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Double-wavelet Transform for Multi-subject Task-induced Functional Magnetic Resonance Imaging Data

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Summary:

The goal of this article is to model multi-subject task-induced fMRI response among predefined regions of interest (ROIs) of the human brain. Conventional approaches to fMRI analysis only take into account temporal correlations, but do not rigorously model the underlying spatial correlation due to the complexity of estimating and inverting the high dimensional spatio-temporal covariance matrix. Other spatio-temporal model approaches estimate the covariance matrix with the assumption of stationary time series, which is not always feasible. To address these limitations, we propose a double-wavelet approach for modeling the spatio-temporal brain process. Working with wavelet coefficients simplifies temporal and spatial covariance structure because under regularity conditions, wavelet coefficients are approximately uncorrelated. different wavelet functions were used to capture different correlation structures in the spatio-temporal model. The main advantages of the wavelet approach are that it is scalable and that it deals with non-stationarity in brain signals. Simulation studies showed that our method could reduce false positive and false negative rates by taking into account spatial and temporal correlations simultaneously. We also applied our method to fMRI data to study activation in pre-specified ROIs in the prefrontal cortex. Data analysis showed that the result using the double-wavelet approach was more consistent than the conventional approach when sample size decreased.

Keywords

Double-wavelet transform; Functional magnetic resonance imaging; multi-subject; spatio-temporal model

1. Introduction

Functional magnetic resonance imaging (fMRI) is a powerful tool for investigating *in vivo* function of the human brain due to its excellent spatial resolution (in mm^3) and reasonable

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⁸Supporting Information

Web Appendices referenced in Section 3.2, 4.2, and 6 and the codes to implement the double-wavelet model in simulation study and data analysis with readme are available at the Biometrics website on Wiley Online Library.

temporal resolution for capturing the evolution of the brain hemodynamic response. Typical fMRI data are generated by scanning the brain every few seconds. During each scan, the signal from the brain is measured on three-dimensional volume elements called voxels.

The conventional analysis of fMRI data (AV-GLM) first applies spatial smoothing on the data to increase the signal-to-noise ratio (SNR) after a series of preprocessing steps, e.g., motion correction, slice timing correction, and co-registration, estimates the parameters from the mean time series of each ROI while taking into account the temporal correlation, e.g., auto-regressive order one (AR(1)) structure, and then uses a simple t-test on the parameters of the model from multiple subjects (Worsley and Friston, 1995; Weiskopf et al., 2003; Huettel et al., 2004). This approach only takes into account the underlying temporal correlation and does not rigorously model the underlying spatial correlation. Dubin (1988) argued that ignoring spatial correlation in data led to smaller standard errors and more Type I errors.

Spatial smoothing and spatio-temporal modeling are two common approaches that account for spatial correlation in fMRI data analysis. Spatial smoothing using a Gaussian kernel was proposed by Worsley et al. (1996). Katanoda et al. (2002) proposed combining information from the six nearest neighboring voxels in the Fourier domain. Though these approaches increased the signal-to-noise ratio in fMRI data, they actually induce more spatial correlation, which may cause a higher error rate. Ombao et al. (2008) developed a spatio-spectral model using the Fourier bases to understand the underlying spatio-temporal processes. Kang et al. (2012) proposed a spatio-spectral mixed-effects model to estimate local and global spatial correlation. These approaches utilized the fact that the Fourier coefficients are approximately uncorrelated across frequencies. However, these approaches require temporal stationarity of the signals and the estimation and inversion of the covariance matrix, both of which are computationally expensive in fMRI data analysis.

Recently, Karaman et al. (2014) used linear operators during spatial and temporal preprocessing and reconstruction operations. Degras and Lindquist (2014) developed a spatio-temporal hierarchical model by estimating the hemodynamic response function (HRF) and voxel activation simultaneously. Lindquist et al. (2009); Zhang et al. (2012, 2013, 2014) proposed both parametric and semi-parametric estimation of the HRF. Although these methods relaxed the stationary time series assumption, they still require stationary spatial correlation across voxels. Hyun et al. (2014) proposed a Gaussian predictive process model using a three-stage estimation to model the spatial correlation and cross-correlation simultaneously. Furthermore, Hyun et al. (2016) applied the spatio-temporal Gaussian process on the longitudinal neuroimaging data. However, the key assumptions of the spatio-temporal Gaussian process must be rigorously validated.

