fMRI alignment based on local functional connectivity patterns

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ABSTRACT

In functional neuroimaging studies, the inter-subject alignment of functional magnetic resonance imaging (fMRI) data is a necessary precursor to improve functional consistency across subjects. Traditional structural MRI based registration methods cannot achieve accurate inter-subject functional consistency in that functional units are not necessarily consistently located relative to anatomical structures due to functional variability across subjects. Although spatial smoothing commonly used in fMRI data preprocessing can reduce the inter-subject functional variability, it may blur the functional signals and thus lose the fine-grained information. In this paper we propose a novel functional signal based fMRI image registration method which aligns local functional connectivity patterns of different subjects to improve the inter-subject functional consistency. Particularly, the functional connectivity is measured using Pearson correlation. For each voxel of an fMRI image, its functional connectivity to every voxel in its local spatial neighborhood, referred to as its local functional connectivity pattern, is characterized by a rotation and shift invariant representation. Based on this representation, the spatial registration of two fMRI images is achieved by minimizing the difference between their corresponding voxels’ local functional connectivity patterns using a deformable image registration model. Experiment results based on simulated fMRI data have demonstrated that the proposed method is more robust and reliable than the existing fMRI image registration methods, including maximizing functional correlations and minimizing difference of global connectivity matrices across different subjects. Experiment results based on real resting-state fMRI data have further demonstrated that the proposed fMRI registration method can statistically significantly improve functional consistency across subjects.

Keywords: fMRI image, image registration, local functional connectivity pattern

1. INTRODUCTION

In group analysis of functional magnetic resonance imaging (fMRI) data, the spatial alignment of fMRI images is often a necessary precursor to improve consistency across subjects. The registration of fMRI images is typically achieved by aligning their corresponding structural MRI (sMRI) images using image registration methods such as Talairach normalization1, FLIRT2, and more advanced non-rigid methods3-5. However, the sMRI based image registration cannot achieve accurate inter-subject functional consistency in that functional units are not necessarily consistently located relative to anatomical structures due to functional variability across different subjects. In order to improve the inter-subject functional consistency, in practice, functional images are often spatially smoothed. However, the adverse effects of image smoothing, including functional signal blurring and loss of fine-grained information, will be brought into the subsequent group analysis. Hence, it is desired to register functional images directly based on functional information in fMRI study.

Recently, several functional information based registration methods have been proposed6-8. Sabuncu et.al proposed a cortical surface alignment method based on functional signals6. In their method, the Pearson correlations of inter-subject functional signals were maximized to register different subjects’ cortex surface meshes based upon the assumption that functional signals are synchronous across different subjects. However, such an assumption is not necessarily true in most cases. In resting-state fMRI (rs-fMRI) images, for instance, even at the same position of same subject, no significant correlations are exhibited between the functional signals of sessions scanned at different time. Thus, this method is not
reliable for rs-fMRI images. Another cortical surface registration method used the whole-brain functional connectivity matrix as a descriptor of the cortical surface and registered different subjects’ cortical surface meshes by minimizing the Frobenius norm of difference of their functional connectivity matrices. However, the global connectivity pattern based functional image registration is not robust since the global connectivity patterns is prone to being severely altered by small local perturbations, such as rotation and shift of functional units in the spatial domain, thus leading to misregistration. Langs et.al extracted features from the whole-brain functional connectivity matrix using spectral embedding technique and then aligned functional images by a point set registration method in the feature space, or, the so called functional space. Although the spectral embedding based feature extraction does not rely on spatial consistency, ad hoc techniques have to be utilized to make the extracted features of different subjects comparable since embedding is defined up to rotation, order and sign of individual coordinate axes.

