Existence of Dynamic Functional Connectivity Variations of Brain Networks in Psychogenic Non-Epileptic Seizures Through Resting-state Functional Magnetic Resonance Imaging

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ABSTRACT

Background: Psychogenic Non-Epileptic Seizures (PNES), is a type of seizure that is caused by emotional factors. Symptoms of PNES are similar to epileptic seizures including disturbance in involuntary movement. Previous studies showed that neural activity altered in PNES detected through the resting-state functional Magnetic Resonance Imaging (rs-fMRI) thus this study was designed for a better understanding of PNES pathophysiology using the rs-fMRI technique.

Objective: This study was conducted to examine dynamic Functional Connectivity (dFC) in the brain networks between PNES and healthy control subjects.

Material and Methods: In this experimental study, the rs-fMRI was collected from 16 PNES subjects and 16 healthy subjects. After surrogating data, the sliding window technique was used for dFC detection in nine brain networks which chosen from Stanford Findlab.

Results: Our results indicate that there were no differences in the presence or absence of dFC between the PNES group and the control group in the ventral Default Mode Network (vDMN), Language Network (LN), and Visuospatial Network (VSN). However, dFC was elevated in the PNES group in comparison to the normal control group within the Sensorimotor Network (SMN), Posterior Salience Network (PSN), and Anterior Salience Network (ASN).

Conclusion: The findings suggest that dFC analyses hold significant potential for uncovering abnormal patterns of brain network connections in the PNES. This offers a promising finding for a better comprehension of PNES.

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Keywords

Dynamic Functional Conne-ctivity; Brain Network; Nonepileptic Seizure; Functional Magnetic Resonance Imaging; Echo-Planar Imaging; Regression Analyses; Seizure Disorder; Default Mode Network

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Introduction

Psychogenic Non-Epileptic Seizures (PNES) is a common type of seizure that especially manifests in young adults caused by emotional factors instead of epileptogenic activity, but resembles epileptic seizures in outpatient diagnoses. PNES is related to brain dysfunction in the psychological processing of distress and pain, which is obvious in altered involuntary movements and decreased self-control

[1, 2]. Despite many advances in the treatment of neuropsychological diseases, due to the gap between the diagnosis and treatment of PNES, the life quality of these patients has decreased [3]. The utilization of functional neuroimaging techniques in identifying epileptogenic foci has been gaining significant prominence in the treatment [4].

Functional Magnetic Resonance Imaging (fMRI) is a useful procedure for the localization of human brain function through changes in the brain tissue blood flow resulting from altered metabolism after neural activity in the resting state or task-based evoked neural responses [5]. fMRI can improve the temporal resolution (based on new imaging protocols) compared to other brain functional evaluation techniques, such as electroencephalography [6]. Recently, attention has been focused on evaluating the function of the brain in the absence of a stimulus or a task (Resting-state (rs)) by fMRI named rs-fMRI [7]. Using the rs-fMRI method, it is possible to study specific brain area networks' function in healthy and pathological conditions during basal brain activity for investigating new aspects of neuropsychiatric disease etiology [8]. In the rs-fMRI method, Functional Connectivity (FC) analysis is utilized to find the association between two separate spatial regions of the brain especially in the PENS through a linear temporal connection [9]. For example, Li et al. reported that PENS patients have stronger FC between the brain area that is included within the control of abnormal emotions, cognitive processing, and motor performance [10]. In addition, Van Der Kruijs et al. reported that there is no significant difference between the activity map of the normal control group and PNES patients, but the FC map between the two groups is statistically different [11].

Some studies reported that the brain network connection is dynamic and the presence or absence of dFC in each brain network can modulate the performance of each network executing brain function [12, 13]. In addition, previous studies showed that the dFC approach leads to a better comprehension of the brain activity at rest, thus providing new insights into brain function in different conditions [14] but dynamism between brain networks in the PENS was not investigated.

Based on these findings, this study was conducted to evaluate of functional dynamics of brain networks between normal individuals and PNES patients for a better understanding of PNES pathophysiology using the rs-fMRI technique.

Material and Methods

Data Acquisition

In this experimental study, using the criteria defined in psychiatry, PNES patients were determined. Also, gender, age, disease duration, and clinical symptoms were also considered as criteria for selecting patients. In total, 32 subjects were included in this study: 16 subjects with PNES and 16 healthy controls. All the participants experienced rs-fMRI scans using a 3.0-tesla (T) scanner (SIEMENS MAGNETOM Prisma) under a closed-eye situation. The scans were done on a 32-channel head coil MRI system at the National Brain Mapping Laboratory (NBML) in Tehran, Iran, through a gradient Echo-Planar Imaging (EPI) method, utilizing this parameter: Repetition Time (TR)/ Echo Time (TE) 2.5 sec/ 33 ms; field-of-view 208×180 mm^2; acquisition matrix 104×90 mm^2, and a voxel dimension 2×2×2 mm^3.

