

Impact of Fixed and Dynamic Factors on Cognitive Ability in Epilepsy

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Annotation: Epilepsy is a major public health problem. Several studies suggest a significant influence of epilepsy and its treatment on the dynamic and functional properties of brain activity. Epilepsy can affect mental development, cognition and behaviour. Patients with epilepsy may have reduced intelligence, attention and problems with memory, language and frontal executive functions.

Keywords: Cognition, epilepsy, mechanisms, neurotransmitters, fixed factors, dynamic factors

Introduction.

Epilepsy is a common, dynamic neurological disorder with an estimated prevalence of approximately 1% [1]. In clinical practice, when managing patients with epilepsy, most neurologists aim to control seizures and select specific antiepileptic drugs based on clinical experience. However, epilepsy is a complex condition. Seizures are just one aspect of epilepsy. Patients with epilepsy may have medical, metabolic [2,3], neuroendocrine [4], and cognitive and behavioural problems [5,6] that can affect their overall quality of life. Neuropsychological, functional and quantitative neuroimaging studies have shown that epilepsy affects the brain as a whole. The mechanisms underlying cognitive dysfunction in epilepsy are poorly understood. Cognitive impairment in epilepsy may be transient, persistent or progressive. Transient cognitive impairment may occur in paroxysmal focal or generalised epileptic discharges, whereas epileptogenesis-related neuronal plasticity, reorganisation, sprouting and disruption of cellular metabolism are fundamental factors determining progressive cognitive impairment. Antiepileptic drugs (AEDs) also have differential, reversible and sometimes cumulative adverse cognitive effects. In addition to reducing neuronal excitability, AEDs can impair neuronal excitability and the release of neurotransmitters, enzymes and factors critical for information processing and memory.

The cognitive comorbidity associated with epilepsy is supported by clinical [7], experimental [8], pathological [9], psychological [10], physiological [11] and imaging studies [12]. Patients with epilepsy may experience problems in several cognitive domains, such as reduced intelligence, attention, memory, language and frontal executive function [5], regardless of the side or location of the lesion [13].

The association between epilepsy and poor cognitive performance, learning and long-term memory is associated with a number of both immutable and dynamic factors. Immutable factors include genetics, underlying brain lesion [14], location and side of structural brain lesion [15], age of onset [16] and duration of epilepsy [17]. Dynamic factors include seizure frequency [18], ictal and interictal transient focal or prolonged electroencephalographic (EEG) epileptic disturbances [19,20], adverse effects of antiepileptic drugs [21] or surgery [22], and psychosocial factors [23,24].

Cognitive aspects of epilepsy

Cognitive function is defined as the ability to work meaningfully with information from the world around us. It involves the mental activity of thinking, learning and remembering. It is the mental process of acquiring knowledge and includes aspects such as awareness, perception, reflection and decision making. Patients with epilepsy have an increased risk of developing cognitive impairment. Memory diffusion is the most common subjective complaint in patients with epilepsy and is also determined by objective measures. Neuropsychological areas at risk include attention, short-term memory and cognitive information processing.

In addition, changes in EEG peak frequency observed on quantitative occipital EEG correlate with subjective cognitive complaints.

Correlation of cognitive ability with static and dynamic factors in epilepsy

The incidence of cognitive dysfunction in epilepsy is difficult to estimate. According to community studies, approximately 26.4-30.0% of children with epilepsy show evidence of subnormal global cognitive function or mental retardation at first diagnosis, with lower school performance [10]. Attention and memory problems are seen in about 30% of newly diagnosed and untreated patients with epilepsy with one or more seizures of cryptogenic origin.

