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Input permutation method to detect active voxels in fMRI study★

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Abstract

Correctly identifying voxels or regions of interest (ROI) that actively respond to a given stimulus is often an important objective/step in many functional magnetic resonance imaging (fMRI) studies. In this article, we study a nonparametric method to detect active voxels, which makes minimal assumption about the distribution of blood oxygen level-dependent (BOLD) signals. Our proposal has several interesting features. It uses time lagged correlation to take into account the delay in response to the stimulus, due to hemodynamic variations. We introduce an input permutation method (IPM), a type of block permutation method, to approximate the null distribution of the test statistic. Also, we propose to pool the permutation-derived statistics of preselected voxels for a better approximation to the null distribution. Finally, we control multiple testing error rate using the local false discovery rate (FDR) by Efron [Correlation and large-scale simultaneous hypothesis testing. *J Am Stat Assoc* 102 (2007) 93–103] and Park et al. [Estimation of empirical null using a mixture of normals and its use in local false discovery rate. *Comput Stat Data Anal* 55 (2011) 2421–2432] to select the active voxels.

Keywords

False discovery rate; fMRI; Input permutation method; Lagged correlation; Time delay

1. Introduction

Functional magnetic resonance imaging (fMRI) permits measurement of local changes in cerebral blood volume [1], flow [2] and oxygenation [3,4] in cortical vasculature. In a typical fMRI study, we observe blocks of images under a baseline condition (e.g., rest) alternating another blocks of images under stimulus presentation or cognitive task performance (stimulus/task). A common goal of fMRI studies is to optimize the detection of signal changes between the experimental stimulus/task and the baseline, and to infer the

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location and the intensity of task-related neural activity. However, it has been reported that there are temporal delays in fMRI responses to the stimulus and the delays vary up to several seconds among activated voxels [5–7].

The common approach within the current literature is to test the association between the BOLD signal and the stimulus function in each voxel and then to select the active voxels by controlling multiple testing error rate such as either the family-wise error rate (FWER) or the false discovery rate (FDR). Among other methods, statistical parametric mapping (SPM [8]) is commonly used in practice. The SPM analyzes fMRI data using the general linear model (GLM). A detailed discussion of this parametric approach based on the GLM is given in Ref. [9]. In the GLM, the stimulus is convoluted with the hemodynamic response function (HRF) to accommodate the delay effect. Hence, the delay and dispersion parameters for the HRF have to be known or estimated. Often, a fixed delay and dispersion are applied to all voxels for the sake of computational efficiency, or the parameters of the HRF per voxel are estimated at the cost of time-consuming computation and the increased complexity of model, which is hard for practitioners to implement ([10] and references therein). Despite its popularity, the validity of GLM technique relies on some strong assumptions, e.g., the normality of residuals and, more importantly, that the HRF is known a priori. When the assumptions are not met, the procedure of the GLM is not optimal [11]. The violation of these assumptions can lead to severe power loss and increase the false-positive rate.

Alternatively, nonparametric methods are proposed by various authors [11–14]. In contrast to parametric methods, nonparametric approaches do not require a specific form of the distributions of the signal or the residuals, e.g., the normal assumption in the GLM. Thus, the nonparametric methods are attractive in fMRI studies since the probability distribution of errors may neither be normal nor be the same over voxels. Ref. [12] suggested a permutation method for multisubject fMRI studies by relabeling subject's index. However, Ref. [12] does not address single-subject fMRI studies. Furthermore, it is difficult to accommodate the voxelwise delay effects in this method, because the delays might be different from subject to subject even at the same voxel. Refs. [13,14] suggested resampling methods based on Fourier and wavelet transforms of the BOLD signal mainly concerning the temporal autocorrelation. These approaches, however, do not consider multiple comparison issues and cannot take into account the delay effect.