Data Pre-processing

The 360-second scan (144 volumes) was done for subjects' analysis. Standard preprocessing of the functional images includes removing space distortions caused by uneven gradients and fixing head movements, we align functional images to a reference image using 6 degrees of freedom. Fixing the bending caused by the B0 field, matching with the T1 weighted image, and adjusting to the 2 mm Montreal Neurological Institute (MNI) space. All the above steps have been applied in one step, minimizing the blur effect. Data are

passed through a temporal high-pass filter with a cutoff frequency of 0.0067 Hz (corresponding to a cutoff time of 150 seconds) to remove the slow drift, data tendency, and frequencies above 0.0067 Hz. Finally, the signal of the white matter and Cerebrospinal Fluid (CSF) has been eliminated from the overall signal. The pre-processing steps were done using Statistical Parametric Mapping (SPM12 (https://www.fil.ion.ucl.ac.uk/spm)). Also, the strength was balanced out and made smoother using a 4 mm FWHM Gaussian filter, and for normalization, a voxel size of 3×3×3 mm^3 was chosen. Upon completion of the pre-processing stages, nine functional networks emerged, in Table 1. The resting-state network regions have been determined from http://findlab.stanford.edu/functional_ROIs.html (Table 1). The dFC between the networks was calculated by the Variation of Information (VI) as a correlation metric and MVPR method for data surrogating.

Variation of Information

The variation of information is a way to measure the distance between two clusters, which shows how far apart they are from each other. It is used to compare the partitions of elements in the clusters. This parameter is used to parameter is used to estimate the distance between two random variables X and Y, and is defined as follows [15]:

$$VI(X,Y) = H(X) + H(Y) - 2I(X,Y) \quad (1)[16]$$

Table 1: Resting-state networks which chosen from Stanford Findlab.

No	Resting state network	Network regions
1	ASN	(MFG.L) - (Ins.L) - (ACC, MPFC, SMA) - (MFG.R- Ins.R) - (Lob.L.IV, Crus.L.I) - (Lob.R.IV, Crus.R.I)
2	dDMN	(MPFC, ACC, OrbFC) - (AngG.L) - (SFG.R) - (PCC, Precu) - (MidCC) - (AngG.R) - (Tha.L, Tha.R) - (Hipoca.L) - (Hipoca.R)
3	LAN	(IFG.L) - (MTG.L) - (MTG.L, AngG.L - MTG.L, STG.L, SmG.L, AngG.L) – (IFG.R) – (SmG.R, STG.R, MTG.R- Crus.L.I)
4	L.ECN	(MFG.L, SFG.L) - (IFG.L,OrbFG.L) - (SPG.L, IPG.L, Precu.L, AngG.L) - (ITG.L, MTG.L) - (Crus.L.I) - (Tha.L)
5	PSN	(MFG.L) - (SmG.L) - (IPG.L) - (Prec.L) - (MidCC.R) - (SPG.R) - (Prec.R) - (SmG.R) - (IPG.R)- (Tha.L) - (Lob.L.VI) - (PIns.L) - (Put.L)- (Tha.R) - (Lob.R.VI) - (PIns.R)
6	R.ECN	(MFG.R, SFG.R) - (MFG.R- IPG.R, SmG.R, AngG.R) - (SFG.R) - (Crus.R.I.II, Lob.R.VI) - (Cau.R).
7	SMN	(Pre/posCenG.L) - (Pre/posCenG.R) - (SMA.R) - (Tha.L) - (Bilat.L.IV.V.VI) - (Tha.R)
8	vDMN	(PCC.L) - (MFG.L) - (ParaHipG.L) - (IPL.L) - (PCC.R) - (Prec) - (SFG.R, MFG.R) - (ParaHipG.R) - (AngG.R) - (Lob.R.IX)
9	VSN	(MFG.L, SFG.L, PreceG.L) - (IPL.L) - (IFG.L) - (ITG.L) - (MFG.R) - (IPL.R) - (IFG.R) - (MTG.R) - (Lob.L.VIII.VIIb) - (Lob.R.VIII.VIIb) - (Lob.R.VI, Crus.I)

ASN: Anterior Salience Network, dDMN: Dorsal Default Mode Network, LAN: Language Network, ECN: Executive Control Network, PSN: Posterior Salience Network, ECN: Executive Control Network, SMN: Sensorimotor Network, vDMN: Ventral Default Mode Network, VSN: Visuospatial Network, MFG: Middle Frontal Gyrus, Ins: Insula, ACC: Anterior Cingulate Cortex, MPFC: Middle Prefrontal Cortex, SMA: Supplementary Motor Area, Lob: Lobule, Crus: First Crus, OrbFC: Orbitofrontal Cortex, AngG: Angular Gyrus, SFG: Superior Frontal Gyrus, PCC: Posterior Cingulate Cortex, Precu: Precuneus, MidCC: Middle Cingulate Cortex, Tha: Thalamus, Hipoca: Hippocampus, IFG: Inferior Frontal, MTG: Middle Temporal Gyrus, SmG: Supramarginal Gyrus, STG: Superior Temporal Gyrus, SPG: Superior Parietal Gyrus, ITG: Inferior Temporal Gyrus, IPG: Inferior Parietal Gyrus, PIns: Posterior Insula, Put: Putamen, Cau: Caudate, Pre/posCenG: Anterior/posterior Central Gyrus, SMA: Supplementary Motor Area, Bilat.L: Bilateral Lobule, ParaHipG: Parahippocampal Gyrus, IPL: Inferior Parietal Lobe, PreceG: Precentral Gyrus. (L: Left, R: Right, I: First, II: Second, IV: Forth, V: Fifth, VI: Sixth, VII: Seventh, VIII: Eight, IX: Ninth)

