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# **Examining Stability of Independent Component Analysis based on Coefficient and Component Matrices for Voxel-based Morphometry of Structural Magnetic Resonance Imaging**

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## **Abstract**

Independent component analysis (ICA) on group-level voxel-based morphometry (VBM) produces the coefficient matrix and the component matrix. The former contains variability among multiple subjects for further statistical analysis, and the latter reveals spatial maps common for all subjects. ICA algorithms converge to local optimization points in practice and the mostly applied stability investigation approach examines the stability of the extracted components. We found that the practically stable components do not guarantee to produce the practically stable coefficients of ICA decomposition for the further statistical analysis.

Consequently, we proposed a novel approach including two steps: 1), the stability index for the coefficient matrix and the stability index for the component matrix were examined, respectively; 2) the two indices were multiplied to analyze the stability of ICA decomposition.

The proposed approach was used to study the sMRI data of Type II diabetes mellitus group (DM) and the healthy control group (HC). Group differences in VBM were found in the superior temporal gyrus. Besides, it was revealed that the VBMs of the region of the HC group were significantly correlated with Montreal Cognitive Assessment (MoCA) describing the level of cognitive disorder.

In contrast to the widely applied approach to investigating the stability of the extracted components for ICA decomposition, we proposed to examine the stability of ICA decomposition by fusion the stability of both coefficient matrix and the component matrix. Therefore, the proposed approach can examine the stability of ICA decomposition sufficiently.

**Keywords:** Diabetes, Voxel-based morphometry, Independent component analysis, Back-projection, Montreal Cognitive Assessment, Stability, Coefficient matrix, Component matrix

# 1. Introduction

The structural Magnetic Resonance Imaging (sMRI) could reflect the real brain shape. Through the preprocessing, we can obtain grey matter volume (GMV). For the reason that grey matter is aggregation of neurons, it is closely related to brain cognition mechanism. The traditional method of GMV processing is mainly based on voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Kurth et al., 2015). An important step in VBM is to reveal group differences voxel by voxel. However, even with the minimum bounding box ( $61 \times 73 \times 61$ ), the number of voxels of the grey matter is still more than 60,000. Due to the numerous multiple comparisons, the phenomenon of false-alarm easily occurs. Even though many statistic scholars have been devoted to solve this problem, the current processing methods of functional MRI dataset are very likely to result in high-level false positive (Eklund et al., 2016).

To solve the problem of false-alarm, one method is to decrease the number of comparison times. Independent component analysis (ICA) is a promising approach that could extract dozens of features of individual regions and one feature is just compared once between groups. Therefore, ICA has been widely used to analyze GMV by using the software called GIFT (<http://mialab.mrn.org/software/gift/>) (Calhoun et al., 2006; Gupta et al., 2015; Luo et al., 2012; Segall et al., 2012; Sui et al., 2012; Xu et al., 2009a, 2009b, 2012).

For the reason that most of ICA decomposition are in terms of self-adaption algorithms and tend to converge to the local optimization points in practice, the results of different times for the same dataset decomposed by ICA with random initialization may change to some extent. For this problem, Himberg et al. developed a software called as ICASSO (Himberg et al., 2004) to evaluate the stability of the extracted component. This issue has been further addressed in many publications such as Correa et al (2007) and Ma et al. (2011). If the extracted components are stably separated out, the ICA decomposition is regarded as to be repeatable. Indeed, when ICA is applied on a matrix, both the coefficient matrix and the component matrix are produced. For example, with ICA on group-level VBM, the coefficient matrix contains the variability among different subjects and is used for the further statistical analysis, and the component matrix reveals the spatial maps. Due to the practically local optimization of ICA decomposition, the practically stable spatial maps extracted by ICA on VBM could not always guarantee that the extracted coefficient matrix is also stable in practice. If the coefficient matrix is not stably extracted out, the further statistical analysis based on it might not be repeatable.

Therefore, in this study, we proposed a novel approach for examining the stability of ICA decomposition, including two steps: 1) the stability index for the coefficient matrix and the stability index for the component matrix were examined, respectively; 2) the two indices were multiplied to analyze the stability of ICA decomposition. The proposed approach was applied to VBM of Diabetes patients and healthy subjects to show its effectiveness.

## 2. Method

### 2.1 Data description

In this experiment, 30 diabetic patients T2 diabetes mellitus (T2DM) and 30 healthy subjects with matched gender and age participate in the T1 image scanning as the structural dataset of brain. The following are the important scanning parameters: TE:2.49, TR:1900ms, FOV: 250\*250, matrix: 256\*256, FA: 9 degree, thickness: 1mm, 176 slices. MoCA (Montreal Cognitive Assessment) was collected for each subject. Its scale describes the level of cognitive disorder, with the full score of 30. If the score is more than 25, the subject would be diagnosed with no cognitive disorder.

### 2.2 Preprocessing and conventional VBM

The sMRI data were preprocessed with the VBM plugin in DPABI (Yan et al., 2016). First of all, the T1 image of brain was segmented as grey matter, white matter and cerebrospinal fluid. Secondly, due to the difference of brain shapes and similarities of anatomy structure among subjects, spatial normalization was performed for further group analysis. Afterwards, the normalized grey matter was registered to the standard MNI template. Then, smooth was done to reduce artifacts as shown in Figure1 (Kurth et al., 2015). For VBM, statistical analysis is conducted for the grey matter volume. Group differences is examined at the voxel level, which corresponded to the AAL (Tzourio-Mazoyer et al., 2002) and Brodmann (Maldjian et al., 2003) encephalic regions. Statistical corrections is done at the voxel level.

