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A Novel Longitudinal Atlas Construction Framework by Groupwise Registration of Subject Image Sequences

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Abstract

Longitudinal atlas construction is a challenging task in medical image analysis. Given a set of longitudinal images of different subjects, the task is how to construct the unbias longitudinal atlas sequence reflecting the anatomical changes over time. In this paper, a novel longitudinal atlas construction framework is proposed. The main contributions of the proposed method lie in the following aspects: (1) Subject-specific longitudinal information is captured by establishing a robust growth model for each subject. (2) The trajectory constraints are enforced for both subject image sequences and the atlas sequence, and only one transformation is needed for each subject to map its image sequence to the atlas sequence while preserving the temporal correspondence. (3) The longitudinal atlases are estimated by groupwise registration and kernel regression, thus no explicit template is used and the atlases are constructed without introducing bias due to the selection of the explicit template. (4) The proposed method is general, where the number of longitudinal images of each subject and the time points at which the images are taken can be different. The proposed method is evaluated on a longitudinal database and compared with a state-of-the-art longitudinal atlas construction method. Experimental results show that the proposed method achieves more consistent spatial-temporal correspondence as well as higher registration accuracy than the compared method.

1 Introduction

Study of longitudinal changes of brain anatomical structures plays an important role in medical image analysis. Observing the anatomical shape variations over time in different subjects can provide important clues to study developmental trends across the life span [10]. For this purpose, images of the same subject at different time points are taken to observe subject-specific longitudinal changes.

Longitudinal atlas construction is an active research topic in longitudinal study in the past decade. It can be broadly classiffied into three categories: (1) Atlas construction by kernel regression [2, 6] over the temporal domain; (2) Joint alignment of image sequences to a selected template space [3, 7]; (3) Atlas construction by registration of cross-sectional images of different time points [4]. Each stream of methods have their own advantages and disadvantages. The proposed method in this paper is mostly related to the methods in [2] and [3].

Davis *et al.* [2] proposed a kernel regression based framework for longitudinal atlas construction. This method extended the Nadaraya-Watson kernel regression method by formulating the regression problem in terms of the Fréchet mean. The longitudinal atlas at a particular time point is constructed by performing kernel regression on the Riemannian manifold represented by diffeomorphisms. The importance of each image during the atlas construction process is reflected by its weight assigned by the kernel. However, in [2], the subject-specific longitudinal information is not considered, thus it may lead to inconsistent temporal correspondence among images of the same subject taken at different time points. Figure 1(a) illustrates the idea of this method.

Durrleman *et al.* proposed a joint spatial-temporal atlas construction framework in [3] to build the longitudinal atlas. In this method, the shape evolution model of each subject is first established by regression (i.e., indicated by the solid lines across the images of the same subject in Figure 1(b)). It is not required in this method that each subject must have the same number of scans, or images must be scanned at the same time point. After building the shape evolution model of each individual subject, pairwise spatial-temporal registration is performed by aligning each subject's image sequence to the atlas sequence. The idea of this method is depicted in Figure 1(b). However, this method requires an explicit template sequence to perform registration instead of estimating the atlas with the groupwise registration scheme, which may lead to bias. Moreover, this approach was evaluated on the 2D human skull profiles only and has not been tested thoroughly on building real human brain atlas.

Therefore, we are motivated to propose a new longitudinal atlas construction method. The proposed method integrates both the subject-specific longitudinal information as well as the population shape variation information to estimate the atlas sequence. More precisely, the temporal correspondence among the image sequence of each subject is represented by its corresponding growth model, which is estimated based on the 4D image registration algorithm. Thus, images belonging to each subject can be warped to any single time point of the subject's image sequence by using the growth model, while enforcing the temporal trajectory constraints. On the other hand, the correspondence among the atlas sequence can also be represented by the evolution model in the atlas space. Specifically, the atlas sequence is estimated by performing groupwise registration from each subject's image sequence to the atlas space. Note that only a single transformation is needed for each subject to map its image sequence to the atlas space while preserving the temporal correspondence. Since the atlas sequence is estimated based on groupwise registration and kernel regression, no explicit template is assumed. Figure 1(c) illustrates the idea of the proposed method. The proposed method is evaluated on the longitudinal dataset in [8] and compared with the state-of-the-art atlas construction method proposed by Davis *et al.* [2]. It is observed that the proposed method achieves higher registration accuracy as well as better temporal correspondence compared with Davis's method [2].

