Diagnosis of Autism Spectrum Disorders Using Regional and Interregional Morphological Features

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Abstract: This article describes a novel approach to identify autism spectrum disorder (ASD) utilizing regional and interregional morphological patterns extracted from structural magnetic resonance images. Two types of features are extracted to characterize the morphological patterns: (1) Regional features, which includes the cortical thickness, volumes of cortical gray matter, and cortical-associated white matter regions, and several subcortical structures extracted from different regions-of-interest (ROIs); (2) Interregional features, which convey the morphological change pattern between pairs of ROIs. We demonstrate that the integration of regional and interregional features via multi-kernel learning technique can significantly improve the classification performance of ASD, compared with using either regional or interregional features alone. Specifically, the proposed framework achieves an accuracy of 96.27% and an area of 0.9952 under the receiver operating characteristic curve, indicating excellent diagnostic power and generalizability. The best performance is achieved when both feature types are weighted approximately equal, indicating complementary between these two feature types. Regions that contributed the most to classification are in line with those reported in the previous studies, particularly the subcortical structures that are highly associated with human emotional modulation and memory formation. The autistic brains demonstrate a significant rightward asymmetry pattern particularly in the auditory language areas. These findings are in agreement with the fact that ASD is a behavioral- and language-related neurodevelopmental disorder. By concurrent consideration of both regional and interregional features, the current work presents an effective means for better characterization of neurobiological underpinnings of ASD that facilitates its identification from typically developing children. Hum Brain Mapp 00:00–000, 2013. © 2013 Wiley Periodicals, Inc.

Key words: autism spectrum disorders (ASD); magnetic resonance imaging (MRI); regional features; interregional features; multiple-kernel learning (MKL); limbic system; rightward asymmetry

INTRODUCTION

Autism spectrum disorder (ASD) is a highly heterogeneous, behaviorally defined neurodevelopmental disorder with multiple causes and courses. It is associated with several comorbid disorders, including intellectual impairment, seizures, and anxiety [Amaral et al., 2008; Ecker et al., 2010a]. Based on the latest report released by the Centers for Disease Control and Prevention, it is estimated that 1 in 88 American children was affected by some forms of ASD, a 78% increase compared to a decade ago, with boys outnumbering girls by a ratio of 5:1 [Centers for Disease
Control and Prevention, 2012]. Although most obvious signs and symptoms of ASD tend to emerge in the first 3 years of life, most children are only diagnosed between ages 4 and 5, when the brain is more mature with less plasticity. Some children with ASD may become depressed or experience behavioral problems during adolescence. People with ASD usually require continued services and supports as they get older, although many of them are able to work and live independently or within a supportive environment.

ASD is characterized, in varying degrees, by difficulties in: (1) verbal and nonverbal communication, (2) social interaction, and (3) repetitive and ritualized behaviors [Gillberg, 1993; Kanner, 1943; Wing, 1997]. Since the behavioral phenotype of ASD is well known, the diagnosis of ASD to date relies entirely on the history, symptoms, and signs of the disorder. Even the latest diagnostic instruments that are proposed in the new editions of the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatry Association [American Psychiatric Association, 2013] and the International Classification of Diseases (ICD-11) of the World Health Organization [Lord and Jones, 2013] and the International Classification of Diseases (ICD-11) are also solely behavioral based. The etiology and pathogenesis of ASD remain elusive, although some brain regions and neural systems have been suggested to be associated with the disorder [Amaral et al., 2008; Toal et al., 2005]. An important drawback of solely behavioral-based diagnostic tools is that many of these behavioral phenotypes are associated with numerous other psychological and psychiatric disorders [Geschwind and Levitt, 2007; Guilmare et al., 2009], such as Fragile X syndrome (which causes mental retardation), tuberous sclerosis, epileptic seizures, Tourette syndrome, learning disabilities, and attention deficit disorder. It has been reported that about 20–30% of children with ASD will develop epilepsy by the time they reach adulthood [Centers for Disease Control and Prevention, 2012]. Moreover, retrospective accounts of past symptoms rely heavily on an informant being both reliable and available [Ecker et al., 2010b]. In addition, problems arise from the fact that some adults being able to modulate symptoms via copying strategies developed over their life spans [Ecker et al., 2010b; Person, 2000]. Therefore, it is assumed that combining biological information with behavioral measurements can provide additional objectivity for ASD diagnosis.

Although group comparisons using whole-brain mass-univariate analyses, such as voxel-based morphometry (VBM), predominantly point toward anomalies in the frontal and parietal lobes, the limbic system, the basal ganglia and the cerebellum [McAlonan et al., 2005; Rojas et al., 2006; Waiter et al., 2004], there are currently no clinical biomarkers for the ASD diagnosis, or for the prediction of treatment response [Anderson et al., 2011; Calderoni et al., 2012; Ecker et al., 2010a,b; Uddin et al., 2011]. Despite its exploratory power, whole brain mass-univariate analysis has only moderate statistical power due to the need for multiple comparison corrections in limiting false positives. More important, VBM-type approaches are unable to provide subject-specific information that is crucial for personalized diagnosis.

