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Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS): Disease State Overview

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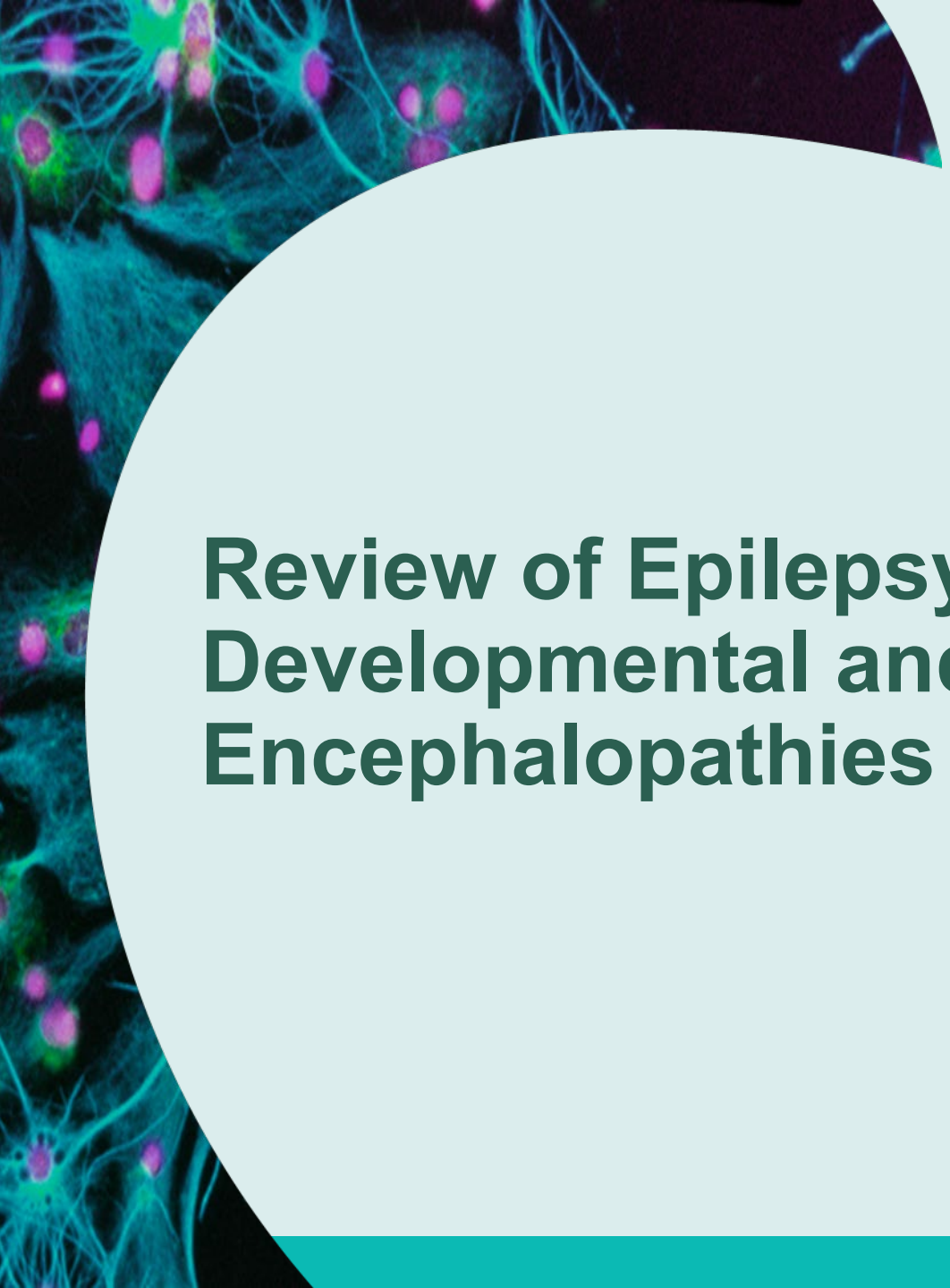