In this article, we propose a nonparametric method to find active voxels in a single-subject, task-based fMRI study. The proposed method has a few interesting features listed below. First, the method takes into account the temporal delay of the fMRI responses by using the maximum lagged correlation (MLCorr) between input stimulus and BOLD signal as a measure of neuronal activity in a voxel. Moreover, the lags producing the maximum correlations, which vary over voxels [7], can be plotted to construct a map of spatial variability of the delay effect in the brain. Second, most importantly, our proposal introduces the input permutation method (IPM) or block permutation method to approximate the null distribution of MLCorr. The IPM permutes on- and off-blocks of input signals, not single scans, to preserve the temporal correlation of BOLD signals. The permutation of single scans introduces extra variability by disregarding the (positive) temporal correlation of BOLD signals and thus it misspecifies the null distribution of the observed test statistic. The statistic obtained by the permutation of single scans has larger variance than the observed statistic. Third, we preselect a set of voxels and pool their permutation-derived statistics to approximate the null distribution of test statistic. Finally, we select a set of active voxels using the local FDR by Ref. [15]. The local FDR procedure estimates the empirical null distribution of z -scores obtained from the P values by applying inverse Gaussian function to P values and finds the threshold of test statistic to control the FDR at a given level.

The article is organized as follows. In Section 2, we provide the technical details of the fMRI experiment analyzed in this article. In Section 3, we propose a nonparametric method to detect voxels which are active during a task. In this section, we introduce the input permutation method and also propose to pool the permutation-derived statistics of predetermined voxels to obtain a good approximation to the null distribution. We also briefly review the local FDR procedure by Efron [15,16] and its modification by Ref. [17]. In Section 4, we apply the proposed method to analyze a finger-tapping fMRI experiment. Summary is presented in Section 5.

2. Materials and methods

2.1. Subjects

Sixteen healthy volunteers (14 males and 2 females between 21 and 36 years of age) with no history of head trauma, neurological disease or hearing disability were scanned. All protocols in this study were approved by an institutional review board. Written consent was obtained from the volunteer after the nature and possible consequences of the study were explained.

2.2. MRI parameters

All images were obtained on a Bruker Medspec 3T/60 cm imaging system. The imaging system was equipped with a three-axis balanced torque head gradient coil and a shielded end-cap quadrature transmit/receive birdcage radiofrequency coil [18]. Volunteers were positioned supine on the gantry with the head in a midline location in the coil. To reduce motion artifacts, foam padding was placed between the forehead and the coil. For each volunteer, echo-planar images were obtained across the motor cortex using a 64×64 matrix, TR/TE=2 s/27.2 ms, FOV=20 cm, slice thickness=5 mm and bandwidth of 125 kHz. The imaging procedure was as follows: sagittal localizer images were first obtained with a conventional gradient-echo sequence. The mid-sagittal image was used to select the axial slice over the motor cortex for functional imaging. In each subject, 75 or 165 echo-planar images were obtained for a total dynamic time of 150 or 330 s. Stimulation task was accomplished by a computer-controlled light signal visible to the volunteer. Subjects were instructed to maintain constant attention during individual experiments.

2.3. Experimental task and data preprocessing

Subjects performed bilateral finger tapping to activate the sensorimotor and its associated cortex. For the periodic bimanual finger-tapping task, participants completed four finger-tapping trials lasting 20 s, each separated by 20 s of rest, and 20 s of finger-tapping preceded the first and followed the last trial. A white circle remained centered on the screen during the rest periods, and to signal the finger-tapping periods, the circle changed color to cyan and began flashing at 0.5 Hz. Participants were instructed to sequentially touch each finger to its respective thumb making one touch and release, as best they could, in synchrony with the flashing circle.

MRI data preprocessing and analysis were performed using analysis of functional neuroimages (AFNI) [19]. AFNI allowed for the analysis of the attained fMRI data and the viewing of activation maps for each subject. Because subject head motion is a concern, prior to any data analysis, motion detection and correction were performed in AFNI (3dvolreg) to ensure the accuracy of the data. Slice timing was also corrected. Data sets were also detrended to eliminate linear drifts caused by motion, scanner-related influences as well as global physiological factors. Spatial smoothing was not performed.

