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Unbiased Group-Wise Image Registration: Applications in Brain Fiber Tract Atlas Construction and Functional Connectivity Analysis

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Abstract

We propose an unbiased implicit-reference group-wise (IRG) image registration method and demonstrate its applications in the construction of a brain white matter fiber tract atlas and the analysis of resting-state functional MRI (fMRI) connectivity. Most image registration techniques pairwise align images to a selected reference image and group analyses are performed in the reference space, which may produce bias. The proposed method jointly estimates transformations, with an elastic deformation model, registering all images to an implicit reference corresponding to the group average. The unbiased registration is applied to build a fiber tract atlas by registering a group of diffusion tensor images. Compared to reference-based registration, the IRG registration improves the fiber track overlap within the group. After applying the method in the fMRI connectivity analysis, results suggest a general improvement in functional connectivity maps at a group level in terms of larger cluster size and higher average *t*-scores.

Keywords

Group-wise image registration; DTI; Fractional anisotropy; Fiber tract; Resting-state fMRI

Introduction

Image registration has widespread interest in accurately relating information in different images and/or imaging modalities for computer-guided surgery, diagnosis, treatment and basic science [1,2]. Most current image registration techniques require the selection of a reference image and pair-wise register images to the reference [3–6]. A strategy to avoid reference selection is to simultaneously estimate transformations for each subject in the group that map them into a common space without choosing any reference image [7,8]. The current work applies an unbiased implicit-reference group-wise (IRG) registration framework [9] to the study of brain white matter fiber tracts and resting-state functional connectivity.

The unbiased IRG registration method jointly estimates transformations from each image in the group to a “hidden” reference by optimizing the intensity difference of each pair of deformed images. A small deformation linear elastic model is used to construct the similarity and regularization cost functions [10]. The basis of the IRG registration method is that transformations take each image to a common coordinate system; therefore, the images

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after deformation should have similar shapes to each other and the intensity difference at the corresponding location should be minimized. By minimizing the intensity differences between the deformed images, they converge to the group average.

Brain fiber tracts can be computed from an emerging magnetic resonance imaging (MRI) technique, diffusion tensor imaging (DTI), that non-invasively measures water diffusion in biological tissues. The diffusion is anisotropic in fibrous tissues such as cerebral white matter and can be quantified by DTI [11,12]. The integration of the tensor field along their principal eigenvectors creates streamlines that sample anatomical fiber tracts.

Fiber tract atlases have been used to study brain white matter alterations and structural connectivity within and between populations [13,14]. Group-wise DTI registration is critical to the construction of an unbiased atlas. To demonstrate the registration effect on building a fiber bundle atlas, the uncinate fasciculus (UF) is constructed after reference-based and the proposed IRG registration methods. The UF is a white matter tract that connects the hippocampus and amygdala in the temporal lobe with frontal regions such as the orbitofrontal cortex. It has been reported that abnormalities in the UF are associated with, for example, social anxiety [15] and schizophrenia [16]. Results show that, after IRG registration, the overlap of the UF bundles is higher compared to reference-based registration.

Resting-state functional MRI (fMRI) has been used extensively to probe the functional connectivity between different brain regions [17]. Functional brain networks are usually identified as regions having synchronous low-frequency fluctuations using either specifically defined “seed” templates [18,19] or data-driven methods without predefined templates [20,21]. For seed-based analyses, the seed regions are typically obtained from activation maps generated by an independent fMRI study or delineated directly from anatomical images in the stereotaxic atlas space (e.g. Talairach space).

For a group analysis of resting-state fMRI, the alignment of brain images across subjects is essential for reducing inter-subject variations caused by individual differences and/or image artifacts. The commonly used method in a group analysis is to obtain a linear affine transformation matrix by matching the high-resolution anatomical images to a template in the atlas space, and then apply the transformation to the low-resolution functional data. In this study, we applied the IRG registration to further deform the functional data across subjects after affine alignment. The results demonstrate a general improvement in functional connectivity maps at a group level in terms of larger cluster size and higher average *t*-scores with IRG registration.

Methods

Unbiased IRG image registration

Conventional reference-based pair-wise image registration methods define the registration problem as finding the transformation h_{ij} from image I_i to I_j by minimizing an energy function such as

$$E(I_i(h_{ij}), I_j) = D(I_i(h_{ij}), I_j) + R(h_{ij}),$$

where D is a similarity cost function to deform I_i to I_j , and R is a regularization term to penalize the transformation h_{ij} .

