An ICA-based framework for joint analysis of cognitive scores and MEG event-related fields

P. Boonyakitanont[1,2], B. Gabrielson[1], I. Belyaeva[1], J. Songsiri[2], Y. P. Wang[3], T. W. Wilson[4], V. D. Calhoun[5,6], J. M. Stephen[5], T. Adalı[1*]

Abstract— **This paper proposes an independent component analysis (ICA)-based framework for exploring associations between neural signals measured with magnetoencephalography (MEG) and non-neuroimaging data of healthy subjects. Our proposed framework contains methods for subject group identification, latent source estimation of MEG, and discriminatory source visualization. Hierarchical clustering on principal components (HCPC) is used to cluster subject groups based on cognitive scores, and ICA is performed on MEG evoked responses such that not only higher-order statistics but also sample dependence within sources is taken into account. The clustered subject labels and estimated sources are jointly analyzed to determine discriminatory sources. Finally, discriminatory sources are used to calculate global difference maps (GDMs) for the summary. Results using a new data set reveal that estimated sources are significantly correlated with cognitive measures and subject demographics. Discriminatory sources have significant correlations with variables that have not been previously used for group identification, and GDMs can effectively identify group differences.**

Index Terms— **MEG, ICA, GDM, HCPC, correlation**

I. Introduction

Magnetoencephalography (MEG) records brain signals that are observed via magnetic flux induced from neural activities. Because of the advantages of high temporal and spatial resolution, MEG has been increasingly utilized in the study of brain function, e.g., MEG was used to determine language dominance in epileptic patients [1]. Blind source separation using MEG and, in particular, independent component analysis (ICA), a matrix decomposition method which demixes a linear mixture of latent sources based on the assumption of their statistical independence [2], has also been of interest to researchers for localizing neural sources [3]. ICA has also been used to reveal subject group differences of brain networks involved in major depressive disorder for MEG [4]. However, the full potential of ICA applied to MEG data, especially by exploiting sample autocorrelation within sources, has not yet been explored. In addition, associations between MEG evoked responses and cognitive characteristics of typical individuals have not been examined. Therefore, we propose an ICA-based framework to jointly analyze MEG and neuropsychological test results. We demonstrate that global difference maps (GDMs) [5], originally developed for functional magnetic resonance imaging analysis, can be effectively used to summarize the analysis results of the MEG data. Results show that sources estimated by ICA can identify subject groups with different neuropsychological scores. Age and social economic status also show significant correlation with the discriminatory sources.

This paper is organized as follows. Section II describes the data set [6] and the analysis methods, including hierarchical clustering on principal components (HCPC), ICA, and GDM, that are used in this work. Section III reports experimental results, and Section IV concludes the summary.

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[1]University of Maryland, Baltimore County, Baltimore, MD, US

[2]Chulalongkorn University, Bangkok, Thailand

[3]Tulane University, New Orleans, LA, US

[4]Boys Town National Research Hospital, Omaha, NE, US

[5]The Mind Research Network a division of Lovelace Biomedical Research Institute, Albuquerque, NM, US

[6]Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, Emory University, Atlanta, GA, US

*Correspond author.

II. Materials and Methods

A. MEG and Non-neuroimaging Data

This study uses MEG, demographics, and cognitive measures of participants in the Developmental Chronnecto-Genomics (Dev-CoG) study [6]; see the list of the cognitive measures in Table I. The Dev-Cog study contains multi-modal neuroimaging data, neuropsychological testing, and parent questionnaires with the aim of understanding brain development from healthy subjects across the age range of 9-14 years. The data was collected from Mind Research Network (MRN) and University of Nebraska Medical Center (UNMC). Each participant was assigned to perform auditory, visual, and multisensory tasks, and neuroimaging data was acquired during these tasks. In each task, participants were asked to press the index finger in response to the auditory and visual stimuli. The visual stimulus was a screen of black and white vertical grids, the auditory stimulus was a 40 Hz modulated 1 kHz sound, and both auditory and visual stimuli simultaneously presented in the multisensory task. MEG recordings were acquired simultaneously using a 306-channel MEG system when participants performed the task. For each trial, the fixation was presented with a red box at the center for a random duration of 2.4-2.6 seconds, followed by a stimulus for 0.8 seconds.

B. Methods

Consider the proposed framework of MEG analysis consisting of group identification, ICA, and GDM as shown in Figure 1. First, groups of subjects are identified by

TABLE I

LIST OF COLLECTED VARIABLES WHERE AGE AND SOCIOECONOMIC STATUS ARE NON-COGNITIVE MEASURES.

