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Review

Cognitive deterioration in adult epilepsy: Does accelerated cognitive ageing exist?

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ABSTRACT

A long-standing concern has been whether epilepsy contributes to cognitive decline or so-called 'epileptic dementia'. Although global cognitive decline is generally reported in the context of chronic refractory epilepsy, it is largely unknown what percentage of patients is at risk for decline. This review is focused on the identification of risk factors and characterization of aberrant cognitive trajectories in epilepsy. Evidence is found that the cognitive trajectory of patients with epilepsy over time differs from processes of cognitive ageing in healthy people, especially in adulthood-onset epilepsy. Cognitive deterioration in these patients seems to develop in a 'second hit model' and occurs when epilepsy hits on a brain that is already vulnerable or vice versa when comorbid problems develop in a person with epilepsy. Processes of ageing may be accelerated due to loss of brain plasticity and cognitive reserve capacity for which we coin the term 'accelerated cognitive ageing'. We believe that the concept of accelerated cognitive ageing can be helpful in providing a framework understanding global cognitive deterioration in epilepsy.

Contents

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1. Introduction

Epilepsy is a neurological disease that, like any human brain disorder, can be complicated by cognitive impairment (Lin et al., 2012). This is found a common comorbidity in epilepsy, ranging from subtle impairments in attention to more severe memory deficits as seen in patients with temporal lobe epilepsy. In fact the following definition of the International League Against Epilepsy incorporates cognitive problems as part of the definition: "*Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition*" (Fisher et al., 2005).

Much research in this field has focused on focal cognitive deficits associated with specific clinical features, specific focus localization or with specific types of epilepsy. The body of literature focuses on memory impairments in temporal lobe epilepsy (Hendriks et al., 2004), impairments in executive function and attention in frontal lobe epilepsy (Braakman et al., 2011), specific impairments such as language deficits in focal epilepsies (Overvliet et al., 2010) or impairments in childhood syndromes such as the language regression in Landau Kleffner (Van Bogaert, 2012). Fewer studies focused on global cognitive effects of epilepsy.

A long-standing concern has been whether epilepsy contributes to cognitive decline or cognitive deterioration (Hermann et al., 2008). Some studies suggest processes of decline of global cognitive function over time. There is even some evidence to suggest that epilepsy increases a person's risk to develop forms of progressive cognitive decline, so-called 'epileptic dementia'. Such processes are generally reported in the context of chronic refractory epilepsies (Jokeit and Ebner, 1999) or in specific symptomatic epilepsies such as in post-stroke epilepsy (De Reuck et al., 2006a; Cordonnier et al., 2007).

The results of the few prospective longitudinal follow-up studies analyzing cognition over time are inconclusive. It seems that the cognitive trajectory of patients with epilepsy over time differs from processes of cognitive ageing in healthy people, revealing impairments in several cognitive domains (e.g. global intelligence, memory, naming, cognitive and psychomotor speed) (Hermann et al., 2007; Jokeit and Ebner, 1999).

This review is focused on evidence that epilepsy may induce cognitive decline or cognitive deterioration. In addition to attempts to characterize these processes, our focus is on the clinical characteristics of the patients showing such decline. Moreover, we attempt to identify the factors that might be considered to have long-term cognitive effects.

2. Age at onset

2.1. Early age at onset

An early age at seizure onset is consistently linked to poorer cognitive function. Bourgeois et al. (1983) found that children with an early age at onset were at higher risk for future reduction in intelligence scores than their peers whose seizure onset was at a later age. More recent research also indicates early seizure onset as a predictor for future impaired intellectual outcome in childhood epilepsy (Korman et al., 2013). In adult studies too, an early age at onset is associated with general intellectual impairment. This seems less predictive of impairment in specific cognitive functions such as memory, language and executive function, but presents more as a global phenomenon (Kaaden and Helmstaedter, 2009; Wang et al., 2011). It is questioned whether this global cognitive impairment should be interpreted as reflecting an altered neurodevelopmental course in early onset epilepsy (interference during sensitive developmental phases) or as cognitive decline due to a longer duration of disease and other confounding factors. Kaaden and Helmstaedter (2009) claim the first.

Some studies present another option. Cognitive impairment and academic underachievement in childhood-onset epilepsy might already be present from the beginning of the disease or even have developed before seizure onset, irrespective of epilepsy syndrome (Hermann et al., 2006a). The same might be true for adult-onset epilepsy, Taylor et al. (2010) found that adults with newly diagnosed epilepsy were already cognitively compromised prior to treatment, which is in line with other research (Pulliainen et al., 2000; Witt and Helmstaedter, 2012). This gives rise to the idea that an underlying neurobiological abnormality could be (partially) responsible for cognitive impairment, rather than cognitive decline being caused by disease progression due to post-onset factors. Indeed, it has been demonstrated that children with new-onset epilepsy already exhibit regional and widespread changes in brain volume at epilepsy onset (Tosun et al., 2011). Also the brain network organization (as measured with functional magnetic resonance imaging (fMRI)) is altered near the time of epilepsy onset, with the most abnormal network organization in children with lower IQ and greater executive dysfunction. Whether this represents a delay in brain maturation or a fixed reorganization of brain function remains to be clarified (Bonilha et al., 2014). We are not aware of studies on pathologic features of brain volume and network organization in newly diagnosed adult epilepsy.

In line with the models that explain cognitive decline as an effect of post-onset factors, much evidence is found that post-onset factors such as effects of persisting seizures (Berg et al., 2012; Dodrill, 2004; Helmstaedter et al., 2003), duration of disease (Coan et al., 2009) and potentially adverse medication-related factors (Baker et al., 2011; Kwan and Brodie, 2001) may accumulate over longer periods of time and further impair cognition in adulthood. This is then related to age at onset as earlier onset allows these factors longer periods to accumulate. Indeed, Berg et al. (2012) found that an early age at seizure onset was associated with poor intellectual outcome, but only in patients with persisting recurrent seizures due to treatment failure.

