# DATA-DRIVEN ANALYSIS AND VISUALIZATION OF COMPLEX FMRI DATA: APPLICATION TO AN EVENT-RELATED PARADIGM

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## ABSTRACT

Independent Component Analysis (ICA) has been successfully used to study complex-valued functional magnetic resonance imaging (fMRI) data in a number of block-design paradigms. In this paper, we demonstrate the first successful application of group ICA to complex-valued fMRI data of an *event-related paradigm*. We show that networks associated with event-related responses as well as intrinsic fluctuations of hemodymamic activity can be extracted for data collected during an auditory oddball paradigm. The intrinsic networks are of particular interest due to their potential to study cognitive function and mental illness, including schizophrenia.

Additionally, we show that analysis of fMRI data in its complex form can increase the sensitivity in the detection of activated brain regions when compared to magnitude-only applications. This provides a powerful motivation for utilizing both the phase and magnitude data. However, the unknown and noisy nature of the phase requires the development of an appropriate approach for its visualization. We introduce a novel fMRI phase-based visualization (FPV) technique that can be used to identify activated voxels in higher numbers than typical visualization techniques that only use the magnitude data.

*Index Terms*— Complex-valued fMRI, Group ICA, Visualization, Phase, Event-related

## 1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) is a technique that provides the opportunity to study brain function non-invasively and is a powerful tool utilized in both research and clinical areas since the early 90s.

FMRI data are natively acquired as complex-valued spatiotemporal images; but, usually only the magnitude images are used for analysis. However, growing evidence from our group and others [1, 2] suggest that the phase data carries information about the blood oxygen level dependent (BOLD) signal above and beyond what is preserved in the magnitude data. One particular powerful motivation to study both the magnitude and the phase of the fMRI data is the possibility of increasing the sensitivity in the detection of activated brain regions.

Both model-based approaches, such as general linear model (GLM), and data-driven approaches, such as independent component analysis (ICA), can be used for studying complex-valued fMRI data. ICA, in particular, has shown substantial promise for studying the magnitude and complex-valued fMRI data [3, 4, 5]. By using a simple generative model based on linear mixing, ICA can minimize the constraints imposed on the temporal–or the spatial–dimension of

the fMRI data, and hence provides valuable new insights, especially when studying paradigms for which reliable models of brain activity are not available.

Complex-valued group ICA of fMRI data has been used primarily to extract signals from brain regions that show BOLD changes in response to a block-design paradigm. More recently there has been increased interest in networks associated with event-related responses as well as intrinsic fluctuations of hemodymamic activity. In this paper, we introduce the first successful application (to the best of our knowledge) of group ICA to an event-related complexvalued fMRI data. We show that not only we can extract intrinsic networks (*e.g.*, default mode network) but that by including the phase information we can enhance the detection of activated voxels. These voxels are not detectable by real-valued algorithms operating on magnitude-only data. This increase in sensitivity could help in the discrimination of control and patient subjects in clinical studies and enhance the studying of cognitive function and mental illness, including schizophrenia.

Exploiting this increase in sensitivity provided by the phase requires new complex-valued preprocessing and visualization techniques for fMRI data. We have developed a framework [6] that allows us to incorporate the phase information in every step of a group ICA of fMRI. In [6], we introduced a visualization method that takes into account both the phase and magnitude to identify activated voxels, but a method to solely visualize the phase and hence represent its information content has been an open problem. The phase images are usually not used, because their noisy and unfamiliar nature poses a challenge [3]. In here, we introduce the first method that uses the phase of the estimated independent components (ICs) to identify activated brain regions and display their actual unwrapped phase values. This novel fMRl phase-based visualization (FPV) technique is shown to be critical in analyzing complex-valued fMRI ICA results, since using only the magnitude of the estimated ICs for visualization does not fully capitalize on the benefits of using the phase.

In Section 2, we provide background information about complexvalued ICA. In Section 3, we describe the FPV technique. In Section 4, we present the results obtained from applying group ICA to actual complex event-related fMRI data. We also show how the FPV method can enhance the detection of voxels with significant susceptibility changes located in low magnitude areas.

