The who, what, when and why of cognitive difficulties in epilepsy

Abstract

Cognitive complaints are very common in people diagnosed with epilepsy. These difficulties are often another manifestation of the same pathology responsible for seizures. They can be further exacerbated by treatments aimed at seizure control. Other common comorbidities of epilepsy such as low mood and elevated anxiety can also contribute to cognitive complaints. There is surprisingly little overlap between memory complaints and performance on formal memory tests in this population. This article examines the multifactorial and heterogeneous nature of cognitive difficulties in epilepsy and makes the case for the provision of basic psychoeducation as the foundation for all interventions aimed at ameliorating these difficulties in this patient population.

Key words: Cognitive impairment; Epilepsy; Memory; Psychoeducation; Trajectory

Submitted: 10 December 2022; accepted following double-blind peer review: 20 February 2023

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Introduction

Cognitive complaints are very common in people diagnosed with epilepsy. This article describes who is affected and why, and covers which cognitive functions are most commonly impacted in adults living with this diagnosis. It also examines when cognitive difficulties are most likely to manifest over the course of the disease.

It may be prudent to start with a brief overview of current terminology, particularly with respect to 'epilepsy' and 'epileptic seizure'. The World Health Organization estimates that up to 10% of people may experience one seizure during their lifetime, commonly as a febrile convulsion in infancy or in response to recreational stimulants or depressants in adolescence and adulthood. A single seizure in these circumstances does not confer a diagnosis of epilepsy. Epilepsy is only diagnosed when someone 'demonstrates a pathologic and enduring tendency to have recurrent seizures' (Fisher et al, 2014). The bar for determining 'recurrent' is set relatively low. Epilepsy is diagnosed when someone has experienced two unprovoked (or reflex) seizures more than 24 hours apart. The condition can also be diagnosed after just one seizure if subsequent investigations indicate that the individual has a greater than 60% chance of another seizure occurring, for example in the presence of clear epileptiform abnormalities on an electroencephalogram or an epileptogenic structural lesion on neuroradiological studies (Fisher et al, 2014).

What is 'cognitive impairment'?

Cognitive impairment can refer to the subjective experience of cognitive difficulties or deficits observed on standardised tests of cognitive function. Subjective complaints can be elicited via clinical interview and can also be recorded on dedicated subjective memory questionnaires (Thompson and Corcoran, 1992) which ask people to rate the frequency of difficulties in common scenarios: for example 'How often do you forget to take your medication?', 'How often do you lose the track of what you are saying in conversation?' and 'How often do you struggle to find the right word in conversation?' Objective cognitive impairment is typically defined as a score below the 5th or 2nd percentile on standardised tests of cognitive function.

Subjective complaints of cognitive impairment are not highly correlated with performance on standardised tests (Hall et al, 2009). In a series of 1186 consecutive patients with confirmed epilepsy referred to the author's specialist epilepsy service for a clinical assessment

How to cite this article:
Baxendale S. The who, what, when and why of cognitive difficulties in epilepsy. Br J Hosp Med. 2023. https://doi.org/10.12968/hmed.2022.0534

