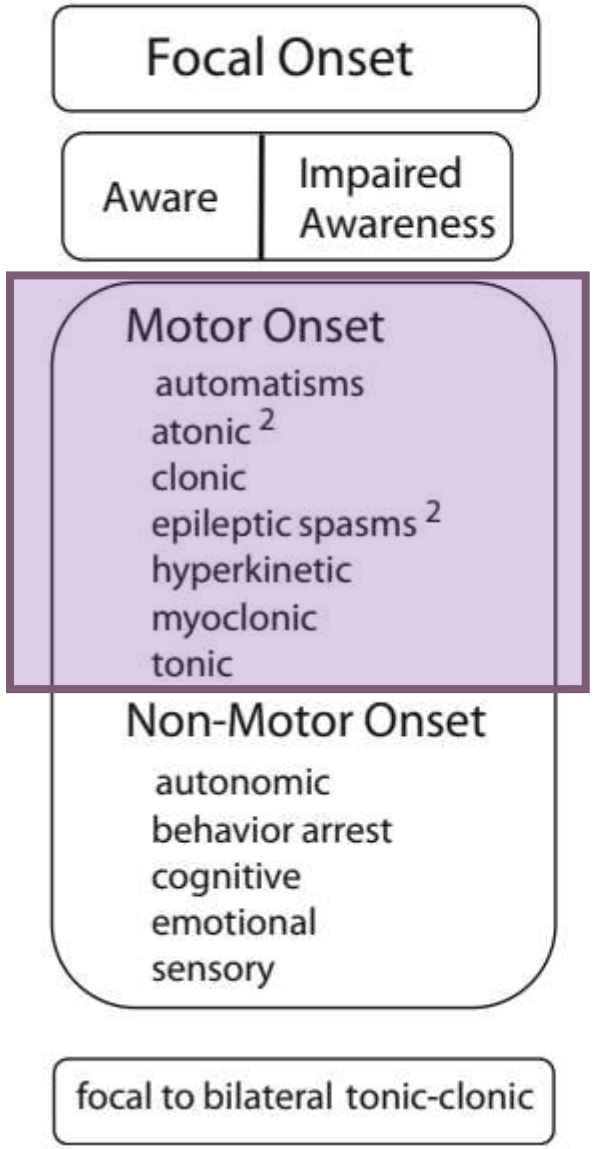
b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Otomatisme a coordinated, repetitive motor activity, often resembling a voluntary movement, but undertaken without volition.

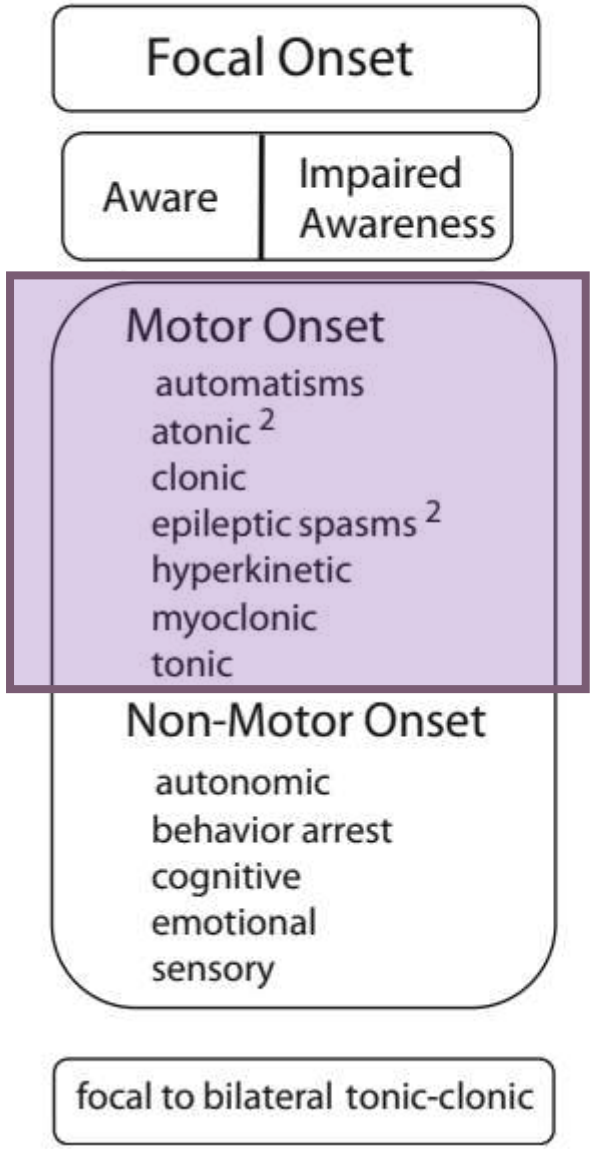
- **Orofacial:** lip smacking, lip pursing, chewing, swallowing, clicking, eye-blinking
- **Manual**: unilateral or bilateral, fumbling, tapping, manipulating or exploratory movements with the hands.
- **Pedal:** bilateral or unilateral movements of the feet/legs, these may include pacing, walking or running. (more reminiscent of normal movements, less frenetic or rapid vs focal hyperkinetic seizures)
- **Perseverative:** an inappropriate continuation of pre-seizure movement.
- **Vocal**: single or repetitive sounds such as shrieks or grunts.
- **Verbal**: single or repetitive words, phrases or brief sentences.
- **Sexual**: sexual behaviours.
- **Other:** automatisms can include head nodding, undressing etc

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



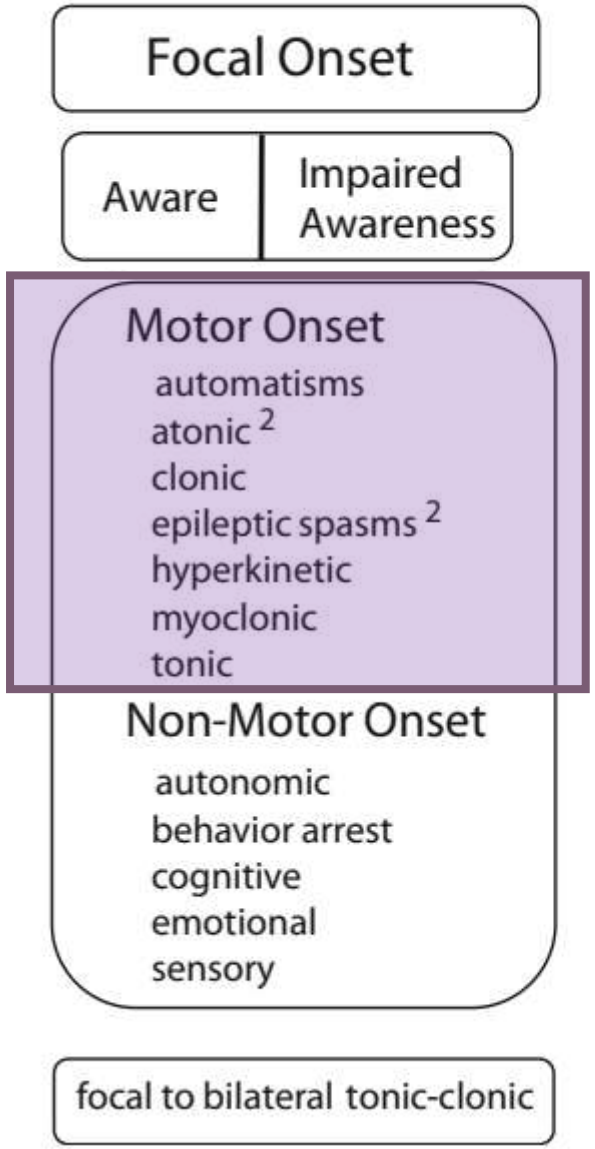
Atonik sudden loss or diminution of muscle tone

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



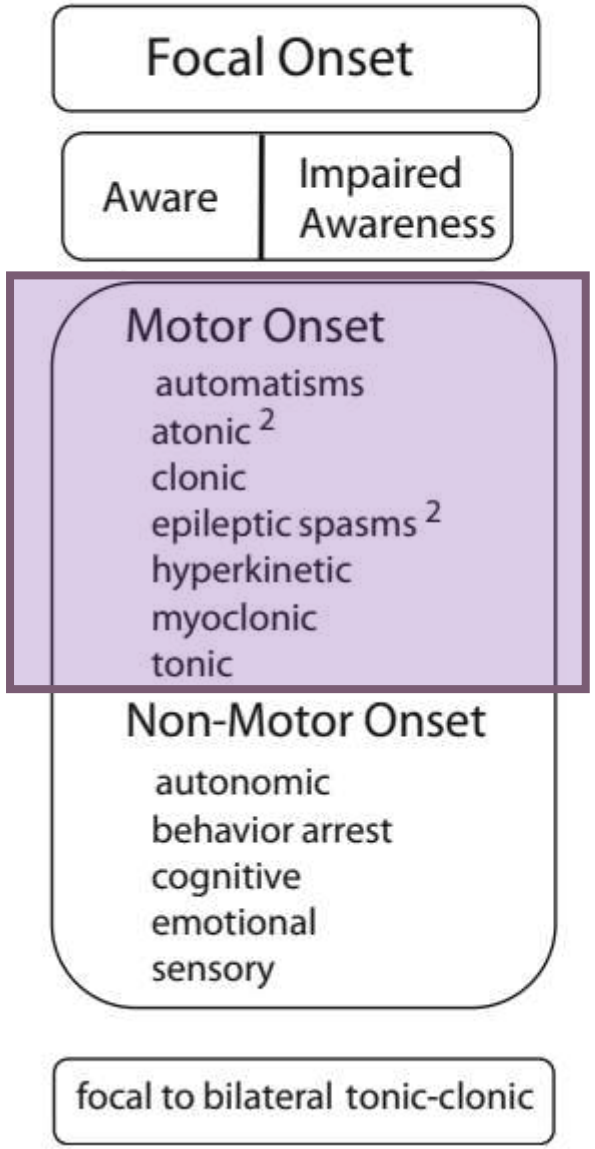
Klonik sustained rhythmic jerking. The jerking may spread to involve parts of the body according to their representation on the motor cortex

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



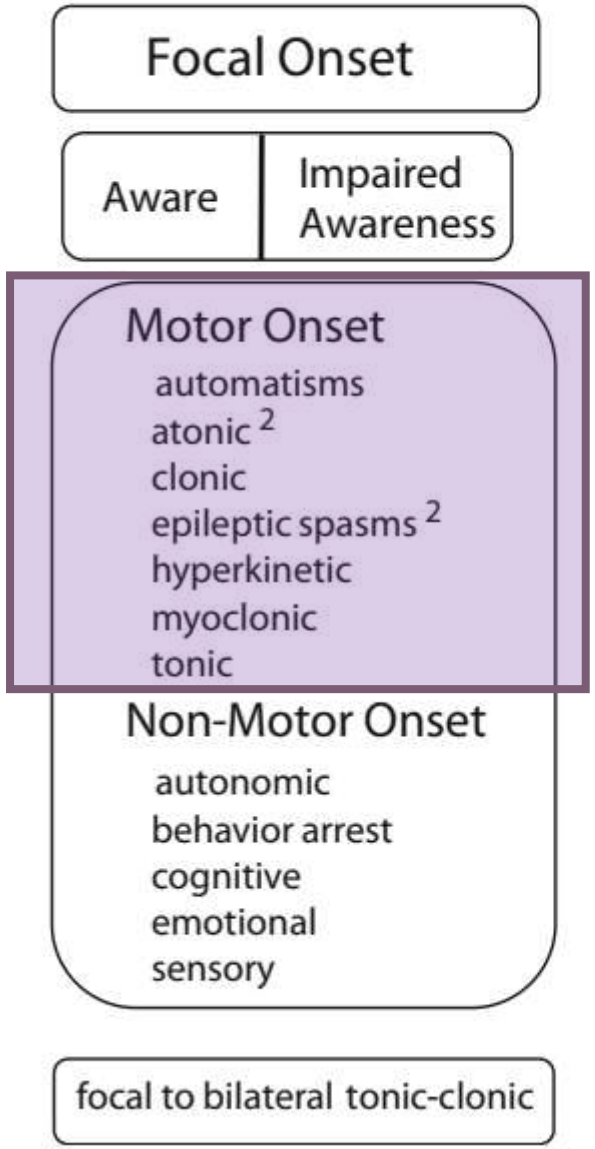
Spasme sudden flexion, extension or mixed flexion-extension of proximal and truncal muscles

