A high performance cluster-based test for subject- and group-level analysis of unsmoothed fMRI data

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Target audience: Researchers interested in statistical modeling and analysis methods, as well as scientists and clinicians whose research focuses on detecting signal changes in functional and structural brain images.

Purpose: Accurately determining the statistical significance of changes in brain images is one of the most critical procedures of functional neuroimaging. Cluster-size tests (CST) have been widely adopted in fMRI data analysis to detect brain activation. However, most existing CST approaches, like the most commonly used 'original' CST (OCST) proposed by Friston in 1994 [1] can only be used appropriately when the image is highly smoothed in the spatial domain. While this improves sensitivity, it is at the expense of spatial specificity. Smith and his colleagues proposed a threshold-free cluster enhancement (TFCE) inference method [2] that does not require spatial smoothing, but this method can only be used for group level analysis. We propose an improved 3D CST approach combining both spatial extent and intensity threshold, named 3D SEe-IT, which is suitable for both subject- and group-level analyses and does not require spatial smoothing. 3D SEe-IT is attractive because it maintains high sensitivity without spatial smoothness and, in turn, without extra spatial smoothing, it retains spatial specificity.

Theory: The probability of clusters with a specific size k or larger, searched over a brain region, and exceeding a given intensity threshold t, $p_v(m \geq k)$, can be computed as one minus the probability that all clusters, i, have less than k voxels, multiplied by the probability of obtaining i clusters:

$$p_v(m \geq k) = \sum_{i=1}^{\infty} \left\{ p(n=i) \left\{ 1 - [1 - p(m \geq k)]^i \right\} \right\} \quad (1)$$

where both $p(n=i)$ and $p(m \geq k)$ are based on smoothness estimation Λ. 3D SEe-IT improves OCST by: (1) modifying the mathematical model for estimating image smoothness Λ; and (2) using a more accurate expression for the probability of observing an individual cluster that is larger than or equal to a specific size $p(m \geq k)$.

The OCST approach is based on the assumption of a continuous random field, with smoothness estimation:

$$\sqrt{|\Lambda|} = \left(\mathrm{FWHM}_x \mathrm{FWHM}_y \mathrm{FWHM}_z\right)^{-1} \left(4\ln(2)\right)^{3/2} \quad (2)$$

However, for most fMRI experiments, the FWHM of the Gaussian kernel is comparable to the voxel size of the acquired image and treating the images as a continuous random field without a correction for voxel size effects is incorrect. In our work, the Λ is modified when the effect of voxel size cannot be ignored (e.g., FWHM < 3 voxels):

$$|\Lambda_t| = \left\{ 2|\Lambda|^{1/3} \Big/ \left(2 + |\Lambda|^{1/3}\right) \right\}^3 \quad (3)$$

and $p(m \geq k)$ based on a Gaussian random field is expressed as:

$$p(m \geq k) = \left(1 + \sqrt{k\gamma}/t^2\right)^2 \exp(-\sqrt{k\gamma} - k\gamma/2t^2) \quad (4)$$

where γ is based on intensity threshold t and smoothness estimation Λ.

Methods: 20 unrelated pre-processed resting-state fMRI (rfMRI) data from the Human Connectome Project (http://www.humanconnectome.org/data) were used to simulate task-activation fMRI data. The ground truth activation spatial pattern we used was the medial visual resting state network spatial map [3]. For the evaluation of task analyses, we followed a strategy similar to that implemented by Woolrich et al. (2001) [4] and Frederick et al. (2012) [5] that utilized dummy paradigms to simulate task activation data. We used: a boxcar design with a period of 161.28 s (20.16-s rest period alternated with a 20.16-s activation period, repeated four times). The activation intensity level used was 2% of the rfMRI data.

All data were analyzed using FSL. The First-level analysis was used to generate the subject-level parameter estimate maps. All paradigms were convolved with the default gamma hemodynamic response function. The application of temporal high-pass filtering and pre-whitening were also tested. Gaussian smoothing kernels of FWHM of 0, 1.5 and 3 voxels were applied to all the images. The resulting parameter estimate maps were further analyzed at the signal-subject level (using OCST and 3D SEe-IT) and at the group level (using 3D SEe-IT and TFCE), respectively.

