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REVIEW

White Matter Structural Connectivity and Its Impact on Psychogenic Non-Epileptic Seizures: An Evidence-Based Review

Daichi Sone

Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan

Correspondence: Daichi Sone, Jikei University School of Medicine, 3-25-8, Nishishimbashi, Minato-ku, Tokyo, Japan, Tel +81-3-3433-1111, Fax +81-3-5401-1879, Email d-sone@jikei.ac.jp

Abstract: Psychiatric non-epileptic seizure (PNES), also known as a form of functional neurological disorders (FND), is a common but still underrecognized disorder presenting seizure-like symptoms and no electrophysiological abnormality. Despite the significant burden of this disorder, the neurobiological mechanisms are not clearly understood, which hinders the development of better diagnosis and treatment. In the recent neuroimaging research on PNES, brain network analysis has become a relevant topic beyond conventional methodologies. The human brain is a highly intricate system of interconnected regions that collaborate to facilitate a wide range of cognitive and behavioral functions. White matter tracts, which are comprised of bundles of axonal fibers, are the primary means by which information is transmitted between different brain regions. As such, comprehending the organization and structure of the brain's white matter network is critical for gaining insight into its functional architecture. This review article aims to provide an overview of the brain mechanisms underlying PNES, with a special focus on analyzing brain networks.

Keywords: psychogenic non-epileptic seizures, functional neurological disorders, neuroimaging, brain network, diffusion tensor imaging

Introduction

Psychiatric non-epileptic seizures (PNES), also known as functional neurological disorders (FND),[1] presents with seizure symptoms similar to epileptic seizures, but there is no evidence that they are caused by abnormal electrical activity in the brain like epileptic seizures, and it is generally assumed that they are caused by psychological factors.[2] Although PNES is a common condition encountered in clinical practice,[3] it is often misunderstood and misdiagnosed, leading to inappropriate treatments and potentially harmful consequences.[2] For example, patients may be mistakenly diagnosed as having epileptic seizures and forced to take unnecessary and potentially harmful antiseizure medications for long periods of time, or they may be inappropriately treated as if they do not have the disease due to lack of objective laboratory findings.

Despite recent progress in the diagnosis and treatment of PNES,[4,5] there are still significant clinical challenges associated with this disorder, including under-recognition, misdiagnosis, and controversies regarding optimal treatment approaches. Moreover, as with many other psychiatric disorders, there are no established objective tests for PNES, and diagnosis is based solely on symptoms. Therefore, investigating the neural mechanisms of PNES can provide insights into diagnostic accuracy, effective treatments, and reduction of misconceptions and under-recognition.

This narrative review article aims to provide an overview of the brain mechanism of PNES, with a focus on brain network analysis. The human brain is a complex network of interconnected regions that work together to facilitate various cognitive and behavioral functions.[6,7] The connectivity between these regions is predominantly mediated by white matter tracts, which are bundles of axonal fibers that transmit information between different brain regions. Therefore, understanding the structure and organization of the brain's white matter network is essential for gaining insights into the brain's functional architecture.[8,9]

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PNES: Epidemiology, Diagnosis, and Treatment

The prevalence of PNES varies considerably from study to study and is estimated at 2–100 per 100,000 persons.[3,4] However, access to diagnostic tests and other factors vary by country and region,[2] so further research is needed to determine the exact figure. It has also been suggested that whether or not PNES is considered a disease may vary by culture,[2] which further complicates research and understanding of the condition. It is consistently reported to be more common in women (60–80%),[10] with most cases occurring in the 20s and 30s.[10] On the other hand, PNES in the elderly is not uncommon,[11] with reports of onset ranging from 4–94 years of age indeed,[3] so it can occur in almost any age group, from children to the elderly.

The gold standard for the diagnosis of PNES is the presence of seizures consistent with PNES and the documentation of seizure symptoms and absence of electroencephalogram (EEG) abnormalities on long-term video-electroencephalography monitoring.[2] In the past, diagnosis was primarily based on exclusion of other abnormalities, but more recently, diagnosis by aggressive rule-in has been advocated.[4] This is a trend toward finding symptoms characteristic of various PNES and positively diagnosing PNES by those characteristic symptoms. However, the problem is that diagnosis remains based solely on symptoms and no objective test has been established, a challenge similar to that of many other psychiatric disorders.

