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## Surface-based shared and distinct resting functional connectivity between attention deficit hyperactivity disorder and autism spectrum disorder

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### Abstract

**Background**—Both attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are neurodevelopmental disorders with high prevalence. They are often comorbid and both exhibit abnormalities in sustained attention, yet common and distinct neural patterns of ASD and ADHD remain unidentified.

**Aims**—To investigate shared and distinct functional connectivity patterns in a relatively large sample of boys (7–15 years old) with ADHD, ASD and typical development (TD) matched by age, gender, and IQ.

**Method**—We applied machine learning techniques to investigate patterns of surface-based brain resting state connectivity in 86 boys with ASD, 83 boys with ADHD, and 125 boys with TD.

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Author Contributions:

M.J. developed the initial idea and design of the study, analysis and interpretation of data, drafting or revising the final manuscript; Y.T. analysis and interpretation of data, drafting or revising the final manuscript; J.P. interpretation of data, drafting or revising the final manuscript; K.J. interpretation of data, drafting or revising the final manuscript; C.L. interpretation of data, drafting or revising the final manuscript; W.S. analysis and interpretation of data, drafting or revising the final manuscript. J.K. developed the initial idea and design of the study, analysis and interpretation of data, drafting or revising the final manuscript.

Conflict of Interest

JK has a disclosure to report (holding equity in a startup company (MNT)); all authors declare no conflict of interest.

**Results**—We observed increased functional connectivity within the limbic and somatomotor networks in boys with ASD compared to boys with TD. We also observed increased functional connectivity within the limbic, visual, default mode, somatomotor, dorsal attention, frontoparietal, and ventral attention networks in boys with ADHD compared to boys with ASD. In addition, using a machine learning approach, we were able to discriminate TD from ASD, TD from ADHD, and ASD from ADHD with accuracy rates of 76.3%, 84.1%, and 79.1%, respectively.

**Conclusion**—Our results may shed new light on the underlying mechanisms of ASD and ADHD and facilitate the development of new diagnostic methods for these disorders.

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## Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention and abnormal hyperactivity and impulsivity, affecting nearly 6% of children<sup>1</sup>. Autism spectrum disorder (ASD) is another highly prevalent neurodevelopmental disorder characterized by difficulties in social communication and social interaction<sup>2</sup>. ADHD and ASD are often comorbid<sup>3,4</sup>, with about 30% of ASD patients having comorbid ADHD characterized by age-inappropriate inattention, impulsiveness, and hyperactivity. Neuroimaging studies have shown that both disorders are associated with abnormal resting state functional brain connectivity<sup>5–12</sup>. For instance, studies have suggested that compared with typical development (TD), 1) children with ADHD showed disrupted functional connectivity patterns in brain regions involved in attention and sensory processing<sup>7,8</sup> and 2) children with ASD displayed increased resting state functional connectivity in the posterior cingulate cortex and salience network, and the strength of functional connectivity was linked to severity of social interaction deficits<sup>5,9,12</sup>. These studies have significantly enhanced the neurophysiological understanding of ADHD and ASD. Nevertheless, the mechanisms underlying the comorbidity and distinction between the two disorders remain unclear. In this study, taking advantage of the Autism Brain Imaging Data Exchange (ABIDE) and ADHD200 data set ([http://fcon\\_1000.projects.nitrc.org/indi/adhd200/](http://fcon_1000.projects.nitrc.org/indi/adhd200/)), we investigated shared and distinct functional connectivity patterns in a relatively large sample of boys (7–15 years old) with ADHD, ASD, and TD matched by age, gender, and IQ. For better functional alignment across subjects, the FreeSurfer image analysis suite was applied to generate a cortical surface for each subject<sup>13</sup>. We hypothesized that 1) children with ASD and ADHD would be associated with altered functional connectivity compared to children with TD, and the altered patterns may be associated with symptoms of ASD and ADHD; and 2) machine learning techniques could be used to identify distinct and common functional connectivity features for both ASD and ADHD.

