ORIGINAL ARTICLE

Detecting ADHD Based on Brain Functional Connectivity Using Resting-State MEG Signals

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Abstract

Purpose: Attention Deficit Hyperactivity Disorder (ADHD) is now recognized as the most common childhood behavioral disorder. This disorder causes school problems and social incompatibility. Thus an accurate diagnosis can help diminish such problems. In this paper, we propose a brain connectomics approach based on eyes-open resting state Magnetoencephalography (rs-MEG) to diagnose subjects with ADHD from Healthy Controls (HC).

Materials and Methods: We used the eyes-open rs-MEG signals recorded from 25 subjects with ADHD and 25 HC. We calculated Coherence (COH) between the MEG sensors in the conventional frequency bands (i.e., delta, theta, alpha, beta, and gamma), selected the most discriminative COH measures by the Neighborhood Component Analysis (NCA), and fed them to three classifiers, including Support Vector Machine (SVM) with Radial Basis Function (RBF) kernel, K-Nearest Neighbors (KNN), and Decision Tree to classify ADHD and HC.

Results: We achieved the best average accuracy of 91.1% for a single-band classifier based on the COH in the delta-band as an input feature of the SVM. However, when we integrated the COH values of all frequency bands as input features, the average accuracy was slightly improved to 92.7% using the SVM classifier.

Conclusion: Our results demonstrate the capability of a functional connectomics approach based on rs-MEG for the diagnosis of ADHD. It is noteworthy that, to the best of our knowledge, COH has not yet been used to diagnose ADHD using rs-MEG data. Furthermore, there is no study on diagnosing ADHD using eyes-open rs-MEG. Thus, a novelty of our proposed method is to use COH and eyes-open rs-MEG data to diagnose ADHD. Moreover, our proposed method showed promising results compared with previous rs-MEG studies for the diagnosis of ADHD.

Keywords: Attention Deficit Hyperactivity Disorder; Resting State Magnetoencephalography; Functional Connectivity; Coherence; Neighborhood Component Analysis; Machine Learning.

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1. Introduction

Behavioral patterns of hyperactivity, impulsivity, and inattention, eventually known as Attention Deficit Hyperactivity Disorder (ADHD), have been described for centuries [1]. ADHD is now recognized as the most common childhood behavioral disorder in the world [2]. ADHD is the most prevalent neurobehavioral disorder in school-age children [3]. The prevalence of ADHD worldwide in children is estimated at 4% among boys and girls [4]. ADHD is characterized by inattention, or excessive activity, and impulsivity or their combination. There has been no effective biomarker to diagnose ADHD accurately [5]. Therefore, the ADHD diagnosis depends entirely on clinical tests that are subjective and prone to different errors. ADHD causes school problems and social incompatibility. The symptoms will remain in adulthood in 50-60% of subjects. In 25% of cases, these symptoms include impulsivity and antisocial behaviors [6]. Although it has apparent medical and social symptoms, there is no neurobiological sign for ADHD yet. Given the prevalence of ADHD and its social consequences in childhood and adulthood, its early diagnosis can make the treatment processes and psychological interventions more effective [7,8].

Magnetoencephalography (MEG) is a non-invasive technology that measures the magnetic fields induced by neuronal current flow in the brain above the scalp [9]. MEG has been shown to be an efficient functional modality to measure neural oscillatory processes due to being non-invasive and having a high temporal and a good spatial resolution. However, limited studies have investigated the feasibility of using MEG for ADHD diagnosis. One approach for automated diagnosis of ADHD is extracting features from the brain signals obtained by functional neuroimaging modalities and applying them to machine learning algorithms to distinguish individuals with ADHD from Healthy Controls (HC). Some previous studies investigating ADHD based on resting-state MEG (rs-MEG) signal are as follows:

In [10], the average of Lempel-Ziv complexity value of the eyes-closed rs-MEG signals in five brain areas was used to diagnose ADHD. The results showed that the Lempel-Ziv complexity value in ADHD was significantly lower than that in HC, and this feature could help to diagnose ADHD with acceptable accuracy. In [11], a different feature in time-space was extracted from the eyes-closed rs-MEG signals with the goal of diagnosing patients with ADHD. Gómez *et al.* proposed an algorithm using sample entropy to diagnose ADHD. They showed that sample entropy was significantly different between HC and ADHD groups. The regularity of MEG signals was significantly lower in HC than in ADHD [11].

