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Adapted estimate of neural activity based on blood-oxygen-level dependent signal by a model-free spatio-temporal clustering analysis

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ABSTRACT

In this study, we detected brain activity by comparing the overall temporal response of the blood oxygen level referring to hemodynamic response with a modeled hemodynamic response (MHR). However, in a conventional analysis by statistical parametric mapping (SPM) method, the MHR is assumed to be a fixed-response function, which may bias the conclusions about brain activation, such as the shapes of the response curve or the different response delays to stimuli. Therefore, to improve detection efficacy, we applied a spatio-temporal clustering analysis (sTCA) to determine the MHR, which is calculated from the prospective voxels with no *a priori* information about the experiment design. With the sTCA method, these prospective voxels are detected by the feature with the largest temporal clustering within which these voxels react simultaneously, irrespective of where the variant hemodynamic response occurs. This estimated MHR (*e*MHR) is then applied to search for brain activation. Preliminary results show that the *e*MHR signal response closely resembles the real signal response of the target area. Moreover, the activation detection using *e*MHR method is more sensitive for the human visual and motor tasks than that with the canonical hemodynamic response embedded in the SPM analysis as the default MHR (*d*MHR). The more precise location of brain activation made possible by the improved sensitivity should provide helpful information about the stimulation of neuron activity.

1. Introduction

Methods of data analysis used in functional magnetic resonance imaging (fMRI) are categorized into paradigm-dependent [1,2] and paradigm-independent [3–10] methods. The former is commonly used when the temporal pattern of a stimulus is known in advance and, thus, the interest signal can be selected with the associated parameters. The latter is used to single out the data-driven features, such as the latent components after analysis of blind source separation, with no *a priori* knowledge about experimental design. The correlated intensity is computed to determine the significance of brain activation with the time course of each voxel and that of a modeled hemodynamic response (MHR), a model for the responsive alternation in the blood caused by physical activities or external stimuli. In general, the MHR is simply the convolution of the hemodynamic response function (HRF) and the stimuli paradigm with an assumption of a fixed delay in response (approximately 2 s). With this model, the effects of the task are determined by calculating the correlation between the MHR and the time response of the activated voxels. In other words, the observed response of blood-oxygen-level dependence (BOLD), which is a common signal acquired in fMRI that reflects the blood-oxygen level, is highly responsive to and dependent on both the evoking stimulus [11,12] and the underlying neuronal activity while the MHR is correctly assessed from the HRF. However, the HRF varies considerably among healthy subjects [13,14], and this phenomenon is even more obvious in certain patient population [15]; for example, the cerebral blood flow is often altered in patients with occlusive cerebrovascular disease and cerebral infarction [16]. Patients with intra- and extracranial vascular obstruction have reportedly had a noncanonical HRF [17] in addition to delayed responses to the task involved. Similarly,

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an unusual HRF often appears in patients who have had a stroke [18]. In contrast, Richter and Richter [19] indicate that the shape of the HRF also changes systematically with age. In conventional statistical parametric mapping (SPM) [2], the HRF is generated by a canonical gamma-variate function that might deviate from the true expression similar to the special cases mentioned above. Under such circumstances, the use of a HRF with fixed shape will bias the detection of a task-induced effect and compromise the power of the analysis. Given the critical role played by the HRF, various delayed intervals of HRF [1] are adjustable in SPM by iteratively calculating the optimal match between the MHR and the measured time course. Moreover, the HRF can also be estimated from a reference waveform, which is derived from a brain area whose cognitive function is well known in many experiment assignments [20,21].

Under special conditions, the MHR is difficult to obtain in drug-abuse cases [22] or epileptic conditions [22,23]. To estimate MHR, it is more appropriate to use paradigm-independent methods, some examples of which are principal component analysis [3,4], fuzzy clustering analysis [5], independent component analysis (ICA) [6], and group-based ICA [7]. In recent years, temporal clustering analysis (TCA) [8–10] has been proposed to detect brain activation. TCA shows high temporal sensitivity for detecting a neural firing with unknown activation location and timing. It is a model-free method in which all prospective voxels represent the area of neuron activity and are clustered according to the temporal feature of synchronization. Accordingly, the TCA method can, for example, detect the neuronal response of glucose ingestion, which is considered as a highly complex situation reflecting hormonal processes as well as neuronal events [24]. Moreover, to improve sensitivity, researchers use signal intensity to enhance the distinction between activated and background voxels [8,10]. In addition, Peng et al. [9] proposed a spatio-TCA (*s*TCA) that incorporates spatial information to enhance the capability of TCA. Based on previous work, sTCA is fourfold more sensitive for temporal detection of activity than both the original TCA [24] and intensity-magnified TCA [8,10]. However, the previous work did not consider whether high-sensitivity detection exists at the location of activity. Therefore, the spatial location of the activation must be confirmed.

