Iran J Psychiatry 2021; 16: 4: 374-382

Original Article

Analysis of Effective Connectivity Strength in Children with Attention Deficit Hyperactivity Disorder Using Phase Transfer Entropy

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Abstract

Objective: This study aimed to investigate differences in brain networks between healthy children and children with attention deficit hyperactivity disorder (ADHD) during an attention test.
Method: To fulfill this, we constructed weighted directed graphs based on Electroencephalography (EEG) signals of 61 children with ADHD and 60 healthy children with the same age. Nodes of graphs were 19 EEG electrodes, and the edges were phase transfer entropy (PTE) between each pair of electrodes. PTE is a measure for directed connectivity that determines the effective relationship between signals in linear and nonlinear coupling. Connectivity graphs of each sample were constructed using PTE in the five frequency bands as follows: delta, theta, alpha, beta, and gamma. To investigate the differences in connectivity strength of each node after the sparsification process with two values (0.5 and 0.25), the permutation statistical test was used with the statistical significance level of p<0.01.
Results: The results indicate stronger inter-regional connectivity in the prefrontal brain regions of the control group compared to the ADHD group. However, the strength of inter-regional connectivity in the central regions of the ADHD group was higher. A comparison of the prefrontal regions between the two groups revealed that the areas of the Fp1 electrode (left prefrontal) in healthy individuals play stronger transmission roles.
Conclusion: Our research can provide new insights into the strength and direction of connectivity in ADHD and healthy individuals during an attention task.

Key words: *Attention Deficit Hyperactivity Disorder (ADHD); Electroencephalography (EEG); Signal Processing*

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Article Information:
Received Date: 2021/01/17, Revised Date: 2021/06/16, Accepted Date: 2021/07/20

Attention Deficit Hyperactivity Disorder (ADHD) is one of the developmental-behavioral disorders in childhood. Individuals with ADHD display some functional and cognitive impairments including inattention, or excessive activity, and impulsivity. These impairments lead to problems in executive function such as staying organized, maintaining concentration and paying attention, regulating emotions, and remembering details (1-3). According to the latest studies of child and adolescent psychiatric disorders in Iran, prevalence of ADHD in Iran is 4%, which is higher in boys than girls (5.2% vs. 2.7%) (4). This value is consistent with estimates of prevalence of ADHD in the world (2 to 7% with an average of 5%) (5). In children, problems related to paying attention may result in poor school performance. So, early recognition of ADHD in children results in early and effective interventions.

Studies using Magnetic Resonance Imaging (MRI) showed that in children with ADHD there was a general reduction of volume in certain brain structures, with a proportionally greater decrease in volume of the left-sided prefrontal cortex (6, 7). Decreased activity in different parts of the brain, especially in the frontal lobes of the brain, was observed in several studies using functional MRI modality in individuals with ADHD disorder (8-10).

Basic research with the Electroencephalogram (EEG) showed that ADHD patients had increased absolute and/or relative delta and theta power as well as decreased absolute and/or relative beta and gamma powers in frontal electrodes as compared to healthy controls (11-13). Most previous studies have reported major differences in brain function in the frontal and prefrontal regions between healthy and ADHD groups. Accordingly, these regions are especially interconnected with brain regions involved with attention, cognition, action, and emotion (14, 15). One way to examine differences between subjects with brain disorders and healthy subjects is by studying functional and effective connectivity between brain areas. Effective connectivity attempts to extract networks of causal influences of one brain region over another region, while functional connectivity extracts patterns of statistical dependence among regions (16) .

Some benefits of EEG include high temporal resolution, portability, and low cost of data recording, suggesting EEG as a proper candidate to study functional and effective connectivity of the brain. In EEG studies, symmetric measures have been used to determine functional connectivity between the brain regions. In this regard, Ahmadlou et al. used Synchronization Likelihood (SL) and Fuzzy Synchronization Likelihood (FSL) to examine the EEG connectivity of ADHD patients (17, 18). Mazaheri et al. showed a specific deficit as a functional disconnection between frontal and occipital cortices in children with ADHD in the attention task with correlation index (19). Recently, Kiiski and Furlong reported the functional EEG connectivity as a neuromarker for adult ADHD symptoms by calculating the Weighted Phase Lag Index (WPLI) (20, 21).