The IRG registration problem can be stated as: estimate $N (>2)$ transformations h_{iR} from each image I_i in a population with N input images to an unknown common space by minimizing the summation of the intensity differences between each pair of deformed images. The unknown common space is defined as the implicit reference space. The energy function can be written as:

$$E = \sigma E_{SIM} + \rho E_{REG}$$

$$= \sigma \sum_i \sum_{j, j < i} \int_{\Omega} \|I_i(h_{iR}(x)) - I_j(h_{jR}(x))\|^2 dx + \rho \sum_i \int_{\Omega} \|L(u_{iR}(x))\|^2 dx \quad (1)$$

where $h_{iR}(x) = u_{iR}(x) + x$ is the transformation from image I_i to the implicit reference R , u_{iR} is the displacement field from I_i to R , $L(u_{iR}(x))$ is a linear differential operator regularization constraint, and σ and ρ are weighting parameters. Following our previous work [9], the linear elasticity operator is used with the form $Lu(s) = -\alpha \nabla^2 u(x) - \beta \nabla (\nabla \cdot u(x)) + \gamma u(x)$, where ∇ is the gradient operator and ∇^2 is the Laplacian operator. Each displacement field $u_{iR}(x)$ is a 3×1 vector-valued function parameterized by the 3D Fourier series

$$u_{iR}(x) = \sum_{k=0}^{d-1} \mu_{i,k} \exp(j2\pi kx/d),$$

where k , d , x and $\mu_{i,k}$ are 3×1 vectors. The basis coefficients $\mu_{i,k} = a_{i,k} + jb_{i,k}$ are initialized to 0, and determined by gradient descenting

$$a_{i,k}^{n+1} = a_{i,k}^n + \varepsilon \frac{\partial E(\mu_{i,k}^n)}{\partial a_{i,k}}, \text{ and } b_{i,k}^{n+1} = b_{i,k}^n + \varepsilon \frac{\partial E(\mu_{i,k}^n)}{\partial b_{i,k}} \quad (2)$$

where ε is the step size, and the superscript n corresponds to the value of the parameters at the n th iteration.

Figure 1 illustrates the unbiased registration method applied to a population of four 2D shapes that consists of a circle, two ellipses and a square. It shows that the transformations bring each shape to the average of all shapes and the deformed shapes are similar to each other.

Data acquisition and preprocessing

Thirty-nine healthy subjects were recruited as part of a protocol approved by the Institutional Review Board (IRB) of the National Institute on Drug Abuse Intramural Research Program and provided written informed consent. All participants underwent a DTI scan, a resting-state fMRI scan, arterial spin labeling perfusion scans (data not shown here), and a high-resolution T₁-weighted anatomical scan within one session on a Siemens 3T Allegra scanner, except for one participant missing the DTI scan. An EPI-based spin-echo pulse sequence was used to acquire diffusion-weighted MRI images. For each subject, 35 axial images were prescribed to cover the whole brain with a 128×128 inplane matrix at a resolution of $1.719 \times 1.719 \times 4$ mm³. Beside the non-diffusion weighted reference image, 12 directions were used to apply the diffusion-sensitive gradients with a b-factor of 1,000 s/mm². For EPI, TR/TE=5000/87 ms, BW=1700 Hz/Pixel, and NEX=4. For resting-state fMRI data, participants were instructed to close their eyes and not to think of anything in

particular during a 6-minute resting scan. The acquisition parameters were: TE/TR=27/2000 ms; FOV=220×220 mm²; image matrix=64×64; slice thickness/gap=4/0 mm; number of slices=39. A set of high-resolution (1×1×1 mm³) T₁-weighted (T_{1w}) anatomical images were also acquired to facilitate the group analysis.

Each structural image was automatically normalized to Talairach space using the AFNI software package [22]. The 12 diffusion weighted images (DWIs) were aligned to their corresponding structure images for correction of motion and image artifacts using mutual information based affine registration. Normalization matrices were applied to DWIs, and the images were resampled to 2×2×2 mm³. Fractional anisotropy (FA) maps were then calculated from the diffusion tensor using AFNI. FA values range from 0 (spherical shape) to 1 (elongate). Each image contains 80×95×75 voxels.