Name	Description
AGE	Age
SES	Socioeconomic Status
INATT	Conners 3 Inattention Score [7]
HYPER	Conners 3 Hyperactivity Score [7]
FSIQ	Full Scale IQ Composite Score [8]
DCCS	Dimensional Card Sorting Score [9]
FICA	Flanker Inhibitory Control and Attention Score [9]
LSWM	List Sorting Working Memory [9]
ORRENG	Oral Reading/Recognition Comprehension Score [9]
PSM	Picture Sequence Memory Score [9]
PICVOCAB	Picture Vocabulary Score [9]

using the cognitive scores. Next, MEG data and the subject groups are jointly used to determine latent sources that can discriminate between the groups by using ICA and false discovery rate (FDR)-controlling procedure. Moreover, correlations are calculated between the estimated MEG sources and behavioral measures. Finally, sources that discriminate between subject groups are summarized by GDMs. With this framework, we can analyze neuroimaging and non-neuroimaging data jointly for cognitive study.

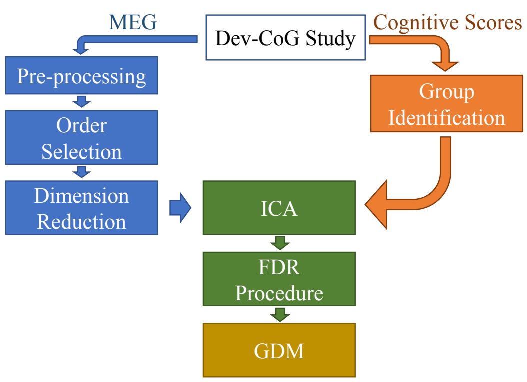


Fig. 1. The proposed framework of MEG analysis.

C. Behavioral Measures Clustering

HCPC is an unsupervised method for clustering data into groups by performing hierarchical clustering on projected inputs [10]. This method can be used for both continuous and categorical variables. Suppose that a feature matrix contains data of M subjects and F features for clustering. The features are projected onto S principal components to reduce dimensions of the data. Subsequently, a hierarchy of the clusters is generated from the projected features using Ward's method [11] and distance correlation [12]. Finally, the optimal number of clusters is determined by an approximately unbiased p-value [13] less than 0.05.

D. MEG Analysis

Artifact and movement were corrected in the MEG data by using the Neuromag Maxfilter software [14]. The Maxfilter software was also used to register each data set to a common head position within the area (average head position across participants) allowing for comparison of sensor level data across participants. Once corrected, epochs that range from -0.1 to 1 second were extracted relative to the presentation of the stimulus triggers with the stimulus presented at time 0. Epochs within the condition were averaged, and the resulting averaged evoked response was used for ICA.

Given an observation matrix $\mathbf{X} \in \mathbb{R}^{N \times T}$ where N and T are the number of mixtures and the number of samples, respectively, the ICA formulation can be expressed as

$$\mathbf{X} = \mathbf{A}\mathbf{S}, \tag{1}$$

where $\mathbf{A} = [\mathbf{a}_1, \ldots, \mathbf{a}_C] \in \mathbb{R}^{N \times C}$ is an unknown mixing matrix, $\mathbf{S} \in \mathbb{R}^{C \times T}$ is a source matrix of which the rows are assumed to be statistically independent [2], and C is the number of latent sources. The i-th column of the mixing matrix, $\mathbf{a}_i$, presents the weight of the i-th source across the mixtures (subjects) . As the goal of this work is to find latent information that describe differences between subject groups, the weights can be used to determine which sources demonstrate significant group differences. To determine the source matrix, a demixing matrix $\mathbf{W}$ that maximizes independence between the sources $\hat{\mathbf{S}} = [\hat{\mathbf{s}}_1, \ldots, \hat{\mathbf{s}}_C]^T \in \mathbb{R}^{C \times T}$, described by $\hat{\mathbf{S}} = \mathbf{W}\mathbf{X}$, is estimated.

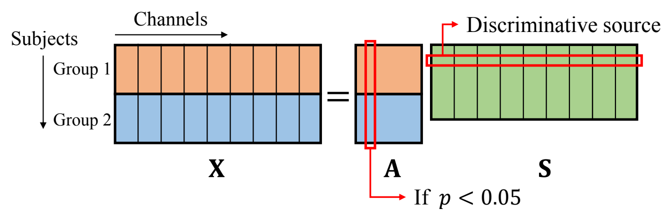


Fig. 2. Observation matrix construction.

