Improved Application of Independent Component Analysis to Functional Magnetic Resonance Imaging Study via Linear Projection Techniques

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Abstract: Spatial Independent component analysis (sICA) has been widely used to analyze functional magnetic resonance imaging (fMRI) data. The well accepted implicit assumption is the spatially statistical independency of intrinsic sources identified by sICA, making the sICA applications difficult for data in which there exist interdependent sources and confounding factors. This interdependency can arise, for instance, from fMRI studies investigating two tasks in a single session. In this study, we introduced a linear projection approach and considered its utilization as a tool to separate task-related components from two-task fMRI data. The robustness and feasibility of the method are substantiated through simulation on computer data and fMRI real rest data. Both simulated and real two-task fMRI experiments demonstrated that sICA in combination with the projection method succeeded in separating spatially dependent components and had better detection power than pure model-based method when estimating activation induced by each task as well as both tasks. *Hum Brain Mapp* 30:417–431, 2009. © 2007 Wiley-Liss, Inc.

Key words: independent component analysis; sICA; fMRI; projection; spatially independent, two-task

INTRODUCTION

As a neuroscientific tool, functional magnetic resonance imaging (fMRI) technique is used to investigate cognitive

functions of human brain and to better understand its underlying neural mechanism. By far, both model-based and data-driven approaches have been applied to analyze fMRI data. One of the most popular model-based methods is the univariate general linear model (GLM) on a voxel-by-voxel basis to reveal brain activation pattern [Bandettini et al., 1993; Friston et al., 1995]. Among various model-free methods, independent component analysis (ICA) [McKeown et al., 1998], aiming at extracting useful cognitive task-related spatial components from the whole spatiotemporal data without any prior model hypothesis, is gaining more attention. In fact, ICA can provide complementary understanding of the data and lead to view brain functions as an interconnected network [Schmithorst, 2005; Schmithorst and Brown, 2004].

Since spatial ICA (sICA) was initially introduced into fMRI data analysis by McKeown et al. [McKeown

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et al., 1998], a number of fMRI applications of sICA have been reported to map brain activations of task-related components [Biswal and Ulmer, 1999a,b; Calhoun et al., 2001a,b; Chad et al., 2000; McKeown et al., 1998] or investigate functional connectivity of brain [Beckmann et al., 2005; Rajapakse et al., 2006; van de Van et al., 2004]. It should be noted a strict assumption is implicated in all the sICA applications. That is the intrinsic sources of fMRI data must be spatially statistically independent. McKeown et al. argued that the sparse distributed nature of the spatial pattern of cognitive activation paradigms and some pro-type confounds would work well with sICA [McKeown et al., 1998]. However, the spatial independency assumption might be violated in some cases. The most two common cases are the interference of some artifacts not spatially independent with task-related components and the spatial interaction of different task-related components in multitask fMRI data. Thus, the sICA results from cases like these two should be interpreted with caution.

It is well known that fMRI signals are often contaminated by a number of error sources and artifacts. The sICA algorithm based on noise free model needs to make the assumption that these error sources and artifacts could be identified as one or more of the independent components [McKeown and Sejnowski, 1998]. Among these error sources or artifacts are the obvious low-frequency fluctuations in the measured fMRI data including the frequency aliasing of some physiological signals, such as cardiac and respiratory pulsations, due to low temporal sampling resolution. These low-frequency fluctuations could have intricate spatial structure [Beckmann et al., 2005], potentially overlapping spatially and temporally with the task-related signals of interests, which are also contaminated by subtle head movements and machine or environmental noise [McKeown and Sejnowski, 1998]. Thus, strictly speaking, the spatial independency of sources could not be guaranteed. The reduction of high-frequency fluctuations [McKeown et al., 1998] or low-frequency fluctuations [Bartels and Zeki, 2004, 2005] or both [Esposito, 2005] contributes to the removal of their interaction with the tasks under investigation.

The “independency” assumption can also be violated when there are multiple tasks in one single fMRI session with some common brain regions activated simultaneously by more than one task. Thus far, successful sICA applications have been mainly analyzing fMRI data containing single-task [Biswal and Ulmer, 1999; Chad et al., 2000]. Multitask cognitive experiment in one session design, however, is gaining its popularity due to its efficient use of resources and the examination of their relationships. Calhoun discussed the analysis of fMRI data containing a pair of task-related waveforms in detail and found that sICA failed for paradigms that were spatially or temporally dependent [Calhoun et al., 2001a]. One approach to apply sICA to a two-task study was via splitting the whole fMRI time series of each session into two datasets in terms of two different tasks [Beckmann et al., 2006]. The limita-

tion of this method is the destruction of the temporal property of the whole fMRI time series. In one of our own previous works, we introduced how to separate two-task fMRI data by analyzing some interesting local regions using both univariate statistical approach and sICA [Long and Yao, 2003]. This current study is our continued effort especially with the use of sICA to examine two-task fMRI data.

Our current focus is to investigate the feasibility of separating the brain network related to each of two tasks in a single fMRI session using sICA in conjunction with our proposed projection approach detailed in this study. In this regard, the introduced linear projection approach is intended to separate spatial overlaps as a result of common activation by two or more tasks. The basic idea of projection is to project raw fMRI data into the subspace perpendicular to the space spanned by the confounding and the factors associated with other tasks, which are not necessarily separable as part of sICA procedure itself. The rest of this article is organized as followings. After this introduction section, the theories of projection and its applications to two-task fMRI data separation are provided in the “Theory” section. Simulated and real fMRI experiments are presented subsequently for their utilization to demonstrate the robustness and feasibility of the method. Some potential issues in the application of sICA in combination with projection method were addressed in the discussion section together with the limitations of the proposed method.

