Received: 14 February 2025 | Revised: 14 May 2025 | Accepted: 26 May 2025

DOI: 10.1002/epi4.70075

Epilepsia Open® Open Access

INVITED ARTICLE

Absence seizures: Update on signaling mechanisms and networks

Ozlem Akman[1] | **Filiz Onat**[2,3]

[1]Department of Physiology, School of Medicine, Demiroglu Bilim University, Istanbul, Türkiye

[2]Department of Medical Pharmacology, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

[3]Department of Neuroscience, Institute of Health Sciences, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

Correspondence
Ozlem Akman, Demiroglu Bilim University, Buyukdere Caddesi, No:120, 34394 Sisli, Istanbul, Türkiye.
Email: ozlem.akman@demiroglu.bilim.edu.tr

Funding information
European Commission Horizon Europe Programme under the call HORIZON-WIDERA-2021-ACCESS-03, Grant/Award Number: 101078981-GEMSTONE

Abstract

Absence seizures (AS) are a hallmark of genetic generalized epilepsies (GGE), characterized by brief episodes of impaired consciousness accompanied by electroencephalographic spike-and-wave discharges (SWDs). Traditionally attributed to cortico-thalamo-cortical (CTC) dysrhythmia, emerging evidence suggests a more intricate pathophysiological framework involving high-order thalamic nuclei, the basal ganglia, limbic structures, and the cerebellum. Rather than arising abruptly from a discrete cortical event, SWDs appear to develop progressively through dynamic network interactions. This paradigm shift underscores the necessity of a network-based approach to comprehensively understand AS pathophysiology. Concurrently, advances in electrophysiology and neuroimaging are refining our understanding of the signaling mechanisms that drive AS generation. This review explores the network dynamics underlying AS, synthesizing recent experimental and clinical findings to provide an integrative framework for future research and the development of novel therapeutic strategies in absence epilepsy.

Plain Language Summary: Absence seizures are brief episodes of staring and unresponsiveness, often beginning in childhood, and are caused by abnormal rhythmic activity in the brain. This review summarizes recent research on how specific brain circuits generate and maintain these seizures. While most studies have focused on the cortex and thalamus, we also highlight the contributions of other regions such as the basal ganglia, cerebellum, and limbic structures. Understanding how these brain networks interact may help explain seizure patterns and guide the development of improved treatments.

KEYWORDS

basal ganglia, cerebellum, idiopathic generalized epilepsies, limbic system, spike-and-wave discharges

1 | INTRODUCTION

Absence seizures (AS) are brief, sudden episodes of impaired consciousness, characterized by a loss of voluntary movement and distinctive spike-and-wave discharges (SWDs) on EEG.[1] SWDs consist of bilaterally synchronous spikes followed by slow waves, typically occurring at 2.5–4 Hz in humans[1] and 5–11 Hz in animal models of idiopathic generalized epilepsy (IGE).[2–4] Traditionally, AS have been attributed to dysfunction within the cortico-thalamo-cortical (CTC) loop. However, growing evidence suggests a broader network involvement, including additional thalamic nuclei beyond the reticular thalamic nucleus (nRT) and ventrobasal thalamus (VB),[5,6] as well as the basal ganglia (BG),[7] limbic system,[8] and cerebellum.[9,10] This perspective shifts the understanding of AS from a localized circuit dysfunction to a disorder involving widespread network interactions.

This review first outlines the clinical and electrographic features of AS within the Genetic Generalized Epilepsies (GGE) spectrum and summarizes relevant rodent models. We then examine AS as a network disorder, integrating recent neurophysiological and neuroimaging advances. Special focus is given to the roles of subcortical structures in seizure generation and propagation, along with emerging insights into thalamic-level signaling mechanisms underlying AS. We primarily discuss inbred rat and mouse models, widely regarded as representative of typical AS, while atypical AS models are not extensively covered. Additionally, due to space constraints, findings from genetic manipulations in nonepileptic rodents and pharmacologically induced AS models are only briefly addressed.

Key points

- Absence seizures (AS) involve widespread brain networks beyond the cortico-thalamo-cortical loop.
- Dynamic preictal cortical activity precedes spike-and-wave discharges, indicating progressive seizure onset.
- Higher-order thalamic nuclei, basal ganglia, and cerebellum play integral roles in AS initiation, propagation, and maintenance.
- Limbic structures are functionally engaged in AS, modulating seizure expression and associated neurocognitive effects.

2 | ABSENCE SEIZURES AND GENETIC GENERALIZED EPILEPSIES

GGE comprise a group of disorders defined by generalized SWDs and are thought to have polygenic inheritance (Table 1).[1] IGE is a distinct subgroup of GGE, consisting of four well-defined syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone. Within the GGE spectrum, AS are most common in IGE, particularly CAE and JAE, which share typical AS but differ in onset, frequency, and EEG characteristics. Other GGE syndromes, such as epilepsy with myoclonic absences and epilepsy with eyelid myoclonia, are often associated with developmental and epileptic encephalopathies (DEEs) and feature AS variants, frequently accompanied by rhythmic myoclonic jerks or eyelid myoclonia.[1] Atypical AS, more common in DEEs like Lennox–Gastaut Syndrome (LGS), typically last longer than typical AS and are characterized by slower (<2.5 Hz), irregular SWDs (such as polyspike preceding slow wave in a SWD episode) on EEG[1] (Figure 1). This review focuses on the mechanisms involved in the generation and maintenance of typical SWDs, whereas those underlying atypical SWDs are discussed in other specialized reviews.[11,12]

3 | RODENT MODELS OF ABSENCE SEIZURES

Animal models have been instrumental in elucidating the cellular, synaptic, and network mechanisms underlying AS. These models are broadly categorized into pharmacologically induced and genetic models, with the latter further divided into spontaneous and induced types. While pharmacological models allow controlled comparisons between seizure and seizure-free states, their transient nature limits validity, failing to replicate the genetic and developmental basis of human AS. Pharmacological models involve four classes of AS-inducing drugs: synaptic $GABA_A$ receptor antagonists, $GABA_B$ receptor agonists, extrasynaptic $GABA_A$ receptor agonists, and GAT-1 transporter antagonists.[3,13] Mechanistically, $GABA_B$ agonists, GAT-1 antagonists, and extrasynaptic $GABA_A$ agonists enhance tonic inhibition, whereas synaptic $GABA_A$ antagonists reduce fast phasic inhibition, collectively promoting SWD generation.[13]

Among genetic models, Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats and Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are widely used Wistar-derived inbred strains with high face, construct, and predictive validity for AS,[14,15] alongside associated behavioral

TABLE 1 Features and EEG findings of absence seizures in ILAE-defined syndromes.[1]

Absence seizures	Main features	Ictal EEG findings	Associated syndrome
Typical absence seizures	Brief (3–30 s), sudden impaired awareness, may have automatisms (eye blinking, lip smacking) JAE has fewer AS	Generalized SWDs (2.5–4 Hz in CAE; 3–5.5 Hz in JAE)	CAE, JAE
Absence seizures in JME	Infrequent, brief (3–8 s), subtle awareness impairment, may be unrecognized AS occur in 1/3 of cases	3–5.5 Hz generalized SWDs and polyspike-wave, may fragment in sleep	JME
Absence seizures in GTCA	Not a defining feature; AS are exclusionary	3–5.5 Hz generalized SWDs or polyspike-wave discharges	GTCA
Myoclonic absence seizures	Absence + rhythmic myoclonic jerks (especially in the arms), ratcheting-up movements of both arms	3–4 Hz generalized SWDs	EMA
Absence seizures with eyelid myoclonia	Absence + eyelid fluttering, eye deviation, often triggered by light or eye closure AS only in some cases	3–6 Hz generalized polyspike-wave discharges	EEM
Atypical absence seizures	Longer duration (>30 s), gradual onset/offset, more pronounced automatisms, less responsive to hyperventilation	<2.5 Hz slow irregular SWDs	LGS, DEEs

Abbreviations: AS, absence seizures; CAE, childhood absence epilepsy; DEEs, developmental and epileptic encephalopathies; EMA; epilepsy with myoclonic absences; GTCA, epilepsy with generalized tonic–clonic seizures alone; JAE, juvenile absence epilepsy; JME; juvenile myoclonic epilepsy; LGS, Lennox–Gastaut Syndrome; SWDs, spike–wave discharges.

and cognitive comorbidities (Table 2).[16] Both exhibit characteristic SWDs on EEG with behavioral arrest. GAERS display longer and more frequent SWDs, whereas WAG/Rij have higher SWD frequency and increased 8–14 Hz power during the pre-SWD period.[4] Their polygenic origin,[17] analogous to human AS, makes them valuable for IGE research and to understand the epileptogenesis process in IGE.

Monogenic mouse models, carrying spontaneous mutations in ion channel subunits and other key genes, provide insights into single-gene effects on neurophysiology and behavior. Well-studied models include *tottering* (Cacna1a), *stargazer* (Cacng2), *lethargic* (Cacnb4), and *coloboma* (Snap25 haploinsufficiency), all of which exhibit early-onset SWDs.[18] However, their motor impairments, such as ataxia and dyskinesia, are absent in human AS. Among mouse models of SWDs, the C3H/HeJ strain offers a distinct advantage due to its relatively pure absence seizure phenotype, without other seizure types or associated neurological deficits such as cerebellar ataxia.[19,20] In this strain, a mutation in the gene encoding the AMPA receptor subunit Gria4 has been identified as the primary driver of SWD generation. Advances in genetic engineering have expanded monogenic rodent AS models, now encompassing over 30 mutations affecting calcium, glutamate, and GABA receptor channels.[18] Recently, Neuroligin-2 knockout mice, which lack a key synaptic adhesion molecule, have been shown to exhibit abnormal SWDs and behavioral arrests, further broadening the scope of AS research.[21]

Developing DEE models remains challenging due to the genetic heterogeneity and environmental factors influencing human disease complexity.[22] Among genetic models, the *Gabrb3*$^{+/D120N}$ knock-in mouse is the most relevant for LGS, as it exhibits atypical AS and neurodevelopmental comorbidities, though its translational potential is limited by the syndrome's heterogeneity in humans.[23] Meanwhile, the multiple-hit infantile spasms model, due to structural etiology, exhibits LGS features, including slow SWDs and motor seizures during sleep, primarily reflecting lesion-based etiologies.[24]

4 | ABSENCE SEIZURE AS A NETWORK DISORDER

The fundamental cellular, synaptic, and network mechanisms underlying AS are well-established, CTC network recognized as the core structure responsible for their generation.[25,26] This basic model comprises three primary

