Group-Wise FMRI Activation Detection on Corresponding Cortical Landmarks

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Abstract. Group-wise activation detection in task-based fMRI has been widely used because of its robustness to noises and statistical power to deal with variability of individual brains. However, current group-wise fMRI activation detection methods typically rely on the spatial alignment established by co-registration of individual brains' fMRI images into the same template space, which has difficulty in dealing with the remarkable anatomic variation of different brains. As a consequence, the resulted misalignment among multiple brains could substantially degrade the accuracy and specificity of group-wise fMRI activation detection. To address these challenges, this paper presents a novel methodology to detect group-wise fMRI activation based on a publicly released dense map of DTI-derived structural cortical landmarks, which possess intrinsic correspondences across individuals and populations. The basic idea here is that a first-level general linear model (GLM) analysis is performed on fMRI signals of each corresponding cortical landmark in each individual brain's own space, and then the single-subject effect size of the same landmark from a group of subjects are statistically integrated and assessed at the group level using the mixed-effects model. As a result, the consistently activated cortical landmarks are determined and declared group-wisely in response to external block-based stimuli. Our experimental results demonstrated that the proposed approach can map meaningful group-wise activation patterns on the atlas of cortical landmarks without image registration between subjects and spatial smoothing.

Keywords: DTI, fMRI, group-wise activation detection, cortical landmarks.

1 Introduction

Task-based fMRI has been widely recognized as a benchmark approach to detecting functional brain regions that are involved in specific cognitive or functional tasks [1]. Due to the individual variability and different sources of noises, deriving consistent activation patterns across different brains and populations has been challenging. To deal with this challenge, researchers in the neuroimaging field have proposed group-wise activation detection methods [2] that leverage the statistical power from multiple brains in order to gain the robustness to noises and the less sensitivity to individual variability. For instance, the FSL FLAME toolkit [2] transforms the single-subject activation maps to the same atlas space via image registration method, and then infers

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the group-wise significantly activated regions from the pooled activation maps. Though these methods have advantages and have been widely used, they are based on image registration algorithms that transform individual fMRI images into the atlas space to achieve spatial alignment, which has been known to have difficulty in dealing with the remarkable anatomical variation of different brains [3]. Consequently, the misalignments between different activation maps from individual brains could significantly deteriorate the sensitivity and specificity of those group-wise fMRI activation detection methods. As a remedy, current group-wise fMRI activation detection methods commonly employ spatial smoothing to account for the misalignments across different brain images by blurring the variability [9].

This paper presents a novel, alternative group-wise fMRI activation detection methodology that employs a dense map of publicly available 358 landmarks named DICCCOL (Dense Individualized and Common Connectivity-based Cortical Landmarks) [4]. It has been shown that the DICCCOLs possess structure consistency and exhibit both anatomical and functional correspondences across subjects and populations [4]. Therefore, we use them as an individualized and common brain atlas system and examine the activation patterns of these common landmarks in task-based fMRI data. Specifically, the first-level general linear model (GLM) analysis is performed on fMRI signal of each corresponding landmark in the individual's own space [5]. Then, the derived effect sizes of each landmark from multiple subjects are pooled together and the consistent activation significance is group-wisely assessed using the mix-effects model [2]. A major advantage of the landmark-based fMRI activation detection is that the activation levels of cortical landmarks in different brains can be directly integrated and pooled with their anatomical correspondence and without the need of image registration across subjects, which essentially avoids the inaccuracies caused by the spatial misalignments across individuals.

The landmark-based activation detection approach has been applied on a working memory task-based fMRI dataset [6], and our experimental results demonstrated that the proposed methods can map meaningful group-wise activations on the landmarks without image registration among subjects and spatial smoothing.

