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# Unlocking the Mysteries of Slumber: Unveiling the Intricate Ties Between Sleep, Epilepsy, and Cognition

**Interaction of Interictal Epileptiform Activity With Sleep Spindles Is Associated With Cognitive Deficits and Adverse Surgical Outcome in Pediatric Focal Epilepsy**

Yu H, Kim W, Park DK, Phi JH, Lim BC, Chae JH, Kim SK, Kim KJ, Provenzano FA, Khodagholy D, Gelinas JN. *Epilepsia*. 2024;65(1):190-203. doi:10.1111/epi.17810. PMID: 37983643

Objective: Temporal coordination between oscillations enables intercortical communication and is implicated in cognition. Focal epileptic activity can affect distributed neural networks and interfere with these interactions. Refractory pediatric epilepsies are often accompanied by substantial cognitive comorbidity, but mechanisms and predictors remain mostly unknown. Here, we investigate oscillatory coupling across large-scale networks in the developing brain. Methods: We analyzed large-scale intracranial electroencephalographic recordings in children with medically refractory epilepsy undergoing presurgical workup ($n = 25$, aged 3–21 years). Interictal epileptiform discharges (IEDs), pathologic high-frequency oscillations (HFOs), and sleep spindles were detected. Spatiotemporal metrics of oscillatory coupling were determined and correlated with age, cognitive function, and postsurgical outcome. Results: Children with epilepsy demonstrated significant temporal coupling of both IEDs and HFOs to sleep spindles in discrete brain regions. HFOs were associated with stronger coupling patterns than IEDs. These interactions involved tissue beyond the clinically identified epileptogenic zone and were ubiquitous across cortical regions. Increased spatial extent of coupling was most prominent in older children. Poor neurocognitive function was significantly correlated with high IED–spindle coupling strength and spatial extent; children with strong pathologic interactions additionally had decreased likelihood of postoperative seizure freedom. Significance: Our findings identify pathologic large-scale oscillatory coupling patterns in the immature brain. These results suggest that such intercortical interactions could predict risk for adverse neurocognitive and surgical outcomes, with the potential to serve as novel therapeutic targets to restore physiologic development.

**Altered Sleep Microarchitecture and Cognitive Impairment in Patients With Temporal Lobe Epilepsy**

Bender AC, Jaleel A, Pellerin KR, Moguilner S, Sarkis RA, Cash SS, Lam AD. *Neurology*. 2023;101(23):e2376-e2387. doi:10.1212/WNL.0000000000207942. PMID: 37848332

Background and Objectives: To investigate the spatiotemporal characteristics of sleep waveforms in temporal lobe epilepsy (TLE) and examine their association with cognition. Methods: In this retrospective, cross-sectional study, we examined overnight EEG data from adult patients with TLE and nonepilepsy comparisons (NECs) admitted to the epilepsy monitoring unit at Mass General Brigham hospitals. Automated algorithms were used to characterize sleep macroarchitecture (sleep stages) and microarchitecture (spindles, slow oscillations [SOs]) on scalp EEG and to detect hippocampal interictal epileptiform discharges (hIEDs) from foramen ovale electrodes simultaneously recorded in a subset of patients with TLE. We examined the association of sleep features and hIEDs with memory and executive function from clinical neuropsychological evaluations. Results: A total of 81 adult patients with TLE and 28 NEC adult patients were included with similar mean ages. There were no significant differences in sleep macroarchitecture between groups, including relative time spent in each sleep stage, sleep efficiency, and sleep fragmentation. By contrast, the spatiotemporal characteristics of sleep microarchitecture were altered in TLE compared with NEC and were associated with cognitive impairments. Specifically, we observed a 30% reduction in spindle density in patients with TLE compared with NEC, which was significantly associated with worse memory performance. Spindle-SO coupling strength was also reduced in TLE and, in contrast to spindles, was associated with diminished executive function. We found no significant association between sleep macroarchitectural and microarchitectural parameters and hIEDs. Discussion: There is a fundamental alteration of sleep microarchitecture in TLE, characterized by a reduction in spindle density and spindle-SO coupling, and these changes may contribute to neurocognitive comorbidity in this disorder.

## Commentary

The interplay between sleep, cognition, and epilepsy represents a complex and multifaceted relationship within the realm of neuroscience. Disruptions in sleep microarchitecture, such as spindle alterations, may impact memory and cognition.[1] Epilepsy and interictal epileptiform discharges (IEDs) independently contribute to cognitive deterioration in both children and adults.[2-4] Nonetheless, the implications of IEDs and seizures on sleep microarchitecture, and their subsequent impact on cognition, remain largely unexplored. This area has recently garnered considerable attention. In a novel study, Yu et al delved into the intricate dynamics involving sleep, epilepsy, IEDs, pathologic high-frequency oscillations (HFOs), and cognitive outcomes in children undergoing intracranial EEG (iEEG).[5] Concurrently, Bender et al examined this relationship in adults with temporal lobe epilepsy (TLE), utilizing scalp EEG and/or foramen ovale electrodes.[6] While these studies provided answers to several critical questions, they also opened up many more new avenues of inquiry along the way.