Since the functional connectivity criteria do not determine the direction of interactions, effective connectivity measures have recently been used to examine the interaction between brain signals in children with ADHD. One of the newly introduced criteria for determining causal interactions between time series (or EEG) is transfer entropy (TE), which is defined based on the information theory (22). TE does not assume a model for input data, thus, it has great ability to determine effective relationship between time series in linear and nonlinear coupling (23, 24). In 2014, Lobier developed TE to Phase Transfer Entropy (PTE), in which the input of the TE function is the instantaneous phase time series of each signal, rather than the signal time series. Due to the use of instantaneous phase of time series, PTE is more robust to noise and linear mixing (25). Recently, studies were conducted on the causal relationships between EEG signals of healthy children and children with ADHD based on directed PTE (dPTE) (26, 27). The dPTE is the normalized value of the PTE estimate introduced by Hillebrand (28). Determining only one value as the amount of information transfer between two systems is the dPTE limit. As the measures for functional and effective connectivity calculate the relationship among brain regions, graph theory can be used to study brain networks. Notably, a brain graph theory network is a mathematical representation of the brain architecture that includes a set of nodes and links interposed between them. In this regard, nodes represent brain regions, while links represent functional or effective connections (29-31).

This study aimed to investigate the differences in the strength of connectivity between brain regions in two groups of healthy children and children with ADHD during task of attention. Thus, we used PTE as a newly introduced effective connectivity measure and used the graph analysis to construct brain networks and to investigate on how the information is transmitted in the brain regions of subjects.

Materials and Methods

Subjects

Since one of the most important disorders in children with ADHD occurs in activities that require visual attention, in this study, we used EEG data of 61 children with ADHD and 60 healthy children (control group) aged between 7 and 12 years old in a visual attention task (32, 33). The ADHD subjects were evaluated by a psychiatrist and received a primary DSM-IV diagnosis (34). Moreover, all children in the healthy group were evaluated by a psychiatrist to ensure absence of psychological disorder, epileptic history, drug abuse, and head injury. All subjects voluntarily participated in the test and their parents signed informed consent for participation in the experiments. This research was approved by the Institutional Review Board (IRB) and Ethics Committee of Tehran University of Medical Sciences (TUMS).

EEG recording was performed based on 10-20 standard by 19 channels with 128 Hz sampling frequency and 16 bits resolution. In this test, the subjects were asked to pay attention to a set of images on the monitor and to count the number of characters in each image. Accordingly, Figure 1 shows an example of these pictures. The duration of recording was dependent on the child's performance. Data is currently available in http://dx.doi.org/10.21227/rzfh-zn36. (35).

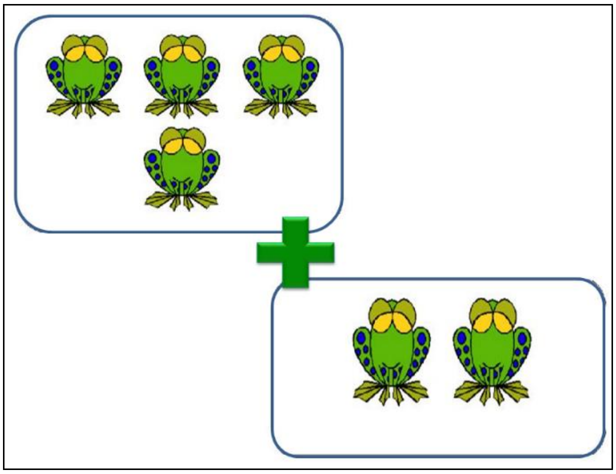


Figure 1. An Example of the Images Shown to Children during Signal Recording

EEG Pre-Processing

After recording these EEG signals, the signal pre-processing was done using the EEGLAB toolbox (version 14.1.1) (36) running on MATLAB 2018a. At first, a band-pass FIR filter of 1 Hz to 48 Hz was applied to continuous EEG data. Afterward, the preprocessed EEG data were decomposed using the Independent Component Analysis (ICA). Eye blinks and muscle artifacts were identified by ICA, which were then removed manually based on their spectra, scalp maps, and time courses. Later, EEG data were filtered with FIR filter with zero phase shift in five frequency bands, including delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13–30 Hz), and gamma (30–45 Hz). Afterward, for each subject, the time series were divided into 8-second segments. The number of segments for each subject was dependent on timing tasks.