Which $H(X)$ is the entropy of the random variable X and is defined as follows:

$$H(X)=\sum_{i=1}^{n}p(X_i)log_2p(X_i) \quad (2)\ [16]$$

Also, $p(X_i)$ is the probability of observing the value of X_i. The quantity $H(Y)$ is defined in the same way. The quantity $I(X, Y)$ is the mutual information (MI) and is calculated by the following relationship:

$$I(X,Y)=\sum_{x\in X}\sum_{y\in Y}p(X,Y)log_2\left(\frac{p(X,Y)}{p(X)p(Y)}\right) \quad (3)\ [16]$$

Also, $p(X, Y)$, $p(X)$, and $p(Y)$ are the joint and marginal Probability Density Function (PDF) of random variables X and Y, respectively. The probability density function is calculated by the histogram of the data, where the number of data is equal to the number of time points of the data. Based on the kernel density method of determining the probability density function and the dimensionality of the data (2D), the minimum sample size required to achieve the minimum error is estimated to be 19 numbers.

Surrogate Data

To put it simply, researchers used a method called multivariate phase randomization to create substitute data. They followed these steps [17]: Let **x** explain the BOLD recordings from different regions of the brain; X explain their discrete Fourier Transform; φ explain a random phase is evenly spread out between 0 and 2π, then calculate the surrogate data, All information measured in terms of frequencies X_k are multiplied by a random phase that is the same for all of them. φ_T. Then, the inverse Fourier transform is calculated, and one surrogate copy is obtained. This method was used to create 250 random copies for each participant [18, 19].

$$x=[x_1,x_2,x_3,\ldots,x_n] \quad (4)$$

$$X=[X_1,X_2,X_3,\ldots,X_n] \quad (5)$$

$$\varphi=[\varphi_1,\varphi_2,\varphi_3,\ldots,\varphi_T] \quad (6)$$

$$\tilde{X}=X_k e^{j\varphi}\ \ k=1,2,\ldots,n \quad (7)$$

Sliding window Methodology Based Dynamic Functional Connectivity

The sliding window approach examines every time-series pair in depth. The length of the sliding window was 75 seconds (for TR 2.5 sec, there are 30 points in sliding window). The FC parameter was calculated for each part of the BOLD signal separated by the sliding window and finally, a set of windowed parameter values was obtained. The ascertained values are subsequently assembled into a three-dimensional matrix (area × area × window), wherein the third dimension is subjected to an averaging process. In the current study, a rectangular window with a 75-second length was used and shifted by a one-time point (1TR).

Null Hypothesis testing

To test the hypothesis, the histogram of the variance of the windowed parameter values dependent on the null hypothesis (stationary FC) was created using surrogate data. As a result, a set of windowed parameter variance was produced, which corresponded to a 4-dimensional matrix (region × region × subject × surrogate). Next, an averaging across individuals was calculated, creating a (region × region × 250) matrix (250 being the number of surrogate data copies) that produced a null hypothesis distribution for each pair of regions. Then the null hypothesis distribution was defined and the statistical hypothesis was expressed as the following formula:

$$H0: dFC\ absence$$
$$H1: dFC\ presence \quad (8)\ [20]$$

In this study, the variance (σ2) of the windowed parameter was included as a measure of dynamic functional relationship, and thus the hypothesis was tested as follows:

$$H0:\sigma 2=0$$
$$H1:\sigma 2>0 \quad (9)\ [20]$$

Results

Dynamic Functional Connectivity in the Sensorimotor network (SMN)

Results showed that the dFC between

the "Pre/posCenG.L" area and the "Pre/posCenG.R", "SMA.R", "Tha.L", "Bilat.LIV.V.VI" was seen in the PNES group. Also the dFC between the "Pre/posCenG.R" area with the "Tha.L", "Tha.R", and "SMA.R" was detected in the PNES group. However, the dFC was seen only between the "Pre/posCenG.L" area and the "Pre/posCenG.R", "Tha.L" and the dFC between the "Pre/posCenG.R" area with the "Tha.R" in the normal control group (Figure 1).

