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Application of a non-linear image registration algorithm to quantitative analysis of T_2 relaxation time in transgenic mouse models of AD pathology

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Abstract

Transgenic mouse models have been essential for understanding the pathogenesis of Alzheimer's disease (AD) including those that model the deposition process of β -amyloid ($A\beta$). Several laboratories have focused on research related to the non-invasive detection of early changes in brains of transgenic mouse models of Alzheimer's pathology. Most of this work has been performed using regional image analysis of individual mouse brains and pooling the results for statistical assessment. Here we report the implementation of a non-linear image registration algorithm to register anatomical and transverse relaxation time (T_2) maps estimated from MR images of transgenic mice. The algorithm successfully registered mouse brain magnetic resonance imaging (MRI) volumes and T_2 maps, allowing reliable estimates of T_2 values for different regions of interest from the resultant combined images. This approach significantly reduced the data processing and analysis time, and improved the ability to statistically discriminate between groups. Additionally, 3D visualization of intra-regional distributions of T_2 of the resultant registered images provided the ability to detect small changes between groups that otherwise would not be possible to detect.

Keywords

MRI; T_2 relaxation; Brain; Image registration; β -Amyloid; Transgenic mice; Alzheimer's disease

1. Introduction

Transgenic mouse models have been essential for understanding the pathogenesis of Alzheimer's disease including those that model the deposition process of β -amyloid ($A\beta$). Recently, we reported a reduction of the transverse relaxation time (T_2) in the cortex and

hippocampus of transgenic mice overexpressing both presenilin and mutant amyloid precursor protein (PS/APP) (Helpert et al., 2004). In that study, the methodological approach used was to assess each animal individually and then pool the results for statistical analysis. This involved drawing regions-of-interest (ROIs) for each mouse brain for each genotype, which proved to be a very time consuming process. In longitudinal studies, the amount of work required to analyze individual brain images in this fashion is enormous and requires more than one person to draw ROIs, which introduces a reliability issue due to the variability between readers. Moreover, individual analysis does not provide the ability to visualize average differences between groups.

An alternative approach, which is widely used in human imaging research, would be to develop a rigorous means for image co-registration. This would allow for image analysis to be performed on the resultant registered image and eliminate much of the inter-rater subjectivity. This is particularly important for computing statistical parametric maps representing group differences of quantitative parameters (e.g., relaxation times, diffusion anisotropy) between different mouse groups.

Three-dimensional (3D) digital image registration algorithms have been developed and tested extensively for inter-subject registration of human brain magnetic resonance imaging (MRI) scans (Collins et al., 1994; Friston et al., 1995; Hellier et al., 2003; Rohlfing et al., 2000). However, the utility of these methods in registering animal brain images is still mostly unexploited. Few studies have focused mostly on creating MRI-based animal brain atlases (Black et al., 2001; MacKenzie-Graham et al., 2003, 2004) or for the spatial comparison between different imaging modalities (Rubins et al., 2003).

We have developed and implemented one such algorithm and applied it to register anatomic MR images and T_2 maps from MRI brain scans of transgenic mice. The objective of the spatial normalization algorithm is to reduce anatomical variability between MRI brain scans from different mice. This variability is due to differences in brain sizes and shapes between mice as well as differences in head position within the imaging matrix. Anatomical normalization allows images of quantitative measurements (e.g., relaxation times) from multiple mice to be more accurately compared. The algorithm successfully registered mouse brain MR images and T_2 maps, allowing a reliable estimates of T_2 values from different ROIs from the resultant combined images. This method reduced the processing time required for data analyses, improved the ability to statistically discriminate between groups and allowed the 3D visualization of intra-regional distributions of T_2 . Additionally, this method provided the ability to detect small changes between groups that otherwise would not have been possible to detect.

2. Materials and methods

2.1. Transgenic mice

We performed our studies using three types of mice: (1) those that overexpress a pathogenic mutation in the presenilin gene (PS), which results in slightly elevated amyloid- β -42 peptide, but do not form amyloid deposits, (2) those that over-express both presenilin and mutant amyloid precursor protein (PS/APP) which have higher levels of human amyloid- β , and as a consequence deposit amyloid in several brain regions from 10 weeks of age onward, and (3) non-transgenic (NTG) mice. Two concurrent studies were performed. In the first study, 27 mice 18 months old ($n = 9$ for each genotype) and three genotypes (PS/APP, PS and non-transgenic) were imaged. In the second study, twelve PS and non-transgenic mice 6 weeks old ($n = 6$ for each genotype) were imaged.

