Original contributions

Improvement of spectral density-based activation detection of event-related fMRI data

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Abstract

For event-related data obtained from an experimental paradigm with a periodic design, spectral density at the fundamental frequency of the paradigm has been used as a template-free activation detection measure. In this article, we build and expand upon this detection measure to create an improved, integrated measure. Such an integrated measure linearly combines information contained in the spectral densities at the fundamental frequency as well as the harmonics of the paradigm and in a spatial correlation function characterizing the degree of co-activation among neighboring voxels. Several figures of merit are described and used to find appropriate values for the coefficients in the linear combination. Using receiver-operating characteristic analysis on simulated functional magnetic resonance imaging (fMRI) data sets, we quantify and validate the improved performance of the integrated measure over the spectral density measure based on the fundamental frequency as well as over some other popular template-free data analysis methods. We then demonstrate the application of the new method on an experimental fMRI data set. Finally, several extensions to this work are suggested.

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1. Introduction

The predominant mode of experimental design for studying brain functions in functional magnetic resonance imaging (fMRI) is the block design, in which the subject alternates back and forth between a control condition and a task condition. Applying standard statistical analysis such as the t test on the resultant data gives us a steady-state view of the neuronal response [1,2]. An alternative mode of experimental design is the event-related fMRI experiment, in which the subject performs a single instance of a task in each epoch while the corresponding transient response is recorded. This approach allows time-resolved measurements of brain activities, enabling the extraction of information regarding transient neuronal events [3–6]. A disadvantage with event-related fMRI experiments is the inherent low signal-to-noise ratio of the resultant data. This can be partially solved by collecting data with repeated epochs and average across these epochs. The detection of neuronal activation in the averaged event-related fMRI data however is still nontrivial because the amplitude of the response is usually small and its precise temporal profile is often unknown [7–10]. As a result, template-based techniques such as cross correlation analysis, which depend on explicit assumption regarding the activation time course, are oftentimes not suitable for these studies. The analysis of event-related fMRI experiments can be greatly facilitated with template-free techniques.

Some examples of template-free methods for fMRI data analysis are (i) cluster analysis techniques using K-means, self-organizing mapping or graph-theoretical approaches, which group voxels into clusters based upon the similarity of their time courses [11–17]; (ii) principal and independent component analyses, which partition the data into orthogonal and independent spatial components respectively [18–22]
and (iii) manifold learning methods, which extract intrinsic low dimensional embedding from high dimensional fMRI data for visualization and further analysis [23,24]. For an event-related experiment with a periodic experimental design, spectral-density based method is a natural choice and has been investigated by a number of researchers [25–29]. In particular, spectral density of the voxel time courses at the fundamental frequency of the periodic experimental paradigm has been used to discriminate between activated and non-activated voxels [26]. In this article, we seek to improve the detection ability of the basic spectral density based method by adding information from the spectral densities at the harmonics of the paradigm and from a spatial correlation measure. This results in a new activation detection measure which is a linear combination of the spectral density of the voxel time course and (iii) subsequently, a spatial correlation measure. This results in a new activation detection measure based on the spatial correlation of a voxel with its neighbors is described; (iii) then, we use the results: canceling out the task related effects, and then concatenating subtracting the adjacent epoch time courses, thereby null fMRI data set described in [26], the degree of task/stimulus-related activation in voxel v can be estimated by evaluating the spectral density of the time course v at frequency f_k,  

\[ C_k(v) = \sum_{j=0}^{MT-1} c_j(v)e^{2\pi j\frac{m}{MT}} \]  

(2)

with \( c_j(v) \equiv x_m(v), \) \( j=(m-1)T+t, \) \( i=\sqrt{-1}, \) \( m\in\{1,2,...,M\}, \) \( r\in\{0,1,...,T-1\}, \) and the term MT is the number of time points in \( \bar{x}(v) \). The periodogram estimate of the spectral density of the time course \( \bar{x}(v) \) at frequency \( f_k \) is simply

\[ P(f_k(v)) = \frac{1}{(MT)^2} \left\{ \left| C_k(v) \right|^2 + \left| C_{MT-k}(v) \right|^2 \right\} \]  

(3)

where \( f_k = \frac{k}{MT} \) and \( \Delta = \) the TR of the MRI data.

For the data set given in Eq. (1), \( P(f_M(v)) \) (ie, setting \( k=M \) in Eq. (3) leading to \( f_M = (T\Delta)^{-1} \), where \( T\Delta \) is simply the time duration of an epoch) yields the spectral density of the time course \( \bar{x}(v) \) at the fundamental frequency. We can apply \( P(f_M) \) over all the brain voxels to create a statistical map. To determine the activated regions, the null distribution associated with \( P(f_M) \) is also needed, so that a proper threshold corresponding to a desired \( p \) value can be set. Then, voxels with their respective \( P(f_M) \) values above the threshold are declared active. 

2.2. Creating the empirical null and activation histograms

While the null distribution mentioned in the previous subsection could be theoretically derived if the correct model describing the baseline is known, we can bypass this theoretical issue by performing the following computationally intensive manipulation of the fMRI data: we first create a null fMRI data set from the data set given in Eq. (1) by subtracting the adjacent epoch time courses, thereby canceling out the task related effects, and then concatenating the results:

\[ \bar{x}^{null}(v) = [x_1^{null}(v); x_2^{null}(v); \ldots; x_M^{null}(v)] \]  

(4.1)

where \( x_m^{null}(v) = [x_m,0(v)x_m,1(v)\ldots x_m,T-1(v)] \) for each brain voxel v. Here, \( \bar{x}_m(v) \) is the mth epoch time course for voxel v, with \( x_m(v) \) being the voxel signal intensity at time point t of epoch m, and T being the total number of time points in an epoch. Thus, \( \bar{x}(v) \) is a time course with \( M\times T \) time points. As described in [26], the degree of task/stimulus-related activation in voxel v can be estimated by evaluating the spectral density of that voxel’s time course at the fundamental frequency of the experimental paradigm. Specifically, we compute the discrete Fourier transform of the time course \( \bar{x}(v) \):

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(3)

where \( f_k = \frac{k}{MT} \) and \( \Delta = \) the TR of the MRI data.
\[ Y_{x \text{act}}^m(v) = \frac{[x_{2m}(v) + x_{2m-1}(v)]}{2} \]

where \( x_{m,t}^\text{act}(v) \) is the time course for voxel \( v \) having \( T \) time points and \( x_{m,0}^\text{act}(v) \) is the complete time course for voxel \( v \) having \( MT/2 \) time points. Analogous to Eq. (2), applying the discrete Fourier transform to the time course \( Y_{x \text{act}}^m(v) \) from Eq. (5.1) yields

\[
C_{k}^{\text{act}}(v) = \sum_{j=0}^{\frac{MT}{2}-1} c_{j}^{\text{act}}(v)e^{2\pi jkT/MT}
\]

with \( c_{j}^{\text{act}}(v) = x_{m,t}^\text{act}(v), j=(m-1)T+t, m \in \{1,2,\ldots,M/2\}, t \in \{0,1,\ldots,T-1\}, \) and the term \( MT/2 \) is the number of time points.

