Which attention-deficit/hyperactivity disorder children will be improved through neurofeedback therapy? A graph theoretical approach to neocortex neuronal network of ADHD

Mehran Ahmadlou\textsuperscript{a,c,d,∗}, Reza Rostami\textsuperscript{a,b}, Vahid Sadeghi\textsuperscript{a,b}

\textsuperscript{a}Atieh Comprehensive Center for Nerve and Psych Disorders, Tehran, Iran
\textsuperscript{b}Department of Psychology and Educational Sciences, University of Tehran, Tehran, Iran
\textsuperscript{c}Department of Biomedical Engineering, Amirkabir University of Technology, Tehran, Iran
\textsuperscript{d}Pediatric Neurorehabilitation Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

\textbf{A B S T R A C T}

Neurofeedback training is increasingly used for ADHD treatment. However some ADHD patients are not treated through the long-time neurofeedback trainings with common protocols. In this paper a new graph theoretical approach is presented for EEG-based prediction of ADHD patients' responses to a common neurofeedback training: rewarding SMR activity (12–15 Hz) with inhibiting theta activity (4–8 Hz) and beta2 activity (18–25 Hz). Eyes closed EEGs of two groups before and after neurofeedback training were studied: ADHD patients with (15 children) and without (15 children) positive response to neurofeedback training. Employing a recent method to measure synchronization, fuzzy synchronization likelihood, functional connectivity graphs of the patients' brains were constructed in the full-band EEGs and 6 common EEG sub-bands produced by wavelet decomposition. Then, efficiencies of the brain networks in synchronization and high speed information transmission were computed based on mean path length of the graphs, before and after neurofeedback training. The results were analyzed by ANOVA and showed synchronizability of the neocortex activity network at beta band in ADHDs with positive response is obviously less than that of ADHDs resistant to neurofeedback therapy, before treatment. The accuracy of linear discriminant analysis (LDA) in distinguishing these patients based on this feature is so high (84.2%) that this feature can be considered as reliable characteristics for prediction of responses of ADHDs to the neurofeedback trainings. Also difference between flexibility of the neocortex in beta band before and after treatment is obviously larger in the ADHDs with positive response in comparison to those with negative response which may be a neuropsychiologic reason for dissatisfaction of the last group to the neurofeedback therapy.

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is known as one of the most common pediatric neuropsychiatric disorders in the world [26]. The main behavioral characteristic of ADHD is a persistent pattern of attentiveness and/or hyperactivity-impulsivity based on the DSM-IV definition [3]. Since it severely affects emotional, educational and social life of the ADHD children [26], an effective treatment is a very important issue. There are three common therapeutic approaches: pharmacological methods, cognitive-behavioral methods, and neurofeedback trainings.

Pharmacological methods have side effects and cognitive-behavioral methods need a high cooperation of parents and teachers, which is hard in general. Neurofeedback aims at obtaining voluntary control over certain brain activity patterns to self-regulate attentional processes and states [18]. Among the therapeutic methods, neurofeedback therapy is known as a roughly effective method without any side effect [7]. It is reported that before 2005 it has been used by at least 1500 practitioners [25], while it is more accepted now and is used increasingly.

Many studies show strong correlations between neuronal synchronization and cognitive processing. Also there are some evidence show the neurofeedback improves the cognitive processing through improving the synchronization neuronal areas and flexibility of the neocortex networks [17,18]. However in practice conventional neurofeedback trainings are not successful in treatment of all ADHD patients [25]. It is not clear yet, why some ADHD children have not positive response to neurofeedback.
therapy and whether their responses to the treatment can be predicted before treatment or not. Answering these questions could help the neurotherapists to tune more effective neurofeedback training protocols or individualize the protocols of ADHDS. The current study attempts to answer these questions. The authors hypothesize structure of neuronal neocortex network of the ADHDS patients in EEG or EEG frequency sub-bands is a determinative characteristic in this prediction, which is responsible to flexibility of the network in the corresponding frequency range.

