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Classification of Healthy Siblings of Bipolar Disorder Patients from Healthy Controls Using MRI

Ozkan Cigdem*, Refik Soyak†, Burhan Aydeniz†, Kaya Oguz‡,
Hasan Demirel§, Omer Kitis¶, Cagdas Eker‖, Ali Saffet Gonul‖, and Devrim Unay**
* Özhak Engineering Ltd. Co., Izmir, Turkey
†Department of Electrical and Electronics Engineering, Izmir University of Economics, Izmir, Turkey
‡Department of Computer Engineering, Izmir University of Economics, Izmir, Turkey
§Department of Electrical and Electronics Engineering, Eastern Mediterranean University, Famagusta, Via Mersin 10, Turkey
¶Department of Neuroradiology, SoCAT Lab and Affective Disorders, School of Medicine, Ege University, Izmir, Turkey
‖Department of Psychiatry, SoCAT Lab and Affective Disorders, School of Medicine, Ege University, Izmir, Turkey
**Department of Biomedical Engineering, Izmir University of Economics, Izmir, Turkey

***Abstract*—Three Dimensional magnetic resonance imaging (3D-MRI) has been utilized to classify patients with neuroanatomical abnormalities apart from healthy controls (HCs). The studies on the diagnosis of Bipolar Disorder (BD) focuses also on the unaffected relatives of BD patients in order to examine the heritable resistance factors associated with the disorder. Hence, the comparison of Healthy Siblings of Bipolar Disorder patients (HSBDs) and HCs is also required owing to the high heritability of BD. In this paper, the classification of 27HSBDs from 38HCs has been studied by using 3D-MRI and Computer-Aided Detection (CAD). The pre-processing of 3D-MRI data is performed by taking advantage of Voxel-Based Morphometry (VBM) and the structural deformations in the Gray Matter (GM) and White Matter (WM) are obtained by using a general linear model. The model is configured by using a two sample t-test technique and Total Intracranial Volume (TIV) as a covariate. The altered voxels between data groups are considered as Voxel of Interests (VOIs) and the 3D masks are generated for GM and WM tissue probability maps. The Relief-F algorithm is utilized to rank the features and a Fisher Criterion (FC) method is considered to determine the number of top-ranked discriminative features. The performances of Support Vector Machines (SVM) and the Naive Bayes (NB) algorithms are compared on the classification of HSBD and HC. The experiments are performed for GM-only, WM-only, and their combinations. The experimental results indicate that the changes between the brain regions of HSBD and HC might provide information on the heritable factors associated with the BD. Additionally, it is concluded that using the combination of GM and WM tissue probability map provides better results than considering them, separately. Finally, it is obtained that the classification accuracy of SVM on HSBD and HC comparison is better than that of NB.**

***Keywords*—Healthy siblings of bipolar disorder patients, SPM12, SVM, Naive Bayes.**

I. INTRODUCTION

The use of a high-resolution 3D-MRI technique has been increased importantly in diagnosis of neuroanatomical abnormalities [1]. BD is one of the most widely encountered disorders and it effects about 1% of the population [2], [3]. The start of BD is generally at the early ages of adolescence or maturity and the disease continues chronically throughout the life of the patients [4], [5]. The studies on the diagnosis of BD focuses also on the unaffacted relatives of BD patients in order to examine the heritable resistance factors associated with the disorder [3], [5]. Hence, the comparison of HSBD and HC is also required owing to the high heritability of BD. In order to determine the deteriorated brain regions, a model needs to be generated using the HSBDs and HCs datasets [6]. To improve the accuracy of clinical examinations, the CAD and 3D-MRI data have been utilized in the diagnosis of neuroanatomical abnormalities [4]. The MRI neuroimaging technique is widely utilized in order to capture the structural deteriorations in brain tissue maps, due to the fact that the contrast and resolution of MRI are high. In this paper, structural MRI (sMRI) has been used for classification of HSBD and HC. The VBM is taken into account to segment, normalize, modulate, and smooth the 3D-MRI data [7]. The altered voxels between the subjects are named as VOIs and they are generated by taking advantage of the VBM [5]. It differentiates HSBD from HC by evaluating group-wise comparisons of sMRI data [7]. A Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL) and VBM are utilized to enhance inter-group registrations and give more accurate localization of alterations of sMRI data [8].