Note that unlike the null data set, the task-related effects are preserved in the activation data. The idea of performing pairing and subtraction has been used in processing fMRI [30] and ERP data [31,32]. Referring to Eqs. (5.1) and (5.2), the resulting voxel time courses in the activation data set can be regarded as comprising of \( M/2 \) epochs, with the \( m \)th epoch time course having \( T \) time points and the complete time course having \( MT/2 \) time points.

**Fig. 1.** Generation of activation maps using the null and activation histograms. Simulated fMRI data were generated by superimposing artificial activations at predetermined spatial locations onto a baseline fMRI data set. (The procedure is detailed in the “Using simulated and experimental fMRI data to evaluate the activation detection measures” subsection.) Panel (A) shows the histogram for the detection measure \( P(f_{M/2}^\text{act}) \) applied on the activation data set, while (B) depicts the corresponding null histogram. In these plots, the horizontal axis indicates the value of the detection measure and the vertical axis indicates the counts. Based on the null histogram in (B), a \( \rho \) value of .05 corresponds to a detection threshold of 179.3, yielding the vertical line in (B) and duplicated on (A). In (A), 451 voxels surpass the threshold. Panel (C) shows the resultant activation map. Panels (D), (E) and (F) are the analogous diagrams for activation detection based on the spectral density at the first harmonic. The same \( \rho \) value of .05 is applied, yielding a detection threshold of 133.6 [the vertical line in (E) and duplicated on (D)], and creating the activation map in Panel (F).
points in $\mathbf{x}^\text{act}(v)$. Analogous to Eq. (3), the periodogram estimate of the spectral density of the time course $\mathbf{x}^\text{act}(v)$ at frequency $f_k^\text{act}$ is

$$P(f_k^\text{act}(v)) = \frac{1}{(MT/2)^2} \left\{ |C_k^\text{act}(v)|^2 + |C_{MT/2-k}^\text{act}(v)|^2 \right\}$$  (7)

where $f_k^\text{act} = \frac{k}{(MT/2)\Delta}$ and $\Delta$ = the TR of the fMRI data.

For the activation data set obtained from Eq. (5.1), $P(f_k^\text{act}(v))$ [i.e., setting $k=M/2$ in Eq. (7) leading to $f_k^\text{act} = (T\Delta)^{-1}$, where $T\Delta$ is again the time duration of one epoch] gives the spectral density of the time course $\mathbf{x}^\text{act}(v)$ at the fundamental frequency. Applying the detection measure $P(f_{M/2}^\text{act})$ to the activation data set over all the brain voxels yields a statistical map.

To determine a proper threshold for $P(f_{M/2}^\text{act})$ so that we can identify activated voxels, we utilize the null data set obtained from Eq. (4.1) to generate the null distribution associated with $P(f_{M/2}^\text{act})$. The procedure is as follows: First, in analogy to Eq. (6), we apply discrete Fourier transform to the time course $\mathbf{x}(v)$ from Eq. (4.1) to get

$$C_{kJ}^\text{null}(v) = \sum_{j=0}^{\frac{M}{2}-1} c_{j}^\text{null}(v)e^{2\pi i j \Delta / (MT/2)}$$  (8)

where $c_{j}^\text{null}(v) = \mathbf{x}_{n}^\text{null}(v)$, $j=(m-1)T+t$, $m\in\{1,2,..,M/2\}$ and $t\in\{0,1,..,T-1\}$. Second, analogous to Eq. (7), the

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**Fig. 2.** The flowchart of the activation detection method. Box A indicates the originally given fMRI data. B shows how the original data is converted into an activation data set and a null data set. Panels C, D and E describe the application of the spectral density based and the spatial correlation measures to the activation and the null data sets. Panel F shows how these individual measures can be combined using a figure of merit.
periodogram estimate of the spectral density of the time course $\hat{x}_{\text{null}}(v)$ at frequency $f_k^\text{null}$ is

$$P(f_k^\text{null}(v)) = \frac{1}{(MT/2)^2} \left\{ |C_k^\text{null}(v)|^2 + |C_{MT/2-k}^\text{null}(v)|^2 \right\}$$  \hspace{1cm} (9)$$

where $f_k^\text{null} = \frac{k}{(MT/2)^2}$ and $\Delta$ is the TR of the fMRI data.

Third, we obtain a histogram which approximates the null distribution associated with $P(f_k^\text{null})$ (hereby denoted as the null histogram) by setting $k=M/2$ in Eq. (9) leading to $f_k^\text{null}=(MT\Delta)^{-1}$ and applying $P(f_k^\text{null}(v))$ to the null data set over all the brain voxels and collecting the resultant values. Finally, we can generate additional samples for the null histogram by modifying the way we select the sets of pairs of epoch time courses to be subtracted in Eq. (4.1), for example, by letting

$$\hat{x}_{\text{null}}^\ast(v) = [\hat{x}_{\text{null}}^\ast(v); \hat{x}_{\text{null}}^\ast(v); \ldots \hat{x}_{M/2}^\ast(v)]$$ \hspace{1cm} (10)$$

where $\hat{x}_{m}^\ast(v) = (\bar{x}_{2m}(v) - \bar{x}_{m}(v))/2$, and then applying

$$P(f_k^\text{null}(v)) = \frac{1}{(MT/2)^2} \left\{ |C_k^\text{null}(v)|^2 + |C_{MT/2-k}^\text{null}(v)|^2 \right\}$$  \hspace{1cm} (11)$$

with $k=M/2$ again to the null data set over all the brain voxels.