The protocols of neurofeedback are based on the slowing EEG rhythms in ADHD children, represented by increase of theta activity and decrease of beta activity [19]. Therefore a common neurofeedback training protocol is used in this study: rewarding Sensorimotor Rhythm (SMR or low beta) (12–15 Hz) activity with inhibiting theta activity (4–8 Hz) and beta2 activity (18–25 Hz) [13,16]. Many studies show training a specific frequency band does not necessarily affect the brain topography at the same frequency band [14]. Therefore, in this study, in order to investigate effects of neurofeedback in each EEG sub-band, EEG is decomposed to 6 conventional sub-bands through a wavelet filter bank. Then the functional connectivity of each electrode pairs is obtained using a recent proposed method by Ahmadlou and Adeli [4] called bivariate fuzzy synchronization likelihood (SL), which is more sensitive to synchronization changes in respect with the conventional SL [24]. Thus, the functional connectivity matrices consist of the fuzzy SLs are computed for the full-band EEG and each EEG sub-band. Since weights of a connectivity graph contain a major part of its structural information [8,20], against most studies, the authors avoid converting it to binary graphs [9,10]. Then efficiency of the weighted graphs, which shows feasibility of Information transmission (flexibility) in the neocortex network [20], is computed for EEGs of both groups (ADHDS with positive response and without positive response) before treatment. Differences of efficiency of the structures between the two groups are analyzed in the full-band EEG and the sub-bands through ANOVA. Also effectiveness of the treatment on changing the structures is investigated through the same analysis based on the EEGs after treatment. At last, a classifier, linear discriminant analysis (LDA), is used to predict responses of ADHD patients to neurofeedback therapy based on the most discriminative features (efficiencies of the neocortex structure) before treatment selected by ANOVA.

2. Method

2.1. Data acquisition and neurofeedback training

The data used in this research were recorded at the Atieh Comprehensive Center for Psych and Nerve Disorders, Tehran, Iran. The data are eyes-closed EEGs of 30 ADHDS children in rest state conditions, 15 subjects (11 males and 4 females), 8–13 years old with average of 11.1, with positive response (improvement) and 15 subjects (12 males and 3 females), 8–13 years old with average of 10.7, with negative response (no-improvement) to neurofeedback therapy. Each subject has 2 recordings of 19-channel EEG with electrodes placed according to the 10–20 system, one EEG before treatment and the other one after treatment. The EEGs were analog filtered from 1 to 70 Hz using a bandpass filter. Also using a notch filter at 50 Hz the electricity line frequency noise was removed. EEGs were digitized to 16 digits with sampling rate of 256 Hz. EEGs are from rest state in eyes-closed condition, sitting on a comfortable chair in a silent room. The EEG recording lasted 5 min (5 × 60 × 256 = 76,800 time samples) to have a large interval free from artifacts, which is needed for the applied nonlinear analysis. Vertical and horizontal Electrooculogram (EOG) was registered simultaneously in order to detect eye-blinking and eye-movement artifacts. An interval of 14,080 points of each EEG data was selected as an appropriate part of the recorded EEG without eye blink and other artifacts. The neurofeedback training protocol used for all patients were rewarding SMR (low beta) (12–15 Hz) activity at Cz, whereas theta (4–8 Hz) and high-beta (18–25 Hz) are inhibited, to remit inattention and hyperactivity [12]. The treatment of each subject lasted 35–40 sessions of 45 min, 3 sessions per week. Video mode was used in all sessions for visual presentation of the biofeedback signal. In this mode, a cartoon is represented while the biofeedback parameter controls size of the cartoon: increase/decrease of the biofeedback parameter results in increase/decrease of the size. The ADHDS patients were diagnosed based on DSM-IV criteria as well as Child Behavior Checklist (CBCL) and Cognitive Assessment System (CAS). Improvement and non-improvement of the subjects, after the treatment sessions, were assessed using ADHD scores of the CBCL (DSM-Oriented Scale) and CAS. The CAS planning (ranged from 45 to 135) and attention (ranged from 45 to 135) standard scores and the CBCL ADHD scores (ranged from 0 to 14) for the improved and non-improved patients, before and after the treatment sessions, have been presented in Table 1. The higher scores of CAS planning and attention, the better performance and the higher ADHD scores of CBCL, the more severe deficits. The successfulness of the treatment was characterized as at least 20% improvement in the scores of the aforementioned behavioral tests after the treatment. Also power spectrum analysis did not show any significant difference between the improved and non-improved ADHDS, before the treatment.

2.2. Data analysis

The proposed predictive method consists of 6 steps as follows.

Step 1. Preprocessing and wavelet decomposition

EEG is decomposed to 6 conventional sub-bands. Gamma (30–70 Hz) (γ), Beta (15–30 Hz) (β), Sensorimotor Rhythm (12–15 Hz) (SMR), Alpha (8–12 Hz) (α), Theta (4–8 Hz) (θ), and Delta (1–4 Hz) (δ), through a wavelet filter bank [1,2]. Details of the data preprocessing and wavelet analysis can be found in Ahmadlou and Adeli [3].

