GROUPWISE FMRI REGISTRATION USING MULTI-RANGE FUNCTIONAL CONNECTIVITY PATTERNS

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ABSTRACT

The inter-subject alignment is an important precursor to improve consistency across subjects for statistical group analysis in functional magnetic resonance imaging (fMRI) studies. To overcome the limitations of existing techniques and further improve inter-subject functional consistency, we propose a novel image registration method for fMRI data based on features of multi-range functional connectivity patterns. To simultaneously align fMRI data of a group of subjects, we also develop a groupwise registration scheme similar to the congealing technique. Experimental results based on simulated fMRI data have demonstrated that our method can achieve superior performance over existing fMRI image registration methods. Experiment results on real resting-state fMRI data have indicated that the proposed method can statistically significantly improve functional consistency across subjects.

Index Terms— fMRI registration, congealing groupwise registration, functional connectivity

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) studies commonly analyze fMRI data across a group of subjects. The spatial consistency across subjects is the basic requirement in most group statistical analysis of fMRI data. To achieve spatial consistency across subjects, one often utilizes structural MRI (sMRI) based registration methods, such as Talairach normalization [1], FLIRT [2] and more advanced non-rigid registration methods [3, 4]. However, this kind of techniques cannot achieve accurate inter-subject functional consistency due to functional variability across subjects [5]. In order to further improve the functional consistency, spatial smoothing the functional image of each subject is commonly used in practice. But the penalty of blurring the functional signals and losing the fine-grained information will be brought into the subsequent group statistical analysis. Hence, it is desirable to develop an image registration method which is directly based on functional information in fMRI studies.

Several registration methods for fMRI data have been proposed recently. A cortical surface alignment method based on fMRI signals was proposed in [5]. In this study, functional signal at each cortical surface location is used as a feature vector, and cortical surfaces of different subjects are registered by maximizing the correlation of inter-subject functional signals. This registration method is built upon the assumption that functional signals are synchronic across different subjects, which is not necessarily true for resting-state fMRI data. A global functional connectivity pattern based registration method was proposed in [6], in which different subjects' cortical surfaces is registered by minimizing the Frobenius norm of difference between the whole-brain connectivity matrices of these subjects. However, the global functional connectivity pattern is not reliable for image registration since small local perturbations of functional units, such as rotation and shift in spatial domain, will change dramatically the global connectivity pattern matrix. In [7], a spectral embedding technique was utilized to extract features from the global functional connectivity matrix and then the registration of fMRI images was accomplished by matching two point sets in the feature space, or, so-called functional space. Although the features extracted using spectral embedding are not dependent on spatial location of voxels, some *ad hoc* techniques have to be utilized to make the features of different subject comparable [7]. In [8], local connectivity pattern was adopted to guide the fMRI image registration to overcome these limitations, but the global functional consistency across subjects might not be achieved by this approach since the spatial range of connectivity patterns is fixed. For registering a group of subjects, an iterative pairwise image registration scheme was adopted in [6, 7]. Such a groupwise image registration scheme is time-consuming and may generate biased results since the images are not warped simultaneously.

To overcome limitations in the existing registration methods for fMRI data, we propose a multi-range functional connectivity pattern based registration method. Instead of maximizing the correlation of inter-subject fMRI signals or similarity of the global connectivity patterns of different subjects, we use local functional connectivity patterns to

guide the registration in a hierarchical way. In other words, at the initial stage of functional image registration, a local functional connectivity pattern is computed in a small spatial local neighborhood of each voxel to describe its functional information, and along the progression of image registration, the local functional connectivity patterns become more consistent across subjects so that the neighborhood size can be gradually increased to capture functional connectivity information in larger scales. In this way, the global consistency can be achieved. Compared with the global functional connectivity pattern which can be changed dramatically by small local perturbations, using the local connectivity pattern at early stage of image registration is much more robust, especially when the neighborhood size is small. To get a rotation and shift invariant representation of functional connectivity patterns, a kernel density estimation technique is utilized to transfer the connectivity pattern into a probability distribution representation [8]. For registering fMRI data of a group of subjects, we jointly align all of them simultaneously to an implicit reference space similar to the congealing algorithm [9, 10].

We compare the proposed method with the inter-subject correlation based method and the global connectivity based method using simulated fMRI data, and the results indicate that the proposed method can achieve superior performance. The experiment results on real resting-state fMRI data further demonstrate that the proposed method can statistically significantly improve functional consistency across subjects.