3. Nonparametric method

3.1. Maximum lagged correlation

Let $\mathbf{X}=(X_1, \dots, X_T)$ be a sequence of BOLD signal and $\mathbf{S}=(S_1, \dots, S_T)$ be its input stimulus, having values of 0 or 1. Here, 0 stands for the resting state and 1 does for the tasking state. The temporal correlation, $\text{corr}(\mathbf{X}, \mathbf{S})$, has been widely used in fMRI study to find the voxels actively responding to various stimuli. However, the fMRI signals are reported to be delayed up to several seconds [7,20,21] with respect to the input stimulus. When delay occurs, the temporal correlation does not fully measure true neural activity.

In this article, we propose to use lagged correlation to take into account the delay effect. Let $\mathbf{S}(\Delta)=(S_{1-\Delta}, \dots, S_{T-\Delta})$ with $S_{t-\Delta}=0$ if $t-\Delta \leq 0$. Then for $\Delta=0, \dots, q$, the lagged correlation between $\mathbf{X}$ and $\mathbf{S}$ is defined as $\tau(\Delta)=\text{corr}(\mathbf{X}, \mathbf{S}(\Delta))$. The ordinary temporal correlation, of course, has $\Delta=0$. In practice, the length of delay Δ is unknown. The statistic to measure the neural activity of the i th voxel is the maximum of its lagged correlations defined as

$$\tau_i=\text{sign}(\tau(\delta_i)) \max_{\Delta \in \{0,1,\dots,q\}} |\tau(\Delta)|=\text{sign}(\text{corr}(X_i, S(\delta_i))) \times \max_{\Delta \in \{0,1,\dots,q\}} |\text{corr}(X_i, S(\Delta))|. \quad (1)$$

where δ_i is the delay at which the maximum occurs. The length of the delay varies over voxels and the maximum lag q is chosen as the length of block of 0 or 1 signal in a block design.

3.2. Permutation test: input permutation method

To decide whether the i th voxel is active, we need to know the null distribution of $\text{MLCorr} \tau_i$ under the assumption that it is not active. In this section, we introduce a procedure based on the IPM to approximate the null distribution of the MLCorr .

There are two interesting features of the permutation procedure we propose. First, the IPM permutes on- and off-blocks of input stimulus, rather than the labels of single scans. Let Π_b be the collection of permutations of on- and off-blocks. Let $T=L \cdot B$, where L is the length of blocks and B is the number of blocks in the task. Then, a permutation $\pi \in \Pi_b$ is indexed by a permutation ψ in Ψ , where Ψ is the set of permutations of $[B]=\{1, 2, \dots, B\}$. To be specific, a permutation $\psi \in \Psi$ induces a permutation $\pi=(\pi(1), \pi(2), \dots, \pi(T)) \in \Pi_b$, which is $((\psi(1)-1)L+1, \dots, (\psi(1)-1)L+L, (\psi(2)-1)L+1, \dots, (\psi(2)-1)L+L, \dots, (\psi(B)-1)L+1, \dots, (\psi(B)-1)L+L)$. In addition, let Π_s be the collection of all possible permutations of $[T]=\{1, 2, \dots, T\}$. We remark that $\Pi_b \subset \Pi_s$.

The permutation method aims to approximate the null distribution of test statistics $\tau=h(\mathbf{X}, \mathbf{S})$ and, thus, the permutation-derived statistic $\tau(\pi)=h(\mathbf{X}, \mathbf{S}(\pi))$ for $\mathbf{S}(\pi)=(S_{\pi(1)}, S_{\pi(2)}, \dots, S_{\pi(T)})$ is expected to have the same distribution as τ regardless of whether the signal $\mathbf{X}$ is active or nonactive to the input stimulus. It is called “permutation invariance” in previous literature [22]. However, the permutation invariance is not satisfied in general when $\mathbf{X}$ is temporally correlated. For example, suppose we consider the simple statistic