Fig. 1(A–C) illustrates the application of the above procedure to determine activated voxels in a simulated fMRI data set: (1) the detection measure $P(f_k^\text{null})$ is applied to the activation data set over all the brain voxels, yielding the activation histogram in Fig. 1A, while $P(f_k^\text{null})$ as well as $P(f_k^\text{null})$ and so on] is applied to the corresponding null data set, leading to the null histogram in Fig. 1B; (2) based on the null histogram, a $p$ value of .05 corresponds to a detection threshold of 179.3 (i.e., 5% of the samples exceed that threshold in the null histogram), yielding the vertical line in Fig. 1B; (3) imposing the same vertical line onto the activation histogram Fig. 1A yields a set of voxels exceeding that threshold and leads to the activation map shown in Fig. 1C, in which the highlighted voxels are deemed active at the significance level of .05.

The above activation detection procedure is summarized in boxes A→B→C in Fig. 2.

2.3. Extracting activation information using the harmonics of the experimental paradigm

It has been mentioned in [26] that spectral density at the first and higher harmonics of an fMRI data set obtained from a periodic paradigm could also be used to detect activation, although that article then focused exclusively on the fundamental frequency in the subsequent formulation of their detection measure. For the activation data set obtained from Eq. (5.1), by setting $k=Mh/2$ with $h=2,3,4$, etc., in Eq. (7), the spectral density of the voxel time courses $\hat{x}_{\text{null}}(v)$ at the harmonics $(2/(MT\Delta))$, $(3/(MT\Delta))$, $(4/(MT\Delta))$, etc., can be obtained, while the corresponding null histograms can be generated by applying Eqs. (9) and (11) (and again, setting $k=Mh/2$ with $h=2,3,4$, etc.) to the associated null data sets [i.e., Eqs. (4.1) and (10)] over all the brain voxels.

Fig. 1(D–F) depicts the use of the first harmonic in extracting activation regions in a simulated fMRI data set. The procedure is also summarized in boxes A→B→D in Fig. 2.

2.4. Using a spatial correlation measure to detect activation regions

Because neuronal activities commonly result in the BOLD signal increase of contiguous voxels, incorporating information regarding voxel connectivity in the image space often enhances the sensitivity and specificity of fMRI data analysis [30,33–36]. It is thus beneficial to augment the spectral density based detection method with spatial consideration. To this end, we employ a simple approach: given a voxel $v$, we characterize the degree of correlation between the voxel’s time course and its nearest spatial neighbors’ using the formula:

$$\hat{s}_{\text{act}}(v) = \frac{1}{Q} \times \sum_{w=\text{[neighboring voxels of } v]} \left\{ \sum_{m=1}^{M/2} \sum_{n=m+1}^{M/2} \text{corr}(\hat{x}_{m}^\text{act}(v), \hat{x}_{n}^\text{act}(w)) \right\}$$ \hspace{1cm} (12)$$

where $Q$ is the number of the nearest spatial neighbors of $v$ (for example, we use $Q=4$ for single slice data set and $Q=6$ for multislice isotropic data set), and following the notation of Eqs. (5.1–2), $\hat{x}_{m}^\text{act}(v)$ and $\hat{x}_{n}^\text{act}(w)$ are the $m$th epoch time course for voxel $v$ and the $n$th epoch time course for voxel $w$ in the activation data set respectively. The term $\text{corr}(\hat{x}_{m}^\text{act}(v), \hat{x}_{n}^\text{act}(w))$ represents the standard linear correlation coefficient between the time courses $\hat{x}_{m}^\text{act}(v)$ and $\hat{x}_{n}^\text{act}(w)$. In Eq. (12), we explicitly exclude the linear correlation values between epoch time courses of the same epoch number (i.e., requiring that $m\neq n$ in the double summation) because we want to minimize the influence of spatial correlation effects other than those due to task/stimulus activation. Qualitatively, if neighboring voxels $v$ and $w$ are both activated in an experimental paradigm under consideration, the response patterns as exhibited in their epoch time courses will be similar and therefore the resulting linear correlation coefficient will be high. On the other hand, if voxels $v$ and $w$ are both nonactive, we expect little correlation between their epoch time courses. In particular, when $m\neq n$, since $\hat{x}_{m}^\text{act}(v)$ and $\hat{x}_{n}^\text{act}(w)$ come from different epochs, $\text{corr}(\hat{x}_{m}^\text{act}(v), \hat{x}_{n}^\text{act}(w))$ will be close to zero. Effectively, since activated voxels usually arise in the form of spatial clusters, the corresponding $s_{\text{act}}$ measure for those voxels will tend to attain high values relative to the null distribution.

Mirroring the development of the previous subsections, we introduce a procedure to estimate the null
distribution associated with the spatial correlation measure. This is achieved by modifying and applying Eq. (12) to the null fMRI data set generated from Eq. (4.1), leading to the formula:

$$s^{\text{null}}(v) = \frac{1}{Q} \times \sum_{w \in \{\text{neighboring voxels of } v\}} \left( \left( \sum_{m,n} corr(z_m^{\text{null}}(v), z_n^{\text{null}}(w)) \right) \right)$$

(13)

The null histogram can then be formed by applying this formula to all the brain voxels v and collecting the resultant $s^{\text{null}}$ values. As before, in order to enhance our estimate of the null distribution, additional samples for the null histogram can be generated by replacing $z_m^{\text{null}}(v)$ and $z_n^{\text{null}}(w)$ [as defined in Eq. (4.1)] with $z_m^{\text{null}}(v)$ and $z_n^{\text{null}}(w)$ [as defined in Eq. (10)] in Eq. (13), applying the resultant formula to all the brain voxels and then incorporating the resultant $s^{\text{null}}$ sample values to the null histogram.

The procedure of using the spatial correlation measure is summarized in boxes A→B→E in Fig. 2.

2.5. Combining spectral density based and spatial correlation detection measures using a figure of merit

The main goal of the paper is to linearly combine the spectral density based and the spatial correlation detection measures introduced in the previous subsections to form a spatiotemporal integrated activation detection measure:

$$\Omega^{\text{act}}(v) = \alpha_1 P(f_{M/2}^{\text{act}}(v)) + \alpha_2 P(f_M^{\text{act}}(v)) + \ldots + \alpha_n P(f_{M/2}^{\text{act}}(v))$$

$$+ \alpha_{n+1} P(v)$$

(14)

where $\alpha_1, \alpha_2, \ldots, \alpha_{n+1}$ are the coefficients to be determined, and the spectral densities of the first (n-1) harmonics for the activation data set are included in the above integrated measure. The key now is to find appropriate values for the $\alpha$’s such that $\Omega^{\text{act}}$ gives good detection ability. To achieve this, we introduce (1) a measure normalization procedure and then (2) a figure of merit to characterize the detection ability of a normalized measure.

