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Neural Network Architectures for Schizophrenia patients-versus-controls Classification based on Amygdala Connectivity

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Abstract

A few recent neuroimaging studies reported the role of amygdala connectivity in patients with schizophrenia. However, thus far in the fMRI literature, the predictive capability of amygdala connectivity in classifying schizophrenia patients and controls has not been explored using advanced machine learning techniques. In this brief report, we present results from analysis utilizing classification methods based on deep neural networks and convolutional neural networks for predicting schizophrenia versus healthy control using the amygdala's connectivity to other brain regions. Median accuracy rates of 62.9%, 60%, and 60% were obtained for classification based on a deep neural network, convolutional neural network, and ResNet34 architectures, respectively.

Keywords*:* Schizophrenia; Amygdala connectivity; fMRI; Deep Neural Networks; Convolutional Neural Networks.

Introduction

Amygdala, with its functional and structural connections to multiple cortical and subcortical regions, is well-known to play a significant role in a large number of behavioral processes [1]. For example, amygdala-median prefrontal cortex (mPFC) circuitry plays a role in the conditioning and extension of averse learning in animals as well as in regulating emotional paradigms in humans [2]. The interaction between the bottom-up and top-down response-control processes arising as a result of such amygdala-mPFC connections, is posited to be impaired in many psychiatric illnesses [2] including schizophrenia [3]. In fact, amygdala abnormality has been long known [4] and repeatedly reported in schizophrenia. Structurally, meta-analyses consistently found smaller amygdala volume in schizophrenia [5-7]. Functionally, the amygdala in schizophrenia has been repeatedly found to be less activated during emotional tasks [8]. Amygdala abnormality in schizophrenia is established. Amygdala dysfunctions can at least partly account for the symptoms of schizophrenia.

A few recent neuroimaging studies reported the role of amygdala connectivity in patients with schizophrenia. Using functional MRI (fMRI) comparing patients (n = 20) and controls (n = 24), Mukherjee and co-authors [9], reported impaired amygdala connectivity with other parts of social brain networks in schizophrenia. In a recent study [10] based on resting state (rs) fMRI, individuals with attenuated psychosis syndrome showed hyperconnectivity between three amygdala subregions and certain cortical subregions compared to healthy controls. Another rs-fMRI study [11] showed different patterns of functional connectivity impairment in the amygdala and hippocampal neural circuits in the schizophrenic cortical-limbic system. Guo and coauthors [12], using the rs-fMRI technique showed abnormal volume and function of the amygdala play important roles in the disease process of schizophrenia. Zheng and coauthors [13], using rs-fMRI showed significant dysfunction in the amygdala in schizophrenia which did not improve with treatment. Evidence for altered functional connectivity of the amygdala during threat anticipation in schizophrenia [14] has also been presented. Hyperconnectivity between amygdala and the visual cortex has been associated with visual hallucinations in patients with schizophrenia as well [15]. However, thus far in the fMRI literature, the predictive capability of amygdala connectivity in classifying schizophrenia patients and controls has not been explored using advanced machine learning techniques. In this study, we attempted to classify based on functional connectivity of the amygdala in schizophrenia and healthy controls, using deep neural networks (DNNs) and convolutional neural networks (CNNs).

Methods

The predictor data consisted of rs-fMRI data tensors of shape 91 x 109 x 91 where each voxel represented Z-score of connectivity to amygdala. The MRI images and the target binary classification variable from the Center for Biomedical Research Excellence in Brain Function and Mental Illness [16] were obtained from Collaborative Informatics and Neuroimaging Suite (http://coins.mrn.org/). Excluding the bipolar patients from the original sample resulted in a total of 173 subjects for the current analysis, with 90 control subjects and 83 patients with schizophrenia or schizoaffective disorder. Resting state echo planner image (EPI) volumes had 32 slices of 4 mm 64x64 matrix with 4-mm thickness (voxel size = 3x3x4 mm), with repetition time (TR) of 2000 milliseconds and echo time (TE) of 29 milliseconds. A total of 150 volumes (5 minutes) were used in the analysis. High-resolution structural T1 volume was acquired as 176 sagittal slices of 256 mm x 256 mm with 1-mm thickness (voxel size = 1x1x1 mm, TR=2530 milliseconds and TE=3.25 milliseconds). Data preprocessing was conducted using FMRIB Software Library (FSL) using procedures very similar to the steps described in [17].

