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fMRG Hacimlerini Kullanarak DEHB'nin 3B ESA Tabanlı Otomatik Teşhisi

3D CNN Based Automatic Diagnosis of ADHD Using fMRI Volumes

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Abstract

Attention deficit hyperactivity disorder (ADHD) is one of the most common mental health disorders and it is threatening especially to the academic performance of children. Its neurobiological diagnosis is essential for clinicians to treat ADHD patients properly. Along with machine learning algorithms, and neuroimaging technologies, especially functional magnetic resonance imaging is increasingly used as biomarker in attention deficit hyperactivity disorder. Also, machine learning methods have been becoming popular at last times. This study presents an optimized 3-dimensional convolutional neural network to classify functional magnetic resonance imaging volumes into two classes to assist experts in diagnosing ADHD. To demonstrate the importance of extracting 3D relationships of data, the method has been tested on ADHD-200 public datasets and its performance on the hold-out testing datasets has been evaluated. Then the network performance has been compared with several recent ADHD detection convolutional neural networks in the literature. It has been observed that the proposed network has a promising performance.

Keywords: *Attention Deficit Hyperactivity Disorder, Functional Magnetic Resonance Imaging, 3D Convolutional Neural Network, ADHD-200 Public Dataset)*

Öz

Dikkat eksikliği hiperaktivite bozukluğu (DEHB) en sık görülen beyin deformasyonlarından biridir ve özellikle çocukların okul başarılarını olumsuz yönde etkilemektedir. Uzmanların, DEHB hastalarına uygun tedavi verebilmeleri için bu hastalığın nörobiyolojik tanısı önemlidir. Makine öğrenimi algoritmaları ile birlikte, nörogörüntüleme teknolojileri, özellikle fonksiyonel manyetik rezonans görüntüleme, dikkat eksikliği hiperaktivite bozukluğunda biyobelirteç olarak giderek daha fazla kullanılmaktadır. Ayrıca, makine öğrenme yöntemleri son zamanlarda popüler hale gelmektedir. Bu çalışma ile, DEHB tanısında uzmanlara yardımcı olmak amacıyla fonksiyonel manyetik rezonans görüntüleme hacimlerini iki sınıfa ayırmak için optimize edilmiş 3 boyutlu evrişimli bir sinir ağı sunulmaktadır. Verilerin 3 boyutlu ilişkilerinin çıkarılmasının önemini göstermek için yöntem, halka açık ADHD-200 veri setlerinin öğrenme ve test verileri kullanılarak test edilmiş ve sinir ağının performansı değerlendirilmiştir. Daha sonra sinir ağının performansı, literatürdeki birkaç yeni DEHB algılama evrişimli sinir ağı ile karşılaştırılmıştır. Kullanılan sinir ağının umut verici bir performansa sahip olduğu gözlemlenmektedir.

Anahtar Kelimeler: *Dikkat Eksikliği Hiperaktivite Bozukluğu, fonksiyonel manyetik rezonans görüntüleme, 3B Evrişimsel Sinir Ağı, Halka Açık ADHD-200 Veri Setleri*

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental health disorders. ADHD affects approximately 5%-10% of school-age children [1]. We can characterize ADHD as excessive impulsive, hyperactive, or inattention behaviors. These symptoms start at childhood and may proceed up to maturity, causing substantial impairments, including significant burdens for families, society, and especially for children themselves, such as not being able to learn lessons quickly and lead an everyday life like their friends. Therefore, there is an urgent need for measurable and objective diagnostic systems for the early diagnosis of ADHD. The conventional diagnosis of ADHD is generally based on clinical evaluations of behavioral symptoms. This matches the Diagnosis and Statistical Manual of Mental Disorders criteria [2-3]. But also, this diagnosis method can be unreliable. Usually, the diagnosis criteria for children depend on the behavior report from teachers or parents. Thus, a measurable and objective biomarker depending on non-invasive imaging would be helpful. Blood-oxygen-level dependent functional magnetic resonance imaging (BOLD fMRI) is a notable non-invasive method. BOLD fMRI successfully shows brain abnormalities of ADHD subjects by obtaining different magnetic properties in the oxygenated and deoxygenated forms of hemoglobin [4]. In particular, resting-state fMRI (rfMRI) is a widely used tool that has strengths in examining the brain's functional organization. Recently, brain functional networks in rfMRI introduced promising outcomes in many brain disorder classification studies [5].