In this study, we construct the observation matrix $\mathbf{X}$ by horizontally concatenating the temporal MEG data from each sensor of one subject into a row vector, and concatenating row vectors from all subjects vertically as shown in Figure 2. This construction allows each of the estimated sources to describe both temporal and spatial variations across subjects, and thus the ICA estimated discriminatory sources can reveal how both the temporal and spatial differences manifest in the different groups. Each row of $\mathbf{X}$ is then standardized to have zero mean and unit variance. Finite memory length model (ER-FM) and autoregressive model (ER-AR) [15] are applied to estimate the model order (the number of latent sources), and principal component analysis (PCA) is then used for dimension reduction using the estimated order C. To perform ICA, the demixing matrix $\mathbf{W}$ is estimated using an entropy rate bound minimization (ERBM) algorithm which exploits not only higher order statistics, but also sample dependence within sources [16]. The sample dependence is especially prevalent in MEG temporal data, and, to the best of our knowledge, has not previously been exploited for MEG analysis.

E. Summarizing MEG Sources via GDM

GDM is a way to effectively summarize group differences using multiple discriminatory sources [5]. The idea is to reveal underlying brain regions that show significant differences between two groups of subjects. When explaining the methodology, due to the permutation ambiguity of ICA, we assume that the first m sources are discriminatory. The GDM is computed by the weighted average of discriminatory sources as follows

$$\hat{\mathbf{s}}_{\mathrm{GDM}} = \sum_{n=1}^{m} \frac{t_n}{\sum_{i=1}^{m} t_i} \hat{\mathbf{s}}_n, \tag{2}$$

where t_n is the t-statistic calculated from the n-th column of $\mathbf{A}$, and t_n is positive or is made to be positive by multiplying -1 to $\mathbf{a}_n$ and $\hat{\mathbf{s}}_n$. Because of the sign ambiguity of ICA, this multiplication does not change the estimated solution (aside from flipping the sign of sources), and keeps the product $t_n\hat{\mathbf{s}}_n$ the same. From temporal and spatial structures in $\hat{\mathbf{s}}_n$, the GDM demonstrates the summary of group differences by signals corresponding to MEG sensors. Note that $\hat{\mathbf{s}}_n$ is standardized to have zero mean and unit variance before the computation. In addition, the weight for the GDM is similarly calculated by

$$\mathbf{a}_{\mathrm{GDM}} = \sum_{n=1}^{m} \frac{t_n}{\sum_{i=1}^{m} t_i} \mathbf{a}_n. \tag{3}$$

This weight is used to calculate the p-value using the two-sample t-test to determine the discriminative power of GDM.

III. Results and Discussion

In this research, we used MEG evoked responses and behavioral scores of 170 healthy subjects from the Dev-CoG study [6]. For MEG analysis, only planar gradiometer sensors were chosen for the analysis, since their peak sensitivity corresponds more closely to the spatial location of the source than magnetometer sensors. As MEG recordings were originally pre-processed with a 60 Hz low-pass filter, we resampled the data from 1000 Hz to 125 Hz to decrease computational complexity without the loss of useful information. In each stimulation task, we selected the demixing matrix $\mathbf{W}$ that was the most similar to others from multiple runs based on inter-symbol interference (ISI). From the order selection, the model orders returned by both ER-AM and ER-FM were 30, 22, and 13 for the auditory, visual, and multisensory tasks, respectively.

Figure 4 reveals that estimated sources are significantly correlated with many non-neuroimaging variables defined in Table I. Specifically, correlations between sources and AGE, INATT, ORRENG, and PSM were common across all tasks. Remarkably, AGE and SES, which are not included in cognitive measures, were also associated with some sources. This means that the estimated sources provide information of not only cognitive measures but also demographic and social standing of participants.

For the group identification, nine cognitive measures, excluding AGE and SES, were used. We validated the optimal number of clusters by using internal cluster validation indices (Dunn index [17], Calinski-Harabasz index [18], Davies-Bouldin index [19], McClain-Rao index [20], Bayesian information criterion, cluster entropy [21]) and external cluster stability index (Jaccard Similarity index [22]). The results showed that the optimal number of clusters was consistently two. Furthermore, as shown in Figure 3, Group 1 is clearly demonstrated by low values of INATT and HYPER and high values of the other cognitive scores compared to Group 2.

