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Automatic Identification of Functional Clusters in fMRI Data using Spatial Information

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Abstract

In independent component analysis (ICA) of functional magnetic resonance imaging (fMRI) data, extracting a large number of maximally independent components provides a more refined functional segmentation of brain. However, such segmentation does not per se establish the relationships among different brain networks, and also selecting and classifying components can be challenging. In this work, we present a multidimensional ICA (MICA) scheme to achieve automatic component clustering. In this MICA framework, stable components are hierarchically grouped into clusters based on spatial information and higher-order statistics, instead of typically used temporal information and second-order correlation. The final cluster membership is determined using a statistical hypothesis testing method. The experimental results from both simulated and real fMRI data sets show that the use of only spatial information with higher-order statistics leads to physiologically meaningful dependence structure of brain networks, which is consistently identified across various ICA model orders and algorithms. In addition, we observe that components related to artifacts, including cerebrospinal fluid (CSF), arteries, and large draining veins, demonstrate a higher degree of dependence among them and encouragingly distinguished from other components of interest using our MICA approach.

Keywords

Independent component analysis; multidimensional ICA; spatial dependence; hierarchical clustering; fMRI

I. Introduction

Functional magnetic resonance imaging (fMRI) data have been successfully analyzed using independent component analysis (ICA) [1], [2]. In these analyses, typically 20–30 independent components (ICs) are extracted, as guided by the information-theoretic criteria [3]. More recently, it has been noted that using high ICA model order, for example, 60 to 70 or higher, a more refined and hence more useful functional segmentation of brain can be achieved [4], [5], [6]. However, without establishing the relationships among ICs, analyzing a large number of ICs is more memory and computer intensive, and also makes component selection more difficult. In this paper, we present an automatic clustering strategy and interpret components in terms of functional clusters such that fine decomposition at high ICA model order is most useful. In contrast to most of previous studies using temporal correlation [7], [8], our approach is based on spatial information and higher-order statistics to increase accuracy and confidence of computed statistics and hence to obtain robust and meaningful assessment of brain connectivity.

In spatial ICA of fMRI data, the underlying components are assumed to be statistically independent to each other. However, not all sources follow ICA model strictly and therefore violation of the independence assumption is observed in real applications. After ICA decomposition, certain levels of dependence among ICs are likely to remain, especially when separating observation data into a large number of source estimates. For example, in [10] the removal of consistently task-related components affects not only the number but also the location of activated voxels in the recomputed transiently task-related components, which indicates that these components are dependent on each other. Therefore, the residual dependence among spatial components after ICA can be used to infer relationships among them [9].

However, to utilize such residual dependence, a relaxation of ICA to allow dependent components is desirable. The first generalization, multidimensional ICA (MICA), has been proposed in [11]. Starting with ICA, MICA suggests grouping ICA source estimates into several clusters, referred to as multidimensional ICs, such that the components within the same cluster are in some way related to each other [12]. For fMRI data analysis, such grouping is in general achieved through visual inspection of spatial maps and corresponding time courses, which is prone to bias and heavily rater dependent. Therefore, we develop an automatic clustering strategy to identify functional clusters.

Other closely related approaches have been proposed in order to incorporate a similar idea, including independent subspace analysis (ISA) [13] and topographic ICA [14]. ISA is a special case of MICA which combines the principle of invariant-feature subspace [15] to maximize the independence between the norms of the projection onto a linear feature subspace, instead of the independence between the projections themselves. Topographic ICA defines the dependence structure graphically by a neighborhood function to express the strength of the connection among components. While the above methods can generate reasonable estimates for MICA decomposition, both of them have limitations: ISA assumes a spherically symmetric distribution for each cluster and topographic ICA requires the size of the neighborhood to be fixed in advance.

Following MICA framework proposed in [11], we integrate ICA, mutual information based hierarchical clustering, and analysis of variance, to achieve MICA decomposition automatically. Compared to ISA and topographic ICA, neither the distribution nor the dimensionality of a multidimensional IC needs to be known beforehand in the presented MICA approach. Since the performance of MICA decomposition mainly depends on ICA source separation, we first handle the algorithmic and statistical uncertainty of ICA source estimates before forming multidimensional ICs, through a modification of the reliability analysis implemented in MATLAB toolbox ICASSO [16], to reduce potential information loss.

To summarize the experimental results, we identify functional clusters of brain networks based on mutual information among spatial components derived from ICA. These clusters, including regions in frontal, parietal, motor, temporal, and visual cortex, respectively, are known to be both functionally and anatomically connected. We find that the obtained dependence structure among different brain networks is consistently identified across various ICA model orders and algorithms. In addition, we show that physiological artifacts from cerebrospinal fluid (CSF), arteries, and large vessels demonstrate a higher degree of spatial dependence among them, which suggests that the proposed MICA approach offers a promising way to automatically compartmentalize these artifacts with other components of interest. These results indicate that the use of only spatial information with higher-order statistics leads to physiologically meaningful dependence structure of brain networks and provides more useful understanding of a large number of components.

