Advances in epileptic network findings of hypothalamic hamartomas

Journal of Central Nervous System Disease
Volume 16: 1–7

DOI: 10.1177/11795735241237627

Di Wang[1,*], Di Lu[2,3,*], Mingtai Zhang[1], Anqi Dai[1], Guangyuan Jin[4], Qiao Wang[4], Yuyang Zhang[5] and Philippe Kahane[6]

[1]School of Engineering Medicine, Beihang University, Beijing, China. [2]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China. [3]Clinical Research Center for Epilepsy, Capital Medical University, Beijing, China. [4]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China. [5]School of Biological Science and Medical Engineering, Beihang University, Beijing, China. [6]Neurology Deparment, CHU Grenoble Alpes, University Grenoble Alpes, Grenoble Institute Neuroscience, Grenoble, France.

ABSTRACT

Hypothalamic hamartomas (HHs) are congenital developmental malformations located in the hypothalamus. They are associated with a characteristic clinical manifestation known as gelastic seizures (GS). However, the traditional understanding of HHs has been limited, resulting in insufficient treatment options and high recurrence rates of seizures after surgery. This is consistent with the network hypothesis of focal epilepsy that the epileptogenic zone is not only limited to HH but may also involve the distant cerebral cortex external to the HH mass. The epilepsy network theory, on the other hand, provides a new perspective. In this study, we aim to explore HH-related epilepsy as a network disease, challenging the conventional notion of being a focal lesional disease. We analyze various aspects of HHs, including genes and signaling pathways, local circuits, the whole-brain level, phenotypical expression in terms of seizure semiology, and comorbidities. By examining HHs through the lens of network theory, we can enhance our understanding of the condition and potentially identify novel approaches for more effective management and treatment of epilepsy associated with HHs.

PLAIN LANGUAGE SUMMARY

Hypothalamic hamartomas (HHs) are unusual brain malformations present from birth in the hypothalamus region. They often lead to a distinctive type of seizures known as GSs. However, our current understanding of HHs is limited, and this has made it challenging to treat them effectively. Many patients continue to experience seizures even after surgery. We've typically considered HH-related epilepsy as a localized problem, but a new theory suggests that it may involve a network of brain areas. In our study, we aim to change the way we view HH-related epilepsy. Instead of thinking of it as a single lesion in the brain, we explore the idea that it's a network disease. To do this, we'll investigate various aspects of HHs, such as the genes and pathways involved, how different parts of the brain interact, the impact on the whole brain, the types of seizures experienced, and any related health issues. By looking at HHs through this network theory, we hope to gain a deeper understanding of the condition and potentially discover new ways to manage and treat epilepsy associated with HHs. This shift in perspective could offer hope to those living with HH-related epilepsy and lead to more effective treatments, ultimately improving their quality of life.

KEYWORDS: Hypothalamic hamartomas, epileptic network, seizure, semiology

RECEIVED: December 29, 2023. **ACCEPTED:** January 16, 2024.

TYPE: Review

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Research Funds for the Beihang University (20300002023145017, 20300002023145007).

CONSENT FOR PUBLICATION: All of the authors have read and agreed with the manuscript for publication.

CORRESPONDING AUTHOR: Di Wang, School of Engineering Medicine, Beihang University, 37 Xueyuan Road, Beijing 100191, China.
Email: wangdi09@126.com

*Di Wang and Di Lu contributed equally to the manuscript.

Introduction

Hypothalamic hamartomas (HHs) are congenital non-progressive developmental malformations in the hypothalamus that occur during fetal development. Hypothalamic hamartomas have been drawing considerable interest for a range of disorders. Particularly, gelastic seizures (GS) have been recognized as characteristic seizure semiology in HH-related epilepsy. After the first description that the origin of ictal discharges associated with GS appears in HH, several studies have confirmed this.[1–3] Moreover, typical GS can be induced by HH direct electrical stimulation.[4] Other seizure types, however, do exist and do not arise from the HH, which indicates that HH-related epilepsy represents a unique and puzzling human epileptic entity.

Although HH neurons exist within local networks that may contribute to ictogenesis, various surgical interventions targeting the hamartoma do not abate seizures systematically.[5] The approach that identified surgery targets in the hamartoma by

resting preoperative resting-state functional MRI has improved freedom from seizures by 45% compared to conventional ablation.[6] By understanding the epileptic network of HHs and tailoring the surgical procedure accordingly, the likelihood of achieving seizure freedom increased.[5] This paper aims to explore HH-related epilepsy as a network disease, challenging the conventional view of being a focal lesional disease.

Epileptic network

Epilepsy was introduced as a network disease due to pathologies affecting a complex system in 2017 by the International League Against Epilepsy Workshop on Neurobiology of Epilepsy (Figure 1).[7] This framework can also be applied to understand the epileptic network associated with HHs. In order to comprehend seizures as a network disease in HHs, it is crucial to grasp the manifestation of pathologies not only at the clinical and electrophysiological scales but also at the genetic and signaling pathway levels. Gene expression plays a crucial role in the production of proteins and is essential for cell signaling. Dysregulation of genes and associated signaling pathways within the HH can lead to abnormal synchronization and hyperexcitability, eventually culminating in the emergence of seizures as a symptomatic manifestation. The interplay between genetic, molecular, cellular, and network-level alterations is crucial for understanding the complex nature of epilepsy in HHs. All these levels of dysfunction interact and contribute to the overall network disturbances and endpoint outcomes observed in HH-related seizures. Traditionally, epilepsy research in HHs has focused on the lesion itself. However, the application of these studies into effective therapies for intractable seizures has been limited. To address this challenge, a network-based approach has been proposed to better understand the pathophysiology of epilepsy. Understanding the epileptic brain network in the context of HHs will contribute to a deeper understanding of the underlying mechanisms and help develop targeted therapeutic interventions to alleviate seizures and associated comorbidities.