Due to the correlated information that the MEG and Electroencephalography (EEG) have, some articles that studied ADHD based on resting-state EEG signals have been reviewed in the following. Authors in [12], using the features extracted from Autoregressive (AR) model of just 2 EEG channels in the eyes-open resting-state condition, achieved a classification accuracy above 90% using a K-Nearest Neighbor (KNN) classifier. In [13], the AR model parameters were extracted from resting-state EEG signals of 30 individuals with ADHD and 30 HC subjects using the Covariance, Burg, and Yule-walker methods. Absolute and relative powers in several frequency bands were calculated using the eigenvector method's power spectral density estimates. The most discriminative feature set was selected using Correlation-based Feature Selection (CFS) and fed to the Support Vector Machine (SVM) and KNN classifiers to classify EEG signals of ADHD and HC subjects. Experimental results demonstrated that the parameters obtained using the Covariance method resulted in the highest classification accuracy of 85%.

Mohammadi *et al.* in [14] extracted Fractal Dimension (FD), approximate entropy, and Lyapunov exponent as non-linear features from EEG signals followed by feature selection using two methods, Double Input Symmetrical Relevance (DISR) and minimum Redundancy Maximum Relevance (mRMR). The Multilayer Perceptron (MLP) was used as the classifier. The results of ADHD classification using DISR and mRMR were 92.28% and 93.56%, respectively.

In recent years, the study of brain function has been performed by measuring connectivity between spatially separate but functionally related brain areas. This approach has become of key interest in investigating brain functional performance. Brain connectivity describes the networks of functional and anatomical connections across the brain. The functional network communications across the brain networks are dependent on neuronal oscillations. Detection of the synchronous activation of neurons can be used to determine the wellbeing or integrity of the functional connectivity in the human brain networks.

A group of studies has studied the brain functional connectivity in individuals with ADHD. Franzen *et al.* [15] investigated the effect of a specific drug on the brain connectivity of ADHD subjects based on the Phase-Locking Value (PLV) of MEG signals. Another study was done on the same dataset and with the aim of assessing brain activity in the Default-Mode Network (DMN) using spectral analyses [16].

Sudre *et al.* [17] investigated the persistence of ADHD symptoms from childhood to adulthood on brain functional connectivity using the Coherence (COH) of eyes-closed rs-MEG data. Khadmaoui *et al.* [18] used PLV and the Euclidean Distance besides COH and showed that these extracted features were significantly different between ADHD and HC subjects [18].

Authors in [19] showed that COH values of the frontal cortex obtained using eyes-open resting state EEG signals are significantly different between ADHD and HC groups. In [20], a study was done based on eyes-closed resting-state EEG signals acquired from 50 individuals with ADHD and 58 HC subjects. Phase Lag Index (PLI) was utilized to construct brain functional networks. PLI values were fed to Convolutional Neural Network (CNN) models as input. This result shows that these connectivity features were efficient for discriminating ADHD and HC. Barry *et al.* [21] also statistically compared the COH of eyes-closed resting-state EEG signals of a total of 40 individuals with ADHD and 40 HC subjects in sensor space. The results showed that the frontal COH value of the ADHD group was statistically lower in delta, alpha, and gamma frequency bands.

It is worth mentioning that COH has not yet been used to diagnose ADHD using rs-MEG data. Only [17] used COH in a statistical comparison framework. Furthermore, there is no study on the diagnosis of ADHD using eyes-open rs-MEG. As mentioned before, there are just two studies on diagnosing ADHD using rs-MEG signals, and in both of them, MEG had been recorded in eyes-closed condition. The objective of the current study is to detect ADHD using the conventional and straightforward functional connectivity measure of COH and eyes-open rs-MEG signals. In fact, we tested the hypothesis that the COH values of sensor-space rs-MEG signals in eyes-open conditions can be used for the accurate diagnosis of ADHD. For this purpose, COH was calculated in conventional MEG frequency bands (i.e., δ, θ, α, β, and γ). Then we used the most discriminative COH values as input features to classify ADHD and HC. Our ultimate goal in this study was to propose a machine learning approach based on functional connectivity of eyes-open rs-MEG for ADHD diagnosis.

