Reconsidering Network Mechanisms in Absence Seizures: Unhitching the Wave Cart From the Spike Horse

Spike-Wave Discharges in Absence Epilepsy: Segregation of Electrographic Components Reveals Distinct Pathways of Seizure Activity

Terlau J, Yang JW, Khashkhodaei Z, et al. J Physiol (Lond.). 2020;598(12):2397-2414. https://doi.org/10.1113/JP279483

Spike and wave discharges (SWDs) are the electrographic hallmark of absence seizures and the major diagnostic criterion for childhood absence epilepsy (CAE). In a widely accepted scheme, the alternating sequence of spikes and waves reflects an iterative progression of neuronal excitation during the spike component and post-excitatory silence during the wave component. Here, we challenge this view by showing that these two components are not necessarily coupled. In a genetic rat model of CAE, self-contained waves occurred in motor cortex in synchrony with SWDs in the somatosensory system during blockade of afferent input from the thalamus. Current source density analyses of multisite local field potentials (LFPs) revealed layer-specific activity, in which thalamic inputs induced a sequence of cellular-synaptic events underlying the spike component, while intracortical oscillations generated the wave component. These findings indicate novel principles of SWDs, where oscillatory cortical waves provide adequate time windows for integration of thalamocortical inputs and feedback responses during generation of seizure activity.

Commentary

Epilepsy is a brain network disorder associated with dysfunction of specific brain regions and the connectivity among them. Identification of seizure networks can help guide targets for network-selective neurostimulation therapies. Because brain stimulation is currently being evaluated for the treatment of generalized epilepsies, it is critical to elucidate the generalized seizure networks.

The network physiology of one type of generalized seizure, absence seizures, and its EEG correlate, spike-wave complexes (SWCs), has been characterized in both animal models and human patients. A simple model holds that increased neuronal firing in the deep layers of the primary somatosensory cortex (S1) coupled with feedforward and feedback interactions among S1 and the thalamic reticular (nRT) and ventrobasal (VB) nuclei produce synchrony and oscillatory neuronal burst firing associated the SWC rhythmic EEG spikes.

This simple model of SWC physiology is incomplete. First, while it accounts for the spike component of the SWC, it does not explain the formation of the characteristic waves. They are often presumed to be formed by hyperpolarization inextricably hitched to the preceding spike. Second, it does not incorporate the role of the centromedian nucleus (CM), the thalamic intralaminar nucleus currently targeted for neurostimulation in generalized epilepsy. Finally, it does not explain the “pre-ictal” oscillations observed several seconds prior to the first SWC spike in several rodent models of absence seizures.

In this article, Terlau and colleagues tested the effects of selective pharmacological (DNQX) deactivation of VB and CM nuclei on SWCs recorded in S1 and secondary motor cortex (M2) in a rat strain that exhibits spontaneous absence seizures. They recorded S1 and M2 electrocorticograms (ECoG), transcortical LFPs, and multiunit activity (MUA). Current source density analyses of the LFPs revealed the time course of current entering (“sinks”) and leaving (“sources”) within the different cortical layers.

With ECoG recordings, the authors found that unilateral CM deactivation reduced SWC incidence at the S1/M2 sites by 44%/49%, values somewhat less than they achieved with VB deactivation (68%/54%). For the SWCs that persisted during VB inactivation, the voltage of both the wave and spike components was reduced at the S1 and M2 sites. In contrast, DNQX applied to CM reduced both spikes and wave voltages in S1 but decreased spike voltage in M2 without changing the waves. Moreover, in 9% of the M2 SWCs, there was no apparent spike component and only a “self-contained wave.” These data demonstrated that spikes could be functionally decoupled (“unhitched”) from the waves. Despite the disassociation of spikes from waves within M2, pairwise phase consistency measurements demonstrated that these
isolated waves behaved as SWCs and were not simply nonepileptic oscillatory activity.