Hypothalamic hamartoma epileptic networks: Genes and signaling pathways

Genetic abnormalities underlie many diseases. Although the HH is a non-neoplastic heterotopic lesion, genetic factors still play an important role in this disease. Previous studies indicate that GLI3, OFD1, PRKACA, DYNC2H1, KIAA0556, and PTPN11 are involved in HHs.[8] GLI3, also known as GLI family zinc finger 3, is a DNA-binding transcription factor and belongs to the Sonic hedgehog (Shh) signaling pathway. Sonic hedgehog participates in the development of the ventral hindbrain, midbrain, and forebrain during the early embryonic period. While in late embryogenesis, Shh expresses in the dentate gyrus of the hippocampus, amygdala, neocortex, and cerebellar Purkinje neurons.[9]

The function of GLI3 appears to be two-faced depending on the length and presence of Shh.[10] Abnormal expression and mutation in the GLI3 gene can lead to different diseases, including HHs, Pallister-Hall syndrome, Greig cephalopolysyndactyly, and polydactyly. Hildebrand et al implicated at least 37% of patients with HH epilepsy have abnormalities in the Shh pathway,[11] such as nonsense change, frameshift indel, in-frame insertion, and large copy-number variants or loss-of-heterozygosity variants. OFD1, encoding a centrosomal/basal body protein, is located on the X chromosome and associated with oral-facial-digital syndrome. It is essential for the formation of left-right asymmetry establishment and primary cilia,

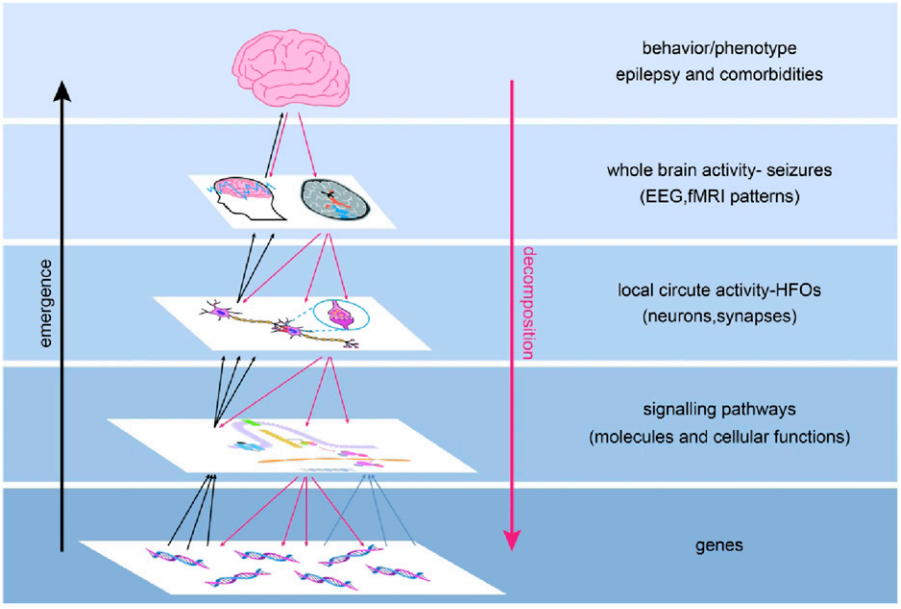

Figure 1. Hierarchical organization of epileptic network. (Adapted from Scott RC, Menendez de la Prida L, Mahoney JM, et al. WONOEP APPRAISAL: The many facets of epilepsy networks. Epilepsia 2018; 59: 1475-1483; with permission).

which is required for Shh signaling.[12] PRKACA encodes one of the catalytic subunits of protein kinase A (PKA). PRKACA mutations repress the GLI3 by increasing phosphorylation and cleavage through the constitutively active form of the PKA.[11] DYNC2H1 encodes a cytoplasmic dynein protein which is important for retrograde transport in the cilium and assembly of ciliary/flagellar.[8] KIAA0556 is also a cilium-associated gene, which is thought to cause Joubert syndrome with multiple congenital anomalies.[13] PTPN11 encodes one type of protein tyrosine phosphatase (PTP). Mutation of this gene can lead to Noonan syndrome and acute myeloid leukemia. Although the causative mechanism is unclear, somatic variants of this gene have been found in some patients with HHs.[8]

Integrating genes and signaling pathways is essential to gain a deeper understanding of epileptogenesis and associated comorbidities in HHs. By exploring the genetic factors and signaling pathways involved, we can identify key molecular mechanisms such as GLI3 and Shh signaling pathway that contribute to the formation and progression of epileptic activity in HHs. Such mechanisms can facilitate the development of novel drugs for seizures and other symptoms in HHs.