THEORY

Summary of Linear Projection

In this section, we will lay out the linear projection as a preprocessing step prior to sICA for fMRI data analysis. sICA is based on a noise free linear model.

$$\mathbf{Y} = \mathbf{A}\mathbf{C} \quad (1)$$

Here $\mathbf{Y} = (y_{ij})_{T \times P}$ is a matrix consisting of fMRI raw data. T is the number of time points in the experiments and P is the number of voxels over the brain volumes. $\mathbf{C} = [C_1, C_2, \dots, C_K]^T$ is the matrix consisting of spatially independent components. Each row of the matrix, C_i , is a spatially independent source. K is the number of total independent components. $\mathbf{A} = [\alpha_1, \alpha_2, \dots, \alpha_K]$ is the mixing matrix. Each column vector of $\mathbf{A}$ can be treated as the time course driving the corresponding spatially independent component.

Suppose that there are some known uninteresting confounds whose spatial distribution may interact with that of interesting sources (i.e., these confounds are not statistically independent to the components of the underlying cognitive factor that we are after). Now the sICA model is no longer suitable due to the independency violation. Under the linear model assumption, however, the data can

still be expressed as (2).

$$\mathbf{Y} = \mathbf{BS} \quad (2)$$

Each column of $\mathbf{B}$ is the time course of each factor and each row of $\mathbf{S}$ denotes the weights of the corresponding factor over the brain volume. The important difference between (1) and (2) is that the rows of $\mathbf{S}$ in (2) can be spatially dependent. To decrease the effects of those confounds, the raw data $\mathbf{Y}$ can be projected into a space perpendicular to the space spanned by the time courses of these confounds. To see this clearly, we first column-wise/row-wise divide the matrices $\mathbf{B}/\mathbf{S}$ into two parts of interest and no interest. Note that these confounding factors are not necessarily spatially independent or even uncorrelated.

$$\mathbf{B} = [\mathbf{X} \ \mathbf{G}] \quad \text{and} \quad \mathbf{S} = [\mathbf{S}_X; \mathbf{S}_G] \quad (3)$$

For the validity of the following derivation, we only need to assume independency for components in $\mathbf{S}_X$, but not for those in $\mathbf{S}_G$ and those between $\mathbf{S}_X$ and $\mathbf{S}_G$.

Then, Eq. (2) becomes

$$\mathbf{Y} = \mathbf{X}\mathbf{S}_X + \mathbf{G}\mathbf{S}_G \quad (4)$$

Assuming $\mathbf{G}$ is of full rank, the projector of the subspace $\text{span}(\mathbf{G})$ is $\mathbf{P} = \mathbf{G}(\mathbf{G}^T\mathbf{G})^{-1}\mathbf{G}^T$, and $\text{span}(\mathbf{G})$ represents the linear subspace spanned by the column vectors in $\mathbf{G}$. Similarly, the orthogonal projector onto $\text{span}(\mathbf{G})^\perp$ is $\mathbf{P}_\perp = \mathbf{I} - \mathbf{P}$. Here $\text{span}(\mathbf{G})^\perp$ represents the subspace perpendicular to $\text{span}(\mathbf{G})$. Left multiply both sides of Eq. (4) by matrix $\mathbf{P}_\perp$.

$$\begin{aligned} \mathbf{Y}_G &= \mathbf{X}_G\mathbf{S}_X \\ \mathbf{Y}_G &= \mathbf{Y} - \mathbf{G}(\mathbf{G}^T\mathbf{G})^{-1}\mathbf{G}^T\mathbf{Y} \quad \mathbf{X}_G = \mathbf{X} - \mathbf{G}(\mathbf{G}^T\mathbf{G})^{-1}\mathbf{G}^T\mathbf{X} \end{aligned} \quad (5)$$

The subscript G in $\mathbf{Y}_G$ and $\mathbf{X}_G$ indicates that they are in the space of $\text{span}(\mathbf{G})^\perp$. Comparing Eqs. (4) with (5), it is clear that the original data matrix $\mathbf{Y}$ and the original mixing matrix $\mathbf{X}$ become $\mathbf{Y}_G$ and $\mathbf{X}_G$, whereas the independent component matrix $\mathbf{S}_X$ remains the same. The conventional sICA can then be performed over the data $\mathbf{Y}_G$, for the easy extraction of the spatially independent components $\mathbf{S}_X$. Note that this preprocessing step is tantamount to first linearly covarying out nuisance variables prior to the sICA analysis. Our primary interest in this current study is to combine this projection approach with sICA to analyze two-task fMRI data as described below.

Separation of Overlapping Components in Two-Task fMRI Data

In the case of multiple tasks in one fMRI session, the independency assumption, as mentioned earlier, may become invalid because the spatial networks of task-related cognitive components could potentially interact with each other. The interaction between components can

Figure 1.

Illustration of spatial overlap including the brain regions activated by only $\mathbf{X}_1$ (area with vertical lines, A_1), only $\mathbf{X}_2$ (area with horizontal lines, A_2) and both $\mathbf{X}_1$ and $\mathbf{X}_2$ (area with oblique lines, A_3).

be in the form of the activation overlapping although the components without overlapping are also possibly dependent. That is the nonoverlapping does not mean that the two components are necessarily statistically independent. The current study will concentrate on discussing the case of spatial overlapping between two components, which often occurs in cognitive fMRI experiment. We will use the proposed method in an attempt to uncover regions that are involved in each of the multiple tasks and those involved in all. In this study, only two-task case is discussed to illustrate the basic underlying principles for simplicity.

