Feature Selection and Classification of Multi-Parametric Medical Images Using Bagging and SVM

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ABSTRACT

This paper presents a framework for brain classification based on multi-parametric medical images. This method takes advantage of multi-parametric imaging to provide a set of discriminative features for classifier construction by using a regional feature extraction method which takes into account joint correlations among different image parameters; in the experiments herein, MRI and PET images of the brain are used. Support vector machine classifiers are then trained based on the most discriminative features selected from the feature set. To facilitate robust classification and optimal selection of parameters involved in classification, in view of the well-known "curse of dimensionality", base classifiers are constructed in a bagging (bootstrap aggregating) framework for building an ensemble classifier and the classification parameters of these base classifiers are optimized by means of maximizing the area under the ROC (receiver operating characteristic) curve estimated from their prediction performance on left-out samples of bootstrap sampling. This classification system is tested on a sex classification problem, where it yields over 90% classification rates for unseen subjects. The proposed classification method is also compared with other commonly used classification algorithms, with favorable results. These results illustrate that the methods built upon information jointly extracted from multi-parametric images have the potential to perform individual classification with high sensitivity and specificity.

Keywords: feature extraction, bagging, SVM, classification and classifier design, multi-parametric imaging, MRI, PET

1. INTRODUCTION

Multi-parametric and multi-modality imaging techniques, such as structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), and positron emission tomography (PET), have been increasingly used in imaging studies to investigate various aspects of structure and function of the brain. Many neuroimaging studies have detected structure–function covariance in a variety of problems via examining brain images of multiple modalities using statistical analysis methods [1-12]. Jointly considering multi-parametric and multi-modality scans may improve the potential for classifying individuals with sufficiently high sensitivity and specificity, although it increases the classification challenge due to the increased dimensionality of the data.

In neuroimage classification studies, the typical input to classifiers is a feature set computed from regions of interest (ROIs), or from whole brain voxel-wise feature maps that might be either spatially normalized functional brain images, or high dimensional morphological measurements computed from the deformation fields that bring individual structural brain images into a template space [13-30]. Compared with features extracted from ROIs chosen based on *a priori* knowledge, the whole brain voxel-wise features measure localized brain alterations in unbiased (hypothesis free) paradigms and are generally applicable. When applying these methods to multi-parametric image studies where different modalities capture brain information complementarily, it is potentially advantageous to jointly consider multi-parametric images in feature extraction.

Support vector machine (SVM) classifiers have been widely used in neuroimaging studies, coupled with feature dimensionality reduction techniques, including principal component analysis (PCA) and feature selection techniques

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[13,14,16,17,19,24,25,28,29,31-36]. PCA is a traditional feature dimensionality reduction technique. However, the PCA features are not necessarily discriminative for classification and their performance is often limited in applications with small number of training samples, high feature dimensionality, and the assumptions that multivariate Gaussian distributions can represent the variation of multi-parametric medical images, which is typically not met in practice. Feature selection methods, which are fundamentally different from PCA in that they directly select features from the original feature set without any transformations or linearity assumptions, have been increasingly used and achieved promising performance in medical image classification studies [20,27,37].

A fundamental challenge that remains in this field is the small sample size problem. Feature extraction and selection, as well as parameter optimization, which are based on a limited training set, are likely to display poor generalization performance on new datasets. To address this challenge, we have used an SVM-based bagging framework for multi-parametric image classification. In particular, the correlations among images of different modalities are taken into account in feature extraction to adaptively capture discriminative regional features, from which the most discriminative ones are selected for SVM classification. Instead of training a single classifier from the training data, we train an ensemble of base classifiers, each derived from a different subset of the training data. The various parameters of the base classifiers are optimized by maximizing the area under the ROC curve (AUC), estimated from the average classification performance of these base classifiers on left-out training samples of bootstrap sampling. Finally, the base classifiers are combined using voting or averaging strategies to classify new (testing) samples. The proposed method is validated on a sex classification problem in an older adult sample, with simultaneous utilization of brain images of structural MRI and PET [^{15}O] water imaging of cerebral blood flow (CBF), and compared with PCA based classification methods.

The remainder of this paper is organized as follows. In Section 2, we detail the methodology. In Section 3, experimental results on sex classification are presented. Conclusion and discussions are provided in Section 4.