FMRIB Software Library (FSL,) as well as Analysis of Functional NeuroImages (AFNI) were used for data preprocessing. The structural T1 volume for each subject was skull stripped, segmented (gray matter, white matter and CSF), and registered to the MNI 2mm standard brain. After removing first four EPI volumes transient signal spikes were removed by de-spiking interpolation. Head motion was corrected by linearly registering all the volumes to the first volume, through which six motion parameters and displacement distance between two consecutive volumes were estimated. Each volume was regressed by white matter and cerebrospinal fluid

signal fluctuations as well as the six motion parameters. EPI volumes were smoothed with a 6mm FWHM Gaussian kernel, resampled and then spatially transformed, and aligned to the MNI 2mm standard brain space through which12 affine parameters were created between rs-fMRI volume and MNI152 2mm space, so that a seed ROI can later be registered to each individual rs-fMRI space. In order to detect excess motion, the root mean square deviation was calculated from motion correction parameters, at an r=40mm spherical surface using FSL's rmsdiff tool [18,19]. Volumes were removed if displacement distance exceeded the threshold (0.3mm) (i.e., scrubbed) from further statistical analyses [20]. Functional connectivity of the amygrala was tested by by ADNI's 3dROIstats, testing every voxel in the whole brain tested using amygdala ROI defined by Harvard_Oxford atlas [21]. The Z-scores were calculated by AFNI's 3dcalc, then registered to the MNI2mm space. Functions in the nibabel Python module were utilized to read in the images and convert them into tensors for neural network inputs. Python modules numpy and tensorflow and Keras API were utilized to further process the data and implement the neural network models.

We present results from three different neural network architectures – 1) deep neural network (DNN), 2) a linear convolutional neural network (CNN) and 3) RESNET-34 which is a nonlinear CNN architecture. Our DNN consisted of 5 hidden layers with 4096 nodes in addition to input and output layers. Our linear CNN is an adaptation of the CNN architecture presented in chapter 14 in [22]. It consisted of two convolutional layers with batch normalization and max-pooling layers in between. The number of square filters (- of sizes 3 and 2, respectively-) in the first and second convolutional layers were 64 and 128. The output from the second convolutional layer was flattened and then transitioned through 5 dense layers, each with 512 nodes. The dense layers were interspersed with dropout-regularization layers with 50% dropout-probability. ResNet-34 is the standard residual learning architecture with 34 layers containing 3 residual units that output 64 feature maps, 4 residual units with 128 maps, 6 residual units with 256 maps, and 3 residual units with 512 maps. The activation function used for all layers (convolutional and dense) in all three architectures was ReLU. The optimizer used for DNN was stochastic gradient descent (SGD), and for linear CNN and RESNET-34 was 'Adam', a variant of SGD. 30 epochs were used for training the first two architectures and 300 epochs used for the ResNet-34 architecture. Performance for all architectures was assessed using random-shuffle cross-validation (CV) with 25 iterations. For each iteration, the 173 samples were split randomly into training, validation and test sets of 120, 18 and 35 samples respectively. Median and inter-quartile range (IQR) values of the accuracy rates are presented as results below. The Python codes and the jupyter-notebook output for all analyses are posted in 'https://github.com/mjohn5/amygdalaconnectivity'.

Results

The median accuracy rate (and IQR) of the DNN architecture based on 25 CV-iterations were 62.9% (60.0%, 65.7%). The median accuracy rate for both the CNN and ResNet architectures was 60.0% with corresponding IQRs being (57.1%, 62.9%) and (57.1%, 65.7%), respectively. The results are graphically represented in Fig. 1.

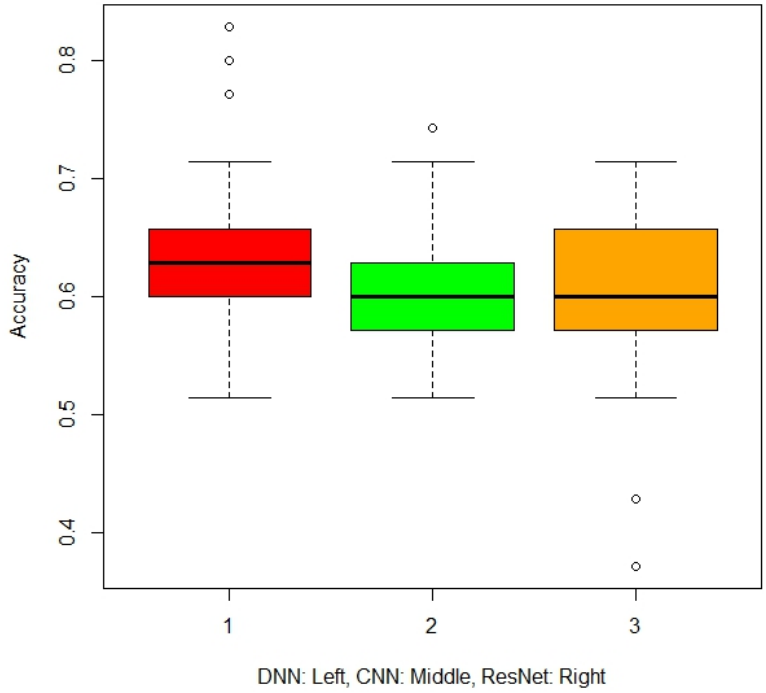

Figure Boxplots of accuracy rates based on the three neural network architectures for 25 cross-validation iterations.

Discussion

Our results show moderate predictive capability of amygdala connectivity for classifying schizophrenia patients and healthy controls. CNN and ResNet achitectures, although well-suited for images as inputs may not be ideal for connectivity matrices as inputs as in the current analysis, which may explain why the accuracy rates based on these two architectures are slightly lower compared to the DNN architecture. Our accuracy rates may also have been limited based on the sample size from a single site. The generalizability of our results based on training and testing with data from multiple sites will also be of interest for future research.

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