Dynamic Functional Connectivity in the Posterior salience network (PSN)

In the PSN, the dFC was seen between the "MFG.L" area with the "SmG.R and IPG.R", "PIns.L" and Put.L" and the dFC between the "SmG.L" and "IPG.R" area with the "SmG.R and IPG.R", "PIns.L and Put.L" and the dFC between the "Prec.L" area with the "MidCC.R", "SPG.R and Prec.R", "Tha.L", "Tha.R", "Lob.L.VI" the dFC between the "MidCC.R" area with the "SPG.R and Prec.R", "PIns.R", the dFC between the "SPG.R and Prec.R" areas with the "Lob.L.VI", "PIns.L and Put.L", "Tha.R", "Lob.R.VI", "PIns.R", the dFC between the "SmG.R and IPG.R" area with the "PIns.R" and the dFC between the "Tha.L" area and " PIns.L and Put.L", "Tha.R", "Lob.R.VI", "PIns.R" and the dFC between the "Lob.L.VI" area with the "PIns.L and Put.L", "Tha.L" and the dFC between the "Tha.R" area with the "PIns.R" was seen in the PNES group.

In the normal control group, the dFC between the "MFG.L" with the "MidCC.R", "SPG.R" and "Prec.R", "Lob.L.VI", "Lob.R.VI" and the dFC between the "SmG.L" and "IPG.L" with the "PIns.L and Put.L" and the dFC between the "Prec.L" area with the "SPG.R" and Prec.R", "SmG.R and the IPG.R", "PIns.L and Put.L" and the dFC between the "SmG.R and the IPG.R" with "Lob.R.VI", "PIns.L and Put.L", "PIns.R", and the dFC between the "Lob.L.VI" area with the "PIns.R" and the dFC between the "Tha.R" area with the "PIns.R" and the dFC between the "Lob.R.VI" area with the "right posterior" was seen (Figure 2).

Dynamic Functional Connectivity Anterior Salience Network (ASN)

In the ASN, in the PNES group, the dFC between the "MFG.L" area with the "Ins.L", "ACC,MPFC,SMA", "MFG.R", "Ins.R", "Lob.L.IV,Crus.L.I" and the dFC between the "Ins.L" area with the "ACC,MPFC,SMA", "MFG.R", "Lob.L.IV,Crus.L.I" and the dFC between the "ACC,MPFC,SMA" with the "MFG.R", "Ins.R", "Lob.L.IV,Crus.L.I", "Lob.R.IV,Crus.R.I" and the dFC between the "MFG.R" area with the "Ins.R",

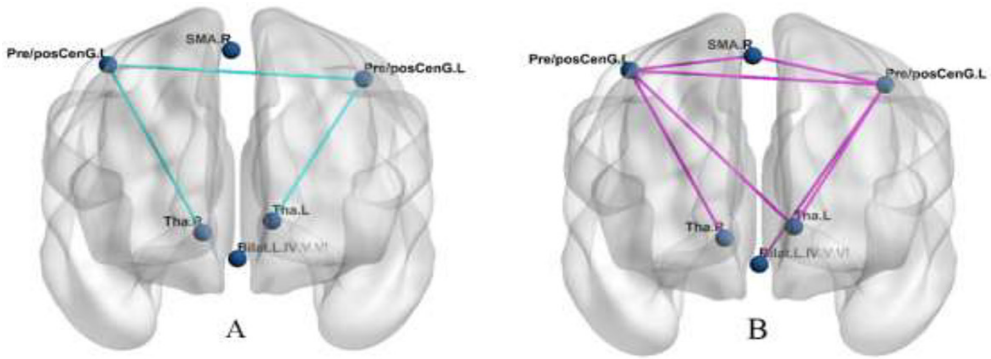

Figure 1: dFC in SMN in normal (**A**) and PNES (**B**) groups.
(dFC: Dynamic Functional Connectivity, SMN: Sensorimotor Network, PNES: Psychogenic Non-Epileptic Seizures, Pre/posCenG: Anterior/posterior Central Gyrus, SMA: Supplementary Motor Area, Tha: Thalamus. Bilat.L.IV.V.VI: Bilateral Lobule, L: Left, R: Right, IV: Forth, V: Fifth, VI: Sixth)