II. Material and Methods

A. Independent Component Analysis of fMRI

The goal of ICA is to find a linear combination of the underlying components that are maximally independent of each other. Consider an M -by- V observation matrix, denoted by $\mathbf{X}$, which is assumed to be generated as the following model,

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

where $\mathbf{S} = [\mathbf{s}_1, \dots, \mathbf{s}_i, \dots, \mathbf{s}_N]^T$, with dimensions of $N \times V$, is the source matrix whose element s_i is the i th independent component (IC) and $\mathbf{A}$ is an M -by- N (usually $M \geq N$) mixing matrix with the i th column ($i = 1, \dots, N$) uniquely denoting the activation level (time course, TC) associated with the i th IC. ICA decomposition of $\mathbf{X}$ can be achieved by estimating a demixing matrix $\mathbf{W} = \mathbf{A}^{-1}$ (when the permutation and scaling ambiguity are ignored) such that the invertible transformation $\widehat{\mathbf{S}} = \mathbf{W}\mathbf{X}$ is a satisfied representation of true sources $\mathbf{S}$. Fig. 1 shows how ICA of fMRI works.

B. Multidimensional Independent Component Analysis

The ICA model presented in previous section can be extended using the following multidimensional ICA (MICA) model [11]:

$$\mathbf{X} = \sum_{i=1}^n \mathbf{X}_i = \sum_{i=1}^n \mathbf{A}_i \mathbf{S}_i$$

where each $\mathbf{S}_i$ is a subset with dimension N_i , $\sum_{i=1}^n N_i = N$ and N is the total number of sources, the same as in ICA model. Correspondingly, each element of mixing matrix, denoted by $\mathbf{A}_i$, is an M -by- N_i matrix which specifies the time-varying contributions of $\mathbf{S}_i$ to the measured fMRI signals. In this MICA model, ICs derived from (1) are grouped into n subsets such that the components within the same subset are allowed to be mutually dependent, while the dependencies among the components of different subsets are minimized. In general, the subset dimension N_i is not necessary to be equal for $\forall i = 1, \dots, n$. Note that this model reduces to the ICA model in (1) when n equals N or equivalently $N_i = 1$, for $\forall i$.

In general definition of MICA, two stages are involved to achieve MICA decomposition: first performing ICA source separation and then grouping the source estimates based on statistical dependence among them [11], spatially or temporally. For spatial grouping, the spatial components from ICA are clustered into a set of groups and these groups are denoted as multidimensional components; on the other hand, permutation on the columns of the mixing matrix are employed to group in terms of temporal correlation [7]. In our study, we focus on spatial ICA and the pairwise dependence between spatial components.

C. MICA Framework for fMRI Data Analysis

In this section, we present a MICA framework for fMRI data analysis to achieve automatic identification of functionally related brain networks. As typically done in fMRI data analysis, we first perform principal component analysis (PCA) to reduce the original dimension of fMRI data set. After this step, three analysis stages are involved: 1) reliability analysis of ICA source estimates; 2) mutual-information based (MI-based) hierarchical clustering; 3) automatic formation of the multidimensional independent components. An

analysis flow chart explaining the whole procedure from fMRI data set to the final multidimensional components is given in Fig. 2.

Our MICA decomposition is based on the statistical dependence among source estimates, hence we introduce the measure of dependence first. Correlation is the most frequently used proximity measure for the post-analysis of ICA of fMRI. Since second-order uncorrelatedness is not the same as statistical independence and the values of the residual correlation after pre-whitening in ICA are usually small enough to neglect, mutual information is an appropriate measure of dependence which takes into account higher order statistical information. We compute a normalized measure of mutual information [17], as the following formula shows,

$$\lambda(s_i, s_j) = (1 - \exp(-2I(s_i, s_j)))^{1/2} \quad (2)$$

where $I(\cdot, \cdot)$ is the mutual information between two components. that $\lambda(\cdot, \cdot)$ is in the interval of $[0, 1]$ and a value of zero means completely independent. In our experiments, mutual information is estimated using a nonparametric kernel density approach [18].

1) Reliability Analysis of ICA Source Estimates—One issue in ICA application is the unknown estimation reliability, which is induced by both the finite sample size and the non-unique ICA solution derived from the local optimal point of the cost function. An approach to this problem has been implemented in the MATLAB toolbox ICASSO [16] where ICA algorithm is investigated by performing multiple runs, say R ($R \in \mathbb{Z}^+$, $R > 1$), at a given ICA model order N with different initial values of demixing matrix and/or bootstrapping data set. The total $R \times N$ source estimates are grouped into N clusters using spatial correlation as the proximity measure. Each ICASSO cluster represents an individual type of source estimate and a reliable estimate corresponds to a tight cluster having an optimal size as same as (or at least close to) the number of runs. A metric I_q , $0 \leq I_q \leq 1$ reflecting the quality of a cluster is introduced and the center or centrotpe for each cluster is provided as the most reliable source estimate of this cluster. For each ICASSO cluster, I_q is calculated as:

$$I_q(n) = \frac{1}{|C_n|^2} \sum_{i,j \in C_n} \lambda(s_i, s_j) - \frac{1}{|C_n||C_{-n}|} \sum_{i \in C_n} \sum_{j \in C_{-n}} \lambda(s_i, s_j)$$

where $|C_n|$ is the number of components within the n th cluster, C_{-n} is the set of indices that do not belong to the n th cluster [16]. Here, we use $\lambda(s_i, s_j)$ introduced in (2) as the similarity measure between the i th and j th components.