The sMRI data is preprocessed and to capture the 3D masks through voxel-by-voxel comparison, a statistical analysis in Computational Anatomy Toolbox (CAT12) is used. In building the general linear model, TIV is used as a covariate and t-contrast is utilized. The 3D masks are generated for GM and WM datasets [7], [9]. The experiments in this study are performed for GM-only, WM-only, and the combination of them to analyze the impacts of GM and WM tissue maps both individually and together. The 3D masking decreases the size of raw data, importantly. However, owing to the number of samples is higher than that of features, a feature selection method needs to be utilized [7]. In this study, the Relief-F feature ranking method is considered to rank the captured 3D masked features and an adaptive Fischer Criterion (FC) scheme is considered to determine the number of top-ranked features. The SVM and NB classification approaches have been used in order to classify HSBDs and HCs. The results of experiments

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indicate that the brain of HSBD generates larger regions in both GM and WM tissue maps comparing to HC. The changes between the brain regions of HSBD and HC might provide information on the heritable and genetic factors associated with the BD. Furthermore, the experimental results represents that SVM provides better results than NB in classification of HSBD from HC. Using SVM as a classifier provides the classification accuracies of 64.17%, 72.92%, and 76.25% and using NB as a classifier gives that of 62.50%, 68.75%, and 71.25% for GM, WM, and the combination of them, respectively. Additionally, the obtained differentiated 3D VOIs between HSBD and HC represent that taking into account the HSBD together with BD might help to the diagnosis of BD.

The paper is organized as follows: in Section II, the statistics of the data and in Section III the methodology of the study have been provided. Section IV gives the results of proposed method, Section V provides the discussion of the experimental results and Section VI gives the conclusions of this study.

II. MATERIALS

All subjects gave written informed consent before participation in the study. Ege University Ethics Committee approved the studies using these data [3].

A. MRI Acquisition

MRI was performed on a 3.0 Tesla scanner (Siemens Magnetom Verio, Numaris/4, Syngo MR B17, Erlangen, Germany) with a 12-channel head matrix coil. The MRI scanning protocol consisted of an axial turbo spin echo (TSE) T2-weighted sequence with the BLADE technique [repetition time (TR) = 2,500 msec, echo time (TE) = 117 msec, slice thickness = 5 mm, number of slices = 20, inter-slice gap = 1.8 mm, voxel size = 0.6x0.6x5.0 mm, field of view (FOV) = 200, Nex = 1, GRAPPA factor = 2], coronal three-dimensional (3D) SPACE Dark Fluid (FLAIR) sequence [TR = 5,000 msec, TE = 399 msec, inversion time (TI) = 1800 msec, slice thickness = 4 mm, number of slices = 44, no inter-slice gap, matrix = 258x256, voxel size = 1x1x4 mm, FOV = 250, Nex = 1, GRAPPA factor = 2], and sagittal T1-weighted 3D magnetization-prepared rapid gradient echo acquisition (MPRAGE) sequence (TR = 1,600 msec, TE = 221 msec, TI = 900 msec, FA = 9, slice thickness = 1 mm, number of slices = 160, no inter-slice gap, matrix = 246x256, voxel size = 1x1x1 mm, FOV = 256, Nex = 1, GRAPPA factor = 2).

B. Subjects

The experiments in this paper are performed by using 27 HSBDs (mean age±standard deviation (SD)= 41.41±9.09, range: 28–63 years, gender: 12M-15F) and 38 HCs (mean age ± standard deviation (SD)= 41.47±8.05 years, range: 29–63 years, gender: 15M-23F).

III. HSBD Classification Method

In this study, to classify the BDHS apart from HCs, a CAD method using 3D-MRI data has been proposed. Firstly, the data is preprocessed by using VBM which compares the brain tissue maps voxel-by-voxel. In order to built a general linear model, TIV is used as a covariate and t-contrast is used to capture the atrophies caused by genetic factors. Then, the Relief-F feature ranking method is used to rank the features from the most to the least important ones and an FC method is utilized to select the number of top-ranked features. Finally, the selected top-ranked features are given to the classification algorithms, In this paper, two different classification approaches, SVM and NB, are used. The scheme of the proposed method is given in Fig. 1.

A. Pre-processing of 3D MRI Data

A statistical parameter mapping (SPM12) package (http://www.fil.ion.ucl.ac.uk/spm) and CAT12 (http://www.neuro.uni-jena.de/cat/) have been considered in pre-processing the 3D MRI data. The data is captured in DICOM format. Using SPM12 package, the DICOM format data are converted into NifTi one. In order to set the central location of all data to the same point, the anterior commissural (AC) part of each data is coregistered to the central point space. The tissue volumes between the two groups are examined by using the automated VBM method. In VBM, the morphology of the brain is considered by comparing it voxel-by-voxel and the deteriorated tissue parts are determined by comparing each subject with the reference brain template obtained from 555 healthy controls. Then the 3D brain data is segmented into six modalities which are GM, WM, CSF, skull, scalp and air cavities. In this paper, the most informative ones, the GM and WM, are considered. After obtaining the segmented data, the VBM normalization and DARTEL method which provides more accurate inter-subject alignment is taken into account [7]. Then the data is registered to standard Montreal neurological institute space, modulated by preserving the total amounts of tissue, and smoothed with an 8 mm full-width-half-maximum (FWHM) Gaussian kernel. In order to generate a model, the general linear model (GLM) in SPM12 package is utilized for GM and WM tissue maps. The data is modeled by utilizing Total Intracranial Volume (TIV) as a covariate and two sample t-test. The parameters of the model is estimated and the volume differences of GM and WM tissue maps are generated by using SPM12 package. A threshold of uncorrected $p<.001$ and none extend threshold voxels are used. The general framework of the process is provided in Fig. 1.