## MATERIALS AND METHODS

### Subject sample

We used an independent sample of individuals with ASD and individuals with TD from the Autism Brain Imaging Data Exchange (ABIDE) and individuals with ADHD from the ADHD200 data set ([http://fcon\\_1000.projects.nitrc.org/indi/adhd200/](http://fcon_1000.projects.nitrc.org/indi/adhd200/)). The inclusion criteria were as follows: i) full scale IQ (F-IQ) scores >80; ii) aged between 7 and 15 years to

minimize potential developmental effects<sup>14</sup>; iii) scanned in a 3T MRI scanner to increase between-site reliability<sup>15</sup>; iv) right-handed; v) diagnosis of ASD based on DSM-IV-TR and assessed with the Autism Diagnostic Observation Schedule (ADOS), the Autism Diagnostic Interview–Revised (ADI-R), or both; vi) children with ASD do not have comorbid ADHD and children with ADHD do not have comorbid ASD; vii) diagnosis of ADHD based on DSM-IV-TR without Axis I disorders. In total, 294 participants fit the above criteria and were included in the present study. Fifty-five children with ASD (65%), sixty-one children with ADHD (73%), and all children with TD were psychotropic medication-naive. Among children with ADHD, 44 met criteria for combined type ADHD, 3 met criteria for hyperactive/impulsive type ADHD, and 36 met criteria for predominantly inattentive type ADHD. Each site was required to confirm that their local Institutional Review Board (IRB) or ethics committee had approved both the initial data collection and sharing the datasets. Details of site-specific protocols, informed consent, and ethical approval at the time of the scan for each data set can be found at [http://fcon\\_1000.projects.nitrc.org](http://fcon_1000.projects.nitrc.org).

### Data preprocessing

Anatomical image data were processed using FreeSurfer, version 5.3.0 software package (<http://surfer.nmr.mgh.harvard.edu/>)<sup>16</sup>. To increase anatomical validation cross individuals with ADHD, ASD, and TD, FreeSurfer was used for segmentation of subcortical structures and automatic tessellation of the cortical surface because cortical surface variability is considerably improved by segmentation. The preprocessing of anatomical data was as follows: 1) motion correction and non-uniformity correction, 2) automatic Talairach transformation, 3) intensity normalization, 4) skull strip and segmentation of the subcortical white matter and gray matter, 5) tessellation of the white matter and gray matter, 6) surface smoothing and inflation, 7) topology correction, and 8) parcellation. Automated segmentation and parcellation results were reviewed for quality and corrected by two trained experts (authors MJ and WS) as necessary.

Resting-state fMRI data sets were processed with the CONN functional connectivity toolbox (<http://www.nitrc.org/projects/conn>)<sup>17</sup>. Preprocessing involved 1) realignment to the mean image, 2) removal of volumes with a mean intensity >1.5% of the mean global signal or 0.5mm/TR framewise displacement to reduce the effect of head movement, 3) CompCor correction to reduce physiological and other noise artifacts<sup>18</sup>, 4) entering segmented CSF and white matter as confounding regressors at the subject-level in FreeSurfer, and 5) band-pass filtering of the functional image (0.01–0.08 Hz).

### ROIs and Connectivity analysis

We used 162 ROIs adopted from the Desikan–Killiany parcellation atlas by FreeSurfer<sup>19</sup> (Supplementary Table 1, Supplementary Figure 1). Mean time series were obtained for each subject by averaging the fMRI time series over all voxels in each of the 162 ROIs. Functional connectivity was estimated based on these regional mean time series by calculating the pairwise Pearson correlation coefficient between all possible (162×161/2=13041) ROI pairs. A symmetric connectivity matrix was constructed to represent these connections. Correlation coefficients were Fisher z-transformed to increase normality for statistical analyses.

## Classification Analysis: Discriminating TD, ASD, and ADHD

To investigate diagnostic features between ADHD and ASD, a feature selection approach combining a univariate t-test and multivariate support vector machine- recursive feature elimination (SVM-RFE) was performed<sup>20</sup>. To avoid the risk of overfitting, all analyses were performed using 10-fold cross validation<sup>21</sup>.

In the first step, we analyzed group-level differences of features between groups. Significant differences for each pair of ROIs were assessed using a mass univariate two sample t-test with a threshold of  $P < 0.001$  and false discovery rate (FDR) correction. Features showing significant difference were retained for the remaining analyses. Our logic was that these features would be the most likely to contribute to the discrimination between groups.