Review of Epilepsy & Developmental and Epileptic Encephalopathies (DEEs)

Epilepsy is a Neurological Disorder Characterized by Unpredictable Seizures

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain that may cause changes in the level of consciousness, movement, behavior, or memory[1,2]

Epilepsy is defined as:

At least two unprovoked seizures occurring greater than 24 hours apart[1]

OR

One unprovoked seizure and a probability of unprovoked seizure recurrence occurring over the next 10 years[1]

Epilepsy occurs on a spectrum with a wide range of presentations, etiologies, and outlooks that can vary from person-to-person[3]

1. Fisher RS, et al. ILAE Official Report: A Practice Clinical Definition of Epilepsy. *Epilepsia*. 2014;55(4):475-82. | 2. Huff JS, Murr N. Seizure. StatPearls. Available online at https://www.ncbi.nlm.nih.gov/books/NBK430765/#_NBK430765_pubdet_. Accessed January 31, 2022. | 3. Epilepsy Foundation. What is Epilepsy. Available online at https://www.epilepsy.com/learn/about-epilepsy-basics/what-epilepsy. Accessed January 31, 2022.

Classification of Epilepsy

Epilepsies are classified by seizure type based on:

Awareness

What is the level of awareness during the seizure?

Location

Where did the seizure begin in the brain?

Other

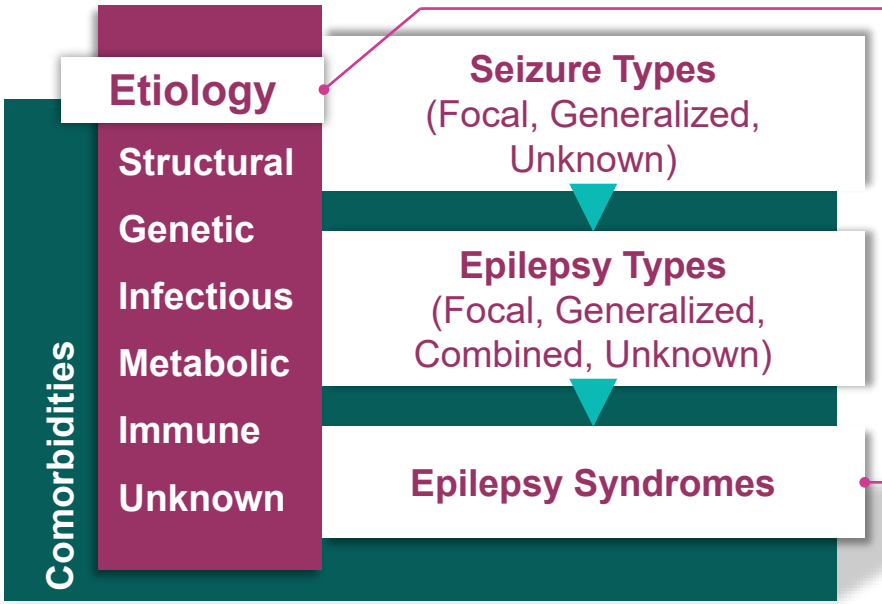
Are there other distinguishing features?

Determining etiology can optimize classification, inform treatment decisions, and aid in syndrome diagnosis

1. Scheffer IE, Berkovic S, Capovilla, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21.

Framework for the Classification of Epilepsies[1]

The ILAE Classification of the Epilepsies is a multilevel system for classifying epilepsy in different clinical environments



Each **etiology** has the potential to affect the expression of epilepsy symptoms in different seizure types, epilepsy types, and epilepsy syndromes

An **epilepsy syndrome** is defined by a group of features that typically occur together, such as:

- Seizure types/triggers
- EEG patterns/imaging features
- Genetic mutations
- Comorbidities
- Age of onset/remission
- Treatment implication

Most identified single gene mutations resulting in epilepsy are ion channel mutations

