REVIEW

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Cognitive dysfunction in patients with epilepsy: focus on clinical variables

Marco Mula*

ABSTRACT A variety of factors can affect cognitive functions in patients with epilepsy, with the majority of cognitive problems having a multifactorial origin. In routine clinical practice, it can be difficult to dissect out the contribution of all of the different variables, because they are often interlinked together. In this article, all of the major variables implicated in cognitive dysfunction in epilepsy are discussed. In general terms, it is widely accepted that cognitive dysfunction in epilepsy can be trait dependent or state dependent. The former is a permanent condition due to the underlying brain damage or disorder, while the latter is a potentially reversible condition due to modifiable factors, such as antiepileptic drugs, seizure frequency and pattern and psychiatric comorbidity. Neuropsychological deficits also represent an important sequela in epilepsy surgery. Visual naming and visual memory loss have been clearly associated with temporal lobe surgery. It seems that the laterality of resection is not a major determinant, while the extension of resection is relevant for visual naming.

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe trait-dependent cognitive dysfunction associated with epilepsy, based on a review
- Discuss state-dependent cognitive dysfunction associated with epilepsy
- Distinguish postsurgical cognitive dysfunction associated with epilepsy

*Epilepsy Group, Atkinson Morley Regional Neuroscience Centre, St George's Hospital, Blackshaw Road, London SW17 0QT, UK; Tel.: +44 2087 254107; Fax: +44 2087 254591; mmula@sgul.ac.uk

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Author & credentials:

M Mula, MD, PhD, Epilepsy Group, Atkinson Morley Regional Neuroscience Centre, St George's Hospital, London, UK

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- epilepsy • memory
- neuropsychology

The issue of cognitive dysfunction in epilepsy is still challenging for clinicians. Patients with epilepsy frequently report some subjective impairment in cognitive functioning, with prevalence rates ranging from 44% for difficulties in learning and psychomotor retardation to 59% for sleepiness or tiredness [1,2]. In addition, 63% of patients perceive that antiepileptic drugs (AEDs) prevent them from achieving activities or goals [1]. However, whether this is a progressive process still remains controversial. In fact, data suggesting a progressive cognitive deterioration in epilepsy are limited to a specific subset of epilepsy syndromes, namely mesial temporal lobe epilepsy and epileptic encephalopathies (EEs) [3]. In this context, the role of AEDs is complex. In fact, on the one hand, seizure control should have a positive impact on cognitive functions. However, AEDs are simply 'seizure suppressants' rather than 'disease-modifying agents'; therefore, they have virtually no impact on the underlying process. In addition, potential cognitive adverse effects due to their mechanisms of action have to be taken into account [2].

Thus, it seems evident that the issue of cognitive dysfunction in epilepsy is quite complex and cannot be explained by a few variables, such as epilepsy itself or AEDs. This article aims to provide an overview of all of the major implicated variables in epilepsy, emphasizing the need for future studies.

Epilepsy-related variables

In general terms, it is widely accepted that cognitive dysfunction in epilepsy can be trait dependent or state dependent (**Figure 1**). The former is a permanent condition due to the underlying brain damage or disorder, while the latter is a potentially reversible condition due to modifiable factors, such as AEDs, seizure frequency and pattern and psychiatric comorbidity. It is obvious that all these factors strongly interact

together and result in the cognitive performance of the individual patient.

In structural/lesional focal epilepsies (e.g., traumatic brain injury, stroke and encephalitis, among others), the underlying cause plays a relevant role, with cognitive deficits in line with the lesion site. The case of focal epilepsies of unknown cause (formerly known as cryptogenic focal epilepsies) is much more complex. Data from the SANAD trial showed that newly diagnosed untreated patients with epilepsy are cognitively compromised before the start of AED medication, independently of the underlying cause, with memory and psychomotor speed being the most severely affected domains [4]. This obviously suggests that something in the epileptogenic process is *per se* implicated in cognitive dysfunction. This hypothesis is also supported by data regarding specific electroclinical syndromes showing a specific spectrum of cognitive impairments. For example, juvenile myoclonic epilepsy seems to be characterized by executive dysfunction [5]; short-term visuospatial memory dysfunction, executive dysfunction and frontal lobe dysfunction have been reported for Unverricht–Lundborg disease [6,7]; language dysfunction has been reported in Landau–Kleffner syndrome [8]; and poor language acquisition and visuospatial defects have been reported in Dravet syndrome [9] and Rett syndrome [10]. Even supposedly 'benign' epilepsies, such as benign epilepsy of childhood with centrotemporal spikes [11] or benign occipital epilepsy [12], seem to be characterized by a specific pattern of cognitive dysfunction.