Machine learning-based techniques have recently been applied to train classifiers, such as support vector machines (SVM), which can reliably distinguish different clinical groups at an individual subject level. These techniques have been successfully applied to classify various diseases, including mild cognitive impairment [Wee et al., 2011, 2012a,b, in press], Alzheimer’s disease [Davatzikos et al., 2008; Kloppel et al., 2008; Magnin et al., 2008; Zhang et al., 2011], Parkinson disease [Haller et al., in press; Pan et al., 2012], depressive illness [Costafreda et al., 2009; Gong et al., 2011], psychosis [Koutsouleris et al., 2009], etc. Of the different imaging modalities used, structural magnetic resonance imaging (MRI) is the most commonly used due to its faster acquisition speed. Because of its ability to detect the anatomical brain abnormalities, structural MRI is a viable alternative for objective ASD diagnosis. Besides using MRI, other neuroimaging techniques such as diffusion tensor imaging (DTI) [Ingatlhalikar et al., 2011; Lange et al., 2010], and electrophysiology techniques such as electroencephalogram (EEG) [Ahmadlou et al., 2012; Bosl et al., 2011; Duffy and Als, 2012] and magnetoencephalography (MEG) [Tsiaras et al., 2011] have been utilized for ASD identification with relatively high diagnosis accuracies. A multimodal classifier, fusing information from DTI and MEG, has also been shown to achieve better performance when compared with using any single modality [Ingatlhalikar et al., 2012].

In this study, we investigate the effectiveness of neuroanatomical information derived from T1-weighted structural MRI scans for ASD classification. Features that are extracted from the T1-weighted images for ASD classification include both the regional and interregional (correlational) features derived from cortical and subcortical regions-of-interest (ROIs). The inclusion of interregional features in addition to the commonly used regional features allows us to take into account the coherence of interregional structural changes for greater sensitivity to the pathologies that are associated with the disorder. We hypothesize that these two types of information are complementary to each other and their integration is better in revealing neuropathological underpinnings of disorder, which helps in facilitating the diagnosis accuracy and efficacy. In order for a more appropriate integration of information, we utilize a multi-kernel learning (MKL) strategy to determine the optimal proportion between two different feature types. A hybrid feature selection approach is utilized to reduce feature dimension and also to select the combination of pertinent features that are most favorable to ASD diagnosis.

The rest of the article is organized as follows: Section Method and Materials provides information on the image dataset, and postprocessing pipeline. This is followed by a description on how the regional and interregional features are extracted and fused via multi-kernel learning.
technique for better classification performance. The proposed ASD classification framework is then evaluated in Section Experimental Results. Interesting findings and their relationships with neurobiological underpinnings of ASD are discussed extensively in Section Discussion. Section Conclusion concludes this article.

### METHOD AND MATERIALS

#### Subjects Characterization and Diagnosis

In this study, MRI scans of 58 ASD patients with different degrees of illness were analyzed with respect to 59 healthy normal controls. The patient data were obtained from the National Database for Autism Research (NDAR), a National Institutes of Health (NIH) funded research data repository that is dedicated to facilitate collaboration across laboratories to help accelerate scientific discovery in autism research. The NDAR consists of various imaging modalities, including T1- and T2-weighted, functional MRI, diffusion tensor imaging, and spectroscopy. The age- and gender-matched healthy subjects were obtained from the Pediatric MRI Data Repository, an NIH archive that aims to foster better understanding of normal brain maturation as a basis for understanding atypical brain development associated with various disorders and diseases. Note that both repositories archive data that were acquired using different scanning protocols and scanners from multiple centers.

Table I provides the demographic and clinical information of all the participants. Note that, even for the same center, the parameter values used were not exactly the same. Table II provides example of scanning parameters of multiple centers for the ASD patients included in this study.

#### Overview of Methodology

Schematic diagram of the proposed ASD classification framework is graphically shown in Figure 1. In this framework, cortical related morphological information was extracted from the MR volume of every subject based on the Desikan–Killiany Cortical Atlas [Desikan et al., 2006], which contains 68 gyral-based ROIs, 34 for each hemisphere. An additional subcortical structural atlas [Fischl et al., 2002] was used to extract subcortical related morphological information. This subcortical structural atlas contains 37 ROIs, however, only left and right thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens areas were included in this study. The morphological information of subcortical structures is included in this study because they have shown significant between-group differences in ASD analyses [Herbert et al., 2003; Qiu et al., 2010]. Essentially, the morphological features extracted from the MR volume can be divided into two categories: (1) **regional features** consisting of regional mean cortical thickness, cerebral cortical GM and cortical associated WM, and subcortical structure volumes; and (2) **interregional (correlative) features** that are derived via constructing a similarity map that signifies the morphological change patterns across different brain regions. A hybrid feature selection method was applied to select the most discriminative features from the regional and interregional features separately. Individual kernel matrices were constructed from the selected optimal features of each feature type before they were integrated to form a single mixed-kernel matrix via multi-kernel SVM. The constructed mixed-kernel matrix was used to train SVM classifier, which can then be used to determine the class to which each new test subject belongs.