Weighted Directed Graph Construction

The first step in constructing a brain graph is determining the nodes and the links between the nodes. Since EEG was used in this study, the nodes of each graph are equal to the number of electrodes or brain channels. Thus, for each graph, 19 nodes were considered. The links between every two nodes in the graph were calculated using the PTE, as an effective connectivity measure. PTE is a measure performed based on transfer entropy that uses the instantaneous phase time series of time series as the input of the TE function. It is noteworthy that TE from a process X to process Y is the amount of uncertainty reduced in future values of Y by knowing the past values of X and past values of Y. The instantaneous phase time-series of the signal X (t) as θ (t) in S (t) = A (t) exp(iθ(t)), where S(t) is analytics form of X(t). θ (t), can be obtained by the Hilbert transform. PTE from X (t) to Y (t) is defined as follows:

$$PTE\ (X \rightarrow Y) = I(\theta_y(t),\theta_x(t')|\theta_y(t')) = H(\theta_y(t'),\theta_x(t')) - H(\theta_y(t),\theta_y(t'),\theta_x(t')) + H(\theta_y(t),(\theta_y(t')) - H(\theta_y(t'))$$

Where H (.,.) is the Shannon entropy that indicates the average level of "information" or "uncertainty" inherent in the variable's possible outcomes, and I(.,.|.) is the conditional mutual information. In Eq (1), δ is prediction delay and θx (t′) and θy (t′) are the past states at time point t′.

$$t' = t - \delta$$
$$\theta_x(t') = \theta_x(t - \delta)$$
$$\theta_y(t') = \theta_y(t - \delta)$$

We used Lobier et al. and similar articles to implement and determine entropy parameters (25, 28, 37). The PTE between each pair of brain channels was calculated for all subjects in each frequency band as well as in each segment. Thereafter, the connectivity matrices of each subject in each frequency band were averaged along with the segments to form a connectivity matrix at the end for each person with dimensions of 19*19 in each frequency band. Each element of the connectivity matrix represented the strength of links between each pair of nodes (channels) in the graph's construction. In this way, a weighted directed graph was constructed for each subject in each frequency band.

Graph Theory Measures

The graph theory provides a mathematical framework to model the pairwise connectivity between the elements of a network. After construction of the connectivity graph for each subject, the sparsification process was performed with two values for each graph. The purpose of the sparsification process was to eliminate spurious and weak edges in the graph through thresholding. For the first case, the threshold was initially considered to be 0.5, and thus for each graph, half of the connections (edges) that were weaker in terms of PTE value were removed. For the second case, the threshold was set at 0.25 to keep a quarter of the strongest connections in the graph of each subject. Then, the graph measure extraction step was performed. The measures related to connectivity strength in each node were used as the extracted feature. Table 1 shows the three measures considered in this regard. Notably, graph measures were calculated using the Brain connectivity toolbox (BCT) (30).

Table1. Node Strength Measures Extracted in PTE-Based Graph for Each Subject of Healthy and Attention Deficit Hyperactivity Disorder (ADHD) Groups

Measures	Description
In-strength	Sum of the weights of inward links connected to a node
Out-strength	Sum of the weights of outward links connected to a node
Strength	Sum of the weights of inward and outward links connected to a node

Statistical Analysis

For statistical comparisons, we used a non-parametric permutation test between the control and ADHD groups in all five frequency bands. This step was performed on the value of each measure in each node to evaluate abnormal changes in the connectivity strength of the ADHD subjects. For each node, we tested the null hypothesis that either the measure of this node has not changed between the two groups or its measure is different between the control group and the subjects with ADHD. In between-group comparisons, null distributions were created with 5,000 permutations and all comparisons were two-tailed. The significance of between-group differences ($p<0.01$) of each measure in each node was determined by comparing the original value with the obtained null histogram. In all the performed analyses, the p-values of pairwise comparisons were corrected by the False Discovery Rate (FDR) (38).

Results

The node's strength (sum of in-strength, out-strength, and total strength of a node) was compared between the two groups to analyze differences in the link weight of brain networks. Since the statistical test was performed between the two groups for each frequency band and also for each measure in each node (channel), the results of the statistical test can be shown on each node. Figures 2 and 3 show the mean values of each node strength feature (according to Table 1) in both groups, in five frequency sub-bands in the graph sparsification of 0.5 and 0.25, respectively. In these figures, the electrodes, which the statistical test showed a statistically significant difference between the two groups in strength measures, were written in the bottom row of each image and marked by Pink Square in each frequency band.