2. METHODOLOGY

A well-known problem in high-dimensional pattern classification, especially pronounced in classifications of 3D and 4D medical scans, has been the robust selection of image features that yield generalizable results. To address this fundamental problem, a classification framework is proposed, consisting of adaptive regional feature extraction, feature selection, SVM classification, and a bagging strategy for building an ensemble classifier.

2.1 Adaptive regional feature extraction from multi-parametric images

To facilitate unbiased, direct comparison among different subjects in multi-parametric neuroimage studies, all images of each individual are first spatially normalized onto a template image, and then morphological and functional measurements are computed from structural and functional brain images. The commonly used morphological measurements include deformation fields, Jacobian determinants, and tissue-density maps [38-44], while the spatially normalized functional images or contrast images are often directly used as functional measurements [14,17,45]. In this way, the multi-parametric images of each subject are represented by voxel-wise morphological and functional maps in the template space.

However, the direct utilization of voxel-wise features in classification, not only renders the classification challenging due to the high feature dimensionality, but also makes it sensitive to image registration error. So, it is advantageous to group voxels into clusters according to their group difference measurements. For this purpose, an adaptive regional feature extraction method was developed to extract volumetric features from brain regions exhibiting similar group differences detected by statistically examining the voxel-wise feature maps in the COMPARE algorithm [25,37]. Herein we extend that approach by treating the multi-parametric image data as an integrative image with vector-valued voxels corresponding to multi-parametric features, which capture the brain morphological and functional information jointly from the vector-valued images.

For jointly examining the multi-parametric images, two-sample Hotelling's T-square statistic of multidimensional feature vectors is used to measure group differences voxel-by-voxel [46]. In this paper, we use a modified Hotelling's T-square statistic to make the group difference measurements robust to group differences in the covariance matrices and the sample sizes [47]. Suppose that we have n training subjects, and each of them is associated with m feature maps $\{ I_j^i$, $i=1,\ldots,n,\ j=1,\ldots,m\}$ and one label $\{ L^i,\ i=1,\ldots,n\}$ which is +1 or -1, then the brain morphological and functional

information on voxel u for each subject is represented by an m-dimensional feature vector $f^i = \{I_j^i(u), j = 1, \cdots, m\}$. Denoting the training information as $f = \{f^i, i = 1, \cdots, n\}$, the modified T-square statistic is defined as

$$T^2(f) = (\mu_1 - \mu_2)'(\Sigma_1 / n_1 + \Sigma_2 / n_2)^{-1}(\mu_1 - \mu_2), \qquad (1)$$

where μ_k, k=1,2, are within-group sample mean vectors, Σ_k, k=1,2, are within-group covariance matrices, and n_k, k=1,2, are the number of samples in each group. This measurement is invariant to linear scale change in any dimension; therefore it can be directly utilized in a group difference test with multiple features. The multivariate nature of the measurement makes it sensitive not only to group difference detectable separately from each feature map, but also to group difference which can not be captured by the univariate measurement from feature maps separately.

The T-square statistical group difference map forms the basis for grouping voxels with similar behavior with respect to discrimination. The brain template space is then partitioned into different regions based on the similarity of the voxels' T-square statistic using a watershed segmentation method, as in the COMPARE approach [48]. The brain clusters (regions) of voxels with significant group difference might contain discriminative morphological and functional information for brain classification. To measure the brain morphological and functional information in each brain region, an m-dimensional feature vector whose elements are corresponding to the multiple feature maps is computed using a selective volume increment method, similar to forward feature selection [37]. In particular, the voxel with the highest T-square statistic within the region under consideration is selected as a starting point of a cluster. Then, its neighboring voxels enter the cluster one by one if the inclusion of a neighboring voxel does not decrease the T-square statistic calculated from the mean of voxels currently selected. This procedure is iterated, similarly to a traditional region growing method, until no more voxels can be added to the set of selected voxels.

