2

The Anatomical Basis of Seizures

Pradip Chauhan[1] • Shalom Elsy Philip[1] • Girish Chauhan[2] • Simmi Mehra[1]

[1]Department of Anatomy, All India Institute of Medical Sciences, Rajkot, Gujarat, India; [2]Department of Oral Pathology, Government Dental College, Jamanagar, Gujarat, India

Author for correspondence: Pradip Chauhan, Department of Anatomy, All India Institute of Medical Sciences, Rajkot, Gujarat, India. Email: prajjawalitresearch@gmail.com

Cite this chapter as: Chauhan P, Philip SE, Chauhan G, Mehra S. The Anatomical Basis of Seizures. In: Czuczwar SJ, editor. *Epilepsy*. Brisbane (AU): Exon Publications. Online first 2022 Feb 25.

Doi: https://doi.org/10.36255/exon-publications-epilepsy-anatomical-basis

Abstract: Paroxysmal alteration of neurological function caused by an excessive hypersynchronous neuronal discharge in the brain is known as seizure. Non-epileptic seizure is short-lived while epilepsy is a neurological condition characterized by two or more provoked seizures. The hippocampus, amygdala, frontal cortex, temporal cortex, and olfactory cortex are the common areas involved in seizures. According to the 'dormant basket cell' theory, loss of excitatory input from the dentate mossy cells makes inhibitory basket cells dormant while according to the 'mossy fiber' theory, mossy fibers induce the formation of excitatory circuits resulting in hyperexcitability. Amygdala is present at the anterior end of the inferior horn of the lateral ventricle; basolateral part plays an important role in temporal lobe epilepsy. The thalamus is an ovoid mass of grey matter; midline nuclei of the thalamus is involved in memory function and arousal, while it plays a crucial role in controlling seizures. Dendrites are short post-synaptic neural processes; in pathological conditions dendrites can cause hyperexcitability in neuronal circuits and lead to decreased seizure thresholds and progressive epileptogenesis. Regions specialized for learning/memory are most prone to seizures, particularly, the neocortical regions and the hippocampus.

Keywords: anatomical basis of seizures; hippocampus and epilepsy; amygdala and epilepsy; temporal lobe epilepsy; epileptic seizure

In: Czuczwar SJ, editor. *Epilepsy*. Exon Publications, Brisbane, Australia.
ISBN: 978-0-6453320-4-9. Doi: https://doi.org/10.36255/exon-publications-epilepsy

Copyright: The Authors.

License: This open access article is licenced under Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) https://creativecommons.org/licenses/by-nc/4.0/

INTRODUCTION

Excessive hypersynchronous neuronal discharge in the brain leading to paroxysmal alteration of neurologic function is known as a seizure. Non-epileptic seizure is short-lived with single occurrence provoked by a reversible insult, whereas epilepsy is a neurological condition characterized by two or more unprovoked seizures (1). About 1% of the population is affected by epilepsy and approximately 75% of epilepsy begins during childhood, reflecting the heightened susceptibility of the developing brain to seizures (2). Hyperexcitability of neurons and hypersynchrony of neural networks are the hallmarks of seizures. Hyperexcitability means that a certain level of excitability, or a threshold, must be exceeded for a seizure to be generated. In other words, when excitation exceeds inhibition, seizures occur. Hypersynchrony is a state where a group of neurons fire at the same time at a similar rate. While individual neurons might be in a state of hyperexcitability and fire rapid, repetitive, paroxysmal discharges, a seizure is a coordinated event, involving numerous neurons firing synchronously. While a plethora of mechanisms have been implicated in the development of seizures, in its simplest form, the primary mechanism may be summarized as the loss or abnormalities of cells that normally inhibit excitatory cells and limit the spread of electrical discharges, or an overproduction of chemicals that causes cells to abnormally discharge electrical signals, or both. Apart from these, to understand the origin of the electrical activity, it is necessary to study the structure and function of those cells in the brain which are generating the activity (2–6). This chapter provides an overview of the anatomical basis of epilepsy.