PNES is known to be associated with a variety of psychiatric disorders,[12–14] including anxiety disorders, post-traumatic stress disorder (PTSD), somatoform disorders, and personality disorders, with an overall reported comorbidity of 53–100%.[15] Past traumatic experiences, especially childhood adverse events such as neglect or sexual abuse, are often associated.[16,17] Intellectual disability is also frequent, and PNES with intellectual disability is sometimes categorized as a subgroup.[2,15] They are also often associated with functional somatic symptoms such as pain and fatigue. On the other hand, patients with traumatic brain injury (TBI) and epilepsy are also known to higher prevalence of comorbid PNES.[15]

In terms of treatment, rehabilitative and psychotherapeutic approaches are known to have therapeutic effects to a certain degree.[4] In addition, stress reduction by modifying the patient's surroundings may help PNES to disappear, especially in patients with intellectual disabilities.[18] While these psychiatric complications and the therapeutic effects of currently available treatments still strongly suggest a link between psychosocial factors and PNES, there are cases in which psychological stress is not always clear, complicating the issue. Regarding prognosis, the overall remission rate of PNES is estimated at 40–50%, which is higher than that of other subtypes of FND, but there is a large variation among studies.[19]

The Mystery of PNES: Why It Occurs?

The neurobiological mechanism of PNES, ie, what exactly is happening in the brain of individuals with PNES, is not clearly understood at this time. However, a growing body of research suggests that abnormal brain activity may play a role in the development and maintenance of these seizures.

Previous studies have implicated a number of brain regions in the pathophysiology of PNES, including the limbic system, and the prefrontal cortex. The limbic system, which includes structures such as the amygdala and the hippocampus, is involved in emotional processing and memory formation, and has been shown to be altered in patients with PNES. Although morphological MRI analysis studies have not reported large abnormalities in these regions,[20] functional and white matter fiber abnormalities have been reported repeatedly. For example, abnormalities in uncinate fasciculus (UF) fibers have suggested increased connectivity in the PNES.[21,22] On the other hand, Diez et al reported reduced limbic white matter integrity in mixed FND patients.[23] Functional MRI studies have also suggested abnormalities in neural activity and connectivity in the hippocampus and amygdala.[24,25]

The prefrontal cortex, which is involved in executive functioning and decision-making, has also been implicated in the pathophysiology of PNES. Decreases in gray matter volume and cortical thickness in prefrontal areas such as the cingulate gyrus, middle frontal gyrus, and superior frontal gyrus have been reported,[26,27] suggesting that these regions may be chronically dysregulated in this patient population. Nuclear imaging studies, including brain glucose metabolism derived from ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) or cerebral blood flow based on single-photon emission computerized tomography (SPECT), also reported reduced uptakes in prefrontal cortex.[28,29] In addition, several functional magnetic resonance imaging (MRI) studies have reported abnormal neural activities in this

area.[24,25,30,31] These abnormalities in the prefrontal cortex may reflect cognitive and emotional aspects and behavioral control difficulties in PNES patients.

There are several areas of abnormality in the PNES outside of the limbic structures and prefrontal cortex, most notably the insular cortex and supplementary motor area (SMA), which have been repeatedly reported. The insular cortex is a region of the brain that is located deep within the lateral sulcus, a fold in the cerebral cortex. It is involved in a wide range of functions, including the processing of sensory information, the integration of emotional and cognitive processes, and the regulation of autonomic functions such as heart rate and blood pressure.[32–34] In fact, insular abnormalities are repeatedly reported in PNES using both structural and functional imaging,[31,35–38] which would support the involvement of emotional and cognitive dysfunctions in PNES.

The SMA is a region of the cerebral cortex that is located in the medial surface of the frontal lobe, anterior to the primary motor cortex. It plays an important role in the planning and execution of movements, particularly complex movements that require the coordination of multiple muscle groups.[39] The reported functional and structural abnormalities within SMA in PNES[26,30,37,40] may accord with the motor symptoms in this disorder.

Taken together, these studies suggest that abnormal brain activity in regions involved in emotional processing, cognitive control, motor, and autonomic regulation may contribute to the development and maintenance of PNES. However, further research is needed to clarify the exact mechanisms underlying PNES and to identify potential targets for treatment.

