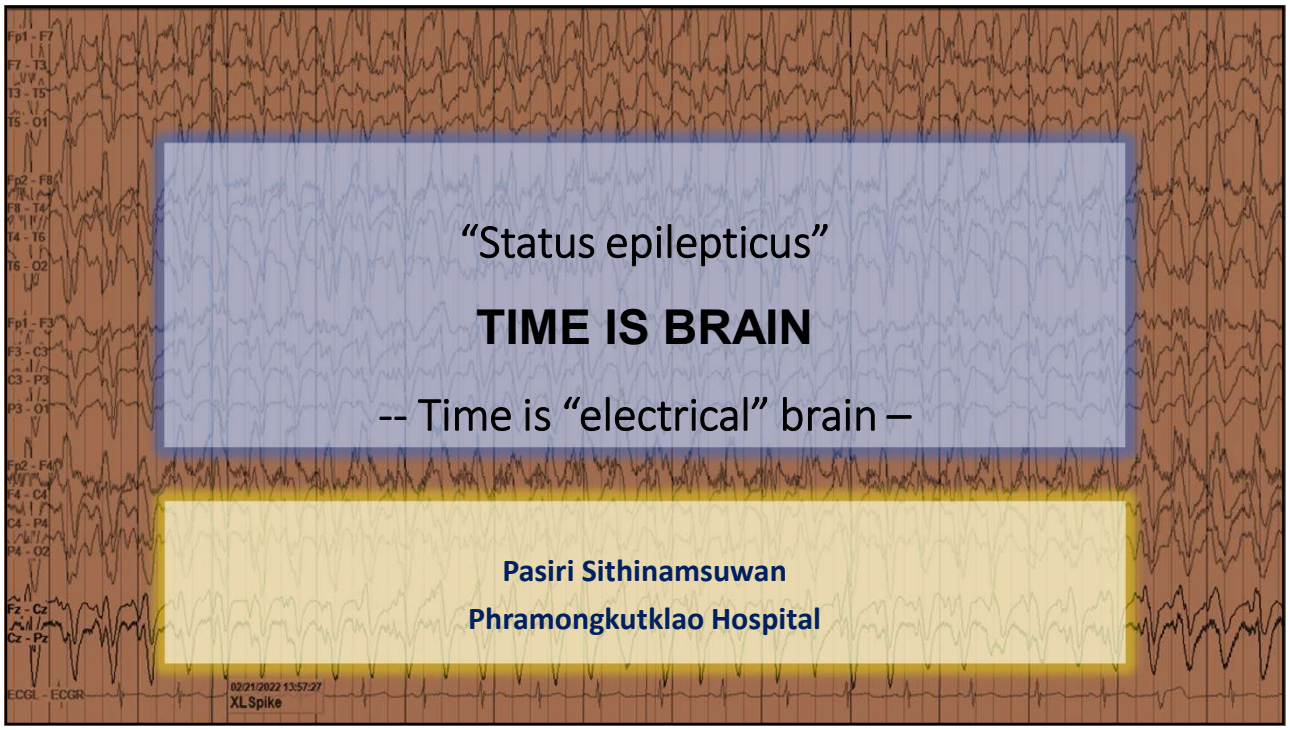


Scope

- Introduction
- Definition
- Pathophysiology
- Neuroimaging
- Consequences

Status epilepticus (SE)

A critical care emergency

- Both convulsive and non-convulsive status epilepticus (CSE >> NCSE)

Current treatment approaches vary dramatically

Status epilepticus remains undertreated

Goal

- Rapid termination of the seizure activity
- To reduce neurological injuries and deaths

High mortality esp. refractory status epilepticus

Trinka E, et al. Epilepsia 2015., Claassen J, et al. Neurology 2004.

Seizure emergency

Definition

- Frequently occurring seizures
- A prolonged seizure or continuous state of seizure
- A bout or cluster of seizures over a short period of time in which the patient regains consciousness between seizures

Types

- Acute repetitive seizures: Evolution into *status epilepticus* ***
  - 40% versus 12% (without ARS)
- Status epilepticus (SE)

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

- Continuous clinical or electrographic seizure activity that lasts at least 5–10 min or recurrent seizure activity without recovery to baseline neurologic status between seizures

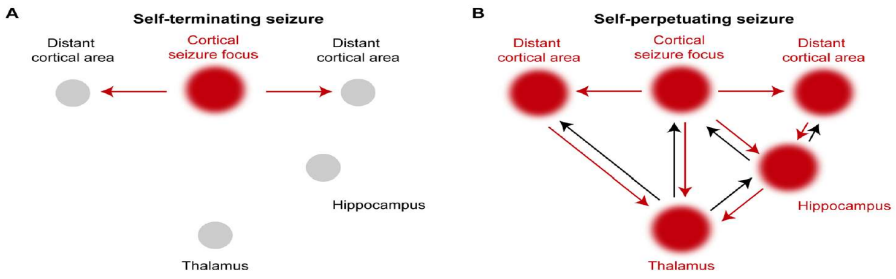
ILAE. Epilepsia 2015

- RSE
  - SE which is refractory to 2 intravenous ASMs, one of which is a benzodiazepine
  - RSE based on the duration of seizure for 1 or 2 hours which may be continuous or intermittent without return to baseline mental status
- SRSE
  - SE that continues for 24 hours or more after the initiation of 3rd line medications (anesthetic therapy), including the cases in whom SE recurs on weaning of anesthesia