2.2. MRI protocol

Animals were anesthetized with isoflurane (2%) in NO₂ (75%) and O₂ (22%). For maintenance of anesthesia, isoflurane was reduced to 1% with a slight correction for body weight. After anesthesia, animals were positioned in a head holder custom designed to fit inside the imaging coil. The head holder included a plastic bite bar on which the animal's front teeth were secured, thus minimizing head movement during imaging. The chest and abdomen of the animal outside the RF coil were covered with a circulating water pad made from silicon tubing connected to a heated water bath to monitor and maintain rectal temperature at 36 °C throughout imaging.

All animals were imaged on a 7 T 40 cm horizontal bore magnet (Magnex Scientific, Abingdon, UK) interfaced to a SMIS console. For T_2 measurements, a multi-slice single spin-echo sequence was used. Imaging parameters were: one signal average, 48 slices, FOV of 2.56 cm $\times$ 2.56 cm, matrix size of 128 $\times$ 96, echo times (TE) of 15, 20, 25, 35, 55 and 75 ms, and repetition time (TR) of 4000 ms. The in-plane resolution was 200 μ m with the slice thickness of 200 μ m and a 100 μ m gap.

2.3. T_2 calculation

T_2 maps were generated via exponential fits to multi-echo data using the MEDx software package (Sensor Systems Inc., Sterling, VA), as previously described by Falangola et al. (2003). Using the image registration algorithm described below, mean brain T_2 maps were generated for each group. Briefly, a mouse brain was chosen as the target brain having the median brain volume amongst all mice. The first echo image (TE = 15 ms) of each mouse was matched to the target brain. The resulting deformation field was then applied to the corresponding T_2 map of each mouse. The registered T_2 maps were averaged to generate a mean T_2 map for each group of mice. Regions of interest were drawn at the level of the cortex and hippocampus on the target brain as well as on each individual mouse brain (first study), and an ROI containing the same amount of pixels was drawn at the level of the lateral ventricles on both average T_2 maps (second study). To estimate T_2 relaxation times for each ROI, a mean image intensity value was computed from the original and warped T_2 maps. Histograms, with 64 bins ranging between 30–120 ms (cortex and hippocampus) and 48–120 ms (brain ventricular area), were also generated from mean T_2 maps. 3D renderings of each averaged registered group of mice were created using the '3D Slicer' software package (Gering, 1999).

2.4. Image registration algorithm

Spatial registration is specified in terms of a 3D transformation or deformation field $\mathbf{w}: \mathbb{R}^3 \rightarrow \mathbb{R}^3$ which is applied to the *subject* or *test* mouse image, $I_s(\mathbf{r})$, to obtain the spatially normalized or warped image $I_w(\mathbf{r}) = I_s(\mathbf{r} + \mathbf{w}(\mathbf{r}))$. The main objective is to find a deformation field $\mathbf{w}$ such that the warped image $I_w(\mathbf{r})$ is as 'similar' as possible to a *target* or *template* mouse image, $I_t(\mathbf{r})$. For a given pair of subject and target images I_s and I_t , image registration algorithms mainly differ in their approach to modeling and estimation of $\mathbf{w}$. In our algorithm, to find a deformation vector $\mathbf{w}(\mathbf{r}) = (u_x(\mathbf{r}), u_y(\mathbf{r}), u_z(\mathbf{r}))$ at each voxel $\mathbf{r}$, each voxel is visited in a raster scan fashion. Let Ω_r be a neighborhood around and including voxel $\mathbf{r}$. The *target feature vector* at voxel $\mathbf{r}$, denoted by $\mathbf{f}_r^t$, is defined to be comprised of elements $\{I_t(\mathbf{v}): \mathbf{v} \in \Omega_r\}$ of the target image. Similarly, the *subject feature vector* at voxel $\mathbf{r}$, denoted by $\mathbf{f}_r^s$, is constructed from the voxel values $\{I_s(\mathbf{v}): \mathbf{v} \in \Omega_r\}$ of the subject image. We define the similarity between two arbitrary vectors $\mathbf{w}_1$ and $\mathbf{w}_2$ of the same dimension to be:

$$S(\mathbf{w}_1, \mathbf{w}_2) = \frac{\mathbf{w}_1^T \mathbf{H} \mathbf{w}_2}{\sqrt{\mathbf{w}_2^T \mathbf{H} \mathbf{w}_2}} \quad (1)$$

