Brain functional connectivity in individuals with psychogenic non epileptic seizures (PNES): An application of graph theory

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Abstract

Objective: To determine brain functional connectivity (FC), based on the graph theory, in individuals with psychogenic nonepileptic seizures (PNES), in order to better understand the mechanisms underlying this disease.

Methods: Twenty-three patients with PNES and twenty-five healthy control subjects were examined. Alterations in FC within the whole brain were examined using resting-state functional magnetic resonance imaging (fMRI). We calculated measures of the nodal degree, a major feature of the graph theory, for all the cortical and subcortical regions in the brain. Pearson correlation was performed to determine the relationship between nodal degree in abnormal brain regions and patient characteristics.

Results: The nodal degrees in the right caudate (CAU), left orbital part of the left inferior frontal gyrus (ORBinf), and right paracentral lobule (PCL) were significantly greater (i.e. hyper-connectivity) in individuals with PNES than in healthy control subjects. On the other hand, a lesser nodal degree (i.e. hypo-connectivity) was detected in several other brain regions including the left and right insula (INS), as well as the right putamen (PUT), and right middle occipital gyrus (MOG).

Conclusion: Our findings suggest that the FC of several major brain regions can be altered in individuals with PNES. Areas with hypo-connectivity may be involved in emotion processing (e.g., INS) and movement regulation (e.g., PUT), whereas areas with hyper-connectivity may play a role in the inhibition of unwanted movements and cognitive processes (e.g., CAU).

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1. Introduction

Psychogenic nonepileptic seizures (PNES) or functional seizures are periods of paroxysmal abnormal events, typically involving altered responsiveness, and impaired cognitive control, emotional or behavioral functions, sensations, and movements [1–3]. These seizures may resemble epileptic seizures, but PNES are not caused by epileptiform discharges in the brain [4]. Patients with PNES are frequently misdiagnosed and treated as if they have epilepsy. The prevalence of PNES is estimated to be 2–33/100,000 persons [1,5].

Despite being the subject of many studies over the past decade, mechanisms underlying PNES are still uncertain due to the complexity of PNES. Evidence that PNES is a disorder of altered brain networks has provided the opportunity to further investigate abnormalities associated with the different patterns of functional connectivity (FC) in the brain networks [3,6,7]. According to recent studies, there is abnormal FC between networks involved in emotion, sensorimotor, and cognitive processes in patients with PNES [1,8,9]. However, there are limited studies regarding alterations in the whole-brain FC network in PNES patients. The FC has a metabolic basis that is coupled with cerebral blood flow (CBF) and metabolism rate [10–12]. Therefore, investigating FC of brain regions (e.g., areas involved in emotion, sensorimotor and cognitive processes) may provide valuable information about the mechanisms underpinning PNES.

In this study, we used functional magnetic resonance imaging (fMRI) to extract FC between the brain regions based on the
blood-oxygen-level-dependent (BOLD) signal at resting state. Graph-theory allows for determining the organization of the brain and characterizing topological properties of the brain networks [13,14]. According to the graph theory, the brain can be modeled by a series of nodes and edges, i.e., the segmented brain regions, and the structural or functional connections between them, respectively [14,15]. The graph theory can be used as an appropriate tool to examine the complexity of brain networks globally or locally; where indeed, the general properties of the whole brain are examined; or the graph features are calculated for specific regions of the brain. Using graph-based network analysis, we compared the functional brain connectivity patterns between patients with PNES and healthy controls. We hypothesized that brain connectivity in people with PNES has different patterns compared with that in healthy individuals.

2. Material and method

2.1. Subjects

Twenty-three patients with PNES (9 males, mean ± SD age: 29.65 ± 10.53 years) and twenty-five healthy controls (HC) (10 males, mean ± SD age: 31.7 ± 6.1 years) were examined. Psychogenic nonepileptic seizures was diagnosed by experienced neurologists and ictal recordings during LTM. Patients with comorbid epilepsy seizure and other neurological or psychiatric disorders (e.g., mood and anxiety disorders, schizophrenia, and psychosis) were excluded. Participant demographics for all patients are shown in Table 1. Only right-handed subjects participated in this study. All subjects gave informed consent to the experimental procedure that was reviewed and approved by the Research Ethics Board of Tehran University of Medical Sciences.

2.2. Data acquisition

All subjects were scanned with a Siemens magnetom Prisma MRI at 3T system. Resting-state functional MRI images covering the whole brain were acquired in the transverse plane using an echo-planar imaging sequence parameters included 240 volumes, 32 slices with 3.5 mm thickness, TR = 2000 ms, TE = 30 ms, flip angle = 90°, voxel size: 3.1 × 3.1 × 3.5 mm, the field of view = 200 × 200 mm and an acquisition matrix of 64 × 64. T1-weighted images were also acquired for the co-registration of functional images. All subjects were asked to keep their eyes open during the scanning process.