2.2. Epilepsia tarda

Also late-onset epilepsy may be associated with global cognitive decline. 'Epilepsia tarda' is the term previously used to describe epilepsy with an onset of seizures after the age of 20. It has long been debated whether this adult-onset epilepsy had to be considered and studied as a distinct disease-group. At present, the annual incidence of seizure disorders at adult age rises and research is being increasingly devoted to this topic.

As the risk of cerebral tumors, cerebrovascular disease, primary neurodegenerative diseases (particularly Alzheimer's disease) and developing serious neurological sequelae of traumatic brain injury increases with age, middle-aged and elderly people are more likely

to develop seizure disorders as a consequence of these conditions (Baram, 2012; Brodie et al., 2009). The risk of seizures increases further through the effect of polypharmacy as well as interactions between drugs on lowering the seizure threshold, thereby considering that use of multiple (potentially proconvulsive) medications in the adult population is more common as concomitant diseases become more prevalent with age (Brodie et al., 2009; Trinka, 2003). Also age-related molecular and metabolic changes might increase seizure susceptibility in the ageing brain (Leppik and Birnbaum, 2010; Palop and Mucke, 2009).

Little is known about the cognitive trajectory of patients with late-onset epilepsy. Most studies on cognition in epilepsy have included patients with chronic epilepsy with an early seizure-onset (hence, childhood epilepsies continuing into adulthood) or no distinction has been made between early- and late-onset epilepsies (Andersson-Roswall et al., 2004; Helmstaedter et al., 2003; Hermann et al., 2006b; Holmes et al., 1998). In a longitudinal study on the cognitive course in newly-diagnosed partial epilepsy with a late-onset (mean age at baseline: 41), approximately one-third of the patients showed global cognitive decline five years after diagnosis (Taylor and Baker, 2010). No decline in memory function was found in another group of newly-diagnosed patients with late-onset temporal lobe epilepsy (average seizure onset at age 31), although memory performance at baseline was already impaired compared with healthy controls. It should be mentioned though, that all patients in this last study were seizure-free on antiepileptic drugs (AED) monotherapy at the time of the 5-year follow-up (Aikia et al., 2001). In the elderly (>60 years of age) with late-onset epilepsy, cognitive function is generally impaired relative to age-matched controls (Piazzini et al., 2006). However, little is known about the cognitive trajectory in new-onset geriatric epilepsy. In cases with known etiology (e.g. post-stroke epilepsy), cognitive impairment may be progressive and exacerbated by the presence of seizures (Roberson et al., 2011).

Our understanding of the pathological mechanisms underlying cognitive impairment and risk factors for possible decline in adult-onset epilepsy are currently expanding as more research is focused on this topic. One might hypothesize that patients with adult- and geriatric-onset epilepsy are at risk for abnormal cognitive ageing since the brain's neuronal plasticity (and thus the cognitive reserve capacity) decreases with age (Elger et al., 2004). The mature brain might be less able to functionally compensate for interference of disease and the pathology underlying the epilepsy. Recent functional imaging research on the effect of age at seizure onset on brain functional organization and connectivity in temporal lobe epilepsy (TLE) revealed significant differences in both global and regional connectivity between adults with early- and late onset seizures (Doucet et al., 2014). In late-onset epilepsy (>20 years of age) with mesial temporal sclerosis, increased global functional integration and both reduced segregation and modularity were seen relative to healthy controls and patients with early seizure onset. At a regional level, differences in functional connectivity were most apparent in the frontal lobe, with again the late-onset group being most impaired. Abnormal brain network organization, specifically decreased functional segregation, has been associated with cognitive decline in epilepsy before (Vlooswijk et al., 2011).

Another age-specific risk for an abnormal cognitive course in adult epilepsy might be the increased inflammatory response to seizures in the ageing brain relative to the younger brain (Baram, 2012). Higher inflammatory markers are associated with age-accelerated cerebral atrophy (Jefferson et al., 2007) as well as global cognitive decline and neurodegenerative disease (Bettcher and Kramer, 2014; Dik et al., 2005; Hermann et al., 2008). Also, patients with adult-onset epilepsy might be at increased risk for metabolic disturbances due to polypharmacy and comorbid disease on top of age-related physiologic changes (Brodie et al., 2009; Leppik and Birnbaum, 2010). It was found that older patients with late-onset epilepsy experience more comorbid diseases than similarly-aged patients with chronic epilepsy and seizure-onset at an earlier age (Stefan et al., 2014). Frequently reported comorbidities include diabetes, tumors (other than brain tumors), arterial hypertension and cardiac infarction (Stefan et al., 2014; Verellen and Cavazos, 2011). Those conditions are known to alter metabolic status, which has been demonstrated to be predictive of cognitive decline and neurodegeneration or dementia in the general population (Hermann et al., 2008).

3. Disease duration (chronic epilepsy)

It is often stated that cognitive impairment in epilepsy increases with duration of disease. A long duration of disease has been associated with decline in specific functions such as memory, naming ability and word fluency, attention and executive functions (Hermann et al., 2006b; Marques et al., 2007; Thompson and Duncan, 2005), but also with global intellectual decline (Jokeit and Ebner, 1999; Marques et al., 2007). However, most studies on cognitive decline have focused on patients with chronic refractory epilepsy, so that a long duration of epilepsy is often entangled with long-lasting poor seizure control and other factors such as specific syndromes, underlying etiology, and chronic antiepileptic drug treatment, often at high drug load. The negative impact of a long duration of epilepsy on cognition in those studies may therefore be in part due to poor seizure control and other underlying factors.

Cognitive decline has long been recognized as a sequel of chronic epilepsy. Recent longitudinal studies, however, found that the degree of cognitive change in epilepsy was frequently characterized by a lack of, or less improvement in cognitive performance compared to healthy control subjects, rather than an absolute decline (Griffith et al., 2007; Hermann et al., 2006b; Seidenberg et al., 2007).