The wavelet transform is a linear transformation. We start with wavelet bases consisting of orthonormal functions. The signal being analyzed is represented in terms of the selected bases. The wavelet coefficients are the inner product (cross-correlation) between the observed signal and each of the wavelet bases functions. Fan (2003) proved that the discrete wavelet transform (DWT) coefficients of both stationary and non-stationary signals were approximately uncorrelated as long as the lengths of the wavelet filter and signals were

sufficient. The wavelet transform was first introduced to fMRI analysis by Brammer (1998) and Ruttimann et al. (1998). Brammer (1998) proposed manipulating the wavelet coefficients in the spatial domain and reconstructing the original data to optimize the detection of activation. Ruttimann et al. (1998) discovered that the sum of the square of standardized wavelet coefficients had a χ^2 distribution. The brain signals were reconstructed using only wavelet coefficients with large magnitude (i.e., those that exceed a theoretically-derived threshold). Bullmore et al. (2003) introduced linear modeling in the wavelet domain to achieve diagonalization of the error covariance matrix by applying wavelet transform on each time series in fMRI data. However, they did not model the spatial correlation and used Bonferroni correction to find the voxel-level activation pattern. Long et al. (2004) performed spatio-temporal wavelet analysis for fMRI data by combining the wavelet transform with calculating the temporal noise parameters using iterative methods. To minimize approximation errors, Ville et al. (2004) proposed using two thresholds: one used before reconstruction and one after. Two thresholds, one in the wavelet domain and the other in the time domain, were simultaneously estimated to produce the reconstructed signal. Perhaps most closely related to the approach we developed, Aston et al. (2005) proposed estimating the model coefficients in the wavelet domain by applying one wavelet transform on the spatial data at each time point. However, their approach still required some linear temporal models to estimate the parameters in the time domain.

In this article, we develop a novel single level double-wavelet framework that takes into account the underlying spatial and temporal correlation in estimating the ROI-level activation patterns in multi-subject fMRI data analysis. Unlike other methods, even those that include wavelet-based methods that do not transform data twice, our approach does not require the estimation of either the spatial covariance matrix or the temporal covariance matrix. As a result, our approach is computationally less demanding. The double-wavelet approach combines the advantages of wavelet transform from Bullmore et al. (2003) and Aston et al. (2005) and reduces the computational burden in modeling the temporal and spatial correlations.

First, we apply one wavelet transform (spatial wavelet function) on the spatial data at each time point. Another wavelet transform (temporal wavelet function) is then applied to the time series of each spatial wavelet coefficient. In this paper, we investigate and validate our approach using a few ROIs. Different wavelet functions can be chosen to capture different correlation structures in the spatial and temporal data. The boxcar stimulus function convolved with the HRF is also transformed using the temporal wavelet function. All estimations and inferences were done using wavelet coefficients. It is worth noting that the order of the computation of the two wavelet transforms has no effect on the result since the wavelet transform is a linear transformation. The double-wavelet transform also simplifies the data structure, where four-dimensional (4-D) data were converted into two-dimensional (2-D) data. We examine the validity of our approach via simulation studies with different spatial correlation structures. Finally, we apply our approach to investigate higher cognitive control function in the anterior premotor cortex (prePMD), the lateral prefrontal cortex (PFC), and the primary visual cortex. The first two regions are expected to be associated with cognitive controls, while the last region serves as a negative control.

2. The Wavelet Transform

First, we introduce the wavelet transform. The wavelet families form a series of orthonormal bases for different dimensional data. Wavelet coefficients are obtained by the inner product of the observed data and wavelet functions which contain the zero-mean “mother” wavelet function and the unit-mean “father” wavelet function. All other wavelet functions are dilated and shifted from the mother and father wavelet functions. For simplicity, we only introduce the one-dimensional (1-D) and two-dimensional (2-D) wavelet transform in the methods and simulation sections.

2.1 One-Dimensional Wavelet Transform

Let $\Psi_{a,b}(x)$ and $\Phi_{a,b}(x)$, $a \in \mathbb{R} \setminus \{0\}$, $b \in \mathbb{R}$ be two families of functions defined as translations and re-scales of functions $\Psi(x)$ and $\Phi(x)$, where

$$\Psi_{a,b}(x) = \frac{1}{\sqrt{a}} \Psi\left(\frac{x-b}{a}\right), \quad \Phi_{a,b}(x) = \frac{1}{\sqrt{a}} \Phi\left(\frac{x-b}{a}\right)$$

The function $\Psi(x)$ is called the wavelet function or the mother wavelet function where $\int \Psi(x) dx = 0$ and $\int \Psi(x)^2 dx = 1$. The function $\Phi(x)$ is called the scaling function or the father wavelet function where $\int \Phi(x) dx = 1$.

For the discrete wavelet transform, we can select discrete values of a and b such that the transformation is invertible, where $a = 2^{-j}$, $b = k2^{-j}$, j indicates the scale, and k indicates the shift. More details can be found in Vidakovic (1999) and Nason (2008). In this paper, we only discuss the single level discrete wavelet transform (SL-DWT), where $j = 1$, $a = \frac{1}{2}$ and $b = \frac{k}{2}$. To simplify the notation, we denote $\varphi_{\omega}(x)$ for all scaled and shifted wavelet functions $\Psi_{a,b}(x)$ and $\Phi_{a,b}(x)$, where $\omega = 1, 2, \dots, \Omega$, and Ω is the total number of 1-D single level wavelet coefficients. different wavelet functions may have different Ω . Suppose we have a time series $g(x)$, the 1-D discrete wavelet transform of $g(x)$ can be expressed as

$$W_{\omega} = \sum_x g(x) \varphi_{\omega}(x)$$

where W_{ω} is a 1-D single level wavelet coefficient.