### 2.3 ICA approach

#### 2.3.1 Data model for ICA

ICA is based on the linear model of unknown source signals  $\mathbf{S}$  and observed signal  $\mathbf{Z}$ . The follow equation could describe the model:

$$\mathbf{Z} = \mathcal{A}\mathbf{S} \quad (1)$$

where  $\mathbf{Z} \in \mathcal{R}^{M \times N}$ ,  $\mathbf{S} \in \mathcal{R}^{R \times N}$ .  $\mathcal{A} \in \mathcal{R}^{M \times R}$  with the full column rank is named as mixing matrix. After preprocessing, the GMV dataset is extracted with grey mask. The GMV data of the  $i_{th}$  subject is defined as the row vector  $\mathbf{z}_i$  which is the row of the matrix  $\mathbf{Z}$ , and the dataset of all subjects composes the matrix  $\mathbf{Z}$ .  $M$  refers to the number of subjects and  $N$  the number of voxels.  $\mathbf{S}$  represents the source signals of ICA decomposition and  $R$  the number of components. Figure2 describes how the

matrix is composed.

The dimension of the observed signal for the matrix is the number of subjects in this study. It is assumed to be larger than that of the source signals, which can be interpreted as  $M$  is larger than  $R$ . In this case, the model can be regarded as the over-determined. Therefore, the first step should be dimension reduction before data decomposition with ICA. After estimating the number of source components, the over-determined model is transformed to the determined model by dimension reduction matrix.

$$\mathbf{X} = \mathbf{V}^T \mathbf{Z} = \mathbf{V}^T \mathbf{A} \mathbf{S} = \mathbf{A} \mathbf{S} \quad (2)$$

In the above formula,  $\mathbf{A} \in \mathcal{R}^{R \times R}$ ,  $\mathbf{A} = \mathbf{V}^T \mathbf{A}$ ,  $\mathbf{X} \in \mathcal{R}^{R \times N}$ ,  $\mathbf{V}^T \in \mathcal{R}^{R \times M}$  refers to the dimension reduction matrix. The dimension reduction matrix usually derives from Principal Component Analysis (PCA), and the  $\mathbf{V}^T$  consists of the first  $R$  eigenvectors of the covariance matrix of the data matrix  $\mathbf{Z}$ . Figure3 depicts the process.

### 2.3.2 ICA decomposition for coefficient matrix and component matrix

The ICA decomposition model is as the following:

$$\mathbf{Y} = \mathbf{W} \mathbf{X} \quad (3)$$

where  $\mathbf{Y} = \mathcal{R}^{R \times N}$  is the estimation of source signals  $\mathbf{S}$  and it is called component matrix in this study. The main purpose of ICA is to find unmixing matrix  $\mathbf{W} \in \mathcal{R}^{R \times R}$  based on the independence of components. For ICA on VBM, each component (each row of  $\mathbf{Y}$ ) represents the spatial map and the variability among different subjects exist in the  $\mathbf{W}$ .

According to different cost functions which aim to obtain the unmixing matrix, Hyvärinen et al. introduced five different ICA algorithms, including Non-Gaussian Maximize based ICA algorithm, Maximum Likelihood Estimation based ICA algorithm, Minimum Mutual Information based ICA algorithm, Tensor based ICA algorithm and Nonlinear Decorrelation and Nonlinear PCA based ICA algorithm (Hyvärinen et al., 2001). Beyond that fixed-point based FastICA (Hyvarinen, 1999) and max mutual information based InfomaxICA (Sejnowski and Bell 1995) also have been widely used in many fields. In this study, the InfomaxICA is used due to its stability advantage. The mutual information equation is listed as the following:

$$I(\mathbf{Y}, \mathbf{X}) = H(\mathbf{Y}) - H(\mathbf{Y}|\mathbf{X}) \quad (4)$$

where  $I$  refers to the mutual information of components and  $H$  the entropy. Based on the above formula, the iterative formula was obtained as follows:

$$\Delta \mathbf{W} \propto [\mathbf{W}^T]^{-1} + (1 - 2\mathbf{Y})\mathbf{X}^T \quad (5)$$

For the reason that dimension reduction has been done before ICA decomposition, the mixing matrix cannot be obtained by the direct inverse of  $\mathbf{W}$ . In Cong et al's study, it has been pointed out that both unmixing matrix and dimension reduction matrix need to be considered in order to obtain coefficient matrix (Cong et al., 2014):

$$\mathbf{U} = \mathbf{V}\mathbf{B} = \mathbf{V}\mathbf{W}^{-1} \quad (6)$$

where  $\mathbf{B} = \mathbf{W}^{-1}$  and  $\mathbf{U} \in \mathcal{R}^{M \times R}$  is named as the coefficient matrix approximating the mixing matrix  $\mathcal{A}$  in (1) and each column of the  $\mathbf{U}$  contains the variability of different subjects.

### 2.3.3 Remark for Equations 1 to 6

In terms of Eqs (1-6), when ICA is applied on group-level VBM, two matrices are generated and they are the component matrix  $\mathbf{Y}$  whose rows represent the spatial maps and the coefficient matrix  $\mathbf{U}$  who columns contain the variability among multiple subjects. It is necessary to analyze whether the stability of the extracted components also indicate the stability of coefficient matrix.