To evaluate the strength of connectivity in different areas of the brain, the electrodes were divided into three regions. Region1 consists of electrodes from the frontal and prefrontal areas of the brain. The region 2 includes electrodes of the central, temporal, and parietal lobes. Region 3 also contains O1 and O2 electrodes located at the occipital lobe. Thus, the number of electrodes in each feature had significant differences counted and listed in Table 2. Division of electrodes in three regions which is based on the 10-20 electrode system is also shown in this table.

Discussion

We used the PTE to investigate the differences in strength of connectivity in brain networks of children with ADHD and healthy children during an attention task. The PTE used the instantaneous phase of time series and TE function to determine the effective connectivity between two systems (in this study, a pair of EEG signals). A connectivity matrix with Phase TE values was constructed for each subject. Thus, the fully connected brain graph for each subject was formed by 19 nodes (equal to the number of electrodes) and edges from each node to the other node with a weight equal to the Phase TE value. By applying the sparsification process, the brain graphs were pruned. In one case, 50% of the weak edges (sparsification value = 0.5) and in the second, 75% of the weak edges (sparsification value = 0.25) were removed to keep the stronger edges in the brain graphs. After sparsification, in-strength, out-strength, and total strength measures were extracted for each node (electrode) to compare these values between the two groups by permutation statistical test .

PTE is a measure for determining causal relationships between pairs of time series that can indicate the direction and strength of information transfer between two signals. In other articles, directed PTE (dPTE) was used to examine differences in connectivity between brain regions in healthy children and children with ADHD (26) and to classify the two groups (27). Due to limitation of dPTE in determining only one value as the information transferred between time series, in the connectivity matrix (formed by the dPTE), the upper part of the triangle and the lower part of the triangle of the matrix do not provide more information (39). In our paper, using PTE, it was possible to examine two-way connectivity between two signals, and the dPTE limit was removed. The sparsification process eliminated the weak connections, but if the two-way connectivity between the two signals are strong, with this method, both connections remain in the calculations.

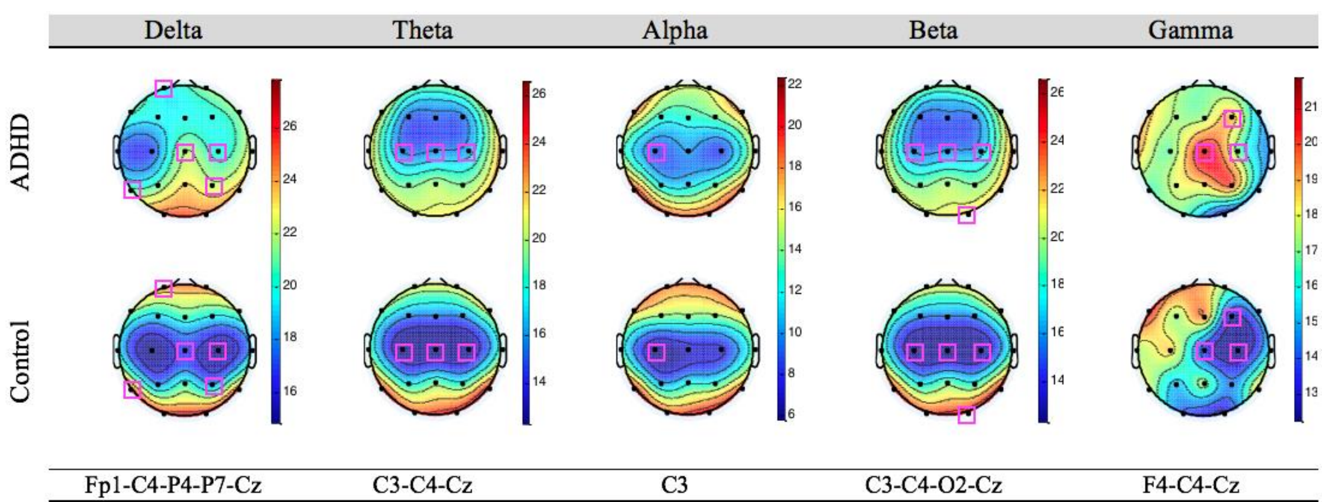
The results of our statistical tests were shown in Figures 2 and 3 and the number of electrodes with values of measures with statistically significant differences between the two groups were indicated in Table 2. From these figures, it can be concluded that in all three measures and in all frequency bands, except the gamma band, values of region 1 (prefrontal and frontal lobe) and region 3 (occipital lobe) are higher than the other regions in both ADHD and control groups. Neuroscience identifies the prefrontal and occipital regions of the brain as the centers of attention and visual processing, respectively (14, 15, 40). Since all subjects participated in a visual cognitive test in this research, the results showed that the strength of connectivity in these areas was higher than the other areas in both groups.