2.2 Ranking based regional feature selection and SVM classification

The adaptive regional feature extraction method typically generates several hundred regional feature vectors, each of them with components corresponding to different modalities. Although these features can be directly used as input for SVM classification, features from brain regions not affected by the problem under study may degrade the classification performance since they are irrelevant for classification. To achieve effective and efficient classification, a small set of features has to be selected. To achieve feature selection in reasonable computation time, we adopted a ranking based feature selection method. In particular, we use the Hotelling's T square statistic (1) as a measure to evaluate the relevance of the regional feature vectors to classification. The number of top ranked feature vectors used in classification is to be determined to optimize the classification performance which could be estimated by cross-validation of classification on the training samples.

2.3. Bagging of multi-parametric neuroimage classifiers and automatic parameter selection

It is common that the available samples in imaging studies are limited, relative to the dimensionality of the acquired images, which has been a challenge to machine learning algorithms. The small sample is typically insufficient for identifying group differences that are stable to sample changes and generalize well in new samples. As a result, the features computed based on unstable group differences lead to "unstable" classification where small changes in the training set result in large changes in predictions [49], although SVM classifiers themselves are not "unstable". Moreover, it is rare to have extra training data for parameter selection using cross-validation. The stability of classification can be effectively improved by bagging (bootstrap aggregating) which determines an aggregated classifier by combining predictions from multiple versions of a classifier which are learned from bootstrap replicates of the training samples [49], whereas the left-out training data of bootstrap sampling can be used to evaluate the classification performance for selecting the classification parameters [50].

To generate multiple versions of the training set, a leave-one-out bootstrap replicate scheme is implemented in this paper due to the limited availability of training data, although other schemes can also be used. For a training set with n samples, n different bootstrap training sets are generated and each of them has n-1 samples. To build a classifier from each training set, denoted as the base classifier, the proposed feature extraction, feature selection, and SVM classification are applied.

Once the base classifiers are built within the bagging framework, an ensemble classifier can be constructed by combining the outputs of these base classifiers. In this paper, we test two schemes for combining these base classifiers: a)

averaging SVM scores and b) voting. Given the outputs of the base classifiers $s_i, i = 1, \cdots, n$, the averaging scheme yields a classification score

$$s = \frac{1}{n}\sum_{i=1}^{n} s_i \,, \qquad (2)$$

and voting scheme yields a classification score

$$s = 2\frac{card\{s_i, i = 1, \cdots, n \mid s_i > 0\}}{n} - 1. \qquad (3)$$

The flowchart of bagging classification is shown in Figure 1.