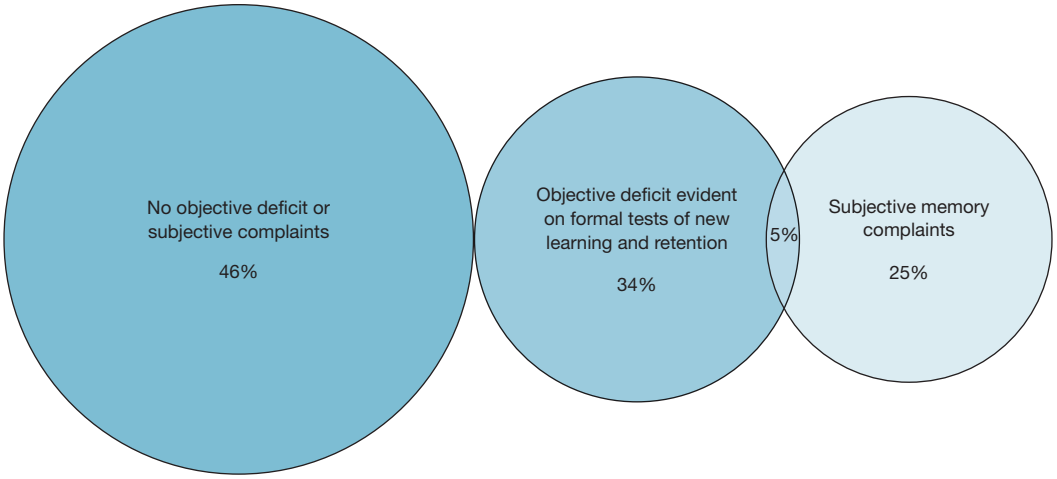

Figure 1. Memory deficits in epilepsy. Objective measures of impairment vs subjective complaints of significant nuisance.

of their memory function, approximately one in three (33%) obtained scores below the 2nd percentile on standardised tests involving the learning and retention of new information (list learning and prose recall tasks; the most commonly used standardised tests of memory function), while one in four (25%) reported that their memory was a serious nuisance in everyday life on a subjective memory questionnaire. The overlap between these groups was limited to the extent that just over half of the sample (54%) either reported significant memory complaints or demonstrated a significant impairment on the formal tests (**Figure 1**).

The majority (80%) of people who reported that their memory was a significant nuisance in their everyday life did not demonstrate clinical impairments on the formal tests. This pattern is likely attributed to a number of factors. It is important to recognise that people with epilepsy and clinicians tend to use language differently when it comes to 'memory'. Patients tend to attribute most cognitive failures to poor memory. However, from a neuropsychological perspective these failures often represent impairments in attention, concentration, language function and executive function, so it is unsurprising that deficits are not always apparent on formal tests of memory function in those who complain about significant 'memory' difficulties in everyday life. The mismatch between memory complaints and function on formal tests may also reflect task specificity (Saling et al, 1993). Each standardised memory test assesses a different aspect of memory, for example, encoding, retrieval or accelerated forgetting. Scores on these tasks can and do dissociate (Saling, 2009). There is no single test of memory that covers all of these processes.

Subjective memory complaints are strongly associated with mood, particularly depression (Grewe et al, 2016). These complaints are also associated with elevated anxiety, where worries about cognitive function can lead to hypervigilance to minor memory lapses and the everyday failures associated with normal age-related changes in function (Baxendale, 2011). Once established, hypervigilance can create a vicious cycle of increased anxiety, leading to further errors and even greater levels of hypervigilance (**Figure 2**). Others have also hypothesised that for some patients, subjective memory complaints may reflect difficulties adjusting to, or coping with, epilepsy (Hall et al, 2009).

It is perhaps more surprising that the majority of people with epilepsy (85%) who demonstrated a significant impairment on the standardised tests of memory function in the author's series did not report that their memory difficulties were a serious nuisance in everyday life. Again, the reasons for this are likely to be multifactorial (Hall et al, 2009). First, standardised tests are deliberately constructed to measure the integrity of underlying processes, not real-life function. In fact, the tests are very deliberately constructed so that they do not reflect life function. Access to all memory aids is denied to the patient. Thus, while difficulties in committing 15 unrelated words to memory may tell us something about the functional integrity of the mesial temporal structures and memory networks, it does not necessarily mean that someone will have difficulties in shopping for 15 items in a supermarket, where they are routinely able to use a number of strategies and aids to help them (eg a written shopping list). It is also the case that many people with epilepsy have longstanding lived

