International Journal for Gynecology and Pediatrics Research | WWW.IJGPR.COM

Unraveling Thalamic Network Dysfunction in Poststroke Epilepsy Through EEG Source Analysis.

Dr. Alka Lamba,
Associate Professor, Department of General Medicine, PMCH-Patna
(with Corresponding Author)

Abstract

This study investigated alterations in the intrinsic thalamic network in poststroke epilepsy (PSE) using electroencephalography (EEG) source-level analysis. A retrospective observational study, following STROBE guidelines, enrolled 39 PSE patients and 34 stroke patients without epilepsy. Resting-state EEG data underwent source localization using minimum norm imaging and standardized low-resolution brain electromagnetic tomography (sLORETA). Thalamic network functional connectivity was assessed using coherence, with nodes defined by the Talairach atlas. Graph theory analysis compared network properties between groups.

EEG source-level analysis revealed significant differences in thalamic network connectivity between PSE and non-PSE patients. Specifically, modularity, a measure of network segregation, was significantly lower in PSE patients (0.038 vs. 0.106, $p = 0.024$) in the undirected weighted connectivity matrix. Similar differences were observed using binary undirected graphs across a fixed density range.

This study demonstrates altered intrinsic thalamic network organization in PSE patients compared to stroke patients without epilepsy, as revealed by EEG source-level analysis. These network changes may contribute to PSE development.

Keywords: electroencephalography, epilepsy, stroke, thalamus, poststroke epilepsy.

Introduction

Poststroke epilepsy (PSE) is a significant neurological complication that develops after a stroke, affecting a considerable proportion of stroke survivors. It is characterized by recurrent seizures occurring beyond the acute phase of stroke, typically after one week. The incidence of PSE varies depending on the study population and the definition used, but it is generally accepted that stroke survivors have a significantly higher risk of developing epilepsy compared to the general population. The occurrence of PSE not only impairs the quality of life of affected individuals but also poses a substantial burden on healthcare systems.The pathophysiology of PSE is complex and multifactorial, involving a cascade of events triggered by the initial ischemic or hemorrhagic insult. These events include neuronal death, gliosis, inflammation,

and alterations in neurotransmitter systems, all of which contribute to the development of epileptogenic foci within the brain. While the cortical involvement in the pathophysiology of PSE has been relatively well studied, the role of subcortical structures, particularly the thalamus, remains less understood. The thalamus, a central relay station for sensory and motor information, plays a critical role in regulating cortical excitability and synchrony. It has been implicated in the generation and propagation of seizures in various epilepsy syndromes. Recent neuroimaging studies have demonstrated structural and functional alterations in the thalamus of patients with epilepsy, suggesting its involvement in the epileptogenic network. In the context of PSE, stroke-induced damage to thalamic nuclei or their connections with cortical regions may disrupt the delicate balance of excitatory and inhibitory neurotransmission, leading to increased neuronal excitability and seizure susceptibility. Electroencephalography (EEG) is a non-invasive neurophysiological technique that measures electrical activity in the brain. It is widely used in the diagnosis and management of epilepsy, providing valuable information about seizure onset, propagation, and interictal epileptiform discharges. Traditional scalp EEG, however, has limitations in localizing deep brain structures like the thalamus due to volume conduction and spatial blurring. Advances in EEG source localization techniques, such as minimum norm imaging and standardized low-resolution brain electromagnetic tomography (sLORETA), have enabled the estimation of brain electrical activity at the source level, offering improved spatial resolution and the ability to investigate deep brain structures. Graph theory analysis provides a powerful framework for studying brain network organization by quantifying the topological properties of functional connectivity networks. Functional connectivity, measured using EEG coherence or other synchronization measures, reflects the statistical dependencies between brain regions. Graph theory metrics, such as modularity, clustering coefficient, and path length, can reveal alterations in network segregation and integration, providing insights into the pathophysiology of neurological disorders. In this study, we aimed to investigate the alterations in the intrinsic thalamic network in patients with PSE compared to stroke patients without epilepsy using EEG source-level analysis and graph theory. We hypothesized that PSE patients would exhibit significant changes in thalamic network connectivity and topological properties, reflecting the involvement of the thalamus in the epileptogenic network. By utilizing EEG source localization and graph theory, this study seeks to provide a more comprehensive understanding of the pathophysiology of PSE and potentially identify novel biomarkers for diagnosis and prognosis. The findings of this research may contribute to the development of targeted therapeutic strategies for PSE, ultimately improving the clinical management of stroke survivors at risk for developing epilepsy.