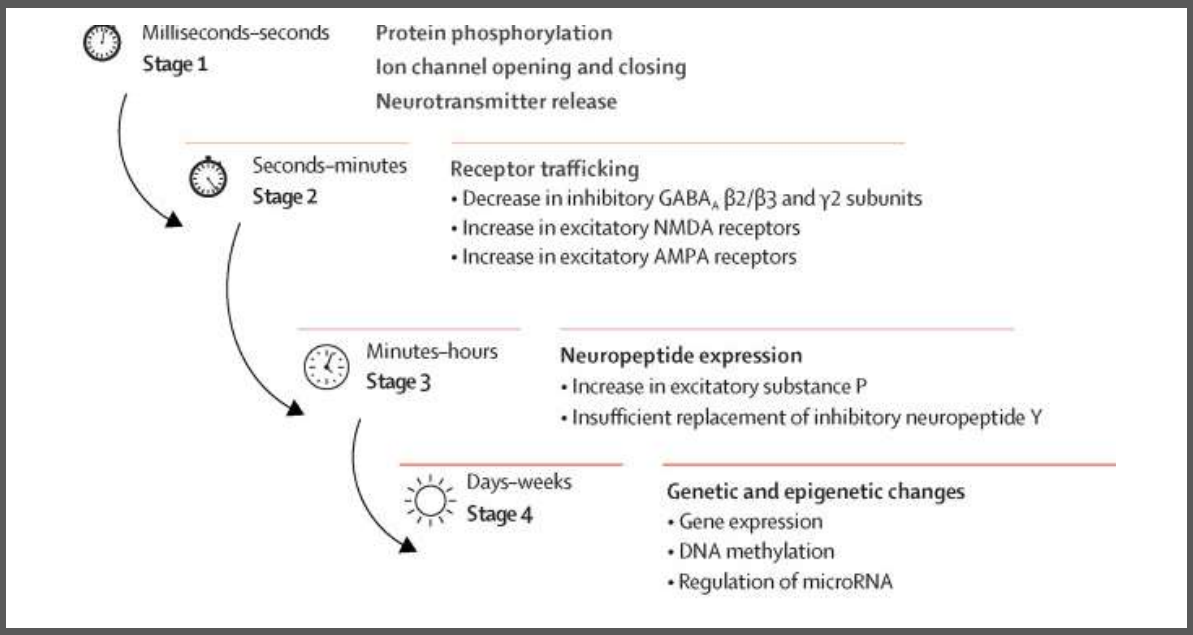
Pathophysiology

The pathophysiology leading to the development of status epilepticus

- SE as a 'seizure that never ends'
- Sustaining epileptic condition, despite the withdrawal of the epileptigenic stimulus
- A complex interaction between mechanisms that operate at both "a cellular and network level"
- Hypersynchronous & hyperexcitability
  - Ion dynamics, neuroenergetics, receptor expression
  - Positive feedback loops that can serve to propagate seizure activity



Burman RJ, et al. Eur J Epilepsy 2020

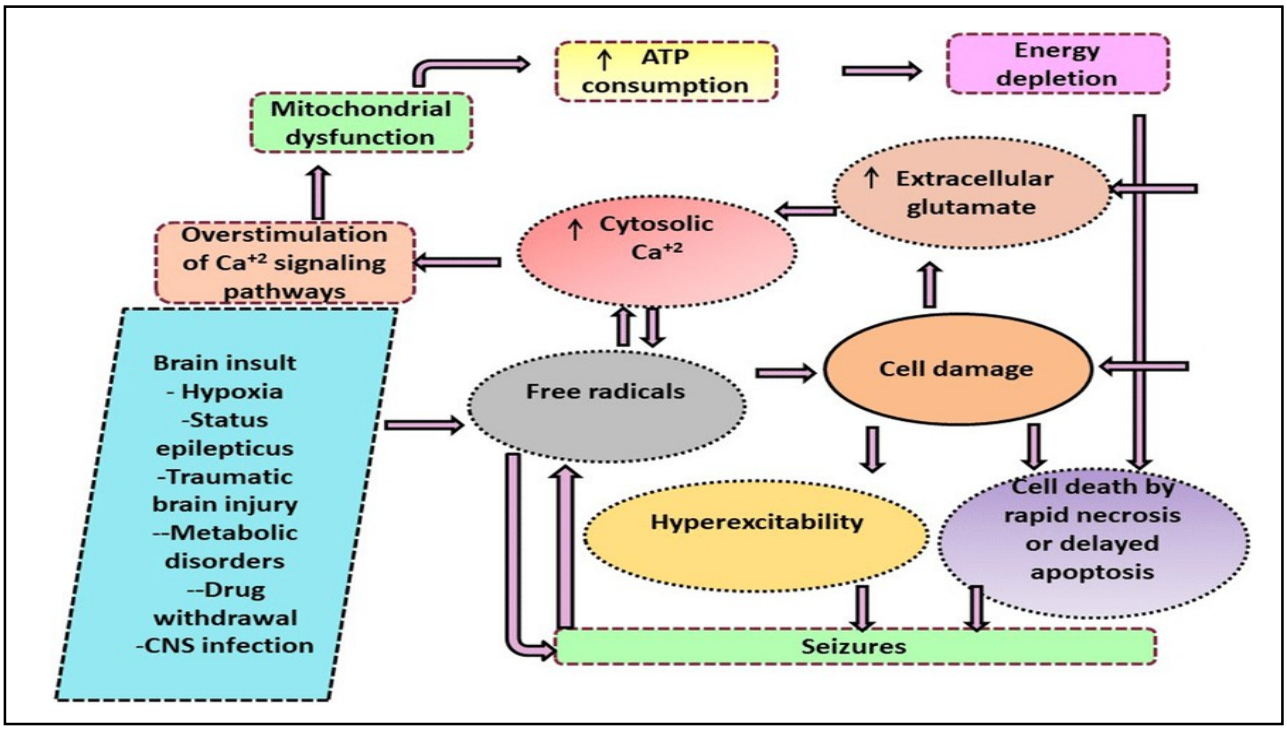


Besjemann JP, et al. The Lancet Neurology 2015.