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



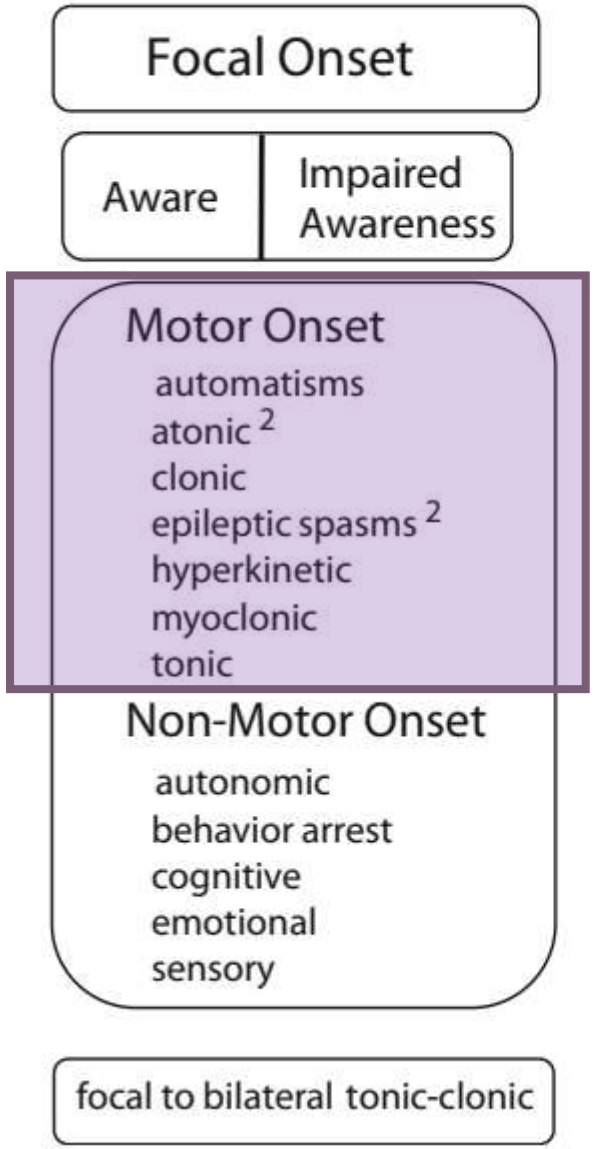
Hiperkinetik movements of proximal limb/ axial muscles irregular large amplitude movements:pedaling, pelvic thrusting, jumping, thrashing and/or rocking

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



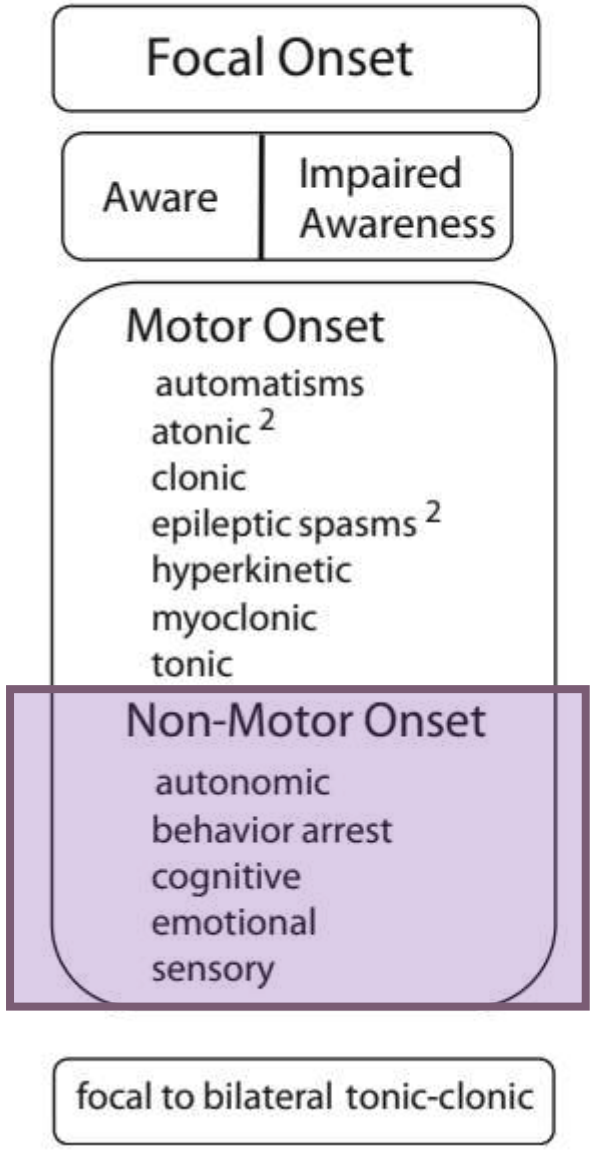
Mioklonik a single or short cluster of brief muscle contractions (unsustained).
Each jerk is typically milliseconds in duration.

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Tonik increased tone of the limbs

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Otonomik

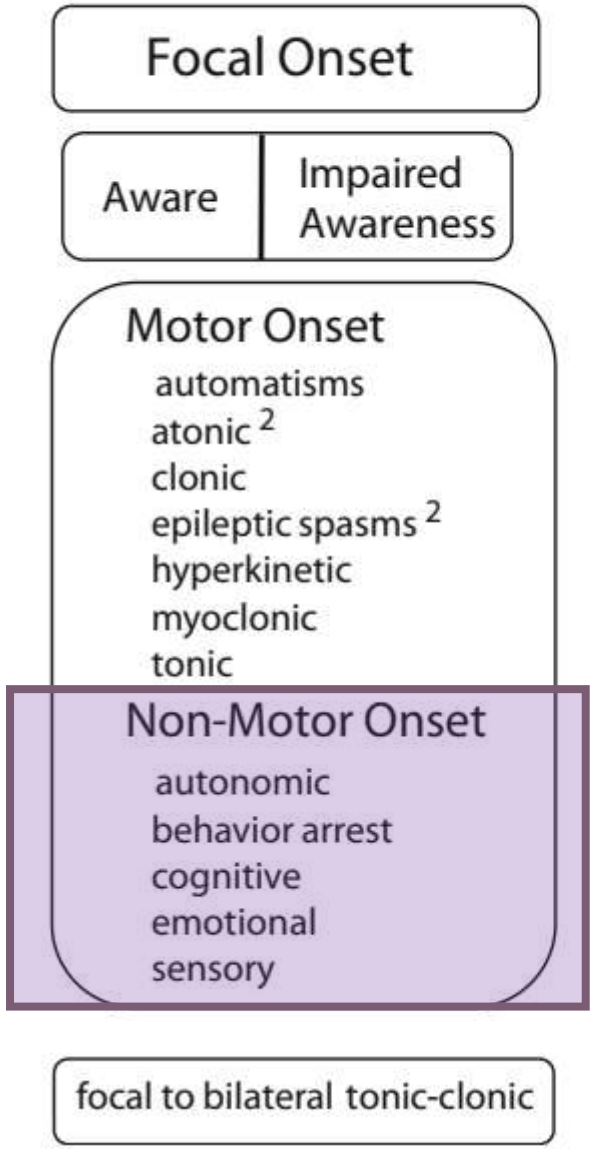
Behavioral arrest

Cognitive

Emotional

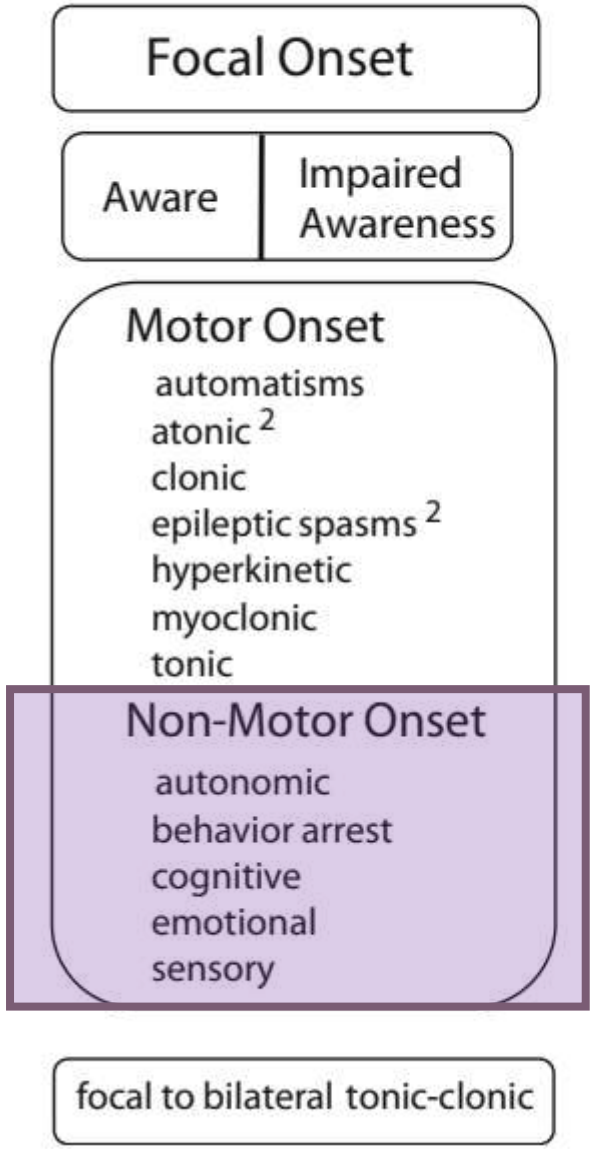
Sensory

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



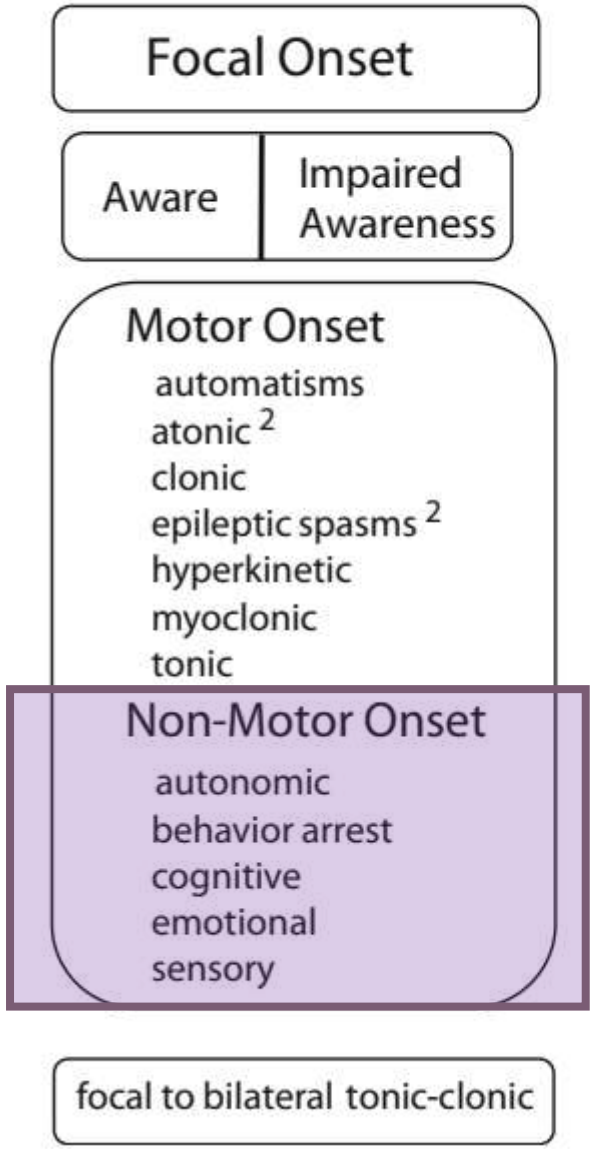
Otonomik heart rate, blood pressure, sweating, skin color, piloerection, gastrointestinal sensations

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Behavioral arrest cessation of movement, sometimes called a freeze or a pause.