The preprocessing of the resting fMRI data was conducted in AFNI including slice-timing correction, motion correction, and low-pass filtering (cutoff frequency=0.1 Hz) to retain the low frequency fluctuation components that contribute to functional connectivity [17,18], spatial normalization, and spatial smoothing (FWHM=6mm). All EPI volumes were resampled to 3×3×3 mm³ and affine aligned to the Talairach space.

Construction of the UF atlas

The unbiased IRG registration was applied to the affine aligned FA maps. To balance the similarity and regularization costs in Eq. (1), the weighting parameter σ of the similarity energy was set to be 1, and the weighting parameter ρ of the regularization constraint was set to be 0.00025 throughout the optimization procedure [9]. A spatial and frequency multi-resolution procedure was used to estimate the transformations to avoid local minima. At each resolution level, the initial and final numbers of harmonics for the transformation are shown in Table 1. The calculation of forward and reverse fast Fourier transforms (FFT) of h_{iR} dominates the computational time at each iteration. Despite the double summation in the similarity cost term, the computational cost is still approximately linear to the number of images to be registered.

Unlike scalar image registration, tensor image registration requires reorienting the deformed tensors such that the orientation of the registered tensors is consistent with the underlying fiber tract direction. The “finite strain” strategy [3] was used in this work. The tensor rotation matrix $R_{iR}(x)$ was calculated using $R(x)=(J(x) \cdot J(x)^T)^{-1/2} J(x)$. $J(x)$ is the Jacobian of the transformation field $h(x)$ with the form:

$$J(x) = \begin{pmatrix} \frac{\partial h(x_1)}{\partial x_1} & \frac{\partial h(x_1)}{\partial x_2} & \frac{\partial h(x_1)}{\partial x_3} \\ \frac{\partial h(x_2)}{\partial x_1} & \frac{\partial h(x_2)}{\partial x_2} & \frac{\partial h(x_2)}{\partial x_3} \\ \frac{\partial h(x_3)}{\partial x_1} & \frac{\partial h(x_3)}{\partial x_2} & \frac{\partial h(x_3)}{\partial x_3} \end{pmatrix}$$

$$= I + \begin{pmatrix} \frac{\partial u(x_1)}{\partial x_1} & \frac{\partial u(x_1)}{\partial x_2} & \frac{\partial u(x_1)}{\partial x_3} \\ \frac{\partial u(x_2)}{\partial x_1} & \frac{\partial u(x_2)}{\partial x_2} & \frac{\partial u(x_2)}{\partial x_3} \\ \frac{\partial u(x_3)}{\partial x_1} & \frac{\partial u(x_3)}{\partial x_2} & \frac{\partial u(x_3)}{\partial x_3} \end{pmatrix}$$

The reorientation of the spatially deformed tensor T was then computed by $T' = R^T T R$.

After all DT images were deformed to the common space, whole brain white matter fibers were generated using the software “Trackvis” [23] from the registered DT images. To extract UF fiber tracks, two regions of interest (ROIs) were selected [24]: right amygdala and orbitalfrontal cortex (OFC). The brain anatomical atlas [25] in AFNI was used, which contains segmentations of cortical and subcortical regions. The T1w images of the 38 subjects were registered using the same IRG registration framework [9], and averaged to

generate the anatomical average. The atlas was affine aligned to the average image, and the right amygdala and OFC ROIs were aligned to the average accordingly. Since the DTI images were aligned to their anatomy in the preprocessing step, the amygdala and OFC were also aligned with the average DTI image. The two gray matter regions were dilated 2 mm along the boundary to including surrounding white matter area. The UF bundles were then extracted for each subject by selecting fibers passing both right amygdala and OFC.

Fiber tracks were represented by lines; each line consists of a list of points. To obtain the fiber bundle atlas, all points on the fiber tracks were projected to the image grid. The number of points in each voxel was counted and the values in each voxel were normalized to 0 to 1, where 0 means no fiber passing the voxel and 1 indicates this voxel has the highest fiber density. We defined the fiber bundle to be the regions with the fiber density greater than 0.5. The group fiber bundle atlas was computed by averaging each binarized fiber bundle. To evaluate the fiber bundle atlas, the relative overlap at each voxel x was computed: $RO(x) = n(x)/N$, where $n(x)$ is the number of subjects that have fibers at x , and N is the total number of subjects.

