



EPILEPSY AND COGNITION: A SYSTEMATIC REVIEW

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ABSTRACT

BACKGROUND: EPILEPSY is a neurological disorder characterized by chronic predisposition Marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, Associated with abnormal electrical activity in the brain, which requires typically two unprovoked seizures. Cognition can be defined as an individual's ability to think, or more precisely, to use information about and from the environment in an adaptive manner. Drugs used to treat epilepsy act by reducing neuronal excitability, which may have the unintended side effect of impairing cognitive function.

OBJECTIVE: This review aims to critically evaluate the existing literature on the relationship between epilepsy and cognitive function.

KEY WORDS: Epilepsy, Cognition, Antiepileptic Drug, Executive Function

METHODS: A systematic search of the MEDLINE database was conducted to identify studies published from 2019 to the present, focusing on the cognitive effects in epilepsy. Out of 108 initial results, 12 studies (including controlled and randomized controlled trials) met the inclusion criteria for review.

CONCLUSION: This review has highlighted the complex relationship between epilepsy and cognitive function, underscoring that seizures and the underlying neurological changes associated with epilepsy can significantly impact cognitive abilities. Key findings indicate that factors such as seizure frequency, type, and the age of onset play critical roles in shaping cognitive outcomes.

I. INTRODUCTION

Epilepsy is a prevalent neurological disorder characterized by recurrent seizures resulting from abnormal electrical activity in the brain. Affecting approximately 50 million people worldwide, epilepsy poses significant challenges not only in terms of seizure management but also in the realm of cognitive functioning. Cognitive impairments are frequently reported among individuals with epilepsy, impacting areas such as attention, memory, language, and executive function.

Cognition comprises a broad range of functions, such as attention, intelligence, visual memory, and fine motor dexterity. Abnormalities in cognition are commonly reported in people with epilepsy. Problems with cognition can be manifested as reductions in attention, IQ, language and perceptual skills, executive functions including problem solving, verbal and visual memory, motor speed, dexterity, and coordination. The poorest cognition is associated with early age at onset and thus, longer duration of epilepsy, especially in the presence of generalized Tonic–Clonic seizures, repeated episodes of status epilepticus, and increased exposure to antiepileptic drugs (AEDs).

Understanding the intricate relationship between epilepsy and cognition is essential for developing effective treatment strategies and improving patient outcomes. Various factors, including the type of epilepsy, age of onset, frequency of seizures, and comorbid conditions, contribute to the cognitive profiles observed in affected individuals. Despite the growing body of research, the mechanisms linking epilepsy and cognitive deficits remain complex and multifaceted.

This review aims to synthesize current literature on the cognitive consequences of epilepsy, exploring both the direct effects of seizures and the broader implications of living with this condition. By examining recent findings and highlighting gaps in knowledge, we hope to provide a comprehensive overview that will inform future research directions and clinical practices? Ultimately, our goal is to enhance the understanding of how epilepsy influences cognitive function and to advocate for integrated approaches that address both neurological and cognitive health in affected individuals.

COGNITION

People with epilepsy (PWE) are also exposed to many other health problems that occur often. For many people, co-morbidity is more burdensome than the seizures themselves. Epileptic seizures can cause both morphological and functional changes in the brain, manifesting as cognitive and neuropsychological disorders. Frequent seizures, especially status epilepticus, repeatedly cause oxidative stress; neuronal loss, mainly in hippocampus or entorhinal cortex, which is another area closely associated to cognitive processing; neurogenesis; changes in growth factors such as BDNF; and inflammation in the brain ^[1,2]. If the epileptic seizures are not properly treated and controlled, they can lead to permanent cognitive dysfunction ^[3]. The difficulty with cognition is one of the most common problems in PWE; however, it is often overlooked. Some studies suggest that between 60% and 70% of people with chronic epilepsy have cognitive impairment ^[4].

According to recent reviews, objective cognitive impairments are frequently present already at the onset of epilepsy or even before ^[5,6]. Objective deficits, mostly in attention, executive function and memory, were registered in up to 70% of untreated adult patients with new-onset epilepsy (not to be confused with patients with just newly diagnosed epilepsy after years of suffering from seizures). A worse cognitive status was associated with lower education, the presence of cerebral lesions, and with generalized-tonic Clonic seizures ^[7].