$$\tau=\sum_{t=1}^T X_t(2S_t-1)=\mathbf{X}(2\mathbf{S}-1)^T. \text{ The permutation invariance implies}$$

$$\tau(\pi)=\sum_{t=1}^T X_t(2S_{\pi(t)}-1)=\mathbf{X}(2\mathbf{S}(\pi)-1)^T \text{ has the same distribution as } \tau. \text{ Then the normality assumption implies that}$$

$$(2\mathbf{S}-1)\Sigma_X(2\mathbf{S}-1)^T=\text{var}_{\pi}\left\{X(2\mathbf{S}(\pi)-1)^T|\mathbf{X}, \mathbf{S}\right\}=\frac{1}{|\Pi|}\sum_{\pi \in \Pi_s}(2\mathbf{S}(\pi)-1)\Sigma_X(2\mathbf{S}(\pi)-1)^T. \quad (2)$$

Eq. (2) is true for very limited choice of $\Sigma_{\mathbf{X}}$. A covariance matrix that satisfies Eq. (2) is the compound symmetry of the form

$$\Sigma_{\mathbf{X}} = \sigma^2 I_T + \eta^2 J_T,$$

where I_T is the T -dimensional identity matrix and J_T is the T -dimensional matrix having all elements as one. On the other hand, Eq. (2) is not true for the “autoregressive” covariance matrix $\Sigma_{\mathbf{X}}$. In particular, if $\mathbf{X}$ has positive temporal correlation, $\text{corr}(X_s, X_t) > 0$ for any $s, t \in [T]$, a simple algebra shows that $(2\mathbf{S}-1)\Sigma_{\mathbf{X}}(2\mathbf{S}-1)^T \neq (1/|\Pi_s|)\Sigma_{\pi \in \Pi}(2\mathbf{S}(\pi)-1)\Sigma_{\mathbf{X}}(2\mathbf{S}(\pi)-1)^T$.

In this article, we propose the IPM to approximate the null distribution of MLCorr, which permutes blocks of input stimulus. The permutation invariance is still not true for the IPM. However, we find that it preserves the temporal correlation within a block and approximates the null distribution well enough. We implemented a numerical study to justify our claim about IPM. For simplicity, the study considers a first-order autoregressive (AR) model. The autocorrelation coefficient is chosen as $\rho=0.1, 0.3, 0.5, 0.7$ to represent different levels of temporal dependence. We generated 200 time series of length $T=90$ from the AR model $X_t = \rho X_{t-1} + \epsilon_t$, where ϵ_t 's are independent and identically distributed from the standard normal distribution. To examine the effect of L on the estimated null distribution, we employed different block lengths ($L=3, 6, 10, 15$). For each time series data set, we computed the permutation-derived statistics (PS) for each L based on IPM and also apply the single-scan permutation method. Based on the histograms of the PSs from all 200 data sets, we estimated the density functions and the results are shown in Fig. 1. In Fig. 1, the true distribution of the MLCorr is evaluated from 2 million time series data sets generated from the true model. The figure shows that as ρ increases the tails of the true distribution become fatter. Also, if the signal has weak or moderate temporal dependence (e.g., $\rho=0.1, 0.3, 0.5$), the large block size, e.g., $L=6$, consistently approximates the null distribution well. The single-scan permutation method, however, completely disregards the temporal correlation in the data and provides the same approximations for different ρ 's. In fMRI studies, temporal dependencies are typically reported as moderate [23]. To this reason, we recommend the reader to use $L=10$ as the size of blocks in the IPM. Interestingly, this happens to be the most common in practice. Experimenters use often a block design of alternating on and off for 20 s ($L=10$) each since the BOLD signal responds to a stimulus slowly and it was found that a stimulus duration of at least 6–8 s resulted in the maximal amplitude response [24]. For our study $L=10$.