Other evidence is provided that actual decline (other than solely the lack of improvement in performance) can be observed only in a subset of patients. For example, in a longitudinal study on the cognitive course in adult-onset epilepsy, 38% of the patients showed significant cognitive decline after five years (Taylor and Baker, 2010). Hermann et al. (2006b) found that 20–25% of the patients with chronic temporal lobe epilepsy exhibited adverse cognitive trajectories over a four-year interval, whereas performance in the remaining patients was stable. Decline was best predicted by increasing chronological age, longer duration of disease, baseline quantitative MRI abnormalities (specifically ventricular enlargement) and lower baseline intellectual capacity, the latter two possibly indicative of reduced cognitive reserve (Dabbs et al., 2012; Oyegbile et al., 2004). From this, the researchers identified three distinct cognitive phenotypes in TLE which were found to be associated with increasingly abnormal prospective cognitive trajectories. The first group consisted of 47% of the TLE patients who showed minimal cognitive difference to healthy controls (minimal impairment in specific cognitive functions such as language, executive function and psychomotor speed). The second group (24%) consisted of patients with mild to moderate cognitive impairment, characterized by additional poor memory performance. Patients in the third group (29%) exhibited a pattern of moderate to severe global cognitive impairment at baseline. These patients were older, had a longer duration of epilepsy, were taking more AEDs and had more abnormal brain volumes than those in the other two groups. After four years, patients in the third group showed the most adverse cognitive course, characterized by actual cognitive decline (Hermann et al., 2007).

Likewise, it has also been suggested that cognitive decline is evident only after a very long duration of disease. Jokeit and Ebner

(1999) found that only a duration of over 30 years of epilepsy was related to cognitive decline. However, Griffith et al. (2007) did not find evidence of decline despite a comparable duration, whereas others did find evidence of decline in patients with a significantly shorter disease duration (Helmstaedter et al., 2003; Hermann et al., 2006b; Holmes et al., 1998).

Another hypothesis concerning cognitive decline in epilepsy is that cognitive deterioration is 'cascadic' rather than progressive, thus: decline occurs around the time of epilepsy onset (causing a neurodevelopmental interruption) but does not deteriorate with a longer duration of disease. Indeed, when comparing the course of verbal learning in relation to age, it appears that the cognitive decline in adult patients with early-onset chronic TLE runs largely parallel to that in healthy controls. However, patients with epilepsy reach their cognitive peak at a much younger age than controls, which means that healthy controls are still improving their performance when patients with epilepsy are already in significant decline (Helmstaedter and Elger, 2009). Because of their lower starting level, patients with epilepsy can become cognitively impaired earlier in life, wrongly suggesting progressive decline (Baxendale et al., 2010). Additional research is needed to examine the age regression performance in patients with adulthood-onset epilepsy, in whom the development of epilepsy might interfere with the ageing process.

4. Seizure type and seizure frequency

A high lifetime number of secondary generalized tonic-clonic seizures is often recognized as a contributor to cognitive decline in epilepsy (Dodrill, 1986; Thompson and Duncan, 2005). To a lesser extent, also frequent complex partial seizures are associated with decline, mainly in specific cognitive subdomains such as memory and executive function, whereas the influence of simple partial and other types of seizures on cognition is less well known (Black et al., 2010; Hermann et al., 1997; Thompson and Duncan, 2005). However, findings on the long-term effect of seizures on cognition are mixed across cross-sectional studies. Longitudinal research has indicated that the connection between seizures and adverse cognitive change is probably only a mild one or shows a high interindividual variability (Dodrill, 2004; Seidenberg et al., 2007). Nonetheless, remission of seizures has been found to stabilize or even improve cognitive function in some studies, the most convincing evidence coming from patients who are completely seizure-free for a longer period of time (Aikia et al., 1999; Dodrill and Wilensky, 1992; Helmstaedter et al., 2003). Although such clear effects have not been obtained in all studies (Engelberts et al., 2002; Loiseau et al., 1983), it is a powerful indicator that seizures may have an accumulating negative effect on cognition over time.

It is debated whether recurrent seizures induce progressive alterations in the epileptic brain leading to neuronal damage, network reorganization and eventually adverse cognitive change (Pitkänen and Sutula, 2002). In human mesial temporal lobe epilepsy (MTLE), a high seizure frequency is associated with progression of gray and white matter brain atrophy that extends beyond the mesial temporal structures, involving frontal, lateral temporal, parietal, and occipital brain regions as well (Bernhardt et al., 2009; Coan et al., 2009). Previous studies have demonstrated a relationship between gray and white matter abnormalities and cognitive decline (Vaessen et al., 2011). However, no causal relationship can be established between the number of seizures, cerebral atrophy and cognitive decline. Moreover, the slope of regression between the number of seizures and structural brain damage appears to be low (Pitkänen and Sutula, 2002). Regarding functional brain connectivity, sparse evidence is provided that a high seizure frequency is associated with alterations in the brain network organization and cognitive impairment (Woodward et al., 2014). To our knowledge, no studies could relate a high frequency of seizures with altered functional connectivity and progressive cognitive decline in adult epilepsy.

