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Attentional Deficits and Absence Epilepsy: A Tale of 2 Interneuronopathies

Prefrontal PV Interneurons Facilitate Attention and Are Linked to Attentional Dysfunction in a Mouse Model of Absence Epilepsy

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Absence seizures are characterized by brief periods of unconsciousness accompanied by lapses in motor function that can occur hundreds of times throughout the day. Outside of these frequent moments of unconsciousness, approximately a third of people living with the disorder experience treatment-resistant attention impairments. Convergent evidence suggests prefrontal cortex (PFC) dysfunction may underlie attention impairments in affected patients. To examine this, we use a combination of slice physiology, fiber photometry, electrocorticography (ECoG), optogenetics, and behavior in the Scn8a+/-mouse model of absence epilepsy. Attention function was measured using a novel visual attention task where a light cue that varied in duration predicted the location of a food reward. In Scn8a+/-mice, we find altered parvalbumin interneuron (PVIN) output in the medial PFC (mPFC) in vitro and PVIN hypoactivity along with reductions in gamma power during cue presentation in vivo. This was associated with poorer attention performance in Scn8a+/-mice that could be rescued by gamma-frequency optogenetic stimulation of PVINs. This highlights cue-related PVIN activity as an important mechanism for attention and suggests PVINs may represent a therapeutic target for cognitive comorbidities in absence epilepsy.

Commentary

Absence seizures are a cardinal feature in multiple forms of generalized epilepsy. They are outwardly manifest by behavioral arrest and have an EEG correlate of generalized spike wave discharges. Attentional deficits are a prominent comorbidity in children and adults who suffer from absence seizures and generalized epilepsy more broadly.[1,2] Notably, attentional ability is prerequisite for academic acheivement,[1] which is also diminished in people with generalized epilepsy, along with employment rate and financial income.[1,3] Despite the established association between generalized epilepsy and attentional impairment, the underlying neurophysiological mechanisms are not understood. In particular, it is not clear whether cognitive comorbidities such as attentional impairment result from seizures or arise independently.

Monogenic mouse models of generalized epilepsy can be used to dissect circuit mechanisms in detail. The authors employed *Scn8a*+/- mice to investigate circuit mechanisms of attentional impairment in the setting of absence seizures.[4] These mice bear the "med" allele of the *Scn8a* gene, leading to expression of a truncated, nonfunctional form of the encoded voltage-gated sodium channel, Nav1.6.[5] Nav1.6 normally serves as a critical determinant of neuronal intrinsic excitability. Mice that are heterozygous for this allele exhibit spontaneous, developmentally dependent absence seizures,[6] characterized by behavioral arrest and 4 to 8 Hz, generalized spike wave discharges on EEG.[7] These mice therefore mirror a human form of generalized epilepsy; people with loss of function variants in *SCN8A* present with mild to moderate intellectual disability and generalized epilepsy, primarily manifest by absence seizures.[8]

It is somewhat counterintuitive that *loss* of function of *Scn8a* could lead to epilepsy, which generally arises from neuronal hyperexcitability. However, the presence of absence seizures in *Scn8a*+/- mice primarily relates to loss of *Scn8a* function in *parvalbumin (PV) inhibitory interneurons*. A 2017 study determined that absence seizures in *Scn8a*+/- mice are a consequence of decreased intrinsic excitability and impaired synaptic output between reticular thalamic nucleus (nRT) PV interneurons. Specifically, *Scn8a* loss of function impairs an important desynchronizing mechanism in which nRT PV interneurons inhibit each other. Excessively synchronous firing of nRT PV interneurons, in turn, leads to self-sustaining and prolonged thalamocortical oscillations that underlie absence seizures.[7]

Could nRT PV interneuron dysfunction that gives rise to seizures, or the seizures themselves, give rise to attentional deficits? To understand the neurophysiological basis of

attentional deficits in the setting of epilepsy, Ferguson and colleagues[4] developed a test of attentional function, in which mice obtain a food reward by attending to a light stimulus of varying duration that indicates the reward location. Shorter light stimuli require greater attention. Compared to *Scn8a*+/+, *Scn8a*+/- mice exhibited fewer accurate responses when challenged with shorter light stimuli. These deficits could not be explained by co-occurring absence seizures, as seizures were infrequent during the test, and task performance was not rescued when seizures were prevented with valproic acid. (One caveat is that among drugs commonly used to treat absence seizures, only valproic acid has been demonstrated to *worsen* attention.)[1] Attention has previously been linked to medial prefrontal cortex (mPFC) function, and specifically to gamma oscillations driven by mPFC PV interneurons.[9] Similarly, the authors localized performance in this behavioral paradigm to mPFC function, and demonstrated deficits in mPFC PV interneuron synaptic output in *Scn8a*+/- mice. Electrocorticography recordings during testing revealed decreased gamma frequency activity in mPFC. Fiber photometry confirmed that mPFC PV interneuron activity evoked by the visual cue was decreased in *Scn8a*+/- mice. Conversely, gamma-frequency stimulation of mPFC PV interneurons improved task performance compared to unstimulated performance. Of note, since the authors demonstrated in a previous experiment that *Scn8a*+/- mPFC PV interneurons in brain slices cannot respond fully to gamma-frequency stimulus trains, it is unlikely that optogenetic stimulation in vivo could completely restore PV interneuron synaptic input, nor attentional performance, to wildtype control levels.

Taken together, the findings convincingly indicate cell autonomous, mPFC PV interneuron synaptic failure that results from loss of normal *Scn8a* expression and is sufficient to impair attention. Moreover, while absence seizures and attentional deficits resulting from *Scn8a* loss of function each stem from synaptic deficits in PV interneurons, the interneurons are located in distinct circuits, and their synaptic deficits play out through distinct mechanisms. In the case of seizures, impaired PV interneuron-to-interneuron synapses in nRT promote thalamocortical hypersynchrony. In the case of attentional deficits, PV interneuron-to-pyramidal neuron synaptic deficits in the mPFC disrupt feedforward inhibition and gamma frequency oscillations.

These findings raise intriguing questions for future study. While the study's findings seem to indicate that dysfunction in mPFC PV interneurons is sufficient for attentional impairment, it remains possible that additional abnormalities also contribute. Examples might include disruption of mPFC excitatory neurons, which also express *Scn8a*, or altered functional connections between the thalamic mediodorsal nucleus and mPFC which are also critical for attention.[10] It also remains to be seen whether deficits of mPFC PV interneuron synaptic output similarly result in attentional deficits in other models of generalized epilepsy, or whether the same circuits are disrupted through distinct mechanisms, for example, involving seizures.

These mechanistic questions have direct relevance for therapeutic strategies. If attentional deficits do not result (either directly or indirectly) from seizures, but arise as an independent process, then it stands to reason that those deficits will not be reversed by symptomatic treatment of seizures. Indeed, it has been observed that attentional deficits in children with absence epilepsy do not resolve with seizure freedom,[1] similar to the findings in this study. This indicates that a separate therapeutic strategy would be needed to address comorbid attention impairment. In contrast, a therapeutic strategy to restore *Scn8a* function could correct seizures and attentional deficits, by addressing the common root cause. This is an argument for precision and/or disease-modifying therapies, particularly in monogenic forms of epilepsy. However, the majority of generalized epilepsies have complex inheritance.[2] In such cases, separate treatments may be necessary to address seizures, cognitive, and neuropsychiatric comorbidities—one mechanism and one circuit at a time.

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Declaration of Conflicting Interests

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