### 2.3.4 Stability of ICA decomposition under global optimization

If both Eqs. (2-3) are merger together, the global matrix  $\mathbf{C}$  links the extracted components and the sources together as the following:

$$\mathbf{Y} = \mathbf{W}\mathbf{X} = \mathbf{W}\mathbf{A}\mathbf{S} = \mathbf{C}\mathbf{S}, \quad (7)$$

where  $\mathbf{C} = \mathbf{W}\mathbf{A}$ .

As shown in (5), the ICA algorithm is adaptive. In theory, for global optimization, in each column and each row of the global matrix  $\mathbf{C}$ , there is only one nonzero elements. Then, the global matrix can be decomposed as the multiplication of a permutation matrix  $\mathbf{P}$  and a diagonal matrix  $\mathbf{D}$  as

$$\mathbf{C} = \mathbf{P}\mathbf{D}, \quad (8)$$

$$\mathbf{Y} = \mathbf{C}\mathbf{S} = \mathbf{P}\mathbf{D}\mathbf{S}, \quad (9)$$

Subsequently, the coefficient matrix turns to be

$$\mathbf{U} = \mathbf{VB} = \mathbf{VW}^{-1} = \mathbf{VAD}^{-1}\mathbf{P}^{-1} = \mathbf{VV}^T\mathcal{A}\mathbf{D}^{-1}\mathbf{P}^{-1} = \mathcal{A}\mathbf{D}^{-1}\mathbf{P}^{-1}, \quad (10)$$

where,  $\mathbf{WA} = \mathbf{PD}$ ,  $\mathbf{A} = \mathbf{V}^T\mathcal{A}$ ,  $\mathbf{VV}^T$  is the identity matrix since  $\mathbf{V}$  contains the eigenvectors of the covariance matrix of the data matrix  $\mathbf{Z}$ ,  $\mathbf{D}^{-1}$  is still the diagonal matrix and  $\mathbf{P}^{-1}$  is the permutation matrix.

Therefore, in theory, if one ICA algorithm is run multiple times with random initialization, the extract components are stable and the coefficient matrix is stable as well. Stability of extracted components indicates the stability of ICA decomposition.

### 2.3.5 Stability of ICA decomposition under local optimization

Since most of ICA algorithms are adaptive and they tend to converge to the local optimization points instead of the global optimization. This results in that the global matrix cannot be decomposed by a permutation matrix and a diagonal matrix. Subsequently,

$$\mathbf{Y} = \mathbf{CS} \neq \mathbf{PDS}, \quad (11)$$

$$\mathbf{U} = \mathbf{VW}^{-1} \neq \mathcal{A}\mathbf{D}^{-1}\mathbf{P}^{-1}. \quad (12)$$

This means some of the extracted components are still mixtures of some sources. For estimating coefficient matrix  $\mathbf{U}$ , the inverse of the unmixing matrix  $\mathbf{W}$  cannot be avoided. It is widely acknowledged that the inverse operation can be not stable, and can amplify the errors in  $\mathbf{W}$ . Therefore, it is necessary to examine whether both the component matrix  $\mathbf{Y}$  and the coefficient matrix  $\mathbf{U}$  are stably extracted out or not.

For example if the number of component is  $R$ , and ICA decomposition is run  $K$  times with random initialization,  $R*K$  components are produced and then, those components can be clustered. A parameter called Iq is calculated in terms of the inner similarity within one cluster and dissimilarity among different clusters. This approach is called ICASSO (Himberg et al., 2004). Here, the Iq for the component is called Comp\_Iq.

For ICA decomposition, each component is associated with each coefficient vector. In order to obtain the stability of the coefficient matrix, the memberships of  $R*K$  components can be used to cluster the  $R*K$  coefficient vectors. The parameter Iq can also be generated for the coefficient matrix. It is called Coef\_Iq in this study.

If both the component and the corresponding coefficient vector are stably extracted, the ICA decomposition for the component and the coefficient vector is repeatable. As a result, the Iq of the ICA decomposition in this study is defined as

$$\text{Iq} = \text{Comp\_Iq} \times \text{Coef\_Iq} \quad (13)$$

Because the range of stability is from 0 to 1, multiplying will not change the range of evaluation of stability. Comp\_Iq can be understood as the probability of the stability of the component matrix. Coef\_Iq can be understood as the probability of the



stability of the coefficient matrix. So the multiplication can be expressed as the stability of the whole.

### 2.3.6 Remark for Equation 13

The range of  $I_q$  for ICA components (Himberg et al, 2004) is from 0 to 1.  $I_q$  for the coefficient matrix also ranges from 0 to 1. From 0 to 1, the stability increases. Therefore, if the two  $I_s$  are multiplied, the product will be closer to 1 if both of them are closer to 1. Otherwise, the lower  $I_q$  will play the role of penalty in the multiplication to result in a lower product, indicating the lower stability of ICA decomposition. In other words, as long as the ICA components are not stable or the coefficient matrix is not stable, the ICA decomposition will not be stable, which is conveyed by the Eq. (13).