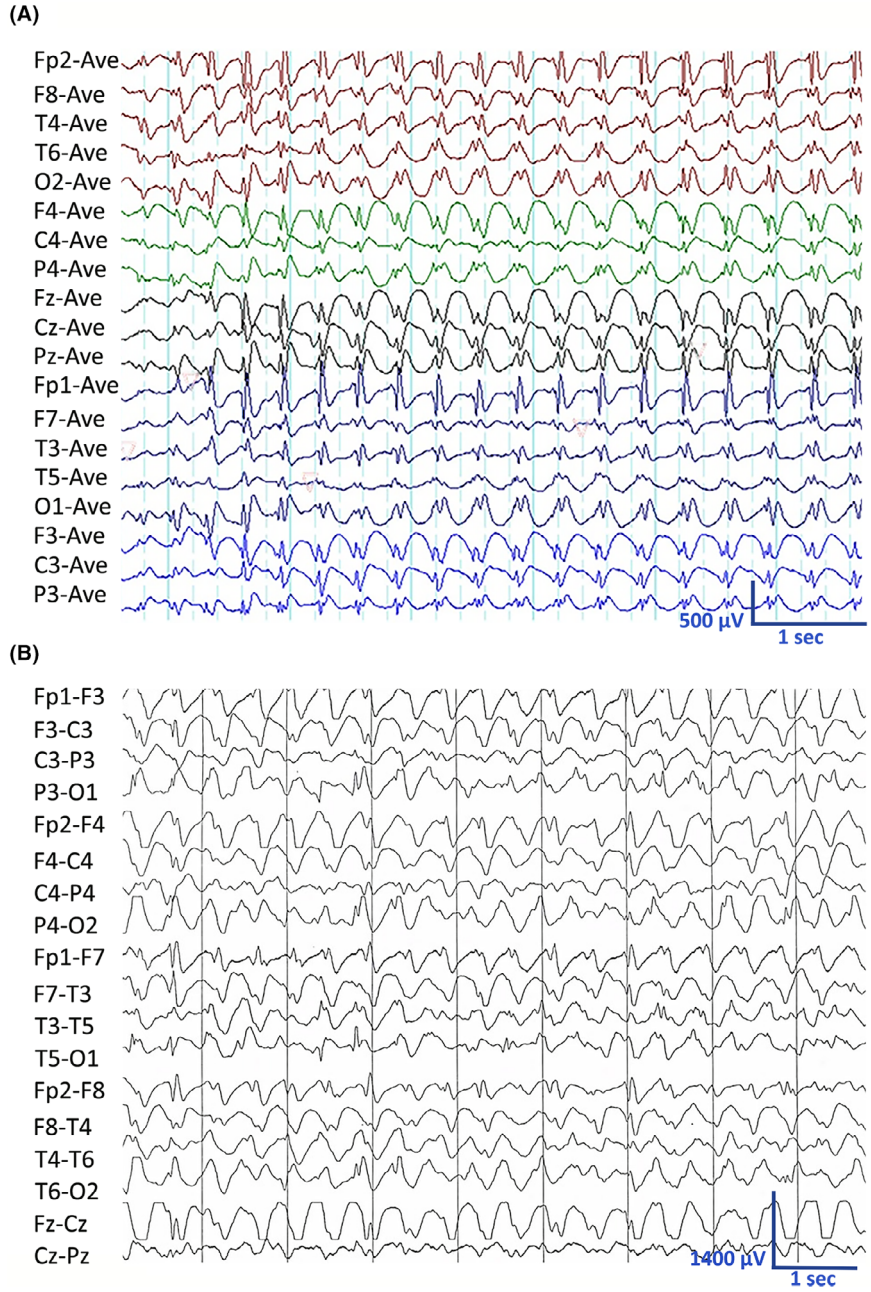

FIGURE 1 Typical and atypical SWDs recorded in human subjects. (A) EEG of a typical absence seizure, illustrating generalized, symmetrical, synchronous, and regular 3-Hz spike-and-wave discharges with frontocentral predominance. *Adapted from: Seneviratne U, Cook MJ, D'Souza WJ*, "*Electroencephalography in the diagnosis of genetic generalized epilepsy syndromes.*"[143] *Licensed under CC BY 4.0* (https://creativecommons.org/licenses/by/4.0/). (B) Slow sharp and spike–wave complexes at 2–2.5 Hz recorded in a patient with LGS. *Reproduced with permission from Bourgeois BFD, Douglass LM, Sankar R*, "*Lennox-Gastaut syndrome: A consensus approach to differential diagnosis.*"[144] License No. 6027380893584.

neuronal populations: cortical pyramidal neurons (CT), thalamocortical relay neurons (TC), and nRT inhibitory neurons (Figure 2). These populations are interconnected through reciprocal excitatory and inhibitory connections that regulate thalamocortical activity and maintain normal oscillatory function.[26,27]

Currently, the prevailing hypothesis suggests that the somatosensory cortex (SoCx) serves as the entry point for initiating aberrant corticothalamic oscillations.[5,28] However, it is also emphasized that both cortical and thalamic dysfunctions can trigger seizures, but neither is strictly necessary for seizure generation, indicating that these pathological oscillations are an intrinsic property of the network.[25,29] Regardless of the entry point, this simplified model does not fully account for the contributions of other interacting networks and subcortical structures. Recent findings highlight the critical role of subcortical structures[7,30] and additional thalamic nuclei,[5,31,32] in both the initiation and maintenance of SWDs, extending beyond the conventional model, as discussed in the following sections.

Advanced neuroimaging techniques have greatly improved our understanding of network-level disruptions underlying AS, revealing widespread structural and functional alterations in both cortical and subcortical regions.[33,34] EEG–functional MRI (EEG-fMRI) fusion studies in CAE and JAE patients, incorporating event-related analysis, time-course analysis, and functional connectivity (FC) assessments, have identified a common network of structures involved in

TABLE 2 Comparison of typical absence seizure features in rodent models and humans.[1,12,49,146]

Typical absence seizure features	Genetic rat models	Human
EEG		
Bilaterally synchronous SWDs	+	+
SWD frequency (Hz)[a]	7–11	2.5–4
SWDs from thalamus and cortex	+	+
SWDs from hippocampus[a]	–	–
Ictal behavior		
Staring; myoclonus, rhythmic twitching of the vibrissae and facial muscles	+	+
Immobility during SWDs[a]	+	+
Precise EEG/Behavioral correlation[a]	+	+
Induction of SWDs		
Intermittent photic stimulation	– (only photic afterdischarges observed)	+
Sleep–wakefulness transition (Spontaneous transition from sleep to waking)	+	+
Severe cognitive disability[a]	–	–
Pharmacology		
Blocked by ETX, VPA, TMD, LMT, CLZ	+	+
Exacerbated by $GABA_{A\&B}R$ agonists	+	+
Blocked by $GABA_BR$ antagonists	+	No data

Abbreviations: CLZ, clonazepam; ETX, ethosuximide; LMT, lamotrigine; SWDs, spike-and-wave discharges; TMD, trimethadione; VPA, valproic acid.
[a]Characteristics that separate atypical absence seizures from typical absence seizures.

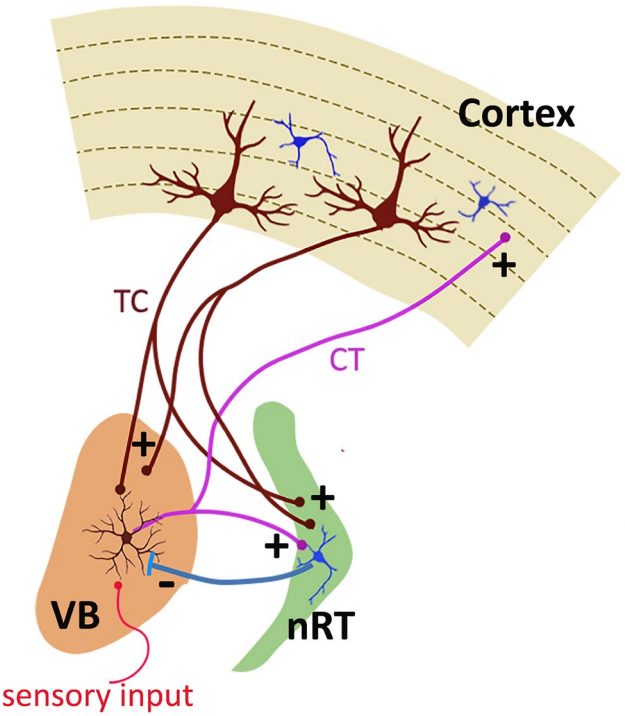

FIGURE 2 Simplified cortico-thalamo-cortical (CTC) circuit. The CTC circuit consists of corticothalamic (CT) neurons, thalamocortical (TC) relay neurons, and GABAergic neurons of the reticular thalamic nucleus (nRT), forming reciprocal excitatory and inhibitory loops.[26] CT neurons, located in cortical layers 5/6, send glutamatergic projections to both TC relay neurons in the ventrobasal thalamus (VB) and inhibitory nRT neurons, which in turn regulate TC activity. TC neurons project excitatory glutamatergic inputs back to cortical layer 4, closing the loop. The nRT provides strong GABAergic inhibition onto TC neurons, shaping their firing patterns through feed-forward (CT→nRT→TC) and feedback (TC→nRT→TC) inhibition.[145] These inhibitory mechanisms, mediated by both $GABA_A$ and $GABA_B$ receptors, control the rhythmic burst firing of TC neurons by inducing hyperpolarization, which relieves the inactivation of T-type Ca^{2+} channels. This allows low-threshold calcium spikes to generate rebound burst firing, driving rhythmic oscillations that can underlie physiological functions or pathological states. The excitatory neurotransmission in the CTC circuit is mediated by ionotropic and metabotropic glutamate receptors.[25] The precise balance of glutamatergic and GABAergic signaling within the CTC circuit is critical for maintaining normal thalamocortical function and preventing pathological oscillatory states.[27]

generalized SWDs. This network includes the anterior and posterior cortices, thalamus, caudate nuclei, cerebellum, and reticular structures of the pons, forming a cohesive system responsible for SWD generation and propagation.[35–37] Phase synchrony analysis of fMRI data has shown that BOLD signal changes occur before, during, and after the electro-clinical onset of SWDs, emphasizing the dynamic involvement of brain networks.[33] Additionally, altered resting-state FC between cortical and subcortical regions has been observed during interictal periods in CAE.[38,39] Similarly, altered FC has been observed across a broad range of cortical and subcortical regions in the GAERS model of AS.[40] These alterations emerge early in life and remain stable over time, reinforcing the concept of persistent network dysfunction associated with AS.

5 | THE CORTEX AS THE PRIMARY DRIVER OF ABSENCE SEIZURES

Substantial evidence, particularly from genetic AS models, indicates that SWDs originate in the deep layers of the SoCx and are sustained through CTC network interactions.[15,41,42] Pyramidal neurons in layers 5/6 of the SoCx, identified as key drivers of epileptic discharges

and termed ictogenic neurons, exhibit heightened excitability and an intrinsic tendency to generate epileptic oscillations.[42,43] The increased excitability and epileptiform oscillations in the SoCx are mechanistically linked to morphological neuronal changes,[44,45] alterations in ion channel expression or function,[15,46] synaptic impairments,[47] neurotransmitter imbalances,[48,49] and inflammatory processes.[50] In GAERS, these neurons show age-related increases in excitability, synaptic activity, and spontaneous firing, which are closely associated with seizure maturation.[51] Aberrant wiring during cortical development[52] may contribute to hyperexcitability and dysfunctional networks in the primary somatosensory cortex (S1).[53] Furthermore, selective deletion of P/Q-type calcium channels in layer VI corticothalamic neurons induces spontaneous SWDs with behavioral arrest in mice, mimicking human absence epilepsy (AE).[54] Elevated T-type calcium currents in postsynaptic thalamic relay and nRT neurons drive this phenomenon, illustrating how a single cortical mutation can remodel the thalamus and promote generalized SWD development.