The anatomical areas related to seizures are important for classification and treatment. The revised classification of the International League Against Epilepsy correlates seizure semiology (signs of clinical manifestation) with anatomical origin (Figure 1) of the seizures (focal vs. generalized) (4). In a study by Fayerstein et al. (4), semiologic features were correlated with the seizure onset zone localization (temporal, prefrontal dorsolateral, prefrontal ventro-mesial, parietal, insular). It showed that dystonia, integrated behavior, and bilateral or unilateral hyperkinetic movements were statistically significant according to localization, and represented parietal, temporal, and prefrontal ventro-mesial seizures. Epilepsy centers around the world have recently reinitiated trials with deep brain stimulation such as vagus nerve stimulation and transcranial magnetic stimulation in different intracerebral structures such as the thalamus, the hippocampus, and the subthalamic nucleus for the treatment of patients with medically or surgically refractory epilepsy (5). The neuroanatomic circuitry is involved in the production of the cardiovascular manifestations of seizures (6).

THE HIPPOCAMPUS AND EPILEPSY

The hippocampus, buried deep in the medial part of the thalamus, plays an important role in memory processing, emotions, spatial navigation, and learning (7). The hippocampal formation comprises part of the uncus, hippocampal proper, gyrus fasciolaris, longitudinal striae, and indusium griseum (8, 9). The hippocampus plays an important role in epilepsy. Sensory impulses from the posterior

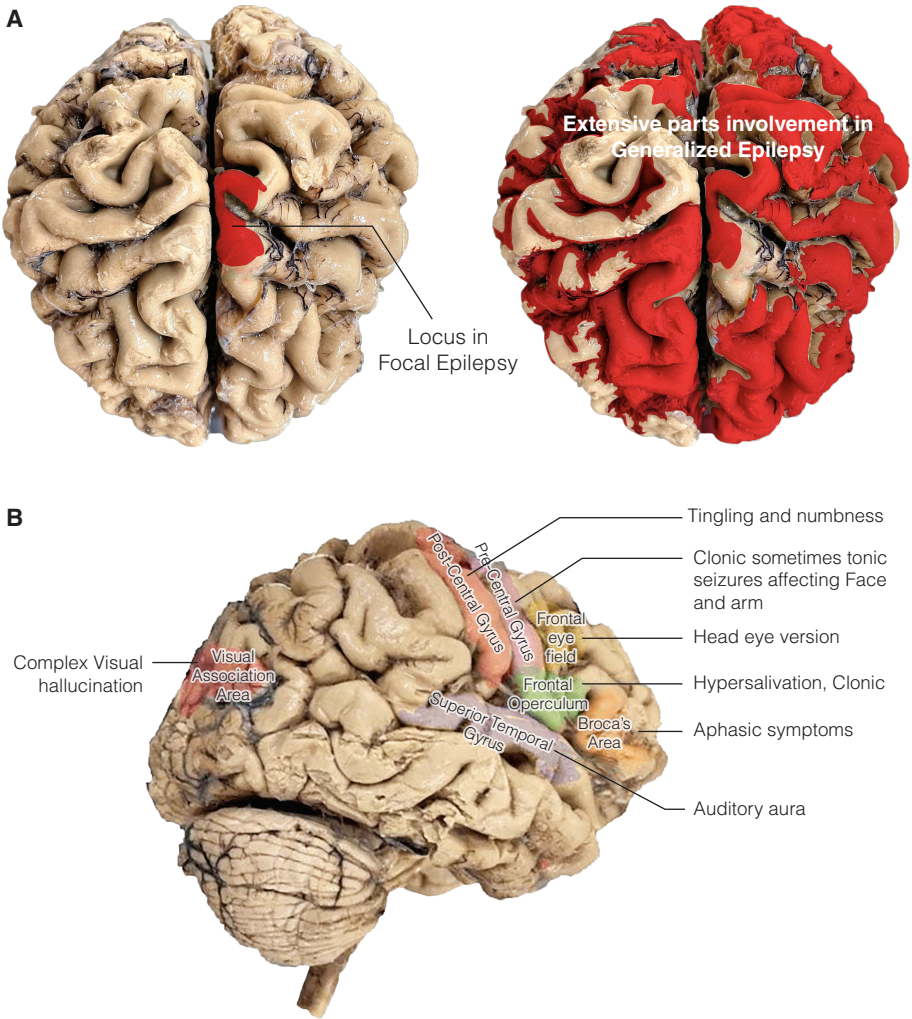

Figure 1. The anatomical basis of epilepsy. A, Structures (marked in red) affected in focal and generalized seizures. **B**, Semiological signs by symptomatogenic areas affected in seizure.