### 2.3.7 Feature extraction for GMV by the ICA approach

For any extracted component of ICA or its associated coefficient vector, i.e., each row of  $\mathbf{Y}$  or each column of  $\mathbf{U}$ , its polarity and variance are not determined (Cong et al., 2011a,b). For ICA on VMB, each row of  $\mathbf{Y}$  represents the spatial map and each column of  $\mathbf{U}$  reveals the variability among multiple subjects. Therefore, the indeterminacy brings difficulty for the interpretation of GMV. In order to overcome the difficulty, the back-projection theory is borrowed from the application of functional brain imaging data (Cong et al., 2011a,b). The back-projection is shown as the following:

$$\mathbf{E}_r = \mathbf{u}_r \mathbf{y}_r \quad (14)$$

where  $r$  refers to the  $r_{th}$  component extracted from ICA,  $\mathbf{u}_r$  is the  $r_{th}$  column of  $\mathbf{U}$  at formula (6),  $\mathbf{y}_r$  the  $r_{th}$  ICA component and is the  $r_{th}$  row of  $\mathbf{Y}$ , and  $\mathbf{E}_r$  the back-projection result of  $r_{th}$  component.

The size of  $\mathbf{E}_r$  and  $\mathbf{Z}$  are the same. Its number of rows is the number of subjects and its number of columns is the number of voxels. Then,  $\mathbf{E}_r$  includes all subjects' data and each row of the  $\mathbf{E}_r$  represents each subject's GMV data estimated from the proposed ICA approach. It should be noted that in  $\mathbf{E}_r$  the variability among different subjects is consistent across all voxels in terms of (14).

Moreover, one row of  $\mathbf{Z}$  actually represents the GMV data of one subject after the conventional preprocessing and probably includes many regions of interest. However, after the proposed ICA approach, one row of the  $\mathbf{E}_r$  only includes one region or very limited regions of interest for one subject. From this perspective, the conventional VBM data is spatially filtered by the proposed ICA approach.

The feature extraction for GMV is in terms of  $\mathbf{E}_r$  in (14) for the ICA approach. An ROI can be generated from the spatial map  $\mathbf{y}_r$  after the setting of a proper threshold. Then, the mean value of GMV in the ROI in each row of  $\mathbf{E}_r$  defined as the

feature of GMV for each subject. Since the variability among different subjects is consistent across all voxels in  $\mathbf{E}_r$ , the averaging is reasonable. Therefore, the features of different groups (DM and HC here) in each ROI are compared only once, which avoids the false-alarm caused by multiple comparisons due to multiple voxels in the conventional VBM method.

### 2.3.8 Data processing steps

The proposed data processing steps in this study are as the following:

- 1) The grey matter was segmented from sMRI data.
- 2) The grey matter was normalized to MNI space and extracted in terms of the grey mask.
- 3) GMV was reshaped into vectors and all the vectors from multiple subjects were grouped together to compose the data matrix  $\mathbf{Z}$  for ICA. In the current study, the size of matrix was  $60 \times 67541$ , the number of subjects was 60 and the number of voxels was 67541.
- 4) InfomaxICA with default parameters of ICASSO was applied on the data matrix  $\mathbf{Z}$  in terms of the equations from (1) to (6), and finally, new features of GMV were obtained according to 2.3.7.
- 5) The stability of ICA decomposition was analyzed by Eq. (13).
- 6) Statistical analysis was conducted to find the components that were significantly different in GMV between groups. After that, correlation analyses were performed between GMV and behavior factors (MoCA here) for each group.
- 7) The component (representing the spatial map) with the significant difference in GMV between two groups of subjects, and meanwhile with the significant correlation between the feature of GMV and any of the behavior factor for any group was selected as the component of interest for the further investigation.

## 3. Result

### 3.1 Stability of ICA decomposition using dataset of ICASSO software

ICASSO provides the dataset of MEG (Himberg et al., 2004). It was used for the demonstration of the proposed method in this study and 20 components were extracted out.

Figure 7 shows the clustering results for the component matrix and the coefficient matrix, as well as the stability index. The index reveals that lower stability of extracted components resulted in even lower stability of the coefficient vectors. This can make the further analysis based on the coefficient matrix is not repeatable.

### **3.2 Stability of ICA decomposition for VBM data in this study**

The Minimum description length (MDL) approach in the previous study (Li et al., 2007) was used to estimate the number of extracted components from the VBM data in this study. The estimated number of components was 15.

Figure 8 shows the clustering results for the component matrix and the coefficient matrix, as well as the stability index. The stability indices for the last two components and coefficient vectors were much lower than others, indicating they might be not repeatable if the same data processing approach was performed again. Therefore, the last two components and the coefficients could not be accepted for the further data analysis.

### **3.2 Statistical analysis of the feature extracted by stable ICA decomposition for VBM data in this study**

The significant differences in the features of GMV between DM and HC were found at superior temporal gyrus from one component (#12) shown in Figure 9. The stability of ICA decomposition for this component and the corresponding coefficient vector (i.e. feature of GMV in this study) was better than five (one third of all 15 components) others. The results by the ICA approach keep in line with the findings from previous studies (Chen et al., 2012; Zhang et al., 2014). Significant correlations were observed in the HC group between the features of GMV and MoCA.

## **4. Discussion**

For global optimization of ICA decomposition, stability of the extracted components indicates the stability of the coefficient matrix. However, since ICA algorithms inevitably converge to the local optimization points in practice, the lower stability of an extracted component can result in even lower stability of the corresponding coefficient vector. Therefore, in this study, we proposed a novel approach for sufficiently examining the stability of ICA decomposition by merging the stability of extracted component matrix and the coefficient matrix together.

