ORIGINAL RESEARCHES

DOI: 10.5281/zenodo.4018890
UDC: 616.853-009.24

Reorganization and resilience of brain networks in focal epilepsy

Dumitru Ciolac

Laboratory of Neurobiology and Medical Genetics
Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova

Author's ORCID iD, academic degree and contributions are available at the end of the article

Corresponding author: dumitru.ciolac@usmf.md
Manuscript received August 10, 2020; revised manuscript September 02, 2020; published online October 02, 2020

Abstract

Background: Epilepsy has been considered as a brain network disorder. Advanced computational tools have granted a non-invasive window to explore the brain networks in epilepsy. Studying the reorganization of brain networks can help in modelling the network topology changes related to focal epilepsy. The present study aimed to explore the reorganization and resilience of brain networks in patients with focal epilepsy.
Material and methods: The structural 3T T1-weighted MR images of 40 patients with focal epilepsy and 40 healthy subjects, were processed by using FreeSurfer. Cortical thickness values were used for the reconstruction of morphometric networks. The topological organization and resilience of brain networks were assessed by applying the graph theoretical analysis.
Results: The topological organization of the brain networks in patients was marked by a higher clustering coefficient, local efficiency and path length (all $p<0.05$) as compared to healthy individuals. The network hubs (i.e. brain regions responsible for network maintenance) were differently distributed in patients (left superior temporal and right paracentral) and healthy subjects (left anterior cingulate and right superior temporal). The brain networks in patients exhibited lower resilience ($p<0.05$) to targeted attacks (i.e. the removal of brain regions depending on their importance for network organization) and similar resilience ($p>0.05$) to random attacks (i.e. random brain area removal).
Conclusions: Brain networks in focal epilepsy were characterized by an increased segregability and a decreased integrability. Reduced resilience to targeted attacks in patients, as compared to healthy subjects, suggests an uneven importance of brain regions for network maintenance in the studied groups.
Key words: epilepsy, brain networks, reorganization, resilience, hubs.

Cite this article
Ciolac D. Reorganization and resilience of brain networks in focal epilepsy. *Mold Med J.* 2020;63(5):5-8. doi: 10.5281/zenodo.4018890.

Introduction

Epilepsy is one of the most common neurological disorders, characterized by susceptibility to generate recurrent seizures. It is widely accepted that focal seizures originate from a brain area and spread along the interconnected tracts to remote regions. However, extensive relevant studies have led to a paradigm shift from the "epileptogenic focus" to the "epileptogenic network". The pathways of interictal discharge propagation involving the thalamo-cortical networks in focal epilepsy have been previously shown [1]. Brain network modelling by using the graph theory is an emerging tool to explore the disease- and brain state-related reorganization processes that mirror the pathological alterations within the epileptogenic networks [2]. At the same time, the mechanisms underlying the vulnerability of networks to recurrent seizures remain poorly understood. A recent work has shown that patients with awake seizures display lower network vulnerability to repeated seizures than patients with sleep seizures [3].

This study aimed to identify the reorganization patterns of brain cortical networks in patients with focal epilepsy. It confirms the hypothesis that epilepsy patients show alterations in cortical networks that implies a higher vulnerability (lower resilience) to recurrent paroxysmal events. Therefore, a reconstruction of cortical networks was carried out, based on cortical thickness measurements from brain magnetic resonance imaging (MRI) and compared to the network topological parameters between the epilepsy patients and healthy subjects. Finally, a random and targeted attack analyses wese performed to assess the resilience of the networks.

Material and methods

Study participants. Forty patients with focal epilepsy (30 ± 6 years; 17 males) were included within the study. Seizure and epilepsy type of the patients were established according to the International League Against Epilepsy criteria [4, 5]. The control group included 40 healthy age- and

gender-matched subjects (28 ± 5 years, 14 males) without any history of neurological disorders. The study protocol was approved by the Ethics Research Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova (notification No 81 of 19.06.2018). All participants were provided with the written informed consent prior to being enrolled in the study.

MRI acquisition. Both patients with epilepsy and healthy subjects underwent a 3T MRI scanning (SIEMENS Skyra, Siemens Healthcare) with a 32-channel head coil according to an approved Epilepsy protocol [1, 3]. This protocol includes 3D T1-weighted (repetition time [TR] = 2000 ms, echo time [TE] = 9 ms, matrix size [MS] = 256 × 256, field of view [FoV] = 256 × 256 mm^2, slice thickness [ST] = 4 mm; T2-weighted (TR = 3800 ms, TE = 117 ms, MS = 256 × 256, FoV = 256 × 256 mm^2, ST = 4 mm) and fluid attenuated inversion recovery (TR = 5000 ms, TE = 388 ms, MS = 256 × 256, FoV = 256 × 256 mm^2, ST = 4 mm).