Deep learning (DL) is becoming popular in various research fields such as pattern recognition, computer vision, natural language processing, and processing and classification of images such as fMRI. Convolutional neural network (CNN) is a very talented DL model for image classification [6-7], face recognition [8], and video captioning [9-10] tasks, image reconstruction for magnetic resonance imaging [11]. CNN extracts representative features from input data automatically. Thus a feature engineering step will not be necessary. And also a CNN is formed of multiple layers, where each module learns the representation from lower level to a higher level.

Two-dimensional CNN (2D-CNN) is the first standard convolutional neural network introduced in the Lenet-5 architecture [12]. It is called a 2D CNN that is usually used for 2D images because the kernel slides along the data in 2 dimensions. Three-dimensional CNN (3D-CNN) is mainly used for 3D images or videos, the kernel slides in 3 dimensions. LeNet-5 [12] CNN network has been used for 2D image classification, and Vu et al. [13] extended this network to 3D fMRI volume classification of four sensorimotor tasks. They showed that three-dimensional feature maps extracted from fMRI volumes represent brain signals better.

This study focuses on the automatic diagnosis of ADHD using fMRI volumes using CNN. In the literature, several CNN-based studies classify ADHD using fMRI. Zou et al. [14] use combined features of MRI and fMRI to classify ADHD by CNN. They first extract some features from the MRI and fMRI data and use these features as input of a CNN. They don't apply a CNN directly to the temporal data of brain regions. Regional homogeneity (ReHo), the normalized amplitude of low-frequency fluctuations (fALFF), and voxel-mirrored homotopic connectivity (VMHC) are the features that are extracted from the fMRI data. The features are calculated using well-known hand-crafted statistical measures. Riaz et al. [15] proposed FCNet. FCNet uses a CNN network to extract functional connectivity (FC) features from rfMRI. The CNN in the FCNet obtains features from time-series signals and a fully connected network that determines the similarity between the obtained features in a Siamese architecture. Riaz et al. [16] also proposed a new network to learn FC features called DeepFMRI. DeepFMRI exploits the representation learning capability of deep learning to classify a neurological disease from fMRI. Their model consists of three networks. These are feature extractor, similarity network, and classification network. DeepFMRI takes raw time-series signals as inputs and gives the predicted labels as outputs and trained using back-propagation. Zhang et al. [17] combine a separated channel convolutional neural network (SC-CNN) with an attention-based network (SC-CNN-attention) to classify ADHD on a large-scale multi-site database. In the first section of their two-stage network, an SC-CNN is used to extract the temporal features of each brain region, and an attention network exploits both intrinsic features and the interactions of temporal dependence in whole-brain rfMRI. The other section is designed to extract temporal-dependent features among regions and obtain fusion features. They use a leave-one-site-out cross-validation framework, although the compared methods use only one site for the training step. Using four times more training sites than other methods seems to have dramatically increased the classification success.

We compare our network with the competitors of ADHD-200 Global Competitors [18], which was held in 2011 to involve researchers from various analytical backgrounds to determine biomarkers of ADHD from rfMRI and structural MRI (s-MRI) data [19]. These studies are published as 3D-CNN [14], FCNet [15], Deep fMRI [16], and SC-CNN-Attention [17]. To make an accurate comparison, NeuroImage (NI) dataset, Peking University (PU) dataset, and New York University (NYU) dataset are used.