4.1. Status epilepticus

A history of convulsive or nonconvulsive status epilepticus (SE) is considered a risk factor for cognitive decline, deteriorated cognitive performance or a lack of improvement in performance in some studies (Dodrill and Wilensky, 1990; Helmstaedter, 2007; Krumholz et al., 1995), although this is not confirmed in other studies (Adachi et al., 2005). Others suggest that cognitive decline after SE is only a marker for potentially progressive underlying pathological conditions that gave rise to the status epilepticus, rather than the SE itself causing adverse cognitive outcome. Thus, a fitter and less vulnerable brain would be less likely to experience a SE (Helmstaedter, 2007). Similarly, it is also hypothesized that SE is an extra hit upon a vulnerable brain with subsequent worsening of cognitive status. Indeed, many retrospective studies that provide evidence for cognitive decline after SE have included patients who exhibited SE as their first epileptic episode following various conditions (e.g. cerebrovascular disease, encephalitis, metabolic disease), rather than SE without a known etiology (Adachi et al., 2005; Krumholz et al., 1995). For example, Krumholz et al. (1995) report marked decline in anterograde memory following a complex partial SE in two patients with viral encephalitis. Dietl et al. (2004) describe two cases of permanent anterograde amnesia following SE after unilateral temporal lobe surgery. Both patients underwent right-sided temporal lobectomy including hippocampectomy for medically intractable seizures before they experienced the SE. After initial improvement (one patient even became seizure-free without AEDs), both patients experienced a SE after which a severe amnesic syndrome remained. Subsequent MRI investigation demonstrated post-SE neural damage in the remaining hippocampus, which is critical in memory formation.

5. Epileptic encephalopathy

Certain epileptic conditions are associated with cognitive deterioration, for example infantile epilepsy-syndromes such as Dravet's, which are clinically manifested by cognitive decline that worsens with persistence of seizures. In some studies, these types of epilepsy are coined as 'cognitive epilepsies'. Also the phenomenon of epileptic encephalopathy (EE) is often referred to. EE is described as the condition in which "the epileptic activity itself (frequent/severe seizures and/or subcontinuous interictal paroxysmal activity on the electroencephalogram (EEG)) may contribute to severe cognitive and behavioral decline above and beyond what might be expected from the underlying pathology alone (e.g. cortical malformation). Diagnosing an individual as having an encephalopathic course requires demonstration of a failure to develop as expected relative to same-aged peers or to regress in abilities" (Berg et al., Report of the ILAE Commission on Classification and Terminology, 2010; Dulac, 2001; Filippini et al., 2013). Although EE is associated mainly with certain infantile and childhood epilepsy syndrome, encephalopathic effects of seizures and subclinical epileptiform discharges on the EEG may potentially occur in association with any form of epilepsy at any age (Berg et al., 2010). However, our search did not reveal community- or population-based studies on EE in adults, but few case-reports describe this condition.

In a long-term follow up study by Fujikawa et al. (2012), four patients with adult-onset idiopathic generalized seizures, cognitive deterioration and an abnormal EEG (marked by frequent or

prolonged bilaterally synchronous spike and slow-wave discharges (SWDs)) repeatedly underwent neuropsychological assessment and routine EEGs in order to determine the relation between chronic subclinical epileptiform activity and cognition. It appeared that the severity of cognitive deterioration was related to the chronicity and amount of SWDs on the EEG and the patients were diagnosed as having a chronic epileptic encephalopathy. Brain MRI showed cerebral atrophy in two of the four cases, possibly due to the chronic frequent and/or prolonged SWDs. Cognitive deterioration in these cases proved to be irreversible, despite apparent successful therapeutic intervention, i.e. significant reduction of SWDs on the EEG.

Villani et al. (2006) describe five patients who suffered from refractory focal epilepsy, persistent deteriorating abnormalities on the EEG, severe unilateral fronto-temporal hypometabolism on positron emission tomography (PET), progressive focal atrophy on brain MRI and cognitive deterioration. They were diagnosed with adult-onset Rasmussen's encephalitis (RE), a rare variation of the childhood syndrome. It has been suggested that in RE too, epileptiform discharges contribute to progressive neurological and cognitive deterioration (Bien et al., 2005), although the pathogenesis of RE is not fully known. Based on the inflammatory responses in the human brain observed in RE, several infectious and immune-mediated mechanisms have been proposed to explain the etiology and development of this disease. Regarding the seizures in RE, it is hypothesized that seizure discharges locally disrupt the protective blood-brain barrier, facilitating entry of pathogenic antibodies into the brain. Through interaction with brain antigens, neuronal injury is induced. Subsequently, epileptic activity increases and so on, maintaining a vicious circle (Andrews et al., 1996; Bien et al., 2005; Dubeau et al., 2008).

6. Coexisting diseases

Several medical and neurological disorders occur more frequently in epilepsy than in the general population. Some diseases not only occur more often in patient with epilepsy but are risk factors themselves for the development of cognitive comorbidity (Gaitatzis et al., 2012). Co-occurrence of multiple diseases has been associated with an accelerated decline in cognitive function in adults (Comijs et al., 2009). Hence, the presence of coexisting conditions in epilepsy can have adverse prognostic implications and might lead to an altered cognitive course.

6.1. Vascular disease

Vascular pathology and associated risk factors are found to be predictive of accelerated cognitive decline and dementia in the ageing adult population (Debette et al., 2011; Gorelick et al., 2011). Epidemiological studies have shown that patients with epilepsy treated with anticonvulsive drugs are at increased risk of both cardiac and cerebrovascular disease (Elliott et al., 2007; Gaitatzis et al., 2004; LoPinto-Khoury and Mintzer, 2010; Olesen et al., 2011) and associated risk factors such as hypertension (Elliott et al., 2007), atherosclerosis and hyperhomocysteinemia (Elliott et al., 2007; Hamed et al., 2007), diabetes mellitus (Elliott et al., 2007; Gaitatzis et al., 2004) and hypercholesterolemia (Hamed et al., 2007; Li et al., 1997).

Vascular disease, especially cerebral stroke, is an important risk factor for the development of epilepsy and accounts for up to 50% of the adult epilepsies with a known cause (Acharya and Acharya, 2014; Brodie et al., 2009; Gaitatzis et al., 2012). In the first year after a stroke, the risk of new-onset seizures increases up to 20-fold, making stroke the most frequent etiology in new-onset epilepsy in the middle-aged and elderly (Tedrus et al., 2012). Also the opposite appears to be true, as the onset of epilepsy in late life is associated with a striking increase in the risk of stroke (Cleary et al., 2004).

