

# MULTIPLE DEEP LEARNING ARCHITECTURES ACHIEVE SUPERIOR PERFORMANCE DIAGNOSING AUTISM SPECTRUM DISORDER USING FEATURES PREVIOUSLY EXTRACTED FROM STRUCTURAL AND FUNCTIONAL MRI

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## ABSTRACT

The diagnosis of Autism Spectrum Disorder (ASD) is a subjective process requiring clinical expertise in neurodevelopmental disorders. Since such expertise is not available at many clinics, automated diagnosis using machine learning (ML) algorithms would be of great value to both clinicians and the imaging community to increase the diagnoses' availability and reproducibility while reducing subjectivity. This research systematically compares the performance of classifiers using over 900 subjects from the IMPAC database [1], using the database's derived anatomical and functional features to diagnose a subject as autistic or healthy. In total 12 classifiers are compared from 3 categories including: 6 non-linear shallow ML models, 3 linear shallow models, and 3 deep learning models. When evaluated with an AUC ROC performance metric, results include: (1) amongst the shallow learning methods, linear models outperformed nonlinear models, agreeing with [2]. (2) Deep learning models outperformed shallow ML models. (3) The best model was a dense feedforward network, achieving 0.80 AUC which compares to the recently reported  $0.79 \pm 0.01$  AUC average of the top 10 methods from the IMPAC challenge [3]. These results demonstrate that even when using features derived from imaging data, deep learning methods can provide additional predictive accuracy over classical methods.

**Index Terms**— autism spectrum disorder, deep learning, machine learning, MRI, neuroimaging

## 1. INTRODUCTION

Autism spectrum disorder (ASD) is a common psychiatric disorder characterized by social and communication deficits and a restricted pattern of interests [4]. It is known that individuals with ASD have altered neuroanatomy and connectivity, though the full extent of these relationships has not been fully elucidated. Currently, the diagnosis of ASD is a subjective process that requires an expert in neurodevelopmental disorders who may be unavailable at many clinics. Non-invasive imaging captures structural and functional aspects of

brain development that are promising for an automated machine learning (ML) based diagnosis. Such automated approaches would reduce subjectivity and increase reproducibility and availability of the diagnosis. Existing literature on automated diagnostics are limited in two ways. First, in these studies, just one category of predictive model is typically proposed and fully optimized; making comparisons to comparable methods biased. Second, they often depend on access to raw image data. Sharing patient images can be problematic due to concerns for patient identifiability. However preprocessed data, such as volumetry and functional connectivity are more easily shared. The Paris IMPAC Autism Challenge [1] is one such sharable dataset containing the derived features from structural MRI (sMRI) and resting state functional MRI (rs-fMRI).

While in many problem domains, such as real world object recognition, deep learning outperforms shallow learning, this increase in performance has been attributed to the replacement of hand-engineered features with learned features. To date there is limited research aimed at understanding how deep learning methods compare in performance to shallow ML methods on datasets with pre-derived features. Elucidating the comparative performance of model categories for such large sharable datasets would be of great significance to guide the image analysis community.

In order to perform a fair comparison, in this study each model is similarly hyperparameter optimized using a random search-based approach. Identical randomly chosen cross-validation splits are used to train each model, ensuring similar training opportunities for each model.

The primary contribution of this work is four-fold. *First* the study provides a systematic comparison of 3 broad categories of methods: linear and nonlinear shallow ML models and deep learning models, and assesses their relative performance. *Second* the study examines the relative performance of anatomical features, functional features and their combination and provides evidence of their level of complementarity. *Third* evidence for the effective level of granularity for deriving regional features from whole brain parcelations is obtained by comparing 7 atlases. *Fourth* the rela-

tive performance of 12 individual classifiers is compared and recommendations for ASD diagnosis is made for a specific winning deep learning model, which achieves greater performance than all other tested models.