2.2 Two-Dimensional Wavelet Transform

Similar to the 1-D wavelet transform, we have a 2-D mother wavelet function $\Psi(x, y)$ such that $\int \int \Psi(x, y) dx dy = 0$, and $\int \int \Psi(x, y)^2 dx dy = 1$, and 2-D father wavelet function $\Phi(x, y)$ such that $\int \int \Phi(x, y) dx dy = 1$. Their scaled and shifted wavelet functions are

$$\begin{aligned} \Psi_{(a,b_1,b_2)}(x,y) &= \frac{1}{\sqrt{|a|}} \Psi\left(\frac{x-ab_1}{2}, \frac{y-ab_2}{a}\right) \\ \Phi_{(a,b_1,b_2)}(x,y) &= \frac{1}{\sqrt{|a|}} \Phi\left(\frac{x-ab_1}{2}, \frac{y-ab_2}{a}\right). \end{aligned}$$

For the discrete wavelet transform, we can select discrete values of a , b_1 and b_2 such that the transformation is invertible, where $a = 2^{-j}$, $b = k 2^{-j}$, j indicates the scale, k_1 and k_2 indicate the shift. We will only use single level wavelet coefficients where $j = 1$, $a = \frac{1}{2}$, $b_1 = \frac{k_1}{2}$, and $b_2 = \frac{k_2}{2}$. We can simplify the notation of all 2-D single level wavelet functions

$\Psi\left(\frac{1}{2}, \frac{k_1}{2}, \frac{k_2}{2}\right)^{(x,y)}$ and $\Phi\left(\frac{1}{2}, \frac{k_1}{2}, \frac{k_2}{2}\right)^{(x,y)}$ as $\phi_r(x, y)$, $r = 1, 2, \dots, R$, and R is the total number of

2-D single level wavelet coefficients. Let $\{\zeta\} = \{x, y\}$ represent all pairs of 2-D data coordinates. Suppose we have 2-D data $g(\zeta) = g(x, y)$, the 2-D discrete wavelet transform of $g(\zeta)$ can be expressed as

$$W_r = \sum_{\zeta} g(\zeta) \phi_r(\zeta)$$

where W_r is a 2-D single level wavelet coefficient. The wavelet transform in higher dimensions can be performed similarly.

3. Methods

3.1 Spatio-temporal Model

We now develop our model in more detail. Suppose that there are N subjects, P external stimuli, C ROIs and V_c voxels within the c -th ROI. Define the time series at voxel v in ROI c for subject n to be $Y_{ncv}(t)$, $t = 1, \dots, T$, where T is the length of time series. We define two functions $\pi_b(\cdot)$ and $\pi_d(\cdot)$ that generate valid covariance matrices. Let $\pi_b(\cdot)$ be a function of the Euclidean distance between voxels within an ROI, and $\pi_d(\cdot)$ is corresponding to the covariance function between ROIs, which does not depend on the Euclidean distance. Using the model described below, we would need to consider three different correlations: the spatial correlation between voxels within an ROI, the temporal correlation within a voxel over time, and the correlation between ROIs. Consider the following spatio-temporal model for the fMRI time series:

$$Y_{ncv}(t) = \sum_{p=1}^P \{\beta_{ncv}^p X^p(t)\} + \epsilon_{ncv}(t), \text{ where} \quad (1)$$

$$\beta_{ncv}^p = \beta_c^p + b_{ncv}^p$$

$$\epsilon_{ncv}(t) = d_{nc} + e_{ncv}(t)$$

- $X^p(t)$ is the expected BOLD response corresponding to the p^{th} stimulus, which is formally the convolution between the hemodynamic response function (HRF) and the p^{th} impulse function. The HRF is the expected neuronal activation function given a stimulus.

- β_c^p is the ROI-specific activation level fixed effect due to stimulus p ;
- b_{ncv}^p is a zero-mean voxel-specific random effect that accounts for the spatial covariance between voxels v and v' within ROI c for subject n , where

$$\text{Cov}(b_{ncv}, b_{n'c'v'}) = \begin{cases} \pi_b(\|v - v'\|), & \text{when } c = c', n = n', \\ 0 & \text{otherwise.} \end{cases} \quad (2)$$

- $\epsilon_{ncv}(t)$ is the noise that accounts for the voxel-specific temporal correlation. d_{nc} is a zero-mean ROI-specific random effect with a covariance structure $\text{Cov}(d_c, d_{c'}) = \pi_d(c, c')$ that is used to model the correlation between ROIs. $e_{ncv}(t)$ is the temporal error that is assumed to follow an AR(1) process.

