

Diffeomorphic MRI-Brain Registration for Automatic Multi Modality Image by Using Mean-Shift Algorithm

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Abstract

A new methods to constrain brain MRI(Magnetic Resonance Imaging) registration, and perform experiments evaluating the alignment of manually-traced structures, reduction of intersubject variance, and morph metric results using group wise registration is compared against traditional MRI.In multistructure diffeomorphic registration to brain registration, where a set of initial segmentations is used as structures along with the MRI. By using image registration, it restrict the scope of structures to those that can be represented volumetrically as images, such as MRI volumes or anatomical segmentations, or those that can be interpolated on a volumetric grid.This method uses Mean Shift algorithm to efficiently segment the gray and white matter.

Index Terms—*Atlases morphometry, brain registration, diffeomorphisms, MRI.*

1. Introduction

WHOLE brain image registration is a useful and often necessary tool for studying morphometry and pooling information in a central space. Registration can be a difficult task considering the anatomical variability and structural complexity present in the human brain, motivating the use of structure-specific information (anatomical guidance) to initialize and constrain registration in a meaningful way. In [1], we described how individual brain structures could be used to perform an initial low- and high-dimensional alignment, leading to improved registration of specific subregions in the brain. More direct shape-matching approaches [2] have shown that using manually traced segmentations to drive the registration instead of MRI intensities can also improve registration of specific cortical and neocortical regions. The main contribution of this study is a registration framework that concurrently employs shape-matching with automated segmentations of multiple structures, and image-matching to obtain an anatomically guided diffeomorphic registration that can more accurately align the individual structures in images.

Previous work integrating registration and segmentation can be categorized into those that perform the tasks simultaneously [3]–[5], and those that perform the tasks in sequence [2], [6]–[9]. Simultaneous, or joint segmentation and registration approaches are attractive because they model the inherent interdependence of each component. However, because of limitations in how the segmentation and registration models can be simultaneously optimized, these methods have not been able to take advantage of more sophisticated or specialized approaches. In contrast, by employing registration and segmentation sequentially, where the contribution becomes how one applies the results of one to aid the other, specialized and potentially disparate techniques, such as surface-based and volume-based segmentation, can be combined to provide a more accurate result. We exploit this idea in this study by making use a segmentations derived from a sophisticated image analysis pipeline employing surface-based registration, namely Freesurfer, and use these to drive a highly deformable large-deformation diffeomorphic registration algorithm [12]. Thus, conceptually the multistructure registration could be thought of as a refinement iteration where a full 3-D diffeomorphism is found using the label constraints generated via an earlier iteration of lower dimensional and surface-based registration techniques.

A key component of many group-based neuroanatomical studies is the extraction of morphometric features that can be used for discrimination or characterization of anatomical variability within or across groups. Whole brain morphometry approaches, such as voxel-based and tensor-based morphometry (TBM) compute morphometric features at a voxel-wise level, which can then be used in mass-univariate or multivariate statistical analyses. Tensor-based morphometry makes use of the transformations obtained from registration to measure the amount of deformation required to match a subject's anatomical features to a template. A subject that is morphologically very different would require a greater amount of deformation in registration to match the template, whereas a subject morphologically similar to the template would require less deforma-

tions. Since the sensitivity of TBM inherently depends on how accurate the underlying registration algorithms are, we also investigate how our proposed registration methods perform when applied to TBM.

We begin by introducing our multistructure registration framework, then describe a groupwise implementation for average atlas building. We then describe how Freesurfer segmentation.

A. Multistructure Registration

Diffeomorphic registration algorithms that ensure the resulting transformations are one to one, invertible and smooth, are desirable because they preserve the topological properties of the underlying anatomy. We employ a large deformation diffeomorphic registration algorithm in this study for these reasons; however, it is possible to implement the proposed

Now, we have additional weights $\lambda^{\text{Seg},i}$ specifying the relative influence of each segmentation in the overall registration. In this study, we chose equal weights, and thus equal contribution for all segmentations and the MRI, $\lambda^{\text{MR}} = \lambda^{\text{Seg},i}$, $i = 1 \dots N$. Note that by employing structure weights, the registration is driven by the intensities of the anatomical MR images, and has been shown to be better than regions such as the medial temporal lobe. In our multistructure registration framework, we add a number of shape-matching terms, each corresponding to a segmentation of a volumetric structure, and register all of these structure channels simultaneously along with the MRI. We now describe how the large deformation diffeomorphic formulation was extended toward multistructure registration.

Let the pair I_a and I_b of whole brain MR images be given, and let segmentations of N structures, $I_a^{\text{Seg},i}$, $i \in [1, \dots, N]$, and $I_b^{\text{Seg},i}$, $i \in [1, \dots, N]$, be available. The diffeomorphic transformation matching I_a and I_b is given by $\phi : \Omega \rightarrow \Omega$ such that $I_a \circ \phi^{-1} \approx I_b$. This transformation ϕ is built from the flow of smooth time-dependent velocity vector field, $v_t \in V$, $t \in [0, 1]$, where V is a Hilbert space of smooth, compactly supported vector fields on Ω . Such a velocity vector field defines the evolution of a curve $\phi_{0,t}$, $t \in [0, 1]$ via the evolution equation $\dot{\phi}_{0,t} = v_t(\phi_{0,t})$ such that the end point $\phi_{0,1}$ of the curve ϕ at time $t = 1$ is the particular transformation $\phi = \phi_{0,1}$ that is sought for registration. Let the notation $\phi_{s,t} : \Omega \rightarrow \Omega$ denote the composition $\phi_{s,t} = \phi_t \circ (\phi_s)^{-1}$ with the interpretation that $\phi_{s,t}(y)$ is the position at time t of a particle that is at position y at time s . Hence, the transformed image I_a is