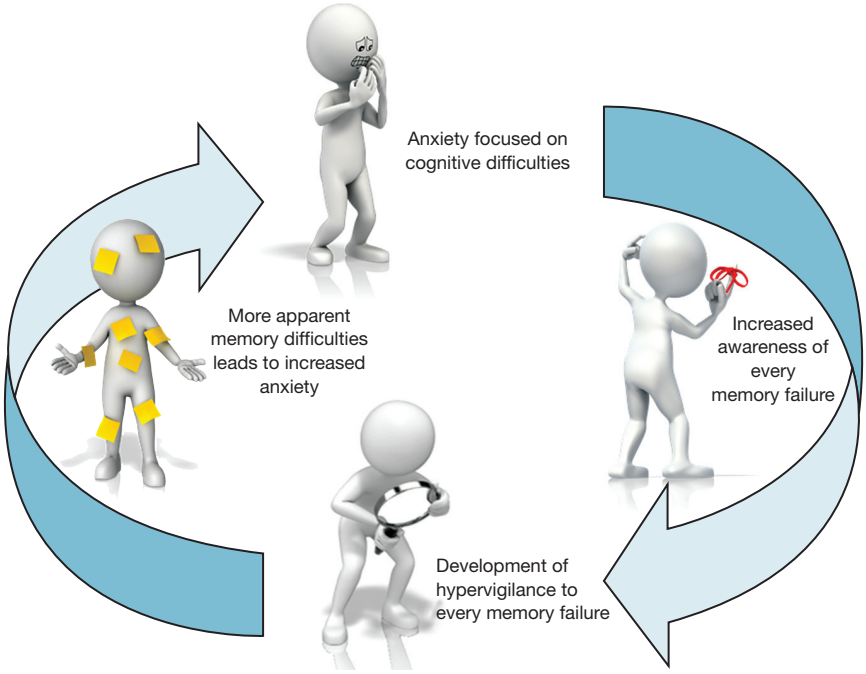

Figure 2. Stages in the development of the vicious circle of hypervigilance with respect to anxiety and cognitive difficulties in epilepsy.

experience with cognitive compromise, and as such have developed many effective adaptations and workarounds to reduce the impact of these on their everyday life, leading to a reduction in disruption and therefore complaints. For a minority of people with epilepsy, the mismatch between objective performance on standardised tests and subjective reports of everyday function may represent a lack of insight, typically associated with frontal lobe dysfunction.

Who experiences cognitive impairment in epilepsy?

While cognitive complaints are common in epilepsy, not all people with epilepsy report cognitive difficulties or demonstrate impairments on psychometric tests. In studies of cognitive phenotypes in temporal lobe epilepsy, studies from a number of centres in the USA and UK indicate that up to one-half of adults do not demonstrate any clinically significant impairments on formal tests of cognitive function (Hermann et al, 2007; Elverman et al, 2019; Baxendale and Thompson, 2020). Up to a third may demonstrate specific deficits in memory function, in the context of otherwise intact cognitive function, with the remainder demonstrating fairly widespread dysfunction with impairment evident in multiple cognitive domains including memory, language and executive function. People with generalised epilepsy often experience similar cognitive impairments in memory and information processing to those with focal epilepsy (Loughman et al, 2017; Simani et al, 2020; Gauffin et al, 2022; Khalife et al, 2022). People with more widespread cognitive impairment tend to have a longer duration of epilepsy, take more medications and have more abnormal brain volumes than those with normal cognitive profiles. Episodes of status epilepticus and frequent generalised tonic-clonic seizures are also associated with more widespread cognitive difficulties (Thompson and Duncan, 2005; Hermann et al, 2020). Caution should be exercised in attributing direct causality to any one of these factors when it comes to cognitive function. It is likely that these factors, like cognitive function itself, are all biomarkers for underlying brain health.

Why is cognitive function compromised in epilepsy?