SWD onset and propagation patterns vary across models. In the JME mouse model (*Gabra1*$^{+/A322D}$)[55] and gamma-Hydroxybutyric acid-induced (GHB) model,[56] SWDs originate in the anterior cortex; whereas in the monogenic PLCβ4 model,[57] they initiate in the SoCx before spreading to the frontal cortex. Notably, the GHB model exhibits multiple cortical SWD foci, suggesting diverse initiation sites across genetic and pharmacological models, paralleling findings in children with AS.[56] These variations may stem from species differences, recording methods, or manipulation techniques but also suggest alternative SWD initiation sites. Indeed, studies on CAE patients have identified dynamic epileptogenic networks, in which one or more hyperexcitable cortical nodes initiate and sustain SWDs in response to thalamic input.[58]

Advanced fMRI and magnetoencephalography MEG analyses suggest that SWDs develop gradually through regional interactions before generalization.[33,34,56,59] A recent study identified a dynamic network where a focal cortical source, typically in the parietal cortex, initiates spatiotemporal changes leading to SWD generalization.[34] Notably, SWD onset location influences treatment response, with parietal/occipital onset linked to better seizure control than frontal/temporal onset. During generalization, a consistent network pattern emerges, with high connectivity in bilateral frontal/parietal areas during spike phases and widespread cortical synchronization during wave phases, reflecting a transition from focal to generalized activity. Consistent with findings in CAE patients,[60] WAG/Rij rats exhibit a progressive increase in intracortical connectivity before SWD onset, preceding thalamocortical engagement.[61] These findings suggest that SWDs are not abrupt, generalized events but rather emerge from a network-driven mechanism that integrates cortical-driven seizure initiation, thalamocortical interactions, and dynamic connectivity shifts, highlighting the necessity of a systems-level perspective in understanding their propagation.

6 | THALAMIC NUCLEI IN ABSENCE SEIZURES: DRIVERS OF NETWORK DYNAMICS

Research on AS models has predominantly focused on the CTC network, which includes the S1, the VB thalamus as a first-order (FO) relay, and the nRT. However, higher-order (HO) thalamic nuclei are also recognized as essential components of this circuitry. Thalamic relay nuclei are classified based on their primary inputs: FO nuclei receive sensory-driven signals from subcortical regions, whereas HO nuclei primarily process input from cortical layer 5 projections.[62,63] Recent studies indicate that HO thalamic nuclei play a role in the initiation and maintenance of SWDs.[6,32,64] Furthermore, advanced signal processing techniques and high-resolution EEG analyses suggest that a simplistic model is insufficient to fully capture the complexity of SWD generation and network dynamics.[5,65] In response, Lüttjohann and van Luijtelaar[5] proposed an extended model incorporating additional thalamic structures (Figure 3). While the role of thalamic nuclei in GGE has been extensively reviewed elsewhere,[5] the following section will focus on recent findings regarding the involvement of the posterior nucleus (PO), the anterior nucleus (ANT), and the centromedian nucleus (CM) in SWD dynamics.

6.1 | The posterior nucleus

The PO serves as a key hub for integrating and relaying information between the thalamus and cortical regions, including S1, secondary somatosensory cortex, and motor cortices.[66,67] Its extensive connectivity modulates thalamocortical and corticothalamic communication.[66] PO stimulation excites cortical pyramidal neurons, enhancing their sensitivity.[68,69] Evidence from GAERS suggests increased driver synapse efficiency between S1 and PO,[70] potentially facilitating recurrent excitation. Recent studies utilizing pharmacological and optogenetic interventions,[32] single-unit recordings,[6] high-resolution EEG, and advanced network analyses[64] have highlighted the PO's critical role in SWD generation, maintenance, and propagation in AS models.

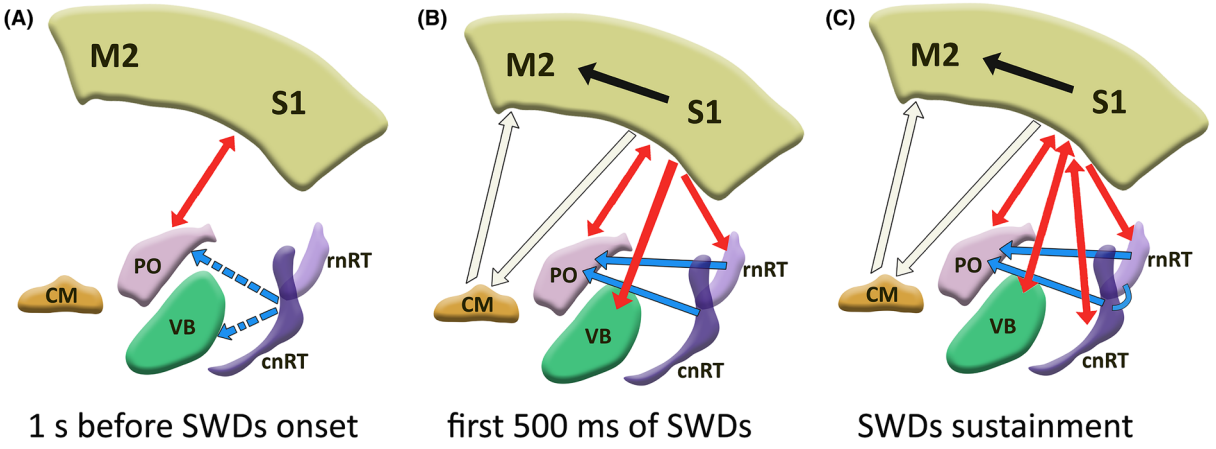

FIGURE 3 The extended model of SWD generation, generalization, and maintenance in genetic absence epilepsy rats, as proposed by Lüttjohann and van Luijtelaar.[5] Unlike the basic CTC model, this framework incorporates dynamic SWD generation. (A) One second before SWD onset, a gradual bidirectional increase in activity emerges between S1 and PO (bidirectional red arrow), potentially leading to transient S1 hyperexcitability. Simultaneously, nRT decreases its inhibitory influence on PO and VB (dashed blue arrows), possibly creating a dormant neuronal population that S1 may recruit into SWD generation. (B) During the first 500 ms of SWDs, S1 predominantly drives most thalamic nuclei (unidirectional red arrows). Meanwhile, nRT enhances its inhibitory influence on PO (blue arrows), promoting conditions that support burst firing. SWD generalization occurs through two distinct pathways: The spike component propagates to distant cortical areas (M2) via the CM (black arrows), while the wave component is transmitted through intracortical pathways. (C) Five hundred milliseconds after SWD onset, communication between S1 and the thalamic nuclei shifts to a bidirectional interaction (bidirectional red arrows), sustaining SWD activity. Concurrently, intra-nRT inhibition (blue line) progressively intensifies, peaking around one second before SWD termination and potentially modulating seizure duration. CM, centromedian thalamic nucleus; cnRT, caudal pole of reticular thalamic nucleus; M2, secondary motor cortex; PO, posterior thalamic nucleus; rnRT, rostral pole of reticular thalamic nucleus; S1, primary somatosensory cortex; VB, ventrobasal thalamus. Adapted from "Extended model on SWD generation, generalization and sustainment" by Lüttjohann A and van Luijtelaar G,[5] licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Nonlinear analysis of preictal to ictal LFPs in freely behaving WAG/Rij rats indicates that S1-PO communication increases before SWD onset, preceding changes in the Ventral–Postero-Medial, rostral and caudal nRT, and ANT.[64] Consistent with prior findings,[41] all other nuclei were driven by S1 during the first 500 ms of SWDs, while PO maintained strong bidirectional communication with S1, sustaining reverberatory activity essential for SWD initiation and maintenance.[64] SWD termination coincided with a sudden cessation of this activity, underscoring PO's role in thalamocortical feedback.[71] Cross-correlation of single-unit recordings in GAERS further confirmed increased SoCx-PO bidirectional coupling in the first 500 ms of SWDs, reinforcing PO's critical involvement in seizure dynamics.[6]

A recent study in freely moving GAERS rats further highlighted the essential role of PO and the lateral posterior nucleus (LP) in SWD propagation and maintenance.[32] Pharmacological inhibition of either nucleus delayed SWD spread from S1 to primary motor cortex (M1), V1, LP, and PO while increasing SWD breaks, defined as ≥500 ms periods where SWDs were absent from all channels except S1. Inhibition also elevated nongeneralized SWDs, restricting activity to S1 alone or S1-M1, without engaging LP or PO. Notably, LP inhibition produced effects similar to PO inhibition despite LP lacking direct input from S1, providing causal evidence that HO thalamic nuclei contribute to SWD propagation independently of reciprocal S1 connectivity. While this study indicates that PO does not initiate SWDs, it suggests that SWD generalization is driven by both intracortical connections and local thalamocortical modules.

6.2 | The Centromedian nucleus

The CM, an intralaminar thalamic nucleus, receives glutamatergic input from the SoCx and projects to the M1 and secondary motor cortex (M2).[72,73] Tractography studies have linked the CM to the anterior insula and frontal operculum, as well as to other thalamic nuclei, including the nRT.[73] In patients with IGE, the CM has been shown to activate during generalized SWDs.[37] Additionally, clinical studies suggest that deep brain stimulation (DBS) targeting the CM may be an effective treatment for individuals with drug-resistant IGE.[74] AS models indicate that the CM contributes to SWD generalization, likely through its extensive cortical connections.[75–77] Findings also suggest that the intralaminar nuclei can trigger AS under hypoxic conditions, indicating that even HO thalamic

nuclei, despite lacking direct recurrent connections with the primary initiation site, may play a crucial role in SWD generation.[78]

Recently, Terlau et al.[31] demonstrated that CM contributes to the rapid spread of SWD activity from S1 in GAERS rats. Local pharmacological inhibition of the CM during epidural ECoG recordings in S1 and M2 significantly reduced SWD incidence at both sites, though less effectively than VB inhibition. For remaining SWDs, the spike amplitude in M2 was reduced, while the wave's amplitude and incidence remained unchanged, and the wave component in M2 remained synchronized with SWDs in S1. Current source density analysis revealed that the spikes were associated with independent current sinks in the upper cortical layers, which were reduced following CM inhibition, whereas the wave component was linked to a deep-layer V current sink that was prolonged by CM inhibition. These findings demonstrate that spikes and waves can be functionally decoupled and propagated through independent pathways. The spikes relay via the CM from S1 to M2, while waves originate from deep-layer V neurons in S1 and propagate through intracortical pathways. As noted by van Luijtelaar,[79] these results align with Guillery and Sherman's[63] theory that intercortical communication occurs largely through HO thalamic nuclei.

6.3 | The anterior thalamic nuclei

The ANT receives input from the hippocampus via the fornix or from the mammillary bodies through the mammillothalamic tract and projects to the cingulate cortex, completing the Papez circuit as information returns to the hippocampus via the cingulate bundle.[80] The ANT serves as a crucial link between prefrontal and limbic functions[81] and has been implicated in various types of generalized epilepsies, as reviewed elsewhere.[5] Neuroimaging studies have reported volume changes in the ANT,[82,83] while EEG-fMRI studies have identified a correlation between the ANT and SWDs in patients with IGE.[37] Although SWDs have been detected in the ANT of WAG/Rij rats,[64] evidence suggests it is not the primary thalamic nucleus involved in SWD generation.[84]

Beyond AE, the ANT plays a key role in propagating and sustaining focal limbic seizures.[85,86] Limbic structures are integral to AS, contributing to the broader epilepsy network.[12] While the ANT is involved in both AS and focal limbic seizures, the networks underlying their generalization may interact oppositely.[87–91] Notably, the ANT is a primary target for DBS in refractory focal epilepsy.[92] Given its role in limbic circuits, ANT DBS is considered a promising approach for modulating seizure networks and thalamocortical excitability.[93]

Recent findings demonstrate that both chemogenetic activation and inhibition of ANT-parvalbumin (PV) neurons exacerbate AS induced by pentilentetrazol (PTZ) in mice.[94] Moreover, chemogenetic inhibition of ANT-PV neurons alone, without PTZ administration, was sufficient to induce generalized SWDs, underscoring the importance of maintaining ANT-PV neuron activity in AS. However, further studies in additional AS models are needed to validate these findings.