2.Methods

Segmentation, we have the energy functional for our multistructure registration

$$(\nabla_v E_t)_V = 2v_t - 2K \left(|D\phi_{t,1}| \left[\lambda^{\text{MR}} \left(\hat{I}_{a,t}^{\text{MR}} - \hat{I}_{b,t}^{\text{MR}} \right) \nabla \hat{I}_{a,t}^{\text{MR}} + \sum_{i=1}^N \lambda^{\text{Seg},i} \left(\hat{I}_{a,t}^{\text{Seg},i} - \hat{I}_{b,t}^{\text{Seg},i} \right) \nabla \hat{I}_{a,t}^{\text{Seg},i} \right] \right) \quad (3)$$

segmentations in the energy functional as such, point correspondences between segmented volumes do not have to

$$E(v) = \int_0^1 \|v_t\|_V^2 dt + \lambda^{\text{MR}} \|I_a^{\text{MR}} \circ \phi_{1,0} - I_b^{\text{MR}}\|_{L^2}^2 + \sum_{i=1}^N \lambda^{\text{Seg},i} \|I_a^{\text{Seg},i} \circ \phi_{1,0} - I_b^{\text{Seg},i}\|_{L^2}^2.$$

V is a compact self-adjoint operator defined by $a, b \in L^2 = K a, b_V$, such that for any smooth vector field $f \in V$, $K(L^{-1})f = f$ is satisfied [12]. The operator L is chosen to be of the Cauchy-Navier type, $L = -\alpha \nabla^2 + \gamma I$, where I is the identity operator and $\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$ is the Laplacian operator. The derivation is a straightforward extension of the previous work [12].

1) Locally Optimal Large Deformation Diffeomorphisms:

An LDDMM optimizes over the full space-time flow and is

thus has heavy computational and memory requirements. When

dealing with large databases of full resolution whole brain MRI

and multiple structures, these requirements can become restric-

given by $I_a \circ \phi^{-1} = I_a \circ \phi_{1,0} \approx I_b$ and the transformed target image is $I_b \circ \phi_{0,1}$.

If it is not necessary to find the shortest geodesic path [12]

connecting two images, that is, if one is interested in diffeomorphic registration and not concerned with computing metric distances, then a locally optimal (or greedy) solution to the variational problem can be used.

Christensen *et al.* [16] proposed a large deformation fluid flow registration exploiting the fact that if the operator L does not differentiate in time, then the space-time optimization can be

split into a sequence of optimizations that solve for the locally optimal velocity at each time index. In this setting as

described in [12], the locally optimal velocity fields satisfy the partial differential equation

$$L^\dagger Lv_t + b_t = 0$$

Here, the weight λ^{MR} enforces how much mismatch in the images is penalized. Adding additional matching terms for each

This can be extended to the multistructure case, LDDMM-MultiStruct, by including additional terms for multiple structures.

Using the optimizer then becomes $v_t = -K(b_t)$, which can be integrated to compute the map $\varphi_{t,0}$.

B. Groupwise Multistructure Registration

When applying pairwise registration to spatially normalize all subjects to a given template, one has to decide which subject to choose as the template. The choice of template also affects how well the pairwise registrations perform, as subjects that are more similar to the template will likely be registered better. To avoid choosing a template, groupwise, or unbiased approaches have been proposed in the past [17]–[20], where the central template is generated and represented as an average of the group. One natural way to define a central template is using the Fréchet mean, where the intrinsic mean of a set of data points x_i is defined as the point \bar{x} that minimizes the sum of squared distances to each data point

$$\bar{x} = \operatorname{argmin}_{x \in X} \sum_{j=1}^M d(x, x_j)^2.$$

Extending this idea to the general problem of template estimation, the central template \bar{I} thus becomes the image that requires the minimal deformation ϕ_i to match each image I_j in the set of images

$$\{\bar{\phi}_j, \bar{I}\} = \operatorname{argmin}_{\phi_j \in G, I \in \mathcal{I}} \sum_{j=1}^M E(I_j \circ \phi_j, I) + D(I_d, \phi_j)^2.$$

We extend this idea to multistructure registration by computing the groupwise average subject, defined as the multistructure image \bar{I} that has minimal distance to each image in the database surface-based atlas. The

To solve for $\{\bar{\phi}_j, \bar{I}\}$ we use an alternating estimation procedure, where 1) $\bar{\phi}_j$ is fixed to find \bar{I} , and 2) \bar{I} is fixed to find $\bar{\phi}_j$. For 1) when transforming the images into the average image space we used the Jacobian to preserve the information regarding the volumes of structures, as was also done in [21], [22]

$$\bar{I} = \frac{\sum_{j=1}^M |D\phi_j| I_j \circ \phi_j}{\sum_{j=1}^M |D\phi_j|}$$

Input: Set of multi-structure images I_1, I_2, \dots, I_M ;

Multi-scale smoothing schedule: $\{\alpha_k, \gamma_k\}$

Output: Ensemble average multi-structure image \bar{I}

Set $\varphi_j^{(0)} = id$;

for $k = 0$ to N_k **do**

$$\bar{I}^{(k)}(x) = \frac{\sum_{j=1}^M |D(\varphi_j^{(k)})| I_j \circ \varphi_j^{(k)}(x)}{\sum_{j=1}^M |D(\varphi_j^{(k)})|};$$

foreach I_j **do**

Compute $\varphi_j^{(k+1)}$ using the body force from equation (6), using differential operator:

$$L_k = -\alpha_k \nabla^2 + \gamma I;$$

end

end

Algorithm 1. Multi-structure group-wise average.