Suppose, in a two-task experiment, task one is $\mathbf{X}_1$ and the other is $\mathbf{X}_2$. Usually, the two tasks are presented orthogonally or uncorrelated in time when designing the experiment. Each task can activate specific brain regions, respectively. Meanwhile both of them may activate some common brain regions. Illustrated in Figure 1, brain regions A_1 and A_3 are assumed to respond to task $\mathbf{X}_1$ while A_2 and A_3 to task $\mathbf{X}_2$. Here, we explicitly introduced the partial spatial overlap between two task-related components. We note that spatial overlap does not necessarily imply spatially dependent as the cases illustrated in [Lund et al., 2006]. This point will be discussed further in the discussion section.

For easy understanding purpose, the two-task fMRI data were assumed to meet a linear mixture model in Eq. (2) (for the robustness of the proposed method to nonlinearity see the simulation section below). Then data $\mathbf{Y}$ and the matrix $\mathbf{B}$ and $\mathbf{S}$ can be written as

$$\begin{aligned} \mathbf{Y} &= \mathbf{BS} = \mathbf{X}_1\mathbf{S}_1 + \mathbf{X}_2\mathbf{S}_2 + \mathbf{X}_N\mathbf{S}_N \\ \mathbf{B} &= [\mathbf{X}_1 \ \mathbf{X}_2 \ \mathbf{X}_N] \quad \mathbf{S} = [\mathbf{S}_1; \mathbf{S}_2; \mathbf{S}_N] \end{aligned} \quad (6)$$

Here $\mathbf{S}_N$ represents other task-unrelated components embedded in the fMRI data $\mathbf{Y}$. If sICA is applied to fMRI data $\mathbf{Y}$ directly, it is impossible to separate two sources $\mathbf{S}_1$ and $\mathbf{S}_2$ when they are not spatially independent. In this model, $\mathbf{S}_1$ and $\mathbf{S}_2$ can interact in any manner, spatially overlapping or not. In the case of $\mathbf{S}_1$ and $\mathbf{S}_2$ overlapping with each other,

the superimposition assumption of the two tasks over the commonly activated brain region is implicated in the linear mixture model as Eq. (6). We will, however, demonstrate that the projection procedure is actually very robust to the violation of this assumption and even to the nonlinearity cases in the simulation section. Furthermore, this assumption is not required for the cases that the two components interact in other nonoverlapping ways.

With the ideas of projection, $\mathbf{X}_2$ can be treated as uninteresting factors and constitute the matrix $\mathbf{G}$ in order to estimate the $\mathbf{X}_1$ -related component. Thus, the matrix $\mathbf{B}$ can be partitioned into $\mathbf{X}$ and $\mathbf{G}$.

$$\mathbf{X} = [\mathbf{X}_1 \ \mathbf{X}_N] \quad \mathbf{G} = [\mathbf{X}_2] \quad (7)$$

Suppose there are total P column vectors distributed in T -dimension temporal space, each vector corresponding to each voxel. When projecting those P vectors into $\text{span}(\mathbf{G})^\perp$ in the temporal space to remove the effect of $\mathbf{X}_2$, $\mathbf{Y}$ is turned into $\mathbf{Y}_G$ with P vectors redistributed in the T -dimension temporal space.

$$\mathbf{Y}_G = \mathbf{X}_{1G}\mathbf{S}_1 + \mathbf{X}_{NG}\mathbf{S}_N \quad (8)$$

Because of the orthogonality between $\mathbf{X}_1$ and $\mathbf{X}_2$, $\mathbf{X}_{1G}$ should be closely related to $\mathbf{X}_1$. Then the $\mathbf{X}_1$ -related component $\mathbf{S}_1$ can be separated from $\mathbf{Y}_G$ by sICA. The same method is suitable for estimating $\mathbf{X}_2$ -related component. Note that the activated region in $\mathbf{X}_1$ -related component $\mathbf{S}_1$ could also contain brain areas where both tasks $\mathbf{X}_1$ and $\mathbf{X}_2$ commonly act on. Thus, the procedure described above is not able to reveal the brain regions responding to $\mathbf{X}_1$ only, $\mathbf{X}_2$ only or both tasks.

Here we present a method to further estimate the regions responding to $\mathbf{X}_1$ only, $\mathbf{X}_2$ only or both tasks from the fMRI data of single-subject when $\mathbf{S}_1$ and $\mathbf{S}_2$ interact in an overlapping manner. Suppose $\mathbf{X}_1$ significantly activate P_1 voxels, some of which also respond to $\mathbf{X}_2$, in $\mathbf{X}_1$ -related component $\mathbf{S}_1$. After estimating $\mathbf{S}_1$, those P_1 voxels activated by $\mathbf{X}_1$ are removed from data $\mathbf{Y}$. The selection of threshold for determining activated voxels to be removed will be illustrated in the simulation section. Then the data $\mathbf{Y}$ becomes $\mathbf{Y}_1$ with only $P-P_1$ vectors remained in the T -dimension temporal space. Applying sICA to the data $\mathbf{Y}_1$, the regions activated by task $\mathbf{X}_2$ only can be estimated from $\mathbf{X}_2$ -related component separated from $\mathbf{Y}_1$. The same procedure is suitable to estimate regions responding to task $\mathbf{X}_1$ only. When voxels activated by task $\mathbf{X}_1$ only and those by task $\mathbf{X}_2$ only are all removed from data $\mathbf{Y}$, the new data $\mathbf{Y}_2$ will include voxels responding to both tasks as well as none of them. Those voxels activated by both tasks can be estimated from the component related to $\mathbf{X}_1+\mathbf{X}_2$ extracted from data $\mathbf{Y}_2$ through sICA.

