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Disruption of hippocampal rhythms via optogenetic stimulation during the critical period for memory development impairs spatial cognition—Michelle L. Kloc, Francisco Velasquez, Rhys W. Niedecker, Jeremy M. Barry, Gregory L. Holmes (Epilepsy Development and Cognition Group, Department of Neurological Sciences, University of Vermont, Larner College of Medicine, Burlington, VT, USA)

Objective: Investigate whether the disruption of normal hippocampal rhythms via optogenetic stimulation of the medial septum (MS) during late postnatal development has enduring effects on the allocentric memory of rat pups.

Methods: Hippocampal theta oscillations were non-endogenously regulated in rat pups using blue light (465-nm) pan-neuronal optogenetic activation of the MS from postnatal day (P)21–25 using random sinewave frequencies ranging from 0.5 to 110 Hz. Non-stimulated and yellow light (590-nm) stimulated rats were used as controls, and local field potentials from the hippocampus and MS were recorded unilaterally during stimulations. In early adulthood, spatial cognition was assessed using the active avoidance task. Rats were perfused and tissue containing the MS and hippocampus was harvested and sectioned to assess cell density. Power spectrum density of both the MS and hippocampus; coherence, and voltage correlation analysis between both structures were used to compare baseline to the disruptive stimulation.

Results: During late postnatal development, non-selective optogenetic activation of the MS tightly regulated hippocampal oscillations. Disruptive stimulation increased power but reduced coherence and voltage correlations; and resulted in impaired spatial learning compared with controls. Impairment of spatial cognition was not attributed to MS or hippocampal cell loss.

Conclusions: These results demonstrate that hippocampal oscillations can be precisely regulated with non-selective optogenetic stimulation of the MS in weanling rats. A disruptive hippocampal stimulation protocol during the critical period of memory development results in long-standing spatial cognitive deficits that is not attributed to cell loss.

Significance: Disruptive activity during postnatal development, such as occurs during early life seizures, has complex effects on developing neural circuits relevant to cognition. By mimicking disruption of MS-hippocampal entrainment in an isolated fashion, it may be possible to pinpoint mechanisms through which ELS may affect cognition.

Effects of early-life seizures on coordination of hippocampal-prefrontal networks: influence of sex and dynamic brain states Rhys W. Niedecker, Michelle L. Kloc, Gregory L. Holmes, Jeremy M. Barry

The development and maturation of neurological circuits associated with learning and memory can be negatively impacted by early life seizures (ELS). While this has been a long-established concept, the pathophysiological mechanism underpinning ELS induced cognitive deficits is not as well understood. Further, the influences of crucial variables such as sex on cognitive outcomes following ELS have not been explored. We hypothesized that when compared to their control (CTL) counterparts, ELS rats would display impairments in spatial cognition as the result of impaired dynamic coordination between the hippocampus and medial prefrontal cortex (mPFC). To test this, flurothyl seizures were induced in both male and female rats at postnatal day (P) 15. We then assessed spatial cognition of the animals as adults using an active avoidance task. After initial testing, the animals were implanted with microwire tetrodes in the mPFC and CA1 of the hippocampus so that single cells and local field potentials could be recorded and analyzed during subsequent active avoidance testing and during sleep. We found that ELS male animals exhibited impairments in the active avoidance task learning while ELS female animals were unaffected. Control female rats had an increased mPFC-hippocampus coherence compared to control males across all bandwidths during active avoidance. ELS males that did not learn the task during training showed significantly lower coherences in all bandwidths than all other groups. ELS male non-learners also showed decreased dynamic coherence and cell modulation specifically in the 8–9 Hz range. Additionally, recordings taking during sleep showed that ELS male non-learners had less coherence and phase locking compared to all other groups. In male animals, ELS decreased hippocampus-mPFC coherence during active cognition and slow wave sleep while female rats showed no differences in these measures. The ELS animals that exhibited the lowest dynamic coherence were also the animals that performed the worst while learning the active avoidance task. Taken in concert, these

results show that there may be a gender dependent influence on the effect of critical period seizures on spatial cognition. Furthermore, incoherent theta signal coordination between the mPFC and hippocampus presents a mechanism for adverse cognitive outcomes following ELS.