2.3. Data analysis

The analyses consist of five major steps as illustrated in Fig. 1 including pre-processing, extracting whole-brain FC matrix (FCM) based on the Automated Anatomical Labeling (AAL) atlas, thresholding, and binary FCM, constructing binary graph network from binary FCM and extracting graph-theoretical features, and finally comparison and statistical analyses.

2.4. Pre-processing

Preprocessing of the rs-fMRI data was performed using the data processing assistant for resting-state fMRI (DPARSF) toolbox version 4.5 based on statistical parametric mapping (SPM12) [16]. Briefly, preprocessing procedures included the following steps: the first 10 volumes of functional images were discarded to allow for magnetization equilibrium. Skull stripping was performed on both functional and structural images to remove non-brain tissue before co-registration of T1 images and functional images for better registration of T1 image to functional space. The slice-timing correction was performed, using slice as a reference and adjusting for interleaved slice acquisition. Spatial realignment was used to reduce extreme head movement using a six-parameter (rigid body) linear transformation. Extreme head movement was corrected using motion scrubbing; Individual structural images were coregistered to mean functional images; The co-registered structural images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and then WM, and CSF [17] and global signals were regressed on the functional images; Spatial normalization was done to the standard template Montreal Neurological Institute (MNI) space. After that, the normalized data were spatially smoothed with a 4-mm full-width at half-maximum (FWHM) Gaussian kernel. Subsequently, the temporal bandpass filter (0.01–0.01 Hz) was performed to reduce the influence of low-frequency drift and high-frequency respiratory and cardiac noise.

2.5. Whole-brain functional connectivity matrix (FCM) and graph construction

Functional connectivity is defined as the temporal correlation between two or more anatomically distinct time-series. The seed regions were chosen based on AAL atlas which divided the whole brain into 116 cortical and subcortical regions [18]. To obtain the weight matrix of FC (size: 116 × 116), the time courses of the brain regions were extracted, the Pearson correlation was used to calculate the FC of each pair, and Fisher’s r-to-z transformation was applied to improve normality. For the analysis of brain connectivity, we used a graph theory software (BRAF tools, Math Work Inc., Natick, MA, United States [19]). For graph construction, negative correlations were set to zero to improve the reliability of graph theoretical measures [20]. Its undirected binary graph format was then calculated by applying a threshold on it. The thresholding was performed at subject level. We applied the proportional thresholding method to construct a binary connectivity matrix. This approach included assigning labels 1 to %5 (density) of the strongest connections in the brain network and 0 to other connections [21]. For the group comparison, unlike the absolute threshold, the use of proportional thresholds ensures that the networks of each group have the same number of nodes and edges [21]. This makes more meaningful comparisons between the two groups.

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Fig. 1. Pipeline of the analyses, preprocessing, extracting functional connectivity matrix (FCM) of networks based on AAL atlas, thresholding for binary FCM, constructing binary graph network from FCM, extracting graph features, and finally comparison and statistical analyses.
Fig. 2. Hyper-connected regions in PNES: Significance of nodal degree differences between the PNES and HC groups. The red points represent the actual nodal degree differences between the PNES and HC group (PNES-HC). The actual difference value (red color points) is significant (p value < 0.05) if it falls outside the confidence intervals (light-blue zone). Right Caudate (CAU), orbital part of the left inferior frontal gyrus (ORBinf), and right paracentral lobule (PCL) are hyper-connected nodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
There are several graph metrics that characterize the graph properties of the brain networks using FC analyses. The importance of each node in a brain network can be determined by centrality metrics, which makes it an appropriate measure to capture the complexity of FC. Several metrics are developed to measure the ‘centrality’ of a brain network, including the clustering coefficient, degree centrality, betweenness centrality, node neighbor’s degree, and closeness centrality [15]. These features have been used to investigate specific changes in the topological properties of the brain graph. Since most of them provide redundant information, we chose the nodal degree as an important centrality measure. For the sake of sensitivity, the nodal degree can be measured locally considering merely the nodes of desired networks. We calculated the ‘nodal degree’ in whole-brain regions in patients with PNES and compared them with that in the healthy control group. For each of these regions, we calculated measures of ‘nodal degree’ as described below.

