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Exploring the Magnetic Resonance Imaging Manifestations of Hippocampal and Amygdala Structures in Temporal Lobe Epilepsy Based on Voxel-Based Morphological Analysis

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***A*bstract:** Temporal lobe epilepsy (TLE) is the most common refractory subtype of epilepsy in clinical practice, with a complex pathogenesis and a lack of precise biomarkers for diagnosis and prognosis evaluation, seriously affecting the quality of life of patients. The hippocampus and amygdala, as the core structures of the limbic system, play a key role in the pathogenesis of TLE. Structural abnormalities in both are considered important pathological bases for the initiation, spread, and progression of epileptic discharges. Although conventional magnetic resonance imaging can detect obvious hippocampal sclerosis, it is difficult to capture microstructural changes and has limited ability to identify hidden damage in areas such as the amygdala, leading to misdiagnosis or missed diagnosis in some patients with hidden TLE. Voxel-based morphological analysis (VBM) can accurately quantify the volume and density changes of the whole brain gray and white matter, providing technical support for analyzing the microstructural damage of the hippocampus and amygdala in TLE patients. Previous studies have suggested that the amygdala is not only a "susceptible area" for epileptic discharges, but may also serve as a "relay station" involved in discharge diffusion. Its structural abnormalities are closely related to the frequency and prognosis of TLE attacks. However, the synergistic effect and specific pathological mechanisms of structural changes in the hippocampus and amygdala still need to be further clarified. Therefore, this study used VBM technology to systematically analyze the magnetic resonance imaging manifestations of the hippocampus and amygdala in TLE patients, aiming to reveal their structural abnormalities and provide imaging evidence for the accurate diagnosis, mechanism research, and prognosis evaluation of TLE.

Keywords: Morphological analysis of voxels; Temporal lobe epilepsy; Magnetic resonance

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1. Introduction

Temporal lobe epilepsy is one of the most common subtypes of adult epilepsy, accounting for about 40% -50% of all epilepsy cases, and up to 60–70% of refractory epilepsy. Its etiology is complex, mainly including hippocampal sclerosis, traumatic brain injury, central nervous system infection, cerebrovascular disease, etc. [1] Among them, hippocampal sclerosis is the most common pathological basis. The disease is characterized by recurrent partial episodes, and long-term episodes not only lead to progressive cognitive decline, especially significant decline in learning and memory abilities, but also trigger emotional disorders such as anxiety and depression, seriously damaging the patient's daily living and social skills, and bringing heavy medical burden and economic pressure to the family and society.

The hippocampus and amygdala, as core components of the limbic system, play crucial roles in physiological processes such as learning, memory encoding, and emotion regulation, and are closely related to the pathogenesis of temporal lobe epilepsy. Clinical studies have confirmed that most patients with temporal lobe epilepsy exhibit sclerosis symptoms such as hippocampal neuron loss and gliosis, accompanied by abnormal morphology of the amygdala [2]. These pathological changes have complex causal relationships with the onset and spread of epileptic seizures, which may be the inducer of epileptic seizures or secondary damage caused by recurrent seizures, becoming the core target area for clinical localization of epileptic foci.

Structural magnetic resonance imaging (sMRI) has been widely used for brain structure assessment and lesion localization in temporal lobe epilepsy due to its high spatial resolution advantage [3]. It can clearly display morphological changes in key structures such as hippocampus and amygdala, providing important imaging evidence for clinical diagnosis. However, traditional sMRI mainly relies on qualitative observation, which lacks sensitivity to early and subtle structural changes, and cannot achieve accurate quantitative analysis of parameters such as brain volume and density, making it difficult to meet the needs of early disease screening, disease progression monitoring, and personalized treatment evaluation. Therefore, it is urgent to introduce precise quantitative analysis techniques to make up for this deficiency.