Second, we propose to pool PSs from preselected nonactive voxels, as opposed to using PSs from all voxels, to obtain a better approximation to the null distribution. The permutation method aims to approximate the distribution of test statistic under the null hypothesis (nonactive). The PSs from a nonactive voxel correctly approximate the true null distribution. However, the PSs from an active voxel do not, as reported in previous literature [25,26]. To illustrate this phenomenon, Fig. 2(A) plots the estimated densities of PSs for two voxels, one has MLCorr above 0.9 (active) and the other has MLCorr below 0.1 (nonactive). The density of PSs from the active voxel has a heavier tail than that from the nonactive voxel.

We propose to preselect voxels which are nonactive with high probability. The preselection procedure we use is based on the rank of the observed absolute value of MLCorr $|\tau_i|$. We select the voxels whose MLCorr's rank among N voxels is lower than $[0.25 \cdot N]$, where $[\cdot]$ is the floor function and N is the total number of voxels. We let $N_0 = [0.25 \cdot N]$ and $\mathcal{Q}$ be the set of preselected voxels. To understand the effect of preselection percentage on the power, we apply different percentages of 0.1, 0.2, 0.25, 0.3 and 0.4, and compare their estimated null

distributions. The results are plotted in Fig. 2(B). It shows that the choice of preselection percentage has minimal influence on the estimation of the null distribution.

We estimate the null distribution of τ_j for the j th voxel using the empirical distribution of the PSs of voxels in $\mathcal{Q}$. Let π_k be a randomly selected permutation in Π_s and

$$\tau_{jk} = \tau_{j(\pi_k)} = \text{sign} \left(\text{corr} \left(X_j, S_{(\pi_k)}(\delta) \right) \right) \max_{\Delta \in \{0,1,\dots,L\}} |\text{corr} \left(X_j, S_{(\pi_k)}(\Delta) \right)|.$$

For each voxel $j \in \mathcal{Q}$, we randomly select K permutations from Π_b with replacement and compute τ_{jk} , $k=1, \dots, K$. We estimate the null distribution of τ_j using the empirical distribution of τ_{jk} 's and, thus, the P value for testing if voxel j is nonactive (say H_{0j}) becomes

$$\hat{p}_j = \frac{1}{|\mathcal{Q}| \cdot K} \sum_{i=1}^{|\mathcal{I}|} \sum_{k=1}^K I(|\tau_{ik}| \geq |\tau_j|). \quad (3)$$

3.3. Local false discovery rate

We should test a large number of hypotheses simultaneously to find a set of active voxels, where the number of hypotheses is equal to that of voxels. Several versions of type I error for multiple testing problem were introduced in previous literature, where FWER and false discovery rate (FDR) are the two most common. In the analysis of brain imaging data, Gaussian random field theory is often used to control the FWER [27], and, recently, FDR approaches are applied [15,16,28–30]. Here, we adopt the FDR approach by Refs. [16,17].

Suppose there are N hypotheses to be tested simultaneously and t_i , $i=1, 2, \dots, N$, is the test statistic for the i th hypothesis. The conventional FDR procedure including Ref. [28] assumes the independence (or the weakly independence) of test statistics t_i 's. In our problem, the test statistics t_i 's (MLCorr) are spatially dependent on each other and this assumption is clearly not true. The empirical Bayes approach for the FDR, first proposed by Ref. [16] and extended later, provides a good remedy for this difficulty. Ref. [16] assumes a two-group mixture model for z -values, which are z -transformed P values, and proposes to estimate the null distribution from the observed z -values itself. Ref. [16] denotes the estimated distribution as the empirical null distribution and uses it to estimate the FDR at a given threshold. Refs. [15,30] improve the estimation procedure for the empirical null distribution. Recently, Ref. [17] extends Ref. [15] to consider a more flexible class of null distribution so that the FDR estimates become robust to the misspecified null distribution by various reasons. Below, we adopt the procedure by Ref. [17], which would explain well the symmetric and bimodal null distribution of MLCorr.