The ‘nodal degree’ of each node equals the total number of edges that are connected to a node [14,15].

\[
(D)_i = \sum_{j=1}^{N} a_{ij}
\]

where \( N \) is the number of all nodes in the network, \( a_{ij} \) is the connection value between a pair of nodes \((i, j)\), with \( a_{ij} = 1 \) when a connection between \((i, j)\) exists, and \( a_{ij} = 0 \) unless otherwise.

2.7. Statistical analyses

The nonparametric permutation test with 1000 resamples was used to evaluate the significance of differences in degree between the HC and PNES groups. Using the non-parametric permutation test, we can determine whether the measured effect is genuine or a statistical glitch due to the randomness associated with the selection of the sample [22]. Permutation testing is an appropriate method for controlling the nominal type I error. The statistical analysis was done using BRAPH, which utilizes a non-parametric permutation test to assess the significance of the differences between groups, and to determine the 95% confidence intervals [19], particularly the permutation test

1. determines the difference between the measures calculated for the two groups,
2. permutes the subjects across the two groups; calculates the difference between the measures in the permuted groups, repeats this procedure several times (1000 times, typically chosen to preserve the degree and the strength distributions of the original graph), and obtains the histogram of the differences,
3. determines whether the calculated difference between the two groups lies within the histogram, then compares this difference with the chosen threshold.

To address multiple comparisons, the false discovery rate (FDR) algorithm was used at the 0.05 significance level [23]. To examine the relationship between the nodal degree of abnormal regions with patient characteristics, Pearson’s correlation coefficients were calculated using the SPSS software (SPSS v24, IBM Corp, USA). The independent sample t-test was also performed for the sex variable.

3. Results

The nodal degree value was calculated from the FC matrix with a density network range of 5–40 for whole-brain regions in the HC and PNES groups. Fig. 2 shows the hyper-connected regions in PNES and the comparison of the nodal degree values in regions that are significantly different between the two groups, using the non-parametric permutation test. The red points represent the actual nodal degree difference between the PNES and HC groups (PNES-HC). The actual difference value (red points) is significant (p-value < 0.05) if it falls outside the confidence intervals (light-blue zone). The nodal degree was significantly greater in the PNES group compared to the HC group in the right caudate (CAU), orbital part of the left inferior frontal gyrus (ORBinf), and right paracentral lobule (PCL) (P-value < 0.05). Furthermore, the nodal degree values in the right CAU were significantly higher in the PNES group than in the HC group in almost all of the network density ranges (8–40%); the biggest nodal degree difference between the two groups was related to this region. The brain schematic view of the regions with significantly different nodal degree values between the HC and PNES groups is shown in Fig. 3. When comparing the PNES group to the HC group, the brain regions with a significantly higher or lower nodal degree are considered as hyper- or hypo-connected areas, respectively. The hyper-connected nodes (nodes with higher nodal degree values) are colored red.

The hypo-connected regions in PNES and the comparison of the nodal degree values in regions that had a significant difference between the two groups of healthy and PNES patients are shown
in Fig. 4. The nodal degree differences were significantly lower in the PNES group than in the HC group in the left and right insula (INS) (P-value < 0.05). Also, the nodal degrees of the right putamen (PUT) and right middle occipital gyrus (MOG) were lower in the PNES group than in the HC group (P-value < 0.05). The abnormal nodal degrees were more evident in the right hemisphere (right CUA, right PUT, right INS, right MOG) in the PNES group. There were no significant differences in other AAL atlas regions between the HC and PNES groups.

Brain views of the regions that had significantly different nodal degree values between the HC and PNES groups are shown in Fig. 5. The hypo-connected nodes (nodes with lower nodal degree values) of the left and right INS, right PUT, and right MOG are colored cyan.

The Pearson correlation coefficients were calculated to determine the association between the nodal degree of hyper- and hypo-connected brain regions in patients with PNES with patient characteristics. For the correlation analysis of each region, we used the nodal degree of the network density in which the most significant difference between the two groups was observed in that region.

We found no association between the nodal degrees and patient characteristics and noticed no significant differences in the nodal degrees of the brain regions between males and females.

4. Discussion

We aimed to investigate the differences of FC in patients with PNES compared with healthy individuals. Using the graph theory, we identified a dissimilar pattern of FC in the brain regions of people with PNES compared to that in healthy people. Our results showed that compared with healthy subjects, patients with PNES exhibited a greater nodal degree (i.e., hyper-connectivity) in several brain regions including the right CUA, left ORBinf, and right PCL. On the other hand, a lesser nodal degree (i.e., hypo-
connectivity) was noted in several other brain regions including the left and right INS, right PUT, and right MOG. These findings may provide evidence that helps better understand the underlying pathophysiological mechanisms in patients with PNES.