A second point that still remains a matter of debate is whether such cognitive dysfunction is a progressive phenomenon [3]. At present, robust data favoring such a hypothesis come from patients with mesial temporal lobe epilepsy [13,14] and some EEs [3]. In such cases, it seems to have been established that progressive cognitive

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Figure 1. Trait-dependent and state-dependent cognitive dysfunction in patients with epilepsy.

deterioration is not limited to memory function, but rather is a more widespread process, and some interventions have been proposed [15]. In some EEs, such as Landau–Kleffner syndrome or continuous spike–wave during slow sleep, a common element is electrical status epilepticus during sleep [3]. It seems now evident that the persistence of epileptic discharges during sleep interferes with cognitive development and cognitive functioning, representing one of the main reasons for progressive cognitive impairment in these patients [16].

Seizure pattern and frequency are strictly interlinked with the underlying epilepsy syndrome, but account for state-dependent cognitive dysfunction. In fact, epileptic seizures themselves may determine transitory cognitive dysfunction with a different magnitude. Generalized tonic–clonic seizures are associated with a greater cognitive impairment than partial seizures [17]. In particular, a generalized tonic–clonic seizure may produce reversible attention deficits for a variable period of time of up to 24 h [18]. In patients with complex partial seizures, such changes seem to last for less time than with generalized tonic–clonic seizures, but it goes without saying that, in patients with frequent seizures, cognitive functioning is highly influenced by such a phenomenon [2].

Finally, age of onset of the epilepsy has been claimed to be a relevant variable, especially in children. In fact, the degree of brain plasticity typical of childhood may enable functional defects to be compensated for by the acquisition of new functions by other brain areas. For example, the hemispheric language dominance

can be switched if the electrophysiological activity of the left hemisphere becomes aberrant [19]. In general terms, an age of onset of epilepsy of younger than 5 years of age has been associated with a high risk for low intelligence quotient [18]. However, this seems to be true for certain syndromes such as Lennox–Gastaut syndrome or West syndrome, but other syndromes that have an early childhood onset, such as childhood absence epilepsy, are not associated with such a severe degree of impairment in intellectual function [20]. Thus, it seems evident that the underlying neurological condition represents the major variable.

AED-related variables

It is usually accepted that AEDs play a major role in state-dependent cognitive dysfunction. However, evidence supporting differences between individual drugs is limited [2,21]. Reasons for conflicting results may be due to the fact that the role of AEDs is not necessarily unidirectional in terms of negative effect. In fact, they can also result in cognitive improvements through the reduction or elimination of seizure activity.

In general terms, it is recognized that AEDs potentiating GABAergic neurotransmission have more detrimental effects on cognitive functions than those modulating voltage-gated channels [2,22]. In this regard, important information is provided by studies on healthy volunteers. In fact, although studies with healthy volunteers may be criticized for their lack of relevance to the clinical situation, they document the specific contribution of the individual compound

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without all of the confounding variables related to the underlying brain disorder. Previous studies on first-generation AEDs showed that barbiturates impair a wide spectrum of cognitive functions, such as attention, memory and mental speed [23–26], while the differences between all of the other first-generation drugs, such as carbamazepine, valproate and phenytoin, are not so striking [25,26]. Among second-generation AEDs, topiramate is probably the AED that is most associated with a significant negative impact on cognitive functions [27–30]. However, it is important to bear in mind that the major limitation of healthy volunteer studies is represented by their short-term perspectives without considering the so-called positive tolerance or habituation phenomenon. In fact, for most drugs, side effects occur early and for a short period (i.e., during the first few days or weeks of drug exposure), after which normalization occurs. Little is known about how tolerance to the cognitive side effects of AEDs develops and whether this phenomenon is relevant in patients with epilepsy. A failure to pay attention to this factor may lead to an overestimation of the negative effects of drugs on cognition. As pointed out by Aldenkamp, in clinical assessment, we should only conclude that a drug has significant ‘cognitive side effects’ if these effects persist over time [31].