where \bar{I} is a multistructure image consisting of \bar{I}^{MR} and N structure-channels, $\bar{I}^{\text{Seg},i}$. For 2) we use pairwise diffeomorphic registration from I_j to the fixed average \bar{I} to obtain the maps ϕ_j . We used a multiscale smoothing schedule by successively decreasing the viscosity parameter, α , in the fluid-flow differential operator L after each iteration. The sequence used was $\alpha = 2, 1, 0.5$, and 0.1 , with a fixed $\gamma = 0.01$, which was chosen based on experiments quantifying effective smoothing to be equivalent to 20, 15, 10, and 5 mm effective smoothing, as shown in [23, Appendix B]. Algorithm 1 describes this procedure.

C. Freesurfer Structure Segmentation

In this section, we describe how we applied our multistructure diffeomorphic registration to brain registration, where a set of initial segmentations were used as structures along with the MRI. Because we are using image registration, we thus restrict our scope of structures to those that can be represented volumetrically as images, such as MRI volumes or anatomical segmentations, or those that can be interpolated on a volumetric surface-based labels are mapped from the atlas using the cortical folding patterns, specifically the curvature of the cortical surface, and are then converted to a volu-

metric representation by projecting the label values from the surface to the voxels labeled as cortical gray matter. The use of these structures from Freesurfer thus, provides the multistructure registration with constraints from a surface-based representation of the cortex, which is known to better represent anatomical structure and function of the highly convoluted cortical topology. We used the following eight subcortical structures, left and right inclusive: lateral ventricles, caudate nucleus, putamen, pallidum, nucleus accumbens, thalamus, hippocampus, and amygdala. For cortical structures, we used the following 34 labels, left and right

inclusive: bankssts (banks around the superior temporal sulcus), caudal anterior cingulate, caudal middle frontal, corpus callosum, cuneus, entorhinal, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lateral orbito-frontal, lingual, medial orbito-frontal, middle temporal, parahippocampal, paracentral, pars opercularis, pars orbitalis, pars triangularis, pericalcarine, postcentral, posterior cingulate, precentral, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, frontal pole, temporal pole, and transverse temporal. Including the MRI as the first structure, we have 43 structure channels for each hemisphere making up our multistructure set.

The segmentation labels making up the multistructure set were extracted from the Freesurfer output images, namely *aparc+aseg.mgz*, 1 mm isotropic voxels, $256 \times 256 \times 256$, smoothed with a Gaussian filter ($\sigma = 2$). Smoothing was performed to mitigate labeling and discretization errors commonly found on the boundaries of the Freesurfer segmentations. For each structure, the labels from both hemispheres were combined into a single image with unique intensities.

D. Initial Affine Registration and Intensity Normalization

Before performing the diffeomorphic multistructure registration, the target subjects were first aligned using a 12-D affine transformation. The registration was performed on the Freesurfer tissue segmentation images of the template and target, which have discrete values of (0, 85, 170, 255) for the background, cerebrospinal fluid, gray matter, and white matter, respectively. The algorithm was implemented in the Insight Toolkit and used regular step gradient descent and a mean-squared error image metric with the transform initialized with the translation bringing the centers of mass into alignment. Once the transform was computed, the target MR images and Freesurfer labels were all transformed to the template space using this 12-parameter transformation and linear interpolation.

To address MRI intensity nonstandardization, we performed a piecewise linear intensity transformation of the target image, where the median white matter, gray matter, and cerebrospinal fluid intensities of the template and target image are used to define the transformation. These median intensities are found by masking the nonuniformity corrected MRI images with the Freesurfer tissue segmentation images, which are first morphologically eroded to avoid voxels that may be susceptible to partial voluming.

E. Diffeomorphi Registration

For pairwise registration, the bounding box was applied to the affine-registered target brain and multistructure set, and multistructure registration was carried out as described in Section II-A, with the parameters of the differential operator being $\alpha = 0.1$ and $\gamma = 0.01$.

For the group-wise approach, a template subject was initially chosen, all targets were affine registered to it, and the bounding box defined on it was applied to all targets. For the registration a multiscale smoothing scheme was used, which successively decreased the viscosity parameter α after each iteration. The sequence used was $\alpha = 2, 1, 0.5$, and 0.1 , with a fixed $\gamma = 0.01$, which was chosen based on experiments quantifying effective smoothing to be equivalent to 20, 15, 10, and 5 mm effective smoothing.

F. Brain Registration Evaluation

The goal of brain registration is to bring structures into alignment with each other; thus, a commonly-used method to evaluate registration performance is to manually segment brain structures in a group of subjects, and measure how well the structures are aligned after registration. To use this label-agreement method of evaluation, we performed fully crossed pairwise brain registrations on a given dataset, that is, each subject I_j is registered to every other subject $I_k = j$ and compared the manual segmentations of this subject, I_{Manual}^j with the propagated manual seg-

mentations, I_{Manual}^k .

To limit computational and memory requirements, we construct a bounding box around the template brain, and use this subvolume in registration instead of the entire $256 \times 256 \times 256$ volume. The bounding box is defined using the extents of the skull-stripped brain allowing for at least 16 voxels (16 mm) of padding at each boundary, and also ensuring the dimensions of the image are divisible by 16, such that this level of data parallelization could be used. The bounding box is applied to both the MRI and multistructure set of the template.