4.1. Role of hyper-connected regions in PNES

A greater nodal degree for a given node within a network indicates a higher ability in local processing and a greater distributed interaction with other nodes within the network (i.e., greater local FC). Our results showed that the nodal degree of the right CAU was significantly higher in people with PNES than that in healthy individuals. The FC has a metabolic basis that is coupled with CBF and metabolism rate \([12,24,25]\). Thus, the increased FC of the right CAU observed in our study is expected to be associated with enhanced metabolism rate and local activity in this region, indicating hyper-activity of the right CAU in PNES patients. This is consistent with the results of previous studies that have shown an increase in metabolism and blood flow in the caudate based on positron emission tomography (PET) \([26,27]\) and hyper-connectivity of the right CAU \([28]\) in individuals with functional neurological disorders (FND). It is noteworthy that PNES is a subtype of FND.

The caudate nucleus is part of the basal ganglia, which is involved in a variety of functions (emotion and movement) \([29,30]\). Since the CAU is involved in the inhibition of unwanted movements, dysfunction in this region can make it more difficult to suppress involuntary movements \([31]\). This is consistent with findings of earlier studies that reported the possible association of caudate dysfunction with movement disorders including Parkinson’s and Huntington’s disease \([26,32]\). We did not find any reports conflicting our findings; to our knowledge, a very limited number of studies have focused on this topic using the nodal degree measure.

Our results also revealed that the degree of the left ORBinf and right PCL were significantly higher in patients with PNES than that in normal individuals. Enhanced FC in the left ORBinf is consistent with similar findings of an earlier study \([6]\). Also, hyper-connectivity of the right PCL confirmed the earlier observation of an increase in the fractional amplitude of low-frequency fluctuations in PNES, which is associated with an increase in local activity in PCL \([3]\).

The left human inferior frontal gyrus is involved in motor control, working memory, language, and empathy processing \([33,34]\). Paracentral lobule is the continuation of the precentral and post-central gyri and has an important role in motor control. Past studies have shown that motor control and cognitive functions, such as working memory are impaired in people with PNES \([35,36]\), which can be explained by hyper-connectivity of the left ORBinf and right PCL observed in this study.

4.2. Role of hypo-connected regions in PNES

Compared to the healthy controls, patients with PNES showed hypo-connectivity in the left and right INS. Our findings are in agreement with the abnormalities found in the structure and function of the in people with PNES \([8,37]\); stronger connectivity values between the insula, inferior frontal gyrus, parietal cortex, and pre-central sulcus were noted based on rs-fMRI in these patients \([1,8]\). Furthermore, an increase in cortical thickness in the left INS \([37]\), and a decrease in strength, efficiency, and betweenness in the left and right INS were observed in PNES patients \([38]\). The insula is involved in a variety of brain functions including socio-emotional processing, empathy, and social cognition, attention, and salience processing \([39]\).

Furthermore, our results revealed hypo-connectivity in the right PUT; this region plays a critical role in motor execution, learning, and memory. Dysfunction in putamen was also previously observed in patients with PNES \([9]\).

4.3. Dysfunctions more lateralized to the right hemisphere in PNES

Our results showed that abnormal nodal degrees were more evident in the right hemisphere (right CAU, right PUT, right INS, right MOG) in the PNES group. This is consistent with prior evidence, pointing toward the right-hemispheric contribution to the pathogenesis of functional disorders and PNES \([240–42]\). Furthermore, emotion regulation, which is associated with the right hemisphere \([43]\), was found to be disrupted in the pathogenesis of PNES \([44]\), confirming our findings.

4.4. Methodological consideration

The evaluation of brain neural activity can aid in better understanding the mechanisms underlying PNES, which has both scientific and clinical significance. The nodal degree of a region is the number of connections to the node, which can quantify FC. Also, the reflection of neuronal activity of a brain region is directly related to the CBF in that region, which can be measured by functional neuroimaging techniques, such as PET and arterial spin labeling (ASL) \([45]\). Earlier studies have shown that FC has a metabolic basis that is coupled with CBF and the rate of metabolism. Thus, a brain region with greater FC has a higher metabolism rate \([12,24,25]\). In this study using the nodal degree, we quantified FC to better understand neural activity in different brain areas in subjects with PNES.