7 | CORTICAL AND THALAMIC CELLULAR ACTIVITY DURING SWDs

Recent electrophysiological and imaging studies in nonanesthetized AS models have provided high-resolution insights into ictal cortical and thalamic activity.[95–98] In *stargazer* mice, most primary visual cortex (V1) neurons exhibit reduced activity during SWDs, while a subset remains unchanged or increases activity, with suppression beginning seconds before onset.[97] Similarly, in GAERS rats, S1 neurons show a net reduction in firing, where spike-phase increases are outweighed by greater wave-phase suppression.[95] Notably, cortical neuron rhythmicity rises well before seizure onset, suggesting a prolonged preictal phase. fMRI studies in nonanesthetized GAERS further reveal widespread cortical suppression,[95] consistent with human AS.[35,36] These findings contradict results from anesthetized models and early in vitro studies, suggesting that the cortical network does not engage uniformly during absence seizures and that neuronal synchrony may be lower than previously thought.[29]

In the C3H/HeJ mouse model, neuronal rhythmicity significantly increases during SWDs, similar to GAERS, yet without a global reduction in cortical firing.[98] This discrepancy may arise from differences in extracellular recording techniques or species-specific neuronal mechanisms underlying AS generation.

Using ensemble recordings in freely moving GAERS and GHB-treated rats, McCafferty et al.[96] demonstrated that cortical excitation primarily drives thalamic activity, while nRT feed-forward inhibition shapes thalamic output synchrony. During AS, TC neurons exhibit an overall reduction in firing, with minimal T-type Ca^{2+} channel-dependent burst activity. TC neuron suppression has been attributed to multiple mechanisms,[7] including enhanced tonic $GABA_A$ inhibition, which prolongs nRT burst-induced IPSPs, effectively silencing TC output for most of the SWD cycle. Additionally, a stronger cortico-nRT than cortico-TC synaptic drive may further contribute to TC neuron suppression. Moreover, increased ictal firing of GABAergic neurons in the substantia nigra pars reticulata

(SNR) may amplify nRT-driven inhibition, reinforcing TC suppression throughout the seizure. Beyond T-type Ca^{2+} channels, HCN channel dysfunction has been implicated in altered TC neuron excitability.[7,99] In AE models, elevated I_h conductance reduces membrane hyperpolarization, thereby limiting T-type Ca^{2+} channel activation and suppressing LTS-mediated burst firing in TC neurons.

Importantly, blocking T-type Ca^{2+} channels in TC neurons does not affect seizure expression or ictal synchrony, whereas their blockade in nRT and cortical neurons suppresses SWDs.[96] This indicates that T-type Ca^{2+} channels in TC neurons are nonessential for AS generation, while their activation in nRT and cortical neurons plays a crucial role.

8 | THE ROLE OF BASAL GANGLIA IN ABSENCE SEIZURES

The BG network consists of interconnected subcortical nuclei that integrate neocortical and subcortical inputs, relaying projections to diverse regions across the diencephalon and brainstem.[100] The striatum and subthalamic nucleus (STN) serve as primary cortical entry points, while the SNR and globus pallidus internus (GPi) function as major output structures. GABAergic neurons of the SNR target over 40 thalamic nuclei, including the ventromedial, ventroanterior, mediodorsal, centrolateral/medial, parafascicular nuclei, nRT, and the zona incerta (ZI).[100,101]

The BG play a crucial role in modulating corticothalamic and limbic networks, influencing seizure susceptibility and propagation across various experimental models.[7,102–104] Pharmacological manipulations in the SNR, striatum, and STN have demonstrated the BG's involvement in AS regulation.[105–107] In GAERS, ictal firing patterns reveal distinct BG dynamics,[108,109] where cortico-striatal neurons exhibit rhythmic depolarization phase-locked to SWD spikes, while striatal GABAergic medium spiny neurons (MSNs) are suppressed due to strong feed-forward inhibition from fast-spiking interneurons (FSIs) synchronized with excitatory cortical inputs.[108] Additionally, STN glutamatergic neurons display high-frequency bursts linked to SWD spikes,[109] enhancing BG output to the thalamus and increasing GABAergic firing in the SNR,[107] promoting ictal inhibition of TC neurons. This extrathalamic inhibition contributes to reduced TC neuron firing during SWDs,[7,96] reinforcing BG circuits in AS pathophysiology.

Recent findings suggest that the SNR regulates AS beyond its thalamic projections, involving GABAergic pathways to additional regions.[110,111] Inhibiting SNR projections to the dorsolateral superior colliculus (SC) mimics the effects of SNR inhibition and dorsolateral SC activation, highlighting their functional interaction.[110] Moreover, optogenetic silencing of SNR projections to the SC and pedunculopontine nucleus replicates the SWD suppression observed with direct SNR inhibition in the GBL model.[110] In WAG/Rij rats, dorsolateral SC activity decreases before SWD onset, followed by an increase during and after seizures.[111] Notably, optogenetic dorsolateral SC stimulation significantly reduces SWDs, emphasizing SC projections in seizure modulation.

The BG-AS relationship extends beyond the ictal period[112] and includes interictal FC alterations in both humans and AS models.[40,113,114] rs-fMRI and causality analyses in IGE patients revealed increased FC between the striatum and thalamus, with a bidirectional relationship between thalamus–striatum and cortical connections, highlighting subcortical involvement in cortical network modulation.[113] Similarly, rs-fMRI in GAERS (under light isoflurane anesthesia, free of SWDs) demonstrated enhanced connectivity and neuronal activity in the cortex, BG, and limbic regions, suggesting a disease-specific resting-state brain network.[40]

Emerging evidence implicates the dopaminergic nigrostriatal pathway in AS modulation.[115–117] The density of dopaminergic neurons in the lateral SNC is negatively correlated with SWD occurrence in WAG/Rij rats,[116] while lesion-induced degeneration of this pathway in GAERS prolongs SWD duration.[115]

The SNR in adult male rats comprises two distinct subregions: the anterior SNR (SNRa) and the posterior SNR (SNRp), each exerting differential effects on seizure propagation and regulation.[103,118] As discussed in the following section, WAG/Rij and GAERS rats exhibit resistance or a delay in the secondary generalization of focal limbic seizures induced by kindling.[87,90] This phenomenon is mediated by the SNRp rather than SNRa and is completely abolished when SNRp is inhibited using lidocaine,[91] suggesting that an altered GABAergic response in GAERS contributes to this resistance mechanism.[119]

A recent study suggests that impaired cortico-striatal excitatory transmission contributes to AS.[30] Conditional deletion of Stxbp1 or Scn2a in cortico-striatal projection neurons induces SWDs in cortical and striatal regions, while pharmacological inhibition of cortico-striatal excitatory transmission to FSIs also triggers SWDs in wild-type mice. These findings support the cortico-striato-thalamocortical circuit as a key epileptogenic pathway, implicating BG involvement through an indirect mechanism. SWD generation linked to reduced cortical excitatory input to FSIs leads to disinhibition of MSNs, activation of the GPi/SNR, excessive thalamic suppression, and ultimately, SWD generation.

Overall, these findings highlight the BG's critical role in AS modulation through direct thalamic inhibition,

SC projections, and dopaminergic regulation from the SNC. AS arise from complex interactions among cortical, striatal, and thalamic circuits, with the BG acting as a central hub. Furthermore, disruptions in cortico-striatal excitatory transmission contribute to AE by disrupting the inhibitory-excitatory balance within these networks.

9 | THE INVOLVEMENT OF LIMBIC STRUCTURES IN ABSENCE SEIZURES

Growing evidence highlights the limbic system's role in modulating typical AS.[12,90,120] While hippocampal SWDs are inconsistent,[121] genetic and pharmacological models indicate increased hippocampal-CTC synchronization, along with altered neurochemical signaling, synaptic plasticity, and oscillatory activity (Table 3). Moreover, studies in JAE patients and GAERS rats demonstrate FC alterations within limbic regions.[40,122] These findings suggest that limbic circuits actively influence seizure dynamics and associated cognitive dysfunction, rather than serving as passive bystanders in AS pathophysiology.

Our group previously demonstrated a functional interaction between limbic structures and the CTC network in both absence and temporal lobe epilepsy models.[12,87–91,123] In GAERS and WAG/Rij rats, resistance to secondary generalization of focal limbic seizures has been observed, particularly following kindling or intra-amygdaloid kainic acid injections.[88,90,123,124] The strong correlation between basal SWD activity and kindling resistance supports the role of limbic structures in AE.[87] Functional alterations in temporal lobe structures, alongside thalamic and neocortical changes, appear to limit kindling-induced seizure progression.[125] Notably, enhanced tonic and phasic GABAergic inhibition in the hippocampus has been implicated in kindling resistance in GAERS.[126] These findings indicate that in typical AE, limbic structures modulate network dynamics, whereas atypical AE is more directly dependent on limbic circuits, influencing both seizure expression and associated cognitive impairments.[3,12,127]

Limbic structures, particularly the hippocampus, are either actively engaged in or dynamically modulated by SWDs in AS models.[8,120,128–131] In the GBL model, SWDs enhance hippocampal–thalamocortical synchronization[128]; increase FC between the hippocampus, thalamus, and sensorimotor cortex[129]; and modulate gamma oscillations, with pronounced effects in the frontal cortex and hippocampus.[120] Similarly, WAG/Rij and GAERS rats exhibit elevated 1–30 Hz coherence between the hippocampal hilus and SoCx during SWDs.[8] In WAG/Rij rats, hippocampal ripples and high-frequency oscillations decrease, with ripple activity nearly absent 4–8 seconds before seizure onset and further suppressed during SWDs.[131]

In GAERS, LFP recordings revealed SWDs in the lateral hypothalamus (LH) with lower amplitude and delayed onset relative to S1. During SWDs, LH neuronal activity decreases, marked by a reduction in firing rates. Notably, many LH neurons project to the dorsal raphe nucleus, a key serotonergic center, suggesting LH involvement in AS modulation and its potential role in comorbidities like depression and altered arousal states.[132] Neuropsychiatric comorbidities, including anxiety and depression, are frequently observed in IGE and its animal models,[16,133,134] further supporting a link between AS networks and limbic dysfunction.

10 | CEREBELLAR INFLUENCE ON ABSENCE SEIZURES

Emerging clinical and experimental evidence suggests that, despite historically not being associated with epilepsy, the cerebellum plays a significant role in seizure networks, including AS.[135,136] It influences epileptogenesis, modulates seizure activity, and may even function as a seizure focus. Electrophysiological studies reveal that subsets of Purkinje cells (PCs) and deep cerebellar nuclei (DCN) neurons exhibit phase-locked firing to SWDs in rodent AS models, including PCs in *tottering* mice,[9] DCN neurons in *tottering*, *C3H/HeOuJ* mice[137] and quirky and purky mice,[10] and both PCs and DCN neurons in WAG/Rij rats.[138] Additionally, SWD-modulated DCN neurons display distinct firing patterns during both ictal and interictal periods.[9] Consistently, increased cerebellar BOLD signals have been observed during SWDs in IGE patients[36] and during polyspike and interictal discharges in LGS patients.[139]

The DCN projects directly to key brain regions, including the thalamus, SC, ZI, and SN, while indirectly influencing cortical and subcortical structures such as the BG, hippocampus, and amygdala.[140] Notably, cerebellar inputs target both motor-related thalamic nuclei and intralaminar regions, including the mediodorsal, parafascicular, and centrolateral nuclei.[141] PCs, the inhibitory output neurons of the cerebellar cortex, exert strong suppressive control over DCN activity, which is crucial for AS modulation.[137,142] Optogenetic or pharmacological DCN inhibition leads to increased SWD incidence, while DCN excitation reduces SWD occurrence in AS models.[137,142] Furthermore, single-pulse optogenetic activation of the cerebello-thalamic pathway during seizures desynchronizes ictal thalamic activity, effectively terminating SWDs

TABLE 3 Neurochemical, morphological, and electrophysiological alterations observed in limbic structures in absence epilepsy models.