EEG, electroencephalogram; ILAE, International League Against Epilepsy

1. Scheffer IE, Berkovic S, Capovilla, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21.

Developmental and Epileptic Encephalopathies (DEEs)*

DEEs are severe epilepsy syndromes in which epileptic activity contributes to pronounced cognitive and behavioral impairments or delays[1,2]

Common Features of DEEs[1-3]

- Multiple seizure types
- EEG paroxysmal activity
- Developmental regression or arrest at seizure onset
- Pharmacoresistance
- Behavioral disturbances
- Progressive psychomotor dysfunction

Many DEEs are **early-onset** (neonatal, infancy, childhood) and have a **genetic or acquired etiology**[1]

DEE patients typically have intractable seizures and neurological deficits that can be unremitting, resulting in early death[1]

**It is suggested that the term "developmental and epileptic encephalopathy" be used where appropriate: developmental encephalopathy where there is just developmental impairment without frequent epileptic activity; epileptic encephalopathy where there is no preexisting developmental delay; and developmental and epileptic encephalopathy where both factors play a role.[2]*

EEG, electroencephalogram

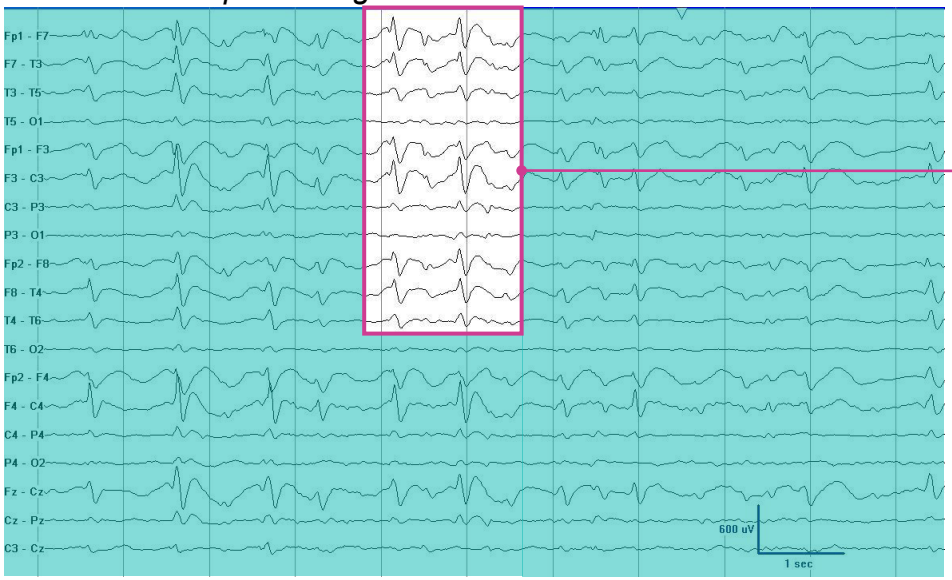
1. Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005. Available at Panayiotopoulos: https://www.ncbi.nlm.nih.gov/books/NBK2611/#ch7.s2 | 2. Scheffer IE, Berkovic S, Capovilla, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21. | 3. Berg, et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. 2010;51(4):676-85.

Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS)

Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS)

EE-CSWS is a rare childhood-onset epilepsy syndrome characterized by an electrical status epilepticus during sleep (ESES) EEG pattern, seizures, and cognitive regression[1]

EEG of child experiencing CSWS



ESES manifests as **diffuse or focal spike and wave discharges** that **appear continuous or nearly continuous** during the non-rapid eye movement (**NREM**) phase of sleep (CSWS)[1,2]

EE-CSWS patients can also experience seizures while awake, which may increase in frequency over time[1]

Image courtesy of The Epilepsy Foundation
EEG, electroencephalogram

1. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021. | 2. Gencpinar P, Dundar NO, Tekgu H. Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) syndrome in children: An electroclinical evaluation according to the EEG patterns. Epilepsy & Behavior. 2016;61:107-11

Patients with EE-CSWS Exhibit Developmental and Cognitive Deficits[1-3]

Over disease progression, EE-CSWS patient experience:[1-3]