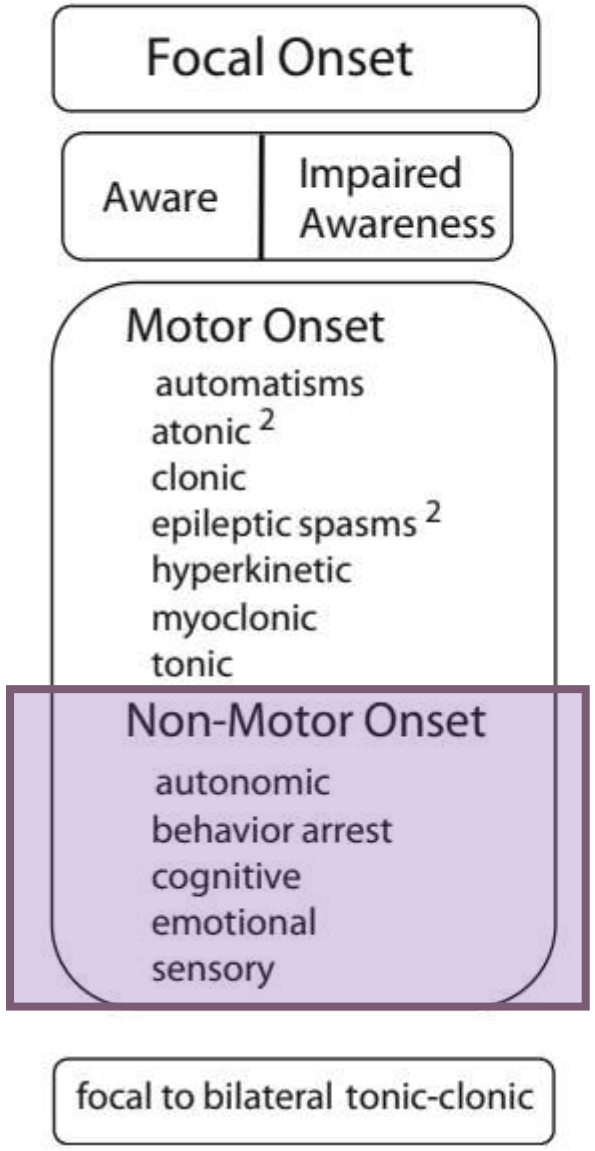
b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Cognitive

- Afasia (motoric, anomik, sensorik, konduksi)
- Aleksia/ agrafia/ akalkulia
- Agnosia auditorik
- Memory impairment
- Déjà vu (familiarity)/ jamais vu (unfamiliarity)
- Halusinasi kompleks (visual, auditoris, somatosensoris)
- Ilusi (alteration of actual perception)
- Disosiasi (being disconnected from, though aware of, self or environment.)
- Forced thinking
- Hemineglect, left right confusion

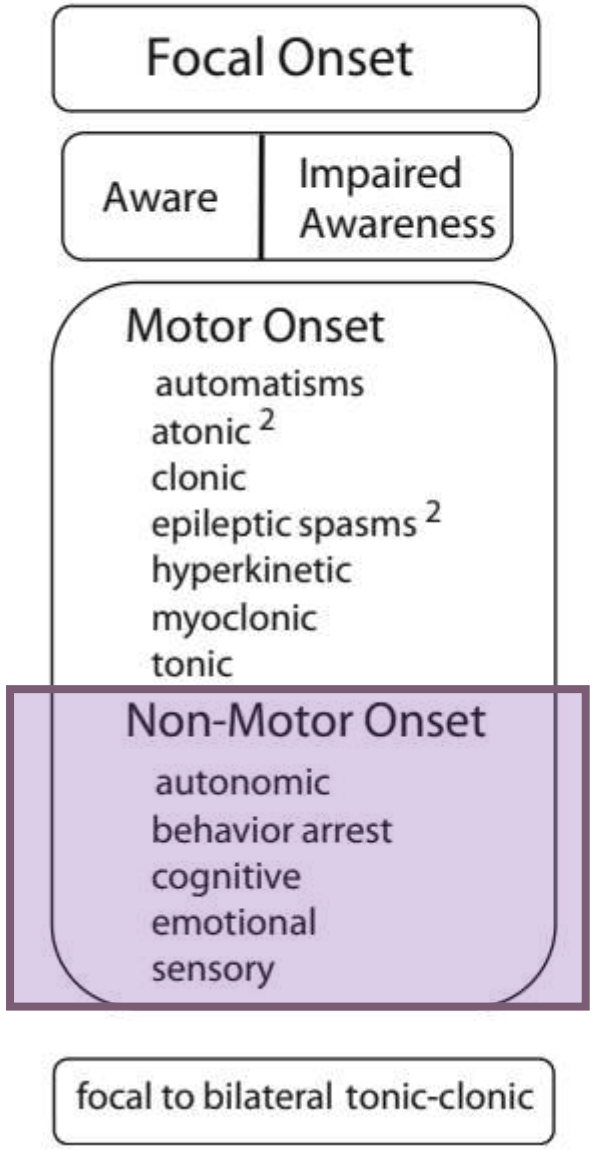
b ILAE 2017 Classification of Seizure Types Expanded Version [1]



Emotional

- Fear/ anxiety/ panic - mTLE, Amygdala
- Laughing (gelastic) - hypothalamus
- Crying (dacrystic) – hypothalamus, frontal, temporal
- Pleasure – anterior insula
- Anger - mTLE

b ILAE 2017 Classification of Seizure Types Expanded Version [1]



- **Somatosensoris:** tingling, numbness, electric-shock like sensation, pain, sense of movement, or desire to move
- **Visual**: elementary visual hallucinations such as flashing or flickering lights/colours, or other shapes, simple patterns, scotomata, or amaurosis
- **Auditori:** elementary auditory phenomena including buzzing, ringing, drumming or single tones.
- **Olfaktorius:** odor, which is often unpleasant
- **Gustatorik**: acidic, bitter, salty, sweet, or metallic tastes
- **Vestibularis**: dizziness, spinning, vertigo or sense of rotation.

Sensory

sensation being experienced at seizure onset, without objective clinical signs of a seizure evident to the observer.

Video pasien epilepsi fokal

Pasien awalnya sedang tidur saat perekaman EEG. Teknisi EEG melihat adanya elektrografik seizure pada monitor EEG dan mendatangi pasien

Yang terjadi pada pasien

Semiologi bangkitan

- Mata pasien terbuka
- Neck lifting
- Kelopak mata fasikulasi
- Mulut kanan tonik
- Leher menoleh tonik ke kanan
- Tangan kanan ekstensi, tonik
- Tangan kiri fleksi, distonik, klonik
- Bilateral tonic clonic

Yang dilakukan operator

Cek kesadaran pasien

- Can you talk?
- Can you say apple?
- Raise your arm up!
- Can you do like this?
- Stick your tongue out

Melaporkan semiologi bangkitan

Melindungi pasien dari cedera

- Bantal di belakang
- Suction
- Oksigenasi
- Melepaskan ikatan tangan

Memasukkan obat untuk menghentikan bangkitan

- Someone quick lorazepam please

Masih ingat adek ini?

Pasien mengeluhkan kesemutan pada ujung mulut →
kelemahan wajah kiri, sehingga liur mengalir dari sudut mulut sebelah kiri →
pasien dapat menuruti perintah dan menjawab pertanyaan tetapi pelo →
Mata berkedip-kedip saat serangan dan kelopak mata kiri lebih menyipit

Apa bentuk kejang pasien ini menurut klasifikasi ILAE?

The ‘sign 4’ position

Video pasien epilepsi fokal non motorik

Yang terjadi pada pasien

Diagnosis klinis: focal aware non motor seizure

Semiologi bangkitan

Ekspresi tampak ketakutan → biasanya pasien aware saat bangkitan

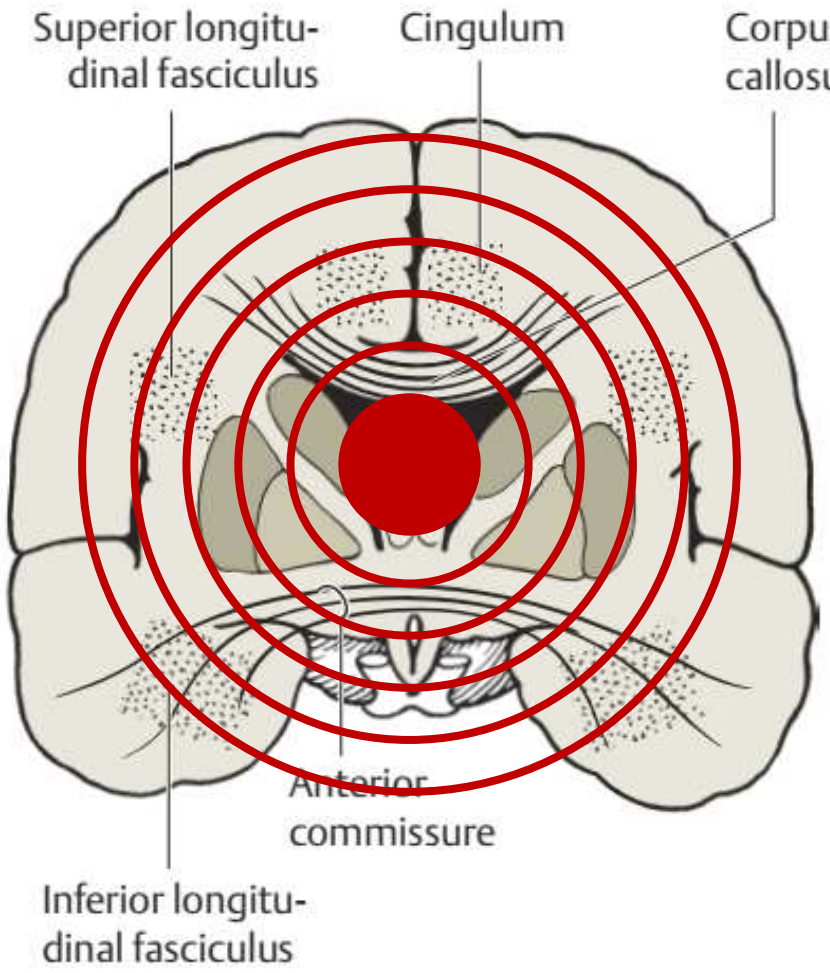
Ictal laughing/ uncontrolled giggling

Diagnosis topis: hipotalamus

Diagnosis etiologis: epilepsi fokal (gelastic epilepsy)

Penyebab terbanyak: hypothalamic hamarthroma

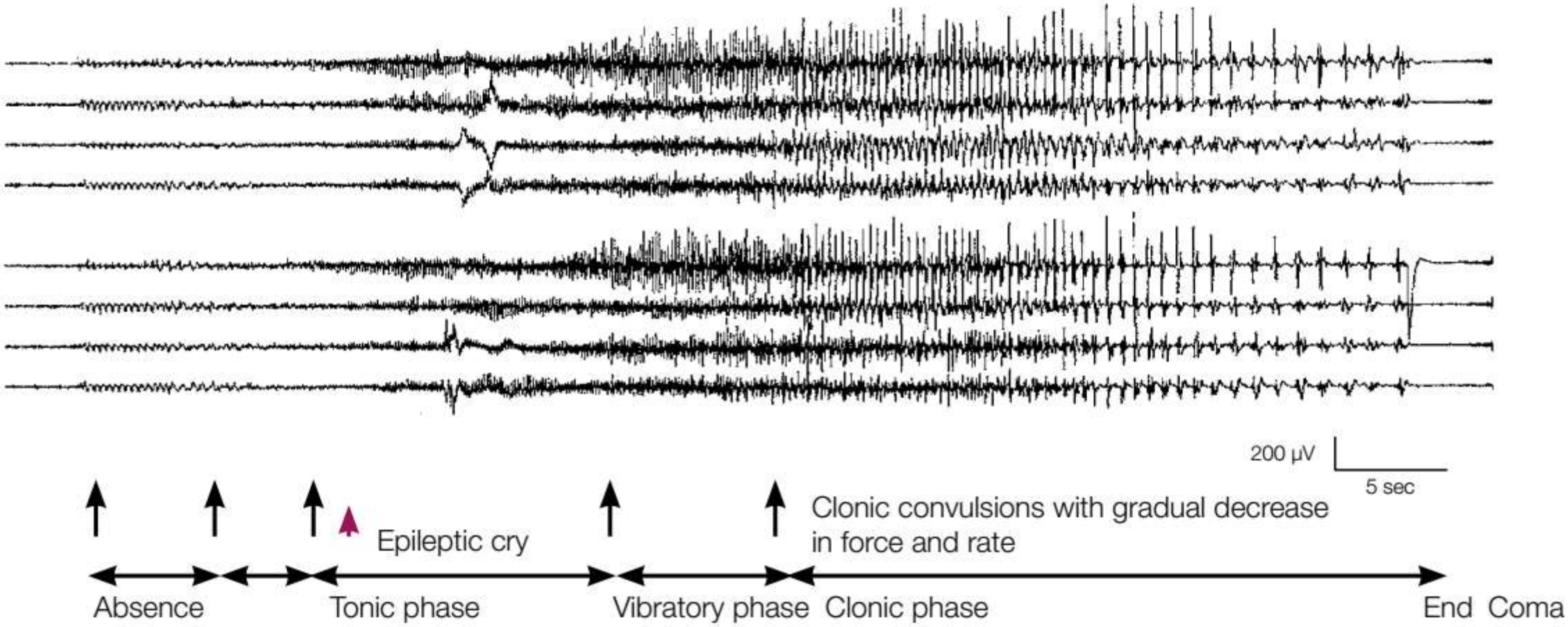
b ILAE 2017 Classification of Seizure Types Expanded Version [1]

