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Review Paper

Neuroimaging Findings in Idiopathic Generalized Epilepsy and Psychogenic Non-epileptic Seizures: A Narrative Review

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ABSTRACT

Background: Psychogenic non-epileptic seizures (PNES) and idiopathic generalized epilepsy (IGE) are two clinical entities that may resemble each other in presentation but differ considerably in their mechanisms, outcomes, and therapeutic approaches. The differential diagnosis between PNES and IGE can be particularly difficult in cases resistant to medical therapy.

Objectives: This review aimed to compare and contrast the neuroimaging findings associated with PNES and IGE to better understand their neurobiological underpinnings and to highlight potential imaging-based differentiators that may assist in clinical diagnosis and treatment planning.

Materials & Methods: We reviewed published reports employing structural and functional neuroimaging modalities—including magnetic resonance imaging (MRI), morphometric studies, diffusion tensor imaging (DTI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI)—in patients with PNES and IGE. The data were synthesized to identify common patterns, divergent findings, and clinical correlations.

Results: While IGE is characterized by thalamocortical dysfunction and white matter disorganization, PNES is more frequently associated with multifocal structural abnormalities

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and disrupted emotion-motor-executive connectivity. Functional imaging demonstrated distinct connectivity and metabolic profiles, with PNES patients showing greater alterations in the insular, cingulate, and prefrontal regions. MRS studies indicated differences in neurochemical profiles, supporting the theory of divergent network-level dysfunctions.

Conclusion: Neuroimaging reveals considerable pathophysiological differences between PNES and IGE. These differences can support more accurate differential diagnosis and help guide personalized treatment strategies. Importantly, neuroimaging findings challenge the historical view of PNES as purely psychogenic, highlighting its organic basis.

Keywords: PNES, Idiopathic generalized epilepsy, Magnetic resonance imaging (MRI), Diffusion tensor imaging (DTI), Positron-emission tomography, Magnetic resonance spectroscopy (MRS)

Highlights

• In structural MRI, PNES patients exhibit multifocal abnormalities across frontal, parietal, temporal, and cerebellar regions, contrasting with the non-specific or absent structural changes typically observed in IGE.

• In fMRI, distinct connectivity profiles are evident, with PNES showing altered emotion-motor-executive network connectivity (e.g. insula, cingulate), while IGE demonstrates thalamocortical dysfunction.

• In DTI, white matter disruptions differ, with PNES involving the uncinate fasciculus and corona radiata, whereas IGE primarily affects thalamocortical and callosal tracts.

● In MRS, PNES is associated with elevated glutamate/creatine ratios in limbic regions, while IGE shows reduced NAA/creatine in thalamic and prefrontal areas.

● Neuroimaging supports PNES as a disorder with organic underpinnings, necessitating distinct therapeutic strategies from IGE.

Introduction

Psychogenic non-epileptic seizures (PNES), also known as functional seizures and previously referred to as pseudo or hysterical seizures, are defined as episodic symptoms that occur without synchronous discharges at the brain cortex level, distinguishing them from epilepsy [1-4]. While this epileptic-mimicking behavior occurs both in people who have epilepsy and in those without epilepsy, the coexistence rate in epileptic patients is 10-13% [3]. Idiopathic generalized epilepsy (IGE) includes generalized epileptic syndromes from childhood to adulthood, like myoclonic, absence, and generalized tonic-clonic seizures (GTCS) [5]. The onset of the spike-wave in IGE originates from the frontal cortex or from thalamic nuclei, based on another study [6]. Principally, in IGE, the genetic basis is much more assumed, while the remaining five, including infection, metabolic, structural, immunologic, and unknown causes, may be considered other etiologies [7].