Cognitive problems in epilepsy are associated with a number of invariant and dynamic factors. Invariant variables include genetics, underlying brain lesion [14], type of epilepsy, location and side of brain lesion [15,18], aetiology of epilepsy, age of onset [16,30] and duration of epilepsy [17]. Dynamic variables include uncontrolled seizures in the epileptic mother [41], seizure frequency and severity [17], ictal and interictal transient focal or prolonged epileptic discharges [19,20], side effects of antiepileptic drugs [21] and psychosocial variables [23,24]. In some patients with epilepsy, many of these factors are interrelated and interdependent, making it difficult to clearly define the relative contribution of one or another (e.g., cognitive impairment in epilepsy occurs regardless of patient age, type and duration of epilepsy, or comorbidities). Limited research suggests that the offspring of mothers with epilepsy may be at increased risk of problems such as prematurity, low birth weight, brain malformations, dysmorphic features and cognitive impairment. An inherited predisposition to abnormal brain activity explains 30-50% of the phenotypic IQ variance in children born to mothers with epilepsy. Koch et al. found abnormal adhesive activity in children born to mothers with epilepsy. Case reports have clearly documented that maternal prolonged seizures and status epilepticus (ES) pose a serious risk to both mother and fetus; however, results from cohort studies, which mainly included mothers with generalised tonic-clonic seizures (GTCS), were inconsistent. Adab et al. found in their retrospective study that verbal IQ in children of women with epilepsy was significantly related to the number of seizures experienced during pregnancy, with a significant reduction in IQ observed in children (17% of the total) who had more than four GTCIs. Uncontrolled maternal GTCIs increase the risk of perinatal anoxia, placental abruption, preterm delivery, intracranial haemorrhage or even death. These risks are high when seizures progress to SE. In addition, the offspring of mothers with epilepsy are vulnerable to the teratogenic effects of AEDs and the social and family conditions associated with having a chronically ill mother.

Cognitive and behavioural functioning in patients with epilepsy is an important area at different ages. Previous studies have reported that the onset of seizures before the age of 14 years is a risk factor for cognitive impairment. Controlled studies have shown significant impairment in neuropsychological function in children and adolescents with chronic epilepsy. However, recent studies have shown that adverse cognitive effects, even progressive cognitive decline, may occur in older adults with chronic partial or generalised seizures. In some studies, adults with epilepsy before AED treatment have shown poor performance on some cognitive tasks, especially tests of visuomotor tasks, motor coordination, mental flexibility and memory. It is possible that epilepsy accelerates general age-related changes, leading to uncertain and understudied outcomes in older adults.

Some studies have found more cognitive problems in patients with generalised seizures than in those with partial seizures, while others have found the opposite. Complaints of memory problems are common in patients with temporal lobe epilepsy (TLE), where memory-related brain structures are directly involved in seizure activity. TLE is associated with more memory impairment than extratemporal epilepsies, and both epilepsies have more memory impairment than those associated with generalised epilepsy. Frontal lobe epilepsy is associated with executive function deficits. However, recent case-control studies have shown that patients with both generalised and localised epilepsy can perform poorly on tests of memory function as well as tests of intelligence, language and executive function, suggesting that cognitive dysfunction is not limited to tasks associated with limbic functions represented in the hippocampus, amygdala or piriform cortex, but extends to different brain regions. The type and location of epilepsy are also important determinants of the degree and type of cognitive impairment. Patients with secondary generalised seizures show more marked