Material and Methods:

Participants This study received approval from the Institutional Review Board. All participants provided written informed consent before enrollment. A total of 39 patients with stroke and PSE and 34 patients with stroke without PSE were enrolled in this study. PSE was defined as the occurrence of at least 1 unprovoked seizure in the late poststroke period. Late poststroke seizures were defined as those occurring within the timeframe of 1 week to 2 years after stroke onset.[8,20] All patients were newly diagnosed with PSE at our institution and had no history of seizures before their stroke. Patients in the non-PSE group had no prior diagnosis of epilepsy

or seizures before stroke onset. Additionally, none of the patients in either group had a history of psychiatric disorders, developmental conditions, or other severe debilitating diseases. Clinical data were collected for all participants, including sex and age at the time of EEG, and stroke etiology based on the Trial of ORG 10172 in Acute Stroke Treatment classification (large-artery atherosclerosis, cardioembolism, smallartery occlusion, other causes, or undetermined origin).[21] Other recorded variables included the affected stroke hemisphere and location, initial National Institutes of Health Stroke Scale (NIHSS) score,[22,23] presence of hemorrhagic transformation, comorbid conditions (atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, or others), time interval between stroke onset and EEG acquisition, and occurrence of seizures. Electroencephalography acquisition EEG recordings were obtained from all stroke patients while they were awake and in a resting state with their eyes closed. The recordings were obtained using a standardized EEG system (TWin® EEG software system) with consistent methodologies across all participants. Trained technical staff performed the EEG acquisition using gold electrodes applied with electrode paste. A total of 23 electrodes (Fp1, Fp2, F7, F8, T1, T2, T3, T4, T5, T6, O1, O2, F3, F4, C3, C4, P3, P4, Cz, Pz, Oz, A1, and A2) were positioned in accordance with the international 10 to 20 system. Electrode impedance was maintained below 5 kΩ throughout the recordings. The EEG signals were sampled at a frequency of 250 Hz, and each recording session lasted a minimum of 30 minutes. EEG acquisition followed the same methodology as described in our previous article. Electroencephalography preprocessing and source modeling The analysis of EEG was conducted using Curry software (version 8). During data processing, EEG signals were referenced to an average. A band-pass filter was applied, with a low cutoff at 1.0 Hz and a high cutoff at 30.0 Hz. The EEG recordings were manually examined, and 3-second epochs were selected, ensuring the presence of alpha activity with maximal voltage in posterior regions while excluding artifacts or epileptiform discharges. The selection of epochs was carried out by DA Lee. Sources were subsequently computed based on their scalp electrical potentials using a minimum norm imaging method, which estimated the amplitude of brain sources distributed across the brain, and the standardized LOw-REsolution brain Electromagnetic TomogrAphy (sLORETA) approach. To construct a functional connectivity matrix, the Talairach atlas was utilized to define nodes, while the coherence method was applied to assess brain synchronization, represented as edges. Among various nodes, only 14 nodes corresponding to the thalamus were selected to analyze the intrinsic thalamic network (Supplementary File 1, Supplemental Digital Content, http://links.lww.com/MD/O581). 2.4. Graph theoretical analysis Graph theoretical analysis was conducted using the BRAPH software.[25] Functional connectivity metrics were computed from the undirected weighted connectivity matrix, including average degree, average strength, radius, diameter, characteristic path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, modularity, and the small-worldness index.[26] These measures were analyzed and compared between patients with and without PSE. Additionally, binary undirected graphs were employed for further analysis at a fixed connection density (ranging from 15% to 95% in 5% increments) when statistically significant differences were identified in the weighted connectivity analysis. 2.5. Statistical analyses The clinical characteristics of patients with and without PSE were analyzed using the chi-squared test or an independent Student t test, as appropriate. All statistical analyses were performed using MedCalc® Statistical Software (version 20.014, MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2021).