However, the direct use of centrotypes can lose information, especially when the ICA model order is high. We note that when ICA model order increases, more and more ICASSO clusters become unreliable to have a size significantly more or less than the number of runs. Since without restriction on cluster size, more than one kind of component may be grouped into the same cluster, but only one type of component can be selected as the centrotpe. For example, as we observed in our study, one ICASSO cluster, represented by a centrotpe in supplementary motor area (SMA), also includes some post-central ICs and one precuneus cluster contains some visual ICs too (hence, the size of such cluster is typically large). This issue is due to interference from the functional connections among different kinds of components, which is the focus in the next stage of our analysis.

Nevertheless, the centrotypes satisfying certain criteria are reliable. We define a cluster in ICASSO as qualified if the cluster size is proper (in our case, 8 to 12 ICs within a cluster are

acceptable since we run the ICA algorithm 10 times) and the index I_q is above a threshold (e.g., 0.7). Instead of centrotypes, we select the ICs from the most stable run based on a metric, denoted by Q , which is the average maximal intra-cluster similarities to centrotypes and calculated as follows:

$$Q(r) = \frac{1}{N_q} \sum_j \max_k \lambda(\mathbf{c}_j, \mathbf{s}_{rjk})$$

where N_q is the total number of qualified clusters, $\mathbf{c}_j, j = 1, \dots, N_q$ is the centrotype of the j th qualified cluster, subscripts on the symbol $\mathbf{s}_{rjk}$ indicate that the k th component derived from the r th run within the j th cluster, and mutual information $\lambda(\cdot, \cdot)$ is defined in (2). Note that I_q is recomputed correspondingly to define the qualified cluster. The close-toone Q for a given run indicates that the ICs from this run are close enough to all centrotypes within the qualified clusters even though they may not be centrotypes.

Using metric Q , we may lose some information. However, our goal in this step is to minimize loss of information by retaining the most reliable information (the most replicated run) while discarding less reliable data.

2) Mutual Information Based Hierarchical Clustering—Based on the normalized mutual information, hierarchical clustering is performed on the N derived ICs from the most reliable run to discover the dependence structure among them. First, the distance or dissimilarity d_{ij} between two components $\mathbf{s}_i$ and $\mathbf{s}_j$ is defined as:

$$d_{ij} = 1 - \lambda(\mathbf{s}_i, \mathbf{s}_j)$$

where mutual information $\lambda(\cdot, \cdot)$ is defined as the same as in (2). Two completely independent sources have the distance d_{ij} of unit. The distance matrix $\mathbf{D}$ is constructed by assigning d_{ij} to the (i, j) th entry of $\mathbf{D}$.

Based on $\mathbf{D}$, the agglomerative hierarchical clustering starts with each component as a separate cluster and merges them into successively larger clusters. The similarity between two clusters is calculated using average-linkage criterion, that is the average $\lambda(\cdot, \cdot)$ of all component pairs from these two clusters. Finally, we obtain the dendrogram, or the tree-like dependence structure for all components.

3) Automatic Formation of Multidimensional Independent Components—After MI-based hierarchical clustering, one of the remaining questions is that the stopping rule to partition the dendrogram is difficult to decide through visual inspection. A robust and effective approach to this type of problem is to incorporate hypothesis testing—analysis of variance (ANOVA) [19]. Using ANOVA-based method, we can decide final members for each cluster using different thresholds. It is possible to use other indices [20], e.g., R-index, to obtain the number of clusters, which is to decide a single threshold to cut the dendrogram. However, in real applications the optimal clustering may not be sufficiently decided by only one specific threshold, especially for a large number of components. We also note that using R-index it is still difficult to decide the optimal number of clusters since R-index may keep decreasing as the number of clusters increases.

We start one-way ANOVA at the two-cluster level of the dendrogram. The null hypothesis is as follows,

$$H_0: \mu_i = \mu_j = \mu_{ij}$$

where μ_i and μ_j are the average values of distance for two possible clusters and μ_{ij} is the average inter-individual distance between them. We reject H_0 in favor of the alternative hypothesis, H_a : at least one inequalities of these three means, where α is the significance threshold. This is the rejection of null hypothesis occurs when $\mu_i < \mu_{ij}$ and $\mu_j < \mu_{ij}$, or when $\mu_i < \mu_{ij}$ but $\mu_j = \mu_{ij}$, or when $\mu_i = \mu_{ij}$ and $\mu_j < \mu_{ij}$. If at least one of the above three cases occurs, then the i th cluster and the j th cluster are believed to be significantly different from each other with a high confidence level. We repeat testing for each branch until the null hypothesis is accepted or the size of two potential clusters is too small (the minimum size is 4 in our experiments); otherwise, we declare two clusters to be the members of one multidimensional IC and stop the test.