Let us assume the test statistics $z_1, z_2, \dots, z_n$ be random samples from the mixture of the null and non-null (alternative) distributions with the density

$$f(z) = p_0 f_0(z) + (1 - p_0) f_1(z), \quad (4)$$

where p_0 is the probability of null, f_0 is the density function under the null hypothesis and f_1 is the density under the non-null hypothesis. Then, the local FDR at t is defined as

$$\text{fdr}(t) = \frac{p_0 f_0(t)}{f(t)}. \quad (5)$$

From Bayesian perspective, $\text{fdr}(t)$ is the posterior probability of a true null hypothesis at $z=t$, i.e., $\text{fdr}(t)=Pr(H_{0,i}|z=t)$. We consider a mixture of normal distributions for f_0 , whereas Ref. [16] assumes it as a single normal distribution. Specifically, we found a three-component normal mixture enough to fit well:

$$f_0(z)=\eta_1\varphi_1(z)+\eta_2\varphi_2(z)+(1-\eta_1-\eta_2)\varphi_3(z) \quad (6)$$

where $\varphi_l(z)=(1/\sigma_{0,l})\varphi((z-\mu_{0,l})/\sigma_{0,l})$, $l=1, 2, 3$, and $\varphi(z)$ is the density of standard normal. We refer to Ref. [17] for more details on the estimation procedure.

4. Results

The threshold for z_i 's of MLCorr is determined for each subject to ensure the local FDR is at a given level α . The thresholds are not the same over subjects. The proposed method using maximum lagged correlation was applied to detect active voxels separately on each subject's data.

For one selected subject, Fig. 3 shows the histogram and the nonparametric density estimate of the null distribution of z -transformed MLCorrs, obtained by the proposed input permutation method using preselected surely nonactive voxels. We observed that the histogram of z -transformed MLCorrs is far from the theoretic null distribution $N(0, 1)$ which is unimodal. Since the estimated null distribution is multimodal (red line curve in Fig. 3), a conventional FDR procedure would not be appropriate. We applied the local FDR procedure of Ref. [17]. Given a local FDR level of 0.05, we identified 1030 voxels as active based on MLCorrs (threshold=6.3910) for the selected subject.

For the purpose of comparison, we applied the GLM and a simple correlation with fixed lag=0, 2 and 4 to the same subject as well. For the GLM method, Gaussian random field theory was used to correct for multiple comparisons at the level of significance $\alpha=0.05$. Fig. 4 displays the active voxels in brain slice no. 67 from the GLM [Fig. 4(A)] and from our MLCorr with IPM procedure [Fig. 4(B)]. The motor cortex in the brain is found accurately with the maximum lagged correlations, whereas the GLM found a broad area, which would not be informative to researchers in this case, i.e., the proposed method has a better specificity compared to the GLM. Furthermore, the identified voxels by our proposed method constitute more contiguous regions. Fig. 5 shows the voxels with $P<.05$ uncorrected for multiple testing when the fixed lags of 0, 2 and 4 for correlation are applied. When we controlled for multiple testing with, say, FDR, none of the voxels was detected as active. This would suggest that the active voxels based on the GLM and the proposed method might be false-positive (incorrectly identified as active).

Fig. 6 shows the lags, at which the maximum correlations are achieved in the voxels identified as active. The figure shows that many of the active voxels have a delay from three to five scans (equivalently, from 6 to 10 s). This emphasizes the importance of taking into account the delay effect in detecting active voxels.

5. Discussion

In this article, we propose a nonparametric method to identify brain areas which are active during an experimental stimulus/task. The method uses the lagged correlations between input stimulus and BOLD signals and tests their significance by permutation methods. The application to a finger-tapping experiment leads to the following observations. First, the proposed method based on maximum lagged correlations identifies contiguous active regions. Second, the identified brain areas by the proposed method were, on average, larger than active areas identified by cross-correlation of fixed lags=0, 2, 4 with the FDR

correction, but smaller than the active areas identified by the GLM with Gaussian random field theory. Third, lags that maximize the correlations (i.e., the delays) are of variable length across voxels. Therefore, a fixed lag, as is often used in fMRI, would not be appropriate. Proper accounting for such varying temporal delays is essential because methods using a fixed lag become too conservative to detect active voxels and result in a suboptimal detection.