The results of the delta frequency band in the sparsification with a value of 0.5 (Figure 2) showed that the highest number of electrodes with statistically significant differences between the two groups was in this frequency band. The results of statistical testing in this frequency band showed that each measure (in-strength, out-strength, and strength) has 5 electrodes in which the measure's value makes a significant difference between the two groups. After delta band, beta and theta frequency bands had the highest number of electrodes with significant differences between the two groups in terms of strength features, respectively. In the sparsification with 0.25 (Figure 3), statistical tests showed that the delta and theta bands had more significantly different channels between the two groups in the values of node strength measures than the other bands.

The results obtained in this study were consistent in two sparsification values in determining the difference in function of brain regions between healthy and ADHD groups. According to statistical test results for both sparsification values (Figure 2, Figure 3, and Table 2), our research indicated that the most significant differences between the two groups occurred in region 2 (specially the central region of the brain, including C4, Cz, and C3) and then in region 1 (specially Fp1 electrode in left prefrontal lobe). In the delta, theta, alpha, and beta frequency bands, the higher mean of all three features in region 2 indicated that children with ADHD had stronger intra-regional connections in the central regions of the brain than healthy children. The results also showed that mean values of all three-nodal strength in region 1 were higher in children in the healthy group than in the ADHD group. Thus, it can be concluded that in the ADHD group, there were weaker intra-region connectivity that were eliminated in the sparsification process. It was also found that healthy children had a stronger intra-regional connection than children with ADHD in the prefrontal and frontal areas of the brain.

Our results of the out-strength measure shown in Figure 2(b) and Figure 3(b) indicated the important role of the Fp1 electrode region (left prefrontal) in transmitting information in the delta, theta, alpha, and beta frequency bands. Statistical testing showed that the areas related to this electrode had more power in transmitting information in the healthy group compared to the ADHD group, which can probably be due to receiving more information in the prefrontal and posterior regions. Previous studies using various modalities such as fMRI and EEG have also reported the decreased function of brain networks in the prefrontal and frontal regions (often in the beta band) of the brain (6-10, 26) .

Additionally, due to the higher average strength of connectivity in the posterior regions in healthy children, it seems like, there is stronger connectivity between the prefrontal and posterior regions compared to children with ADHD. These results were identified in the delta and theta frequency bands. Several previous studies have shown functional disconnection of the frontal cortex (or anterior region of brain) and visual cortex (or posterior region of brain) in children with ADHD during the attention test (19). Accordingly, they used cross-frequency amplitude correlations to investigate differences in functional connectivity between the studied groups. The result of our research is consistent with results of previous studies on stronger connections between prefrontal and posterior brain in healthy children compared to ADHD patients.