Step 2. Computation of bivariate fuzzy synchronization likelihood (fuzzy SL)

In contrast to linear synchronization measurements such as coherence [21] and cross correlation [23], SL is an unbiased measurement of both linear and nonlinear synchronizations among two or more coupled systems [24]. Recently Ahmadlou and Adeli [4] proposed the fuzzyfied version of SL, called fuzzy SL, as more precise measurement of synchronization and interdependencies between coupled systems. Indeed it measures generalized synchronization. When there is generalized synchronization between two signals, a pattern present in one signal tends to repeat itself in the other signal, at the same times, directly or indirectly using a mapping function [24]. In this paper, fuzzy SL is used as a bivariate measurement which quantifies likelihood and similarity between dynamics of signals of each electrode pair.

Let X_t and X_p be time series of two different systems (e.g. two electrodes), A and B. They are reconstructed in a state space, respectively, as trajectories X_t and X_p. According to Taken's reconstruction method [11], n'th point of X_t (where k ∈ [A, B]), X_k,n, is represented in the form: X_k,n = (x_k,n, x_k,n+1, ..., x_k,n+(d−1)t); in which x_k,n is the n'th sample of the time series X_t; The state space is reconstructed based on two parameters, d and τ, time lag (the time delay between the elements of the space) and embedding dimension (the dimension of the space). They are computed so that the reconstructed trajectories have no folding and self-intersection to avoid incorrectly considered close points of the trajectories which...
can hamper the computation of closeness in the fuzzy SL method. Also, both of them are assumed to have the same value for all signals in order to compute similarities among the trajectories in the same state space for meaningful comparisons [6,22]. Consequently, the number of points of a trajectory (N) is equal to M – (d – 1)r; where M is number of sampling points of the signal. A window, W_{w}^{n}(k, n), around the reference state (reference state is the point of the constructed trajectory at the center of the window.), X_{k,n}, contains all states, X_{k,m}, which their indices, m, satisfy the condition: w_{1} < |n - m| < w_{2}. W_{1} is the Theiler correction [9] to prevent information redundancy in the similarity computation (similarity of the states means closeness of the states to the trajectory to the reference state.). Therefore Z(w_{2} - w_{1}) is the number of points restricted in the window and \( W_{w}^{n}(k, n) \) determines the maximum temporal distance that a state can have from the reference state.

In the window W_{w}^{n}(k, n), a Gaussian membership function with center at the reference state and a standard deviation of \( \varepsilon_{k,n} \) is employed [4]:

\[
\mu_{k,n}(X_{k,m}) = \exp \left( - \frac{|X_{k,m} - X_{k,n}|^{2}}{\varepsilon_{k,n}} \right)
\]

where \( \mu_{k,n}(X_{k,m}) \) is the membership value of the state \( X_{k,m} \) in the d dimensional Gaussian function of the time series \( k \) in the window and \( |X_{k,m} - X_{k,n}| \) indicates Euclidean distance between the states \( X_{k,m} \) and \( X_{k,n} \). Then, the probability that a state \( X_{k,m} \) is closer to the reference state \( X_{k,n} \) than a distance \( \varepsilon_{k,n} \) in the window is computed as follows [4]:

\[
P_{k,n} = \frac{1}{2(z_{w2} - z_{w1})} \sum_{m=1}^{N} \mu_{k,n}(X_{k,m})
\]

For all \( k \), \( \varepsilon_{k,n} \) is obtained by making \( P_{k,n} \) equal to a small \( P_{ref} \) << 1. Through application of the Gaussian function to the states, values of the similarity of the states to the reference state are indicated through their Euclidean distances to the reference state. Standard deviations of the Gaussian functions are set equal to \( \varepsilon_{A,n} \) and \( \varepsilon_{B,n} \) for \( X_{A} \) and \( X_{B} \), respectively. Centers of the functions are the reference states.

Then fuzzy SL between \( X_{A} \) and \( X_{B} \) restricted in the windows with centers \( X_{A,n} \) and \( X_{B,n} \), respectively, is computed as follows [4]:

\[
S_{A,n} = S_{B,n} = \frac{1}{2P_{ref}(z_{w2} - z_{w1})} \sum_{m=1}^{N} [\mu_{A,n}(X_{A,m})\mu_{B,n}(X_{B,m})]
\]

Sliding the window overall the time series (shifting the window with a step), computing the SL in each shifted window and averaging the SLs of all shifted windows leads to the SL between the signals \( X_{A} \) and \( X_{B} \).