2. Research progress of VBM in hippocampal structure analysis of temporal lobe epilepsy

2.1. Core findings of VBM research on changes in hippocampal volume and density

Based on Voxel-based morphological analysis (VBM), with the quantitative advantage of voxel levels, specific changes in the hippocampal structure of patients with temporal lobe epilepsy (TLE) were clearly revealed [4]. The core findings focused on the lateral and regional specificity of volume atrophy and density abnormalities. Most studies have confirmed that patients with unilateral TLE have significantly reduced hippocampal volume on the epileptic side, and the degree of atrophy is higher than that on the non epileptic side. This feature is particularly prominent in medial temporal lobe epilepsy. VBM further discovered that hippocampal atrophy is not uniformly distributed, but is more pronounced in subregions such as CA1, CA3, and the dentate gyrus, which may be related to the susceptibility of neurons in these regions to abnormal discharge damage. For patients with bilateral TLE, there is heterogeneity in hippocampal structural changes, with some patients showing symmetrical atrophy on both sides and others showing asymmetrical changes mainly on one side [5]. This difference may be related to the pathogenesis and progression of the disease. In addition, the decrease in hippocampal gray matter density detected by VBM often occurs earlier than visible volume atrophy, providing a sensitive indicator for early pathological change identification of TLE. However, the differences in sample size, scanning parameters, and analysis software

among different studies have led to slight discrepancies in some results, which require further validation through large-scale standardized research.

2.2. Correlation study between hippocampal structural abnormalities and clinical features of TLE

The quantitative analysis of VBM provides precise evidence for the association between hippocampal structural abnormalities and clinical features of TLE, with core correlation dimensions covering seizure characteristics, cognitive function, and drug effects. In terms of seizure-related characteristics, research has shown that the degree of hippocampal atrophy is positively correlated with the frequency and duration of epileptic seizures [6]. Patients with a course of more than 5 years have a significantly higher rate of hippocampal volume reduction than those with short-term seizures, suggesting that long-term abnormal discharges may exacerbate hippocampal neuronal damage. In terms of cognitive function correlation, VBM found that patients with decreased gray matter density in the hippocampal CA1 region and dentate gyrus had significantly lower episodic memory and spatial memory scores than those with normal structure, and the degree of cognitive impairment was positively correlated with the degree of hippocampal structural abnormalities, revealing the key role of hippocampal structural integrity in cognitive function. In terms of drug effects, some studies have found through VBM comparison that patients who regularly take antiepileptic drugs for a long time have a slower progression of hippocampal atrophy than those who do not regularly use drugs. However, there are differences in the protective effects of different drugs on hippocampal structures, and there is a lack of large-scale, long-term follow-up data support. In addition, a few studies suggest that hippocampal structural abnormalities may also be related to seizure types, and patients with complex partial seizures have a wider range of hippocampal abnormalities.

2.3. Differences in VBM research on hippocampal structural changes in different subtypes of TLE

The precise quantitative ability of VBM technology clearly distinguishes the specific differences in hippocampal structural changes among different subtypes of TLE patients, providing an objective basis for TLE subtype classification [7]. In the comparison between medial temporal lobe epilepsy (mTLE) and lateral temporal lobe epilepsy (lTLE), VBM studies showed that the incidence of hippocampal volume atrophy in mTLE patients was as high as 70% -80%, and it was mostly significant atrophy on the epileptic side. Significant gray matter density reduction was observed in various subregions of the hippocampus; However, the hippocampal structural changes in patients with lTLE are relatively mild, with only some patients showing mild bilateral hippocampal volume reduction, without obvious lateral specificity. This is related to the fact that mTLE has the hippocampus as the core of the epileptic foci, and lTLE's epileptic foci are mostly located in the lateral temporal lobe. In the comparison of TLE subtypes with and without hippocampal sclerosis (HS), the differences are more significant: TLE patients with HS show a significant reduction in hippocampal volume on the epileptic side, a significant decrease in gray matter density, and often accompanied by irregular hippocampal morphology in VBM; For TLE patients without HS, there may not be a significant reduction in hippocampal volume, but some patients can detect subtle gray matter density abnormalities in local subregions (such as CA3) through VBM. In addition, studies have found through VBM that there are differences in the pattern of hippocampal structural changes between patients with familial TLE and those with sporadic TLE, and familial patients are more likely to experience bilateral contralateral neuropathy.

