FLEXIBLE LARGE-SCALE FMRI ANALYSIS: A SURVEY

Seung-Jun Kim[1], *Vince D. Calhoun*[2,3], *and Tülay Adalı*[1]

[1]Department of Computer Science and Electrical Engineering
University of Maryland, Baltimore County, Baltimore, MD 21250
[2]The Mind Research Network, Albuquerque, NM 87106
[3]Department of Electrical and Computer Engineering
The University of New Mexico, Albuquerque, NM 87131

ABSTRACT

Functional magnetic resonance imaging (fMRI) has provided a window into the brain with wide adoption in research and even clinical settings. Data-driven methods such as those based on latent variable models and matrix/tensor factorizations are being increasingly used for fMRI data analysis. There is increasing availability of large-scale multi-subject repositories involving 1,000+ individuals. Studies with large numbers of data sets promise effective comparisons across different conditions, groups, and time points, further increasing the utility of fMRI in human brain research. In this context, there is a pressing need for innovative ideas to develop flexible analysis methods that can scale to handle large-volume fMRI data, process the data in a distributed and policy-compliant manner, and capture diverse global and local patterns leveraging the big pool of fMRI data. This paper is a survey of some of the recent research in this direction.

***Index Terms*—** Functional MRI, data-driven analysis, large-scale data.

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) provides a noninvasive window into the brain. The technique has been widely adopted in research since its inception a couple of decades ago, and more recently in clinical settings. The most popular method involves observing the blood oxygenation level-dependent (BOLD) contrast, where the distinct magnetic properties of (de-)oxygenated hemoglobin are exploited. The premise is that the vascular hemodynamics can be linked to the brain neural activities with high spatial resolution [1].

Brain regions responsible for specific functions have been identified by task-based fMRI analysis, where the subjects perform active tasks or get exposed to sensory stimulations during the imaging process [2]. More recently, resting-state fMRI analysis has attracted significant attention, where participants do not engage in specific tasks but are instructed to rest quietly. Low-frequency synchronous oscillations observed across brain regions in the resting-state time courses reveal functional connectivity in the brain, often ascribed to spontaneous cognitive processes [3].

Brain functional networks are, at a high level, relatively consistent across different healthy subjects and stages of consciousness [4]. On the other hand, significant heterogeneity exists across different individuals within healthy or patient groups. The variability in brain functional networks across subjects is both significant and consistent like fingerprints [5]. Biomarkers of neural connectivity can thus be used to predict individual differences in various cognitive processes [6].

There exist multiple methods for analyzing resting-state fMRI datasets. The most straightforward one is to use region-of-interest (ROI) or seed-based methods, which correlate the fMRI time courses from predefined ROIs or voxels to obtain functional connectivity maps [7, 8]. Although such approaches can produce readily interpretable results, they are hypothesis-driven, and thus their findings are limited by the *a priori* definition of the ROIs and seed regions.

An alternative is to adopt a fully multivariate *data-driven* paradigm, of which blind source separation (BSS) is a major one. Independent component analysis (ICA) is the most popular way to achieve BSS, which aims at discovering latent factors from a set of measurements such that the factors have maximal statistical independence. ICA has proven very useful for fMRI analysis as it can find non-overlapping, temporally consistent brain regions without prior knowledge on temporal structures [9, 10]. When it comes to analyzing fMRI data from multiple subjects, the group ICA method has been widely used. It obtains a decomposition for a common signal subspace, which can be further used to obtain subject-specific spatial maps and time courses [11, 12]. Independent vector analysis (IVA) generalizes ICA to achieve joint decomposition of multi-subject data and estimates individual mixing matrices and spatial maps, and better preserves subject variability as it eliminates the need to define a common group subspace as in group ICA [13, 14, 15, 16, 17].

