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REGULAR PAPER

Identification of changes in grey matter volume using an evolutionary approach: an MRI study of schizophrenia

Indranath Chatterjee[1,2] · Virendra Kumar[3] · Bharti Rana[4] · Manoj Agarwal[4] · Naveen Kumar[1]

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Abstract

Schizophrenia, a serious psychological disorder, causes auditory and visual hallucinations, and delusions in a person. Several studies have shown that schizophrenia imposes structural changes in human brain. Relative changes in the grey matter volume of the schizophrenia patients in comparison to healthy controls have been well explored. However, identification of relevant brain regions that exhibit grey matter atrophy and also aid in the classification of schizophrenic patients and healthy controls has not been extensively investigated. In this study, a novel application of the non-dominated sorting genetic algorithm has been developed to select a set of relevant features (voxels) that show grey matter changes in the brain regions attributable to schizophrenia. This study uses MRI data of 32 healthy controls and 28 schizophrenia patients. The results show notable shrink in the gray matter volume in the brain of the schizophrenia patients, mostly in inferior frontal gyrus, superior temporal gyrus, middle occipital gyrus, and insula. The proposed approach yields a mean classification accuracy close to 90% with a feature set having around 70 voxels. This study may open a means of investigation of underlying neurobiology of schizophrenic brain for effective clinical intervention.

Keywords Evolutionary algorithm · NSGA-II · Magnetic resonance imaging (MRI) · Schizophrenia · Grey matter atrophy

1 Introduction

Schizophrenia is a serious mental illness presenting symptoms of hallucinations and delusions related to auditory, visual, social and emotional dullness [5, 6]. Psychological and neurological disorders such as schizophrenia may induce structural changes in the human brain. In this direction, several neuroimaging studies [16, 29, 30, 44] have been reported, which investigate the structural changes with respect to grey matter volume (GMV) [16, 44], white matter (WM) tracts [25], and cerebrospinal fluid (CSF) [9]. In schizophrenia studies, grey matter analysis is an active area of research. Grey matter is a major component of the brain, mainly comprising of neuronal cell bodies. It includes the regions of the brain which control muscles, and sensory functions such as visual, auditory, speech, emotions, memory, and decision making. Grey matter deficits in the range of 2–4% have been found in the patients suffering from schizophrenia as compared to healthy subjects [23, 47]. Volumetric grey matter loss in several regions like insula and superior temporal gyrus regions of the brain has been reported in several cross-sectional studies on schizophrenia

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✉ Indranath Chatterjee
indranath.cs.du@gmail.com

Virendra Kumar
vrndra@gmail.com

Bharti Rana
bhartirana.it@gmail.com

Manoj Agarwal
agar.manoj@gmail.com

Naveen Kumar
nk.cs.du@gmail.com

1 Department of Computer Science, University of Delhi, New Delhi 110007, India

2 Department of Computer Engineering, Tongmyong University, Busan 48520, South Korea

3 Department of NMR and MRI Facility, All India Institute of Medical Sciences, New Delhi 110029, India

4 Department of Computer Science, Hans Raj College, University of Delhi, New Delhi 110007, India

patients [16, 41, 44] using magnetic resonance imaging (MRI) [14, 26, 29, 32, 42].

Because of its ability to depict anatomy and soft tissue contrast in a non-invasive manner, MRI is used for studying structural changes. Wright et al. [46] studied the global and regional grey matter changes in the whole brain with the help of structural MRI data of 42 schizophrenia patients and 52 healthy controls. They found significant reductions in regional grey matter in the medial temporal lobe. Job et al. [17] reported grey matter deficiency in schizophrenia patients compared to healthy controls using voxel-based morphometry (VBM) analysis of grey matter volume determined from MRI of 34 first episode schizophrenia patients and 36 controls. Grey matter volumes of subcortical brain regions were studied by Khodaei et al. [18]. With the help of whole brain segmentation, they compared the brain volumes of the MRI data of 12 schizophrenia patients with an equal number of healthy subjects. They identified a reduction in brain volume in the patient group.

Gender influences brain anatomy and age-related structural changes associated with it. Ruigrok et al. [39] found significant differences in size and volume of the brain of males and females in terms of grey matter. Bora et al. [1] conducted a meta-analysis study on schizophrenia patients with bipolar disorder to observe the effect of gender on the grey matter. The authors reported that grey matter abnormalities were more pronounced in data sets having a skewed gender ratio in favour of male patients. In a region-of-interest based study to investigate the influence of gender on first-episode schizophrenia patients, Duggal et al. [11] found greater reduction in insular volume in female patients in comparison to male subjects. Similarly, aging also influences the structural properties of the human brain. Premkumar et al. [38] found that longer duration of illness was associated with GM deficit in several regions of schizophrenic brain.

The above-mentioned studies were based on group analysis of schizophrenic patients. However, individual differential diagnosis of schizophrenic patients and healthy subjects have also been an active area of research. Since MRI captures a detailed 3D image of brain anatomy, MRI images are voluminous ($\approx 10^6$ voxels). The number of subjects being low in comparison to number of voxels, discriminative analysis cannot be carried out efficiently. To handle this problem of high dimensionality, several works [34, 40] employed feature selection techniques before proceeding to classification of schizophrenia patients and healthy controls. Efficient feature selection techniques lead to high classification accuracy and also helps in better identification of affected brain regions [8]. Lu et al. [27] proposed a classification of schizophrenia and healthy controls using support vector machine (SVM) with recursive feature elimination to find the changes in GM and WM in the brain. The classification model yielded 88.4% accuracy. Nieuwenhuis et al. [34] used whole grey matter density images for classification of schizophrenia and healthy subjects. Feature selection was performed by selecting the top-ranked features, based on absolute values of the element of weight vectors of the SVM model.

Feature selection of MRI data has also been performed using meta-heuristic approaches. Recently, in a study, Tas et al. [42] used Ant Colony Optimization (ACO) as a feature selection tool in discrimination of schizophrenia and schizo-obsessive disorder patients. Classification of 23 schizophrenia and an equal number of schizo-obsessive disorder patients was performed using MRI data. However, to the best of our knowledge, evolutionary approaches have not been explored for grey matter analysis of schizophrenia patients. Since traditional feature selection methods get stuck in local optima and/or incur high computational cost [48], an efficient global search technique may be better suited to solve the feature selection problem for MRI data sets. Evolutionary approaches which possess global search ability have established themselves as an important class of search algorithms that have problem-invariant searching capabilities, i.e., they can efficiently search for optimal or near optimal solutions in any problem domain.

