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The impact of epilepsy on brain structure and function

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Abstract

Epilepsies are disorders that are characterized by the dysfunction of brain neural network integrity, leading to alterations in physiological interactions and the possible emergence of pathological neural networks. Various mechanisms may be associated with these network changes in epilepsy, including the recurrence of abnormal synchronous neuronal activity during seizures or interictal discharges. Factors such as the underlying etiology, stage of neurodevelopment at which these alterations occur, and use of antiseizure medication are also pivotal contributors to these abnormalities. Additionally, neural network alterations in epilepsy may have a significant correlation with the clinical phenotype, contributing to the unsatisfactory response to pharmacological treatment and the frequent occurrence of neuropsychiatric comorbidities within these patients. This study reviewed structural and functional brain network changes in epilepsies, their relationship with specific phenotypes, and their potential impact on the neurodevelopment of children and adolescents.

Keywords: Neural network, comorbidities, neurodevelopment, clinical phenotype.

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Introduction: brain damage and epilepsy

Epilepsies are brain network disorders with abnormal connectivity, which explains the seizure semiology and common comorbidities that are associated with these conditions [1]. Therefore, epilepsy can be defined as a dysfunction in the integrity of brain neural networks, leading to changes in physiological interactions and the possible emergence of pathological neural networks [2]. The advent of magnetic resonance imaging (MRI) and the development of specialized computer programs and algorithms have confirmed that diffuse brain damage occurs in patients with epilepsy [3, 4]. When compared with the brains of healthy individuals, individuals with epilepsy have a network of subtle but consistent structural and functional brain damage [5, 6]. Recently, the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium confirmed the presence of structural gray and white matter damage through brain MRIs of over 2000 individuals [7]. Furthermore, ENIGMA-epilepsy not only confirmed brain structural damage in patients with epilepsy but also identified its variability based on the type of epilepsy [7]. Moreover, the impact of white matter-damaged brain networks may be even more significant in early-onset epilepsies [8].

Functional damage also occurs in epilepsy patients, as studies have shown that brain activation and deactivation networks are associated with interictal or ictal discharges and the dysfunction of long-distance cognitive brain networks [6, 9]. This diffuse functional and structural brain damage, as detected through neuroimaging, supports the clinical and neuropsychological understanding that epilepsy negatively affects both the development and maintenance of cognition to varying degrees in distinct epilepsy syndromes [10].

Structural and functional changes in neural networks in epilepsy may be attributed to numerous mechanisms, including the recurrence of abnormal synchronous neuronal activity during seizures or interictal discharges [11, 12]. However, the underlying etiology, stage of neurodevelopment at which these changes occur, and other factors, such as the use of antiseizure medications, likely also play significant roles in these abnormalities [13, 14]. Additionally, changes in neural networks in epilepsy possibly have a significant relationship with the clinical phenotype, contributing to an unsatisfactory response to pharmacological treatment and the presence of neuropsychiatric comorbidities.

Consequently, the following sections of this manuscript reviewed the data on the impact of abnormal structural and functional brain networks on the neurodevelopment of children and adolescents with epilepsy and their association with specific phenotypes and epileptic syndromes.

Epilepsy and brain development

Children who experience the onset of epilepsy in the first years of life are at a heightened risk of neurodevelopmental delays, learning disorders, or intellectual disability. Studies have indi-

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cated that cognitive comorbidities are prevalent in 28% to 38% of children with epilepsy [15]. Multiple factors potentially contribute to these neurodevelopmental delays, including the underlying etiology, epileptic seizure frequency, adverse effects of antiseizure medications, and the social impact of epilepsy. Notably, the cognitive and behavioral comorbidities in children with epilepsy have a significant impact on their quality of life, often surpassing the impact of the epileptic seizures themselves [15].