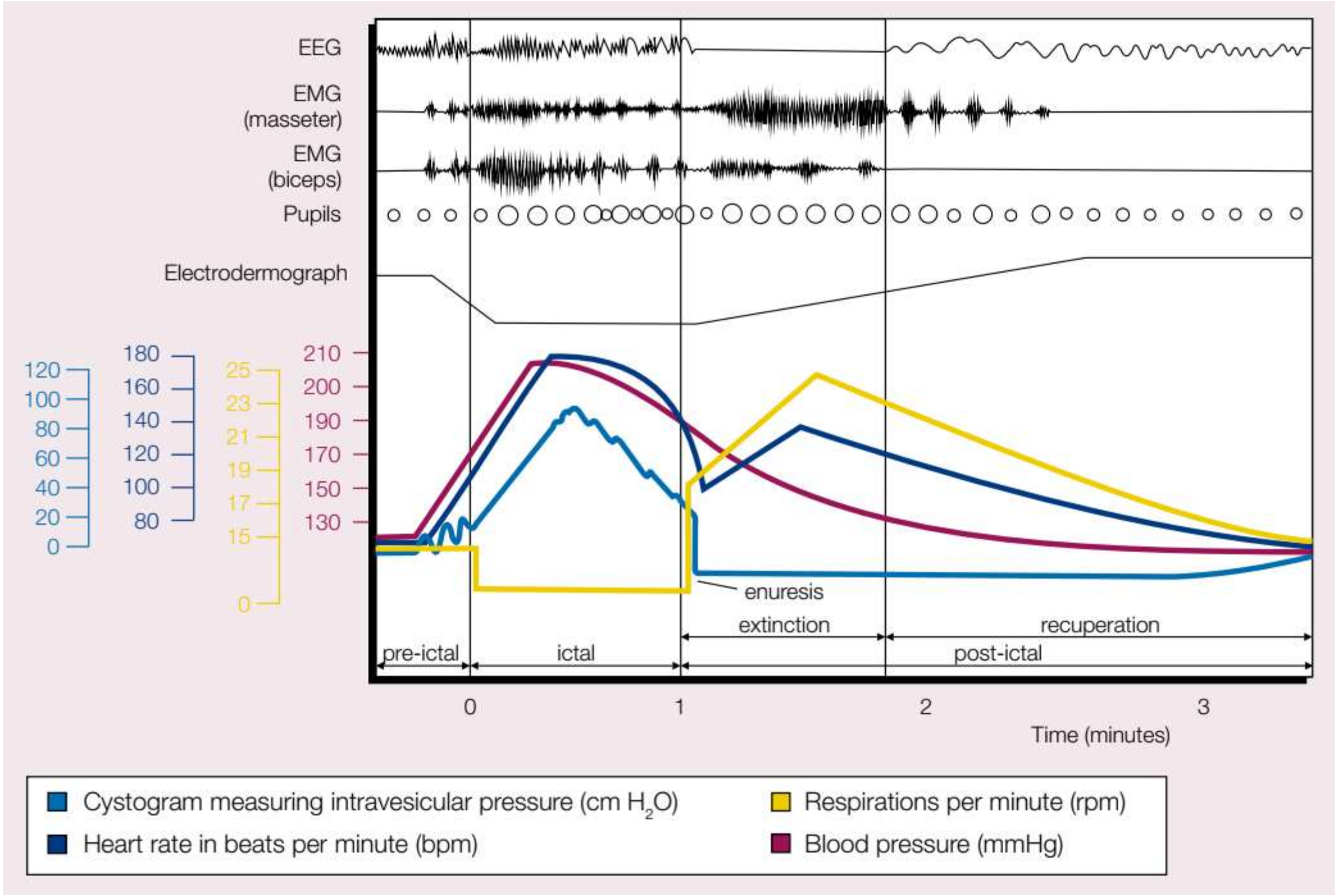


Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia


200 µV
5 sec
Epileptic cry
Clonic convulsions with gradual decrease
in force and rate
Absence
Tonic phase
Vibratory phase
Clonic phase
End Coma


EEG
EMG (masseter)
EMG (biceps)
Pupils
Electrodermograph
120
100
80
60
40
20
0
180
160
140
120
100
80
25
23
21
19
17
15
0
210
200
190
170
150
130
enuresis
extinction
recuperation
pre-ictal
ictal
post-ictal
0
1
2
3
Time (minutes)
Cystogram measuring intravesicular pressure (cm H_2O)
Heart rate in beats per minute (bpm)
Respirations per minute (rpm)
Blood pressure (mmHg)

Onset and sequence of a GTCS

Pre-ictal: In this example the patient is relaxing in bed and eyes are closed

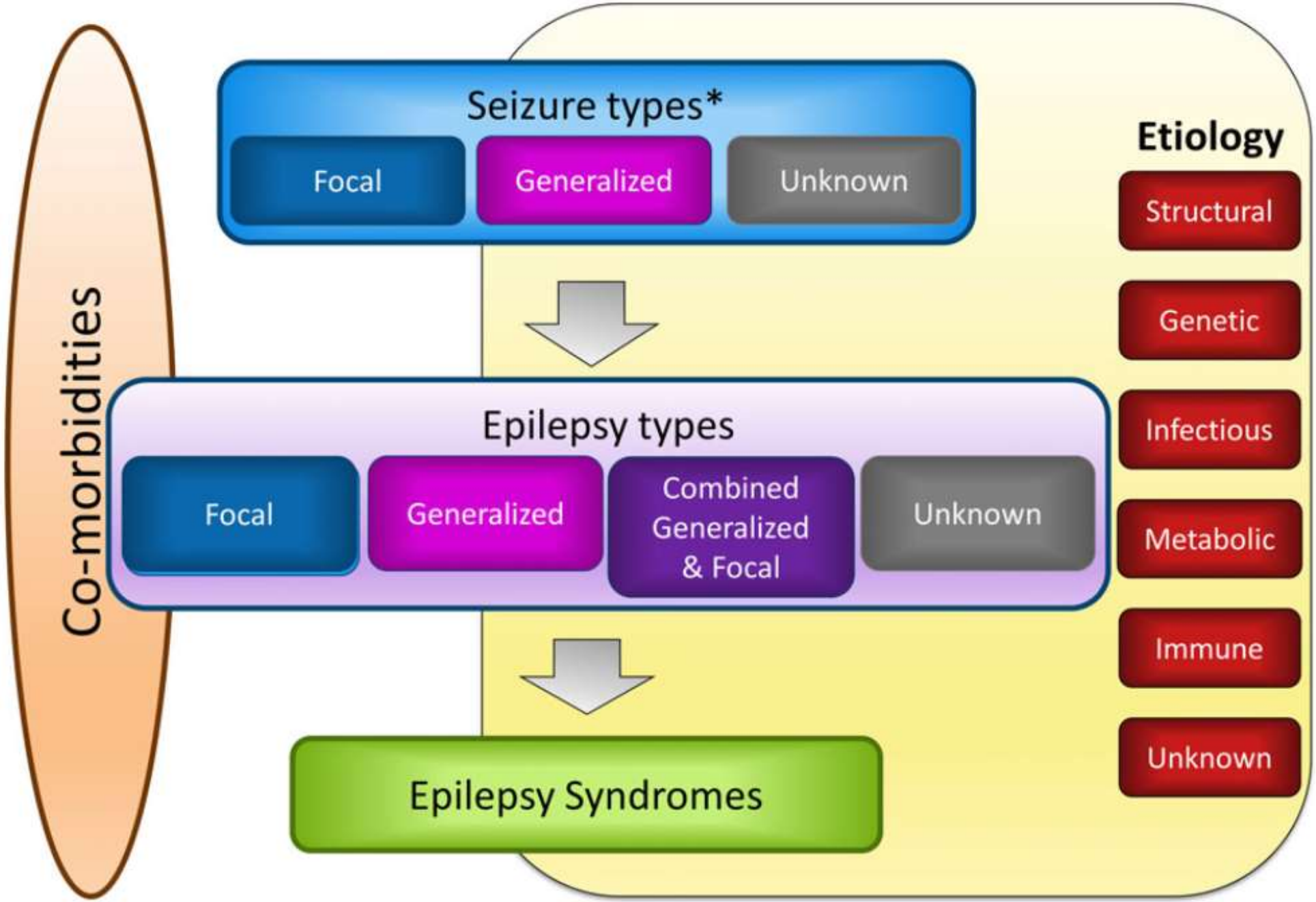
Initial stage of tonic phase in flexion

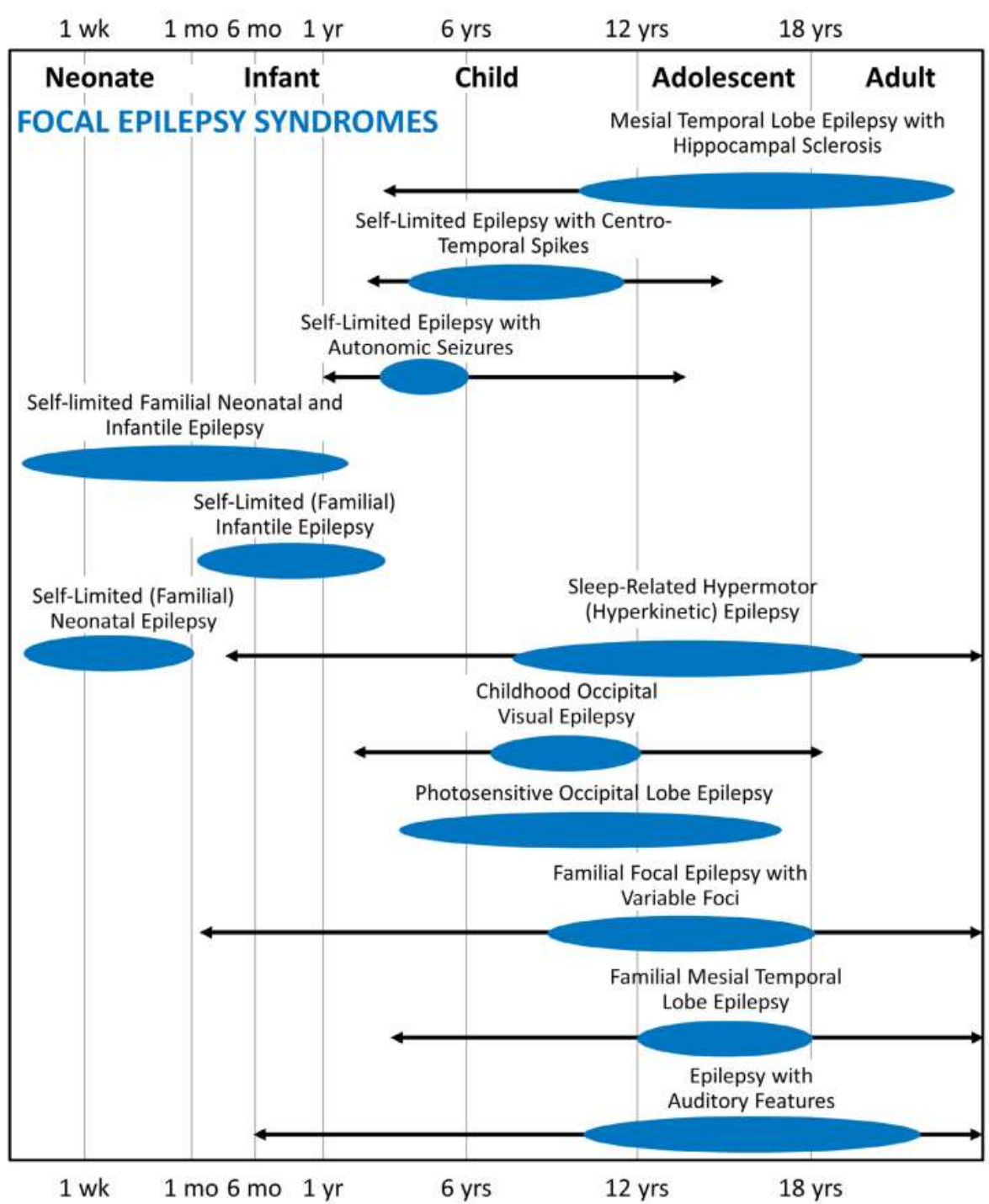
The eyes open immediately after the onset and remain open during the whole period of a GTCS. They usually close post-ictally. Asymmetrical postures may occur both in PGTCS and SGTCS

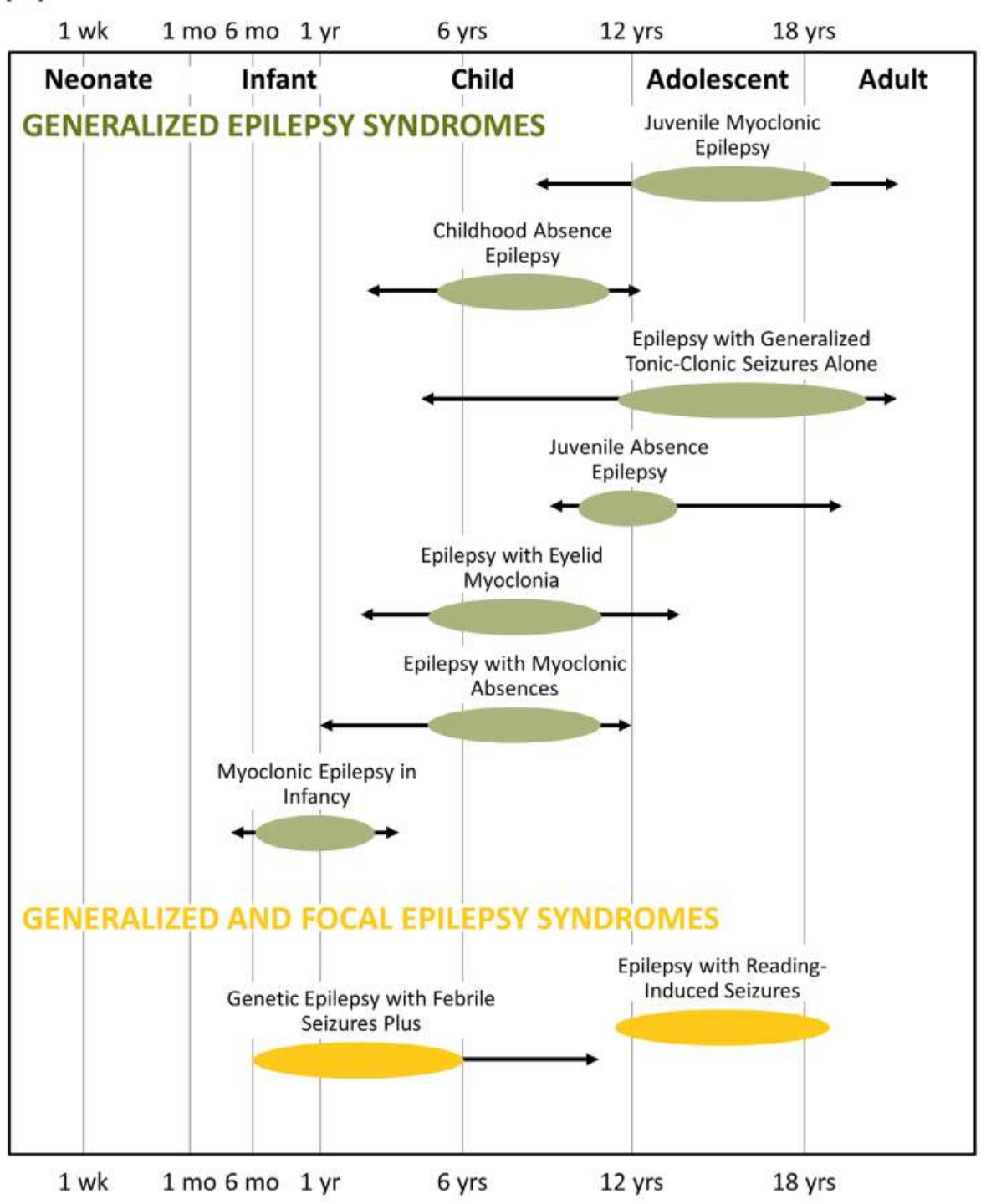
Second stage of tonic phase in extension

