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Research Article

The Thinning Brain In Pediatric Epilepsy: A Systematic Review on Cortical and Sub-Cortical Thickness Alterations

Short Title: Cortical Alterations In Epilepsy

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ABSTRACT

Background: Epilepsy is a common neurological disorder in children, resulting in morphological changes in the brain and its different regions. This systematic review aimed to examine the recent articles regarding epilepsy-related cortex changes to look for a pattern of cortical changes in the brain.

Methods: This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and the principle of non-bias was respected. All the articles from 2020-2022 were extracted from the Web of Science, PubMed and Scopus databases. Subsequently, sleep disorders and alterations in the anatomy of cortical and gray matter in children up to 18 years were identified and documented.

Results: Eight studies established inclusion criteria encompassing breathing disorders, obstructive sleep apnea and periodic sleep disorders. The mean age of the children involved in the studies was 11.45±1.01 (P=0.4) for generalized epilepsies and 11.49±0.831 (P=0.5) for focal epilepsies. Notable findings included reduced cortical thickness in the frontal lobe and the right hemisphere in cases of generalized epilepsy. Conversely, in the absence of epilepsy, an observed increase existed in cortical thickness in both the right and left hemispheres. Reduced cortical thickness was reported in each type of focal epilepsies. Additionally, both types of epilepsy are associated with a significant decrease in cortical volume compared to healthy individuals.

Conclusion: The volume and thickness of the cortex and sub-cortical areas change during epilepsy in children. Depending on the type of epilepsy, these changes are different. Changes in the cortex in different brain areas are reduced in focal epilepsies. The changes followed a punctate pattern, with each point of involvement showing a different response to the seizure.

Keywords: Epilepsy, Cortical Thickness, Pediatric, Focal Epilepsy, Cortical Volume

1. Introduction

Epilepsy is characterized by chronic convulsive attacks, revealing the involvement of brain lobes and changes in central and peripheral nerve function[1]. Focal epilepsies are mainly confined to a specific part of the brain, meaning they can spread from one point to another. Focal epilepsies have the potential to spread in the brain tissue, in which case the second type of epilepsy is known as generalized epilepsy[2]. Seizure is generally

classified as generalized or focal, where generalized seizures involve the entire cerebral hemispheres[3]. In the context of epilepsy pathology, the initiation of seizures is typically linked to an external factor. In pediatric cases, a significant contributor is the elevation of body temperature accompanied by fever[4], which can trigger convulsive episodes. If these episodes persist over time, they may ultimately result in developing epilepsy. Genetic predispositions are indeed influential in the manifestation of epilepsy; however, brain injuries, stemming from trauma or surgical interventions and inflammation within brain tissue are recognized as key contributors to the disorder. Electroencephalography (EEG) serves as the primary diagnostic tool for epilepsy[5], complemented by other imaging modalities such as Computer Tomography (CT) and Magnetic Resonance Imaging (MRI)[6].

Epilepsy is one of the common neurological disorders in children that can have profound effects on the structure and function of the brain. Morphological changes in the brain in patients with epilepsy, specifically during development, are prominent due to the presence of abnormal electrical oscillations[7,8]. These changes include increasing or decreasing the volume of specific brain areas, changes in the thickness of the cortex and changes in sub-cortical structures[9]. Children with epilepsy may experience atrophy or enlargement of certain areas of the brain, which can be due to abnormal electrical activity or drug effects[10]. In addition, these changes may affect the child's cognitive and behavioral development and lead to learning and social problems[11]. A detailed examination of these morphological changes can help us to better understand the underlying mechanisms of the disease and how it affects brain development. Additionally, monitoring the thickness of the brain cortex in children with epilepsy is of particular importance because this characteristic can indicate the severity and type of epilepsy and be effective in predicting treatment results. Considering that the cerebral cortex plays a crucial role in information processing and cognitive functions, the analysis of changes in its volume and thickness can aid in identifying specific patterns of pathology in epilepsy[12,13]. Therefore, addressing these changes not only facilitates understanding the disease better but can also lead to the development of new and more effective treatment methods for children with epilepsy.

Unfortunately, the results of previous studies on changes in the cortex are different, making it challenging to decide. A significant lack of studies exists regarding cortical changes associated with all forms of epilepsy. However, a systematic examination has been conducted on cortical changes in Rolandic epilepsy, indicating that these changes are still poorly defined[14]. In light of this, the current study sought to investigate the alterations in cortical thickness across different types of epilepsy in children, with the research question formulated according to the Patient/Population, Intervention, Comparison, Outcomes (PICO) criteria.