To test whether ROI c is activated when the p^{th} stimulus is presented, we are interested in the hypothesis:

$$H_0: \beta_c^p - \beta_c^1 = 0 \quad (3)$$

where β_c^1 indicates the baseline condition at ROI c .

3.2 Double-Wavelet Transform

The main idea of the double-wavelet transform is to first apply the 2-D/3-D wavelet transform on the spatial image/volume data at each time point, then apply the 1-D wavelet transform on the time series of each wavelet coefficient in the previous step. We also apply the 1-D wavelet transform on the stimulus function. Then we build all models and analyses using the double-wavelet coefficients instead of the original data. For simplicity, we assume our data at each time point are two dimensional and we use the 2-D wavelet transform here.

In this paper, we used equation (1) to generate the data for our simulation study. We did not use it to model the spatio-temporal correlation for double wavelet approach, which did not require modeling the spatio-temporal correlation. We applied wavelet transform on both sides of equation (1), resulting in equation (4) for double wavelet approach. First we apply the 2-D discrete wavelet transform on the data at each time point. Assume that $\phi_r(v)$ are families of one specific 2-D wavelet transform function, then for ROI c , we have

$$U_{ncr}(t) = \sum_v Y_{ncv}(t) \phi_r(v) = \sum_{p=1}^P \lambda_{ncr}^p X^p(t) + e_{ncv}(t) \text{ where}$$

$r = 1, 2, \dots, R$, and R is the total number of 2-D wavelet coefficients at each time point.

$\lambda_{ncr}^p = \sum_v \beta_{ncv}^p \phi_r(v)$ is the 2-D wavelet coefficient by applying the 2-D wavelet transform on the spatially dependent parameter β_{ncv}^p in ROI c for subject n .

Secondly, we apply the 1-D wavelet transform on the time series of each 2-D wavelet coefficient $U_{ncr}(t)$. Assume that $\varphi_{\omega}(t)$ are families of one specific 1-D wavelet transform function, then we have

$$W_{ncr\omega} = \sum_t U_{ncr}(t) \varphi_{\omega}(t) = \sum_{p=1}^P \lambda_{ncr}^p V_{\omega}^p + \delta_{ncr\omega} \quad \text{where} \quad (4)$$

$\omega = 1, 2, \dots, \Omega$, and Ω is the total number of 1-D wavelet coefficients for the time series of each 2-D wavelet coefficient. $V_{\omega}^p = \sum_t X^p(t) \varphi_{\omega}(t)$ is the 1-D wavelet coefficients by applying the 1-D wavelet transform on the stimulus function $X^p(t)$. $\delta_{ncr\omega} = \sum_t \epsilon_{ncr}(t) \varphi_{\omega}(t)$ is the 1-D wavelet coefficients by applying the 1-D wavelet transform on the time dependent error term $\epsilon_{ncr}(t)$ at the 2-D wavelet coefficient r in ROI c for subject n . An example of the double-wavelet coefficients $W_{ncr\omega}$ in ROI c for subject n of an activated ROI ($\beta^1 - \beta^2 > 0$, equivalently $\lambda^1 - \lambda^2 > 0$ in equation (4)) in simulation is illustrated in Figure 1(a). After the double-wavelet transform, all $\delta_{ncr\omega}$ are approximately uncorrelated, as long as the two wavelet filters are long enough (Fan, 2003). We indirectly assessed how much of the temporal correlation in the data would be reduced with the wavelet transform via estimating AR(1) parameters before and after the transform in simulation study. Additional supporting information may be found online in the Supporting Information section at the end of the article.

3.3 Denoising

The wavelet transform naturally decomposes data into different scales. Each scale corresponds to different frequency bands for both spatial and temporal data. The single level discrete wavelet transform (SL-DWT) decomposes data into two frequency bands at each dimension. For example, a 1-D signal would be transformed into wavelet coefficients indicating information from one high frequency band and one low frequency band by SLDWT. A 2-D image would be decomposed into high and low frequency bands on both vertical and horizontal directions by SL-DWT, which results into four parts, a low-low (horizontal-vertical) frequency band (LL), a low-high (horizontal-vertical) frequency band (LH), a high-low (horizontal-vertical) frequency band (HL), and a high-high (horizontal-vertical) frequency band (HH). For subject n at ROI c , $W_{ncr\omega}$ in equation (4) would have the same shape as in Figure 1(b), where S indicates the wavelet coefficients from the 2-D wavelet transform on the spatial data and T indicates the wavelet coefficients from the 1-D wavelet transform on the temporal data.