In analyzing actual fMRI data, the prior knowledge of $\mathbf{X}_1$ and $\mathbf{X}_2$ necessary to the projection steps could come from the convolution of the ideal stimulus paradigm with hemodynamic response function (HRF) consisting of two γ

functions [Friston et al., 1998]. Thus, the sICA with projection could not be characterized as a pure data-driven approach.

It is worth noting that the projection method can also be used as the preprocessing step to reduce the effects of the low frequency fluctuations. In this regard, discrete cosine transform (DCT) functions was used to approximate the characteristics of the low frequency part [Frackowiak et al., 2004] and entered into the columns of $\mathbf{G}$ matrix before each sICA processing. The cut-off frequency of DCT is often determined by the cycle of task paradigm [Frackowiak et al., 2004]. Therefore, before each sICA process, data can be preprocessed to remove the low frequency effects by using the same projection method.

SIMULATIONS

In this section, simulated data were generated in order to illustrate the robustness and the feasibility of the proposed method. For simplicity, the spatial activation pattern associated with each task is assumed to be nonzero only over a sub-brain volume defined via a binary mask in all simulations. That is the weight of a specific task outside that binary mask is zero. Only the voxels within the mask are activated by the task and the corresponding weight can vary from voxel to voxel within the mask. We also assume that the weights of $\mathbf{X}_1$ and $\mathbf{X}_2$ activating common region are compatible. In the following experiments, the threshold of Z score was set to 2 when mapping spatial activation of independent components. That is, all the voxels with Z score higher than 2 were considered as activation. However, when making mask to remove the voxels responding to a specific task, the threshold of Z score was reduce to 1.5. The use of this threshold will be validated in the two-task fMRI simulation section. Like the regular sICA applications, data dimension was first reduced by principal component analysis to 20 components with 95% information maintained. The informax sICA algorithm [Bell and Sejnowski, 1995] embedded in FMRLAB software (<http://www.sccn.ucsd.edu/fmrlab/>) was utilized to process all the data.

Robustness of the Projection Method

When two task-related components spatially overlap in some common regions, the projection method is relied on the superimposition assumption that the two tasks $\mathbf{X}_1$ and $\mathbf{X}_2$ activate the common brain region in a linear addition manner. The prior information of $\mathbf{X}_1$ and $\mathbf{X}_2$ is an essential factor to determine the applicability of the projection method. However, in the case of noises, the true sources relevant to each task embedded in the data may vary across voxels and deviate from each of the ideal $\mathbf{X}_1$, $\mathbf{X}_2$ and their simple summation. High degree of variation and deviation will lead to the violation of the assumption and the failure of the projection method.

Figure 2.

Time courses (**A** and **B**) of sources and the corresponding activated spatial regions (**C**). **A** shows the time courses of two task X_1 and X_2 . **B** shows the time courses of four task-unrelated components.

Furthermore, X_1 and X_2 can act on the common region in a very general form that could be nonlinear contributing to the departure from the superimposition assumption, or the general linear assumption. Apparently, noiseless and linear superimposition assumptions are unrealistic for most of the real fMRI data. The simulations described here are designed to demonstrate the robustness of our proposed method in terms of the effects of noises and the nonlinearity that X_1 and X_2 act on the common brain region.

The receiver operation characteristic (ROC) method [Constable et al., 1995] was utilized to investigate the detection power of sICA with projection in the case of superimposition assumption violation. The relationship between the false positive ratio and the true positive ratio can be drawn as ROC curves. The area under the curve is a useful statistic summary of the accuracy of the method. Larger area means the detection of the method is more accurate.

Robustness to noise magnitude

A. The robustness of the superimposition assumption to different noise levels. Under noise-free condition, theoretical consideration guarantees that when two tasks X_1 and X_2 uniquely act on distinct brain regions as well as commonly on the same brain region, the true time courses underlying this common brain region would be the linear addition of the time course underlying the region only responding to X_1 and that underlying the region only to

X_2 if the linear superimposition assumption was met. However, that same conclusion can not be assured with the presence of noises. The simulation here was conducted to investigate the possible deviation of superimposition assumption under different noise levels.

A two-dimensional 128×128 matrix with each pixel's intensity of 100 was duplicated 65 times, one for each time point, as a real fMRI time series data. Gaussian noises with zero mean and specific standard deviation (SD) were added to all pixels at every time point to simulate system noises. As shown in Figure 2C, seven rectangular regions of interests (ROIs) (the binary masks) over this matrix were constructed for the introduction of brain activations by tasks or some task-unrelated factors comprised by periodic temporal fluctuations. The two tasks were supposed to occur in ABABAB sequence. The entire temporal paradigm of all stimuli, starting with an "off" half cycle, consists of six and a half 10-frame cycles. Each cycle includes five-frame task block and five-frame rest block. The simulated fMRI response X_1 or X_2 (See Fig. 2A) was derived from convolution of the stimulus paradigm of each task with HRF.

Three fMRI sessions were simulated in each functional experiment. In the first session, only task X_1 was presented and evoked the region SA. In the second session, only task X_2 was presented and evoked the region SB. In the third session, both tasks were presented and only evoked the region SC separately. Four task-unrelated time courses G_1 to G_4 (See Fig. 2B) activating the corresponding four regions S1 to S4 (See Fig. 2C) were added to each dataset

Figure 3.