Stroke is associated with long-term cognitive decline in the general population (Comijs et al., 2009; Rafnsson et al., 2007). When complicated by subsequent epileptic seizures, cognitive function may further deteriorate. De Reuck et al. (2006a) found that the long-term cognitive outcome is worse in patients with repeated post-stroke seizures compared to those without subsequent epilepsy, even though the degree of cognitive impairment in patients after a single seizure is similar to that of non-seizure stroke patients. Furthermore, the occurrence of seizures following stroke is associated with an increased risk of developing dementia (Cordonnier et al., 2007). One might hypothesize that this seemingly more extensive cognitive deterioration in post-stroke epilepsy is due to a more severe underlying neurological pathology as defined by the initial severity, size and location of the infarction. However, it has been demonstrated that in patients with post-stroke seizures, the severity of ischemic changes in the infarcted brain area is more pronounced compared to patients with similar neurological impairment but without seizures (De Reuck et al., 2006b). Recurrent seizures after stroke have been associated with additional ischemic changes and long-lasting worsening of the initial neurological sequelae, potentially adversely affecting clinical outcome (Kumral et al., 2013). Prospective studies are needed to characterize directions of causality in these studies and to further explore the relationship between seizures and cognitive deterioration following cerebral stroke.

6.2. Dementia (Alzheimer's disease)

Dementia and neurodegenerative disorders are estimated to be an etiological factor in 10–20% of all epilepsies in the elderly population. Patients with Alzheimer's disease (AD) are up to ten times more likely to develop seizures than those without Alzheimer's and the rate of epilepsy in this disease is higher than in other dementias (Acharya and Acharya, 2014; Brodie et al., 2009; Verellen and Cavazos, 2011). Vice-versa, people with epilepsy are at increased risk of developing AD (Gaitatzis et al., 2012).

Although it is often assumed that seizures in AD are a secondary process resulting from advanced stages of neurodegeneration, seizures can occur at any stage of disease and the occurrence of seizures does not necessarily correlate with severity or duration of illness (Friedman et al., 2012; Gaitatzis et al., 2012; Palop and Mucke, 2009). It is questioned whether epileptic seizures have a disadvantageous effect on the course of AD. In terms of progression of non-cognitive symptoms and mortality, findings vary (Förstl et al., 1992; Friedman et al., 2012).

Little research has been conducted on the cognitive course in AD in relation to epilepsy. Several studies have found that the cognitive decline in patients with Mild Cognitive Impairment (MCI) or AD begins several years earlier in patients who also have seizures compared to those who do not develop epilepsy (Amatniek et al., 2006; Irizarry et al., 2012; Vossel et al., 2013). Remarkably, Vossel et al. (2013) found the same being true for patients with AD who have subclinical epileptiform activity as shown on the EEG, even though they clinically have no obvious seizures. A recent study provides evidence that seizures potentially lower the pathologic threshold for the development of cognitive impairment and early dementia in AD (Patrick et al., 2014). At autopsy, patients with a history of seizures had less AD brain pathology than seen in the patients without seizures, whereas the degree of cognitive impairment was similar between the two groups. It was suggested that seizures may act as an additive factor contributing to cognitive decline in the earliest stages of AD progression. AEDs may also worsen cognitive function in AD, specifically phenytoin, carbamazepine, phenobarbital and several benzodiazepines (Vossel et al., 2013). No studies

have been found on the consequences of seizures or AEDs on cognitive function in patients with dementia other than Alzheimer's disease.

The mechanisms underlying seizures and possible exacerbated or accelerated cognitive decline in AD remain to be determined. It has been suspected that accumulation of amyloid β plaques, neurofibrillary tangles and neuronal loss in limbic and association cortices contribute to an imbalance between excitation and inhibition in the brain, inducing epileptiform activity. In response to epileptic activity and chronic excitability, compensatory changes such as network reorganization take place, particularly in the dentate gyrus (Chin and Scharfman, 2013; Friedman et al., 2012; Hommet et al., 2008; Palop and Mucke, 2009; Roberson et al., 2011). The severity of these compensatory responses correlates with the degree of cognitive impairment in the early stages of AD and may be linked to exacerbated cognitive decline (Roberson et al., 2011). However, whether seizures are indeed an integral part of the emerging pathophysiology and progression of cognitive impairment in human AD is still debated.

6.3. Traumatic brain injury

About 6% of all cases of epilepsies can be attributed to head trauma (Szaflarski et al., 2014). Older age has been identified as a risk factor for developing epilepsy after traumatic brain injury (TBI) and up to 20% of all epilepsy in the elderly is post-traumatic (Acharya and Acharya, 2014; Brodie et al., 2009). Other risk factors for subsequent epilepsy are penetrating injury, intracranial hematoma, skull fracture, loss of consciousness, amnesia for more than 24 h and early seizures occurring within the first seven days after trauma (Brodie et al., 2009; Szaflarski et al., 2014). The risk of developing post-traumatic epilepsy (PTE) is highest during the first two years after the injury, but remains elevated for up to more than ten years after injury compared to people without TBI (Annegers et al., 1998). Post-traumatic seizures have a significant effect on long-term outcome after TBI and adversely affect quality of life, independency, employment and psychosocial integration (Kolakowsky-Hayner et al., 2013; Szaflarski et al., 2014).

Raymont et al. (2010) found that PTE is also associated with exacerbated cognitive outcome in later life, patients who developed epilepsy after TBI showed a greater level of cognitive decline 35 years post-TBI compared to those without subsequent epilepsy, regardless of the amount of total brain volume loss. Intellectual decline was predicted by duration of PTE and was worse in patients with frequent generalized seizures. Another study found no differences in neuropsychological outcome 1 year post-injury between patients with PTE and those who remained seizure free when the severity of the head injury was taken into account (Haltiner et al., 1996). It remains debated whether long-term cognitive decline in PTE largely reflects the severity of the neurological injury that caused the seizures or the deleterious effects of seizures on the existing cognitive weakness resulting from TBI.