Figure 2 shows that when the AR(1) parameter is greater than 0.5, more than 90% of the wavelet periodograms were contained in the $S_{LL} \cdot T_L$ part, which included 1/8 of the original data. The data in $S_{LL} \cdot T_L$ were the double-wavelet coefficients from the father wavelet (low-pass filter) in both time domain and spatial domain. The double-wavelet coefficients other than $S_{LL} \cdot T_L$ were the wavelet coefficients passing at least one high-pass filter in time domain or spatial domain. To remove this noise from the data, we simply excluded the wavelet coefficients not in the $S_{LL} \cdot T_L$ part when estimating parameters; we only used the

double-wavelet coefficients in the $S_{LL} \cdot T_L$ part, where $r = 1, 2, \dots, R/4$ and $\omega = 1, 2, \dots, \Omega/2$.

3.4 Estimation

First, we define some notations. We define $N_q(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ as multi-variate normal distribution with $q \times 1$ mean vector $\boldsymbol{\mu}$, and covariance matrix $\boldsymbol{\Sigma}$, and denote the $q \times q$ identity matrix by $\mathbf{I}_q$

We can rewrite equation (4) in matrix notation, we have

$$\mathbf{W}_{ncr} = \mathbf{V}^T \boldsymbol{\lambda}_{ncr} + \boldsymbol{\delta}_{ncr}, \text{ where } (5)$$

- $\mathbf{W}_{ncr} = [W_{ncr1}, W_{ncr2}, \dots, W_{ncr(\Omega/2)}]^T$ is a $\Omega/2 \times 1$ vector, which are the double-wavelet coefficients in the $S_{LL} \cdot T_L$ part by performing double-wavelet transform on data Y_{ncv} for subject n in ROI c . We assume that $\mathbf{W}_{ncr} \sim N_{\Omega/2}(\mathbf{V}^T \boldsymbol{\lambda}_{ncr}, \text{Cov}(\boldsymbol{\delta}_{ncr}))$

$$\mathbf{V} = \begin{bmatrix} \mathbf{v}^1 \\ \mathbf{v}^2 \\ \dots \\ \mathbf{v}^P \end{bmatrix} = \begin{bmatrix} v_1^1 & v_2^1 & v_3^1 & \dots & v_{\Omega/2}^1 \\ v_1^2 & v_2^2 & v_3^2 & \dots & v_{\Omega/2}^2 \\ \dots & \dots & \dots & \dots & \dots \\ v_1^P & v_2^P & v_3^P & \dots & v_{\Omega/2}^P \end{bmatrix}_{P \times \Omega/2}$$

where $\mathbf{V}$ is a $P \times \Omega/2$ matrix, in which elements are the 1-D wavelet coefficients by performing 1-D wavelet transform on $X^p(t)$ corresponding the p^{th} stimulus function;

- $\boldsymbol{\lambda}_{ncr} = [\lambda_{ncr}^1, \lambda_{ncr}^2, \dots, \lambda_{ncr}^P]^T$ is a $P \times 1$ vector, consisting of the 2-D wavelet coefficients by performing 2-D wavelet transform on the β_{ncv}^p ;
- $\boldsymbol{\delta}_{ncr} = [\delta_{ncr1}, \delta_{ncr2}, \dots, \delta_{ncr(\Omega/2)}]^T$ is a $\Omega/2 \times 1$ vector, consisting of the 1-D wavelet coefficients by performing 1-D wavelet transform on the error term $\boldsymbol{\epsilon}_{ncv}$, and $\boldsymbol{\delta}_{ncr} \sim N_{\Omega/2}(0, \sigma^2 \mathbf{I}_{\Omega/2})$, where σ^2 is the variance of the wavelet coefficients $\boldsymbol{\delta}_{ncr}$.

Then, we estimate $\hat{\boldsymbol{\lambda}}_{ncr}$ by using the ordinary least squares estimator

$$\hat{\boldsymbol{\lambda}}_{ncr} = (\mathbf{V}\mathbf{V}^T)^{-1} \mathbf{V}\mathbf{W}_{ncr}$$

The boxcar stimuli are orthogonal to each other in task-induced fMRI data, which means $\mathbf{X}^{p'} \cdot (\mathbf{X}^p)^T = 0$ when $p \neq p'$, then

$$\mathbf{V}^{p'} \cdot (\mathbf{V}^p)^T = \{\phi(x)\mathbf{X}^{p'}\} \{\phi(x)\mathbf{X}^p\}^T = \phi(x)\mathbf{X}^{p'}(\mathbf{X}^p)^T \phi(x)^T$$

where $\phi(x) = [\phi_1(x) \ \phi_2(x) \ \dots \ \phi_{\Omega/2}(x)]$ and $\phi_k(x)$, $k = 1, 2, \dots, \Omega/2$ are wavelet functions. Then we have $V^{p'} \cdot (V^p)^T = 0$ and $(VV^T)^{-1}$ is a diagonal matrix.