Neuropsychiatric Symptoms **+** Global **Regression**

Early signs of EE-CSWS also include:
Developmental delay
Autism-like episodes
Declining behavioral and cognitive skills

Early diagnosis is critical to cognitive development

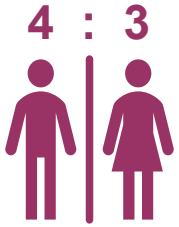
EE-CSWS, epileptic encephalopathy with continuous spike and wave during sleep

1. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed February 12, 2021. | 2. Gencpinar P, Dundar NO, Tekgu H. Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) syndrome in children: An electroclinical evaluation according to the EEG patterns. Epilepsy & Behavior. 2016;61:107-11. | 3. De Giorgis V, et al. Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: A pattern of developmental hindrance. Epilepsy & Behavior. 2017;74:1-9.

EE-CSWS was Designated a Rare Pediatric Disease in 2018 by the FDA

The exact frequency of EE-CSWS is difficult to assess due to differences in inclusion criteria and methods across clinical trials, as well as missed or incorrect diagnoses[1]

Accounts for **~0.2-0.5%** of all childhood epilepsies[2]



Higher incidence among **males**[1]

EE-CSWS has been associated with structural abnormalities of the brain, as well as genetic variants[3]

- The ESES EEG pattern is also observed in epilepsy syndromes including Landau-Kleffner syndrome (LKS) and benign pediatric focal epilepsy (also known as benign childhood epilepsy with centrotemporal spikes or benign Rolandic epilepsy)[1]
  - LKS is an epileptic encephalopathy associated with ESES in which cognitive regression primarily affects language and speech development, rather than global regression[1]

EE-CSWS, epileptic encephalopathy with continuous spike and wave during sleep; ESES, electrical status epilepticus during sleep; FDA, US Food and Drug Administration

1. Sanchez Fernandez I, Chapman KE, Peters JM, et al. Continuous Spikes and Waves during Sleep: Electroclinical Presentation and Suggestions for Management. Epilepsy Res Treat. 2013;2013:583531. | 2 . Nieuwenhuis L, Nicolai J. The pathophysiological mechanisms of cognitive and behavioral disturbances in children with Landau–Kleffner syndrome or epilepsy with continuous spike-and-waves during slow-wave sleep. Seizure. 2006;15(4):249-58. | 3. De Giorgis V, et al. Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: A pattern of developmental hindrance. Epilepsy & Behavior. 2017;74:1-9

EE-CSWS Clinical Features[1-3]

Dormant Stage

- **Ages: Birth to Onset**
- No seizures; EEG generally not performed
- Normal to moderately abnormal baseline development

Prodromal Stage

- **Ages: 2 – 4 years**
- Seizures typically infrequent & mild; EEG pattern of infrequent spikes and waves
- ≥2 seizure types seen in only 20% of patients

Acute Stage

- **Ages: 5 – 12 years**
- Increase in frequency and types of seizures and definitive ESES EEG
- Severe neurocognitive global regression (peaks at age 5-6)

Residual Stage

- **Ages: Puberty**
- Gradual disappearance of seizures and progressive normalization of EEG
- Mild to moderate improvement in cognition; developmental delays often remain

EEG, electroencephalogram; ESES, electrical status epilepticus during sleep

1. Sanchez Fernandez I, Chapman KE, Peters JM, et al. Continuous Spikes and Waves during Sleep: Electroclinical Presentation and Suggestions for Management. Epilepsy Res Treat. 2013;2013:583531. | 2. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021. | 3. De Giorgis V, et al. Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: A pattern of developmental hindrance. Epilepsy & Behavior. 2017;74:1-9.

