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Thalamocortical circuits in generalized epilepsy: Pathophysiologic mechanisms and therapeutic targets

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Abstract

Generalized epilepsy affects 24 million people globally; at least 25% of cases remain medically refractory. The thalamus, with widespread connections throughout the brain, plays a critical role in generalized epilepsy. The intrinsic properties of thalamic neurons and the synaptic connections between populations of neurons in the nucleus reticularis thalami and thalamocortical relay nuclei help generate different firing patterns that influence brain states. In particular, transitions from tonic firing to highly synchronized burst firing mode in thalamic neurons can cause seizures that rapidly generalize and cause altered awareness and unconsciousness. Here, we review the most recent advances in our understanding of how thalamic activity is regulated and discuss the gaps in our understanding of the mechanisms of generalized epilepsy syndromes. Elucidating the role of the thalamus in generalized epilepsy syndromes may lead to new opportunities to better treat pharmaco-resistant generalized epilepsy by thalamic modulation and dietary therapy.

Keywords

Absence epilepsy; Burst firing; Generalized spike-and-wave discharge; Oscillation; Thalamus; Genetic generalized epilepsy; Idiopathic generalized epilepsy

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None. The authors have no competing interests to declare.

1. Introduction

Epilepsy comprises a broad category of diseases occurring across the lifespan, united by a common tendency toward unprovoked seizures (Fisher et al., 2017). Generalized epilepsy disorders affect 24 million individuals worldwide (GBDN Collaborators, 2019). Unlike focal epilepsy, which remains localized to specific parts of the brain, generalized epilepsy involves the whole brain. The thalamus is thought to be a key contributor to generalized epilepsy because it has widespread connections to the cortex and other brain regions.

Most, if not all, generalized epilepsy syndromes have a genetic or presumed genetic etiology. Thus, the latest ILAE Task Force classified these disorders as genetic generalized epilepsies (GGEs). GGE is characterized by generalized seizure semiologies (myoclonic, absence, myoclonic-tonic-clonic, and/or generalized tonic-clonic) and generalized discharges at 2.5–5.5 Hz on electrographic recordings outside of seizures (Hirsch et al., 2022). GGE includes the defined clinical syndromes known as idiopathic generalized epilepsies (IGEs); some developmental epileptic encephalopathies (DEEs) also meet the criteria of GGE (Hirsch et al., 2022; Wirrell et al., 2022). IGEs and DEEs differ in etiology—largely unknown genetic factors in IGE vs. known causal mutations for many DEEs—and in clinical presentation—age of onset, comorbidities, and response to treatment (Fig. 1). In addition, a number of IGEs have been modeled in animals, whereas many DEEs lack validated models. Therefore, much of our review summarizes work on IGEs, as animal models of IGEs have established the foundation for our understanding of intrathalamic circuits and long-range projections between the thalamus and other structures in generalized epilepsy. Nevertheless, we also draw parallels with generalized DEEs, as the presence of generalized seizure semiologies in DEEs suggests there may be overlap in pathogenic mechanisms with IGEs.

The aim of this review is to summarize our current knowledge about mechanisms of GGEs and to identify remaining gaps in our understanding of pathogenesis and potential treatment targets. First, we provide an overview of the epidemiology and clinical features of GGEs, contrasting IGEs and DEEs (Fig. 1). Then, we summarize the functional neuroanatomy of intrathalamic and thalamo-cortico-thalamic circuits and their modulation by local metabolic conditions, inputs from other brain regions, and systemic factors, highlighting evidence implicating these pathways in GGE. We also report recent preclinical work on thalamocortical mechanisms in DEEs, which will be important in identifying treatment targets for syndromes that currently lack highly effective medical therapies. Finally, we discuss unresolved questions in the field relevant to the pathogenesis of GGEs and emerging treatment approaches targeting the thalamus.

2. Key features of idiopathic generalized epilepsies (IGEs)

There are four key IGE syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures alone. These syndromes differ in their age of onset, time course, prognosis, and major seizure types. Despite this heterogeneity, pharmacologic treatments largely overlap, including ethosuximide for absence seizures and lamotrigine, valproic acid, or levetiracetam for convulsive (i.e.,

generalized tonic-clonic) seizures (Beydoun and D'Souza, 2012; Mastroianni et al., 2021). However, a large portion of IGEs are refractory to these approaches and require better treatments or new drug targets. Below we review the common clinical features and pathophysiologic mechanisms of these four IGE syndromes, current drug targets, and the unresolved gaps that need to be addressed to generate better treatments.

2.1. Childhood absence epilepsy

2.1.1. Epidemiology—Childhood absence epilepsy (CAE) occurs in 6.3–8.0 children per 100,000 and is more common in girls (60–75% of cases) than in boys (ILAE, 1989; Wirrell et al., 1996). CAE accounts for approximately 18% of epilepsy in school-aged children, with onset typically at 4–10 years of age (Blom et al., 1978; Cavazzuti, 1980; Olsson, 1988; ILAE, 1989; Loiseau et al., 1990; Wirrell et al., 1996; Grosso et al., 2005; Valentin et al., 2007; Ma et al., 2011; Hirsch et al., 2022).

2.1.2. Features and natural history—CAE clinical features include daily typical absence seizures associated with 2.5–4-Hz generalized spike-and-wave discharges (SWDs), which can be reliably provoked by hyperventilation (Salvati and Beenhakker, 2019), and an interictal (between seizures) generalized spike-and-wave pattern, often occurring during drowsiness and sleep. Typical absence seizures are characterized by abrupt onset and loss of awareness lasting 3–20 seconds, followed by an instant return to normal activity with possible confusion (Panayiotopoulos et al., 1989b; Wirrell et al., 1996; Sadleir et al., 2006; Sadleir et al., 2009; Kessler et al., 2017; Seneviratne et al., 2017; Elmali et al., 2020). The seizures are accompanied by inert facial expression, staring, behavioral arrest (interruption of activity), and sometimes manual automatisms and eye involvement. Incontinence and loss of postural control are rare (Kessler et al., 2017; Elmali et al., 2020). Antecedent febrile seizures occur in 10–15% of children with CAE (Livingston et al., 1965; Dieterich et al., 1985; Marini et al., 2003). Generalized tonic-clonic seizures may occur later during adolescence, and myoclonic seizures, by definition, do not occur in CAE patients (Wirrell et al., 1996; Ma et al., 2011; Elmali et al., 2020).

Children with CAE show typical development; however, subtle learning difficulties and attention deficit hyperactivity disorder (ADHD) might be present, with an increased risk for depression and anxiety (Wirrell et al., 1997; Austin et al., 2001; Hermann et al., 2007; Caplan et al., 2008; Shinnar et al., 2017; Abarrategui et al., 2018). CAE is usually drug-responsive (Table 1); first-line agents for treatment are ethosuximide, valproic acid, and lamotrigine. Sixty percent of patients achieve spontaneous remission in early adolescence. The remainder continue to require treatment or develop other generalized epilepsy syndromes; in one longitudinal study, 7% required medication after 12–17 years of follow-up (Wirrell et al., 1996; Trinka et al., 2004; Grosso et al., 2005; Valentin et al., 2007; Callenbach et al., 2009; Morse et al., 2019). Why remission occurs in some patients but not others is not well understood.

2.2. Juvenile absence epilepsy

2.2.1. Epidemiology—Juvenile absence epilepsy (JAE) is less common than CAE, accounting for 2.4–3.1% of child and adolescent epilepsy, with onset typically at 9–13 years of age (Berg et al., 1999; Jallon and Latour, 2005; Wirrell et al., 2011).

2.2.2. Features and natural history—JAE clinical features include both absence seizures, with ≥3–Hz generalized SWDs, and generalized tonic-clonic seizures. A history of febrile seizures is noted in 6–33% of patients (Marini et al., 2004; Asadi-Pooya et al., 2013; Asadi-Pooya and Homayoun, 2020). JAE has fewer (less than daily) absence seizures, and seizures are associated with less loss of awareness than in CAE; seizures are also provoked by drowsiness. Seizure duration in JAE is 5–30 s, during which patients can usually respond to commands but cannot perform complex tasks (Trinka et al., 2004; Beghi et al., 2006). Similar to CAE, absence seizures in JAE are accompanied by an unreactive facial expression and motor automatisms. With seizure offset, EEG activity immediately returns to normal (Beghi et al., 2006; Elmali et al., 2020). Absence status epilepticus, generalized tonic-clonic seizures, and myoclonic seizures occur in 20%, >90%, and 0% of patients, respectively (Agathonikou et al., 1998; Trinka et al., 2004).

Children with JAE develop without major cognitive impairment; however, learning problems, ADHD, depression, and anxiety are prominent comorbidities (Marini et al., 2004; Henkin et al., 2005; Prassouli et al., 2007; Asadi-Pooya et al., 2013; Abarrategui et al., 2018; Asadi-Pooya and Homayoun, 2020). JAE is usually drug-responsive, though some patients require lifelong treatment (Trinka et al., 2004; Table 1). Ethosuximide as a monotherapy is not recommended due to high likelihood of generalized tonic-clonic seizures for which ethosuximide is ineffective; rather, broad-spectrum antiseizure medications for generalized epilepsies should be used (Trinka et al., 2004; Vorderwülbecke et al., 2017; Healy et al., 2018; Hirsch et al., 2022).

2.3. Juvenile myoclonic epilepsy

2.3.1. Epidemiology—Juvenile myoclonic epilepsy (JME) is common, with a prevalence of 1–3 per 10,000 people, accounting for 9.3% of all epilepsies (Juul-Jensen and Foldspang, 1983; Syvertsen et al., 2015; Syvertsen et al., 2017). The typical age at onset is 10–24 years, females are represented slightly more than males, and 5–15% of cases evolve from CAE (Juul-Jensen and Foldspang, 1983; Wirrell et al., 1996; Syvertsen et al., 2015; Syvertsen et al., 2017).

2.3.2. Features and natural history—JME clinical features include myoclonic seizures, usually occurring within the first hour of awakening. Seizures can be triggered by sleep deprivation (Hirsch et al., 2022). Electroencephalography features 3–3.5-Hz interictal spike-and-wave and polyspike-and-wave signatures (Elmali et al., 2020). Generalized tonic-clonic seizures (>90% of patients) are common, and febrile seizures occur in 4–5% of patients (Jain et al., 1998). In one third of patients, absence seizures occur, less than daily, with subtle impairment to awareness (Panayiotopoulos et al., 1989a; Yacubian, 2017).

