



Published in final edited form as:

Mach Learn Med Imaging. 2018 September ; 11046: 303–309. doi:10.1007/978-3-030-00919-9_35.

Early Diagnosis of Autism Disease by Multi-channel CNNs

Guannan Li^{1,2}, Mingxia Liu², Quansen Sun¹, Dinggang Shen², and Li Wang²

¹School of Computer Science and Engineering, Nanjing University of Science and Technology, Nanjing 210094, China

²Department of Radiology and Biomedical Research Imaging Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Abstract

Currently there are still no early biomarkers to detect infants with risk of autism spectrum disorder (ASD), which is mainly diagnosed based on behavior observations at three or four years old. Since intervention efforts may miss a critical developmental window after 2 years old, it is significant to identify imaging-based biomarkers for early diagnosis of ASD. Although some methods using magnetic resonance imaging (MRI) for brain disease prediction have been proposed in the last decade, few of them were developed for predicting ASD in early age. Inspired by deep multi-instance learning, in this paper, we propose a patch-level data-expanding strategy for multi-channel convolutional neural networks to automatically identify infants with risk of ASD in early age. Experiments were conducted on the National Database for Autism Research (NDAR), with results showing that our proposed method can significantly improve the performance of early diagnosis of ASD.

Keywords

Autism; Convolutional neural network; Early diagnosis Deep multi-instance learning

1 Introduction

Autism, or autism spectrum disorder (ASD), refers to a range of conditions characterized by challenges with social skills, repetitive behaviors, speech and nonverbal communication, as well as by unique strengths and differences. Globally, autism is estimated to affect 24.8 million people as of 2015 [1]. The diagnosis of ASD is mainly based on behaviors. Studies demonstrate that behavioral signs can begin to emerge as early as 6–12 months [2].

However, most professionals who specialize in diagnosing the disorder won't attempt to make a definite diagnosis until 2 or 3 years old [3]. As a result, the window of opportunity for effective intervention may have passed when the disorder is detected. Thus, it is of great importance to detect ASD earlier in life for better intervention.

Magnetic resonance (MR) examination allows researchers and clinicians to noninvasively examine brain anatomy. Structural MR examination is widely used to investigate brain morphology because of its high contrast sensitivity and spatial resolution [4]. Imaging plays an increasingly pivotal role in early diagnosis and intervention of ASD. Many neuroscience studies on children and young adults with ASD demonstrate abnormalities in the

hippocampus [5], precentral gyrus [6], and anterior cingulate gyrus [7]. These researches demonstrate that it is highly feasible to detect ASD in early age.

In recent years, deep learning has demonstrated outstanding performances in a wide range of computer vision and image analysis applications. Many methods based on convolutional neural networks (CNNs) [8] are proposed for MRI analysis, e.g., classification of the Alzheimer's disease (AD). For example, Sarraf *et al.* [9] proposed a DeepAD for AD diagnosis, where the existing CNN architectures, LeNet [10] and GoogleNet [11], were used for MR brain scans on the slice level and subject level, respectively. But feature representations defined at whole-brain level may not be effective in characterizing early structural changes of the brain. Several patch-level (an intermediate scale between voxel level and region of interest (ROI)) features have been proposed to represent structural MR images for brain disease diagnosis. For example, a deep multi-instance learning framework for AD classification using MRI was proposed by Liu *et al.* [12], achieving promising results in AD diagnosis.

Compared with adult brains, the analysis of infant brains is more difficult due to the low tissue contrast caused by the largely immature myelination. Furthermore, the number of autistic subjects is usually very limited, making the task of computer-aided diagnosis of ASD more challenging.

Motivated by deep multi-instance learning [12], in this paper, we propose a patch-level data-expanding strategy in multi-channel CNN for prediction of ASD in early age. Figure 1 shows a schematic diagram of our method. We first preprocess MR images and then identify anatomical landmarks in a data-driven manner. In the patch extraction step, we utilize a patch-level data expanding strategy based on identified landmarks. In the last step, we use the multi-channel CNNs for ASD classification. Experimental results on 276 subjects with MRIs show that our method outperforms conventional methods in ASD classification.