Another issue is to determine the major brain regions within each multidimensional IC. We incorporate automated anatomical labeling (AAL) [21] to label final clusters. First, each spatial component is converted into Z-score. For each spatial component within a given cluster, we set value of a voxel above a Z-score threshold as 1, otherwise as 0. Then each survived voxel is labeled by AAL mask using element-by-element product of thresholded spatial component and mask. In this way, we obtain 116 labeled regions of interest (ROIs) for each component. Next, average Z-score for each ROI is calculated and based on these average values, ROIs within each spatial component are sorted in a descending order. We select top ten ROIs for each component as candidates for labeling. Finally, across all components within one cluster, we use dominant ROIs to label the whole cluster. Here, dominant ROIs are those that are common in at least 50% of the components within a given cluster.

III. Experimental Results

A. Simulated fMRI Data

We first apply our proposed analysis scheme to a simulated data set generated using the MATLAB toolbox, SimTB [22], where observations are expressed as product of time courses and super-Gaussian sources. To simulate an auditory oddball task (AOD), we generate 20 sources including sensorimotor, auditory, frontoparietal, frontal, visual, precuneus, dorsal attention network (DAN), default mode network (DMN), ventricle and subcortical nuclei sources. Each source has 148×148 voxels and is independently rotated, translated, and contracted or expanded for each of 12 subjects. Noise is added relative to two levels of specified contrast-to-noise ratio (CNR): standard level is uniformly generated from 0.8 to 2 and lower level is within the range [0.4, 0.8]. Time courses are simulated as the convolution of “neural” events with a canonical hemodynamic response function [23] and each one includes 150 time points collected during a repetition time of 2 seconds. For each participant, time courses are scaled to have a peak-to-peak range of one. The event-related paradigm task consists of three auditory stimuli (standard, target, and novel) with specified probability to appear. Standard events are mapped to auditory sources with amplitude 1 and other sources (frontal and DAN) with amplitude 0.7. Target events are mapped to auditory sources with amplitude 1.2, motor sources with unit amplitude, and other sources (frontal: 1; DAN: 0.8; precuneus: 0.5). Novel events are mapped to two auditory sources with amplitude 1.5, motor sources with small amplitude (0.5), and other sources (frontal source has unit amplitude and DAN has amplitude 1.2). DMN source is negatively activated with three events having amplitude -0.3 . In addition to three task event types, two cerebrospinal fluid (CSF) sources have unit amplitude using a spike model.

After obtaining simulated data, we first perform ICA decomposition ten times with randomly initialized demixing matrix and bootstrapping and select the run with the highest stability index Q . We then perform mutual information based hierarchical clustering to group 20 estimated components and ANOVA-based approach to determine the final clusters. Four ICA algorithms we use are Infomax [24], ICA by entropy bound minimization (ICA-EBM) [25], [26], FastICA [27], and joint approximate diagonalization of eigenmatrices (JADE) [28]. Infomax (or maximum likelihood ICA) is one of the most widely used algorithms and with sigmoid nonlinearity, it works well in estimating super-Gaussian sources; ICA-EBM is a flexible approach providing various options for source density matching; FastICA is based on a fixed-point iteration scheme maximizing non-Gaussianity as a measure of statistical independence; JADE performs ICA by joint diagonalization. Due to space limitation, we present Infomax and ICA-EBM results and give a brief review of FastICA and JADE results.

The dendrograms for Infomax components at two noise levels are shown in Fig. 3. (a) and (b). Comparing these two dendrograms, we find that CSF and nuclei components, sensorimotor and frontoparietal components, two auditory components, four frontal components, precuneus and visual components are grouped into clusters, respectively; DAN component is also grouped with visual and precuneus components; these physiologically meaningful clusters are not well retained when grouping using temporal correlations among component time courses. We also note that when CNR decreases only DMN component changes cluster to be grouped with frontoparietal and motor components. Hence, it indicates that the obtained dependence structure of brain networks presents consistency to different noise levels in the data.

Due to the characteristics of ICA algorithms, the decompositions might be different. For example, ICA-EBM components are less sparse than Infomax components such that sources with high temporal correlation are estimated as one ICA-EBM component. However, similar clusters of ICA-EBM components are obtained as in Infomax decomposition. Comparing dendrograms of Infomax and ICA-EBM (Fig. 3. (a) and (c)), we find that in ICA-EBM decomposition, only DMN component changes its cluster and is grouped with frontal components. For FastICA and JADE components, we obtain similar clusters to Infomax and ICA-EBM, with slight difference: left/right motor and left/right temporal components present higher dependence due to structural overlap of them. However, it is important to note that inherently different decompositions result in slight differences in the final groupings.