Patients with JME develop typically, and intellectual disability is rare (Wandschneider et al., 2012; Iqbal et al., 2015; Abarrategui et al., 2018; Sezikli et al., 2018; Almane et al., 2019; Chawla et al., 2021). Some cognitive domains might be altered (e.g., executive function), and depression, anxiety, impulsivity, and social or psychiatric problems are common (Wandschneider et al., 2012; de Araujo Filho and Yacubian, 2013; Iqbal et al., 2015; Abarrategui et al., 2018; Sezikli et al., 2018; Almane et al., 2019; Syvertsen et al., 2019; Gama et al., 2020; Taura et al., 2020; Chawla et al., 2021). JME is responsive to anti-seizure medications in 65–92% of patients, though it often requires lifelong treatment (Yacubian, 2017; see Table 1). Myoclonic seizures may be more difficult to control than generalized tonic-clonic seizures: sodium channel blockers often aggravate both myoclonic and absence seizures in JME, and lamotrigine (which has multiple mechanisms of action, including sodium channel blockade) may aggravate myoclonic seizures in some patients (Geithner et al., 2012; Senf et al., 2013; Höfler et al., 2014; Yacubian, 2017; Stevelink et al., 2019; Zhang et al., 2019; Pietrafusa et al., 2021; Hirsch et al., 2022). The mechanisms by which sodium channel blockers exacerbate seizures are not well understood but may relate to inhibition of $Na_v1.1$ channels on GABAergic neurons implicated in generalized epilepsies (Catterall, 2014).

2.4. Generalized tonic-clonic seizures alone

2.4.1. Epidemiology—Generalized tonic-clonic seizures alone (GTCA) accounts for one-third of all adolescent-onset IGEs (Vorderwülbecke et al., 2017). The typical age at onset is 10–25 years, later than in JAE or JME (Beghi et al., 2006; Vorderwülbecke et al., 2017).

2.4.2. Features and natural history—GTCA clinical features include generalized tonic-clonic seizures and interictal 3–5.5-Hz generalized spike-and-wave or polyspike-and-wave signatures. Seizures usually occur within 2 hours of awakening but can happen at other times. Seizures are infrequent, occurring yearly or less, and are sometimes triggered by sleep deprivation, fatigue, or alcohol (Holtkamp et al., 2014).

Patients' cognition is grossly normal interictally; however, specific cognitive domains might be altered (e.g., attention or decision-making) (Abarrategui et al., 2018). Antiseizure medications, including valproic acid, lamotrigine, levetiracetam, topiramate, perampanel, and zonisamide, are used to treat seizures in GTCA (Beydoun and D'Souza, 2012; Rohracher et al., 2016). Many patients with GTCA require medication throughout their adult lives.

In summary, IGEs share key clinical features, including seizures with impaired awareness and increased susceptibility surrounding sleep-wake transitions. While most IGEs are managed with medications, current therapies have off-target effects (for instance, sleep perturbations), and a substantial fraction of cases are refractory to treatment, motivating the pursuit of mechanistic investigations in animal models that will aid the discovery of more effective drug targets.

The factors that provoke seizures provide valuable clues to underlying mechanisms. For example, absence seizures provoked by hyperventilation suggest pH-dependent processes,

and the association between drowsiness and seizure susceptibility may be linked to high adenosine tone and low acetylcholine and norepinephrine levels during these periods. In addition, to understand why some drugs are ineffective or exacerbate a particular seizure type, it is important to investigate their effects on specific cells and brain circuits. In the sections that follow, we highlight recent developments linking clinical observations with mechanistic studies.

3. Contrasts and parallels between IGEs and DEEs

DEEs are a heterogeneous group of disorders characterized by early-onset, often severe seizures and developmental impairment, and encephalopathy that tends to worsen with increasing seizure burden (reviewed in Guerrini et al., 2023). While some DEEs are caused by focal structural changes and have a largely focal EEG pattern, others include generalized seizure types and display generalized interictal patterns on EEG, consistent with GGEs (Wirrell et al., 2022; Guerrini et al., 2023).

The latest ILAE Task Force on Nosology and Definitions for epilepsy syndromes defined 18 syndromes as DEEs, subcategorized by age of onset (Guerrini et al., 2023; for detailed review, see Guerrini et al., 2023). Here we highlight those DEEs that meet criteria for GGE (such as epilepsy with myoclonic-atonic seizures), and also those that prominently feature generalized seizure types (such as Dravet syndrome), because they are the most likely to have any mechanistic overlap with IGEs. There is also genetic overlap between DEEs with generalized features and IGEs, including mutations in *GABRA1* and *GABRG2* associated with both familial IGE syndromes and Dravet syndrome (Helbig, 2015).

The neonatal- and infantile-onset DEEs with generalized features include clinically defined syndromes with multiple etiologies (such as early infantile developmental and epileptic encephalopathy (EIDEE) or Dravet syndrome), and a growing list of etiology-specific syndromes such as those with an identified genetic cause (i.e., KCNQ2 and glucose transporter-1 deficiency (Glu1DS)). Childhood-onset DEEs with generalized features include clinically defined syndromes with multiple etiologies (Lennox-Gastaut Syndrome (LGS), epilepsy with myoclonic-atonic seizures, spike-and-wave activation in sleep). DEEs with generalized features that present at variable ages include progressive myoclonic epilepsy, which has multiple genetic and metabolic causes such as mitochondrial disease (myoclonus epilepsy and ragged red fibers), and lysosome- and glycogen-storage disorders (including Lafora disease and Unverrict-Lundborg disease). This is not an exhaustive list of the DEEs, and we direct the reader to a recent review for a more detailed enumeration of the genetic associations identified so far (Guerrini et al., 2023).(Guerrini et al., 2023).

3.1. Epidemiology

The true prevalence of DEEs is not well established, although it has been estimated that the overall annual incidence of monogenic epilepsies is around 1 per 2100 live births (Symonds et al., 2019; Aledo-Serrano et al., 2021).

3.2. Features and natural history

DEE clinical features encompass a broad spectrum of severity, seizure types, and developmental comorbidities. Currently, most therapies for DEEs target individual symptoms such as seizures and not the underlying disease mechanisms (with a few notable exceptions, such as the ketogenic diet for Glu1DS). By contrast with IGEs, which are largely drug-responsive, seizure control is elusive for many individuals with DEEs, even when anti-seizure medications are optimized for the underlying etiology. First-line treatments for IGEs such as ethosuximide, valproate, and lamotrigine are often ineffective in DEEs and can cause neuropsychiatric side effects, adding to comorbid developmental impairment (Strzelczyk and Schubert-Bast, 2022). By contrast, there are medications with specific indications for DEEs that are not typically used in IGEs, including cannabidiol and fenfluramine for Dravet syndrome, and ganaxolone for CDKL5 (Elkommos and Mula, 2022). Despite combination therapy (i.e., >50% of patients with LGS take three or more anti-seizure medications concurrently (Spoor et al., 2021), many patients with DEEs still experience untreated symptoms and turn to nonspecific treatments such as the ketogenic diet (Sondhi et al., 2020). In DEE patients in whom seizure control is achieved, developmental impairments and other comorbidities often remain severe (McTague et al., 2016; Stamberger et al., 2016).

4. Animal models of generalized epilepsy

Foundational work on mechanisms of GGEs was made possible by studying animal models with generalized SWDs and behavioral arrest that recapitulate absence epilepsy. SWDs are an electrographic pattern composed of a bilaterally synchronous spike and after-going slow wave; in humans, absence seizures are associated with 2.5–5 Hz SWDs while in animal models of IGE, SWDs tend to occur faster, at 5–11 Hz (Jafarian et al., 2020; Hirsch et al., 2021; Hirsch et al., 2022).

Animal models of IGEs were initially obtained by inbreeding rat and mouse strains and screening them for features of IGEs, including absence-type seizures and SWDs. The resulting models include Genetic Absence Epilepsy Rat from Strasbourg (GAERS, Marescaux et al., 1992), Wistar Albino Glaxo Rijswijk rats (WAG/Rij), *tottering*, *lethargic*, *coloboma*, and *stargazer* (reviewed in Crunelli and Leresche, 2002b, and in Maheshwari and Noebels, 2014). Eventually, the disease-conferring loci were identified in these strains by forward genetics. As molecular biology technologies advanced and reverse genetics became possible, epileptic mice (and, to a lesser degree, rats) were generated with targeted mutations in pathways implicated in IGEs (for example, *Gabrg2* missense (R43Q) mutation, encoding the GABA-Aγ_2 subunit (Petrou and Reid, 2012); *Gabra1* knock-out, encoding the GABA-Aα_{1A} subunit (Arain et al., 2012); *Cacna1g* knock-out, encoding the T-type Ca^{2+} channel (Kim et al., 2001); *Hcn2* missense (R591E, T592A) mutation, ablating cAMP sensitivity (Hammelmann et al., 2019). These models reproduce the seizure semiology (behavioral arrest) and electroencephalographic pattern (generalized SWDs) common to CAE and JAE, although the SWD frequency is faster in rodents than in humans, and persists beyond the development window seen in humans.

Nevertheless, important gaps remain in animal models of GGEs. The rodent models of JME (Ding and Gallagher, 2016; McCarthy et al., 2020) and GTCA (Harada et al., 2013) have not been as exhaustively characterized as the absence epilepsy models, and could yield additional important insights into how pathogenic mechanisms differ between absence and convulsive seizures. Moreover, developing animal models of DEEs is challenging due to the sheer number and variety of insults that are known to cause clinical disease. For example, Dravet syndrome can be caused by thousands of mutations in numerous genes (He et al., 2022). A Dravet syndrome model induced by a mutation in *Scn1a* may not translate to the same clinical syndrome as induced with a *Gabra1* mutation and vice versa (He et al., 2022). Many etiology-specific DEEs now have animal models in which patient-derived mutations have been introduced, but the resulting animal phenotype and seizure repertoire do not always phenocopy the human disease (for review of genetic models see Wang and Frankel, 2021).

5. Neuroanatomical basis for the role of the thalamus in generalized epilepsy

Here we summarize the functional neuroanatomy of the thalamus as it relates to normal physiology and its disruption in GGEs. We describe the intrinsic properties of thalamocortical (TC) and nucleus reticularis thalami (nRT) neurons and their modulation by larger regulatory loops connecting thalamus and cortex.