cingulate cortex, contralateral hippocampus, occipital, temporal, and parietal lobe converge on the hippocampus through the lateral and medial perforant pathways (9, 10). Seizures have been known to cause abnormal neurogenesis in the hippocampus and form faulty circuits that disrupt its function (11). The term hippocampal sclerosis (HS) and mesial temporal lobe epilepsy (MLTE) are used synonymously and is involved in epilepsy-related cognitive dysfunction (12). Sclerosis is a macroscopic and descriptive one, indicating shrinkage and induration of the structure and selective neuronal loss with secondary astroglial proliferation that affects various sectors of hippocampus. The International League against Epilepsy in 2004 proposed there should be neuronal cell loss and gliosis at CA1 and end-folium

areas of the hippocampus with relative sparing of the transitional cortex measured at the mid-body of the anterior-posterior axis as the minimum criteria of MTLE-HS (13). It often involves the amygdala, uncus, and parahippocampal gyrus. Thom (14) classified hippocampal sclerosis into: (i) classical—neuronal loss and gliosis mainly in CA1, CA3, and end-folium; (ii) total—severe neuronal loss in all hippocampal subfields and the dentate gyrus; and (iii) end-folium—neuronal loss and gliosis restricted to the hilum of the dentate gyrus.

Theories

The two theories associated with hippocampal sclerosis in epileptogenesis is the 'dormant basket cell' and 'mossy fiber' theory. According to the 'dormant basket cell' theory, loss of excitatory input from the dentate mossy cells makes inhibitory basket cells dormant. This excitatory input can cause excessive firing and neuronal death and initiate epileptic focus in the absence of inhibitory (GABA) action (15–17). The 'mossy fiber' hypothesis suggests that sprouts of aberrant mossy fiber originating in the dentate granule cells and terminating in the supragranular area of the inner molecular layer of the dentate induce the formation of excitatory circuits resulting in hyperexcitability (15, 18). Kainic acid epilepsy models in rats and human epilepsy surgery resections of the sclerotic hippocampus have shown mossy fiber sprouting (19, 20). However, the role of various hippocampal changes in epilepsy is still the subject of ongoing research.

Pathophysiology

The part having the least seizure threshold is the hippocampus. Hippocampal sclerosis is presented as tissue shrinkage, loss of cells, and reactive gliosis in the hippocampus. Neuronal losses involve the hilar mossy cells, and hilar somatostatin containing interneurons (16–20). When the CA3 cells burst, the bursting spreads from cell to cell and results in a synchronisation leading to tonic depolarization. In the cortex, epileptiform discharges originate near histological layer IV. The capacity of some populations of neurons to generate high-frequency synchronous discharges underlies the development of focal cortical epileptogenesis (16–20). Neurons surrounding the epileptogenic focus are hyperpolarized and GABAergic, inhibiting the neurons within the focus. Seizure spread probably depends on any factor or agent that activates neurons in the focus or inhibits those surrounding it. Once the intensity of the seizure discharges exceeds a certain point, it overcomes the inhibitory influence of surrounding neurons and spreads to neighboring cortical and subcortical regions via short cortico-cortical synaptic connections. The spread of excitation to the cortical, thalamic, and brain stem centers correspond with the tonic phase of the seizure and loss of consciousness, as well as with the signs of the autonomic nervous system (16–20).

THE TEMPORAL LOBE, THALAMUS, AMYGDALA AND EPILEPSY

Temporal lobe epilepsy (TLE) is the commonest form of focal epilepsy and represents almost 2/3 of cases of intractable epilepsy managed surgically. Temporal lobe

epilepsy can be classified as mesial temporal lobe epilepsy (mTLE) and neocortical temporal lobe epilepsy (nTLE); nTLE is also called extrahippocampal, nonlesional or lateral neocortical epilepsy. The mTLE is associated with cortical atrophy and loss of volume in the hippocampus and the anterior thalamus. Aberrant white matter tracts and connections may be observed TLE in addition to the grey matter abnormalities. Fronto-temporal, fronto-occipital, fornix or temporo-occipital fasciculus may present diffuse network in TLE. (21, 22).

The anterior thalamus is involved in memory processing, spatial navigation, and communication with the hippocampus. The mediodorsal thalamic nucleus plays a major role in goal-directed behavior, and the intralaminar thalamic nucleus and the perifascicular thalamus are involved in behavioral flexibility (23). Studies have shown that baseline thalamic volumes are lower in patients with TLE. The thalamic lesion in seizure is associated with the limbic system atrophy (24).