Due to technical limitations, there is no optimum network density to calculate the most accurate nodal degree and characterize FC the best. Alternatively, FC should be described over a range of network density; we chose a network density range of 5–40% for interpretation since this range was found to be consistent with the biological background of brain functional networks \([46,47]\). The 5% lower bound was selected to avoid excessive network fragmentation at lower density, while the 40% upper bound was considerably chosen as the brain networks have a tendency of moving toward randomness at higher densities. Despite this, the interpretation of FC as a function of network density is complicated, difficult, and application dependent. In this study, the degree of several brain regions as a function of network density varied between the PNES and HC groups; in the right caudate, the differences in the degree were significant for approximately all of the network densities, whereas in the left orbitofrontal, it was significantly only for the low-range densities. These changes must be considered carefully to provide a reliable interpretation based on the application. For example, in this case, hyper-connectivity of the right caudate in PNES was evident, whereas hyper-connectivity of the left orbitofrontal was cautiously taken into consideration.

One of the major challenges facing the measurement of FCs is the reliability of the graph-theoretical analysis with respect to parcellation schemes. This is related to the selection of an atlas with an appropriate number of parcels. In this regard, we chose the AAL atlas with 116 nodes, which is popular for this type of application. However, we did not quantify the influence of different parcellation schemes on nodal degree centrality because the nodes across different parcellation schemes were difficult to match due to their different spatial locations and network sizes (e.g., the insula is parcellated into one node in the AAL atlas and in six nodes in the Brainnetome (246 nodes) atlas \([48]\), which makes the interpretation of results difficult. Despite this, to furthermore investigate the influence of the parcellation scale on different network parameters, we calculated the network topological metrics for two different brain atlases (AAL and Brainnetome). Network topological metrics, including the global coefficient, local efficiency,
clustering, and modularity were measured [49] for two different brain parcellation atlases in the PNES group. The results showed that the trends of topological parameters were the same for both atlases with each having a different number of nodes (Fig. 6). These findings were consistent with previous studies, which showed that whole-brain topological parameters were quite robust over different scale [46,50,51].

Another challenge facing the graph-theoretical analyses is how to handle or interpret negative edge weights in resting-state FC. Based on a meta-analysis [20], 57% of the studies reported insufficient or no information regarding how negative edges can be handled in graph analyses. Before analysis, twenty-one percent of studies deleted negative edges, and only 9% took the absolute value of the negative weights and handled the negative correlations as positive. More importantly, a recent study reported that negative FC has the lowest consistency among all connectivity types, which may be interpreted as evidence against the presence of a biological basis for negative FC [52]. We, therefore, decided to zero out all the negative correlations merely based on the findings of previous articles and existing consensus among the peers.

4.5. Limitations and future directions

The limited number of male subjects with PNES was one of the limitations of this study. It was impractical to balance the gender in the PNES group because PNES is more prevalent among females (female-to-male ratio (3:1)) [53,54]. Despite this, the gender imbalance in the PNES group would be expected to have a minimal impact on the reported results, since we found no significant correlations in the nodal degrees between the males and females in both the PNES and HC groups. Furthermore, to minimize the gender dependence impact, we recruited PNES and HC subjects with a similar ratio of male-to-female subjects (9/23 in the PNES group vs. 10/25 in the HC group).

Fig. 6. Topological metrics: global coefficient, local efficiency, clustering and modularity in the PNES group for AAL (blue) and Brainnetome (red) atlas.

Fig. 7. The imbalances of functional connectivity in cognitive and emotion processing in patients with PNES. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Furthermore, although we excluded PNES patients with an obvious clinical detection of major depressive disorder, we did not evaluate our patients with structured instruments for psychiatric comorbidities (e.g., depression) that may frequently exist in people with PNES and may alter brain connectivity. Therefore, our results may not be specific to people with PNES.

Finally, due to the limitations of this study, further studies with a larger sample size are required to confirm the findings of this study.

5. Clinical significant

Fig. 7 shows the schematic views indicating the imbalances in FC in cognitive and emotion processing in patients with PNES. Our findings suggest that people with PNES may have different FC patterns compared with that in healthy individuals; regions involved in cognitive processing and movement regulation (hypo-connectivity in INS and PUT) or inhibition of unwanted movements and emotion processes (hyper-connectivity in CAU) are particularly interesting avenues for further investigation. This information may provide a better understanding of the mechanisms underlying PNES, which may assist practitioners in improving diagnosis and treatment.

6. Conclusion

Further knowledge of the etiology of PNES is necessary for more accurate clinical management of PNES diagnosis and treatment. Our results indicated that the graph theory was a robust tool, capable of quantifying the FC of brain regions for detecting abnormal activities of areas associated with PNES. Our findings demonstrate suggest that the nodal degree measure may have the potential to be used as an appropriate parameter to further investigate the mechanisms underlying PNES.

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Declaration of conflicting interests

The authors expressed no conflicts of interest for the authorship, research, and publication of this study.

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