Head trauma initiates a sequence of responses that includes altered blood flow and vasoregulation, increase in intracranial pressure, focal and diffuse ischemic hemorrhage, inflammation, and disruption of the blood-brain barrier (BBB) (Gupta and Gupta, 2006). The latter is associated with delayed neuronal dysfunction and degeneration and long-term cognitive decline. It is indicated that BBB breakdown after TBI contributes to long-term complications such as Alzheimer's disease (Shlosberg et al., 2010). It may also mediate the development of PTE. In patients with PTE, both frequency and extent of long-lasting disruption of the BBB are increased compared to non-epileptic TBI patients (Tomkins et al., 2011). To date there is no information addressing the course of cognitive function or brain structure in these patients and it remains unclear whether patients with PTE are at increased risk of age-accelerated cognitive changes and dementia.

Similarly, it has been questioned whether the occurrence of TBI in pre-existent epilepsy increases the risk of exacerbated cognitive decline, since TBI alone might lead to accelerated cognitive decline and increases a person's risk of developing dementia in later life (Moretti et al., 2012). In a post-mortem study exploring brain ageing and cognition, evidence was found that the presence of TBI in chronic epilepsy can lead to accelerated brain ageing. Patients with contusional brain injury on top of their epilepsy were found to have increased neurofibrillary tangle pathology (age-accelerated tau-protein accumulation) and cognitive decline, compared to those without TBI (Thom et al., 2011).

7. Antiepileptic drugs

Antiepileptic drugs (AED) affect cognition by modulating neuronal excitability and inhibitory neurotransmission (Ortinski and Meador, 2004). Common cognitive side effects are psychomotor slowing, decreased alertness and slowing of the central information processing speed, although impairment is considered mild to moderate for most AEDs (Aldenkamp, 2011). Only few studies found evidence for possible AED-induced cognitive decline. It should be noted however, that due to several methodological difficulties, the adverse effects of antiepileptic's on cognition could have been both over- and under-rated in the past (see Vermeulen and Aldenkamp, 1995). Only few AEDs have to be discussed in the context of this review as potential cause of global cognitive decline or deterioration of higher order cognitive function. For most AEDs, adverse effects were limited to fluid function.

Long-term administration of phenobarbital (PB), a long-acting barbiturate, is associated with cognitive decline in some studies. In an early study of Bourgeois et al. (1983), a decrease in intelligence scores was observed in a group of young patients with epilepsy. It was assumed that this was related to treatment with high doses of PB, since it was not seen in patients receiving other AEDs. It remains unclear though whether this deterioration was indeed related to the prescription of PB or that the patients treated with PB suffered from a more severe type of epilepsy. In two additional studies, including one with a double-blind crossover design, prolonged use of PB was clearly associated with global cognitive decline in both verbal and performance IQ in comparison with long-term valproate therapy (Calandre et al., 1990; Vining et al., 1987). Decline in attention and information processing speed was reported in patients who were seizure-free on PB-monotherapy for several years compared to healthy controls (Manni et al., 1993). However, PB-related cognitive decline has been more consistently demonstrated in children rather than adult patients and some authors suggest that exposure to PB might have a differentially damaging effect at certain critical stages of development (Sulzbacher et al., 1999). It has also been stated that the adverse cognitive effects of PB are more deleterious in the elderly population. Elderly patients with epilepsy and Alzheimer's disease showed significant cognitive decline and aggravation of existing cognitive impairment after 12 months of treatment with PB compared to healthy controls and patients treated with levetiracetam or lamotrigine (Cumbo and Ligori, 2010).

Phenytoin (PHT) has been implicated in decline in visuomotor functions, memory and especially mental speed (Aldenkamp et al., 1994; Gillham et al., 1990). In contrast to PB however, long-term effects of PHT appear not to include global intellectual decline. Pulliainen and Jokelainen (1995) even state that the effects of long-term administration of PHT on cognition are small and restricted mainly to some visually guided motor functions, which is in line

with other longitudinal studies (Aikia et al., 1992; Dodrill and Wilensky, 1992).

Long-term use of topiramate (TPM), a relatively new AED, is associated with decline of higher-order cognitive function. In a study of Thompson et al. (2000), repeated neuropsychological assessment revealed a significant decline in verbal IQ, verbal fluency and verbal memory in epilepsy patients treated with TPM. Also declines in verbal working memory, spatial working memory, verbal comprehension and attention are reported (Fritz et al., 2005), even in low-dose TPM monotherapy (Lee et al., 2006). Since all patients included in the aforementioned studies were treated with TPM for at least three months but predominantly longer, cognitive changes do not reflect an acute effect that is expected to diminish over time as described by Meador et al. (2003). Impairment seems at least partially reversible though, as withdrawal or reduction of TPM resulted in improved cognitive performance in several studies (Lee et al., 2006, 2003; Thompson et al., 2000).

8. Discussion

There is sufficient evidence that, in addition to specific impairments in locally organized functions (especially memory), also global cognitive decline or deterioration may occur in epilepsy. It is largely unknown what percentage of patients is at risk and show forms of cognitive decline, neither the typical form of cognitive decline has been described sufficiently. Identification of risk factors and characterization of aberrant trajectories may be a first step towards a better understanding of this group.

Early *age at onset of epilepsy* is a factor associated with poorer cognitive outcome in later life. Children with an early age at onset are at higher risk for future reduction in intelligence scores. The same appears to be true for adult onset epilepsies. Of course it can be debated whether this is confounded by the onset of specific epilepsy syndromes or whether this is the result of interference with sensitive developmental phases. There is even some evidence that some cognitive problems have a pre-onset origin and may be entangled in the process of epileptogenesis. The body of evidence, however, shows that that post-onset factors such as the effects of persisting seizures, duration of disease and long-term adverse effects of some of the AEDs may accumulate over longer periods of time and result in impaired cognition in adulthood. This is then related to age at onset as earlier onset allows these factors longer periods to accumulate.