A simple t-test is used on a linear contrast of λ_{ncr} based on multi-subject data. Since there is a one-to-one relationship between β_{ncv}^p and λ_{ncr}^p , the hypothesis in equation (3) is equivalent to

$$H_0: \lambda_c^p - \lambda_c^1 = 0$$

where λ_c^1 is the mean of the estimator λ_{ncr}^1 and λ_c^p is the mean of the estimator λ_{ncr}^p across subjects for ROI c using double-wavelet coefficients in the $S_{LL} \cdot T_L$ part as discussed in Section 3.3.

4. Simulation Study

We explored and validated our approach via simulation studies. We generated multi-subject spatially and temporally correlated data. Then, we compared our double-wavelet (DW) approach with the conventional AV-GLM approach in terms of false positive and false negative rates at each ROI.

4.1 Data Generation

In the simulation, we generated data using the spatio-temporal model (1) in Section 3.1. For the sake of simplicity, we assumed that there were only two ROIs. One ROI was assumed to be a null ROI ($\beta^2 - \beta^1 = 0$) and the other ROI was assumed to be a non-null ROI ($\beta^2 - \beta^1 \neq 0$). We varied the effect size ($\beta^2 - \beta^1$) from 0 to 1. The correlation between ROIs was 0.2. Between three and fifteen subjects were used in the analysis.

Each ROI contained 100 voxels (10×10). At each voxel, spatially and temporally correlated time series with $T = 128$ were generated using AR(1) structure with the variance of white noise 1. The parameter of AR(1) model was 0.6. Two boxcar external stimuli were used to generate each signal. The HRF we used to generate data in simulation was estimated by inverse logit (IL) model (Lindquist et al., 2009) using the data in Section 5.

We considered three different spatial correlations. First we assumed all voxels were independent within an ROI, where $\pi_b(\cdot) = 0$ in equation (2). Secondly, we assumed that $\pi_b(\cdot)$ was an exponential covariance function with the decaying parameter 2. Thirdly, we assumed that all observations were the same across voxels, meaning that all voxels were highly correlated with one another. All results were based on 500 repetitions for each simulation scenario.

4.2 Estimation and Results

We tried 54 different wavelet functions in the MATLAB (MathWorks, Natick, MA) wavelet toolbox for both 2-D wavelet transform and 1-D wavelet transform. There were a total of

2916 (54×54) combinations of the double-wavelet transform. We present the result of some combinations of the double-wavelet transform in this section.

Figure 3 shows the Type I errors and the Type II errors for the double-wavelet and AV-GLM approach based on 12 subjects under three different spatial correlations when the effect size ($\beta^1 - \beta^2$) was 0.6. When all voxels were uncorrelated, some combinations of the double-wavelet transform have more Type I errors than the AV-GLM approach and others have fewer. When the spatial correlations among voxels were based on the exponential covariance function, all combinations of the double-wavelet transform have fewer Type I errors than the AV-GLM approach. The AV-GLM approach produces the fewest Type I errors when all voxels were identical. The Type II error using double-wavelet and AV-GLM approach were similar under all three different spatial correlations.

Figure 4 shows the Type I and Type II errors for the double-wavelet and AV-GLM approach based on 12 subjects when the effect size ($\beta_1 - \beta_2$) changed from 0.2 to 1 and the spatial correlations among voxels were based on the exponential covariance function. The AVGLM approach usually has the most Type I errors when effect size changes. There were no differences between the two methods in terms of Type II errors when the effect size is greater than 0.3. When all voxels were uncorrelated or identical, there were no difference between the two methods. It is worth noting that uncorrelated and identical voxels are based on two extreme scenarios and not realistic, whereas the spatial correlation based on exponential covariance function is more plausible. Details about more simulation results can be found in Supporting Information.

The simulation studies showed that the double-wavelet approach outperformed the AV-GLM approach when the spatial correlations among voxels were based on the exponential covariance function. The double-wavelet approach outperformed the AV-GLM approach in our simulation, partly because it did not require two assumptions. The AV-GLM approach assumed (1) that the mean time series of each ROI had AR(1) structure and (2) that all voxels were uncorrelated by not rigorously modeling the underlying spatial correlations in estimating model parameters. These two assumptions used in our simulation studies can be violated in common fMRI data analysis.

5. Data Analysis

We applied our proposed double-wavelet transform approach to a study designed to test cognitive control related activation in the prefrontal cortex (PFC) of the human brain. Here we describe the background, motivation, study design and data.

In a previous study (e.g., Badre and D'Esposito, 2007; Long and Badre, 2009), the anterior premotor cortex (prePMd) was activated in an experimental situation. Fifteen healthy subjects (ten women), right-handed, aged 18 – 25 years, were recruited in the study. No subjects reported any history of a neurological or psychiatric disorder. During the experiment, each participant first selected one of two perceptual dimensions (i.e., shape or texture) of a stimulus and then selected a response. All participants were trained to press one of four buttons while seeing four stimulus shapes and four stimulus textures (e.g., webbed,

streaked). Since the response sets associated with shape and texture overlap, the participant needed to first select whether shape or texture was the relevant cue dimension to make a correct response. Participants also needed to link two colors with the texture dimension and two colors with the shape dimension. In the experiment, they would see a shape with a particular texture within a colored box. They would choose one of the four buttons based on the color of the box and the associations they learned for shape or for texture.