5.1. Neuronal components of intrathalamic circuits underlying adaptive and maladaptive rhythmic oscillations

There are two functionally distinct populations of neurons in the thalamus implicated in generalized epilepsy: TC neurons and nRT neurons.

TC neurons are intrinsically oscillatory, due in part to the alternating activation and deactivation of hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN) and TWIK-related acid-sensitive K^+ (TASK) channels (Meuth et al., 2006), interacting with T-type Ca^{2+} channels (Coulter et al., 1989; Tissone et al., 2021). TC neurons in the ventrobasal (VB) thalamus are glutamatergic projection neurons that innervate neocortical neurons in layer 4 and receive glutamatergic input from corticothalamic (CT) neurons in neocortical layers 5 and 6 (Sherman and Guillery, 1996; Fig. 2A and discussed below). The glutamate signal from CT neurons acts on two types of receptors expressed on the TC neurons' surface: ionotropic glutamate receptors are essential to the flow of information through the thalamocortical circuit (Koerner et al., 1996; Paz et al., 2011; Barad et al., 2012), and metabotropic glutamate receptors contribute to the regulation of the firing mode of TC neurons (McCormick and von Krosigk, 1992; Bertaso et al., 2008; Cheong et al., 2009).

The activity of TC neurons is influenced by GABAergic inputs from nRT neurons, and $GABA_A$ and $GABA_B$ receptor activation in the thalamocortical circuit has long been implicated in the generation of SWDs (Coulter et al., 1990b; Hosford et al., 1997; Kim et al., 1997).

The nRT, composed of GABAergic neurons spatially arranged as a capsule around and between projection nuclei, forms an important input to TC neurons (Fig. 2A). Like TC neurons, nRT neurons are also intrinsically oscillatory (Steriade et al., 1987; Fuentealba et al., 2005) due to the presence of low-voltage-activated T-type Ca^{2+} channels, Ca^{2+}-activated small conductance potassium (SK) channels (Cueni et al., 2008), and Ca^{2+}-activated cation TRPM4 channels (O'Malley et al., 2020).

TC and CT neurons send glutamatergic collaterals to the nRT (Fig. 2A), which also expresses both ionotropic and metabotropic glutamate receptors. The inhibition caused by the CT->nRT->TC pathway is referred to as feedforward inhibition, whereas inhibition from the TC->nRT->TC pathway is referred to as feedback inhibition (for review see Paz and Huguenard, 2015a). Fast AMPA-receptor (AMPAR)-mediated currents are critical for CT-nRT-TC feedforward inhibition. Evidence for the importance of this pathway in epilepsy comes from the *stargazer* mouse, which lacks an auxiliary AMPAR subunit and displays absence epilepsy (Bats et al., 2007; Lacey et al., 2012). AMPARs that include the GluR4 subunit are particularly enriched on nRT neurons, opposite CT presynaptic elements, and loss of GluR4 is sufficient to cause loss of CT-nRT-TC feedforward inhibition and absence epilepsy (Paz et al., 2011). Both feedforward and feedback inhibition can result in a powerful GABAergic input to TC neurons, promoting a recurrent cycle of hyperpolarization followed by a burst of Na^{+} action potentials; the mechanisms underlying burst firing and their disruption in SWDs are discussed below.

5.2. Tonic and burst firing in the intrathalamic circuit

TC and nRT neurons operate in two modes: burst firing (predominant during sleep, seizures, and anesthesia) and tonic firing (during wakefulness).

The tonic firing mode allows TC neurons to integrate and relay activity between cortical regions and the subcortical regions to which they are connected (Whitmire et al., 2021). Tonic firing occurs when the TC membrane is at resting potential (~60 mV). With T-type Ca^{2+} channels inactivated, the TC neurons generate Na^{+}-channel-dependent action potentials in response to excitatory stimuli.

The burst firing mode allows the thalamus to entrain wide regions of the brain into hypersynchronous activity, as occurs normally during sleep. Burst firing occurs when the TC membrane is hyperpolarized (Sorokin et al., 2017; Whitmire et al., 2021). Hyperpolarization of TC neurons, which can result from GABAergic inputs from the nRT, relieves the inactivation of T-type Ca^{2+} channels and activates HCN channels. These conditions permit TC cells to fire a rebound Ca^{2+} spike with an overriding burst of high-frequency Na^{+}-mediated action potentials (Fig. 2B, C). The volley of high-frequency action potentials from TC neurons excites distant targets throughout the brain. CT projection neurons then send glutamatergic inputs back to the thalamus (Fig. 2A).

Key to the burst firing mode in both TC and nRT neurons, T-type Ca^{2+} channels voltage-activate in response to low voltage depolarization (−50 mV), inactivate with further depolarization (−30 mV), and require hyperpolarization (−90 mV and below) to relieve voltage inactivation, as was demonstrated in acutely dissociated rat TC neurons (Coulter

et al., 1989). Enhanced T-type Ca^{2+} currents are implicated in many rodent models of absence epilepsy. For example, T-type Ca^{2+} current is augmented in nRT in GAERS rats, resulting in more powerful hyperpolarizing output onto TC neurons (Tsakiridou et al., 1995). T-type Ca^{2+} current is also augmented in the *tottering*, *stargazer*, *lethargic*, *coloboma*, and *Cacna1a*$^{-/-}$ models (Ernst et al., 2009). Thus, monogenic mouse models of epilepsy, such as those with deficient or dysfunctional P/Q Ca^{2+} channels ($Ca_v2.1$ α_{1A}), may cause epilepsy via a compensatory increase in T-type Ca^{2+} channels (Zhang et al., 2002; Song et al., 2004; Zhang et al., 2004). Deletion of functional α_{1G}-containing T-type Ca^{2+} channels on TC neurons is protective against SWDs (Kim et al., 2001; Miao et al., 2020), and overexpression of this subunit is sufficient to cause an absence epilepsy phenotype in mice (Ernst et al., 2009). T-type Ca^{2+} channels are one of the targets of ethosuximide, which is effective in treating absence seizures in IGE (Huguenard, 1999; Table 1).

In spite of these observations, other lines of evidence call into question the primacy of TC T-type Ca^{2+} channels: 1) ethosuximide is a relatively weak T-type Ca^{2+} channel blocker (Coulter et al., 1990a), and it has been suggested that its anti-absence effects could be mediated by modifying other channels (Crunelli and Leresche, 2002a); 2) a recent absence epilepsy model generated by deletion of P/Q channels in adult mice failed to show the expected increases in T-type Ca^{2+} current or burst-firing (Miao et al., 2020); 3) It has been observed that some TC neurons can remain in tonic firing mode during SWDs (Pinault et al., 1998; McCafferty et al., 2018).

In the GAERS rat model of absence epilepsy, nRT neurons fire in burst mode during SWDs, as measured using either intracellular (Slaght et al., 2002) or extracellular recordings (McCafferty et al., 2018). The burst firing in nRT neurons is critical for SWDs *in vivo* (McCafferty et al., 2018) and in SWD-like activity in brain slices from GAERS rats (Cain et al., 2018). Burst firing mode is also observed in TC neurons in the motor thalamus during SWDs in GAERS rats (Paz et al., 2007). However, burst firing in single TC neurons is not commonly observed during SWDs in the VB thalamus (McCafferty et al., 2018). Although the results between brain regions seem variable as to the proportion of burst firing in TC cells, there is consensus that universal burst firing in every single TC neuron is not necessary for the expression of SWDs, but that switching the firing of a population of TC neurons from synchronized to non-synchronized is sufficient to interrupt SWDs in both the rat and mouse models of absence epilepsy (Sorokin et al., 2017).

Activation of GABA receptors in TC neurons can be pro-epileptic, because $GABA_A$ and $GABA_B$ receptors hyperpolarize TC neurons with differing time courses and promote post-hyperpolarization rebound firing (Kim et al., 1997). Consistent with this idea, enhancing the bioavailability of endogenous GABA with reuptake inhibitors (D'Amore et al., 2015), loss-of-function mutations in *Slc6a1* (a mutation encoding GABA transporter GAT-1 and implicated in a generalized DEE, epilepsy with myoclonic-atonic seizures) (Pirttimaki et al., 2013), or administering GABA pro-drug GHB (Godschalk et al., 1977; Liu et al., 1991), can all provoke SWDs. Burst firing in TC neurons is key to understanding the mechanism by which clinical GABA reuptake inhibitors, such as tiagabine and vigabatrin, which provoke absence status in patients with IGE (Knake et al., 1999).

In contrast to the seizure-promoting effects of GABA receptor activation on TC neurons, $GABA_A$ receptor activation in the nRT is antiepileptic. This effect probably reflects lateral inhibition between nRT neurons, which desynchronizes GABAergic output to TC neurons and decreases the duration of bursts in thalamic slices (Sohal et al., 2000; Beenhakker and Huguenard, 2009); loss of lateral inhibition is a putative pathogenic mechanism of GGE in *Scn8a*$^{+/-}$ mice (Makinson et al., 2017). Indeed, overactivity of nRT cells, which results in increased GABAergic output to TC neurons, is implicated in several animal models of IGE and DEE (GAERS Tsakiridou et al., 1995, and Bessaih et al., 2006, Scn1a$^{+/-}$ Ritter-Makinson et al., 2019). Thus, the therapeutic effect of benzodiazepines such as clonazepam on absence seizures is thought to be due to enhancement of α3-containing $GABA_A$ receptor current within the nRT (Sohal et al., 2003; Schofield et al., 2009).

The difficulty in selectively promoting anti-epileptic vs. pro-epileptic actions of GABA within the thalamus underlines the need for cell-type specific targeting of therapeutics in GGEs.

5.3. The role of thalamo-cortico-thalamic loops in spike-and-wave discharges

SWDs result from synchronized oscillations in thalamo-cortico-thalamic loops. Bursting TC neurons cause excitatory postsynaptic potentials in neocortical neurons, which generates a time-locked extracellular negative potential seen as a “spike” on a surface electroencephalogram (Staak and Pape, 2001; Terlau et al., 2020). The spike is followed by a slow wave representing complex intracortical polysynaptic excitatory and inhibitory postsynaptic potentials (Terlau et al., 2020).