A key issue addressed by these studies is the potential correlations between epilepsy and sleep macro- and microarchitecture. Bender et al found no significant differences in sleep macroarchitecture, such as sleep efficiency, fragmentation, and time spent in different stages of sleep, between TLE and controls.[6] However, they did observe a notable reduction in sleep microarchitecture, specifically spindle density, in TLE patients, particularly ipsilateral to the side of the ictal onset.[6] This finding suggests a possible link between alteration in sleep microarchitecture and abnormal epileptic network. Known for modulating spindles, cortical slow oscillations (SO, 0.5-2 Hz)[1] during non-rapid eye movement sleep were also found to have reduced coupling with spindles in TLE.[6] These findings indicate that epilepsy might impact sleep microarchitecture without necessarily altering macroarchitecture and sleep disturbances that are commonly assessed in clinical practice. Thus, these findings underscore the importance of incorporating sleep microarchitecture analysis into routine epilepsy care and suggest that a quantitative evaluation of sleep microarchitecture might be vital for a thorough assessment of cognition.

Regarding the relationship between IEDs and sleep features, Bender et al found no association between hippocampal IEDs (hIEDs) and sleep efficiency, fragmentation, or time spent in each stage.[6] As for sleep microarchitecture, in contrast to prior studies that demonstrated strong coupling of IEDs with spindles in TLE,[7] Bender et al did not find an association between hIED rate and spindle density or spindle-SO coupling.[6] On the other hand, pediatric research in this area was largely uncharted territory until Yu et al's current study.[5] Utilizing iEEG in children, Yu et al discovered that both IEDs and HFOs had a significant correlation with spindles and observed a vigorous coupling of IEDs or HFOs with spindles.[5] Authors found that IEDs/HFOs were coupled to the spindle as early as 3 years in immature brains with an increase in the spatial extent of coupling with increasing age.[5] In contrast, Bender et al reported a weak inverse relationship between hIED-spindle coupling and age in adult TLE.[6] Additionally, HFOs showed a stronger correlation with spindles compared to IEDs,[5] likely because HFOs more accurately predict epileptogenic zones.[8] The IEDs/HFO coupling interactions were not confined to certain brain areas but rather spanned both short and distant anatomic connections of the neocortex.[5] These IED and HFO coupling interactions with spindles not only involved the ictal network but often extended well beyond the extent of regions producing ictal activity.[5] High-frequency oscillations, in comparison to IEDs, also demonstrated a broader spatial extent of spindle coupling.[5] Understanding these interactions is crucial as they could impact brain networks both during early development and later in life, play a role in disease course and progression, and have implications for treatment outcomes. However, to determine if therapeutic strategies targeting these altered sleep microarchitectures and network dysfunctions could improve epilepsy outcomes, longitudinal studies are needed.

Another key area examined by both studies is the interaction between epilepsy, IEDs, sleep, and neuro-cognitive outcomes. Numerous studies have established an association between IEDs and poor cognition in both pediatric and adult populations.[2-4] Echoing these findings, Bender et al identified an inverse correlation between hIED rate and executive function,[6] and Yu et al noted a similar relationship between IEDs and IQ.[5] Exploring the more complex trinity of epilepsy, sleep, and cognition, Bender et al also found that decreased spindle density in TLE was associated with worse memory but not necessarily executive function.[6] Moreover, they observed a positive association between spindle-SO coupling and executive function, noting that the extent of disrupted spindle-SO coupling observed in TLE paralleled the degree of executive dysfunction.[6] Similarly, on iEEG, Yu et al found that the strength and spatial extent of IED/HFO-spindle coupling were associated with worse neuro-cognitive outcomes.[5] These findings lead to numerous questions regarding the potential role of spindles as biomarkers for therapeutic intervention to alleviate cognitive impairment in epilepsy and whether targeting the IED burden could improve executive function. Further clinical trials are required to explore these possibilities.

Finally, the impact of this interaction triad on surgical outcomes is also noteworthy. Yu et al reported that increased strength and spatial extent of IED/HFO-spindle coupling correlated with poor surgical outcomes.[5] This suggests that alteration of coupling across epileptic networks over time in children might contribute to a higher degree of drug resistance in chronic epilepsies. These findings could be valuable in predicting surgical outcomes and assisting in clinical decision-making. These results naturally lead us to a critical inquiry: Should sleep architecture be incorporated into tools that predict surgical outcomes in epilepsy? This remains yet another important area for future research.

Lastly, it is crucial to recognize some shortcomings in both studies. Both Bender et al and Yu et al conducted single-center, retrospective cross-sectional studies. Bender et al's research was carried out in the epilepsy monitoring unit, which differs from the patient's home environment, and several uncontrollable factors in the hospital setting, such as anti-seizure medication use and nightly sleep disruptions, could have influenced the results of the study. Furthermore, they did not assess sleep-dependent memory tasks or compare EEG variables with cognitive tasks conducted at the same time. Yu et al's study lacked a control group, which is another significant limitation.

Nevertheless, both Bender et al and Yu et al have made strides in enhancing our understanding of the intricate connections between sleep, cognition, and epilepsy. They provide evidence of an association between sleep microarchitecture, epilepsy, and cognitive outcomes in both children and adults with TLE. These findings suggest that epileptic networks, IEDs, and HFO likely change sleep microarchitecture and networks in a fashion that can impact memory, cognition, and executive function. These findings are significant not only for their implications on cognition but also for predicting surgical outcomes and seizure freedom following epilepsy surgery. Future longitudinal studies are essential to confirm the prognostic potential of these interactions for cognitive and surgical outcomes in both children and adults.

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