UNIFIED ICA-SPM ANALYSIS OF FMRI EXPERIMENTS
Implementation of an ICA Graphical User Interface for the SPM Pipeline

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Abstract: We present a toolbox for exploratory analysis of functional magnetic resonance imaging (fMRI) data using independent component analysis (ICA) within the widely used SPM analysis pipeline. The toolbox enables dimensional reduction using principal component analysis, ICA using several different ICA algorithms, selection of the number of components using the Bayesian information criterion (BIC), visualization of ICA components, and extraction of components for subsequent analysis using the standard general linear model. We demonstrate how the toolbox is capable of identifying activity and nuisance effects in fMRI data from a visual experiment.

1 INTRODUCTION

Statistical parametric mapping (SPM) is the dominant tool for analysis of functional brain data acquired from medical imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (Frackowiak et al., 2003), and is aimed at identification of functionally specialized brain regions. SPM is a voxel based hypothesis driven method that examines regionally specific responses on the basis of standard inferential statistics.

The typical functional imaging experiment involves a group of subjects undergoing a common set of stimuli the stimuli time course is referred to as the 'paradigm'. Among *hypothesis-driven methods* the far most common model employed is the general linear model (GLM), where the response in each voxel is modeled as a linear combination of a number of explanatory variables, typically derived from the paradigm, and a noise term. Since each voxel is treated individually this approach is commonly referred to as a mass-univariate approach. In fMRI changes in the blood oxygen level dependent (BOLD) signal can be modeled by incorporation of information regarding the experimental paradigm, physiological- (e.g., cardiac and respiratory effects) and non-physiological artifacts (e.g. head movement and hardware instabilities) into the design matrix (Frackowiak et al., 2003; Lund et al., 2006).
Data-driven methods are less committed, explorative, and aim to discover the underlying structure of the data rather than impose given *a priori* knowledge on the model. Principal component analysis (PCA) and independent component analysis (ICA) are *multivariate* methods that take interactions between voxels into account, and hereby characterize brain responses as spatial-temporal patterns (McKeown et al., 2003a). ICA allows for discovery of *components* that are statistically independent, where each component is characterized by a spatial map and a time course. The technique has proven to be useful in extraction of independent components (ICs) related to the experimental design, physiological and non-physiological noise as well as being capable of identification of brain activations that have been difficult to specify beforehand, for a review, see e.g., (McKeown et al., 2003a).

This paper concerns a software tool for the combination of hypothesis- and a data-driven strategies.

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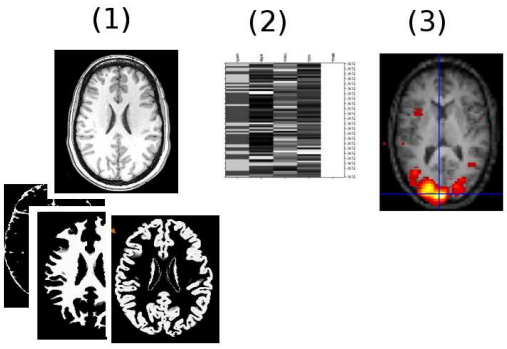

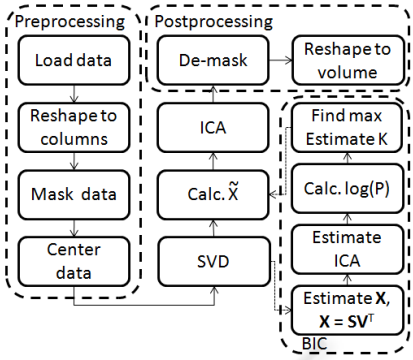

Figure 1: **Left;** The SPM data analysis pipeline. First step (1) is preprocessing, second step (2) is model design and parameter estimation and third step (3) is the statistical inference. The `ica4spm` toolbox is aimed as a intermediate step between the first and second step. **Right;** Flow chart for the `ica4spm` toolbox. Signal processing includes dimensionality reduction via PCA, ICA decomposition and BIC model order estimation. The final volumes contain images of the different components activation magnitude.

Based on ICA decomposition of the image set, both 'neural response' or 'noise' components are determined and hereafter incorporated as explanatory variables in the model specification in a conventional SPM analysis. This unified methodology is not novel and has earlier been proposed by e.g., (Hu et al., 2005). In their approach, univariate SPM is combined with multivariate ICA, where inference of statistical significance of ICs obtained from an ICA analysis is conducted within the mass-univariate SPM framework.

While there are excellent tools available for fMRI analysis that parallels the present toolbox, such as the Group ICA of fMRI Toolbox (GIFT) by Calhoun et al. (http://icatb.sourceforge.net), the toolbox presented here is the first to fully integrate ICA (and PCA) linear multivariate methods into SPM.