Results of robustness to various noise level. (A) shows the variation of mean correlation between $X_{1E}+X_{2E}$ and X_{3E} with SNR, (B) shows the variation of mean ROC areas with SNR. The error bar represents the SD.

in each session. The signal change of each task was presumed to randomly range from 0.5–2% that is consistent with the observed fMRI responses at 1.5T [Lange et al., 1999], relative to the mean intensity value of the individual pixel. The mean signal change for each task was equal to 1.25% for each dataset. sICA was directly applied to the three datasets from three sessions separately. Three time courses X_{1E} , X_{2E} , X_{3E} corresponding to X_1 -related, X_2 -related, and X_1+X_2 -related components were extracted from the three datasets, respectively. The correlation coefficient R between $X_{1E}+X_{2E}$ and X_{3E} can be calculated from each functional experiment.

Each functional experiment consisting of three sessions was repeated 50 times under various noise levels expressed as signal to noise ratios (SNR). The SNR varied from 0.2 to 1.4 with the decreasing of the SD of Gaussian noises across different functional experiments. The mean and SD of 50 correlation coefficients between $X_{1E}+X_{2E}$ and X_{3E} were yielded and plotted in Figure 3A.

It is evident that the mean correlation coefficient increased and its SD decreased dramatically with the increasing of SNR. When SNR is less than 0.4, the very low mean correlation between $X_{1E}+X_{2E}$ and X_{3E} with large variations suggested that sICA with the projection could failed as a result of high degree of departure from the superimposition assumption at high noise level. However, the mean correlation reached above 0.9 with SNR equal to 0.5 and was very close to 1 indicating $X_{1E}+X_{2E} \propto X_{3E}$ in the case of SNR larger than 1.

B. The variation of detection power with different noise levels. This simulation aimed at revealing the robustness of the proposed approach by investigating the variation of its detection power with various noise levels. The simulated data was generated through the same procedure as

the above one, except that each functional experiment consisted of only one session with both tasks evoking distinct regions as well as common region. The simulated fMRI response X_1 (See Fig. 2A) was added to the ROIs labeled as SA and SC while the fMRI response X_2 (See Fig. 2A) was delivered to SB and SC.

For a given SNR, each functional experiment was repeated 50 times. The sICA with the projection method was applied to each of the 50 simulated dataset to estimate the regions activated by task X_1 and derive the corresponding ROC area. The mean and SD of 50 ROC areas at each SNR level was shown in Figure 3B.

As the SNR increased, the mean of ROC areas increased from 0.59 to 0.99 and the SD decreased from 0.023 to 0.009. This result indicated that the detection power of sICA with projection was raised rapidly with the increasing of SNR. However, in the case of large noises with SNR < 0.4, the performance of the method could be degenerated greatly by the noises because their mean ROC areas are less than 0.75. The results provide additional evidence to support that large noises (SNR < 0.4) would contribute to the high deviation from the superimposition assumption and the failure of the proposed approach.

Robustness for nonlinearity

This simulation concentrated on examining the nonlinear impact of the two tasks on the sICA with projection method. The generation of simulated data was almost the same as the prior one with one session in each functional experiment, except that the additional nonlinear factor was included and the SNR was remained constant in this simulation. The time courses and spatial activation of X_1 , X_2 and G1 to G4 were kept the same. The nonlinear factor

Figure 4. Results of robustness for nonlinearity. (A) the variation of mean performance ratio with the nonlinear coefficient k . (B) the variation of mean ROC area with k . The error bar represents the SD.

kX_1^2 and kX_2^2 was supposed to evoke the ROI labeled as SC that was also activated by the linear combination of X_1 and X_2 as in the simulation described above. The signal change randomly ranged from 0.5–2%.

The nonlinear coefficient k was varied from 0 to 1.5 with the SNR was kept constant at 0.8 across different functional experiments. For a given value of k , the functional experiment was repeated 50 times. sICA with the projection method was applied to each dataset to estimate the regions responding to task X_1 . Meanwhile, the ROC area and the number of activated voxels for each dataset were yielded. To measure the detection variation in the case of nonlinearity relative to linearity, a performance ratio for nonzero k was defined as N_k/N_0 where N_k was the number of activated voxels estimated at a given nonzero k and N_0 was the mean number of activated voxels averaged across the 50 datasets with k equal to zero. The mean and SD of the performance ratio and ROC area for each nonzero k were displayed in Figure 4A,B, respectively.

The results showed that the ROC area and the number of activated voxels detected by sICA with projection reduced gradually with the increasing of k . However, even for $k = 0.8$, the detected voxels were still about 75% of those for $k = 0$ and its ROC area was up to 0.93. This suggests that the method is very robust for a wide range of degree of nonlinearity (indexed as parameter k here).

Validation Using Simulated Two-Task fMRI Data

Human rest data

All simulated data below were built on an fMRI baseline dataset acquired from a healthy volunteer who signed the consent form for the study. The data was acquired in a

2.0 T GE/Elscint Prestige whole-body MRI scanner (GE/Elscint, Haifa, Israel) using gradient-echo echo-planar imaging protocol and consisting of 19 axial slices (TR = 3,000 ms, TE = 60 ms, field of view $375 \times 210 \text{ mm}^2$, matrix size $128 \times 72.6 \text{ mm}^2$ thickness, no gap). The healthy volunteer was asked simply to relax and remain still while 70 whole-brain baseline scans were collected. The first five scans were eliminated in the simulation experiments as a result of their instability at the beginning of scanning.

Generation of simulated data

The simulated fMRI responses to task X_1 or X_2 (see panel A in Fig. 2) were identical to the prior simulations. It was supposed that task X_1 activated the predefined ROI in slice 13 and 14 whereas X_2 activated the ROIs in slice 14 and 15 as seen in Figure 5. Those ROIs were specified by using 3D ROI tool in MRicro software (<http://www.sph.sc.edu/comd/rorden/mricro.html>). Total 13 datasets with the same task paradigm but different SNR were generated. The 13 datasets had the same minimum signal change (0.5%) and the varied maximum signal change from 1.4 to 2.6% with increment of 0.1%, relative to

Figure 5. The ROIs activated by task X_1 or X_2 in the two-task fMRI simulation.