Again, most of the schizophrenic studies cited above either focused on improving the classification accuracy or on the identification of relevant brain regions having grey matter atrophy. However, to the best of our knowledge, no study has modeled the problem as a multi-objective optimization problem in which one can investigate the effect of a minimal set of features on the classification accuracy of schizophrenic patients and healthy subjects. Also, the analysis of the trade-off feature set obtained throws light on the most relevant discriminating features that exhibit grey matter atrophy. Non-dominated Sorting Genetic Algorithm (NSGA-II) [10] has been the most popular evolutionary multi-objective algorithm for obtaining trade-off solutions in a variety of problem domains.

In this study, we explore the suitability of NSGA-II algorithm for generating trade-off solutions in the domain of neuroimaging for studying grey matter atrophy. It yields a high classification accuracy by using a very small set of features. Thus, we are able to obtain features (voxels) that identify the relevant regions of the brain exhibiting grey matter atrophy.

Table 1 Demographic details of the dataset

	No. of subjects	Age group (mean ± std dev)	Male/female
Healthy	32	40.4 ± 12.29	20/12
Schizophrenia	28	42.3 ± 10.81	22/6

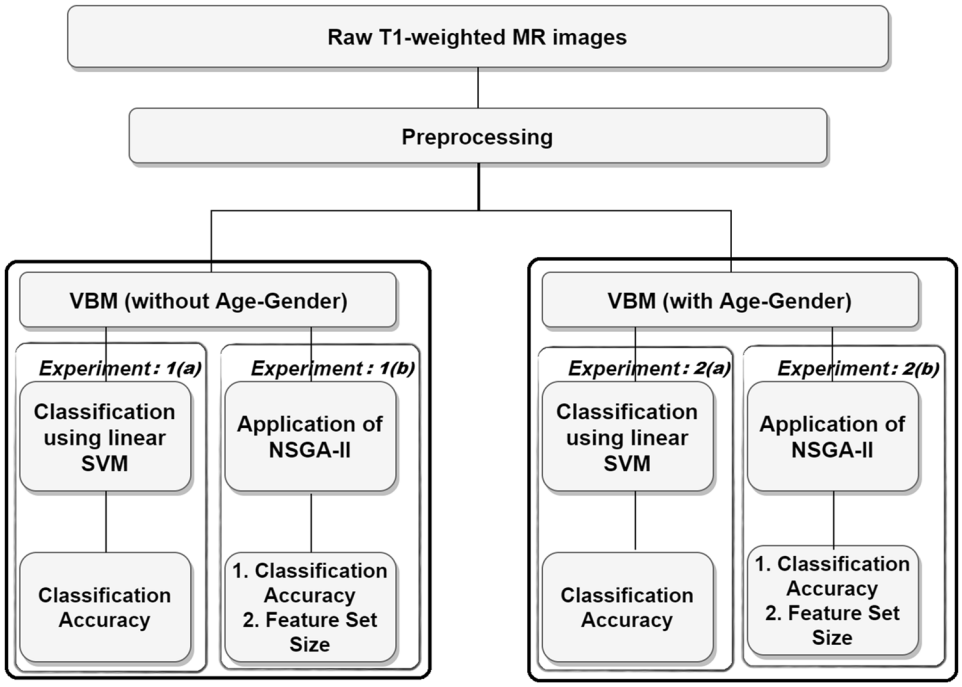


Fig. 1 Scheme of experiments for the study

2 Material and methods

2.1 Dataset

The MRI data used in this study was obtained from the Functional Biomedical Informatics Research Network (FBIRN) Phase II dataset.[1] This was a multi-site neuroimaging dataset acquired across different centers [37]. In this data, all subjects had sufficient eyesight, regular hearing levels, and were able to perform the cognitive tasks. Healthy subjects were excluded if they had a recent or past history of head injury or any major medical illness. All the healthy subjects were free from antipsychotic exposure and they had no recent history of medication effect. Patients with schizophrenia and schizoaffective disorder meeting Diagnostic and Statistical Manual of Mental Disorders, fourth version revised (DSM-IV-TR) criteria were included in this FBIRN study. The research group of FBIRN had determined the symptom scores by using the Schedule for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms assessment measures [19]. In this study, we have employed T1-weighted MRI images of schizophrenia and healthy subjects acquired using machine having 1.5 T with the scanning parameters as follows: 256×256 matrix, 24 cm field of view (FOV), 160–170 slices to cover the entire head in sagittal orientation, and slice thickness ranging from 1.2 to 1.5 mm [37]. Demographic details of the utilized dataset is shown in Table 1.

2.2 Proposed approach

Our approach to identify grey matter atrophy in schizophrenic patients is outlined in Fig. 1. The steps of the proposed approach are described below.

2.2.1 Preprocessing

For preprocessing the raw MRI dataset, we have used the Statistical Parametric Mapping version 8 (SPM8, Wellcome Trust Centre for Neuroimaging, University College London, UK)[2] [36] toolbox in MATLAB-R2014a (Mathworks Inc., Natick, MA, USA).

Firstly, normalization of the MRI data was performed using the SPM's default T1-weighted image by preserving the total amount of signal in the images keeping the voxel size as $2 \times 2 \times 2$ mm^3. Next, we have segmented the normalized images into modulated probability map volumes of grey matter, white matter and cerebrospinal fluid. Finally, as the present study focuses on the analysis of grey matter atrophy, smoothing was done on the modulated normalized grey matter volumes using full-width half maximum (FWHM) Gaussian filter at window size $10 \times 10 \times 10$. Voxel values in the smoothed segmented volume lie between 0 and 1. Higher

[1] Dataset: http://fbirnbdr.birncommunity.org:8080/BDR.

[2] SPM8: http://www.fil.ion.ucl.ac.uk/spm/software/spm8/.

the voxel value, higher is the probability of the voxel to be a part of grey matter. Resulting smoothed modulated normalized grey matter volumes were then used for further analysis.

2.2.2 The application of voxel based morphometry

Voxel-based morphometry (VBM) is a technique to identify the structural changes in the brain. It is based on the statistical analysis of brain in voxel-by-voxel manner to trace the structural changes between two groups (population) of data. It is used to localize the changes, and make inferences about the group differences. The resulting output from the VBM analysis is a statistical parametric map which shows brain regions that differ significantly between the two populations. For statistical analysis, the method uses the general linear model (GLM) approach, which further uses the Gaussian random fields [13, 45].

For VBM analysis, normalized, segmented, and smoothed grey matter images were used. For the purpose of statistical analysis, we performed two sample t test over the two groups of data. While the first group of data comprised of schizophrenia patients, the second group was of healthy subjects. As we have hypothesized that reduction of grey matter concentration takes place in schizophrenia patients vis-a-vis healthy subjects, we set [−1&1] as t-contrast that represents a right-tailed (group2 > group1) t test. We have taken the level of significance (α), as $\alpha = 0.001$, uncorrected, and 25 as threshold value for cluster size to eliminate less significant voxels.

Age is an important parameter as ageing eventually deteriorates the anatomical structure of the brain and also leads to functional decline due to the gradual death of neurons [31]. Also, the female human brain is slightly smaller in size than the male human brain [39]. Further, the male human brain is around 100 g heavier than a female human brain [28]. Thus, it is important to neutralize the effects of both age and gender in a study on the anatomical changes in the human brain caused by schizophrenia. Therefore, we have introduced two variables namely, age and gender, as covariates during the VBM analysis.

It is evident from Table 1 that the dataset has a mean age of 40.4 and 42.3 years for healthy and schizophrenic subjects respectively. The high standard deviation values suggest that there is a significant variability in age. Similarly, an imbalanced gender ratio can be seen in Table 1.

Finally, VBM analysis generates voxel-wise statistical parametric map that identifies the brain voxels that represent anatomical changes in the grey matter volume. This map has been used for further analysis.

2.2.3 The application of NSGA-II

As the VBM analysis produces a statistical parametric map involving a large number of affected or malfunctioning voxels (features) in different parts of the brain, we have used Non-dominated Sorting Genetic Algorithm (NSGA-II) [10] for identification of relevant voxels that exhibit grey matter atrophy.

Algorithm 1 Non-dominated Sorting Genetic Algorithm (NSGA-II)

INPUT:

1. N = Number of chromosomes (population size)
2. $MaxGen$ = Maximum number of generations allowed
3. f^1 = Objective function to be maximized
4. f^2 = Objective function to be minimized

OUTPUT:
Pareto-optimal set of chromosomes

1: Randomly generate initial binary population, P_0, of size N
2: Compute fitness values for $f^1(P_0)$ and $f^2(P_0)$ // /*For each chromosome belonging to P_0*/
3: **for** $i = 0$ to $MaxGen$ **do**
4: $S_i \leftarrow$ BinaryTournamentSelection (P_i) // /*S_i is the population after tournament selection*/
5: $C_i \leftarrow$ Crossover (S_i) // /*C_i is the population after one-point crossover*/
6: $M_i \leftarrow$ Mutation (C_i) // /*M_i is the mutated population*/
7: Compute fitness values for $f^1(M_i)$ and $f^2(M_i)$ // /*For each mutated chromosome belonging to M_i*/
8: $T_i \leftarrow P_i \bigcup M_i$ // /*T_i denotes the pooled population*/
9: $P_{i+1} \leftarrow$ NonDominatedSort (T_i) and select the top most N chromosomes
10: **end for**
11: Generate set of pareto-optimal solutions

NSGA-II is a popular multi-objective genetic algorithm. In addition to the genetic operators—selection, crossover and mutation, NSGA-II uses non-dominated sorting and crowding distance measure to generate trade-off solutions. The algorithm starts with initialization of a population of size N. After initialization, we identify the most potent chromosomes by employing tournament selection and the resulting chromosomes are crossed over and finally, mutated to generate an offspring population of size N. A new population comprising of the parent population and current offsprings is formed and sorted using the non-dominated sorting mechanism to select the best N chromosomes for next generation. The population of chromosomes thus sorted splits the entire combined population into multiple fronts $(F_1, F_2, F_3, ...)$. The first front (F_1) is the first level non-dominant set, while the second front (F_2) is dominated only by F_1, and so on. This process is repeated for a given number of generations or till a specific criterion is met.

In our experiment, we have applied the NSGA-II as a feature selection tool in a bi-objective framework [7]. We have identified the following two conflicting objective functions for the study:

- f^1: Maximization of classification accuracy
- f^2: Minimization of number of features.

Based on experimental exploration with selection of different numbers of features, finally top 300 features (rank wise) obtained from the VBM analysis were selected. We created a population of binary chromosomes, each having a size of 300 bits. A one (1) at a position in the chromosome indicates the presence of the corresponding feature and zero (0) bit indicates its absence. Initially, for each chromosome, 20% of the randomly selected bits were set as one (1), and the remaining 80% of the bits as zero (0). In these experiments, the population size (N) was kept as 200. The fitness value of a chromosome for the first objective function, f^1, was evaluated with the help of SVM with linear kernel. The fitness value of the second objective function, f^2, for a chromosome was computed by counting the number of ones in the chromosome. Candidate chromosomes for the child population were generated using binary tournament selection. One-point crossover was applied on the selected chromosome set, followed by application of mutation at the rate of 0.01. The fitness values of the resulting child population (M_i) were computed, and a pooled population (T_i) comprising of the initial (P_i) and child population (M_i) was created. Non-dominated sort was performed on the pooled population (T_i) to find the set of non-dominated solutions. The best N chromosomes representing the trade-off solutions were passed to the next generation population (P_{i+1}). Algorithm 1 outlines the steps of standard NSGA-II used in this study. The maximum number of iterations (MaxGen) was set to 500. We have used 80–20 hold-out scheme for learning the decision model, i.e., for every run of the experiment, 80% of the data was randomly selected for training and the rest 20% for testing. The experiment was repeated 20 times to examine the variability in the results.

Table 2 Mean classification accuracy of the four experiments

Strategy	Experiment (1): excluding age–gender		Experiment (2): including age–gender	
	Accuracy	Feature size	Accuracy	Feature size
(a) VBM	52.5%	16,227	60.83 %	12,035
(b) VBM + NSGA-II	88.33%	72	90.0 %	65

Experiments 1(a) and 2(a) correspond to the VBM analysis excluding age & gender, and including age & gender as covariates, respectively (first row). Experiments 1(b) and 2(b) correspond to VBM analysis in conjunction with NSGA-II excluding age & gender, and including age & gender as covariates, respectively (second row)

By applying NSGA-II as feature selection tool, we obtained a small set of relevant features which yielded high classification accuracy to distinguish the patients from the healthy controls. The features, obtained in each independent run of the experiments, were analysed and accumulated. These accumulated features were then backtracked to the original Cartesian coordinate system. To find the brain voxels corresponding to these coordinates, these Cartesian coordinates were mapped to the MNI coordinate system, and then finally, to Talairach coordinate system to map to the brain space. Thus, we could identify the most affected brain regions in schizophrenia patients.

3 Results

All the experiments conducted in this study have been implemented in MATLAB-R2014a. We have used SPM8 toolbox for preprocessing and VBM analysis of MRI images; libsvm [4] package for the classification task; Talairach Daemon [21] for mapping of brain regions; and Multi-image Analysis GUI (Mango) [22] for visualization of the identified regions in the brain. We have used the C-Support Vector Classification (C-SVC) [2] tool for the classification task. We have experimented with several values of the regularization parameter C in the range [0.01, 1000] in multiple of 10, and obtained the best classification accuracy results for $C = 100$.

In experiments 1(a) and 2(a), the set of voxels obtained from VBM analysis were fed into the SVM classifier. VBM analysis excluding the age and gender as covariates resulted in 16227 voxels. When age and gender were included as covariates, it resulted in 12035 voxels. Experiment 1(a), using 16227 voxels, generated a mean classification

Table 3 Mean and median values of grey matter volume loss in schizophrenic patients obtained in Experiment 1(b)

Level	Regions	Voxel count	Mean GM change	Median GM change
Hemisphere	*	49	− 0.215	− 0.230
	Left cerebrum	41	− 0.174	− 0.192
	Right cerebrum	202	− 0.164	− 0.159
Lobes	*	51	− 0.216	− 0.234
	Frontal lobe	2	− 0.205	− 0.192
	Occipital lobe	46	− 0.177	− 0.205
	Sub-lobar	5	− 0.232	− 0.223
	Temporal lobe	188	− 0.161	− 0.154
Gyrus	*	53	− 0.217	− 0.235
	Extra-nuclear	5	− 0.232	− 0.223
	Inferior frontal gyrus	1	− 0.249	− 0.209
	Inferior temporal gyrus	15	− 0.158	− 0.175
	Medial frontal gyrus	1	− 0.128	− 0.131
	Middle occipital gyrus	43	− 0.177	− 0.204
	Middle temporal gyrus	97	− 0.146	− 0.155
	Sub-gyral	2	− 0.240	− 0.229
	Superior temporal gyrus	75	− 0.179	− 0.160
Cell type	*	147	− 0.175	− 0.164
	Brodmann area 18	14	− 0.186	− 0.179
	Brodmann area 19	11	− 0.193	− 0.227
	Brodmann area 20	8	− 0.176	− 0.179
	Brodmann area 21	50	− 0.150	− 0.180
	Brodmann area 37	10	− 0.136	− 0.155
	Brodmann area 38	51	− 0.177	− 0.162
	Brodmann area 47	1	− 0.249	− 0.209

accuracy of 52.50%. While experiment 2(*a*), using 12035 voxels, resulted a mean classification accuracy of 60.83% (see Table 2).

In experiments 1(b) and 2(b), NSGA-II was applied on the 16,227 voxels and 12,035 voxels, respectively. Experiment 1(b) resulted in a mean classification accuracy of 88.33% using a mean feature set of size 72, and experiment 2b resulted in a mean classification accuracy of 90% using a mean feature set of size 65 (see Table 2).

In experiment 1(b), the features over all runs of the experiment were accumulated, and backtracked to the Talairach's space enabling us to study brain regions at several level of hierarchy starting from hemisphere levels to the cell level. We found 21 brain regions as being affected. We also observed that about 17% of voxels were outside the of grey matter regions (see Table 3). Similarly, experiment 2(b) also resulted in accumulated features which were mapped to the brain regions in Talairach's space. We identified 26 different brain regions as the most affected (see Table 4). The identified brain regions are visualized in Fig. 2.

Grey matter atrophy was computed as percentage of volume loss in schizophrenia patients as compared to healthy subjects (see Tables 3 and 4). Comparison of the grey matter values for each of the identified brain region showed a drop in grey matter concentration in the patient group. The negative values indicate loss of grey matter. The variation in grey matter loss has been visualized in boxplot diagrams as shown in Figs. 3, 4, and 5. At the hemisphere level, we found that both the left and right hemisphere showed reduced grey matter concentration in schizophrenia patients compared to healthy subjects. We found no changes in grey matter volume (GMV) in the brain stem or cerebellum region. The box plots in the Fig. 3 shows the difference in GMV at hemisphere level of the brain. At the lobular level of the brain, frontal lobe, occipital lobe, sub-lobar region and temporal lobe showed reduced grey matter (see Fig. 3) in the patient group. Gyral regions including inferior frontal gyrus, inferior temporal gyrus, superior temporal gyrus, middle occipital gyrus, middle temporal gyrus, middle frontal gyrus, sub-gyral, insula and extra-nuclear regions were found to have atrophy in grey matter volume (see Fig. 4). At cell level, Brodmann's area 13, BA 18, BA 19, BA 20, BA 21, BA 37, BA 38, BA 47, BA 6 and BA 9 showed a drop in grey matter concentration of these areas in patient group compared to healthy controls (see Fig. 5). The box plots (Figs. 3, 4 and 5) show the magnitude of the atrophy of

Table 4 Mean and median values of grey matter volume loss in schizophrenic patients obtained in Experiment 2(b)

Level	Regions	Voxel count	Mean GM change	Median GM change
Hemisphere	Left cerebrum	50	− 0.206	− 0.233
	Right cerebrum	242	− 0.180	− 0.181
Lobes	Frontal lobe	12	− 0.240	− 0.222
	Occipital lobe	60	− 0.202	− 0.220
	Sub-lobar	11	− 0.208	− 0.188
	Temporal lobe	209	− 0.175	− 0.166
Gyrus	Extra-nuclear	9	− 0.207	− 0.189
	Inferior frontal gyrus	9	− 0.249	− 0.234
	Inferior temporal gyrus	37	− 0.189	− 0.187
	Insula	2	− 0.212	− 0.215
	Middle frontal gyrus	2	− 0.213	− 0.149
	Middle occipital gyrus	60	− 0.202	− 0.220
	Middle temporal gyrus	65	− 0.153	− 0.167
	Sub-gyral	10	− 0.140	− 0.133
	Superior frontal gyrus	1	− 0.128	− 0.131
	Superior temporal gyrus	97	− 0.189	− 0.156
Cell type	Brodmann area 13	14	− 0.196	− 0.170
	Brodmann area 18	21	− 0.234	− 0.197
	Brodmann area 19	39	− 0.194	− 0.196
	Brodmann area 20	32	− 0.192	− 0.195
	Brodmann area 21	74	− 0.152	− 0.161
	Brodmann area 37	3	− 0.144	− 0.132
	Brodmann area 38	97	− 0.189	− 0.158
	Brodmann area 47	9	− 0.249	− 0.234
	Brodmann area 6	1	− 0.128	− 0.131
	Brodmann area 9	2	− 0.213	− 0.149

GMV in the schizophrenic brain. Tables 3 and 4 show the mean and median values of voxel intensity for schizophrenia patients showing negative (loss) change in grey matter volume compared to healthy controls.

Each of the experiments (experiments 1(b) and 2(b)), as depicted in Fig. 1, was repeated 20 times using 80–20 hold-out scheme to check robustness in classification accuracy and variability of selected features. The variations in mean classification accuracy and the size of feature set for each independent run are shown in Fig. 6a, b. The features obtained from all the runs of the algorithm were aggregated and the brain regions appearing in at least 80% of the runs were identified. For each of the regions so obtained, the Student's paired t test was applied group wise across healthy subjects and schizophrenia patients, considering 95% confidence level. We found that all the identified brain regions show significantly difference in grey matter volume in schizophrenia patients resulting the P value < 0.05. The Table 5 shows the statistically significant difference in grey matter volume when compared between healthy and schizophrenia subjects.

4 Discussion

The study of structural changes in the brain of schizophrenia patients is an important research area. In this cross-sectional study, we have identified the brain regions, typically affected by schizophrenia, showing shrinkage in grey matter volume. With the help of voxel-based morphometry, we obtained a reduced set of features (voxels). When these features were fed as input to the bi-objective NSGA-II, a much reduced set of discriminating features was obtained. Using these features high classification accuracy was achieved. Further, the features obtained using the NSGA-II algorithm were successfully used to identify the affected brain regions.

As mentioned above, the experiments 1(b) and 2(b) were repeated 20 times to observe the changes in different feature sets obtained in independent runs. The most frequently occurring features (brain regions) were taken into account. We found little variation in terms of brain regions at different runs of the experiment. The voxels identified in experiment 1(b) when mapped to Talairach's space showed 21 brain regions. Similarly, we obtained 26 brain regions from

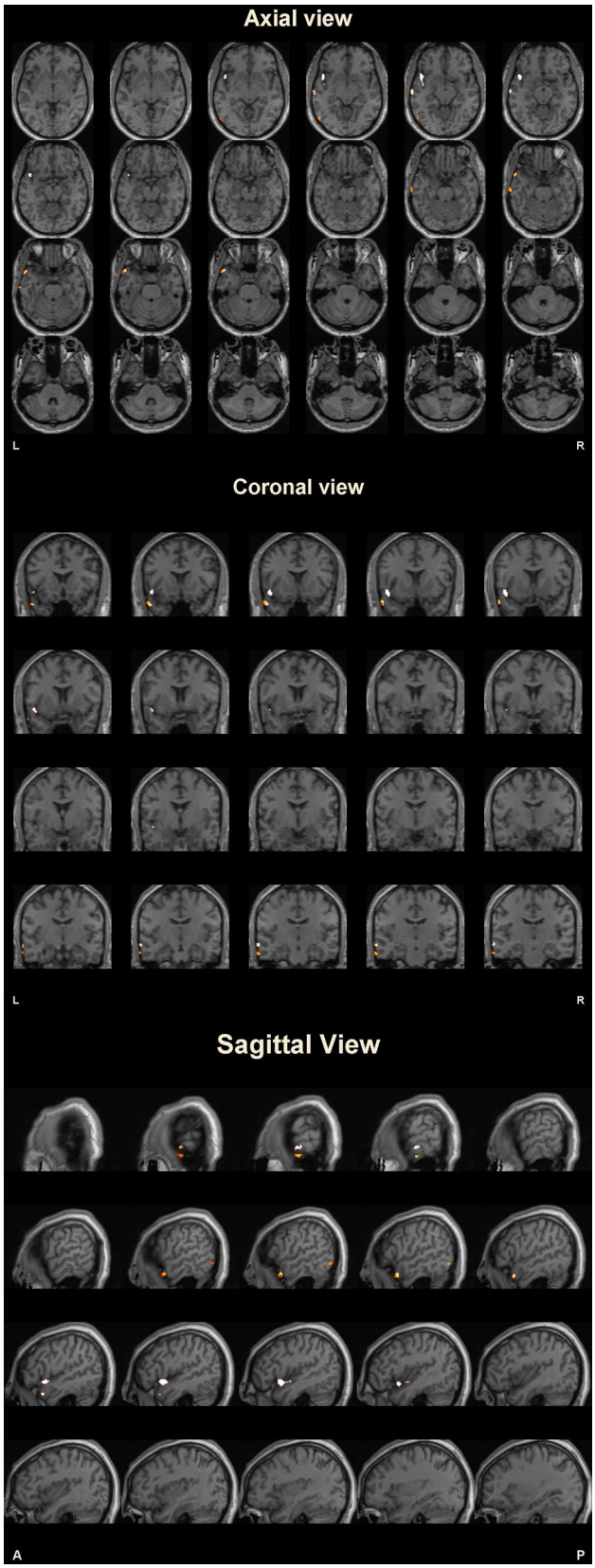


Fig. 2 An overlay of mask of identified voxels on T1-weighted image showing the regions having grey matter atrophy in schizophrenia patients in axial, coronal and sagittal view of brain

experiment 2(b). It was noted that a significant number of identified regions in experiment 2(b) can be attributed to age and gender as covariates. This suggests that these covariates should be included while conducting VBM analysis. Further, the grey matter loss in the identified regions for experiment 1(b) is less in comparison to experiment 2(b) (Tables 3 and 4).

Table 4 shows that both the left (− 0.20) and right hemisphere (− 0.18) exhibit grey matter loss in the schizophrenia patients. Studies [33, 43] suggest that the hemispheric grey matter loss is noticeable in early-onset schizophrenia patients compared to healthy controls. At the lobe level brain map, frontal lobe (− 0.24), occipital lobe (− 0.20), sub-lobar region (− 0.20) and temporal lobe (− 0.17) show grey matter atrophy in accordance to the previous studies on schizophrenia [3, 15, 20, 33]. Inferior frontal gyrus (− 0.24), inferior temporal gyrus (− 0.18), superior temporal gyrus (− 0.12), middle occipital gyrus (− 0.20), middle temporal gyrus (− 0.15), insula (− 0.21), sub-gyral (− 0.14) and extra-nuclear (− 0.20) regions show a reduction in grey matter concentration. In addition to regions mentioned in literature [3, 33, 46], we find that insula and extra-nuclear region also show a reduction in grey matter volume when compared to healthy controls. Fornito et al. [12] found that insula showed more consistent grey matter reduction. In another study, Lei et al. [24] suggested that lower volume in the extra-nuclear white matter may be a biological sign of schizophrenia. But in our study, we find extra-nuclear region showing prominent grey matter loss. We infer from our study that more research on the extra-nuclear region for identification of a change in grey matter is an open area of investigation. When we see the brain mapping at cell level, we find Brodmann's areas (BA) showing a change in grey matter concentration. Brodmann's areas like BA 18 (− 0.23) and BA 47 (− 0.24) show atrophy in grey matter volume. These regions are also mentioned in a previous study [35]. BA 38 (− 0.18) also shows a reduction in grey matter in the patient group. Literature suggests that this region is also affected in schizophrenia [3, 35]. We also found some regions like BA 13 (− 0.19), BA 19 (− 0.19), BA 37 (− 0.14), BA 20 (− 0.19), BA 6 (− 0.12), BA 9 (− 0.21) and BA 21 (− 0.15) showing a prominent loss of grey matter.

This study opens up a new approach for identifying the brain regions that exhibit grey matter atrophy in schizophrenia. Most of the regions identified in this study are in compliance with the existing studies on grey matter changes in schizophrenia patients. The identified regions may serve as cues for further investigation for effective clinical intervention with localized medication. Our study of schizophrenia patients and healthy controls using the MRI data also includes some new findings that might help in devising a more effective treatment strategy for schizophrenia. Although we have considered age and gender as two

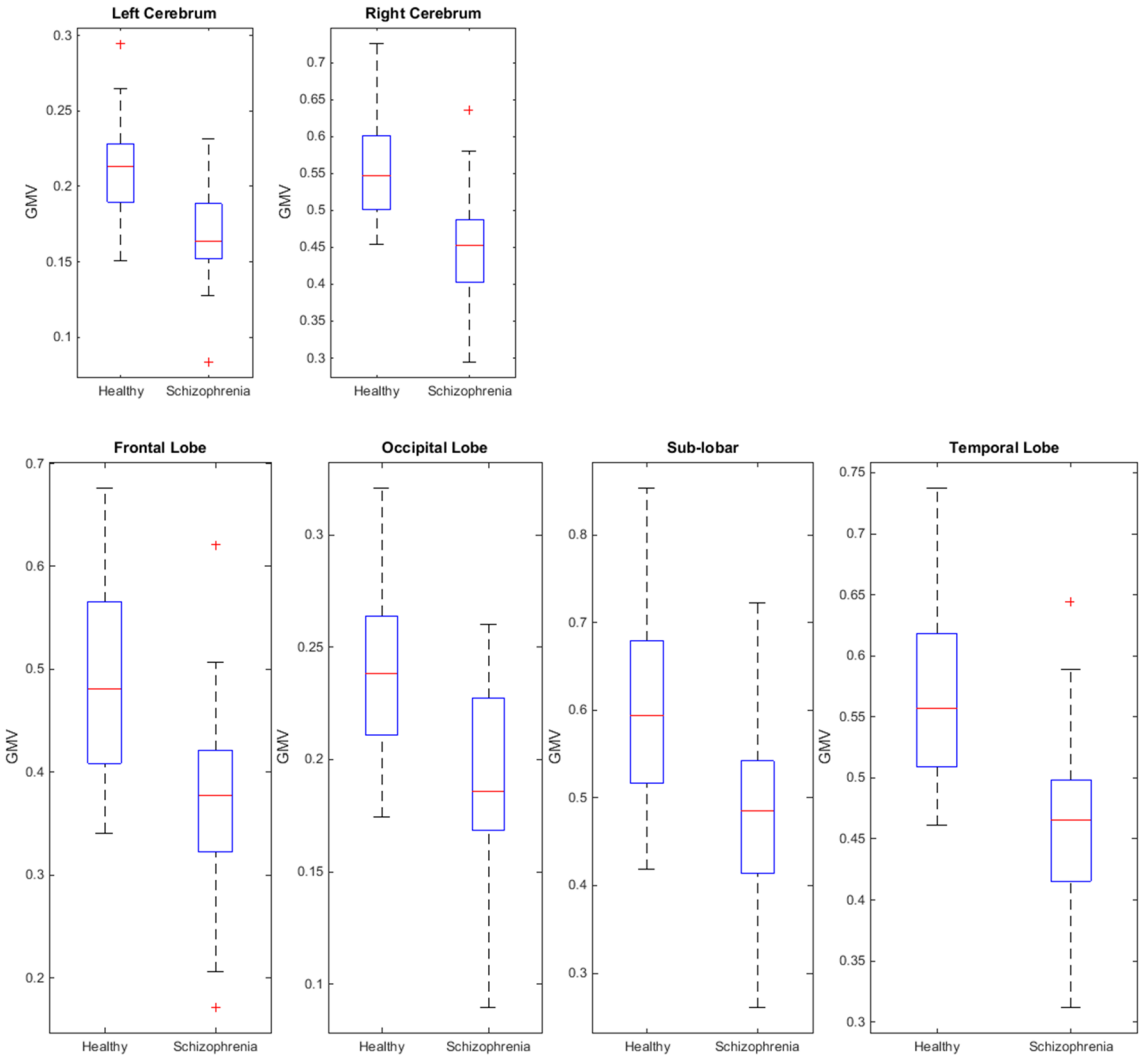


Fig. 3 Box plots showing brain regions having grey matter atrophy in schizophrenia patients for hemisphere and lobes regions

covariates in VBM, we have used them only to nullify their effect in this study. To understand the specific influences of age and gender on human brain, further studies may be conducted.

5 Conclusion

In this paper, we explored the applicability of evolutionary feature selection approach to study variations in grey matter volume in the brain regions of schizophrenia patients vis-a-vis healthy subjects. We also explored the effect of including age and gender as covariates in VBM analysis. The use of NSGA-II after the VBM analysis phase, led to improvement in classification accuracy from 52.5 to 88.33% when age and gender were not included as covariates during VBM analysis. Whereas, the use of NSGA-II after the VBM analysis, with age and gender as covariates, improved the classification accuracy from 60.83 to 90%. In summary, the NSGA-II based model that included age and gender as covariates during the VBM analysis yielded a better classification accuracy with a smaller set of features. The identified regions exhibiting grey matter atrophy may be further investigated to identify the causes that may play an adverse role in schizophrenia. Our study of schizophrenia patients and healthy controls using the MRI data also includes some new findings that might help in devising a more effective treatment strategy for schizophrenia.

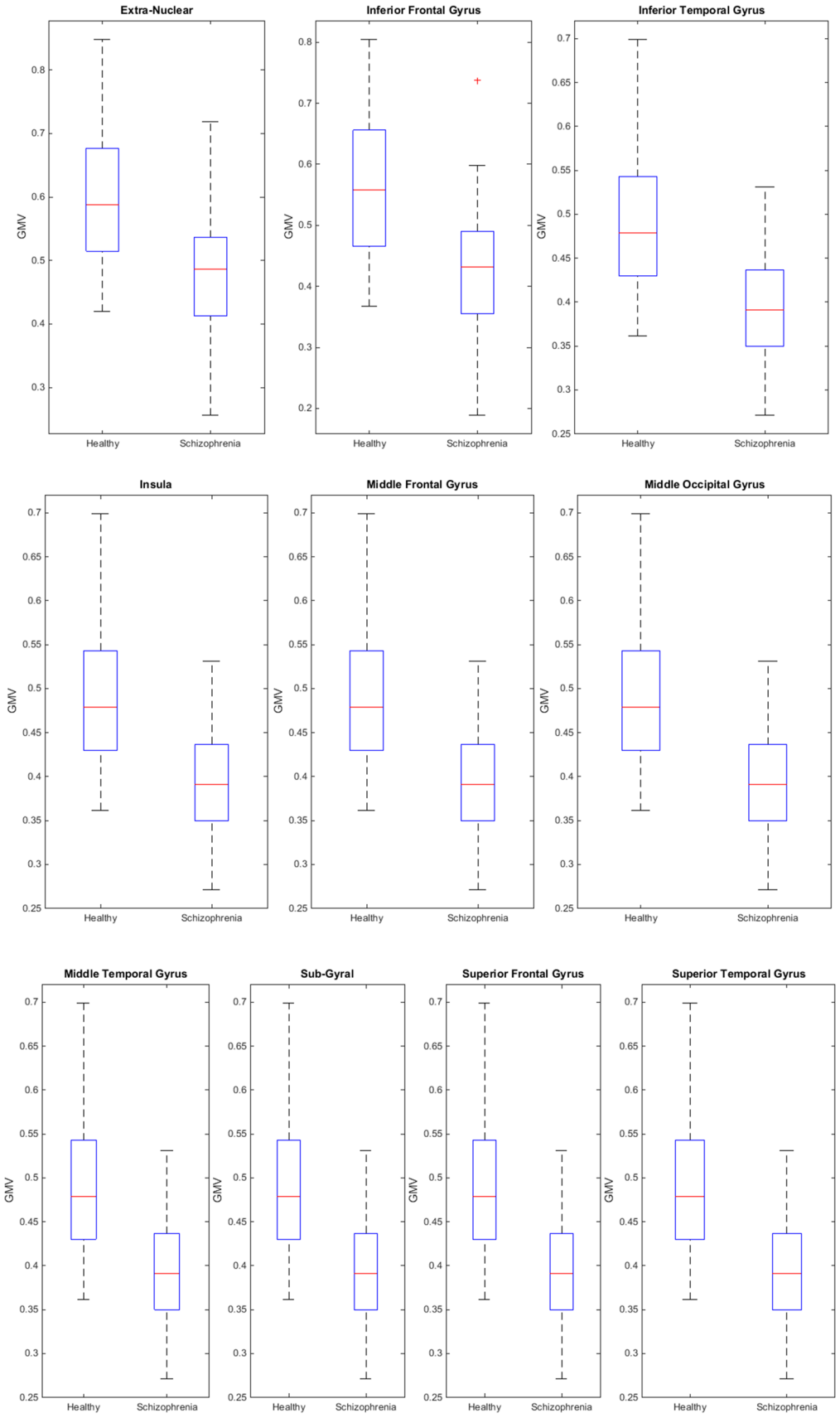


Fig. 4 Box plots showing brain regions having grey matter atrophy in schizophrenia patients for gyrus level

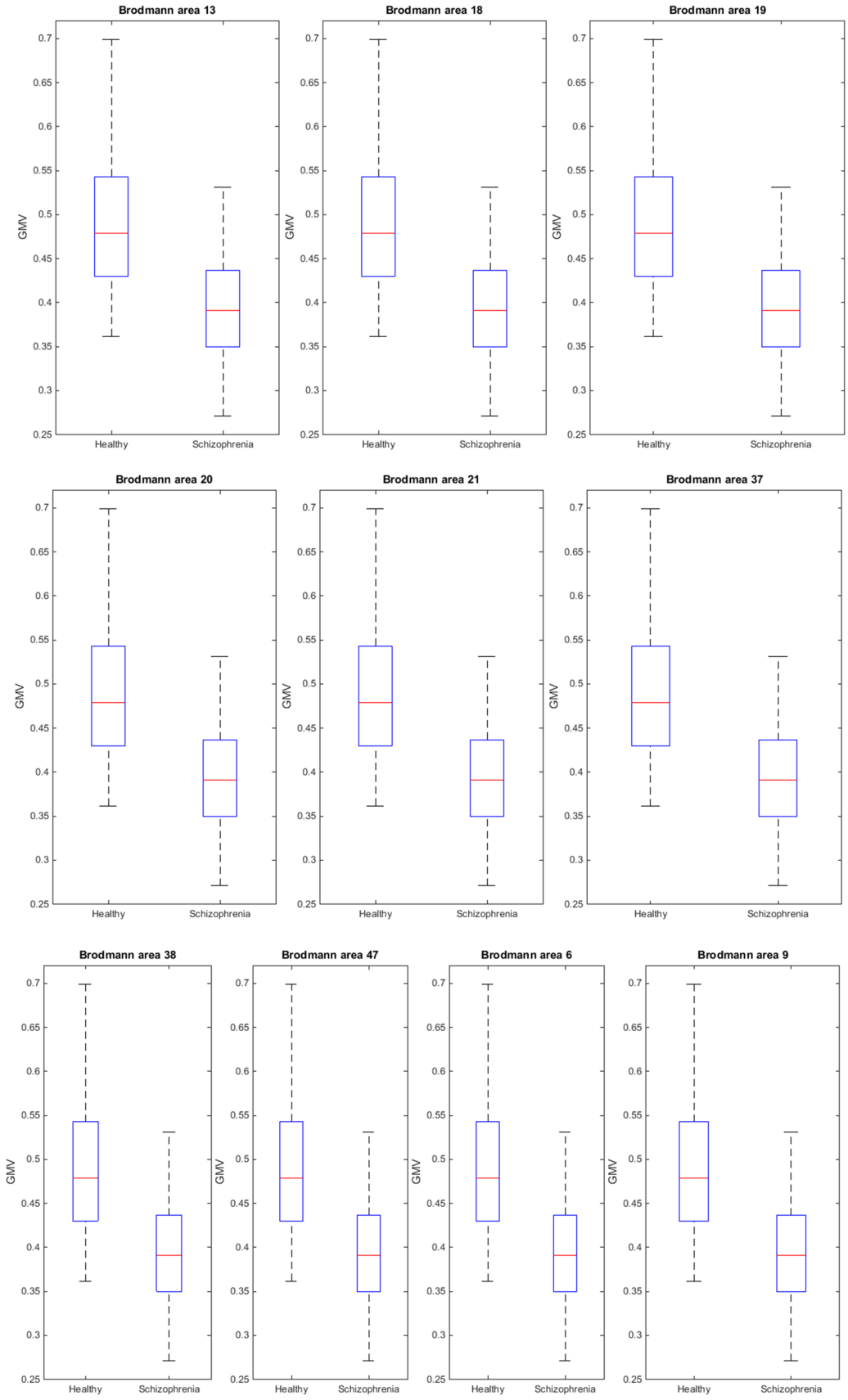
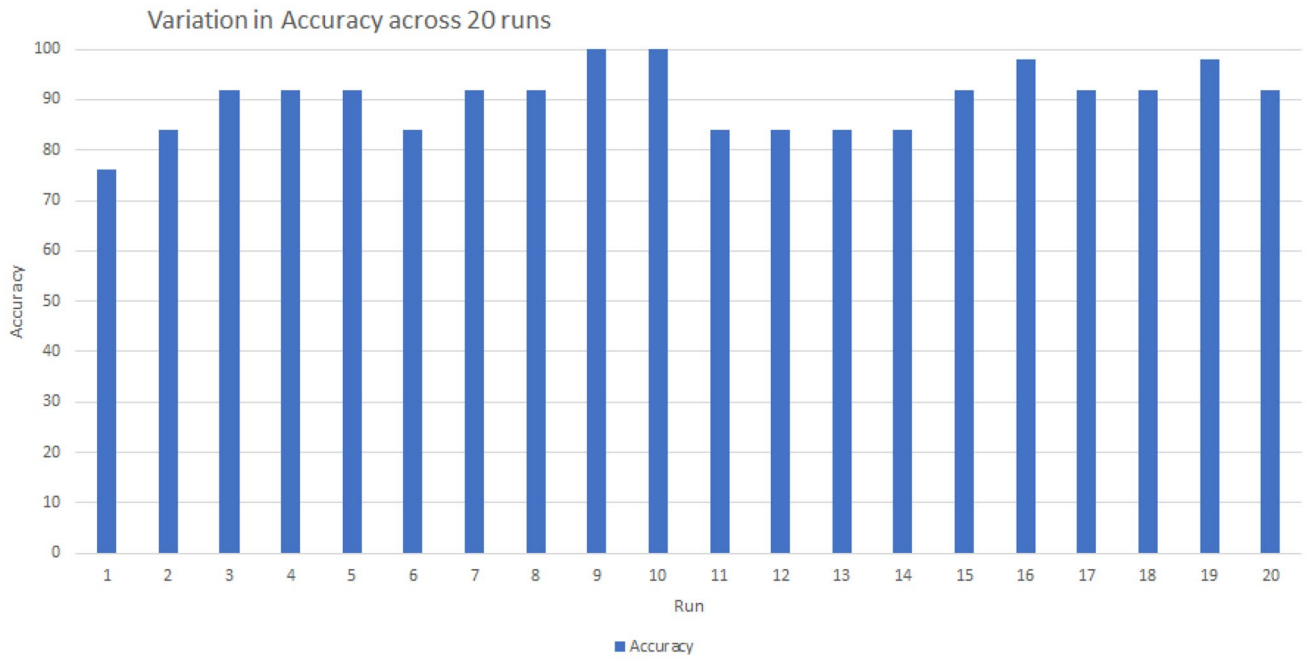
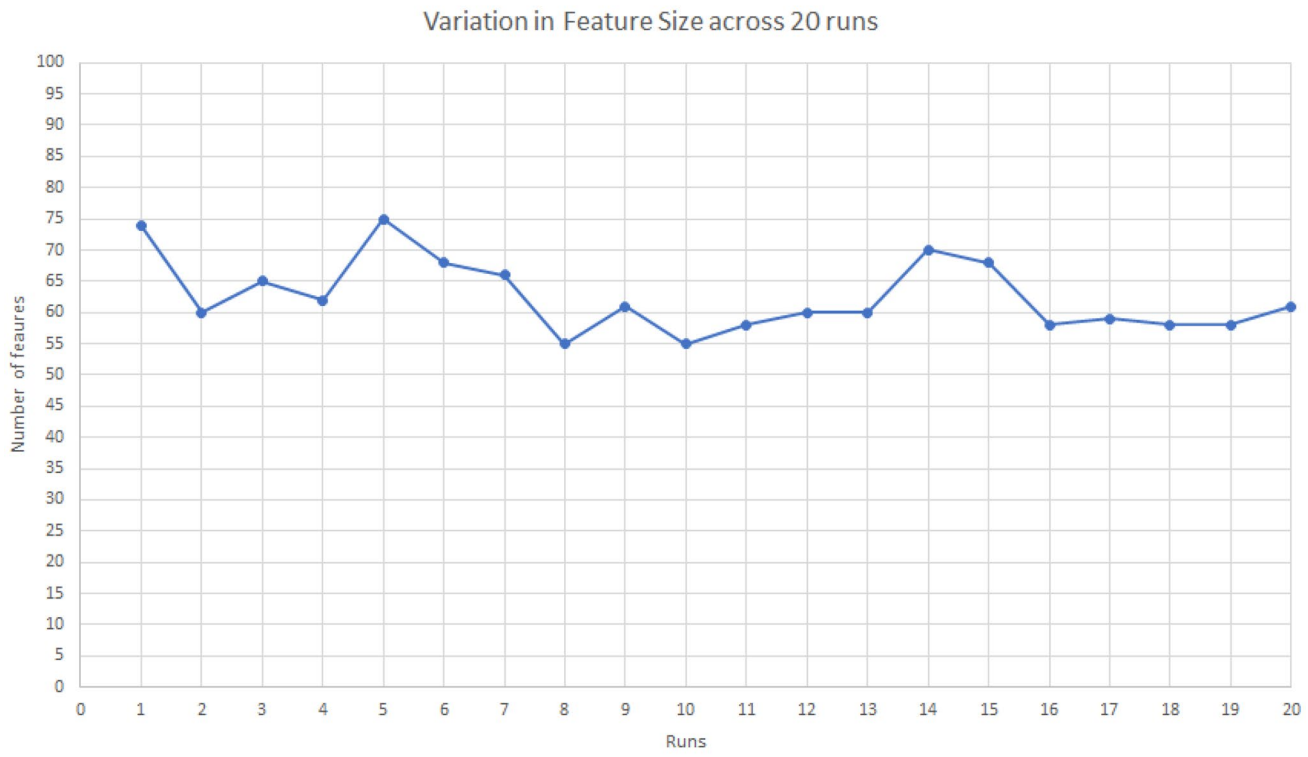


Fig. 5 Box plots showing brain regions having grey matter atrophy in schizophrenia patients for Brodmann's areas



a Accuracy across 20 runs



b Number of selected features across 20 runs

Fig. 6 Variation of mean classification accuracy and feature set size for each independent run of the Experiment 2(b). **a** The variation of mean accuracy. **b** The variation in the number of features across all the runs

Table 5 Identified brain regions showing statistically significant difference in grey matter volume when compared between healthy and schizophrenia subjects

Brain regions	*P* value
Left cerebrum	7.83E−07
Right cerebrum	5.17E−07
Frontal lobe	1.26E−05
Occipital lobe	1.75E−06
Sub-lobar	1.40E−05
Temporal lobe	4.84E−07
Extra-nuclear	1.95E−05
Inferior frontal gyrus	2.02E−05
Inferior temporal gyrus	4.19E−06
Insula	6.45E−06
Middle frontal gyrus	2.88E−05
Middle occipital gyrus	1.75E−06
Middle temporal gyrus	3.93E−07
Sub-gyral	6.43E−06
Superior frontal gyrus	2.72E−05
Superior temporal gyrus	2.10E−06
Brodmann area 13	1.50E−05
Brodmann area 18	3.29E−06
Brodmann area 19	1.72E−06
Brodmann area 20	5.91E−06
Brodmann area 21	5.28E−07
Brodmann area 37	3.68E−06
Brodmann area 38	1.97E−06
Brodmann area 47	2.02E−05
Brodmann area 6	2.72E−05
Brodmann area 9	2.88E−05

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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