In discussing the normalization procedure, for concreteness, let us focus on the spectral density at the fundamental frequency $P(f_{M/2}^{\text{act}})$ and the first harmonic $P(f_M^{\text{act}})$ for the time courses $z^{\text{act}}(v)$ obtained from our activation data set [i.e., from Eq. (5.1)]. As described in a previous subsection, the null histograms associated with the measures $P(f_{M/2}^{\text{null}})$ and $P(f_M^{\text{null}})$ can be generated by applying $P(f_{M/2}^{\text{null}})$ and $P(f_M^{\text{null}})$ based on Eqs. (4.1) and (9) to the corresponding null data set over all the brain voxels. Moreover, estimates for the means and the standard deviations of the null distributions associated with measures $P(f_{M/2}^{\text{null}})$ and $P(f_M^{\text{null}})$, hereby denoted as $\mu_{P(f_{M/2}^{\text{null}})}$, $\sigma_{P(f_{M/2}^{\text{null}})}$, $\mu_{P(f_M^{\text{null}})}$, and $\sigma_{P(f_M^{\text{null}})}$, can be computed directly from these null histograms. We can then normalize the spectral density based activation detection measures $P(f_{M/2}^{\text{act}})$ and $P(f_M^{\text{act}})$ using the following formulas:

$$\tilde{P}(f_{M/2}^{\text{act}}) = \frac{P(f_{M/2}^{\text{act}}) - \mu_{P(f_{M/2}^{\text{null}})}}{\sigma_{P(f_{M/2}^{\text{null}})}}$$

(15.1)

and

$$\tilde{P}(f_M^{\text{act}}) = \frac{P(f_M^{\text{act}}) - \mu_{P(f_M^{\text{null}})}}{\sigma_{P(f_M^{\text{null}})}}$$

(15.2)

where

$$\mu_{P(f_{M/2}^{\text{null}})} = \frac{1}{(\text{total # of brain voxels})} \sum_{v \in \{\text{brain voxels}\}} P(f_{M/2}^{\text{null}}(v))$$

(15.3)

and

$$\sigma_{P(f_{M/2}^{\text{null}})} = \frac{1}{(\text{total # of brain voxels})} \times \sum_{v \in \{\text{brain voxels}\}} \left( P(f_{M/2}^{\text{null}}(v)) - \mu_{P(f_{M/2}^{\text{null}})} \right)^2$$

(15.4)

$\mu_{P(f_M^{\text{null}})}$ and $\sigma_{P(f_M^{\text{null}})}$ are analogously defined. Let us further suppose a synthetic scenario in which in our activation data set, the epoch time courses of the activated voxels take the form of a sinusoid: Fig. 3A shows such a noiseless temporal profile, while Fig. 3B shows the time course from a typical activated voxel in this activation data set. It can be shown by direct calculation that the spectral density for this temporal profile (Fig. 3A) is positive at the fundamental frequency $f_{M/2}^{\text{null}}(1/T\Delta)$ and zero at the first harmonic $f_M^{\text{null}}(2/T\Delta)$. By computing $P(f_{M/2}^{\text{null}})$ and $P(f_M^{\text{null}})$ over all the brain voxels in the activation data set and collecting the results, we obtain the histograms shown in Fig. 3C–D. On the other hand, calculating $P(f_{M/2}^{\text{null}})$ and $P(f_M^{\text{null}})$ over the corresponding null data set yields the null histograms shown in Fig. 3E, F. Comparing Fig. 3C and E [i.e., the “activation” and the null histograms associated with $P(f_{M/2}^{\text{null}})$], we see that the cluster representing the activated voxels (enclosed by an oval in Fig. 3C) is located to the right of the null histogram (Fig. 3E). Hence, by setting appropriate threshold, we can use $P(f_{M/2}^{\text{null}})$ to help discriminate the activated from the nonactive voxels. Meanwhile, as depicted in Fig. 3D and F, the activation and the null histograms for the measure $P(f_M^{\text{null}})$ are largely identical. Thus, $P(f_{M}^{\text{null}})$ is not a useful measure for isolating activated voxels. These observations
lead us to define a figure of merit $F$ quantifying how much an activation distribution for a measure [e.g., the histogram for $P(f_M^{act})$ as shown in Fig. 3D] deviates from its associated null distribution [e.g., the null histogram associated with $P(f_M^{null})$, as shown in Fig. 3F]:

$$F\left(\tilde{P}(f_M^{act})\right) = \frac{1}{v} \sum_{v \in \text{brain voxels}} \left\{\tilde{P}(f_M^{act}(v))\right\}^2 
\times \left\{\frac{1}{\text{total # of brain voxels}} \sum_{v \in \text{brain voxels}} \left\{\tilde{P}(f_M^{act}(v))\right\}^2 - 1\right\} \quad (16)$$

For our present case, substituting Eq. (15.2) into Eq. (16) and performing algebraic manipulation yields

$$F\left(\tilde{P}(f_M^{act})\right) = \sum_{v \in \text{brain voxels}} \left\{P(f_M^{act}(v)) - \mu_{P(f_M^{null})}\right\}^2 \quad \sum_{v \in \text{brain voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2 \quad (17.1)$$

Using the observation that the distributions of $P(f_M^{act})$ and $P(f_M^{null})$ are identical, we obtain $F(\tilde{P}(f_M^{act})) = 1$ from Eq. (17.1). For the measure $P(f_M^{null})$, it can be shown (as we have observed in Fig. 3C and E) that the $P(f_M^{null})$ values of the activated voxels are generally larger than their corresponding $P(f_M^{null})$ values, while the distributions of $P(f_M^{act})$ and $P(f_M^{null})$ for the nonactive voxels are identical. Hence, in computing the figure of merit for $P(f_M^{null})$, we have

$$F\left(\tilde{P}(f_M^{null})\right) = \sum_{v \in \text{brain voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2 \quad \sum_{v \in \text{brain voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2 \quad (17.2)$$

where

$$A = \sum_{v \in \text{non active voxels}} \left\{P(f_M^{act}(v)) - \mu_{P(f_M^{null})}\right\}^2, \quad B = \sum_{v \in \text{active voxels}} \left\{P(f_M^{act}(v)) - \mu_{P(f_M^{null})}\right\}^2, \quad C = \sum_{v \in \text{null voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2, \quad D = \sum_{v \in \text{null voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2 \quad$$

we have $A = C$. Letting $\varepsilon(v) = P(f_M^{act}) - P(f_M^{null})$, we obtain

$$B = \sum_{v \in \text{active voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})} + \varepsilon(v)\right\}^2 = \sum_{v \in \text{active voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2 + \left\{\varepsilon(v)\right\}^2 + 2\left\{P(f_M^{null}(v))\right\} \varepsilon(v)$$

$$= D + \sum_{v \in \text{null voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\}^2 + 2\sum_{v \in \text{active voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\} \varepsilon(v) \quad (17.3)$$

