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STRUCTURAL REMODELING OF THE EPILEPTIC BRAIN: AN ANATOMICAL AND HISTOPATHOLOGICAL REVIEW

Oluwaseyi Emmanuel Kolawole, Oluseyi Sunday Fabiyi, Olugbenga Olawole Olayinka, Caroline Ifeoluwa Olakanmi, Kehinde Lawal and Onyema Kelechi Roselyn *

Department of Anatomy, School of Basic Medical Sciences, Babcock University, Ilishan Remo, Ogun State, Nigeria.
* Corresponding Author; Email: onyemak@babcock.edu.ng.

ORCID Details
Oluwaseyi Emmanuel Kolawole: https://orcid.org/0009-0005-4849-7030
Oluseyi Sunday Fabiyi: https://orcid.org/0000-0003-4938-0908
Olugbenga Olawole Olayinka: https://orcid.org/0000-0002-1008-9593
Caroline Ifeoluwa Olakanmi: https://orcid.org/0009-0006-0300-3305
Kehinde Lawal: https://orcid.org/0009-0009-9445-1390
Kelechi Roselyn Onyema: https://orcid.org/0009-0003-1946-0226

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ABSTRACT

Epilepsy is increasingly recognized not merely as a functional electrical disorder but as a condition associated with progressive and, in many cases, region-specific structural reorganization of the brain. Neuroimaging and histopathological studies over the past two decades have demonstrated that recurrent seizures are accompanied by hippocampal sclerosis, mossy fiber sprouting, granule cell dispersion, cortical thinning, white matter tract disruption, and, in some models, alterations extending to extra-limbic and even extra-cranial structures. These structural alterations are not static end-points but evolve dynamically with disease duration, seizure frequency, and etiology, and they carry important implications for diagnosis, prognosis, and surgical planning. This review synthesizes current evidence on structural brain changes in epilepsy, drawing on human neuroimaging and histopathology literature as well as preclinical rodent studies, including several recent Nigerian experimental studies using lithium chloride-pilocarpine and kainic acid models that have examined hippocampal, prefrontal cortical, and limbic architecture following induced seizures and after treatment with plant-derived neuroprotective agents. We discuss the cellular and molecular underpinnings of hippocampal sclerosis, cortical and subcortical atrophy, white matter and network level changes, and the emerging use of structural biomarkers, while highlighting therapeutic strategies, including antiepileptic drugs, ketogenic diet, and Phyto therapeutic agents, that may attenuate or reverse these structural sequelae.

Keywords: Hippocampal Sclerosis; Mossy Fiber Sprouting; Granule Cell Dispersion; Cortical Atrophy; Epileptogenesis; Neuroimaging; Epilepsy

1 INTRODUCTION

Epilepsy affects over 50 million people worldwide and is defined clinically by the recurrence of unprovoked seizures [1]. Beyond its electrophysiological hallmark, chronic epilepsy-particularly temporal lobe epilepsy (TLE) is associated with structural brain changes that can be detected macroscopically on magnetic resonance imaging (MRI) and microscopically at the cellular level [2]. These structural alterations were historically considered secondary consequences of recurrent seizures, but growing evidence suggests a bidirectional relationship: pre-existing developmental or acquired structural abnormalities can lower seizure threshold, while recurrent seizures themselves drive further structural reorganization, a phenomenon central to the concept of epileptogenesis [3].

The most extensively studied structural change is hippocampal sclerosis (HS), the histopathological correlate of mesial temporal lobe epilepsy (MTLE) and the most common finding in surgical specimens from patients with drug-resistant focal epilepsy [4,5]. However, structural changes in epilepsy are not confined to the hippocampus; cortical thinning, amygdala and thalamic volume loss, white matter tract disruption, and even extra-cranial structural changes observed in some experimental models illustrate that epilepsy exerts a widespread anatomical footprint [6,7]. This review provides an integrated account of the structural neuropathology of epilepsy, from the classical hippocampal sclerosis to network-level and extra-hippocampal changes, and reviews evidence from preclinical models including several recent Nigerian studies using plant-derived agents that inform both the mechanisms and potential reversibility of these structural alterations.