#### Regional Morphological Features

Regional morphological features, i.e., regional mean cortical thickness, cerebral cortical GM, cortical associated WM, and subcortical structure volumes, were extracted in an automated manner using the Freesurfer software suite (http://surfer.nmr.mgh.harvard.edu/, version 4.5.0) on servers with Red Hat Enterprise Linux version 5.7. Free- surfer is effective in performing volumetric segmentation
and cortical surface reconstruction [Desikan et al., 2006; Fischl and Dale, 2000; Fischl et al., 2002, 1999a,b]. Both intensity and continuity information from the entire three dimensional MR volumes are used in the segmentation and deformation procedures to produce representations of cortical thickness [Dale et al., 1999; Fischl et al., 1999a]. Cortical thickness measurement of this package has been thoroughly validated against histological analysis [Rosas et al., 2002] and manual measurements [Kuperberg et al., 2003; Salat et al., 2004], and demonstrated a good test-retest reliability across different scanners and field strengths [Dickerson et al., 2008; Han et al., 2006]. The regional mean cortical thickness feature for each ROI, defined in the Desikan–Killiany cortical atlas [Desikan et al., 2006], was normalized with respect to the standard deviation.

The cerebral cortical GM and cortical associated WM volumes were extracted using the same cortical atlas. Volumes of seven subcortical structures, i.e., thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens areas, were extracted from both hemispheres based on the ROIs defined in the subcortical structural atlas [Fischl et al., 2002]. The cortical and subcortical volumes of each subject were normalized with respect to the intracranial volume to minimize the effects of intersubject variation [Whitwell et al., 2001].

### Interregional Morphological Features

Connection abnormalities have been suggested to be associated with a wide range of neurological and psychiatric brain disorders, e.g., Alzheimer’s disease, Parkinson disease, and schizophrenia. Brain communication efficiency and capacity are affected in a different manner in each disease [Bosboom et al., 2009; He et al., 2008; Lynall et al., 2010; Stam et al., 2007; van den Heuvel et al., 2010; Zalesky et al., 2011]. A study based on FDG-PET imaging suggested that the brain of ASD children is damaged in a large-scale network level, in addition to abnormality in isolated regions [Lee et al., 2011]. In view of this, we hypothesize that interregional morphological information, which conveys higher order information of disease pathology, can be integrated with regional information to improve the diagnosis accuracy of ASD.

In this study, interregional features were computed between pairs of ROIs using their mean cortical thickness. A 68 × 68 correlative matrix map was constructed with every element representing the relative change pattern of regional mean cortical thicknesses between a pair of ROIs. The constructed correlative map is symmetric with ones along its diagonal. Because of this symmetrical property, only the upper triangular of the correlative map was used. For each subject, all elements of the upper triangular part of the correlative map were concatenated to form a long feature vector. Details of extracting the interregional features can be found in Wee et al. [in press].

### Feature Selection

Neuroimage classification using high-dimensional data is a challenging task. Because of the possible presence of irrelevant or redundant features, learning models tend to overfit data and become less generalizable. Feature selection is a critical step in reducing dimensionality while preserving discriminative information. The selection of relevant features is essential for improving the performance of the classification model. In this study, feature selection was performed using a combination of filtering and wrapper methods. Filtering methods assess the relevance of features independently of the classifier, while wrapper methods incorporate the classifier into the selection process. This hybrid approach allows for a more efficient and effective feature selection, ultimately leading to improved classification accuracy.
selection is commonly used to identify relevant features for dimensionality reduction and improving generalization performance [Guyon and Elisseeff, 2003; Liu and Yu, 2005]. Since two feature types both with high dimensionality are included in the proposed framework, we utilized a hybrid feature selection method, which combines filter- and wrapper-based approaches, to identify the most relevant features for ASD classification. Two filter-based methods were initially used to reduce the number of features based on the general characteristics of data. Specifically, in the first filter-based feature selection method, only features that differ significantly between ASD patients and healthy controls, measured using $t$-tests, were retained. Then, the second filter-based feature selection method, regarded as minimum redundancy and maximum relevance (mRMR) [Ding and Peng, 2005; Peng et al., 2005], was applied to further reduce the feature dimensionality by minimizing their intercorrelation. The mRMR model provides a balance between two aspects of feature selection: (1) efficiency that ensures the data characteristics