More recently, another matrix decomposition approach

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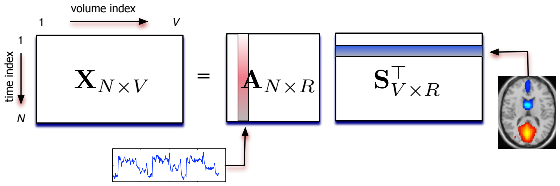

Fig. 1. Matrix factorization of fMRI data. The spatial maps of functional activity and their temporal modulation are given as the columns of $\mathbf{S}$ and $\mathbf{A}$, respectively ($\cdot^{\top}$: transposition).

imposes the notion of sparsity to ensure identifiability, as in dictionary learning (DL) [18, 19]. The idea is not only intuitively appealing in the sense that the simplest explanation is preferred, but is also attractive from the efficiency viewpoint of neuronal encoding [20]. More importantly, the model accommodates an *overcomplete* representation—a representation that consists of more components than the ambient data dimension. Thus, the fine-grained variability due to individual and group heterogeneity can be captured as long as the components are distinct and consistently present in the dataset. A promising idea may be to carefully balance the statistical diversity from these two sources of statistical prior information, i.e., independence and sparsity, leveraging their complementary strengths.

The benefits of fine-grained analysis will be particularly critical in large-scale studies, involving thousands of subjects, which is becoming feasible through large-scale repositories such as the human connectome project (HCP) [21] or the collaborative informatics and neuroimaging suite (COINS; http://coins.mrn.org) [22]. There is also a pressing need to develop scalable analysis platforms linking multi-site repositories to enable even larger-scale studies. The present paper is a survey of some of the recent works toward this direction.

The rest of this paper is organized as follows. In Sec. 2, the data-driven fMRI analysis methods are reviewed. Methods for group analysis are discussed in Sec. 3. Challenges and opportunities for large-scale multi-subject fMRI analysis are surveyed in Sec. 4. The conclusion is provided in Sec. 5.

2. FMRI DATA ANALYSIS METHODS

FMRI data allow us to study hemodynamic changes as a function of time, during well-defined tasks with on/off periods, as shown in the box-car time course in Fig. 1, or even during a resting state. A standard approach for analyzing fMRI data is to correlate the time-series data with an assumed reference signal, as in the general linear model (GLM) implemented in the statistical parametric mapping (SPM) software [23]. However, such an approach is heavily dependent on the reliability of the prior information. Many generalizations of this model-based method have been proposed, typically involving an estimate of the hemodynamic response, which is known to change depending on the functional areas. Data-driven methods, on the other hand, minimize the need for such prior information, and when working with resting-state data, a model time course to use as a regressor is simply not available. In this case, the methods based on matrix factorization have proven very effective as they enable a fully multivariate analysis of the data as opposed to the seed- and ROI-based methods. Next, we describe the application of ICA to fMRI data, as well as of the DL approach, which has been applied more recently.

2.1. Independent Component Analysis

Statistically motivated methods such as BSS make use of various statistical properties of the data to achieve matrix factorization. ICA has been the most widely used BSS technique. By assuming that the observations are a linear mixture of independent sources/components, ICA can recover the original sources up to an ordering and scaling ambiguity. Following the work of McKeown *et al.* [9], ICA has been widely applied to fMRI analysis [12, 10]. Spatial ICA can estimate systematically non-overlapping, temporally coherent brain regions without constraining the temporal domain. The spatial ICA model is shown in Fig. 1, where each row of the observation matrix is formed by flattening the voxels of the scanned brain at a given time. The number of time points is typically reduced using principal component analysis (PCA) often with information-theoretic criteria (ITC) to determine the signal space in which ICA is performed. Since ICA can be cast in a maximum likelihood framework, ITC-based order selection is a natural fit [13].

More precisely, the linear mixing model for mixture $\mathbf{x}(v) \in \mathbb{R}^N$ observed over N time points at voxel v is given in terms of the mixing matrix $\mathbf{A} \in \mathbb{R}^{N\times R}$ and R sources $\{s_r(v)\}$ constituting $\mathbf{s}(v) := [s_1(v), s_2(v), \ldots, s_R(v)]^{\top}$ as

$$\mathbf{x}(v) = \mathbf{A}\mathbf{s}(v),\ v = 1, 2, \ldots, V \tag{1}$$

which can be written of matrices $\mathbf{X} := [\mathbf{x}(1), \ldots, \mathbf{x}(V)]$ and $\mathbf{S} = [\mathbf{s}(1), \ldots, \mathbf{s}(V)]^{\top}$ as $\mathbf{X} = \mathbf{A}\mathbf{S}^{\top}$. Based on the assumption that the source components $\{s_r(v)\}$ are statistically independent, ICA estimates component vector $\mathbf{u}(v)$ via a linear unmixing matrix $\mathbf{W} \in \mathbb{R}^{R\times N}$ as $\mathbf{u}(v) = \mathbf{W}\mathbf{x}(v)$.