Figure 6.

Results of two-task fMRI simulation. ICAp represents the sICA with the projection method. (A) is the time course (upper) and the spatial activation of task-related component (lower) estimated directly from raw data without projection. The results from (B) to (E) are those estimated by sICA with the projection method and SPM. Each panel consists of both time courses of task-related components (upper) for sICA with projection and

activation pattern (lower) of components estimated from sICA with projection and SPM. Results in (B) and (C) are activations by task X_1 and by task X_2 respectively. Panels (D), (E) and (F) show the activations invoked by both tasks, task X_1 only, task X_2 only. The solid line indicates the time courses of task-related components whereas the dotted line indicates the reference function.

the mean intensity value of the individual voxel. The ranges of signal change for the two tasks are the same in each dataset.

Data processing

All 13 datasets underwent exactly the same processing. The high-pass filter composed of the DCT functions with

the cut-off period 120s and a three-point hanning low-pass filter were applied to the simulated data before each sICA process. The data were processed separately by standard sICA (i.e., without the projection) and by sICA with the proposed projection method. In addition, GLM analysis was applied to the data processed by high-frequency filter and global scaling through SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>). The threshold adopted was $P < 0.001$ uncorrected.

Figure 7.

The comparison between sICA with projection and SPM (A) and the determination of optimal threshold (B). (A) shows the mean ROC areas of sICA with projection and SPM in five cases. X1_O, X2_O and X1&X2 represent the case of task X₁ only,

X₂ only and both tasks. B shows the variation of mean ROC area with different thresholds when estimating activation induced by task X₂ only. The error bar represents the SD. Note: asterisk represents $P < 0.01$.

Finally, the ROC method was utilized to measure the accuracy of detection by sICA with projection and GLM method.

Results

Figure 6 shows the results of one dataset with maximum signal change of 2% processed by standard (or conventional) sICA, sICA with projection and SPM. When sICA was used alone without the proposed projection procedure, only one task-related component was unearthed. The time course and corresponding spatial mapping are shown in Figure 6A. Although the time course is highly correlated with reference function X₁+X₂, its spatial mapping consists of not only the regions activated by X₁+X₂, but also some only by X₁ or X₂ respectively. When sICA was used in conjunction with the projection method, brain regions associated with each of the two tasks as well as the regions jointly activated by both were revealed. The results are shown in Figure 6 together with the corresponding SPM spatial activation results (panels B to F). Both sICA with the projection and SPM were able to detect most of the voxels participating in each of the two tasks or both.

The ROC areas of each dataset were obtained from the estimation of activation induced by task X₁, task X₂, task X₁ only, task X₂ only and both tasks through sICA with projection and SPM method. The mean and SD of ROC areas for the two methods across the 13 datasets were shown in Figure 7A. To examine the difference of detection power between these two methods in each case, the nonparametric Wilcoxon test for paired sample was performed. The means of ROC areas for sICA with projection were significantly greater than SPM in the case of task X₁, task X₂ and both tasks ($P = 0.001$ for all three cases). No significant difference was found between these two methods in the case of task

X₁ only and task X₂ only. The results show that the sICA with projection is better at detecting regions responding to task X₁, task X₂ or both tasks than SPM.

Determination of the Threshold

To obtain the regions activated only by one task using the proposed projection procedure, the activation of the other task must be removed from the raw data. High threshold could result in the good specificity and the removal of less voxels responding to the noninterest task whereas low threshold would contribute to good sensitivity and the removal of more nonactivated voxels. As a result, it is essential to seek an optimal threshold achieving a compromise between sensitivity and specificity to properly mask out the voxels responding to the task to be removed. Because ROC method is a good way to delineate the relationship between sensitivity and specificity, it was utilized to determine the optimal one among various thresholds based on two-task fMRI simulation data.

The same 13 datasets with different SNR as the above were used again. For each datasets, the sICA with the projection method was conducted to estimate the regions activated by the task X₂ only and the threshold of removing task X₁ was varied from 1.1 to 2.3. Under each threshold, the ROC areas of 13 datasets were calculated separately. The means and SD of the ROC areas across the 13 datasets were plotted in Figure 7B.

The results showed that the means of the ROC areas for the threshold equal to 1.4, 1.5, and 1.6 were very close and reached the highest relative to the other thresholds. As a result of the relatively smaller SD for threshold 1.5 compared to 1.4 and 1.6, 1.5 was selected as the optimal one in the entire simulation and real fMRI experiment.

Figure 8.

The mean time courses (upper row) of task-related component for ICA with projection and spatial activation (lower row) estimated by sICA with projection and SPM for three subjects. Left column shows the brain regions engaged in visual motion only,

middle column shows the regions engaged in color perception only and right column shows regions engaged in both visual tasks. The solid line indicates the time courses of task-related components whereas the dotted line indicates the reference function.

REAL fMRI EXPERIMENT

In this section, real fMRI data were used to examine the capacity of the proposed projection method to separate components related to two tasks. All the scanning parameters were the same as the fMRI data used in the simulation.

Three healthy subjects (one male and two females, 22–25 years old, right-handed) were recruited. They all agreed to participate in the fMRI experiment and signed the consent form.