This paper is organized as follows. The MEG dataset used in this study and our machine learning approach for diagnosing AHDH using COH of eyes-open rs-MEG signals will be introduced in Section 2. Then in Section 3, the results will be presented. Afterward, we will discuss the proposed method and its results in Section 4. Finally, in section 5, we will conclude the paper, and some ideas for future works will be suggested.

2. Materials and Methods

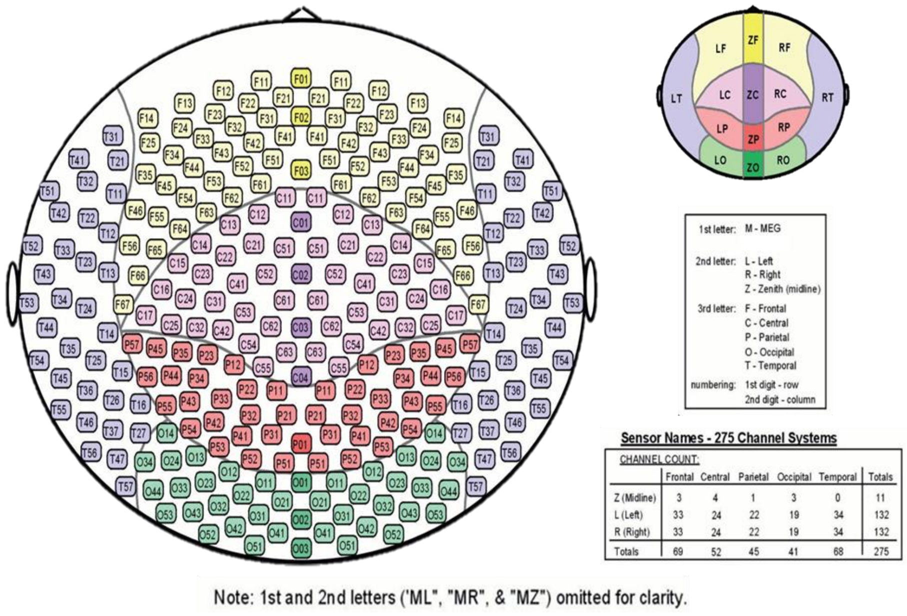
2.1. Participants

In this study, we used the Open MEG Archive (OMEGA), a free MEG dataset provided by the McConnell Brain Imaging Centre of the Montreal Neurological Institute and the Université de Montréal [22]. The dataset can be freely downloaded from [23]. We conducted our analysis on a subset of data with 25 healthy participants (age: 20.6 ± 2.35 years; mean ± standard deviation), including 14 boys and 9 girls and 25 patients with ADHD (age: 20.6 ± 3.04 years; mean ± standard deviation) including 10 boys and 15 girls. All the subjects were strictly right-handed.

The medical history of the ADHD participants was evaluated to ensure the absence of any psychotropic drugs or received psychotherapy. Each subject's MEG assessment was obtained during an eyes-open resting condition for about 5 minutes at a sampling frequency of 2400 Hz. The data were low passed at 600 Hz. The participants were instructed to remain awake and refrain from head and eye movements. The data was recorded by a CTF MEG system (VSM MedTech Inc., Coquitlam, Canada) using 275 axial gradiometers. Figure 1 is a map with the full list of sensor names for this CTF system. Moreover, bipolar Electrocardiogram (ECG) and vertical and horizontal Electrooculogram (EOG) were recorded from all subjects.