Controversy has persisted for decades regarding the brain region—cortex or thalamus—that instigates absence seizures in susceptible animals (Meeren et al., 2002; Manning et al., 2004; Polack et al., 2009). Multi-electrode arrays in GAERS rats demonstrated that precursor activity could be recorded in the somatosensory cortex, before the appearance of SWDs (Seidenbecher et al., 1998). Similar studies in WAG/Rij rats showed that SWDs appear earliest in the peri-oral region of the somatosensory cortex, then rapidly generalize to other cortical regions (Meeren et al., 2002; Polack et al., 2009). These observations gave rise to the “cortical focus theory,” which has accumulated additional evidence from network approaches such as cross-correlation, phase synchronization analysis and Granger causality (Luttjohann and van Luijtelaar, 2012; Luttjohann et al., 2013; Sysoeva et al., 2016; Luttjohann and Pape, 2019). The early involvement of the somatosensory cortex was demonstrated for both absence seizures and myoclonic seizures, in a mouse model of JME (Ding and Gallagher, 2016).

One caveat to the interpretation of cortically recorded SWDs is that standard electrode arrays lack the spatial resolution to resolve which neuronal population(s) generate the signals. Thus, local field recordings could reflect the postsynaptic responses of layer IV neurons (the target of thalamocortical inputs), layer II/III (thalamocortical and corticocortical inputs), or layer VI neurons (which receive a mix of both thalamocortical and intracolumnar cortical input), while unit activity recordings could indicate intracortical (layer II/III) or corticofugal (layer V & VI) neuronal spikes. Thus, single-electrode techniques cannot distinguish a cortical focus firing autonomously vs a cortical focus driven

by thalamocortical stimuli. Efforts to disentangle these possibilities might be enhanced by current source density analysis. Terlau et al. (2020) have recently described depth profiles in the somatosensory cortex and mapped current sources and sinks during SWDs in GAERS rats using high-density multi-contact electrodes. The same approach could be used to characterize the precursor activity and initiation of SWD in the somatosensory cortical focus (Luttjohann and van Luijtelaar, 2012; Luttjohann and Pape, 2019). Furthermore, the cortical focus theory should be evaluated in animal models of generalized DEEs, as the existence of a cortical focus, if confirmed, could inform clinical approaches to treatment such as placement of electrodes for responsive neurostimulation or other neuromodulatory interventions.

The current consensus is that thalamus and cortex are both needed for the expression of generalized seizures. Intervening at any point in the thalamo-cortico-thalamic loop is likely to interrupt SWDs as long as a critical mass of neurons is affected. Thus, absence seizures in animal models can be attenuated by ablative lesions of the nRT (Banerjee and Snead 3rd, 1994) or an infusion of glutamate receptor antagonists into thalamic relay nuclei (Seidenbecher and Pape, 2001; Terlau et al., 2020), but also by lesioning the ipsilateral cortex (Scicchitano et al., 2015) or silencing it with lidocaine, tetrodotoxin or cortical spreading depression (Vergnes and Marescaux, 1992; Sitnikova and van Luijtelaar, 2004; Polack et al., 2009). Wherever the seizures start, they almost instantaneously generalize throughout the bilateral thalamo-cortico-thalamic loops and cause unconsciousness by disrupting the tonic firing mode required for awake awareness (Paz and Huguenard, 2015a; Paz and Huguenard, 2015b; Sorokin et al., 2017).

Thus, the thalamus remains a potent therapeutic target because it is a key gatekeeper to seizure maintenance, whether the SWDs started there or not. Indeed, the first real-time optogenetic disruption of thalamic output during SWDs showed that switching the output of the thalamus from bursting to tonic firing mode is sufficient to instantaneously interrupt SWDs and behavioral absences in multiple rodent models of absence epilepsy (Sorokin et al., 2017). This on-demand switch in the firing mode of TC neurons can be achieved simply by manipulating the membrane voltage of TC neurons: by expressing the inhibitory halorhodopsin in TC neurons of various rodent models of absence epilepsy – WAG/Rij rats and stargazer mice – were able to cause a short hyperpolarization of TC neurons with a brief yellow light pulse delivered in the thalamus with an optical fiber, which caused rebound burst firing in TC neurons and an SWD accompanied by a behavioral arrest. In contrast, by expressing the excitatory stabilized step function opsin in TC neurons in these rodent models, Sorokin et al. (2017) were able to depolarize TC neurons with a brief blue light pulse delivered to the thalamus, which caused a switch from bursting to tonic firing mode, instantaneously ending the SWD and the associated behavioral absence. Thus, depolarizing TC neurons is a powerful way to interrupt the high-frequency burst firing in TC neurons, which is due to the fact that depolarization inactivates T-type Ca^{2+} channels in these neurons. These first real-time optogenetic perturbations of thalamic firing mode revealed that synchronized output from the thalamus is *necessary* to maintain an SWD. Whether single TC neurons fire in bursts or not, their collective output from the thalamus is “bursty” during SWDs because the output of a mass of TC neurons is highly synchronized, which is sufficient to cause an SWD in mice prone to absence epilepsy.

Emerging literature is beginning to clarify how mode switching is accomplished endogenously and where those processes can go wrong and contribute to GGEs.

6. Intrinsic properties and synaptic inputs that influence firing states of intrathalamic circuits in healthy states and epilepsy

Several factors regulate thalamic neuron membrane potential and, thus, their firing mode.

6.1. Metabotropic glutamate receptors in TC and nRT neurons

Metabotropic glutamate receptors on TC neurons can switch these cells' firing mode from tonic to burst firing. For example, group I metabotropic glutamate receptors (mGluR1 and mGluR5) activate phospholipase C (PLC), which activates protein kinase C (PKC) and modifies the function of T- and L-type Ca^{2+} channels in TC neurons (Cheong et al., 2009). In the absence of this downstream signaling, PLC β4 knockout animals demonstrate increased voltage sensitivity of T-type Ca^{2+} channels, more easily generate bursts of spikes, and develop spontaneous absence seizures, which can be rescued by PKC activation (Cheong et al., 2009). Disrupting the subcellular targeting of mGluR7, a group III metabotropic glutamate receptor coupled to the $G_{i/o}$ second messenger system, and expressed presynaptically in both nRT and TC neurons, decreases neurotransmitter release at multiple synapses in the intrathalamic circuit, and also leads to absence epilepsy (Okamoto et al., 1994; Bertaso et al., 2008; Tassin et al., 2016).

6.2. Hyperpolarization-activated cyclic nucleotide-gated nonselective (HCN) in TC neurons

HCN channels carry a nonselective (depolarizing) current that activates at hyperpolarized membrane potentials and inactivates at depolarized membrane potentials (He et al., 2014). This property makes HCN channels well-positioned to stabilize the resting membrane potential of TC neurons. In the presence of cAMP, the voltage sensitivity of the channel shifts to more depolarized potentials, such that the TC neuron resting membrane potential is maintained above the threshold for T-type Ca^{2+} channel deinactivation, favoring tonic firing over burst firing (Budde et al., 2005; Zobeiri et al., 2019).

Hyperpolarization-activated cAMP nucleotide-gated (HCN) channels have been implicated in generalized epilepsy by genetic and pharmacologic studies (Ludwig et al., 2003; Budde et al., 2005; David et al., 2018; Hammelmann et al., 2019; Nishitani et al., 2019; Iacone et al., 2021). HCN channels' cAMP sensitivity provides a candidate mechanism for state-dependent susceptibility to SWDs during drowsiness and sleep, as neuromodulators linked to wakefulness (norepinephrine α2 and β receptors, acetylcholine mAChRs 2/4) and sleep pressure (adenosine receptors A1, 2A/B, 3) are coupled to G_i and G_s proteins that control adenylyl cyclase activity. HCN channels are sensitive to intracellular pH, and their voltage sensitivity is shifted by lamotrigine (Table 1). HCN channels make an attractive target for rational drug therapy if their modulation can reduce burst-firing in drowsy states without disrupting neuronal function during alert wakefulness.

6.3. TWIK-related potassium (TREK) and TWIK-related acid-sensitive potassium (TASK) channels in TC neurons

Together with HCN channels, TREK and TASK channels on TC neurons contribute to resting membrane potential and facilitate switching between tonic and burst firing modes (Meuth et al., 2006; Bista et al., 2012; Bista et al., 2015). TASK and TREK channels contribute to the background potassium leak current (Enyedi and Czirjak, 2010). When this leak current is inhibited, as by Gq-coupled receptors (Bista et al., 2012, Bista et al., 2015), resting membrane potential shifts upward, and T-type Ca^{2+} channels are maintained in an inactivated state, thus favoring tonic firing. Tonic firing is thereby favored over burst firing (Meuth et al., 2006; Bista et al., 2012). Conversely, under conditions of extracellular or intracellular alkalinization, TASK channels open (Niemeyer et al., 2010), hyperpolarizing the resting membrane potential and favoring burst firing. TASK channel mutations have not, to our knowledge, been reported in generalized epilepsy cohorts (Kananura et al., 2002), but TASK and TREK channels should be explored as potential therapeutic targets for much-needed treatments.

6.4. Ca^{2+}-activated potassium channels in nRT neurons

Ca^{2+} activated small conductance K^+ currents (SK) in nRT reticular thalamic neurons regulate GABAergic input to TC neurons (Ying and Goldstein, 2005; Kleiman-Weiner et al., 2009), thus influencing firing mode in the thalamocortical circuit (Wong et al., 2013). SK channels are critical for the afterhyperpolarization (Debarbieux et al., 1998; Zaman et al., 2011) in nRT neurons following each low threshold Ca^{2+} spike. This afterhyperpolarization relieves voltage inactivation of T-type Ca^{2+} channels, restoring conditions required to initiate the next burst (Debarbieux et al., 1998, Zaman et al., 2011). The role of these channels in epilepsy pathogenesis is less well understood, but diminished SK current and hyperactive nRT output are seen in brain slices from mice with a model of Dravet syndrome induced by *Scn1a* deficiency (Ritter-Makinson et al., 2019). Further study is needed on the role of SK currents in epilepsy to inform anti-seizure medication development.

6.5. Non-neuronal modulators of intrathalamic circuits: thalamic glia

Astrocytes are an important non-neuronal cell type that regulates ion concentrations and neurotransmitter levels, stores glycogen, and provides metabolic support for neurons during high energy demands of seizures (Walz, 2000; Pirttimaki et al., 2013; Crunelli et al., 2015; Philippot et al., 2021; Dienel et al., 2023). More than just “support cells,” astrocytes demonstrate intrinsic oscillations, carry Ca^{2+} waves, release signals of their own, and have been implicated in the pathogenesis of some types of epilepsy (Parri and Crunelli, 2001; Cho et al., 2022).