(a) In-Strength

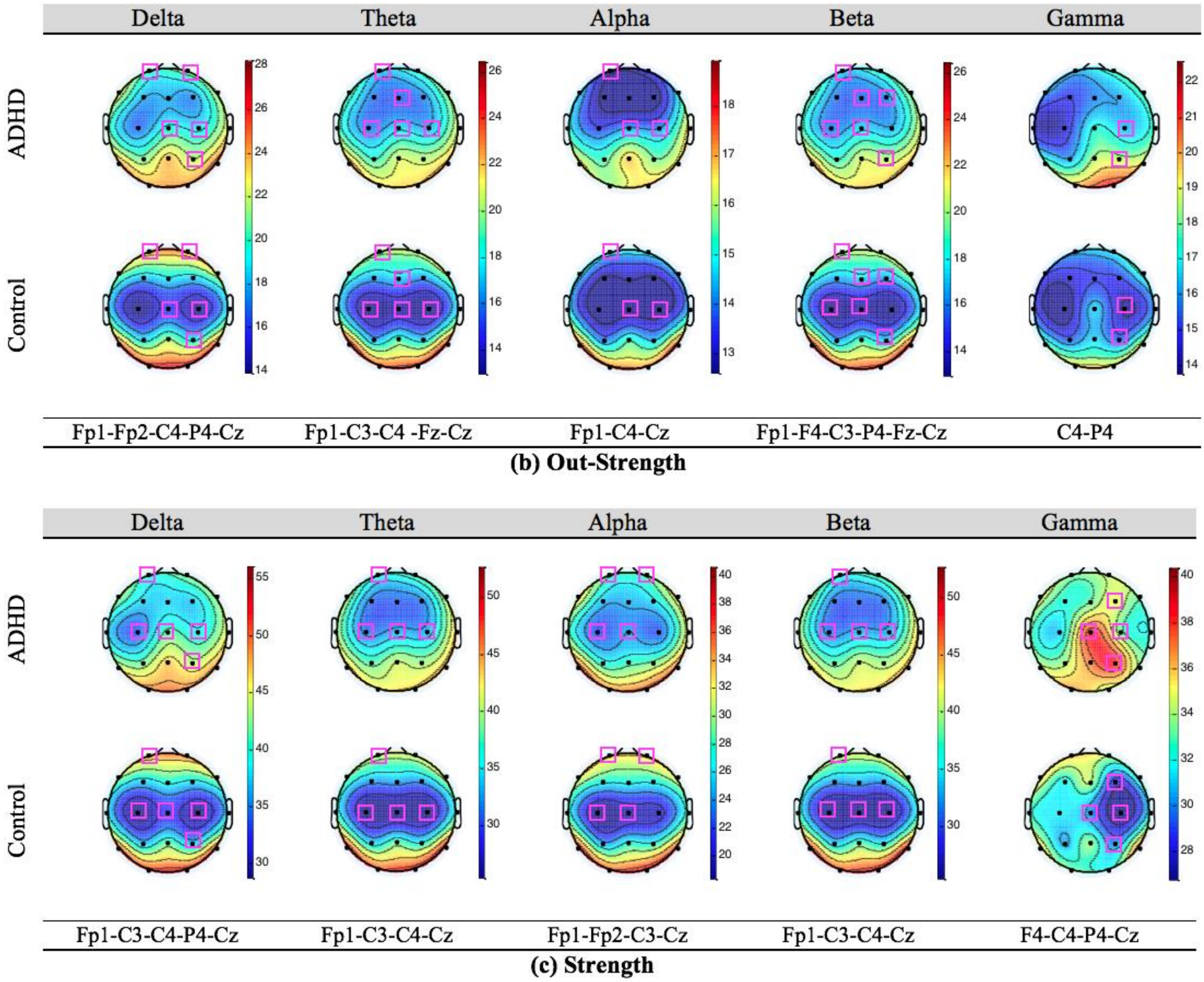
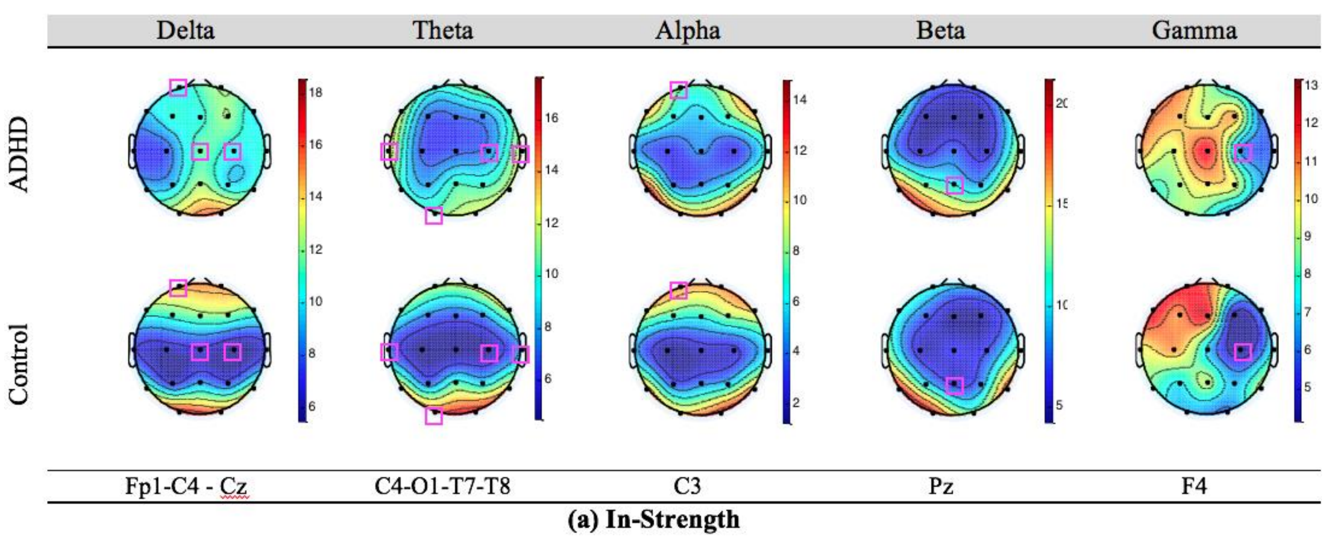