2 Formulation and Properties of the Proposed Method

In this section, we describe the design details and advantages of the proposed longitudinal atlas construction framework. The whole framework can be summarized by Figure 2. The preprocessing step shown in Figure 2 includes histogram matching and rigid alignment of all the other time point images to the first time point image of each subject.

Suppose there are C different subjects, and each subject i ($i = 1, \ldots, C$) has n_i longitudinal images taken at different time points. Let $S_{t_j^i}$ denote the jth time point image of subject i. The number of longitudinal images and the earliest time point of each subject are not necessarily the same. The task is to simultaneously estimate an atlas sequence which can reflect the longitudinal changes of the population.

Suppose there are N different time points $t_1, \dots t_N$ where we want to construct the atlas sequence, and let $T = \{t_1, \dots, t_N\}$ and the atlas at different time point t denoted as M_t, where $t \in T$. The whole framework to construct the longitudinal atlas can be formulated as the energy minimization problem as expressed in Equation 1:

$$E(M_t, \varphi^i, \chi) = \sum_{t \in T} \sum_{i=1}^{C} \left\{ \frac{\sum\limits_{t_0^i \le t_j^i \le t_{n_i-1}^i} d(M_t, \chi_{t_0^i \to t}(I_{t_j^i}))^2 K_h(t - t_j^i)}{\sum\limits_{t_0^i \le t_j^i \le t_{n_i-1}^i} K_h(t - t_j^i)} + \Psi(\varphi^i, \chi) \right\}, \tag{1}$$

where $I_{t_j^i}$ is the transformed image of $S_{t_j^i}$ to the time point t_0^i in the atlas space defined by Equation 2:

$$I_{t_j^i} = \varphi^i \circ V^i_{(t_j^i \to t_0^i)}(S_{t_j^i}), \tag{2}$$

where $V^i_{(t_j^i \to t_0^i)}$ denotes the underlying growth model of subject i which can warp image $S_{t_j^i}$ of subject i to its first time point image $S_{t_0^i}$ while preserving the temporal smoothness. The growth model only needs to be estimated once. φ^i is the transformation which maps subject i's space to the atlas space, and $\circ$ denotes the operation of compositing deformations.

In Equation 1, χ is the underlying evolution model in the atlas space. $K_h(t)$ is the kernel satisfying $K_h(t) = \frac{1}{h} K(\frac{t}{h})$, where h is the bandwidth of the kernel and K is a function satisfying $\int K(t)dt = 1$. $d(\cdot)$ is the distance metric between images defined based on diffeomorphisms. $\Psi(\varphi^i, \chi)$ is the overall regularization term defined by Equation 3.

$$\Psi(\varphi^i, \chi) = \gamma_{\varphi^i} Reg(\varphi^i) + \gamma_\chi Reg(\chi), \tag{3}$$

where $Reg(\cdot)$ denotes the regularization function, and γ_{φ^i} and γ_χ are constants trading off the accuracies in image matching and the smoothness of the deformation field.

The physical meaning beneath Equation 1 is: all the longitudinal images of each subject are jointly considered as a sequence with trajectory constraints established by its growth model V^i. Each subject i's image sequence can be transformed to the atlas space by using a single transformation φ^i, and the transformed images can be further warped to any time point t in the atlas space by the evolution model χ. Finally the atlas sequence is estimated based on groupwise registration and kernel regression over all subject image sequences.

There are four main advantages of the proposed framework compared to conventional atlas construction approaches proposed in [2] and [3]. First, subject-specific longitudinal information is considered by building a growth model for each subject, which is different from the method proposed in [2], where subject-specific longitudinal information is not considered and thus possibly leads to inconsistent temporal correspondence. Second, the trajectory constraints are enforced by considering each subject's image sequence as a group to map to the atlas sequence, thus only one transformation φ^i is needed for each subject i to map its image sequence to the atlas sequence. Third, the atlas sequence is estimated based on groupwise registration and kernel regression over all subject image sequences, therefore the unbias atlas sequence can be obtained, which is different from the method proposed in

[3] where an explicit template is used. Finally, the proposed method is general, as the number of longitudinal images of each subject and the time points at which the images are taken can be different.