In the second step, we used SVM-RFE to select the features with the most discriminative power for the classifier itself. SVM-RFE was used to train the classification model and obtain weights for each feature. The features were ranked according to the absolute values of weights, and the lowest ranking feature was discarded. Then the classification model was trained using the new feature set (i.e. without the discarded feature). This procedure was repeatedly performed until the feature set was empty. We conducted a full backward elimination procedure to further select the features with the highest classification accuracy. Since we used a 10-fold cross validation strategy to estimate the performance of the classifiers and feature ranking and each iteration was based on a slightly different dataset, the selected feature sets differed slightly from iteration to iteration.

To determine the most discriminative features, a consensus discrimination map which aggregated features selected in all cross validation iterations was used. Regional weight, which represents the contribution of each feature for discriminating different groups, was denoted by the number of ROI occurrences in the consensus discrimination map<sup>22</sup>. The discriminative power of each feature was denoted by the average of its classification weights across all iterations. We conducted linear regression analyses of group-level differences to select features based on SVM-RFE and core symptom severity in ASD (total SRS scores), adjusting for data collection site, FIQ, and age using SPSS. Regression analyses were corrected for multiple comparisons using FDR correction ( $p < 0.05$ ).

Features with the most discriminative power were fed to an SVM with a linear kernel, which was implemented using LIBSVM. The classification (ASD vs. TD; ADHD vs. TD; ADHD vs. ASD) was also based on 10-fold cross validation, and the performance of the classifier was evaluated by accuracy, sensitivity, and specificity. Nonparametric permutation tests (1000 times) were used to estimate the statistical significance of the observed classification accuracy. We randomly permuted the class labels of the data prior to training. Cross validation was then performed on the permuted dataset and the procedure was repeated 1000 times. If the classifier trained on real class labels had an accuracy exceeding the 95% confidence interval generated from the accuracies of the classifiers trained on randomly relabeled class labels, this classifier was considered to be well-performing.

## RESULTS

### Demographic and Clinical Characteristics

294 subjects (86 boys with ASD, 83 boys with ADHD, and 125 boys with TD) were included in the study. There were no significant differences between the three groups for FIQ ( $p=0.51$ ) and age ( $p=0.26$ ). Demographic and clinical characteristics for all participants included in the analyses are presented in Table 1. There was a significant difference between ASD and TD groups for SRS total scores ( $p<0.001$ ).

### Diagnostic features of ROI-to-ROI functional connectivity analysis

Comparison of the TD and ASD groups showed 72 ROI-to-ROI increased connectivities in the ASD group compared to the TD group (Figure 1). The ASD group showed increased connectivity in brain areas associated with the limbic, visual, default mode, somatomotor, dorsal attention, frontoparietal, and ventral attention networks. The TD group only showed 9 ROI-to-ROI increased connectivities in brain areas associated with the visual, default mode, dorsal attention, frontoparietal, and ventral attention networks. The classification accuracy of discriminating TD from ASD was 76.3% ( $p < 0.001$ ; see Table 2).

Comparison of the TD and ADHD groups showed 8 ROI-to-ROI increased connectivities in the ADHD group compared to the TD group (Figure 2). Specifically, the ADHD group showed increased connectivity in brain areas associated with the limbic, ventral attention, visual, and default mode networks. In addition, the TD group showed 2 ROI-to-ROI increased connectivities in brain areas associated with the default mode and visual networks. The classification accuracy of discriminating TD from ADHD was 84.1% ( $p < 0.001$ ; see Table 2).

Comparison of the ASD and ADHD groups showed 9 ROI-to-ROI increased connectivities in the ADHD group compared to the ASD group (Supplementary Figure 2). Specifically, the ADHD group showed increased functional connectivity between brain regions associated with the limbic, visual, default mode, somatomotor, dorsal attention, frontoparietal, ventral attention networks. In addition, we found that the ASD group showed increased functional connectivity in the left middle occipital sulcus and right precentral sulcus associated with the somatomotor and dorsal attention networks. The classification accuracy of discriminating ADHD from ASD was 79.3% ( $p < 0.001$ ; see Table 2).