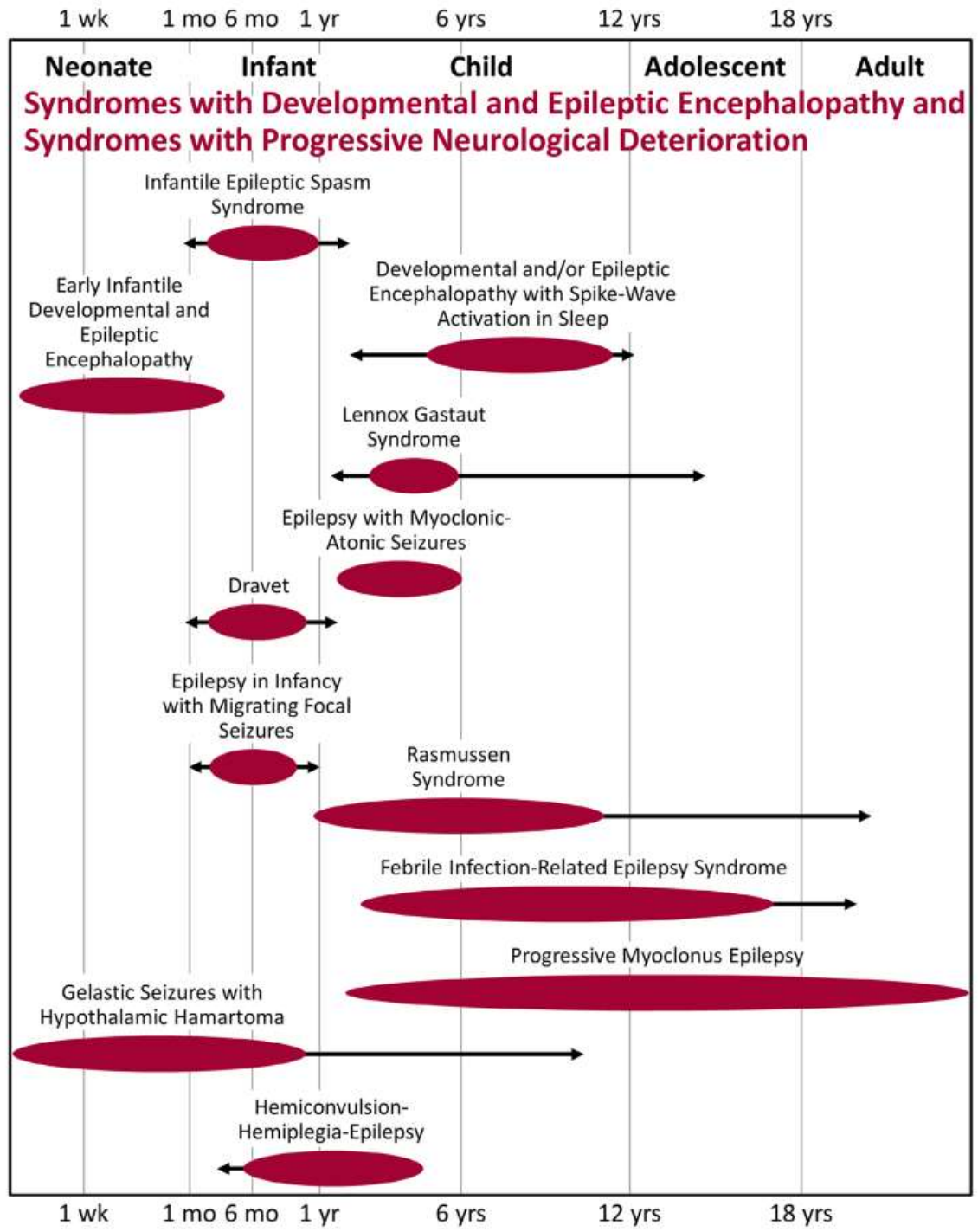
Immediate post-ictal stage with urinary incontinence

Urinary incontinence occurs in the immediate post-ictal stage and not during the convulsions

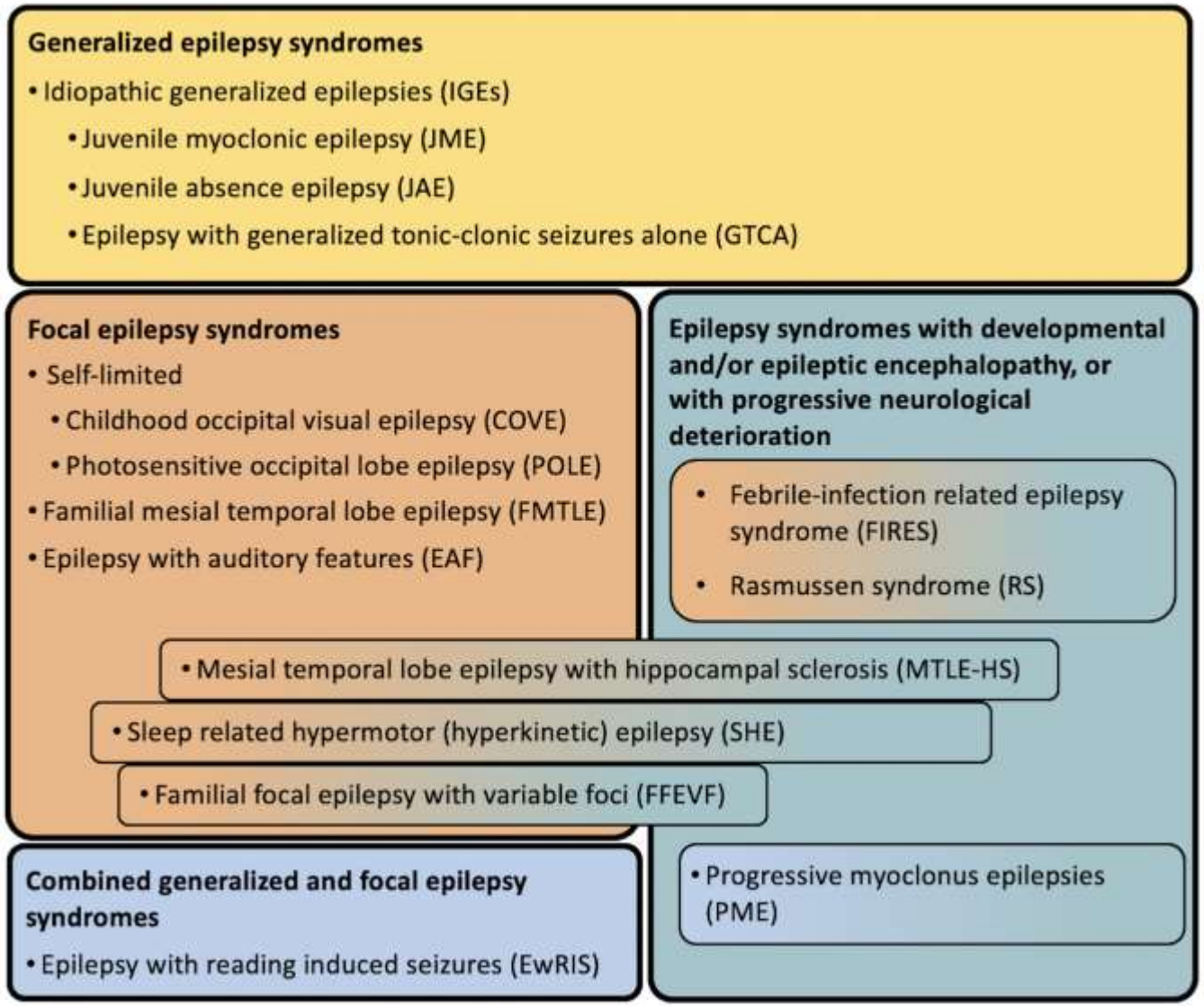

Co-morbidities
Seizure types*
Focal
Generalized
Unknown
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown


1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
FOCAL EPILEPSY SYNDROMES
Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
Self-Limited Epilepsy with Centro-Temporal Spikes
Self-Limited Epilepsy with Autonomic Seizures
Self-limited Familial Neonatal and Infantile Epilepsy
Self-Limited (Familial) Infantile Epilepsy
Self-Limited (Familial) Neonatal Epilepsy
Sleep-Related Hypermotor (Hyperkinetic) Epilepsy
Childhood Occipital Visual Epilepsy
Photosensitive Occipital Lobe Epilepsy
Familial Focal Epilepsy with Variable Foci
Familial Mesial Temporal Lobe Epilepsy
Epilepsy with Auditory Features
1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs


1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
GENERALIZED EPILEPSY SYNDROMES
Juvenile Myoclonic Epilepsy
Childhood Absence Epilepsy
Epilepsy with Generalized Tonic-Clonic Seizures Alone
Juvenile Absence Epilepsy
Epilepsy with Eyelid Myoclonia
Epilepsy with Myoclonic Absences
Myoclonic Epilepsy in Infancy
GENERALIZED AND FOCAL EPILEPSY SYNDROMES
Epilepsy with Reading-Induced Seizures
Genetic Epilepsy with Febrile Seizures Plus
1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs


1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
Syndromes with Developmental and Epileptic Encephalopathy and Syndromes with Progressive Neurological Deterioration
Infantile Epileptic Spasm Syndrome
Early Infantile Developmental and Epileptic Encephalopathy
Developmental and/or Epileptic Encephalopathy with Spike-Wave Activation in Sleep
Lennox Gastaut Syndrome
Epilepsy with Myoclonic-Atonic Seizures
Dravet
Epilepsy in Infancy with Migrating Focal Seizures
Rasmussen Syndrome
Febrile Infection-Related Epilepsy Syndrome
Progressive Myoclonus Epilepsy
Gelastic Seizures with Hypothalamic Hamartoma
Hemiconvulsion-Hemiplegia-Epilepsy
1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs

Sindrom epilepsi dengan onset neonatus dan anak



Etiologi epilepsi

structural :
hippocampal sclerosis, tumors, malformations, vascular lesions, traumatic brain injury

genetic :
monogenic or polygenic inheritance, germline or somatic mutations

infection :
bacterial, fungal, viral, parasites → geographical impact

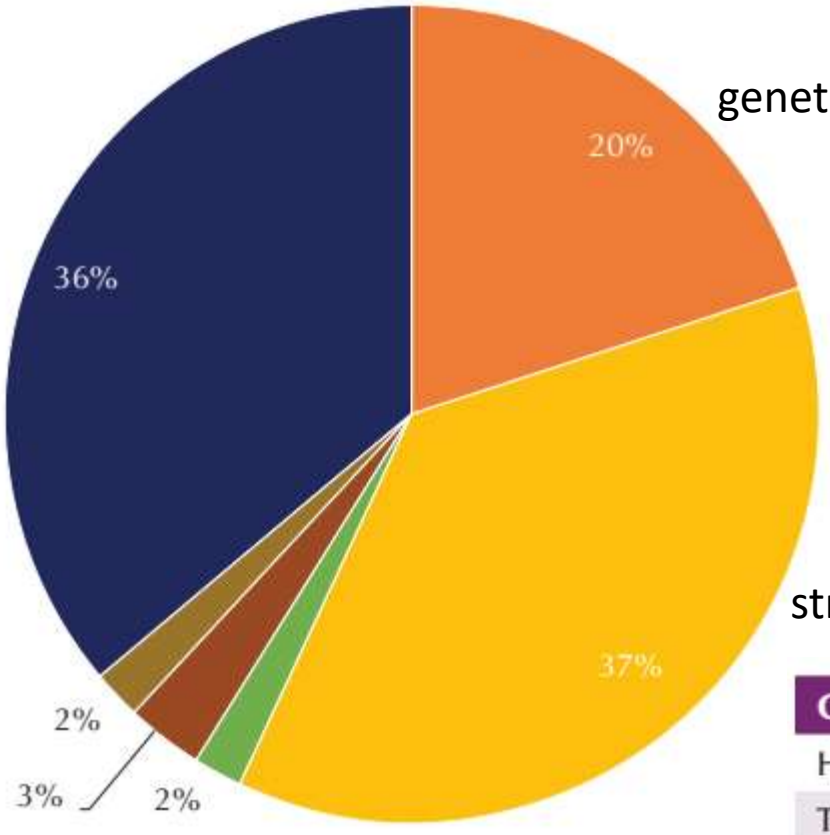
metabolic :
inborn errors of metabolism, glucose transport defects, pyridoxine-dependent seizures, mitochondrial pathologies

immune :
Rasmussen encephalitis, LGI1 antibodies, NMDA antibodies

neurodegenerative :
Alzheimer's disease, Down syndrome, progressive myoclonic epilepsies