For many people, cognitive dysfunction is an essential comorbidity of epilepsy (Wilson and Baxendale, 2016). The same underlying pathology that is responsible for recurrent seizures also disrupts functions subserved by that region of the brain and its key networks. Thus, people with temporal lobe epilepsy may experience memory problems, while those with frontal

lobe epilepsy may present with features of executive dysfunction. In many ways, the term 'comorbidity' in its traditional sense is a misnomer in this situation, since seizures and cognitive difficulties are both manifestations or symptoms of the same underlying brain abnormality.

The impact of the underlying pathology on cognitive function will be mediated by its extent, location and type. The developmental context of the pathology is an important factor in shaping any associated deficit. In some cases, neuronal plasticity and reorganisation in the developing brain allow some cognitive functions to develop around the lesion, or for other more distant structures to take over functions if the lesion occurs early enough in the neurodevelopmental trajectory (Serrano-Castro et al, 2020). However, the capacity of the developing brain to reorganise function is not a panacea when it comes to cognitive compromise in epilepsy. This reorganisation can sometimes lead to the compromise of functions typically subserved by the newly recruited region. Low-grade developmental and epilepsy-associated tumours are often (but not always) associated with an onset of seizures before 13 years of age (Slegers and Blumcke, 2020). An onset of seizures in childhood can lead to hindrance in the development of cognitive function, whereby the child with epilepsy never quite reaches the full potential seen in their peers (Helmstaedter and Elger, 2009) (Figure 3). Epileptogenic pathology that develops later in life, for example vascular lesions or tumours, can lead to much more focal deficits in cognitive function, as the pathology disrupts and destroys functions and networks which developed normally before its formation.

Pathology does not have to be observable to disrupt function. Approximately 30% of people with temporal lobe epilepsy have no observable pathology evident on high resolution magnetic resonance imaging (Muhlhofer et al, 2017). The proportion is higher in extra-temporal cases. Nevertheless, these people can also experience cognitive difficulties. Epilepsy is a networked disorder (Kramer and Cash, 2012) and whatever abnormality is responsible for the seizures can also disrupt the associated cognitive networks. While the underlying pathology lays a critical foundation in shaping any associated cognitive deficit, the influence is complex and determined by more than just the location and laterality of any pathology, observable or otherwise.

Cognitive difficulties can also be exacerbated by many of the treatments offered for seizures, and concerns about the impact of anti-seizure medications on cognitive function are frequently raised in the epilepsy clinic by patients and their families. Methodological shortcomings in the literature on anti-seizure medication and cognitive function can make it difficult to draw firm conclusions from single, pragmatic studies. Similarly, like-for-like comparisons between medications are very difficult to draw because of differences in test selection, variable performance at baseline and small sample sizes which cannot account