Of particular relevance to the pathophysiology of GGEs, thalamic astrocytes are key modifiers of thalamo-cortico-thalamic oscillations; they regulate glutamate and GABA synthesis (Bryant et al., 2009) and clearance (Beenhakker and Huguenard, 2010; Pirttimaki et al., 2013), thus shaping the kinetics of synaptic neurotransmission. GABA reuptake, in particular, has been implicated in absence epilepsy: for instance, reduced GAT-1 function in thalamic astrocytes prolongs neuronal $GABA_A$ and $GABA_B$ receptor activation and promotes SWDs (Pirttimaki et al., 2013).

Interactions between astrocytes and neurons in the development of generalized seizures could be bidirectional. For instance, in various IGE models (Akbar et al., 1998; Dutuit et al., 2000; Dutuit et al., 2002; Cavdar et al., 2019; Kose et al., 2022; Thompson et al., 2022), as well as in some models of DEEs (Scn8a epileptic encephalopathy Thompson et al., 2022, Dravet syndrome Uchino et al., 2023), thalamic astrocytes proliferate and take on a reactive phenotype – downregulating glutamate and GABA transporters, and decreasing potassium uptake – while spontaneous seizures develop. Experimental work has now extended these observations and established a role for thalamic astrocytes in thalamocortical circuit physiology and generalized seizures. Thus, optogenetic depolarization of astrocytes in the VB relay thalamus prolongs SWDs in GAERS rats (Ozgur et al., 2022), whereas ablating glial function (with fluorocitrate or a glutamine shuttle toxin) disrupts intrathalamic oscillations elicited in brain slices from normal rats (Yang and Cox, 2011).

Electrolyte homeostasis by astrocytes may contribute to seizures in the Noda epileptic rat, a model of GTCA that shows decreased astrocyte expression of *Kir4.1* in thalamus and amygdala (Harada et al., 2013). In the special case of Lafora disease, a rare glycogen storage disorder causing progressive myoclonus epilepsy with neurodevelopmental impairment, toxic accumulation of glycogen in astrocytes results in impaired neurotransmitter clearance (Munoz-Ballester et al., 2016; Munoz-Ballester et al., 2019), and the disease can be rescued by astrocyte-specific deletion of glycogen synthase (Duran et al., 2021); whether manipulations of thalamic astrocytes are sufficient to rescue the epileptic phenotype is not known and should be investigated.

In conclusion, thalamic astrocytes represent an important therapeutic target for GGEs that is not currently targeted by existing anti-seizure medications, and should be researched further.

7. Neuromodulation in the thalamus

Thalamic modulation occurs through neuromodulators released by a heterogeneous group of afferents, and through systemic drivers (Sherman and Guillery, 1998; Varela, 2014). Examples of thalamic modulators include local purinergic, afferent noradrenergic, cholinergic, serotonergic, dopaminergic, and histaminergic projections, and systemic carbon dioxide and blood pH (CO_2/pH), among others. Here, we focus on purinergic, noradrenergic, cholinergic, and CO_2/pH modulation (Fig. 3) due to their prominent role in vigilance state changes controlled by the thalamus.

7.1. Norepinephrine

The adrenergic neuromodulator norepinephrine (NE) has potent and long-lasting effects on thalamocortical circuits and is released from NE axons to all thalamic nuclei (McCormick et al., 1991; Pérez-Santos et al., 2021) under conditions of alert wakefulness (Berridge et al., 2012). NE axons project from the locus coeruleus (LC) in the brainstem reticular formation (Simpson et al., 1997) and the A5 noradrenergic region in the brainstem (Swanson and Hartman, 1975; Morrison and Foote, 1986; Byrum and Guyenet, 1987; De Lima and Singer, 1987; Simpson et al., 1997; Vogt et al., 2008; Varela, 2014).

In acute thalamic slices from guinea pig and cat brains, norepinephrine application evokes a slow depolarization, reduced burst firing, and increased tonic activity by decreasing K^+ leak current (likely via TASK and TREK channels) and changing voltage sensitivity of I_h (likely reflecting HCN channels) which remains active at resting membrane potential and makes it more difficult to switch to burst mode (McCormick and Prince, 1988; Pape and McCormick, 1989; McCormick and Pape, 1990; Varela, 2014). In addition, norepinephrine increases synaptic strength in thalamocortical synapses (Varela, 2013).

In vivo, LC stimulation increases thalamocortical response to whisker stimulation (Moxon et al., 2007; Devilbiss and Waterhouse, 2011), and phasic LC stimulation sensitizes TC neurons to low-level stimuli (Devilbiss and Waterhouse, 2011). However, 20–40% of TC neurons show suppression of their response to whisker stimulation when LC is stimulated (Moxon et al., 2007, Devilbiss and Waterhouse, 2011), congruent with i*n vivo* iontophoretic delivery of noradrenergic agonists inhibiting TC neurons (Grasso et al., 2006).

Taken together, these data support an antiepileptic role of endogenous NE, though this has not yet been exploited therapeutically (reviewed in Giorgi et al., 2004).

7.2. Acetylcholine

Acetylcholine, released by widespread nerve terminals arising from cell bodies in brainstem nuclei (pedunculopontine nucleus (PPT), laterodorsal tegmentum (LDT), parabigeminal nucleus (PBG)), and the basal forebrain (BF), is high during alert wakefulness when absence seizures and SWDs are least likely to occur. Acetylcholine powerfully switches the firing patterns of thalamic neurons, inhibiting nRT neurons and activating tonic firing in TC projection neurons (Ben-Ari et al., 1976). Acetylcholine effects are mediated through Gq-coupled muscarinic M1 and M3 receptors, which close TASK and TREK channels (Bista et al., 2012), thus decreasing membrane conductance and depolarizing TC cells above the threshold of T-type channel deinactivation (McCormick and von Krosigk, 1992; Broicher et al., 2008). Importantly, acetylcholine mimics like pilocarpine (an M3 receptor agonist) provoke convulsive seizures (Levesque et al., 2021), but may exert contrasting effects on absence seizures due to intrathalamic signaling. Similar to norepinephrine, potential cholinergic antiepileptic mechanisms have not yet been explored therapeutically, but will have to be targeted to the appropriate patient population, and to the correct brain structure and cell type.

7.3. Adenosine

The purinergic neuromodulator adenosine regulates neural activity via four subtypes of G-protein coupled receptors. Adenosine is a low-energy metabolite released into the extracellular milieu by equilibrative and concentrative transporters (Lovatt et al., 2012; Wall and Dale, 2013) and under some conditions in the form of ATP by neurons (Pankratov et al., 2007) and glia (Newman, 2004; Pascual et al., 2005; Wall and Dale, 2013). A1 receptors are widely expressed in the brain, and A1R activation inhibits synaptic transmission and hyperpolarizes the membrane potential via the activation of K^+ channels (Dunwiddie and Masino, 2001; Borea et al., 2018; Wall et al., 2022).

Adenosine has a well-established role as an endogenous anti-epileptic neuromodulator in focal and convulsive seizures (Weltha et al., 2019). Adenosine accumulates during seizures and provides negative feedback to terminate bursts of neuronal activity and delay the next event (During and Spencer, 1992; Boison, 2008). The role of adenosine in the thalamocortical circuit and generalized seizures is less clear.

In the thalamus, A1Rs are highly expressed, particularly in the VB thalamus and the nRT, supporting a role for adenosine signaling in modulating oscillations in thalamic microcircuit and TC neurons. A recent study showed that endogenous adenosine is released during thalamic oscillations and acts via A1 receptors to feedback and reduce thalamic oscillatory activity in acute thalamic slices from mice (Wall et al., 2022).

However, adenosine also accumulates with sleep pressure and drowsiness, which may contribute to its observed pro-epileptic role in absence seizures. Exogenous agonists of adenosine receptors increase SWDs, while antagonists (i.e., caffeine) decrease SWDs in rodent models of absence epilepsy (Ilbay et al., 2001; Ates et al., 2004; Germé et al., 2015; Dede et al., 2019).

7.4. CO_2/pH

Voluntary hyperventilation provokes SWDs in 90% of patients with absence epilepsy and can be useful as a bedside diagnostic maneuver (Holowach et al., 1962; Panayiotopoulos, 1999; Caplan et al., 2008; Glauser et al., 2013; Caplan, 2015; Salvati and Beenhakker, 2019). This physiological response to hyperventilation is caused by the intimate relationship between carbon dioxide (CO_2) and blood pH. After CO_2 is formed as a waste product of aerobic respiration, CO_2 diffuses out of tissues into blood plasma and then red blood cells. Plasma CO_2 is in equilibrium with carbonic acid (H_2CO_3), bicarbonate ions (HCO_3^-), and hydrogen ions (H^+) (Svichar and Chesler, 2003). These free H^+ ions determine blood plasma pH. Hyperventilation causes CO_2 plasma to drop, promoting the reverse formation of H_2CO_3 from HCO_3^- and H^+ ions. This decrease of H^+ ions in the blood is called respiratory alkalosis, which was shown to directly provoke SWDs in seizure-prone rats (Salvati et al., 2022). Importantly, absence seizures are induced by hyperventilation at a low metabolic state and not during exercise, during which increased breathing does not induce respiratory alkalosis (Esquivel et al., 1991; Salvati and Beenhakker, 2019).