2 Materials and Methods

2.1 Overview

The computational pipeline of our methods is summarized in Fig. 1. First, DTI data is registered into fMRI image space using the FSL FLIRT registration toolkit (http://www.fmrib.ox.ac.uk/fsl/). Then, white matter streamline fibers are tracked from DTI data via MEDINRIA (http://www-sop.inria.fr/asclepios/software/MedINRIA/). Afterwards, we locate 358 DICCCOL landmarks on individual white matter cortical surfaces via the approach in [4] with the aim that each landmark possesses similar fiber connection patterns across subjects. With the co-registered DTI and task-based fMRI data, we extract fMRI BOLD

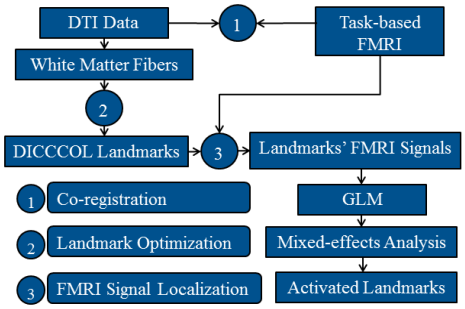

Fig. 1. The pipeline of cortical landmark-based activation detection

signal for each landmark. The commonly used GLM model is then applied on these fMRI signals individually to estimate the single-subject effect size in response to stimulus for each landmark. As the 358 DICCCOL landmarks were validated to possess intrinsic structural correspondences [4], we perform mixed-effects model [2] on each landmark's effect sizes obtained from different brains for the purpose of detecting group-wise consistently activated landmarks.

2.2 Data Acquisition and Pre-processing

In an IRB approved operational span (OSPAN) working memory task-based fMRI experiment [6], fMRI images of 19 subjects were scanned on a 3T GE Signa scanner. Briefly, acquisition parameters are as follows: fMRI: 64×64 matrix, 4mm slice thickness, 220mm FOV, 30 slices, TR=1.5s, TE=25ms, ASSET=2. Each participant performs a modified version of the OSPAN task (3 block types: OSPAN, Arithmetic, and Baseline) while fMRI data is acquired. DTI data was acquired with dimensionality 128×128×60, spatial resolution 2mm×2mm×2mm; parameters are TR 15.5s and TE 89.5ms, with 30 DWI gradient directions and 3 B0 volumes acquired. The DTI data was co-registered to the fMRI space using a linear transformation via FSL FLIRT. For fMRI images, the preprocessing pipeline includes motion correction, slice time correction, temporal pre-whitening, and global drift removal. For DTI data, preprocessing includes skull removal, motion correction and eddy current correction. The brain tissue segmentations are performed on the DTI-derived images via the approaches in [7].

2.3 Group-Wise Activation Detection to Cortical Landmarks

As the cortical landmarks are located cortical surfaces, which are reconstructed from DTI brain tissue maps, we first translate the landmark locations into voxels of

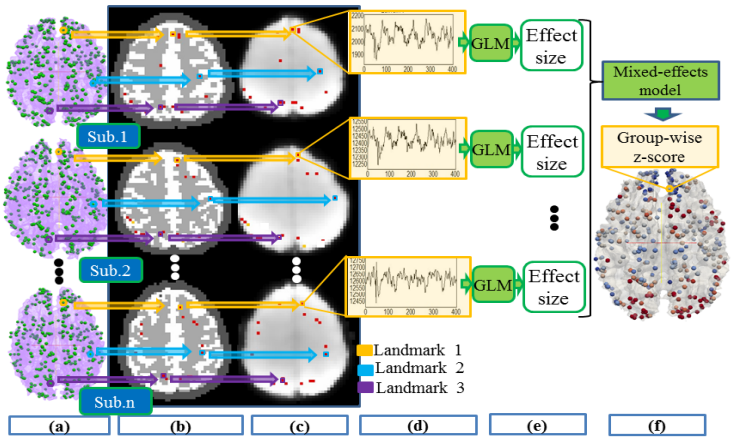

Fig. 2. Illustration of landmark-based group-wise activation detection method. (a) 358 landmarks (green spheres) on the cortical surfaces of 3 subjects. (b) Landmarks (red dots) on the DTI-derived brain tissue maps. (c) Landmark locations (red dots) on fMRI images. Circles and boxes in yellow, blue and purple colors highlight three examples of corresponding landmarks from different subjects. (d) FMRI signals of one example landmark in 3 subjects. (e) GLM analysis applied to each signal. (f) Mixed-effects analysis and group-wise z-score map of 358 landmarks.