In the absence of DNQX, the LFP recordings in S1 revealed a prominent spike-associated sink in layers II/III and IV and a prominent wave-associated sink in layer VI, results that qualitatively agreed with a previous study in another SWC rat model. Additional S1 spike-associated sinks were identified in layers I and V. In M2 cortex, a region with minimal layer IV, a prominent spike-associated sink was identified in layer II/III with an additional region in layer I. A wave-associated sink was present in M2 layer V. In both S1 and M2, MUA was prominent in layers II to VI during the SWC spike component and markedly attenuated during the wave.

With CM deactivation by DNQX, LFPs recorded during the self-contained waves confirmed the initial assignment of the spike-associated sinks, both the layer II/III and layer I sinks were significantly reduced. Interestingly, the wave associated layer V sink was prolonged, a result that demonstrated that the cortical current flow produced during waves was not simply a consequence of a preceding spike.

Multiunit activity during the self-contained waves was significantly reduced compared to baseline. Interestingly, the paper’s figures suggest that the remaining MUA was more prevalent during the first part of the self-contained wave, the time when the spike would have occurred, than during the latter half of the wave.

The first important result from this article is the finding that CM inactivation significantly reduced the incidence of SWCs. Although several previous investigators found that modulation of S1, nRT, and VB activity reduced SWCs, these brain regions have not been therapeutically targeted in human patients with drug-resistant generalized epilepsy. Conversely, while a few studies tested the effects of deactivating various midline thalamic nuclei on generalized seizures, to my knowledge, the studies tested the effects of deactivating various midline thalamic nuclei on generalized seizures.

In conclusion, by pharmacologically unhitching SWC spike and wave components, this article extends our understanding of the basic neurophysiology of absence seizures and provides important, clinically translatable data applicable to trials of CM neurostimulation. It will be important for follow-up studies to determine the ability of open- and closed-loop CM deactivation to more effectively inhibit SWCs and to elucidate the effects of waves on the intrinsic physiology of cortical neurons.

Martin J. Gallagher

ORCID iD

Martin J. Gallagher https://orcid.org/0000-0002-3537-4200

References
1. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. Epilepsia. 2018;59(2):273-290. doi:10.1111/epi.13964
2. Huguenard J. Current controversy: spikes, bursts, and synchrony in generalized absence epilepsy: unresolved questions regarding thalamocortical synchrony in absence epilepsy. Epilepsy Curr. 2019;19(2):105-111. doi:10.1177/1535759719835355

3. Lüttjohann A, Schoffelen J-M, van Luijtelaar G. Peri-ictal network dynamics of spike-wave discharges: phase and spectral characteristics. Exp Neurol. 2013;239(1):235-247. doi:10.1016/j.expneurol.2012.10.021

4. Sorokin JM, Paz JT, Huguenard JR. Absence seizure susceptibility correlates with pre-ictal β oscillations. J Physiol. Paris. 2016;110 (4 pt A):372-381. https://doi.org/10.1016/j.jphysparis.2017.05.004

5. Ding L, Satish S, Zhou C, Gallagher MJ. Cortical activation in generalized seizures. Epilepsia. 2019;60 (9):1932-1941. doi:10.1111/epi.16306

6. Terlau J, Yang J-W, Khashkhodaei Z, et al. Spike-wave discharges in absence epilepsy: segregation of electrographic components reveals distinct pathways of seizure activity. J Physiol (Lond.). 2020;598(12):2397-2414. doi:10.1113/JP279483

7. Kandel A, Buzsáki G. Cellular-synaptic generation of sleep spindles, spike-and-wave discharges, and evoked thalamocortical responses in the neocortex of the rat. J Neurosci. 1997;17(17):6783-6797.

8. 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(8):1537-1546. doi:10.1046/j.0953-816x.2001.01537.x

9. Wang X, Stewart L, Cortez MA, et al. The circuitry of atypical absence seizures in GABABR1a transgenic mice. Pharmacol Biochem Behav. 2009;94(1):124-130. doi:10.1016/j.pbb.2009.07.017

10. Maksimenko VA, van Heukelum S, Makarov VV, et al. Absence seizure control by a brain computer interface. Sci Rep. 2017;7(1):1-8. doi:10.1038/s41598-017-02626-y