Pathophysiology of SE

- Neurotransmitter and modulators release (msec to sec)
- Receptor trafficking: GABA and glutamate receptor (Sec – min)
- Maladaptive change in neuropeptide expression (min - hour)
- Neuronal injury/death and epileptogenesis (hour - day)

CG **Wasterlain, et al. Epilepsia 2008**



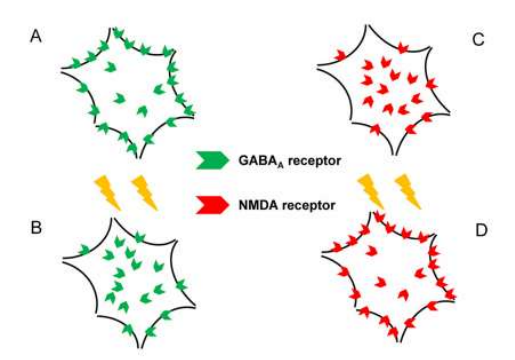
Neurotransmitter and modulators release

- First milliseconds to seconds
- Set the stage for a potentially prolonged seizure
- Release of neurotransmitters and modulators: massive GABA release
- The opening and closing of ion channels
- Receptor phosphorylation and desensitization

CG Wasterlain, et al. Epilepsia 2008

Receptor trafficking: GABA and glutamate receptor

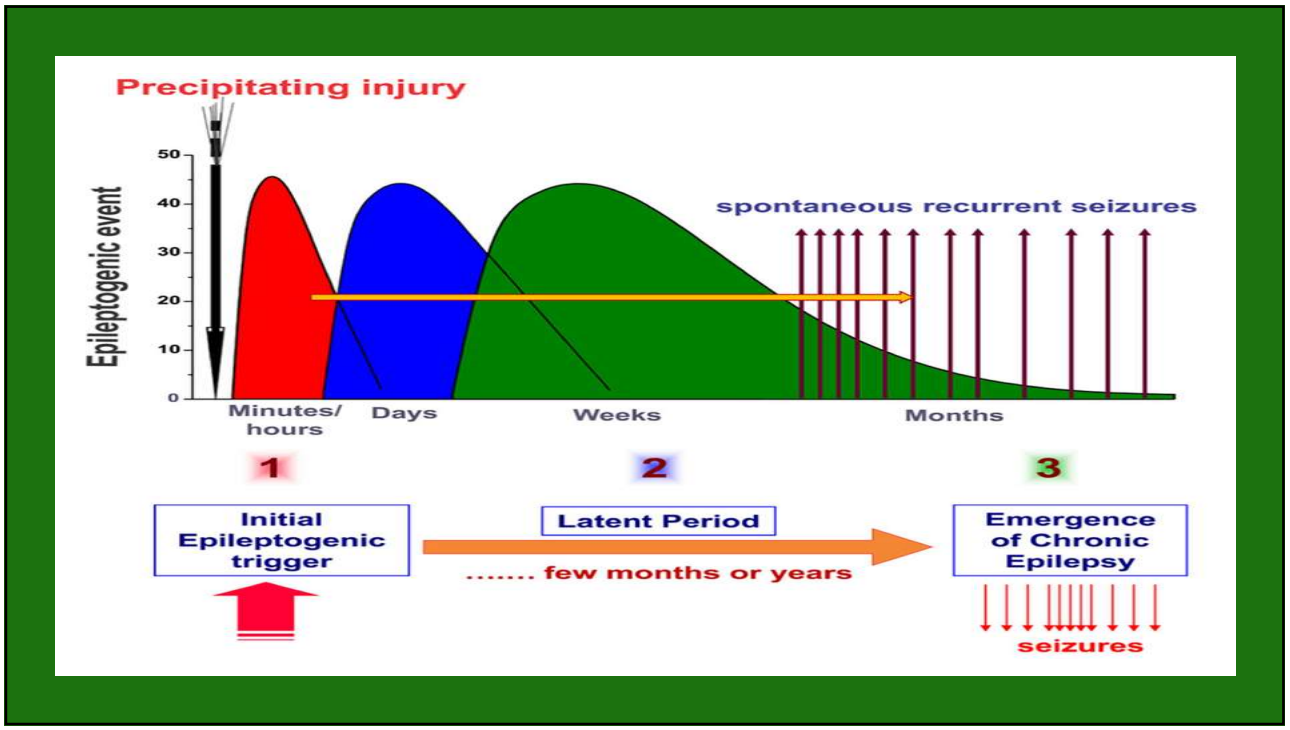
- Seconds to minutes
- Receptor relocation
  - Internalization (from synaptic membrane to interior of cell) → inactive GABA-A
  - Expression (from storage sites to synaptic membrane) → active Glutamate - NMDA
- This process enhance brain activity (promote SSSE) and explain pharmacoresistance