The main contribution of this study is to use raw fMRI as input data to diagnose ADHD without extracting any handcrafted features. Therefore, showing that CNN can learn helpful information from raw data without any extra steps. Also, we introduce the use of the 3D-CNN model for sensorimotor classification proposed by Vu et al.'s [13] with hyperparameter optimization. Finally, the network performance is tested with the publicly available ADHD datasets and compared with some state-of-the-art models [14-17] in the literature.

The rest of the paper is structured as follows. We present an overview of the fMRI data used in this study with preprocessing steps, the proposed method, including optimized parameters, and used evaluation criteria as a performance measure in Section 2. Section 3 presents the experimental study and results. Section 4 concludes the paper.

2. Material and Method

This section demonstrates the data used in this study and summarizes the methods for classifying ADHD data.

2.1. ADHD data

fMRI data from the ADHD-200 consortium. 776 fMRI scans and associated T1-weighted structural scans are available were used in this study, thanks to this consortium. They obtain 491 of them from typically developing subjects and 285 from ADHD. The characteristic information of individuals is also available such as age, gender, handedness, and IQ scores. Eight institutions around the world collect the data and share them anonymously without any protected health information, following the Health Insurance Portability and Accountability Act (HIPAA) guidelines and the 1000 Functional Connectomes Project (FCP) protocols [20]. All of these datasets have different numbers of subjects. And also, these datasets have various scan parameters and equipment. This study uses the NI, PU_1, and NYU datasets to compare correctly. PU consists of 3 datasets. PU_1 is one of these three datasets. PU_1 dataset is used in this study to provide the same conditions as the compared studies. Riaz et al. [16] use the PU_1 dataset in their research. However, the other studies don't mention which set of PU is used. The details of the data used in this study are described in table 1. As can be seen from the table, there is a major imbalance PU_1 train dataset.

The ADHD-200 consortium has provided training datasets and discretely independent testing datasets for all of the imaging sites. So, these provided datasets a, as in other studies, these provided datasets are used in the study son result. Used fMRI data are in Neuroimaging Informatics Tool Initiative (NIFTI) format. NIFTI is one of the three most important medical imaging data formats. The distinguishing feature in the NIFTI format is a way to represent the relationship between voxel indices and spatial locations in the MRI scanner. This helps to accurately determine which side of the image represents the left or right side of the brain [21].

Table 1. Subject and volume numbers of the datasets.

	Train		Test	
	Healthy	**ADHD**	**Healthy**	**ADHD**
NI	**23 Subjects**	**25 Subjects**	**14 Subjects**	**11 Subjects**
	5888 fMRI Volumes	**6400 fMRI Volumes**	**3584 fMRI Volumes**	**2816 fMRI Volumes**
PU_1	**61 Subjects**	**24 Subjects**	**27 Subjects**	**23 Subjects**
	14091 fMRI Volumes	**5544 fMRI Volumes**	**6237 fMRI Volumes**	**5313 fMRI Volumes**
NYU	**98 Subjects**	**118 Subjects**	**12 Subjects**	**29 Subjects**
	31648 fMRI Volumes with 2nd runs	**36464 fMRI Volumes with 2nd runs**	**2052 fMRI Volumes**	**4959 fMRI Volumes**

In the phase of preparing fMRI data for the training process, fMRI data in NIFTI format are taken into the Matlab environment by a function in our algorithm. 4D fMRI data is converted to 3D. And the fMRI data in the provided train and test datasets are randomly mixed before the train and test processes without losing labels of them.

For all experiments, preprocessed data publicly available from the Preprocessed Connectomes Project [22] is used. In 2011, the ADHD-200 Consortium organized a competition to determine biomarkers of ADHD using the ADHD-200 data. The Preprocessed Connectomes Project started as an attempt to bring competitiveness to more researchers by preprocessing the data and openly sharing the results. The ADHD-200 data are preprocessed by three different teams using their preferred tools. NIAK team's preprocessed data are used in this study as in Zhang et al.'s study [17]. The NIAK pipeline uses the Neuroimaging Analysis Kit on CBRAIN. Preprocessing details and preprocessed datasets can be accessed on the Preprocessed Connectomes Project site [23].