There is well-established evidence that the thalamus is responsible for hyperventilation-induced absence seizures. In 1965, hyperventilation-induced SWDs were shown to be abolished by severing connections between the cortex and subcortical structures, and in 1967, the thalamus was shown to be the responsible pH sensor (Sherwin, 1965; Sherwin, 1967). TC neurons express HCN and TASK channels which are pH-sensitive (Soltesz et al., 1991; Meuth et al., 2006). Their respective currents, I_h and I_{TASK}, are blocked by extracellular acidification (Meuth et al., 2006; Biel et al., 2009). However, since the I_h is depolarizing (reversal potential is around −20 mV) and I_{TASK} is hyperpolarizing (reversal potential is around −70 mV), the net result of extracellular acidification is minimal, and neither the resting membrane potential nor firing properties of TC neurons change much during extracellular acidification (Meuth et al., 2006). Thus, it remains unclear how TC neurons are responsible for hyperventilation-induced absence seizures (Salvati and

Beenhakker, 2019). The possible proposed mechanisms include, but are not limited to, 1) unbalanced HCN and TASK1/3 channel expression in TC sub-populations (Salvati and Beenhakker, 2019); 2) differences in HCN and TASK 1/3 channel responses to extracellular alkalization (Salvati and Beenhakker, 2019); or 3) TC neurons' modulation by nitric oxide (NO) produced by vasculature in response to blood pH changes (Najarian et al., 2000; Yang and Cox, 2007; Yang and Cox, 2008), 4) cell-specific response of thalamic nuclei to hyperventilation (Salvati et al., 2022). Interestingly, the most recent study to date on thalamic pH-sensitivity determined that hypoxia-induced hyperventilation consistently activates neurons within the intralaminar nuclei (Salvati et al., 2022). pH effects may be particularly potent because the intralaminar nuclei – along with other nonspecific thalamic nuclei – have such broad connections throughout the cortex.

8. Inputs to the thalamus from the basal ganglia, cerebellum, and limbic system are disrupted in generalized epilepsy

The thalamus is extensively connected to other brain regions. Here we focus on the afferent connections that modulate the activity of the thalamus and are implicated in the pathogenesis of seizures (Fig. 3), as well as the outputs from the thalamus to cortex that form thalamo-cortico-thalamic loops which are activated in SWDs. Thalamic projections play an important role in numerous other cortical and subcortical circuits, which are beyond the scope of this review (reviewed in Castro-Alamancos and Connors, 1997, and Haber and McFarland, 2001).

8.1. The role of the basal ganglia in regulating thalamic circuits in generalized epilepsy

Parallel direct and indirect pathways through the basal ganglia form inhibitory inputs to TC neurons in circuits critical for the control of behavior and implicated in the pathogenesis of neurodegenerative, movement, and neuropsychiatric disorders (Graybiel, 2000). Within these circuits, inhibitory projections from the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr) are organized topographically in the thalamic mediodorsal (MD), ventral anterior (VA) and ventral lateral (VL) nuclei (Haber and Calzavara, 2009). In turn, TC neurons in MD innervate the prefrontal cortex, while TC neurons in VA and VL largely target motor and premotor cortices (Haber and Calzavara, 2009).

The role of increased inhibitory output from SNr to the thalamus in the pathogenesis of generalized seizures has been demonstrated in the GAERS rat model of absence epilepsy. In freely behaving GAERS rats, multi-unit recordings of SNr neurons revealed a change in firing properties time-locked with spontaneous SWDs, with an increase in firing rates and a switch to burst firing (Deransart et al., 2003). The impact of this change in the firing pattern of nigral neurons was further elucidated through recordings of ventral medial thalamic neurons in GAERS rats, which also show an increase in burst firing during SWDs, and demonstrate tonic firing with disruption of SWDs when glutamatergic signaling in SNr is blocked (Paz et al., 2007).

Alterations in basal ganglia-thalamic pathways have also been implicated in secondary seizure generalization in focal epilepsy (reviewed in Gale, 1992). Patients with recent

focal to bilateral tonic-clonic seizures have shown decreased pallidal–thalamic interaction through the indirect pathway in measures of resting state functional connectivity, compared with patients with exclusively focal seizures or only remote history of focal to bilateral tonic-clonic seizures (He et al., 2020).

8.2. Altered cerebellothalamic pathways in generalized epilepsy

The efferent pathways from the cerebellum form a major excitatory input to thalamic neurons, originating in the projection neurons of the deep cerebellar nuclei, and altered intrinsic cerebellar firing has been implicated in generalized epilepsy (reviewed in Streng and Krook-Magnuson, 2021). Cerebellar projection neuron activity is largely modulated by inhibitory input from Purkinje neurons. In rodent models of absence epilepsy, subsets of Purkinje neurons and cerebellar nuclei projection neurons show firing patterns phase-locked to SWDs (Kandel and Buzsáki, 1993; Kros et al., 2015), and genetic manipulation of cerebellar neurons can cause SWDs (Schwitalla et al., 2022). Pharmacologic or optogenetic modulation of cerebellar projection neurons has shown that decreasing cerebellar projection neuron output leads to an increase in SWDs, while conversely, increasing firing reduces SWDs (Kros et al., 2015; Eelkman Rooda et al., 2021).

8.3. Limbic-thalamic pathways implicated in generalized epilepsy

The epileptogenic role of limbic pathways involving the hippocampus and amygdala have been well-defined through clinical data and animal models of focal temporal lobe epilepsy but may also be disrupted in generalized epilepsy (reviewed in Nayel et al., 1991, Jefferys et al., 2012). Specifically, the connections between limbic cortical and subcortical regions with the nRT and limbic thalamic nuclei (including anterior and midline nuclei) are likely to be altered in some GGEs (reviewed in Onat et al., 2013).

The strongest evidence for the role of limbic pathways in generalized epilepsy comes from models of atypical absence epilepsy. This has been studied through a mouse model generated through a mutation in the R1 subunit of the metabotropic $GABA_B$ receptor (Wang et al., 2009). SWDs were recorded in vivo from the midline thalamus, hippocampal CA1 and nRT; the nRT and midline thalamus were necessary for the generation of SWDs (Wang et al., 2009). Though not directly implicated in epileptogenesis, there is also evidence for disrupted limbic pathways in typical absence epilepsy models: data from WAG/Rij rats suggests a lower threshold to trigger the spread of SWDs to limbic pathways, and GAERS rats are resistant to secondary generalized seizures after amygdala kindling (Eşkazan et al., 2002; Tolmacheva et al., 2004). Further strengthening the link between alterations in the limbic system and generalized epilepsy is the presence of comorbid mood disorders. Neuropsychiatric comorbidities, including anxiety and depression, are common in patients with IGE, and anxious and depressive behaviors have also been described in corresponding animal models (Gruenbaum et al., 2021).

9. Mechanistic overlap between seizures and sleep

Additional clues to the pathogenesis of IGEs have come from studying the mechanisms of sleep. The thalamocortical circuits underlying abnormal rhythmic activity in generalized

seizures are also thought to generate the physiologic rhythms of sleep (reviewed in Beenhakker and Huguenard, 2009). Specifically, sleep spindles, brief bursts of rhythmic waveforms seen on scalp EEG during non-REM sleep, are generated through recurrent loops between the nRT and TC neurons (Steriade et al., 1985; Contreras et al., 1997). Disconnection experiments have demonstrated that similar to the pathways generating SWDs, the circuit connecting cortex, nRT, and thalamocortical neurons is necessary to generate synchronized spindles within the thalamus and cortex (Steriade et al., 1985, Contreras et al., 1997). Specifically, excitatory corticothalamic projections targeting the inhibitory nRT drive burst firing in thalamocortical neurons, and ablating the cortical input to the thalamus or the inhibitory nRT input to thalamocortical neurons disrupts spindle synchronization in healthy cats (Contreras et al., 1997).

In addition to sharing underlying pathways, sleep spindles and SWDs can arise in similar brain states. SWDs are often observed at sleep-wake transitions and can be seen in non-REM sleep, similar to the temporal pattern of sleep spindles (Kostopoulos, 2000). Further supporting the mechanistic links between sleep spindles and generalized seizures, there is evidence that spindle oscillations directly transform into SWDs in feline and rodent models of epilepsy (reviewed in Kostopoulos, 2000, Halasz et al., 2002). Lesional studies targeting these pathways have demonstrated that ablating the nRT and thalamocortical relay nuclei suppresses both sleep spindles and SWDs ipsilateral to the lesion (Meeren et al., 2009). Further work is needed to determine the relationship between sleep spindles and SWDs in humans, but there is evidence that sleep spindles are disrupted in patients with focal and generalized epilepsy (Drake et al., 1991; Tezer et al., 2014; Kramer et al., 2021).

Further supporting the link between sleep and epilepsy, sleep is often disrupted in patients with epilepsy, and anti-seizure medications commonly cause disordered sleep, including insomnia or daytime sleepiness (reviewed in Liguori et al., 2021). These differential effects on sleep do not clearly cluster by drug mechanism, and additional research is needed to identify potential mechanisms underlying these side effects and reduce or eliminate them in newer anti-seizure treatments. Data from functional imaging implicates alterations in thalamic metabolism in sleep disorders, including hypersomnia and insomnia (Nofzinger, 2005). Given the key role of the thalamus in both sleep and epilepsy, alterations in thalamocortical circuits likely play a role in these symptoms in patients with epilepsy.

10. Discussion: unresolved questions and opportunities

Our understanding of TC circuits in GGEs has been advanced by genetic, histologic, anatomic, electrophysiological, pharmacological, and molecular approaches, as summarized above. However, important questions for the field remain unanswered.

10.1. Thalamic circuits in developmental and epileptic encephalopathies

There is limited research on the role of the TC circuit in developmental and epileptic encephalopathies (DEEs). Lennox-Gastaut Syndrome (LGS), characterized by slow spike-and-wave and commonly including generalized seizure types, is an area of research using surgical ablation and functional modulation (Velasco et al., 2006). Intracranial recordings from patients with LGS show ictal discharges in the centromedian thalamic nucleus (CM)

during generalized seizures, including tonic, tonic-clonic, and myoclonic seizures (Velasco et al., 1991). In Dravet syndrome resulting from *SCN1A* mutations (predominantly affecting $Na_V1.1$ on inhibitory neurons), an association has been demonstrated between loss of SK current, hyperactivity in nRT neurons, and downstream enhancement of TC neuron bursting (Ritter-Makinson et al., 2019; Studtmann et al., 2022). $Na_V1.2$, by contrast, is predominantly expressed on excitatory cells, and mutations in the *SCN2A* gene encoding $Na_V1.2$ are also associated with DEEs with predominantly focal seizures (Wolff et al., 2017), though animals carrying these mutations have absence-type seizures (Ogiwara et al., 2018). The mechanisms remain unknown. Further studies are needed to investigate the role of TC neuron disruption in the pathogenesis of these syndromes and the many other syndromes caused by other channelopathies (*SCN8A*, *SCN1B*, etc.) and to discover new therapeutic options for these conditions.