In order to overcome the limitations in the existing registration methods for fMRI data, we propose a novel functional signal based registration algorithm. Instead of maximizing correlation of functional signals or similarity of global connectivity patterns of different subjects, in our method, local functional connectivity pattern, which is computed in a small local neighborhood of each voxel to describe its functional information, is adopted to guide the image registration. Since the global connectivity patterns can be dramatically changed by the local spatial perturbations of functional units, using the local connectivity patterns is much robust in the fMRI registration task, especially when the spatial neighborhood size is small. To get a rotation and shift invariant representation of functional connectivity patterns, a kernel density estimation technique is further utilized to transfer the local connectivity pattern into a probability distribution representation. The distance between the probability distributions of different subjects is then minimized under a deformable registration model to achieve image registration. Experiment results based on simulated fMRI data have demonstrated that, compared with the fMRI registration methods based on maximizing functional correlations and minimizing difference of global connectivity matrices across different subjects, the proposed method is more robust and reliable and capable of achieving superior image registration performance. Experiment results based on real resting-state fMRI data have further demonstrated that the proposed fMRI registration method can statistically significantly improve functional consistency across subjects.

2. METHOD

The proposed local connectivity pattern based fMRI image registration algorithm consists of feature extraction and feature based image registration. The section of Feature Extraction details the computation of local connectivity patterns and the strategy of getting the rotation and shift invariant representation of the local connectivity pattern. The section of Image Registration describes the definition of the registration objective function and its optimization. In addition, the difference between local and global connectivity patterns is illustrated in the section 2.3.

2.1 Feature extraction

Let be a volumetric functional image, and its spatial domain is denoted by , . Thus, the volumetric functional image can be seen as a vector function over the spatial domain , , with a vector value , where is the local range (local spatial neighborhood of each voxel) rather than the global range (whole brain), this set of connectivity measures is referred to as a local connectivity pattern. The size and the shape of the spatial neighborhood of every voxel can be the same throughout the image spatial domain, or, can be adaptive to different image locations. The neighborhood size also can be gradually increased as the registration process proceeds, to capture functional information in larger scales. In experiments reported in this paper, for simplicity, the spatial neighborhood is chosen as a cube with the edge length of 5 voxels, and is fixed throughout the image domain and the cube size stays the same in the whole registration process.

1) As illustrated in Fig.1a, for each voxel , we compute its functional connectivity to every neighboring voxel in its local spatial neighborhood of , denoted by , generating a set of functional connectivity measures , which serves as a descriptor of the functional connectivity information of voxel . Since the functional connectivity information is computed at the local range (local spatial neighborhood of each voxel) rather than the global range (whole brain), this set of connectivity measures is referred to as a local connectivity pattern. The size and the shape of the spatial neighborhood of every voxel can be the same throughout the image spatial domain, or, can be adaptive to different image locations. The neighborhood size also can be gradually increased as the registration process proceeds, to capture functional information in larger scales. In experiments reported in this paper, for simplicity, the spatial neighborhood is chosen as a cube with the edge length of 5 voxels, and is fixed throughout the image domain and the cube size stays the same in the whole registration process.
2) A voxel's local connectivity pattern can be affected by the spatial rotation and shift of its neighboring voxels, since the neighboring voxels' change at the spatial domain relative to the neighborhood center will alter the order of the brain functional connectivity measures. As shown in Fig.1b, the black dot is referred to as an image voxel, while others of different colors around it are referred to as its neighboring voxels. The numbers marked on the neighboring voxels indicate the order of the functional connectivity measures. As the neighboring voxels rotate counterclockwise for 120° from the left panel to the right panel of Fig.1b, the order of connectivity measures has been altered (bottom of Fig.1b, the connectivity measures of left and right panels have different orders). Thus, to achieve effective image registration, a rotation and shift invariant feature has to be adopted based on the local connectivity pattern. To do so, for each voxel, the set of functional connectivity measures is modeled as a set of sample points of a specific probability distribution, and then the probability distribution is estimated using the kernel density estimation technique\(^\text{11}\). Herein, Gaussian kernel is used as the kernel function. For a image voxel \(x_i\) and a given sampling point \(p_k \in [-1,1]\) (since the Pearson correlation coefficient is between -1 and 1), the probability density at \(p_k\) is:

\[
f^k(x_i) = \frac{1}{|n(i) \setminus x_i|} \sum_{f \in n(i), f \neq x_i} \frac{1}{(2\pi)^{d/2}} \exp \left\{ -\frac{||p_k - C(i,f)||^2}{2\sigma^2} \right\},
\]

where \(|n(i) \setminus x_i|\) is the number of neighboring voxels in the spatial neighborhood of voxel \(x_i\). Thus, the probability distribution is represented by a feature vector, \(f(x_i) = [f^1(x_i), f^2(x_i), \ldots, f^M(x_i)]\) for each voxel \(x_i\). These feature vectors are then used to guide the image registration. The whole feature extraction strategy is illustrated schematically in Fig.1c.

![Fig.1. Feature extraction. a) Functional connectivity is computed in a local spatial neighborhood of voxel \(x_s\), referred to as a local connectivity pattern. The red line segments stand for the functional connectivity. b) Local connectivity pattern can be altered by spatial rotation (or shift) of the neighboring voxels. c) Schematic diagram of our feature extraction strategy.](image)

### 2.2 Image registration

Let \(T,S\) be the target and source functional images respectively. To register the source image \(S\) to the target image \(T\), we need to find a spatial transformation \(g: \Omega_T \rightarrow \Omega_S\) that warps the target image onto the source image space following the Euler reference frame criterion\(^\text{12}\). Image registration is commonly modeled as an optimization problem for finding the optimal spatial transformation \(g\). The optimization objective function often contains a fidelity term and a regularization term. The fidelity term is minimized when the best correspondence between the source and target images has been established. Thus, a metric should be defined to measure the distance between the features belong to a pair of images. A lot of metrics, such as Euclidian distance in the feature space, KL-divergence, Chi-square metric, can be adopted here to measure distance between a pair of local connectivity patterns. In the experiments reported in this paper, for simplicity, the Euclidian distance is adopted, which is defined as eqn. (1),

\[
\text{dist}(f_T(x), f_S(y)) = \sum_{k=1}^{M} (f^k_T(x) - f^k_S(y))^2.
\]

where \(M\) is the dimension of the feature vectors of local functional connectivity patterns, and \(f^k(x)\) is the probability density estimated at \(k\)th sampling point \(p_k\). It is worth noting that for the Euclidean distance measure, feature vectors of all image voxels should have the same dimension, i.e., in the feature extraction step, the probability density should be estimated at the same sampling points for all the voxels.

To solve the optimization problem, the spatial transformation should be parameterized. Here, the spatial transformation \(g\) is represented as a dense deformation field, i.e., \(g(x) = x + u(x)\), and \(u(x)\) is the displacement at point \(x\). By this parameterization of \(g\), the fidelity term can be written as:

\[
E_f = \int_\Omega_T \text{dist}(f_T(x), f_S(x + u(x)))dx.
\]
In addition to the fidelity term, the transformation, i.e. the deformation field, has to be regularized, in order to prevent it from severe spatial distortions. Thus, a regularization term, \( E_r(u) \), is needed in the image registration objective function. There are many choices for \( E_r(u) \) here, for instance, the fluid-like regularization\(^5\), the diffusion-like regularization\(^4\), as well as diffeomorphic regularization\(^5,15,16\). Besides these regularization techniques, Thirion’s demons registration model\(^3\) does not have an explicit regularization term in its objective function, as it regularizes the displacement field by a Gaussian convolution filter. Cashier et.al\(^17\) introduced a hidden variable into the demons model and turned it into a two-step optimization problem so that its objective function contained a regularization term and a likelihood term. This demons registration model with the fluid-like or, the incremental regularization\(^17\), is adopted here for its excellent image registration performance. Combining the fidelity term and the regularization term, we have the image registration objective function

\[
E = E_f + E_d + E_r = \int_{\Omega} \text{dist}(f_T(x), f_S(x + \tilde{u})) dx + \int_{\Omega} \|\tilde{u} - u\|^2 dx + E_r(u),
\]

where \( \tilde{u} \) is the hidden variable, \( E_d \) is the likelyhood term and \( E_r(u) \) is a quadratic form which regularizes the incremental \( u^n - u^{n-1} \) between \( n^{th} \) and \( (n-1)^{th} \) iteration. Thus, we follow the two-step optimization strategy to find a local optimum of the deformation field and regularize it by the Gaussian convolution filter at every iteration. This optimization strategy is summarized in table 1.