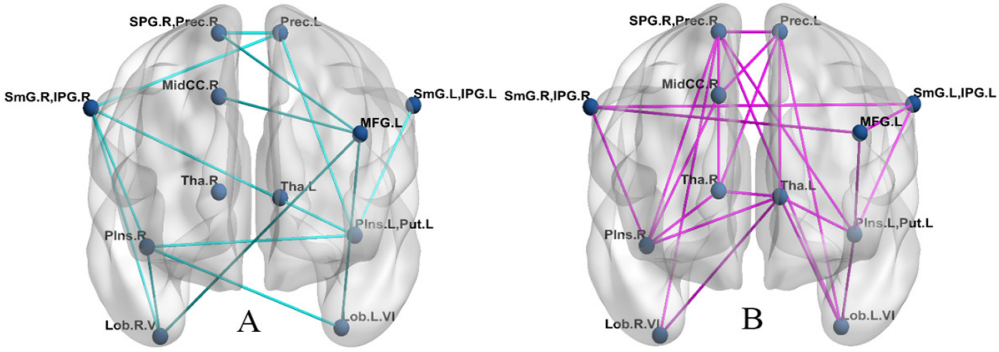

Figure 2: dFC in the PSN in normal (**A**) and PNES (**B**) groups.
(dFC: Dynamic Functional Connectivity, PSN: Posterior Salience Network, PNES: Psychogenic Non-Epileptic Seizures, MFG: Middle Frontal Gyrus, SmG: Supramarginal Gyrus, IPG: Inferior Parietal Gyrus. Prec: Precuneus, MidCC: Middle Cingulate Cortex, SPG: Superior Parietal Gyrus, Tha: Thalamus, Lob: Lobule, PIns: Posterior Insula, Put: Putamen, L: Left, R: Right)

"Lob.L.IV,Crus.L.I", "Lob.R.IV,Crus.R.I" and the dFC between the "Ins.R" area with the "Lob.R.IV,Crus.R.I" and the dFC between the "Lob.L.IV,Crus.L.I" area with the "Lob.R.IV,Crus.R.I" are presented. The dFC between the "MFG.L" area with the "MFG.R", "Ins.R", "Lob.L.IV,Crus.L.I" and the dFC between the "Ins.L" area with the "Lob.L.IV,Crus.L.I" and the dFC between the "ACC,MPFC,SMA" with the "MFG.R", "Lob.R.IV,Crus.R.I" and the dFC between the "Ins.R" area with the "Lob.R.IV,Crus.R.I" and the dFC between the "Lob.L.IV,Crus.L.I" area with the "Lob.R.IV,Crus.R.I" are presented in the normal subjects (Figure 3 a).

Dynamic Functional Connectivity in the Dorsal Default Mode Network (dDMN)

In the dDMN, in the PNES group, the dFC between the "MPfC,ACC,OrbfC" area with the "AngG.L", "Hipoca.L" and the dFC between the "AngG.L" area with the "Tha.R, Tha.L" and the dFC between the "SFG.R" area with the "PCC,Precu", "MidCC", "Hipoca.R" and the dFC between the "PCC,Precu" area with the "Hipoca.L", "Hipoca.R" and the dFC between "Tha.R, Tha.L" area with the "Hipoca.L", "Hipoca.R" was seen. Instead, in the normal control group, the dFC between the "MPfC,ACC,OrbfC" area with the "AngG.L", "AngG.R", "Hipoca.L", "Hipoca.R" and the dFC between the "AngG.L" area with the "PCC,Precu", "MidCC", "AngG.R", "Hipoca.L" and the dFC between "SFG.R" area with the "PCC,Precu", "Hipoca.R" and the dFC between "PCC,Precu" area with the "Hipoca.L", "Hipoca.R" and the dFC between the "MidCC" area with the "Hipoca.L" and the dFC between the "AngG.R" area with the "Tha.R, Tha.L", "Hipoca.L", "Hipoca.R" and the dFC between the "Tha.R, Tha.L" area with the "Hipoca.L", "Hipoca.R" are presented (Figure 3b).

Dynamic Functional Connectivity in the Left and Right Executive Control Network (LECN and RECN)

In the LECN, in the PNES group, there is no dFC between different areas of this network. Instead, in the normal control group, the dFC between the "IFG.L,OrbFG.L" area with the "Tha.L" and the dFC between the "SPG.L, IPG.L, Precu.L, AngG.L" area with the "Tha.L" and the dFC between the "ITG.L, MTG.L" with the "Tha.L" is presented (Figure 4a).

In the RECN, in the PNES group, the dFC between the "MFG.R, SFG.R" area with the "MFG.R" is presented. Instead, in the normal