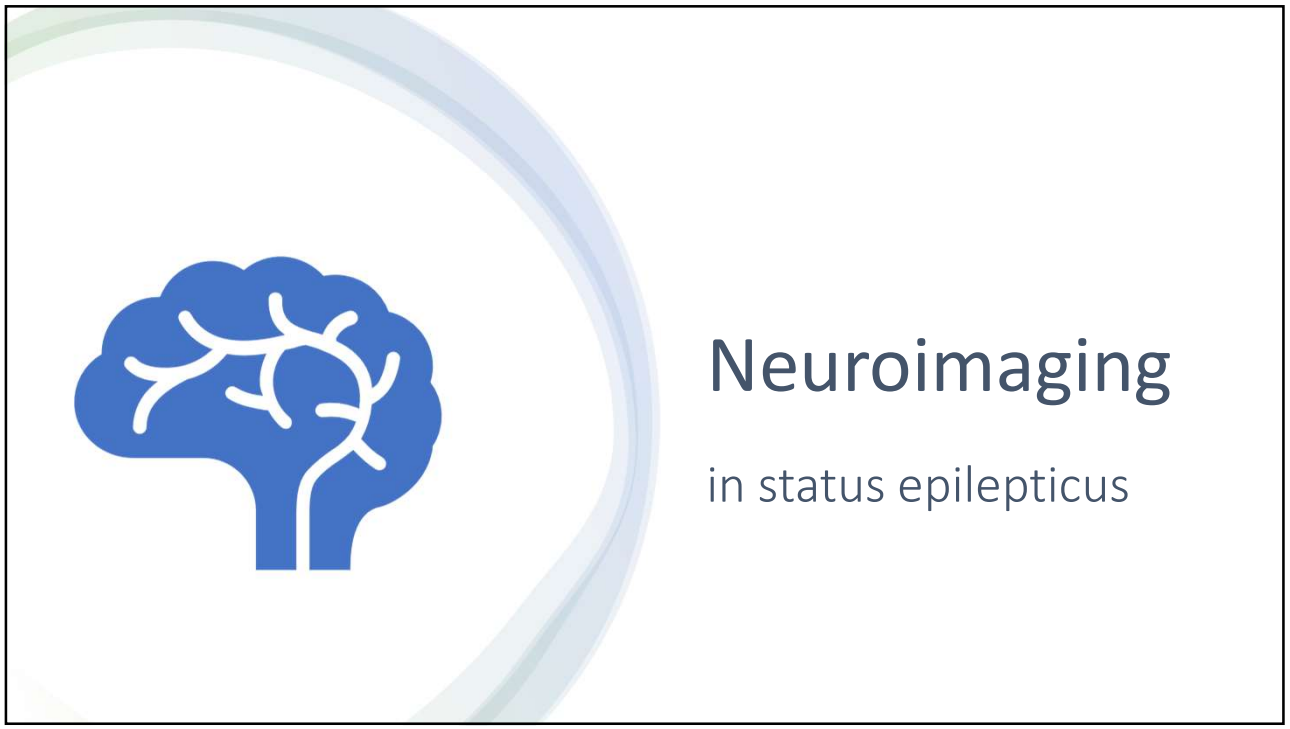


CG **Wasterlain, et al. Epilepsia 2008**

Pathophysiology of epileptogenesis

- Epileptogenesis
  - The process whereby a normal brain becomes progressively epileptic because of precipitating injury or risk factors such as TBI, stroke, brain infections, or prolonged seizures
  - An interaction of acute and delayed anatomic, molecular, and physiological events that are both complex and multifaceted
- Epilepsy development: unclear: ? 3 stages
  - (1) the initial injury (epileptogenic event)
    - Inflammation, oxidation, apoptosis, neurogenesis, and synaptic plasticity
  - (2) the latent period (silent period with no seizure activity)
    - Structural and functional changes in neurons
  - (3) chronic period with spontaneous recurrent seizures
    - Abnormal hyperexcitability and spontaneous seizures


Precipitating injury
Epileptogenic event
50
40
30
20
10
0
spontaneous recurrent seizures
Minutes/ hours
Days
Weeks
Months
1
2
3
Initial Epileptogenic trigger
Latent Period
..... few months or years
Emergence of Chronic Epilepsy
seizures


Neuroimaging
in status epilepticus

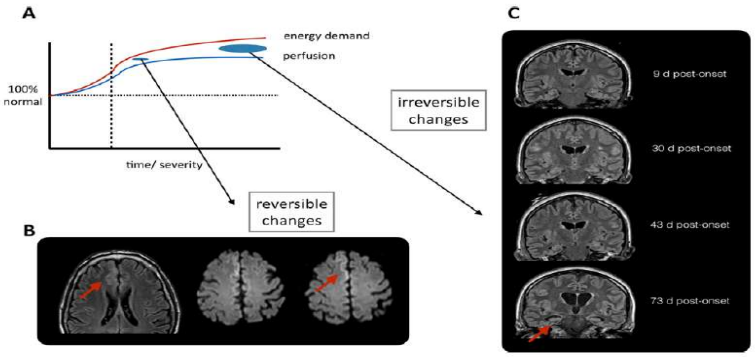


FIGURE 1 A, Conceptual cartoon illustrating a possible relation between energy supply, energy demand, and observed periictal imaging changes. After the initial coupling between energy demand and perfusion (dotted line), a mismatch between the 2 can be observed. Depending on the duration of the status and of the increased energy demand, reversible or irreversible tissue changes can develop (B and C, respectively). To meet the increased glucose and oxygen demand of the epileptogenic cortex (network), ictal hyperperfusion first appears, secondarily vasogenic and cytotoxic edema (changes in diffusion-weighted sequences) follows, resulting from uncoupling between metabolism and circulation. B, Axial fluid-attenuated inversion recovery (FLAIR, left) showing signal hyperintensity involving the right frontomesial cortex, with correspondent increased signal on diffusion-weighted image (DWI, right). These reversible abnormalities were observed on the MRI acquired the day after the end of an NCSE of 6 hour duration in a 64-year-old woman. Follow-up MRI was normal (not shown). C, Coronal FLAIR sequences showing progressive diffuse atrophic evolution and development of bilateral hippocampal sclerosis in a long-lasting super-refractory status epilepticus in a 36-year-old woman. d, days from status onset