2 Materials and Methods

Data description.

A total of 276 subjects gathered from National Database for Autism Research (NDAR) [13] were used in the study. More specifically, the dataset consists of 215 normal controls (NCs), 31 mild condition autism spectrum subjects, and 30 autistic subjects, as listed in Table 1. In the experiments, we regard the last two types as one group. All images were acquired at around 24 months of age on a Siemens 3T scanner, while subjects were naturally sleeping and fitted with ear protection, with their heads secured in a vacuum-fixation device. T1-weighted MR images were acquired with 160 sagittal slices using parameters: TR/TE = 2400/3.16 ms and voxel resolution = $1 \times 1 \times 1 \text{ mm}^3$. T2-weighted MR images were obtained with 160 sagittal slices using parameters: TR/TE = 3200/499 ms and voxel resolution = $1 \times 1 \times 1 \text{ mm}^3$.

MRI Pre-processing.

We use in-house tools to perform skull stripping and histogram matching for T1 MR images. After skull stripping, we can estimate the whole brain volume for each subject. This pre-processing step is important for subsequent analysis steps.

Data-Driven Anatomical Landmark Identification.

To extract informative patches from MRI for model training, we first identify discriminative ASD-related landmark locations using a data-driven landmark discovery algorithm [14]. The aim is to identify the landmarks with statistically significant group difference between ASD and NC subjects in local brain structures. The pipeline for defining ASD landmarks is shown in Fig. 2. Specifically, we first choose one T1-weighted image with high quality as a template. Then, a linear registration is used to locate the same location across all training images in the pre-processing step. Since the linearly-aligned images are not voxel-wisely comparable, nonlinear registration is further used for spatial normalization, thus corresponding relationship among voxels can be established. To identify local morphological patterns with statistically significant differences between groups, we use the histogram of oriented gradients (HOG) features as morphological patterns. Finally, the Hotelling's T2 statistic [15] is adopted for group comparison. Accordingly, each voxel in the template is assigned with a p -value. Any voxels in the template with p -values smaller than 0.001 are regarded as significantly different positions. To avoid redundancy, only local minimum (whose p -values are also smaller than 0.001) are defined as ASD landmarks in the template image.

Patch Extraction from MRI.

By using the deformation field from nonlinear registration, we can get the corresponding patches in each linearly-aligned image. To address the issue of the limited number of autistic subjects, we propose a data expansion strategy on autistic subjects to have comparable number of samples as the number of NC subjects. As shown in Fig. 3(b), for each landmark, we randomly extract $N (> 1)$ image patches as ASD training samples, but only 1 image patch as NC training sample (Fig. 3(c)). In the datasets, since the NC sample size is about 4 times larger than the ASD, we set $N = 4$ in the experiment.

Multi-Channel Convolutional Neural Networks.

In this study, both local and global features are used for classification. We use a multi-channel CNN model as shown in Fig. 4 for diagnosis. Given a subject, the input data are L patches extracted from L landmarks. To learn representations of individual image patch in one group, we first run multiple sub-CNN architectures. More specifically, we embed L parallel sub-CNN architectures with a series of 5 convolutional layers with stride size 1 and 0-padding (i.e., Conv1, Conv2, Conv3, Conv4, and Conv5), and a fully-connected (FC) layer (FC7). The rectified linear unit (ReLU) activation function is used after convolutional layers, while Conv2 and Conv4 are followed by max-pooling procedures to conduct the down-sampling operation for their outputs, respectively. To model global structural information of MRI, we further concatenate the outputs of L FC7 layers and add two additional FC layers (i.e., FC9, and FC10) to capture global structural information of MRI. Moreover, we use a

concatenated representation comprising the output of FC8, personal information (gender) and the whole-brain volume into FC9 layer. Finally, FC11 layer is used to predict class probability (via soft-max).