### Association between functional connectivity and core symptom severity

Regression analysis showed a positive association between increased connectivity in the ASD group compared to the TD group and SRS scores, specifically 1) with the right insula and post transverse collateral sulcus functional connectivity ( $p = 0.0004$ ,  $p = 0.01$  FDR corrected;  $r = 0.376$ ) and 2) with the right orbital gyrus and right horizontal ramus of the lateral sulcus functional connectivity ( $p = 0.0076$ ,  $p = 0.025$  FDR corrected;  $r = 0.309$ ) (Supplementary Figure 3, Supplementary Table 2).

## Discussion

In this study, we investigated shared and distinct patterns of dysconnectivity in boys with ASD and ADHD. We found that 1) children with ASD showed increased functional connectivity compared to children with TD, and children with ADHD showed increased functional connectivity compared to children with ASD and children with TD; and 2) machine learning approaches can discriminate ASD and ADHD with accuracies of 76.3% (ASD from TD), 84.1% (ADHD from TD) and 79.6% (ADHD from ASD). Our results may deepen our understanding of the neurophysiological mechanisms underlying the comorbidity and distinction between ADHD and ASD.

Our findings of increased functional connectivity patterns within the limbic regions and the somatomotor network in ASD compared to TD are consistent with previous studies<sup>12</sup>. For instance, Cerliani and colleagues found increased functional connectivity in the limbic area and sensory-motor area in male ASD patients<sup>12</sup>. Likewise, the DSM-5 manual also includes abnormal responses to sensory stimulation as a diagnostic criterion of ASD. Our results suggest that increased functional connectivity in the limbic and sensory-motor areas might reflect this abnormal response. The finding of increased functional connectivity patterns in children with ADHD compared to TD is also consistent with previous studies of ADHD<sup>6</sup>. Studies have suggested that the default network and limbic area are associated with regulation of attention<sup>23</sup>, self-cognition<sup>24</sup>, and external cognition<sup>25</sup>. We thus speculate that increased functional connectivity may underlie impairments in “sharing attention with other people,” which is a core symptom of ADHD.

We also found increased functional connectivity in the frontal lobe, temporal lobe, occipital lobe, parietal lobes, frontoparietal network, and ventral attention network in the ADHD group compared to the TD group. Rubia *et al.* found that temporal lobe and parietal lobe dysfunction in boys with ADHD during an attention allocation task is associated with symptoms of ADHD<sup>26</sup>. We believe that abnormal functional connectivity in the temporal lobe and parietal lobe might disrupt or delay maturation of the regulation of attention in ADHD.

Nonetheless, our findings are inconsistent with other studies indicating that the ADHD cohort showed decreased functional connectivity in the posterior cingulate cortex<sup>7</sup> and increased functional connectivity within frontal regions of the executive control network<sup>8</sup> as compared to the TD cohort. These conflicting findings may be due to inconsistent methodologies or variability in the ADHD sample population. For instance, Kyeong *et al.*<sup>7</sup> used graph theory analysis to estimate degree centrality in the stratifying ADHD subgroups with mild symptom ADHD and severe symptom ADHD. Francx *et al.*<sup>8</sup> used independent component analysis to detect components or networks in the persistent ADHD subgroups and remittent ADHD subgroups. These discrepancies illustrate the importance of methodology and clinical subgroup differences during the interpretation of neuroimaging study findings.

We found that children with ASD showed increased functional connectivity between the left middle occipital sulcus and right precentral sulcus compared to ADHD. The occipital lobe



and parietal lobe are involved in communication processing, including emotion perception<sup>27</sup> and face discrimination<sup>28</sup>, as well as the pathophysiology of autism<sup>29</sup>. A previous study indicated that ASD involves a different cognitive process during social interactions<sup>30</sup>. We speculate that this may be due to the increased functional connectivity between the occipital and parietal lobes compared to ADHD and TD. These results may provide an explanation for the altered communication processing at the neural level in individuals with ASD.