Regarding the influence of epileptic seizures on brain development, most of the current knowledge is derived from animal models. It is established that during the first months of life, there is a progressive increase in the formation and maturation of synapses, which gradually organize into diffusely distributed neural networks. While genetic factors strongly influence the formation of synapses and the organization of neural networks, extrinsic factors also play a role [16]. Paradoxically, results from animal models indicate that the brain in the first years of life is less susceptible to neuronal loss and hippocampal injury following prolonged seizures than adult brains. Nevertheless , recurrent seizures can reduce neurogenesis, leading to the morphological alteration of dendritic spines and changes in the distribution of the glutamatergic receptors [16]. Consequently, the influence of epilepsies on the developing brain is associated with a "brain-epilepsy paradox." Children have significantly higher brain plasticity than adults, and the brain adapts to various insults. The earlier the insult occurs, the better the plasticity. However, it is possible that recurrent seizures at an early age, when brain plasticity is at its peak, can impair brain development due to an increase in abnormal connections and oligodendroglia disorganization [16].

Neuroimaging studies have shown that epilepsy onset during the first decade of life is associated with more severe gray and white matter brain abnormalities [13, 14]. Similarly, neuropsychological studies have indicated that intelligence quotient (IQ) scores may decrease in children with epilepsy [10]. Therefore, epilepsy negatively impacts the maturation of cognitive functions in children [10]. Additionally, irrespective of cognitive impairment, children with epilepsy tend to exhibit lower academic performance than their age-matched controls, and these difficulties may manifest shortly after the diagnosis of epilepsy or even precede it [17].

Cognitive alterations in children and adolescents with epilepsy vary widely, with some individuals with chronic epilepsy experiencing minimal impact on cognition and others having severe intellectual deficits and behavioral changes. Among the several factors that are potentially associated with these comorbidities, the cognitive profile of children with epilepsy appears most strongly linked to the underlying etiology and the age at seizure onset [10]. Additionally, the presence of neuropsychological abnormalities in children with self-limited childhood epilepsies, where mean scores for memory, visual perception, verbal fluency, and fine motor function are lower than those of children without epilepsy, provides further evidence that factors other than seizures impact cognitive function in children [18].

Regarding white matter in childhood epilepsies, the corpus callosum is the most significantly affected structure, and this damage may potentially predate the initial diagnosis. The integrity of the corpus callosum plays a crucial role in the proper execution of cognitive functions, with its dimensions exhibiting a positive correlation with IQ [19]. Children with newly diagnosed idiopathic generalized and non-lesional focal epilepsies had microstructural alteration in the corpus callosum and cingulate, without concomitant changes in the macrostructure of the white and gray matter [20]. Moreover, a volumetric reduction in the corpus callosum has been noted in adults with temporal lobe epilepsy with seizure onset in the first decade of life but not in those with a later onset of epilepsy [21]. Furthermore, many studies have consistently demonstrated the possible impact of epilepsy on brain maturation. For example, Hermann et al. demonstrated that despite the absence of abnormalities in the volume of white and gray matter in children with newly diagnosed epilepsy, the correlation between cognitive development and brain volume, which normally occurs in controls, was altered [17]. Longitudinal studies further support the negative role of epilepsy in brain development. For instance, Tosun et al. demonstrated in a two-year prospective evaluation that there was slower white matter expansion and an abnormal pattern of gray matter volume increase in children newly diagnosed with epilepsy [22].

The functioning of large-scale cognitive brain networks is also affected in children with epilepsy. The default mode network (DMN), a large-scale brain network comprising highly connected regions, exhibits activity during wakeful rest and heightened activity during introspection or self-referential thinking. These regions include the medial prefrontal cortex, posterior cingulate, inferior parietal lobe, lateral temporal cortex, and bilateral hippocampus [23]. Alterations in the functional connectivity of the DMN have been described in children with distinct types of epilepsies, both with pharmacoresistant seizures or self-limited evolution [24, 25, 26]. Notably, abnormal DMN connectivity is also present in distinct types of neuropsychiatric disorders [27, 28], demonstrating that it must be a common and early pathway of brain disturbance.

