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Neuropsychology of epilepsy in old age – English Version

Carina Heerwig · Hendrik Möller · Katja Brückner
Epilepsy Center Alsterdorf, Protestant Hospital Alsterdorf, Hamburg, Germany

Abstract

As a result of demographic change, the frequency of epilepsy in older age is increasing. In addition, a connection between epilepsy and an accelerated cognitive aging process is assumed. Cognitive impairments mainly affect memory and executive functions. The older patient group represents a challenge for neuropsychological diagnostics since only few test procedures with age-specific norms are available and, in addition to the diagnosis of epilepsy, other risk factors for cognitive performance decline must be taken into account. Older people with epilepsy may suffer from associated comorbid affective disorders in addition to cognitive impairment. In older (50+ years) and aged (65+ years) people with epilepsy, these impairments may increase and have a greater impact on daily life and daily living skills than in younger people. Because of increasing limitations as well as a higher risk of cognitive consequences and complications, epilepsy surgery remains controversial in old people; however, several studies have observed a postoperative stable cognitive performance profile and improvement in mood in older people with epilepsy.

Keywords
Cognition · Performance decline · Elderly · Memory · Executive function

Cognitive and neuropsychological testing

Although there are a multitude of studies and reviews on cognitive impairment in childhood and adult epilepsy [1–3], the number of studies with individuals of older age is modest [4]. This is partly due to the fact that neuropsychological testing in this patient group is challenging. Test procedures with current, age-specific, and education-adjusted norms are generally rare and even rarer for the 65+ age group. Apart from the verbal learning and memory test (VLMT; [5]) and the change-sensitive cognitive screening to assess attention and executive functions for quality and outcome monitoring of treatment in patients with epilepsy (EpiTrack; [6]), there are few epilepsy-validated neuropsychological procedures. Moreover, with increasing age, there is an accumulation of risk factors for cognition independent of epilepsy. Diseases of the cardiovascular system, vascular events, metabolic diseases, as well as oncological and degenerative diseases increase and can have a (usually negative) effect on cognition, as can their treatment.

People with epilepsy are subject to normal aging processes. The classic non-pathological age-related decline in cognitive performance in people with chronic epilepsy runs relatively parallel to that in people without epilepsy [7–10]. However, individuals with epilepsy often have disease-related limitations. Deficits in memory, in executive functions, and in psychomotor speed are often found both in new-onset epilepsy after the age of 65 and in chronic epilepsy [9, 11, 12]. Therefore, as part of the normal aging process, people with epilepsy often reach a critical threshold sooner than healthy individuals, at which point the decline in cognitive performance can have an impact on coping with the demands of everyday life [7–10].

The most common cause of new-onset epilepsy in older age is vascular disease, followed by degenerative disease. Both are disease groups that are often (in the case

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of strokes) or by diagnosis inevitably (in the case of dementia) associated with cognitive deficits and limitations in daily living skills [13, 14]. It is now believed that there is even a bidirectional relationship between epilepsy in older age and an accelerated cognitive aging process: For example, people aged between 50 and 75 years have an increased risk of developing dementia, and people with Alzheimer's disease or vascular dementia have an increased risk of experiencing epileptic seizures. In these cases, the seizures are a symptom of degenerative decline, which further manifests in cognitive impairment, mental health problems, and other physical illnesses [15]. Therefore, it was recently proposed that older people with epilepsy should also be given the diagnosis of mild cognitive impairment (MCI) and should be required to undergo a follow-up examination. This would enable a distinction to be made between possible degenerative decline in the setting of dementia and cognitive deficits in the setting of epilepsy [4, 16]. In the case of new-onset epileptic seizures in older age, autoimmune limbic encephalitis should also be ruled out on the basis of cerebrospinal fluid (CSF) diagnostics. Neuropsychological diagnostics of limbic encephalitis reveal in particular impairments of long-term memory, deficits in the recognition of learned material, impaired recognition of emotions, and executive deficits [17]. In addition, affective disorders and psychiatric symptoms may also develop [18, 19]. A detailed neuropsychological diagnostic work-up should be carried out in these cases both before the start of treatment and in the event of cognitive changes or changes in therapy [19].

Independent of the aforementioned factors, people who have had epilepsy for a longer period—some for their entire lives—are exposed to additional risk factors for cognition that may accumulate over the years: critical events such as head injury, status epilepticus, frequent tonic–clonic seizures, psychiatric comorbidities, treatment sequelae from epilepsy surgery, and adverse effects from anticonvulsant medications [20, 21]. In particular, treatment with phenytoin, phenobarbital, carbamazepine, or valproate may induce vascular risk factors such as hypertension, diabetes, elevated cholesterol, and inflammation—factors that in turn are associated with conditions such as vascular dementia. In addition, people with chronic epilepsy are more likely to be overweight and have elevated body mass index (BMI) levels. Their lifestyle tends to be unfavorable from a health perspective: They are less physically active, have reduced muscle strength and endurance, have fewer social contacts and networks, and show reduced mental activity [15, 22]. All these factors correlate with an increased risk of developing dementia and thus with a reduction in cognitive performance.