Our machine-learning algorithms confirmed common classification features between ASD and ADHD in the limbic, ventral attention, visual, and default mode networks. This finding is consistent with previous studies that found abnormal functional connectivity in these networks in both ASD and ADHD<sup>5,6,31</sup>. Recent studies indicate that ADHD may be associated with difficulties in social interaction<sup>32</sup>. Symptoms of ADHD (e.g., attention deficits, impulse control, hyper-activity) are also frequently observed in ASD, demonstrating that the two disorders share some common manifestations. Taken together, the common classification features between ASD and ADHD may reflect shared neural mechanisms and clinical manifestations in the two disorders.

Translational neuroimaging studies have provided a basis for identifying neurophysiological features of ASD and showed potential clinical utility<sup>33</sup>. Specifically, advanced machine learning techniques have been introduced to extract meaningful features from neuroimaging data and subsequently make an objective diagnosis for ASD. Anderson and colleagues used univariate t-tests to exclude irrelevant FCs and achieved an accuracy of 79%. Nielsen et al. used a leave-one-out classifier with a general linear model on the multisite ABIDE dataset and obtained accuracies of up to 60% for different sites.

More recently, Yahata and his colleagues developed a machine learning algorithm combining  $L_1$ -regularized sparse canonical correlation analysis and sparse logistic regression for selecting a subset of FCs to obtain a classification accuracy of around 85% in a Japanese dataset, but generalization for independent cohorts using two independent validation cohorts obtained from the ABIDE dataset showed lower accuracy (75%). In the present study, we combined univariate t-tests and multivariate SVM-RFE to identify the most discriminative features between ASD, ADHD, and TD using 7 independent cohorts and obtained accuracies of 76.3% between TD and ASD, 84.1% between TD and ADHD, and 79.1% between ASD and ADHD. Our results demonstrated that a classifier developed using surface-based functional connectivity also showed high classification for ASD and ADHD across other independent cohorts.

We found that the increased functional connectivity in the right insula and right orbital cortex was associated with SRS scores. Functional and structural imaging studies of ASD have identified abnormalities in the insula, explaining the emotion dysregulation and social avoidance symptoms of ASD<sup>34,35</sup>. The orbital cortex, a critical brain region in social cognition, has been associated with high levels of autistic traits<sup>36</sup>. Taken together, these results suggest that atypical connectivity in the insula and orbital cortex are related to emotion dysregulation and social cognition.

There are several limitations in this study. First, our analyses were performed on boys with ASD who did not have comorbid ADHD and boys with ADHD who did not have comorbid ASD. Yet, we did not have ADHD symptom scores of subjects with ASD or ASD scores of subjects with ADHD. We thus cannot exclude the possibility that the disorders were comorbid. Further research including both ASD and ADHD symptom scores is needed. Second, this study only included boys with TD, ASD, and ADHD; thus, the results may not be generalizable to girls. Future studies including both boys and girls with ASD and ADHD are needed.