2. METHODS

Supposing $\{I_1, \dots, I_N\}$ is a set of functional images, each of them containing functional signals $I_i(x) = \{I_i^t(x)\}_{t=1}^T$ over the image space Ω_i, $i = 1, \dots, N$. For any reference image I_R, I_i can be registered to I_R by a spatial transformation $g_i: \Omega_R \to \Omega_i$ through maximizing the similarity between $f(I_i(g_i(x)))$ and $f(I_R(x))$ for somehow defined image feature f.

2.1. Feature Extraction

The features used in the proposed registration method are extracted from fMRI images based on connectivity patterns. Given an fMRI image *I*, the functional connectivity between two voxels x, y can be measured using Pearson correlation between their time courses, denoted as $C(x,y) = corr(I(x), I(y))$. For each voxel $x \in \Omega$, we compute its functional connectivity to every voxel in its spatial neighborhood $nh(x)$, generateing a set of functional connectivity measures $\{C(x,y)\}_{y \in nh(x)}$,, which serves as a functional descriptor of voxel *x*, and is referred to as a local connectivity pattern. The spatial neighborhood size can vary to compute functional connectivity patterns at different ranges.

The local functional connectivity pattern is more robust for spatial image registration than the global one as schematically illustrated in Fig.1. Fig.1a shows two simulated fMRI data, each of them containing one square and one circle regions located spatially differently. Supposing that regions of the same shape in two images are corresponding regions across subjects, we study the images' local and global functional patterns. The square patches extracted from images (Fig.1b, c) stand for the spatial neighborhoods of pixel A, B, from which the connectivity patterns are computed. As shown in Fig.1b, the local functional patterns across different subjects can be highly similar since the small neighborhoods contain the same functional units. However, when the spatial neighborhood size increases to a certain range, its associated functional patterns across different subjects may have low similarity since the relatively large neighborhoods may contain different mixtures of functional units, as illustrated in Fig.1c, indicating that functional connectivity pattern of large range cannot be robust for image registration.

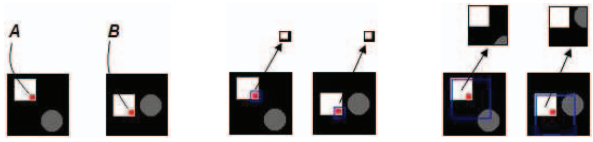


Fig.1. Comparison between local and global functional connectivity patterns. a) Simulated functional images of two different subjects, same shapes representing corresponding functional regions between subjects, A and B are corresponding pixels. b) Small neighborhoods contain the same functional units. c) Large neighborhoods contain different mixtures of functional units.

For achieving robust functional image registration, at the initial stage, the neighborhood size for computing functional connectivity pattern should be relatively small. Along the progression of image registration, as the local patterns become much more consistent across subjects, the neighborhood size can be increased and larger range connectivity patterns can be used for achieving global consistency.



Fig.2. Schematic diagram of a) our feature extraction strategy, b) a pixel stack of a group of images.

Since the local connectivity patterns can still be affected by spatial rotation and shift of neighboring voxels, to achieve effective image registration, a rotation and shift invariant feature should be adopted. To do so, for each voxel, measures of its functional connectivity to other voxels within its spatial neighborhood are modeled as a set of sampling points of a specific probability distribution, and

then the distribution is estimated using kernel density estimation method. Herein, for voxel x, its local functional connectivity pattern's probability distribution is used as feature $f(I(x))$ to guide the registration. This feature extraction strategy is shown schematically in Fig.2a, where the red line segments stand for a voxel's connectivity to its neighboring voxels.

2.2. Groupwise Registration

To register a group of subjects, we adopt a scheme similar to the congealing algorithm [9, 10]. Particularly, all images are aligned simultaneously to an implicit common space by minimizing the sum of voxelwise entropies along pixel stacks as illustrated by Fig.2b.