2. Methods

2.1. Protocol and registration

This systematic study was performed based on the accepted criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Additionally, to comply with the principle of non-bias, this study used the Cochrane Manual for Systematic Reviewers 5.1.0 for clinical studies and reviewed the studies regarding allocation concealment, blinding of participants, study personnel and outcome assessors. The research question was based on Patient/Population, Intervention, Comparison, Outcomes (PICO) criteria.

2.2. Eligibility criteria and search strategy

We assessed published studies from January٢٠٢٠- to ٢٠٢٢ in databases such as Web of Science, PubMed and Scopus. epilepsy was defined based on the ILAE Classification of Epilepsies, based on this definition, which were completed based on International Classification of Diseases 11th (ICD-11). This systematic review has investigated the structural and morphological changes of the brain cortex and cortical thickness in children with epilepsy. Studies with the following characters were eliminated:

- review studies, case reports, letters to the editor
- studies that did not have open access and whose basic information was unavailable in abstract
- Non-English studies were excluded entirely.
- Studies that examined epilepsy after accidents, tumors or head trauma.
- Studies that examined gray matter volume and cognitive impairments after epilepsy surgery.
- Studies whose participant age range included cases above 18 were excluded. These studies only included children between the ages of one day and 18.
- All studies included neuropsychiatric, neurodegenerative, neuroautoimmune diseases and congenital cranial and spinal disorders.
- Studies that examined psychological (as: stress, anxiety, bipolar disorder, depression and etc.) disorders along with epilepsy were excluded to ensure that psychological disorders did not cause gray matter volume.
- Studies that investigated gray matter volume as a side effect of anti-seizure drugs were eliminated, these studies examined the side effects of drugs.

An examination of our title was conducted in the Cochrane Database to identify similarities and assess comparable systematic studies. Keywords were extracted from the MeSH database. Two teams, each comprising two members, performed independent searches across the databases, beginning with Web of Science and then extending to PubMed and Scopus, utilizing keywords related to epilepsy and cortical/gray matter changes in the brain. Following the PRISMA guidelines, duplicate and non-English entries were initially excluded, after which both teams screened the titles and abstracts. The co-author was provided with the articles that met the inclusion criteria to assist in compiling the studies. For articles without subscription access, they were reviewed under the supervision of the first author and the issue was resolved. In the end, eight studies were selected and the full texts of all these studies were assessed; however, no additional articles were found through manual citation searches.

2.3. Data extraction, study selection and methodological quality assessment

The first and corresponding author built the summary table, sizing up studies with Cochrane's risk of bias 2 (RoB 2)[15]. Three authors tackled data extraction epilepsy types, cortical/gray matter shifts, anatomy changes, cognitive links, average age, gender working solo, no chatter. Results faced dual review from

the first and corresponding author, sticking to Cochrane rules to cut bias and lock in reliability.

2.4. Processing

After eliminating all types of review studies, case reports and letters to the editor from the PubMed, Scopus and Web of Science databases, a two-member team removed duplicate titles and then screened their abstracts.

Initially, all studies examining gray matter and sleep disorders were selected and the AIM and CONCLUSION sections of each article were reviewed. Using this approach, approximately eighty-six studies were evaluated to exclude those that did not meet the criteria outlined in the methods section (exclusion studies). Subsequently, two authors independently conducted a thorough review of the remaining studies and extracted the necessary data. In total, twenty-six studies underwent full-text assessment **(Figure 1)**.

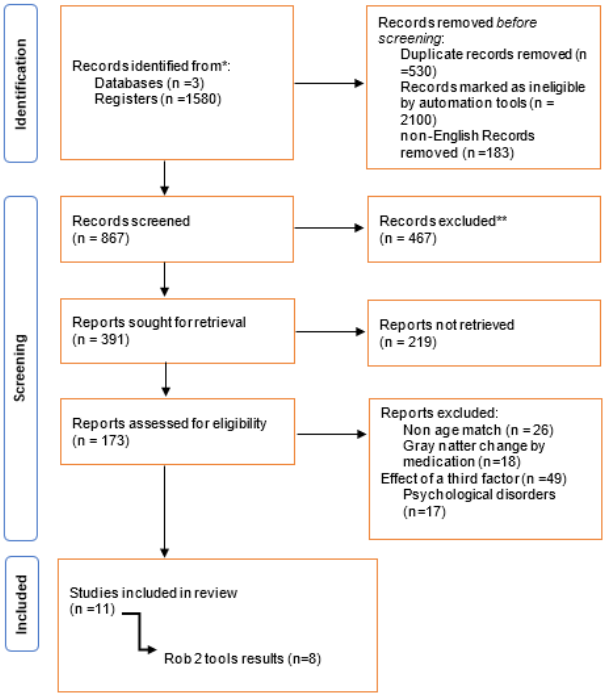

Figure 1: PRISMA 2020 flow diagram for systematic reviews.