10.2. Dietary approaches may reveal untapped mechanisms

The ketogenic diet is effective for a wide range of epilepsies and represents an important tool in the clinical management of pharmaco-resistant seizures (Kinsman et al., 1992; Martin-McGill et al., 2020). A few randomized clinical trials (Kim et al., 2016; Sondhi et al., 2020) and innumerable clinical case reports suggest that ketogenic diets improve GGEs, including typical (Clemens et al., 2013) and atypical absence epilepsy (Ross et al., 1985), juvenile myoclonic epilepsy (Kverneland et al., 2015), and LGS (Caraballo et al., 2011), Dravet syndrome (Caraballo et al., 2005), and epilepsy with myoclonic-atonic seizures (Wiemer-Kruel et al., 2017). The ketogenic diet is pleiotropic, and the mechanisms of action so far identified include the provision of ketone bodies as an alternative metabolic substrate (Klepper, 2008), shifting the glutamate-glutamine equilibrium (Melo et al., 2006; Yudkoff et al., 2007), decreasing quantal content of glutamatergic vesicles (Juge et al., 2010), acidification of the brain parenchyma (Choudhary et al., 2021) and activation of ATP-sensitive potassium channels (Fogle et al., 2016). The extent to which these mechanisms act on TC circuits is not well understood, but the pH sensitivity of TASK and HCN channels provides one possible link.

10.3. Therapeutic thalamic stimulation in refractory epilepsy

Thalamic stimulation with deep brain stimulation (DBS) and responsive neurostimulation (RNS) are emerging treatments for refractory generalized epilepsy syndromes, and the efficacy of these treatments further supports a central role for the thalamus in generalized epilepsies. Chronic stimulation with DBS in the centromedian (CM) thalamic nucleus has been shown to reduce the frequency of generalized seizures, including absence and generalized tonic-clonic seizures in patients with GGE, multifocal epilepsy, or LGS (Velasco et al., 1987; Velasco et al., 2006; Dalic et al., 2022). There is also evidence for improvement of cognitive symptoms in patients with LGS after CM neurostimulation (Velasco et al., 2006). This effect on generalized epilepsy through stimulating CM is thought to be mediated by the widespread cortical connections of CM, including prefrontal, orbitofrontal, insular, motor, and sensory cortices (reviewed in Velasco et al., 2021). In contrast, targeting the anterior thalamic nucleus, with its largely temporal and frontal lobe connections, reduces seizure frequency in refractory temporal lobe epilepsy (Fisher et al., 2010; Salanova et al., 2021).

Closed-loop neurostimulation with RNS has also been used to target thalamic nuclei in patients with refractory epilepsy, recording thalamic ictal discharges and delivering stimulation in response to seizure detection. In case reports of patients with LGS, RNS targeting bilateral CM reduced the frequency of generalized seizures, including tonic, atonic, myoclonic, and generalized tonic-clonic seizures (Kwon et al., 2020; Welch et al., 2021).

In addition to modifying thalamic network activity with RNS or DBS, thalamic ablation has also been studied as a treatment for refractory epilepsy (Aguado-Carrillo et al., 2021). In a case series of patients with refractory generalized or multifocal epilepsy, bilateral radiofrequency ablation of CM significantly reduced the frequency of generalized seizures and was well tolerated, with only transient feeding difficulties after surgery (Aguado-Carrillo et al., 2021). Together, these results support the key role of the thalamus, and specifically the broad reciprocal cortical connections of CM, in generalized seizures and open new avenues for treating generalized epilepsy through thalamic modulation.

Further refinement of thalamic targets for neurostimulation is needed to improve treatment options in refractory epilepsy. Hypothesis-driven intracranial recordings from thalamic nuclei may help guide patient selection and improve outcomes as this technique becomes more widespread (Chaitanya et al., 2020). Furthermore, additional work in preclinical models is needed to study the therapeutic impact of modulating other thalamic nuclei. Potential candidates include the mediodorsal nucleus, with its widespread frontal connections, or nRT, with its key role in modulating thalamocortical loops.

10.4. Charting a path to future therapeutic breakthroughs

A number of technical and conceptual barriers should be addressed to improve treatments for GGE. One conceptual challenge is the remarkable clinical heterogeneity in the causes, expression, and treatments of the GGE syndromes. On the technical side, our understanding of the pathophysiology of generalized seizures would benefit from more widespread implementation of optogenetics and miniaturized probes and amplifiers that can record electrophysiologic signals in awake, behaving animals with high spatial and temporal resolution.

The rodent strains with susceptibility to absence epilepsy, which have served as powerful prototype disease models for the IGEs, have limited utility for the study of DEEs. Monogenic knock-in and knock-out genetic mouse models are helpful for identifying mechanisms and screening treatments for DEEs, but these approaches remain hampered by their low throughput. DEEs tend to be rare diseases, with only a handful of patients sharing any given mutation – it would be a staggering task to develop a unique mouse strain for every pathogenic human mutation. High-throughput assays and personalized medicine approaches should be leveraged where possible.

Current pharmacologic approaches to epilepsy treatment do not take full advantage of our knowledge about pathophysiologic mechanisms. More selective T-type Ca^{2+} channel antagonists are needed. Notable gaps exist in medication classes that target reactive astrocytes, shift membrane potential, influence second messenger systems downstream of metabotropic glutamate receptors, adenosine receptors, adrenergic receptors, and muscarinic

acetylcholine receptors, and modulate emerging targets such as HCN and TASK channels. As highlighted above, we suggest that broader use of direct thalamic stimulation may expand therapeutic options for GGEs.

11. Conclusion

The unique physiologic properties of thalamic neurons and the widespread cortical and subcortical connections of the thalamus are dysregulated in generalized epilepsy syndromes and animal models of epilepsy. However, a more nuanced understanding of the relationship between TC circuit dysfunction and epilepsy is needed to identify new pharmacologic, dietary, gene therapy, surgical, and neuromodulation therapeutic targets to treat refractory generalized epilepsy. In particular, more studies are required to dissect thalamocortical cellular heterogeneity in health and epilepsy through single-cell and spatial transcriptomics. The rapid development of research tools to address these questions, including molecular and genetic models combined with optogenetics and advancements in recording techniques, makes this a pivotal time for the field.

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Data availability

No data were used for the research described in the article.

Abbreviations:

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CAE	childhood absence epilepsy
cAMP	cyclic adenosine monophosphate
CT	corticothalamic
DBS	deep brain stimulation
DEE	developmental and epileptic encephalopathy

EEG	electroencephalogram
GABA	γ-aminobutyric acid
GAERS	genetic absence epilepsy rat from Strasbourg
GGE	genetic generalized epilepsy
GPe	globus pallidus pars externa
GTCA	generalized tonic clonic seizures alone
HCN	hyperpolarization-activated cyclic nucleotide-gated channel
IGE	idiopathic generalized epilepsy
JAE	juvenile absence epilepsy
JME	juvenile myoclonic epilepsy
LGS	Lennox-Gastaut syndrome
NE	norepinephrine
NMDA	N-methyl-D-aspartic acid
nRT	nucleus reticularis thalami
RNS	responsive neurostimulation
SWD	spike-and-wave discharge
TASK	TWIK-related acid-sensitive potassium channel
TC	thalamocortical
TREK	TWIK-related potassium channel
WAG/Rij	Wistar Albino Glaxo rats from Rijswijk.

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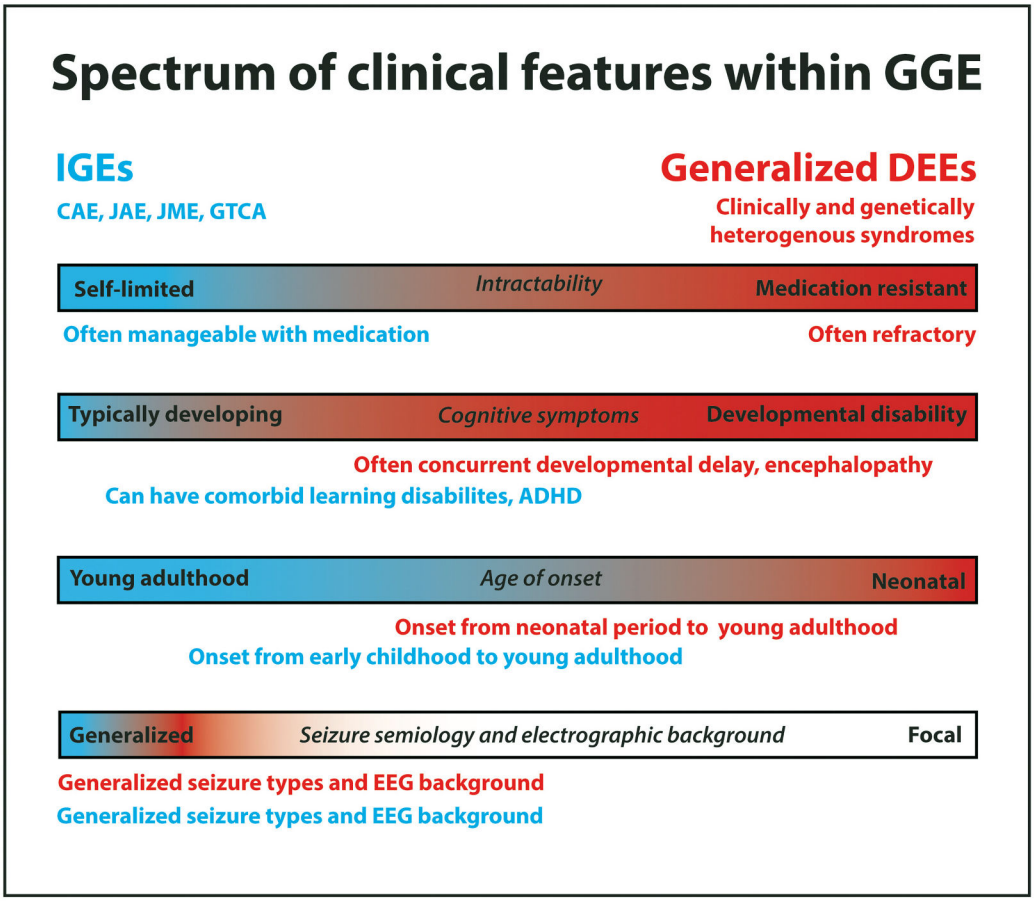

Fig. 1.