Experimental Design

The experimental paradigm was a boxcar function with the start of 30s baseline. The durations for each experiment block and baseline block were 30s. Two sorts of visual stim-

uli were presented to each subject in a single session. Task A was passively viewing radially moving dots and task B was passively viewing the color of a square displayed in the center of the screen. The order of the two tasks was in ABABAB sequence. The entire session consist of six 30s task blocks interspersed with six 30s rest blocks and lasted 6 min. During the rest, a fixation cross was constantly presented in the centre of the screen. The subjects were instructed to maintain fixation through the whole rest condition. The total 120 scans were acquired during the whole 360-s experimental session.

Data Preprocessing

Those functional images were first realigned, spatially normalized into the standard MNI template space, resliced to

TABLE 1. Talairach coordinates of results through ICA with the projection method for each subject

Subject	Region	BA	Talairach coordinates			Z score
			<i>x</i>	<i>y</i>	<i>z</i>	
Subject1	Visual motion					
	Left middle temporal gyrus	37	-50	-66	4	2.51
Subject2	Right inferior temporal gyrus	37	44	-71	2	4.38
	Left middle occipital gyrus	19	-50	-72	4	3.47
Subject3	Right middle occipital gyrus	37	56	-70	4	4.11
	Right middle occipital gyrus	19	48	-74	4	3.78
Subject1	Color perception					
	Left fusiform gyrus	37	-32	-52	-14	3.39
Subject2	Right fusiform gyrus	37	39	-57	-14	3.10
	Left fusiform gyrus	37	-36	-48	-20	2.39
Subject3	Right fusiform gyrus	37	36	-52	-18	2.44
	Left fusiform gyrus	37	-34	48	-20	2.10
Subject1	Visual motion and color perception					
	Left inferior occipital gyrus	17	-28	-93	-6	12.74
Subject2	Right inferior occipital gyrus	18	32	-96	-6	11.26
	Left inferior occipital gyrus	18	-24	-100	-6	11.23
Subject3	Right inferior occipital gyrus	18	21	-96	-6	8.01
	Left inferior occipital gyrus	18	-24	-99	-6	8.10
	Right inferior occipital gyrus	18	32	-93	-6	8.43

$3 \times 3 \times 4 \text{ mm}^3$ voxels and smoothed with a $8 \times 8 \times 8 \text{ mm}^3$ full-width at half maximum Gaussian kernel through SPM2. The first five scans were excluded from further statistical analysis.

Data Analysis

After preprocessing, the data were processed by sICA with and without the projection method. The high-pass filter composed of the DCT functions with the cut-off period 120s and a three-point hanning low-pass filter were applied to the simulated data before each sICA process. For the SPM analysis, the smoothed data went through the high-frequency filter, global scaling and GLM analysis. The threshold adopted in SPM was $P < 0.001$ uncorrected.

Results

The brain regions of three subjects activated by visual motion only, color perception only and both tasks for sICA with the projection and SPM were shown in the 3 lower rows of Figure 8. The corresponding time courses of task-related components averaged across the three subjects in the three cases were plotted in the upper row of Figure 8. The talairach coordinates of the crucial regions were listed in Table I and Table II.

Many previous studies have substantiated that different visual stimuli selectively activate different part of extrastriate visual cortex. For instance, the color center that is V4 area in fusiform gyrus is involved in color perception [McKeefry and Zeki, 1997] whereas V5/MT that is located

TABLE 2. Talairach coordinates of SPM results for each subject

Subject	Region	BA	Talairach coordinates			T score
			<i>x</i>	<i>y</i>	<i>z</i>	
Subject1	Visual motion					
	Right middle occipital gyrus	37	45	-70	4	3.23
Subject2	Left middle occipital gyrus	19	-50	-72	4	3.23
	Right inferior temporal gyrus	37	50	-64	0	4.11
Subject3	Left middle occipital gyrus	37	-50	-70	4	3.85
	Right middle occipital gyrus	19	48	-70	6	4.49
Subject1	Color perception					
	Left fusiform gyrus	37	-36	-53	-18	3.68
Subject2						
	Left fusiform gyrus	19	-25	-75	-14	3.76
Subject1	Visual motion and color perception					
	Left inferior occipital gyrus	17	-21	-99	-12	3.68
Subject2	Left inferior occipital gyrus	18	-21	-97	-6	6.74
	Right inferior occipital gyrus	18	25	-98	-6	6.55
Subject3	Left inferior occipital gyrus	17	-27	-94	-6	10.17
	Right inferior occipital gyrus	17	27	-95	-6	8.58

Figure 9.

The time courses (**A** and **C**) and their corresponding spatial mappings (**B** and **D**) of two task-related components estimated by sICA without projection for subject 1. The solid line indicates the time courses of task-related components whereas the dotted line indicates the reference function.

in the intersection of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus [Dumoulin et al., 2000] responds to visual motion [Salzman et al., 1990; Snowden, 1994]. Primary visual cortex V1/V2 is mainly engaged in the early visual processing.

For sICA with projection, subject 1 and subject 2 showed strong activation in bilateral V5/MT for visual motion and bilateral V4 for color perception. However, only right V5/MT responded to visual motion and left V4 responded to color perception in subject 3. Furthermore, the bilateral primary visual cortex (V1/V2) was found to consistently participate in two visual tasks for all the three subjects (See Table I).

Larger individual differences were seen in SPM results in contrast to sICA with projection. The activation in bilateral V5/MT was observed in subjects 2 and 3, whereas only right V5/MT in subject 1 was found to respond to

visual motion. Color perception induced significant activity in the left V4 for subject 1 and subject 3. However, the activity of V4 was absent in subject 2. Both visual motion and color perception invoked the bilateral V1/V2 activation in subject 2 and subject 3 although only the activity of left V1 were observed in subject 1 (See Table II).