B. Resting-state fMRI Data

We also apply the proposed MICA scheme to a resting-state fMRI data set obtained from 28 healthy participants (23 males and 5 females; average age, 32 ± 13 years). All participants provided written, IRB-approved consent at Hartford Hospital. They were asked to relax and open their eyes to avoid falling into sleep. Scans were acquired on a 1.5 T dedicated head scanner (Siemens) with single echo planar imaging, using 1.5 s repeat time, 27 ms echo time, 24 cm field of view, 64×64 acquisition matrix, 70° flip angle, $3.75 \times 3.75 \times 4$ mm³ voxel size, 4 mm slice thickness, 1 mm gap, 29 slices, and ascending acquisition. Images were realigned with INRIalign [29], spatially normalized into the standard Montreal Neurological Institute (MNI) space [23] and smoothed with $9 \times 9 \times 9$ -mm full width at half-maximum Gaussian kernel, and then resampled $3 \times 3 \times 3$ -mm, resulting in $53 \times 63 \times 46$ voxels. For more details, see Calhoun et al. [30].

Since we apply our method to a multi-subject data set, we perform group ICA [31], at three model orders 20, 40, and a relatively high order 60. The derived ICs we show here are the group results. We again use two ICA algorithms: Infomax [24] and ICA-EBM [25], [26].

1) Reliability Analysis of ICA Source Estimates—Before identifying the latent multidimensional ICs, we first evaluate the reliability of source estimates by performing group ICA ten times with random initialization of demixing matrix and bootstrapping on the whole group. We use the metric Q to select one run of ICA as the most stable run, instead of using ICASSO centrotypes from different runs. The average values and standard deviation of Q for each algorithm at three orders are shown in Fig. 4. We note that decomposition at lower order may yield more reliable ICA estimates than at higher order. However, there is a recent trend in this field to analyze refined separation of brain networks obtained at higher order [4], [5], [6]. Hence, we focus on the results obtained at order 60 and give a brief overview of results at lower order.

For ICA-EBM at order 60, there are 18 qualified ICASSO clusters and 42 other clusters either with inappropriate sizes (< 8 or > 12) or having undesirable quality ($I_q < 0.7$) or both. The fifth run, contributing centrotypes to four qualified clusters, has the highest value of Q score (0.94) indicating that even though the ICs from this run are not centrotypes in the other qualified clusters, they are much closer to the centrotypes than ICs derived from other runs and therefore more reliable and reproducible. The least reliable run of ICA-EBM algorithm has a value of 0.81. Hence, we perform our subsequent analysis, including mutual information based hierarchical clustering and hypothesis testing, on the ICA-EBM ICs from the fifth run of group ICA at order 60. Compared to Infomax, ICA-EBM is slightly less stable than Infomax due to inherent flexibility of ICA-EBM in density matching.

2) Mutual Information Based Hierarchical Clustering—The hierarchies of 60 ICA-EBM ICs and Infomax ICs produced by MI-based hierarchical clustering are demonstrated in Fig. 6. Due to space limitations, we only present the dendrogram produced at this high order and give a brief overview of the MICA results at other orders. Mutual information between two ICs are estimated using nonparametric Gaussian kernel density matching method and the average mutual information among ICA-EBM and Infomax ICs is 0.21 ± 0.07 and 0.26 ± 0.06 , respectively. For ICA-EBM, the most dependent ICs are #17 and #6, both of which cover the sensorimotor cortex, while the least dependent pair is #3 (artifact) and #34 (superior frontal) with value of mutual information 0.05. Similarly for Infomax, two sensorimotor ICs have the highest mutual information and the lowest dependence exists between one artificial IC and one IC of interest.

3) Automatic Formation of Multidimensional Independent Components—The final clusters decided using ANOVA with significance level $\alpha = 0.05$ are differentiated by various colors and labels in dendrogram. Spatial maps for ICA-EBM and Infomax ICs within each cluster are shown in Fig. 6 and Fig. 7. Although two algorithms derive different decompositions, the overall dependence structures of ICA-EBM ICs and Infomax ICs are similar to each other. Both of these two hierarchies contain several major clusters (multidimensional ICs) of interest; for example, the motor cluster includes supplementary motor area (SMA) and post-central gyrus. The dominant AAL labels for each cluster of ICA-EBM ICs at order 60 are shown in Table I. Other clusters cover the visual cortex, temporal gyrus, parietal lobule, precuneus and posterior cingulum, frontal lobe and frontoparietal regions, all of which characterize the rest state of the brain. ICs within the parietal, precuneus, and frontal clusters are related to DMN [32].