We thus present a MATLAB R2007b (The MathWorks, Natick, Massachusetts, USA) implementation of a unified methodology comprising of the following steps: *I*) Dimension reduction with PCA. *II*) ICA decomposition, with model order selection by the Bayesian information criterion (BIC) (Hansen et al., 2001a). *III*) Visualization of spatial map, time course and frequency content of ICs. *IV*) Export of relevant ICs for easy inclusion in specification of the GLM in a conventional SPM analysis. The toolbox and a user manual can be downloaded from `http://isp.imm.dtu.dk/toolbox/ica/`.

Our design goals for the `ica4spm` toolbox were to develop a toolbox that is easy and intuitive for the neuroscience researcher to use and compatible with the SPM5 software package (Wellcome Department of Imaging Neuroscience, University College London). The toolbox is intended as an intermediate step in the conventional SPM pipeline outlined in Fig. 1. Our toolbox facilitates identification and extraction of ICs related to noise or the paradigm. Relevant ICs can conveniently be exported and included in the design matrix specification in SPM. Hereby our toolbox is not a 'direct competitor' to the GIFT toolbox, which has many additional functions and statistical tests, but rather an intuitive tool for researchers familiar with the SPM software package and the statistical inference framework in SPM. The presentation is organized as follow. First, we briefly review the theory behind multivariate methods such as PCA, ICA and model selection based on BIC. Secondly, we give some general considerations about the combined approach. Finally, we present our implementation and an example of an analysis of an fMRI data set.

2 THEORY

Let the response variable in a given voxel be defined by the random variable Y_i, where $i \in [1:N]$ are the observations. The GLM General Linear Model expresses the response variable as a linear combination of L explanatory variables, where $L < N$ plus an error term (Frackowiak et al., 2003)

$$Y_i = x_{i1}\beta_1 + x_{i2}\beta_2 + \ldots + x_{iL}\beta_L + \varepsilon_i, \qquad (1)$$

where β_l are unknown parameters. It is assumed, that the errors ε_i are independent and identically distributed (i.i.d.) normal random variables with zero mean and variance σ^2, that is $\varepsilon_i \sim \mathcal{N}(0,\sigma^2)$. In matrix notation the GLM is written as $Y = \mathbf{X}\beta + \varepsilon$, where $\mathbf{X} \in \mathbb{R}^{N\times L}$ is the design matrix and $\beta \in \mathbb{R}^{L\times 1}$ is the parameter vector. The design matrix contains the explanatory variables. These variables could be directly related to the paradigm or related to confoun-

ding effects. Model parameters are determined by least square estimation.

2.1 Principal Components Analysis

Principal Components Analysis (PCA) is a multivariate statistical method for analysis or dimension reduction of multidimensional data sets. It is based on an orthogonal linear transformation of the data into a new coordinate system, where the data is projected in the directions with the most variance defined by the eigenvectors corresponding to the largest eigenvalues of the covariance matrix, see e.g., (Hansen et al., 1999). A basic tool for PCA is singular value decomposition (SVD) of the data matrix, see e.g., (Smith, 2002). An fMRI data set describes a temporal development of the acquisition volume, thus forms a 4D data structure of dimensions $\mathbf{X} \in \mathbb{R}^{L\times M\times N\times T}$, where L, M, and N are the physical dimensions of a single recorded volume at a given time, while T is the time dimension. Before performing PCA and ICA, this data set is reshaped into two dimensions $\mathbf{X} \in \mathbb{R}^{P\times T}$, where $P = L \times M \times N$ denotes the number of voxels. The SVD of the matrix $\mathbf{X} \in \mathbb{R}^{P\times T}$ is given as $\mathbf{X} = \mathbf{USV}^T$, where $\mathbf{U} \in \mathbb{R}^{P\times T}$ and $\mathbf{V} \in \mathbb{R}^{T\times T}$ are orthogonal matrices with the sorted eigenvectors of $\frac{1}{T}\mathbf{XX}^T$ and $\frac{1}{P}\mathbf{X}^T\mathbf{X}$ respectively (McKeown et al., 1998). $\mathbf{S} \in \mathbb{R}^{T\times T}$ is a diagonal matrix with the sorted singular values, which are the standard deviation values in the different directions. The dimensions of $\mathbf{U}$, $\mathbf{S}$ and $\mathbf{V}$ described here, are those obtained by performing the so-called thin PCA decomposition where only the first T instead of P columns of $\mathbf{U}$ and T instead of P rows of $\mathbf{S}$ are calculated. When the variance of the noise is small, the dimensionality reduction from $\mathbf{X} \in \mathbb{R}^{P\times T}$ to $\mathbf{X} \in \mathbb{R}^{K\times T}$ is performed by linear transformation to the sub-space spanned by the K eigenvectors of $\mathbf{U}$ corresponding to the K largest eigenvalues of $\mathbf{S}$, i.e., $\tilde{\mathbf{X}} = \tilde{\mathbf{U}}^T\mathbf{X}$. After the PCA transformation, dimensionality reduction is carried out by retaining the lowest order principal components, hence, the dimensions of the data set that contribute most to its variance.

