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Age-Specific Diagnostic Classification of ASD Using Deep Learning Approaches

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Abstract. Autism Spectrum Disorder (ASD) is a highly heterogeneous condition, due to high variance in its etiology, comorbidity, pathogenesis, severity, genetics, and brain functional connectivity (FC). This makes it devoid of any robust universal biomarker. This study aims to analyze the role of age and multivariate patterns in brain FC and their accountability in diagnosing ASD by deep learning algorithms. We utilized functional magnetic resonance imaging data of three age groups (6 to 11, 11 to 18, and 6 to 18 years), available with public databases ABIDE-I and ABIDE-II, to discriminate between ASD and typically developing. The blood-oxygen-level dependent time series were extracted using the Gordon's, Harvard Oxford and Diedrichsen's atlases, over 236 regions of interest, as 236x236 sized FC matrices for each participant, with Pearson correlations. The feature sets, in the form of FC heat maps were computed with respect to each age group and were fed to a convolutional neural network, such as MobileNetV2 and DenseNet201 to build age-specific diagnostic models. The results revealed that DenseNet201 was able to adapt and extract better features from the heat maps, and hence returned better accuracy scores. The age-specific dataset, with participants of ages 6 to 11 years, performed best, followed by 11 to 18 years and 6 to 18 years, with accuracy scores of 72.19%, 71.88%, and 69.74% respectively, when tested using the DenseNet201. Our results suggest that age-specific diagnostic models are able to counter heterogeneity present in ASD, and that enables better discrimination.

Keywords. Autism Spectrum Disorder; fMRI; Functional Connectivity; Deep Learning

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that influences social communication and interaction. Autistic individuals exhibit restricted, repetitive patterns of behavior, interests, or activities [1]. The neurobiological differences in ASD persist lifelong, due to genetic, epigenetic, and environmental factors contributing to the condition. Behavioral observations and developmental assessments are typical diagnostic techniques, which are highly subjective and prone to misdiagnosis or overdiagnosis [2]. Brain functional connectivity (FC) features computed from functional magnetic resonance imaging (fMRI) data, with the aid of deep learning (DL)

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can help detect biomarkers, which can distinguish ASD from typical developing (TD) [3]. The potential biomarkers describing ASD are local under-connectivity and cortical over-connectivity [4,5]. However, there is an inconsistency among studies in identifying a global biomarker for identifying ASD. Varying methodologies and demographic differences are possible reasons for such heterogeneities to exist, which considerably affect the results of the group comparisons. Continual research has pointed towards neural plasticity as a crucial driver of brain development with advancing age. This highlights the possibility of neuroanatomical differences between ASD and TD individuals being substantially age-dependent, supported by the abnormal FC patterns of resting state networks in ASD participants of different age groups [6]. Hence, there is a need for further investigation into heterogeneity by age and age-dependent atypical neurobiology in ASD.

The objective of this study is to utilize temporal correlations of FC data to identify patterns within fMRI to diagnose ASD. This helps us examine atypical neural differences of ASD arising with age. The neuronal activation patterns from fMRI data are identified and then input to pre-trained convolutional neural networks (CNN) in the form of heat maps to classify ASD and TD participants.

2. Methodology

Autism Brain Image Data Exchange I and II (ABIDE I and ABIDE II) offer multi-modal data for autistic participants collected globally and reviewed by local institutional review boards [7]. The resting-state fMRI data of participants aged 6-18 was recorded with their eyes open. The current study only included data collected at 7 sites, including age, gender, and intelligence quotient information. The participants were so chosen that the root mean square deviation (motion) was minimal (less than 0.2), and a minimum of 80% of the original volume was retained after filtering, so as to avoid motion artifacts during the recording of the BOLD signals. Three different datasets are created, on the basis of the age of participants and the corresponding data demographics are shown in Table 1.