Meletti S, et al. Epilepsia 2017

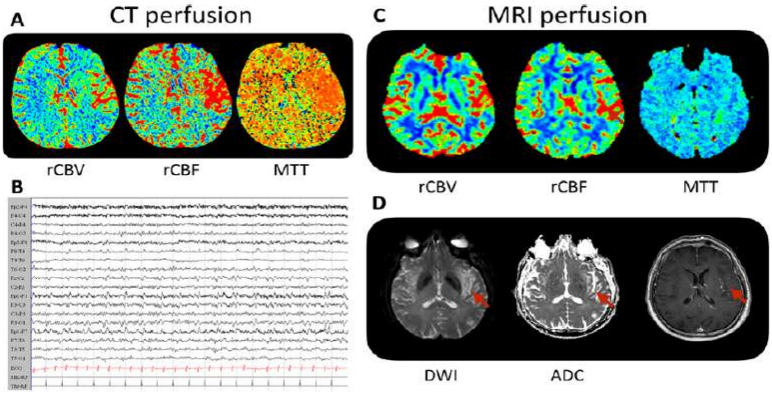


FIGURE 2 Multimodal imaging in a 65-year-old man presenting to the emergency department with acute aphasia and right hemiparesis. A, Ictal computed tomography perfusion (CTP) showing increased relative cerebral blood volume (rCBV), increased relative cerebral blood flow (rCBF), and decreased mean transit time (MTT) over the left frontoinsular region. B, The corresponding EEG (1 h form CTP) shows left frontocentral periodic epileptic discharges. The patients also presented brief focal faciobrachial dystonic seizures (not shown). C, Magnetic resonance perfusion (MRP) shows increased left insular (arrow) rCBV, rCBF, with conserved MTT values. D, Axial diffusion-weighted image (DWI) with apparent diffusion coefficient (ADC) shows signal hyperintensity involving bilaterally the insular region, external capsule, and claustrum, more pronounced on the left side. On the right it is subtle contrast enhancement of the left insular cortex, demonstrating a breakdown of the blood-brain barrier

Meletti S, et al. Epilepsia 2017

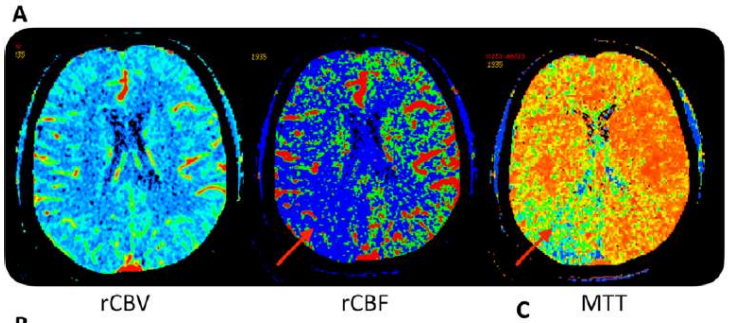


FIGURE 3 Postictal hypoperfusion. A 77-year-old woman presented to the emergency department for acute confusional state and left hemiparesis. A, Computer tomography perfusion shows, on the right hemisphere, normal rCBV, diffuse reduction of rCBF, and increased MTT in the parietal region. B, The EEG shows diffuse right hemisphere slowing. C, The FLAIR sequence on the MRI performed 24 h after the admission shows mild temporoparietal right cortical signal hyperintensity

Meletti S, et al. Epilepsia 2017

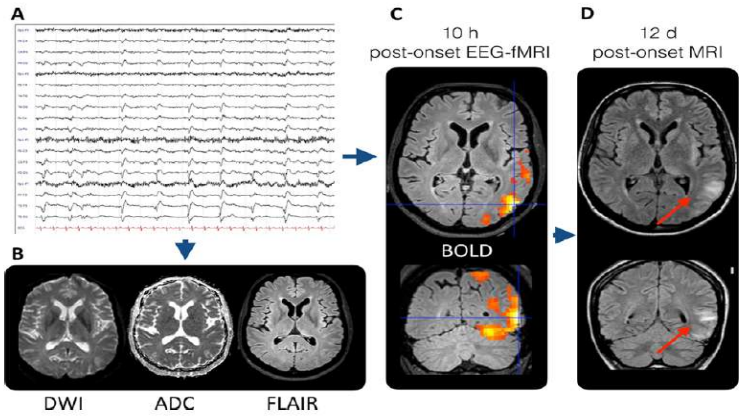
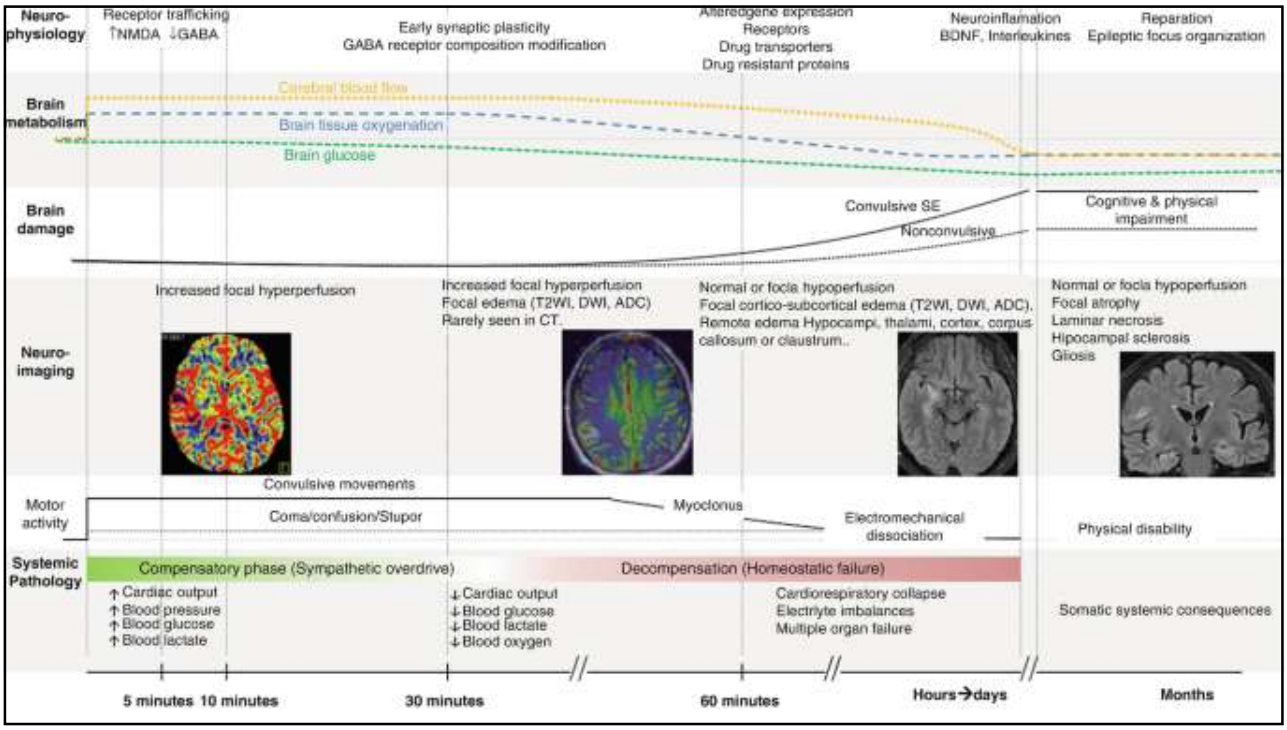