For the special case where $\varepsilon(v) = \varepsilon$ is constant, $\sum_{v \in \text{active voxels}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\} \varepsilon = 0$. In general, the terms $\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\}$ and $\varepsilon(v)$ are not correlated, and thus

$$\sum_{v \in \text{activation distribution}} \left\{P(f_M^{null}(v)) - \mu_{P(f_M^{null})}\right\} \varepsilon(v)$$

is close to zero. Therefore, from Eq. (17.3), we have $B = D$, leading to $F(\tilde{P}(f_M^{null})) > 1$ from Eq. (17.2).

Heuristically, the better a given detection measure $\Omega^{act}$ is in isolating the activated from the nonactive voxels, the larger the $\Omega^{act}(v)$ values of the activated voxels will attain relative to their corresponding $\Omega^{null}(v)$ values, resulting in a large value of $F(\Omega^{act})$. In this light, $F$ can also be used as a figure of merit characterizing the detection ability of a given detection measure.

Hence, our original problem of determining the coefficients $\alpha_1, \alpha_2, ..., \alpha_n$ in Eq. (14) can be transformed into an auxiliary problem of maximizing the figure of merit $F(\Omega^{act})$, defined as

$$F\left(\Omega^{act}\right) = \frac{1}{v} \sum_{v \in \text{brain voxels}} \left\{\tilde{\Omega}^{act}(v)\right\}^2 \quad (18)$$

with $\tilde{\Omega}^{act}(v) = \frac{\Omega^{act}(v) - \Omega^{null}(v)}{\sigma^{act}(v) + \sigma^{null}(v)}$ by searching for appropriate values for $\alpha_1, \alpha_2, ..., \alpha_n$. Here, $\mu^{null}$ and $\alpha^{null}$ are the histograms estimates of the mean and the standard deviation of the distribution for $\Omega^{null}$, which, in turn is defined as:

$$\Omega^{null}(v) = \alpha_1 P(f_M^{null}(v)) + \alpha_2 P(f_M^{null}(v)) + ... + \alpha_n P(f_M^{null}(v)) + \alpha_{n+1} P(f_M^{null}(v))$$

A greedy algorithm can be used to search for appropriate values for the $\alpha$’s. First, following Eq. (16), we compute $F(\tilde{P}(f_M^{act}))$, $F(\tilde{P}(f_M^{null}))$,...,$F(\tilde{P}(f_M^{null}))$ and $F(\tilde{P}(f_M^{null}))$ individually to determine which of the measures $P(f_M^{act}), P(f_M^{null}), P(f_M^{act}), P(f_M^{null})$, and $P(s^{act})$, and $s^{act}$ yields the largest figure-of-merit value. Second, we fix the $\alpha$ coefficient associated with that measure to 1. For concreteness, let us suppose that measure is $P(f_M^{act})$ and we set $\alpha_1 = 1$. Third, we initialize $\alpha_2,...,\alpha_{n+1} = 0$. We then search for a value for $\alpha_2$ (denoted as $\tilde{\alpha}_2$) such that $F(\Omega^{act})$ is under the constraint $\alpha_1 = 1, \alpha_2 = 2 \alpha_2$ and $\alpha_4,...,\alpha_{n+1} = 0$ and so on. Once $\alpha_{n+1}$ is processed, we iterate the entire algorithm by going back again to searching and updating the best value for $\alpha_2$ while setting $\alpha_1 = 1, \alpha_3 = 2 \alpha_3,...,\alpha_{n+1} = 2 \alpha_{n+1}$ and then searching and updating the best values for $\alpha_3, \alpha_4, ..., \alpha_{n+1}$, etc., until convergence is achieved. By the linearity of the integrated measure and the fact that the coefficient for the component with the largest figure of merit is set to one, all the $\tilde{\alpha}$’s so obtained are finite.

The procedure of using the figure of merit $F$ to construct the combined measure $\Omega^{act}$ is summarized in box F in Fig. 2.
A variation of Eq. (18) can be used as an alternative figure of merit to optimize the coefficients $\alpha_1, \ldots, \alpha_{n+1}$ in Eq. (14):

$$F'\left(\tilde{\Omega}^{\text{act}}\right) = \frac{1}{(\text{total # of brain voxels})} \sum_{v \in \{\text{brain voxels}\}} |\tilde{\Omega}^{\text{act}}(v)| \quad (20)$$

where $\tilde{\Omega}^{\text{act}}(v) = \Omega^{\text{act}}(v) - \bar{\Omega}^{\text{null}}$.

$$\mu_{\Omega^{\text{null}}} = \frac{1}{(\text{total # of brain voxels})} \sum_{v \in \{\text{brain voxels}\}} \Omega^{\text{null}}(v)$$

and

$$\pi_{\Omega^{\text{null}}} = \frac{1}{(\text{total # of brain voxels})} \sum_{v \in \{\text{brain voxels}\}} |\Omega^{\text{null}}(v) - \mu_{\Omega^{\text{null}}}|$$

The summing of the squares in Eq. (18) is replaced by the summing of the absolute values in Eq. (20). $\pi_{\Omega^{\text{null}}}$ is the mean absolute deviation of the null distribution associated with $\Omega^{\text{act}}$.