DTI-derived brain tissue maps (Fig.2(b)). With the help of intra-subject registration, we locate landmarks on fMRI images (Fig.2(c)) to the corresponding voxels and extract fMRI signal from the voxel for each landmark (Fig.2(d)), avoiding uncertainty caused by averaging signals in a region. Then, the GLM model is employed to estimate the single-subject effect size of each fMRI signal for the task –based block design [6].

We use the mixed-effects model to explore the group-wise activation significance of each landmark from a group of brains. As illustrated in Figs.2(e-f) , for each landmark, we first set single-subject effect sizes from a group of subjects, which are generated from the application of GLM in individual brains, as the input of mixed-effects analysis via the tool of FSL FLAME [2]. Then, the derived z-scores are used to measure the group-wise activation significance of each landmark. Afterwards, we determine the activated landmarks using a threshold.

3 Experimental Results

Here, we designed a series of experiments to investigate the influences of image registration and spatial smoothing in traditional group-wise activation detections (Sections 3.1-3.2), perform group-wise activation detection method on corresponding DICCCOL landmarks and compare it with traditional methods (Section 3.3).

3.1 The Influence of Image Registration in Traditional Method

In traditional group-wise fMRI activation detection, image registration is typically employed to obtain correspondences across subjects. But it is widely recognized that image registration cannot deal with anatomical variations quite well. As shown in Fig.3, 3 subjects are registered to the MNI space. They have voxel alignment

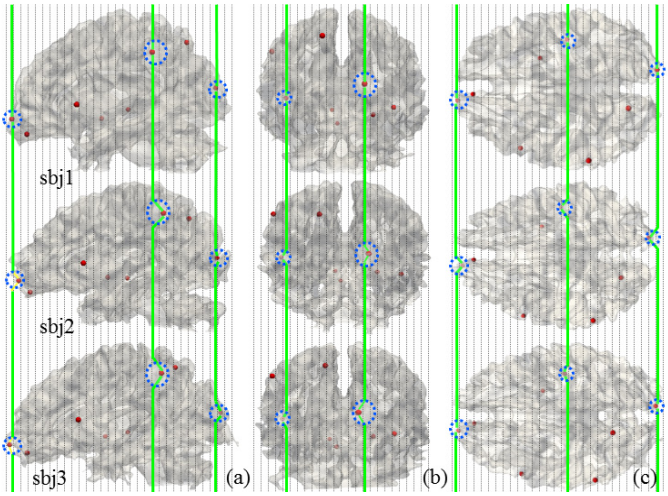

Fig. 3. Illustration that image registration misses anatomical correspondences of the landmarks. Three example brains were linearly transformed into the MNI atlas space. (a) (b) and (c) show 3 perspectives of 8 randomly selected landmarks on the 3 brains.

across subjects as illustrated by the gray dash grids, but the voxel-level correspondence is not necessarily true anatomical correspondence of brains, as the cortical landmarks possess. Actually, the brains' anatomical correspondences can be achieved by the cortical landmarks (red spheres) as highlighted by the green curves. This means image registration could miss actual anatomical correspondence of the landmarks, which could cause inaccuracy during group-wise statistics of activations. Usually, as a remedy, spatial smoothing has been implemented and used before group-wise activation detection [9], in order to blur the misalignment. The blue dash circles show the possible sizes of regions needed to be blurred with spatial smoothing in order to gain actual anatomical correspondence.

3.2 The Influence of Spatial Smoothing in Traditional Method

In traditional group-wise activation detection, spatial smoothing [8, 9] is usually used during the pre-processing of each brain in the group, which makes it easy to detect commonly activated regions across subjects. However, this process involves much uncertainty for the group-wise statistics. Fig.4 presents a series of z-score maps when the Gaussian kernels in different FWHM (Full Width Half Maximum) (0 mm means no spatial smoothing) are used during smoothing. In this figure, the bright regions with high z-scores are potential activations.