Based on the neuropsychological and neuroimaging investigations, studies demonstrated impairment in thalamo-frontal and corticolimbic pathways, which are shared pathways in both IGE and PNES [8]. Impaired cognitive function is often found in patients with epilepsy, and these patients show impaired function in memory, attention, and data processing in the ictal, postictal, and interictal phases [9]. Likewise, in functional movement disorders, like PNES, the premotor areas, prefrontal cortex (PFC), insular cortex, posterior parietal cortex/temporoparietal junction (PPC/TPJ), and amygdala, along with their networks, are considered the principal structures [10].

Although the incidence of epilepsy is generally higher in men, both PNES and IGE have a higher prevalence in women. The incidence and prevalence rates of PNES are 1.4 to 4.9 and 33 patients per 100,000 cases, respectively. Also, among individuals with drug-resistant epilepsy, 20-40% are diagnosed with PNES. As previously mentioned, PNES is more common in women during their second and third decades of life and is uncommon

in individuals under the age of six and over 50 years [10, 11]. IGE accounts for 20% of epilepsies and has a prevalence of one case per 100 people, with the majority of diagnoses (approximately 92%) occurring in the third decade of life [12].

Psychiatric comorbidities further distinguish the two disorders. PNES patients frequently present with anxiety, post-traumatic stress disorder, and personality disorders, and may also experience depression and suicidal ideation. In contrast, mood disorders and anxiety-panic syndromes are the most commonly reported psychiatric comorbidities among individuals with IGE [2, 11, 12].

Given these complexities, neuroimaging studies provide a valuable framework for comparing the two conditions. While earlier research has often examined PNES and IGE separately, a comparative perspective may help clarify their distinct neurobiological mechanisms and clinical implications. This review, therefore, synthesizes the available evidence across multiple imaging modalities—including magnetic resonance imaging (MRI), morphometry, diffusion tensor imaging (DTI), Positron emission tomography (PET), single-photon emission computed tomography (SPECT), Magnetic resonance spectroscopy (MRS), and functional MRI (fMRI)—to highlight differences and potential diagnostic markers between PNES and IGE, as summarized in Table 1 and Figure 1.

MRI Neuroimaging Findings

Brain structural abnormalities

MRI is widely applied in the study of epilepsy to better understand its underlying mechanisms. Various MRI modalities allow for the assessment of different aspects of brain structure and function. These include volumetric and morphometric analyses to assess gray matter, diffusion-based techniques to evaluate white matter integrity, fMRI to measure neuronal activity, and MR spectroscopy for metabolic profiling [13].

Previous studies on PNES, while scarce in number, reported no brain structural abnormalities [14-17]; nevertheless, 40% of patients with PNES had brain lesions, and there is limited information on the etiology and effect of these lesions on PNES. However, they may impact PNES and its consequences. More specifically, Bolen et al. reported anatomic abnormalities in 38% of patients with PNES, including encephalomalacia or chronic infarct, areas of parenchymal focal T2 hyperintensity, and cerebral volume loss [14]. The prevalence of MRI abnormalities has been reported as 15% by Szaflarski et al. [17]. Moreover, as stated by Kanner et al., the presence of structural abnormalities on MRI can predict the prognosis and recurrence of PNES [15].

In contrast, IGE is usually associated with a structurally normal brain on conventional MRI. Nevertheless, a study of 134 individuals with IGE identified abnormalities in 33 patients. Reported changes included arachnoid cysts, cortical atrophy, signal alterations in the basal ganglia, enlargement of perivascular spaces, ventricular enlargement, white matter hyperintensities in the frontal lobes, hippocampal volume loss, focal gyral malformations, and gliosis in the frontal lobe area, although most of these (88%) were non-specific [6].

In addition, multifocal abnormalities were observed in the frontal, parietal, temporal, cerebellar, brainstem, and occipital areas in patients with PNES (47.8%) compared to the group with IGE (21.9%). However, IGE patients exhibited more significant temporal abnormalities in comparison to those with PNES (57.8% vs 21.7%) [2].