**Step 3.** Creating functional connectivity matrices

In this step, functional connectivity matrices are created with values of the fuzzy SL between signals of all pair-wise combinations of the channels obtained in the previous step. A connectivity matrix is calculated for each EEG sub-band and for the full-band EEG. As such, each patient has 7 functional connectivity matrices corresponding to the full-band EEG and 6 EEG sub-bands.

**Step 4.** Computing efficiency of the neuronal network’s structures

Efficiency of a weighted graph indicates speed of information transition from a node to another node of the graph which is defined in the following way [20]:

\[
L = \frac{1}{N(N-1)/2} \sum_{1<j<i<N} \left( \frac{1}{d_{ij}} \right)^{k}
\]

where \( d_{ij} \) is defined as inverse of the weight between \( i \)th node and \( j \)th node. \( L \) is known as overall routing efficiency characteristics of the graph which is responsible for feasibility of information transmission (flexibility) in the network. That is, in our application, \( L \) is a measure of the extent of average connectivity or overall routing efficiency and flexibility of the neocortex network which helps the different neuronal areas of the network to easily be synchronized to each other in different situations. This feasibility in synchronization is a key point in information transmission and accomplishment of all of behavioral and cognitive activities. The \( L \) value closer to 1 indicates higher flexibility and the \( L \) value higher than 1 means less flexibility. In this way efficiency of functional connectivity matrices, which correspond to neuronal network’s structures in the full-band EEG and corresponding sub-bands, are computed.

**Step 5.** Statistical analysis

In this study one-way ANOVA is used to find the most discriminative efficiencies of the neocortex neuronal network (which EEG sub-bands or full-band EEG) \( (L_{S}) \) before treatment in distinguishing the ADHD patients with positive response from those resistant to the treatment. Also ANOVA is used to investigate effectiveness of the treatment in changing the neocortex neuronal network in both groups.

**Step 6.** Classification

In order to predict responses of the ADHD patients to the neurofeedback treatment, a linear discriminant analysis (LDA) is used [5,15]. Inputs of the LDA are the most discriminative features \( (L_{S}) \) recognized by ANOVA based on the EEGs before treatment. LDA is an analysis to separate groups based on a linear combination of features. In this study Fisher’s LDA is used which attempts to discriminate the groups (ADHDs with positive response to the treatment and those without positive response) based on finding a direction with maximum ratio of variations of between groups to variations of within groups in that direction.

**3. Results**

EEGs were recorded two times: before and after treatment. Wavelet analysis in the first step resulted in 210 [30 × (ADHD with positive response) + 15 (ADHD with negative response)] × 7 [6 (EEG sub-bands) + 1 (full-band EEG)] signals for each time (before treatment and after treatment), a total of 420 signals for all ADHD patients. The first step in computation of bivariate fuzzy SL is determining embedding dimension and time delay. An embedding dimension of \( d = 24 \) was used for all EEGs and EEG sub-bands for
Fig. 1. (a) Distribution of patients with positive and negative responses to neurofeedback therapy in terms of mean length (L) of neocortex's network in beta band, before treatment. (b) Mean length (L) of neocortex's network at beta band in patients with positive (filled line) and negative (dashed line) responses to neurofeedback therapy, before and after treatment.

all channels based on the maximum of the embedding dimensions found for all channels and EEG data. Also, after trying several different values from 1 to 10 (recommended values for SLs in the literature), a time delay of $\tau = 5$ was used because of representing higher ability of the extracted SLs, based on this time delay, in distinguishing ADHDs with positive response from ADHDs with negative response at the final step. Then all EEG sub-bands and the full-band EEGs were reconstructed in their embedded space. The values of $W_2 = 400$ and $P_{ref} = 0.05$ were selected after trying several different values following the ranges of recommended values in the literature. The number of calculated fuzzy SLs is equal to $(15 + 15) \times 19 \times 7 = 3990 \times (\text{number of channels}) \times (\text{number of sub-bands as well as the full-band EEG}).$ Then 7 connectivity matrices consist of the computed fuzzy SLs were constructed for each individual EEG record $[6 \times (\text{EEG sub-bands}) + 1 \{\text{full-band EEG}\}]$. The feature $L$ is computed for all signals. The results for EEGs of before and after treatment were analyzed through one-way ANOVA test with the objective of discovering sub-bands (or full-band) in which $L$ is discriminative in distinguishing the groups, ADHDs with positive response and ADHDs with negative response to neurofeedback, in each time, before and after treatment.