The proposed method allows investigators to vary the time delay parameter across voxels to maximize the correlation. Making inferences regarding the task/stimuli-related brain activation is based on permutation methods. The IPM proposed here is efficient in that it permutes only the stimulus. The effect of multiple testing is controlled using the local FDR procedure suggested by Ref. [17]. The local FDR more adequately estimated the distribution of the lagged correlations under the null hypothesis (no activation) than the standard FDR. The local FDR accounts for the possible dependence between the multiple tests, which is important in lagged correlations as Fig. 3 shows. Finally, as a by-product of the proposed method, a voxel-wise hemodynamic delay map across the whole brain can also be generated. Such maps can provide quantitative information about the differences (between two or more regions or voxels) in hemodynamic delays corresponding to a particular task/stimulus. This will be informative as to how the task/stimulus activation might be delayed in different parts of the brain.

The goal of this article was to reliably and accurately estimate the task-induced signal changes. Independent component analysis (ICA), due to the simplicity and ease of use in available software applications like MELODIC and GIFT, is increasingly being applied in research. The nonparametric nature of this methodology gives researchers flexibility and provides estimates that are robust to the violations of typical model assumption as in the GLM. Yet, because of the lack of parameters for delays in activation, which might vary over the voxels, ICA can miss important effects. More importantly, since the cut-off value in ICA is set somewhat arbitrary, ICA does not provide the significance of levels for the activation nor does it control the FDR as our proposed method does. To summarize, the main contributions of this work are (i) a method for more accurate assessment of brain activation for task-based fMRI studies, which takes the delay into account, and (ii) controlling the FDR more effectively by accounting for the dependence among voxels.

As fMRI becomes more commonly used in clinical setting, patients with different diagnoses are routinely scanned under various tasks/stimuli. Individual activation maps are then obtained and can be used, for example, to evaluate differences between diagnostic groups. The assumption is that activation differences reflect underlying neural differences between the groups. It is, however, possible that, in some diseases, such as brain tumor, the differences in brain activation reflect altered brain vasculature, which would have an impact of length of delay, rather than neural changes. With the lagged correlation method, more comparable maps between the two groups can be obtained.

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Fig. 1.

Estimated density function of true null distribution (red) of the Z transformed MLCorr, empirical null distribution generated by block-wise permutations of different L 's ($=3, 6, 10, 15$; pink for $L=1$, blue for $L=10$) and one (black) by scan-wise permutation as ρ increases from 0.1 to 0.7. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

(A) Estimated density function of empirical null distribution of the Z-transformed MLCorr from nonactive voxels (red) and one from active voxels (blue). (B) Estimated density functions of empirical null distributions using nonactive voxels selected by different cut-off values of 0.10, 0.20, 0.25, 0.30 and 0.40. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3.

Histogram of Z -transformed MLCorr with superimposed $\hat{\kappa}$ (smooth red curve) and empirical mixture of three normals (smooth blue curve). Histogram shows that the empirical distributions of $z\hat{\kappa}$'s are far from the theoretic null distribution $\mathcal{N}(0,1)$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 4.
Comparison of results from MLCorr and GLM in slice no. 67: (A) GLM, (B) MLCorr analysis.

Fig. 5. Fixed lag analysis in slice no. 67 without FDR correction at the significance level of .05: (A) lag=0, (B) lag=2, (C) lag=4. Note that there is no active voxel detected with the FDR correction at the significance level of .05.

Fig. 6. (A) Delay map, (B) histogram of lags for active voxels: majority of voxels have lags of 3, 4 or 5 in scan.