We find that functionally related components, e.g., IC #17 (blue, SMA) and #32 (pink, paracentral lobule) in Fig. 6 (a), are grouped together to reflect a localized network, which appears to be consistent with the principles of functional organization of the brain. This kind of functional grouping was also found in our previous studies where for a data set acquired during a visuomotor task, three task-related ICs (bilateral visuomotor cortex and medial occipital) and four DMN ICs (frontal pole, frontoparietal, posterior cingulate and

precuneus), respectively, had higher dependence among them [9]. Recently, we also applied mutual information based hierarchical clustering to another real fMRI data set acquired during an AOD task and we observe consistent groupings of components [33]. All these experimental results from several fMRI data sets indicate that our component clustering scheme generalizes to different tasks.

Due to the characteristics of ICA algorithms, the decompositions might be different. We note that for ICA-EBM, the head motion artifact and SMA are estimated as one component (green in Fig. 6. (a)), which is often observed in SPM regression and ICA applications; while for Infomax, although these two regions are estimated as two separate components, they are grouped together probably resulting from the involvement of body movement, especially for a task requiring contingent movement. For ICA-EBM, another component, including both frontal and left parietal lobes as shown in light blue in Fig. 6. (c), is grouped into frontal cluster since the frontal regions of this component has high dependence with ICs within the frontal cluster.

Besides the functional dependence, we note that structurally related ICs are also grouped together according to the inherent nature of MI-based clustering. An example is the multidimensional IC containing both temporal and motor regions, as shown in Fig. 6. (g). The cerebellum ICs are also grouped together with some artificial ICs for the same reason.

Another intriguing result is that components related to physiological artifacts in vicinity of cerebellum are consistently clustered together across different orders and algorithms, which is not observed when using temporal correlation. As shown in Fig. 8, those components caused by the presence of arteries, large blood vessels, and CSF are grouped into subcortical/cerebellar cluster, together with several physiological plausible components in cerebellum, insular, and pallidum areas, due to inherent structural dependence. The verification of CSF artifacts is based on the criterion that the spatial correlation of an IC of interest with grey matter (GM) template is bigger than that with CSF MNI template [34]. The GM and CSF templates are registered to the same dimensions as IC; voxel value of the template is retained if it is the largest among GM, white matter, and CSF and otherwise is set to zero. We calculate two correlation coefficients for each IC: $Corr_{GM}$ and $Corr_{CSF}$. Within subcortical/cerebellar cluster for ICA-EBM and Infomax, 63% and 59% ICs have $Corr_{GM} < Corr_{CSF}$. Outside this cluster, only three ICA-EBM ICs and two Infomax ICs have larger correlation with CSF template than with GM template. Furthermore, we compute average temporal power spectrum of each IC within low-frequency band (< 0.1 Hz) and within high-frequency band (> 0.15 Hz) and calculate the power ratio according to the criterion that task-related activity is usually characterized by lower frequencies (0 to 0.1 Hz) than those in the respiratory cycles (0.1 to 0.5 Hz) and cardiac cycles (0.6 to 1.2 Hz) [35], [6]. At order 60, more than 76% ICA-EBM ICs and 88% Infomax ICs within the subcortical/cerebellar cluster have the ratio less than median value (0.43/0.44 for ICA-EBM/Infomax, dynamic range 0.03/0.05), while only 33% and 34% ICs outside this cluster have temporal power ratio less than median.

It is important to note that inherently different decompositions result in slight differences in the final groupings. We compare spatial components derived from two algorithms and find a total 43 common components, of which 86% (37 common components) are from the same kind of clusters in two dendrograms shown in Fig. 5. Using ANOVA, we also cross-check the similarity between the corresponding clusters derived from different algorithms. All the comparable pairs of clusters obtained from ICA-EBM and Infomax are significantly similar to each other ($p < 0.05$).

Finally, we observe that the dependence patterns are consistent across different ICA model orders. Although the number of ICs within one cluster at low order might be smaller than it at high order, which results from the splitting of components at high order decomposition [3], the major clustering structure is retained. For example, the visual, frontal, motor and temporal clusters, are consistently estimated at orders 20 and 40. Furthermore, at low order, artifacts are still more dependent on each other when compared with ICs of interest.

IV. Discussion

We present a MICA framework for fMRI data analysis to automatically investigate relationships among a large number of ICA components using spatial information and higher-order statistics, while most previous studies focus on the use of temporal information and second-order statistics [7], [8] and also are not automatic. After ICA, time courses are usually noisy. Moreover, time courses contain smaller set of samples compared to the spatial maps (hundreds compared to tens of thousands). The small sample size and inherent noise reduce accuracy of computed statistics. Also, second-order statistics does not take full-order statistical information into account. In contrast, we use mutual information among spatial components for quantification of similarity and for constructing the subspaces, i.e., for detecting relationships among different brain networks.