Comparative analyses highlight some distinctions between PNES and IGE. Multifocal abnormalities affecting the frontal, parietal, temporal, cerebellar, brainstem, and occipital regions appear more common in PNES, whereas temporal lobe involvement is more frequently observed in epilepsy. Specifically, one study noted multifocal abnormalities in nearly half of PNES patients but in only one-fifth of those with epilepsy, while temporal lobe abnormalities were far more prevalent in the epilepsy group than in PNES [14].

Morphometric changes

Morphometric analyses provide further insights into brain structure in PNES and IGE. Labate et al. reported reductions in gray matter volume within several regions in PNES patients, including the bilateral cerebellum, the right precentral and middle frontal gyri, as well as the right ACC and supplementary motor area [18]. Additionally, cortical thinning was observed in areas, such as the right precentral and superior frontal gyri, the right precuneus, and the right paracentral gyrus.

Other studies, however, have reported somewhat different findings. For instance, Ristić et al. noted decreased cortical thickness in the bilateral precentral, right entorhinal, and right lateral occipital regions of PNES patients but also reported increased thickness in the insula and medial orbitofrontal cortices on both sides, along with the left lateral orbitofrontal cortex [18, 19].

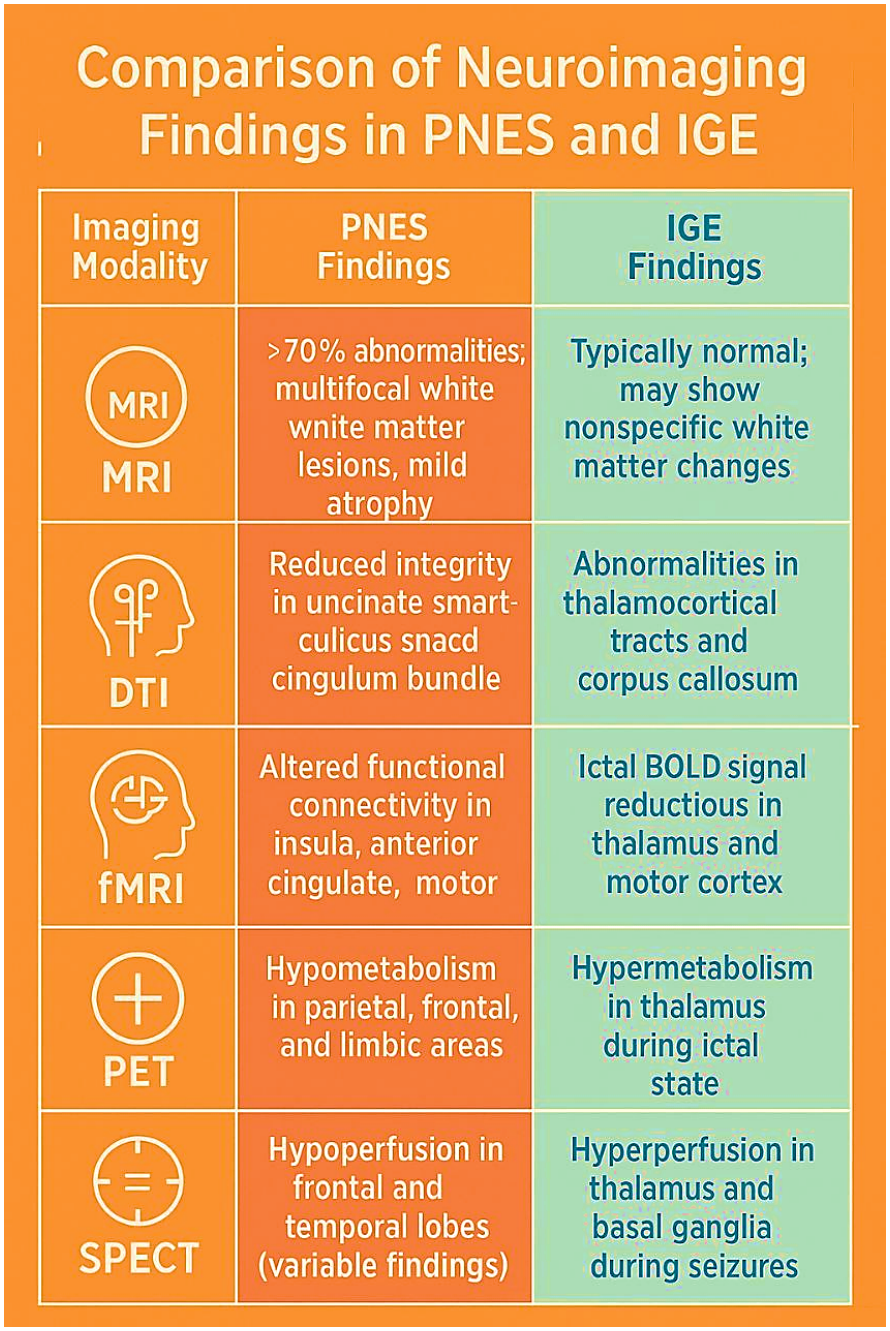

Figure 1. Comparison of neuroimaging findings in PNES and IGE across five key imaging modalities

Abbreviations: MRI: Magnetic resonance imaging; DTI: Diffusion tensor imaging; fMRI: Functional MRI; PET: Positron emission tomography; SPECT: Single-photon emission computed tomography.

However, there were no differences in cortical thickness or gray-white matter contrast in IGE patients compared to control groups. It has also been demonstrated that the thalamo-prefrontal network integrity has remained intact, despite alterations in functional activity reported in IGE patients [5].

A broader review of PNES-related neuroimaging has further highlighted associations between morphometric changes and psychiatric comorbidity. For example, higher depression scores have been linked to reduced volume in the right premotor cortex, thinner orbitofrontal and superior frontal gyri, and decreased paracentral gyrus thickness. Moreover, disease duration has shown an inverse correlation with cortical thickness in the left

Table 1. Summary of the neuroimaging findings in IGE and PNES

Brain Imaging Modality		IGE	PNES
MRI	Brain structural abnormality	Usually, there are no structural brain abnormalities in IGE; however, non-specific brain lesions have been reported, including arachnoid cysts, widespread cortical atrophy, basal ganglia abnormalities, white matter abnormalities (an enhanced T2 signal in the frontal lobes), decreased hippocampal volume, focal gyral abnormalities, and areas of gliosis in the frontal lobe.	Multifocal abnormalities in frontal, temporal, parietal, occipital, cerebellar, and brainstem areas have been observed in 40% of PNES-only patients (no cause and effect has been proven).