2.2 Independent Component Analysis

The nature of the BOLD fMRI signal suggests that blind source separation (BSS) techniques are relevant for reconstructing individual signal components (McKeown et al., 1998). In BSS, source signals are recovered from mixtures without knowing the mixing coefficients. The source signals can be related to, e.g., stimulus response, the heartbeat, respiratory related confounds, and motion artifacts. ICA is a method for solving the BSS problem, where multivariate signals are separated into components or sources that are statistically independent (McKeown et al., 1998; Hyvärinen and Oja, 2000). In general, the ICA decomposition can be written as:

$$\mathbf{X} = \mathbf{AS} \qquad \mathbf{X}_{n,t} = \sum_{k=1}^{K} A_{n,k}S_{k,t}, \tag{2}$$

where $\mathbf{X}_{n,t}$ is the signal at the n'th voxel and K is the number of independent components. In matrix notation $\mathbf{A} \in \mathbb{R}^{K\times K}$ is the mixing matrix and $\mathbf{S} \in \mathbb{R}^{K\times N}$ is the source matrix. In (2), the sources as well as the mixing coefficients are unknown, hence, the mixing matrix can be determined up to scaling and permutation (Hyvärinen and Oja, 2000).

ICA can be used to separate either spatially or temporally independent sources (McKeown et al., 2003b; Hu et al., 2005). In temporal ICA (tICA), a single independent component is a set of voxels in $\mathbf{A}$ that are activated by an independent time function in $\mathbf{S}$. In spatial ICA (sICA) the time courses in $\mathbf{S}$ of each voxel are derived in such a way, that the columns in $\mathbf{A}$ are statistically independent.

Numerous approaches exist for solving the ICA problem. The toolbox `ica4spm` offers the following algorithms:

- Maximum Likelihood (also known as Infomax) (Bell and Sejnowski, 1995; Hansen et al., 2001b)
- Molgedey-Schuster (Molgedey and Schuster, 1994; Hansen et al., 2001b; Kolenda et al., 2001)
- Joint approximate diagonalization of eigenmatrices (JADE) (Cardoso, 1999)
- Fast Fixed-Point Algorithm for Independent Component Analysis (FastICA) (Hyvärinen and Oja, 1997)

These algorithms have all been evaluated in fMRI contexts, see e.g., (Correa et al., 2007).

2.3 Probabilistic Model Selection

The conditional probability $P(m|\mathbf{X})$ of a specific model hypothesis $m = 0,..,T$ given the observed data $\mathbf{X}$ can be calculated using Bayes' theorem,

$$P(m|\mathbf{X}) = \frac{P(\mathbf{X}|m)P(m)}{\sum_m P(\mathbf{X}|m)P(m)}, \tag{3}$$

where $P(m)$ is the prior probability of the specific model given by $P(m) = 1/(T+1)$ if there is no prior knowledge. $P(\mathbf{X}|m)$ is the conditional probability of the measured data using the hypothesis of the specific model. In (Kolenda et al., 2001; Højen-Sørensen et al., 2002; Hu et al., 2005) BIC Bayes Information

Criterion was proposed for model order selection in order to select the number of independent component in fMRI data sets. Let θ be the parameters that describe a specific ICA model. Then the optimal model is found by maximizing the BIC approximation to (3), $BIC = \log(P(\mathbf{X} \mid \theta_{MAP}, m) - \frac{1}{2} W \log(N)$, where m is a specific model, θ_{MAP} are the maximum likelihood parameters, W is the number of parameters and N is the number of data points. In `ica4spm` we offer model order estimation for the Maximum Likelihood and the Molgedey-Schuster algorithms.