3. Research progress of VBM in amygdala structure analysis of temporal lobe epilepsy

3.1. Core findings of VBM research on changes in amygdala volume and density

The voxel-based morphometric measurement (VBM) technique, with its advantages of automation and whole-brain coverage, has become a core tool for analyzing the microstructural changes in the amygdala of patients with temporal lobe epilepsy (TLE). Its core findings focus on two dimensions: volume atrophy and density abnormalities. Most studies have confirmed that the volume of the amygdala on the affected side of TLE patients is significantly reduced, and the degree of reduction is positively correlated with the course of the disease [8]. The volume reduction rate in patients with a course of more than 10 years can reach 15–20%. More importantly, VBM can detect a decrease in grayscale values that are difficult to detect with conventional MRI, indicating neuronal loss, gliosis, and reduced synaptic connections in the amygdala. In patients with unilateral TLE, about 30–40% will experience a mild reduction in the volume of the contralateral amygdala, indicating that epileptic discharges may cause bilateral structural damage. In addition, there are differences in amygdala changes among different subtypes of TLE: amygdala atrophy is more pronounced in hippocampal sclerosis-related TLEs, while non-hippocampal sclerosis type TLEs may only exhibit local density abnormalities. These findings provide imaging biomarkers for the objective diagnosis of TLE, especially for occult cases without clear hippocampal lesions, which have important reference value [9].

3.2. Study on the correlation between abnormal amygdala structure and clinical features of TLE

Existing imaging evidence suggests that some TLE patients exhibit ipsilateral amygdala volume atrophy or contralateral compensatory changes, but the relationship between these morphological changes and clinical symptoms has not been fully elucidated and there are significant individual differences. [10] Analysis has found that in some patients, the significant reduction in amygdala (especially ipsilateral) volume may be related to longer disease duration or higher frequency of epileptic seizures. This may reflect the cumulative effect of neuronal damage or remodeling caused by repeated epileptic activity. However, this association is not absolutely linear, and other factors such as age of onset and medication history may constitute important confounding variables. Meanwhile, preliminary observations suggest that abnormalities in the amygdala structure may be potentially associated with certain specific symptom dimensions. For example, some TLE patients with obvious anxiety or emotional regulation difficulties have more common signal abnormalities or connectivity changes in the amygdala (often involving both sides). This supports the neurobiological hypothesis that the dysfunction of the amygdala as a hub of the limbic system may be involved in the comorbidity of emotional symptoms in TLE. In addition, studies have reported that the synergistic atrophy of the amygdala and hippocampus may be associated with complaints of memory impairment, but the causal relationship and directionality still need further verification.

3.3. Exploration of the role of the amygdala in the pathogenesis of TLE

Combining VBM research results with neurophysiological mechanisms, the dual role of the amygdala in the pathogenesis of TLE can be indirectly inferred, serving as both a “susceptible area” for epileptic discharges and a “relay station” for discharge diffusion. Firstly, the decrease in grayscale values and neuronal loss detected by VBM in the amygdala may be due to excitotoxic damage caused by long-term epileptic discharges: excessive release of glutamate leads to calcium influx imbalance, which in turn destroys neuronal structure and forms a vicious cycle of “discharge damage easier discharge”. This explains why patients with amygdala structural abnormalities have

more frequent seizures. Secondly, the abnormal structure of the bilateral amygdala in patients with unilateral TLE suggests that the amygdala may serve as a diffusion pathway for epileptic discharges, transmitting discharges to the contralateral hemisphere through the limbic system connection and participating in the formation of global cerebral seizures. In addition, abnormal structural connections between the amygdala and regions such as the hippocampus and temporal pole (confirmed by VBM combined with diffusion tensor imaging) may exacerbate the formation of epileptic networks and enhance the synchronicity of discharges. At the same time, the ion microenvironment disorder caused by amygdala gliosis further reduces the neuronal firing threshold and promotes the maintenance of epileptic foci. This indirect evidence suggests that structural abnormalities in the amygdala are not secondary changes to TLE, but rather a key link involved in its pathogenesis.