For a given block of trials, participants would be cued either one dimension (D1) or two dimensions (D2). On D2 blocks, they were required to select the relevant dimension based on color. On D1 blocks, minimal cognitive control was required because the same dimension was always relevant. Based on prior studies (Badre and D'Esposito, 2007; Badre et al., 2009), prePMd should be activated with the contrast of $D2 > D1$. We defined this as ROI 1. Regions rostral to prePMd (e.g., lateral frontal cortex, Brodmann area 9/46) were suggested to have less activation by this specific control demand by hierarchical theories of rostro-caudal frontal organization. These regions were more involved in more abstract control (Koechlin et al., 2003; Badre, 2008). One region rostral to prePMd in lateral PFC was associated with higher order control (e.g., Badre and D'Esposito, 2007). We defined this as ROI 2. We also defined an ROI in the primary visual cortex (ROI 3) whose D2 versus D1 contrast should not be different in low-level perceptual demands. This ROI 3 was not expected to show activation. The three ROIs were illustrated in Figure 5, where ROI 1, ROI 2, and ROI 3 were denoted by colored boxes in each axial slice of the brain image. Their x-, y-, and z-coordinates in the brain were also included, where the origin was at the center of the brain.

There were 144 trials (2 sec/trial) for each dimension condition (D1, D2). The inter-trial interval was 0 – 8 sec. Six scanning runs (4 min/run) contained 48 trials each. Each run had 4 blocks (12 trials/block), which followed an ABBA format for dimension type (e.g., D1, D2, D2, D1). The subject's order of dimension conditions were counterbalanced.

Functional images were acquired using a gradient-echo echo-planar sequence (TR = 2 sec; TE = 30 msec; flip angle = 90; 33 axial slices, $3 \times 3 \times 3.5$ mm) on the Siemens 3T TIM Trio MRI system at the Brown University MRI Research Facility. High-resolution T1-weighted (MP-RAGE) anatomical images were collected (TR = 1900 msec; TE = 2.98 sec; flip angle = 9; 160 sagittal slices, $1 \times 1 \times 1$ mm) after each run. Participants would see visual stimuli through a mirror attached to a matrix eight-channel head coil.

Data were preprocessed and analyzed using SPM12 and MATLAB (MathWorks, Natick, MA). To correct for differences in slice acquisition timing, all images of slice in time were resampled to match the first slice. Images were then motion corrected and normalized to Montreal Neurological Institute stereotaxic space, and spatially smoothed for the AV-GLM approach (FWHM=4) but not for the double-wavelet approach.

We applied the 3-D wavelet transform using the Db3 wavelet on the volume of the brain at each time point, and then applied the 1-D wavelet transform using the Sym8 wavelet on the time series of each 3-D wavelet coefficient. We had three stimuli: D1, D2, and the instruction period (IP). The three stimuli were convolved with the estimated HRF described

in Section 4.1 and then transformed using the 1-D Sym8 wavelet, which were denoted by V_{D1} , V_{D2} and V_{DIP} . We then applied equation (5) to the data collected from 15 subjects to see if we could find any activated ROI(s) among the three given ROIs. Each ROI contained 343 ($7 \times 7 \times 7$) voxels. The corresponding regression coefficients were λ_c^{D1} , λ_c^{D2} and λ_c^{DIP} in ROI c , where $c \in \{1, 2, 3\}$. $\lambda_c^{D2} - \lambda_c^{D1}$ was of primary interest to test the hypothesis $H_0: \lambda_c^{D2} - \lambda_c^{D1} > 0$ which was equivalent to $H_0: \beta_c^{D2} - \beta_c^{D1} > 0$ in equation (1). Given the point estimates of $\lambda_c^{D2} - \lambda_c^{D1}$ at each ROI for each subject, p-values were computed based on a t-test. To manage the multiple comparisons, we controlled the False Discovery Rate (FDR) at 0.05 level.

To see which method was more robust when sample size decreased, we compared the results using a different number of subjects to the result using all 15 subjects for each ROI. A full description of this approach, called data decimation, can be found in Yang et al. (2010). We calculated the rejection rates based on all possible combinations of different subjects. For example, the rejection rate at 6 subjects was based on $C(15, 6) = 5005$ tests. The rejection rates are illustrated in Figure 6. We defined the rejection rate as the *correct* rejection rate if the test was rejected using all 15 subjects. Otherwise, the rejection rate was called the *incorrect* rejection rate. For ROI 1 and ROI 2, the *correct* rejection rates went up when the number of subjects increased. For ROI 3, the *incorrect* rejection rates went down when the number of subjects increased, as we expected to see no difference between D2 versus D1 contrast. For ROI 1, the DW approach had slightly lower *correct* rejection rates (82.6% and 92.7%) than the AV-GLM approach (85.5% and 94.7%) for 3 and 4 subjects. For ROI 2, the DW approach had slightly lower *correct* rejection rates (94.1% and 99.4%) than the AV-GLM approach (97.4% and 99.9%) for 3 and 4 subjects. For ROI 3, the DW approach had much smaller *incorrect* rejection rates (9.7%, 4.2%, 1.5% and 0.5%) than the AV-GLM approach (20.4%, 10.3%, 7.1% and 4.9%) for 3, 5, 7 and 9 subjects. After 10 subjects, there was no difference between the two methods for all three ROIs.