Fig. 1a shows distribution of $L$ at beta sub-band for ADHDs with positive and negative responses to neurofeedback, separately. Very low $p$-value of $3.72 \times 10^{-5}$ obtained for $L$ of beta sub-band for discriminating the groups (ADHDs with positive and negative responses to neurofeedback) while $p$-values of $L$s in other sub-bands and full-band EEG are not meaningful (more than 0.1). It shows obvious deficit in synchronizability of the positive group's network of neocortex activity at beta band in comparison to negative group. Also, $p$-values of $L$s in any sub-bands or full-band EEG are not meaningful (more than 0.85) at all after treatment.

Fig. 1b shows effect of neurofeedback therapy on synchronizability in neocortex activity network at beta band of both positive and negative groups. Mean length (L) of neocortex's graph at beta band in patients with positive (filled line) and negative (dashed line) responses to neurofeedback therapy, before and after treatment. It shows reduction of $L$ in both groups after treatment in comparison with that before treatment, which implies on influence of the neurofeedback training in increasing synchronizability of neocortex activity at beta band. Interestingly synchronizability of neocortex activity at beta band for both groups increases to the same value by neurofeedback training.

For evaluation of the classification accuracy using Fisher's LDA, about 60% of the data (data for 18 subjects) were selected randomly and used for training and the remaining 40% of the data (data for 12 subjects) were used for testing. This random selection was repeated 100 times and the average value was considered as the final accuracy. A high accuracy of 84.2% is obtained for prediction of the ADHD patients' responses, based on the $L$ of beta band EEGs recorded before treatment, with a high specificity of 80.6% and the highest sensitivity of 88.2%.

4. Conclusion

Among the therapeutic methods for ADHD, neurofeedback therapy is increasingly used due to its high performance in treatment without any side effect. But it is not actually and in practice completely accepted yet, because there is still a percent of patients not improved by at least common neurofeedback trainings (if not improved by any neurofeedback training). To the best of the author’s knowledge, there is not any study to predict responses of ADHD patients to neurofeedback trainings. The purpose of this study was to solve this prediction problem and to discover whether there is a neurophysiologic reason or not. The authors hypothesized that neurofeedback training affects global structure of neocortex activity network, which is responsible for synchronizability of the network and its ability in information transmission, at least in certain frequency bands. Therefore responses of the ADHDs to the neurofeedback training correlate with improvement of the global structure of their neocortex activity network. Hence EEGs of two groups of ADHDs with positive response and negative response to two simultaneous common neurofeedback (long-time) trainings were analyzed before and after treatment. Using a wavelet filter-bank the EEGs were decomposed to 6 common EEG frequency bands and the functional connectivity graphs were constructed, based on the recent proposed fuzzy SL, in those sub-bands as well as the full-band EEG. In the sake of quantifying synchronizability of the constructed neocortex activity networks in the corresponding frequency bands, mean path length of the networks was computed. The results were analyzed by ANOVA and showed synchronizability of the neocortex activity network at beta band in ADHDs with positive response is obviously less than that of ADHDs with
negative response, before treatment. The accuracy of a linear classifier (LDA) in distinguishing these patients based on this feature is so high (84.2%) that this feature can be considered as reliable characteristics for prediction of responses of ADHDs to the neurofeedback trainings.

Some studies show beta activity is increased in alert conditions and attention performance [13]. Therefore the current finding may show much less needed flexibility of the neocortex for alert conditions and attentive tasks when comparing ADHDs with negative response. On the other hand the findings based on EEGs of after treatment showed improvement of the mentioned deficit in both groups (Fig. 1b). But it seems the most effect of the neurofeedback trainings on the global structure of the neocortex activity in beta band has limitation, as it was eventually reached to the same final structure for all patients (either with positive response or with negative response) (Fig. 1b). Therefore difference between synchronizability of the neocortex before and after treatment is obviously larger and more sensible in the ADHDs with positive response in comparison to those with negative response. The psychiatric tests (such as CBCL) which commonly monitor effects of the neurofeedback trainings on the ADHDs are majorly dependent on what their parents and teachers sense and observe from their behaviors. Hence we hypothesize that the improvement of the synchronizability of the neocortex in the ADHDs resistant to neurofeedback therapy is so little that cannot result in observable and sensible behavioral improvements.

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