As with all drugs, cognitive adverse effects are dose dependent in the majority of cases. For this reason, data on plasma levels should always be taken into account when discussing the impact of AEDs on cognition. Thompson and Trimble performed one of the first studies demonstrating an association between cognitive performance and plasma levels, assessing a number of subjects at both low and high serum levels of AEDs, but both within the therapeutic range [32]. In this regard, the pharmacokinetic properties of the individual drug have to be considered. For example, the controlled-release formulation of carbamazepine has a more favorable cognitive profile than conventional forms that display less marked and rapid fluctuations of plasma levels [33], but this has not been demonstrated for controlled-release valproate [34].

Finally, the issue of polytherapy still needs to be clarified. For a long time, it has been thought that cognitive adverse effects are more likely to occur on polytherapy than on monotherapy [35,36]. However, recent evidence suggests that polytherapy is not a specific risk factor for adverse effects [37]. Theoretically,

two AEDs with a similar spectrum of adverse effects on cognition may show a potentiation of tolerability problems, thus leading to serious cognitive impairment when used in combination [38]. However, it has to be acknowledged that polytherapy is adopted for patients with drug-resistant epileptic syndromes in which the aforementioned epilepsy-related variables play a relevant role.

Patient-related variables

Children and the elderly represent special population of patients. In these subgroups, epilepsy-related variables play a different role, as already discussed. However, it has to be considered that the impact of AEDs is also different. In fact, children and the elderly are not only more susceptible than adults to the cognitive effects of AEDs, but the phenomenology may be also different, with sedative AEDs being occasionally characterized by paradoxical hyperactivity and excitation [39]. In children, AEDs may have additional deleterious consequences on cognition due to the effect on neurodevelopment [40], and this notion has also been supported by animal studies [41]. Most importantly, it has to be taken into account that even modest cognitive side effects in children may have significant cumulative consequences if they restrict the rate at which academic skills are subsequently mastered (e.g., through multiple school absences, among other factors).

Finally, the presence of a psychiatric comorbidity represents another important variable. First, some psychiatric disorders are associated *per se* with neuropsychological deficits [42]. For example, several studies highlighted a dysfunction within the orbitofrontal loop circuit in patients with mood disorders, leading to a specific pattern of impairment in executive functions and attention [42]. Second, in some cases, patients with psychiatric disorders may have a poor understanding of their own cognitive abilities or, especially in mood and anxiety disorders, cognitive complaints are an integral part of the condition [43]. In fact, patients often believe that their cognitive problems are caused by external factors, such as the drug they have to take, instead of by internal factors, such as their seizures or their mood state. Several clinical situations signify the relationship between mood state, cognition and subjective complaints, and cases of patients doing better but feeling worse, and *vice versa*, when changing to another drug is an example of this.

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Cognitive dysfunction & epilepsy surgery

Epilepsy surgery has been demonstrated to be an effective and safe treatment in selected populations of patients [44], with clinically important sequelae occurring in a limited number of patients [45]. In the context of epilepsy surgery, the role of neuropsychology is still relevant in terms of providing further information regarding localization (temporal vs pre/postcentral structures), laterality and functional adequacy and reserve [46]. The ratio between adequacy and reserve seems to be a good estimate for neuropsychological deficits after surgery in patients with temporal lobe epilepsy. For example, in the case of temporal lobe surgery, adequacy represents the ability of the mesial temporal lobe structures on side of resection to support memory function, while reserve is the ability of the contralateral side of resection to support memory function. Postoperative memory decline is less likely with low adequacy and high reserve rather than *vice versa* [47].