There are Currently no Guidelines or Approved Treatments for EE-CSWS

Primary treatment goals:[1]

Suppression of EEG Abnormalities +/- **Improved Seizure Control** → **Improved Cognitive Function**

Current treatment consists of traditional ASMs, benzodiazepines, corticosteroids, epilepsy surgery, and other non-pharmacological therapies[3]

Most Common ASMs:
Valproate
Levetiracetam
Ethosuximide

Some AESs such as phenytoin, phenobarbital, and carbamazepine can **worsen seizure control**[3]

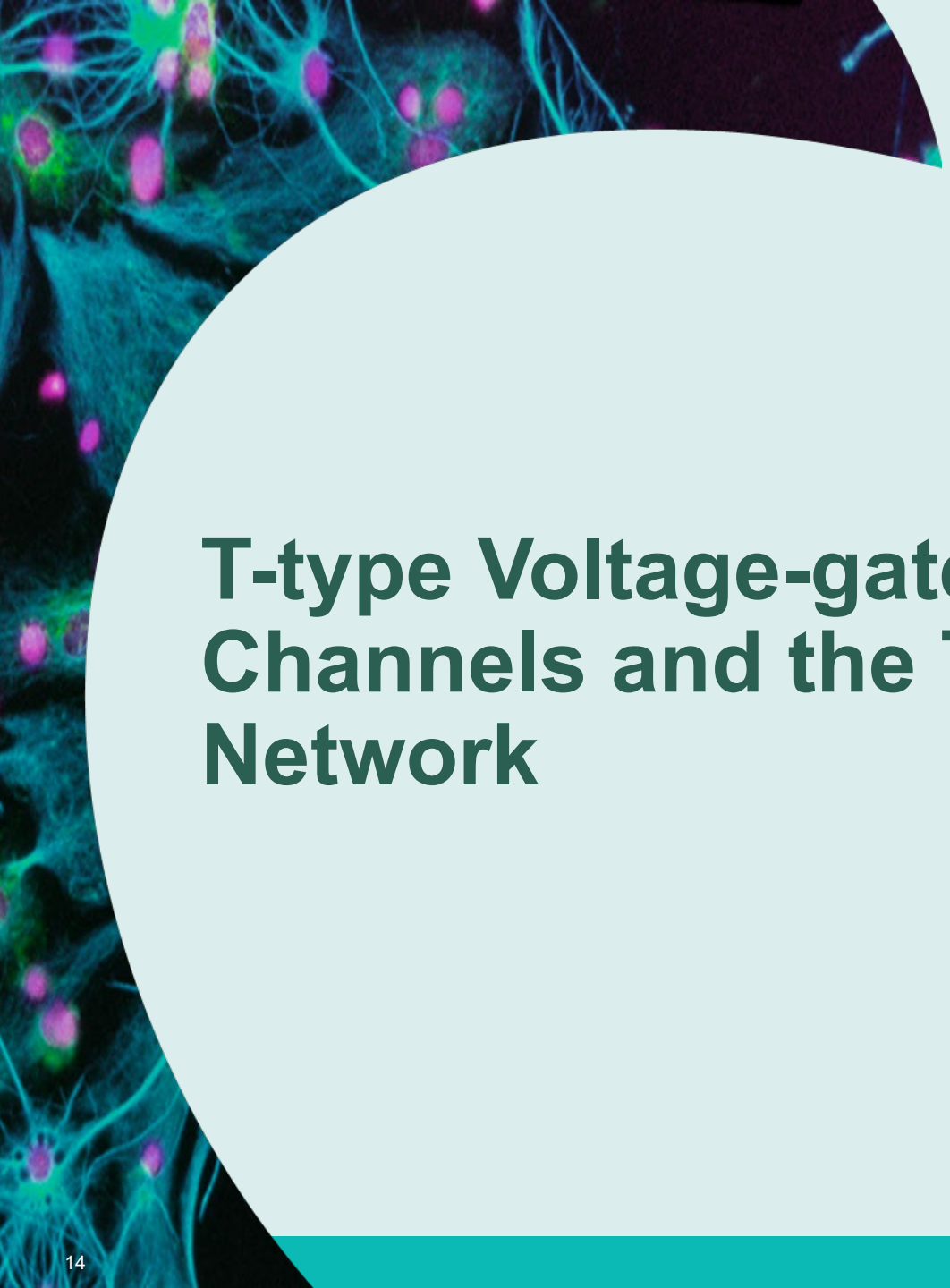
Effects of Analyzed Treatments on Cognition and EEG in Patients with ESES/CSWS[1,2]