Figure 2. Average of Strength Graph Measures (In-Strength (a), Out-Strength (b), and Strength(c) in Five Frequency Bands) for ADHD and Healthy Groups with PTE in the Graph Sparsification of 0.50. Pink Squares Show Electrodes Indicating A Statistically Significant Difference (p<0.01) between the Two Groups.



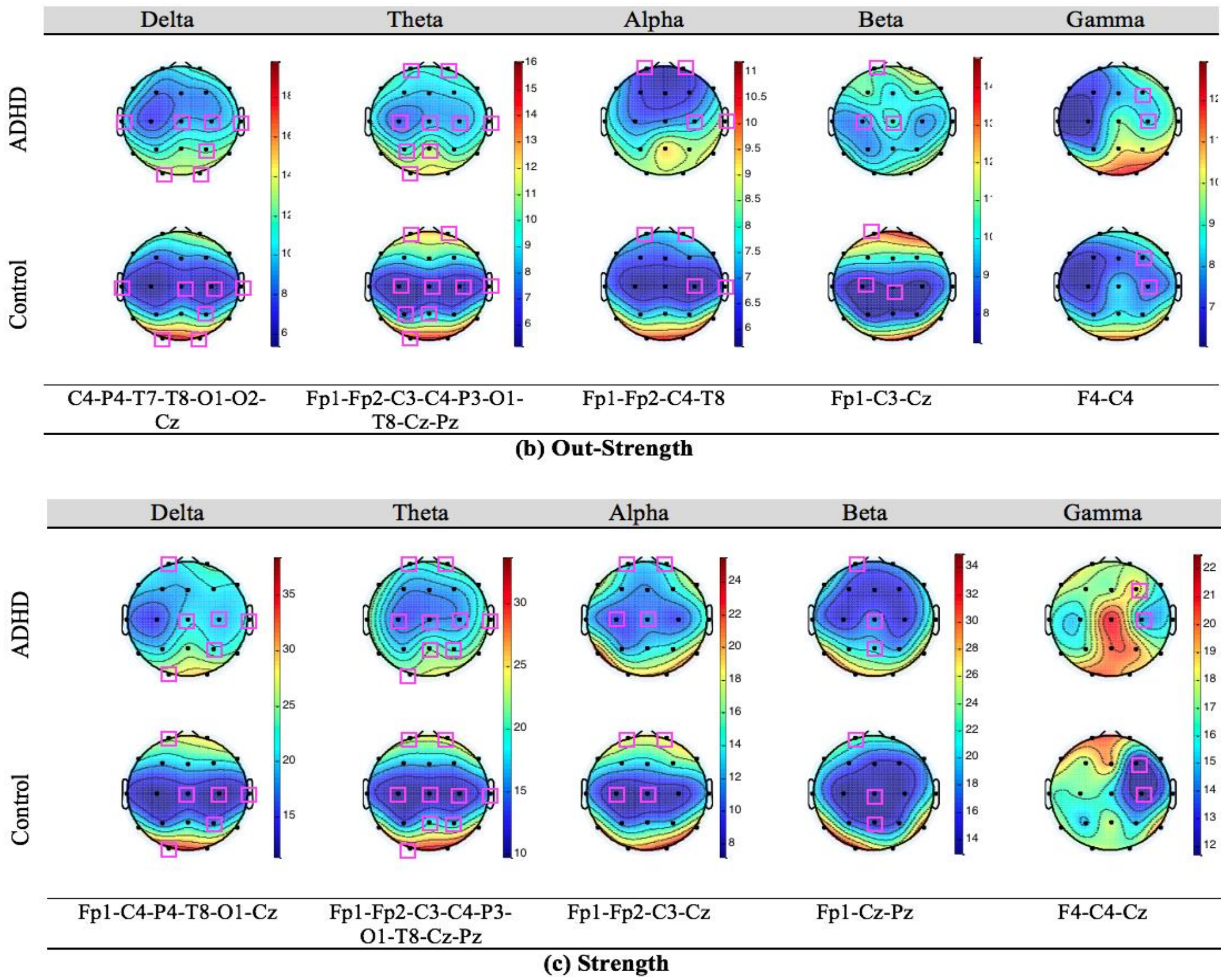
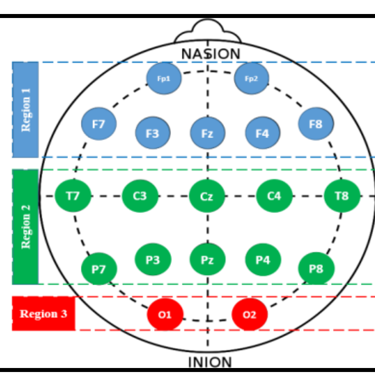


