

Absence seizures: Update on signaling mechanisms and networks

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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 humans¹ 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.

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

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.

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 EEG¹ (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 (3–30s), 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 (3–8s), 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 (>30s), 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,

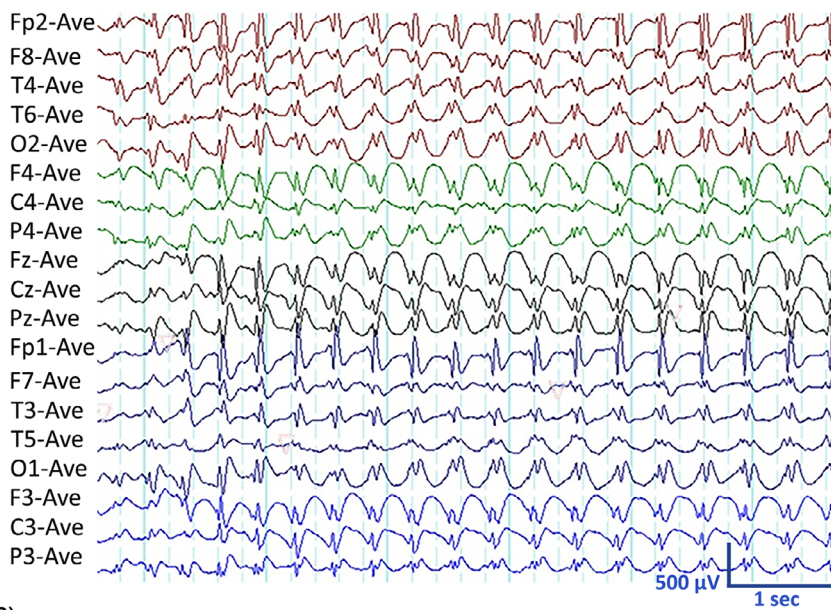
and GABA receptor channels.¹⁸ Recently, Neuroligin-2 knockout mice, which lack a key synaptic adhesion molecule, have been shown to exhibit abnormal SWDs and behavioral arrests, further broadening the scope of AS research.²¹

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

(A)



(B)

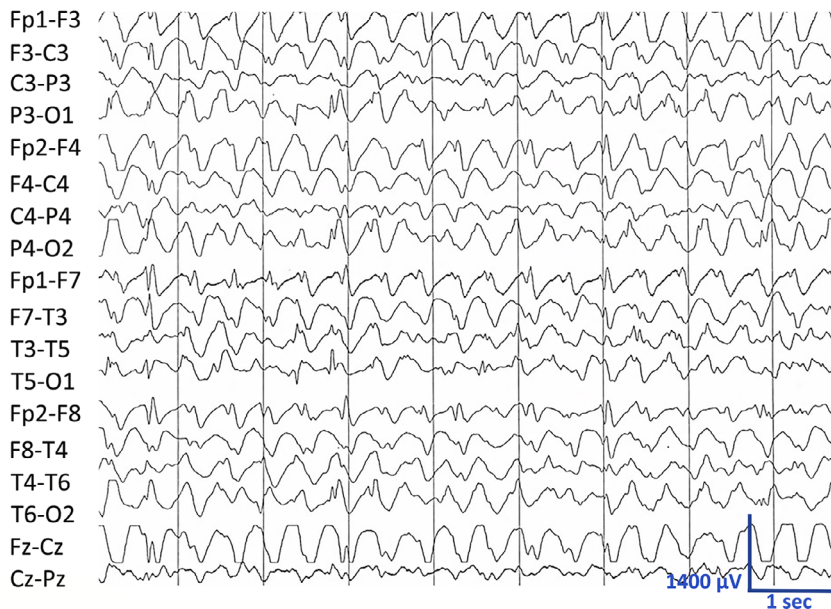


FIGURE 1 Typical and atypical SWDs recorded in human subjects. (A) EEG of a typical absence seizure, illustrating generalized, symmetrical, synchronous, and regular 3-Hz spike-and-wave discharges with frontocentral predominance. Adapted from: Seneviratne U, Cook MJ, D'Souza WJ, "Electroencephalography 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 _B R antagonists	+	No data

Abbreviations: CLZ, clonazepam; ETX, ethosuximide; LMT, lamotrigine; SWDs, spike-and-wave discharges; TMD, trimethadione; VPA, valproic acid.

^aCharacteristics that separate atypical absence seizures from typical absence seizures.

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.