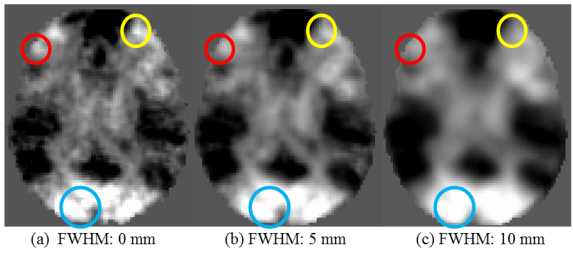

Fig. 4. Example z-score slices of different sizes of smoothing windows for a working memory task fMRI

We can observe from the comparisons in Fig.4 that with the increase of FWHM of Gaussian kernel, the borders of white regions in the blue circles become blurred and finally disappear, which makes different bright regions merge into one. Meanwhile, the small activation region in red circles is weakened and even disappears, and the activation center in yellow circles shifts. Here, we can see that the spatial smoothing process before group-wise analysis could result in possible false positive effects including border blurring, weakening small activation region, and shifting activation centers. We also map the group-wise z-scores without using spatial smoothing (FWHM: 0mm) and using spatial smoothing (FWHM: 5mm) back to the cortical surfaces overlaid with the cortical landmarks (green spheres), as shown in Fig.5. In Fig.5, with spatial smoothing, red areas with high z-scores will expand and involve more landmarks, which we believe are inaccuracy, as illustrated by the black dash circles in Fig.5. All of these results provide evidence that spatial smoothing would potentially result in uncertainty and inaccuracy.

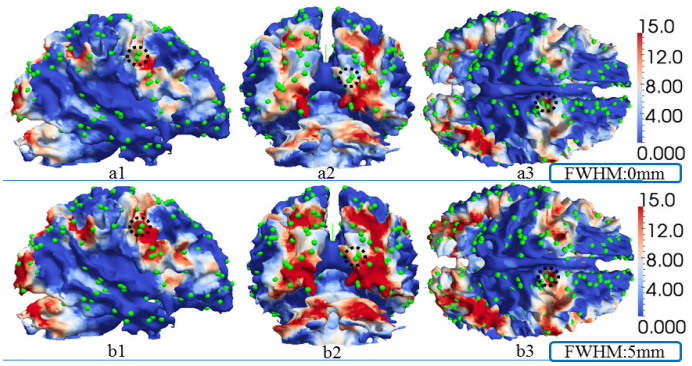

Fig. 5. Z-score maps of traditional group-wise activation detection with different levels of FWHM spatial smoothing. Rows of **a** and **b** are with FWHM 0mm and 5mm respectively. Columns 1, 2 and 3 show three different views of the subject. Green spheres represent the cortical landmarks.

3.3 Group-Wise Activation Detection on the Cortical Landmarks

With the task design paradigm [6], we first perform individual activation detection using FSL FEAT toolkit on the landmarks of each individual brain and color-code landmarks of each subject with the derived z-scores. Similar patterns of z-score distributions on landmarks can be observed for different subjects, as shown in Fig.6(a). Here, four subjects are randomly selected from a group of 19, from which we can infer that although these 358 landmarks' z-scores show different magnitudes across different brains, the spatial distributions of highly activated landmarks are reasonably similar. This result suggests the feasibility of group-wise activation detection using the DICCCOL landmark system. Further, we use our method detailed in section 2.3 to perform group-wise activation detection on the landmark system, and in Fig.6(b), the derived z-scores are mapped back to each landmark with their colors. It's evident that the spatial distribution of group-wise z-scores of landmarks preserves similar pattern of individual distribution, which is also in agreement with activation