These results were consistent with our claim supported via simulation studies in Figure 4. When the voxel-level spatial correlation was based on the exponential covariance function, the DW approach outperformed the AV-GLM approach in terms of the Type I errors, while the Type II errors resulting from the two methods were similar. We can conclude that ignoring the underlying spatial correlation in fMRI data results in misleading scientific findings for a small sample size by potentially underestimating the variance of estimators of interest, as shown in Dubin (1988).

6. Conclusion

In this article, we proposed a double-wavelet transform approach, where we transformed the data twice using different wavelet functions. The stimulus functions were also transformed into a wavelet domain. The advantages of our wavelet model over existing models are as follows. First, we took into account the spatial-temporal correlation in fMRI data by transforming the data twice. Second, stationary assumptions on both spatial and temporal data were not required using the double-wavelet transform. Third, our approach did not

require the estimation and inversion of the covariance matrix because wavelet coefficients were approximately uncorrelated, which significantly reduced the computational burden in the fMRI data analysis. Fourth, the double-wavelet transform converted 4-D data into 2-D data, which simplified the fMRI data structure.

In simulation, we suggested using the Daubechies 3 wavelet on the spatial data and the Symlets 8 wavelet on the temporal data. When there were two ROIs, we found that the DW approach outperformed the AV-GLM approach when there existed underlying spatial correlation. We found the similar results with six ROIs, as illustrated in Supporting Information. In the data analysis, we used data decimation to show that the results using the DW approach were less sensitive to a decrease in sample size, compared to the AV-GLM approach. These results were consistent with our simulation study, meaning that the DW approach made fewer mistakes than the conventional AV-GLM approach by properly taking into account the spatio-temporal correlation for a small sample size.

One limitation of our approach is that it requires ROIs to be cubic or rectangular. However irregular ROIs can be transformed into rectangular to perform the double wavelet approach. The other limitation of our approach is that we only investigate single level discrete wavelet transform (SL-DWT). More levels can be used to further improve the signal-to-noise ratio and model performance. In practice, data decimation can be employed as an objective tool of selecting the optimal combination of wavelet functions to apply the double-wavelet model to analyze task-induced fMRI data. The inference based on the chosen wavelet combination is expected to be most insensitive to a decrease in sample size.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(a) Example of double-wavelet coefficients

(b) Double-wavelet coefficient structure

Figure 1.

The double-wavelet coefficient structure. (a) is an example using the Daubechies 3 wavelet (spatial wavelet function) and the Symlet 8 wavelet (temporal wavelet function) on an activated 3-D ROI data ($\beta^1 - \beta^2 > 0$) in simulation (2-D in spatial domain and 1-D in temporal domain). (b): S_{LL} , S_{LH} , S_{HL} and S_{HH} represent the wavelet coefficients from the 2-D wavelet transform on the spatial data in low-low (horizontal-vertical) frequency band (LL), low-high (horizontal-vertical) frequency band (LH), high-low (horizontal-vertical) frequency band (HL), and high-high (horizontal-vertical) frequency band (HH) respectively; T_L and T_H represent the wavelet coefficients from the 1-D wavelet transform on the temporal data in low and high frequency band respectively.

Figure 2.

The wavelet periodograms of different double-wavelet coefficient parts using simulated data when the AR(1) parameter varies from 0 to 1.

Figure 3.

Type I and Type II errors for the double-wavelet and AV-GLM approach based on 12 subjects with different spatial correlation structures, when the effect size ($\beta^1 - \beta^2$) was 0.6 and the correlation between the two ROIs was 0.

Figure 4.

Type I and Type II errors for the DW and AV-GLM approach based on 12 subjects with different effect size ($\beta^1 - \beta^2$), when the spatial correlations among voxels were based on the exponential covariance function.

Figure 5.

Colored boxes on the axial slices of the brain illustrate the location of three ROIs: the red box indicates ROI 1, the blue box indicates ROI 2 and the green box indicates ROI3; their coordinates are also included: (a) ROI 1 $(-40,4,3)$, (b) ROI 2 $(-42,28,24)$, (c) ROI 3 $(14,-100,0)$.

Figure 6.

Rejection rates for ROI 1, ROI 2 and ROI 3 using different numbers of subjects for the DW and AV-GLM approach.