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**Figure 1.**
Schematic overview of the proposed ASD classification framework using multi-kernel SVM with features derived from T1-weighted MRI images. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
can be represented with a minimal number of features, and (2) broadness that ensures the selected feature subset can maximally represent the original space covered by the entire dataset. Specifically, mRMR minimizes the total relevance of each feature–feature pairs to achieve minimum redundancy condition, while simultaneously maximizes the total relevance of each feature–class pairs to achieve maximum relevance condition. Finally, support vector machine based recursive feature elimination (SVM-RFE) [Guyon et al., 2004; Rakotomamonjy, 2003], an effective wrapper-based model, was utilized to determine a subset of features that optimizes the performance of the SVM classifier. The basic principle of SVM-RFE is to remove features to make the classification error smallest. Note that hybrid feature selection was performed separately on each feature type (i.e., regional and interregional features) as shown in Figure 1.

Features Integration

To provide a more comprehensive way of characterizing the whole feature space, we utilized an MKL-based approach to combine the selected regional and interregional features with appropriate weighting. This approach enables the utilization of different types of kernels or feature types concurrently in one single classifier instance. Specifically, in this study a kernel matrix was first constructed for each individual feature type based on radial basic function (RBF) before they were integrated via a multi-kernel SVM to form a mixed-kernel matrix with appropriate weighting factor, \( \beta_m \geq 0 \) [Wee et al., 2012b]. The optimal SVM model and unbiased estimation of the generalization performance were obtained via a nested crossvalidation scheme.

Statistical Measures and Performance Evaluation

In addition to classification accuracy (ACC) and area under receiver operating characteristic curve (AUC), other statistical measures were also been adopted to evaluate the diagnostic power of compared methods more comprehensively, including Balanced ACCuracy (BAC), Youden’s index (Y), and F-score (F) [Sokolova et al., 2006; Wee et al., 2012b]. F-score provides a composite measure that favors algorithms with higher sensitivity while challenges those with higher specificity. Youden’s index evaluates the ability of an algorithm to avoid failure by equally weighting its performance on positive and negative samples.

In order to provide a more conservative evaluation on classification performance, a twofold crossvalidation was adopted in our study to access the discriminative power of each compared method. Specifically, at the beginning of experiment, the whole dataset was randomly partitioned into two sets, one for training and one for testing, with similar number of subjects from each class in each set. The training set was used to construct the optimal SVM model based on the nested crossvalidation approach. Then, the constructed optimal SVM model was used to identify the ASD patients from healthy controls from the testing set. The same training and testing procedures were repeated by swapping the training and testing sets. The crossvalidation classification performance was determined by averaging the statistical measures over the twofold. This procedure was repeated for 100 times to obtain the final mean classification performance. The superiority of the proposed method with respect to other compared methods was evaluated via a paired t-test on the mean classification accuracy over these 100 repetitions.

EXPERIMENTAL RESULTS

ASD Classification Performance

ASD classification was performed using different feature types, i.e., regional mean cortical thickness, cortical GM volume, cortical associated WM volume, combination of GM and WM volumes, subcortical volume, correlative morphological feature, and the proposed integrated morphological feature. The combined GM and WM volumes were constructed by concatenating the cortical GM and cortical associated WM volumes into a long feature vector. We included all the subjects listed in Table I by combining all the ASD subgroups into a bigger patient group. The mean classification performance of all compared feature types over 100 repetitions, as well as the \( P \) values obtained from the paired t-test on ACC, were provided in Table III. The boxplot of ACC for all compared feature types are provided in Figure 2.

The WM volume performed the worst among all the compared feature types in ASD classification. For the case of regional mean cortical thickness, the mean classification performance was improved significantly when the interregional information was extracted and used for classification. The interregional features performed similarly with the combination of GM and WM volumes. It is interesting to know that the subcortical volume performed significantly better than any other feature type alone with a relatively high mean accuracy of 94.4%. The proposed method, which integrates the regional and interregional features with appropriate weight, performed the best in ASD classification with 96.3% mean accuracy. The improvement over all other methods is significant (\( P < 0.0001 \)), indicating the superiority of the proposed method in better characterizing the brain structural anomalies in ASD patients. Furthermore, the proposed approach shows much higher mean AUC value of 0.9952 than any other individual feature types. Also, the proposed approach always exhibits much better prediction on patients and healthy individuals as reflected by its significantly higher sensitivity and specificity values compared with other approaches.