In late-onset epilepsies, especially in the geriatric age-range, such processes may be strengthened due to diminished cognitive reserve capacity. In other words, here the same processes of accumulation occur, however with effects noticeable in a shorter time-span as mechanisms of neuronal adjustment and plasticity fail. The mature brain might be less able to functionally compensate for interference of disease and the pathology underlying the epilepsy. Patients with adult- and geriatric-onset epilepsy are thus at risk for cognitive deterioration since the brain's neuronal plasticity decreases with age. Another factor, not to be underestimated, is that in late-onset epilepsies many factors converge in addition to the reduced neuronal plasticity: increased risks for metabolic disturbances, increased inflammatory brain response to seizures, higher risks for neurological diseases and comorbidity (most of them with a known impact on cognition), and the use of polypharmacy often with complex interactions. The risk of cognitive deterioration is therefore large in this group. Accordingly, Piazzini et al. (2006) showed that in the elderly with late-onset epilepsy, cognitive function is generally impaired relative to age-matched controls. Taylor et al. (2010) found that adults with newly diagnosed epilepsy were already cognitively compromised prior to treatment, which is in line with other research (Pulliainen et al., 2000; Witt and Helmstaedter, 2012). This points to the effects of the aforementioned loss of reserve capacity. In combination with the expected changes of normal ageing, this might lead to a very specific process of cognitive decline: accelerated cognitive ageing.

Duration of epilepsy is a second factor, although confounded with age at onset. Most studies describing cognitive decline, focus on chronic epilepsy in which results must be interpreted with great caution. Many confounders are simultaneously active in this group, such as treatment issues, underlying etiology, the effect of specific syndromes etc. However, some studies did identify cognitive decline in chronic epilepsy specifically in patients that were older, had a longer duration of epilepsy, were taking more AEDs and had more abnormal brain volumes (Hermann et al., 2006b). So again, ageing and cognitive deterioration seem to be inseparably connected and especially in adulthood-onset chronic epilepsy, the development of epilepsy might interfere with the ageing process.

The third factor *seizure type and seizure frequency* does not provide much additional information, except the findings following status epilepticus. Patients with cognitive decline after a SE are generally patients who exhibited a SE following various conditions (e.g. cerebrovascular disease, encephalitis, metabolic disease), rather than a SE without a known etiology. Thus suggests that a SE on an already vulnerable brain changes cognitive status through preceding loss of cognitive reserve capacity.

Epileptic encephalopathy, the fourth factor, generally has cognitive deterioration as an inherent characteristic. The rare studies in adult encephalopathies show the role of inflammation in relation to cognitive deterioration. In Rasmussen's encephalitis several infectious and immune-mediated mechanisms have been proposed to explain the etiology and development of this disease. Regarding the seizures in RE, it is hypothesized that seizure discharges locally disrupt the protective blood-brain barrier, facilitating entry of pathogenic antibodies into the brain, eventually leading to neuronal injury (Andrews et al., 1996; Bien et al., 2005; Dubeau et al., 2008).

The role of the fifth factor, *coexisting diseases*,is essential in our opinion. Patients with seizures after stroke or traumatic brain injury show more severe cognitive decline than those without seizures. Seizures can therefore be seen as an amplifying factor on an already vulnerable brain. Several studies have found that cognitive decline in patients with Mild Cognitive Impairment or AD begins several years earlier in patients who also have seizures compared to those who do not develop epilepsy (Amatniek et al., 2006; Irizarry et al., 2012; Patrick et al., 2014; Vossel et al., 2013). This again points to a mechanism which accelerates ageing processes due to loss of cognitive reserve capacity.

The sixth factor is *AED treatment* that seems to be able to induce cognitive decline, however as an idiosyncratic reaction to treatment. This is also only valid for a minority of the available treatment options.

When combining the effects of the first five factors involved in cognitive decline, then some findings are apparent: post-onset factors of childhood epilepsies may accumulate and result in poor cognitive outcome in adult life. Here accumulation and thereby gradual decline as a consequence of chronicity is the key factor. This is what Gowers has labeled as 'epileptic dementia' in the past. However, definitive conclusions about the relationship between the accumulating effect of epilepsy/seizures and cognitive decline are difficult in such chronic epilepsies due to the existence of many confounding factors.

In addition to this 'accumulation chronic model', cognitive decline may also develop in a 'second hit model' and occurs when epilepsy hits on an already vulnerable brain. This pertains to the concept of 'reserve capacity' or loss of brain plasticity. Probably the most important factor here is 'ageing'. The mature brain might be less able to functionally compensate for interference of disease