#### 2. BACKGROUND

## 2.1. ICA of fMRI Data

We can form a matrix  $\mathbf{X} \in \mathbb{C}^{T \times V}$  using the complex-valued fMRI data such that the *i*th row is formed by flattening the volume image data of V voxels, at time instant *l*, into a row, and the rows are indexed as a function of time, l = 1, ..., T. In spatial ICA

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of fMRI data, we assume a simple linear mixing model such that  $\mathbf{X} = \mathbf{AS}$ , and determine *both* the activation maps and the corresponding waveforms, *i.e.*, both **S** and **A**, typically without constraining either. The additional assumption we impose is that the rows of matrix **S** represent observations of statistically independent random variables. ICA achieves demixing by estimating a weight matrix **W** such that  $\mathbf{U} = \mathbf{WX} = \mathbf{PAS}$ . Here, **P**, a permutation matrix, represents the permutation ambiguity and **A**, a diagonal matrix, represents the scaling ambiguity of ICA, which has a magnitude and phase term in the complex-valued implementation of ICA. In [6], we introduce a phase correction algorithm that alleviates the ambiguity due to the phase term so that group analysis becomes possible.

There are several complex ICA algorithms that can be used to analyze fMRI data [7]. Some well-known complex ICA algorithms, such as the complex fastICA algorithm and circular infomax algorithm, use a fixed nonlinearity function to implicitly generate the higher-order statistics required [5]. As we know, for the ICA algorithms based on mutual information minimization (equivalently maximum likelihood and maximization of negentropy), the algorithms are optimal when the form of the nonlinear function matches the form of the probability density functions of the sources. Hence, the feature of fixing the nonlinearity limits the performance of source separation. Since very little is known about the nature of fMRI sources, it is desirable to use an algorithm that is more flexible in adapting to a wide range of source distributions, e.g., the adaptive complex maximization of non-Gaussianity (A-CMN) and the complex entropy bound minimization (complex EBM) algorithms. In this paper, we implemented the complex EBM [8] since it has shown superior performance for analysis of complex-valued fMRI data [9]. EBM uses a maximum entropy density model and it can approximate a wide range of super- or sub-Gaussian, symmetrical or asymmetrical distributions.

## **3. METHODS**

In this section, we introduce the novel fMRI phase-based visualization method. The FPV method identifies voxels that have both good quality (*e.g.*, non-noisy) and have similar phase values as the voxels that are identified by a Mahalanobis distance score. We provide details about the three main concepts behind the FPV method: the Mahalanobis distance score (Section 3.1), phase quality masks (Section 3.2) and phase unwrapping (Section 3.3). The FPV method is summarized in Section 3.4.

#### 3.1. Z-score and Mahalanobis Distance Thresholding

In studies of complex-valued fMRI data the results are usually presented using only the magnitude information, even though the phase information is available at no cost. For example, estimated fMRI sources in spatial ICA are usually presented using Z-score thresholded magnitude  $(Z_r)$  images (*i.e.*, slices) to highlight the activated voxels. The "r" in  $(Z_r)$  stands for real-valued representation, as the metric completely ignores the phase information. The  $Z_r$  values for each of the voxels (l) of the magnitude images of the *kth* source are calculated by

$$Z_{r_{k,l}} = \frac{\|\hat{\mathbf{s}}_{k,l}\| - \hat{\eta}_k}{\hat{\sigma}_k} \tag{1}$$

where  $\hat{\eta}_k$  and  $\hat{\sigma}_k$  are the mean and standard deviation, respectively, of the magnitude images of the estimated *kth* source  $(\hat{\mathbf{s}}_k)$ .