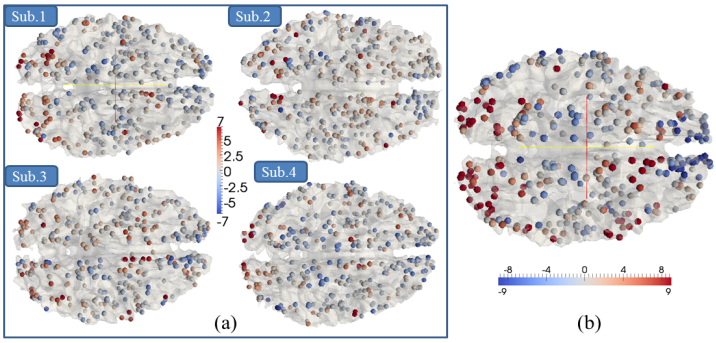

Fig. 6. (a) Randomly selected 4 cases of z-score maps on landmarks by individual activation detection. (b) Z-score map of landmarks by our group-wise method.

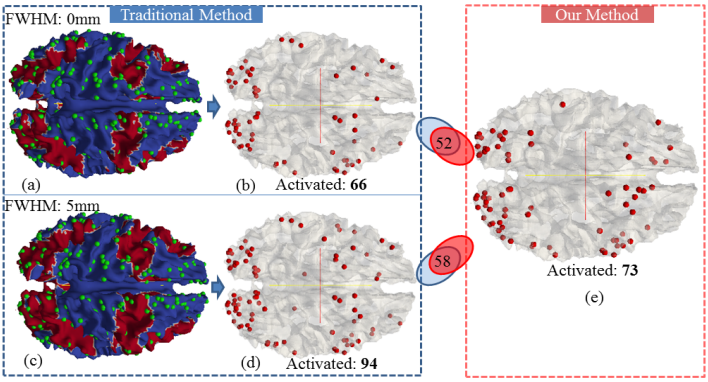

Fig. 7. Comparison of activation from traditional method and our method on cortical landmarks. (a)-(b): Activation detected using T-0mm method. (c)-(d): Activation detected using T-5mm method. (a) and (c): Cortical surfaces mapped with activations by traditional method, on which red area represents activation and green spheres are landmark locations. (b) and (d): Selected activated landmarks when they locate in red areas of (a) and (c). (e): Activated landmarks by our method. T-0mm denotes traditional method with spatial smoothing of FWHM 0mm, and T-5mm is alike.

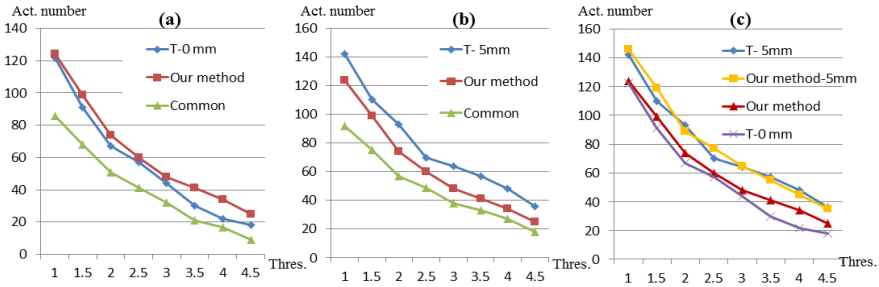

Fig. 8. (a-b) Quantitative comparison of activated landmark numbers via our method and traditional method [2] using different thresholds of z-score. The x-axis represents threshold values of z-score and the y-axis represents activated landmark number. The curves "common" represents number of commonly activated landmarks of two methods. (c) Activated number of four methods. Our method-5mm represents results from our method with the spatial smoothing of 5mm while preprocessing.

results in [6]. Then a threshold is used to the landmarks in Fig.6(b) to determine activations. As shown in Fig.7(e), with a threshold of z-value>2.0 and p-value=0.05, 73 landmarks are detected as activation foci and are colored in red.