Treatment	N	Any Improvement	Cognitive Improvement
Conventional ASMs	310	34%	32%
BZDs	107	59%	45%
Corticosteroids	100	75%	70%
Surgery*	30	93%	83%
Other	38	58%	71%

*Only indicated for a subset of EE-CSWS patients

ASM, anti seizure medication; CSWS, continuous spike and wake during sleep; EEG, electroencephalography; ESES, electrical status epilepticus in sleep; BZD, benzodiazepine

1. Sanchez Fernandez I, Chapman K, Peters JM, et al. Treatment for continuous spikes and waves during sleep (CSWS): Survey on treatment choices in North America. Epilepsia. 2014;55(7):1099-108. | 2. Kotagal P. Current Status of Treatments for Children with Electrical Status in Slow-Wave Sleep (ESES/CSWS). Epilepsy Curr. 2017;17(4):214-16. | 3. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021.



T-type Voltage-gated Calcium Channels and the Thalamocortical Network

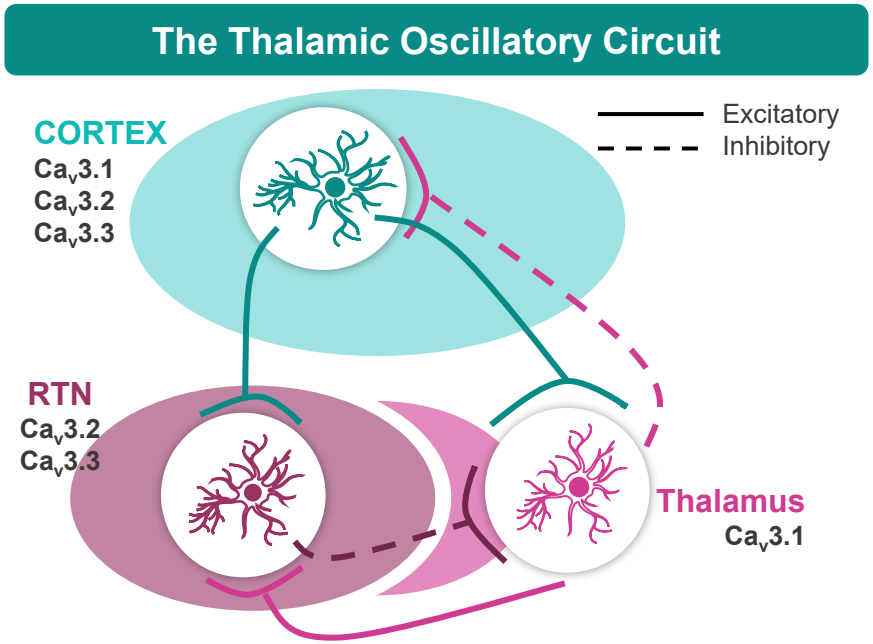
T-type Voltage-gated Calcium ($Ca_v3.x$) Channels and the Thalamocortical Network

Low-voltage activated (LVA) calcium channels mediate low-threshold Ca^{2+} spikes in neurons, leading to burst firing and rhythmic oscillations[1,2]

LVAs are inactive during regular neuronal firing and thus do not contribute to "normal" neuronal activity

T-type Ca^{2+} channels regulate synchronized oscillations within the thalamocortical circuit (including sleep spindles and non-REM sleep)[1]

HVA	$Ca_v1.1$	L-type	
	$Ca_v1.2$		
	$Ca_v1.3$		
	$Ca_v1.4$		
	$Ca_v2.1$	P/Q-type	
	$Ca_v2.2$	N-type	
	$Ca_v2.3$	R-type	
LVA	**$Ca_v3.1$**	**T-type**	
	$Ca_v3.2$		
	$Ca_v3.3$		