3 Experiments and Results

In this section, we present our experimental results using the proposed data-expanding multi-channel CNNs (DE-MC) scheme. We also evaluate performance *with respect to* landmark number and learning rate. Ten-fold cross-validation was used in the experiment. In each fold, we selected 264 subjects, with 55 ASD training samples and 209 NC training samples for training, and used 6 ASD subjects and 6 NC subjects as testing samples. The patch size was set as $24 \times 24 \times 24$. Since both T1w and T2w images are available, we concatenated the extracted T1w and T2w image patches as input to the multi-channel framework. The cross-entropy loss was used to train the network.

First, we compared our DE-MC method with 3D convolutional neural networks (3D CNN). The input of 3D CNN is the whole linearly aligned MR image and the network has 10 convolutional layers and 3 fully connection layers, and we have optimized all parameters for fair comparison. The performance of classification is evaluated by the overall classification accuracy (ACC), as shown in Table 2. We can see that, compared with 3D CNN, our method can get a much higher accuracy. In terms of overall accuracy, DE-MC achieves 24% improvement over 3D CNN. To evaluate the contributions of the proposed strategies, we further compare the DE-MC with its two variants: (1) multi-channel learning without patch-level data expansion (MC), and (2) multi-channel learning using data expansion without additional information (i.e., gender information and whole-brain volume) (DE-MC₂). They all share the same $L = 50$ landmarks and learning rate $lr = 0.0001$. Compared multi-channel learning without patch-level data expansion (MC), the proposed method can get better result. It proves that the data expanding strategy can help get more useful information for classification and improve the performance. Compared with the proposed methods *with* and *without* additional information (i.e., gender information and whole-brain volume), we can see this additional information is useful for ASD diagnosis.

Hyper parameters, e.g., number of landmarks and learning rate, in the deep learning may significantly impact the performance, and hence they should be carefully chosen. Table 3 shows the results *with respect to* the use of different combination of learning rate and landmark number.

4 Conclusion

In this paper, we proposed a patch-level data-expanding strategy to multi-channel CNN for early ASD diagnosis. In the patch extraction step, we utilized a patch-level data expanding strategy to balance the samples from NC and autistic groups, and the experiments show that this strategy is effective. The experiment results also showed that our proposed networks can achieve reasonable diagnosis accuracy. In our future work, we will further validate the proposed model on 6-month-old infant subjects with risk of ASD.

Acknowledgments.

Data used in the preparation of this manuscript were obtained from the NIH-supported National Database for Autism Research (NDAR). NDAR is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in autism. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDAR.

This work was supported in part by National Institutes of Health grants MH109773, MH100217, MH070890, EB006733, EB008374, EB009634, AG041721, AG042599, MH088520, MH108914, MH107815, and MH113255.