In light of the sICA without projection, one or two task-related components that were highly correlated with two-task time courses were found in each subject. The time courses and activation of the two task-related components for the first subject was shown in Figure 9. Actually, the component similar to that in Figure 9C,D could also be observed consistently in the other two subjects. The other component in Figure 9A,B showed more variability across the three subjects. The time courses of the two components in Figure 9 indicated that they participated in both visual motion and color perception. Meanwhile, there were some

Figure 10.

The instances of different overlap resulting in different dependency. (A) and (B) provide two nearly independent components with small spatial overlap. (C) and (D) provide two dependent components with large spatial overlap.

overlap and differences between the activated brain regions in these two components. The vagueness of the results compromised their interpretation.

DISCUSSION

In this study, we proposed a projection procedure which can be utilized in conjunction with sICA approach to separate tasks whose involved spatial activation patterns are not statistically independent. We illustrated the robustness of the method in the case of noises and nonlinearity of the two tasks. Results from both simulated and the real fMRI data demonstrated the increased sensitivity of the method in comparison to univariate SPM and the sICA procedure without the proposed projection method. Several issues related to our investigation procedure are further elaborated here.

It should be noted that spatial overlap does not necessarily imply spatial dependency. When the overlap region of two components is relatively small, the two components may still be almost statistically independent in a practical criterion. For example, the normalized mutual information (NMI) [Studholme et al., 1999] can be used to measure the independency between two components, with value of 1.0 being indicative of independency and value of 2.0 being identity. Therefore, larger NMI indicates stronger dependency between two components. For instance, although A and B in Figure 10 have small overlap, the NMI between them is 1.01 that means they are nearly independent. By contrast, large overlap between C and D in Figure 10 result in their stronger spatial dependency with NMI equal to 1.38 that is indicative of statistical dependency. Note that the MNI between the spatial patterns activated by X_1 or X_2 in our two-task fMRI simulation is equal to 1.386.

One advantage of sICA over GLM is that it is a useful exploratory tool to identify unexpected brain activity patterns without any prior hypothesis about the data [De Luca, 2006]. Though the projection method introduced in our study can separate out patterns that are associated with individual tasks in the cases of multitask fMRI data with spatially dependent components, the fact that the feasibility of the projection method depends on the prior hypothesis of the experimental model makes the sICA proce-

cedure in conjunction with the proposed projection method not purely exploratory any more. Previous studies [Hu et al., 2005; McKeown, 2002] demonstrated more accurate statistical model derived from fitting those task-related components of sICA into the unexpected HRF contribute to better detection power for model-driven method (GLM). By contrast, sICA with the projection method provides a way to integrate prior model with data-driven method. The projection making use of the prior hemodynamic response model helps sICA succeed in the situations it may fail. Simulation experiments revealed that the sICA with the projection can achieve more robust and higher detection power compared to the pure hypothesis-driven method GLM or sICA alone when estimating regions responding to each tasks or both rather than each task only. Another significance of sICA with projection is that it provides us a potential way for functional connectivity analysis in two-task fMRI data to extract the spatially distributed networks driven by each task even though these two networks are not spatially independent.

Although all our simulations were both based on the assumption that components are constrained to binary spatial distributions, the results of our real fMRI data, on the other hand, strongly support that the general applicability of the proposed projection method to data having components with a general spatial distribution. The potential issue associated with the general applicability is the optimal threshold for removing the voxels responding to one task and yet preserve those for another. The commonly adopted Z threshold value of 2 that is suitable to activation detection was demonstrated in our simulation to be too restrictive to remove activated voxels effectively. Instead, our choice of 1.5 seemed a reasonable compromise, and the results of our real fMRI data analysis also support its use for nonbinary distributions. Nevertheless, separate study is needed to further investigate the nonbinary distribution issue in light of the optimal threshold.

For easy understanding and simple illustration of our proposed projection method, the current study also assumed that there is only one component related to each task in our data. In reality, there potentially exist several task-related components that are often called as consistently task-related and transiently task-related (TTR) components [McKeown et al., 1998]. However, a closer examination of our derivation of the procedure reveals that it is generalizable to multicomponent situation as long as projection matrix can be predetermined. Practically, because all the TTR components are also highly correlated with a specific task (or its time course), such as task X_1 , the influence of these components would be reduced dramatically after projecting the data to the space perpendicular to the task X_1 . Meanwhile the TTR components of task X_2 can be preserved and are correlated with task X_2 . Therefore, we claim that the projection approach is feasible in such situation.

When designing two-task fMRI experiment, the two tasks are usually presented in a way so that the tasks are

orthogonal to each other to minimize the potential interaction between them. Our previous theoretical discussion on the two tasks separation relied upon the orthogonal assumption. However, this criterion is not as critical for linear projection separation method, which means it may work well with the two tasks that are not exactly orthogonal to each other when they interact in an additive manner.

Another crucial point we need to notice is that not all components with overlapped activation are definitely spatially dependent. In the case of the common activation relatively much less than the single task activation, sICA may be able to dissociate the components associated with each single task directly.

LIMITATIONS

Though, as demonstrated in the current study, the projection preprocessing can be used for the separation of two-task fMRI data, there is one underlying assumption about this method, making its general use somewhat limited. This is the assumption of linearity that assumes the effects of the two tasks are purely additive (e.g., all the inputs to the commonly activated brain area are linearly and simultaneously added). Further studies are needed for the feasibility of the method to deal with more general situations.

Like any other statistical method, the projection may fail when the noises are highly related to signal or when the SNR is very low.

CONCLUSION

We demonstrated that sICA in combination with the projection method can be used to reduce the effects of artifacts, to enhance activation detection power and to analyze two-task fMRI data with spatially dependent components. Further studies are needed to probe its applicability to more complicated multitask cognitive experiments.

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