After reviewing the full texts, eight studies focusing on the effects of neuropsychiatric disorders and treatment were excluded. Following an evaluation based on Cochrane's bias assessment guidelines for non-randomized clinical trials and Rob 2 analysis, three studies with a high risk of bias[16-18] were also excluded **(Figure 2)**. Ultimately, eight studies were included in our systematic review to address the research question.

2.5. Participants

The average age of children with general epilepsy was 11.45 ± 1.01. The number of boys (53%) suffering from general epilepsy was more than that of girls (47%). The disparity is minimized in focal epilepsies, resulting in a negligible difference between the two sexes. All studies mentioned referenced unanimously indicated that age does not play a role in the difference in the volume and thickness of the cortex in the course of epilepsy. However, the age mean of children with generalized epilepsy was higher than that of children with localized type. Generally, children with epilepsy at any age show morphologic changes in the cortex. Nevertheless, focal epilepsies at older ages are associated with a decrease in thickness loss; in other words, as age increases and brain tissue growth follows, the loss of thickness decreases. Notably, age does not play a role in thickness changes compared to healthy children, but at any age, children with epilepsy show less thickness than their healthy counterparts, although this thickness reduction may decrease with age.

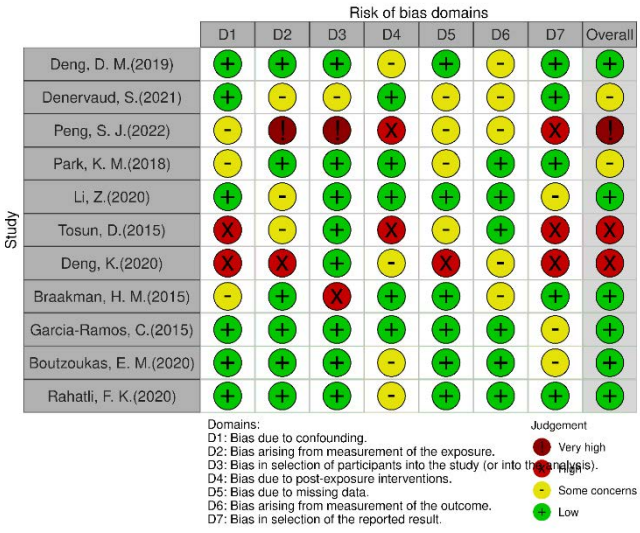

Figure 2: Rob 2 plot for our article. High and very high overall marks were removed.

2.6. Assessment tools

Two studies used MRI scans with a 3.0 T MR system and one used the T1-weighted technique. The measurement tools in focal and general epilepsies were the same.

2.7. Cortical thickness in general epilepsy

Myoclonic atonic seizure has generally reduced children's Cortical Volume (CV) and Cortical Thickness (CT). CV decreases in the frontal, temporal and parietal lobes and the cingulate gyrus. Reducing cortex thickness in the frontal lobe, right hemisphere, including precentral, Para-hippocampal, superior frontal, insula and caudal middle frontal cortex and in the left hemisphere, including superior frontal, precentral and fusiform cortex, left rostral middle frontal gyrus, was reported by studies in general epilepsy[19,20]. Park Kang Min also reported that the thickness increase in the cerebral cortex in the right hemisphere, including the lateral orbitofrontal and precentral cortex and in the left hemisphere, including the middle rostral frontal and the superior frontal cortex, is seen in Childhood Absence Epilepsy (CAE)[21]. This increase in Juvenile Absence Epilepsy (JAE) leads to the right hemisphere, including precuneus, postcentral, middle temporal, rostral middle frontal, inferior parietal, lateral orbitofrontal, supramarginal, inferior temporal and pars triangularis cortex; in the left hemisphere, including pars triangularis, middle temporal, precuneus, supramarginal, middle temporal, superior parietal, inferior parietal, rostral middle frontal, superior temporal, postcentral, caudal middle frontal and lateral orbitofrontal cortex.