2.2. Preprocessing

Pre-processing of the brain signals was done by Brainstorm toolbox in MATLAB 2020b software. At first, a 60 Hz notch filter and a 0.3-90 Hz bandpass filter were applied to eliminate powerline noise and remove the fluctuations of non-neural origin, respectively. Then physiological artifacts (e.g., eye blinks and heartbeats) were removed using both visual inspection and Signal-Space Projectors (SSP) [25]. After all, the signals were divided into artifact-free epochs of 5-sec duration (12000-



	Frontal	Central	Parietal	Occipital	Temporal	Totals
Z (Midline)	3	4	1	3	0	11
L (Left)	33	24	22	19	34	132
R (Right)	33	24	22	19	34	132
Totals	69	52	45	41	68	275

Figure 1. The map of a full list of sensor names for this CTF system [24]

time samples) for further analyses. An average of 7 clean epochs was selected from the MEG signals of each subject. The maximum number of epochs extracted from each subject was 9, and the minimum number of epochs was 5. In fact, the number of epochs was restricted due to the noisiness of ADHD data which made the selection of clean 5s epochs from total data a challenging process.

Afterward, MEG data were decomposed to five frequency bands, including delta (0.3-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12–30 Hz), and gamma (30–60 Hz) using 3rd order Butterworth filters.

2.3. Feature Extraction

The human brain is an enormous network of connected pathways. It communicates through synchronized electric brain activity along fiber tracts. The synchronized activity within this neuronal network can be detected by MEG and investigated using network connectivity analysis. Connectivity analyses of the brain map out the brain communication networks in which the brain function. In the frequency domain, functional connectivity measurements can be analyzed with methods such as COH which is a mathematical index that somehow quantifies the synchronicity of neuronal patterns of brain activity oscillating. This technique quantifies the neuronal patterns of synchronicity measured between spatially separated MEG sensors and is a normalized linear measure of functional connectivity [26].

In this study, COH is used as input features of various classifiers. The COH provides information about the degree of linear coupling between two signals in a specific frequency band. The COH between two MEG sensors (t) and $y(t)$ in each frequency band can be calculated as follows (Equation 1) [26]:

$$COH_{xy}^{band} = \sum_{f\in band} \frac{|S_{xy}(f)|^2}{S_{xx}(f).S_{yy}(f)}; \quad band = \{\delta,\theta,\alpha,\beta,\gamma\} \tag{1}$$

Where $S_{xx}(f)$ is the cross-power spectral density, and $S_{xx}(f)$ and $S_{yy}(f)$ are the respective auto-power spectral densities. COH values vary between 0 and 1. The closer this value is to 0, the weaker the linear dependence between MEG sensors, whereas the closer this value is to 1, the stronger the linear coupling between them. COH was calculated between the time series of each two sensors in each frequency band (Figure 2). In order to calculate COH, Brainstorm (A Matlab toolbox for the processing of MEG and EEG signals) was used. It is worth mentioning that just common sensors between all subjects were considered for the estimation of COH. Therefore, 36046 COH features were extracted from each epoch between all pairs of MEG sensors.

2.4. Feature Selection

All of the COH values extracted from MEG may not be appropriate for classification. Additionally, the presence of inefficient features leads to a burden for any classifier. In this study, the Neighborhood Component Analysis (NCA) was employed as a nonparametric and supervised feature selection algorithm to select the most

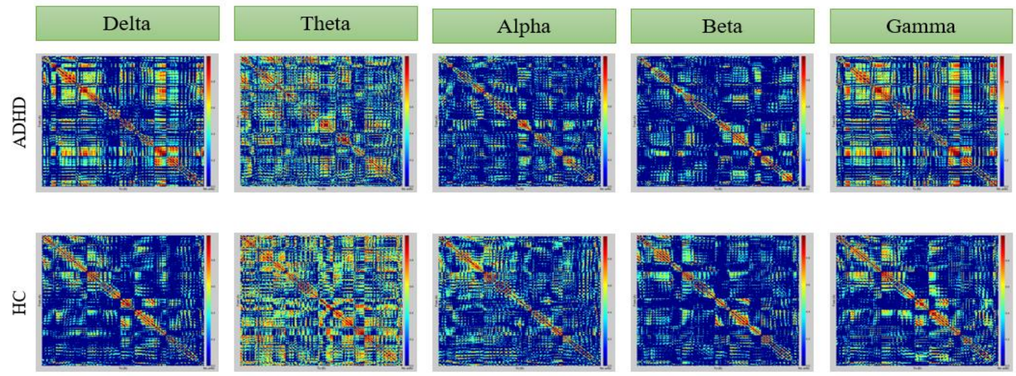


Figure 2. An example of COH values of one subject from the ADHD group versus a subject from the HC group

discriminative features. This algorithm is based on the KNN algorithm and aims to obtain a weight vector based on the importance of features by maximizing the mean Leave-One-Out (LOO) classification accuracy across the training data with an optimized regulation parameter [27].