Amygdala is primarily associated with emotions. Stimulation of the lateral amygdala has shown experiential symptoms in patients with TLE (24). Lesions of the lateral amygdala may lead to deficits in emotional appraisal in TLE. In children with temporal lobe epilepsy, grey matter thinning has been reported in the hippocampus, lateral temporal lobes, thalamus, posterior cingulum, and cerebellum. Neuronal injury to lateral septal nuclei, amygdala, ventral subiculum/CA1 is seen in neonatal or early life seizures (25).

Autosomal dominant lateral temporal lobe epilepsy (ADLTE) is a genetic condition characterized by onset in early adulthood or in adolescence of temporal seizures. The condition presents auditory auras triggered by external noises without any visible pathological finding in conventional magnetic resonance imaging. About 50% of ADLTE families and 2% of sporadic cases show LGI1 gene (one of the ion channel gene) mutation on chromosome 10 q24 (26).

OLFACTORY CORTEX AND EPILEPSY

Piriform cortex (primary olfactory cortex) is an epileptogenic structure and increased glial cell densities in the layers of piriform have been noted in postmortem cases with epilepsy (8, 9, 27). Seizures involving the olfactory cortex present reduced olfactory functioning, confusion in test, and unpleasant auras. Olfactory auras in the pre-ictal period are associated with hyperresponsiveness of neurons (27).

FRONTAL CORTEX AND EPILEPSY

The frontal lobe is divided into dorsolateral, medial orbital, and inferior orbital. Dorsolateral frontal lobe is further subdivided into primary motor, premotor and prefrontal cortex. Frontal lobe seizures originating in the primary motor area has early motor manifestations, it may occur during sleep, and lack post-ictal phase. It consists of unilateral spreading clonic activity beginning on face, spreading to arm, and speech arrest. Frontal lobe epilepsy is one of the commonest types of focal epilepsy (27, 28). The premotor cortex is further subdivided into the frontal eye field, secondary motor cortex and Broca's language area (Figure 1) (28, 29).

Seizure affecting the frontal eye field leads to lateral deviation to eyes. Involvement of Broca's language area represents aphasic seizures. Involvement of premotor area represents versive seizures with forced head turn characterized by involuntary head deviation. Frontal lobe pathology may lead to atrophy of the rostral corpus callosum in juvenile myoclonic epilepsy (30). Frontal lobe epilepsy is presented as contralateral clonic movement, unilateral or bilateral tonic activity or complex automatism. Locus foci in medial frontal lobe in frontal lobe epilepsy may be responsible for paradoxical lateralization. Abnormal thalamus and frontal lobe volumes are seen in children with idiopathic generalized epilepsies (30).

CEREBELLUM AND EPILEPSY

Patients with epilepsy often have cerebellar atrophy. Cerebellar stimulation in the anterior lobe is found to be effective in patients with intractable epilepsy (31). The concept of cerebellar stimulation is based on that Purkinje cell inhibition can be prosthetically induced to modify neurologic activity that is abnormally and undesirably heightened by pathologic facilitation or disinhibition (31). Cerebellar biopsies taken at the time of stimulation showed reduced molecular layer, decreased stellate cells and Purkinje cells.

DENDRITIC PATHOLOGY AND EPILEPSY

Dendritic spines are thin protrusions from the surface of neurons that make point of contact between the neurons. They are indeed postsynaptic structures that establish synaptic contact with axon terminals (32). They are major targets of excitatory synapses in the brain. Dendritic spine density indicates the cellular process involved in neural plasticity, and cognitive functions such as memory and learning (33). The dendritic spine undergoes changes in pathological conditions and can cause hyperexcitability in neuronal circuits which leads to decreased seizure thresholds and progressive epileptogenesis (34). Neurons show a wide range of firing patterns and dendritic morphology and play an important role in modulating firing patterns. Computational models of neocortical pyramidal cells showed that total length of apical dendrite and branching pattern significantly influences the burst spike intervals and determines if a cell exhibit burst firing. Either reducing or enlarging the dendritic tree or modifying its topological structure without changing total dendritic length, can transform a cell's firing pattern from bursting to tonic firing (35). Alterations in size or topology of pyramidal cell morphology in epilepsy could change neuronal burst firing and affect information processing and cognition (35).