2.8. Cortical thickness in focal epilepsy

In contrast to generalized epilepsies, all studies reporting focal epilepsies agreed on reduced cortical thickness. In point epilepsies, changes in the thickness and volume of the cortex were first directed to the area of the epileptic focus and then to the closely related areas. Children with Rolandic epilepsy show thickness reduction in bilateral frontal, temporal regions and limbic systems[22,23]. More precisely, the superior frontal gyrus, rostral middle frontal gyrus, pars orbitalis gyrus, medial orbitofrontal gyrus, precentral gyrus, fusiform gyrus, middle temporal gyrus in the bilateral hemisphere, Para hippocampal gyrus, temporal pole, pars opercular is gyrus, caudal middle frontal gyrus, caudal anterior cingulate gyrus, lateral occipital gyrus and insula in the left hemisphere, as well as superior temporal gyrus, paracentral lobule, inferior parietal gyrus, posterior cingulate gyrus and inferior temporal gyrus in the right hemisphere are the areas involved in this epilepsy. Frontal epilepsy thins the bilateral middle frontal gyrus, bilateral occipitotemporal and medial lingual gyrus, left subcallosal gyrus, left short insular gyrus and right long insular gyrus[24]. Supramarginal, paracentral and superior frontal gyri changes, as well as the parieto-occipital junction in children with left hemisphere focal epilepsy, are examples of widespread changes in epilepsies[25]. Whereas in another study, children with FLE showed changes only in the frontal region[26].

The volume of gray and white matter decreases in frontal epilepsy and the pattern of volume reduction follows the pattern of focal where thickness is reduced. Garcia-Ramos also states that putamen in Rolandic epilepsy shows increased volume bilaterally.

3. Discussions

The present study's results identify areas of cortex changes in both types of epilepsy in children. Depending on whether the epilepsy is focal or generalized, the cerebral cortex is associated with a reduction in thickness and volume in children with epilepsy. Although the sub-cortical areas may show a different pattern, such as an increase in the putamen volume, the changes in the cerebral cortex in both types of epilepsy follow a specific pattern.

In general epilepsies, a decrease in thickness and volume was observed, although one study reports an increase in thickness in some places in addition to the decrease. However, these findings can be explained by the general patterns of point changes observed in epilepsy. A comparative analysis of the changes highlighted in the studies reveals that the opposing changes do not entirely align, reflecting a variable response in different regions concerning epilepsy. This results in a pattern of point changes that contributes to inconsistent findings in adult studies. In the right hemisphere, alterations are observed in the precentral, Para hippocampal, superior frontal, insula and caudal middle frontal cortex regions, where a reduction in thickness occurs, while the lateral orbitofrontal region exhibits an increase. Notably, both increases and decreases were identified in the right hemisphere's precentral cortex, a phenomenon that can also be observed in the left hemisphere and several other areas. Although these studies used the same tool for their analysis, these changes may be attributed to the difference in their general epilepsy patterns. The observed increase in cortical thickness has been documented in cases of absence epilepsy, whereas a reduction in thickness is noted in myoclonic epilepsy. Conversely, in focal epilepsies, alterations have been similarly reported, typically indicating a decrease in both volume and thickness of the cortex. A noteworthy point in the studies is the change in the thickness of the cortex in areas other than the epileptic focus, which can be essential in managing epilepsy complications in children and the prognosis of subsequent disorders.

Reducing cortex thickness in adults with opercula-insular epilepsy is significantly evident in the regions of the orbitofrontal gyrus, rectus gyrus, olfactory cortex, cingulate gyrus and lateral frontal cortices[27]. Moreover, in TLE, cluster changes are evident in the left hemisphere in the caudal and rostral anterior cingulate, superior frontal, lateral orbitofrontal points and in parallel in the other hemisphere[28,29]. Although Curwood generally does not consider brain network changes related to cortical thickness changes in children, the obtained results were consistent with the thickness changes in adults[30]. Zelinski also states in a more recent study that the difference in thickness is not significantly evident[31]. However, these two studies examining anatomical and functional brain network changes clearly measured disorders resulting from brain morphological changes in the gyri and sub-cortical areas. Each of the brain components in the more extensive network is connected to each other to help regulate many functional and cognitive activities[32] and damage in each area results in behavioral and functional changes in the child. Epilepsy is associated with damage to nerves and brain tissue structure, which may be in the form of inflammation of cortical or sub-cortical areas (inflammation of the hippocampus and amygdala) or tissue disorders[33-35]. These alterations result in alterations to the anatomical networks formed by the interconnections within the brain structure. Ultimately, such damage can lead to morphological changes in the brain, which may subsequently induce alterations in the cortex[28]. Seemingly, the pattern of thickness changes in children and adults follows a specific adaptation, giving us an extraordinary prognosis to detect possible injuries in epilepsy. Moreover, in absence epilepsies, where disorders become more severe in the long term, examining the disturbed areas based on the mentioned pattern can be a key to rehabilitation both in childhood and adulthood.