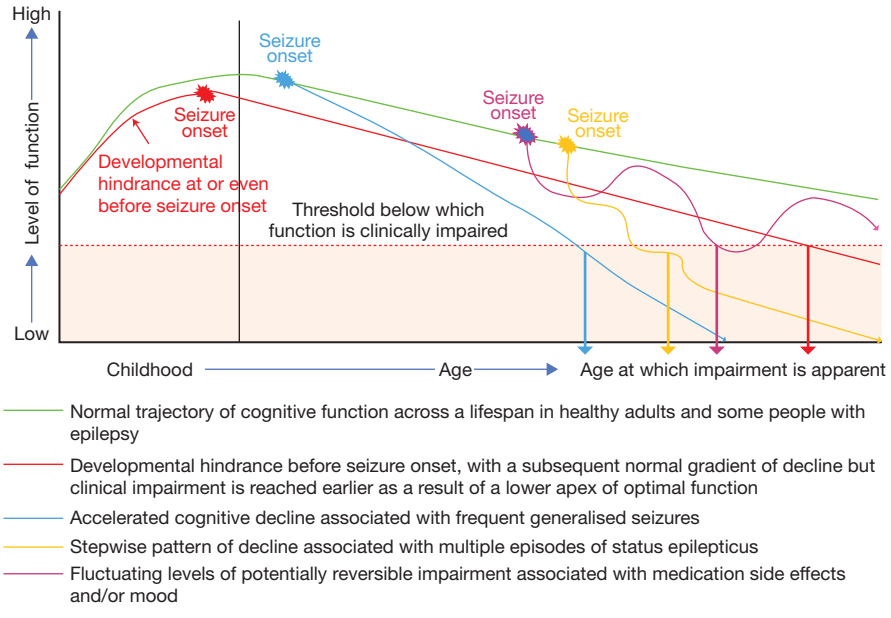

Figure 3. Some of the possible trajectories of cognitive decline in epilepsy across a lifespan.

for the multiple factors that impact cognitive function in people with epilepsy. Nevertheless, some consistent themes emerge from the literature. While some anti-seizure medications are associated with decline in specific functions, such as verbal fluency (Thompson et al, 2000), working memory (Fritz et al, 2005) and processing speed (Hessen et al, 2006), as a general rule of thumb higher doses and polytherapy tend to be associated with greater deficits (Witt et al, 2015; Quon et al, 2020), with processing speed, attention and vigilance particularly affected (Park and Kwon, 2008). These difficulties may be lessened in some cases if drugs are titrated slowly to the maximum dose (Witt and Helmstaedter, 2017). However, cognitive complaints are often cited as the primary reason for discontinuation of anti-seizure medications, even in the context of efficacy in terms of seizure control (Bootsma et al, 2004). Cognitive difficulties that are secondary to drug effects, be they direct side effects or the result of other effects of the drug such as somnolence or fatigue, tend to resolve once the medication is reduced or withdrawn (Witt and Helmstaedter, 2017), although the impact of these side effects can be lifelong if they occur at critical periods of education and training (Brückner, 2020). Pseudodementia related to sodium valproate is a rare but serious condition whereby an individual may present with very severe cognitive difficulties resembling advanced dementia but caused by drug toxicity.

Epilepsy surgery is increasingly recognised as a viable treatment for carefully selected people with medically intractable epilepsy (Jehi et al, 2022) but is often associated with a cost when it comes to cognitive function (Baxendale, 2020a). Postoperative deteriorations in memory and language functions are most frequently reported in patients who undergo temporal lobe resection, while changes in executive function and social cognition can result from resections of more anterior regions (Ljunggren et al, 2021). The nature and extent of postoperative decline depends on preoperative clinical and demographic variables, and can be accurately predicted before surgery (Busch et al, 2018). While prehabilitation can be implemented before surgery – using functions before they are lost to prepare patients for anticipated changes – these programmes are essentially palliative, reducing the impact of the impairment on everyday function (Baxendale, 2020b). In the adult population, surgically-induced cognitive impairments should, for the most part, be viewed as permanent, notwithstanding the improvements that are sometimes seen following the cessation of seizures and consequent reduction of medications in some cases.

Treatments for seizures are not the only factors that exacerbate cognitive difficulties in people with epilepsy. The seizures themselves disrupt cognitive function. Focal seizures with a loss of awareness (previously known as complex partial seizures) and generalised motor seizures (Fisher et al, 2017) are invariably associated with peri-ictal cognitive disturbance and amnesia for the events that occurred during the seizure. Cognitive functions can take some time to return to baseline following a seizure, with some patients experiencing long periods of postictal disturbance. Nocturnal seizures can disrupt memory consolidation during sleep and lead to losses from the autobiographical memory store over time. Subclinical electroencephalogram discharges can also have a significant impact on attention and the encoding of new information, leading to significant and unpredictable fluctuations and variations in cognitive function over the course of a day or longer time period.