Brain Network Analysis: An Emerging Biomarker for Neuropsychiatry

Network analysis has emerged as a powerful tool for characterizing the complex organization of brain connectivity. In the human brain, which has about 86 billion neurons and 100 trillion synapses,[41,42] pathological changes are rarely confined to a single point and often spread to other areas via axons.[43] Therefore, the limitations of discussing the brain only locally and the need for network analysis have been proposed in recent years. While network analysis is expected in epilepsy due to the presence of abnormal neuronal circuit by seizures,[44] PNES is believed to result from dysfunctions in the brain networks that control emotional and cognitive processing, which can lead to the manifestation of seizure-like symptoms. Therefore, network analysis may help identify the specific brain regions and pathways that are involved in PNES and how they are connected to each other, which could provide insights into the underlying mechanisms of the disorder.

In particular, graph theory has become a popular framework for analyzing brain networks due to its ability to quantify the topology of complex systems.[45] Graph theoretical analysis involves the construction of a network model, using the different brain regions as nodes and the connectivity as edges. The topological properties of the network can then be analyzed using graph theoretical measures, such as network density, clustering coefficient, and betweenness centrality, to gain insights into the organization and efficiency of the network.

In brain imaging research, various imaging modalities can be applied to network analysis.[46] In functional MRI, connectivity can be calculated from the correlation of signal changes over time in each region, and in diffusion MRI, connectivity can be calculated from the strength of white matter fiber connections between regions. In structural MRI and perfusion/metabolic imaging, connectivity can be calculated from the correlation of gray matter volume and blood flow at each site (Figure 1). Furthermore, in recent years, networks based on similarity can also be calculated from structural MRI on an individual level,[47] revealing the effects of age and abnormalities in brain diseases.[48,49]

Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique that has revolutionized our ability to investigate the white matter integrity of the brain.[50] This technique is sensitive to the diffusion of water molecules in brain tissue and can be used to infer the orientation and integrity of white matter tracts. This information can be used to construct a structural network model of the brain's white matter connectivity. White matter structural network analysis using DTI and graph theoretical analysis provides a unique perspective on the brain's structural connectivity and organization. The human brain comprises interconnected regions, which are predominantly connected by white matter tracts that serve as conduits for transmitting information between different brain regions. Thus, comprehending the structure and organization of the brain's white matter network is crucial to gain insights into its functional architecture.[8,9]

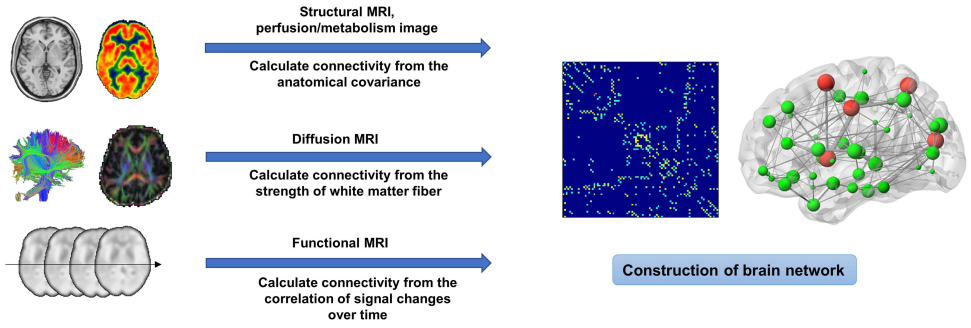

Figure 1 Brain network construction using neuroimaging modalities.

Network Abnormalities in PNES

There are already several neuroimaging studies on PNES using network analysis, most of which utilized functional MRI.[51] Despite the relatively small sample size in each study, these studies have provided important initial evidence into the neural mechanisms of PNES. Findings of functional connectivity (FC) in PNES included reduced coupling strength with structural connectivity,[52] abnormal FC density,[30] stronger connectivity in emotion, executive function, and movement areas,[36] altered FC patterns in the insular subregions,[37] Increased FC of the amygdalae to various brain regions,[53] or reduced connectivity in the visual networks.[54]

Regarding the white matter structural network analysis derived from DTI, our previous study showed reduced global and local network efficiency as well as reduced network connectivity in the right posterior region[55] (Figure 2A). The abnormal structural network area in PNES involved the right precuneus and parahippocampal gyrus, suggesting some specific impairment of this region such as default mode network dysfunction.[56] Patients with PNES also showed widely reduced integrity in the deep white matters (Figure 2B), and the reduced deep white matter integrity in PNES was later reported by another study using advanced diffusion imaging, ie, neurite orientation dispersion and density imaging (NODDI).[57] On the other hand, earlier studies on DTI in PNES reported an increase or no difference in fractional anisotropy (FA).[21,22] In fact, it is said that white matter analysis by DTI in PNES is in its early stages,[58] and the accumulation of evidence is expected in the future.