Another figure of merit can be obtained from the modified ROC method of Nandy and Cordes [37]: concisely, given a test statistic and for a desired $\rho$ value, the corresponding test statistic threshold can be determined since we can estimate the null distribution of the test statistic using the subtraction procedure [e.g., Eq. (4.1)] described in the previous subsections. And with the test statistics threshold determined, the number of voxels surpassing that threshold in the
activation data set can be simply counted in the activation histogram. Hence, a figure of merit can be defined as:

\[
F''(P(f_{M/2}^{act})) = \int_{p=0.0}^{0.1} \chi_p(P(f_{M/2}^{act})) dp
\]

where \( \chi_p(P(f_{M/2}^{act})) \) represents the fraction of the brain voxels in the activation data set with their test statistic \( P(f_{M/2}^{act}) \) surpassing the threshold corresponding to a \( p \) value of \( P \). For example, in Fig. 1A, 451 out of 1564 voxels have their \( P(f_{M/2}^{act}) \) values surpassing the vertical line representing a \( p \) value of .05. Thus, in that case, \( \chi_{0.05}(P(f_{M/2}^{act}))=451/1564=0.288 \). In general, the larger the fraction, the better the measure is in isolating the activated from the nonactive voxels. In Eq. (21), the term \( \chi_p(P(f_{M/2}^{act})) \) is integrated from \( p=0 \) to \( p=0.1 \) because for activation detection in fMRI, we primarily focus on this range of small \( p \) values only. To compute \( F''(P(f_{M/2}^{act})) \) numerically, we perform the following summation:

\[
F''(P(f_{M/2}^{act})) \approx \sum_{j=1}^{100} \chi_j \Delta(P(f_{M/2}^{act})) \Delta
\]

with \( \Delta=0.001 \).

2.6 Using simulated and experimental fMRI data to evaluate the activation detection measures

We have implemented the integrated activation detection method described in the previous subsections in MATLAB (The MathWorks Inc., Natick, MA, USA). In order to validate the method, it was applied to simulated and experimental data. All fMRI data sets were previously acquired in the Center for Magnetic Resonance Research at the University of Minnesota, with informed consent from the subjects and approved by the university institutional review board. To generate simulated data, we employed a method described in [38]. First, a baseline data set from a healthy volunteer in a resting state was collected (T2*-weighted EPI images at 1.5 T, with TR=300 ms, TE=55 ms, matrix size 64×64, field of view 20×20 cm²). Then, eight epochs of artificial activation (each epoch having duration of 64 images) with a temporal activation signal pattern of the form (see Fig. 4B):

\[
\chi_t = \left\{ 1 - \exp\left(\frac{-t}{T_*}\right) \right\}^3 \exp\left(\frac{-t}{T^{**}}\right)
\]

and a preassigned contrast level ranging from 1% to 4% were superimposed onto the baseline data set. \( T_* \) and \( T^{**} \) are
constants that can be adjusted to obtain the desired shape (we set $T_*=20$ and $T_{**}=30$), and $\tau$ is the time point within an epoch. Besides Eq. (23), we also used temporal signal patterns of the box-car and the half-sinusoid to create additional types of simulated data sets. The spatial locations of the activated voxels corresponded to a grid of squares in the image space, with a range in sizes of 4, 9, 16, 25 and 36 voxels. Finally, we delineated a region of interest enclosing the entire extent of the brain, and the voxels inside the ROI were subsequently analyzed with the activation detection algorithm (refer to Fig. 4A for the detail configuration). Before submitting a given fMRI data set to our activation detection algorithm, all the voxel time courses were detrended using high-pass filtering, by (i) Fourier-transform each voxel time course, (ii) setting the Fourier coefficients which correspond to frequencies less than $(T\Delta)^{-1}$ to zero and then (iii) inverse Fourier-transform the results back to the time domain.

We used the ROC analysis to assess the performance of the integrated activation detection measure in the following manner. Once we have optimized the figure of merit $F(\Omega^\text{act})$ and determine the appropriate values for the coefficients $\alpha_1, \alpha_2, \ldots, \alpha_{n+1}$ for a given fMRI data set, the $\Omega^\text{act}$ measure for all voxels in the ROI were calculated. We then ordered these voxels according to their $\Omega^\text{act}$ values.

The true-positive fraction (TPF) and the false-positive fraction (FPF) were determined at each successive step and plotted against each other to generate the ROC curve. The area under the truncated ROC curve (integrating from FPF=0 to FPF=0.1) was then computed and taken as a measure of the detection ability of the integrated detection measure. In order to quantify the improvement in performance, the results were compared with those obtained by using the spectral density measure based on the fundamental frequency.

It is also desirable to understand the influence of activation cluster size on the behavior of the algorithm. Thus, in a second set of simulation studies, the cluster size was varied from 1, 4, 9, 16, 25 to 36 voxels in six separate types of simulated fMRI data sets. The performances of the integrated measure and the spectral density based measure were again compared.

In order to demonstrate the practical utility of the integrated detection algorithm, it was applied to experimental data acquired from a healthy volunteer. The experimental task consisted of performing rapid finger movement using the dominant right hand when cued with flashing red LED goggles for a brief duration. T2*-weighted EPI images of a single oblique brain slice traversing the occipital cortex and the motor cortex were collected (TR=300 ms, TE=60 ms, matrix size 64×64, and field of view 22×22 cm²). Eight epochs were used in the computation of the activation detection measures, and appropriate threshold was selected to isolate the activation regions.

As an additional validation of our method, we finally compared the performance of the integrated measure with those of the Icasso method [39] and the Spatiotemporal ICA method [40] using both simulated and experimental data.

3. Results and discussion

3.1. Performance of the detection measures on simulated fMRI data

We first examine the detection ability of integrated detection measures of the form

$$\Omega^\text{act}_{\text{spectral},1}(v) = \alpha_1 P(f_M^\text{act}(v)) + \alpha_2 P(f_M^\text{act}(v)) + \ldots + \alpha_n P(f_M^\text{act}(v))$$

(24)

i.e., the individual components of such measures are composed of spectral densities at the fundamental frequency and the harmonics only. In Fig. 5, the performances of two of these integrated measures are depicted. The symbol $\Delta$ corresponds to the normalized version of the integrated measure

$$\Omega^\text{act}_{\text{spectral},2}(v) = \alpha_1 P(f_M^\text{act}(v)) + \alpha_2 P(f_M^\text{act}(v))$$

(25.1)

while the symbol $\circ$ represents the normalized version of the integrated measure

$$\Omega^\text{act}_{\text{spectral},3}(v) = \alpha_1 P(f_M^\text{act}(v)) + \alpha_2 P(f_M^\text{act}(v)) + \alpha_3 P(f_M^\text{act}(v))$$

(25.2)

The results for three “singleton” measures $P(f_M^\text{act})$, $P(f_M^\text{act})$ and $P(f_M^\text{act})$, representing activation detection based on the