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Sleep and memory consolidation in temporal lobe epilepsy—Samantha Audrain, Richard Wennberg, Apameh Tarazi, Mary Pat McAndrews (Krembil Brain Institute, University Health Network, Toronto, Canada)

Objectives: Work in our lab and others have found that individuals with temporal-lobe epilepsy show Accelerated Long-Term Forgetting, a situation characterized by normal memory at short intervals (15–30 mins, which is typical of clinical assessments) but a rapid rate of forgetting relative to controls over hours and days afterward. These findings suggest disruption to a process involving hippocampal-neocortical interaction enabling 'consolidation' of memory traces in the neocortex over time. Indeed, we have reported that functional connectivity between the affected hippocampus and temporal neocortex is positively associated with recall after 72 hours (Audrain & McAndrews, Cortex 2018). Here, we investigated how slow-wave sleep (SWS) might moderate these effects.

Methods: We examined associative recognition memory in 19 patients with temporal lobe epilepsy on the Epilepsy Monitoring Unit at the Toronto Western Hospital. Critically, we focused on forgetting over a period of 6 hours to 16 hours as a function of duration of SWS overnight and frequency of frontotemporal interictal epileptic discharges (IEDs) during the same period. We also compared behavioral forgetting rates against age-matched healthy controls.

Results: While there was no significant difference between patients and controls in forgetting rates over that interval, most controls showed a facilitative impact whereas there was considerable variability amongst the patient group. In patients, there was a significant relationship between duration of SWS and forgetting ($r = 0.60$), such that greater SWS was associated with greater forgetting, which is opposite to the typical facilitative effect of SWS on retention in controls. We hypothesized that IEDs might mediate this effect, as they might serve as disruptive signals to consolidation processes during sleep and are more abundant during SWS. However, while IEDs did correlate with forgetting ($r = 0.42$), this did not prove to be a significant independent mediator.

Conclusions: The counter-intuitive effects of SWS on memory retention in individuals with temporal lobe epilepsy found here replicates one previous study. We consider the possibility that hippocampal IEDs, not captured adequately by scalp recordings, may play a significant role and we plan to investigate this in a subsequent study.

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The effects of cannabidiol, Δ9-tetrahydrocannabinol, and combinations of cannabidiol and Δ9-tetrahydrocannabinol in the open field test and forced swim test—Lukasz Dlugosz, Brian W. Scott, W. McIntyre Burnham (University of Toronto, Canada)

Background: Depression is the most common psychiatric comorbidity in people living with epilepsy, affecting approximately 25–35% of patients. Antidepressants are typically prescribed for depression, but they only provide relief in about two-thirds of patients. Recent research suggests that the cannabinoids might provide a new therapy for depression in both epileptic and non-epileptic patients.

Methods: The effects of cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC), and combinations of CBD and THC were tested in a mouse model of depression (the forced swim test, FST) and locomotor activity (the open field test, OFT). Adult, male CD-1 mice were injected intraperitoneally with CBD (0 or 30 mg/kg), THC (0 or 2 mg/kg) or CBD + THC (0 + 0, 30 + 1, 30 + 2 mg/kg). They were then tested for 30 minutes in the OFT and for 6 min in the FST.

Results: As compared to vehicle, CBD, and THC both significantly decreased the time spent immobile and increased the time spent swimming in the FST. THC, however, also significantly increased locomotor activity in the OFT, suggesting a non-specific effect. In combination, CBD and THC lost their effects in both tests and did not differ from vehicle.

Conclusions: These results suggest that CBD might be potentially useful for people living with depression. In the present study, however, combinations of CBD and THC had an infra-additive effect rather than the supra-additive effect reported in a previous study. Since CBD and THC in combination produced effects that are less than the sum of the drugs alone ($1 + 1 > 2$), this may suggest the presence of antagonistic interactions between these two cannabinoids.

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