There are also brain network studies on PNES using neurophysiological data, such as EEG or magnetoencephalography (MEG).[59–64] The accumulation of studies using multiple modalities is expected to further contribute to the elucidation of the mechanism of PNES. On the other hand, as we have seen, there is some variation in the results obtained by various methods of network analysis, and it is important to examine and standardize the methods in addition to accumulating research.

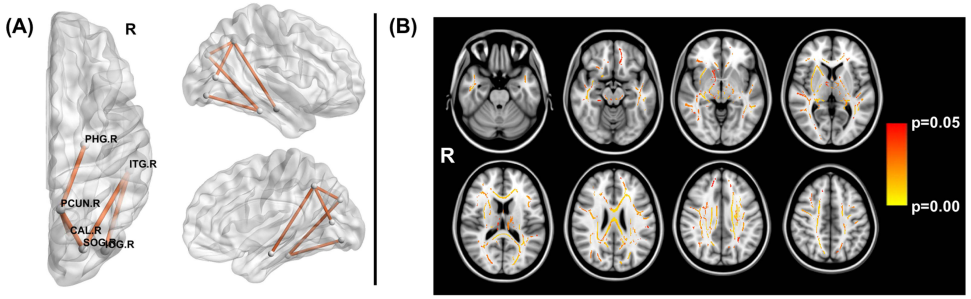

Figure 2 White matter integrity and network abnormalities in PNES.
Notes: (**A**) Reduced network connectivity in the right posterior region. (**B**) Widely reduced fractional anisotropy (FA) particularly in deep white matters. The yellow-red color denotes p-values in the comparison with healthy controls. Adapted from Sone D, Sato N, Ota M, Kimura Y, Matsuda H. Widely Impaired White Matter Integrity and Altered Structural Brain Networks in Psychogenic Non-Epileptic Seizures. *Neuropsychiatr Dis Treat*. 2019;15:3549–3555.[55]
Abbreviations: PHG, parahippocampal gyrus; ITG, inferior temporal gyrus; PCUN, precuneus; CAL, calcarine; SOG, superior occipital gyrus; IOG, inferior occipital gyrus.

Problems and Future Directions

These studies are still in their early stages, with small sample sizes and low levels of evidence.[51] The requirement for long-term video-EEG monitoring to obtain a definitive diagnosis of PNES may hinder the ability to obtain a large sample size, adding to the challenges posed by the condition's under-recognition and lack of attention. In addition, the presence or absence of intellectual disability, diverse onset age, and various comorbid psychiatric disorders may affect the results of the analysis as confounding factors.

One of the biggest problems, again, is that the diagnosis is based solely on symptoms, and no objective test abnormalities have been established. We do not even know for sure if PNES is a biologically valid disease category, and the same is true for FND and its subcategories, eg, functional movement disorder and functional seizure. It is assumed that emotion regulation problems are involved in the development of symptoms in PNES,[65] but since PNES has not been biologically established, this too may be a matter of speculation.

Future directions include the use of large, multicenter studies to ensure sample size and external validity, and longitudinal data analysis to investigate changes over time and predict associations with symptoms and treatment response. Combining multimodal imaging may provide further relevant evidence. Advances in analytical methods are also important, with machine learning, for example, another major trend in neurobiological research.

Conclusion

PNES remains a clinical challenge due to its under-recognition and misdiagnosis, and the lack of objective diagnostic tests. However, advances in brain network analysis have shed light on the neural mechanisms of PNES, providing potential avenues for improved diagnostic accuracy and effective treatments. Further research is needed to reveal the pathophysiology of PNES and to develop better interventions for patients with this disorder.

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Disclosure

The author reports no conflicts of interest in this work.

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