Resting-state fMRI connectivity analysis

Seed-based functional connectivity analysis was performed in this work. Three spherical seed ROIs (radius=3 mm) were defined in left amygdala, motor cortex and posterior cingulate cortex (PCC), respectively, to assess the effects of the IRG registration on inter-subject alignment in subcortical and cortical regions. The weighting parameters were the same as that used in the DTI registration. The fMRI data has less contrast and coarser image resolution compared to DTI data, therefore the optimization was performed only at the full spatial resolution. The initial and final numbers of harmonics for the transformation coefficients are shown in Table 1.

Two cross-correlation coefficient (CC) maps were calculated for each seed ROI on the data with or without IRG registration and then were transferred to z -value maps using fisher's z transformation to improve the normality of the data distribution. Six motion parameter time courses and the two sets of the first three principal components, each from the cohorts of white matter and cerebrospinal fluid (CSF) time courses separately, were regressed out during the CC calculation. One-sample two-tailed t -tests were performed to obtain two sets of group functional connectivity maps for each data set with $t > 6.8$ and a cluster size of 9 voxels ($p_{\text{corrected}} < 0.05$). Ten brain areas (3 from the amygdala network, 3 from the sensorimotor network, and 4 from the default-mode network) were selected from the overlapped group connectivity maps (with and without IRG) to evaluate the effects of the IRG registration. Average t -scores and z -values were calculated in these ten regions.

Results

Figure 2 shows FA images from three randomly selected subjects and their deformed images after reference-based (with a randomly selected image as the reference) and IRG registration. The deformed images using reference-based registration have similar shapes as the reference, whereas the ones using IRG have similar shapes to each other, having been proved to converge to the group mean [26].

Figure 3 shows an example of a whole brain fiber tracking and the UF bundle defined by passing both through the right amygdala and OFC. The UF atlas after the IRG registration is shown in Fig. 4(a). The UF bundle was thresholded at 0.5. The enlarged group UF bundles constructed using affine, reference-based, and IRG registration are shown in Fig. 4(b), (c) and (d). The average overlap of the bundle obtained by affine, reference-based and IRG registration is 0.627, 0.664 and 0.678 respectively. The IRG registration has an 8%

improvement compared to affine, and 2% improvement compared to the reference-based registration.

Figure 5 shows the group functional connectivity maps for seed ROIs located at (a) left amygdala, (b) left motor cortex, and (c) left PCC. The group connectivity maps obtained with and without IRG registration overlapped in large extent, although group maps with IRG registration generally showed larger connected regions than those without IRG, except in the area of ACC/medial prefrontal cortex (MPFC) for the left amygdala seed, as indicated by the cluster size in Table 2. Paired two-tailed t -test showed that 6 out of 10 regions (i.e. left amygdala, right amygdala, left motor cortex, right motor cortex, supplemental motor area (SMA), PCC, and left inferior parietal cortex (IPC)) had significant improvement ($p < 0.05$) with IRG registration in terms of the average z -values, while the remaining 4 regions had no significant changes. In terms of average t -scores, most of the investigated regions showed higher average t -scores with IRG registration, except for the ACC/MPFC in the amygdala network and the right IPC in the default-mode network, as shown in Table 2.

Discussion and conclusions

An unbiased group-wise registration algorithm with a small deformation elastic model was applied to build a white matter fiber tract atlas and align resting-state EPI data sets across participants. Compared to commonly used reference-based registration method, the unbiased IRG registration produced a higher overlap of the registered UF bundles resulting in a sharper UF atlas, which enables more accurate atlas based white matter analyses. The fMRI results demonstrate a general improvement of the proposed registration in group functional connectivity map in terms of larger cluster size and higher average t -scores compared with the affine alignment, which may improve the sensitivity of group functional connectivity studies.