Several results are of interest. First, multidimensional ICs containing functionally and anatomically dependent components are identified using only spatial information. This observation is consistent with our previous study in an fMRI data set acquired during the cognitive task that physiologically meaningful clusters, e.g., task-related (visuomotor) cluster and DMN cluster, are obtained. Hence our MICA results are unbiased toward a particular data set and task [9]. Second, we find that the dependent patterns among ICs are retained across various ICA model orders and algorithms, which implies that our approach is robust to different ICA source estimates. Third, physiological artifacts from CSF, vessels, arteries, and large draining veins have higher dependence when compared to cortical ICs. Several physiological plausible ICs, for example, cerebellum, pallidum, and putamen, are also grouped together with the artifacts in the vicinity of cerebellum which is due to the structural dependence among those regions. Further artifact separation within such cluster can be achieved by incorporating other features, e.g., including spatial templates [34], kurtosis, skewness, temporal spectral feature [36], and temporal correlation [7], [8], and training a classifier using these features. Nevertheless, our results indicate that using only spatial dependence, the proposed MICA method promises to be effective for the automatic compartmentalization of physiological artifacts from other ICs of interest in fMRI data.

In the proposed framework, we perform ICA multiple runs, handle the reliable uncertainty of the derived components, and incorporate mutual information based hierarchical clustering in conjunction with a hypothesis testing method, to determine the underlying multidimensional ICs, which represent the functional clusters in the brain. Other popular clustering approaches, for example, fuzzy k -means clustering, may also be applicable. However, hierarchical clustering explicitly explores and visualizes the tree-like relationships among ICs, similar to the transformation to make ICs fit the graphical model presented in tree-dependent component analysis (TCA) [37].

In the reliability analysis of ICA source estimates, we select all the ICs from the most stable run instead of centrotypes due to the selection confidence of them. A metric Q is defined to evaluate the stability of each run of ICA algorithm. Indeed, this metric can be extended since in current work we only assess the reliability within the clusters with proper size and high quality. In our future study, we will consider the incorporation of the performance within those unqualified clusters as a penalty into this metric. Nevertheless, this reliability analysis

to some extent is useful to quantitatively evaluate the performance of ICA algorithm. Our experimental results show that the source estimates derived from Infomax are more stable than that obtained from ICA-EBM. It is reasonable according to the nature of the two algorithms: ICA-EBM provides flexible options for density matching [25], [26], while Infomax assumes a super-Gaussian density model to consistently produce stable ICs [38], [39].

One issue for hierarchical clustering is that how to cut dendrogram is difficult to decide only through visual inspection. We adopt ANOVA to test the significant difference between the mean of the within-group distance and the between-group distance. Such a statistical procedure provides objective stopping conditions for partitioning the dendrogram. Besides the rejection of our null hypothesis, another desirable stopping rule is the minimum dimension of each multidimensional IC to avoid small-size cluster. Our experience working with different algorithms and orders suggests that a threshold 4 is a good choice to produce plausible clusters. After determining the membership of each multidimensional IC, we label them based on the AAL atlas to provide a descriptive symbol for each functional cluster. Other atlas, including the Talairach atlas [40] and Wake Forest (WFU pick atlas) [41], can also be used to report the ROIs within a cluster.

The main advantage of the presented MICA scheme is that we achieve an efficient and effective grouping of ICA components using only spatial information, which is usually a time-consuming task and requires a high demand for expertise in both brain functional segmentation and fMRI data analysis. Our approach facilitates the study of brain network interrelationships in terms of identifying functional clusters of them, in spite of task, model order, and algorithm. Although we propose for fMRI data analysis, our approach can be easily applied to other kinds of neuroimaging data, e.g., electroencephalography.

A number of previous studies show evidence that many brain diseases, including schizophrenia, Alzheimer, and bipolar, show dysfunctional connectivity in various regions, for example, temporal lobe, default mode networks, and occipital cortex [42], [43], [44], [45]. All these regions have been found to be multidimensional ICs in our MICA results. Therefore, we will apply the proposed approach to fMRI data set acquired from patient participants and compare the normal and pathological brain networks in our future study.

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Fig. 1.
ICA decomposes fMRI data into a product of a set of time courses and spatial components.

Fig. 2.

The flow chart explaining how to form multidimensional components from fMRI data.

Usually, data set is multi-subject; therefore, a preprocessing step to reduce the dimension of raw data is required.

Fig. 3. Dendrogram for 20 components estimated from simulated data: (a) Infomax with standard contrast-to-noise ratio (CNR) $\sim U[0.8, 2]$; (b) Infomax with low CNR $\sim U[0.4, 0.8]$; (c) ICA-EBM with standard CNR $\sim U[0.8, 2]$. The final clusters are determined using ANOVA-based approach presented in Section II. C. In spatial maps, red and blue regions represent voxels with positive and negative values, respectively.

Fig. 4.

The average stability metric Q for ten runs of ICA-EBM and Infomax at three model orders, 20, 40, and 60, respectively. As order increases, the stability for each algorithm decreases.

Fig. 5. Dendrogram for 60 ICs derived from algorithms: (a) ICA-EBM; (b) Infomax. Corresponding clusters in these two hierarchies are labeled in the same color and text. Although the component indices in these two figures do not correspond to each other, in most cases the spatial maps are quite similar for the two algorithms, as shown in Fig. 6 and Fig. 7.