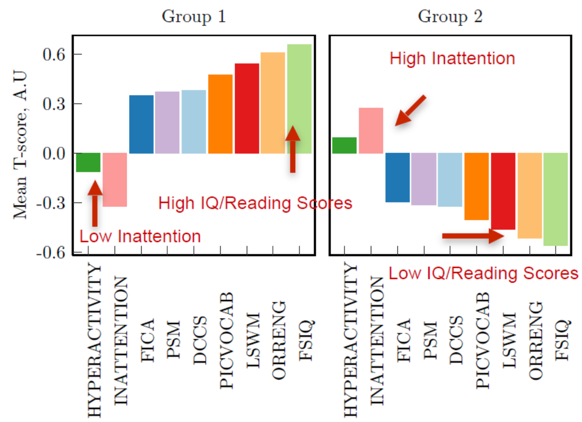


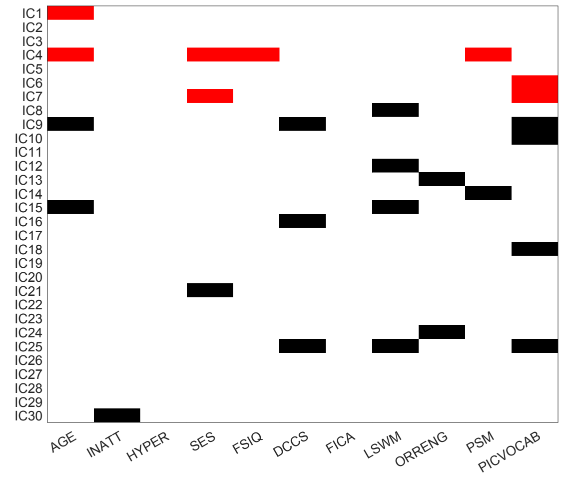
Fig. 3. Differences of cognitive scores in group identification.

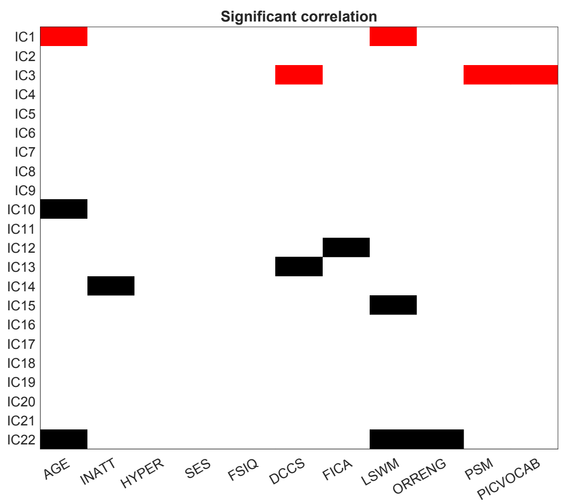
According to the number of subject groups, discriminatory sources were consequently determined by two-sample t-tests performed on the columns of $\mathbf{A}$, and corrected for multiple comparisons using a FDR-controlling procedure with $p < 0.05$ [23]. As a result, the numbers of the discriminatory sources for auditory, visual, and multisensory tasks were 7, 3, and 4, respectively. As illustrated in Figure 4, discriminatory sources are associated with AGE and PSM for all tasks. It is worth noting that AGE, a variable not included in the cognitive scores, is involved with the subject groups identified by those scores. This underlines the importance of including participants' age in studies of brain development.

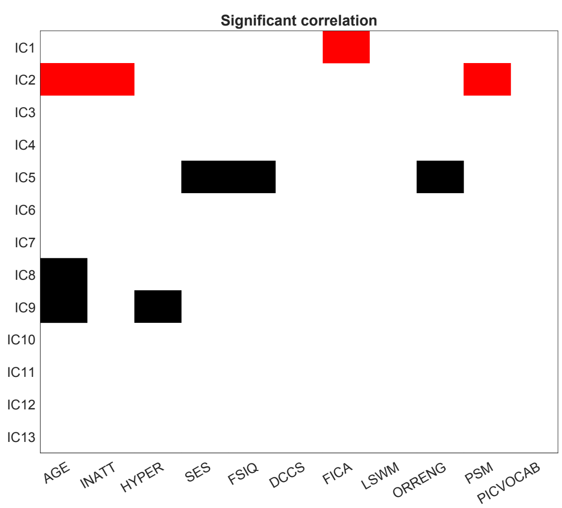
In addition, Figure 5 illustrates that, from the p-values calculated using $\mathbf{a}_{\mathrm{GDM}}$, GDMs significantly demonstrate group differences across subjects with different cognitive scores. The GDMs show that discriminatory sources start to respond about 0.1 seconds after the stimulation. The estimated activity was dominant over temporal lobe in the auditory task, while occipital lobe and surrounding regions were active in the visual and multisensory tasks, consistent with the expected behaviors for these tasks. This suggests that these brain areas reflect brain development and are influenced by the participants' age during a simple multisensory task.