The proposed approach was applied to find the differences in GMV between Type II diabetes mellitus group (DM) and the healthy control group (HC). The scores of MoCA were taken as behavioral factor since they can reflect the level of cognition ability and the GMV results of interesting were supposed to be correlated with the

scores of MoCA. The features of GMV by the proposed ICA approach in HC groups were significantly and positively correlated with the HC groups, and GMV was significantly reduced in DM group in contrast to HC group.

Type 2 diabetes mellitus (T2DM) is a chronic, metabolic disease characterized by hyperglycemia which leads over time to serious damage to the blood vessels in brain. T2DM is associated with cognitive decrements and an increased risk to develop dementia (Mccrimmon et al., 2012; Spauwen et al., 2013). And it displays structural changes in the brain such as cortical atrophy. It has shown more prominent DM-related regional gray matter loss (Erus et al., 2015; Moran et al., 2013). Diabetes-related cognitive impairment is attributable to the structural changes (Kim et al., 2016). Since MoCA assesses a broader range of cognitive domains including abstraction and executive function, it may be sensitive to diagnose MCI in DM subjects (Alagiakrishnan et al., 2014). In this study, the GMV results by the proposed ICA approach match the previous findings. There are two advantages of the new approach as the following.

In future study, tensor decomposition (Cong et al., 2015) can be employed in MRI dataset processing. The current data-driven method may not fully exploit the structure information of MRI dataset through reshaping data from multi-dimensions to vectors. Hence, tensor, which operates on high-order structure directly, may generate more reasonable results (Barnathan et al., 2011). Furthermore, the study is devoted to the structural imaging data and the proposed idea can also be applied to functional and psychological imaging data for different time scales (Dđi et al., 2017).

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## Figure captions:

Figure 1: Original sMRI data and the data after preprocessing

Figure 2: Vectorization and matrix of GMV of multiple subjects

Figure 3: Dimension reduction by PCA

Figure 4: ICA decomposition model for GMV data

Figure 5: Calculation of coefficient matrix approximating the mixing matrix

Figure 6: Feature extraction for GMV by the ICA approach

Figure 7: Stability of ICA decomposition using dataset of ICASSO software. Each black convex hull represents one cluster. The intensity of red shade shows the degree of similarity among components.

Figure 8: Stability of ICA decomposition for VBM data in this study

Figure 9: Statistical results of Component#12 at superior temporal gyrus and the corresponding coefficient vector, i.e., the feature of GMV. The coefficient vector of the DM group shows a significant correlation with the MoCA value. This means that the feature is associated with diabetes.