To minimize the energy function in Equation 1 with respect to M_t, φ^i and χ, the four step optimization strategy is adopted: (1) Growth model V^i estimation, (2) subject-specific transformation φ^i estimation, (3) atlas M_t construction by kernel regression, and (4) evolution model χ estimation in the atlas space. The proposed method is consisted of these four major components, as highlighted by red rectangles shown in Figure 2. Note that the growth model in the first step only needs to be computed once, and the last three steps need to be updated iteratively, which is also illustrated in Figure 2. In the following sections, details of each component are given on how to optimize Equation 1.

2.1 Growth Model Estimation for Each Subject

The first step of the proposed framework is to estimate the growth model of each subject after the preprocessing step as shown in Figure 2. The goal of this step is to recover the geometric changes of anatomical structures over time of each subject image sequence.

The growth model of each subject can be estimated based on 4D image registration methods (i.e., a method proposed in [9]). Therefore, after the 4D registration, temporal correspondences are established among the entire image sequence, which are represented by the respective deformation field from each time point image to the first time point image. This step can be summarized by Algorithm 1 below.

After estimating the growth model for each subject i by Algorithm 1, the longitudinal information of subject i contained in the image sequence can be propagated and aggregated to any time point based on the growth model. Without loss of generality, in this paper the images of each subject are all warped to its earliest time point.

The growth model provides smooth and consistent temporal correspondence among image sequence of each subject. Another advantage of building the growth model for each subject is that if the longitudinal data of a particular subject is taken sparsely with large time gap (e.g., more than 3 years), the geometric changes of brain structures can be dramatic; In this case, the growth model can bridge the gap of the dramatic changes of anatomical structures by interpolating longitudinal images between two consecutive time points. The growth model estimation step for each subject only needs to be calculated once, which is also illustrated by Figure 2.

2.2 Transformation of Subject Image Sequence to the Atlas Space

After building the subject-specific growth model described in Section 2.1, the next step is to estimate the transformation from each subject space to the atlas space (i.e. φ^i in Equations 1 and 2) by fixing the rest of the variables such as M_t and χ in Equation 1.

To estimate φ^i, the image matching term $d(M_t, \chi_{t_0^i \to t}(I_{t_j^i}))$ in Equation 1 can be redefined as $d((\chi_{t_0^i \to t})^{-1} M_t, I_{t_j^i})$ (i.e., each atlas is first warped to the earliest time point t_0^i of subject i in the atlas space, and the warped images of subject i at the same time point t_0^i are then matched to the warped atlases by the transformation φ^i). This redefinition is valid only when the evolution model χ is a diffeomorphic transformation. Therefore, Equation 1 now becomes:

$$J(\varphi^i)=\sum_{t\in T}\left\{\frac{\sum\limits_{t_0^i\le t_j^i\le t_{n_i-1}^i} d((\chi_{t_0^i\to t})^{-1}M_t, I_{t_j^i})^2 K_h(t-t_j^i)}{\sum\limits_{t_0^i\le t_j^i\le t_{n_i-1}^i} K_h(t-t_j^i)}+\gamma_{\varphi^i}Reg(\varphi^i)\right\}, \quad (4)$$

where $I_{t_j^i}=\varphi^i \circ V^i_{(t_j^i\to t_0^i)}(S_{t_j^i})$. Equation 4 reflects that atlases at different time points are inversely warped to the time point t_0^i by the reversed evolution model $(\chi_{t_0^i\to t})^{-1}$. Each image $S_{t_j^i}$ of subject i is aligned to the first time point t_0^i of subject i by its growth model $V^i_{(t_j^i\to t_0^i)}$. Thus φ^i can be estimated by groupwise registration between the warped images of subject i at the first time point t_0^i and all the warped atlases M_t also at time point t_0^i. This procedure can be summarized by Figure 3. In Figure 3, we aim to estimate the transformation from the subject space to the atlas space for subject i, where t_0^i denotes the earliest time point of subject i. We only need to estimate one transformation from the subject space to the atlas space at time t_0^i as images of the same subject can be warped to the earliest time point t_0^i based on the growth model built in Section 2.1.

After estimating φ^i for each subject, we can transform images in each subject's space to the common atlas space to construct and update the atlas sequence, which will be described in the next section.