Most studies evaluating brain damage in children with epilepsy have included individuals with chronic conditions and antiseizure medication. However, some researchers have had the opportunity to evaluate children with newly diagnosed epilepsy and, occasionally, epilepsy without the use of medication. These studies have yielded contrasting results, with some reporting volumetric brain changes and others not observing such changes [17, 29]. Notably, the presence of brain abnormalities in children with newly diagnosed epilepsy is significantly more subtle than those that are observed in adults, even when comparing the same etiology [30].

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Brain functional abnormalities and phenotypes: the epileptic syndromes

When examining specific epilepsy syndromes and brain abnormalities, most studies have been conducted on self-limited epilepsies, especially self-limited epilepsy with centrotemporal spikes (SeLECTS). Structural MRI studies of SeLECTS have shown either decreased cortical thickness in the perisylvian region [31] or an increase in gray matter volume within the frontoparietal regions [32]. Additionally, studies have revealed reduced connectivity between the motor networks and the frontostriatal circuit and between the DMN and language areas [32]. Functional neuroimaging studies have also suggested that interictal epileptiform activity interferes with cognitive functioning in SeLECTS, which was previously questioned by clinical studies [33, 34]. In childhood absence epilepsy, concomitant electroencephalogram and functional fMRI (EEG-fMRI) studies of generalized spike-and-wave discharges (GSW) have consistently shown thalamic activation and both activation and deactivation in cortical regions during the discharges. Moreover, a negative hemodynamic response, potentially indicating suppression of neuronal activity, occurs time-locked to the discharges in the DMN [35].

This demonstration of DMN deactivation during GSW was the first step in understanding how epileptiform discharges can compromise normal brain function and contribute to the phenotype of a lapse of responsiveness [35]. Interestingly, although thalamic activation during GSW is consistent, the presence and localization of cortical activation vary among patients, and GSW does not consistently adhere to the frontocentral predominance that is usually seen in electroencephalograms (EEGs). However, in the same patient, the whole-brain hemodynamic response, including cortical activation, is consistently reproducible in different generalized complexes [36]. Additionally, the hemodynamic response to GSW is not only consistent across studies but is also unaffected by factors such as age, epilepsy duration, or the use of antiepileptic drugs . In patients with drug-naive epilepsy patients, the hemodynamic response to GSW is similar to that in patients receiving medication [37].

Developmental and epileptic encephalopathies (DEEs) are a group of disorders in which both the underlying cause of epilepsy and the ictal and/or interictal epileptiform activity may contribute to behavioral and cognitive impairment [38, 39]. Despite the existence of electroclinical syndromes that are specifically associated with cognitive impairment resulting from seizures, such as infantile epileptic spasms syndrome (IESS), the deleterious effects on the development and cognition of epileptic seizures can be associated with any form of epilepsy [40]. However, not all severe cognitive alterations in individuals with epilepsy are due to seizures. In some encephalopathies linked to epilepsy, an underlying disease is responsible for both the occurrence of epileptic seizures and the resulting impact on cognition and neurodevelopment [38, 41]. Thus, the term DEE refers to children with severe early-onset epilepsies, where neurodevelopmental alterations can be attributed to the underlying cause and the effects of uncontrolled epileptic activity [39].

Over the past decade, genetic and neuroimaging studies have provided a greater understanding of the role of underlying disease mechanisms and their relationship with epileptic activity in DEEs, particularly in cases with severe cognitive impairment and behavioral abnormalities [42, 43]. Nevertheless, despite the knowledge that has been accumulated over the last two decades on the phenotypic characteristics, natural history, and underlying etiologies of DEEs, the understanding of the mechanisms that are associated with neurodevelopmental disorders remains incomplete. For instance, some researchers justify that in DEEs, diffuse brain alterations lead to a failure in thalamocortical communication, resulting in secondary dysregulation of “cortical tone” or dysfunction of the interneurons, with increased cortical excitability [44]. More recently, new advances in understanding the pathophysiology of DEEs have emerged from structural and functional neuroimaging studies and the concomitant evaluation of electroencephalographic changes and functional brain abnormalities within these syndromes. Neuroimaging studies have contributed to the hypothesis that epileptic discharges cause transitory effects on information processing in the brain and inhibit some distant brain areas in the long term [45]. Currently, only a few studies have described the specific neural networks underlying DEEs [46, 47], but new hypotheses regarding the cognitive deficits that are associated with the phenotype are continuing to proliferate.