Factors influencing cognitive dysfunction

- 1. *Biologic factors***
- 2. *Psychosocial factors***
- 3. *Treatment-related factors***
- 4. *Epilepsy surgery***

1. *Biological Factors*

a) Seizure type and etiology

Different epilepsy syndromes have different effects on cognition. Symptomatic epilepsies can affect certain aspects of cognition and behavior depending on the location and nature of the neuropathology. While a small stroke or tumor may not involve any measurable neurocognitive impairment, seizures associated with lesions in the frontal lobe or limbic system can result in memory, language or psychologic disturbances ^[9]. A recent study in patients with post traumatic epilepsy showed the presence of personality disorder, disinhibited behavior, irritability, agitation, and aggressive behavior but no deterioration in memory, language, intelligence, attention, and spatial cognition ^[10]

b) Neuropathology

The type and anatomic location of the brain pathology have crucial impact on the type of cognitive deficit. Verbal memory deficit is more commonly associated with left-sided TLE and nonverbal or visual memory is typically affected in right temporal seizures ^[10,11]. Similarly, frontal lobe seizures may induce executive dysfunction (i.e., difficulties with attention and problem solving) or motor incoordination ^[12].

c) Age at seizure onset

Studies in both humans and animals suggest that immature brain, although resistant to the development of mesial temporal sclerosis (MTS), may develop age specific functional and anatomic pathologies in the hippocampus ^[13]. Patients with childhood-onset TLE have reduced total white matter volume associated with poorer cognitive status ^[14]. These findings suggest that different pathologies at different ages of epilepsy onset and during different stages of development may induce different types of neuropsychologic impairments ^[15].

d) Seizure frequency

Evaluation of the effects of seizure frequency independent from effects of duration or severity of epilepsy may not be feasible. However, there is convincing evidence showing that higher frequency and duration of TLE are associated with more severe hippocampal atrophy and cognitive deficiency, possibly through secondary neuronal metabolic and structural deterioration ^[16–19]. Generalized cognitive impairment with global decline in attention, memory, and general intelligence is more likely to be seen with increasing seizure frequency and epilepsy duration ^[20]. Seizure frequency has also been reported as among the most relevant determinants of poor QoL scores in chronic epilepsy ^[21].

e) Seizure severity

Status epilepticus and prolonged or repetitive seizures may induce permanent neuronal injury and result in neurocognitive damage ^[16].

2. Psychosocial factors

A variety of psychosocial problems associated with epilepsy can give rise to, or exacerbate, cognitive and behavioral dysfunction. Although the true incidence and prevalence of morbid psychologic disturbance in epileptic patients are not clear, they are more common in patients with epilepsy than in the general population. The most common forms of psychologic morbidity in these patients are depression, anxiety, psychosis, and attention deficit disorder. The incidence of depression and suicide is four to five times higher in epilepsy patients as compared with the general population. A recent study suggested that depression contributed more to poor QoL than did ongoing seizure activity. Health-related quality of life (HRQoL) in patients with psychogenic non-epileptic seizures is lower than in epilepsy patients. It has been shown that psychiatric history, depression, and mood disturbance are more common in the former group and that they have a lower HRQoL than epilepsy patients. Mood problems are a strong predictor of low HRQoL that may explain the lower HRQoL in non-epileptic seizure patients compared with those with epilepsy [22-23].

3. Treatment-related factors

Although cognitive and behavioral side effects of epilepsy have been known for a long time, new therapeutic Interventions, such as pharmacotherapy and epilepsy surgery, are also associated with cognitive and behavioral effects. These treatments may have both negative and positive effects on cognition and behavior. Seizure reduction may improve cognition and behavior, although it may be somewhat counteracted by inducing changes in the underlying neurochemical systems that control thinking and mood. Appropriate management of AED therapy can minimize side effects of the AEDs, and potential cognitive deficits after epilepsy surgery can be minimized by tailoring the resection to the individual patients condition. We review the neurocognitive side effects of the currently available therapeutic antiepileptic modalities, i.e., AEDs, epilepsy surgery, and vagal nerve stimulation.

4. AEDs:

Adverse cognitive and behavioral effects are most common with some of the older drugs, i.e., barbiturates and benzodiazepines, while data regarding other first generation AEDs, carbamazepine, phenytoin, and valproate, have been somewhat controversial. Barbiturates and benzodiazepines seem to have the worst cognitive profiles, including decreased arousal and deterioration in most areas of cognitive performance [26].

5. Epilepsy surgery

The laterality and locality of the resection influence deficits following epilepsy surgery. The most common epilepsy surgery is temporal lobectomy. Typically, left-sided temporal lobectomy induces verbal memory and learning deficits, while right-sided resections are associated with visual-spatial memory and cognitive declines; however, the changes are more consistent in left-sided resections. It appears the potential deficits are affected by the degree of seizure control, level of functioning, and duration of seizure prior to surgery [24].