Hypothalamic hamartoma epileptic networks: Local circuits and HFOs

In HH tissue, there are 2 distinct cellular populations. Most of them are small, with short, unbranched processes. They can lead to spontaneous pacemaker-like firing activity, and their primary neurotransmitter is Gamma-aminobutyric acid (GABA). The rest are large with pleomorphic dendrites. They can depolarize and fire in response to GABA.[14] It has been shown that GABA-mediated excitation results in epileptogenesis in HHs.[15] Through $GABA_A$ and $GABA_B$ receptors, GABA can suppress neuronal firing and is of vital importance to epileptic activity.[16] With the perforated patch-clamp technique, Li et al found a functional rundown of transmembrane currents mediated by $GABA_A$ receptor after GABA agonist exposure in the surgical removal of HH tissue.[17] Gamma-aminobutyric acid, typically an inhibitory neurotransmitter, has a dual role in HH-related epilepsy. The reversal of the intracellular chloride ion gradient due to cation-chloride transporters may be responsible for the paradoxical excitation in response to GABA. Specifically, differential expression of the cation-chloride co-transporters and activation of L-type calcium channels also result in GABA receptor-mediated epilepsy in HH.[18]

A variety of electrophysiological indicators are helpful for the study of HH epileptic networks, including high-frequency oscillations (HFOs, ripples, and fast ripples), field potentials, and multiunit activity.[19] High-frequency oscillations, characterized by 80-600 Hz signals, are a potentially valuable candidate for the identification of epileptogenic tissue.[20] There is a lack of a strict definition of HFOs due to the different spectral frequency ranges and sampling rates. However, studies have shown that HFOs are strongly associated with a number of conditions, including the development of epilepsy, the occurrence of seizures, the severity of epilepsy, and the outcome of treatment.[21] The presence of HFOs observed in vivo within the HH highlights the intricate interplay among multiple distinct neuronal types within complex neuronal networks.[22]

In addition to HFOs, heterogeneous interictal discharges are observed within the HH, with spikes or sharp waves being more frequently detected. Specifically, the ictal pattern is characterized by abrupt giant direct current shifts superimposed with low-voltage fast activity in the beta-gamma range, which can be preceded by variable numbers of preictal discharges with high amplitude.[22] Furthermore, HHs demonstrate the ability to induce typical GS through direct electrical stimulation, revealing the primary role of HHs in GS genesis.[4]

In constructing animal models of epilepsy, repeated application of subconvulsive electrical stimulations can result in spontaneous seizures, which is called "kindling".[23] Despite the failure of the animal model in HHs, "kindling-like" seizures can be found in patients with HH. Some patients with HHs do not achieve the expected improvement after surgery and still have seizures (Figure 2), suggesting that distant cortical regions may be involved. The underlying mechanism may be kindling-like secondary epileptogenesis. According to the definition of epileptic networks, secondary epileptogenesis refers to epileptic activities in cellular elements of a previously normal network induced by discharging epileptogenic region.[24] Freeman et al indicated that GS arise from the hamartoma itself, while the interictal spike-wave and generalized seizures may reflect secondary epileptogenesis.[25] Scholly et al considered that there may be "kindling-like" relationships between the HH and the neocortex based on a dynamic ictal network.[26]

Hypothalamic hamartoma epileptic networks: Whole brain level

The mammillothalamic tract originates from the mammillary body in the hypothalamus and extends towards the anterior nucleus of the thalamus. It further establishes connections with the cingulate gyrus. On the other hand, the fornix extends from the hypothalamus to the hippocampus. Additionally, there are smaller fibers that connect the hypothalamus to the ventral septum and the nucleus retroambiguus within the pons[27] (Figure 3).

Voxel-based morphometry (VBM) analysis is widely used to detect structural changes in gray matter volume. Using VBM of T1 weighted MRI, researchers found significantly greater white matter density in the temporal lobes and cerebellum in HH patients with multiple seizure types. It may be an important cause of the spread of seizure activity in patients with HH, contributing to the evolvement of seizure types.[28] Moreover, VBM can predict the prognosis of patients with HH. When treated with stereotactic radiosurgery, higher pretherapeutic gray matter density (GMD) in the mesencephalic tegmentum, as well as lower pretherapeutic GMD in the right cerebellar

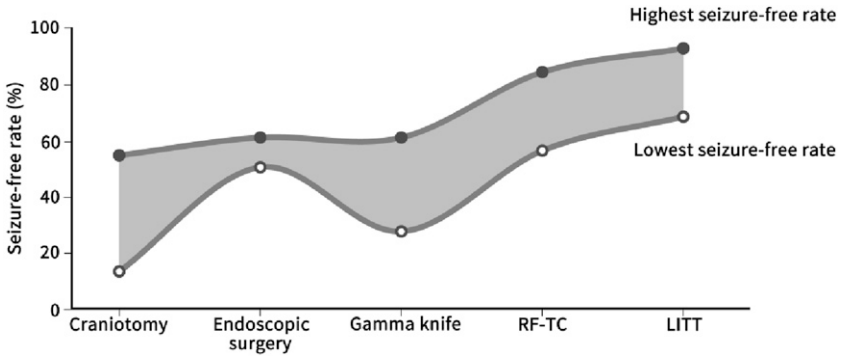

Figure 2. Seizure-free range of various surgical interventions targeting HH. The unfilled dot indicates the lowest seizure-free rate, while the solid dot indicates the highest seizure-free rate. The shaded region delineates the range of seizure-free rates associated with different surgical interventions.