2.3 Atlas Construction by Kernel Regression

After estimating the transformation φ^i from each subject i's space to the atlas space, the next step is to construct and update the atlas sequence M_t by fixing the variables φ^i and χ in Equation 1.

By fixing φ^i and χ, the energy minimization problem in Equation 1 with respect to M_t now becomes:

$$J(M_t)=\sum_{i=1}^{C}\left\{\frac{\sum\limits_{t_0^i\le t_j^i\le t_{n_i-1}^i} d(M_t,\chi_{t_0^i\to t}(I_{t_j^i}))^2 K_h(t-t_j^i)}{\sum\limits_{t_0^i\le t_j^i\le t_{n_i-1}^i} K_h(t-t_j^i)}\right\}. \quad (5)$$

The optimal solution M_t of Equation 5 can be obtained by Equation 6:

$$M_t=\arg\min_{M_{opt}\in\Lambda}\sum_{i=1}^{C}\left(\frac{\sum_{j=0}^{n_i-1}K_h(t-t_j^i)d(M_{opt},\chi_{t_0^i\to t}(I_{t_j^i}))^2}{\sum_{j=0}^{n_i-1}K_h(t-t_j^i)}\right), \quad (6)$$

where Λ denotes the whole possible image space, C denotes the number of subjects, n_i denotes the number of longitudinal images belonging to the subject i, and t_j^i denotes the time point at which the jth longitudinal image of subject i is taken. $K_h(\cdot)$ is the kernel function, and the Gaussian kernel is adopted in this paper. $d(\cdot)$ is the distance metric between images defined based on diffeomorphisms.

Equation 6 actually denotes a kernel regression procedure to estimate M_t. In this paper, the greedy iterative algorithm proposed in [5] is adopted to estimate the optimal solution of Equation 6.

2.4 Evolution Model Estimation in the Atlas Space

After constructing the atlas sequence by kernel regression in Section 2.3, the last step of the proposed method is to estimate and update the evolution model χ in the atlas space by fixing variables φ^i and M_t in Equation 1. When φ^i and M_t are fixed, Equation 1 becomes:

$$J(\chi)=\sum_{t\in T}\sum_{i=1}^{C}\left\{\frac{\sum_{t_0^i\le t_j^i\le t_{n_i-1}^i} d(M_t,\chi_{t_0^i\to t}(I_{t_j^i}))^2 K_h(t-t_j^i)}{\sum_{t_0^i\le t_j^i\le t_{n_i-1}^i} K_h(t-t_j^i)}+\gamma_\chi Reg(\chi)\right\}. \tag{7}$$

Therefore, to estimate χ, first all images of each subject i are warped to the atlas space of the first time point of subject i by $\varphi^i\circ V^i_{(t_j^i\to t_0^i)}(S_{t_j^i})$. Then, we can estimate $\chi_{t_0^i\to t}$ by registering all these warped images of subject i with M_t, thus the overall χ can be obtained by stitching all $\chi_{t_0^i\to t}$. Note that the kernel $K_h(\cdot)$ will be used to constrain the weight of these warped images.

3 Experimental Results

The proposed method is evaluated by building longitudinal atlases from the longitudinal dataset in [8]. Ten subjects are selected, with the ages ranging from 67 to 85 when the first time point images were taken. Each subject has around ten longitudinal images taken at different time points, and the period between each pair of consecutive time points is around one year. Each image is with resolution 256 × 256 × 124. The first row in Figure 4 shows longitudinal images scanned from the same subject from ages 67 to 74, where significant longitudinal changes can be observed, especially at the ventricle region. Images shown in the second row of Figure 4 are taken from different subjects to demonstrate the large population shape variations in this dataset. The segmentation results of each image into three different types of tissues: white matter (WM), gray matter (GM) and ventricular CSF, are also available.

The proposed method is also compared with the state-of-the-art atlas construction algorithm proposed by Davis *et al.* [2]. Both methods were implemented based on the Insight Segmentation and Registration Toolkit (ITK) [1]. In this paper, the proposed method was evaluated both on the ability to capture the global shape variations among all the images and the ability to preserve the temporal correspondence among the longitudinal data of the same subject.