## 2. MATERIALS AND METHODS

### 2.1. Materials

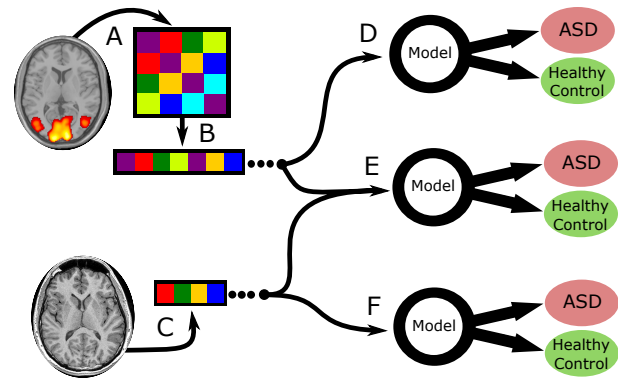
This study uses 915 subjects from the IMPAC dataset [1] that received both sMRI and rs-fMRI and were identified by the IMPAC organizers as having satisfactory images. The focus of this study is the comparison of two-category classifiers for diagnosing ASD or healthy control. The IMPAC dataset includes the clinical diagnosis (the classifier target) for which there were 418 ASD patients and 497 healthy control subjects. Structural MRI (sMRI) and resting state functional MRI (rs-fMRI) were acquired for each subject. Figure 1 illustrates how the features were derived from the MRI. From the sMRI, 207 features were extracted, including volumes of cortical and subcortical structures, cortical thickness, and area per region of interest (ROI) defined by the Desikan-Killiany gyral atlas [5]. From the rs-fMRI, functional connectivity matrices were derived. For this derivation, the rs-fMRI was first parcellated into ROIs using seven different atlases including: atlases (1-3) The BASC Atlas, whose regions are defined by k-means clustering of stable coherent groups [6] for  $k=64, 122,$  and 197 ROIs, atlas (4) the Craddock atlas, which defines 249 ROIs by coherence of local graph connectivity [7], atlas (5) the Harvard-Oxford Anatomical atlas, which defines 69 ROIs using anatomical features, atlas (6) the MSDL atlas, which has 39 ROIs defined by correlations of spontaneous activity [8], and atlas (7) the Power atlas [9], which is defined by local graph-connectivity into 264 ROIs. The rs-fMRI time signals from each region were converted into a connectivity matrix by projection into tangent space, a procedure which captures connectivity aspects from both the correlation and partial correlation [10]. Clinical data including patient gender and age were also collected.

### 2.2. Data partitioning

Subjects were randomly partitioned with 80% assigned to a training set and 20% to a test set with the split having matching proportions of diagnosis (ASD/healthy) and gender (male/female). The test subjects were set aside and not used during training or model selection. The training set was further split into validation and training folds using a 3-fold stratified cross validation approach. To ensure fair subsequent model comparison, the same splits were used for all tested machine learning models.

### 2.3. Model construction

Systematic testing of a broad array of 12 machine learning classifiers was conducted. This included 6 nonlinear shallow



**Fig. 1.** Combinations of derived features used by the predictive models tested in this study. Image data (rs-fMRI and sMRI) and was gathered externally by IMPAC organizers. (A) The rs-fMRI was transformed into a symmetric connectivity matrix for each atlas. (B) Upper triangular elements of matrix were flattened into a 1D vector. (C) The sMRI was transformed into a vector of cortical/subcortical ROI volumes and cortical thickness features. In (D) the connectivity matrix vector is used as the sole input for the predictive model, in (E) both anatomical and connectivity derived feature vectors are appended and used, while in (F) the anatomical features are used as the sole input for the predictive model.

machine learning methods: a naïve Bayes classifier, a support vector machine with a Gaussian kernel, a random forest classifier, an extremely randomized trees classifier, adaptive boosting, and gradient boosting with decision tree base models; 3 linear shallow models; a support vector machine with a linear kernel, logistic regression with ridge regularization, logistic regression with lasso regularization; and 3 deep learning approaches: a fully connected dense feedforward (FeedFWD) network, and a long-short term memory (LSTM) based recurrent neural network classifier (RNN), and the BrainNetCNN [11]. Classical models were constructed using the scikit-learn and XGBoost packages, while the deep learning models used the keras, tensorflow, and caffe packages. The LSTM classifier uses an LSTM network followed by a dense feedforward layer for classification like [12] which can succeed even on non-sequential fixed vector data, as suggested by [13]. The BrainNetCNN classifier is a graph-convolutional network classifier [11]. The models were trained on an NVIDIA Tesla p100.

### 2.4. Random search

To optimize each ML model, a random search was conducted over the model's hyperparameter space. A total of 50 random points in hyperparameter space were sampled for each model. To illustrate, consider the examples of simple and complex dense FeedFWD networks that were tested are illustrated in Table 1, in the left and middle columns respectively. In de-

**Table 1.** Examples of dense FeedFWD network architectures tested in the random search. Hyperparameters shown include the regularization coefficient, # of layers, # of neurons/layer, and dropout fraction. Left column illustrates a simple network. Middle shows a complex network. Right column shows the architecture of the highest performing network.