G. Tensor-Based Morphometry

We applied TBM to investigate how well the multistructure and MRI-only registration methods can detect the expected differences between a group of demented patients and cognitively normal patients. Groupwise registration was carried out as described in the previous section to obtain transformations and log-determinant Jacobian maps from the average to each subject.

The SurfStat package¹, is capable of random-field theory analysis with general linear and multivariate modelling on both volumetric and surface data. In this software, the linear model is specified for example as

$$P = \text{Group} + \text{Age} + \text{Gender}$$

where *Age* and *Gender* are nuisance covariates in the model testing for group differences, obviating the need to specify a design matrix. We use SurfStat to generate statistical parametric maps for our TBM results using the log-determinant Jacobians.

3. Materials

We used freely available MR imaging datasets to evaluate our brain registration methods. These datasets are available online to researchers, and provide an open repository for data sharing and method comparison.

The Internet brain segmentation repository (IBSR) 1.5T Dataset consists of 18 healthy controls, provided by the Center for Morphometric Analysis at Massachusetts General Hospital. The ages of the subjects ranged from juvenile to 71 years. Manual segmentations were provided for 48 cortical regions.

The Laboratory of Neuro Imaging Probabilistic Brain Atlas (LPBA40) [24] consists of 40 healthy controls, provided by the University of California, Los Angeles Laboratory of Neuro Imaging. Subjects were scanned on a GE 1.5T scanner, with average age at time of acquisition 29.20 ± 6.30 (mean \pm S.D.) years (min = 19.3, max = 39.5 years). Manual segmentations of 56 structures, mainly cortical, were provided, with a manual segmentation protocol defined by Shattuck *et al.* [24].

These two datasets were recently used to evaluate brain registration accuracy for 14 commonly used registration methods [25]. Note that two other smaller datasets (CUMC12, MGH10) were also used in that study; however, we only used the two largest datasets here. Since we used the same datasets, methodology, and evaluation metrics as the Klein *et al.* evaluation, we can directly compare our results to the leading brain registration methods applied in that study.

For evaluating group-wise average atlas construction and morphometry, we used MRI datasets from the Open Access Series of Imaging Studies (OASIS), freely available online (<http://www.oasis-brains.org>). We used baseline scans from a dataset consisting of 150 subjects, aged 60–96 years with 64 of the subjects characterized with very mild to mild Alzheimer's disease [26].

4. Results

A. Brain Registration Evaluation

Figs. 1 and 2 plot the Dice overlaps for the LPBA and IBSR datasets, averaged over all pairwise registrations in each dataset. Since we did not observe a significant difference between left and right structures, the mean dice scores for bilateral structures were also averaged to summarize the results further. We compared locally optimal LDDMM registration using multi-structure (LDDMM Multistucture) and MRI-only (LDDMM MRI) costs against the four top ranked registration methods from the [25] evaluation: SyN [27], ART [28], IRTK [15], and SPM Dartelet [29]. One of the most significant findings of that study was that the relative performances of the registration methods under comparison appear to be little affected by the choice of subject population, labeling protocol, and type of overlap measure, thus our choice of only using the two largest datasets and the Dice overlap measure is justified. On the LPBA dataset, we see that our multistucture approach improves accuracy over our MRI-based approach for nearly all structures, except for the gyrus rectus and lateral orbitofrontal gyrus, both located in the frontal lobe. The improvement is especially notable in the hippocampus and postcentral gyrus, where the MRI-based method is the worst performing of the group and the multistucture method is one of the best performing. Comparing to the other methods, our Dice overlaps are generally in the same range except for the cerebellum and brainstem, where both LDDMM and LDDMM MultiStruct are consider-

ably higher. This could be attributed to the fact that our brains were not skull-stripped prior to registration, whereas [25] used the manual labels to generate a brainmask for skull-stripping; it is possible that the additional information in the neck aids in registration of the mid-brain regions.

For the IBSR dataset, we see multistucture generally has higher overlaps than MRI-based for most regions, except for the temporal pole, temporal gyrus, parietal lobule, supramarginal gyrus, frontal orbital gyrus, and Heschl's gyrus. The reduced performance in the frontal lobe was also seen in the LPBA dataset. Comparing to the other methods, our methods have higher overlaps for all structures.