FIGURE 4 Multimodal imaging in a 44-year-old woman with cryptogenic temporal lobe epilepsy. The patient presented during the night to the emergency unit with aphasic status epilepticus. A, EEG performed the morning after emergency ward presentation showing lateralized periodic discharges (LPDs) over the left temporo-occipital region. B, MRI acquired immediately after the EEG in A showed no abnormalities on FLAIR, DWI, and ADC images. C, The results of EEG co-registered with functional MRI (EEG-fMRI) the same day of A and B are shown. The hemodynamic changes related to LPDs, which were the event of interest in the fMRI analysis, show an increased blood oxygen level-dependant (BOLD) signal in the left temporoparieto-occipital cortex ($P < .05$ family wise error corrected). D, Follow-up MRI acquired 12 days post-SE (normal EEG, not shown) shows irreversible hyperintense corticosubcortical lesions that were located exactly in the regions previously involved by BOLD signal changes during continuous LPDs on EEG

Meletti S, et al. Epilepsia 2017



Consequences of status epilepticus

Esp. delayed SE termination

Complications of SE

In animal models

- Convulsive SE causes extensive neuronal necrosis.
- Nonconvulsive SE also leads to widespread neuronal necrosis in vulnerable regions, although lesions develop more slowly than convulsive SE or anoxia
- Lesions induced by SE may be epileptogenic by leading to misdirected regeneration

Human status epilepticus (SE)

- Associated with cognitive problems
- Widespread neuronal necrosis in hippocampus and other brain regions

Wasterlain C, et al. Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 1993

Major complications of status epilepticus

Mortality rates

- 15% to 20% in adults
- 3% to 15% in children

Acute complications

- Hyperthermia
- Pulmonary edema
- Cardiac arrhythmias, cardiovascular collapse

Long-term complications

- Epilepsy (20% to 40%)
- Encephalopathy (6% to 15%)
- Focal neurologic deficits (9% to 11%)