Regarding specific DEE syndromes, the most comprehensive studies to date on brain mechanisms that are associated with epileptic encephalopathies include patients with Lennox-Gastaut syndrome (LGS). In this specific type of DEE, studies suggest that epileptic activity interferes with the functioning of neural networks, and this is reflected in both the phenotype and cognitive and behavioral comorbidities [48]. Findings from studies on adults with LGS suggest that epileptic activity can lead to dysfunction of the associative cortical areas and interfere with the proper functioning of neuronal networks, such as the attention network and the DMN. Another hypothesis posits that these changes in the proper functioning of neural networks are secondary to epileptic activity in a developing brain in the first years of life [49]. In contrast, in children with LGS, interictal epileptiform activity appears to be associated with brainstem and thalamus activation independently of the type and distribution of these discharges [50]. For example, Pillay et al. showed, in a group of adult patients with LGS, that the hemodynamic responses to EEG patterns manifest as distinct types of discharges that are characteristic of LGS. They demonstrated that while paroxysmal fast activity shows increased hemodynamic responses in the thalamus, brainstem, and specific cortical regions, mainly the associative cortex, GSW shows decreased hemodynamic responses in the primary cortical regions, such as the motor and visual cortex [51].

The EEG-fMRI analysis of infants with IESS showed that the interictal epileptiform discharges in these children presented with neocortical activations in the cerebral regions consistent with the spike distribution in the EEG [52]. More interestingly, the occipital activations were present in all the infants, irrespective of concomitant occipital epileptiform discharges in the EEG

or occipital lesions that were detected via a structural MRI. Regarding the slow waves of hypsarrhythmia, there was a positive correlation between the EEG delta power and the activity in the brainstem, thalamus, putamen, and different cortical areas, mostly in the frontal and parietal regions. Overall, these results agree with previous findings of metabolic changes in the different cortical and subcortical regions, including the putamen and brainstem, in children with IESS [52]. Moreover, they corroborate the significant involvement of the posterior cortex in IESS and hypsarrhythmia [53]. Among the hypotheses regarding the pathogenesis of IESS, it is postulated that epileptic spasms result from abnormalities in descending and ascending brainstem projections with abnormal function in the raphe striatal pathways, which are possibly triggered by focal or diffuse cortical abnormalities. Accordingly, Siniatchkin et al. demonstrated that high-voltage slow waves are a hypsarrhythmia electrographic pattern that is possibly associated with the pathogenesis of IESS [53].

In DEE with spike-and-wave activation during sleep (DEE-SWAS), EEG-fMRI studies have identified activation in the perisylvian region, insula, and cingulate gyrus during spikes in the neuronal networks [54]. These findings confirm previous evidence supporting the involvement of the perisylvian region in DEE-SWAS. The study also revealed that spikes have different cortical generators but share a common pattern of propagation involving the perisylvian region. Moreover, other brain regions that are involved during these discharges, such as the prefrontal cortex and cingulate, may also contribute to the complex neuropsychological disturbances in these patients [54].

Conclusion

Individuals with epilepsy have a network of structural and functional brain abnormalities. Early-onset epilepsy impacts brain development and leads to worse cognitive outcomes, possibly resulting in abnormal white matter development and disrupted patterns of connectivity. The precise effects of seizures and the underlying etiology within each type of epilepsy are still not fully understood. While abnormal structural and functional networks can explain the clinical phenotype, they are not specific markers of a particular epileptic syndrome. The overlap of phenotypes in epilepsies with distinct etiologies might be attributed to the occurrence of specific abnormal networks. The accumulated knowledge that was presented in this review can provide us with a basis for further research on how to prevent or reduce brain damage in children with early-onset epilepsies.

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Competing interests

The author has no competing interests to declare.

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