Assume that $T = \{(x_1, y_1), \dots, (x_i, y_i), \dots (x_N, y_N)\}$ is the training subject set, where x_i is a feature vector, y_i is its corresponding class label, and N is the number of training subjects. The weighted distance between the two samples x_i and x_j is computed as follows (Equation 2):

$$D_w(x_i, x_j) = \sum_{r=1}^{d} w_r^2 |x_{ir} - x_{jr}| \tag{2}$$

Where w_r is a weight associated with r^{th} feature. The NCA algorithm aims to maximize its LOO classification accuracy on the training set T.

The probability of data point x_i selects another data point x_j as its nearest neighbor is defined as (Equation 3):

$$p_{ij} = \begin{cases} \dfrac{k\left(D_w(x_i, x_j)\right)}{\sum_{k \neq i} k\left(D_w(x_i, x_j)\right)} & if\ i \neq j \\ 0 & if\ i = j \end{cases} \tag{3}$$

where $k(.)$ is a kernel function, hence, the probability of x_i being accurately classified with the correct class label is as follows (Equation 4):

$$p_i = \sum_j y_{ij} p_{ij} \ ; \ y_{ij} = \begin{cases} 1, & if\ \ y_j = y_i \\ 0, & otherwise \end{cases} \tag{4}$$

Moreover, to perform feature selection and alleviate overfitting, a regularization term is introduced and hence the following object function is obtained (Equation 5):

$$f(w) = \sum_i \sum_j y_{ij} p_{ij} - \lambda \sum_r^d w_r^2 \tag{5}$$

Where λ is a non-negative regularization parameter tuned via cross-validation. Using $f(w)$ derivate with respect to w_r leads to the weights of features. Ultimately features weighing more than a preset threshold are selected [27].

2.5. Classification

Three classifiers: (1) SVM with Radial Based Function (RBF), (2) KNN (K = 3), and (3) decision tree were used in the current study to classify ADHD and HC subjects. We used the COH of 269 MEG sensors in each of the five conventional frequency bands as the input feature set for the classifiers. These five feature sets were also integrated to likely achieve better performance. The NCA algorithm selected the most discriminative features. Then the selected features were fed to the three classifiers to identify ADHD and HC subjects. We used the Leave-One-Subject-Out Cross-Validation (LOSO-CV) to evaluate the performance of the classifiers. It is noteworthy that, from all the features provided by the NCA algorithm among all repetitions of LOSO-CV, we selected the most replicated ones, which were repeated in at least 50% of repetitions. Consequently, five features were selected for each frequency band and also for the all-band case. The LOSO-CV results across all subjects were used to calculate the accuracy, sensitivity, specificity, and Cohen's kappa coefficient of the proposed method. Figure 3 demonstrates a summary of the proposed method.

3. Results

The selected features, inputs of classifiers for both single-band and all-band cases are shown in Table 1. The performance criteria of the three classifiers based on LOSO-CV using selected features are also reported in Tables 2, 3, and 4.

The best classification accuracy using the single-band COH measures was obtained using the delta band that shows the importance of this frequency band for ADHD diagnosis. In addition, SVM outperformed other classifiers. By integrating features of all five frequency bands, the average accuracy of the SVM classifier was slightly improved from 91.1% to 92.7%.