	Morphometric changes	No difference in cortical thickness or gray-white matter contrast.	Decreased gray matter volume in the bilateral cerebellum, right precentral gyrus, right middle frontal gyrus, right anterior cingulate cortex, and right supplementary area in PNES brains. Reduced cortical thickness in the right precentral gyrus, right superior frontal gyrus, right precuneus, and right paracentral gyrus. An increase in cortical thickness in the left insula and bilateral medial orbitofrontal regions, along with a decrease in the right precentral gyrus, right entorhinal area, right lateral occipital area, and left precentral areas
	DTI	Deterioration in the uncinate fasciculus and fornix white matter pathways. Thalamic and corpus callosum abnormalities in absence seizures. Changes in the frontal lobe in predominant myoclonic seizures. Diffuse white matter alterations in the temporal and occipital areas. Decreased FC in the medial PFC and limbic regions.	More right-sided uncinate fasciculus streamlines. Increased FC in the left superior temporal gyrus, corona radiata, internal and external capsules, and uncinate fasciculus is linked to motor function.
	fMRI	Decreased fALFF of the BOLD signal in the thalamic-PFC-connecting subregion. BOLD signal decreases in the motor and temporal cortices and increases in the ventro-basal thalamus and sensory cortex during the ictal phase of absence seizures. Altered regional cerebral blood flow (a decrease) has been reported in the thalamus, cingulate, cerebellum, and upper brainstem (superior colliculi) (no cause and effect has been proven).	Increased FC values of brain regions related to attention, the default mode network (DMN), and sensorimotor areas. Enhanced synchronous regional activity was detected in the DLPFC, parietal, and motor areas in a study of PNES patients, while lower activity was found in the right triangular inferior frontal gyrus. Elevated FC values were observed in the right dorsal anterior insula (dAI) and posterior insula (PI), as well as the left putamen and superior parietal gyrus. The left ventral anterior insula (vAI) showed better FC with the right lingual gyrus, left postcentral gyrus, and bilateral supplementary motor area (SMA).
	PET	Diffuse hypermetabolism and a rise in cerebral blood flow in the entire brain, particularly in the thalamus.	Hypometabolism in the right inferior parietal brain areas and bilateral anterior cingulate.
	SPECT	There is an increase in cerebral blood flow during the ictal phase and a decrease in blood flow in the cerebellum, brainstem, thalamus, and cingulate gyrus during the interictal phase.	Hypoperfusion in the bifrontal, left frontoparietal, right medial temporal, right posterolateral frontal, and right insular areas.
	MRS	Lower NAA/Cr ratio in the right and left thalamus, right DMPFC, and right ACC; lower choline (Cho)/Cr ratio in the right ACC; decreased levels of NAA and NAA/Cr in patients with JME.	Lower NAA/Cr ratio in the right and left thalamus, right DMPFC, and right ACC; higher NAA/Cr ratio in the right DLPFC and lower NAA/Cr ratio in the left DMPFC; lower Cho/Cr ratio in the right ACC; and an increase in the ratio of glutamate and glutamine to creatinine in the anterior cingulate and medial PFC.