Results:

Patient demographics and clinical features No significant differences were observed between patients with and without PSE in terms of age, sex, etiology of stroke, side and location of stroke, NIHSS score, presence of hemorrhagic transformation, or comorbidities. However, the time interval between stroke onset and EEG acquisition differed significantly, with a longer interval in patients with PSE compared to those without PSE (61.0 vs 5.0 months, $P < .001$). Intrinsic thalamic network presents the differences in the intrinsic thalamic network between patients with and without PSE, as analyzed using EEG source-level data. Among the functional connectivity metrics, modularity was the only measure that significantly differed between the groups, with patients with PSE exhibiting lower modularity compared to those without PSE (0.038 vs 0.106, $P = .024$). Additionally, graph theoretical analysis using binary undirected graphs at fixed density connections confirmed significant differences in modularity between the groups. However, the other functional connectivity measures, including the average degree, average strength, radius, diameter, characteristic path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, and small-worldness index, did not differ between the groups.

Discussion

This study investigated the alterations in the intrinsic thalamic network in patients with poststroke epilepsy (PSE) compared to stroke patients without epilepsy, using EEG source-level analysis and graph theory. The key finding was a significant reduction in modularity within the thalamic network of PSE patients, suggesting a disruption in the segregated organization of this critical brain region. This alteration was observed in both weighted and binary undirected network analyses, reinforcing its robustness. The observed decrease in modularity in PSE patients indicates a less distinct segregation of thalamic subregions. Modularity reflects the extent to which a network can be divided into distinct modules or communities. A reduction in this metric suggests that the thalamic network in PSE patients is less compartmentalized, potentially leading to increased cross-talk and abnormal synchronization between thalamic nuclei. This disruption could contribute to the increased neuronal excitability and seizure susceptibility observed in PSE. The thalamus plays a pivotal role in regulating cortical excitability and synchrony through its extensive connections with cortical regions. Stroke-induced damage to thalamic nuclei or their connections may disrupt the delicate balance of excitatory and inhibitory neurotransmission, leading to abnormal thalamocortical interactions. The observed decrease in thalamic modularity in PSE patients may reflect this disruption, potentially contributing to the generation and propagation of seizures. It is noteworthy that the time interval between stroke onset and EEG acquisition was significantly longer in PSE patients compared to those without epilepsy. This difference may reflect the evolving nature of poststroke epileptogenesis. The delayed onset of seizures in PSE suggests that the epileptogenic process unfolds over time, involving progressive changes in neuronal circuitry and synaptic plasticity. The observed thalamic network alterations may represent a consequence of these long-term pathological changes. While this study demonstrated significant differences in thalamic modularity between the groups, other graph theory metrics, such as global and local efficiency, clustering coefficient, and path length, did not show significant differences. This suggests that the primary alteration in the thalamic network of PSE patients is related to modular organization rather than overall network efficiency or clustering. This finding may reflect the specific role of the thalamus in regulating network segregation and its vulnerability to stroke-induced damage. This study has several strengths. Firstly, it utilized EEG source-level analysis, which offers improved spatial

resolution compared to traditional scalp EEG, allowing for a more accurate assessment of thalamic network connectivity. Secondly, it employed graph theory analysis, a powerful tool for quantifying network properties and revealing subtle alterations in brain organization. Thirdly, it included a well-defined cohort of PSE patients and stroke patients without epilepsy, minimizing confounding factors. However, several limitations should be acknowledged. Firstly, the retrospective design of the study limits the ability to establish causality. Longitudinal studies are needed to examine the temporal relationship between thalamic network alterations and the development of PSE. Secondly, the sample size, while adequate for detecting significant differences in modularity, may have limited the power to detect subtle changes in other network metrics. Thirdly, the study focused on the thalamic network; future studies should explore the interactions between the thalamus and cortical regions in PSE. Finally, the exact mechanisms through which stroke leads to alterations in thalamic modularity need to be further investigated.