References

1. Newschaffer CJ, et al.: The epidemiology of autism spectrum disorders. *Dev. Disab. Res. Rev* 8, 151–161 (2002)
2. Filipek PA, et al.: The screening and diagnosis of autistic spectrum disorders. *J. Autism Dev. Disorders* 29, 439–484 (1999)
3. Baird G, Cass H, Slonims V: Diagnosis of autism. *BMJ Brit. Med. J* 327, 488–493 (2003) [PubMed: 12946972]
4. Chen R, Jiao Y, Herskovits EH: Structural MRI in autism spectrum disorder. *Pediatr. Res* 69, 63R (2011)
5. Schumann CM, et al.: The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *J. Neurosci* 24, 6392 (2004) [PubMed: 15254095]
6. Greimel E, et al.: Changes in grey matter development in autism spectrum disorder. *Brain Struct. Funct* 218, 929–942 (2013) [PubMed: 22777602]
7. Thakkar KN, et al.: Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD). *Brain* 131, 2464–2478 (2008) [PubMed: 18550622]
8. Ciresan DC, Meier U, Masci J, Maria Gambardella L, Schmidhuber J: Flexible, high performance convolutional neural networks for image classification In: *IJCAI Proceedings-International Joint Conference on Artificial Intelligence*, pp. 1237 Barcelona, Spain, (2011)
9. Sarraf S, Tofighi G: DeepAD: Alzheimer’s Disease Classification via Deep Convolutional Neural Networks using MRI and fMRI. *bioRxiv* 070441 (2016)
10. LeCun Y: LeNet-5, convolutional neural networks (2015). <http://yann.lecun.com/exdb/lenet20>
11. Zhong Z, Jin L, Xie Z: High performance offline handwritten chinese character recognition using googlenet and directional feature maps. In: *13th International Conference on Document Analysis and Recognition (ICDAR)*, pp. 846–850. IEEE (2015)
12. Liu M, Zhang J, Adeli E, Shen D: Landmark-based deep multi-instance learning for brain disease diagnosis. *Med. Image Anal* 43, 157–168 (2018) [PubMed: 29107865]
13. Payakachat N, Tilford JM, Ungar WJ: National Database for Autism Research (NDAR): Big data opportunities for health services research and health technology assessment. *PharmacoEconomics* 34, 127–138 (2016) [PubMed: 26446859]
14. Zhang J, Gao Y, Gao Y, Munsell BC, Shen D: Detecting anatomical landmarks for fast Alzheimer’s disease diagnosis. *IEEE Trans. Med. Imaging* 35, 2524 (2016) [PubMed: 27333602]
15. Mardia K: Assessment of multinormality and the robustness of Hotelling’s T2 test. *Appl. Stat.* 163–171 (1975)



Fig. 1.
Block diagram of the proposed scheme for automatic classification of ASD.