3.1 Experiments on Measuring Global Registration Accuracy

In this section, the proposed method is evaluated on measuring the global registration accuracy among all the aligned images together. Figure 5 shows the same cross section of the atlas constructed by the proposed method across different ages. It can be observed that the expansion of the lateral ventricle is captured.

[1]http://www.itk.org/

To visually compare the atlas construction performance of the proposed method and the method proposed by Davis *et al.* [2], Figure 6 shows the 3D rendering of the atlas of age 74 constructed by both the proposed method and the method proposed by Davis *et al.* [2]. It can be observed that the atlas constructed by using the proposed method is sharper and preserves more anatomical details than the atlas constructed by the approach proposed by Davis *et al.* [2], where the regions with significant differences are highlighted by the green circles.

In this paper, we also quantitatively evaluate the proposed method by using the tissue overlap ratio [1]. It is defined as $P=\frac{\#(A\cap B)}{\#(A\cup B)}$, where A and B denote the regions of a specific tissue in the two images, and $\#(\cdot)$ denotes the number of voxels inside a region. In this paper, since there is no explicit template used for both Davis's method [2] and the proposed method, the segmentation result of the template image was obtained by majority voting from all aligned images by setting the tissue type of each voxel in the template image as the majority of tissue labels from all aligned images. The average values of P for WM, GM and ventricular CSF across different ages using Davis's method [2] and the proposed method are shown in Figures 7(a) to (c). It can be observed that the proposed method consistently achieves higher tissue overlap ratio than Davis's method [2]. More precisely, for each type of tissue and for each age, the tissue overlap ratio obtained by the proposed method is normally 2% to 3% higher than that obtained by Davis's method [2], which is a significant improvement as the standard deviation of the tissue overlap ratios for each type of tissue at different age is no more than 0.1%.

3.2 Experiments on Measuring Individual Temporal Smoothness

Besides evaluating the global registration accuracy among all the images of the proposed method, we also measure the registration accuracy within each subject. We adopt the tissue overlap ratio measure similar to Section 3.1, but now each subject is considered as a separate group, and the overlap ratios for WM, GM and ventricular CSF are measured for each group.

The average tissue overlap ratios of WM, GM and ventricular CSF across the 10 groups (i.e., there are 10 subjects in total) are shown in Figures 8(a) to (c) for different ages. It can be observed that the average subject-specific tissue overlap ratios are generally higher than those obtained from the whole population shown in Section 3.1, as the longitudinal changes within each subject are much smaller than the shape variations across different subjects. It is demonstrated that the proposed method still maintains higher tissue overlap ratios than Davis's method, which implies the more accurate registration results by the proposed method within each subject's image sequence.

Moreover, to measure the temporal consistency across different ages of each subject, the temporal consistency (TC) factor of different types of tissues is calculated. The average TC factor is defined as: $TC=\frac{1}{\|(\Omega)\|}\sum_{i\in\Omega}(1-L_i/(Y-1))$, where Ω is the voxel set of region of interest to measure the temporal consistency, and $\|\Omega\|$ denotes the number of voxels in Ω. L_i denotes the number of tissue label changes of the corresponding voxel i across time, and Y denotes the number of longitudinal images of the subject. The average TC values for WM, GM and ventricular CSF of different approaches for each subject are shown in Figures 9(a) to (c). It is observed that the proposed method consistently achieves higher TC values for different types of tissues for each subject compared to Davis's method, which strongly implies the better temporal correspondence established by the proposed method. The improvement of the temporal consistency of the proposed method is significant as the average TC values for the proposed method are normally 2% to 3% higher than Davis's method, while the standard deviations of the TC values are no more than 0.1%.

4 Conclusion

In this paper, a new framework to construct the longitudinal atlas is proposed. The proposed method takes both the subject-specific longitudinal changes and population shape variations information into account when estimating the longitudinal atlas. The subject-specific longitudinal information is captured by establishing a growth model for each subject based on the 4D image registration algorithm. Then, transformations which map each subject's image sequence to the atlas space are estimated by performing diffeomorphic groupwise registration between the warped subject images and the warped atlases. Images of each subject are transformed to the atlas space by the estimated diffeomorphic transformations and warped to the time point of interest to build the atlas by the evolution model in the atlas space. The atlas is then estimated based on the kernel regression procedure. The proposed method is qualitatively and quantitatively compared with the state-of-the-art atlas building algorithm proposed by Davis *et al.* [2] on the longitudinal dataset. Experimental results show that the proposed method achieves higher registration accuracy as well as better temporal correspondence. Future work includes testing the proposed method to measure the longitudinal changes of deep brain structures such as hippocampus.