![Fig. 5. Comparison amongst the spectral density based detection measures. Simulated fMRI data sets were generated by superimposing artificial activations [of the temporal signal pattern of Eq. (23)] at predetermined spatial locations (Fig. 4A) onto the baseline fMRI data. The horizontal axis indicates contrast level of the artificial activation imposed on the baseline data, and the vertical axis indicates the performance of the various detection measures. The symbol * corresponds to activation detection using spectral density at the fundamental frequency; □, the first harmonic and ○, the second harmonic. ● represents an integrated measure combining the spectral densities at the fundamental frequency and the first harmonic, and ○ an integrated measure combining the spectral densities at the fundamental frequency, the first harmonic and the second harmonic.](image-url)
fundamental frequency, the first and the second harmonics, are also plotted and are denoted by the symbols *, □ and ◊ respectively. We see that the two integrated measures generally outperform the singleton measures for the various contrast levels tested (lines for Δ and ○ are generally above lines for *, □ and ◊ in Fig. 5). On the other hand, the detection ability of the two integrated measures are largely identical (lines for Δ and ○ largely coincide with each other), indicating that the spectral density at the second harmonic [i.e., the third term on the right hand side of Eq. (25.2)] provides very little additional information in aiding activation detection. Therefore, in our subsequent discussion, we simplify the weighted sum in Eq. (14) and exclusively focus on the following spatiospectral integrated measure:

$$\Omega_{\text{act}}(v) = \alpha_1 P(f_{M/2}^{\text{act}}(v)) + \alpha_2 P(f_M^{\text{act}}(v)) + \alpha_3 s^{\text{act}}(v)$$  \hspace{1cm} (26)$$

where only the spectral densities at the fundamental frequency and the first harmonic and the spatial correlation term are included.

Fig. 6 depicts the performances of the full spatiospectral integrated measure [i.e., Eq. (26)] and the spectral density measure based on the fundamental frequency [i.e., \(P(f_M^{\text{act}})\)]. We see that across all 21 simulated fMRI data sets (seven different activation contrast levels ranging from 1\% to 4\%×3 types of temporal activation signal patterns: Eq. (23), boxcar, and half-sinusoid), the integrated measure (denoted by the solid lines, with ○ representing the simulated data sets with activation signal pattern of Eq. (23), * for the data sets with activation signal pattern of the boxcar and Δ for the data sets with signal pattern of the half-sinusoid) has a higher detection ability than the spectral density measure (denoted by the dashed lines). For example, the solid line with ○ is positioned above the dashed line with the same symbol. As a further illustration, we select a simulated data set with a temporal activation signal pattern of Eq. (23) and the activation contrast level of 3.0\%. The ROC curves for both the integrated (solid lines) and the spectral density measure (dashed line) are plotted in (A). Points x and y are the optimal classification points on the respective ROC curves. Panel (B) depicts the activation map corresponding to point x, and (C) depicts the activation map corresponding to point y. Comparing (B) and (C) with on the spatial activation template in Fig. 4A, we observe that the integrated detection measure leads to a more accurate activation map.

![Fig. 6](image1)

Fig. 6. ROC analyses of the spatiospectral integrated detection measure. Simulated fMRI data sets were generated by superimposing artificial activations at predetermined spatial locations (Fig. 4A) onto the baseline fMRI data. Three different types of temporal activation signal patterns [signal pattern of Eq. (23), boxcar and half-sinusoid] were used to create the simulated data, indicated by ○, * and Δ respectively. The horizontal axis indicates the contrast level of the artificial activation imposed on the baseline data, while the vertical axis indicates the detection ability of the various measures. Solid lines depict the performances of the spatiospectral integrated detection measure, and the dashed lines the performance of the spectral density measure based on the fundamental frequency.

![Fig. 7](image2)

Fig. 7. Illustration of activation detection using the spatiospectral integrated measure and the spectral density measure based on the fundamental frequency. A simulated fMRI data set with artificial activation contrast level set at 3\% is used. The ROC curves for the integrated measure (solid line) and the spectral density measure (dashed line) are plotted in (A). Points x and y are the optimal classification points on the respective ROC curves. Panel (B) depicts the activation map corresponding to point x, and (C) depicts the activation map corresponding to point y. Comparing (B) and (C) with on the spatial activation template in Fig. 4A, we observe that the integrated detection measure leads to a more accurate activation map.
singleton activated voxels (1×1), activation clusters in
groups of 2×2=4 voxels, in groups of 3×3=9 voxels, in
groups of 4×4=16 voxels, in groups of 5×5=25 voxels and
in groups of 6×6=36 voxels were separately superimposed
onto the baseline fMRI data sets, leading to six different sets
of simulated fMRI data for each activation contrast level
tested. The ROC analyses results are displayed in Fig. 8, in
which the solid lines delineate the performances of the
integrated measure and the dashed lines the performances
of the spectral density measure based on the fundamental
frequency. Different symbols (i.e., ○, *, Δ, □, × and ◊)
represent simulated data sets with activation contrast level
set at different levels (i.e., 1.5%, 2.0%, 2.5%, 3.0%, 3.5%
and 4.0%, respectively). We observe that the solid lines
generally position above the corresponding dashed lines,
indicating that across the various contrast levels and cluster
sizes, the integrated measure has better detection ability than
the spectral density measure.

In our discussion so far, eight epochs of artificial
activation were imposed in creating the simulated fMRI
data. In Fig. 9, we study the influence of varying the number of epochs on the detection ability of the activation measures. As expected, for each contrast level tested (○=1.5%, *=2.0%, Δ=2.5%, □=3.0%, ×=3.5% and ◊=4.0%), the performances of both the integrated and the spectral density measures improve as the number of epochs increases (each individual line is monotonically increasing). Furthermore, the integrated measure again outperforms the spectral density measure across the various number of epochs and contrast levels, as the solid lines (representing the integrated measure) generally place above the corresponding dashed lines (representing the spectral density measure).

We also compared the performance of the integrated
measure with those of the Icasso method [39] and the
Spatiotemporal ICA method [40], two template-free fMRI
data analysis methods. Icasso is based on the repeated
application of the FastICA algorithm [41] and the clustering of the results to enhance the reliability of the obtained components. (We applied resampling 25 times and employed the Gaussian function as the nonlinearity function in their fixed point algorithm. The other two nonlinearity functions available in their software package gave the worse performance for our data sets.) The Spatiotemporal ICA method simultaneously maximizes statistical independence of the components temporally and spatially. (We used the default parameters with the skew spatial-temporal ICA option and with \( \alpha = 0.5 \).) Each execution of the Icasso method (as well as the Spatiotemporal method) results in a number of independent components. To find the component most

Fig. 10. Comparison of the spatiotemporal integrated detection measure with other template-free data analysis methods. To generate simulated fMRI data sets, three different types of temporal activation signal patterns [signal pattern of Eq. (23), boxcar and half-sinusoid] were used, leading to the results in (A), (B) and (C) respectively. The horizontal axes indicate the contrast level of the artificial activation imposed on the baseline data, and the vertical axes indicate the detection ability of the various measures. ○ depicts the performance of the spatiotemporal integrated detection measure; *, the performance of the Icasso method and \( \Delta \), the performance of the Spatiotemporal ICA method.