Fig. 6. Spatial maps for ICA-EBM ICs within seven clusters: (a) motor; (b) parietal; (c) frontal; (d) frontal parietal; (e) occipital; (f) precuneus; (g) temporal. ICs are obtained at model order 60. Both positive and negative voxel values ($|Z| \geq 2.5$) are shown. AAL labels for these clusters are demonstrated in Table I.

Fig. 7. Spatial maps for Infomax ICs within seven corresponding clusters shown in Fig. 6, with same ICA model order and Z score threshold of ICA spatial maps. Compared with Fig. 6, the color of similar regions for two algorithms is made to be more consistent. Since corresponding clusters from two algorithms may have different dimensions, different regions may have the same color.

Fig. 8. Spatial maps for ICA-EBM ICs within the subcortical/cerebellar cluster. Sub clusters include (a) vessel/artery; (b) cerebellum; (c) midline CSF; (d) nuclei. For Infomax at order 60, four similar clusters including physiological artifacts in the vicinity of cerebellum and subcortical/cerebellar ICs are consistently obtained.

AAL labeling for ICA-EBM functional clusters at model order 60. Both maximal positive and minimal negative Z-score values of ICA spatial maps are shown and ns means no voxel survives. ROI prevalence is appearance percentage of ROIs across all components within one cluster

Table 1

ROI	ROI No.	Pos. max. R/L	Neg. min. R/L	Voxel No.	ROI prevalence
Motor cluster					
Supplementary motor area	19, 20	2.95/2.54	ns	1839	3/4(75%)
Superior/inferior parietal lobule	59 – 62	ns/4.09	-2.59/-2.52	1686	3/4(75%)
Paracentral Lobule	69, 70	5.25/6.4	-3.99/-3.27	1446	3/4(75%)
Parietal cluster					
Superior/inferior parietal lobule	59 – 62	3.78/3.26	-5.41/-4.94	3440	3/3(100%)
Precuneus	69, 70	5.36/4.32	ns	574	3/3(100%)
Frontal cluster					
Superior/middle frontal gyrus	3, 7, 8	2.71/3.93	ns	5774	4/7(57%)
Superior frontal gyrus medial part	23, 24	4.55/5.17	-3.99/ns	4050	5/7(71%)
Anterior/posterior cingulate gyrus	31, 32, 35, 36	5.46/5.06	ns/-3.72	2020	5/7(71%)
Frontal gyrus orbital part	9, 10, 25, 26	5.93/4.68	-3.84/-2.65	1629	5/7(71%)
Frontal parietal cluster					
Frontal lobule	8, 15, 24, 25	3.02/ns	ns	1783	3/3(100%)
Superior/inferior parietal	60, 62	ns/5.51	ns	1290	2/3(67%)
Occipital cluster					
Superior/middle/inferior occipital	49 – 54	3.47/3.32	-2.84/ns	4281	3/4(75%)
Lingual gyrus	47, 48	ns/3.14	-3.66/-2.77	2561	3/4(75%)
Precuneus cluster					
Precuneus	67, 68	3.04/3.9	ns	2563	2/3(67%)
Posterior cingulum	35, 36	5.35/3.33	ns	950	2/3(67%)
Temporal cluster					
Superior/middle temporal gyrus	81, 82, 85	4.88/4.2	ns	4013	3/6(50%)
Superior/middle frontal gyrus	3 – 8	4.81/4.36	ns/-3.32	1581	5/6(83%)
Transverse temporal gyrus	79, 80	4.7/3.92	ns	286	3/6(50%)
Subcortical/cerebellar cluster Vessel/artery cluster					
Parahippocampal gyrus	39, 40	3.33/3.86	ns	1430	4/5(80%)
Superior temporal pole	83, 84	4.89/5.51	ns	1378	4/5(80%)

ROI	ROI No.	Pos. max. R/L	Neg. min. R/L	Voxel No.	ROI prevalence
Lobule of vermis	109, 115, 116	5.01	ns	341	5/5(100%)
Amygdala	41, 42	4.59/6.22	ns	299	4/5(80%)
Cerebellum cluster					
Cerebellar lobule	95	ns/3.11	ns	1689	3/3(100%)
Lobule of vermis	109, 112 – 116	8.19	ns	676	3/3(100%)
Midline CSF cluster					
Cerebellar lobule	95 – 98	4.26/4.19	ns	1246	4/4(100%)
Lobule of vermis	109 – 113	6.85	ns	989	4/4(100%)
Cingulate gyrus	33 – 36	2.53/ns	ns/-2.61	434	4/4(100%)
Nuclei cluster					
Caudate nucleus	71, 72	3.86/3.0	-4.15/-3.33	1982	4/6(67%)
Thalamus	77, 78	5.48/5.79	-5.6/-3.91	1809	4/6(67%)
Putamen	73, 74	3.42/3.57	ns	867	3/6(50%)
Pallidum	75, 76	3.53/3.72	-2.33/-2.19	303	5/6(83%)