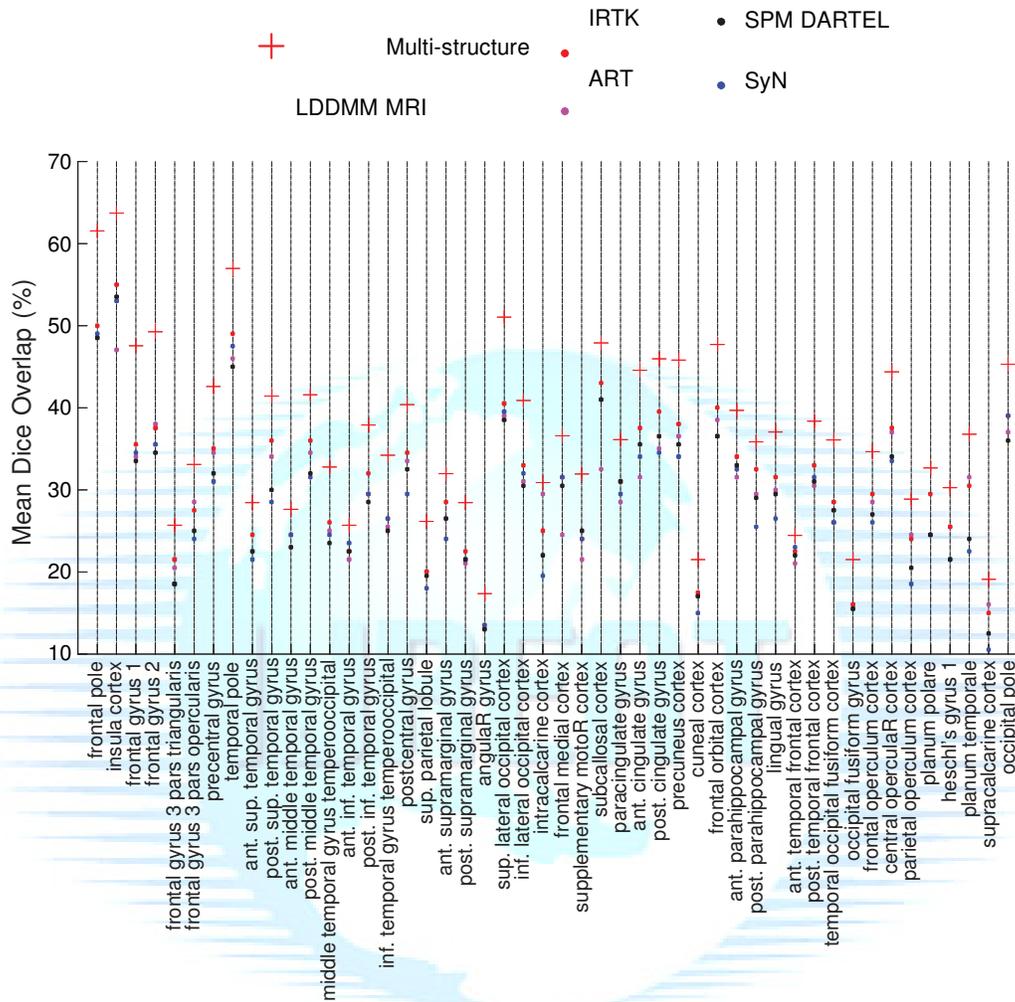


Fig. 2. Mean Dice overlap scores for each manually traced structure (bilateral structures combined) from fully crossed pairwise registrations of the 18 subjects in the IBSR dataset (324 pairwise registrations). Our locally optimal LDDMM registration with multistructure and MRI-based cost functions are compared against the top performing registration methods: SPM DarteL, SyN, IRTK, and ART.

B. Groupwise Average Atlas

To qualitatively evaluate the performance of our multistructure and MRI-based groupwise average atlas generation, we performed them on the OASIS 150 subject set, generating an LDDMM MultiStruct average and an LDDMM MRI average. Fig. 3 shows representative axial slices of the average T1 MRI image, generated by transforming each subject's T1 MRI image to the average space, using the final mappings from the group-wise average, and performing voxel-wise averaging. In regions where the anatomy is not well aligned and thus has a mixture of different tissue types from the subjects, the image is effectively blurred. In contrast, where the anatomy is well aligned the anatomical boundaries are effectively sharper. We see here that the multistructure approach improves registration in many regions, especially cortical regions, as can be seen by

the sharp and well-defined boundaries. To further investigate this effect, we transformed the gray matter segmentations from each subject to the average space to generate an average gray matter mask, as shown in Fig. 4. We see a similar pattern here, with greater definition of cortical folding patterns in the average generated by multistructure registration.

To further inspect alignment of cortical anatomy with our approaches, we performed a cortical surface reconstruction of the average MRI images using the Freesurfer image analysis suite. This processing also includes a cortical labeling using curvature-based surface registration to an atlas. Fig. 5 shows the cortical surface reconstructions for the average images from MRI-based and multistructure group-wise registration. Here, we see that the multistructure-based cortical surface shows much greater detail and consistency, closer to what one would see

in an individual's cortical surface, demonstrating the superior alignment of cortical regions as compared to single-channel MRI-based registration.

We can quantify the alignment of these group-wise ap-

proaches by computing the residual variance in the intensities of the aligned MRI images. We computed the variance of prenormalized MRI intensities at each voxel, and thresholded at $\sigma = 20$ to generate a map that can be overlaid on the average