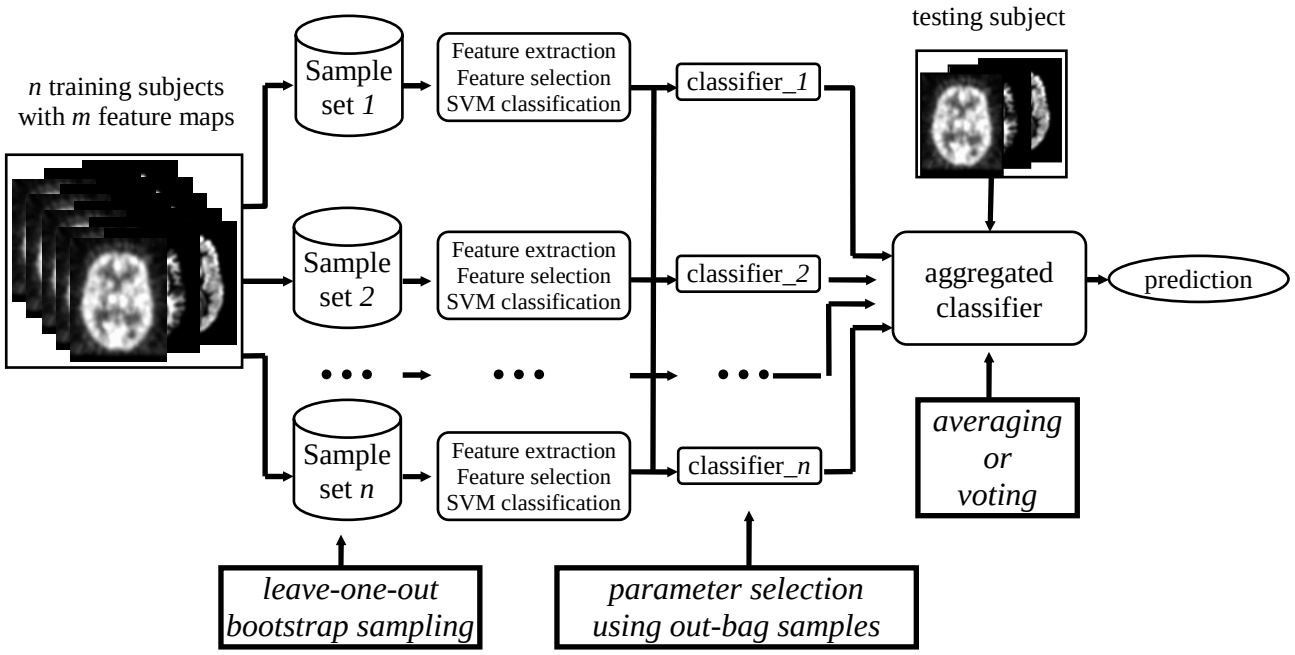

Figure 1. Flowchart of bagging classification.

3. RESULTS

The proposed method is applied to a sex classification problem, with simultaneous utilization of structural MRI and PET [^{15}O] water imaging of cerebral blood flow (CBF). MRI scans and PET images from 30 older individuals were obtained as part of the Baltimore Longitudinal Study of Aging neuroimaging substudy, including 15 males (mean age ± std. deviation 67.62±1.40) and 15 females (67.49±1.38).

MR acquisition procedures are detailed in [51]. MR scanning was performed on a GE Signa 1.5 Tesla scanner. MR images were obtained by using a high-resolution volumetric "spoiled grass" (SPGR) series (axial acquisition, TR = 35, TE = 5, flip angle = 45, FOV = 24, matrix = 256 x 256, NEX = 1, voxel dimensions of .94 X .94 X 1.5 mm slice thickness). Resting PET images of participants were acquired on a GE 4096+ scanner which provides 15 slices of 6.5mm thickness. During scanning, participants were instructed to keep their eyes open and focused on a computer screen covered by a black cloth. PET measures of regional cerebral blood flow were obtained using [^{15}O] water. Images were acquired for 60s from the time the total radioactivity counts in brain reached threshold level. A transmission scan acquired before the emission scans was used to perform attenuation correction.

The morphological representation of brain anatomy is computed by spatial normalization of the MRI scan for each subject to a template space within a mass-preserving shape transformation framework [41,52]. First, each skull-stripped MR brain image is segmented into three tissues, namely gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), by a brain tissue segmentation method proposed in [53]. Next, each tissue-segmented brain image is spatially normalized into a template space, using a high-dimensional image warping method, called HAMMER [52]. The total tissue mass is preserved in each region during the image warping, which is achieved by increasing the respective density when a region was compressed, and vice versa. With this procedure, three tissue density maps are generated in the template space, each reflecting local volumetric measurements corresponding to GM, WM, and ventricular CSF, respectively. These tissue density maps, which have been called RAVENS maps in [41], give a quantitative representation of the spatial distribution of tissues in a brain, with brightness being proportional to the amount of local tissue volume before warping. In order to account for variations in head size, RAVENS maps are normalized by total intra-cranial volume (ICV). Although head size might be a good feature for sex classification, here we focus on local sex differences in the brain to allow generalization to conditions characterized by local differences in brain morphology and function. By the same spatial transformation obtained above, the co-registered PET scan is spatially normalized to the same template. The intensities of PET scans are normalized using proportional scaling to adjust for global CBF. Finally, all the tissue density maps and PET images are smoothed by Gaussian filters of 8mm full-width at half-maximum (FWHM).

3.1 Discriminative analysis

To evaluate the discrimination ability of the proposed method, a leave-one-out cross-validation is performed. In each leave-one-out cross-validation experiment, one sample is first selected as a testing sample, and the remaining subjects are used for regional feature extraction, feature selection, and linear SVM classifier training. Then, the classification result on the testing subject predicted by the trained SVM classifier is compared with the ground-truth class label, to evaluate the classification performance. By repeatedly leaving each subject out as a testing subject, we obtained the average classification rate from 30 leave-one-out experiments. The classification rates as a function of the number of regions used in a linear SVM classification are shown in the left column of Figure 2, demonstrating over 95% classification rates of brain images of men versus women. The ROC curve of the classifier achieving the best average classification rate with the minimal number of features is shown in the right column of Figure 2, indicating good classification performance (AUC is close to 0.98).