2.2. Proposed method

A revised and optimized 3D-CNN model which is formed by Vu et al [13] is used in this study. LeNet-5 [12] CNN network has been used for 2D image classification and Vu et al. extended this network to 3D fMRI volume classification. Figure 1 shows their 3D CNN network. There are three 3D convolutional (Conv) layers, two fully-connected layers, and one output layer with four output nodes in the network. The 1st Conv layer has 8 filters with 7×7×7 kernel size, the 2nd Conv layer has 16 filters with 5×5×5 kernel size, and the 3rd Conv layer has 32 filters with 3×3×3 kernel size. 1st fully connected layer consists of 128 hidden nodes (in the hidden layer). Four output nodes classify each of the four tasks in the model. The output nodes are revised to two for binary classification as ADHD or healthy subjects. 3D volumes used in this study are in the size of 53×64×46. When these volumes are applied to the network, the dimension of the output pattern is 24x29x20 at the 1st Conv layer, 10x13x8 at the 2nd Conv layer, and 4x6x3 at the 3rd Conv layer. The stride of 2 is used in each Conv layer. And also, there are 8 channels (filters) in the 1st Conv layer, 16 channels in the 2nd Conv layer, and 32 channels in the 3rd Conv layer. The relations between slices which are extremely important are taken into consideration by 3D filters. After Conv layers, the output pattern is converted into a 1D vector with 2304 elements (=4×6×3×32). And this vector is applied to the fully connected layer.

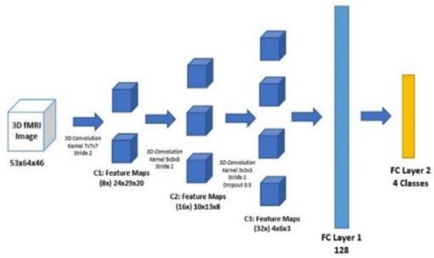

Figure 1. The 3D CNN network

The network is revised according to the ADHD diagnosis problem at hand in this study. For most training algorithms, the learning rate, mini-batch size, and momentum are the most important hyperparameters to set. For this reason, the hyperparameters of the network such as learning rate and mini-batch size are optimized by grid search. Different learning rates such as

10^{-3}, $5x10^{-3}$, and 10^{-2} are searched with different mini-batch size combinations such as 50, 25, 17, and 13. It is observed that momentum revisions did not affect the results positively, therefore this parameter has not been revised. Parameters, without revisions, used to train the 3D-CNN network are given in table 2.

Table 2. Network parameters without revisions

Parameters	Choices
Activation Function	ReLU
Loss Function	Cross entropy
Learning Algorithm	Stochastic Gradient Descent
Annealing	At the end of 50 epochs by a minimum learning rate of 10^{-6}
Dropout	Probability of 0.5 in the 3rd Conv layer

2.3. Evaluation criteria

The accuracy, specificity, and sensitivity are used as the metrics to compare the performance of some of the state-of-the-art machine learning models [14-17] in the literature. The accuracy of a test is its capability to recognize the patient and normal subjects correctly. The specificity of a test is its capability to define the healthy subjects correctly. The sensitivity of a test is its capability to define the patient subjects correctly [24]. We select ADHD subjects as positive and healthy subjects as negative. In this case, the number of subjects correctly determined as ADHD is called true positive (TP), the number of subjects incorrectly determined as ADHD is called false positive (FP), and the number of subjects correctly determined as healthy is called true negative (TN), and the number of individuals incorrectly determined as healthy is called as false negative (FN). The accuracy, specificity, and sensitivity are calculated as follows based on their definitions:

$$Accuracy = (TP + TN)/(TP + TN + FP + FN) \quad (1)$$

$$Specificity = TN/(TN + FP) \quad (2)$$

$$Sensitivity = TP/(TP + FN) \quad (3)$$

3. Results

The confusion matrix including the definitions explained in the evaluation criteria section is shown in Figure 2. The confusion matrix given in the figure belongs to the NI dataset classified with the parameters of the highest accuracy rate obtained.