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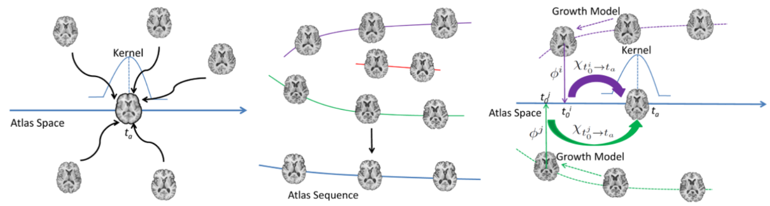

(a) Davis *et al.* [2] (b) Durrleman *et al.* [3] (c) Our method.

Fig. 1.

(a) The method proposed by Davis *et al.* [2], where the atlas is built by kernel regression, and the contribution of each image to build the atlas is determined by the kernel. However, the subject-specific longitudinal information is not considered in this approach. (b) The approach proposed by Durrleman *et al.* [3], where the shape evolution model is constructed for each subject first, as indicated by solid lines, and then each subject's image sequence is registered to the atlas sequence. (c) The proposed method. In this method, for each subject, its corresponding growth model is first estimated based on 4D image registration method to establish the temporal correspondence within the image sequence. A single transformation φ_i is then estimated to map subject *i's* image sequence to the atlas space. Each image can be warped to the atlas space of a certain time point by the composite deformation field formed by φ_i and its subject's growth model. It can be further warped to any time points in the atlas space by the evolution model χ of the atlas. Finally the atlas at each time point is built by performing kernel regression with respect to all the warped images.

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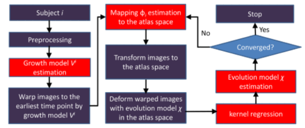

Fig. 2.

Flow chart of the proposed method, where rectangles highlighted with red color denote the major components of the proposed approach.

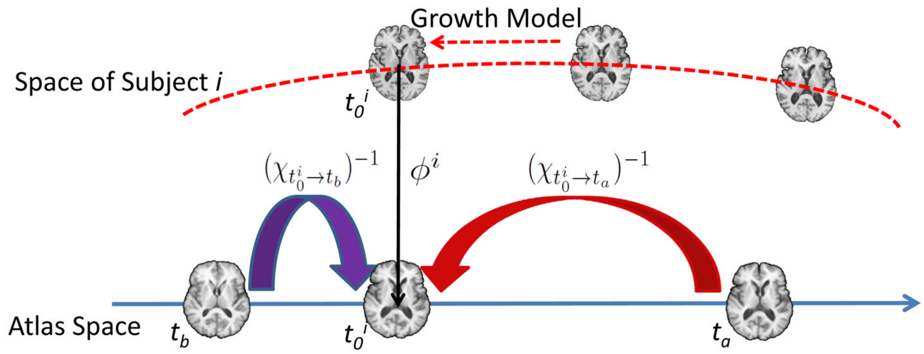

Fig. 3.

Illustration of how to estimate the transformation φ^i from the subject space to the atlas space. First, each image of subject *i* is warped to the earliest time point t_0^i of subject *i* by the growth model. Then, for the current atlas sequence, each atlas at different time point is first warped to the subject *i's* earliest time point t_0^i in the atlas space by applying the reversed evolution model $(\chi_{t_0^i \to t})^{-1}$. The transformation mapping from the subject space to the atlas space φ^i can be estimated by performing group wise diffeomorphic registration from the warped images of subject *i* to the warped atlases both at t_0^i.