Balestrini, et al. Epileptic Disord 2021; 23 (1): 1-16

Etiologi epilepsi



#1

structural

Category	Number (%)
HS	2,144 (36.3)
Tumour	1,680 (28.4)
Malformation	1,238 (20.9)
Vascular	369 (6.2)
Scar	344 (5.8)
Encephalitis	138 (2.3)

#1

*** HS : hippocampal sclerosis**

anamnesis

- Bentuk bangkitan
- Durasi bangkitan
- Gejala sebelum, selama, setelah bangkitan
- Frekuensi bangkitan
- Pencetus bangkitan
- Penyakit lain yang diderita
- Usia bangkitan pertama
- Riwayat ante-, peri-, post-natal, tumbuh kembang
- Riwayat pengobatan epilepsi
- Riwayat epilepsi keluarga

Anamnesis Pemeriksaan Fisik

- Riwayat trauma kepala
- Sumber infeksi otak: infeksi telinga/ sinus
- Gangguan kongenital
- Riwayat dan tanda kecanduan alkohol
- Riwayat dan tanda keganasan
- Defisit neurologis fokal
- Defisit neurologis difus

Pemeriksaan penunjang

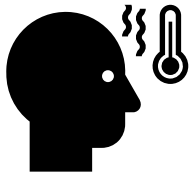
Elektroensefalografi	Membantu penegakan diagnosis epilepsi dan sindrom epilepsi, menentukan letak fokus (fokal/general), menentukan prognosis, pertimbangan saat penghentian ASM, membedakan dengan *seizure mimic,* membantu penegakan diagnosis status epilepticus non konvulsif
Brain imaging: CT scan, MRI kepala, PET, SPECT, fMRI	Sklerosis hipokampus, disgenesis kortikal, tumor, hemangioma kavernosa, AVM **CT scan:** superior dalam menilai kalsifikasi, perdarahan, kista, ventrikel otak **MRI:** gambran struktur otak lebih spesifik dan sensitif
Laboratorium	*Complete blood count* (hemoglobin, leukosit, trombosit), hapusan darah tepi, elektrolit, faal hati, faal ginjal. **Kadar obat**
Video iktal	

Diagnosis banding kejang

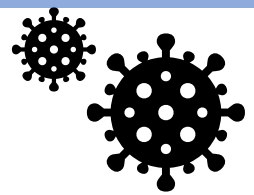
True seizure

- EPILEPSI

- KEJANG DEMAM



- KEJANG SIMTOMATIK AKUT



mimic seizure

- SINKOP

- PSIKOGENIK

- SLEEP DISORDER
- MOVEMENT DISORDER
- MIGRAINE RELATED
- STROKE/ TIA

Tatalaksana epilepsi

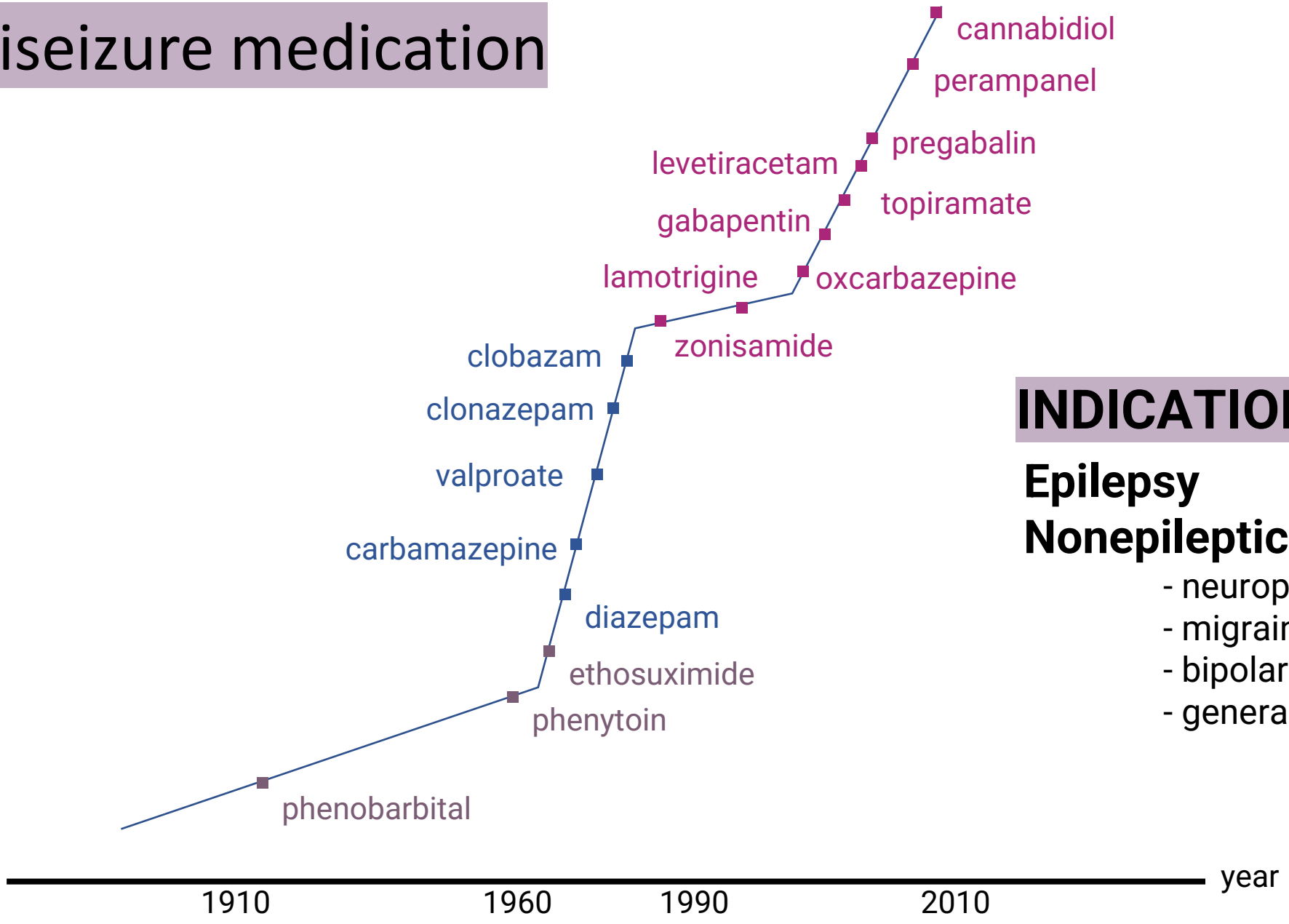
Farmakologis: antiseizure medication

Nutrition: ketogenic diet, gluten free diet, caloric restriction

Neurostimulation: Vagal nerve ST, responsive nerve ST, deep brain ST

Surgery: intractable epilepsy

Antiseizure medication



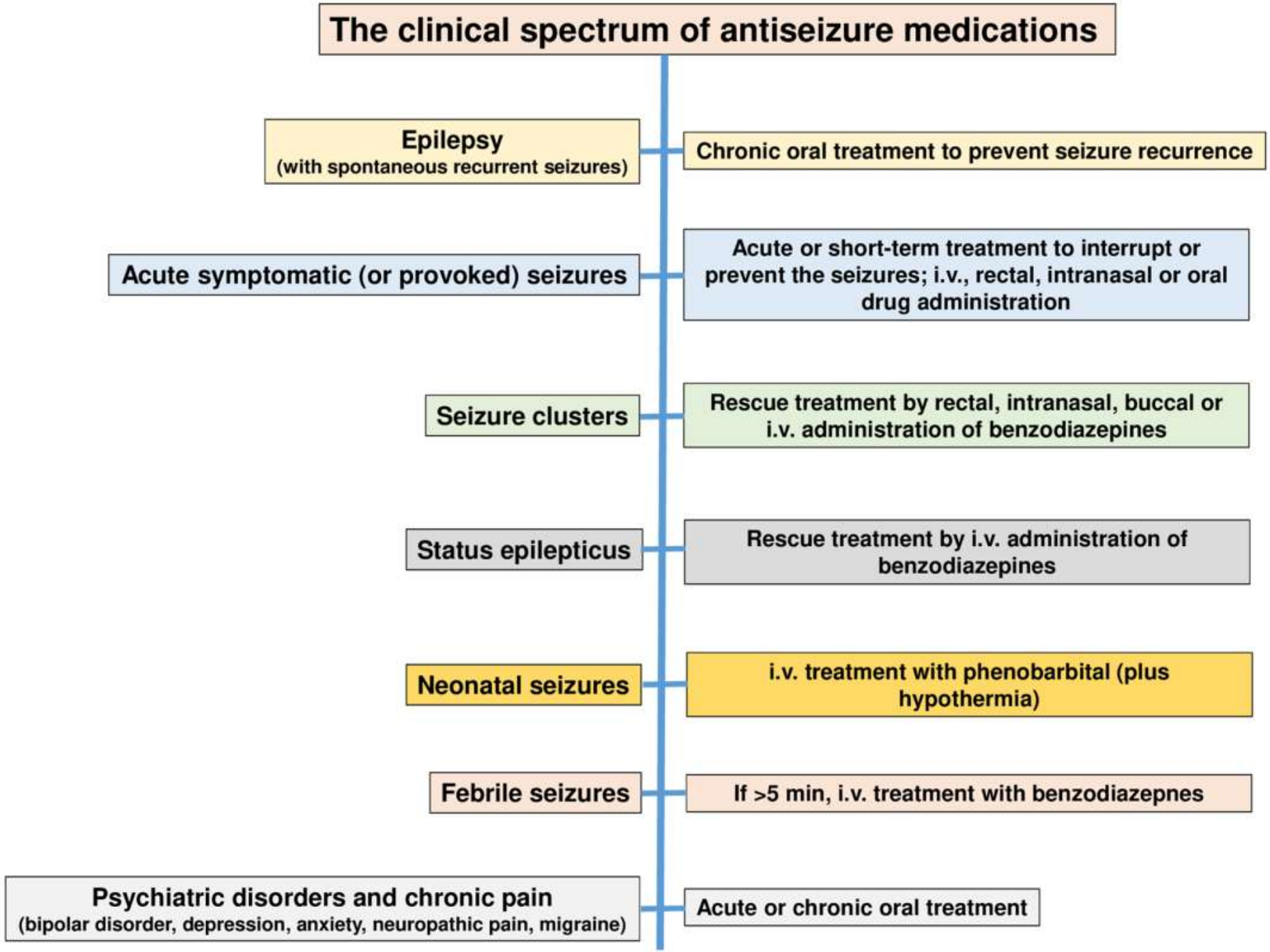
INDICATION:

Epilepsy

Nonepileptic conditions

- neuropathic pain
- migraine
- bipolar disorder
- generalized anxiety disorder.

Löscher and Klein. The Pharmacology and Clinical Efficacy of Antiseizure Medications: From Bromide Salts to Cenobamate and Beyond. *CNS Drugs* **35**, 935–963 (2021).