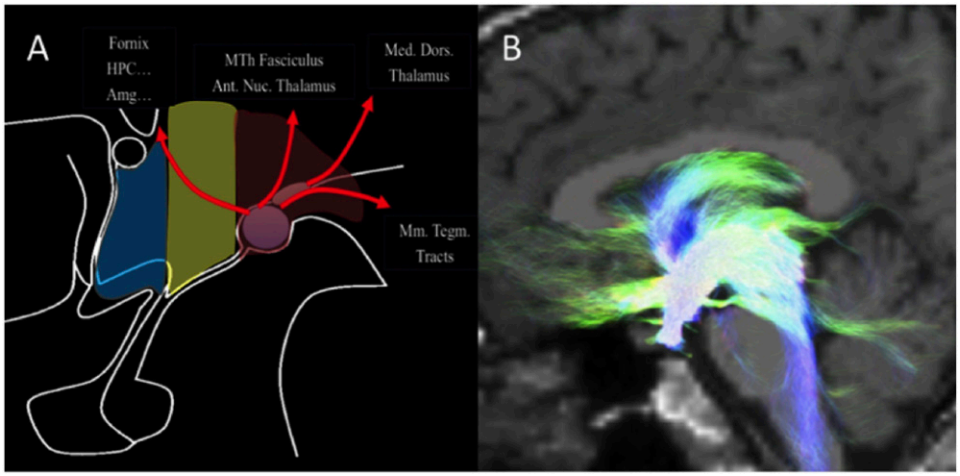

Figure 3. Schematic anatomic connectivity of the mammillary bodies (A) and connectivity of the HH according to DTI (B). (from Régis J, Helen Cross J and Kerrigan JF. Achieving a cure for hypothalamic hamartomas: a Sisyphean quest? Epilepsia 2017; 58 Suppl 2: 7-11; with permission).

lobule, was associated with a better prognosis for seizure freedom.[29]

Given that HHs typically exhibit asymmetry and tend to predominate on one side, the overall brain glucose metabolic pattern also revealed reductions in the neocortex, primarily in the ipsilateral hemisphere to the HH, as well as in bilateral subcortical regions, the cingulate gyrus, and the cerebellum. The dentatothalamic tract and cortico-ponto-cerebellar tract are thought to play a role in facilitating intercommunication between the cerebral cortex, subcortical regions, and cerebellar regions. The characteristics of glucose hypometabolism differ across seizure types. Hypothalamic hamartoma patients with focal to bilateral tonic-clonic seizures (FBTCS) show significant hypometabolism in both sides of the precentral gyrus and insular lobe ipsilateral to the HH compared with the patients with focal aware/impaired awareness seizures.[30] Another study using positron emission tomography (PET) revealed that the final cortical hypometabolic pattern depended on the neuroanatomic location of the HH mass and was consistent with the main involved cortex of the interictal and ictal discharges.[31]

Functional magnetic resonance imaging (fMRI), using seed-based connectivity measures, revealed that the left amygdala-parahippocampal gyrus area, cingulate gyrus, and occipito-temporal gyrus demonstrated the highest derangement in connectivity with the hypothalamus in patients with HHs. These findings align with the regions mentioned earlier that have direct anatomical connections to the hypothalamus.[32]

EEG-fMRI, a combination of electroencephalography (EEG) and fMRI, can detect blood oxygen level-dependent (BOLD) changes that are related to interictal discharges identified from scalp EEG. This technique has been reported to be clinically valuable in localizing the epileptic focus and investigating epileptic networks. Group analysis of EEG-fMRI data from patients with HHs has revealed common activation in the ipsilateral hypothalamus, brainstem tegmentum, and contralateral cerebellum. Conversely, deactivation predominantly occurred in the default mode network (DMN) and bilateral hippocampus. These activated-deactivated networks suggest that frequent epileptic spikes may lead to the deactivation of the DMN and alteration in the network in the hippocampus, which might be an interruption of the normal cognitive development process.[33] Ictal networks from the

hypothalamus have been studied via EEG-fMRI. Detailed evidence of the pathway has been obtained through simultaneous EEG-fMRI recordings capturing approximately 60 seizures in a single individual. The signal was observed to originate from the HH, traveled through the left fornix to the temporal lobe, and subsequently passed through the left cingulate to the dorsal-lateral frontal lobe.[34] Another patient with HHs had ictal EEG-fMRI capturing 21 seizures, with increased BOLD in the precuneus, anterior cingulate, and medial occipital areas.[35]

Group analysis of single-photon emission computed tomography (SPECT) data comparing interictal and ictal states revealed significant hyperperfusion in several regions. These included the ipsilateral hypothalamus, mediodorsal nucleus of the thalamus, putamen, bilateral pontine tegmentum, and contralateral cerebellum. However, contrary to previous reports suggesting that HH lesions connect to the anterior thalamic nucleus, no hyperperfusion was observed in the mammillo-thalamo-cingulate pathway, which could be attributed to the limited sensitivity of SPECT in detecting seizure activity coming from small HH lesions.[36]

The mammillo-thalamo-cingulate circuit had previously been proposed by Kahane et al to be involved in secondary epileptogenesis after GS based on intracranial EEG recordings.[4] For investigating the dynamic ictal network organization, invasive EEG, which allows for deeper and more precise recordings, is a more practical and useful tool for deep and small hamartoma. In the Marseille series, 2 cases studied by using stereo-electroencephalography (SEEG) provided evidence of epileptogenicity extending beyond the boundaries of the HH. In the first case, the HH still triggered clusters of seizures that spread to neocortex, whereas in the second case, the HH was not found to be involved in spontaneous seizures.[26] These findings suggest the possible "kindling-like" relationships between the HH and the neocortex or widespread epileptogenesis. Our recent study showed that independent epileptic ictal discharges arising from the mesial temporal lobe in 3 patients with HHs were thus largely suggestive of extended epileptogenicity outside the limits of the HH. Repetitive intra-hamartoma interictal or ictal discharges are assumed to contribute to the development of dependent or independent epileptogenesis on extra-HH structures.[22]