The improvement for building the UF atlas can be explained by the fact that the unbiased IRG registration produces smaller registration errors compared to affine and reference-based methods. Our previous study shows that the deformed FA maps have smaller shape variation compared to other methods [9]. The smaller registration error of the IRG registration can be explained by the following: Starting with the registration of two images, the similarity objective function for the implicit reference method is defined as $D(I_1(h_{1R}), I_2(h_{2R}))$, and the similarity cost for the reference-based method can be written as $D(I_1(h_{12}), I_2)$, which is equal to $D(I_1(h_{12}), I_2(h_{id}))$, where h_{id} is the identity map from I_2 to I_2 . The optimization of the former cost function searches the optimal transformations h_{1R} and h_{2R} to minimize the similarity cost between $I_1(h_{1R})$ and $I_2(h_{2R})$. The optimization of the latter cost function searches the optimal transformation h_{12} that minimizes the similarity cost between $I_1(h_{12})$ and $I_2(h_{id})$. Therefore, the minimizer of the latter can be considered as a local minimizer of the former, which means that the similarity error between $I_1(h_{12})$ and I_2 is no smaller than the error between $I_1(h_{1R})$ and $I_2(h_{2R})$. Similar analysis can be extended to the registration of more than two images.

In the resting-state functional connectivity study, the average z -values in the six out of ten selected ROIs elevated significantly after the IRG registration. Also, most of the investigated regions showed higher average t -scores with IRG registration, except for the ACC/MPFC in the amygdala network. These results demonstrated that with better across-subject registration, it not only increases the within-network average correlation, but also reduces correlation variation across subjects.

A limitation of the fiber tract atlas construction performed in this work is that the fiber bundles are generated from tensors, which have limitations to model intra-voxel fiber

crossings [27,28]. Fiber trackings based on higher order models may identify fiber tracts in complex brain regions. Image registration considering crossing fibers has the potential to better align these complex regions [28].

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Fig. 1. Unbiased IRG registration of four 2D phantom shapes. I_i : original shapes; $I(h_{iR})$: deformed shapes; h_{iR} : transformations estimated by the IRG registration

Fig. 2.

FA images before and after reference-based and IRG registration. The circled regions show closer spacing of the bilateral internal capsules after reference-based registration due to the bias from the single subject reference

Fig. 3. The right amygdala and OFC in the group average anatomical image (*top row*) and the whole brain and UF fiber tracks of a subject (*bottom row*)

Fig. 4. The UF atlas built by different registration methods. **a** the UF atlas by IRG registration at axial, sagittal and coronal views. **b–d** the enlarged UF atlases by affine, reference-based and IRG registrations, respectively

Fig. 5. Group functional connectivity maps for seeds at **a** left amygdala, **b** left motor cortex, and **c** left PCC. Ten regions chosen to assess the effects of IRG registration are labeled in the maps (left amygdala, right amygdala, and ACC/ MPFC in **(a)**, left motor cortex, right motor cortex, and SMA cortex in **(b)**, PCC, ACC/MPFC, left IPC, and right IPC in **(c)**). Black crosses indicate the locations of the seeds

Table 1

Multi-resolution parameters for DTI and fMRI registration

	Voxel dims	Resolution	Initial # harmonics	Final # harmonics
DTI	80×95×75	¼	1	5
		½	5	9
		1	9	13
fMRI	64×64×50	1	1	9

Table 2

Comparison of functional connectivity maps in cluster size, average *t*-score and average *z*-value with and without IRG registration

Seed	Connected Region	Cluster Size (mm ³)		Avg. <i>t</i> -score		Avg. <i>z</i> -value (mean±std)	
		wo IRG	w IRG	wo IRG	w IRG	wo IRG	w IRG
Left Amy	L. Amyg.*	28566	41175	10.7	11.6	0.31±0.08	0.35±0.09
	R. Amyg.*	24435	38799	9.11	9.97	0.26±0.09	0.29±0.10
	ACC/MPFC	1944	837	7.52	7.19	0.21±0.14	0.20±0.14
Left Motor Cortex	L. Motor*	12474	17712	10.5	11.6	0.39±0.12	0.43±0.14
	R. Motor*	7776	10503	7.78	8.28	0.28±0.16	0.31±0.17
Left PCC	SMA	405	648	7.27	7.53	0.19±0.15	0.20±0.16
	PCC*	26946	30132	11.4	12.5	0.43±0.13	0.46±0.14
	ACC/MPFC	14985	17847	7.86	8.05	0.27±0.14	0.28±0.14
	L. IPC*	9666	11367	8.22	9.12	0.32±0.17	0.34±0.15
	R. IPC	3753	5022	7.61	8.20	0.27±0.17	0.29±0.17

* Regions showing significant improvement on average *z*-score with IRG registration