Clinical differences and areas of overlap within GGE, between IGEs and generalized DEEs. CAE: childhood absence epilepsy, DEE: developmental and epileptic encephalopathy, GTCA: generalized tonic-clonic seizures alone, IGE: idiopathic generalized epilepsy, JAE: juvenile absence epilepsy, JME: juvenile myoclonic epilepsy. Blue: features associated with IGE, red: features associated with generalized DEEs.

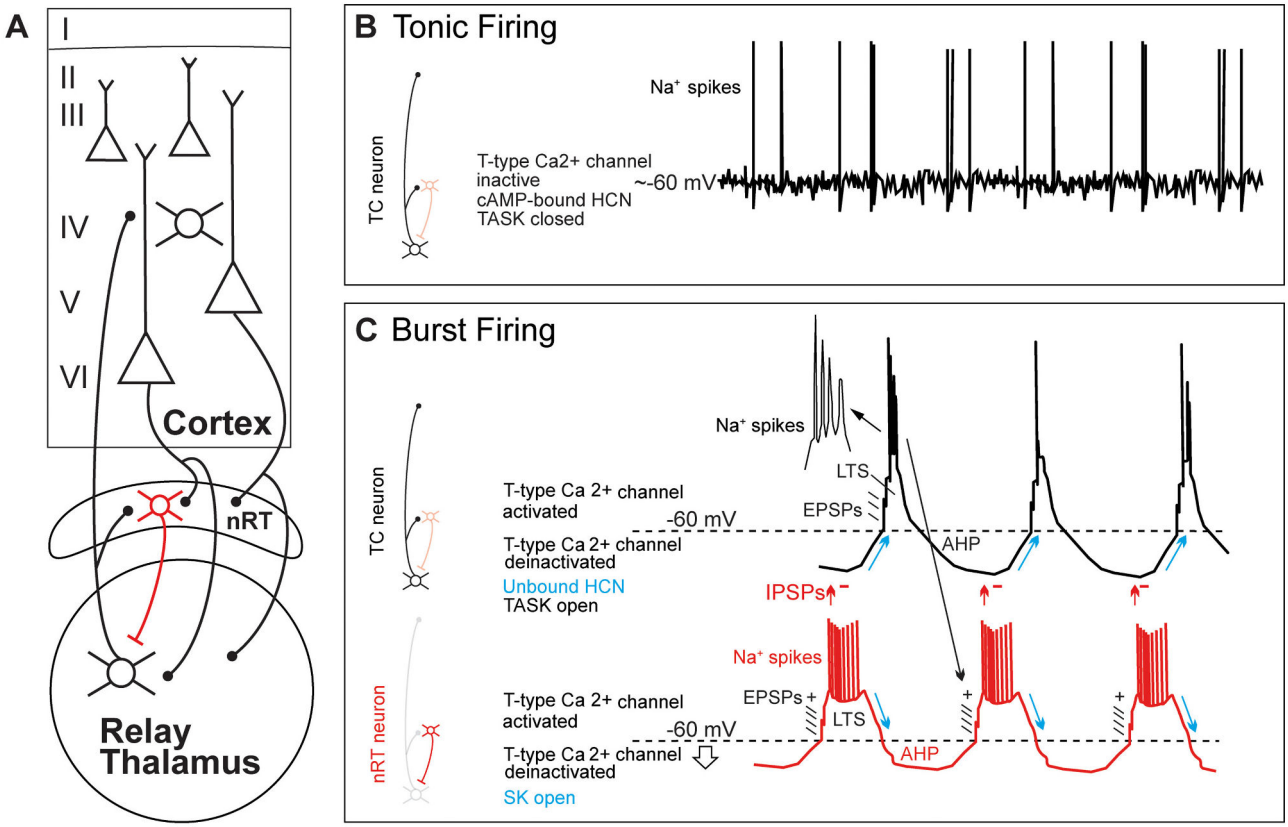

Fig. 2.

Simplified diagram of the major thalamocortical circuit and schematic representation of burst-firing and tonic-firing modes regulating thalamocortical output. A. Feedforward axons from TC neurons target middle cortical layers (e.g., a VB TC neuron targeting cortical layer IV), while corticothalamic (CT) pyramidal neurons in layers V and VI project to the thalamus. Both projection neurons also synapse on inhibitory neurons in the nucleus reticularis thalami (nRT). Intra-nRT lateral inhibitory projections are omitted for clarity. B. Schematic of tonic firing mode. During alert wakefulness, under conditions of high acetylcholine and high norepinephrine tone, TASK channels close (inhibited by Gq-coupled signaling cascades), and cAMP-bound HCN channels open at higher voltages (downstream of Gs-coupled signaling cascades), resulting in a relatively depolarized TC membrane potential. Consequently, T-type Ca^{2+} channels remain inactivated. Under these conditions, TC neurons fire Na^{+}-mediated action potentials in response to excitatory synaptic inputs. C. Schematic of burst firing observed when neurons are exposed to conditions of low acetylcholine and low norepinephrine tone: TASK channels are open, contributing to outward potassium “leak current,” and cAMP-unbound HCN channels require lower voltages to open; TC membrane potential is dynamically regulated around a relatively hyperpolarized set-point, and this relieves the inactivation of T-type Ca^{2+} channels. In these conditions, excitatory post-synaptic potentials (EPSPs) depolarize the membrane to the activation threshold of T-type Ca^{2+} channels, which elicits a low-threshold Ca^{2+} spike (LTS) and a burst of Na^{+} action potentials in nRT and variable responses in TC neurons, which can fire either bursts of action potentials or single action potentials during a SWD.

An intrathalamic network oscillation is generated by interactions between bursting nRT and TC neurons: nRT neuron firing leads to GABA-mediated inhibitory post-synaptic potentials (IPSPs) in TC neurons, leading to activation of HCN channels, resulting in membrane depolarization to the activation threshold of T-type Ca^{2+} channels. A subsequent LTS and train of Na^{+} spikes lead to glutamate release from the TC neurons onto the nRT neurons and the next cycle of burst firing. In nRT, Ca^{2+} influx activates SK channels, resulting in afterhyperpolarization of nRT neurons which makes T-type Ca^{2+} available for another burst and perpetuates the cycle.

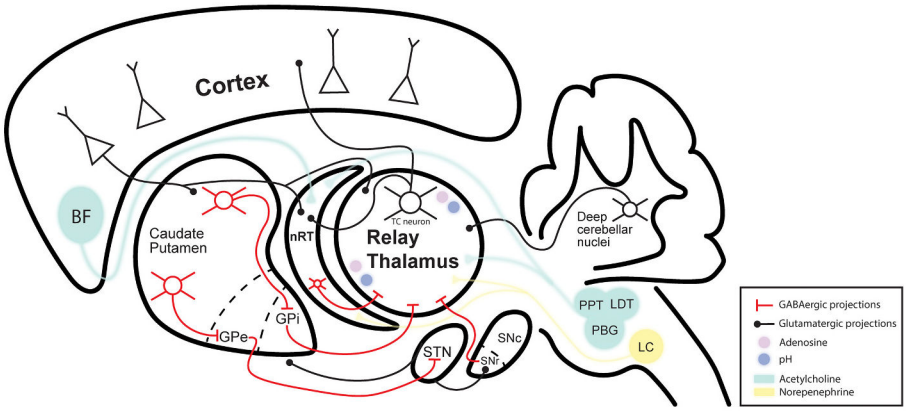

Fig. 3.

Simplified diagram of the major glutamatergic, GABAergic, and neuromodulatory inputs to the thalamus. Projections from the cortex, basal ganglia, cerebellum, and brainstem converge on TC neurons. BF: basal forebrain, GPe: globus pallidus externa, GPi: globus pallidus interna, LC: locus coeruleus, LDT: laterodorsal tegmentum, nRT: nucleus reticularis thalami, PBG: parabigeminal nucleus, PPT: pedunculopontine tegmentum, STN: subthalamic nucleus, SNc: substantia nigra pars compacta, SNr: substantia nigra pars reticulata.

Table 1

Clinical and electrographic features differ between IGEs, though first-line medications and putative targets of current treatments overlap (Jallon and Latour, 2005; Mastroianni et al., 2021; Hirsch et al., 2022).

IGE	Epidemiology	Seizure type and age of onset	Susceptible brain state(s)	Medications	Putative medication targets
CAE	Prevalence: 5–50 per 100,000	Typical absence seizures, generalized tonic-clonic seizures may occur in adolescence	Hyperventilation	ETX	T-type Ca^{2+} channels
	Accounts for 18% of children with epilepsy		Drowsiness and sleep	VPA	Na^+, K^+, and Ca^{2+} channels, GABA
		Age of onset: 4–10 (range: 2–13)		LTG	Na^+ channels, HCN channels
JAE	Prevalence: 10 per 100,000	Typical absence seizures, generalized tonic-clonic seizures (>90%)	Upon waking	VPA	Na^+, K^+, and Ca^{2+} channels, GABA
	Accounts for 2.4–3.1% of children and adolescents with epilepsy		Drowsiness and sleep	LTG	Na^+ channels, HCN channels
		Age of onset: 9–13 (range: 8–20)		ETX (adjunctive therapy for absence seizures)	T-type Ca^{2+} channels
JME	Prevalence: 1–3 per 100,000	Myoclonic seizures, generalized tonic-clonic seizures (>90%), absence seizures (33%)	Soon after waking	VPA	Na^+, K^+, and Ca^{2+} channels, GABA
	Accounts for 9.3% of all epilepsies		Increased risk with sleep deprivation and photic stimulation	LEV	Presynaptic glutamate release
		Age of onset: 10–24 (range: 8–40)	Sleep	LTG	HCN channels, Na^+ channels
				CZP	$GABA_A$ receptors
				TPM, ZNS	Carbonic anhydrase
GTCA	Prevalence: 1.8 per 100,000	Generalized tonic-clonic seizures	Soon after waking	VPA	Na^+, K^+, and Ca^{2+} channels, GABA
	Accounts for 33% of all adolescent epilepsies	Age of onset: 10–25 (range: 5–40)	Increased risk with sleep deprivation, fatigue, and alcohol use, photic stimulation	LEV	Presynaptic glutamate release
				LTG	HCN channels, Na^+ channels
			Sleep	TPM, ZNS	Carbonic anhydrase

CZP: clonazepam, ETX: ethosuximide, LEV: levetiracetam, LTG: lamotrigine, TPM: topiramate, VPA: valproic acid, ZNS: zonisamide.