3 MATERIALS AND METHODS

The fMRI data set used in the demonstration of the `ica4spm` toolbox was collected from a single subject with a 3T scanner (Magnetom Trio, Siemens, Erlangen Germany) using a gradient echo EPI sequence. The following settings were used: Echo time TE = 30 ms, repetition time TR = 2.37 s, in-plane resolution 3×3 mm, flip angle $\alpha = 90^{\circ}$, slice thickness 3 mm, and interleaved acquisition without gaps. The subject was visually stimulated during the scan using an 8 Hz reversing checkerboard with an expanding ring, where each period lasted 30 s. The activation is therefore expected to be present in the occipital cortex at a frequency of 1/30 Hz with phase depending on the position in the visual cortices. Rigid-body realignment of the data was done using SPM2 (Wellcome Department of Imaging Neuroscience, University College London) to minimize movement artifacts and the data was spatially smoothed with a Gaussian kernel in order to suppress high frequency noise. An overview of the signal processing is shown in Fig. 1. We performed two ICAs on the demonstration data set, one on the entire dataset (381 volumes) selected ICs from this analysis is displayed in Fig. 3. In the second analysis we aim to show how ICA can be used to identify signal components to be used in a subsequent analysis. In order to be able to test for activation in the subsequent analysis unbiased we divide the data set into a training set and a test set. Relevant ICs were identified with the toolbox in the training set and included in a subsequent SPM analysis of the test data set (using SPM5). The statistical inference was done using an F-test with voxels activations considered significant for p-values < 0.001. Results from this analysis is displayed in Fig. 3. In both cases we used a temporal MS ICA with automatically selected τ and a number of components based on BIC. The `ica4spm` toolbox is designed and tested in MATLAB R2007b as a GUI add-on to the SPM software package. The front end is set up by the script `ica4spm`. The objects in the user interface have different callbacks enabling different functions depending on the task required. If possible, SPM5 functionalities have been used in the toolbox interface to ease the use for potential users already familiar with SPM5. Three global variables are used. These are: a structure containing all handles to the GUI-figure and its controls, a structure containing all input variables and calculated parameters by the PCA, ICA and BIC, and finally a structure with the handles and variables containing parameters for the SPM-visualization.

4 RESULTS

The user interface consist of two windows, the main window `ica4spm` and the component visualization window `ICA visualization` displayed in Fig. 2. The main window gives the user the ability to setup an appropriate ICA. The initial step of the ICA will be to reduce the dimensionality with PCA. The toolbox gives the user the option to automatically select the dimensionality based on the optimal numbers of principal components calculated by BIC, or use the BIC as a guidance when specifying the dimension for the data set entering ICA.

In order to support large data sets and reduce the computational workload it is possible to mask the data to only include relevant parts of the images. Masking can be performed based on the mean value or variance of the voxels in the images across time. The data is thresholded so either a fraction of voxels with highest mean values or a fraction with greatest variance is included in the analysis. The toolbox enables the user to manually review the masks before the actual processing. Masks obtained from other sources such as SPM5 can also be loaded and used.

The toolbox offers the possibility of selecting either temporal or spatial ICA, currently four ICA algorithms are implemented in the toolbox: Maximum Likelihood (ML), Molgedey Schuster (MS), JADE, and FastICA. For the MS algorithm the user has the ability to manually define a desirable value of τ. As default the MS algorithm estimates an optimal value. When the user has selected the desired analysis, ICA will be performed automatically by pressing *Start Analysis*. After processing the results will be displayed in the component visualization window.

The visualization window enables the user to investigate the individual ICs superimposed on a co-registered anatomical volume. The superimposed components are shown in the transverse, coronal, and sagittal planes. The user has the ability to threshold the visualization of a component, so only a percentage

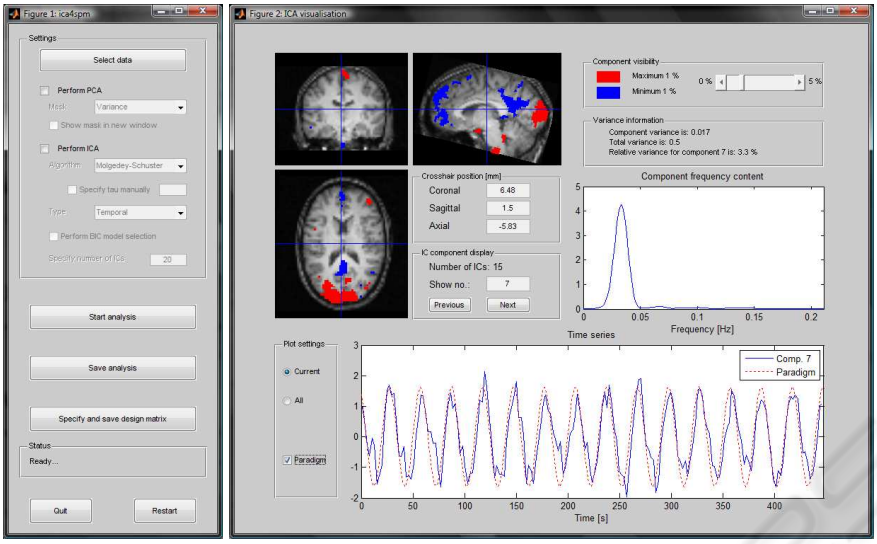

Figure 2: **Left;** The main user interface for the `ica4spm` toolbox. **Right;** Example of the *ICA visualization* user interface of the `ica4spm` toolbox showing a temporal MS ICA component.