2.2. Dictionary Learning

DL aims at finding in a data-driven manner the set of subspaces that allows a parsimonious representation of a given dataset. Recently, the DL approach has attracted significant attention as a tool for fMRI data analysis [24, 25, 26]. The typical setup of DL for fMRI analysis postulates the linear mixing model in Fig. 1, with R potentially larger than N, allowing overcomplete representation. Sparseness is encouraged in the spatial maps $\mathbf{S}$, encoding the notion that the neural activities are parsimonious and confined to localized brain regions. Specifically, DL for fMRI analysis can be formulated using the noisy measurement model

$$\mathbf{x}(v) = \mathbf{A}\mathbf{s}(v) + \mathbf{e}(v),\ v = 1, 2, \ldots, V \tag{2}$$

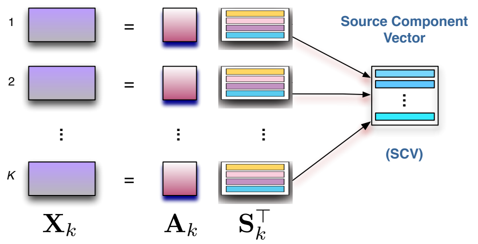

Fig. 2. IVA model allows for individual mixing matrices $\mathbf{A}_k$ and spatial maps $\mathbf{S}_k^\top$. The SCV effectively exploits dataset dependence.

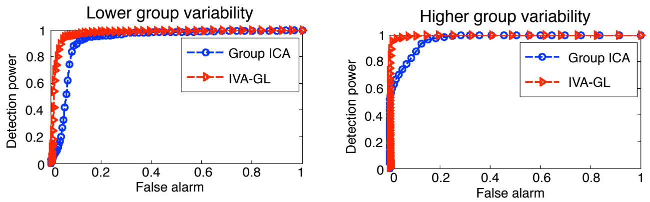

Fig. 3. Receiver operating characteristic curves for IVA and group ICA. IVA leads to better performance in capturing group differences, especially with increasing group variability compared to group ICA.

where $\mathbf{A}$ plays the role of the dictionary, $\{\mathbf{s}(v)\}$ are assumed to be sparse, and $\mathbf{e}(v)$ is the noise, typically modeled as independent from voxel to voxel. A maximum-likelihood estimation approach is taken in [26], where $\mathbf{A}$ and $\mathbf{S}$ were estimated jointly with the noise covariance, and the sparsity level is determined based on the minimum description length (MDL) criterion thus alleviating the issue with selecting multiple parameters for the DL decomposition. Additional processing to prevent strongly correlated time courses may be also useful [24]. It is also worth noting that the sparsity imposed in the DL framework is tantamount to introducing a super-Gaussian prior, allowing DL to capture higher-order statistical (HOS) information as well [27]. The simple Infomax algorithm [28] has proven very effective for ICA of fMRI data for this simple reason as the fixed nonlinearity used in Infomax is a good match for sources with highly super-Gaussian distributions.

3. GROUP ANALYSIS METHODS

Thanks to continued fMRI data collection efforts including HCP and the growth of data repositories like COINS, there is increasing availability of large-scale multi-subject datasets involving more than 1000 individuals. We review multi-subject fMRI data analysis methods with a focus on the ICA and DL-based approaches.

3.1. ICA for Group Analysis

Multi-set generalizations of ICA include group ICA [11] and IVA [13, 29]. Group ICA performs ICA on the vertically concatenated data. Let $\mathbf{X}_k \in \mathbb{R}^{N_k \times V}$ be the fMRI dataset for subject $k = 1, \ldots, K$ spanning N_k time instants and V voxels. Group ICA captures a group subspace with spatially independent (systematically non-overlapping) spatial maps and time courses. These are then used to back-reconstruct subject-specific spatial maps $\mathbf{S}_k$ and time courses $\mathbf{A}_k$ [10, 11].