Feature	Model, sex, age	Brain region	Findings	Interpretation
Glutamate signaling				
Glutamate level	GAERS, F, 13 week-old	Ventral hippocampus	Higher extracellular glutamate levels compared to Wistar	Increased excitatory neurotransmission[147]
Glutamate density	GAERS, M, 6–12 months-old	CA3, DG	Increased glutamate density in CA3; decreased glutamate density in MFTs of the DG compared to Wistar	Imbalance between DG and CA3 glutamatergic transmission may contribute to altered hippocampal network dynamics[148,149]
NR2B subunits of NMDA receptor	WAG/Rij, M, 2 months-old, 6 months-old	CA1	At 6 month, reduction in NR2B expression compared to age-matched Wistar	Impaired excitatory transmission may contribute to cognitive deficits[150]
mGlu2/3 receptors	WAG/Rij, M, 2 months-old, 6 months-old	CA1, CA3, DG	At 6 month, increased expression of mGlu2/3 receptors and functional deficits in receptor signaling compared to Wistar	Impaired mGlu2/3 receptor function may contribute to cognitive deficits[151]
Glutamatergic metabolism	GAERS, M, 5 months-old	Hippocampus	Higher levels of labeled glutamate, glutamine, and aspartate compared to NEC	Increased glutamate metabolism may enhance synaptic plasticity[152]
GABA signaling				
PV^+ interneurons, CR^+ interneurons	GAERS, WAG/Rij, M, F, 8 months-old	Dorsal hippocampus	Reduced density of PV^+ and CR^+ interneurons in the hippocampal hilus compared to NEC	Neuronal loss or dysfunction may contribute to cognitive deficits[8]
GABA-ir	GAERS, M, 6 months-old	CA3	Increased GABA-ir in mossy fiber terminals compared to Wistar	Higher GABA content may contribute to resistance to convulsive seizures[153]
Other signaling systems				
MT1 and MT2 melatonin receptors	WAG/Rij rats, M, 6 months-old	Hippocampus	Lower endogenous melatonin levels; higher MT1 and MT2 expression compared to Wistar	Dysfunction in the hippocampal melatonergic system may contribute to the depression-like phenotype[154]
Histamine H1 receptor	WAG/Rij rats, M, 7–9 months-old	CA1, CA2, CA3	Increased H1 receptor densities compared to Wistar	Histaminergic modulation of the limbic system may be involved in both seizure propagation and cognitive effects of epilepsy[155]
D2-like dopamine receptors	WAG/Rij, M, 7 months-old	CA3	Reduction in D2-like receptor density compared to ACI	Dopaminergic dysfunction may contribute to increased excitability, impaired cognitive function, and altered emotional regulation[156]
Morphology, neurogenesis, and apoptosis				
Dendrite morphology	GAERS, M, 6 months-old	CA1	Excessive dendritic branching and increased synaptic density, particularly stubby-type spines, compared to Wistar	Hyperconnectivity and excitatory overdrive may contribute to cognitive deficits and altered hippocampal function[157]
Cell density	WAG/Rij, M, 6 months-old	CA1, CA3, Hilus	Significant cell loss compared to Wistar	Hippocampal atrophy linked to prolonged seizure activity, contributing to cognitive and mood disturbances[154]

(Continues)

TABLE 3 (Continued)

Feature	Model, sex, age	Brain region	Findings	Interpretation
Morphometric abnormalities	GAERS, F, 14 weeks-old	Amygdala, hippocampus	Increased amygdala volume, regional hippocampal volume loss (no overall volume loss) compared to NEC	Amygdala enlargement may contribute to cognitive and emotional disturbances[158]
Neurogenesis	GAERS, M, 21 days-old, 3 months-old	DG	Enhanced neurogenesis in young GAERS compared to age-matched Wistar	Early hippocampal plasticity changes could be linked to epileptogenesis[159]
Neurogenesis, mTOR pathway activation	WAG/Rij, M, 1 month-old, 6 months-old	Hippocampus	At 1 month, higher phospho-mTOR expression compared to age-matched Wistar	mTOR activation and hippocampal progenitor cell proliferation changes may contribute to epileptogenesis[160]
Neuronal injury and apoptosis	WAG/Rij, M, 2 months-old, 6 months-old	CA1, CA3	At 6 month, increased caspase-3 activity and higher numbers of dark neurons to Wistar	Neuronal injury correlated with age-dependent cognitive deficits[161]
Synaptic plasticity				
LTD	WAG/Rij, M, 4–6 weeks-old and 5–6 months-old	CA1	At 5-6 month, reduced metabotropic Glu1/5 receptor-mediated LTD compared to Wistar	Impaired hippocampal plasticity[162]
Inhibitory synaptic activity	GAERS, M, 13 weeks-old	CA1	Greater paired-pulse depression compared to Wistar	Increased inhibitory activity may contribute to seizure resistance[126]
Electrophysiology-Neuroimaging				
Hippocampal high frequency	WAG/Rij, M, 8–12 months-old	DG	Reduced hippocampal high-frequency oscillations and ripples before, during, and after SWDs	SWD-related seizure mechanisms actively suppress hippocampal oscillations[131]
Hippocampal coupling	WAG/Rij, M, 8–10 months-old	Dorsal hippocampus	Decrease in coupling strength from the hippocampus to the frontal cortex during SWDs	Hippocampus may have a modulatory role in AS[130]
Coherence between hippocampus and S1	GAERS, WAG/Rij, M, F, 8 months-old	Dorsal hippocampus	Increased synchronization between the S1 and hippocampus during SWDs	Hippocampus is functionally impacted during AS[8]
Coherence between hippocampus and cortex/ thalamus	GBL, Long–Evans, M, adult	CA1	Increased hippocampal coherence with the thalamus/ cortex during SWDs	Hippocampus plays an active role in AS[128]
FC	GBL, Sprague Dawley, 6–8 weeks-old	Hippocampus	Increased FC between the hippocampus and thalamus/cortex during SWDs	Hippocampus is actively engaged during AS[129]
FC	GAERS, F, 3–8 months-old	Limbic structures	Stronger FC in limbic regions Functional alterations in the septum, hypothalamus, periaqueductal gray, CA1 and CA3	Widespread functional and structural brain network alterations in AS already present at early ages[40]

Abbreviations: ACI, August Copenhagen Irish; AS, absence seizures; CR+, Calretinin positive interneuron; DG, dentate gyrus; F, female; FC, functional connectivity; GAERS, Genetic Absence Epilepsy Rats from Strasbourg; GBL, gamma-butyrolactone; H1, histamine H1 receptor; LTD, long-term depression; M, male; MFTs, mossy fiber terminals; mGlu, metabotropic glutamate receptor; MT1, MT2, melatonin receptors 1 and 2; mTOR, mechanistic target of rapamycin; NEC, nonepileptic control; NMDA, N-Methyl-D-Aspartate; nRT, reticular thalamic nucleus; PAG, Periaqueductal Gray; PV^{+}, parvalbumin-positive interneuron; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SWDs, spike-and-wave discharges; TLE, temporal lobe epilepsy; WAG/Rij, Wistar Albino Glaxo from Rijswijk.

in *tottering* mice.[142] Although direct stimulation of DCN fibers within thalamic nuclei can also disrupt generalized SWDs, this approach is less effective than direct DCN modulation.[142]

Recent studies show that genetic ablation of P/Q-type calcium channels in cerebellar granule cells (quirky) or PCs (purky) induces recurrent bilateral SWDs in mice similar to other AS models.[10] Enhancing DCN activity via excitatory Gq-coupled designer receptors exclusively activated by designer drugs (Gq-DREADDs) or mGluR1 activation reduced SWD incidence, whereas inhibitory Gi-DREADDs exacerbate seizure activity. These findings highlight the bidirectional role of DCN in seizure modulation, supporting the notion that cerebellar circuit dysfunction contributes to SWD generation.

The cerebellum, particularly DCN neurons, plays a crucial role in AS modulation, influencing both SWD generation and seizure inhibition. While cerebello-thalamic pathways contribute significantly to seizure suppression, nonthalamic DCN projections may further regulate network-level epileptogenic mechanisms, highlighting the cerebellum as a key player in AS pathophysiology.

11 | CONCLUSIONS

AS are increasingly recognized as a network-level disorder, extending beyond the classical CTC model. Evidence from neuroimaging and experimental models highlights the critical involvement of additional subcortical structures and network interactions in the generation and propagation of SWDs. Experimental models continue to provide essential insights into the cellular and circuit-level mechanisms underlying AS, offering a deeper understanding of its pathophysiology. The reconsideration of TC burst firing[96] as a fundamental mechanism for SWD maintenance further necessitates a paradigm shift in AS research and treatment approaches.

Future research should integrate advanced circuit-mapping techniques such as optogenetics, chemogenetics, and multiregional in vivo recordings with computational modeling to elucidate the causal mechanisms of absence seizures across diverse models. These approaches will help clarify the specific roles of cortical, thalamic, basal ganglia, cerebellar, and limbic circuits in seizure dynamics. Concurrently, translational studies employing EEG-fMRI, MEG, and machine learning-based connectivity analyses may identify reliable network-level biomarkers and therapeutic targets. Computational modeling of seizure evolution can further guide the development of circuit-based interventions. Bridging preclinical and clinical findings through cross-species models and multimodal strategies will be essential for advancing precision therapies in AS.

ACKNOWLEDGMENTS

The work, performed in the Filiz Onat's laboratory, was funded by the European Commission Horizon Europe Programme under the call HORIZON-WIDERA-2021-ACCESS-03 [Grant Number 101078981-GEMSTONE].

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Ozlem Akman https://orcid.org/0000-0002-0610-7955

REFERENCES

1. Hirsch E, French J, Scheffer IE, Bogacz A, Alsaadi T, Sperling MR, et al. ILAE definition of the idiopathic generalized epilepsy syndromes: position statement by the ILAE task force on nosology and definitions. Epilepsia. 2022;63:1475–99.
2. Jafarian M, Alipour ME, Karimzadeh F. Experimental models of absence epilepsy. Basic Clin Neurosci. 2020;11:715–26.
3. Cortez MA, Kostopoulos GK, Snead OC. Acute and chronic pharmacological models of generalized absence seizures. J Neurosci Methods. 2016;260:175–84.
4. Akman O, Demiralp T, Ates N, Onat FY. Electroencephalographic differences between WAG/Rij and GAERS rat models of absence epilepsy. Epilepsy Res. 2010;89(MAY 2010):185–93.
5. Lüttjohann A, van Luijtelaar G. The role of thalamic nuclei in genetic generalized epilepsies. Epilepsy Res. 2022;182:106918.
6. Lüttjohann A, Pape HC. Regional specificity of cortico-thalamic coupling strength and directionality during waxing and waning of spike and wave discharges. Sci Rep. 2019;9:2100.
7. Crunelli V, Lőrincz ML, McCafferty C, Lambert RC, Leresche N, Di Giovanni G, et al. Clinical and experimental insight into pathophysiology, comorbidity and therapy of absence seizures. Brain. 2020;143:2341–68.
8. Papp P, Kovács Z, Szocsics P, Juhász G, Maglóczky Z. Alterations in hippocampal and cortical densities of functionally different interneurons in rat models of absence epilepsy. Epilepsy Res. 2018;145:40–50.
9. Kros L, Lindeman S, Eelkman Rooda OHJ, Murugesan P, Bina L, Bosman LWJ, et al. Synchronicity and rhythmicity of Purkinje cell firing during generalized spike-and-wave discharges in a natural mouse model of absence epilepsy. Front Cell Neurosci. 2017;11:346.
10. Schwitalla JC, Pakusch J, Mücher B, Brückner A, Depke DA, Fenzl T, et al. Controlling absence seizures from the cerebellar nuclei via activation of the G. Cell Mol Life Sci. 2022;79:197.
11. Zhao X, He Z, Li Y, Yang X, Li B. Atypical absence seizures and gene variants: a gene-based review of etiology, electro-clinical features, and associated epilepsy syndrome. Epilepsy Behav. 2024;151:109636.