To investigate the connectivity between the HH and cortex more thoroughly, HH-cortical evoked potentials were applied to evaluate the direct electrophysiological connectivity between the HH and the cortex in vivo. In our recent study, repetitive single-pulse direct electrical stimulation was performed in 2 representative patients through the contacts implanted into the hamartoma. In the patient with prominent GS, the N1 component of averaged evoked potentials to HH stimulation was more remarkable in the orbitofrontal cortex than in the other distributed structures (Figure 4A). Located on the ventral surface of the frontal lobe, the orbitofrontal cortex is involved in emotion and executive function.[37] In another patient suffering from seizures with impaired awareness and GS, the N1 component of averaged evoked potentials to HH stimulation was mainly detected in the amygdala ipsilateral to the attachment of the HH[22] (Figure 4B). Research on the amygdala consistently highlights its pivotal role as a crucial hub that connects various cortical and subcortical structures within the brain.[38,39] This region consistently evaluates and integrates diverse sensory inputs from the environment, assigning them meaningful values such as valence, intensity, and approachability, and contributing to a wide array of behaviors. Consequently, the amygdala plays an important role in the network of the limbic system and various emotional and cognitive functions are thought to be related to the amygdala.[40,41] These results suggested that the spatial distribution of the N1 component was related to seizure semiology.

Hypothalamic hamartoma epileptic networks: Phenotypical expression-seizure semiology and comorbidities

It has been shown that the morphological features may affect the clinical presentations in HHs. HHs are located at the parahypothalamic position without affecting the third ventricle in most patients with central precocious puberty (PP). However, a sessile intrahypothalamic hamartoma may be associated with seizures.[42]

Patients diagnosed with HHs and epilepsy frequently experience cognitive deficits. Frattali et al demonstrated that the conduction pathways in HHs were related to cortical association areas and amygdala and hippocampal formation, which affect cognitive functions and affective/emotional states.[43] Other associated comorbidities in patients with HHs, such as attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder, which manifest with disruptive or aggressive behaviour, were associated with epilepsy and sex(male).[44] Epileptiform activity seem to cause cognitive and behavioral deterioration.[44,45] More than half of the patients with HHs were below the average of global intellectual abilities, mainly in verbal and visual learning and memory.[46] After surgery, there are mild to moderate improvements in patients' intelligence.[47]

The gelastic and sometimes dacrystic seizure is a special and unique clinical manifestation in HHs, in which small HHs are more prone to produce discrete symptoms, such as pressure to laugh. Dacrystic seizures, often referred to as 'crying seizures', are characterized by paroxysmal episodes of stereotyped crying and often co-occur with GS in HHs.[48] At the group level, our recent study of SEEG showed that GS propagated mainly through orbitofrontal areas, the cingulate gyrus and/or the neighboring limbic system.[22] At present, the pathophysiology of GS is still not completely understood. Typically, onset occurs during early infancy, averaging at 6 months of age.[25,49] The utility of scalp EEG is not favorable in the evaluation of GS.[50] Studies on GS should be inseparable from the research on the physiological mechanism of laughter. Laughter comprises 2 components, including motor and emotion. The emotional or involuntary components are associated with the amygdala, thalamic/hypo- and subthalamic areas and the

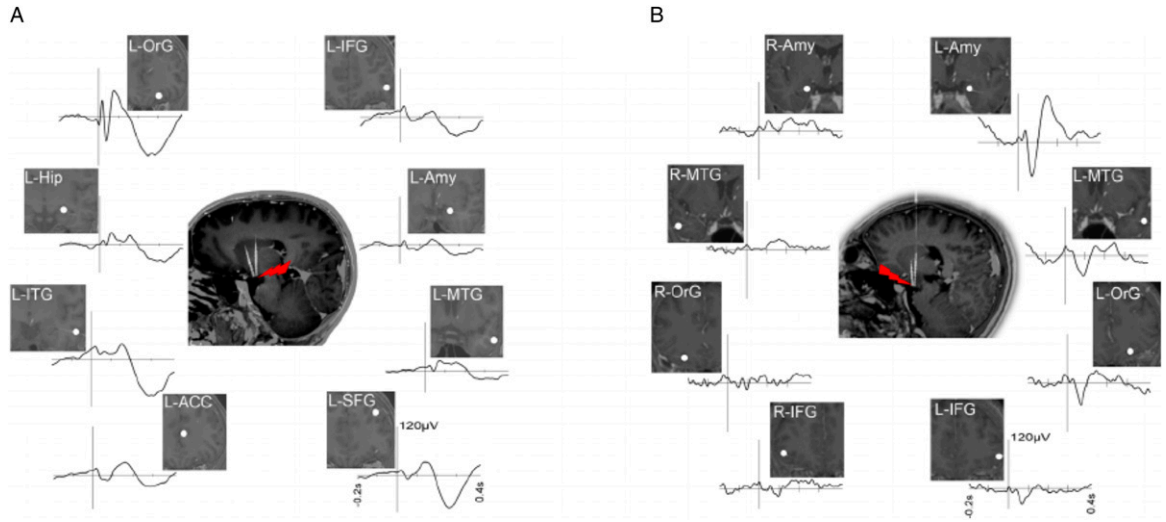

Figure 4. HH-cortical evoked potentials in a patient with prominent GS (A) and HH-cortical evoked potentials in a patient with FIAS and GS (B). (from Wang D, Shan Y, Bartolomei F, et al. Electrophysiological properties and seizure networks in hypothalamic hamartoma. Ann Clin Transl Neurol 2020; 7: 653-666; with permission).

dorsal/tegmental brainstem.[51] Impaired functional connections in mesial temporal structures (hippocampus and amygdala) can result in asymmetric emotional facial movements.[52] The motor or voluntary components are associated with the premotor/frontal opercular areas, motor cortex and the ventral brainstem.[51] Gelastic seizure originating from the HH are not associated with emotion.[53]

In the absence of surgical intervention, GS, commonly observed during childhood, have the potential to evolve into various seizure types. Therefore, HHs are associated with a diverse spectrum of epileptic seizure manifestations, including FBTCS, focal seizures, atonic seizures, tonic seizures, atypical absences, and infantile spasms.[54] Moreover, these seizures are often related to extra-HH origin and exhibit resistance to conventional antiseizure medications. These scenarios suggest that the nature of HHs is complex and multifaceted.