As quantitative comparisons, we carry out traditional full-level group-wise activation detection using the FSL FEAT [2] on volumes of the same group of subjects with different spatial smoothing settings. With the same threshold of z-value>2.0 and p-value=0.05, activation regions are mapped onto surfaces with red color in Figs.7(a) and 7(c). Traditional method without spatial smoothing (T-0mm method) detects reasonable regions in spite of inaccuracy induced by registration. But with spatial smoothing of FWHM 5mm (T-5mm method), the resolution of activation

is reduced because of uncertainty caused by smoothing. For ease of comparison, we further overlaid landmarks (green spheres in Figs.7(a) and 7(c)) on the cortical surfaces and the cortical landmarks in red regions are selected as activation, as visualized in Figs.7(b) and 7(d). Fig.7(b) shows 66 activated landmarks using T-0mm method, and the common activation number with the result by our method (Fig.7(e)) is 52, which is majority of both methods. In contrast, the activated landmarks using T-5mm method only have 58 of 94 in common with our method. Further we performed similar comparison with different thresholds of z-values, and the activated landmark numbers are plotted in Fig.8. In Fig.8(a), the red and blue curves almost match together before the threshold of z-value=3.0. As the threshold increases above 3.0, the blue curve trends closer to green curve, suggesting that our method has similar spatial resolution with T-0mm method. But with higher threshold, the T-0mm method will be less powerful because of inaccuracy caused by image registration. However our method is able to keep the spatial resolution. In Fig.8(b), the blue curve is above the red curve, and the deviation of them grows larger above the threshold of 3.0. In contrast, the red curve approximates the green curve, which implies that our method has higher sensitivity and specification than the T-5mm method, especially when the threshold is high. For the T-5mm method even with high threshold, the uncertainty caused by spatial smoothing cannot be prevented. In addition, we applied our proposed method with spatial smoothing of FWHM=5mm in the preprocessing step (Our method-5mm), and the activated numbers are curved with yellow color in Fig.8(c), which performs similar or more activated number than the T-5mm method. This is another evidence for the uncertainty caused by spatial smoothing. Here, experimental results demonstrated that our landmark-based method is able to avoid the image registration inaccuracy without the need of spatial smoothing.

4 Conclusion

The development and validation of robust, effective and accurate approaches for fMRI activation detection have been investigated for decades. Due to the challenges of remarkable variability in brain structure and function across individuals and the lack of quantitative representation of common brain architectures, novel fMRI activation detection methods have been still in active research in the neuroimaging community. The major novel insight obtained from this work is that an individualized representation of common structural brain architectures across different brains, e.g., by the 358 DICCCOL landmarks, can substantially improve the reliability and accuracy of fMRI activation detection. Although 358 landmarks are limited quantity of samples from fMRI image, their group correspondence and signal quality are guaranteed in our approach. With the development of imaging technology and improvement of DICCCOL system, the limitation will be remedied.

References

1. Logothetis, N.K.: What we can do and what we cannot do with fMRI. Nature 453, 869–878 (2008)

2. Beckmann, C.F., Jenkinson, M., Smith, S.M.: General multi-level linear modelling for group analysis in FMRI. NeuroImage 20, 1052–1063 (2003)
3. Derrfuss, J., Mar, R.A.: Lost in localization: the need for a universal coordinate database. NeuroImage 48(1), 1–7 (2009)
4. Zhu, D., et al.: DICCCOL: Dense Individualized and Common Connectivity-Based Cortical Landmarks. Cerebral cortex (2012), http://dicccol.cs.uga.edu/
5. Friston, K.J., et al.: Statistical parametric maps in functional imaging: a general linear approach. Human Brain Mapping 2(4), 189–210 (1994)
6. Faraco, C.C., et al.: Complex span tasks and hippocampal recruitment during working memory. NeuroImage 55(2), 773–787 (2011)
7. Liu, T., Li, H., Wong, K., et al.: Brain Tissue Segmentation Based on DTI Data. NeuroImage 38(1), 114–123 (2007)
8. Frison, K.J., Holmes, A., et al.: Detecting activations in PET and fMRI: levels of inference and power. Neuroimage 4(3), 223–235 (1996)
9. Mikl, M., et al.: Effects of spatial smoothing on fMRI group inferences. Magn. Reson. Imaging 26(4), 490–503 (2008)