The present results show that focal and general epilepsies affect different points and the affected areas may be different according to the pattern of epilepsy and other brain disorders. Evidently, age does not influence the pattern of changes and heredity does not contribute to this pattern[36]. Attention-deficit/hyperactivity disorder (ADHD) or neurodegenerative diseases may contribute to alterations in the thickness and volume of the cortex; however, if we exclude these factors, it is evident that each form of epilepsy exhibits a distinct pattern of cortical changes[37,38]. The obtained results showed that these disorders follow the pattern of point changes in cortical areas, which in turn cause disorders in brain networks that lead to cognitive and functional problems. epilepsy is associated with cognitive disorders, including intelligence and language skills[39], as well as disorders of the child's perception and understanding of the environment[40] and these changes in the volume and thickness of the cortex and sub-cortical areas justify these disorders. Knowing the pattern of point changes in types of epilepsy primarily requires the study of the community on the morphological changes in each of the epilepsy patterns, but it is considered a turning point in the control and prognosis of epilepsy.

Point changes, localized alterations at the cellular and molecular levels that occur in the brain after epileptic seizures[41]. These changes can provide insights into the mechanisms of epilepsy, its progression and potential therapeutic target seizures can stimulate neurogenesis, the generation of new neurons in specific brain regions such as the hippocampus[42]. However, this neurogenesis is often aberrant, with newly generated neurons integrating improperly into existing circuits, potentially contributing to hyperexcitability. Concurrently, seizures can lead to gliosis, the proliferation of glial cells (astrocytes and microglia), which can alter the extracellular environment and impair neuronal function[43].

Dendritic spines, which are critical for synaptic communication, may undergo morphological changes, leading to enhanced or weakened synaptic connections[44]. These alterations can create a hyperexcitable network, increasing the likelihood of future seizures. In the hippocampus, a common site of seizure activity, seizures can induce mossy fiber sprouting. This phenomenon involves the abnormal growth of axons from granule cells in the dentate gyrus, which form new synaptic connections with other neurons[45]. Our results show that epileptic stimulation will be different in each subcortical location and therefore the response to these synaptic changes will not be similar to each other and will be different in different locations.

Eventually, the present findings support the changes in the volume and thickness of the cortex in all types of epilepsy. This study extracted the details of the changes in different types of epilepsy and resolved the conflicting results. In order to justify the disorders, this review assumed the results were based on a pattern of point changes based on the epilepsy pattern. In this case, each area of the brain cortex may increase or decrease in thickness compared to the type of epilepsy, which leads to brain network disorders.

4. Conclusion

The brain cortex and sub-cortical areas in children with epilepsy are associated with thickness and volume changes based on a specific pattern caused by the type of epilepsy. Certain regions demonstrate a reduction in thickness, while others show an increase. Additionally, the areas with reduced thickness may either align with these changes or exhibit alterations in the opposite direction.

5. Declarations

All procedures performed in this study involving human participants studies, were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

6. Consent for publication

Not applicable.

7. Availability of data and materials

The datasets used or analyzed during the current study available from the corresponding author on reasonable request.

8. Competing interests

The authors declare no competing interests.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

10. Author contribution

H.T.A. the study design and protocol development; oversaw the clinical trial implementation; contributed to data interpretation and manuscript writing. M.S. and N.P.A. Managed participant recruitment and retention; performed statistical analysis; drafted sections of the results and discussion. M.S.H. Conducted literature review and provided expertise in clinical methodology; assisted in data collection and quality assurance; contributed to manuscript revisions. F.SH. Supervised the overall project and ensured compliance with ethical standards; reviewed and approved the final manuscript.

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12. Conflict

There is no conflict of interest for this investigation.

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