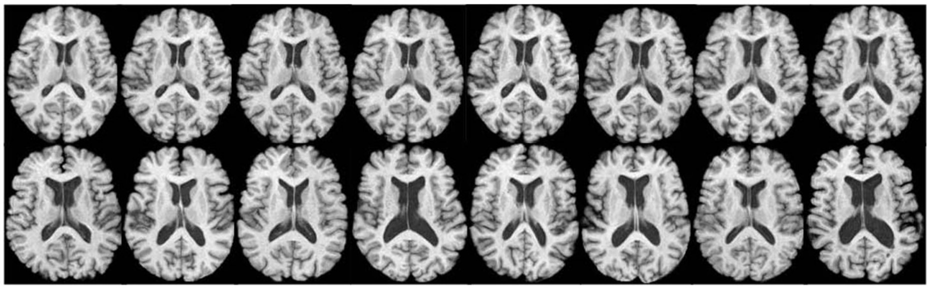

Fig. 4.

First row shows images taken from the same subject from age 67 to age 74. Significant longitudinal changes can be observed. Second row shows images taken from different subjects, demonstrating the large structural variations across different subjects in the dataset.

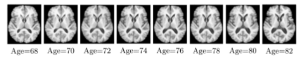

Fig. 5.

The same cross-sectional images obtained from the atlas constructed by the proposed method at different ages. The expansion behavior of the lateral ventricle is captured.

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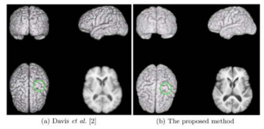


Fig. 6.

3D rendering of the atlas of age 74 constructed by: (a) the method proposed by Davis *et al.* [2] and (b) the proposed method. Significant differences are highlighted with the green circles.

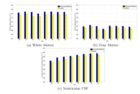
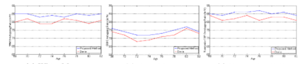


Fig. 7.

Mean tissue overlap ratios for: (a) white matter, (b) gray matter, and (c) ventricular CSF across different ages by using Davis's method [2] (yellow bars) and the proposed method (blue bars).



(a) White Matter (b) Gray Matter (c) Ventricular CSF

Fig. 8.

Subject-specific mean tissue overlap ratios for: (a) white matter, (b) gray matter, and (c) ventricular CSF across different ages with Davis's method [2] and the proposed method.

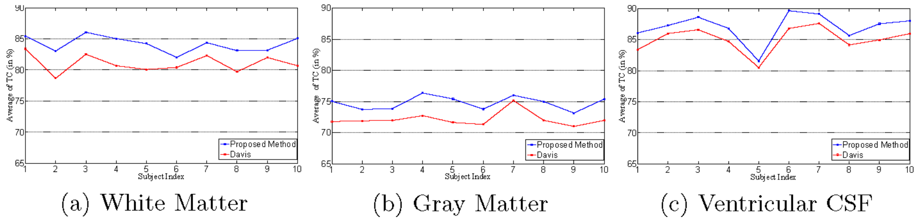


Fig. 9.
Mean temporal consistency (TC) values for different subjects of: (a) white matter, (b) gray matter, and (c) ventricular CSF with Davis's method [2] and the proposed method.

Algorithm 1

Growth Model Estimation for Subject *i*

Input: The rigidly-aligned and histogram-matched image sequence $S_{t_0^i}, S_{t_1^i}, \ldots, S_{t_{n_i-1}^i}$ of subject i, where n_i denotes the total number of images in the image sequence of subject i.

Output: Deformation fields $V^i_{(t_0^i \to t_0^i)}, V^i_{(t_1^i \to t_0^i)}, \ldots, V^i_{(t_{n_i-1}^i \to t_0^i)}$ mapping from $S_{t_0^i}, S_{t_1^i}, \ldots, S_{t_{n_i-1}^i}$ to $S_{t_0^i}$

1. Construct the moving image sequence as $S_{t_0^i}, S_{t_1^i}, \ldots, S_{t_{n_i-1}^i}$.

2. Construct the reference image sequence by repeating the first time point image as $S_{t_0^i}, S_{t_0^i}, \ldots, S_{t_0^i}$.

3. Register the moving image sequence to the reference image sequence using the 4D registration method in [9]. Denote the resulting deformation field that warps $S_{t_j^i}\ (j=0, \ldots, n_i - 1)$ to $S_{t_0^i}$ as $V^i_{(t_j^i \to t_0^i)}$, where $V^i_{(t_0^i \to t_0^i)}$ is the identity deformation field.

4. Return $V^i_{(t_0^i \to t_0^i)}, V^i_{(t_1^i \to t_0^i)}, \ldots, V^i_{(t_{n_i-1}^i \to t_0^i)}$.