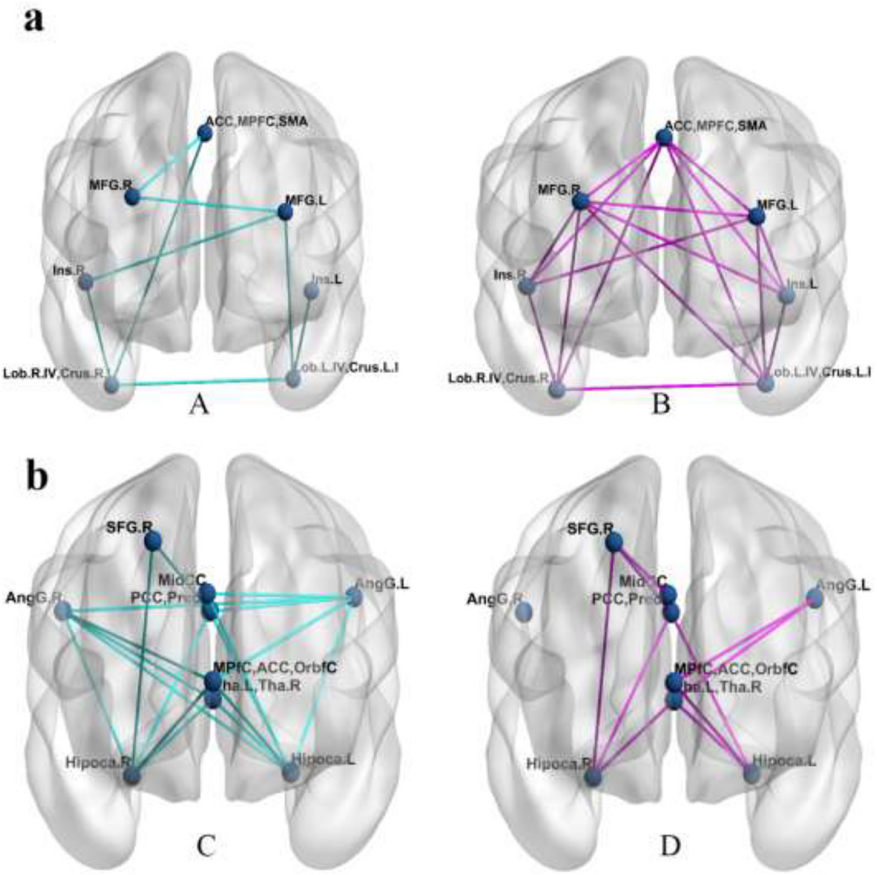

Figure 3: a: dFC in ASN in normal (**A**) and PNES (**B**) groups. **b:** dFC in dDMN in normal (**C**) and PNES (**D**) groups.
(dFC: Dynamic Functional Connectivity, ASN: Anterior Salience Network, PNES: Psychogenic Non-Epileptic Seizures, ACC: Anterior Cingulate Cortex, MPFC: Medial Prefrontal Cortex, SMA: Supplementary Motor Area, MFG: Middle Frontal Gyrus, Ins: Insula, Lob: Lobule, Crus: Crus, OrbfC: Orbitofrontal Cortex, AngG: Angular Gyrus, SFG: Superior Frontal Gyrus, PCC: Posterior Cingulate Cortex, Precu: Precuneus, MidCC: Middle Cingulate Cortex, Hipoca: Hippocampus, Tha: Thalamus, L: Left, R: Right, I: First, IV: Forth)

control group, the dFC between the "MFG.R, SFG.R" area with the "MFG.R", "Crus.R.I.II, Lob.R.VI", "right caudate" and the dFC between the "SFG.R" with the "Cau.R" are presented (Figure 4b).

Discussion

This study was conducted to the evaluation of dFC between some brain networks in PNES patients through the rs-fMRI method. Our findings indicate that the distribution and the numbers of presented dFC in the PNES group were significantly higher than in the normal control group in the SMN, PSN, and ASN. Also, in the networks of the dorsal DMN (dDMN), RECN network, and the LECN, the distribution and the numbers of presented dFC were higher in the normal control group than in the PNES group. These showed significant changes in the brain networks during rest state conditions.

The DMN is a large-scale functional brain network that distributes brain regions in the frontal, temporal, and parietal cortex that have low-frequency oscillations during the resting state. The DMN is usually activated during internal mental processes such as memory