**Table 1.** Summary of the image registration algorithm.

| **Initialize** | \( n \leftarrow 0, \quad u^0 \leftarrow \text{zero field} \).
| **Given maximum iteration** | \( \text{max} \) and tolerance \( \varepsilon \).
| **Given the current deformation field** | \( u^n \), compute the update field \( v \) by optimizing \( E_f + E_d = \int_{\Omega} \text{dist}(f_T(x), f_S(x + u^n + v)) dx + \int_{\Omega} \|v\|^2 dx \).
| **Update** | \( v = K_{\text{gauss}} \ast v \).
| \( u^{n+1} = u^n + t \cdot v \). | The time step \( t \) is adaptive at each iteration as suggested by B. C. Vemuri, et.al\(^{18}\).
| If | \( n > \text{max} \) or \( \text{abs}(E_f^{n+1} - E_f^n) < \varepsilon \), stop; else, \( n \leftarrow n + 1 \) and go to the first step.

**Fig.2.** Schematic illustration of the computation of local and global functional connectivity patterns. a) Simulated functional images of two different subjects, objects in the images with the same shape denote corresponding functional regions across subjects, \( A \) and \( B \) are corresponding pixels. b) Small neighborhoods contain the same functional units so that the functional connectivity patterns computed based on them can be highly similar across subjects. c) Large neighborhoods contain different mixtures of functional units so that the functional connectivity patterns computed based on them may have low similarity across subjects.

2.3 Why the local functional connectivity pattern instead of global?

The performance of image registration with local and global functional connectivity patterns is investigated using simulated images as schematically illustrated in Fig.2. Fig.2a shows two simulated images, each of them containing one square region and one circle region at different locations. We denote the left simulated image as Image 1 and the right one as Image 2. Supposing that regions of the same shape in the two images are corresponding regions across subjects, we study the images’ local and global functional patterns. For mapping pixel \( A \) of Image 1 to its corresponding pixel \( B \) of the Image 2 by means of the image registration process, these two pixels should be highly similar to each other with respect to their functional connectivity patterns. The blue squares shown in the images of Fig.2b and Fig.2c schematically illustrate the spatial neighborhoods used in the computation of functional connectivity patterns. As shown in Fig.2b, the functional connectivity patterns of corresponding pixels across different subjects can be highly similar to...
each other since the small neighborhood patches contain the same functional units. However, when the spatial neighborhood size increases to a certain range, its associated functional connectivity patterns across different subjects may have lower similarity since the relatively large neighborhoods may contain different mixtures of functional units, as illustrated in Fig.2c. The schematic illustration of Fig.2 indicates that the global connectivity pattern can also be altered by local perturbations such as spatial shift of the corresponding regions, thus might be less robust for image registration.

To further illustrate the problem associated with the computation of functional connectivity patterns when the spatial neighborhood size used is relatively large, simulated images with real fMRI signals are generated based on Image 1 and Image 2 shown in Fig.2a. Particularly, three functional signals are randomly picked from a real fMRI image and filled into the square and circle regions of Image 1 and Image 2, as well as the black background, as shown in Fig.3a, with same signals filled into corresponding regions. For each pixel of these two images, a local functional connectivity pattern and a global functional connectivity are computed by the method described in Section 2.1. The connectivity patterns of Image 1 and Image 2 are compared using Pearson correlation as the similarity measure and squared difference as a distance measure, respectively. Fig.3b shows the similarity measures of pixel A of Image 1 to all pixels of Image 2 with the local and global functional connectivity patterns. The similarity maps shown in Fig.3b indicate that pixel A have the highest similarity to its corresponding pixel B when measured with their local connectivity patterns, however when measured with their global connectivity patterns, all pixels in the square region of Image 2 have the same similarity to pixel A. Fig.3c shows the distance measures pixel A of Image 1 to all pixels of Image 2 with local and global functional connectivity patterns. The distance maps shown in Fig.3c also indicate the local functional connectivity patterns can better establish correspondence between pixels across images.

