



Mind the Gate to Improve Comorbid Cognitive Impairments in Epilepsy

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Circuit-Based Interventions in the Dentate Gyrus Rescue Epilepsy-Associated Cognitive Dysfunction

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Temporal lobe epilepsy is associated with significant structural pathology in the hippocampus. In the dentate gyrus, the summative effect of these pathologies is massive hyperexcitability in the granule cells, generating both increased seizure susceptibility and cognitive deficits. To date, therapeutic approaches have failed to improve the cognitive symptoms in fully developed, chronic epilepsy. As the dentate's principal signaling population, the granule cells' aggregate excitability has the potential to provide a mechanistically independent downstream target. We examined whether normalizing epilepsy-associated granule cell hyperexcitability—without correcting the underlying structural circuit disruptions—would constitute an effective therapeutic approach for cognitive dysfunction. In the systemic pilocarpine mouse model of temporal lobe epilepsy, the epileptic dentate gyrus excessively recruits granule cells in behavioral contexts, not just during seizure events, and these mice fail to perform on a dentate-mediated spatial discrimination task. Acutely reducing dorsal granule cell hyperactivity in chronically epileptic mice via either of 2 distinct inhibitory chemogenetic receptors rescued behavioral performance such that they responded comparably to wild-type mice. Furthermore, recreating granule cell hyperexcitability in control mice via excitatory chemogenetic receptors, without altering normal circuit anatomy, recapitulated spatial memory deficits observed in epileptic mice. However, making the granule cells overly quiescent in both epileptic and control mice again disrupted behavioral performance. These bidirectional manipulations reveal that there is a permissive excitability window for granule cells that is necessary to support successful behavioral performance. Chemogenetic effects were specific to the targeted dorsal hippocampus, as hippocampal-independent and ventral hippocampal-dependent behaviors remained unaffected. Fos expression demonstrated that chemogenetics can modulate granule cell recruitment via behaviorally relevant inputs. Rather than driving cell activity deterministically or spontaneously, chemogenetic intervention merely modulates the behaviorally permissive activity window in which the circuit operates. We conclude that restoring appropriate principal cell tuning via circuit-based therapies, irrespective of the mechanisms generating the disease-related hyperactivity, is a promising translational approach.

Commentary

Cognitive impairments associated with epilepsy are estimated to impact nearly 70% to 80% of patients and include a range of symptoms from processing difficulties to profound memory impairments and decreased IQ (for review, see the study by Helmstaedter and Witt¹). Numerous mechanisms have been implicated in cognitive impairments associated with epilepsy, including insults associated with the underlying etiology of the epilepsy, such as brain trauma, or due to damage caused by the seizures themselves, such as mesial temporal sclerosis. Cognitive disturbances may also result from abnormal ictal/interictal activity or antiepileptic drug treatment. Comorbidities associated with epilepsy, including cognitive impairments, have been reported to be more burdensome than seizures in patients with epilepsy and negatively impact their quality of life.² Despite

the high incidence of cognitive impairments associated with epilepsy and the negative impact on the quality of life of patients, research into the underlying mechanisms mediating these comorbidities remains the minority of research in the epilepsy field and there is a need for more research in this area.

The highlighted study tackles comorbid cognitive dysfunction in epilepsy investigating the role of circuit dysfunction in brain regions relevant to cognition, focusing on the hippocampal dentate gyrus. Network dysfunction has been extensively studied in relation to abnormal epileptiform activity within the area of the seizure focus and the impact on ictal generation; however, network dysfunction in epilepsy is more widespread and network abnormalities may also contribute to other pathological features of epilepsy. Although ictal activity is the most pronounced manifestation of circuit dysfunction in epilepsy,



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subtler deficits in circuit function likely contribute to the comorbidities of epilepsy, including cognitive deficits. Recent evidence outside of the epilepsy field points to a role for specific patterns of network activity in mediating behavioral output, such as in mediating fear and anxiety (for review, see the study by Stujenske et al and Tovote et al^{3,4}); however, this idea has not been extensively explored in relation to epilepsy. Prolonged or recurrent seizures could induce network dysfunction contributing to, or that worsen, cognitive impairment in epilepsy. Thus, the neurobiological mechanisms underlying cognitive deficits in epilepsy may be distinct from the pathological processes contributing to seizure activity.² Another possibility is that the underlying neurobiological mechanisms leading to epilepsy also contribute to cognitive impairments. For example, the hippocampus is an obvious candidate for mediating both seizure generation and cognitive impairments.