Theoretically, in sTCA, when the responsive peak is determined, the responsive time window (TW) can be defined by Gaussian fitting of the clustered voxels. A t statistic is then applied to each voxel to test the signal differences between two time-separated peaks that represent areas within and outside of the TW. As a result, activation is detected with higher sensitivity, allowing many joined activations to be detected instead of just those under a single temporal peak. In the spatial analysis of brain activity, a TW interval is necessary to detect activation in the brain [2]. Unfortunately, for studies with a low contrast-to-noise ratio (*CNR*) or with a few activated voxels, Gaussian fitting is more likely to lead to inaccurate inferences, resulting in an incorrect estimate of the TW, thereby losing the sensitivity and the specificity of activation detection. Under such circumstances, the meaning of the selected cluster must be further validated.

Given that the detection of brain activation can be improved with sTCA, in this study, we integrated the advantages of sTCA in the SPM method to generate a modified assessment of neural activation. While assessing the MHR, we use sTCA [9] to obtain the TW with the most voxels that show statistical significance within the range of a full width at half maximum (FWHM) of the characteristic curve; subsequently, we estimate the MHR from the time courses of these voxels. We thus refine the hemodynamic response by avoiding flawed data acquired from a single canonical hemodynamic response and for the various situations of the stimulation. This allows us to estimate a genuine MHR based on the signal and also improves the resolution, which facilitates differentiating between hemodynamic responses in various conditions.

2. Methods and materials

2.1. Spatio-temporal clustering analysis (sTCA)

This section describes sTCA; for more detail, see Ref. [9]. The data matrix of a series of fMRIs can be presented as a two dimensional data matrix S, where $S_{i,j}$ are the signal strengths of voxel i at time j. When a given $S_{i,j}$ reaches maximum intensity over the entire time course, its status $W_{i,j} = 1$ in a remark matrix W and $W_{\neq i,j} = 0$. Next, we calculate $\sum_i W_{ij}$ to generate a temporal clustering distribution K as a characteristic curve, in which K_j is the number of voxels whose intensity simultaneously reaches their maximum at time j. Because of the temporal clustering property, the peak of the K histogram implies that the task-related responses occurred simultaneously at these voxels. As a result, the responsive TW can be set around peaks. Furthermore, to increase the sensitivity with which the TW is detected, both signal intensity [8,10] and spatial information [9] are incorporated into the calculation of K_j:

$$K_j = \sum_i W_{i,j} \times r_i \times S_{i,j} \tag{1}$$

where the correlation r_i of voxel i and its surrounding neighbors, defined as a 5×5 voxel group around the single voxel i, weights the signal intensity. To calculate the correlation (r_i), a reference time course of neighborhood $G_{i,j}$ is derived from the adjacent voxels with the same temporal property as the pinpointed voxel (i.e., maximum intensity at time j) [8]. Thereafter, the temporal correlation coefficient r_i can be calculated from $S_{i,j}$ and $G_{i,j}$. Given that the spatial relationship is highly bounded to any other voxel in the neighborhood, the temporal correlation is enhanced within the activated region instead of in the region with spurious, noisy, or background signals. As a result, the detection of the TW for the K histogram is enhanced by considering the r_i factor.

2.2. Estimate of modeled hemodynamic response (eMHR)

Theoretically, an ideal MHR (*i*MHR) should be in close accord with the time courses of activated voxels and should generate a highly correlated relationship with the manipulation task. To be specific, we hypothesize that, when the brain is stimulated, the signals of most activated voxels arise simultaneously, and these responsive voxels can be detected by the clustering expression at a certain point in the K histogram. Because voxels under the peak of the K histogram represent the most likely activated response induced by the task, their time courses closely approach that of the *i*MHR. Consequently, the *e*MHR (as opposed to the *i*MHR) can be calculated from the time courses of these indicated voxels.

By considering the slight deviation at the onset of the response time and the sensitivity of peak detection, the prospective activated voxels are determined within the peak regime of the K histogram, which spans between the two peaks nearest in time. Moreover, the clusters are checked again to exclude noisy voxels from the group for which the cluster size is less than five voxels.

Therefore, the MHR at time j is

$$MHR_j = \frac{\sum_{\substack{i \in \mathbf{K}_P \\ r_i > 0.2}} r_i \times S_{i,j}}{\sum_{\substack{i \in \mathbf{K}_P \\ r_i > 0.2}} r_i}. \tag{2}$$

In this formula, $\mathbf{K}_P$ represents the set of all voxels under the peak of the K histogram. The correlation r_i serves as a weighting factor to reduce the influence of background noise in the estimate. Moreover, the time span, equal to a FWHM of the MHR, served as the responsive TW to the stimulation. By using this scheme, we can detect the temporal response automatically with no *a priori* knowledge of the activation