The clinical spectrum of antiseizure medications
Epilepsy
(with spontaneous recurrent seizures)
Chronic oral treatment to prevent seizure recurrence
Acute symptomatic (or provoked) seizures
Acute or short-term treatment to interrupt or prevent the seizures; i.v., rectal, intranasal or oral drug administration
Seizure clusters
Rescue treatment by rectal, intranasal, buccal or i.v. administration of benzodiazepines
Status epilepticus
Rescue treatment by i.v. administration of benzodiazepines
Neonatal seizures
i.v. treatment with phenobarbital (plus hypothermia)
Febrile seizures
If >5 min, i.v. treatment with benzodiazepnes
Psychiatric disorders and chronic pain
(bipolar disorder, depression, anxiety, neuropathic pain, migraine)
Acute or chronic oral treatment

pemilihan

Antiseizure medication

Jenis kejang: focal epilepsy/ general epilepsy

Sindrom epilepsi khusus

Kondisi pasien : usia subur, kehamilan, gangguan ginjal, liver, geriatri

Harga obat, ketersediaan

Focal epilepsy

Hampir semua ASM dapat diberikan

Carbamazepin adalah obat dengan level of evidence A

Pilihan lain: phenytoin (A), levetiracetam (A) Valproat (B)

general epilepsy

Perhatian khusus pada epilepsi dengan tonic/ atonic/ absence seizuer

Valproate	
Levetiracetam*	(-) absence, tonic, or atonic
Lamotrigine*	< absence seizures (-)myoclonic seizures
Topiramate	
Zonisamide	
Felbamate	
Perampanel	
Lacosamide	

Tetapi tidak ada pilihan obat yang level of evidence nya A

Sindrom epilepsi khusus

Pediatric genetic epilepsies

- Lennox–Gastaut syndrome
- Infantile spasms (West syndrome)
- Dravet syndrome,
- Tuberosclerosis complex (TSC)

Difficult to treat

Specific regiment

absence seizures (childhood or juvenile absence epilepsy) : General seizure
Drug of choice : **Ethosuximide** → valproate → other ASMs used for GE

Infantile spasms : General seizure
Drug of choice**:** hormone therapy **(ACTH)** → prednisone → vigabatrin

Lennox-Gastaut Syndrome: multiple seizure type
Drug of choice**:** benzodiazepine, cannabiol

valproate

weight gain → ASM lain penyebab **weight gain**:
Gabapentin, pregabalin, carbamazepine, vigabatrine

Hyperandrogenemia: hirsutism

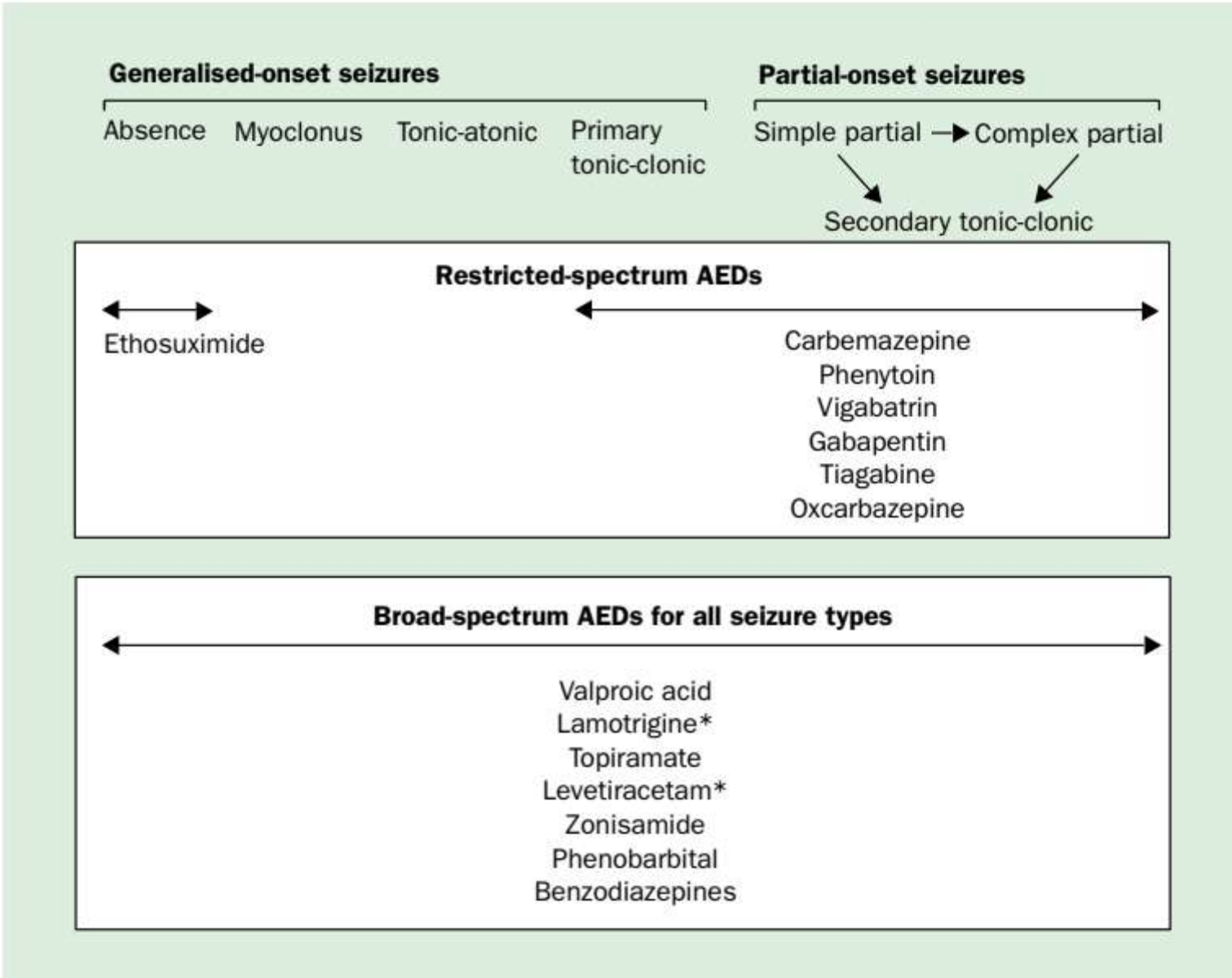
Metabolic syndrome

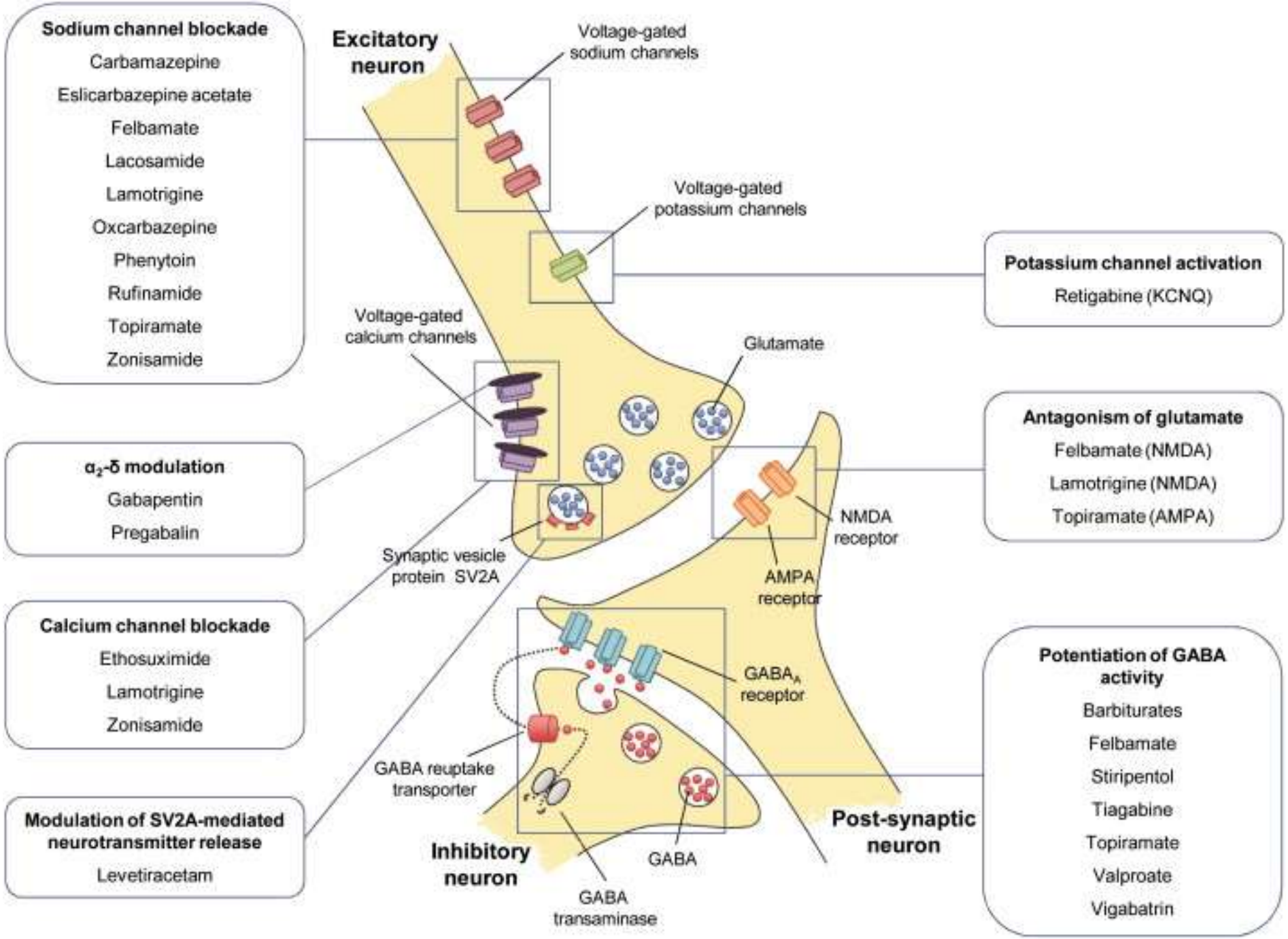
Exacerbation of diabetes

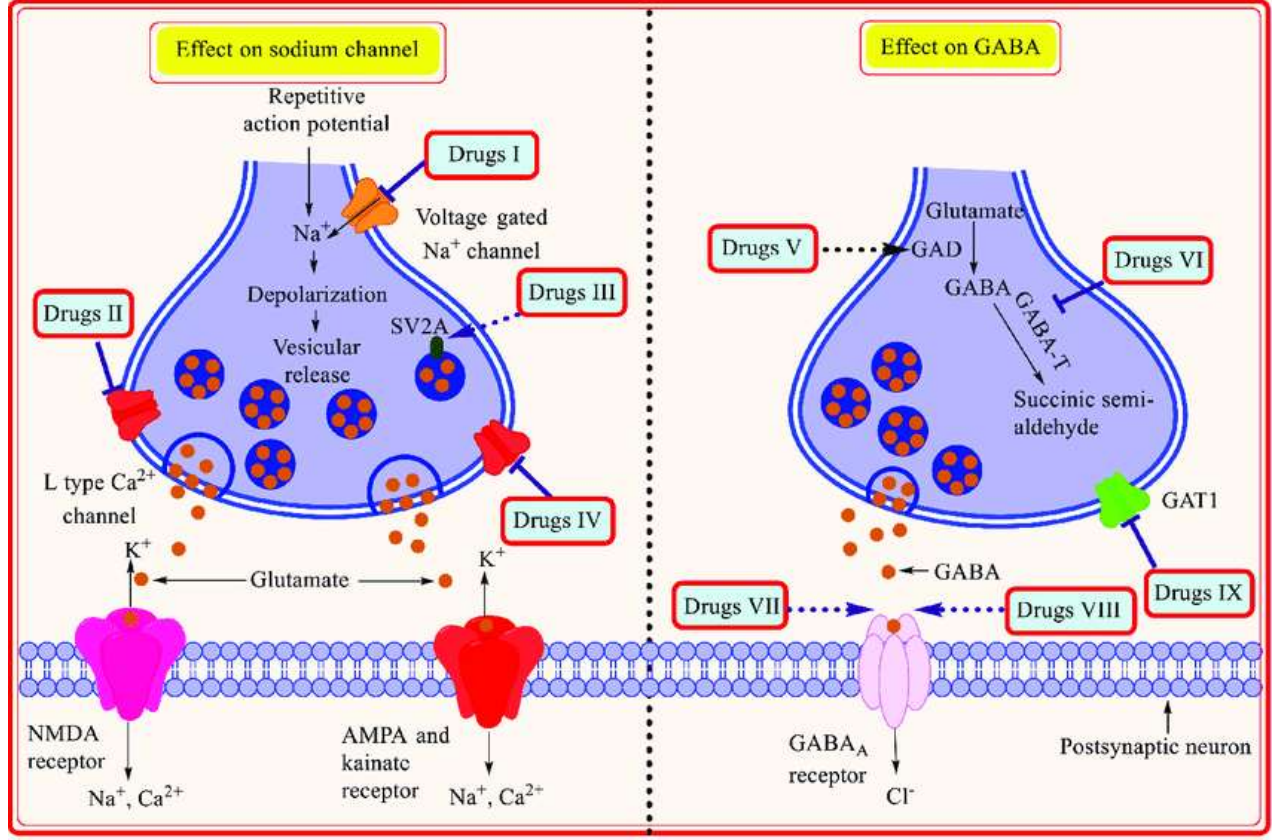
Polycystic ovarian syndrome

Hepatitis → Risiko lebih tinggi pada mutasi gen **POLG1**

pancreatitis


Generalised-onset seizures
Absence
Myoclonus
Tonic-atonic
Primary tonic-clonic
Partial-onset seizures
Simple partial
Complex partial
Secondary tonic-clonic
Restricted-spectrum AEDs
Ethosuximide
Carbemazepine
Phenytoin
Vigabatrin
Gabapentin
Tiagabine
Oxcarbazepine
Broad-spectrum AEDs for all seizure types
Valproic acid
Lamotrigine*
Topiramate
Levetiracetam*
Zonisamide
Phenobarbital
Benzodiazepines