**Figure 1**

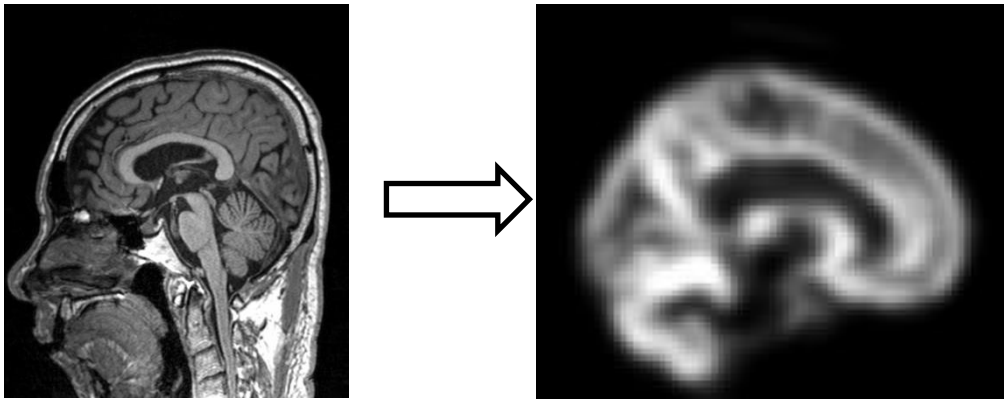
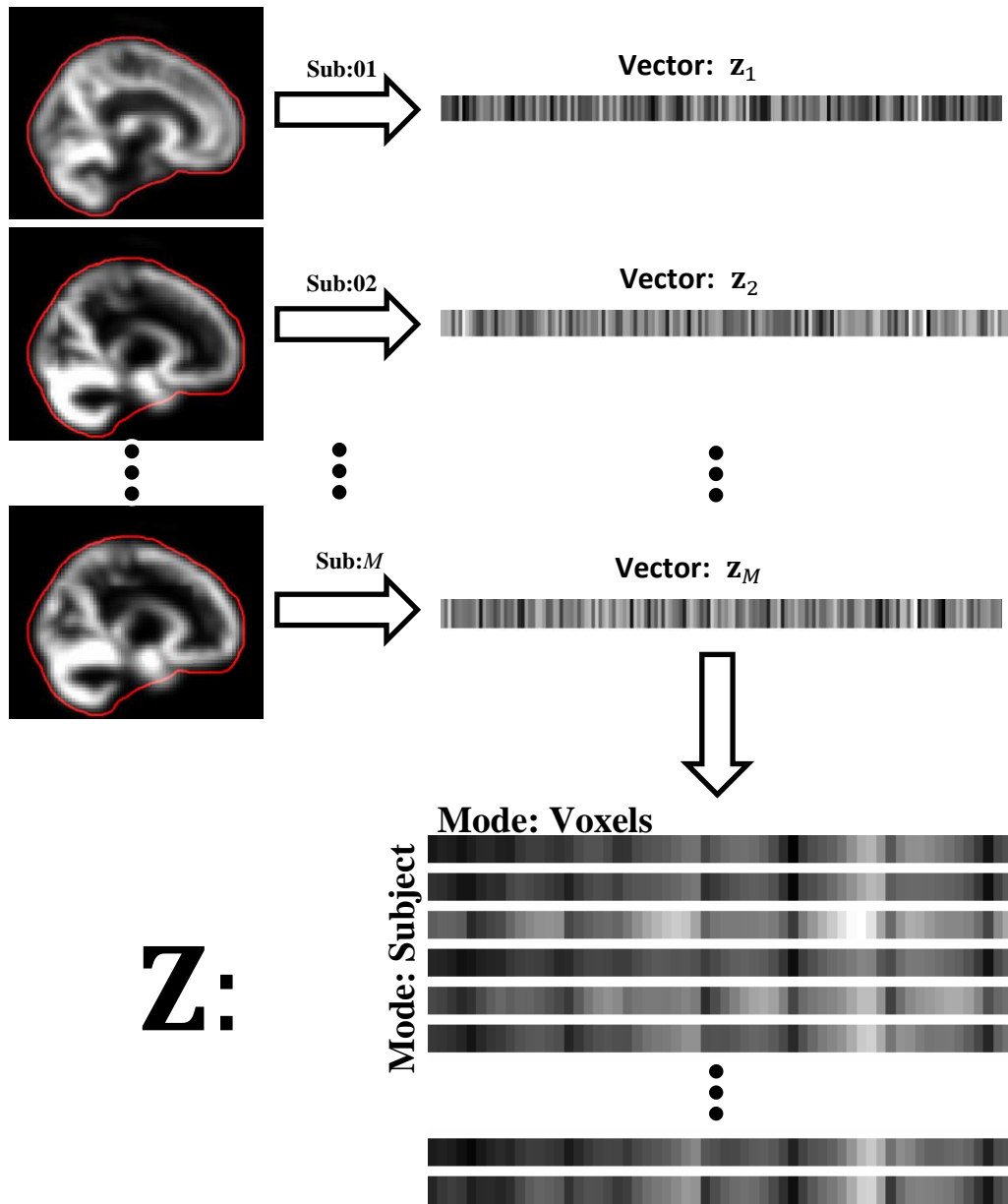
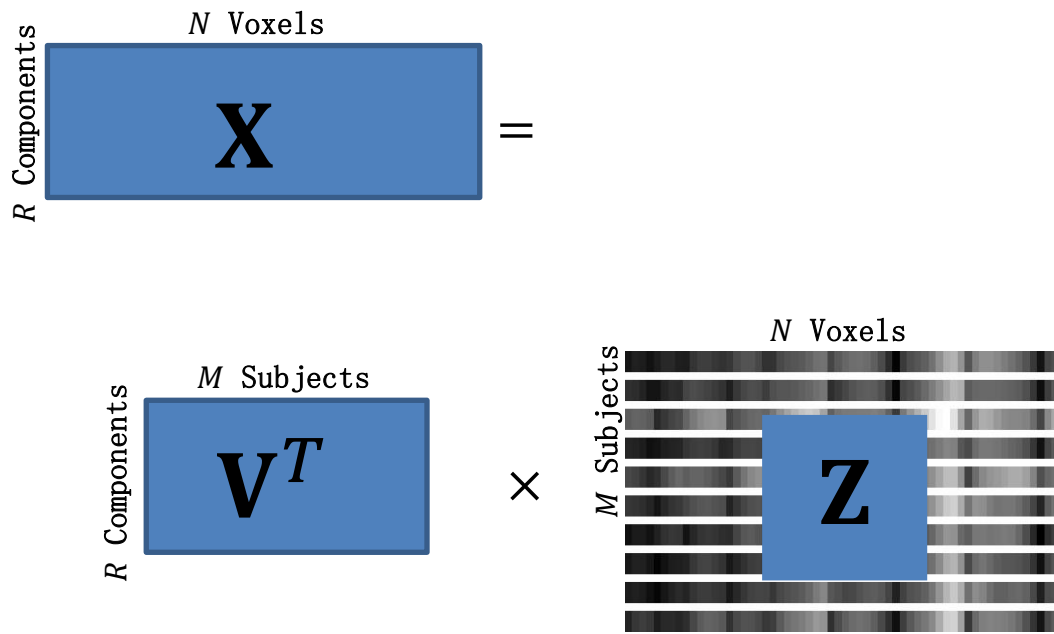