12. Onat FY, van Luijtelaar G, Nehlig A, Snead OC. The involvement of limbic structures in typical and atypical absence epilepsy. Epilepsy Res. 2013;103:111–23.
13. Noebels JL, Avoli M, Rogawski MA, Vezzani A, Delgado-Escueta AV. Jasper's basic mechanisms of the epilepsies. Oxford: Oxford University Press; 2024.
14. van Luijtelaar G, Oijen G. Establishing drug effects on electrocorticographic activity in a genetic absence epilepsy model: advances and pitfalls. Front Pharmacol. 2020;11:395.
15. Depaulis A, David O, Charpier S. The genetic absence epilepsy rat from Strasbourg as a model to decipher the neuronal and network mechanisms of generalized idiopathic epilepsies. J Neurosci Methods. 2016;260:159–74.
16. Russo E, Citraro R. Pharmacology of epileptogenesis and related comorbidities in the WAG/Rij rat model of genetic absence epilepsy. J Neurosci Methods. 2018;310:54–62.
17. Rudolf G, Bihoreau MT, Godfrey RF, Wilder SP, Cox RD, Lathrop M, et al. Polygenic control of idiopathic generalized epilepsy phenotypes in the genetic absence rats from Strasbourg (GAERS). Epilepsia. 2004;45:301–8.
18. Maheshwari A, Noebels JL. Monogenic models of absence epilepsy: windows into the complex balance between inhibition and excitation in thalamocortical microcircuits. Prog Brain Res. 2014;213:223–52.
19. Ellens DJ, Hong E, Giblin K, Singleton MJ, Bashyal C, Englot DJ, et al. Development of spike-wave seizures in C3H/HeJ mice. Epilepsy Res. 2009;85:53–9.
20. Beyer B, Deleuze C, Letts VA, Mahaffey CL, Boumil RM, Lew TA, et al. Absence seizures in C3H/HeJ and knockout mice caused by mutation of the AMPA receptor subunit Gria4. Hum Mol Genet. 2008;17:1738–49.
21. Cao F, Liu JJ, Zhou S, Cortez MA, Snead OC, Han J, et al. Neuroligin 2 regulates absence seizures and behavioral arrests through GABAergic transmission within the thalamocortical circuitry. Nat Commun. 2020;11:3744.
22. Wang W, Frankel WN. Overlaps, gaps, and complexities of mouse models of developmental and epileptic encephalopathy. Neurobiol Dis. 2021;148:105220.
23. Qu S, Catron M, Zhou C, Janve V, Shen W, Howe RK, et al. GABAA receptor β3 subunit mutation D120N causes Lennox–Gastaut syndrome in knock-in mice. Brain Commun. 2020;2:fcaa028.
24. Akman O, Briggs SW, Mowrey WB, Moshé SL, Galanopoulou AS. Antiepileptogenic effects of rapamycin in a model of infantile spasms due to structural lesions. Epilepsia. 2021;62:1985–99.
25. Lindquist BE, Timbie C, Voskobiynyk Y, Paz JT. Thalamocortical circuits in generalized epilepsy: pathophysiologic mechanisms and therapeutic targets. Neurobiol Dis. 2023;181:106094.
26. Huguenard J. Current controversy: spikes, bursts, and synchrony in generalized absence epilepsy: unresolved questions regarding thalamocortical synchrony in absence epilepsy. Epilepsy Curr. 2019;19:105–11.
27. Fogerson PM, Huguenard JR. Tapping the brakes: cellular and synaptic mechanisms that regulate thalamic oscillations. Neuron. 2016;92:687–704.
28. Depaulis A, Charpier S. Pathophysiology of absence epilepsy: insights from genetic models. Neurosci Lett. 2018;667:53–65.
29. Huguenard JR. Perspective: is cortical hyperexcitability the only path to generalized absence epilepsy? Epilepsy Curr. 2020;20:59S–61S.
30. Miyamoto H, Tatsukawa T, Shimohata A, Yamagata T, Suzuki T, Amano K, et al. Impaired cortico-striatal excitatory transmission triggers epilepsy. Nat Commun. 2019;10:1917.
31. Terlau J, Yang JW, Khastkhodaei Z, Seidenbecher T, Luhmann HJ, Pape HC, et al. Spike-wave discharges in absence epilepsy: segregation of electrographic components reveals distinct pathways of seizure activity. J Physiol. 2020;598:2397–414.
32. Atherton Z, Nagy O, Barcsai L, Sere P, Zsigri N, Földi T, et al. Higher-order thalamic nuclei facilitate the generalization and maintenance of spike-and-wave discharges of absence seizures. Neurobiol Dis. 2023;178:106025.
33. Tangwiriyasakul C, Perani S, Centeno M, Yaakub SN, Abela E, Carmichael DW, et al. Dynamic brain network states in human generalized spike-wave discharges. Brain. 2018;141:2981–94.
34. Ossenblok P, van Houdt P, Colon A, Stroink H, van Luijtelaar G. A network approach to investigate the bi-hemispheric synchrony in absence epilepsy. Clin Neurophysiol. 2019;130:1611–9.
35. Salek-Haddadi A, Lemieux L, Merschhemke M, Friston KJ, Duncan JS, Fish DR. Functional magnetic resonance imaging of human absence seizures. Ann Neurol. 2003;53:663–7.
36. Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc Natl Acad Sci USA. 2005;102:15236–40.
37. Tyvaert L, Chassagnon S, Sadikot A, LeVan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: an EEG-fMRI study. Neurology. 2009;73:2018–22.
38. Wang Y, Li Y, Sun F, Xu Y, Xu F, Wang S, et al. Altered neuromagnetic activity in default mode network in childhood absence epilepsy. Front Neurosci. 2023;17:1133064.
39. Wu C, Xiang J, Jiang W, Huang S, Gao Y, Tang L, et al. Altered effective connectivity network in childhood absence epilepsy: a multi-frequency MEG study. Brain Topogr. 2017;30:673–84.
40. Wachsmuth L, Hebbelmann L, Prade J, Kohnert LC, Lambers H, Lüttjohann A, et al. Epilepsy-related functional brain network alterations are already present at an early age in the GAERS rat model of genetic absence epilepsy. Front Neurol. 2024;15:1355862.
41. Meeren HK, Pijn JP, Van Luijtelaar EL, Coenen AM, Lopes da Silva FH. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. J Neurosci. 2002;22:1480–95.
42. Polack PO, Guillemain I, Hu E, Deransart C, Depaulis A, Charpier S. Deep layer somatosensory cortical neurons initiate spike-and-wave discharges in a genetic model of absence seizures. J Neurosci. 2007;27:6590–9.
43. Polack PO, Mahon S, Chavez M, Charpier S. Inactivation of the somatosensory cortex prevents paroxysmal oscillations in cortical and related thalamic neurons in a genetic model of absence epilepsy. Cereb Cortex. 2009;19:2078–91.
44. Karpova AV, Bikbaev AF, Coenen AM, van Luijtelaar G. Morphometric Golgi study of cortical locations in WAG/Rij rats: the cortical focus theory. Neurosci Res. 2005;51:119–28.