IV. Conclusion

This study aimed to examine associations between neural activities observed via MEG and cognitive test outcomes of healthy participants taken from the Dev-CoG study. We applied HCPC to cognitive scores for clustering subjects, and performed ICA on MEG data to estimate latent sources. The application of ICA to the MEG data revealed estimated sources which described variation in both spatial and temporal domains. Furthermore, we implemented ICA-ERBM to exploit not just higher order statistics, but also the strong

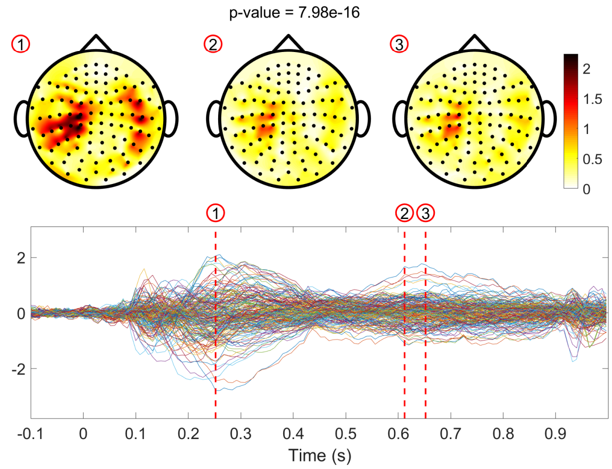




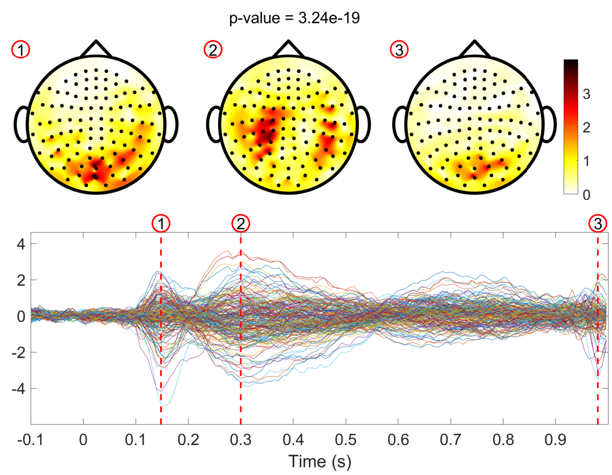


(c) Multisensory task.

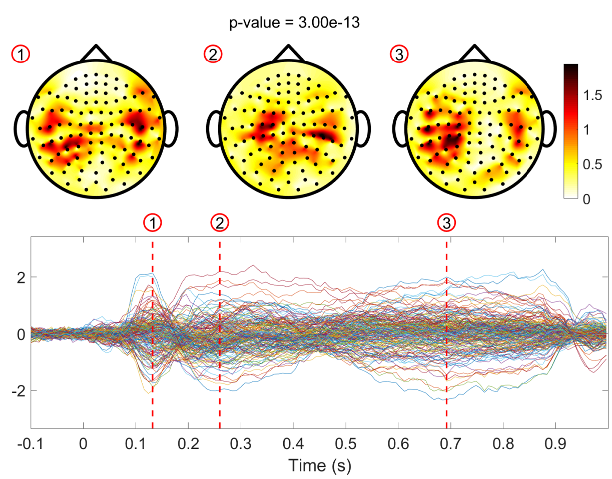
Fig. 4. Significant correlations between sources (ICs) and subject characteristics where discriminatory sources are emphasized in red. The sources are sorted by p-values from two-sample t-tests for determining the discriminatory sources.



(a) Auditory task.



(b) Visual task.



(c) Multisensory task.

Fig. 5. GDMs calculated using discriminatory sources. Signals are GDMs corresponding to MEG channels, and topographical maps show the absolute values of the GDMs at peaks of global field potentials as marked. The stimuli start at time 0.

prevalence of sample dependence within the MEG data. The clusters and latent sources were jointly analyzed to determine sources that can discriminate between groups. All estimated discriminatory sources were then used to calculate GDMs that summarize their discriminative power. Experimental results showed that the estimated sources were significantly correlated with cognitive test results without prior information, and age had most associations with discriminatory sources. These results are interesting because sensory responses are typically viewed as developing early, and less emphasis is put on examining basic sensory-level development in the 9-14 year age range. These results also indicate that sensory and cognitive processes continue to develop throughout adolescence. Furthermore, the GDMs revealed brain networks involved in the underlying group differences. In addition, the proposed method, which was performed in sensor space, could be extended to analyze MEG evoked responses in source space to obtain more specific details of spatial localization of brain regions.

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