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Review

Cognition in the early stages of adult epilepsy☆

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ABSTRACT

Purpose: The impact of duration of epilepsy on cognition has been discussed for a long time. More recently, it has been recognized that cognitive deficits are often already present at the onset of epilepsy or even before. From an etiological point of view it is now understood that it is not really the question what comes first, epilepsy or cognitive comorbidity. Instead the evidence suggests that both problems rather originate from a common underlying pathology.
Methods: We selected studies addressing cognition in adult new-onset or newly diagnosed epilepsies before treatment initiation. Potential factors are outlined that affect cognition prior to, around or after epilepsy onset.
Results: Most studies investigated newly diagnosed patients, but many included individuals who already had a long history of seizures at the time of diagnosis. Fewer studies focused on new-onset epilepsies. Overall, cognitive problems in the early stages of adult onset epilepsy were found to be common. The occurrence of seizures may initially cause greater concern and lead to an underreporting of cognitive problems prior to or around the time of diagnosis.
Conclusion: The high prevalence of objective cognitive impairments present at epilepsy onset calls for early neuropsychological assessments soon after the diagnosis of epilepsy, and at best before medical treatment is initiated. Without such baseline assessments subsequent neuropsychological testing during follow-up is difficult to interpret in regard to the effects of treatment success or the course of underlying disease processes. Beyond that, the baseline assessment may also guide treatment choices and serve as an early indicator of the need for support or rehabilitation. In this way neuropsychological monitoring can improve individual medical care, and increase tolerability, adherence, and treatment retention from the point of diagnosis.

Cognitive deficits in epilepsy are frequent and can have negative effects on daily functioning. The etiology of cognitive deficits is often multi-factorial, since static and dynamic factors can synergistically affect cognition [1,2]. Static factors primarily refer to the presence of developmental or acquired cerebral lesions causing both, epilepsy and cognitive impairment. Dynamic factors contributing to cognitive impairment are (1) active epilepsy, i.e. seizures and interictal epileptic discharges, (2) antiepileptic drug treatment (AEDs), and (3) psychiatric comorbidities. However, these factors are not necessarily independent of each other. Age at first hit or onset of epilepsy must be considered as an important moderator variable, since early epilepsy and underlying pathologies can negatively affect brain maturation and development [3,4]. Additionally, individual reserve capacities and age- and sex-dependent neural plasticity need to be considered [5].

Against the background of this etiological model of cognitive deficits in epilepsy, the situation apparently becomes more and more complex with an increasing duration of epilepsy (see Table 1 for an overview of the potential factors that may affect cognition in the course of time). In the later stages of chronic epilepsy, and without repeated standardized assessment, it is hardly possible to retrospectively attribute cognitive deficits to particular factors which may be involved (cf. [6] for an attempt on a group level). This emphasizes the need for neuropsychological assessments at an early stage of epilepsy to be able to disentangle the complex interactions of the factors contributing to cognitive problems [7]. Ideally, cognition should be assessed shortly after the onset of epilepsy and, at the latest, before treatment initiation. Such a baseline assessment is required for a subsequent monitoring of

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Table 1
Potential factors affecting cognition before and at epilepsy onset, and thereafter. Gray boxes indicate a potential impact.

	Prior to epilepsy onset	At epilepsy onset	Controlled epilepsy (100% seizure control)	Cured epilepsy (seizure free, AEDs withdrawn)	Chronic refractory epilepsy
Cerebral lesions					
Covert epileptic dysfunction					
Overt epileptic seizures					
Antiepileptic treatment					
Behavioral/ psychiatric problems					

treatment success and the course of the disease. Furthermore, information on the cognitive status can also indicate the need for rehabilitative procedures, or it can direct treatment choices. By means of cognitive monitoring, neuropsychology allows for quality and outcome control of medical interventions striving for an improved individual medical care [2].