45. Ilbay G, Balıkcı A, Köktürk S, Yılmaz MY, Ates N, Baydemır C, et al. Neonatal tactile stimulation downregulates dendritic spines in layer V pyramidal neurons of the WAG/Rij rat somatosensory cortex. Neural Plast. 2022;2022:7251460.
46. Kole MH, Bräuer AU, Stuart GJ. Inherited cortical HCN1 channel loss amplifies dendritic calcium electrogenesis and burst firing in a rat absence epilepsy model. J Physiol. 2007;578:507–25.
47. D'Antuono M, Inaba Y, Biagini G, D'Arcangelo G, Tancredi V, Avoli M. Synaptic hyperexcitability of deep layer neocortical cells in a genetic model of absence seizures. Genes Brain Behav. 2006;5:73–84.
48. Arkan S, Kasap M, Akman Ö, Akpınar G, Ateş N, Karson A. The lower expression of parvalbumin in the primary somatosensory cortex of WAG/Rij rats may facilitate the occurrence of absence seizures. Neurosci Lett. 2019;709:134299.
49. Russo E, Citraro R, Constanti A, Leo A, Lüttjohann A, van Luijtelaar G, et al. Upholding WAG/Rij rats as a model of absence epileptogenesis: hidden mechanisms and a new theory on seizure development. Neurosci Biobehav Rev. 2016;71:388–408.
50. Dutuit M, Didier-Bazès M, Vergnes M, Mutin M, Conjard A, Akaoka H, et al. Specific alteration in the expression of glial fibrillary acidic protein, glutamate dehydrogenase, and glutamine synthetase in rats with genetic absence epilepsy. Glia. 2000;32:15–24.
51. Jarre G, Altwegg-Boussac T, Williams MS, Studer F, Chipaux M, David O, et al. Building up absence seizures in the somatosensory cortex: from network to cellular epileptogenic processes. Cereb Cortex. 2017;27:4607–23.
52. Plutino S, Laghouati E, Jarre G, Depaulis A, Guillemain I, Bureau I. Barrel cortex development lacks a key stage of hyperconnectivity from deep to superficial layers in a rat model of absence epilepsy. Prog Neurobiol. 2024;234:102564.
53. Studer F, Jarre G, Pouyatos B, Nemoz C, Brauer-Krisch E, Muzelle C, et al. Aberrant neuronal connectivity in the cortex drives generation of seizures in rat absence epilepsy. Brain. 2022;145:1978–91.
54. Bomben VC, Aiba I, Qian J, Mark MD, Herlitze S, Noebels JL. Isolated P/Q Calcium Channel deletion in layer VI corticothalamic neurons generates absence epilepsy. J Neurosci. 2016;36:405–18.
55. Ding L, Satish S, Zhou C, Gallagher MJ. Cortical activation in generalized seizures. Epilepsia. 2019;60:1932–41.
56. Westmijse I, Ossenblok P, Gunning B, van Luijtelaar G. Onset and propagation of spike and slow wave discharges in human absence epilepsy: a MEG study. Epilepsia. 2009;50:2538–48.
57. Lee S, Hwang E, Lee M, Choi JH. Distinct topographical patterns of spike-wave discharge in transgenic and pharmacologically induced absence seizure models. Exp Neurobiol. 2019;28:474–84.
58. Kokkinos V, Koupparis AM, Koutroumanidis M, Kostopoulos GK. Spatiotemporal propagation patterns of generalized ictal spikes in childhood absence epilepsy. Clin Neurophysiol. 2017;128:1553–62.
59. Gupta D, Ossenblok P, van Luijtelaar G. Space-time network connectivity and cortical activations preceding spike wave discharges in human absence epilepsy: a MEG study. Med Biol Eng Comput. 2011;49:555–65.
60. Wu C, Xiang J, Sun J, Huang S, Tang L, Miao A, et al. Quantify neuromagnetic network changes from pre-ictal to ictal activities in absence seizures. Neuroscience. 2017;357:134–44.
61. Sysoeva MV, Lüttjohann A, van Luijtelaar G, Sysoev IV. Dynamics of directional coupling underlying spike-wave discharges. Neuroscience. 2016;314:75–89.
62. Halassa MM, Sherman SM. Thalamocortical circuit motifs: a general framework. Neuron. 2019;103:762–70.
63. Guillery RW, Sherman SM. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron. 2002;33:163–75.
64. Lüttjohann A, van Luijtelaar G. The dynamics of cortico-thalamo-cortical interactions at the transition from pre-ictal to ictal LFPs in absence epilepsy. Neurobiol Dis. 2012;47:49–60.
65. Gallagher MJ. Reconsidering network mechanisms in absence seizures: unhitching the wave cart from the spike horse. Epilepsy Curr. 2021;21:64–6.
66. Casas-Torremocha D, Porrero C, Rodriguez-Moreno J, García-Amado M, Lübke JHR, Núñez Á, et al. Posterior thalamic nucleus axon terminals have different structure and functional impact in the motor and somatosensory vibrissal cortices. Brain Struct Funct. 2019;224:1627–45.
67. Sherman SM, Guillery RW. On the actions that one nerve cell can have on another: distinguishing "drivers" from "modulators". Proc Natl Acad Sci USA. 1998;95:7121–6.
68. Zhang W, Bruno RM. High-order thalamic inputs to primary somatosensory cortex are stronger and longer lasting than cortical inputs. elife. 2019;8:e44158.
69. Mease RA, Metz M, Groh A. Cortical sensory responses are enhanced by the higher-order thalamus. Cell Rep. 2016;14:208–15.
70. Cavdar S, Hacıoğlu H, Doğukan SY, Onat F. Do the quantitative relationships of synaptic junctions and terminals in the thalamus of genetic absence epilepsy rats from Strasbourg (GAERS) differ from those in normal control Wistar rats. Neurol Sci. 2012;33:251–9.
71. Lüttjohann A, Schoffelen JM, van Luijtelaar G. Termination of ongoing spike-wave discharges investigated by cortico-thalamic network analyses. Neurobiol Dis. 2014;70:127–37.
72. Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res Brain Res Rev. 2002;39:107–40.
73. Ilyas A, Pizarro D, Romeo AK, Riley KO, Pati S. The centromedian nucleus: anatomy, physiology, and clinical implications. J Clin Neurosci. 2019;63:1–7.
74. Park S, Permezel F, Agashe S, Osman G, Simpson HD, Miller KJ, et al. Centromedian thalamic deep brain stimulation for idiopathic generalized epilepsy: connectivity and target optimization. Epilepsia. 2024;65:e197–e203.
75. Gorji A, Mittag C, Shahabi P, Seidenbecher T, Pape HC. Seizure-related activity of intralaminar thalamic neurons in a genetic model of absence epilepsy. Neurobiol Dis. 2011;43:266–74.
76. Inoue M, Duysens J, Vossen JM, Coenen AM. Thalamic multiple-unit activity underlying spike-wave discharges in anesthetized rats. Brain Res. 1993;612:35–40.
77. Seidenbecher T, Pape HC. Contribution of intralaminar thalamic nuclei to spike-and-wave-discharges during spontaneous seizures in a genetic rat model of absence epilepsy. Eur J Neurosci. 2001;13:1537–46.

78. Salvati KA, Souza GMPR, Lu AC, Ritger ML, Guyenet P, Abbott SB, et al. Respiratory alkalosis provokes spike-wave discharges in seizure-prone rats. elife. 2022;11:e72898.
79. van Luijtelaar G. On the yin and Yang of spike and waves. J Physiol. 2020;598:2279–80.
80. Weininger J, Roman E, Tierney P, Barry D, Gallagher H, Murphy P, et al. Papez's forgotten tract: 80 years of unreconciled findings concerning the thalamocingulate tract. Front Neuroanat. 2019;13:14.
81. Child ND, Benarroch EE. Anterior nucleus of the thalamus: functional organization and clinical implications. Neurology. 2013;81:1869–76.
82. Chen Y, Fallon N, Kreilkamp BAK, Denby C, Bracewell M, Das K, et al. Probabilistic mapping of thalamic nuclei and thalamocortical functional connectivity in idiopathic generalised epilepsy. Hum Brain Mapp. 2021;42:5648–64.
83. Betting LE, Mory SB, Lopes-Cendes I, Li LM, Guerreiro MM, Guerreiro CA, et al. MRI volumetry shows increased anterior thalamic volumes in patients with absence seizures. Epilepsy Behav. 2006;8:575–80.
84. Lüttjohann A, van Luijtelaar G. Dynamics of networks during absence seizure's on- and offset in rodents and man. Front Physiol. 2015;6:16.
85. Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery. 2004;54:191–5; discussion 195–197.
86. Takebayashi S, Hashizume K, Tanaka T, Hodozuka A. The effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal cortical seizure status in rats. Epilepsia. 2007;48:348–58.
87. Onat FY, Aker RG, Gurbanova AA, Ateş N, van Luijtelaar G. The effect of generalized absence seizures on the progression of kindling in the rat. Epilepsia. 2007;48(Suppl 5):150–6.
88. Gurbanova AA, Aker RG, Sirvanci S, Demiralp T, Onat FY. Intra-amygdaloid injection of kainic acid in rats with genetic absence epilepsy: the relationship of typical absence epilepsy and temporal lobe epilepsy. J Neurosci. 2008;28:7828–36.
89. Akman O, Karson A, Aker RG, Ates N, Onat FY. Perirhinal cortical kindling in rats with genetic absence epilepsy. Neurosci Lett. 2010;479:74–8.
90. Akman O, Karson A, Aker RG, Ates N, Onat FY. Hippocampal kindling in rats with absence epilepsy resembles amygdaloid kindling. Epilepsy Res. 2008;81:211–9.
91. Akman O, Gulcebi MI, Carcak N, Ketenci Ozatman S, Eryigit T, Moshé SL, et al. The role of the substantia nigra pars reticulata in kindling resistance in rats with genetic absence epilepsy. Epilepsia. 2015;56:1793–802.
92. Olaciregui Dague K, Witt JA, von Wrede R, Helmstaedter C, Surges R. DBS of the ANT for refractory epilepsy: a single center experience of seizure reduction, side effects and neuropsychological outcomes. Front Neurol. 2023;14:1106511.
93. Laxpati NG, Kasoff WS, Gross RE. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. Neurotherapeutics. 2014;11:508–26.
94. Zhang X, Yu X, Tuo M, Zhao Z, Wang J, Jiang T, et al. Parvalbumin neurons in the anterior nucleus of thalamus control absence seizures. Epilepsia Open. 2023;8:1002–12.
95. McCafferty C, Gruenbaum BF, Tung R, Li JJ, Zheng X, Salvino P, et al. Decreased but diverse activity of cortical and thalamic neurons in consciousness-impairing rodent absence seizures. Nat Commun. 2023;14:117.
96. McCafferty C, David F, Venzi M, Lőrincz ML, Delicata F, Atherton Z, et al. Cortical drive and thalamic feed-forward inhibition control thalamic output synchrony during absence seizures. Nat Neurosci. 2018;21:744–56.
97. Meyer J, Maheshwari A, Noebels J, Smirnakis S. Asynchronous suppression of visual cortex during absence seizures in stargazer mice. Nat Commun. 2018;9:1938.
98. Khan W, Chopra S, Zheng X, Liu S, Paszkowski P, Valcarce-Aspegren M, et al. Neuronal rhythmicity and cortical arousal in a mouse model of absence epilepsy. Exp Neurol. 2024;381:114925.
99. Crunelli V, David F, Morais TP, Lorincz ML. HCN channels and absence seizures. Neurobiol Dis. 2023;181:106107.
100. McElvain LE, Chen Y, Moore JD, Brigidi GS, Bloodgood BL, Lim BK, et al. Specific populations of basal ganglia output neurons target distinct brain stem areas while collateralizing throughout the diencephalon. Neuron. 2021;109:1721–38.
101. Gulcebi MI, Ketenci S, Linke R, Hacıoğlu H, Yanalı H, Veliskova J, et al. Topographical connections of the substantia nigra pars reticulata to higher-order thalamic nuclei in the rat. Brain Res Bull. 2012;87:312–8.
102. Akman O, Moshé SL, Galanopoulou AS. Sex-specific consequences of early life seizures. Neurobiol Dis. 2014;72:153–66.
103. Giorgi FS, Galanopoulou AS, Moshé SL. Sex dimorphism in seizure-controlling networks. Neurobiol Dis. 2014;72:144–52.
104. Vuong J, Devergnas A. The role of the basal ganglia in the control of seizure. J Neural Transm Vienna. 2018;125:531–45.
105. Deransart C, Depaulis A. The control of seizures by the basal ganglia? A review of experimental data. Epileptic Disord. 2002;4(Suppl 3):S61–S72.
106. Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. Nat Rev Neurosci. 2002;3:371–82.
107. Deransart C, Hellwig B, Heupel-Reuter M, Léger JF, Heck D, Lücking CH. Single-unit analysis of substantia nigra pars reticulata neurons in freely behaving rats with genetic absence epilepsy. Epilepsia. 2003;44:1513–20.
108. Slaght SJ, Paz T, Chavez M, Deniau JM, Mahon S, Charpier S. On the activity of the corticostriatal networks during spike-and-wave discharges in a genetic model of absence epilepsy. J Neurosci. 2004;24:6816–25.
109. Paz JT, Deniau JM, Charpier S. Rhythmic bursting in the cortico-subthalamo-pallidal network during spontaneous genetically determined spike and wave discharges. J Neurosci. 2005;25:2092–101.
110. Wicker E, Beck VC, Kulick-Soper C, Kulick-Soper CV, Hyder SK, Campos-Rodriguez C, et al. Descending projections from the. Proc Natl Acad Sci USA. 2019;116:27084–94.
111. Campos-Rodriguez C, Palmer D, Forcelli PA. Optogenetic stimulation of the superior colliculus suppresses genetic absence seizures. Brain. 2023;146:4320–35.
112. Berman R, Negishi M, Vestal M, Spann M, Chung MH, Bai X, et al. Simultaneous EEG, fMRI, and behavior in typical childhood absence seizures. Epilepsia. 2010;51:2011–22.