Sodium channel blockade
Carbamazepine
Eslicarbazepine acetate
Felbamate
Lacosamide
Lamotrigine
Oxcarbazepine
Phenytoin
Rufinamide
Topiramate
Zonisamide
α2-δ modulation
Gabapentin
Pregabalin
Calcium channel blockade
Ethosuximide
Lamotrigine
Zonisamide
Modulation of SV2A-mediated neurotransmitter release
Levetiracetam
Excitatory neuron
Voltage-gated sodium channels
Voltage-gated potassium channels
Voltage-gated calcium channels
Glutamate
Synaptic vesicle protein SV2A
NMDA receptor
AMPA receptor
GABAA receptor
GABA reuptake transporter
GABA
GABA transaminase
Inhibitory neuron
Post-synaptic neuron
Potassium channel activation
Retigabine (KCNQ)
Antagonism of glutamate
Felbamate (NMDA)
Lamotrigine (NMDA)
Topiramate (AMPA)
Potentiation of GABA activity
Barbiturates
Felbamate
Stiripentol
Tiagabine
Topiramate
Valproate
Vigabatrin



DRUGS	MECHANISM OF ACTION
Drugs I:- Phenytoin, Fosphenytoin, Carbamazepine, Topiramate, Oxcarbazepine, Sodium Valproate, Lamotrigine, Zonisamide, Lacosamide	Bind to voltage-dependent Na^+ channel and prevent further entry of Na^+ into neurons. Thus, inhibit repetitive action potential. Thus, reduce the spread of seizures.
Drugs II:- Gabapentin, Pregabalin	Reduce Ca^{2+} influx
Drugs III:- Levetiracetam	Only drug that binds to SV2A
Drugs IV:- Ethosuxamide	Inhibit T type Ca2+ current in thalamic neurons
Drugs V:- Sodium Valproate	Stimulates GAD and increases GABA activity
Drugs VI:-- Vigabatrin, Sodium Valproate	Inhibits GABA-T and increases GABA activity
Drugs VII:- Benzodiazepines	Facilitate GABA activity
Drugs VIII:- Phenobarbitones	Facilitate GABA activity and have GABA mimetic activity
Drugs IX:- Tiagabin	Block uptake of GABA into the neurons

Represents release/facilitation Represents inhibition

carbamazepin

oxcarbazepin

Asam valproat

phenytoin

Clonazepam*

gabapentin

pregabalin

phenobarbital

levetiracetam

lamotrigin

topiramate

perampanel

zonisamide

cannabidiol

clobazam*

Focal epilepsy/ to bilateral
General tonic clonic seizure

Terutama untuk focal epilepsy
Dapat untuk general epilepsy

Lennox-Gastaut syndrome
Dravet syndrome

Adjunctive therapy

- Lennox-Gastaut syndrome
- Focal epilepsy
- Generalized tonic clonic seizure

carbamazepin

oxcarbazepin

Asam valproat

phenytoin

Clonazepam*

gabapentin

pregabalin

phenobarbital

levetiracetam

lamotrigin

topiramate

perampanel

zonisamide

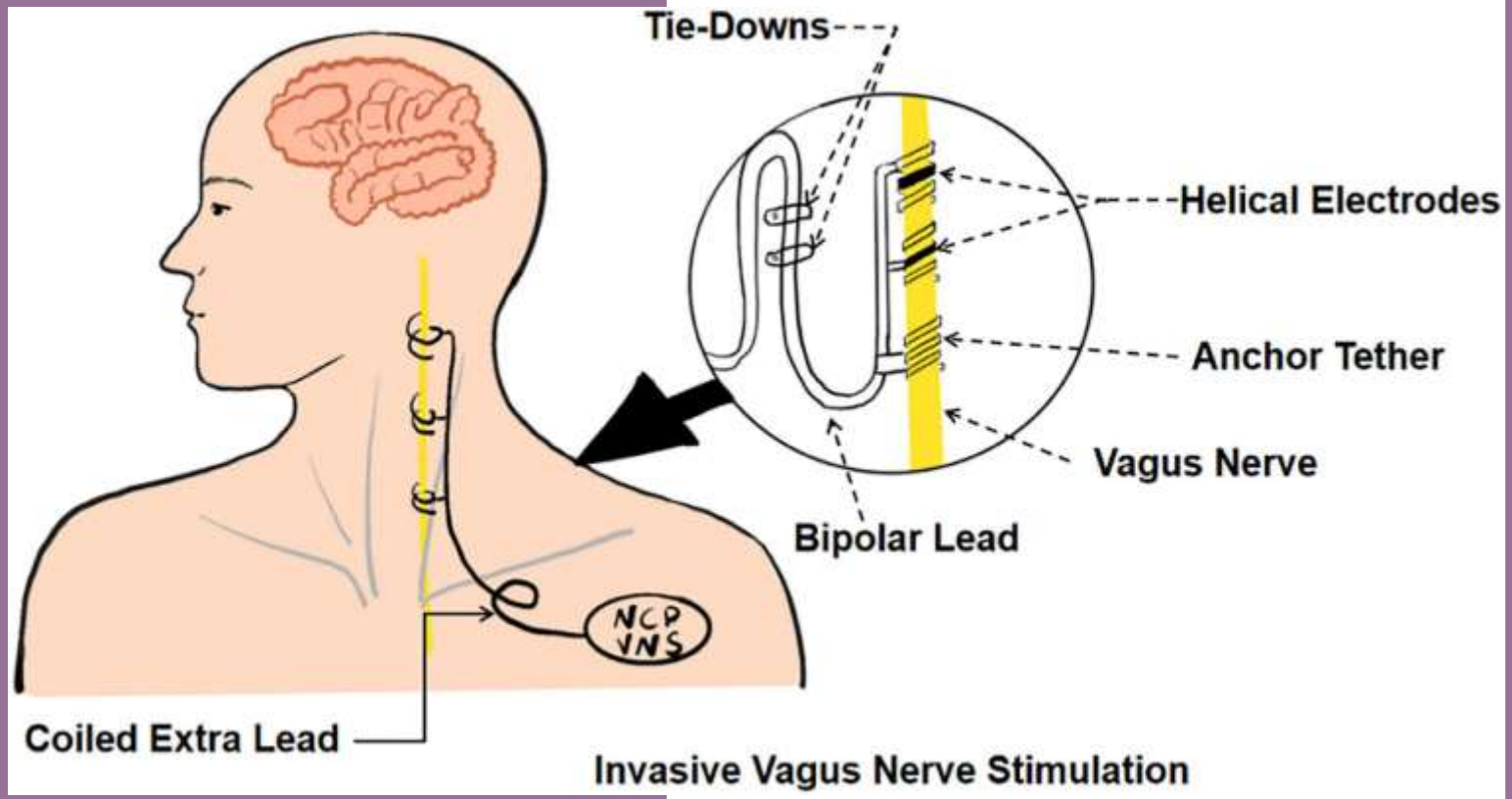
cannabidiol

clobazam*

Obat antibangkitan juga digunakan untuk penyakit2 lain:

- neuropathic pain: gabapentin
- Trigeminal neuralgia: carbamazepine
- Migraine: topiramate
- bipolar disorder valproate
- generalized anxiety disorder clobazam, clonazepam

Vagal nerve stimulation



indikasi

Epilepsy
Depression
Cluster headache
Migraine

jenis

Invasive
Transcutaneus
- Cervical
- auricular

Nutrition therapy: restrictive diet

- Ketogenic diet + variants
  - Pediatric refractory epilepsy
  - Infantile spasm
  - Less study in adult
- Gluten-free diet
- Caloric restriction

Surgery in epilepsy

- **Focal resection:** temporal lobectomy/ extra-temporal
  (Non eloquent area)
- **Lesionectomy:** symptomatic epilepsy (tumor, AVM)
- **Multiple subpial transections:** epilepsy focus in the eloquent area (memory, speech, movement, visual)
- **Laser interstitial thermal therapy** (ablation surgery): less invasive
- Hemispherectomy (anatomy/ functional): large seizure area, children
- **Corpus callosotomy:** atonic/ falls
- **Stereotactic radiosurgery**: less invasive

Antiseizure medication withdrawal

Seizure free 2-5 year

EEG: No epileptiform discharge

Risk of seizure recurrence after withdrawal:
- Multiple seizure type, juvenile myoclonic epilepsy
- Onset seizure: adolescent, adult
- Abnormal neurology exam, IQ<70
- Underlying cerebral substrate of seizure

ASD Withdrawal:
- Stable time
- Minimal stress/ provoking factor

Seizure relapse:
- Mostly within 12 months

Prognosis

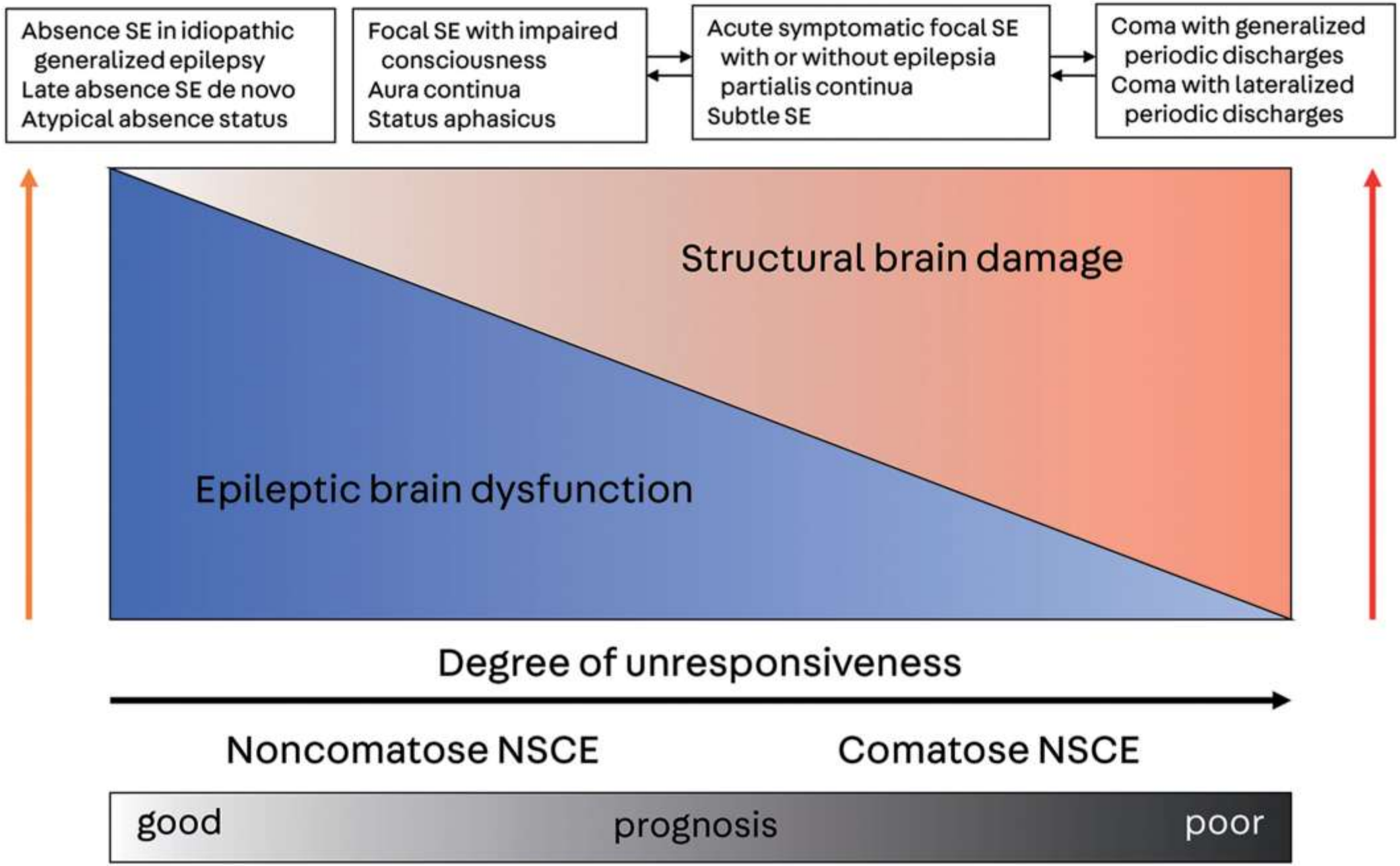
Remission in epilepsy

70% pasien mencapai remisi

The International League Against Epilepsy (ILAE) has proposed to expand the definition of remission to 10 years seizure-free with the last 5 years off antiepileptic drugs (AEDs).

possible predictors of seizure prognosis:

- age of onset
- Gender
- Etiology
- Seizure type
- EEG patterns
- Number of seizures prior to treatment
- Early response to treatment


Absence SE in idiopathic generalized epilepsy
Late absence SE de novo
Atypical absence status
Focal SE with impaired consciousness
Aura continua
Status aphasicus
Acute symptomatic focal SE with or without epilepsia partialis continua
Subtle SE
Coma with generalized periodic discharges
Coma with lateralized periodic discharges
Structural brain damage
Epileptic brain dysfunction
Degree of unresponsiveness
Noncomatose NSCE
Comatose NSCE
good
prognosis
poor