Since each voxelwise functional connectivity pattern's probability distribution can be represented by a *D*-dimensional feature vector, for a voxel stack, Shannon entropies can be estimated along each dimension separately. Given a voxel in the reference space, $x \in \Omega_R$, the voxel stack at spatial location *x* can be represented by $\{g_i(x)\}_{i=1}^N$ for the images to be registered. By employing the kernel density estimation technique, the Shannon entropy along *d*th dimension can be written as:

$$H_d(x) = -\frac{1}{N}\sum_{i=1}^{N} log \frac{1}{N}\sum_{j=1}^{N} G_\sigma[f^d(I_i(g_i(x))) - f^d(I_j(g_j(x)))].$$

Thus, the total entropy for each voxel stack and the groupwise registration objective can be written as:

$$E = \sum_{x\in\Omega_R} E(x), in\ which, E(x) = \sum_{d=1}^{D} H_d(x).$$

The objective function achieves its minimum when the features of different images become similar along every dimension of feature space. By representing transforms as dense deformation fields, i.e. $g_i(x) = x + u_i(x)$, the objective function can be optimized with respect to u_n using gradient descent method. Kernel density estimation allows us to obtain analytical expressions for the derivative of the objective function with respect to u_n.

To make the deformation fields smooth, we adopt the fluid-like demons scheme [4] for minimizing the objective function and use a Gaussian filter to spatially smooth the velocity fields at every iteration before updating the deformation fields. The deformation fields are further regularized by composing each of them with the inverse of the mean deformation field so that unbiased registration results can be achieved.

3. EXPERIMENTAL RESULTS

The proposed algorithm is validated using both simulated and real resting-state fMRI data, and is compared with the inter-subject correlation based method and the global connectivity pattern based method. The resting-state fMRI (rs-fMRI) data were obtained from INDI database (fcon_1000.projects.nitrc.org), consisting of 20 healthy subjects, each subject's image has 175 time points with TR=2s. The data were preprocessed using the standard protocol, including slice timing, head movement correction, band-pass filtering, spatially normalization based on structure images, and regressing out the nuisance covariant. However, the data were not smoothed spatially.

3.1. Simulated Experiment

We first compare the proposed algorithm with the inter-subject correlation based method [5]. In this experiment, we try to demonstrate that the inter-subject correlation based method cannot work well due to asynchrony of resting-state functional signals across different subjects.

From each subject's fMRI data, two simulated functional images are generated, one consisting of its first 150 time points and the other consisting of its last 150 time points. The first 150-time-points image is then registered to the last 150-time-points image pairwisely by the two algorithms respectively for each subject. Since each pair of simulated images is built from same subject's functional signals, we expect that the resultant deformation displacement is closed to zero. Both methods run 100 iterations in this experiment. The mean deformation displacement generated by our method is 0.58mm (variance = 0.06), 86.2% of the voxels are with displacements less than 1mm, and only 0.7% of the voxels are with displacements than the image spatial resolution (3mm). In contrast, the mean deformation displacement generated by the correlation based method is 4.36mm (variance = 0.81), only 6.73% of the voxels are with displacements less than 1mm, and 52.4% of the voxels are with displacements larger than the image spatial resolution. The histograms of displacements are shown in Fig.3, indicating that the inter-subject correlation based method may get biased registration results for resting state fMRI data.

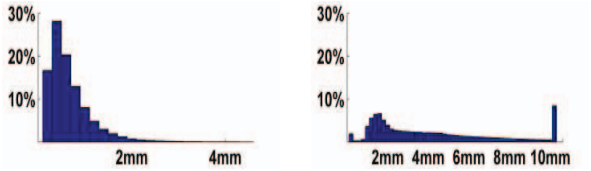


Fig.3. Histogram of displacements generated by different methods. Left: the proposed method. Right: inter-subject correlation based method.

To compare with the global connectivity based method [6], another experiment is performed based on the simulated functional images shown in Fig.4. We randomly pick three time series from the real rs-fMRI data, and fill them respectively into the square and the circle region, and as well as the black background (Fig.4a). The left simulated image is then registered to the right one by the global connectivity based method and our method respectively (Fig.4a). The registration result of our method is shown in Fig.4b, and result of the global connectivity based method is shown in Fig.4c. It can be seen that the global connectivity

based method failed to register the two images while our method yielding a promising result.

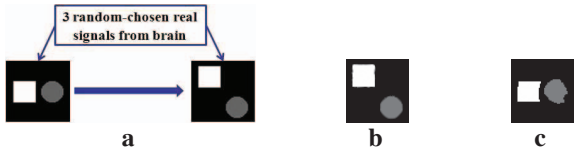


Fig.4. Simulated experiments for comparison between local connectivity and global connectivity.