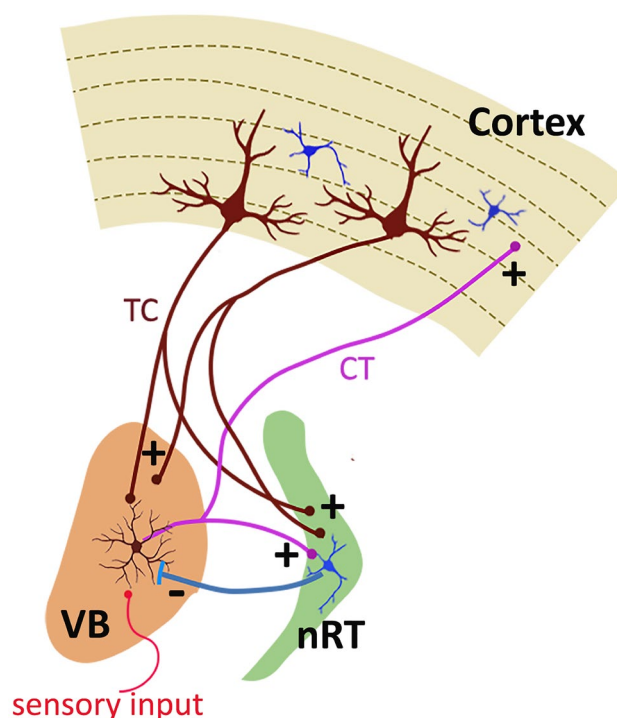


FIGURE 2 Simplified cortico-thalamo-cortical (CTC) circuit. The CTC circuit consists of corticothalamic (CT) neurons, thalamocortical (TC) relay neurons, and GABAergic neurons of the reticular thalamic nucleus (nRT), forming reciprocal excitatory and inhibitory loops.²⁶ CT neurons, located in cortical 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 Ca²⁺ 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

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 development⁵² 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 Luijtelaar⁵ 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 analyses⁶⁴ have highlighted the PO's critical role in SWD generation, maintenance, and propagation in AS models.

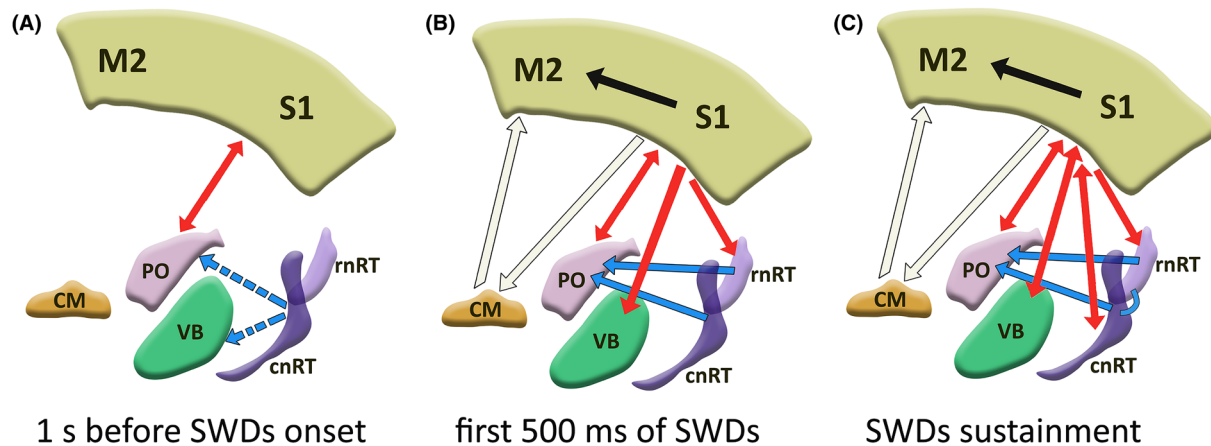


FIGURE 3 The extended model of SWD generation, generalization, and maintenance in genetic absence epilepsy rats, as proposed by Lüttjohann and van Luijtelar.⁵ Unlike the basic CTC model, this framework incorporates dynamic SWD generation. (A) One second before SWD onset, a gradual bidirectional increase 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 Luijtelar 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 Luijckelaar,⁷⁹ these results align with Guillery and Sherman's⁶³ 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 functions⁸¹ 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 pentylenetetrazol (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 non-anesthetized 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 pre-ictal 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 corticostriatal 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 period¹¹² 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-thalamo-cortical 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 synchronization¹²⁸; increase FC between the hippocampus, thalamus, and sensorimotor cortex¹²⁹; 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* mice¹³⁷ 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 patients³⁶ 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: AC1, 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 firing⁹⁶ 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.

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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.

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