**Fig.3.** Similarity/distance map comparison between local and global connectivity pattern. a) Simulated functional images. b) Similarity between pixel A and all pixels in Image 2, where Pearson correlation is adopted as the similarity measure. Left: similarity map computed using global connectivity pattern. Right: similarity map computed using local connectivity pattern. c) Distance measure between pixel A and all pixels in Image 2, where squared difference is adopted as the distance measure. Left: distance map computed using global connectivity pattern. Right: distance map computed using local connectivity pattern. The squared differences have been normalized to [0,1]

### 3. EXPERIMENTAL RESULTS

The proposed algorithm is validated using both simulated and real resting-state fMRI (rs-fMRI) data. Based on the simulated fMRI data, the proposed method is compared with fMRI image registration methods which achieve image registration based on maximizing functional correlation and minimizing difference of the global connectivity matrices across subjects. The real rs-fMRI data is used to demonstrate that the inter-subject functional consistency can be improved statistically significantly by the proposed method. The real rs-fMRI dataset consists of 13 healthy subjects, each of them also having a volumetric structural MRI data. The rs-fMRI images have 197 time points with TR=2s. The data were preprocessed using the standard protocol, including slice timing, head movement correction, band-pass filtering, spatially normalization to 3mm MNI space based on structure images, and regressing out the nuisance covariant. However, the data were not smoothed spatially.

#### 3.1 Simulated experiments

We first compare the proposed fMRI registration algorithm with the method which is based on minimizing the difference of the global connectivity matrices across different subjects. The simulated images used in the experiment are Image 1 and Image 2 constructed in Section 2.3, as shown in Fig.3a. The functional signals filled into different regions of the simulated images are randomly picked from a subject from the real rs-fMRI dataset. As shown in Fig.4a, the simulated functional image Image 1 is registered to Image 2 by two methods respectively. As mentioned above, the global
connectivity patterns have been altered by the spatial shift of the corresponding functional region so that the corresponding pixels can have very different global connectivity patterns, thus cannot lead to correct image registration. As shown in Fig.4b, the registration method based on the global connectivity patterns has failed to align these simulated images. It is worth noting that the global connectivity pattern based method failed to converge, so the result shown in Fig.4b is the output of 100 iterations of the image registration algorithm. The registration result of our method is shown in Fig.4c. Since the local connectivity patterns adopted in our method are computed in small spatial neighborhoods and are modeled to be invariant to rotation and shift of the neighboring pixels, it is more robust against the local spatial perturbations so that the proposed method has yielded a promising result.

![Fig.4. Comparison between the proposed method and the global connectivity pattern based method based on simulated data. a) Image 1 is registered to Image 2 by two methods respectively. b) The result of the global connectivity based method. c) The result of the proposed local connectivity based method.](image)

To compare the proposed algorithm with the inter-subject functional correlation based method, another simulated experiment is performed. In this experiment, we try to demonstrate that the inter-subject correlation based method cannot work well due to asynchrony of the resting-state functional signals.