Image processing and cortical thickness reconstruction. The FreeSurfer software (version 5.3.0, http://surfer.nmr.mgh.harvard.edu/) was used to reconstruct the cortical surface from T1-weighted images. The FreeSurfer pipeline runs in a fully automated fashion, followed by visual inspection at various processing steps for quality control. Briefly, the surface-based processing stream consists of skull stripping, transformation into Talairach space, optimization of boundaries between gray matter and white matter and between gray matter and cerebrospinal fluid, segmentation of subcortical white matter and deep gray matter structures, and tessellation [6]. Cortical thickness at each vertex was calculated (in mm) as the average of the shortest distance between the gray matter-white matter surface and gray matter-cerebrospinal fluid surface. Afterwards, cerebral cortex was parcellated into anatomical labels according to the Desikan-Killiany atlas for regional cortical thickness measurements [7].

Cortical network reconstruction. The cortical thickness from each cortical region of interest (according to Desikan-Killiany atlas) was extracted and served for the construction of cortical connectivity matrices. For both groups, connectivity matrices (size 68 × 68 regions) were obtained by computing the Pearson's correlation coefficient between the anatomical regions. The Graph Analysis Toolbox was used to threshold the matrices into multiple densities, ranging from 0.38 to 0.48, and compute the network measures [8].

Network measures. Topological organization of cortical networks was assessed by computing the following parameters: clustering coefficient, path length, local efficiency and global efficiency [9]. Clustering coefficient represents the measure of network's local organization, which indicates the number of connections between the neighboring nodes. Path length is the minimal number of edges that must be passed to reach the given region (node). Local efficiency reflects the efficiency of neural communication within the network at local level. Global efficiency is the average inverse distance matrix of all brain networks and reflects the global network efficiency. The resilience of cortical networks was evaluated via random and targeted attack analysis.

Statistical analysis. All statistical analyses were performed in MATLAB R2012b (Mathworks, Natick, Mass). The normal distribution of the analyzed variables was assessed by using Shapiro-Wilk test. Assessment of between-group differences in parametric and non-parametric variables was based on t-test, Mann-Whitney U or Pearson's χ^2 tests, where appropriate. A p value of < 0.05 was considered statistically significant.

Results

Patients and healthy controls were comparable in terms of age ($t = 2.1$, $p = 0.23$) and gender ($\chi^2 = 0.04$, $p = 0.82$). Thirty-one patients had temporal and nine patients extra-temporal epilepsy.

The topological organization of brain networks in patients with epilepsy exhibited a higher clustering coefficient, local efficiency and path length (all $p < 0.05$) but lower global efficiency ($t = 2.8$, $p = 0.008$; fig. 1) as compared to the healthy subjects. The network hubs (i .e. brain regions, responsible for the functional maintenance of the whole network) had a different distribution in patients (left superior temporal, right paracentral cortex) and healthy subjects (left rostral anterior cingulate, right superior temporal, right supramarginal cortex).

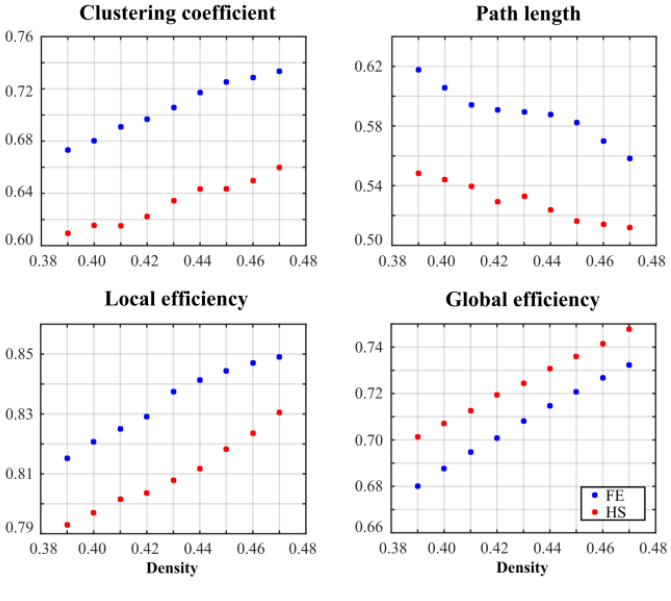

Fig. 1. Network topological parameters.

Mean values across densities of clustering coefficient, path length, local efficiency and global efficiency in patients with focal epilepsy (FE) as compared to healthy subjects (HS)

The brain networks in epilepsy patients were characterized by lower resilience (i.e. higher vulnerability) ($p < 0.05$) to targeted attacks (i.e. removal of brain regions depending on their importance for network organization) and similar resilience ($p > 0.05$) to random attacks (i.e. random removal of brain regions; fig. 2).

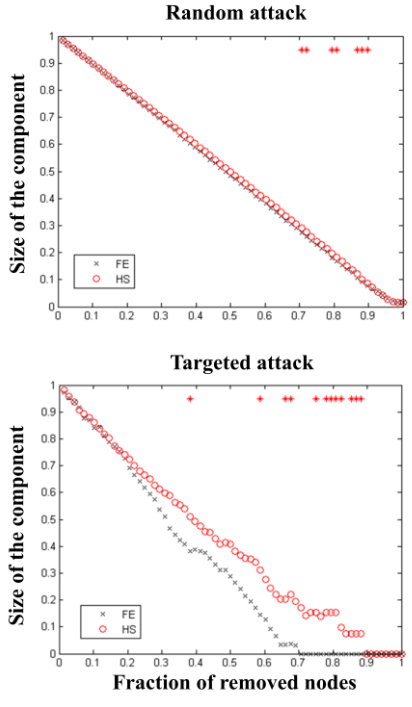

Fig. 2. Network attack analysis.