Effect of Weighting Factor, \( \beta_m \)

The weighting factor, \( \beta_m \), determines the contribution of each feature type in the proposed integrated classification
Diagnosis of ASD Using Morphological Features

The most discriminative regions that were selected using the proposed classification framework for identifying the ASD patients from healthy controls are reported. The top 15 selected regional and interregional morphological features are listed in Table IV. It is found that the selected regional features include features from the regional mean cortical thickness, the regional cortical GM volume, the cortical associated WM volume, and the regional mean subcortical volume, indicating existence of complementary information between different regional morphological feature types. It is also observed that the selected features are from both brain hemispheres and all four lobes, indicating the spread of morphological abnormalities over whole brain in ASD patients. Based on these selected features,
the regions that contribute for accurate ASD classification include the subcortical structures (bilateral putamen, bilateral accumbens, right hippocampus, right caudate, and right amygdala), GM regions (bilateral parahippocampal, left precentral gyrus, right supramarginal gyrus, and left lateral occipital gyrus), cortical thickness (left caudal middle frontal gyrus, and right paracentral gyrus), and WM region (right rostral anterior cingulate gyrus). It is interesting to know that most of the selected regional features are the subcortical structures and GM regions, indicating more significant morphological anomalies of the subcortical structures and GM regions than other regions in the autistic brains. Figure 4 illustrates the selected regional features after projecting them onto the cortical surface.

Figure 5 graphically shows the connectogram, generated using a circular representation tool called Circos (www.cpan.org/ports) [Krzywinski et al., 2009], of the most selected interregional features after filtering out some

Table IV. Top 15 most discriminative regional and correlative features that were selected using the proposed classification framework

<table>
<thead>
<tr>
<th>No.</th>
<th>Region-based features</th>
<th>Freq</th>
<th>Correlation-based features</th>
<th>Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Putamen_L</td>
<td>200</td>
<td>CaudalMiddleFrontal_R-InferiorTemporal_R</td>
<td>194</td>
</tr>
<tr>
<td>2</td>
<td>Accumbens_R</td>
<td>200</td>
<td>Paracentral_L-SuperiorFrontal_R</td>
<td>186</td>
</tr>
<tr>
<td>3</td>
<td>Accumbens_L</td>
<td>197</td>
<td>CaudalMiddleFrontal_L-Precentral_L</td>
<td>143</td>
</tr>
<tr>
<td>4</td>
<td>Parahippocampal_R_G</td>
<td>180</td>
<td>Precentral_L-SuperiorFrontal_R</td>
<td>138</td>
</tr>
<tr>
<td>5</td>
<td>Precentral_L_G</td>
<td>164</td>
<td>Fusiform_R-RostralMiddleFrontal_R</td>
<td>137</td>
</tr>
<tr>
<td>6</td>
<td>Hippocampus_R</td>
<td>153</td>
<td>Lingual_R-RostralMiddleFrontal_R</td>
<td>116</td>
</tr>
<tr>
<td>7</td>
<td>Amygdala_R</td>
<td>108</td>
<td>Cuneus_R-RostralMiddleFrontal_R</td>
<td>111</td>
</tr>
<tr>
<td>8</td>
<td>Caudate_R</td>
<td>107</td>
<td>SuperiorFrontal_L-Paracentral_R</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>Parahippocampal_L_G</td>
<td>105</td>
<td>Postcentral_R-RostralMiddleFrontal_R</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>Supramarginal_L_G</td>
<td>102</td>
<td>Precentral_R-SuperiorFrontal_R</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>CaudalMiddleFrontal_L_T</td>
<td>99</td>
<td>MiddleTemporal_L-Fusiform_R</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>Paracentral_R_T</td>
<td>94</td>
<td>Paracentral_L-ParsOpercularis_R (Inferior Frontal Gyrus)</td>
<td>54</td>
</tr>
<tr>
<td>13</td>
<td>Putamen_R</td>
<td>82</td>
<td>CaudalMiddleFrontal_R-Paracentral_R</td>
<td>53</td>
</tr>
<tr>
<td>14</td>
<td>LateralOccipital_L_G</td>
<td>76</td>
<td>Paracentral_R-SuperiorFrontal_R</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>RostralAnteriorCingulate_R_W</td>
<td>72</td>
<td>Postcentral_R-RostralMiddleFrontal_R</td>
<td>50</td>
</tr>
</tbody>
</table>

L = left hemisphere; R = right hemisphere; G = GM; W = WM; T = cortical thickness; Freq = selected frequency over 100 repetitions of twofold crossvalidation.
connections that are with low selection frequency. It can be clearly observed that pairs of regions (links in the connectogram) that contributed for accurate ASD classification are not only restricted within the same hemisphere or same lobe, but across all hemispheres and lobes, particularly between the left and right frontal lobes, right frontal and left parietal lobes, right and left temporal lobes, right frontal and right temporal lobes, right frontal and right occipital lobes, and right frontal and right parietal lobes. It is interesting to observe that most of the selected interregional features are within the right hemisphere of the brain, as indicated by thicker and more frequent links connecting between regions located in the right hemisphere as shown in Figure 5. In addition, most of the within lobe interregional features connect regions located in the bilateral frontal lobes. It can also be observed that some of the regions associated with the selected interregional features are same as those associated with the selected regional features.