B. Feature Extraction

The dimensions of the extracted GM and WM data are reduced significantly through feature extraction. In this study, GM and WM VOIs are concatenated to investigate the effects of both modalities. The pipeline of the procedure is given in Fig. 1.

C. Feature Ranking

3D masking reduces the size of raw data, importantly. However, to remove the irrelevant features independently from the learning approach, alleviate the effects of curse of dimensionality and reduce the process time, the use of a feture

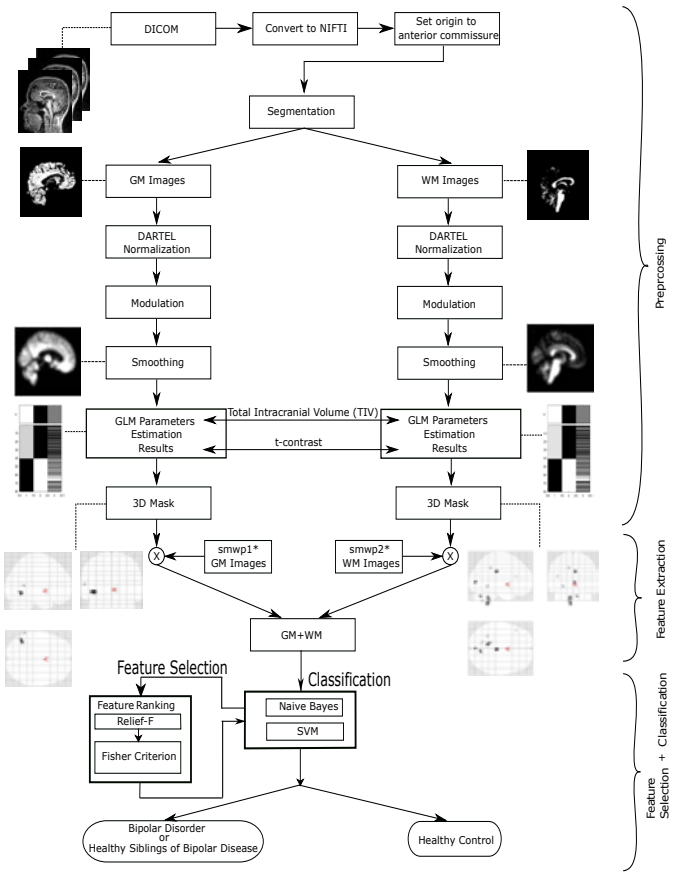

Fig. 1. The general framework of classifying HSBD apart from HC
smwp1*=DARTEL warped, modulated, smoothed GM tissue.
smwp2*=DARTEL warped, modulated, smoothed WM tissue

selection method is required [7]. In this paper, the Relief-F filter technique is used to rank the features.

1) Relief-F: Relief-F is a supervised, randomized, iterative, and noise tolerant method in which the quality of the features are estimated according to how well the values of the features separate close data samples [7].

D. Feature Selection Based on Fisher Criterion Methods

The goal of FS is to determine the feature subset of a precise size that leads to the largest possible generalization or minimal risk [10]. To identify the optimal feature subset which has the number of the most discriminative features, a method utilizing the FC, J(w), provided in Eq. 1 is considered [7].

$$J(w) = \frac{w^T S_B w}{w^T S_W w} \tag{1}$$

where S_B and S_W indicate the determinant of between and within class scatter matrices, respectively. The between class scatter and within class scatter matrixes for y_1 and y_2 classes are defined as follows:

$$S_B = (\mu_{y_1} - \mu_{y_2})(\mu_{y_1} - \mu_{y_2})^T$$
$$S_W = \sum_{x_i \epsilon y_1} (x_i - \mu_{y_1})(x_i - \mu_{y_1})^T + \sum_{x_i \epsilon y_2} (x_i - \mu_{y_2})(x_i - \mu_{y_2})^T \tag{2}$$

where $w = {S_w}^{-1}(\mu_{y_1} - \mu_{y_2})$ and μ_{y_i} is the mean value of the data in each group. In each training set, the most discriminative features are chosen instead of a fixed number of features. The number of features increases in each loop and a FC value is calculated for each iteration. The iterations are finished when the maximum FC value is achieved.

E. Classification Methods

In order to classify the HSBD patients apart from the HCs, a classification algorithm needs to be used. In this paper, SVM and NB classification methods are utilized for training the model. To evaluate the performance of the classifier, 10-fold cross-validation is used.