impairment of concentration and mental flexibility than patients with complex partial seizures. Delayed word recall problems have been observed in newly diagnosed partial seizure patients prior to medication. VE is associated with cognitive impairment in confrontation naming, visual memory, verbal memory and motor speed. VE affects declarative memory systems (i.e. episodic memory, including contextual, autobiographical information, and semantic memory, including abstract knowledge), whereas non-declarative learning (e.g. procedural learning) remains more or less unaffected. Episodic memory, in turn, depends on hippocampal function. Semantic performance is clearly related to the language dominant hemisphere, as expressed in language-related tasks (e.g. semantic fluency, naming and vocabulary). Verbal-oriented problems are specifically involved in left-sided epileptogenic foci. In left-sided RE, verbal episodic memory (e.g. recall of a word list), long-term verbal associations, recall of semantically related verbal information, learning speed and delayed memory with deficits in verbal information consolidation are particularly impaired. Visual-constructive memory deficits have been found in patients with right-sided VE. Silva et al. found that epileptic patients with mesial temporal lesions had poor cognitive performance in the areas of concentration, memory, language and everyday problem solving, whereas patients without lesions showed more compensated cognitive performance, except for mild attentional changes. Some cross-sectional cohort studies have reported an association between cognitive impairment and smaller hippocampal volume in RE (58). Reduced hippocampal volume has been associated with longer duration of epilepsy and is considered both a marker and a predictor of cognitive decline in patients with epilepsy. However, recent quantitative volumetric magnetic resonance imaging (MRI) studies have confirmed the presence of volumetric abnormalities in temporal and extratemporal regions, consistent with the generalised cognitive impairment associated with early localised epilepsy syndromes such as VE. Abnormalities were found in the amygdala, fornix, entorhinal cortex, parahippocampus, thalamus and basal ganglia, cerebellum and whole brain. Herrmann et al. found a decrease in total cerebral white matter volume, an increase in total cerebrospinal fluid volume and a decrease in grey matter volume both ipsilateral and contralateral to the side of temporal lobe seizure onset. In a prospective study by Liu et al, a longitudinal follow-up of 122 patients with chronic epilepsy, in which serial MRI scans were obtained at 3.5 year intervals, new focal or generalised neocortical volume loss was detected in 54% of patients with chronic epilepsy and in 39% of patients with newly diagnosed epilepsy. Seidenberg et al. reported bilateral thalamic volume reduction in chronic unilateral VE. Thalamic atrophy correlated significantly with cognitive, memory and non-memory scores. Rzezak et al [13] found frontal lobe dysfunction in children with VE, with worse scores in children with mesial VE, early onset, longer duration and use of polytherapy. The authors suggested that epileptogenic activity in the temporal lobe affects extratemporal areas mediating attention and executive function. Guimaraes et al. conducted a comprehensive neuropsychological assessment in a population of children with TLE, including IQ, direct numeracy, Traceability Test for Children Part B, Wisconsin Card Sorting Test, Block Design, Boston Naming Test, fluency, and a broad assessment of memory and learning, including visual learning, verbal memory, visual memorisation, delayed recall of verbal learning, delayed recall of stories, and recognition of stories. The authors found that there are several neuropsychological deficits in TLE, despite a normal IQ. The authors conclude that there may be abnormalities in brain regions other than the temporal lobe in TLE, particularly in the frontal lobes. In addition, a generalised reduction in brain volume is observed in children with mixed seizures and focal temporal and frontal lobe epilepsy, which are associated with neurodevelopmental delays. Branching networks and connections between cortical areas are thought to contribute to widespread cerebral atrophy distant from the presumed epileptic focus. Functional MRI studies have shown that retrieval of information from working memory is associated with activation of the dorsolateral frontal cortex. Other cortical and thalamic areas are also activated, including the anterior cingulate cortex, which is associated with executive function, and the posterior parietal cortex, which is associated with attention. Results from volumetric quantitative MRI studies are consistent with a general decline in neuropsychological functions, including intelligence, language, visual perception, memory and executive function in the same group of patients studied. Cross-sectional and longitudinal studies of cognitive changes in epilepsy show that longer duration of epilepsy is associated with impairment in many cognitive domains [17]. Cognitive impairment is more common in symptomatic and cryptogenic epilepsy than in idiopathic epilepsy. Mood states in people with epilepsy may be an additional factor affecting cognitive function. People with epilepsy who suffer from depression may experience a double burden of cognitive

impairment. Seizures at school or work can lead to poor self-image and reduced social interaction. The stigma of epilepsy and learning difficulties can lower the expectations of parents and teachers. Reduced expectations can have a negative impact on academic effort and therefore academic performance. School failure, intellectual disability, reduced educational attainment and possible mental retardation are long-term consequences in children with epilepsy, whereas low functional status, reduced educational attainment, low employment and poor quality of life are long-term consequences in adults with epilepsy [17,18].

Conclusion: The mechanism of cognitive impairment in epilepsy is complex. Negative effects on cognition may be manifested by the presence or absence of clinically significant seizures, convulsive or non-convulsive SE occurring during wakefulness or sleep, and may result from focal or generalised EEG epileptic discharges in the absence of epileptic symptoms. Cognitive impairment associated with epilepsy and epileptic EEG discharges may be transient, persistent or progressive [6].

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