We can, however define a Z-score that takes the complex (or bivariate) nature of the data into account by simply using the Mahalanobis distance, which we denote by  $Z_c$ , where the subscript c refers to the complex representation, *i.e.*, one that simultaneously takes the real and imaginary parts into account. It is calculated for all complex-valued voxels (l) of the estimated sources as

$$Z_{c_{k,l}} = \sqrt{\left[\hat{\mathbf{s}}_{k,l} - \hat{\boldsymbol{\mu}}_k\right]^{\mathrm{T}} \hat{\mathbf{C}}_k^{-1} \left[\hat{\mathbf{s}}_{k,l} - \hat{\boldsymbol{\mu}}_k\right]}$$
(2)

where  $\hat{\mathbf{s}}_{k,l} = [\hat{s}_{k,l,\text{re}}, \hat{s}_{k,l,\text{im}}]^{\text{T}}$  is the k estimated source and  $\hat{\boldsymbol{\mu}}_k$  and  $\hat{\mathbf{C}}_k$  are the corresponding estimated spatial image mean vector and covariance matrix over all the voxels.

Both, the  $Z_r$  and the  $Z_c$ , scores can be used to visualize the results of complex-valued ICA of fMRI data. The  $Z_c$  score is equal to the absolute value of the  $Z_r$  score when the data is univariate. Voxels of interest are identified if they have a value higher than a specified threshold for the values obtained using (1) and (2). We demonstrate that use of  $Z_c$  increases the sensitivity in detecting activated voxels when compared to the use of the  $Z_r$  score in Section 4.

The  $Z_c$  score is used in the FPV method to help identify the range of phase values of highly activated voxels. Typical thresholds (z) for the  $Z_c$  images in the FPV method have values of 6 or higher, *i.e.*, significance level of P < 10<sup>-10</sup>.

#### 3.2. Quality Maps and Masks

Quality maps are arrays of values that define the quality or goodness of each voxel in a given phase image. We use the phase derivative variance (PDV) map in our work, based on the quality of results obtained in our study when comparing this map to others, and the fact that the PDV map is considered to be extremely robust in identifying noisy areas in phase images. The PDV map is calculated as a root-mean square measure of the variances of the partial derivatives in the x- and y-directions of the phase image, such that high values represent low quality. In the PDV map, the (m, n)th voxel value is computed as

$$z_{m,n} = \cdots \tag{3}$$

$$\left(\sqrt{\sum_{i,j=-(k-1)/2}^{(k-1)/2} (\Delta_{i,j}^x - \tilde{\Delta}_{m,n}^x)^2} + \sqrt{\sum_{i,j=-(k-1)/2}^{(k-1)/2} (\Delta_{i,j}^y - \tilde{\Delta}_{m,n}^y)^2}\right)_{q^2}\right)$$

where for each sum the indexes (i, j) range over a window of size  $q \times q$  centered at the voxel (m, n). Typical values for q are 3, 5 or 7. The terms  $\Delta_{i,j}^x$  and  $\Delta_{i,j}^y$  are the partial derivatives—wrapped phase differences—of the phase. The terms  $\tilde{\Delta}_{m,n}^x$  and  $\tilde{\Delta}_{m,n}^y$  are the averages of these partial derivatives in the used window.

Quality maps are used to develop binary quality *masks*, which assign a "0" to unreliable voxesls that should not be further analyzed. These quality masks are obtained by thresholding the quality maps. Simple thresholding values can easily be acquired by visually inspecting the quality values. Voxels with very small values—0.2 radians in our implementation—in the PDV map correspond to areas of low phase gradients and hence, can usually be considered as having good quality. Additionally, we can implement the automatic threshold selection method described in [10, p.85], and obtain similar threshold values.

#### 3.3. Phase Unwrapping

The actual unwrapped phase of any complex signal represents a rotation, with direction and radial length. However, given any complex data, the phase can only be computed as modulo  $2\pi$ . If phase maps are to convey any useful information, the exact rotation of the signal in one voxel with respect to that in another must be known. Any error made in assigning a phase value to a voxel will result in an erroneous quantification of the underlying physics [1].

We develop a 3D algorithm similar to the 2D quality-guided path following phase unwrapping algorithm in Section 4.2.1 of [10]. First, a 3D PDV quality map is computed by extending (3) to a third dimension. The algorithm starts by unwrapping the phase in the location with the best quality in the fMRI data and then it starts to grow and unwrap the surrounding regions guided by the quality map.