Fountain NB. Epilepsia 2000

Complications of RSE and SRSE

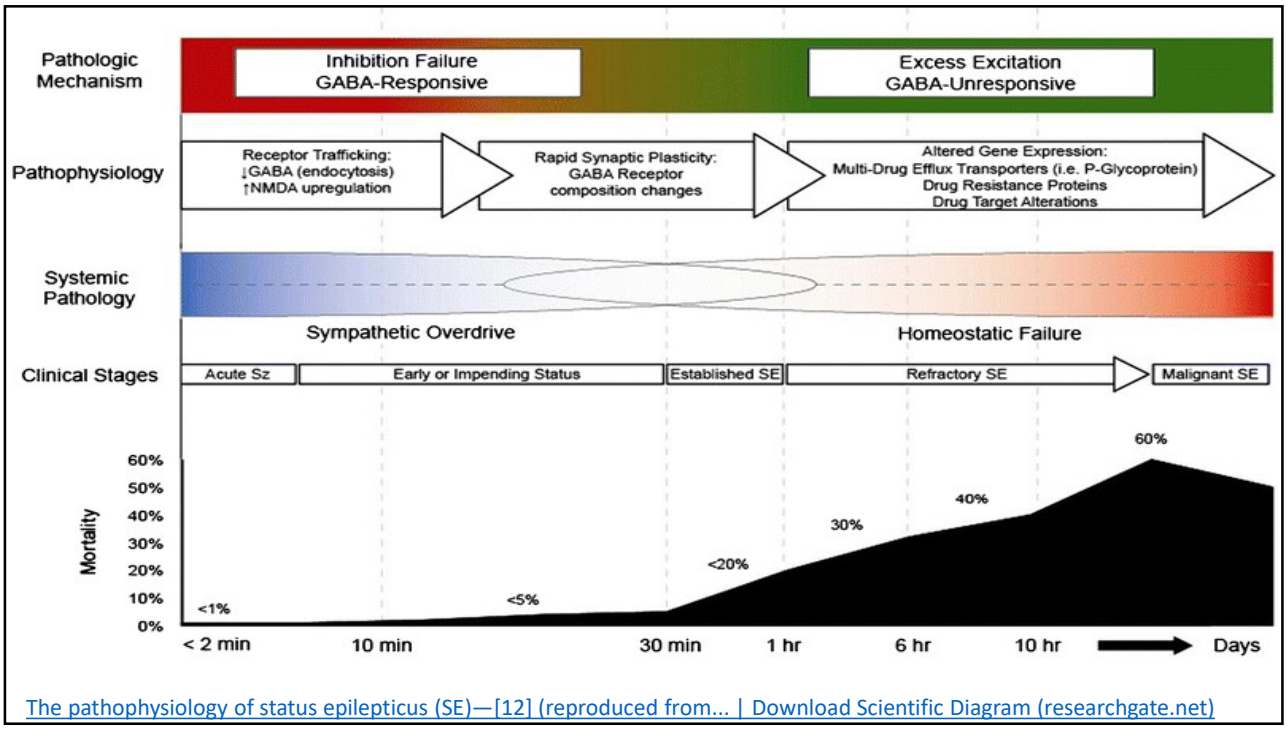
RSE

- High mortality: The short-term mortality of RSE is 16%-39% approximately 3 times higher compared to non-RSE
- A 30–40% mortality → serious neurological emergencies

SRSE

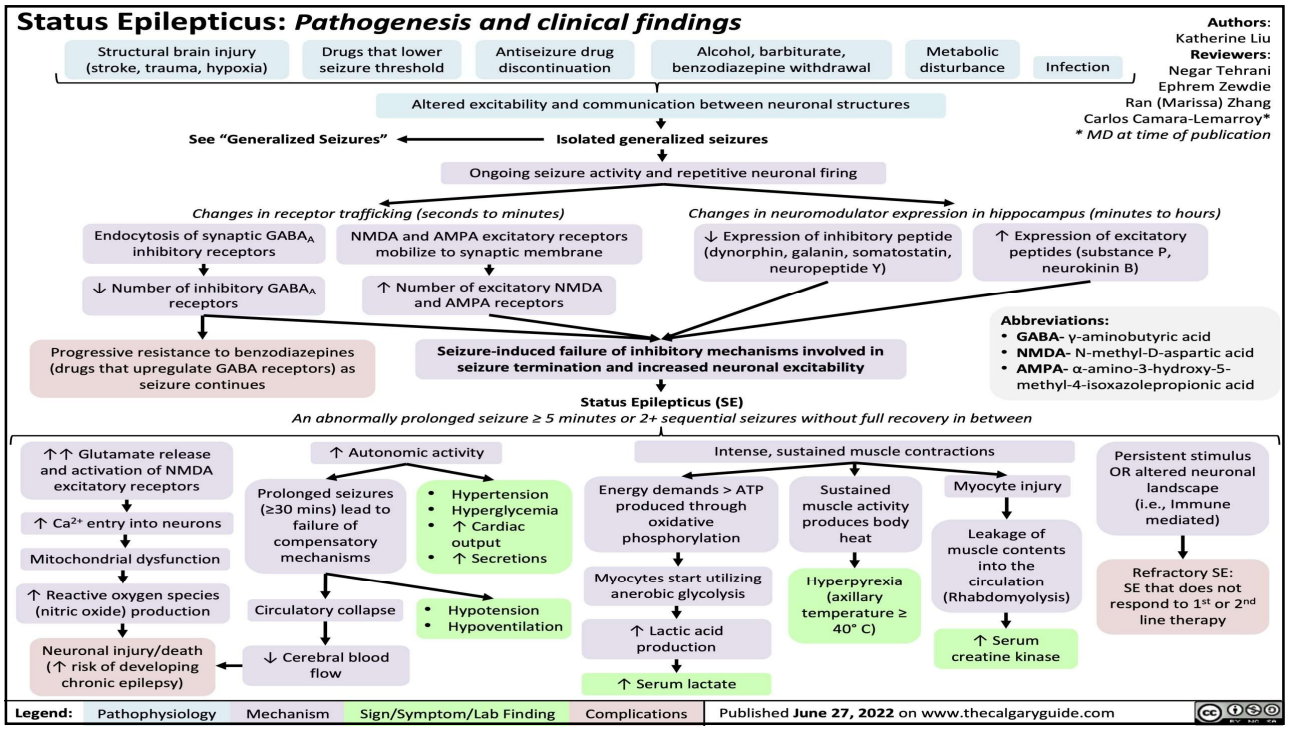
- Short-term mortality of 12%-27%, Long-term disability and epilepsy
- A substantial risk for poor neurological outcome with mortality of 35%