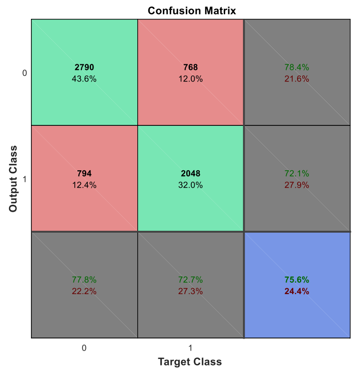

Figure 2. Confusion matrix for NI dataset.

The success criteria of the proposed network for ADHD classification employing rfMRI is evaluated by searching different learning rates and mini-batch sizes and also, by comparing our results with some other models. Different learning rates such as 10^{-3}, $5x10^{-3}$, and 10^{-2} are searched with different mini-batch size combinations such as 50, 25, 17, and 13, heuristically. We compare our network with 3D-CNN[14], FCNet[15], Deep fMRI[16], SC-CNN-Attention[17], and ADHD-200 Global Competition[18].

Figures 3-a to c show the accuracy results for different learning rates and different minibatch sizes for the datasets individually as NI, PU_1, and NYU, respectively.

Figure 3-a. Accuracy results for different learning rates and different mini-batch sizes for NI dataset.

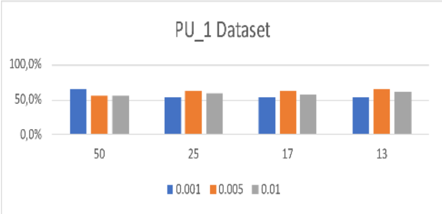

Figure 3-b. Accuracy results for different learning rates and different mini-batch sizes for PU_1 dataset.

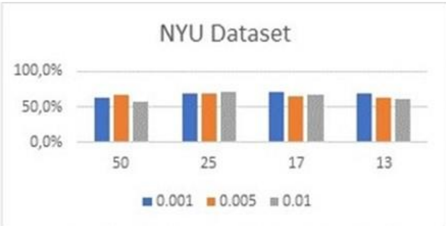

Figure 3-c. Accuracy results for different learning rates and different mini-batch sizes for NYU dataset.

As a result of these studies carried out to determine the optimum learning rates and mini-batch sizes for different datasets, it is determined that the revised optimum learning rate is 10^{-3}, and the mini-batch size is 50 for NI dataset, the revised optimum learning rate is $5x10^{-3}$ and mini-batch size is 13 for PU_1 datasets, and the revised optimum learning rate is 10^{-2}, and mini-batch size is 25 for NYU dataset as listed in table 3.

Table 3. Optimized learning rates and mini-batch sizes for different datasets.

	Learning Rate	**Mini-Batch Size**	**Accuracy Result**
NI Dataset	10^{-3}	50	75.6%
PU_1 Dataset	$5x10^{-3}$	13	65.0%
NYU Dataset	10^{-2}	25	70.9%

The accuracy, specificity, and sensitivity are used as the metrics to compare the performance of some of the state-of-the-art machine learning models [14-17] in the literature. To make a correct comparison with these studies, NI, PU_1, and NYU datasets are used providing the same conditions. Also, the same train and test datasets are used as in other studies to make a correct comparison. The fMRI data in the provided train and test datasets are randomly mixed before train and test processes without losing labels of them.

Because specificity and sensitivity results are not included in other studies, these comparisons can only be performed with the Deep fMRI study.

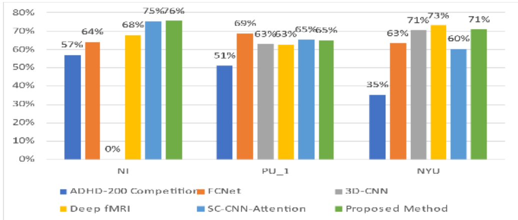

Figure 4. Accuracy comparison for optimum hyperparameters and different datasets with various state-of-the-art methods [14-17].