**DISCUSSION**

Neuroimaging-based ASD classification frameworks proposed recently were essentially based on either volumetric information [Akshoomoff et al., 2004; Uddin et al., 2011], cortical surface information [Ecker et al., 2010a,b] or functional connectivity of GM region [Anderson et al., 2011]. The highest ASD classification accuracy achieved using these frameworks are slightly greater than 90%, but with relatively low sensitivity and/or specificity values. Furthermore, the datasets used in these studies are relatively small, with the total number of ASD patients and healthy subjects slightly more than 60. These datasets were also acquired in relatively well-controlled conditions, using the same scanner with the same acquisition protocols.

In the present study, the proposed method extracts, in addition to regional information, interregional (or correlative) morphological information [Wee et al., in press], and

![Figure 4.](image1.png)

The most discriminative regional features projected onto the cortical surface. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

![Figure 5.](image2.png)

Connectogram of the most discriminative connections selected from the correlative features. Red color lines are intrahemispheric links, and gray color lines are interhemispheric links. Thickness of each line reflects its selection frequency, e.g., a thicker line indicates a higher selection frequency. For the abbreviations of the regions, please refer to Table V. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
most of the individual regional features in discriminating yield performance that is comparable or even better than our study, it was found that this feature extraction method regional morphological change patterns of entire brain. In the brain anomaly caused by diseases through the interregional underpinnings of ASD. This approach addresses might convey information that is associated with neurobiology, 2011, and the relative changes between pairs of ROIs areas, but widely spread over the whole brain [Lee et al., 2011], and the relative changes between pairs of ROIs might convey information that is associated with neurobiological underpinnings of ASD. This approach addresses the brain anomaly caused by diseases through the interregional morphological change patterns of entire brain. In our study, it was found that this feature extraction method yield performance that is comparable or even better than most of the individual regional features in discriminating ASD patients from healthy controls, except the subcortical structure volume. To fully utilize information conveyed by different feature types and hence further enhance the classification performance, we suggested to fusing both the regional and interregional features with appropriate weights via multi-kernel learning technique. Promising classification results were obtained using the proposed fused (or integrated) regional and interregional features on the NDAR dataset: ACC = 96.27%, AUC = 0.9952, SEN = 0.9553, and SPE = 0.9700. Almost perfect AUC value was achieved, indicating excellent diagnostic power and generalizability of the proposed framework to future unseen subjects.

To determine whether site protocol variance or individual variance drives classification errors, we have performed three additional experiments: (1) classification using samples from each site individually; (2) classification between ASD samples of two largest sites; and (3) permutation test by perturbing the clinical label of the samples. The proposed method performs similarly when the classification is performed on the samples from each site separately. Specifically, the classification accuracies for the NYSPI and NYUSM sites are 86.0% and 84.0%, respectively. For the experiment to distinguish ASD samples from NYPsi and from NYUSM, a near-random performance with accuracy of 66.8% is achieved, indicating the nondifferentiability of ASD samples from these two sites. Finally, in the permutation test, the proposed framework is statistically significant in the context of discriminative analysis compared with random classifiers at the 1% significance level, computing using 10,000 repetitions.

The integration of regional and interregional morphological features provided the best classification results when the weighting factor between two feature types is within the range (0.30 ≤ βm ≤ 0.65), suggesting that the interregional features convey additional and complementary ASD-related information to the regional features. High and consistent classification performance over this wide weighting factor range demonstrates that the proposed approach is relatively robust with respect to the parameter that determines the contribution of each feature type. This also implies that the difficulty of determining the most appropriate weighting factor for fusing the regional and interregional features in our proposed approach can somewhat be reduced.

High accuracy predictive classification, as reported in this study, is important from the clinical perspective, as ASD is still regarded by many as a functional mental disorder, lacking a robust neurological or structural basis. This view persists despite many reports of differences in brain structure at a group level between autistic and normal brains. However, group level differences provide little useful information for individual patients and there has, furthermore, been marked heterogeneity of reported group level abnormalities [Amaral et al., 2008; Lainhart, 2006; Salmond et al., 2007; Toal et al., 2005]. Consequently, these findings have had limited impact on