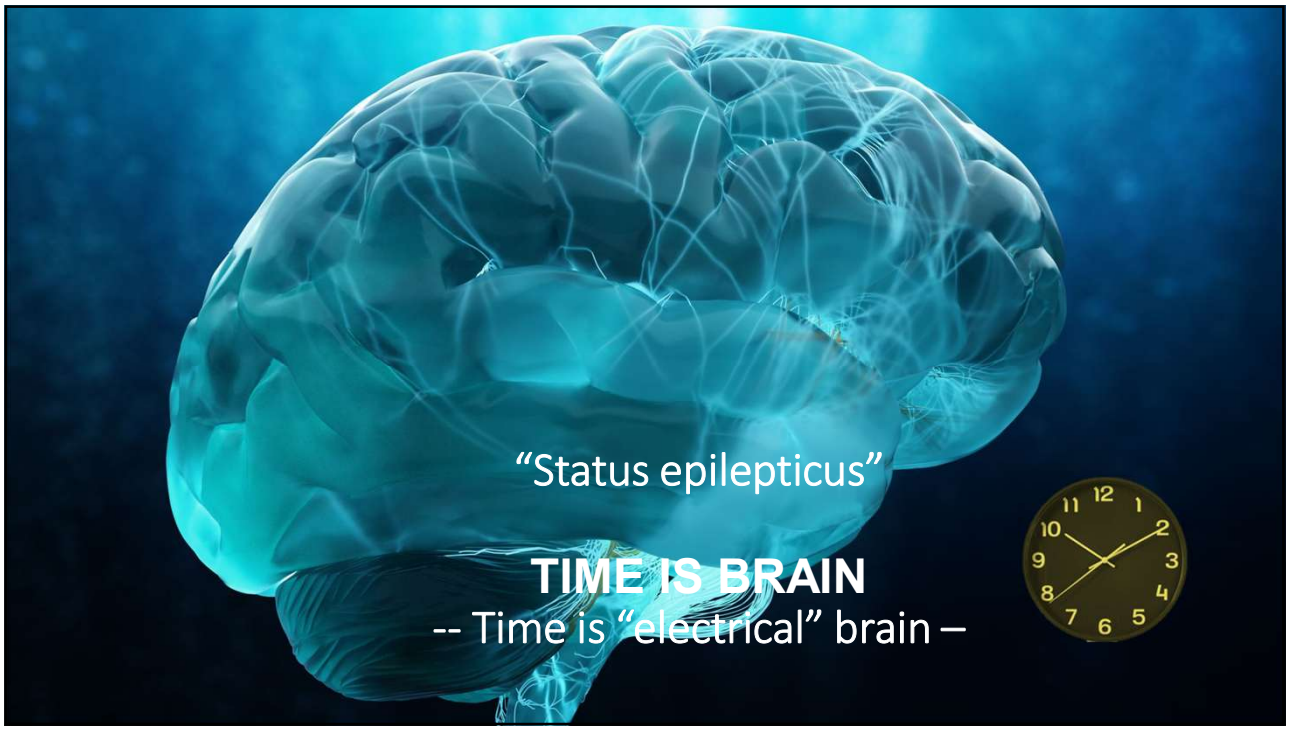
Rossetti AO, et al. Lancet Neurology 2011, Kirmani BF, et al. Aging disease 2021, Ochao JG, et al. Epilepsy Currents 2021



The pathophysiology of status epilepticus (SE)—[12] (reproduced from... | Download Scientific Diagram (researchgate.net)


Summary
Signature


Status Epilepticus: Pathogenesis and clinical findings
Authors: Katherine Liu
Reviewers: Negar Tehrani, Ephrem Zewdie, Ran (Marissa) Zhang, Carlos Camara-Lemarroy*
* MD at time of publication
Structural brain injury (stroke, trauma, hypoxia)
Drugs that lower seizure threshold
Antiseizure drug discontinuation
Alcohol, barbiturate, benzodiazepine withdrawal
Metabolic disturbance
Infection
Altered excitability and communication between neuronal structures
See "Generalized Seizures"
Isolated generalized seizures
Ongoing seizure activity and repetitive neuronal firing
Changes in receptor trafficking (seconds to minutes)
Changes in neuromodulator expression in hippocampus (minutes to hours)
Endocytosis of synaptic GABAA inhibitory receptors
↓ Number of inhibitory GABAA receptors
NMDA and AMPA excitatory receptors mobilize to synaptic membrane
↑ Number of excitatory NMDA and AMPA receptors
↓ Expression of inhibitory peptide (dynorphin, galanin, somatostatin, neuropeptide Y)
↑ Expression of excitatory peptides (substance P, neurokinin B)
Progressive resistance to benzodiazepines (drugs that upregulate GABA receptors) as seizure continues
Seizure-induced failure of inhibitory mechanisms involved in seizure termination and increased neuronal excitability
Abbreviations:
• GABA- γ-aminobutyric acid
• NMDA- N-methyl-D-aspartic acid
• AMPA- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Status Epilepticus (SE)
An abnormally prolonged seizure ≥ 5 minutes or 2+ sequential seizures without full recovery in between
↑↑ Glutamate release and activation of NMDA excitatory receptors
↑ Ca2+ entry into neurons
Mitochondrial dysfunction
↑ Reactive oxygen species (nitric oxide) production
Neuronal injury/death (↑ risk of developing chronic epilepsy)
↑ Autonomic activity
Prolonged seizures (≥30 mins) lead to failure of compensatory mechanisms
• Hypertension
• Hyperglycemia
• ↑ Cardiac output
• ↑ Secretions
Circulatory collapse
↓ Cerebral blood flow
• Hypotension
• Hypoventilation
Intense, sustained muscle contractions
Energy demands > ATP produced through oxidative phosphorylation
Myocytes start utilizing anerobic glycolysis
↑ Lactic acid production
↑ Serum lactate
Sustained muscle activity produces body heat
Hyperpyrexia (axillary temperature ≥ 40° C)
Myocyte injury
Leakage of muscle contents into the circulation (Rhabdomyolysis)
↑ Serum creatine kinase
Persistent stimulus OR altered neuronal landscape (i.e., Immune mediated)
Refractory SE: SE that does not respond to 1st or 2nd line therapy
Legend: Pathophysiology Mechanism Sign/Symptom/Lab Finding Complications
Published June 27, 2022 on www.thecalgaryguide.com


"Status epilepticus"
TIME IS BRAIN
-- Time is "electrical" brain –