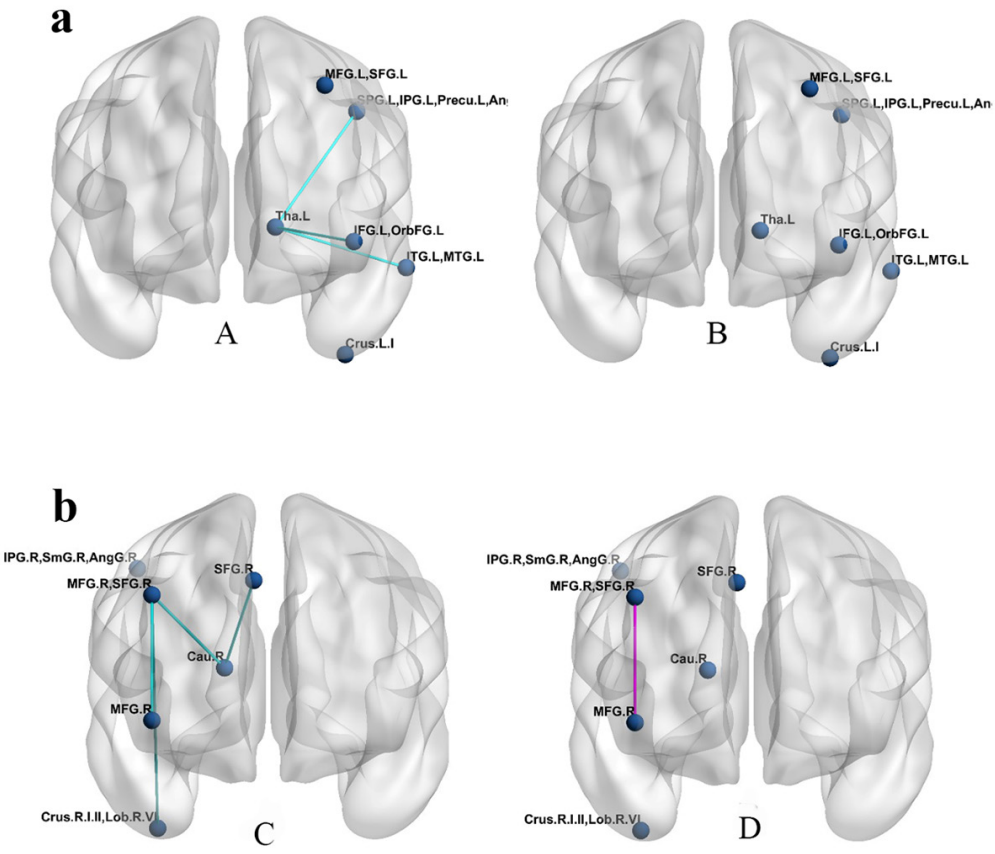

Figure 4: a: dFC in LECN in normal (**A**) and PNES (**B**) groups. **b:** dFC in RECN in normal (**C**) and PNES (**D**) groups.
(dFC: Dynamic Functional Connectivity, PNES: Psychogenic Non-Epileptic Seizures, ECN: Executive Control Network, MFG: Middle Frontal Gyrus, SFG: Superior Frontal Gyrus, SPG: Superior Parietal Gyrus, IPG: Inferior Parietal Gyrus, Precu: Precuneus, IFG: Inferior Frontal Gyrus, OrbFG: Orbitofrontal Gyrus, ITG: Inferior Temporal Gyrus, MTG: Middle Temporal Gyrus, Crus: Crus. Tha: Thalamus, SmG: Supramarginal Gyrus, AngG: Angular Gyrus, Lob: Lobule, Cau: Caudate. L: Left, R: Right, I: First, II: Second, IV: Forth)

processing and spatial navigation. Li et al. showed that the FC of the DMN has changed in the PNES which can reflect the causes and symptoms including abnormalities of neural synchrony in PNES [21,22]. Our results showed that the dFC was detected between the different regions of dDMN in the normal control group, while not seen in the PNES group. According to these results, it considers the dDMN has undergone changes in the PNES group.

The FC change in the ECN-related regions, such as the cingulate cortex, amygdala, thalamus, and hippocampus can change ECN control in different situations such as anxiety [23]. Van Der Kruijs et al. reported that stronger connectivity values in the PNES were seen which leads to emotion processing dysfunction [11]. Also, dFC changes in the Precu region and cingulate cortex which affects the function of consciousness, self-awareness, and self-related mental representations. Therefore, it leads to impaired consciousness [24]. This study shows changes in the dFC of the cingulate cortex, which can affect the DMN, sensorimotor, and ECN. These can lead to changes in brain focus on physical functions because previous studies showed that the cingulate cortex is involved in self-control, cognitive processing, and

attention. Also, it has a critical role in the recognition of novelty, the implementation of tasks through the selection of an appropriate motor response to the task, and or the change in inhibition of responses (inhibitory control). Zhao et al. showed that FC of ECN was different in Alzheimer's Disease (AD) suggesting that AD affects the brain functions and changes connections in various areas of the brain [24, 25]. Our results showed that the dFC between the "MFG.R, SFG.R" area with the "Crus.L.I.II, Lob.L.VI" and "Cau.R" was seen in the RECN of the normal control group, while these are not detected in PNES group. Also, the dFC between the "Tha.L" with the "IFG.L, OrbFG.L" and "SPG.L, IPG.L, Precu.L, AngG" and "ITG.L, MTG.L" was seen in the LECN normal control group, while these are not presented in PNES group. Therefore, the difference between the normal control group and the PNES was detected. The absence of the dFC in some the of frontal regions in executive control is related to the disability of unusual behavior [26]. These networks also play an important role in controlling external stimuli in cognitive tasks [27]. The frontal regions can influence emotion control (inhibitory control functions) and play a role in functions such as problem-solving ability, language skills, impulse control, and judgment [27]. Changes in FC patterns of some parts of the parietal lobe ("SPG.L, IPG.L") are involved in the processing function of sensory information and organizing subsequent actions (motor planning) which are also observed in the ECN, and changes in their dFC lead to changes in conscious motor control and then it appears in form of episodes of inefficient behaviors with the occurrence of epilepsy [28].