<table>
<thead>
<tr>
<th>Index</th>
<th>Region</th>
<th>Abbrev.</th>
</tr>
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<tbody>
<tr>
<td>1, 35</td>
<td>Superior frontal gyrus</td>
<td>SFG</td>
</tr>
<tr>
<td>2, 36</td>
<td>Caudal middle frontal gyrus</td>
<td>CMFG</td>
</tr>
<tr>
<td>3, 37</td>
<td>Rostral middle frontal gyrus</td>
<td>RMFG</td>
</tr>
<tr>
<td>4, 38</td>
<td>Paras orbitalis gyrus</td>
<td>PORB</td>
</tr>
<tr>
<td>5, 39</td>
<td>Pars opercularis gyrus</td>
<td>POPE</td>
</tr>
<tr>
<td>6, 40</td>
<td>Pars triangularis gyrus</td>
<td>PTRI</td>
</tr>
<tr>
<td>7, 41</td>
<td>Lateral orbitofrontal cortex</td>
<td>LOF</td>
</tr>
<tr>
<td>8, 42</td>
<td>Medial orbitofrontal cortex</td>
<td>MOF</td>
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<tr>
<td>9, 43</td>
<td>Frontal pole</td>
<td>FP</td>
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<td>10, 44</td>
<td>Precentral gyrus</td>
<td>PREC</td>
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<tr>
<td>11, 45</td>
<td>Paracentral lobule</td>
<td>PARC</td>
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clinical practice. Development of a high accuracy predictive classification framework that can identify ASD patients from healthy controls, with results replicable across scanners and subjects, is therefore a significant advance.

The brain regions that are associated with the ASD pathology have already been extensively reported in previous studies, either based on between-group comparison [Hardan et al., 2006; McAlonan et al., 2005; Nordahl et al., 2007; Redcay and Courchesne, 2008] or individual-level classification [Akshoomoff et al., 2004; Anderson et al., 2011; Ecker et al., 2010a,b]. Regions, which are associated with the selected regional features, are spread over the whole brain, not restricted to particular brain hemispheres or lobes. These regions have been widely reported in the literature to be associated with ASD, including bilateral putamen [Haznedar et al., 2006; Langen et al., 2009; Qiu et al., 2010; Toal et al., 2009], bilateral accumbens [Dichter et al., 2012; Langen et al., 2009], right hippocampus [Aylward et al., 1999; Baron-Cohen, 2004; Sparks et al., 2002], right caudate [Langen et al., 2007, 2009; Qiu et al., 2010; Sears et al., 1999], right amygdala [Ashwin et al., 2007; Aylward et al., 1999; Baron-Cohen, 2004; Baron-Cohen et al., 2000; Sparks et al., 2002], bilateral parahippocampal [Ecker et al., 2010a; Toal et al., 2009], left precentral gyrus [Cauda et al., 2011; Rojas et al., 2006; Scheel et al., 2011; Toal et al., 2009], right supramarginal gyrus [Bolling et al., 2011; Brieber et al., 2007], left lateral occipital gyrus [Ecker et al., 2010a; Greene et al., 2011], left caudal middle frontal gyrus [Baron-Cohen, 2004; Rojas et al., 2006; Schmitz et al., 2008], right paracentral gyrus [Cheng et al., 2011; Scheel et al., 2011; Toal et al., 2009], and right rostral anterior cingulate gyrus [Ashwin et al., 2007; Cauda et al., 2011; Cheng et al., 2011; Toal et al., 2009].

Some of the regions that are associated with the selected interregional features have also been detected in the selected interregional features, including the left caudal middle frontal gyrus, right paracentral lobule, and left precentral gyrus. Regions that are associated only with the selected interregional features are: frontal lobe (i.e., right caudal middle frontal gyrus [Ecker et al., 2010a; Gomot et al., 2006; Turner et al., 2006], left paracentral lobule [Bolling et al., 2011; Hyde et al., 2010], bilateral superior frontal gyrus [Cheng et al., 2010; Hyde et al., 2010], right rostral middle frontal gyrus [Ecker et al., 2010b], right precentral gyrus [Ecker et al., 2010b; Hyde et al., 2010], and right pars opercularis [Dapretto et al., 2005; Nordahl et al., 2007; Yamasaki et al., 2010]), temporal lobe (temporal inferior temporal gyrus [Abell et al., 1999; Ecker et al., 2010a; Peterson et al., 2006], left middle temporal gyrus [Abell et al., 1999; Ecker et al., 2010a,b] and right fusiform gyrus [Ecker et al., 2010a,b; Hall et al., 2003; Hyde et al., 2010]), occipital lobe (right lingual gyrus [Cheng et al., 2011; Ecker et al., 2010b] and right cuneus cortex [Greene et al., 2011; Luders et al., 2012]), and parietal lobe (bilateral postcentral gyrus [Chen et al., 2010b; Hyde et al., 2010]). The fact that our findings are consistent with results reported in previous studies demonstrates the efficacy of our proposed framework also in identifying disease-related biomarkers for ASD classification. Furthermore, the morphological change patterns between region pairs together with the regional features provide crucial yet complementary information for better understanding of the neurobiological underpinnings of ASD.