1) The Support Vector Machines Classifier: An SVM classification algorithm is used in order to classify HSBDs apart from HCs. The aim of SVM classifier is to search an optimal class-separation hyperplane with a maximal margin [7]. In this paper, the RBF-SVM classification approach is used.

F. The Naive Bayes Classifier

NB is a classification algorithm which assumes the independence of the predictors. The effect of a feature in a given class is unrelated to the many other existing features [7]. Hence, the computational cost is reduced.

IV. EXPERIMENTAL RESULTS AND DISCUSSION

The preprocessed sMRI data is utilized to generate the 3D masks for GM-only and WM-only tissue probablity maps by taking advantage of the SPM12 and the CAT12 toolbox. The VOIs are the 3D masks which are the most discriminative voxels between HSBD and HC. The t-contrast in model building is configured as [HSBD HC]=[1 -1] which searches for the differentiated brain regions between the HSBD and HC. In other words, the brain regions in which they are larger in HSBD than HC are obtained. The generated 3D masks are provided in Fig. 2. In order to take into account the effects of both GM and WM data, the 3D masked GM and WM are concatenated and the combined GM+WM dataset is generated.

From Fig. 2, it is concluded that the brain of HSBD generates larger regions in both GM and WM tissue maps comparing to HC. The alterations between the brain regions of HSBD and HC might give information on the heritable factors associated with the BD. As stated in [3], comparing to HSBD and HC, the volumetric differences unique to BD patients might occur and these volumetric differences constitute disease markers. Also the risk markers, the volumetric differences shared by BD patients and HSBD, and markers of resistance to BD, the volumetric differences unique to HSBD, are studied. Hence, the brain regions found in this study provide information on the probable disease markers. Differently from [3] and [5],

TABLE I
CLASSIFICATION OF HSBD FROM HC USING SVM AND NB CLASSIFIERS FOR GM, WM, AND COMBINATION OF GM AS WELL AS WM.

	GM			WM			GM+WM		
Cov*	**ACC***	**SEN***	**SPE***	**ACC***	**SEN***	**SPE***	**ACC***	**SEN***	**SPE***
SVM	**64.17**	78.33	50.00	**72.92**	68.33	77.50	**76.25**	75.00	77.50
NB	62.50	75.00	50.00	68.75	65.00	72.50	71.25	65.00	77.50

* ACC:accuracy(%), SEN:sensitivity(%), SPE:specificity(%), Cov:Covariate.

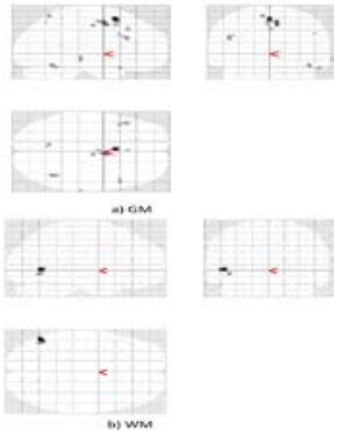

Fig. 2. The 3D VOIs of GM and WM tissue maps for t-contrast of [HSBD HC]=[1 -1].

in this study, the classification of HSBD apart from HC are performed by using an automated feature selection method and two different classification approaches.

In this study, instead of analyzing GM-only data, also the WM-only data and the concatenation of GM and WM data are studied. The experimental results from Table I indicate that using WM-only data has more impact on the detection of HSBD than using GM-only one and utilizing the combination of GM and WM data improves the classification accuracy of detection of HSBD comparing to considering each tissue maps, separately. Since taking into account changes in both maps together gives more information to compare, the combination of GM and WM tissue probability maps enhances the classification accuracy. Additionally, since there is limited number of data used in this study and NB mostly performs better with more data, the classification accuracy of SVM is better than that of NB.

V. CONCLUSIONS

The neuroanatomical abnormality detection by taking advantage of computer-aided methods with MRI imaging techniques has been widely studied, recently. In this paper, the classification of HSBD from HC is studied in order to investigate the heritable factors associated with the BD. The VBM is utilized to extract the altered 3D VOIs between HSBD abd HC. The experiments are performed for GM-only, WM-only, and their combination. The Relief-F approach is used to rank the features and a FC technique is considered to select the top-rank features. The performance of SVM and NB are compared. From the obtained 3D masks, it is obtained that the brain of HSBD has larger regions comparing to that of HCs which might be used as probable disease markers on the diagnosis of BD. Additionally, the experimental results indicate that combination of GM and WM tissue maps enhances the classification accuracy of considering them individually and the classification accuracy of SVM is better than that of NB. In future work, the comparison of BD and HSBD will be studied and instead of considering only the larger brain regions, all differentiated brain regions will be examined. Furthermore, the performance of various feature selection and classification methods will be compared.

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