insula and left precentral gyrus. Conversely, a thicker entorhinal cortex on the right side and atrophy in the left central sulcus and inferior frontal gyrus were associated with greater dissociation scores, suggesting a relationship between structural alterations and the clinical expression of PNES [2].

DTI

DTI has been employed to investigate structural and connectivity changes in both IGE and PNES. By measuring indices, such as fractional anisotropy (FA) and performing tractography, DTI provides a means of assessing whether alterations in white matter pathways contribute to the clinical features of these conditions [5].

For example, Hernando et al. reported that PNES patients exhibited a greater number of streamlines in the right uncinate fasciculus compared to the left, a pattern not seen in healthy controls [20]. In contrast, Lee et al. observed enhanced connectivity in the left uncinate fasciculus and superior temporal gyrus, but not on the right side [21]. The controversial data may be due to very small patient populations in these studies. In the investigation by McGill et al. [5], DTI revealed that the anterior thalamic radiation (ATR) connecting tracts in the anterior limb of the internal capsule between the thalamo-prefrontal areas were intact in IGE patients compared to the control group. Nevertheless, structural abnormalities in the thalamus and corpus callosum have been observed in individuals with IGE exhibiting absence seizures. Additionally, alterations in the frontal region have been documented in patients primarily suffering from myoclonic seizures. In IGE patients, more diffuse impairments in white matter integrity have been identified in the temporal and occipital areas [22].

Functional connectivity (FC) analyses further highlight network disruptions in IGE. Reduced connectivity between prefrontal regions and limbic structures has been associated with higher seizure frequency. Moreover, degeneration has been reported in key white matter pathways, such as the uncinate fasciculus, which links the PFC to the amygdala, and the fornix, which connects the hippocampus with the hypothalamus. These changes underscore the involvement of fronto-limbic circuits in the pathophysiology of generalized epilepsies [23-26].

fMRI

This method utilizes fluctuations in the blood-oxygen-level-dependent (BOLD) signal to assess patterns of neural activity. It can be applied both in task-based settings and at rest to examine FC, which reflects the degree of synchronization and communication among brain regions [5].