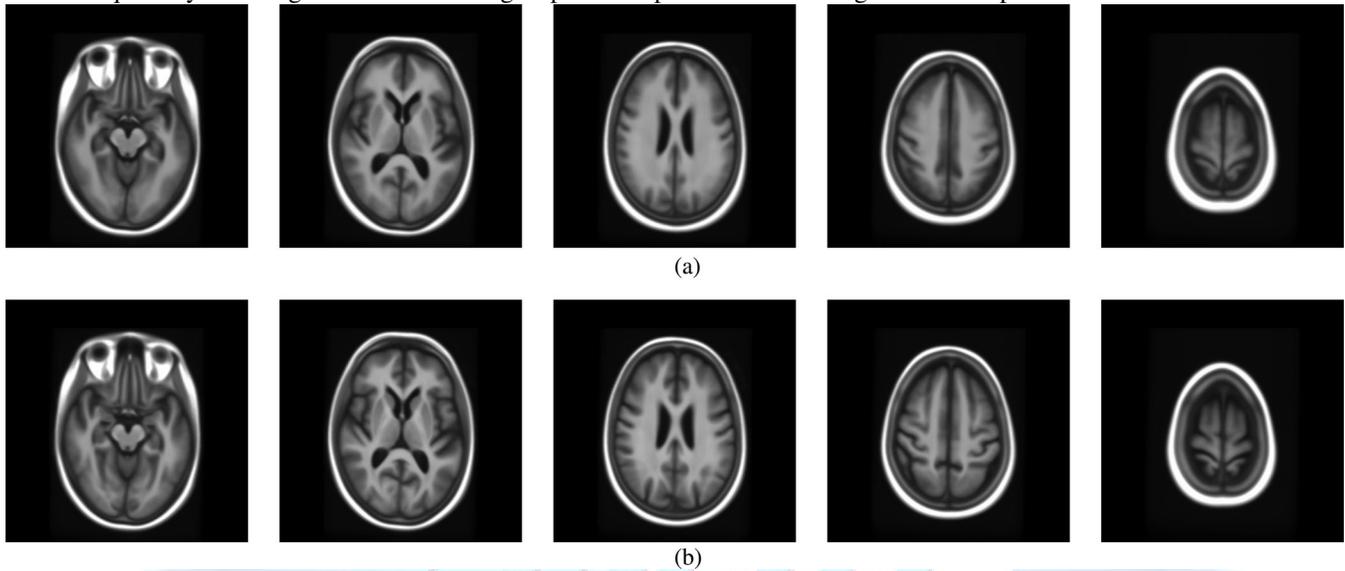
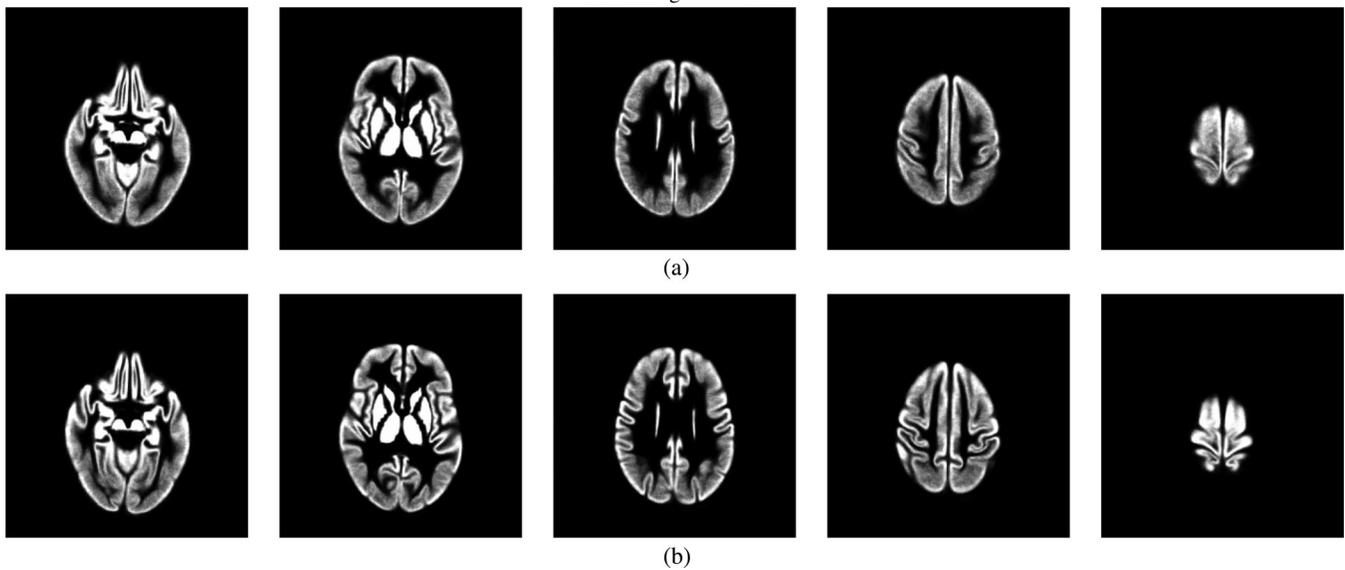


Fig. 3. Average T1 MRI images from groupwise registration of all subjects in the OASIS database (150 subjects), comparing the average obtained via (a) MRI-based (single-channel) and (b) multistucture registration, both using locally optimal LDDMM registration. Registration performance can be assessed by whether the anatomical features are sharp (high accuracy) or blurred (low accuracy). Both methods show good alignment in the subcortical regions but the multistucture variant exhibits much better cortical alignment resulting in sharper delineation of cortical folds in the averaged brain MR image.

Fig. 4. Average gray matter segmentations from groupwise registration of all subjects in the OASIS database (150 subjects), comparing the average obtained via (a) MRI-based (single-channel) and (b) multistucture registration, both using locally optimal LDDMM registration. Registration performance can be assessed by whether the anatomical features are sharp (high accuracy) or blurred (low accuracy). We can see better definition of the cortical folding patterns with multistucture registration.



MRI image to compare residual variance for the multistructure and MRI-based registration approaches, as shown in Fig. 6.