113. Qin Y, Li S, Yao D, Luo C. Causality analysis to the abnormal subcortical-cortical connections in idiopathic-generalized epilepsy. Front Neurosci. 2022;16:925968.
114. Wachsmuth L, Datunashvili M, Kemper K, Albers F, Lambers H, Lüttjohann A, et al. Retrosplenial cortex contributes to network changes during seizures in the GAERS absence epilepsy rat model. Cereb Cortex Commun. 2021;2:tgab023.
115. Tugba EK, Medine GIO, Ozlem A, Deniz K, Filiz OY. Prolongation of absence seizures and changes in serotonergic and dopaminergic neurotransmission by nigrostriatal pathway degeneration in genetic absence epilepsy rats. Pharmacol Biochem Behav. 2022;213:173317.
116. Birioukova LM, Tsvetaeva DA, Midzyanovskaya IS, Raevsky VV, Sitnikova E. The neuronal density in the rostral pole of substantia nigra pars compacta in Wistar albino rats from Rijswijk rats: a link to spike-wave seizures. J Biol Methods. 2024;11:e99010022.
117. de Bruin NM, van Luijtelaar EL, Jansen SJ, Cools AR, Ellenbroek BA. Dopamine characteristics in different rat genotypes: the relation to absence epilepsy. Neurosci Res. 2000;38:165–73.
118. Velísková J, Moshé SL. Update on the role of substantia nigra pars reticulata in the regulation of seizures. Epilepsy Curr. 2006;6:83–7.
119. Gulcebi M, Akman O, Carcak N, Karamahmutoglu T, Onat F. Evaluation of GAD67 immunoreactivity in the region of substantia nigra pars reticulata in resistance to development of convulsive seizure in genetic absence epilepsy rats. North Clin Istanb. 2016;3:161–7.
120. Ajaz R, Mousavi SR, Mirsattari SM, Leung LS. Paroxysmal slow-wave discharges in a model of absence seizure are coupled to gamma oscillations in the thalamocortical and limbic systems. Epilepsy Res. 2023;191:107103.
121. Velazquez JL, Huo JZ, Dominguez LG, Leshchenko Y, Snead OC. Typical versus atypical absence seizures: network mechanisms of the spread of paroxysms. Epilepsia. 2007;48:1585–93.
122. Zhang T, Zhang Y, Ren J, Yang C, Zhou H, Li L, et al. Aberrant basal ganglia-thalamo-cortical network topology in juvenile absence epilepsy: a resting-state EEG-fMRI study. Seizure. 2021;84:78–83.
123. Eşkazan E, Onat FY, Aker R, Oner G. Resistance to propagation of amygdaloid kindling seizures in rats with genetic absence epilepsy. Epilepsia. 2002;43:1115–9.
124. Aker RG, Yananli HR, Gurbanova AA, Ozkaynakçi AE, Ateş N, van Luijtelaar G, et al. Amygdala kindling in the WAG/Rij rat model of absence epilepsy. Epilepsia. 2006;47:33–40.
125. Carçak N, Ferrandon A, Koning E, Aker RG, Ozdemir O, Onat FY, et al. Effect of stage 2 kindling on local cerebral blood flow rates in rats with genetic absence epilepsy. Epilepsia. 2009;50:33–43.
126. Çarçak N, Dileköz E, Gülhan R, Onur R, Onat FY, Sara Y. Increased inhibitory synaptic activity in the hippocampus (CA1) of genetic absence epilepsy rats: relevance of kindling resistance. Epilepsy Res. 2016;126:70–7.
127. Wang X, Stewart L, Cortez MA, Wu Y, Velazquez JL, Liu CC, et al. The circuitry of atypical absence seizures in GABA(B)R1a transgenic mice. Pharmacol Biochem Behav. 2009;94:124–30.
128. Arcaro J, Ma J, Chu L, Kuo M, Mirsattari SM, Stan LL. The hippocampus participates in a pharmacological rat model of absence seizures. Epilepsy Res. 2016;120:79–90.
129. Mousavi SR, Arcaro JA, Leung LS, Tenney JR, Mirsattari SM. Functional connectivity of the hippocampus to the thalamocortical circuitry in an animal model of absence seizures. Epilepsy Res. 2017;137:19–24.
130. Sysoeva MV, Kuznetsova GD, Sysoev IV, Ngomba RT, Vinogradova LV, Grishchenko AA, et al. Network analysis reveals a role of the hippocampus in absence seizures: the effects of a cannabinoid agonist. Epilepsy Res. 2023;192:107135.
131. Sitnikova E, Perevozniuk D, Rutskova E, Uzakov S, Korshunov VA. Reduction of hippocampal high-frequency activity in wag/Rij rats with a genetic predisposition to absence epilepsy. Diagnostics. 2022;12:2798.
132. Sere P, Zsigri N, Raffai T, Furdan S, Győri F, Crunelli V, et al. Activity of the lateral hypothalamus during genetically determined absence seizures. Int J Mol Sci. 2021;22:9466.
133. Karson A, Utkan T, Şahin TD, Balcı F, Arkan S, Ateş N. Etanercept rescues cognitive deficits, depression-like symptoms, and spike-wave discharge incidence in WAG/Rij rat model of absence epilepsy. Epilepsy Behav. 2021;115:107532.
134. Gruenbaum BF, Sandhu MRS, Bertasi RAO, Bertasi TGO, Schonwald A, Kurup A, et al. Absence seizures and their relationship to depression and anxiety: evidence for bidirectionality. Epilepsia. 2021;62:1041–56.
135. Streng ML, Froula JM, Krook-Magnuson E. The cerebellum's understated role and influences in the epilepsies. Neurobiol Dis. 2023;183:106160.
136. Leitch B. Molecular mechanisms underlying the generation of absence seizures: identification of potential targets for therapeutic intervention. Int J Mol Sci. 2024;25:9821.
137. Kros L, Eelkman Rooda OH, Spanke JK, Alva P, van Dongen MN, Karapatis A, et al. Cerebellar output controls generalized spike-and-wave discharge occurrence. Ann Neurol. 2015;77:1027–49.
138. Kandel A, Buzsáki G. Cerebellar neuronal activity correlates with spike and wave EEG patterns in the rat. Epilepsy Res. 1993;16:1–9.
139. Siniatchkin M, Coropceanu D, Moeller F, Boor R, Stephani U. EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox-Gastaut syndrome. Epilepsia. 2011;52:766–74.
140. Kang S, Jun S, Baek SJ, Park H, Yamamoto Y, Tanaka-Yamamoto K. Recent advances in the understanding of specific efferent pathways emerging from the cerebellum. Front Neuroanat. 2021;15:759948.
141. Gornati SV, Schäfer CB, Eelkman Rooda OHJ, Nigg AL, De Zeeuw CI, Hoebeek FE. Differentiating cerebellar impact on thalamic nuclei. Cell Rep. 2018;23:2690–704.
142. Eelkman Rooda OHJ, Kros L, Faneyte SJ, Holland PJ, Gornati SV, Poelman HJ, et al. Single-pulse stimulation of cerebellar nuclei stops epileptic thalamic activity. Brain Stimul. 2021;14:861–72.
143. Seneviratne U, Cook MJ, D'Souza WJ. Electroencephalography in the diagnosis of genetic generalized epilepsy syndromes. Front Neurol. 2017;8:499.
144. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. Epilepsia. 2014;55(Suppl 4):4–9.
145. Paz JT, Huguenard JR. Microcircuits and their interactions in epilepsy: is the focus out of focus? Nat Neurosci. 2015;18:351–9.

146. Mastroianni G, Ascoli M, Gasparini S, Brigo F, Cianci V, Neri S, et al. Therapeutic approach to difficult-to-treat typical absences and related epilepsy syndromes. Expert Rev Clin Pharmacol. 2021;14:1427–33.
147. Richards DA, Morrone LA, Bowery NG. Hippocampal extracellular amino acids and EEG spectral analysis in a genetic rat model of absence epilepsy. Neuropharmacology. 2000;39:2433–41.
148. Sirvanci S, Meshul CK, Onat F, San T. Immunocytochemical analysis of glutamate and GABA in hippocampus of genetic absence epilepsy rats (GAERS). Brain Res. 2003;988:180–8.
149. Sirvanci S, Meshul CK, Onat F, San T. Glutamate and GABA immunocytochemical electron microscopy in the hippocampal dentate gyrus of normal and genetic absence epilepsy rats. Brain Res. 2005;1053:108–15.
150. Karimzadeh F, Soleimani M, Mehdizadeh M, Jafarian M, Mohamadpour M, Kazemi H, et al. Diminution of the NMDA receptor NR2B subunit in cortical and subcortical areas of WAG/Rij rats. Synapse. 2013;67:839–46.
151. Ngomba RT, Biagioni F, Casciato S, Willems-van Bree E, Battaglia G, Bruno V, et al. The preferential mGlu2/3 receptor antagonist, LY341495, reduces the frequency of spike-wave discharges in the WAG/Rij rat model of absence epilepsy. Neuropharmacology. 2005;49(Suppl 1):89–103.
152. Melø TM, Sonnewald U, Touret M, Nehlig A. Cortical glutamate metabolism is enhanced in a genetic model of absence epilepsy. J Cereb Blood Flow Metab. 2006;26:1496–506.
153. Akakin D, Sirvanci S, Gurbanova A, Aker R, Onat F, San T. Ultrastructural GABA immunocytochemistry in the mossy fiber terminals of Wistar and genetic absence epileptic rats receiving amygdaloid kindling stimulations. Brain Res. 2011;1377:101–8.
154. Moyanova S, De Fusco A, Santolini I, Celli R, Bucci D, Mastroiacovo F, et al. Abnormal hippocampal Melatoninergic system: a potential link between absence epilepsy and depression-like behavior in WAG/Rij rats? Int J Mol Sci. 2018;19:1973.
155. Midzyanovskaya IS, Birioukova LM, Shatskova AB, van Luijtelaar G, Tuomisto LM. H1 histamine receptor densities are increased in brain regions of rats with genetically generalized epilepsies. Epilepsy Res. 2016;127:135–40.
156. Birioukova LM, Midzyanovskaya IS, Lensu S, Tuomisto L, van Luijtelaar G. Distribution of D1-like and D2-like dopamine receptors in the brain of genetic epileptic WAG/Rij rats. Epilepsy Res. 2005;63:89–96.
157. Yazi S, Sehirli US, Gulhan R, Onat F, Kirazli O. Evaluation of dendrite morphology in Wistar and genetic absence epileptic rats. Brain Struct Funct. 2024;230:5.
158. Bouilleret V, Hogan RE, Velakoulis D, Salzberg MR, Wang L, Egan GF, et al. Morphometric abnormalities and hyperanxiety in genetically epileptic rats: a model of psychiatric comorbidity? NeuroImage. 2009;45:267–74.
159. Cilingir-Kaya OT, Moore C, Meshul CK, Gursoy D, Onat F, Sirvanci S. Neurogenesis is enhanced in young rats with genetic absence epilepsy: an Immuno-electron microscopic study. Turk Neurosurg. 2021;31:623–33.
160. Russo E, Follesa P, Citraro R, Camastra C, Donato A, Isola D, et al. The mTOR signaling pathway and neuronal stem/progenitor cell proliferation in the hippocampus are altered during the development of absence epilepsy in a genetic animal model. Neurol Sci. 2014;35:1793–9.
161. Jafarian M, Karimzadeh F, Alipour F, Attari F, Lotfinia AA, Speckmann EJ, et al. Cognitive impairments and neuronal injury in different brain regions of a genetic rat model of absence epilepsy. Neuroscience. 2015;298:161–70.
162. Di Cicco G, Marzano E, Iacovelli L, Celli R, van Luijtelaar G, Nicoletti F, et al. Group I metabotropic glutamate receptor-mediated long term depression is disrupted in the hippocampus of WAG/Rij rats modelling absence epilepsy. Neuropharmacology. 2021;196:108686.

How to cite this article: Akman O, Onat F. Absence seizures: Update on signaling mechanisms and networks. Epilepsia Open. 2025;00:1–18. https://doi.org/10.1002/epi4.70075