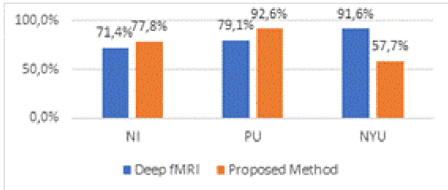

Figure 5. Specificity comparison for optimum hyperparameters and different datasets with Deep fMRI study.

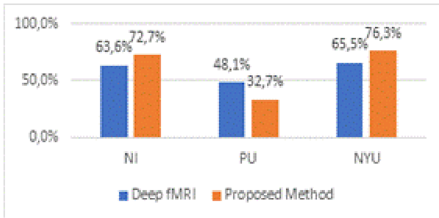

Figure 6. Sensitivity comparison for optimum hyperparameters and different datasets with Deep fMRI study.

In addition, all comparison results are shown in table 4 so that the quantitative values could be observed easily.

As can be seen, all methods have better achievements than ADHD-200 competition teams in terms of accuracy. As listed in table 4, different algorithms get the highest accuracies for different datasets. This reflects that the characteristics of the data are changing with the dataset. Thus, the proposed network is optimized for each dataset individually.

Table 4. Accuracy, specificity and sensitivity comparison with various state-of-the-art methods [14-17].

Method vs. Data	NI (%)	PU_1 (%)	NYU (%)	Evaluation Criteria
3D-CNN [14]	-	63.0	70.5	**ACC**
	-	-	-	**SPEC**
	-	-	-	**SEN**
FCNet [15]	64.0	**68.6**	63.4	**ACC**
	-	-	-	**SPEC**
	-	-	-	**SEN**
Deep fMRI [16]	67.9	62.7	**73.1**	**ACC**
	71.4	79.1	**91.6**	**SPEC**
	63.6	**48.1**	65.5	**SEN**
SC-CNN-Attention [17]	75.3	65.2	60.4	**ACC**
	-	-	-	**SPEC**
	-	-	-	**SEN**
ADHD-200 Competition [18]	57.0	51.1	35.2	**ACC**
	-	-	-	**SPEC**
	-	-	-	**SEN**
Proposed Method	**75.6**	65.0	70.9	**ACC**
	77.8	**92.6**	57.7	**SPEC**
	72.7	32.7	**76.3**	**SEN**

When the NI dataset is considered, it has been observed that it has balanced healthy and ADHD subjects. And the proposed method outperforms previous methods in all measures as expected.

PU_1 dataset has a severe imbalance between the number of healthy and ADHD subjects for both train and test sets. In terms of accuracy, FCNet has slightly better results, however, the sensitivity of the proposed method is quite low and the specificity is too high which indicates an imbalance in data. Also, the results of the Deep fMRI method for the PU_1 dataset support this finding.

For a relatively larger NYU dataset, Deep fMRI gives the best results with slightly better accuracies than the proposed method.

4. Discussion and Conclusion

Raw fMRI is used as input data to diagnose ADHD without extracting features with the learning ability of CNN from data. To demonstrate this 3D-CNN model is revised and hyperparameters are optimized for common ADHD datasets. It has been observed that the 3D-CNN model considers the relations between slices by 3D filters which are extremely important for ADHD diagnosis. As a result of the study, it has been seen that 3D-CNN has tremendous potential for fMRI classification.

One of the most important inferences of this study is that the performance of classification is drastically affected by the balance of the number of samples in each class. Artificial data generation methods will be employed in the future to create a more balanced dataset. And also, the network will be tested by applying it to other ADHD-200 datasets such as KKI and OHSU, which are used in other studies.

5. Ethics committee approval ve conflicts of interest

<u>The authors declare no need for an ethics committee approval and no conflict of interest in this paper.</u>

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