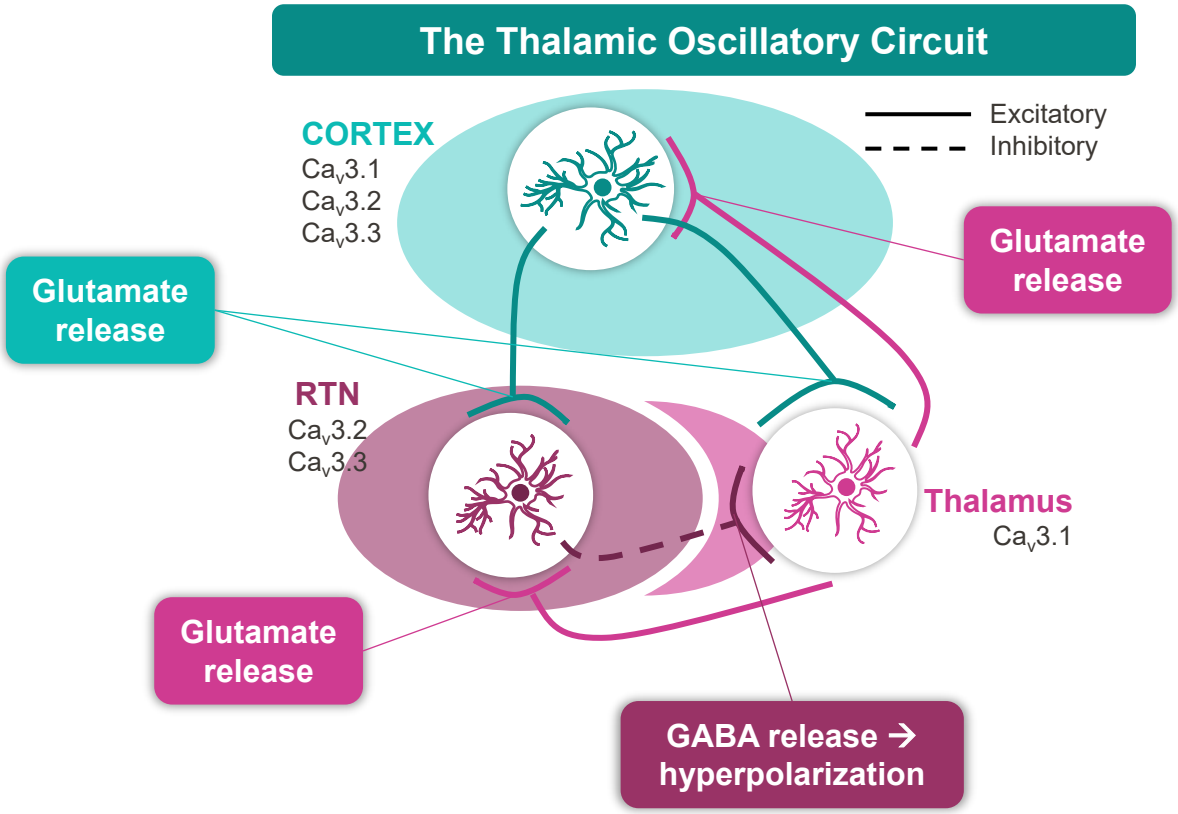


Ca_v, voltage-gated calcium ion channel; EEG, electroencephalogram; ESES electrical status epilepticus during sleep; RTN, reticular thalamic neurons

1. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021. | 2. Chen Y, Parker WD, Wang K. The role of T-type calcium channel genes in absence seizures. Front. Neurol. 2014;5:45.