It has been shown that in PNES, there is abnormal FC in the cingulate gyrus, insula, occipital cortex, frontal cortex, and sensorimotor cortex. Additionally, the occipital cortex's FC density also showed a correlation with disease duration [27]. Other investigations demonstrated increased activity in regions, such as the dorsolateral PFC (DLPFC), motor cortex, and parietal lobes, while simultaneously reporting reduced activation in the right inferior frontal gyrus—an area linked to inhibitory control and sensory processing. This imbalance may underlie the impaired regulation of involuntary behaviors observed in PNES. Further evidence indicates that PNES patients may exhibit elevated FC within the dorsal anterior insula and posterior insula, as well as heightened connectivity involving the putamen and superior parietal lobule. Left-sided ventral anterior insula activity has also been linked to stronger interactions with the lingual gyrus, postcentral cortex, and supplementary motor areas [28-32].

Amiri et al. demonstrated that limbic and emotional circuits exert inhibitory effects on executive and motor regions, which could explain the prevalence of abnormal motor behaviors in PNES. These alterations were further associated with disease chronicity and cognitive deficits, highlighting the clinical relevance of FC disruptions [33].

In IGE, fMRI results emphasize the dysfunction of thalamo-cortical circuits. Reduced fractional amplitude of low-frequency fluctuations (fALFF) has been reported within thalamic–prefrontal networks [5]. During absence seizures, dynamic changes in the BOLD signal have been observed, with decreases in motor and temporal cortices coupled with increased activation in the ventro-basal thalamus and sensory cortices [34]. Cerebral blood flow studies using fMRI have additionally revealed hypoperfusion in structures, such as the thalamus, cingulate cortex, cerebellum, and superior colliculi, though it remains unresolved whether these represent primary causes or secondary effects of epileptic activity [35].

Collectively, fMRI investigations underscore clear differences between PNES and IGE. Although PNES is characterized by disrupted connectivity across networks involved in emotion, motor control, and executive functioning, IGE is primarily associated with alterations in thalamo-cortical oscillatory activity. These findings pro-

vide mechanistic insight into the divergent clinical manifestations of the two disorders.

MRS

MRS offers a non-invasive method to evaluate biochemical changes in the brain and has been particularly useful in distinguishing between IGE and PNES [8].

Several studies have documented abnormalities in these metabolites in IGE. Cevik et al., for example, demonstrated significantly reduced N-acetylaspartate (NAA) concentrations in both the frontal cortex and thalamus, along with decreased NAA/creatine (Cr) ratios in patients with juvenile myoclonic epilepsy (JME). These reductions were independent of age, age at seizure onset, or disease duration. Moreover, neuropsychological correlations revealed that higher prefrontal NAA/Cr levels were associated with better performance on attention and memory tasks, while thalamic NAA/Cr correlated positively with executive functions, including performance on the Wisconsin card sorting test [36].

In contrast, PNES has been linked to distinct metabolic signatures. Studies have reported elevated Glx/Cr ratios within the ACC and medial prefrontal regions, which were found to correlate with measures of alexithymia, anxiety, and symptom severity. These findings support the notion that PNES involves dysfunction within emotion-regulation networks [37].

Simani et al. further compared metabolic alterations across both disorders. Their results indicated decreased NAA/Cr ratios in the bilateral thalamus, right dorsomedial PFC (DMPFC), and right ACC in both PNES and IGE groups. Additional disorder-specific differences were also observed: PNES patients exhibited reduced NAA/Cr ratios in the left DMPFC and increased NAA/Cr ratios in the right dorsolateral PFC (DLPFC), whereas IGE patients did not show these patterns. In both groups, decreased NAA/Cr ratios were linked to worse cognitive outcomes, reinforcing the association between metabolic dysfunction and impaired network performance [8].