It is interesting to observe that several components in the limbic system have been selected in the proposed framework as important features for ASD classification. The human limbic system is primarily responsible for regulating the human emotions as well as the formation of memories, indicating the capability of the proposed framework in reflecting the relationships between behavioral impairments and structural abnormalities. Amygdala, component of the limbic system that is located in the medial temporal lobe of the brain, is the brain area that concerns with the autonomic responses associated with fear, emotional responses, sexual arousal, and hormonal secretions [Amunts et al., 2006]. It has been strongly supported, particularly in functional neuroimaging analysis, that amygdala plays a critical role in emotional processing, without lateralization in terms of gender or valence [Sergerie et al., 2008]. Specifically, the amygdala parallelly involves implicit emotional learning and memory, emotional modulation of memory, emotional influences on attention and perception, emotion and social behavior, and emotion inhibition and regulation [Davis and Whalen, 2001; Phelps and LeDoux, 2005]. Based on a postmortem study, the dysfunction of amygdala, which may lead to changes in the aggressive and emotional behavior, might be explained by the significant reduced number of neurons in this area of the autistic brain when compared with age-matched typically developing children [Schulkin, 2007; Schumann and Amaral, 2006]. In addition, based on MRI studies the amygdala appears to undergo an abnormal pattern of development that includes early enlargement and a decreased number of neurons in adulthood [Schumann et al., 2004]. Impairment of the amygdala usually results in inappropriate behavioral and emotional reactions that eventually lead to physical harm to the patients and others. In fact, most of such patients need to be under supervised care and cannot function alone in society [Lee et al., 1988, 1995].

Other components of the human limbic system that were selected by the proposed framework include the cingulate gyrus, orbitofrontal cortex, nucleus accumbens, and parahippocampus. The developmental dysfunction of the orbitofrontal-amygdala circuit of the brain is a critical factor in the development of autism, particularly for persons with autism in socio-emotional cognition and behavioral self-regulation [Bachevalier and Loveland, 2006]. A review of cases with early prefrontal damage by [Eslinger et al., 2004] suggested that early injury to the orbitofrontal cortex is associated with intractable deficits in the regulation of emotions and social functioning. Developmental trajectories of the caudate nucleus, putamen, and nucleus
respect to gender. This demonstrates the robustness of our framework with patients, both from the mildly affected subgroup, are ratio as 3.5:1) was used in this study, only two female dataset with highly imbalance gender ratio (male to female patients decreases with the degree of illness. Although that the difficulty of identifying the mildly affected both subgroups. This finding is in agreement with the fact acrossvalidation, although the sample size is similar for ASD patients when they achieve adulthood. Since the age range of ASD subjects used in this study is between 4 and 26 years old, the proposed diagnosis framework has only been tested with subjects who are older than 4 years old. Because of the importance of early diagnosis, future research will be directed to extending the current framework to the diagnosis of children prior to 4 years of age.

The performance of the proposed ASD identification method is limited by the accuracy of the segmentation results given by Freesurfer. Several recent publications have indicated that segmentation by Freesurfer in subcortical regions is incorrect, particularly for deep structures such as amygdala [Khan et al., 2008; Klauschen et al., 2009; Morey et al., 2009, 2010; Zhong et al., 2010]. Subcortical segmentation errors may result in the inability to correctly capture the true biological differences between patient and control groups, and eventually influencing disease identification accuracy. Since precise measurement of biological differences is crucial for improving identification accuracy, we expect that the performance of the proposed method can be further improved by utilizing better segmentation algorithms in the future.

Artifacts caused by head motion can be a significant impediment to acquiring the in vivo MRI scans of the human brain. Motion artifacts adversely affect the ability to accurately characterize the size, shape, and tissue properties of brain structures [Brown et al., 2010; Kuperman et al., 2011]. This issue is particularly severe for pediatric patients who have difficulties remaining still in the scanner during data acquisition. We have visually inspected the quality of all MRI scans from both groups and found no significant motion artifact. We believe that the investigators who contributed to these archives have performed certain quality control procedures before uploading their datasets to the repositories.

**CONCLUSIONS**

In this article, a new classification framework has been proposed to differentiate ASD patients from healthy controls using regional and interregional morphological features derived from T1-weighted MRI scans. This framework fuses the regional and interregional (correlative) morphological features using multiple kernel learning for accurate classification of ASD, which is a highly heterogeneous neurodevelopmental disorder. Significant improvement in classification performance demonstrates the reliability and robustness of our proposed framework. Furthermore, the regions that were selected for accurate classification are similar to those reported in the previous ASD studies, particularly components in the human limbic...
system, demonstrating the capability of our framework also in determining the biologically meaningful and disease-associated biomarkers. Furthermore, the observed rightward asymmetry anatomically anomalies pattern, particularly in auditory language cortex, provides supportive evidence that the ASD is a neurodevelopmental disorder that is closely related to language problem. The promising results obtained demonstrate the effectiveness of integrating regional and interregional information for diagnosis of highly heterogeneous neurodevelopmental disorders such as ASD. While these findings in this study are intriguing, they are preliminary and require further study particularly using larger dataset.

**REFERENCES**


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