Another essential clinical manifestation is precocious puberty, which results from early activation of the hypothalamic-pituitary-gonadal axis by HHs, as it may produce and release luteinizing-hormone-releasing factor, also named gonadotropin-releasing hormone (GnRH) into blood spontaneously.[55,56] Potential explanations for this symptom may include GABA-mediated excitation and glial factors (like transforming growth factor α). Other less common endocrine symptoms in HHs include growth hormone deficiency, hypothyroidism, and adrenal insufficiency.[56]

Rage attacks are characterized by sudden episodes of explosive anger or aggressive behavior. Rage attacks can also be a concomitant symptom of HHs. It is a common externalizing symptom in HHs.[44] The exact mechanisms underlying rage attacks in individuals with HHs are not fully understood and may be attributed to the abnormal activity of the HHs and its impact on emotional network.

Conclusions

HHs are congenital non-progressive developmental malformations located in the hypothalamus, which can manifest as GS and other seizure types, cognitive and behavioral problems, and precocious puberty. This study provides an in-depth investigation and analysis of the pathogenic mechanisms of HHs from the perspective of epileptic networks. Multiple aspects, including genes and signaling pathways, local circuits, whole-brain level analysis, phenotypical expression in terms of seizure semiology, and comorbidities, have been thoroughly examined. The study of HH epileptic networks contributes to a deeper understanding of this disorder and holds the potential to advance the development of minimally invasive surgical treatments for HHs.

Author contributions

Di Wang performed the conceptualization, investigation, and supervision, wrote the original draft, and reviewed and edited the manuscript. Di Lu performed the investigation and methodology, wrote the original draft, and reviewed and edited the manuscript. Mingtai Zhang performed the investigation and methodology, and wrote the original draft. Anqi Dai performed the formal analysis and investigation, and wrote the original draft. Guangyuan Jin performed the conceptualization and reviewed and edited the manuscript. Qiao Wang performed the methodology and reviewed and edited the manuscript. Yuyang Zhang performed the investigation and reviewed and edited the manuscript. Philippe Kahane performed the conceptualization and investigation, and reviewed and edited the manuscript.

ORCID iDs

Di Wang https://orcid.org/0000-0002-7202-2474
Di Lu https://orcid.org/0009-0002-5499-260X