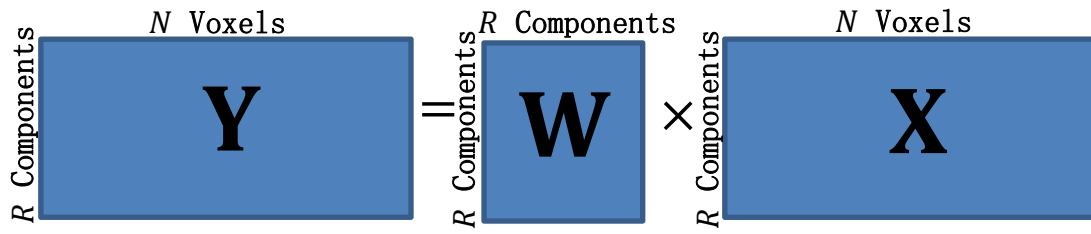
Figure 2



**Figure 3**



**Figure 4**



**Figure 5**

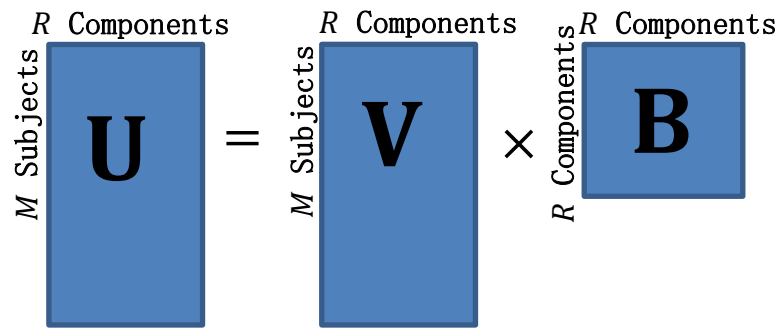
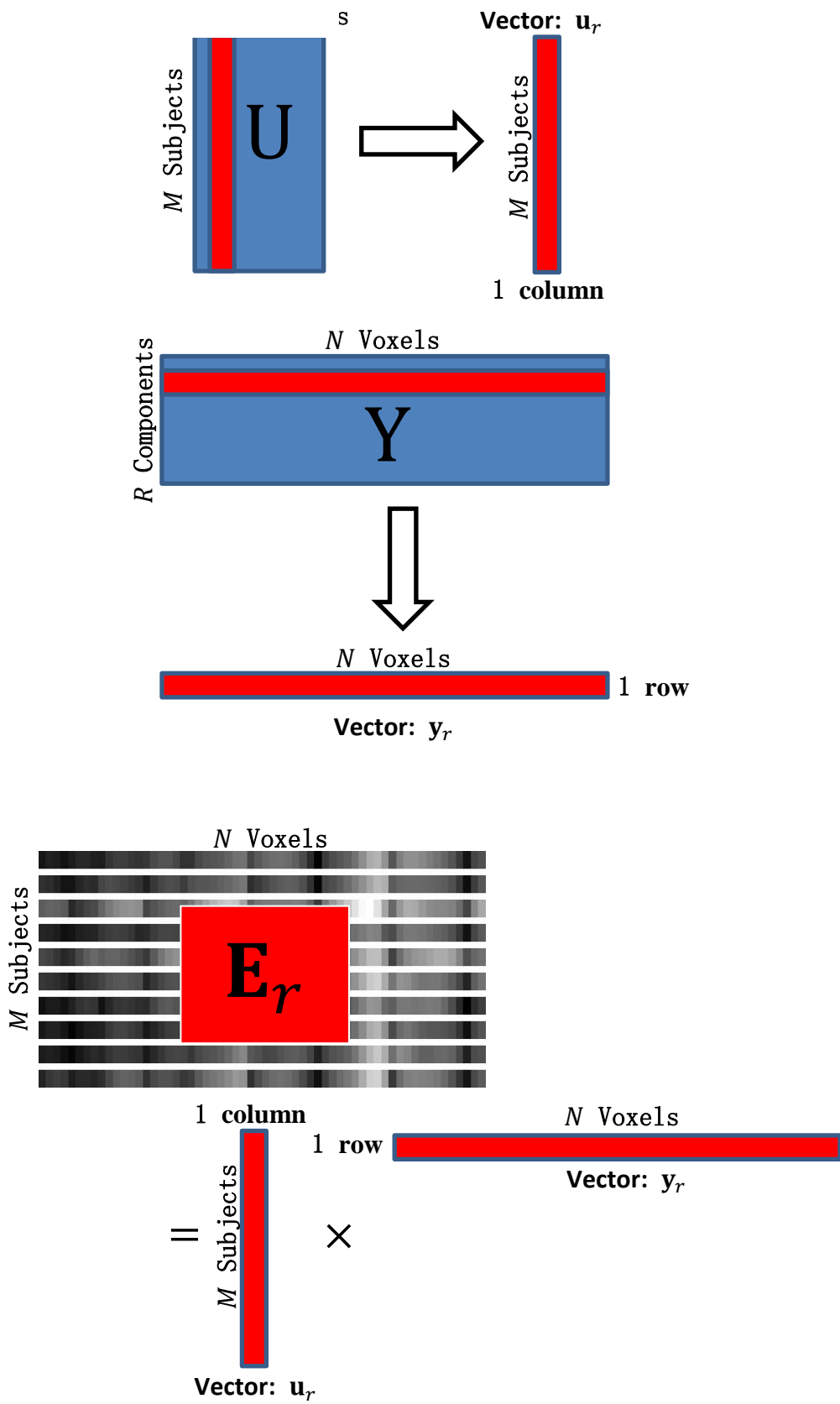
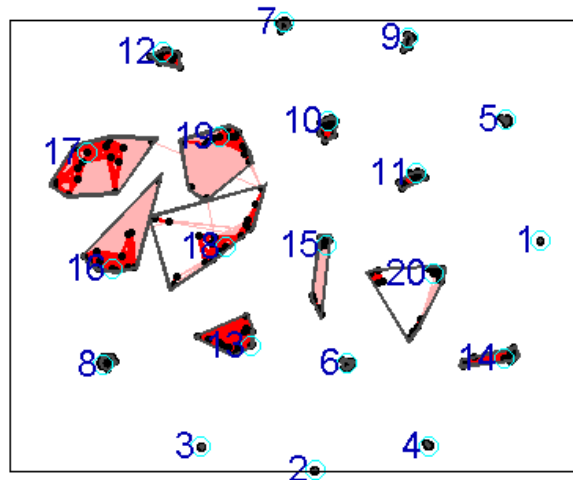