Neuropsychological aspects of drug treatment

It is well known that anticonvulsant medications, especially in polytherapy, can have adverse drug effects (ADE) on cognition [23–27]. These are also possible in older age. In the group of very old individuals, anticonvulsant drugs are far more frequently combined with other drugs than in younger people. The general drug load is thus often significantly higher in older people, which can lead to increased drug interactions. Since it is known that older adults are more sensitive to medication and more susceptible to adverse effects such as fatigue, dizziness, and gait disturbances, but may complain less about such adverse effects, it is important that the practitioner is particularly attuned to this constellation. As in younger patients, polytherapy should be avoided if possible, as any additional medication increases the likelihood of ADE and may exacerbate pre-existing cognitive deficits [15, 27].

Unfortunately, there are only a handful of drug studies to date that consider the group of older adults with the associated problem constellations in sufficient size. It is known that in particular carbamazepine, clobazam, eslicarbazepine, oxcarbazepine, phenytoin, valproate, topiramate, and zonisamide can have a negative effect on cognition in older people, and that clobazam, levetiracetam, lacosamide, perampanel, phenytoin, topiramate, and zonisamide can have a negative impact on mental well-being. On the other hand, carbamazepine, lamotrigine, gabapentin, pregabalin, and valproate can have more of a positive or stabilizing effect on mood [15].

In order to control ADE on cognition, older adults should also undergo a neuropsychological examination at the time of a new diagnosis of epilepsy and, ideally, before the start of drug treatment. In this way, possible ADE as well as future deterioration of cognitive performance can be identified, classified and, in the best case, positively influenced. The distinction between cognitive performance that is impaired by epilepsy but comparatively stable over time and performance that deteriorates progressively in the setting of dementia, as well as reversible cognitive impairment caused by medication, is much easier if a preliminary examination has been carried out than if it has not [15, 28].

Excursus: TEA

In transient epileptic amnesia (TEA), memory is absent for a period of time, similar to transient global amnesia. However, in TEA, there is a time relationship to an epileptic seizure, usually a temporal seizure. Transient epileptic amnesia is a comparatively rare presentation, but is more common in older age (especially in men). People with TEA may also have interictal memory impairment, mainly affecting autobiographical memory and accelerated forgetting over time. A link to dementia could not be found in long-term studies, although it should be noted that these studies do not go beyond individual case descriptions due to the rarity of TEA. However, one can assume that these phenomena (TEA, accelerated forgetting) will continue to become more prevalent as the life expectancy of the world population increases [28–30].

Neuropsychological aspects of surgical interventions for epilepsy

In pharmacoresistant focal epilepsy, resective epilepsy surgery has been established as an alternative treatment option and offers a good chance of permanent freedom from seizures [31, 32]. However, in addition to the good prospect of success, there is always a risk of cognitive impairment as a result of resection [33–35]. Surgical intervention in older adults is controver-

sial, partly due to the fact that older age and longer duration of epilepsy are associated with postoperative cognitive deficits [36–39]. There is also concern about a deterioration in quality of life (QoL; [40, 41]).

The current body of studies on cognitive sequelae following epilepsy surgery in older people reflects a heterogeneous picture of neuropsychological outcomes. In some studies [42–44], no significant difference in cognitive performance after resection was found compared to younger people. Older individuals showed a stable to at most slightly worsened cognitive performance profile postoperatively [45, 46]. However, younger affected individuals had a better preoperative performance profile, especially in verbal memory [46, 47]. By contrast, other studies described deficits in pre- and postoperative verbal memory performance in older compared to younger individuals [47, 48]. A correlation was found between age, duration of epilepsy before surgery, and deficits in verbal memory performance. Predictors of stability or even improvement in long-term verbal memory performance included younger age and lower preoperative seizure frequency [49].

Studies investigating neuropsychological consequences following epilepsy surgery in older individuals without making comparisons with a younger cohort found that impairments in figural and verbal memory performance, attentional performance, visuospatial constructional ability, and language performance were already present preoperatively compared to the average age [50–52]. In particular, epileptogenic areas in the language-dominant hemisphere had a relevant impact on verbal memory and language functions, which again significantly deteriorated postoperatively [50, 51]. By contrast, when surgery was performed in the non-language dominant hemisphere, stable to improved memory performance was observed even in the older age group [50–52]. The fact that postoperative deterioration of performance is not necessarily limited to this group is shown by a study that observed stable to even improved performance in visuospatial constructional ability, attention, and figural memory performance—irrespective of the side of epilepsy surgery [50].