Table 1. Demographic information of the dataset

	6 to 11 years		11 to 18 years		6 to 18 years	
	TD	**ASD**	**TD**	**ASD**	**TD**	**ASD**
Count	187	136	213	181	400	317
Gender	126 M; 61 F	112 M; 24 F	171 M; 42 F	165 M; 16 F	297 M; 103 F	277 M; 40 F
PIQ/ FIQ (Mean ± SD)	114.37 ±12.61	106.32 ±18.48	109.38 ±13.76	104.46 ±16.03	111.71 ±13.46	105.26 ±17.15

M: Male; F: Female; SD: Standard deviation; PIQ: Performance intelligence quotient; FIQ: Full-scale intelligence quotient

Functional Neuroimaging Analysis Software Packages AFNI and FSL 5.0 were used for pre-processing of resting-state fMRI data. The images underwent trimming for T1 equilibrium maintenance, sinc interpolation, and FLIRT, for alignment to the anatomical space, followed by normalization using FNIRT and standardization (MNI 152, 3mm isotropic resolution). Spatial smoothing, band pass filtering (0.008 to 0.08 Hz), and signal regression were part of the pipeline to reduce the signal-to-noise ratio, added as a result of using fMRI data from multiple sites, as followed by Ronicko et al. [8]. Mean time series, extracted from 236 cerebellar, cortical, and subcortical regions of

interest (ROIs), of which 213 out of 333 were from Gordon's cortical, 9 out of 26 from Harvard Oxford's subcortical and all 14 Diedrichsen's cerebellar atlases, were used to create the final 236x236 Fischer transformed Pearson-correlation connectivity matrices. The FC matrices are translated into heat maps, resulting in an image dataset with 717 participants with 317 ASD and 400 TD samples. The dataset is further expanded by including various data augmentation techniques, such as rotation, blurring, edge enhancement, cropping, zooming, etc. The high-dimensional images are resized to the standard 224x224x3 before feeding them to a pre-trained CNN model using transfer learning. The dataset is then divided into three parts, the training data (75% of the total); validation data (12.5% of the total); and test data (12.5% of the total). Two standard classifier convolutional networks, MobileNetV2 and DenseNet201 [9, 10], with weights initialized using the ImageNet dataset, were trained using Tensorflow on NVIDIA RTX A200 GPUs. These were deployed first without fine-tuning (500 epochs), and then with fine-tuning (500 epochs) to classify ASD and TD on all three datasets. We fine-tuned 54 layers out of 154, and 57 layers out of 707 in the case of MobileNetV2 and DenseNet201, respectively. This helps the models extract high-level texture features from the training images, which helps the models learn to identify biomarkers and improves the performance of the classifier. The process pipeline followed in the study is shown in Figure 1.

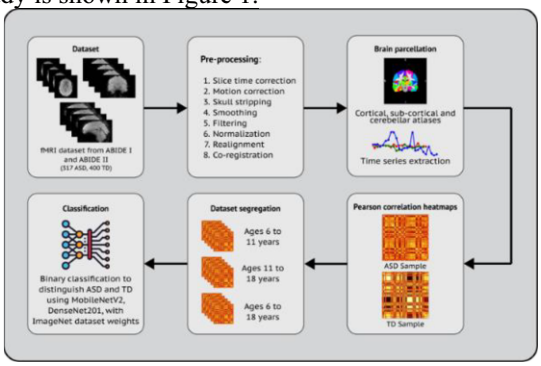

Figure 1. Process pipeline for the proposed methodology

3. Results and Discussion

The FC heat maps for TD and ASD participants are generated and fed as input to the deep-learning models. We tested the model performance on all the datasets under similar conditions, i.e. using the same weights (ImageNet) and architectures (MobileNetV2 and DenseNet201), with similar augmentation techniques. The age-specific dataset, "ages 6 to 11 years" returns the highest accuracy of 72.19% after fine tuning. It was followed by the "ages 11 to 18 years" dataset and lastly by the total dataset "ages 6 to 18 years", with accuracy scores of 71.88% and 69.74% respectively. In all cases, DenseNet201 performed better than MobileNetV2. The classification results with both classifiers, for all three datasets are shown in Fig 2 (a-c).