Cognitive difficulties are further compounded by the other primary comorbidities of epilepsy, particularly anxiety and depression. Both are very common in epilepsy, with estimates as high as 40% of people with epilepsy experiencing elevated levels of anxiety (Pham et al, 2017) and one in four experiencing depression (Fiest et al, 2013). Depression has a bidirectional relationship with epilepsy (Kanner et al, 2012) and can have a very significant impact on cognitive function in this group, exacerbating difficulties that are already compromised as a result of the factors discussed above, with memory, attention and language functions being particularly vulnerable. Similarly, high levels of anxiety are associated with increased difficulties with attentional control and working memory (Robinson et al, 2013).

When does cognitive impairment manifest in epilepsy?

The onset of cognitive impairment in epilepsy and the subsequent trajectories of cognitive decline in this group is very varied (Figure 3). For some, the underlying pathology that

Key points

- Cognitive difficulties are common in people with epilepsy and are often another symptom of the underlying pathology that is responsible for the seizures. They are an essential comorbidity of the disease.
- These difficulties can be further exacerbated by treatments aimed at seizure control.
- Different factors drive subjective complaints of cognitive impairment and objective measures of impairment on psychometric tests.
- The trajectories of cognitive impairment in epilepsy are heterogenous and dependent on the interactions of a number of biopsychosocial factors for each individual.
- While specialist neuropsychological evaluation is the gold standard in the assessment of cognitive impairment in epilepsy, all clinicians involved in the care of this group play an important role in psychoeducation, helping the patient and their family to understand the complex nature of these difficulties.

eventually leads to seizures will have had an impact on the development of cognitive function long before the onset of seizures (Baxendale et al, 2013). In these patients cognitive impairment is often present at the onset of seizures, before the instigation of any treatments and the impact of seizures themselves on cognition (Taylor et al, 2010). Subsequent decline in cognitive function in adulthood may follow the same gradient as those without epilepsy (Elger et al, 2004), but these people will hit the level at which impairments become problematic earlier than their peers. Others may demonstrate a stepwise pattern of deterioration in response to epilepsy related phenomena, such as head injuries sustained in seizure-related falls or periods of status epilepticus. A minority of people with epilepsy demonstrate accelerated decline over time at a much steeper gradient than their peers. This patten is typically seen in those with frequent generalised convulsions (Thompson and Duncan, 2005) or other neurological comorbidities, particularly those with a vascular basis. Superimposed upon these individual trajectories are the factors that can exacerbate impairments in function, including (but by no means limited to) treatment effects, mood related factors, including anxiety and low mood, and menopause in women.

A comprehensive, specialist neuropsychological assessment can help to delineate the contribution of each of these factors when someone with epilepsy presents in the clinic with cognitive complaints. However, even in the absence of these specialist assessments, careful questioning at the bedside or in the clinic can help to identify some of the factors that may be contributing to reported difficulties. In the majority of cases, therapeutic input will involve a combination of psychoeducation about the causes of cognitive difficulties in epilepsy and acceptance that many of these issues are part of the condition, before the implementation of any targeted neurorehabilitation (Baxendale, 2020b).

Conclusions

Cognitive difficulties are common in epilepsy. Up to 50% of people with the diagnosis demonstrate clinical impairments on standardised tests or report that memory difficulties are a significant nuisance in their everyday life. These difficulties are multifactorial in their aetiology. Many intrinsic and extrinsic factors influence the trajectories of cognitive development and decline across one's lifespan. Developing an understanding and acceptance that cognitive difficulties are an essential comorbidity of epilepsy is an important first-step in the amelioration of these difficulties in this population. Effective treatment of other comorbidities, particularly depression and anxiety, may lead to a reduction in subjective complaints, while training in the use of strategies, outsourcing and social support can reduce the impact of cognitive difficulties on everyday function.

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Conflicts of interest

Sallie Baxendale has received speaker honoraria from UCB Pharma, Neurodiem and International Medical Press for her participation in their educational programs for epilepsy professionals. She is currently the chair of the International League Against Epilepsy Diagnostic Methods Commission and serves on the Board of Governors for the International Neuropsychological Society.

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