REFERENCES

1. Munari C, Kahane P, Francione S, et al. Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study). *Electroencephalogr Clin Neurophysiol*. 1995;95:154-160.
2. Kuzniecky R, Guthrie B, Mountz J, et al. Intrinsic epileptogenesis of hypothalamic hamartomas in gelastic epilepsy. *Ann Neurol*. 1997;42:60-67. doi:10.1002/ana.410420111.
3. Mullatti N, Selway R, Nashef L, et al. The clinical spectrum of epilepsy in children and adults with hypothalamic hamartoma. *Epilepsia*. 2003;44:1310-1319.
4. Kahane P, Ryvlin P, Hoffmann D, et al. From hypothalamic hamartoma to cortex: what can be learnt from depth recordings and stimulation? *Epileptic Disord*. 2003;5:205-217.
5. Bourdillon P, Ferrand-Sorbet S, Apra C, et al. Surgical treatment of hypothalamic hamartomas. *Neurosurg Rev*. 2020;44:753. doi:10.1007/s10143-020-01298-z.
6. Boerwinkle VL, Foldes ST, Torrisi SJ, et al. Subcentimeter epilepsy surgery targets by resting state functional magnetic resonance imaging can improve outcomes in hypothalamic hamartoma. *Epilepsia*. 2018;59:2284-2295. doi:10.1111/epi.14583.
7. Scott RC, Menendez de la Prida L, Mahoney JM, et al. WONOEP APPRAISAL: the many facets of epilepsy networks. *Epilepsia*. 2018;59:1475-1483. doi:10.1111/epi.14503.
8. Fujita A, Higashijima T, Shirozu H, et al. Pathogenic variants of DYNC2H1, KIAA0556, and PTPN11 associated with hypothalamic hamartoma. *Neurology*. 2019;93:e237-e251. doi:10.1212/WNL.0000000000007774.
9. Ruiz i Altaba A, Palma V, Dahmane N. Hedgehog-Gli signalling and the growth of the brain. *Nat Rev Neurosci*. 2002;3:24-33. doi:10.1038/nrn704.
10. Saitsu H, Sonoda M, Higashijima T, et al. Somatic mutations in GLI3 and OFD1 involved in sonic hedgehog signaling cause hypothalamic hamartoma. *Ann Clin Transl Neurol*. 2016;3:356-365. doi:10.1002/acn3.300.
11. Hildebrand MS, Griffin NG, Damiano JA, et al. Mutations of the sonic hedgehog pathway underlie hypothalamic hamartoma with gelastic epilepsy. *Am J Hum Genet*. 2016;99:423-429. doi:10.1016/j.ajhg.2016.05.031.
12. Pezzella N, Bove G, Tammaro R, et al. OFD1: one gene, several disorders. *Am J Med Genet C Semin Med Genet* 2022; 190: 57-71. doi:10.1002/ajmg.c.31962.
13. Niceta M, Dentici ML, Ciolfi A, et al. Co-occurrence of mutations in KIF7 and KIAA0556 in Joubert syndrome with ocular coloboma, pituitary malformation and growth hormone deficiency: a case report and literature review. *BMC Pediatr* 2020; 20: 120. doi:10.1186/s12887-020-2019-0.
14. Kerrigan JF, Parsons A, Tsang C, et al. Hypothalamic hamartoma: neuropathology and epileptogenesis. *Epilepsia*. 2017;58(Suppl 2):22-31. doi:10.1111/epi.13752.
15. Wu J, Gao M, Shen JX, et al. Mechanisms of intrinsic epileptogenesis in human gelastic seizures with hypothalamic hamartoma. *CNS Neurosci Ther*. 2015;21:104-111. doi:10.1111/cns.12348.
16. Treiman DM. GABAergic mechanisms in epilepsy. *Epilepsia*. 2001;42(Suppl 3):8-12. doi:10.1046/j.1528-1157.2001.042suppl.3008.x.
17. Li G, Yang K, Zheng C, et al. Functional rundown of gamma-aminobutyric acid(A) receptors in human hypothalamic hamartomas. *Ann Neurol*. 2011;69:664-672. doi:10.1002/ana.22298.
18. Kim DY, Fenoglio KA, Simeone TA, et al. GABAA receptor-mediated activation of L-type calcium channels induces neuronal excitation in surgically resected human hypothalamic hamartomas. *Epilepsia*. 2008;49:861-871. doi:10.1111/j.1528-1167.2007.01455.x.
19. Simeone KA, Sabesan S, Kim DY, et al. L-Type calcium channel blockade reduces network activity in human epileptic hypothalamic hamartoma tissue. *Epilepsia*. 2011;52:531-540. doi:10.1111/j.1528-1167.2010.02942.x.
20. Li X, Zhang H, Lai H, et al. High-frequency oscillations and epileptogenic network. *Curr Neuropharmacol*. 2022;20:1687-1703. doi:10.2174/1570159X19666210908165641.
21. Jacobs J, Zijlmans M. HFO to measure seizure propensity and improve prognostication in patients with epilepsy. *Epilepsy Curr*. 2020;20:338-347. doi:10.1177/1535759720957308.
22. Wang D, Shan Y, Bartolomei F, et al. Electrophysiological properties and seizure networks in hypothalamic hamartoma. *Ann Clin Transl Neurol*. 2020;7:653-666. doi:10.1002/acn3.51033.
23. McNamara JO. Analyses of the molecular basis of kindling development. *Psychiatry Clin Neurosci*. 1995;49:S175-178. doi:10.1111/j.1440-1819.1995.tb02167.x.
24. Morrell F. Secondary epileptogenesis in man. *Arch Neurol*. 1985;42:318-335. doi:10.1001/archneur.1985.04060040028009.
25. Freeman JL, Harvey AS, Rosenfeld JV, et al. Generalized epilepsy in hypothalamic hamartoma: evolution and postoperative resolution. *Neurology*. 2003;60:762-767. doi:10.1212/01.wnl.0000049457.05670.7d.
26. Scholly J, Staack AM, Kahane P, et al. Hypothalamic hamartoma: epileptogenesis beyond the lesion? *Epilepsia*. 2017;58(Suppl 2):32-40. doi:10.1111/epi.13755.
27. Régis J, Helen Cross J, Kerrigan JF. Achieving a cure for hypothalamic hamartomas: a Sisyphean quest? *Epilepsia*. 2017;58(Suppl 2):7-11. doi:10.1111/epi.13773.
28. Losey TE, Beeman SC, Ng YT, et al. White matter density is increased in patients with hypothalamic hamartoma and multiple seizure types. *Epilepsy Res*. 2011;93:212-215. doi:10.1016/j.eplepsyres.2010.12.006.
29. Tuleasca C, Hamdi H, Daquin G, et al. Increased gray matter density in the right mesencephalic tegmentum is associated with better engel classes I and II after radiosurgery for hypothalamic hamartomas. *Neurosurgery*. 2022;90:180-185. doi:10.1227/NEU.0000000000001738.