The SMN is responsible for our body's response to stimuli. It does this by taking information from our senses, both from the outside world and from inside our body. It then analyzes this information and helps us decide how to move or react [29]. Our results indicated that dFC between the "Pre/posCenG.L" area with the "SMA.R" and "Bilat.L.IV.V.VI" and "Pre/posCenG.R" region with the "SMA.R" and "Tha.L" regions are shown in the SMN of in the PNES group, while these are not shown in the normal control group. The precentral gyrus plays an important role in movement control. Changes in this network in the PNES indicate that the process of movement control has changed and led to manifesting episodes of altered movement and sensation [30]. During PNES, patients' sensorimotor and cognitive processes are affected and are not properly integrated, resulting in involuntary behavioral patterns [31]. These changes create abnormal sensorimotor interactions that are beyond the patient's conscious control. For most patients, the involuntary behavior patterns are avoidance coping strategies used to handle stressors and to abstain from experiencing stressful events or from memories of those events [32].

PSN has a critical role in consciousness and attention. Lou et al. provide evidence in favor of the disruption of inherent neural activity within the SN, which could potentially be associated with the obstruction of consequential information processing processes and linked to the manifestation of attentional impairments in childhood absence epilepsy [32, 33]. Similar to these data, our results showed that the dFC between some regions such as "MFG.L" area with the "MidCC.R" was seen in the PSN of the normal control group while was not seen in the PNES group. Also, the dFC between some regions of PSN such as "MFG.L" region with the "SmG.R, IPG.R" was detected in the PNES while these are not presented in the normal control group. These results indicated a significant difference in the dFC between both groups and ensured that the PSN in the PNES group has a different dFC distribution. It seems that the "PIns.L, Put.L", "Tha.R" and "PIns.R" regions are more active in this network.

Also, the dFC between the "MFG.L" area with "Ins.L", "ACC, MPFC, SMA", "Ins.L" area with the "ACC, MPFC, SMA" and "MFG.R" and "Ins.R" area with the "ACC, MPFC, SMA" and "MFG.R" was detected in the PNES group while these are not recorded in the normal control group. These results show it

is possible to observe a significant difference in the dFC between both groups and ensure that the ASN in the PNES group has a different distribution of dFC. It seems that the "PIns.L", "Tha.R" and "PIns.R" regions are more active in this network. The insula is an important multisensory integrator area that mediates the interpretation of sensory information received from the body, and then it is related to the function of emotion regulation; so the changes in its FC lead to unbalancing in emotional and cognitive functions [34]. Also, according to previous studies, the changes in insula connectivity are associated with impairment in "consciousness of error perception" [35]. The insula modulates emotional and behavioral activities, and its different connectivity distribution can lead to functional abnormalities [35]. The different dFC of the insula in the PNES group can be related to the different emotional processing in disorders such as major depression [36].

Based on this study, the activity of dFC in the DMN, RECN, and LECN was lesser in the PNES group than in the normal control group, and the activity of dFC in the SMN, PSN, and ASN was more than in the normal control group. However, there was no significant difference between both groups in the dFC of the 3 networks. PNES patients are more stressed and have a range of involuntary behavior patterns along with motor signs because they cannot deny psychological stress experiences and cannot choose avoidance-based coping strategies like behavioral efforts to avoid conflict or stress, so they have a range of involuntary behavior patterns [37]. Also, due to the changes in brain networks due to the disease, PNES patients cannot have the optimal ability to integrate information [38].

Increasing activity of the networks related to the functions of receiving sensory signals, emotion processing, and movement controlling. Reducing the activity of the networks related to internal functions such as self-awareness and consciousness and inhibitory functions, were the main cause of PNES symptoms like involuntary movement and inability to control. Therefore, our results agree with the results of previous studies and confirm the idea of unbalanced functions in the networks of related to emotional-motor-executive control functions in the PNES [38]. Also, the results confirm the theory that PNES patients overreact to external stimuli and cannot consider the conditions related to social emotions and leads to impairment and inefficiency in mental and social processing [31].

Conclusion

This study aimed to explicit the dynamics of neural activity of the brain networks as a function of time and focused on within-network FC dynamics. Our results show that the functional dynamics of some of the brain networks in PNES changed. This changed characteristic is related to FC dynamics of each network (within network interregional coupling) rather than regional brain activation and this issue is considered as altered network dynamism. dDMN, LCN, and RCN are the networks associated with reduced dynamism (lesser activation and/or connection), and the SMN, ASN, and PSN are also the networks associated with increased dynamism (more activation and/or connection). Furthermore, in contrast with the healthy control group, there are also aberrant connectivity dynamics in PNES. Our data revealed new aspects of PNES which may help shed light on its pathophysiology.

Authors' Contribution

M. Vardian and MA. Oghabian conceived the presented idea. MA. Oghabian developed the theory and performed the computations. Material preparation, data collection, and analysis were performed by MA. Oghabian and M. Arbabi. All authors wrote and reviewed the manuscript.

Ethical Approval

This study was approved by the local ethical committee, Tehran University of Medical Sciences (TUMS), Tehran, Iran (Approval number: IR.TUMS.MEDICINE.REC.1398.496).

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Conflict of Interest

None

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