2 HIPPOCAMPAL SCLEROSIS: THE CLASSICAL STRUCTURAL SIGNATURE OF EPILEPSY

2.1 Histopathological Features

Hippocampal sclerosis is characterized by segmental neuronal loss, most severe in the CA1 and CA4/hilar subfields, with relative sparing of CA2 and the dentate granule cell layer, accompanied by reactive astrogliosis that gives the tissue its characteristic firmness ("Ammon's horn sclerosis") [8,9]. The International League Against Epilepsy (ILAE) classification system stratifies hippocampal sclerosis into three histopathological subtypes based on the pattern of subfield involvement: ILAE type 1 (classical, with combined CA1 and CA4 loss, accounting for 60–80% of surgical cases), ILAE type 2 (predominant CA1 loss), and ILAE type 3 (predominant CA4/dentate loss), alongside a fourth category of "gliosis only" without significant neuronal loss [8]. Cell loss and gliosis frequently extend into adjacent structures, including the subiculum, entorhinal cortex, and amygdala, although the subiculum tends to be relatively preserved and has been proposed to act as a hub for the synchronization and propagation of hyperexcitable activity to extrahippocampal regions [10].

2.2 Mossy Fiber Sprouting and Granule Cell Dispersion

A hallmark reorganizational feature accompanying hippocampal sclerosis is mossy fiber sprouting (MFS), in which dentate granule cell axons, having lost their normal hilar targets to cell death, aberrantly sprout into the inner molecular layer, forming new excitatory synapses onto granule cell dendrites, surviving mossy cells, and interneurons [11,12]. This aberrant circuitry has been proposed to create a recurrent excitatory network capable of sustaining hyperexcitability, although its precise pro- or anti-epileptogenic role remains debated, since blocking sprouting pharmacologically does not consistently reduce seizure frequency in animal models [11]. A recent human histopathological study using resected hippocampi from patients with drug-resistant MTLE demonstrated putative long-range mossy fiber sprouting extending toward the subiculum, accompanied by regional increases in cytochrome c oxidase expression, suggesting a hypermetabolic state that may facilitate network hyperexcitability [13].

Granule cell dispersion (a widening and disorganization of the normally compact dentate granule cell layer) frequently co-occurs with mossy fiber sprouting and is thought to result from aberrant migration of newly generated granule cells in the seizing hippocampus, possibly compounded by altered reelin signaling [9,14].

2.3 Neuroimaging Correlates

On MRI, hippocampal sclerosis manifests as hippocampal atrophy with T2-weighted hyperintensity and loss of internal architecture, and is the most frequent structural abnormality identified in patients undergoing presurgical evaluation for drug-resistant epilepsy [14]. Longitudinal imaging studies indicate that while some hippocampal damage precedes seizure onset (reflecting an initial precipitating injury such as prolonged febrile seizures, CNS infection, or trauma), a component of atrophy can progress with ongoing seizures, supporting the concept of seizure-induced structural injury superimposed on a pre-existing vulnerability [14,15]. Laterality of hippocampal atrophy also correlates with specific cognitive deficits, with dominant-hemisphere (typically left) hippocampal atrophy associated with verbal memory impairment and non-dominant hippocampal atrophy associated with visuospatial memory deficits [14].

3 EXTRA-HIPPOCAMPAL AND CORTICAL STRUCTURAL CHANGES

Although the hippocampus is the most studied structure, epilepsy-associated structural change extends into extrahippocampal and cortical regions. Cortical thinning has been documented in the ipsilateral temporal pole, insula, and orbitofrontal cortex in patients with TLE, and in some cases, extends to contralateral and even remote cortical regions, consistent with epilepsy's characterization as a network, rather than purely focal, disorder [6]. Amygdala enlargement or atrophy, thalamic volume reduction, and reduction in cerebellar volume have also been reported in chronic epilepsy, particularly in cases of long disease duration and high seizure burden [6,7].

Preclinical studies utilizing chemo convulsant models have been valuable in characterizing structural change in extrahippocampal limbic structures. Several Nigerian experimental studies using the lithium chloride-pilocarpine and kainic acid models have demonstrated that seizures induce histoarchitectural derangement in the prefrontal cortex, characterized by neuronal degeneration, pyknosis, vacuolation, and disrupted cortical lamination, alongside behavioral deficits in memory and anxiety-related paradigms [16,17,18]. For instance, Kolawole *et al.* (2026) reported prefrontal cortical damage following lithium-pilocarpine-induced seizures in Wistar rats, with the plant extract *Aframomum melegueta* attenuating neuronal degeneration and improving cortical cytoarchitecture [16]. Similarly, Fabiyi *et al.* (2025) demonstrated that *Bryophyllum pinnatum* ameliorated lithium-pilocarpine-induced prefrontal cortical alterations, supporting a structural neuroprotective effect of Phyto therapeutic intervention [17]. Adelakin *et al.* (2022), using the kainic acid model, compared the structural effects of *Bryophyllum pinnatum*, a ketogenic diet, and carbamazepine on the frontal lobe cortex, finding that all three interventions reduced seizure-associated cortical histoarchitectural derangement to varying degrees, with the ketogenic diet showing comparable benefit to the standard antiepileptic drug [18].