Collectively, MRS findings emphasize that while IGE and PNES share some neurochemical alterations, particularly within thalamo-prefrontal networks, each disorder also displays unique metabolic profiles. These differences may serve as potential biomarkers for differential diagnosis.

PET

PET, using 18FDG or fluorodeoxyglucose F 18, can indirectly measure brain activity by quantifying glucose uptake in the brain regions of patients with PNES and IGE. This imaging modality allows for assessing hyper- and hypometabolism in these regions, providing insight into their metabolic differences [2].

Interictal 18F-FDG-PET in PNES patients has demonstrated bilateral anterior cingulate and right inferior parietal hypometabolism. However, these findings can be due to psychiatric comorbidities [38].

Diffuse hypermetabolism has been observed in IGE patients during the ictal phase compared to healthy individuals and during the interictal phase. In addition, during hyperventilation-induced absence with generalized spike-wave discharge, cerebral blood flow increases in the entire brain (14.9%), particularly in the thalamus (3.9-7.8%) [34].

SPECT

SPECT enables the evaluation of cerebral blood flow and metabolic activity and has been used in both PNES and IGE. In PNES, studies employing SPECT and subtraction ictal SPECT co-registered with MRI (SISCOM) have identified areas of hypoperfusion in up to one-third of patients. The most commonly affected regions include the bifrontal cortex, left frontoparietal areas, right medial temporal lobe, posterolateral frontal cortex, and right insula. These abnormalities further support the involvement of distributed cortical and subcortical networks in PNES pathophysiology [39-41].

A SPECT investigation of pediatric absence epilepsy (IGE subtype) found an increase in cerebral blood flow with the incidence of absences, but no localized increases [34]. Using SPECT, Joo et al. discovered a decrease in blood flow in the cerebellum, brain stem, thalamus, and cingulate gyrus during the interictal phase [35].

Conclusion

The pathophysiology of PNES and IGE appears to be different based on imaging and functional differences. As a result, it is best to consider distinct treatment and management strategies for each. Furthermore, based on imaging abnormalities in PNES patients, the condition is assumed to be of a more organic nature, and patient care should be based on this understanding.

Limitations

The present review has several limitations. First, it concentrated exclusively on imaging findings and did not address other biological, psychological, or social contributors to PNES and IGE. Second, many of the studies included were based on relatively small cohorts, which may reduce the generalizability of their conclusions. Third, potential confounders, such as antiepileptic medication use, psychiatric comorbidities, or other neurological conditions, were not uniformly controlled across studies. Fourth, while imaging abnormalities are described, the precise mechanisms linking these changes to clinical symptoms remain insufficiently explained. Finally, because the review did not include a comparison group with other seizure disorders, its ability to distinguish PNES and IGE from additional epilepsy subtypes is limited.

This paper primarily focuses on the use of imaging techniques and does not explore other potential factors that may contribute to the development and manifestation of PNES and IGE. The sample size of the study may be small, limiting the generalizability of the findings. The paper did not consider potential confounding variables, such as medication use or comorbidities, which may impact the results. Additionally, this paper did not provide a clear explanation of the mechanisms underlying the observed brain abnormalities in PNES and IGE patients. Also, the study did not include a control group of individuals with other types of seizures, making it difficult to compare the findings between PNES and IGE patients.

Ethical Considerations

Compliance with ethical guidelines

This review was conducted in accordance with ethical research principles.

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Authors contributions

Conceptualization: Mehrdad Roozbeh; Methodology: Parnian Shobeiri and Farzan SafiDahaj; Investigation: Mahrooz Roozbeh and Mobina Fathi; Data curation: Farzan SafiDahaj; Writing the original draft: Farzan SafiDahaj, Mehrdad Roozbeh, and Parnian Shobeiri; Review, and editing: Mehrdad Roozbeh and Farzad Ashrafi; Supervision: Hossein Pakdaman and Farzad Ashrafi; Project administration: Farzan SafiDahaj.

Conflict of interest

The authors declared no conflict of interest.

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