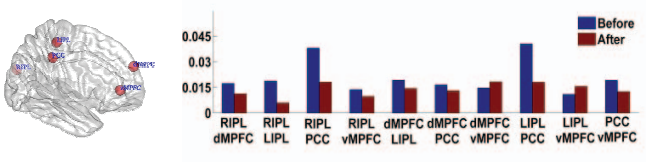


Fig.5. Comparison results for functional connectivities among 5 hub nodes of DMN. a) PCC, RIPL, LIPL, dMPFC, vMPFC. b) Connectivity variance across subjects. Bars in blue are corresponding to the results of before fMRI image registration, and those in red are corresponding to the results of fMRI image registration performed by the proposed method.

3.2. Real Data Experiment

The real rs-fMRI data of 20 subjects are groupwisely registered using the proposed method after they are aligned based on their structural T1 images. The quality of the alignment is evaluated by assessing the inter-subject consistency of Default Mode Network (DMN) consisting of 13 nodes.

For each pair of nodes, the variance of node-to-node connectivity among 20 subjects is computed and then used to assess the inter-subject consistency, i.e. lower variance indicating improved inter-subject consistency. We compare the node-to-node connectivity variances before and after the groupwise alignment by our method. That is, the comparison is performed between the standard registration methods based on structural information and our registration method based on functional information. The results indicate that the node-to-node connectivity variances are statistically significantly lower after alignment with $p < 6 \times 10^{-8}$ for paired t-test. Due to the space limitation, only the comparison histogram for 5 hub nodes of DMN (posterior cingulate cortex (PCC), left and right inferior parietal lobule (LIPL & RIPL), dorsal medial prefrontal cortex (dMPFC) and ventromedial prefrontal cortex (vMPFC)) are shown in Fig.5. This result indicates that our proposed method can statistically significantly improve the functional consistency across subjects. The proposed method is implemented based on ITK and parallelized using openMP. The computational time for these 20 fMRI data is about 32hs on a 16-core 32G ram server.

4. CONCLUSION

In this paper, a novel groupwise registration algorithm for fMRI data is proposed. The proposed method has several advantages compared with existing fMRI image registration techniques. First, the image registration is driven by multi-range connectivity patterns that are robust against small local perturbations compared with the global connectivity pattern and can overcome the problem of asynchrony of functional signals across different subjects. Second, the groupwise registration is performed within the framework of congealing, enabling bias-free registration of a group of images. The experiment results indicate that the proposed method can statistically significantly improve the inter-subject functional consistency.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

[1] J. Talairach and P. Tournoux, Co-planar stereotaxic atlas of the human brain. Stuttgart & New York: Georg Thieme, 1988.

[2] B. Fischer and J. Modersitzki, "FLIRT: A flexible image registration toolbox," Biomedical Image Registration, vol. 2717, pp. 261-270, 2003.

[3] M. F. Beg, et al., "Computing large deformation metric mappings via geodesic flows of diffeomorphisms," International Journal of Computer Vision, vol. 61, pp. 139-157, Feb 2005.

[4] J. P. Thirion, "Image matching as a diffusion process: an analogy with Maxwell's demons," Med Image Anal, vol. 2, pp. 243-60, Sep 1998.

[5] M. R. Sabuncu, et al., "Function-based intersubject alignment of human cortical anatomy," Cereb Cortex, vol. 20, pp. 130-40, Jan 2010.

[6] B. Conroy, et al., "fMRI-Based Inter-Subject Cortical Alignment Using Functional Connectivity," Advances in Neural Information Processing Systems 22, pp. 378-386, 2009.

[7] G. Langs, et al., "Functional Geometry Alignment and Localization of Brain Areas," Advances in Neural Information Processing Systems 23, pp. 1225-1233, 2010.

[8] D. Jiang, et al., "fMRI Alignment Based on Local Functional Connectivity Patterns," in SPIE 2012 Medical Imaging Accepted.

[9] S. K. Balci, et al., "Free-Form B-spline Deformation Model for Groupwise Registration," Med Image Comput Comput Assist Interv, vol. 10, pp. 23-30, 2007.

[10] E. G. Learned-Miller, "Data driven image models through continuous joint alignment," IEEE Transactions on Pattern Analysis and Machine Intelligence, vol. 28, pp. 236-250, Feb 2006.