The currently highlighted study investigates the mechanisms contributing to cognitive dysfunction in epilepsy, focusing on the role of the dentate gyrus. The dentate gyrus acts as a “gate,” controlling information flow through the hippocampus^{5,6} (for review, see the study by Scharfman⁷). The authors investigated whether circuit-level interventions, controlling the “gate” of hippocampal activity, could overcome cognitive impairments in chronically epileptic mice. Consistent with subversive network dysfunction, this study demonstrates altered activation of dentate gyrus granule cells independent of ictal activity. Using FoxTRAP to get a snapshot of *in vivo* activity, the authors demonstrate an increase in the activation of dentate granule cells in epileptic mice after exploring a novel environment compared to controls, a pattern of activity distinct from seizures. These data suggest that the dentate “gate” may be compromised in chronically epileptic mice, a pathological change which may contribute to cognitive dysfunction. Consistent with this notion, the authors demonstrate that reducing dentate gyrus hyperexcitability utilizing designer receptors exclusively activated by designer drugs (DREADDs) to modulate dentate gyrus activity improves cognitive impairments in chronically epileptic mice.

It is important to note that the potential off-target effects of clozapine-n-oxide (CNO) used to target DREADDs has recently been the focus of a controversy regarding the utility of this approach.⁸ The current study employs important controls to alleviate concerns regarding the approach, including treating non-DREADD expressing mice with CNO and the use of a kappa opioid receptor DREADD (KORD) which employs a different ligand (salvinorin B). An interesting observation from this study is that the DREADD approach did not alter neuronal activity in the absence of a physiological stimulus but rather exerted a modulatory effect that influenced responses to stimulation. This is an important distinction since this approach is often utilized to “activate” or “silence” cells,⁹ but DREADDs are G-protein-coupled receptors that rely on well-established intracellular signaling cascades which should be appreciated when employing this methodology.


This work demonstrates that the activity of the dentate gyrus needs to be finely tuned for optimal cognitive performance, as

evident by the findings that enhancing dentate gyrus activity in wild-type mice or making the dentate gyrus overly quiescent in epileptic mice compromised cognitive performance. Thus, the data presented here suggest the importance of an optimal window of excitability for appropriate hippocampus-dependent cognitive processing in nonepileptic animals as well as in chronically epileptic mice. These data also suggest that the ability of dentate gyrus modulation to improve cognitive performance is not merely due to a suppression of seizure activity. If the improved cognitive performance was indirectly due to seizure suppression, one would anticipate that further reducing dentate gyrus activity would be beneficial; however, the authors found that making the dentate gyrus overly quiescent in epileptic mice compromised cognitive performance. Further, these acute manipulations were performed in mice that did not exhibit seizure activity for at least 1 hour prior to behavioral testing. Thus, it appears that there is a permissive window of excitability in which the dentate gyrus can optimally encode information.

Interestingly, the dentate gyrus retains the ability to encode information properly under the right “permissive” conditions despite the neuropathological features associated with epilepsy, which are particularly pronounced in the hippocampus. These data suggest that modulating dentate gyrus activity could be beneficial in improving cognitive performance even in cases where there is damage to the hippocampus, underscoring the potential therapeutic implications of this study. Notably, the work focuses solely on normalizing circuit activity in the dorsal dentate gyrus and the resultant impact on dorsal hippocampus-dependent behaviors. It remains unclear whether restoring the appropriate window of excitability in other networks will attenuate other pathological features of epilepsy, such as psychiatric comorbidities, which are evident in epilepsy models with insults to the ventral hippocampus.¹⁰ For instance, does restoration of normal ventral hippocampal activity improve anxiety-like and/or depression-like behaviors comorbid in chronically epileptic animals? Nonetheless, this study demonstrates the importance of a “permissive excitability window” in granule cells for optimal encoding and cognitive function. The dentate granule cells become hyperexcitable in chronically epileptic mice, which contributes to deficits in cognitive performance. Circuit-level modulation of excitability to counteract these changes is a novel translational approach to intervene in comorbidities associated with epilepsy.

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