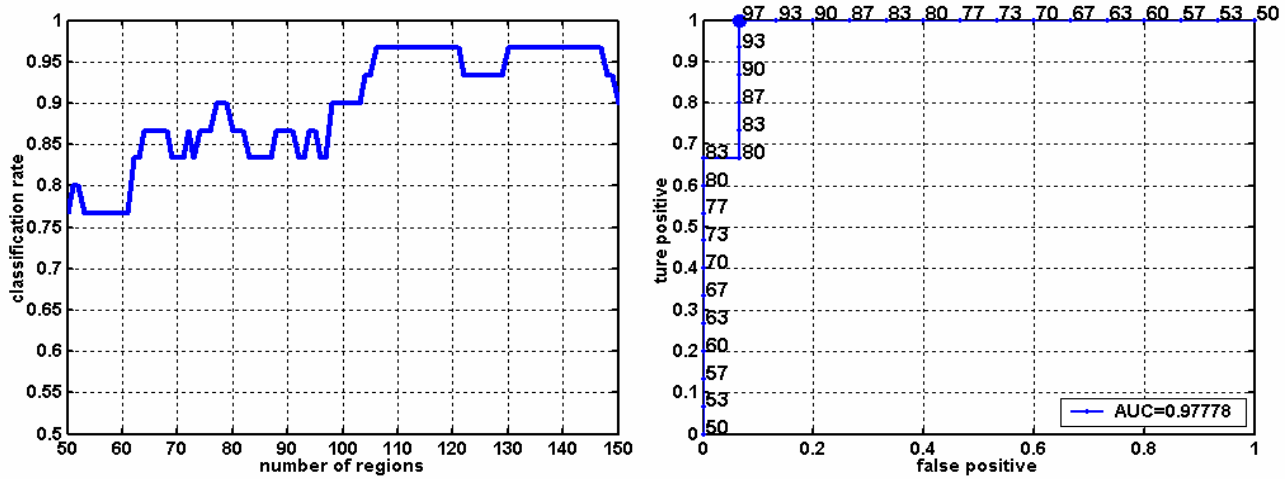

Figure 2. Left column: the classification rates as a function of the number of regions used in classification. Right column: ROC curve of the classifiers achieving the best classification performance with the minimal number of features. Numbers around the curves are the correct classification rates (%) corresponding to different sensitivities and specificities. The bold face point on the curve corresponds to the classification result with zero as the classification threshold. The area under the ROC is close to 0.98.

We compare the proposed method with a principal component analysis (PCA) based classification method [19] and our previous method, referred to as COMPARE, in which regional features were independently extracted from morphological and functional representations [37]. In the PCA method, morphological representations, or functional

representations, or both of them, are used to compute a PCA projection, respectively. Then the coefficients of principal components of respective feature maps or their combination are used to build linear SVM classifiers. Different numbers of top ranked coefficients based upon absolute value of Pearson correlation are tested to achieve the best classification rate in leave-one-out cross-validation. Similarly in COMPARE, regional features are extracted independently from morphological and functional maps by the feature extraction method of COMPARE, and are ranked separately within the morphological feature set, the functional feature set, and the pool of both feature sets using absolute value of Pearson correlation as the ranking criterion. The number of features used in classification to achieve the best linear SVM classification is determined by the same strategy used in the PCA method. In Table 1, the best leave-one-out cross-validation performances of these methods with different combinations of imaging modalities are summarized. Although promising performances are achieved by these methods, they are slightly worse than that achieved by the proposed multi-parametric classification method.

Table 1. Comparison on different feature extraction methods and different combinations of imaging modalities in brain classification.