![Fig.5. Simulated functional images construction and histogram of deformation distance generated by two methods. a) Two images are simulated with different time points of each real rs-fMRI dataset, one with the first 150 time points volume and the other with the last 150 time points volume. b) Histogram of deformation distances generated by the functional correlation based method. c) Histogram of deformation distances generated by the proposed method.](image)

From each real rs-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, as shown schematically in Fig.5a. The first 150-time-points image is then registered to the last 150-time-points image pairwisely for each pair of simulated images by the two algorithms, respectively. Since each pair of simulated images is built from same subject’s functional signals, we expect that the resultant deformation displacement should be closed to zero. Both methods run 100 iterations in this experiment. The mean deformation displacement generated by our method is 0.2mm (variance = 0.14), 95.52% of the voxels are with displacements less than 1mm, and only 0.59% 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 1.33mm (variance = 0.71), only 48.12% of the voxels are with displacements less than 1mm, and 6.62% of the voxels are with displacements larger than the image spatial resolution. The histograms of displacements shown in Fig.5b and 5c demonstrate that the proposed method has yielded much smaller deformations than the functional correlation based method in this experiment, indicating that the functional correlation based method may get biased registration results for rs-fMRI data.
3.2 Real fMRI data experiments

The proposed method has also been validated based on the real rs-fMRI dataset. We randomly pick one subject to be the target template, and register other images to the template using the proposed algorithm. The image registration is initialized by the structural image based registration technique, SyN, implemented in ANTs software (Advanced Normalization Tools). The comparison is performed between results of the sMRI based registration method (ANTS) and those further registered by the proposed method.

The quality of image registration is evaluated by inter-subject consistency of Default Mode Network (DMN). Particularly, we choose 5 hub nodes of default mode network (DMN), namely, posterior cingulate cortex (PCC), dorsal medial prefrontal cortex (dMPFC), ventromedial prefrontal cortex (vMPFC), left and right inferior parietal lobule (LIPL & RIPL) as shown in Fig.6a, and for each pair of these hub nodes, the variance of node-to-node functional connectivity measures among 13 subjects is computed and then used to assess the inter-subject consistency, i.e. lower variance indicating improved inter-subject consistency. The node-to-node functional connectivity can be computed using eqn. (5),

\[ C(node_p, node_q) = \left( \frac{1}{K_{p,q}} \right) \sum_{x_i \in node_p, x_j \in node_q} C(i, j), \]  

where \( K_{p,q} \) stands for the number of voxel pairs \( \{(x_i, x_j) | x_i \in node_p, x_j \in node_q\} \).

We compute every node-to-node connectivity variance among subjects before and after the alignment of fMRI data by the proposed method, respectively. The comparison results indicate that the node-to-node connectivity variances are statistically significantly lower after alignment with \( p = 4.73 \times 10^{-8} \) for paired t-test. The detailed variance comparison histogram is shown in Fig.6b. This result indicates that our proposed method can statistically significantly improve the functional consistency across subjects.

![Fig.6. Inter-subject consistency comparison for functional connectivity measures among 5 hub nodes of DMN between before and after functional alignment by the proposed method. a) 5 hub nodes of DMN, dMPFC, vMPFC, PCC, RIPL & LIPL. b) Variances of node-to-node functional connectivity among subjects. The blue bars are variances of 10 node-to-node connectivity among subjects before functional alignment by the proposed method. The red bars are variances among subjects after functional alignment by the proposed method.](image)

4. CONCLUSION

This paper presents a novel fMRI image alignment method, aiming to achieve functional consistency across subjects. The image registration is guided by a local functional connectivity pattern which is computed in a small spatial neighborhood of each voxel for characterizing its functional information. The local functional connectivity is modeled as a probability distribution to generate a feature invariant to spatial rotation and shift of its neighboring voxels. The simulated experiment results demonstrate that the proposed method outperformed the existing fMRI registration methods, since it is more robust against local spatial perturbations and can overcome the problem of the asynchrony of the resting-state functional signals. Experiment result based on real fMRI data further demonstrates that the proposed method has improved the inter-subject functional consistency statistically significantly. We expect that better performances may be obtained if the neighborhood size used in defining local connectivity patterns is adaptive at different image locations or gradually increased from local to global as the registration process proceeds and also, if a bias-free groupwise registration strategy is adopted.
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