IVA, on the other hand, admits individual time courses $\{\mathbf{A}_k\}$ and spatial maps $\{\mathbf{S}_k\}$ by directly generalizing the ICA model for K datasets, where

$$\mathbf{X}_k = \mathbf{A}_k \mathbf{S}_k^\top \quad (\text{or, } \mathbf{x}_k(v) = \mathbf{A}_k \mathbf{s}_k(v),\ v = 1, \ldots, V). \quad (3)$$

for $k = 1, \ldots, K$. Then, as shown in Fig. 2, source component vector (SCV) $\mathbf{s}^{[r]}(v) \in \mathbb{R}^K$ for $r = 1, 2, \ldots, R$ is formed by collecting the r-th components of $\mathbf{s}_k(v)$, $k = 1, 2, \ldots, K$. The dependence across the multiple datasets are captured through the definition of a cost function that achieves a decomposition with maximally independent SCVs. IVA essentially performs ICA for each dataset $\mathbf{X}_k$, while maximizing the dependence of the entries within each SCV.

Both ICA and IVA can be formulated using the mutual information rate [13], which allows maximally exploiting all available diversity *within* (in the case of ICA and IVA) and *across* (IVA) datasets. Moreover, both group ICA and IVA provide fully multivariate approaches for multiset data analysis. IVA provides a more flexible approach than group ICA at the cost of increased computational time by avoiding a rigid definition of a common subspace, which allows the algorithm to better capture subject variability as demonstrated by multiple examples, both with simulated fMRI-like data and with real data from patients with schizophrenia and stroke [16, 15]. In Fig. 3, IVA is seen to be more effective in capturing differences in two groups of subjects simulated via SimTB [13, 30].

3.2. DL for Group Analysis

Matrix factorization has been extended for multi-set data fusion. Matrix co-factorization is shown to be effective for analyzing multi-set multi-modal datasets [31, 32, 33]. Some results on using DL for multi-subject fMRI data analysis were reported in [34, 35]. One approach is to introduce common spatial maps $\bar{\mathbf{S}}$ shared across the subjects but allow slight individual variations [34]. Specifically,

$$\mathbf{X}_k = \mathbf{A}_k \mathbf{S}_k^\top + \mathbf{E}_k,\ \mathbf{S}_k = \bar{\mathbf{S}} + \mathbf{F}_k,\ k = 1, 2, \ldots, K \quad (4)$$

where $\mathbf{E}_k$ and $\mathbf{F}_k$ are Gaussian perturbations. In addition to sparsity, spatial smoothness can be encouraged on the spatial map $\bar{\mathbf{S}}$ using a graph Laplacian-based regularizer. However, in this model, distinct individual subspaces are not jointly extracted from the data, which may be informative for various personalized prediction tasks. An alternative is to respect variability in different datasets by pursuing a hybrid of DL and multiset canonical correlation analysis (MCCA) [35], where individualized factors are obtained for each dataset while correlations are maximized across the factors in different datasets. Note that IVA significantly expands the benefits of MCCA by taking HOS into account and includes MCCA as a special case [13].

4. LARGE-SCALE FMRI ANALYSIS: CHALLENGES AND OPPORTUNITIES

Given that large-scale multi-subject data have become available across multiple repositories, there is a growing need for the development of a flexible analysis framework for large-scale fMRI data that can capture the global traits in brain activity, while not losing the individual aspects of a given brain. Accurate estimation of each subject's functional connectivity allows leveraging large and distributed fMRI repositories while also offering effective comparisons across different conditions, groups, and time points, further increasing the usefulness of fMRI in brain research. However, there are challenges associated with analyzing such large-scale data.