Methods \ Modalities	MRI	PET	MRI/PET
PCA	86.7%	90.0%	86.7%
COMPARE	90.0%	90.0%	93.3%

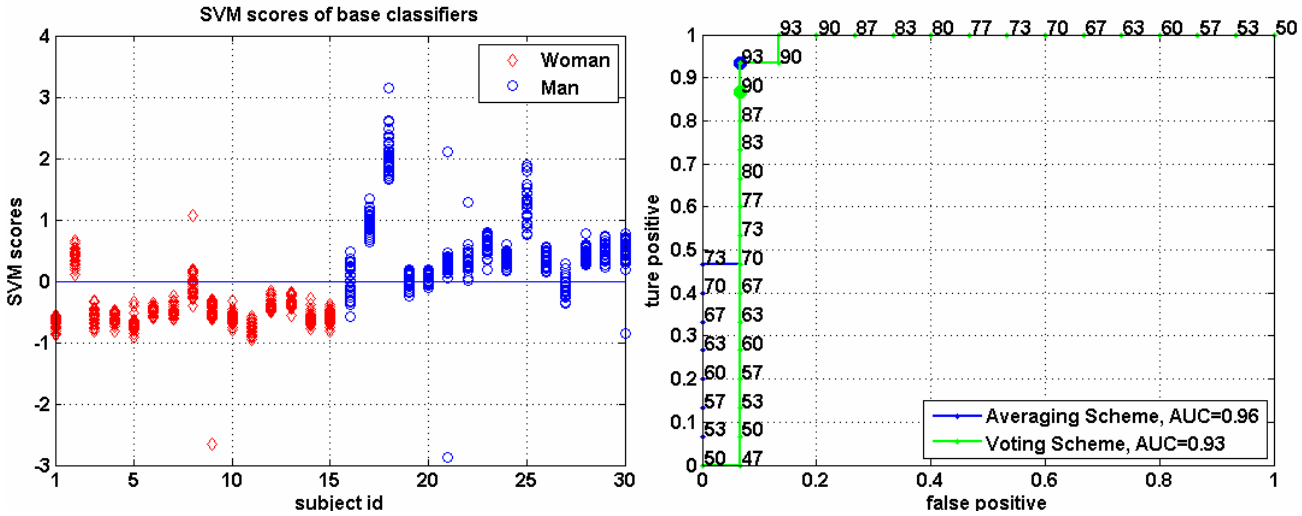

Figure 3. Left column: Distribution of SVM scores of testing samples predicted by base classifiers which constitute the ensemble classifiers. Right column: ROC curves of the averaging and voting schemes of the ensemble classifiers. Numbers around the curves are the correct classification rates (%) corresponding to different sensitivities and specificities. The bold face points on the curves correspond to the classification results with zero as the classification threshold.

3.2 Classification of unseen subjects

In above section of discriminative analysis, the proposed method demonstrates its potential to achieve good classification performance, however these classifiers might be not stable when applied to unseen subjects due to the small size of training dataset. To overcome this problem, ensemble classifiers can be built with base classifiers constructed by the proposed method. To evaluate the classification accuracy of the ensemble classifiers, a different leave-one-out cross-validation is implemented to test the generalizability of the ensemble classifiers. In each leave-one-out validation experiment, one subject is first selected as a testing subject, and the remaining subjects were used for building an ensemble classifier whose parameters are automatically optimized in the bagging framework. By repeatedly leaving each subject out as a testing subject, we obtain the average classification performance from 30 leave-one-out experiments. Each leave-one-out ensemble classifier consists of 29 base classifiers whose parameters are automatically

selected within the bagging framework. When applying the ensemble classifier to the sample excluded from the training set, we obtain 29 SVM scores. The performance of the ensemble classifier whose parameters are selected by means of optimizing the AUC is summarized in Figure 3. The ROC curves of the averaging and voting strategies of the ensemble classifiers indicate the classifiers achieve over 90% classification rates, which are more accurate estimates of the classification accuracy on new samples since the ensemble classifiers are built fully independent on the testing samples.

The performance of ensemble classifiers with base classifiers built upon the PCA based feature extraction is also evaluated in the same way. In this method, the absolute value of Pearson correlation based feature ranking is used to select the most discriminative PCA features, and the linear SVM is used to build base classifiers. The same classification parameter selection strategy by means of optimizing the AUC is used to find the optimal parameters for base classifiers. As summarized in Figure 4, the PCA based ensemble classifiers performs inferior to those built upon the proposed feature extraction and selection methods.