The method of surgery is considered to have a crucial impact on neuropsychological outcome in older patients [47, 53]. A clear advantage is shown here for selective amygdalohippocampectomy (SAH) compared to anterior temporal lobectomy (ATL). While older individuals with SAH showed similar losses in verbal memory performance to younger individuals, the postoperative losses in verbal memory performance were significantly more severe in older individuals with ATL. Thus, the older group appears to compensate less well for the loss of neocortical areas and most likely has fewer compensatory resources than their younger counterparts [54, 55].

Psychopathology

The treatment of epilepsy, whether pharmacological or surgical, should ultimately serve to increase QoL via the subgoal of seizure control and minimization. For older people with epilepsy, psychopathological mechanisms emerge that differ from general psychopathological findings primarily in terms of the severity of their impact. In view of demographic changes and the rise in the incidence of epilepsy with increasing age [56], the consideration of this older age group is of considerable relevance. Psychogenic nonepileptic seizures (PNES) also represent a relevant differential diagnosis in older age. These occur with similar frequency in this age group to that in younger people and should be distinguished from epileptic seizures [57].

It is not uncommon for epilepsy to be associated with cognitive and affective comorbidities [58]. This association is particularly evident in older adults [15], although studies on the incidence of comorbid affective disorders in this group are rare. The limited data suggest that, on the one hand, pre-existing psychiatric diagnoses increase the likelihood of epilepsy onset [59]. On the other hand, the onset of an epileptic disorder in older adults increases the likelihood of prospectively developing a psychiatric syndrome. In addition, effects of epilepsy on QoL and the perception of stigmatization are evident [15]. At the same time, affective distress is considered the strongest predictor of QoL in affected individuals [60]. Driving bans are reported to be one of the most frequently mentioned stressors regarding QoL. Even in older age, the car remains the most important means of transportation. In addition to mobility, effects of epilepsy on living together with a partner are also mentioned.

In older people with epilepsy, one can assume that varying mechanisms of action are at work with regard to the psychological burden of the disease. For example, as described above, this group has fewer social contacts, reduced cognitive abilities, physical limitations, and they are more affected by somatic diseases. Limitations in autonomy are also to be expected, which may be due, for example, to the greater impact caused by driving bans or living alone (e.g., after the death of a partner). One can assume that epilepsy thus has a stronger impact on psychopathology, QoL, and mood, given that affected individuals are as it is particularly vulnerable [15]. It can also be assumed that the already more frequent cognitive impairments in people with epilepsy [9] are mutually reinforced by the reduced QoL and accompanying affective disorders [15].

Having said that, older people are not per se to be described as "victims" of their age. For example, life experience also confers an advantage: Older people succeed in psychologically adjusting to their chronic illness better than younger people do [60]. A number of studies even found depressive symptoms to be of lower clinical relevance in older than in younger people. Some of the less severe social effects of epilepsy have been discussed as a reason for the lower disease burden on older people, for example, in terms of epilepsy-related losses in monthly income [61]. However, the impact of having epilepsy may affect older individuals in other ways. It is not uncommon for epilepsy surgery to be excluded in the older age group despite its potential to improve QoL and mood [37, 50, 62]. However, the following study on the effect of epilepsy surgery in terms of psychological well-being in people aged over 50 years demonstrates that this should be reconsidered in the future: It was found that, prior to the procedures, nearly half of the affected individuals were rated by their practitioners as having psychopathological abnormalities—based on

screening instruments, psychopathological findings, and a psychological assessment. During follow-up at least 1 year after the respective interventions, only 25% of this cohort were still assessed as psychopathologically abnormal according to the same criteria. The transition from an abnormal to an ultimately unremarkable psychopathology finding was statistically significant. Further analyses failed to identify clear predictors for the improvement in psychopathological findings. However, a reduction in anticonvulsant medication, cognitive changes, and general seizure outcome following surgery were discussed as possible preconditions for improvement [52].

Practical conclusion

- **Older people with epilepsy show cognitive deficits both at the onset of epilepsy and in the long-term course, especially in memory and executive performance as well as in psychomotor speed.**
- **Due to older age, risk factors for cognition accumulate, and patients are more vulnerable to adverse drug effects.**
- **Compared to younger persons, older individuals already have a worse neuropsychological test profile preoperatively, but show a stable level of performance postoperatively in most studies.**
- **Older people with epilepsy also frequently suffer from comorbid affective disorders. The impact of concomitant mental disorders on quality of life is often immense and should therefore be taken into account during treatment planning.**
- **Individual studies suggest that older people may also benefit from epilepsy surgery in terms of mood.**

Corresponding address

Katja Brückner
Epilepsy Center Alsterdorf, Protestant Hospital Alsterdorf
Elisabeth-Flügge-Str. 1, 22337 Hamburg, Germany
k.brueckner@eka.alsterdorf.de

Declarations

Conflict of interest. C. Heerwig, H. Möller and K. Brückner declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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