T-type Voltage-gated Calcium ($Ca_v3.x$) Channels and the Thalamocortical Network

De-inactivation of T-type channels in the thalamocortical network leads to the generation of rebound burst of action potentials



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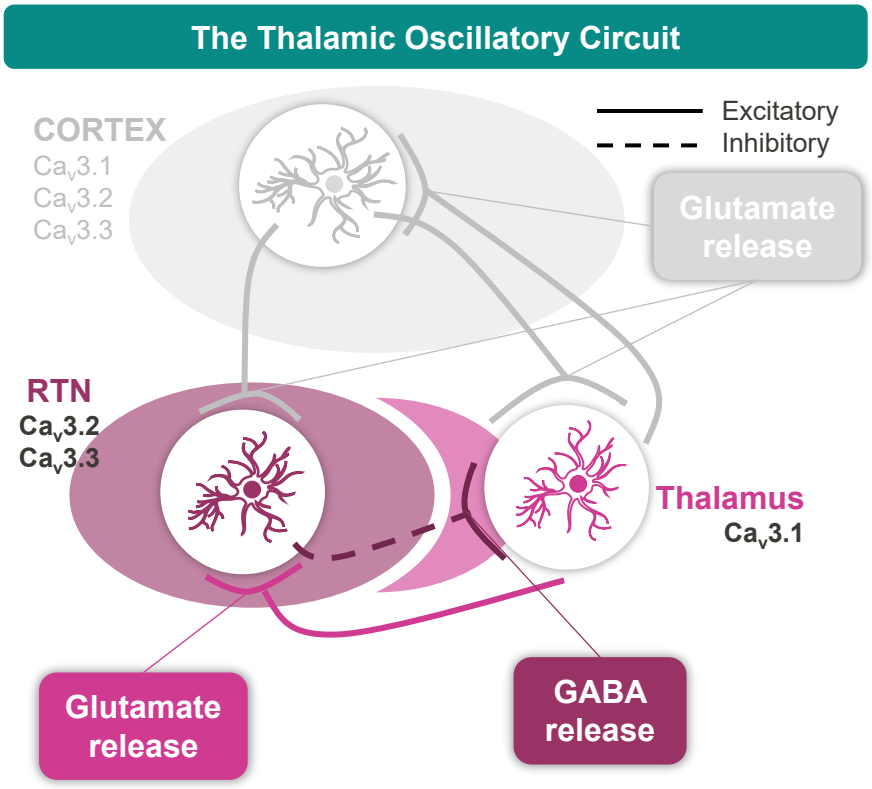
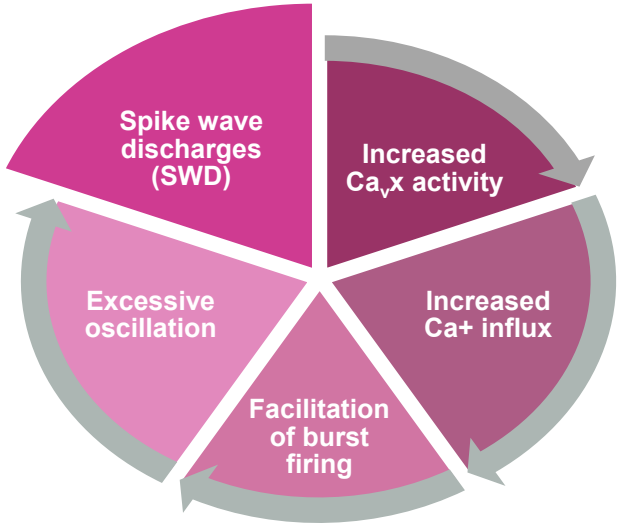
ESES EEG is Correlated with Abnormal Thalamic Oscillatory Circuit Activity[1]

ESES is due to probable interplay between inhibitory GABAergic reticular thalamic neurons and excitatory glutaminergic dorsal thalamic neurons[1]





Increased activity in $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ facilitate excessive oscillation in the thalamocortical loop and is associated with spike wave discharges (SWD)[1]

Ca_v, voltage-gated calcium ion channel; EEG, electroencephalogram; ESES electrical status epilepticus during sleep; RTN, reticular thalamic neurons

1. Fogerson PM, et al. Tapping the brakes: cellular and synaptic mechanisms that regulate thalamic oscillations. *Neuron*. 2016;92(4):687-704.