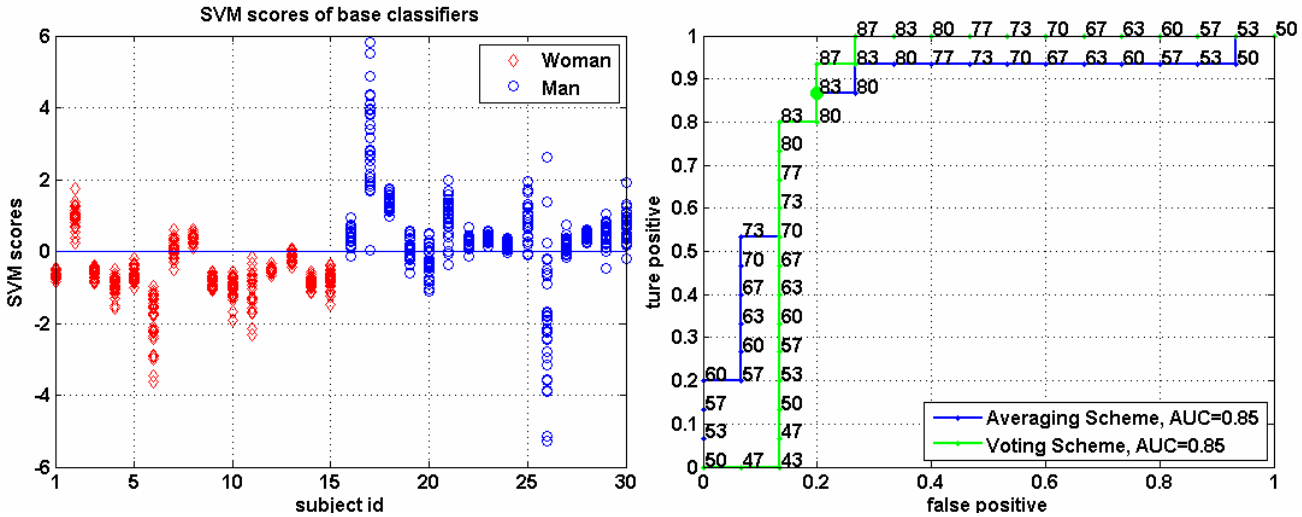

Figure 4. Left column: Distribution of SVM scores of testing samples predicted by PCA base classifiers which constitute the ensemble classifiers. Right column: ROC curves of the averaging and voting schemes of the ensemble classifiers. Numbers around the curves are the correct classification rates (%) corresponding to different sensitivities and specificities. The bold face points on the curves correspond to the classification results with zero as the classification threshold.

4. CONCLUSION

This paper presents a general framework for multi-parametric and multi-modality image based classification and evaluates the proposed approach in a study aiming to distinguish male from female brain images. Beyond considering multi-parametric images, the main contribution of this study is in the use of a bagging technique, aiming to overcome the relatively insufficient training due to limited training samples, relative to the image data dimensionality, a persistent problem in high-dimensional neuroimage classification. The bagging technique, proposed to improve performance of "unstable" classifiers [49], has been successfully adopted herein to overcome this problem. As Figure 2 and 3 showed, there is a great variance in the classification scores produced by individual base classifiers, which indicates the instability inherent to small sample size classification schemes applied to high-dimensionality data, and further speaks to the need for ensemble classifiers, as the one used herein. The bagging framework for building ensemble classifiers not only facilitates robust classification and good generalization performance, but also enables automatic parameter selection which has been often overlooked in neuroimaging classification studies.

In the current study, the base classifiers are built using the linear SVM techniques which is computational efficient and tends to generalize well. Nonlinear SVM might be able to further improve the classification performance of the ensemble classifier; however the increased complexity of the classification might hamper its generalization ability,

especially when the training sample size is small. Moreover, non-linear SVM has more parameters to be evaluated during bagging, which might render it prohibitively computationally expensive in our framework.

In conclusion, this study presents strong evidence that multi-parametric imaging coupled with advanced high-dimensional pattern classification and bagging methods can achieve promising classification of individuals into groups. Current and future work focuses on application of this methodology to a variety of clinical studies utilizing imaging as a biomarker for diagnosis, prognosis, and disease progression.

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