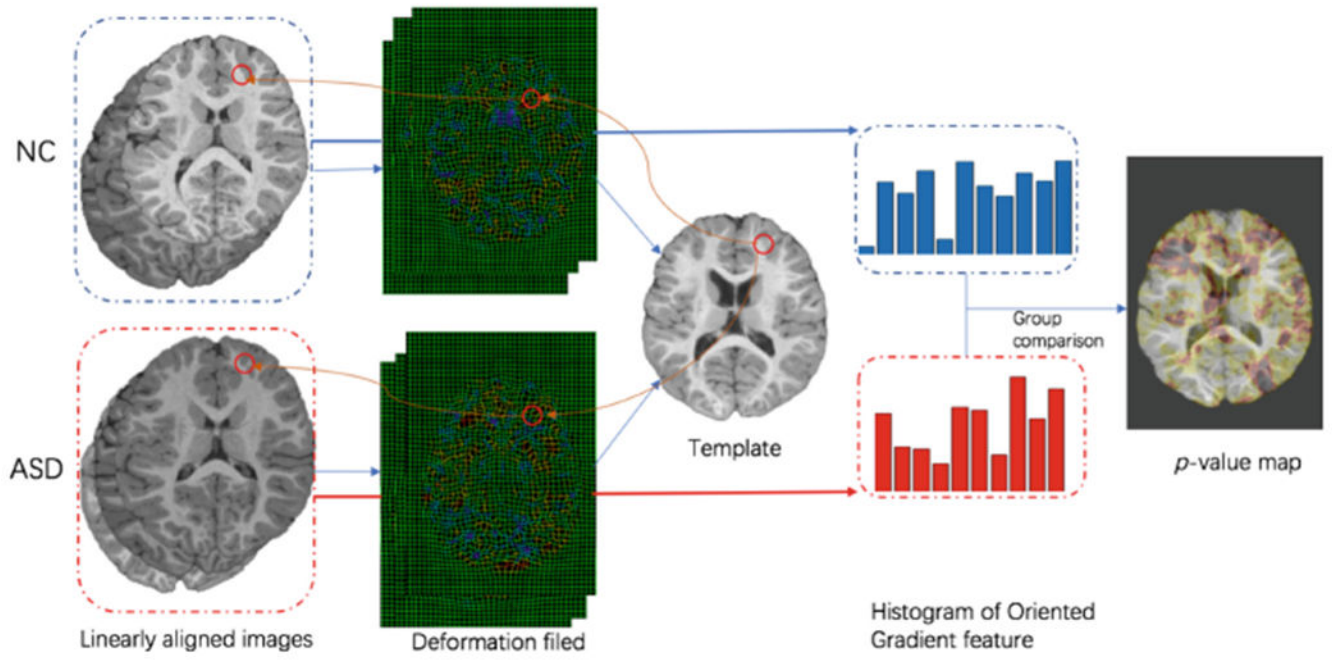


Fig. 2.
The proposed pipeline for anatomical landmark definition.

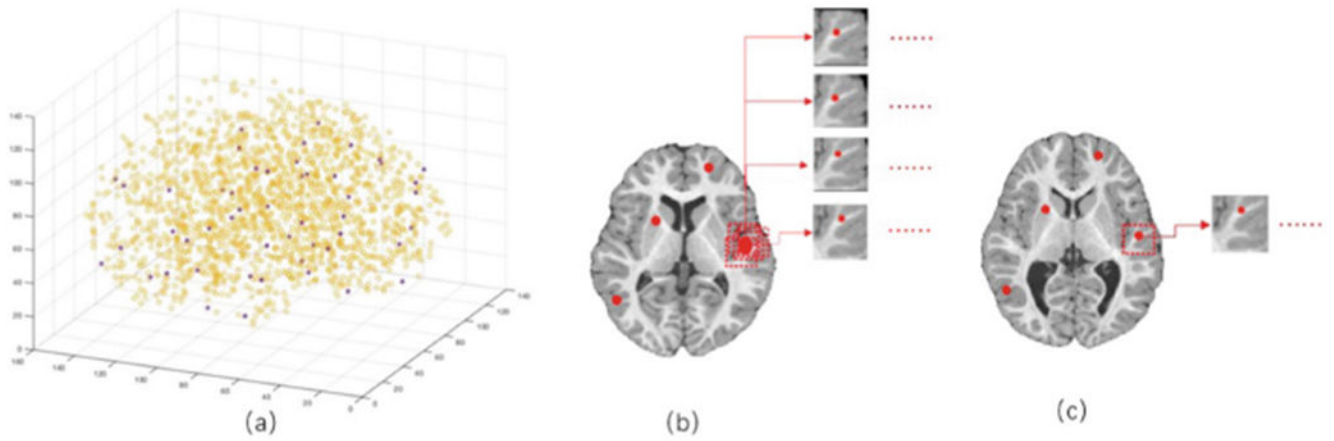


Fig. 3. Illustration of landmarks selection and patch extraction. The yellow color in **a** is the illustration of all identified anatomical landmarks, and the red points show the selected 50 landmarks which are chosen by both their p-values and spatial distances from other nearby points. **b** shows 4 randomly extracted patches around a landmark which are as ASD training samples, and **c** shows 1 randomly extracted patch which is used as NC training sample.