Patients with focal epilepsy (FE) were comparable to healthy subjects (HS) in terms of random attack but showed reduced resilience to targeted attack

Discussion

The current study analyzed the reorganization of cortical networks based on MRI-derived cortical morphometric measures in patients with focal epilepsy in order to identify the possible network mechanims of network vulnerability. The research results point towards a network reorganization pattern that is characterized by increased segregation (higher clustering coefficient and local efficiency) and decreased integration (higher path length and lower global efficiency). Additionally, patients with focal epilepsy had a different distribution of network hubs. The remodelling of brain networks in focal epilepsy might be due to an increased vulnerability to recurrent seizures as evidenced from the targeted network analysis.

The cortical networks in epilepsy patients displayed higher clustering coefficient, path length and local efficiency. Clustering coefficient is a parameter of network segregation that quantifies the number of connections between the neighbouring nodes [9]. The increased clustering coefficient in patients with focal epilepsy has been previously reported [2, 10]. In conditions of increased clustering coefficient, the network nodes are more likely to be connected to each other in order to maintain the local information processing. Thus, the increased clustering coefficient might be considered as a compensatory increase in the number of local connections as a response to the reduction of long-range connections [11]. The path length is a measure of network's integration and denotes the minimal number of connections that must be traversed to travel from one node to another [9]. An increased path length implies that the networks are less integrated [2]. As shown by Bernhardt et al. [10] the increased clustering coefficient and path length were associated with seizure recurrence after epilepsy surgery. Local efficiency is the average of the inverse distance in the network that describes the efficiency of information processing within a network [9]. Thus, it can be hypothesized that the identified increased local efficiency might also be a compensatory response to long-range disconnections that is directed to maintain local functionality of the network.

Different hubs were identified in patients with focal epilepsy (left superior temporal, right paracentral cortex) compared to healthy subjects. This suggests that along with local network reorganization, hub redistribution also occurs. In patients with temporal lobe epilepsy (TLE), 2 hubs were located in paralimbic and 3 hubs in primary cortical areas (left TLE) and 1 hub was identified in paralimbic and 5 in association areas (right TLE) [10]. The predominant distribution of the hubs in temporal association cortices might stem from the altered connectivity between temporolimbic and extratemporal networks [10].

To investigate the resilience properties of networks in epilepsy, the network attack analysis was performed. This implies virtual random or targeted removing of one node from the network and measuring the network alteration thereafter [8]. Patients with focal epilepsy displayed lower resilience to targeted attacks as compared to healthy subjects, thus suggesting an unequal importance of brain regions for network maintenance in the studied groups. Similar results were reported by Bernhardt et al. [10]. However, another study showed that epilepsy patients had a higher network resilience to random attack and targeted attack than the control group [12]. This might be explained by the study methodological differences – inclusion of children into the analysis and use of different image processing algorithms. It can be assumed that the increased vulnerability of brain networks in epilepsy patients might be the precondition for the recurrent generation of seizures. The altered distribution of the hub together with the increased path length and clustering coefficient may compromise the efficiency of global information transfer [13, 10].

Evaluation of the network measures was found to be useful to predict the clinical outcomes of the epilepsy patients [11]. In patients with TLE, both the decreased clustering coefficient and the increased path length were associated with lower cognitive performance [14]. These results suggest that local and global reduced information processing partially underlie the mechanisms of cognitive decline in TLE [11]. Consequently, these network measures may be used as biomarkers to predict the cognitive status in patients with epilepsy.

Several limitations were encountered within the present study. First, due to the group network analysis, individual values of the network topology were not available, thus, we couldn't relate the seizure frequency to the alterations of network topology. Second, the patients didn't undergo the

neuropsychological tests; hence, their cognitive performance couldn't be correlated with the network reorganization. Thirdly, the network parameters were derived only from structural MRI without analysing the functional data from electroencephalography. Fourthly, patients presented various structural causes of their focal seizures that could in a specific manner impact the reorganization of cortical networks. Patients' antiepileptic drugs could influence the network parameters, as well.

Conclusions

Patients with focal epilepsy show more segregated and less integrated network architecture. The increased vulnerability (reduced resilience) of brain networks in focal epilepsy may stem from the reorganized network topology and serve as mechanism facilitating seizure recurrence. Characterization of network topology reorganization patterns might be an important biomarker to assess individual epilepsy courses and treatment responses.

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Author's ORCID iD and academic degree
Dumitru Ciolac, MD, PhD Applicant – https://orcid.org/0000-0003-1243-313X.

Author's contribution
DC designed the study, collected, processed, and interpreted the data and drafted the manuscript.

Ethics approval and consent to participate
The research was approved by the Ethics Research Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (protocol No 81 of 19.06.2018).

Conflict of Interests
Nothing to disclose.