In summary, we found that boys with ASD are associated with increased functional connectivity in the limbic area, while boys with ADHD are associated with increased functional connectivity in the frontal and temporal areas. Machine learning-derived classification methods hold the potential to uncover neuroimaging biomarkers for ASD and ADHD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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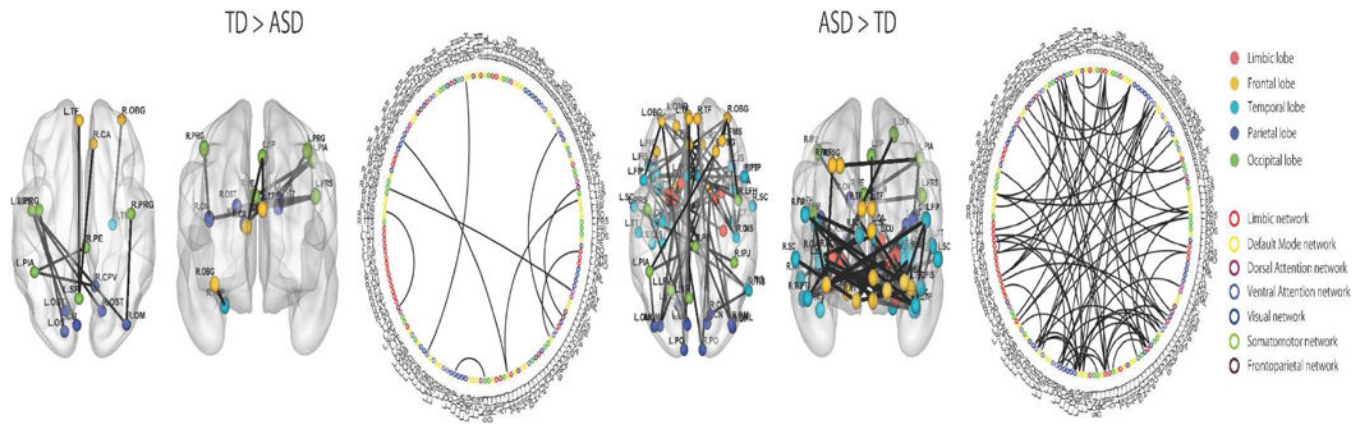
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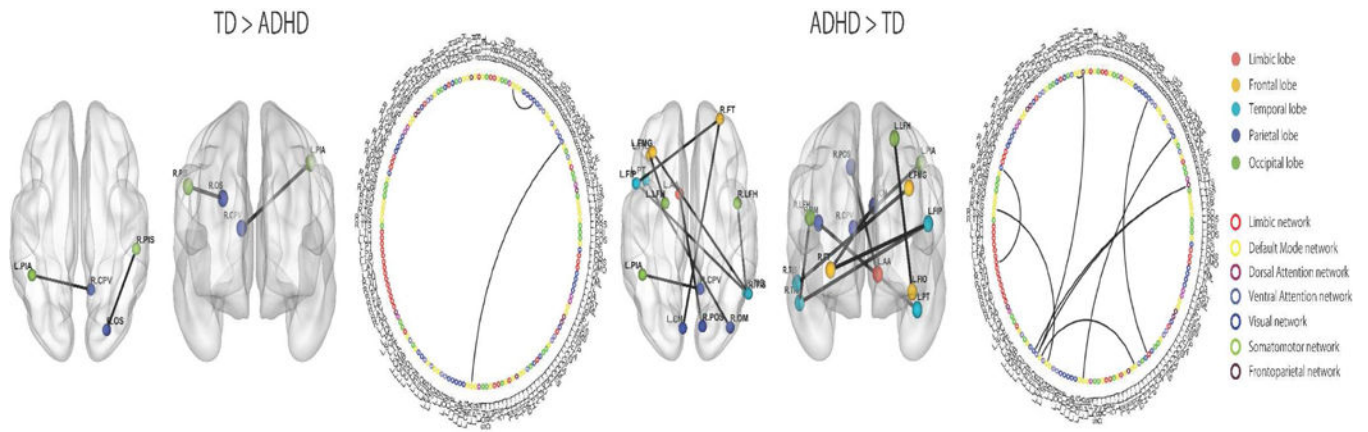
**Figure 1.** ROI-to-ROI functional connectivity analysis between TD and ASD. The ASD group showed predominantly higher connectivity than the TD group. Colored circles indicate brain regions. Colored lines indicate networks.

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**Figure 2.** ROI-to-ROI functional connectivity analysis between TD and ADHD. The ADHD group showed predominantly higher connectivity than the TD group. Colored circles indicate brain regions. Colored lines indicate networks.

**Table 1**

Demographic and Clinical Characteristics

Measure	ASD n = 86		TD n = 125		ADHD n = 83		Group Comparisons	
	Mean	SD	Mean	SD	Mean	SD	F value	P value
Age (years)	11.4	2.1	10.9	1.6	11.2	1.8	1.32	0.267
Full IQ	110.4	13.2	111.7	9.7	109.9	13.1	0.67	0.512
ADI-R								
Social	18.9	4.9	0					
Non-verbal	8.34	3.1						
Verbal	14.9	4.3						
SRS total scores	91.8	25.7	19.2	12.4			t = 26.3	< 0.0001

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; LR: likelihood ratios; TD: typically developed

**Table 2.**

## Results of machine learning analysis

Method	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
TD_AS	76.3	79.2	63.9	2.19	0.33
TD_AD	84.1	88.8	76.1	3.72	0.15
ASD_AD	79.3	75.6	83.1	4.47	0.29

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; LR: likelihood ratios; TD: typically developed