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Sleeping High and Getting Lost on the Spiky Road: What Affects Visual Memory in Older Adults With Epilepsy, and What Can We Do About It?

Epilepsy and Sleep Characteristics Are Associated With Diminished 24-h Memory Retention in Older Adults With Epilepsy

Sarkis RA, Lam AD, Pavlova M, Locascio JJ, Putta S, Puri N, Pham J, Yih A, Marshall GA, Stickgold R. *Epilepsia*. 2023;64(10):2771-2780. doi:10.1111/epi.17707

Objective: Individuals with epilepsy often have memory difficulties, and older adults with epilepsy are especially vulnerable, due to the additive effect of aging. The goal of this study was to assess factors that are associated with 24-h memory retention in older adults with epilepsy. Methods: Fifty-five adults with epilepsy, all aged >50 years, performed a declarative memory task involving the recall of the positions of 15 card pairs on a computer screen prior to a 24-h ambulatory electroencephalogram (EEG). We assessed the percentage of encoded card pairs that were correctly recalled after 24 h (24-h retention rate). EEGs were evaluated for the presence and frequency of scalp interictal epileptiform activity (IEA) and scored for total sleep. Global slow wave activity (SWA) power during non-rapid eye movement sleep was also calculated. Results: Forty-four participants successfully completed the memory task. Two were subsequently excluded due to seizures on EEG. The final cohort ($n = 42$) had a mean age of 64.3 $\pm$ 7.5 years, was 52% female, and had an average 24-h retention rate of 70.9% $\pm$ 30.2%. Predictors of 24-h retention based on multivariate regression analysis when controlling for age, sex, and education included number of antiseizure medications ($\beta = -.20$, $p = .013$), IEA frequency ($\beta = -.08$, $p = .0094$), and SWA power ($\beta = +.002$, $p = .02$). Significance: In older adults with epilepsy, greater frequency of IEA, reduced SWA power, and higher burden of antiseizure medications correlated with worse 24-h memory retention. These factors represent potential treatment targets to improve memory in older adults with epilepsy. This study provides Class I evidence supporting that, in adults with First Single Unprovoked Seizure (FSUS), 24-h ambulatory EEG has increased sensitivity when compared with routine and repeated EEG.

Commentary

Epilepsy is so much more than just the sum of its seizures.

While "responder rates" and "seizure freedom" are important outcome markers, the actual destination is the improved quality of life for people with epilepsy (PWE). The path to this goal is not uniform; it is a tailored journey that addresses psychiatric conditions, bolsters social support, and lessens the side effects of anti-seizure medications (ASMs).

Cognitive impairment is an often-overlooked companion of epilepsy, especially in older adults whose cognitive reserves are already strained by factors such as aging, accumulated brain pathologies, polypharmacy, and the forgetful elephant at the crossroads—dementias.

Nevertheless, how do you choose which older adults with epilepsy should you perform cognitive screening on? The answer *should be* simple—all those with no previous cognitive impairment diagnosis. However, a more practical answer is—every older adult with epilepsy that time and resources allow. While popular cognitive screening tools such as Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment test (MoCA) are not validated in PWE, neurologists use them commonly.[1] They can be insensitive to cognitive impairment confirmed on neuropsychological evaluation and ASM changes. Systematic screening in older adults with epilepsy will reveal previously undiagnosed cognitive impairment.[2] Upon discovery, modifying what we can is crucial, even though the list is short: ASM burden, seizure frequency, psychiatric health, and sleep quality. Neurologists should screen for sleep quality or excessive daytime sleepiness when cognitive impairment is present.

The importance of sleep in cognition was highlighted in this study by Sarkis et al.[3] It included 55 older adults >50 years

who were assessed for visual memory by recalling 15 card pairs before and after a 24-hour ambulatory electroencephalogram (EEG). They analyzed EEGs for the presence and frequency of interictal epileptiform activity (IEA), total sleep, and global slow wave activity (SWA) power during non-rapid eye movement (NREM) sleep. Their findings were as follows: Within the 42 older adults who qualified for the final analysis, the average retention of the paired cards (a marker for declarative visual memory) was around 71%. The caravan of the number of ASMs, IEA frequency, and SWA power predicts how often these older adults can retain visual information at the end of 24 hours. To simplify, the more ASMs used, the more the IEAs/hour, and the lower the SWA power (a marker of quality of NREM sleep), the lower the proportion of paired cards correctly identified the next day. While these seem like easy modifiable targets to improve cognition, it is essentially a traffic jam.

Treatment of IEAs to improve cognition with ASMs in adults is controversial.[4] Interestingly, the presence of IEAs can worsen the trajectory of the cognitive decline in Alzheimer's disease.[5] In people with Alzheimer's disease and epilepsy, medium-term treatment with ASMs has not been found to improve cognition,[6] but some other studies have shown improvement in spatial memory and executive function in people with Alzheimer's disease and IEA (without epilepsy) with levetiracetam.[7] Furthermore, as reported in this study, more ASMs are associated with worse cognition. Interictal epileptiform activities can worsen cognition even in ASM-naïve older adults with epilepsy.[8] But that is only part of the story; some ASMs (e.g., lamotrigine) can be associated with worse slow wave sleep, but many are not.[9] Anti-seizure medication polypharmacy likely affects slow wave sleep[10]—a key factor found to worsen cognition in this study. Thus, the likely best strategy to maintain or improve cognition in older adults with epilepsy is ASM monotherapy when possible and maximization of the dose as tolerated.

Ambulatory EEG or sleep studies can affect sleep quality. However, the study by Sarkis et al confirmed that the ambulatory EEG did not compromise sleep quality, maintaining consistency over the test period. However, the study has its blind spots. The epilepsy etiology in participants was not delved into, and cognitive baselines were assessed up to a year prior, leaving some ambiguity regarding the range of cognitive impairment. In patients with Alzheimer's disease, MMSE and MoCA scores can decline by 1 to 2 points per year.[5] The speed of decline can be worse in other dementias. Specifically, few patients had an abnormal MoCA score (<26). It's unclear if the study patients had dementia or if the cognitive impairment was due to epilepsy and/or comorbidities.

Anti-seizure medications traditionally linked to cognitive decline (benzodiazepines, topiramate, phenytoin) did not show the expected impact, nor did the visual memory-associated nondominant epilepsy lateralization (presumed to be right hemisphere in the study). This finding is not completely surprising. Topiramate usually causes impairment in verbal fluency and verbal memory rather than visual memory.[11] Phenytoin affects visually guided motor functions rather than visual memory.[12] The lack of findings may also be attributed to the study's small sample size.

The findings highlight the complexity of epilepsy's cognitive footprint. In certain patients, visual memory impairment is significant but of limited practical use in clinic visits concerning detection and management. While the commonly used cognitive screening tests such as MMSE and MoCA have visual recognition and visuospatial components, there are no specific declarative visual memory tasks. In addition, these tests focus on short-term memory, while the study focuses on medium-term memory, which is affected by the accelerated long-term forgetting phenomenon.[13] Thus, no rapid cognitive test detects medium-term visual memory impairment in routine clinical practice.

Despite some limitations, the study's insights are vital and address aspects of cognition not usually tested. Awareness of the detrimental roles of IEAs, sleep quality, and ASM burden on cognition is critical, and optimizing these factors should be a priority. Encouraging non-pharmacological interventions like exercise and meditation can also be beneficial.[14]

In essence, the study by Sarkis et al not only sheds light on the intricate dynamics influencing cognitive health in epilepsy but also underscores the importance of a holistic, personalized approach to care—one that goes beyond mere seizure control to truly uplift the lives of those affected.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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