Fig. 11. Comparison of the three figures of merit. ○ indicates the performance of the integrated measure optimized using the figure of merit of Eq. (18) * that optimized using the figure of merit of Eq. (20) and \( \Delta \) that optimized using the figure of merit of Eq. (21). The detection abilities of the three versions are very similar and hence the corresponding lines virtually overlap. ■ indicates the performance of \( P(t_2) \). As before, simulated fMRI data sets were generated by superimposing artificial activations [of the signal pattern of Eq. (23)] at pre-determined spatial locations (Fig. 4A) on the baseline fMRI data.

relevant to activation, we calculate the correlation of the each of the resulting components with the true spatial activation template (i.e., Fig. 4A) and select the component with the best correlation, yielding the performance results in Fig. 10 (○: integrated measure, *: Icasso, Δ: Spatiotemporal ICA). The ROC analyses were done over seven different activation contrast levels (1–4%) and three different types of temporal activation signal pattern [Fig. 10A: pattern of Eq. (23), 10B: boxcar, 10C: half-sinusoid]. We see that the integrated detection measure generally outperforms the Icasso and the Spatiotemporal ICA methods, except for the case with the contrast level at 1.5% in subplot (c).

In all the analyses discussed thus far in this section, the integrated detection measure Eq. (26) was optimized with the figure of merit described in Eq. (18). When we instead used the figure of merits described in Eqs. (20) and (21) to optimize the integrated measure, the resulting detection abilities are very similar. For example, Fig. 11 shows the performances of the integrated measure optimized with Eq. (18) (denoted by ○), that optimized with Eq. (20) (denoted by *), and that optimized with Eq. (21) (denoted by Δ). Again, the analyses were done over various contrast levels and three temporal activation signal patterns, leading to the three subplots. These lines largely overlap with one another for the various contrast levels and activation signal patterns tested. Lines with □ indicate the detection ability of $P(f_{M/2})$ and are included in the figure to serve as a reference.

3.2. Using the activation detection measures on experimental data

In Fig. 12, we depict the results of applying the integrated detection measure, the spectral density measure, the Icasso method and the Spatiotemporal ICA method on an experimental data set obtained from a visually cued motor paradigm. Using the procedure described in the Methods section to generate the null histogram for the integrated measure, a threshold corresponding to a $p$ value of .005 was chosen. Fig. 12A displays the corresponding activation map, which shows activation in both the V1 and M1 regions. A total of 90 voxels pass that threshold and are highlighted in the figure. On the other hand, the 90 best scoring voxels based on their spectral density measure values at the fundamental frequency are highlighted in Fig. 12B. Fig. 12C, D show the top 90 voxels (in terms of voxel intensity) in the activation related independent components generated by the Icasso and Spatiotemporal methods respectively. On the whole, Fig. 12 shows that qualitatively, the activation map produced by the integrated measure is less noisy than the other three maps, in agreement with the quantitative assessment obtained from the ROC analyses of the simulated fMRI data.

4. Conclusion

In this article, we have improved upon a spectral density based activation detection measure for event-related fMRI data by constructing a new, integrated detection measure. The spectral density-based measure estimates the degree of task/stimulus related activation in a brain voxel by calculating the spectral density at the fundamental frequency of a periodic experimental paradigm. The new measure, termed the spatio-spectral integrated measure, linearly combines the spectral densities at the fundamental frequency and the harmonics and a spatial correlation term. Furthermore, several figures of merit have been described and used to determine appropriate values for the coefficients in such a linear combination.

The motivation for extending the original spectral density based measure is that additional information regarding task/stimulus related activation in the fMRI data may be contained in and extractable from the first and higher harmonics of the experimental paradigm. Moreover, many past fMRI studies have indicated the benefits of exploiting voxel connectivity in data analysis because the sites corresponding to neuronal activities often exist as spatial clusters rather than occur in isolation.

We have used both simulated fMRI and experimental fMRI data to illustrate the utility of the spatio-spectral integrated detection measure. A variety of simulated fMRI
data sets were generated by superimposing artificial activation of various temporal signal patterns with various contrast levels at various spatial locations onto baseline fMRI data. ROC analysis of the results quantified and demonstrated the improved detection ability of the integrated measure over the original spectral density based measure over a range of testing conditions. Our experimental fMRI data obtained using a visually guided motor paradigm depicted qualitatively that we can obtain a more sensitive and specific activation map using the new measure. The present measure also compares quite favorably with the Spatiotemporal ICA and the Icasso methods, which are useful template-free fMRI data analysis methods themselves.

The present method depends on the existence of reproducible response patterns across epochs. Fortunately, even with this limitation, the method is still applicable to fMRI data sets obtained from a large subclass of useful experimental paradigms. The performances of the integrated as well as the purely spectral density based measures will of course deteriorate if the activation patterns in the epochs are not exactly in phase, with the degree of reduction dependent upon how out of phase the activation patterns are. For the generation of null data sets under these circumstances, resampling techniques such as wavelet resampling [42,43] can be applied as an additional step after the pairing and subtraction procedure described in Eq. (4.1) to further remove any residual activation signals.

Finally, the integrated measure can be expanded to include terms other than the spectral densities and the spatial correlation. For example, the statistical map generated from the present integrated measure can be used to identify the activation related independent components obtained from the Icasso and the Spatiotemporal ICA methods. The statistical map and the components can then be combined linearly to produce a further improved activation map. A caveat is that overfitting might possibly occur if we include too many terms in the integrated measure. Fortunately, this problem can be overcome by testing whether the coefficient for each term is significantly different from zero using resampling or cross-validation. Moreover, moving away from the domain of spectral densities, we can utilize the figures of merit to choose an appropriate subset of wavelet basis in the wavelet analysis of event-related fMRI data, to choose appropriate kernel width for spatial smoothing of fMRI data (Refs. [44–46] are examples of attempts in finding optimal spatial smoothing) and to determine an optimal neighborhood size for the computing spatial correlation measure [referring to Eq. (12), we currently impose a neighborhood size of Q=4 for single slice data]. Some of these topics will be discussed in a separate article.

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