Since the mutual relationship between pathology, epilepsy, and cognition has become increasingly recognized, cognition in people with new-onset epilepsy has been studied more intensively. In 2011, this issue was identified as a theme of major importance for neuropsychological research in the field of epilepsy [8]. Beforehand it is important to point out that a careful distinction needs to be made between research relating to children and adults. In children, neuropediatric services and parents are concerned with brain and mental development as soon as a patient is diagnosed with epilepsy. For a review focusing on cognition in pediatric patients with new-onset seizures please see Hermann et al. [9]. In children it has been demonstrated how early assessment allows for the monitoring of the subsequent course of epilepsy [10,11]. This may well serve as a model for adult epileptology. However, in adults it is still common practice at the stage of diagnosis to explore the etiology of seizures and focus on rapid seizure control but not to take account of comorbidities such as cognitive difficulties.

For this review we performed a literature search (medline) for original articles investigating cognition in "untreated" "adult patients" with "new-onset epilepsy" or "newly-diagnosed epilepsy". Only studies with an objective cognitive assessment were considered. A total of 11 studies met these criteria. Most of them addressed at least attention and memory and reported respective impairments in these domains [12–22] (for overview see Table 2). However, the studies differed considerably in regard to patient selection, sample sizes, etiologies, assessment tools, the question of any pretreatment, and most importantly in regard to the duration of untreated epilepsy. A point of major importance is that most studies investigated newly diagnosed patients and not patients with new-onset epilepsies, emphasizing the need for a clear terminology [23]. Indeed the mean duration of epilepsy in the different patient cohorts ranged from 92 days to 7 years. Even the newly diagnosed patients of the SANAD study presented with a mean epilepsy duration of 5 years [18]. The same is true for an early study performed at our center comparing the cognitive effects of first treatment on lesional versus non-lesional patients [22]. This means that the neuropsychological findings from such studies cannot tell us much about new-onset epilepsy. Another factor which needs to be considered is age at the onset of epilepsy, which ranges on average between 27 and 71 years. The age at the onset of epilepsy is strongly connected to its etiology. Therefore the results obtained in early versus late onset epilepsies can hardly be compared without taking pathology and the interaction of pathology with the maturing versus aging brain into consideration. In the light of the increasing incidence of epilepsy with older age, a recent study investigated elderly patients with new-onset epilepsy aged between 60 and 95 years. As expected elderly patients showed greater impairments than the younger sample [20].

Some studies analyzed patients without evidence of brain pathology in order to disclose the sole effect of active epilepsy on cognition [12,14,18]. One study considered epilepsy syndromes and compared the neuropsychological results between idiopathic, symptomatic and cryptogenic epilepsies [19]: Among these subtypes, symptomatic epilepsies presented with the worst performance in executive function. Finally, most studies simply compared the cognitive performance of patients with newly diagnosed epilepsy and healthy controls on a group level. Only five of the 11 studies assessed more than 100 patients, a minority had larger reference groups of healthy subjects, and only six studies provide prevalences/frequencies of cognitive deficits on an individual level according to normative data or healthy controls [18–20]. Taylor et al. report impaired performance in 1–18% of all measures of the employed test battery [18]. Fifty-four percent of the patients versus 21% of the healthy controls were impaired in at least one test score. A study in 247 middle-aged patients with new-onset epilepsy found impairments in attention and memory in 48–49% of the sample [19]. Less than one third was unimpaired in both domains. Subjective deficits in the respective domains were complained by 25–29% of the patients only. This indicates an underreporting of cognitive deficits at this early stage of epilepsy. Comparable underreporting was evident in 257 elderly patients with new-onset epilepsy [20]: The prevalence of objective deficits in executive function was 58%, whereas subjective deficits were reported in only up to 27% of the patients. The independent observation in two studies that cognitive problems were underreported when compared to objective assessment may be interpreted in a way that in the patients' view and at that early stage of the disease the diagnosis of seizures and their expected consequences are of pressing relevance. In chronic epilepsies cognitive complaints are much more frequent [24,25].

The finding that cognitive-behavioral deficits may precede seizure onset [26], raises the question of whether there is a