Figure 3. Average of Strength Graph Measures (In-Strength (a), Out-Strength (b), and Strength(c) in Five Frequency Bands) for ADHD and Healthy Groups with PTE in the Graph Sparsification of 0.25. Pink Squares Show Electrodes Indicating A Statistically Significant Difference (p<0.01) between the Two Groups.

Table2. Number of Channels with Statistical Significant Differences in Graph Measures between ADHD and Healthy Groups

	In Strength						Out Strength						Strength					
	Reg1		Reg2		Reg3		Reg1		Reg2		Reg3		Reg1		Reg2		Reg3	
	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**
Delta	1	1	4	2	0	0	2	0	3	5	0	2	1	1	4	4	0	1
Theta	0	0	3	3	0	1	2	2	3	8	0	1	1	2	3	6	0	1
Alpha	0	1	1	0	0	0	1	2	2	2	0	0	2	2	2	2	0	0
Beta	0	0	3	1	1	0	3	1	3	2	0	0	1	1	3	2	0	0
Gamma	1	0	2	1	0	0	0	1	2	1	0	0	1	1	3	1	0	0



* sparsification value = 0.5
** sparsification value = 0.25

Limitation

One of the limitations of our study was that the strength of brain networks between ADHD types was not examined, specifically inattentive, hyperactive-impulsive, and combination types. By increasing the number of subjects in the experiment and using their clinical information, the differences in the strength of brain networks between the three types of ADHD can be investigated. Another limitation of this study was the use of 19-channel EEG recordings, while with the increase of EEG channels, a more accurate representation of brain activity will be provided.

Conclusion

In this study, using Phase Transfer Entropy (PTE), the differences in characteristics of brain graphs of healthy children and children with ADHD during an attention test were investigated. For this purpose, after recording the brain signals of the subjects in both groups, their brain connectivity graphs were constructed. The graph sparsification process was used to eliminate weak and possibly noisy connectivity. One of the features of a graph that can explain aspects of brain networks is the strength of connectivity. Since the PTE shows the strength and direction of connectivity, the strength of nodes can be investigated using in-strength, out-strength, and total strength measures. The results of statistical tests showed that in the prefrontal regions of the brains of the control group, there was stronger inter-regional connectivity in the delta, theta, alpha, and beta frequency bands compared to the ADHD group, while in the same frequency bands in the ADHD subjects, the strength of inter-regional connectivity in the central regions of the brain was higher. A comparison of the prefrontal regions of the brain between these two groups revealed that the areas of the Fp1 electrode (left prefrontal lobe) in healthy individuals play stronger transmission roles compared to the rest of the brain. Due to the higher average strength of connections in the occipital lobe of healthy people in our results, it also seems there are stronger connections between the prefrontal regions and posterior regions of the brain in healthy children compared to patients. Our research can provide new insights into the strength and direction of connectivity in ADHD and healthy individuals during an attention task.

Acknowledgment

The authors would like to thank the Psychiatric and Psychological Research Center of Tehran University of Medical Sciences for their cooperation and recording parts of the EEG data.

Conflict of Interest

None.

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