CONCLUSION

Epilepsy is a neurological condition characterized by two or more unprovoked seizures. About 75% of epilepsy occurs during childhood, reflecting the heightened susceptibility of the developing brain to seizures. Brain regions specialized

for learning and memory, particularly the neocortical regions and the hippocampus, are comparatively more prone to seizures. Epilepsy is associated with anatomical changes in the hippocampus, amygdala, frontal cortex, temporal cortex, and olfactory cortex. Knowledge of the anatomical basis of epilepsy will enable the understanding of the origin of the electrical activity, help accurate diagnosis, and guide appropriate management strategies.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

Copyright and Permission Statement: The authors confirm that the materials included in this chapter do not violate copyright laws. Where relevant, appropriate permissions have been obtained from the original copyright holder(s), and all original sources have been appropriately acknowledged or referenced.

REFERENCES

1. Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harb Perspect Med. 2015;5(6):a022426. https://doi.org/10.1101/cshperspect.a022426
2. Wu Q, Zhao CW, Long Z, Xiao B, Feng L. Anatomy Based Networks and Topology Alteration in Seizure-Related Cognitive Outcomes. Front Neuroanat. 2018;12:25. https://doi.org/10.3389/fnana.2018.00025
3. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522-530. https://doi.org/10.1111/epi.13670
4. Fayerstein J, McGonigal A, Pizzo F, Bonini F, Lagarde S, Braquet A et al. Quantitative analysis of hyperkinetic seizures and correlation with seizure onset zone. Epilepsia. 2020;61(5):1019-1026. https://doi.org/10.1111/epi.16510
5. Vonck K, Boon P, Van Roost D. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy. Acta Neurochir Suppl. 2007;97(Pt 2):321-328. https://doi.org/10.1007/978-3-211-33081-4_35
6. Britton JW, Benarroch E. Seizures and syncope: anatomic basis and diagnostic considerations. Clin Auton Res. 2006;16(1):18-28. https://doi.org/10.1007/s10286-006-0277-z
7. Tatu L, Vuillier F. Structure and vascularization of the human hippocampus. Front Neurol Neurosci. 2014;34:18-25. https://doi.org/10.1159/000356440
8. Chauhan P, Jethwa K, Rathawa A, Chauhan G, Mehra S. The Anatomy of the Hippocampus. In: Pluta R, editor. Cerebral Ischemia [Internet]. Brisbane (AU): Exon Publications; 2021 Nov 6. Chapter 2. https://doi.org/10.36255/exonpublications.cerebralischemia.2021.hippocampus
9. Aggleton JP. Multiple anatomical systems embedded within the primate medial temporal lobe: implications for hippocampal function. Neurosci Biobehav Rev. 2012;36(7):1579-1596. https://doi.org/10.1016/j.neubiorev.2011.09.005
10. Fournier NM, Botterill JJ, Marks WN, Guskjolen AJ, Kalynchuk LE. Impaired recruitment of seizure-generated neurons into functional memory networks of the adult dentate gyrus following long-term amygdala kindling. Exp Neurol. 2013;244:96-104. https://doi.org/10.1016/j.expneurol.2012.11.031
11. Blümcke I, Coras R, Miyata H, Ozkara C. Defining clinico-neuropathological subtypes of mesial temporal lobe epilepsy with hippocampal sclerosis. Brain Pathol. 2012;22(3):402-411. https://doi.org/10.1111/j.1750-3639.2012.00583.x
12. Wieser HG: ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 2004;45:695-714. https://doi.org/10.1111/j.0013-9580.2004.09004.x
13. Thom M: Recent advances in the neuropathology of focal lesions in epilepsy. Expert Rev Neurother 2004;4:973-984. https://doi.org/10.1586/14737175.4.6.973