Deep learning models classified ASD and TD most accurately on the dataset group, "ages 6 to 11 years", followed by the groups, "ages 11 to 18 years" and "ages 6 to 18 years". These results can be attributed to the fact that neuroplasticity plays a crucial role in brain development. Its effect varies with age, as it is a dominant factor in brain

development during childhood, and its prominence reduces with age. Our results are consistent with the findings of Al-Hiyali MI et al. [11] where significant differences in FC patterns were observed in children with ASD, compared to adolescents. These studies have implemented age-specific analysis on ABIDE databases and achieved higher classification accuracy, but only used one site from the database for their analysis. Our results suggest that DenseNet201 outperforms MobileNetV2 in all three datasets. DenseNet201 has a more complex architecture and is able to reuse feature information more efficiently within layers. It has significantly more number of trainable parameters and has also been extensively pre-trained, which it leverages to extract a wider range of features from a dataset. ASD studies have reported high classification accuracies using DenseNet201 on structural MRI [8] and fMRI [9]. However, till now, no study has employed MobileNetV2 for diagnostic classification of ASD on neuroimaging data.

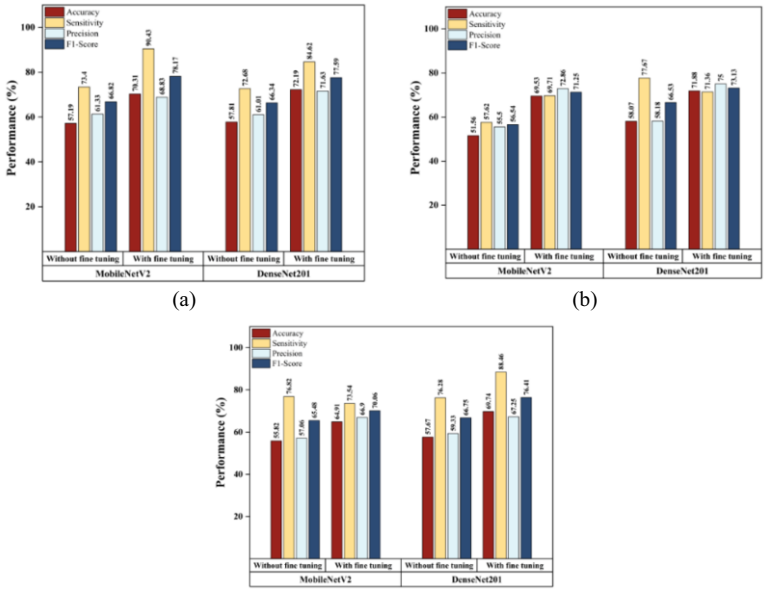

Figure 2. Performance of MobileNetV2 and DenseNet201 for (a) Ages 6 to 11 years; (b) Ages 11 to 18 years; (c) Ages 6 to 18 years

4. Limitations and Future Work

The process pipeline proposed above clearly indicates its efficacy in diagnosing ASD; however, this pipeline comes with a few shortcomings. The training dataset is relatively small and comprises only 7 sites. The rest of the sites from ABIDE database were not considered for analysis due to the stringent inclusion criteria followed for this study. Further, we never considered the participants aged more than 18 years in our analysis, due to limited data availability of this age group in the database. The computational complexity of model training could not allow for cross-validation of the data. Moreover, the testing dataset also included augmented images. This research can be further extended to include more participants. The datasets can be further separated

on the basis of other demographic features to reduce heterogeneity, which might help the classifiers perform better in discriminating ASD from TD. Further work could also include feature ranking and selection, to include only relevant features for the classifier.

5. Conclusions

This research highlights the effect of age on the diagnostic classification of ASD. The FC matrices were computed from the time series' BOLD signal of fMRI data using Pearson correlation. These were converted to heat maps and used to train two classification models, MobileNetV2 and DenseNet201. Age-specific dataset with participants, "ages 6 to 11 years", returned the best results, compared to the "ages 11 to 18 years" and "ages 6 to 18 years". The CNN network, DenseNet201 returned the best results with an accuracy, sensitivity, precision, and F1-Score of 72.19%, 84.62%, 71.63%, and 77.58%, respectively. It is observed that a dataset with reduced heterogeneity, when fed to a deep network with high information flow within layers, results in better accuracy scores. Our investigations imply that the inconsistency in neuroanatomical reports observed in ASD could be attributed to age variability in the study cohorts. Hence, future studies elucidating the underlying neural mechanisms of ASD should meticulously take into account the effects of age, as well as its biological and methodological implications.

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