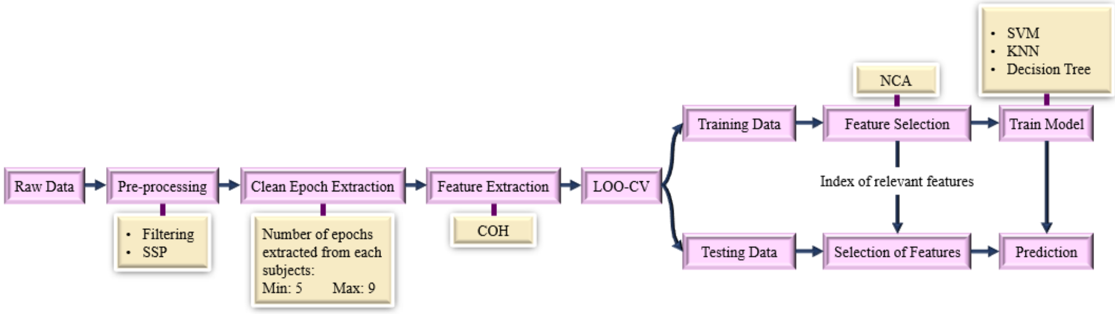


Figure 3. Block diagram of the proposed method

Table 1. Selected features by NCA algorithm

Frequency band	Features (COH values between two MEG sensors)
δ	(MRF23,MRF21)-(MRO22,MRO23) (MLF51,MLC11)-(MRF22,MRF12)-(MRF12,MRF11)
θ	(MRT51,MRT32)-(MRT51,MRT42) (MRP31,MLP31)-(MLO32,MLO22)-(MRT52,MRT42)
α	(MZF01,MRF13)-(MRF12-MLF32) (MRF11-MLF23)-(MRF22,MLF23)-(MZF03,MRF41)
β	(MRT52,MRT53)-(MLP23,MLO33) (MLP22,MLP12)-(MRF44,MRF41)-(MZF01,MRF13)
γ	(MLP32,MLP22)-(MLP43,MLP33)-(MRT52,MRT43) (MRP43,MRP44)-(MRT52,MRT53)
All-band	(γ:MRT52,MRT43)-(γ:MRP43,MRP44) (γ:MLP32,MLP22) (δ:MRF12,MRF11)-(β:MRT52,MRT53)

Table 2. Classification performance of KNN (mean %± std%)

Frequency Band	Accuracy	Sensitivity	Specificity	Kappa
δ	87.7 ± 1.9	96.2 ± 1.8	79.7 ± 2.3	0.75 ± 0.03
θ	72.5 ± 2.3	84.2 ± 1.7	61.4 ± 2.2	0.45 ± 0.04
α	71.7 ± 2.8	82.5 ± 2	61.4 ± 3.1	0.44 ± 0.04
β	72.3 ± 2.9	83.8 ± 2	61.4 ± 3.1	0.45 ± 0.04
γ	84.2 ± 2.2	92.7 ± 1.4	76.1 ± 2.6	0.68 ± 0.03
All-band	89.6 ± 2	94.9 ± 1.1	84.6 ± 2.6	0.79 ± 0.03

Table 3. Classification performance of Decision Tree (mean% ± std%)

Frequency Band	Accuracy	Sensitivity	Specificity	Kappa
δ	86.1 ± 1.4	87.7 ± 1.3	82.5 ± 1.6	0.72 ± 0.03
θ	75.6 ± 2	78.6 ± 1.7	72.8 ± 2	0.51 ± 0.04
α	80.4 ± 2.1	81.2 ± 2	79.7 ± 2.8	0.61 ± 0.04
β	80.8 ± 2.4	80.8 ± 2.4	80.9 ± 2.2	0.62 ± 0.04
γ	85.6 ± 1.9	85.5 ± 1.5	85.8 ± 2.3	0.71 ± 0.03
All-band	88.3 ± 1.8	90.2 ± 1.7	86.6 ± 1.8	0.77 ± 0.03

4. Discussion

In this paper, the identification of ADHD using eyes-open rs-MEG signals was performed by computing the COH in sensor-space in five conventional frequency bands using three classifiers. To the best of our knowledge, there has been no study on the diagnosis of ADHD using eyes-open rs-MEG, and just two studies used eyes-closed rs-MEG data [10] and [11]. Their best accuracy, sensitivity, and specificity were 85.6%, 92.7%, and 78.5%, respectively in [10] and 85.7%, 64.29%, and 75%, respectively in [11]. According to Table 5, we achieved better performance in the current study compared to the two previous studies as our best results were accuracy of 92.7%, sensitivity of 93.6%, and specificity of 91.9% on a larger dataset than theirs. Thus our proposed algorithm may be considered more reliable than the previous methods and seems to be a promising step toward designing an accurate machine learning approach of low computational cost for ADHD.