Simple Dense Network	Complex Dense Network	Highest Performing Dense Network
L2 Regularization: 2.3e-4 Dense 16 neurons Dropout: 53% removed Dense 16 neurons Dense 1 neuron	L2 Regularization: 2.3e-4 Dense 128 neurons Dropout 18% removed Dense 128 neurons Dropout 18% removed Dense 64 neurons Dropout 18% removed Dense 42 neurons Dense 1 neuron	L2 Regularization: 1.1e-4 Dense 64 neurons Dropout 13% removed Dense 64 neurons Dense 1 neuron

tail, for the models tested these hyperparameter points were randomly chosen from the following dimensions and ranges: Random Forest: number of estimators [50, 5000], max nodes [5, 50]; Extremely Random Trees: number of estimators [50, 5000], max nodes [5, 50]; Adaptive Boosting: number of estimators [20, 2000], learning rate [0.1, 0.9]; Gradient Boosting: number of estimators [5, 5000], max depth [1, 10], subsampling fraction per tree [0.2, 0.8], fraction of columns per tree [0.2, 1], learning rate [0.01, 1]; SVM with Gaussian Kernel: C [0.0001, 10000], maximum iterations: [10000, 100000], gamma [0.01, 100]; SVM with Linear Kernel: C [0.0001, 10000], maximum iterations: [10000, 100000]; logistic regression with lasso regularization: C [0.0001, 10000], maximum iterations [1000, 100000]; logistic regression with ridge regularization: C [0.0001, 10000], maximum iterations [1000, 100000]; dense FeedFWD network: number of hidden layers [1, 3], layer width [16, 256]; dropout fraction [0.1, 0.6], L2 regularization coefficient [0.0001, 0.02], LSTM: number of hidden layers [1, 3], layer width [16, 256], dropout fraction [0.1, 0.6], L2 regularization coefficient [0.0001, 0.02]; BrainNetCNN: number of hidden layers [0, 2], layer width [16, 64], dropout fraction [0.1, 0.6], ReLU slope for  $x < 1$  [0.1, 0.5]. Deep learning models used the leaky ReLU activation function, early stopping, the Nesterov ADAM optimizer, a batch size of 128, and the binary cross-entropy loss function.

Each of our 12 models types was trained on 15 different feature sets, for a total of 180 model type  $\times$  feature set combinations. The feature sets contain measures of anatomical volume and functional connectivity from the IMPAC dataset. These feature sets included: (1) 207 measures of regional volume and thickness, (2-8) functional connectivity measured between regions defined by one of the 7 atlases described in the materials section above, (9-15) the union of the anatomical with one of the functional feature sets. The model with the highest average area under ROC curve over the cross validation folds was selected as the best model for each model type  $\times$  feature set combination. This model was then trained on all training data and evaluated on the held out test set not used in training.

### 3. RESULTS

The results are summarized in Figure 2, which shows the area under the ROC curve of different machine learning models predicting ASD vs healthy control on the test data that was held out from training.

#### 3.1. The importance of feature set combination

Comparing the 15 feature sets (rows of Figure 2), it can be observed that the anatomical features yielded the lowest prediction accuracy by area under the ROC curve, while the rs-fMRI functional connectivity features alone yielded models with higher predictive power than anatomical features. For functional connectivity data alone, the BASC atlas with any number of parcellations and the Power atlas generated models with more predictive power than other atlases. However the combination of anatomical and functional features yielded models with even higher predictive power, suggesting their complementarity. The best performing models used the anatomical features with connectivity features from the Power atlas, Craddock atlas, or BASC atlas. Models trained on the Harvard-Oxford atlas connectivity data and volumetric data are notably lower performing, and models trained on the MSDL atlas were slightly better than those trained on the Harvard-Oxford atlas.

#### 3.2. The importance of model type

The most accurate shallow machine learning algorithm was logistic regression with ridge regularization, which had a maximum ROC AUC of 0.773. Of the nonlinear methods, the extremely randomized trees performed the highest, and the adaptive boosting methods performed the lowest. Overall, deep learning outperformed shallow learning, and the highest performing shallow linear methods outperformed the highest performing shallow nonlinear methods.

As shown in the columns towards the right of Figure 2, the deep learning methods performed higher than the other categories of models. The most successful deep learning algorithms were the dense FeedFWD network which achieved an ROC AUC of 0.804 and LSTM, which achieved an ROC AUC of 0.776. The BrainNetCNN model is only defined for functional connectivity input features, but on those features it performed lower than the other deep learning models with a performance similar to the linear models. Like the shallow methods, the deep learning methods performed best when using the combination of functional and anatomical features. The highest overall performance was the dense FeedFWD network, whose architecture is shown in Table 1 right column, using the rs-fMRI connectivity data with the BASC atlas with 122 ROIs and the sMRI volumetric data combined, achieving an AUC of 0.804. Other permutations using the BASC atlases, Craddock atlas, and Power atlas as training data for the dense FeedFWD network also performed well.



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