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Memories in Persons with Epilepsy: They Are More Fragile Than You Think

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"Hidden Objective Memory Deficits Behind Subjective Memory Complaints in Patients with Temporal Lobe Epilepsy"

Lemesle B, Barbeau EJ, Milongo Rigal E, Denuelle M, Valton L, Pariente J, Curot J. *Neurology*. 2022 Feb 22;98(8):e818-e828. doi: 10.1212/WNL.0000000000013212. Epub 2021 Dec 14. PMID: 34906979.

"Background and objectives: The aim of this work was to test the hypothesis that patients with temporal lobe epilepsy (TLE) with subjective initial memory complaints (not confirmed by an objective standard assessment) and various phenotypes also show objective very long-term memory deficit with accelerated long-term forgetting. We tested patients with TLE with 2 surprise memory tests after 3 weeks: the standard Free and Cued Selective Reminding Test (FCSRT) and Epireal, a new test specifically designed to capture more ecologic aspects of autobiographical memory. Methods: Forty-seven patients with TLE (12 with hippocampal sclerosis, 12 with amygdala enlargement, 11 with extensive lesions, 12 with normal MRI) who complained about their memory, but for whom the standard neuropsychological assessment did not reveal any memory impairment after a standard delay of 20 minutes, underwent 2 surprise memory tests after 3 weeks. They were compared to 35 healthy controls. Results: After 3 weeks, FCSRT and Epireal recall scores were significantly lower in patients than in controls ($P < .001$). There was no significant correlation between FCSRT and Epireal scores ($P = .99$). Seventy-six percent of patients with TLE had objective impairment on at least 1 of these very long-term memory tests, regardless of the existence and type of lesion or response to antiseizure medication. Easily applicable, Epireal had a higher effect size, detected deficits in 28% more patients, and is a useful addition to the standard workup. Discussion: Assessing long-term memory should be broadened to a wide spectrum of patients with TLE with a memory complaint, regardless of the epileptic syndrome, regardless of whether it is associated with a lesion. This could lead to rethinking TLE nosology associated with memory."

Commentary

Memory complaints are one of the most common complaints in the epilepsy clinic and have a negative impact on quality of life.[1] There has been a perception in the epilepsy field that patients who perform well on neuropsychological testing do not have an underlying memory issue. As a result, in patients with "normal performance", the complaints are often attributed to co-morbid mood disorders or psychosocial factors. This has created a large discrepancy between the prevalence of subjective memory complaints and objective impairment on testing.[2]

The standard neuropsychological battery has served us well so far in identifying phenotypes of cognitive impairment in epilepsy, predicting risk of decline after epilepsy surgery, identifying cognitive domains that might benefit from more support, and planning treatment strategies/accommodations, among other benefits.[3] However, the standard battery that we have relied on has some blind spots; we do not perform an adequate assessment of autobiographical memory and our "long term" memory assessments occur 10 to 30 minutes after the information is encoded. It is these blind spots that Lemesle et al. try to address.[4] The authors prospectively recruited 47 patients with temporal lobe epilepsy (TLE) who had: 1- subjective memory complaints corroborated by a family member; 2- a normal performance on standard neuropsychological testing defined as a score within 2 standard deviations on the free and cued selective reminding test (FCSRT) which is a 16 word list verbal memory test; 3- mini mental status exam >25.

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Thirty-five control subjects were also enrolled in the study for comparison. Eligible patients were invited to return for another assessment 3 weeks later which is where this study's novelty and creativity lies. This time subjects were asked about the FCSRT again to determine how many words from the 16-word list they recalled, and then the Epireal protocol was implemented. Epireal consists of a total of 8 induced events during the assessment that would be asked about 3 weeks later. An example of these events includes the examiner offering the subject a drink, the examiner leaving the room and changing their gown, the phone ringing twice during the visit, asking the subject to retrieve a questionnaire from a shelf and providing the subject with a green binder from a specific location. Elements that were tested later included content, context, and timing of these events. In the absence of spontaneous recall, cues were then provided followed by recognition questions such as "did the phone ring once or twice?', and a score out of 39 was generated.[4]

After using the controls to establish impaired performance cut-offs on Epireal, seventy-six percent of epilepsy patients were shown to have impairment on either the Epireal, the FCSRT or both. There was no correlation between performance on the FCSRT and Epireal likely because the tests are assessing different aspects of memory. The presence or absence of lesions did not affect outcomes, curiously 12 patients had amygdala enlargement on MRI which is not a very common finding seen in TLE.[5] These findings were still significant after adjusting for mood, anxiety, and motivation using standard questionnaires. The authors highlight Epireal as an easy to use, multisensory protocol, that can supplement a standard neuropsychological battery and identify objective impairments in long term memory.[4]

The phenomenon of accelerated long term forgetting (ALF) was first described in temporal lobe epilepsy and is characterized by normal encoding over delays up to 30 minutes with accelerated decay of information over a period of hours, days, and weeks.[6] This phenomenon has been identified across different epilepsy populations and age groups and has also been noted in older adults without epilepsy. Memories once encoded are fragile and need to be consolidated. The process of memory consolidation is heavily dependent on sleep and allows the transfer of memories from the hippocampus to a more distributed neocortical network.[7] Studies looking at long term memory consolidation often use word lists and images, the advantage of Epireal is that it is testing an episodic memory in which the subject was an observer or participant. Epireal seems easy to use but still requires reproducibility. There are also questions about whether the events in Epireal are truly encoded in the first place, and how attentional difficulties which are prevalent in epilepsy can affect performance.[8] An additional concern revolves around the saliency of the induced events and the fact that subjects are not forewarned about the protocol.[9] Our brains need to prioritize which autobiographical memories need consolidation, and the memory of being offered a glass of orange juice during a neuropsychological assessment might not always make the cut.

One of the main messages of this study is that patients who have subjective memory complaints should be taken seriously. In the dementia literature, the concept of subjective cognitive decline has received attention because a subset of patients were found to have underlying neurodegenerative pathologies despite normal performance on neuropsychological testing.[10] Studies focusing on cohorts with subjective cognitive decline have shown an increased risk of mild cognitive impairment or Alzheimer's dementia with longitudinal follow up.[10] We should extrapolate this concern to our epilepsy clinic and perform a thorough work up in patients with subjective memory complaints. The differential diagnosis is broad and includes a cogniform disorder, impact of a mood disorder, medication effects, or as this study suggests impairments in long term consolidation.

The pathophysiology of ALF in epilepsy is still poorly understood which is why we need to start by establishing the ideal battery of tests to assess long term memory, identify factors that correlate with impaired consolidation and determine whether any interventions will help. Given the need for serial testing, an ideal battery would be self-administered. Certain at home tablet-based cognitive batteries are already being investigated in elderly cohorts and performance on these tests has been correlated with Alzheimer's disease biomarker status.[11]

With regards to contributing factors to ALF, seizures whether clinical or subclinical are likely top of the list. There is also interest in the role of interictal epileptiform discharges especially those in sleep.[12] Given the prevalence of sleep disordered breathing in epilepsy, and its disruption of sleep architecture, one would also expect it to play a role. Identifying patients who might benefit from prolonged EEG or a sleep study to better examine their memory complaints would be a good first step. Studies have already started looking at ways to improve the process of memory consolidation during sleep with medications, electrical stimulation or tagging memories with odors or sounds. If successful they present appealing therapeutic opportunities.

This study is another reminder that we should listen closely to our patients' complaints, and that our gold standards need to be updated as our understanding of memory evolves.

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