4. The value and challenges of VBM technology in the clinical application of temporal lobe epilepsy

4.1. Clinical diagnosis and differential diagnostic value

Voxel-based morphometry (VBM) technology, with its advantages of automation and quantification, has become an important auxiliary tool for clinical diagnosis of temporal lobe epilepsy (TLE). Traditional imaging has low sensitivity to early or mild changes in brain structure, while VBM can accurately detect gray matter volume atrophy in peripheral system structures such as hippocampus and amygdala in TLE patients through whole brain voxel level analysis, and even identify subclinical brain structural abnormalities in patients with atypical clinical symptoms, providing objective imaging evidence for early diagnosis of TLE. In terms of differential diagnosis, TLE often needs to be distinguished from frontal lobe epilepsy, epileptic seizures caused by mental and psychological disorders, etc. The brain structural changes of these diseases have different characteristics. For example, frontal lobe epilepsy is often manifested as abnormal gray matter volume in the frontal lobe, while VBM can significantly improve the accuracy of differential diagnosis by comparing the brain structural morphological characteristics of different diseases, combining clinical symptoms and EEG results. In addition, for cryptogenic TLEs without clear lesions, VBM can detect potential brain structural changes, providing direction for further etiological exploration and compensating for the shortcomings of traditional imaging.

4.2. Classification and prognostic evaluation value

VBM technology may provide a certain reference basis for the classification and prognosis evaluation of temporal lobe epilepsy (TLE), but its conclusions need to be comprehensively judged in combination with other clinical indicators, and it is difficult to use it alone as an absolute classification or prognosis judgment standard. In terms of subtyping assistance, there may be subtle differences in the VBM changes of key structures such as the amygdala and hippocampus in patients with different subtypes of TLE. For patients with TLE related to hippocampal sclerosis, the volume shrinkage of the amygdala and hippocampus on the affected side may be more pronounced, and the range of gray value reduction may be wider. Patients with non-hippocampal sclerosis type TLE may only present with localized density abnormalities in the amygdala or no significant volume changes. This structural difference may assist in clinical differentiation of TLE subtypes, especially for cases with atypical imaging findings, which may improve the accuracy of classification. However, the sample size of relevant studies is still relatively limited, and there are slight differences in the conclusions of different studies. A unified classification threshold has not yet been formed. In terms of prognostic assessment, the degree of structural abnormalities detected by VBM may serve as one of the reference dimensions for prognostic judgment. For example, patients

with mild amygdala volume atrophy and no significant decrease in grayscale values before treatment may have a relatively better response to drug therapy and a higher probability of seizure control; Patients with severe structural damage may have an increased risk of developing drug resistance.

4.3. Challenges currently faced in clinical translation

Although VBM technology has made significant progress in TLE research, clinical translation still faces multiple challenges. Firstly, standardization issues urgently need to be addressed: there are differences in scanning parameters, post-processing software, and analysis methods used in different studies, resulting in poor comparability of results, a lack of unified clinical diagnostic thresholds, and difficulty in forming standardized clinical application processes. Secondly, insufficient specificity limits its independent application. The gray matter volume atrophy detected by VBM is not unique to TLE, and similar changes may also occur in diseases such as Alzheimer's disease and schizophrenia. Relying solely on VBM results cannot diagnose TLE, and other examination results need to be combined, increasing the complexity of clinical application. Furthermore, the technical interpretation threshold is relatively high: VBM results need to be comprehensively analyzed based on neuroanatomical knowledge and clinical experience, and grassroots hospitals lack professional image interpretation talents, making it difficult to popularize and apply. In addition, the issue of sample size and heterogeneity is prominent: existing studies are mostly small sample single-center studies, and TLE patients have heterogeneity in disease duration, seizure type, treatment history, etc., which limits the generalizability of research results. Finally, the dynamic monitoring capability is insufficient, and currently VBM is mostly used for static brain structure analysis, which is difficult to reflect the dynamic changes in brain structure during epileptic seizures in real time, and has limited value for dynamic evaluation of treatment effectiveness.

5. Conclusion

Based on Voxel-based morphological analysis (VBM), with the advantage of precise quantification, the specificity of hippocampal structural changes in patients with different subtypes of temporal lobe epilepsy (TLE) has been clarified. Patients with medial TLE exhibit significant hippocampal atrophy and extensive involvement of subregions on the epileptic side, while those with lateral TLE have mild hippocampal abnormalities and no significant lateral differences; Patients with hippocampal sclerosis have significantly reduced hippocampal volume and density, while those without sclerosis only show subtle abnormalities in local subregions; There are also differences in the hippocampal change patterns between familial and sporadic TLEs. In summary, VBM can provide objective imaging evidence for the subtyping of TLE, help deepen the understanding of the pathological mechanism of TLE, and lay the foundation for accurate clinical diagnosis and treatment.

Disclosure statement

The authors declare no conflict of interest.

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