14. Fisher PD, Sperber EF, Moshe SL: Hippocampal sclerosis revisited. Brain Dev 1998;20:563–573. https://doi.org/10.1016/S0387-7604(98)00069-2
15. Sloviter RS: Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. Science 1987;235:73–76. https://doi.org/10.1126/science.2879352
16. Sloviter RS: On the relationship between neuropathology and pathophysiology in the epileptic hippocampus of humans and experimental animals. Hippocampus 1994;4:250–253. https://doi.org/10.1002/hipo.450040304
17. Nadler JV, Perry BW, Cotman CW: Selective reinnervation of hippocampal area CA1 and the fascia dentata after destruction of CA3-CA4 afferents with kainic acid. Brain Res 1980;182:1–9. https://doi.org/10.1016/0006-8993(80)90825-2
18. Tauck DL, Nadler JV: Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid-treated rats. J Neurosci 1985;5:1016–1022. https://doi.org/10.1523/JNEUROSCI.05-04-01016.1985
19. Franck JE, Pokorny J, Kunkel DD, Schwartzkroin PA: Physiologic and morphologic characteristics of granule cell circuitry in human epileptic hippocampus. Epilepsia 1995;36:543–558. https://doi.org/10.1111/j.1528-1157.1995.tb02566.x
20. Mueller SG, Laxer KD, Barakos J, et al. Involvement of the thalamocortical network in TLE with and without mesiotemporal sclerosis. Epilepsia. 2010;51(8):1436–1445. https://doi.org/10.1111/j.1528-1167.2009.02413.x
21. Saniya K, Patil BG, Chavan MD, et al. Neuroanatomical Changes in Brain Structures Related to Cognition in Epilepsy: An Update. J Nat Sci Biol Med. 2017;8(2):139–143. https://doi.org/10.4103/0976-9668.210016
22. Bercovici E, Kumar BS, Mirsattari SM. Neocortical temporal lobe epilepsy. Epilepsy Res Treat. 2012;2012:103160. https://doi.org/10.1155/2012/103160
23. Tuchscherer V, Seidenberg M, Pulsipher D, Lancaster M, Guidotti L, Hermann B. Extrahippocampal integrity in temporal lobe epilepsy and cognition: thalamus and executive functioning. Epilepsy Behav. 2010;17(4):478–482. https://doi.org/10.1016/j.yebeh.2010.01.019
24. Cormack F, Gadian DG, Vargha-Khadem F, Cross JH, Connelly A, Baldeweg T. Extra-hippocampal grey matter density abnormalities in paediatric mesial temporal sclerosis. Neuroimage. 2005;27(3):635–643. https://doi.org/10.1016/j.neuroimage.2005.05.023
25. Menassa DA, Sloan C, Chance SA. Primary olfactory cortex in autism and epilepsy: increased glial cells in autism. Brain Pathol. 2017;27(4):437–448. https://doi.org/10.1111/bpa.12415
26. Bercovici E, Kumar BS, Mirsattari SM. Neocortical temporal lobe epilepsy. Epilepsy Res Treat. 2012;2012:103160. doi: 10.1155/2012/103160. Epub 2012 Jul 16. https://doi.org/10.1155/2012/103160
27. Centeno M, Vollmar C, Stretton J, Symms MR, Thompson PJ, Richardson MP et al. Structural changes in the temporal lobe and piriform cortex in frontal lobe epilepsy. Epilepsy Res. 2014;108(5):978–981. https://doi.org/10.1016/j.eplepsyres.2014.03.001
28. Engel J Jr. The current place of epilepsy surgery. Curr Opin Neurol. 2018 Apr;31(2):192–197. https://doi.org/10.1097/WCO.0000000000000528
29. Widjaja E, Mahmoodabadi SZ, Snead OC 3rd, Almehdar A, Smith ML. Widespread cortical thinning in children with frontal lobe epilepsy. Epilepsia. 2011;52(9):1685–1691. https://doi.org/10.1111/j.1528-1167.2011.03085.x
30. Tae WS, Hong, SB, Joo, EY. Han SJ, Cho JW, Seo DW, et al. Structural brain abnormalities in juvenile myoclonic epilepsy patients: volumetry and voxel-based morphometry. Korean J Radiol. 2006;7(3):162–172. https://doi.org/10.3348/kjr.2006.7.3.162
31. Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. Arch Neurol. 1976;33(8):559–570. https://doi.org/10.1001/archneur.1976.00500080037006
32. Heck N, Benavides-Piccione R. Editorial: Dendritic spines: from shape to function. Front Neuroanat. 2015;9:101. Published 2015 Jul 28. https://doi.org/10.3389/fnana.2015.00101

33. Mancuso JJ, Cheng J, Yin Z, Gilliam JC, Xia X, Li X et al. Integration of multiscale dendritic spine structure and function data into systems biology models. Front Neuroanat. 2014;8:130. Published 2014 Nov 12. https://doi.org/10.3389/fnana.2014.00130
34. Wang Z, Dai Z, Gong G, Zhou C, He Y. Understanding structural-functional relationships in the human brain: a large-scale network perspective. Neuroscientist. 2015;21(3):290–305. https://doi.org/10.1177/1073858414537560
35. Van Elburg RA, Van Ooyen A. Impact of dendritic size and dendritic topology on burst firing in pyramidal cells. PLoS Comput Biol. 2010;6(5):e1000781. https://doi.org/10.1371/journal.pcbi.1000781