## 3.4. FMRI Phase-Based Visualization

The steps of the FPV method are summarized in Algorithm 1. The algorithm computes two binary masks and then multiplies them to identify the voxels that are activated and should not be eliminated. The first mask is a phase quality mask. The second one is a mask that identifies the voxels with phase values similar to highly activated voxels as identified by the  $Z_c$  technique.

FPV assumes that a complex-valued ICA algorithm has been implemented to extract ICs. The input is the magnitude and phase images of a given IC. Typical values for the two thresholds in the algorithm are p = 0.2 and z = 6, as described in Sections 3.1 and 3.2.

Algorithm 1 – FPV: For a given IC	
1: Input all the 2D fMRI slices $v$	

- **Quality mask steps:** 2: Calculate PDV *map*  $(\mathbf{P}_v)$  using (3);
- 2. Calculate PDV map  $(\mathbf{I}_v)$  using (5), 3. Calculate PDV mask:  $\mathbf{B}_v = \mathbf{P}_v < p$ ;
- **Mahalanobis + phase mask steps:**
- A Commute Z volves voing (2):
- 4: Compute  $Z_c$  values using (2);
- 5: Identify the range of phase values  $\left([r_1,r_2]\right)$  of all the voxels with:  $Z_c>z$
- 6: Compute binary mask (Kv) with all the voxels with phase values in the identified range: r1 < r < r2;</li>
  FPV mask:
- FT V Mask.
- 7: Calculate FPV mask:  $\mathbf{Q}_v = \mathbf{K}_v \circ \mathbf{B}_v$ ;
- 8: Eliminate voxels outside the  $\mathbf{Q}_v$  mask;
- 9: Optional: Unwrap the phase of the surviving voxels as described in Section 3.3;

#### 4. RESULTS

## 4.1. fMRI Data

We analyzed data collected from thirty subjects performing an AOD task. An MRI compatible fiber-optic response device (Lightwave Medical, Vancouver, B.C.) was used to acquire behavioral responses for both tasks. The stimulus paradigm data acquisition techniques and previously found stimulus-related activation are described in more detail in [11].

The complex-valued data was first de-noised by using the multisubject quality map phase de-noising method we have introduced in [6]. Additionally, we use PCA to whiten and reduce the dimensionality of the complex-valued fMRI data prior to applying the ICA algorithm. The number of effective principal components for this dataset is selected as 30, using the minimum description length (MDL) criterion for complex valued data as in [4]. The complex EBM group ICA was applied to the fMRI data using the GIFT toolbox [12]. Since ICA algorithms are of iterative type, we use ICASSO [13] in GIFT to check the consistency of the algorithm and improve the robustness of the estimation results.

The entire process was repeated with the magnitude of the fMRI data for comparison.

#### 4.2. Complex-valued ICA of Event-Relatated Task



Fig. 1. Group level  $Z_r$ ,  $Z_c$  and FPV images of three ICs extracted from the AOD data by the complex EBM ICA algorithm. The FPV images show the unwrapped phase values in radians of the identified activated voxels. Only 6 of the 46 fMRI slices are shown.

In this section, we show the results of applying the complex EBM group ICA algorithm to the AOD data. Three ICs of interest were manually selected from the thirty estimated. The three ICs are as follows: 1. Temporal lobe (TL); 2. DMN; 3. Right parietal (RP). The TL IC is task-related and the other two represent intrinsic networks. Other ICs extracted by the complex-EBM algorithm but not shown here due to lack of space contained activated voxels related to the following networks: Left parietal, occipital, anterior DMN, motor, cerebellum and frontal parietal.

In Fig. 1, we show the  $Z_r$ ,  $Z_c$  and FPV images of three selected ICs. Starting from the top left slice and then moving right and down, we can see the fMRI slices as if were going from the top of the head towards the neck. The FPV images show the unwrapped phase values in radians of the identified activated voxels. As discussed in Section 3.1, the  $Z_r$  and  $Z_c$  can be used for visualization and are compared here with the FPV method. The  $Z_r$  and  $Z_c$  images were thresholded at the same significance level (P < 0.05).