A recent systematic review presented pooled estimates for different neuropsychological functions that could be used in clinical settings to aid in surgical decision-making [48]. The authors performed an extensive literature search using PubMed, EMBASE and the Cochrane database, identifying 5061 articles on epilepsy surgery, with 193 focusing on neuropsychological outcomes. Of these, 23 met the final eligibility criteria, with 22 studies involving temporal surgery only. They showed that visual naming and verbal memory loss occur in approximately 40% of patients with left temporal lobe epilepsy. Visual memory loss was reported in 20% of patients and seemed to be independent of laterality. Verbal fluency was surprisingly not related to laterality of resection, and whether it might represent a neuropsychological sequela is still controversial, reportedly being improved in 25% of patients. Extension of resection was shown to be relevant only for visual naming, and a significant

risk was reported for extensive resections (i.e., larger than 5.6 cm) [48]. Obviously, the limited number of studies in this analysis represents a major limitation. However, the review clearly suggests the need for further studies in homogeneous clinical samples. In addition, as compared with temporal lobe epilepsy surgery, other cases have been poorly studied and data are very limited [47,48] and, for example, patients undergoing callosotomy or hemispherectomy are also those with more severe epilepsy syndromes in which epilepsy-related variables play a considerable role. Systematic data collection is urgently needed in order to obtain meaningful results and estimates.

Conclusion

Cognitive dysfunction in epilepsy represents an important factor that complicates clinical management and contributes to quality of life and outcome measures. A number of variables related to the individual patient, the underlying brain disorder and the AED treatment play a role. All of these factors need to be considered when discussing the cognitive problems of patients with epilepsy. Tailored treatment approaches addressing comorbidities and modifiable factors represent important strategies. Further studies and systematic data collection will enable further insight into this problem.

Future perspective

Cognitive problems in epilepsy have represented and will continue to represent an important issue in patients with epilepsy. New AEDs and treatment strategies will have to take these aspects into consideration, possibly being as crucially as efficacy. Systematic data collection and standardized protocols of assessment will enable proper clinical intervention. Future studies will also focus on cognitive rehabilitation in order to improve quality of life, minimize side effects and maximize recovery after surgery.

EXECUTIVE SUMMARY

- Subjective cognitive impairment is reported in more than half of patients with epilepsy.
- Cognitive dysfunction in epilepsy is multifactorial in origin, with multiple variables being involved, including epilepsy-related, antiepileptic drug-related and patient-related variables.
- Visual memory and visual naming loss represent the most frequently reported cognitive sequelae after temporal lobe epilepsy surgery.
- Cognitive rehabilitation will represent a new area of epilepsy research.

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The activity was presented objectively and free of commercial bias.					

1. Your patient is a 23-year-old man with seizures secondary to a traumatic brain injury. He also has symptoms of cognitive impairment. According to the review by Mula, which of the following statements about trait-dependent cognitive dysfunction associated with epilepsy is correct?

- ☐ A In structural focal epilepsies such as those from traumatic brain injury, stroke, or encephalitis, cognitive deficits are usually those expected from the lesion site
- ☐ B Trait-dependent cognitive dysfunction in epilepsy is usually reversible
- ☐ C Memory and psychomotor speed are usually unaffected in focal epilepsies of unknown cause
- ☐ D Rett syndrome is associated with executive dysfunction

2. According to the review by Mula, which of the following statements about state-dependent cognitive dysfunction associated with epilepsy is correct?

- ☐ A Potentially modifiable factors contributing to state-dependent cognitive dysfunction in epilepsy may include AEDs, seizure frequency and pattern, and psychiatric comorbidity
- ☐ B Epileptic seizures themselves are not implicated in transient cognitive dysfunction
- ☐ C A single generalized tonic-clonic seizure may produce reversible attention deficits for up to 3 days
- ☐ D AEDs modulating voltage-gated channels have more detrimental effects on cognitive functions than those potentiating GABAergic neurotransmission

3. According to the review by Mula, which of the following statements about postsurgical cognitive dysfunction associated with epilepsy would **most** likely be correct?

- ☐ A Temporal lobe surgery is not associated with visual memory loss
- ☐ B Frontal lobe surgery is associated with visual naming deficits
- ☐ C The laterality of temporal lobe resection is a major determinant of visual memory loss
- ☐ D The extent of temporal lobe resection is relevant to postoperative visual naming deficits