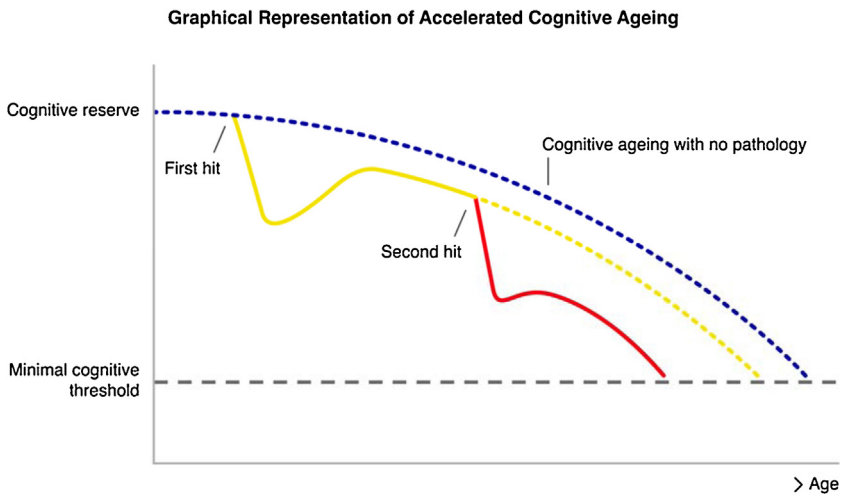

Fig. 1. Graphical representation of Accelerated Cognitive Ageing. The broken blue line represents the cognitive ageing trajectory without pathology. With increasing age, cognitive functioning is declining until the minimal cognitive threshold is reached. Two alternative cognitive ageing trajectories are shown. The yellow line depicts the cognitive trajectory after one hit (e.g. TBI). There is decline in cognitive function which recovers. Recovery is, however, not complete and results in a loss of functional reserve. This is followed by a normal rate of subsequent ageing. The red line represents Accelerated Cognitive Ageing in the second-hit model. After a second hit (e.g. epilepsy), cascadic deterioration takes place and does not recover due to the diminished cognitive reserve capacity. In combination and interaction with the expected changes of normal ageing, cognitive ageing is accelerated and the patient's cognitive profile resembles that of an older individual. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Based on: Smith (2013).

and the pathology underlying the epilepsy. Patients with adult- and geriatric-onset epilepsy are at risk for cognitive deterioration and accelerated cognitive ageing since the brain's neuronal plasticity decreases with age. In addition, many factors converge in late-onset epilepsies: comorbidity (and especially stroke and other (cardio) vascular disease), metabolic disturbances, increased inflammatory response to seizures, and the use of polypharmacy (Baram, 2012; Brodie et al., 2009; Trinka, 2003; Leppik and Birnbaum, 2010; Palop and Mucke, 2009; Stefan et al., 2014). All these conditions in conjunction with ageing may serve as a first hit, reducing reserve capacity. When epilepsy has it's onset in such a vulnerable brain, or vice versa, cognitive deterioration may occur, accelerating the effects of ageing by diminishing cognitive reserve. Fig. 1 graphically represents this second hit model.

An important distinction between the 'chronic accumulation model' (Gowers' epileptic dementia) and the 'second hit model' with accelerated cognitive ageing is the time scale. Cognitive decline occurs gradually over a long period of time in the chronic accumulation model, whereas it occurs as a form of cascadic deterioration (decline in a relatively short period of time) in the 'second hit model'. The typical trajectory of cognitive decline in the late-onset epilepsies may therefore present as a form of speeded ageing. Epilepsy as a first or second hit on a vulnerable brain accelerates the effects of ageing by diminishing cognitive reserve, for which we coin the term 'accelerated cognitive ageing'.

An important issue is why this cognitive deterioration is not reported more frequently, especially in the late-onset epilepsies. Under-detection is possible as deteriorated function may be attributed to 'normal ageing effects' or, in case of severe deterioration, to a form of dementia.

The key finding to collaborate with the concept of accelerated cognitive ageing (ACA) would be the demonstration of neuropsychological and MRI changes in brain organization that would resemble ageing processes in normal individuals, but in an accelerated mode. With respect to the neuropsychological profile, Helmstaedter and Elger (2009) found that cognitive ageing in TLE runs largely parallel to that in healthy controls. However, because of cascadic deterioration around the time of epilepsy onset, patients with epilepsy reach their cognitive peak at a much younger age than controls. In other words, their cognitive profile at a certain age resembles that of an older individual, as they become cognitively impaired earlier in life. The group of Taylor et al. (2010) confirmed that adults with newly diagnosed epilepsy were already cognitively compromised prior to treatment, which is in line with other research (Pulliainen et al., 2000; Witt and Helmstaedter, 2012). Additional research is needed to examine the age regression performance in those patients. With respect to brain organization, functional imaging-research showed significant differences in both global and regional connectivity between adults with early- and late seizure onset (Doucet et al., 2014). In late-onset epilepsy, increased global functional integration and both reduced segregation and modularity were seen relative to healthy controls and patients with early seizure onset. At a regional level, differences in functional connectivity were most apparent in the frontal lobe. Such abnormal brain network organization, specifically decreased functional segregation, has been associated with cognitive deterioration in epilepsy before by our own group (Vlooswijk et al., 2011).

The mechanisms underlying ACA remain to be elucidated. We hypothesize that first and second hits (e.g. epilepsy, vascular disease, traumatic brain injury) trigger a sequence of neurobiological events that cause neuronal changes or injury that can be exacerbated through an ongoing interaction with the normal ageing process, especially in older adults. For example, traumatic brain injury (TBI) initiates a sequence of responses that includes disruption or dysregulation of the blood-brain barrier (BBB) (Gupta and Gupta, 2006). This is associated with delayed neuronal dysfunction and degeneration. This effect can be magnified by the effects of 'second-hit' epilepsy on the permeability of the BBB (Tomkins et al., 2011). In interaction with the neuronal ageing process, this might lead to pathologically BBB leakage, facilitating the entry of pathogenic antibodies into the brain. This leads to cognitive deterioration, aggravated by the initial severity of the TBI and epilepsy and lack of cognitive reserve capacity (Moretti et al., 2012). Also (cardio) vascular disease or an immune response may cause ongoing neuronal injury, inflammation, and oxidative stress, contributing to cognitive deterioration and abnormalities in brain structure and metabolism. In older adults this might be exacerbated

through age-related changes, e.g. the sensitization to neuroinflammatory response (Rosano et al., 2012).

Although prospective studies combining analysis of function profiles and brain organization will be needed, we believe that the concept of accelerated cognitive ageing can be helpful in providing a framework for understanding global cognitive decline in epilepsy.

In conclusion: two forms of global cognitive deterioration may occur in epilepsy. Decline that can be explained using an 'accumulation chronic model', with slow and gradual decline as a consequence of chronicity and consequently the accumulation of the negative effects of seizures, treatment and other epilepsy-related factors. This is what Gowers has labeled as 'epileptic dementia' in the past. Another form of decline can only be explained in the 'second hit model' with accelerated cognitive ageing in the form of cascadic deterioration as the key clinical hallmark.

Conflicts of interest

There are no conflicts of interest.

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