II. RESEARCH METHODOLOGY

LITERATURE SEARCH: A vigorous, maximum sensitive and online search of the literature was performed using the PubMed, Scopus, PsycINFO, MEDLINE and Web of Science Data Bases. The search strategy was limited to published articles in the last 10 years (JUNE 2014–JUNE 2024) to include the most recent, up-to-date data that reflect the current clinical practice in English. The search terms used were, “Epilepsy”, “Cognitive Side Effects”, “Behavioral Effects”, “Cognition in Epilepsy”, “Cognition” “Psychosocial Factors”, “Temporal Lobe Epilepsy”, and “epileptic surgery” “combined with Boolean operators “AND” and “OR” as appropriate.

STUDY SELECTION: Initial screening of titles and abstracts of the retrieved articles were independently screened by two reviewers to assess their relevance to the review topic. The first stage of screening was performed based on the titles and abstracts. Eligible studies were screened based on the full text in the second stage.

DATA EXTRACTION: Data extraction was performed by two reviewers using a standardized data extraction. Extracted data included the details such as study characteristics, participant characteristics, anti-epileptic drugs investigated, cognitive and neuropsychological outcomes measured and the key findings related to the side effects.

DATA SYNTHESIS: The findings from the synthesized data were performed to find out the cognitive and behavioral adverse effects of various anti-epileptic drugs.

IV. RESULTS AND DISCUSSION

Cognitive and behavioral deficits are more common in patients with epilepsy than in the general population. These deficits are multifactorial in etiology, ranging from biologic factors, such as the type of seizures, neuropathology, or age of onset, to a variety of psychosocial problems and, in particular, therapeutic interventions that may adversely affect epilepsy patients. While treating epilepsy it is necessary and by itself may resolve or alleviate the cognitive and behavioral deficits of the disease, it may also be associated with its own side effects ^[24].

The major therapeutic modalities (i.e., AEDs and epilepsy surgery) are associated with cognitive and behavioral risks. While the majority of such dysfunctions are reversible, some are not remediable or even avoidable. Currently, there are no effective treatments that are available for cognitive deficits of epilepsy ^[22].

Therefore, treatment of epilepsy must be tailored to the individual patient with the potential risks in mind. Treating physicians should be aware of these risks and the contributing factors to avoid or minimize negative consequences ^[24].

In patients with medically refractory epilepsy, a meticulous and comprehensive pre surgical evaluation can predict and reduce the cognitive and behavioral risks of epilepsy surgery ^[25].

In summary, recognizing and addressing cognitive impairments in patients with epilepsy is crucial, and ongoing studies will be vital in shaping effective management strategies and improving life quality for

those affected.

CONCLUSION

In conclusion, the interplay between epilepsy and cognition is complex and multifaceted. This review highlights that individuals with epilepsy often face significant cognitive challenges, influenced by factors such as seizure frequency, type of epilepsy, and treatment regimens. While some patients may experience minimal cognitive impairment, others may struggle with memory, attention, and executive functioning, which can profoundly impact their quality of life.

Furthermore, the neurobiological mechanisms underlying cognitive dysfunction in epilepsy remain an active area of research. Advances in neuroimaging and cognitive assessments have shed light on how seizure activity and interictal abnormalities affect cognitive processes. Importantly, this review underscores the necessity for a multidisciplinary approach to patient care that includes neuropsychological evaluation and tailored interventions aimed at improving cognitive outcomes.

Future research should focus on identifying specific risk factors for cognitive decline in epilepsy, as well as developing targeted therapies that address these cognitive deficits. By enhancing our understanding of the relationship between epilepsy and cognition, we can better support individuals living with this condition and improve their overall well-being.

In summary, recognizing and addressing cognitive impairments in patients with epilepsy is crucial, and ongoing studies will be vital in shaping effective management strategies and improving life quality for those affected.

Moreover, the review emphasizes the importance of early diagnosis and intervention, as well as tailored therapeutic strategies that can mitigate cognitive decline. Ongoing research into the neurobiological mechanisms underlying cognitive impairment in epilepsy is essential for developing targeted treatments.

In summary, this review has highlighted the complex relationship between epilepsy and cognitive function, underscoring that seizures and the underlying neurological changes associated with epilepsy can significantly impact cognitive abilities. Key findings indicate that factors such as seizure frequency, type, and the age of onset play critical roles in shaping cognitive outcomes.

Future studies should focus on longitudinal assessments and explore the impact of emerging therapies on cognitive function. By enhancing our understanding of how epilepsy affects cognition, we can improve quality of life for those living with this condition and inform clinical practices. Ultimately, a comprehensive approach that addresses both seizure management and cognitive health is crucial for optimizing patient care.

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