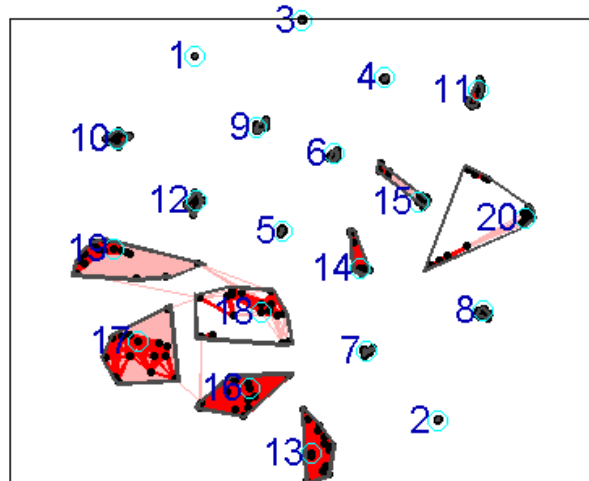
Figure 6



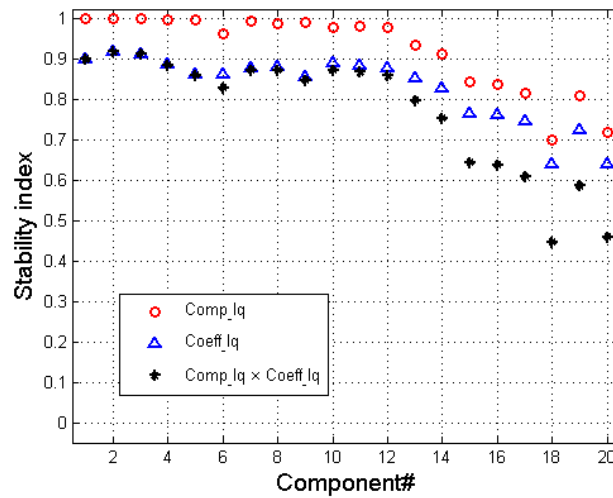
**Figure 7**



(a) Clustering of the component matrix



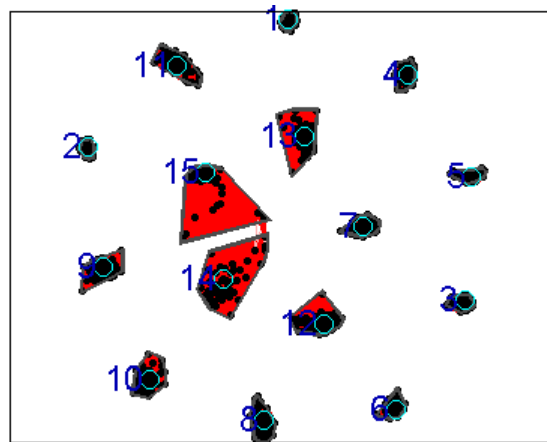
(b) Clustering of the coefficient matrix



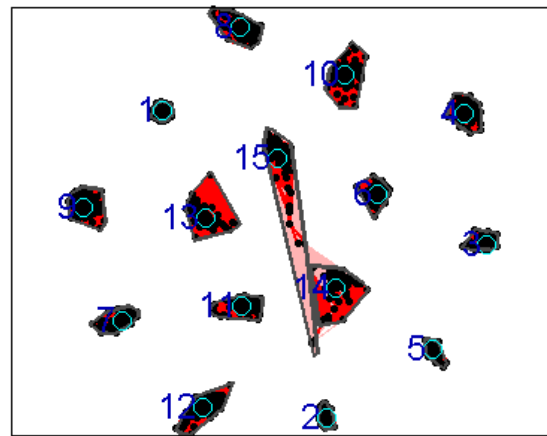
(c) Stability indices for ICA decomposition



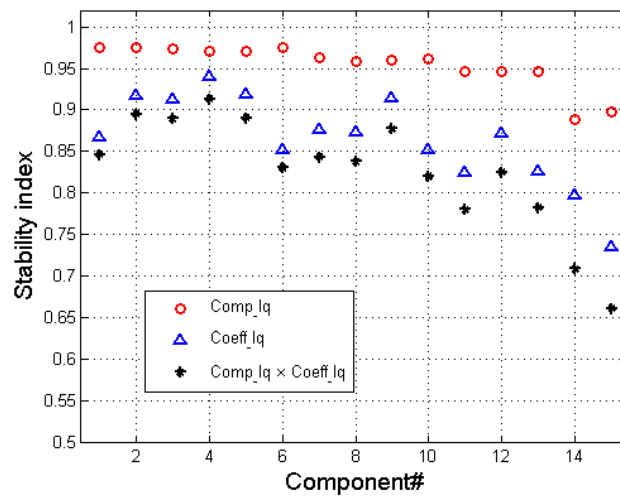
Figure 8



(a) Clustering of the component matrix



(b) Clustering of the coefficient matrix



(c) Stability indices for ICA decomposition



**Figure 9**