The results of all three classifiers indicated that the COH values in delta bands are the most discriminative features for diagnosing ADHD, which manifests that ADHD may affect the connectivity of the delta band more. This claim is consistent with the hypothesis that ADHD affects the delta band asserted in [18,21,28]. In [18], the results showed that interaction among MEG channels in resting state conditions is statistically different at delta and gamma bands. Our results confirm this claim as we achieved the highest accuracy using these frequency bands, especially the delta band. Also, Monge et al. in [28] showed that fuzzy entropy of rs-MEG is statistically different in the delta band between ADHD and HC. In the other another study, the EEG profile of adults with ADHD and HC was investigated using an eyes-open resting condition. The results showed that the absolute amplitude of the delta band is statistically different between the two groups [29].

It is worth mentioning that, according to Table 4, the selected features of each frequency band generally belong to a limited region which is a part of the frontal cortex. It may be hypothesized the nearly focal disorganization of the brain connectivity in ADHD. In [21,19], as mentioned in the introduction section, COH values between EEG sensors were significantly different in the delta band and frontal brain region, which supports the hypothesis that the most different COH values are mainly in this region. We believe that ADHD may cause dysfunction in this area which needs to be more studied more in future researches. As a result, it seems that focusing on these areas and further studying them may help diagnose ADHD more accurately.

5. Conclusion

In conclusion, the present study showed a difference in COH values in sensor-space between HC and ADHD,

Table 4. Classification performance of SVM (mean% ± std%)

Frequency Band	Accuracy	Sensitivity	Specificity	Kappa
δ	91.1 ± 1.4	94.4 ± 1.1	87.8 ± 1.6	0.82 ± 0.03
θ	78.8 ± 2.1	85.5 ± 1.9	72.4 ± 2	0.58 ± 0.04
α	74.6 ± 2.5	73.9 ± 2	75.2 ± 2.8	0.49 ± 0.04
β	81.7 ± 2.4	79.1 ± 2.6	84.1 ± 2.2	0.63 ± 0.04
γ	86.1 ± 2	89.3 ± 1.7	82.9 ± 2.3	0.72 ± 0.03
All-band	92.7 ± 1.6	93.6 ± 1.3	91.9 ± 1.9	0.85 ± 0.02

Table 5. Important information about the previous studies on ADHD diagnosis using rs-MEG

	Participants No. (HC + ADHD)	Resting mode	Epoch length	Features	Classifier
[6]	14+17	Eyes-closed	20 sec	Average of LZC scores in Anterior brain regions	Logistic regression
[7]	14+14	Eyes-closed	5 sec	Average of Sample Entropy in Anterior brain regions	Thresholding
The proposed work	25+25	Eyes-open	5 sec	COH	KNN, Decision tree, SVM with RBF, kernel

especially in the delta frequency band. The proposed algorithm was performed based on three different classifiers. The results showed that ADHD may cause dysfunction in connectivity of the delta band more than the other frequency bands. Moreover, the selected COH values between MEG sensors are mainly focused on just one of the brain regions, which is a part of the frontal brain region. We hypothesize that the functional connectivity of this area is disorganized due to ADHD. These hypotheses are consistent with previous studies based on resting resting-state MEG and EEG signals and need to be studied in more details in future works.

It is noteworthy that fine-tuning the proposed algorithm may provide better results in predicting ADHD. Also, investigating the use of different linear and non-linear connectivity measures, phase synchronization measures, different graph parameters, and source-space connectivity features are some future works. Moreover, proposing age-specific or gender-specific Computer-Aided Diagnosis Systems (CADS) for ADHD may lead to better classification performance. In addition, different classifiers, feature extraction, and selection methods can be investigated in the future to obtain better results.

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