Beyond the prefrontal cortex, structural derangement of the hippocampus itself has been documented in these rodent models. Onyema *et al*. (2026) showed that *Crinum jagus* ethanol leaf extract mitigated lithium chloride-pilocarpine-induced epilepsy by improving hippocampal architecture alongside behavioral and neurochemical parameters, reinforcing the hippocampus as the primary structural target in this model [19]. Olatunji *et al.* (2024) similarly reported that *Diospyros mespiliformis* modulated both hippocampal and prefrontal cortical histoarchitecture following lithium chloride-pilocarpine-induced epilepsy [20], while Owolabi *et al.* (2019) demonstrated ameliorative effects of *Bryophyllum pinnatum* on structural correlates of kainic acid-induced temporal lobe epilepsy [21]. Collectively, these preclinical findings corroborate human histopathological data in confirming that seizure activity produces measurable, region-specific structural injury that is at least partially preventable or reversible with appropriate pharmacological or Phyto therapeutic intervention.

4 WHITE MATTER AND NETWORK-LEVEL STRUCTURAL ALTERATIONS

Diffusion tensor imaging (DTI) studies have revealed disruption of white matter integrity in tracts connecting the temporal lobe to extratemporal regions, including the fornix, cingulum, and uncinate fasciculus, in patients with TLE [6]. These changes are consistent with epilepsy being conceptualized as a network disorder, wherein structural and functional connectivity abnormalities extend well beyond the presumed epileptogenic focus [10,22]. Such widespread network disruption may underlie the cognitive and psychiatric comorbidities frequently observed in chronic epilepsy, including memory impairment, depression, and psychosis [14].

5 CELLULAR AND MOLECULAR MECHANISMS DRIVING STRUCTURAL REORGANIZATION

The structural changes discussed above are underpinned by processes including excitotoxic neuronal death (mediated by excessive glutamatergic signaling and calcium influx during status epilepticus), neuroinflammation with sustained microglial and astrocytic activation, oxidative stress, and impaired neurogenesis and aberrant migration of newly formed granule cells [3,9]. These processes, discussed extensively in the companion mechanistic literature on neuroinflammation, oxidative stress, and mitochondrial dysfunction in epilepsy, converge to produce the histopathological picture of hippocampal sclerosis, mossy fiber sprouting, and cortical injury described here, underscoring those pathways as attractive therapeutic targets not only for seizure control but also for structural neuroprotection [3].

6 THERAPEUTIC AND NEUROPROTECTIVE STRATEGIES AGAINST STRUCTURAL INJURY

Beyond conventional antiepileptic drugs, several strategies have shown promise in limiting or reversing seizure-associated structural damage in preclinical models. The ketogenic diet has demonstrated structural neuroprotective effects comparable to carbamazepine in the kainic acid model, potentially through improved mitochondrial function and reduced oxidative injury [18]. Plant-derived agents rich in antioxidant and anti-inflammatory phytochemicals including *Bryophyllum pinnatum, Aframomum melegueta, Crinum jagus, and Diospyros mespiliformis* have consistently

been shown across multiple Nigerian experimental studies to attenuate hippocampal and prefrontal cortical histoarchitectural derangement in lithium chloride-pilocarpine and kainic acid models [16,17,18,19,20,21]. In humans, early and effective seizure control, together with surgical resection of the epileptogenic zone in appropriately selected drug-resistant cases, remains central to limiting the extent and consequences of hippocampal sclerosis and network-level structural injury [5,14].

7 CONCLUSION

Structural change is a defining, though under-recognized, feature of chronic epilepsy, extending from the classical hippocampal sclerosis and mossy fiber sprouting of mesial temporal lobe epilepsy to cortical thinning, subcortical volume loss, and white matter network disruption. Convergent evidence from human neuroimaging, human histopathology, and preclinical rodent models including several Nigerian studies employing lithium chloride-pilocarpine and kainic acid paradigms demonstrates that these structural alterations are, at least in part, mechanistically linked to excitotoxicity, neuroinflammation, and oxidative injury, and that they can be attenuated by antiepileptic drugs, ketogenic diet, and plant-derived neuroprotective agents. Future research should prioritize longitudinal human imaging studies correlating structural progression with seizure burden and treatment response, alongside translational studies validating Phyto therapeutic and dietary interventions as adjuncts for structural neuroprotection in epilepsy.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflict of Interest.

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