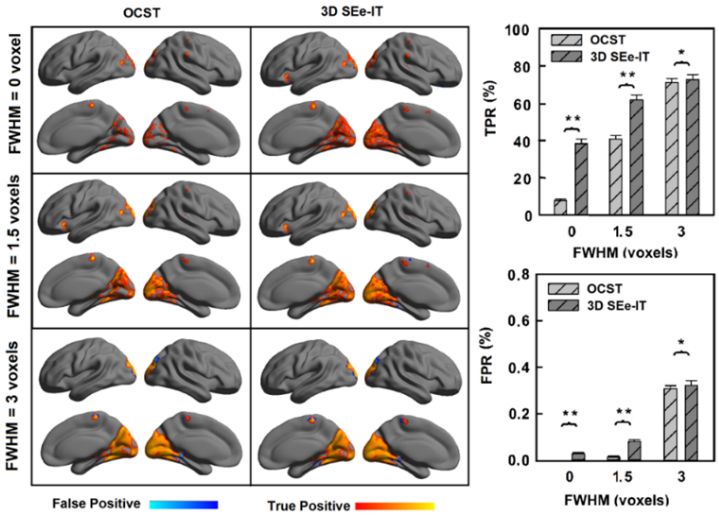

Fig. 1. The representative result of single-subject analysis. The result was detected by OCST and 3D SEe-IT methods at the significance level of 0.05.

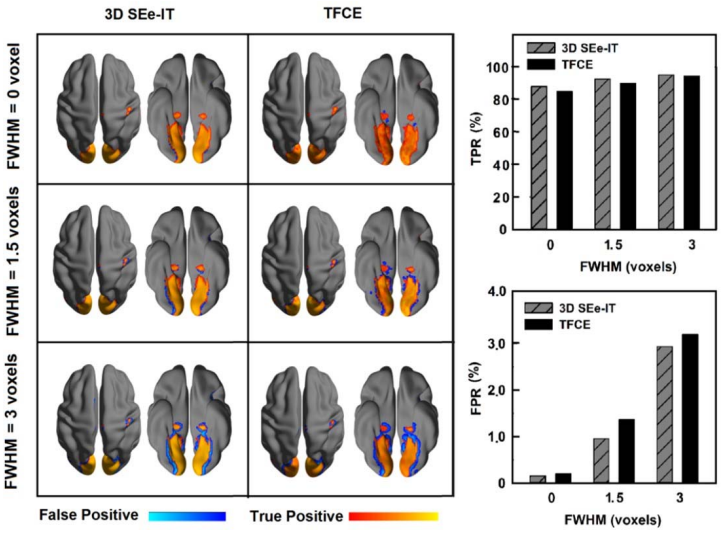

Fig. 2. The result of group level analysis. The result was detected by 3D SEe-IT and TFCE methods at the significance level of 0.05.

Results and Discussion: Fig. 1 shows the single-subject level analysis results. The cluster size thresholds of 3D SEe-IT were the same as OCST for each smoothness level at the significance level of 0.05. As shown in the results, OCST is conservative with no spatial smoothness. The performance of 3D SEe-IT is significantly better than OCST with low spatial smoothness (FWHM ≤ 1.5 voxels). Fig. 2 presents the group level analysis results. The intensity threshold for 3D SEe-IT was 3.65 for each smoothness level. Results show that with a suitable intensity threshold, 3D SEe-IT achieves slightly better sensitivity and specificity than TFCE at each smoothness level.

Conclusion: In this report, a reliable and effective improved cluster-size method was introduced and benchmarked for use in assessing significance in three-dimensional functional images. Unlike the standard approach to CST, which requires heavy spatial smoothing, and TFCE, which can only be used for group level fMRI data analysis, the 3D SEe-IT approach has a higher sensitivity for localizing activation regions for both single-subject and group level analysis without the requirement of spatial smoothness.

References: [1] Friston K.J, et al. Hum Brain Mapp. 1994; 1:210-20. [2] Smith S.M, et al. NeuroImage. 2009; 44:83-98. [3] Beckmann, C.F, et al. Philos Trans R Soc Lond B Biol Sci. 2005; 360: 1001-13. [4] Woolrich, M.W, et al. NeuroImage. 2001; 14:1370-86. [5] Frederick, B.d, et al. NeuroImage. 2012; 60: 1913-23.