4.1. Independence or Sparsity?

A promising idea may be to carefully balance the two sources of diversity so as to capture the *global* traits in the brain activities robustly, while not losing the *local* details that entail the individual/group-specific features. In fact, there has been a lively debate as to whether ICA indeed leverages source independence, or rather exploits sparsity, especially in the context of fMRI data analysis [36, 37]. It was argued in [36] that ICA may be seeking sparsity rather than independence and thus the success of the ICA methods in fMRI analysis indicated that sparse representations offer a more promising framework. Although most of these claims were countered in a later detailed rebuttal [37], the healthy ingredient in the debate is the finding that both forms of diversity are extremely valuable for fine-grained flexible fMRI analysis.

To elaborate, it is noted that group ICA provides reliable performance in general and also scales well for a sizable number of datasets, but uses back-reconstruction to produce subject-specific spatial maps [38]. In contrast, IVA can directly produce subject-specific mixing matrices and spatial maps, and as a result captures subject variability well. However, IVA incurs a high computational cost, especially when the goal is to leverage HOS information. On the other hand, the fine-grained variability from individual heterogeneity can be extracted using a sparse overcomplete DL framework at a reasonable computational cost. Therefore, synergistically combining the strengths of the BSS and DL approaches has the potential to provide multi-resolution understanding of the brain's functional connectivity, encapsulating both the structures that are globally coherent, as well as the patterns that emerge at a local scale.

4.2. Multi-site fMRI Data Sharing

For carrying out large-scale fMRI data analysis, it is crucial to capitalize on the vast collection of datasets that reside in different sites and databases. Although the field of neuroimaging has been embracing the need for data sharing and now there are a multitude of data repositories and neuroinformatics consortia, they mainly subscribe to a centralized sharing model, which entails significant computational and storage requirements, lacking scalability. Furthermore, there are regulatory barriers due to constraints on post-hoc sharing, institutional review board (IRB) issues, and governmental or proprietary restrictions that hinder open sharing and collaboration. As the traditional data usage agreements are extremely diverse and dataset-dependent, the time frame needed to undergo necessary approval processes often exceeds the feasible research schedule. Allowing the reuse of datasets collected for past projects while respecting the participants, principal investigator permissions, and IRB regulations is critically desired.

A promising alternative is a decentralized sharing model, where the data themselves are kept at the respective repositories but local analyses are coordinated so as to achieve the computational quality on par with what would have been obtained with centrally pooled data. Recent frameworks in this direction include ViPAR [39], ENIGMA [40], and COINSTAC [41]. In particular, COINSTAC encompasses the benefits of the existing successful platforms with numerous added strengths such as quantifiable privacy assurance, comprehensive preprocessing, and ease of anonymizing data.

4.3. Decentralized Analysis

Under the decentralized data sharing model, decentralized fMRI data analysis algorithms must be developed. Key issues include the fidelity of analysis compared to centralized solutions, amount of information exchange between repositories, parallelism in processing for scalability, privacy/policy compliance for data sharing. A single-shot approach entails individual nodes performing local analysis, whose results are then combined by a fusion site. More accurate results are obtained by a multi-shot/iterative approach at the expense of multiple stages of data access and information exchange [41]. A decentralized iterative ICA method was tested for temporal ICA of large-scale multi-subject data in [42]. Computationally efficient local dimensionality reduction was employed prior to global DL analysis in [43]. Decentralized DL algorithms have been developed in different contexts as well [44, 45].

5. CONCLUSION

Data-driven fMRI analysis methods have been reviewed with a focus on matrix factorization approaches exploiting source independence and sparsity. ICA captures a variety of statistical diversity including HOS information and sample dependence. Multi-subject extensions such as group ICA and IVA can additionally exploit dependence across datasets. Recent DL-based methods admit overcomplete representations and have the potential to obtain more detailed component maps. Joint analysis of multi-subject data using DL is under active research. A synergistic approach to combine the strengths of BSS and DL may provide a flexible multi-resolution method for large-scale fMRI data analysis. Distributed sharing platforms mitigate the barriers for integrative multi-repository analysis including various regulatory and data sharing restrictions. Under such frameworks, managing the disparity of site-specific preprocessing stages, developing efficient decentralized processing algorithms, and ensuring policy-compliant data sharing are important research issues.

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