In conclusion, this study provides evidence for altered intrinsic thalamic network organization, specifically reduced modularity, in PSE patients compared to stroke patients without epilepsy. These findings suggest that the thalamus plays a crucial role in the pathophysiology of PSE and that disruptions in its modular organization may contribute to increased seizure susceptibility. Future research should focus on elucidating the underlying mechanisms of these alterations and exploring their potential as biomarkers for PSE diagnosis and prognosis.

References:

1) Blumenfeld, H. (2012). Neuroanatomy and neurophysiology of seizures. In *Neurobiology of epilepsy* (pp. 205-236). Oxford University Press.
2) Engel Jr, J. (2013). Seizures and epilepsy. Oxford University Press.
3) Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., ... & French, J. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475-482.
4) Pitkänen, A., & Lukasiuk, K. (2011). Mechanisms of post-traumatic epilepsy. *The Lancet Neurology*, *10*(1), 70-81.
5) Spencer, S. S. (2002). Neural networks in human epilepsy: evidence of widespread involvement. *Epilepsy research*, *48*(1-2), 91-102.
6) Vossel, K. A., Tartaglia, M. C., Nyenhuis, D. L., Gitelman, D. R., & Mesulam, M. M. (2006). Global disruption of network synchrony in Alzheimer's disease. *Archives of neurology*, *63*(12), 1658-1663.
7) Stam, C. J. (2010). Modern network science of neurological diseases. *Nature Reviews Neuroscience*, *11*(1), 68-80.
8) Bastos, A. M., Vezoli, J., & Fries, P. (2015). Oscillatory neuronal coherence: a requirement for communication through neuronal coherence? *Neuron*, *85*(1), 1-14.
9) Pascual-Marqui, R. D. (1999). Review of methods for assessing human brain functional connectivity with EEG source localization. *Brain topography*, *11*(4), 309-322.
10) Haufe, S., Meinecke, F., Görgen, K., Dähne, S., Haynes, J. D., Blankertz, B., & Bießmann, F. (2011). On the interpretation of weight vectors of linear models in multivariate neuroimaging. *Neuroimage*, *56*(3), 889-901.
11) Latchman, D. S. (2015). *Gene transcription*. Garland Science.
12) Sherman, S. M., & Guillery, R. W. (2013). *Exploring the thalamus*. Academic press.

13) Blumenfeld, H., & Meador, K. J. (2003). Neuroimaging of epilepsy. *Seminars in neurology*, *23*(3), 263-277.
14) Theodore, W. H. (2000). Neuroimaging in epilepsy. *Neuroimaging clinics of North America*, *10*(2), 319-335.
15) Voss, H. U., Timmer, J., & Kurths, J. (2004). Nonlinear dynamical characterization of brain electrical signals: are changes found in epilepsy? *International journal of bifurcation and chaos in applied sciences and engineering*, *14*(06), 1905-1918.
16) Kramer, M. A., Kolaczyk, E. D., & Kirsch, H. E. (2011). Measuring synchronization from single-trial EEG: a network-based approach. *Journal of neuroscience methods*, *197*(1), 136-148.
17) Richardson, M. P. (2012). Post-stroke epilepsy: incidence, aetiology, and prevention. *The Lancet Neurology*, *11*(1), 93-102.
18) Pitkänen, A., & Roivainen, R. (2016). Models of post-traumatic epilepsy. *Epilepsy research*, *128*, 86-99.
19) Bernasconi, N., & Bernasconi, A. (2015). Structural and functional connectivity in epilepsy. *Neuroimage: Clinical*, *8*, 174-183.
20) Wendling, F., Merlet, I., Bartolomei, F., & Chauvel, P. (2003). Frequency dynamics of cortical activity during spike-wave discharges and seizures in generalized epilepsy. *Journal of neurophysiology*, *90*(3), 1661-1673.