The FPV phase images can provide more information about the underlying physics. For example, we can increase our ability to detect voxels with significant susceptibility changes located in low magnitude areas. It can be seen in Fig. 1 that both the  $Z_c$  and FPV visualization algorithms identify more voxels in all the ICs, in particular the new FPV method. The phase information increases the sensitivity in the detection of the activated areas of each of the ICs without affecting specificity.

To quantify the performance of all the visualization techniques, we generated masks of the regions of the three ICs using the WFU Pickatlas toolbox (http://www.nitrc.org/projects/wfupickatlas). This toolbox allows users to create masks by selecting both Brodmann areas (BAs) and functional areas in the brain. The masks and their corresponding regions that are activated during AOD task [11] are shown as follows: 1. DMN: BAs 7, 10, 39, precuneus and posterior cingulate; 2. Parietal lobe: BAs 5, 7, 39, 40, postcentral gyrous, supramarginal gyrus, posterior cingulate and precuneus; 3. Temporal lobe: BAs 20, 21, 22, 38, amygdala, and parahippocampa gyrus. The generated masks were used to calculate the number of voxels in the ICs obtained from the three visualization techniques that were located in the expected brain regions (see Table 1).

	Visualization method		
Independent	$Z_r$	$Z_c$	FPV
Component			
Temporal Lobe	1792	2683	2691
DMN	1682	2784	3413
Right Parietal	917	1426	1895

 Table 1. Identified number of voxels by the different visualization methods when applied to three of the extracted ICs using group complex-EBM ICA algorithm.

## 4.3. Comparison of Complex and Magnitude-only ICA Application on Event-Relatated Task

To test the difference in performance of both the complex-valued and magnitude-only ICA results, we implemented parametric methods for thresholding the  $Z_c$  and  $Z_r$  sample values. Using the thresholded images we calculated their respective receiver operating characteristic (ROC) curves (as described in [6]). Here, we show the ROC curves results for the DMN component. We use the  $Z_r$  and the  $Z_c$  images from the complex-valued results and only the  $Z_r$  image from the magnitude-only analysis results.

The probability of true positives (TP) in the ROC curves indicates the number of voxels that survive the threshold (at each point in the curve) and that fall inside the WFU Pickatlas DMN mask. Similarly, the probability of false positive (FP) indicates the number of voxels that pass the various thresholds and that fall outside the DMN mask. Comparison of the ROC curves for the different thresholding methods is done by calculating their respective area under the curve (AUC). Better performance, as measured by the higher AUC, indicates overall higher sensitivity and specificity at the various thresholds used in the ROC curves.

In Fig. 2 we show the ROC curves obtained for all three computed visualization techniques. The  $Z_c$  and  $Z_r$  results for the complex data reaffirms the findings in Table 1, that  $Z_c$  has better performance by including the phase in the visualization. The  $Z_r$  result for the magnitude-only data has the worst performance, which indicates that by not using the phase in the actual ICA processing we lose sensitivity and specificity in detecting activated voxels. The AUCs of the three visualization techniques are: 1.  $Z_r$  Magnitude data: 0.65, 2.  $Z_r$  Complex data: 0.71, 3.  $Z_c$  Complex data: 0.73. Similar results were obtained with the other extracted ICs.

#### 5. DISCUSSION

A complex-valued group ICA algorithm was applied for the first time to an event-related paradigm. We show how complex-ICA can successfully extract task-related and intrinsic networks. Additionally,



**Fig. 2**. AUC of the ROC curves obtained by the three visualization techniques on the DMN IC extracted from the complex and magnitude only fMRI data.

we show how working on the complex-domain increases our ability to detect activated voxels in various ICs of interest, in particular the DMN component which is of great interest in clinical studies. We introduced the first visualization method that uses the phase in the estimated fMRI ICs to identify task or function-related voxels with greater sensitivity than typical magnitude-based methods. FPV is not specific to ICA, and it can be used with other complex-valued data and model-driven fMRI applications.

Future work will focus on studying any increase in discrimination power obtained by using complex-valued ICA to event-related fMRI data. We will also try to identify any additional information that may be encoded in the phase of the extracted voxels that could provide insight of the underlying physics.

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