30. Lu C, Wang K, Meng F, et al. ^{18}F-FDG-PET glucose hypometabolism pattern in patients with epileptogenic hypothalamic hamartoma. *Front Med*. 2021;15:913-921. doi:10.1007/s11684-021-0874-1.
31. Yang YF, Wei PH, Meng F, et al. Glucose metabolism characteristics of extra-hypothalamic cortex in patients with hypothalamic hamartomas (HH) undergoing epilepsy evaluation: a retrospective study of 16 cases. *Front Neurol*. 2020;11:587622. doi:10.3389/fneur.2020.587622.
32. Boerwinkle VL, Wilfong AA, Curry DJ. Resting-state functional connectivity by independent component analysis-based markers corresponds to areas of initial seizure propagation established by prior modalities from the hypothalamus. *Brain Connect*. 2016; 6: 642-651. doi:10.1089/brain.2015.0404.
33. Usami K, Matsumoto R, Sawamoto N, et al. Epileptic network of hypothalamic hamartoma: an EEG-fMRI study. *Epilepsy Res*. 2016;125:1-9. doi:10.1016/j.eplepsyres.2016.05.011.
34. Leal AJ, Monteiro JP, Secca MF, et al. Functional brain mapping of ictal activity in gelastic epilepsy associated with hypothalamic hamartoma: a case report. *Epilepsia*. 2009;50:1624-1631. doi:10.1111/j.1528-1167.2008.01810.x.
35. Kokkinos V, Zountsas B, Kontogiannis K, et al. Epileptogenic networks in two patients with hypothalamic hamartoma. *Brain Topogr*. 2012;25:327-331. doi:10.1007/s10548-011-0214-x.
36. Kameyama S, Masuda H, Murakami H. Ictogenesis and symptomatogenesis of gelastic seizures in hypothalamic hamartomas: an ictal SPECT study. *Epilepsia*. 2010;51:2270-2279. doi:10.1111/j.1528-1167.2010.02739.x.
37. Rudebeck PH, Rich EL. Orbitofrontal cortex. *Curr Biol*. 2018;28:R1083-R1088. doi:10.1016/j.cub.2018.07.018.
38. Sawada M, Adolphs R, Dlouhy BJ, et al. Mapping effective connectivity of human amygdala subdivisions with intracranial stimulation. *Nat Commun*. 2022;13:4909. doi:10.1038/s41467-022-32644-y.
39. Zhang H, Wang D, Wei P, et al. Integrative roles of human amygdala subdivisions: insight from direct intracerebral stimulations via stereotactic EEG. *Hum Brain Mapp* 2023; 44: 3610-3623. doi:10.1002/hbm.26300.
40. Janak PH, Tye KM. From circuits to behaviour in the amygdala. *Nature*. 2015;517:284-292. doi:10.1038/nature14188.
41. Simic G, Tkalcic M, Vukic V, et al. Understanding emotions: origins and roles of the amygdala. *Biomolecules*. 2021;11:823. doi:10.3390/biom11060823.
42. Jung H, Neumaier Probst E, Hauffa BP, et al. Association of morphological characteristics with precocious puberty and/or gelastic seizures in hypothalamic hamartoma. *J Clin Endocrinol Metab*. 2003;88:4590-4595. doi:10.1210/jc.2002-022018.
43. Frattali CM, Liow K, Craig GH, et al. Cognitive deficits in children with gelastic seizures and hypothalamic hamartoma. *Neurology*. 2001;57:43-46. doi:10.1212/wnl.57.1.43.
44. Corbet Burcher G, Liang H, Lancaster R, et al. Neuropsychiatric profile of paediatric hypothalamic hamartoma: systematic review and case series. *Dev Med Child Neurol*. 2019;61:1377-1385. doi:10.1111/dmcn.14241.
45. Noeker M, Haverkamp-Krois A, Haverkamp F. Development of mental health dysfunction in childhood epilepsy. *Brain Dev*. 2005;27:5-16. doi:10.1016/j.braindev.2004.02.008.
46. Quiske A, Frings L, Wagner K, et al. Cognitive functions in juvenile and adult patients with gelastic epilepsy due to hypothalamic hamartoma. *Epilepsia*. 2006;47:153-158. doi:10.1111/j.1528-1167.2006.00381.x.
47. Wethe JV, Prigatano GP, Gray J, et al. Cognitive functioning before and after surgical resection for hypothalamic hamartoma and epilepsy. *Neurology*. 2013;81:1044-1050. doi:10.1212/WNL.0b013e3182a4a3e3.
48. Offen ML, Davidoff RA, Troost BT, et al. Dacrystic epilepsy. *J Neurol Neurosurg Psychiatry*. 1976;39:829-834. doi:10.1136/jnnp.39.9.829.
49. Striano S, Striano P. Clinical features and evolution of the gelastic seizures-hypothalamic hamartoma syndrome. *Epilepsia*. 2017;58(Suppl 2):12-15. doi:10.1111/epi.13753.
50. Troester M, Haine-Schlagel R, Ng YT, et al. EEG and video-EEG seizure monitoring has limited utility in patients with hypothalamic hamartoma and epilepsy. *Epilepsia*. 2011;52:1137-1143. doi:10.1111/j.1528-1167.2011.03095.x.
51. Wild B, Rodden FA, Grodd W, et al. Neural correlates of laughter and humour. *Brain*. 2003;126:2121-2138. doi:10.1093/brain/awg226.
52. Yamao Y, Matsumoto R, Kunieda T, et al. Neural correlates of mirth and laughter: a direct electrical cortical stimulation study. *Cortex*. 2015;66:134-140. doi:10.1016/j.cortex.2014.11.008.
53. Lu D, Wang T, Yang Y, et al. Advances in hypothalamic hamartoma research over the past 30 years (1992-2021): a bibliometric analysis. *Front Neurol*. 2023;14:1176459. doi:10.3389/fneur.2023.1176459.
54. Parvizi J, Le S, Foster BL, et al. Gelastic epilepsy and hypothalamic hamartomas: neuroanatomical analysis of brain lesions in 100 patients. *Brain*. 2011;134:2960-2968. doi:10.1093/brain/awr235.
55. Judge DM, Kulin HE, Page R, et al. Hypothalamic hamartoma: a source of luteinizing-hormone-releasing factor in precocious puberty. *N Engl J Med*. 1977;296:7-10. doi:10.1056/NEJM197701062960102.
56. Harrison VS, Oatman O, Kerrigan JF. Hypothalamic hamartoma with epilepsy: review of endocrine comorbidity. *Epilepsia*. 2017;58(Suppl 2):50-59. doi:10.1111/epi.13756.