C. Tensor-Based Morphometry

We tested for the effect of group using SurfStat with the linear model, $M = 1 + Group$, and examined differences between nondemented ($CDR = 0$) and demented subjects ($CDR = 0.5/1$). Fig. 7 shows the T-statistics for the comparison of the demented group to the nondemented group, showing greater differences in the medial temporal regions using the multistructure approach. Fig. 8 shows the significant ($P < 0.05$) clusters

of relative volume contraction in the demented group found by the MRI-based and multistructure groupwise registration methods, with significance level correction using RFT. We see large significant clusters in the medial temporal lobe and hippocampus as detected by the multistructure registration, whereas the MRI-based registration detects a small cluster in the posterior

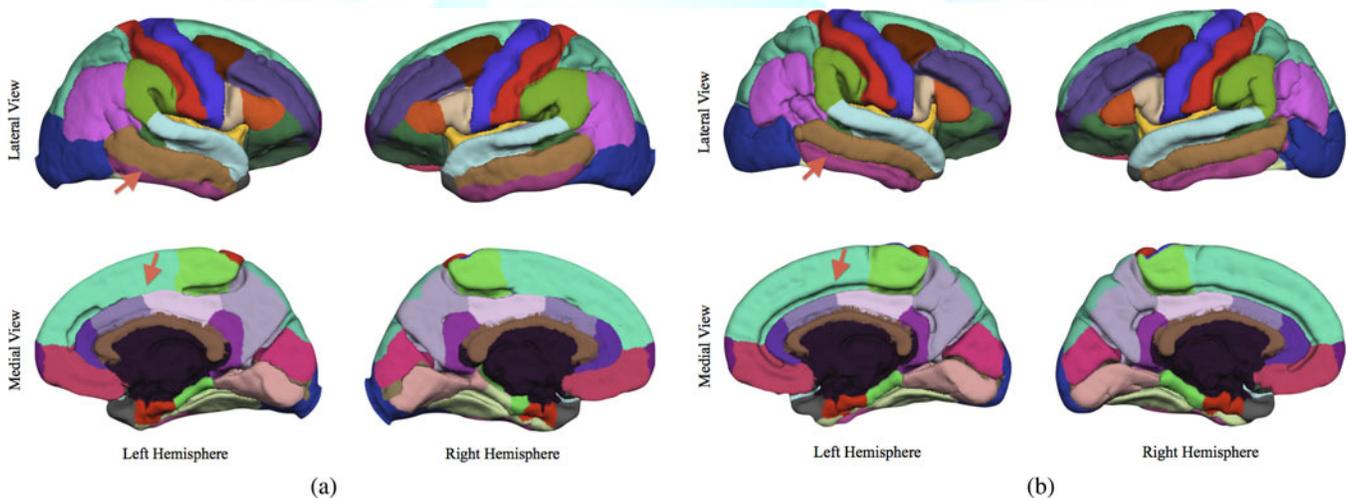


Fig. 5. Cortical surface reconstructions of the average MRI images generated using (a) MRI-based (single-channel) and (b) multistructure group-wise registration generated by Freesurfer. Cortical regions were labeled by surface-based registration to the Freesurfer cortical parcellation atlas. These visualizations show greater detail and consistency with expected cortical anatomy, demonstrating that the multi-structure registration aligns the cortical regions better than the MRI-based registration. (a) Cortical surface of MRI-based average. (b) Cortical surface of multistructure average.

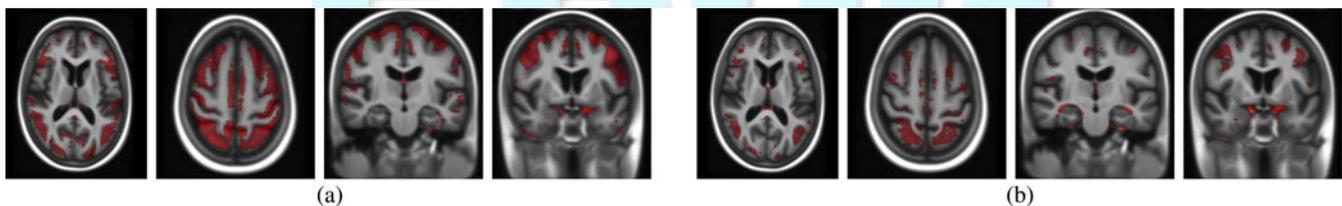


Fig. 6. Visualization of the residual variance from groupwise registration of all subjects in the OASIS database (150 subjects) comparing the (a) MRI-based approach (b) to the multistructure approach. The variance at each voxel was computed using the MRI image intensities of all subjects in the average space, and the visualization is showing the variance thresholded at $\sigma = 20$ to aid comparison. We see that the multistructure approach results in less overall residual variance, and that variance is generally greater in the posterior regions of the brain.

cingulate gyrus. Both methods failed to detect any differences of relative volume expansion in the demented group.

5. Discussion

Our multistructure framework has the significant advantage of being flexible enough to allow use of computed features derived from MRI images, such as white matter tract-based labels and diffusion tensor metrics or additional modalities such as BOLD functional images, susceptibility weighted images, magnetization transfer images, or quantitative relaxation-based maps. A multicontrast LDDMM approach specific to the problem of diffusion tensor image registration [30] has also been proposed. In this approach, whole brain registration was performed with diffusion-tensor derived images such as b_0 , fractional anisotropy (FA) and combined b_0 , and FA with the goal of better aligning whole brain white matter regions and ventricles for DTI normalization. The findings of this study are similar to ours in that the incorporation of multiple streams of information improves registration. Our approach of using multiple structure segmentations to drive local whole brain registration shows for the first time that, as expected, incorporation of individual segmentations into the registration further improves local registration accuracy. A drawback of this approach is the additional burden to provide initial structure segmentations; however, employing a tool such as FreeSurfer, which is highly automated, free, and commonly used in the neuroimaging community, this additional burden is placed on increased computational time only.