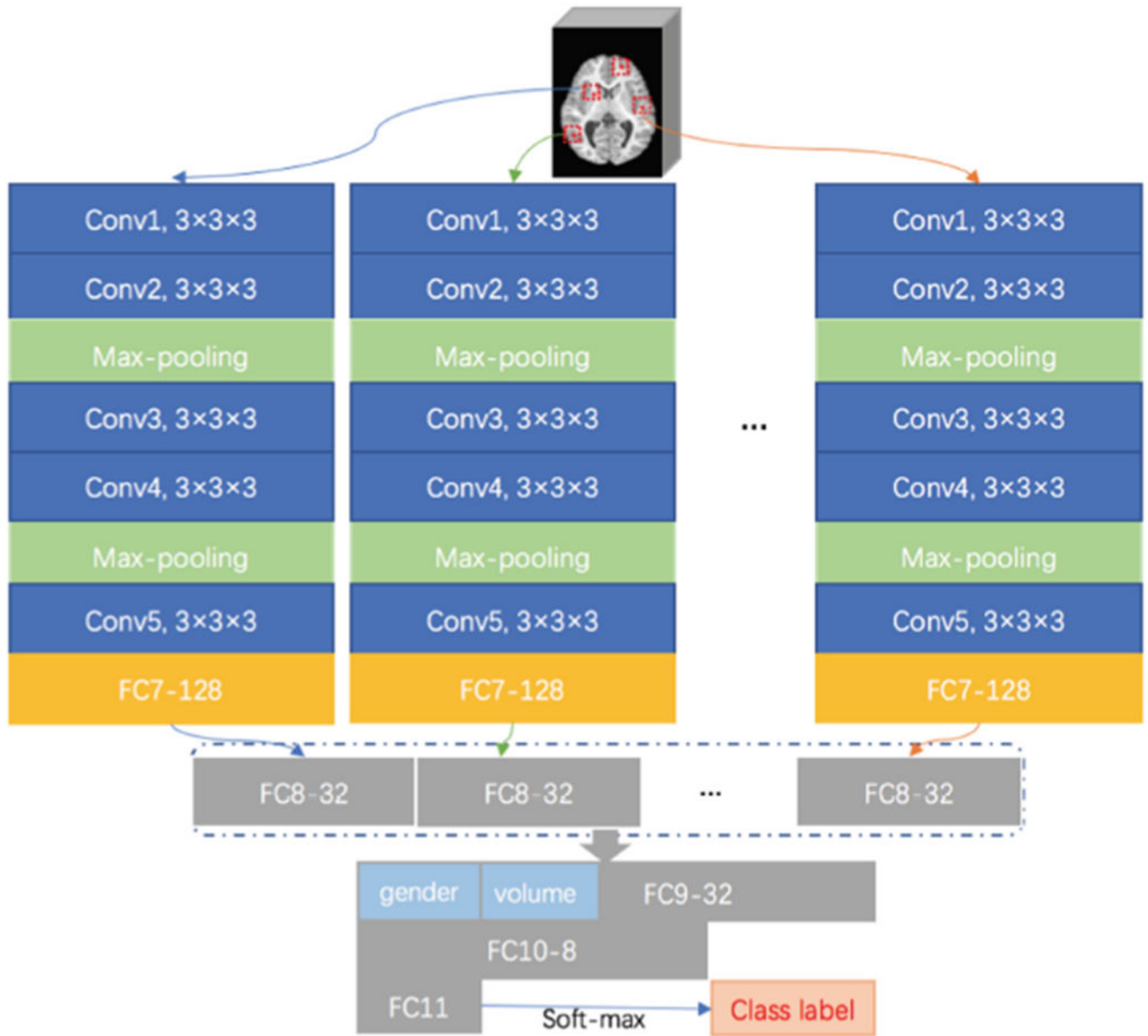


Fig. 4. Architecture of the proposed multi-channel CNN for ASD diagnosis. In each channel CNN, there is a sequence of convolutional (Conv) layers and fully connected (FC) layers.

Table 1.

Description of 24-month subjects in the NADR datasets.

Category	Male/female
Autism	25/5
Autism spectrum	21/10
Normal control	133/82

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Classification results achieved by different methods.

Method	3D CNN	DE-MC	MC	DE-MC ₂
ACC	0.5234	0.7624	0.6231	0.7432

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3.

Classification accuracy of our method with different hyperparameters.

L	lr	0.0001	0.001	0.01
30		0.6132	0.5244	0.4243
50		0.7624	0.6138	0.5471
100		0.7620	0.6249	0.5731
200		0.7431	0.6169	0.5708

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript