BioMarker Identification for Diagnosis of Schizophrenia with Integrated Analysis of fMRI and SNPs

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***Abstract*—It is important to identify significant biomarkers such as SNPs for medical diagnosis and treatment. However, the size of a biological sample is usually far less than the number of measurements, which makes the problem more challenging. To overcome this difficulty, we propose a sparse representation based variable selection (SRVS) approach. A simulated data set was first tested to demonstrate the advantages and properties of the proposed method. Then, we applied the algorithm to a joint analysis of 759075 SNPs and 153594 functional magnetic resonance imaging (fMRI) voxels in 208 subjects (92 cases/116 controls) to identify significant biomarkers for schizophrenia (SZ). When compared with previous studies, our proposed method located 20 genes out of the top 45 SZ genes that are publicly reported. We also detected some interesting functional brain regions from the fMRI study. In addition, a leave one out (LOO) cross-validation was performed and the results were compared with that of a previously reported method, which showed that our method gave significantly higher classification accuracy. In addition, the identification accuracy with integrative analysis is much better than that of using single type of data, suggesting that integrative analysis may lead to better diagnostic accuracy by combining complementary SNP and fMRI data.**

Keywords-Sparse representations, SNP, fMRI, Variable selection, Integrated analysis.

I. INTRODUCTION

Sparse representation has received a great attention in recent years [1]-[7]. For example, Kidron et. al. used sparse regression for cross-modal localizations of sound-related region in the video [4]. We recently developed sparse representation based clustering algorithms for sub-typing of leukemia using gene expression data [5], for M-FISH image segmentation [7] and for integrative analysis of gene copy number variation and gene expression data [6].

In applications such as signal recovery [8] [9] and significant components identification [10], the analysis ability of the sparse representation is limited by the number of samples. Generally speaking, the number of signals to be recovered or the significant components to be detected cannot be more than the number of samples. On the other hand, the number of samples in genomic data or other biomedical data (e.g. fMRI data) is usually far less than the number of variables. Thus, the existing methods cannot be used to effectively analyze the data in such cases.

Li et al. recently proposed a sparse representation based variable selection method and applied it to the voxel selection in fMRI data [10]. Their method is capable of getting the sparse solution when the number of samples is large. However, in many biomedical problems, the number of samples is far less than the number of variables.

In this work, we proposed a novel sparse representation based variable selection (SRVS) model that can select significant biomarkers at different detection resolutions. This extends the detection ability for small sample sizes. The analysis was performed by using a flexible window, the size of which determines the detection resolution. The SRVS algorithm has been proved to be convergent generating a unique sparse solution at any given detection resolution. To study the effect of the window size and the error term on the solution, we applied the SRVS to a simulated data set with 10000 variables and 100 samples (50 cases/50 controls). Then, we applied the algorithm to a joint analysis of 759075 SNPs and 153594 fMRI voxels in 208 subjects (92 cases and 116 controls) to identify significant biomarkers for schizophrenia (SZ).

Schizophrenia is a complex disease, caused by the interaction of a number of genetic factors (e.g. change of gene regulation, alteration of mRNA and SNPs) and environmental effects. In recent years, many studies focus on exploring critical genes or SNPs associated with schizophrenia. Many potential genetic markers of great importance have been reported to cause susceptibility to schizophrenia such as the G72/G30 gene locus on chromosome 13q [11], Gene DISC1 variation [12] and copy number variations on gene GRIK3, EFNA5, AKAP5 and CACNG2[13]. In addition to genetic studies, fMRI has been widely used for the study of schizophrenia because of its ability to identify both structural and functional abnormalities in brain regions of SZ patients [14] [15]. However, in most of the studies SNPs and fMRI have been used independently. In this work, we combined both fMRI and SNP information using our proposed SRVS method to get more comprehensive results.

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Two steps were taken to validate the selected variables (SNPs/fMRI voxels). Firstly, we compared our results with that of previous SZ studies. Our proposed SRVS method identified 20 genes (e.g. 'PRSS16', ' NOTCH4, 'PDE4B', 'TCF4') out of the top 45 SZ genes that are publicly available (http://www.szgene.org/default.asp). We also detected some interesting functional areas of the brain from the fMRI study. Secondly, a leave one out cross validation (LOO) was performed and the results were compared with a previously reported sparse representation based variable selection method [10]. The LOO results showed that our method gives significantly higher classification accuracy. In addition, the identification accuracy with integrative analysis is much better than using a single type of data; This suggests that SNP data and fMRI data have complementary information, which can be used for integrative analysis to have better diagnosis accuracy.

II. METHODS

In this section, we first describe the proposed algorithm and study its properties (Section *A*), then we apply the proposed SRVS method to the integrative analysis of SNP data and fMRI data (Section *B*), and finally we describe the validation method for the selected variables (Section *C*).

A. SRVS algorithm and its properties

Identifying significant biomarkers based on a small number of observations is a fundamental problem in signal processing [10]. In general, the sparse representation of a signal can be modeled by

$$y = X\delta + \varepsilon, \tag{1}$$

where $y \in R^{n\times 1}$ is the observation vector; $X \in R^{n\times p}$ are measurements of the data and $p \gg n$. $\varepsilon \in R^{n\times 1}$ is the measurement error caused by noise. The goal is to reconstruct the unknown vector $\delta \in R^{p\times 1}$ based on y and X.

To best approximate y by choosing a small number of non-zeros entries of δ for the model give by Eq. (1), we consider the following L_p minimization problem (P0):

$$(\text{P0}) \quad min \|\delta\|_p \; subject\; to \; \|y - X\delta\|_2 \le \varepsilon \tag{2}$$

where $\|*\|_p$ is the L_p norm, and $p \in [0,1]$. The following algorithm is designed to solve the minimization problem (P0) given by Eq. (2) and detect the columns of X relevant to y.

SRVS Algorithm

1. Initial $\delta^{(0)} = 0$;
2. For the Step l, randomly choose k columns from $X = \{x_1, \ldots, x_p\} \in R^{n\times p}$ to construct a $n \times k$ sub-matrix denoted as $X_l \in R^{n\times k}$; and mark the selected columns' indexes as $I_l \in R^{1\times k}$;
3. Solve the following L_p minimization problem to find the optimal sparse solution $\delta_l \in R^{k\times 1}$:

$$min\|\delta_l\|_p \quad \text{s.t.} \quad \|y - X_l\delta_l\|_2 \le \varepsilon \tag{3}$$

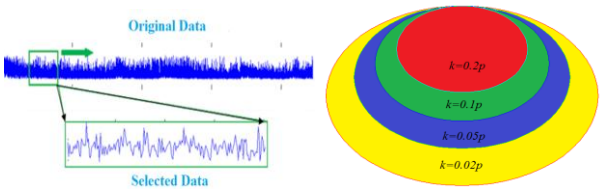
4. Update $\delta^{(l)} \in R^{p\times 1}$ with δ_l: $\delta^{(l)}(I_l) = \delta^{(l-1)}(I_l) + \delta_l$; where $\delta^{(l)}(I_l)$ and $\delta^{(l-1)}(I_l)$ denote the I_l th entries in $\delta^{(l)}$ and $\delta^{(l-1)}$ respectively;
5. If $\left\|\delta^{(l)}/l - \delta^{(l-1)}/(l-1)\right\|_2 > \alpha$, where α is a predefined constant, update $l = l + 1$, and go to Step 2. Otherwise, set $\delta = \delta^{(l)}/l$. The non-zero entries in δ correspond to the column vectors selected.

In Step 3, there are many proposed methods for solving the L_p minimization problem, such as Homotopy method [16] for $p = 1$, and orthogonal matching pursuit (OMP) algorithm [9] for $p = 0$.

In the following sections, we discussed the multiple resolution property of the method and the influence of the error term ε on the solution of δ.

The multiple resolution properties

One of the advantages of the proposed SRVS method is its multiple resolution characteristic. In Step 2 of the ***SRVS Algorithm***, one way to achieve the random selection of k columns from X is by shuffling the data with Fisher-Yates Shuffling algorithm[17], and then using a window of length k to select variables at a random position along the columns of the data, as shown in Fig. 1 (a). The length k of the sub-matrix $X_l \in R^{n\times k}$ is a resolution factor for the column variable selection process. The smaller the k, the higher the resolution of the detection process and the greater the number of selected variables. The variables selected with lower resolution (larger k) are subsets of variables selected with higher resolution (smaller k), as is shown in Fig. 1 (b). This is expected since the most important variables will be selected at any resolution. This multi-scale analysis gives a flexible method to select variables at different significance levels.



(a) (b)

Fig. 1 Diagram for the variables selected using SRVS method with different window lengths. (a) is a k-column selection process using a selection window; (b) is the influence of window length on the variables selected, where p is the total number of variables/columns.; The plot was generated with the results from simulated random white noise data set with column number p = 1e6, and row number m = 100 (case/control=50/50).

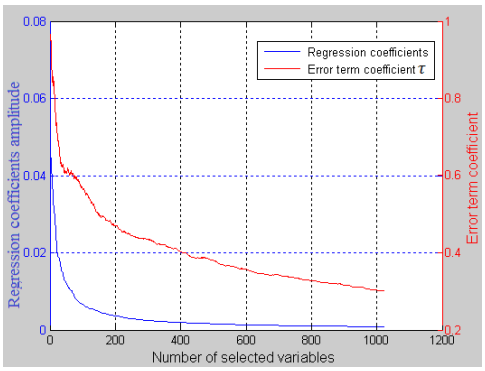


Fig. 2 The relationships among error term coefficient τ, amplitude of the regression coefficients δ_i and the number of selected variables/columns. The plot was generated with simulated white noise data set with column number p = 10e5 , row number m = 100 (case/control=50/50) and k = 0.02p.

Influence of error term ε on the solution δ

Once a group of variables are selected, the magnitude of the ith entry of δ reflects the significance of the ith column of X within the group [10]. However, Cai et al. showed that, if we set $\varepsilon = 0$, the selected columns may involve noise [9]. In this work, we set $\varepsilon = \tau\|y\|_2$ ($\tau \in (0,1)$ is the error term coefficient) and select the first m non-zero entries with highest magnitude from δ that satisfy Eq. (2). The relationships among error term ε, amplitude of regression coefficients δ_i(We sorted the entries of δ according to their amplitude and $\delta = \{\delta_i\}$) and the number of selected variables/columns are shown in Fig. 2. The 'Regression coefficients' line gives the relationship between amplitude of δ_i and the order that it has been selected. The 'Error term coefficient' line gives the relationship between error term ε and the number of selected variables. The larger the error term ε, the lower the number of selected variables and the more significant the selected variables. While ε decides how many significant variables should be selected, the significance of each selected variables was given by δ_i, as shown by the 'Regression coefficients' line (left axis) in Fig. 2.

B. *Variable selection in schizophrenia data*

We applied our proposed SRVS algorithm to an integrative analysis of 759075 SNPs and 153594 fMRI voxels in 208 subjects (92 cases and 116 controls) to identify significant biomarkers for schizophrenia (SZ).

Participants for the data collection

In this study, participant recruitment and data collection were conducted by The Mind Clinical Imaging consortium (MCIC). Two types of data (SNP and fMRI) were collected from 208 subjects including 96 schizophrenia patients (age: 34 ± 1 , 22 females) and 112 healthy controls (age: 32 ± 1, 44 females). All of them provided written informed consents. Healthy participants were free of any medical, neurological or psychiatric illnesses and had no history of substance abuse. By the clinical interview of patients for DSM IV-TR Disorders (22) or the Comprehensive Assessment of Symptoms and History, patients met criteria for DSM-IV-TR schizophrenia (23). Antipsychotic history was collected as part of the psychiatric assessment.

fMRI data collecting and preprocessing

fMRI data was collected during a sensorimotor task, a block-design motor response to auditory stimulation. During the on-block, 200 msec tones presented a 500 msec stimulus onset asynchrony (SOA). A total of 16 different tones were presented in each on-block, with frequency ranging from 236 Hz to 1318 Hz. The fMRI images were acquired on Siemens 3T Trio Scanners and a 1.5T Sonata with echo-planar imaging (EPI) sequences using the following parameters (TR = 2000msec, TE = 30msec (3.0T)/40msec (1.5T), field of view = 22cm, slice thickness = 4mm, 1mm skip, 27 slices, acquisition matrix = 64 × 64, flip angle = 90^o.) Data was pre-processed in SPM5 (http://www.fil.ion.ucl.ac.uk/spm) and was realigned, spatially normalized and resliced to 3 × 3 × 3 mm, smoothed with a 10×10×10 mm^3 Gaussian kernel to reduce spatial noise, and analyzed by multiple regression considering the stimulus and their temporal derivatives plus an intercept term as regressors. Finally the stimulus-on versus stimulus-off contrast images were extracted with 53 × 63 × 46 voxels and all of the voxels with missing measurements were excluded.

SNPs data

A blood sample was obtained for each participant and DNA was extracted. Genotyping for all participants was performed at the Mind Research Network using the Illumina Infinium HumanOmni1-Quad assay covering 1,140,419 SNP loci. Bead Studio was used to make the final genotype calls. Next, the PLINK software package ((27); http://pngu.mgh.harvard.edu/~purcell/plink) was used to perform a series of standard quality control procedures (28), resulting in the final dataset spanning 777,635 SNP loci. Each SNP was categorized into three clusters based on their genotype and was represented with discrete numbers: 0 for 'BB' (no minor allele), 1 for 'AB' (one minor allele) and 2 for 'AA' (two minor alleles).

Generalized SLR model for integrative analysis

We extended the sparse representation model given by Eq. (1) for the integrative analysis of two types of data sets:

$$y = [\alpha_1 X_1, \alpha_2 X_2] \begin{bmatrix} \delta_1 \\ \delta_2 \end{bmatrix} + \varepsilon = X\delta + \varepsilon \qquad (7)$$

where, $y \in R^{n\times 1}$ is the observation vector (phenotypes of the subjects); $X_1 \in R^{n\times p_1}$ and $X_2 \in R^{n\times p_2}$ are measurements of two different data types with their columns normalized to have unit L_2 norm; $X = [\alpha_1 X_1, \alpha_2 X_2] \in R^{n\times p}$; $\alpha_1 + \alpha_2 = 1$, and $\alpha_1, \alpha_2 > 0$ are the weight factors for the two types of data. $\varepsilon \in R^{n\times 1}$ is the measurement error caused by noise. The goal is to reconstruct the unknown vector $\delta = \begin{bmatrix} \delta_1 \\ \delta_2 \end{bmatrix} \in$

$R^{p\times 1}$ based on y and X, where $\delta_1 \in R^{p_1\times 1}$, $\delta_2 \in R^{p_2\times 1}$, , and $p_1 + p_2 = p$.

In this work, we consider the OMP algorithm [9] to solve a L_0 minimization problem in the Step 3 of the ***SRVS algorithm***. The OMP, with its simplicity and fast implementation, has been widely used for signal recovery and approximation[8], [18]-[21]. Donoho and Tsaig further proved that OMP and other alternative L_1 minimization based methods (e.g. LARS and Homotopy methods) are closely linked and under similar conditions both L_1 minimization and OMP recover the sparsest solution [16].

C. Validation

Two steps were taken to validate the selected variables (SNPs/fMRI voxels). Firstly, comparisons between our results and previous studies were performed for both selected SNPs and fMRI voxels. Secondly, identification of SZ patients using the selected variables has been done. We used the SRC classifier proposed by us [7], followed by the leave one out (LOO) cross validation. The results were compared with a previously reported SR based variable selection method [10]. In addition, we compared the LOO results using one type of data and using both types of data.

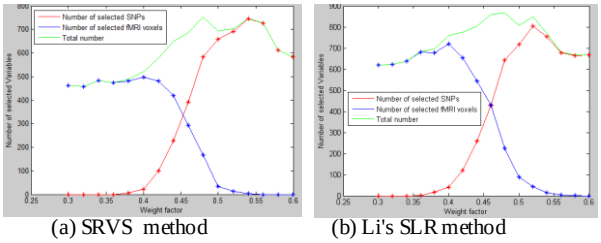
III. Results

We applied our method to an integrative analysis of two SZ data sets: SNP data and fMRI data. To validate the variables selected, we compared the results from our proposed SRVS method with that from previous SZ studies. We also compared the analysis results with that of using a SR based method by Li et al. [10].

A. Influence of weight factor on δ

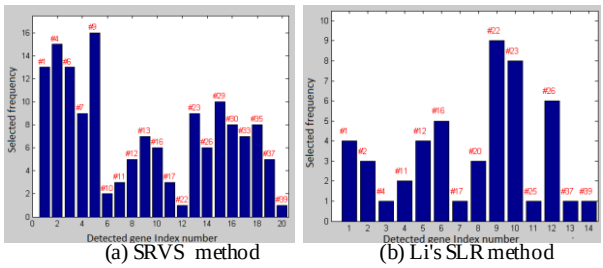
We tested the influence of weight factors on the variable selection results. Fig. 3 gives the plot of the number of SNPs and fMRI voxels selected against the SNP data weight factor α_1 (fMRI data weight factor $\alpha_2 = 1 - \alpha_1$). When the weight factor is small (e.g. $\alpha_1 = 0$), the selection is performed only using one type of data. Here we tested the range of α_1 from 0.3 to 0.6, and used a step length of 0.02 with a total of 16 different values.

To select the most important biomarkers, we set $\varepsilon = 0.3\|y\|_2$ and $k = 0.05$ in our proposed method. For Li's SLR method [10], the number of subjects selected in each



(a) SRVS method (b) Li's SLR method

Fig. 3 The influence of the weight factor α_1 on the variable selection.



(a) SRVS method (b) Li's SLR method

Fig. 4 Comparison of the selected genes with the reported top 45 SZ genes. The number above each bar is the order of the selected genes in the top 45 reported genes list.

run is $0.1n$, where n is the number of total subjects; and the threshold θ for δ is 0.01(please refer to [10] for the meaning of θ). From Fig. 3 (a) and (b) we can see that when α_1 is small, only a few SNPs were selected. Those SNPs should be the most important ones since they were identified in both two data sets with smaller weight factors. When α_1 is big, only a few fMRI voxels were selected. For the same reason, these pixels should be the most important ones.

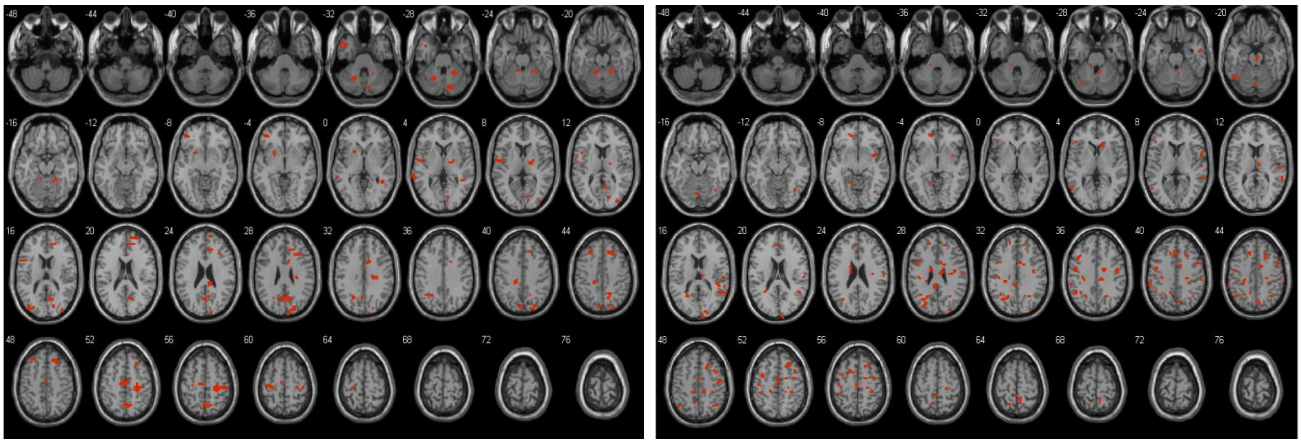
B. Comparison with Li's method

We compared our selected genes with the top 45 genes reported (http://www.szgene.org/default.asp). For the 16 trials we tested (α_1 is from 0.3 to 0.6; Step length = 0.02), our proposed method selected 20 reported genes (e.g. 'PRSS16', ' NOTCH4, 'PDE4B', 'TCF4') with high frequencies, as shown in Fig. 4 (a). Since significant biomarkers should be selected in most of the trials, the frequencies can be used as significance label for the variables For Li's SLR method, 14 reported genes were located with relatively lower frequencies (Fig. 4(b)).

We compared the fMRI voxels selected by our proposed SRVS method with that of Li's method, as shown in Fig. 5. It can be seen that the voxels selected by SRVS method are more clustered at specific regions such as temporal lobe, lateral frontal lobe, occipital lobe, and motor cortex, which are SZ related brain regions [22]-[24]. However, the voxels selected by Li's method are scattered over the whole brain, which provides less instructive information for identifying SZ related brain regions.

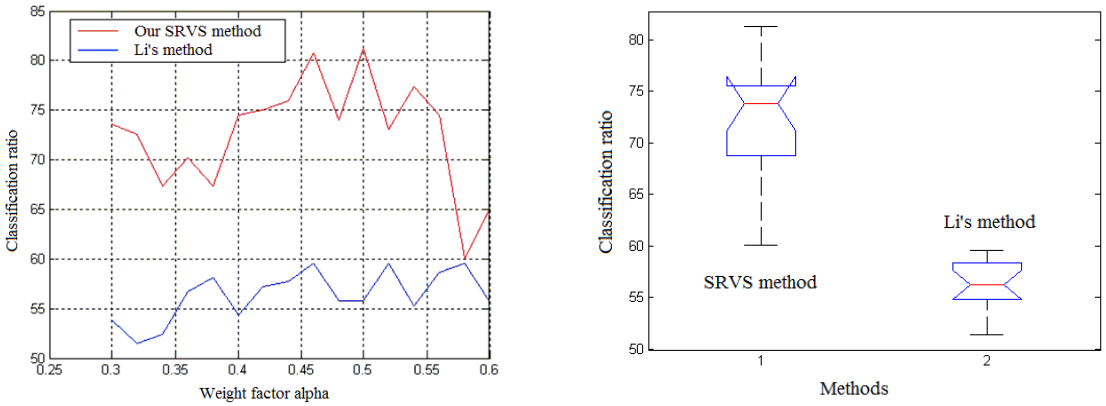
C. LOO validation

To further validate the selected variables (SNPs/fMRI voxels), we performed classification of SZ data sets with a sparse representation based classifier (SRC) [7] followed by the LOO cross validation. In the LOO validation, one sample was used for testing in each run and the rest of the samples were used for variable selection. Fig. 6 shows the results of our proposed SRVS method and those of Li's SLR method for the 16 trials given in Fig.3. It can be seen from Fig. 6 (b) that our method provides a much higher classification ratio (p-value $< 1e-11$).



(a) SRVS method (b) Li's SLR method

Fig. 5 The selected fMRI voxels from the two methods



(a) SRVS method (b) Li's SLR method

Fig.6 A comparison of the cross validation results of two methods. (a) gives the classification ratio of the two methods with different weight factors; (b) is the box plot generated with ANOVA analysis of the classification ratios from the two different methods

It should also be noted that when the weight factor is around 0.4 to 0.5, the classification ratios are higher than observed with other weight factors. This may be due to the fact that it employed both the most significant SNPs and fMRI voxels for the classification (see Fig. 3). When the weight factor is too small (close to 0) or too large (close to 1), variables mostly correspond to one type of data. This test demonstrates the advantages of integrative analysis.

IV. Discussion and Conclusion

In this work, we proposed a novel sparse representation based variable selection algorithm, which has the following advantages: 1. It uses a variable window, allowing one to detect variables at different significance levels; 2. It can be generalized to include more than two types of data for the integrative analysis.

In the ***SRVS Algorithm***, two parameters were introduced: the widow length k and error term ε. It is provable that our proposed SRVS algorithm converges for any given k and ε, generating a solution that effectively satisfies the sparse representation problem given by Eq. (2). However, we did not provide a detailed description of it due to the lack of space.

The introduction of a variable window in the SRVS algorithm is one of the advantages of our method. For the vast amount of measurements in the data, one may be interested in looking for significant variables at different significance levels. By simply varying the window length in the SRVS algorithm, the detection process will be performed at different resolutions. Consequently variables of different significance levels can be identified.

In the sparse representation based biomarker selection, the selected variables correspond to the non-zeros entries in δ, and their significances will be reflected by the magnitude of those entries [10] [9].Thus, by selecting a proper error ε, one can identify the most important variables among the selected biomarkers at a given resolution (see Fig. 2).

In addition to the advantages discussed above, our proposed SRVS algorithm can be generalized to include multiple types of data for the integrative analysis. As is shown in Fig. 3, when the weight factors for the SNP data and fMRI data are close to each other, the most important variables of each data sets are identified. Using those significant variables from both types of data produces a much better classification ratio, as shown in Fig. 6 (a).

When compared to the previous SZ studies, our method effectively identified 20 genes out of the top 45 SZ genes. Moreover, most of those genes were detected regardless of variability of the weight factor α_1 of SNP data, which were selected at high frequencies(as can be seen from Fig. 5 (a)). This proves the validity of our proposed method. We also located some interesting functional regions of the brain from the fMRI study, which further suggests the effectiveness of our method. In addition, the LOO cross validation results showed that our method generated significantly higher classification ratio in the LOO cross validation (Fig. 6 (b), p value $< 1e-11$), which suggests that our method is more effective for significant variable selection.

In this work, we consider the OMP algorithm [9] to solve a L_0 minimization problem in Step 3 of the ***SRVS algorithm***. However, different L_p minimization problems ($p \in [0,1]$) may lead to different results, which is worth further study.

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