Group-wise registration approaches that solely use the MRI image intensities to generate an average template are susceptible to partial volume effects that occur when intensities from different tissue types are averaged together as a result of mis-registration. This can lead to the generation of false anatomy,

if for example, CSF intensities were averaged with WM intensities, the average obtained would be interpreted as a GM intensity. Our multistructure approach helps alleviate this problem by using separate channels for each cortical gray-matter parcellation, such that when these are averaged together there is no partial-voluming of different tissue types. This effect could explain the much higher cortical registration accuracy seen with the group-wise multistructure approach. Previous studies on using segmentation shape matching for cortical alignment, such as [2] also support this conclusion.

The combination of different structure segmentations in the whole brain registration as we have proposed allows the incorporation of *a priori* relative weights reflecting confidence levels for variability of individual ROIs as well as confidence in segmentation accuracy. At this time, these weights are fixed to be equal; however, these could be optimized over a small training database for best whole brain registration in a principled

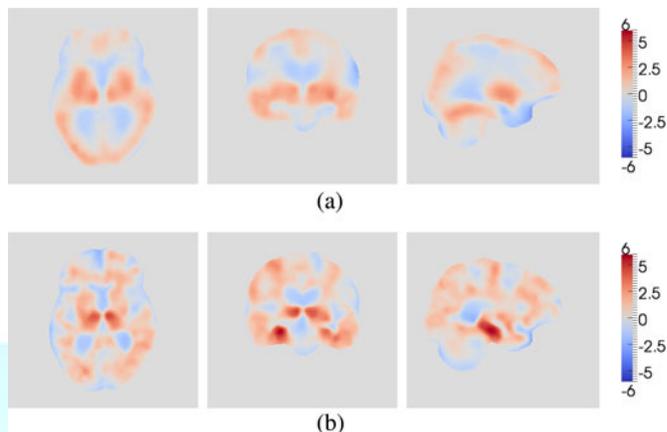


Fig. 7. T-statistic maps showing TBM-based group differences between nondemented and demented subjects in the OASIS database, comparing results from (a) MRI-based group-wise registration (b) to multistructure group-wise registration. Cool colors indicate regions where relative expansion is greater in demented subjects, and warm colors show where relative contraction is greater in demented subjects. We see relative expansion in the ventricles using both methods, and a high level of contraction in regions occupied by the hippocampus, thalamus, and medial temporal lobe detected by the multistructure method only.

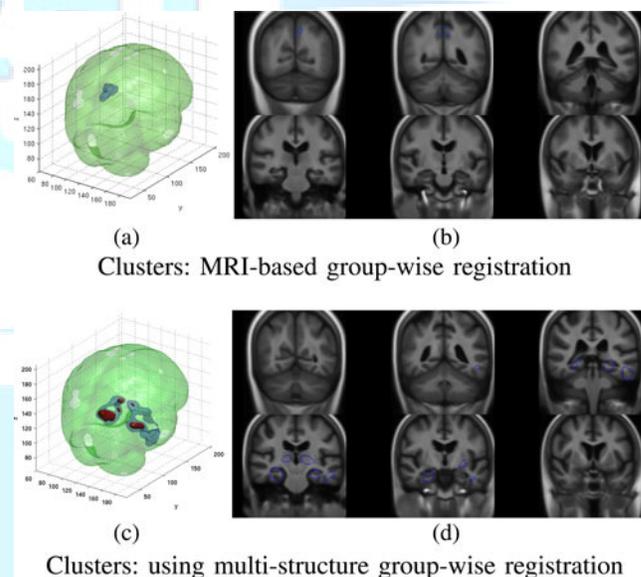


Fig. 8. Visualizations showing regions of significant ($P < 0.05$) TBM-based group differences between nondemented and demented subjects in the OASIS database, comparing results from (a) and (b) MRI-based group-wise registration to (c) and (d) multistructure group-wise registration. The surface visualizations, (a) and (c), depict significant regions of voxel-wise significance (red) and cluster-wise significance (blue). The orthoslice visualizations, (b) and (d), show the average MRI overlaid with outlines surrounding all significant regions (both voxel-wise and cluster-wise significant). These clusters relate to the positive T-statistics shown in Fig. 7, showing where demented subjects experience greater relative contraction than nondemented subjects. We see large clusters in the temporal lobe, hippocampus, and thalamus with the multistructure approach, and a single small cluster in the posterior cingulate with the MRI-based approach.

way. Another approach would be to weigh the relative channel contributions of the segmentation channels to be inversely proportional to the size of the structures, so errors in alignment over smaller structures are penalized more heavily. In the evaluation of cortical overlap metrics, we had seen reduced performance of frontal lobe alignment with the multistructure approach. This could be due to the relatively larger size of Freesurfer cortical parcellations in the frontal region; if the parcellations are smaller, the effective correspondences through shape matching are at a finer scale. Conversely, if the parcellations are larger and encompass more cortical folding variability, their effectiveness is reduced since they would be more susceptible to local minima. Adaptive weighting of the structure channels could thus potentially aid in addressing this problem as well.

Another limitation of our approach is the large amount of computational resources required for multistructure registration. Although the computational time and memory requirements increase linearly with the number of structures, or channels, in the multistructure approach, we do, however, use a large number of structures for our brain registration, with 37 cortical parcellations and 8 subcortical structures. If we were to include further modalities, such as diffusion tensor or functional data, the total number of channels would further increase. Also, the FreeSurfer processing pipeline often takes several hours to complete cortical reconstruction and segmentation for a single brain. However, thanks to significantly increasing hardware capabilities in face of rapidly decreasing hardware costs, and to several national and international high-performance computing (HPC) initiatives that now allow easy access to computational resources; the tradeoff between computational cost and enhanced accuracy of whole brain registration, as demonstrated in Figs. 1 and 2, is increasingly acceptable.

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