of the greatest/least intense voxels are superimposed. In addition, it is possible to examine the temporal pattern and frequency content of each IC and compare that to a paradigm. If the user finds it relevant to include a given IC in the GLM, the toolbox facilitates specification and export of the IC for use in a subsequent SPM analysis. Fig. 3 shows three selected components from a temporal MS ICA performed on the demonstration data set. The temporal profile and frequency contents of the two first components clearly indicate that these components are related to the visual paradigm with a 30 second period and the spatial map show activity restricted to the visual areas of the brain. The analysis has split visual activity into two components allowing it to capture activity regardless of the phase. The last component shows how the ICA has also captured nuisance signal variation related to the cardiac cycle. Notice, that the temporal profile of this component appears aliased due the low sampling rate. Figure 3 shows a test for significant effects in the test data set based on paradigm related ICs identified in the training data set.

5 DISCUSSION & CONCLUSION

Our `ica4spm` toolbox facilitates easy unsupervised exploratory analysis and visualization of relevant signal components from a data set and the use of extracted ICs in a SPM analysis. From the `ica4spm` main GUI, it is easy to load fMRI data and select which settings to use for the ICA. If selected, PCA is performed for dimensionality reduction of the data set and BIC can be used to automatically for determining the number of relevant signal components. This makes it easy to ensure that all relevant signal components are discovered. The components of interest can be saved to a design matrix and loaded in SPM5. Generally, the use of structures in the program have made it possible to access all data and variables at all times.

ICA was found useful when applied to a real fMRI data set, as it was able to identify both paradigm and nuisance related effects. The activation related to the paradigm was split into two components with different phases in order to model any phase of the visual stimuli. In subsequent SPM analysis with the time series as regressors in the design matrix, we found strong visual cortex as expected, see Fig. 3. Our findings are equivalent to those found in (Lund et al., 2006) for the same data set. Furthermore, it was possible to recognize ICs containing the pulse and respiration, making it possible to include these as confounding effects in the design matrix. In conclusion, we found that the GUI may prove useful in the analysis of fMRI data.

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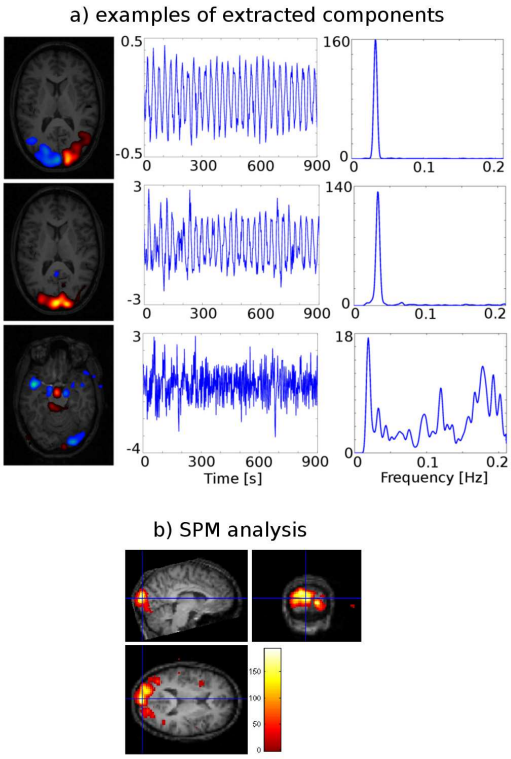

Figure 3: **Top;** Three selected components from ICA performed on the demonstration dataset. To the left the spatial map from each component is showed as an overlay on the anatomical scan. For the first two components a slice near the calcarine sulcus is shown whereas a slice near the circle of Willis is shown for the last component. The middle column of figures shows the temporal profile for each of the components and the right column shows the power spectrum (Welch method). The first two components are clearly related to the visual paradigm with prominent activity in the occipital cortex whereas the last component is related to cardiac nuisance effects. **Buttom;** F-test conducted in SPM5 on test data set for significant effects of paradigm related ICs identified in the training data set. Thresholded at $p < 0.001$ uncorrected.

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