where $\mathbf{H}$ is an idempotent ($\mathbf{H}^2 = \mathbf{H}$) symmetric centering matrix defined so that it removes the mean of the vector it pre-multiplies. Next consider a *search neighborhood*, $\psi_{\mathbf{r}}$, around and including voxel $\mathbf{r}$. Let voxel $\mathbf{q} \in \psi_{\mathbf{r}}$ be the voxel in this neighborhood at which the similarity measure $S(\mathbf{f}_{\mathbf{r}}^t, \mathbf{f}_{\mathbf{q}}^s)$ is maximum, that is:

$$S(\mathbf{f}_{\mathbf{r}}^t, \mathbf{f}_{\mathbf{q}}^s) = \max_{v \in \psi_{\mathbf{r}}} S(\mathbf{f}_{\mathbf{r}}^t, \mathbf{f}_{\mathbf{v}}^s) \quad (2)$$

Our initial estimate of the deformation field at voxel $\mathbf{r}$ is $\mathbf{w}(\mathbf{r}) = \mathbf{q} - \mathbf{r}$. Note that Eq. (1) can be made symmetric by dividing the right-hand side by $\sqrt{\mathbf{w}_1^T \mathbf{H} \mathbf{w}_1}$. This does not, however, change the voxel $\mathbf{q}$ at which S attains its maximum and will only increase the computational burden.

Described above is the essence of the registration algorithm implemented. However, there still remain a number of very important details that need to be addressed. First, the registration algorithm can benefit from an initial linear registration, either a 6-parameter rigid-body, or a 12-parameter affine transformation. In our implementation, there is an option for performing an initial rigid-body registration using the method described by Ardekani et al. (1995).

Next is the issue of speed. The speed of the algorithm depends on several factors including the number of image voxels, size of the feature neighborhood $\Omega_{\mathbf{r}}$, and size of the search neighborhood $\psi_{\mathbf{r}}$. In our implementation, the neighborhoods $\Omega_{\mathbf{r}}$ and $\psi_{\mathbf{r}}$ are cubic and centered on voxel $\mathbf{r}$. Initially the search neighborhood $\psi_{\mathbf{r}}$ must be large enough to enable the algorithm to find large scale deformations. The search neighborhood is shrunk iteratively and the computations repeated for finding finer scale deformations. In practice, this is achieved through a multiresolution approach. In other words, the image is processed in multiple resolution levels (Fig. 1) using scale-space theory (Lindeberg, 1994). Thus, the initial image is low-pass filtered with Gaussian kernels of various widths to form the scale-space. The core registration process that is described above is repeated in scale-space starting from coarse resolutions towards the finest resolution. At each step, the deformation field found is applied to the subject image before starting the next interaction. The number of iterations is an option to the program. At coarse resolution levels, the algorithm is fast because: (1) the image is represented by fewer voxels with a proportionally larger voxel size, and (2) the search neighborhood $\psi_{\mathbf{r}}$ can be large but comprised of few voxels because of the larger voxel size. In order to use the deformation field obtained at a lower resolution level as the starting point for the next stage, the field components (u_x, u_y, u_z) need to be interpolated to match the voxel size at the higher resolution level. In the present method, this is achieved by using a fast digital filter implementation of the cubic spline interpolation method (Unser, 1999). Overall, the multiresolution approach improves the speed and robustness of the algorithm.

An additional strategy for increasing the computational efficiency of the algorithm was implemented by computing the template image gradient L_2 norm, $\|\nabla I_t(\mathbf{r})\|$, at the highest resolution level and only updating the deformation field in those voxels where the gradient norm is in a certain upper percentile of the gradient magnitude histogram of the template image. The percentile level can be specified as an optional argument to the program. This is

only done at the iteration corresponding to the finest resolution level that is the most computationally intensive iteration. The philosophy behind this approach is that voxels with low spatial derivatives $\|\nabla I_t(\mathbf{r})\|$ are located in featureless ‘planes’ of the image and contain little information for guiding the algorithm and may even result in errors. The gradient vector $\nabla I_t(\mathbf{r})$ is calculated by approximating the template image using cubic splines (Unser, 1999) enabling us to easily compute the necessary partial derivatives.

The next point to consider when implementing the algorithm is the regularization of the deformation field. Intuitively speaking, regularization is necessary to ensure that points that are close to each other in the subject image $I_s(\mathbf{r})$ remain close in the warped image $I_w(\mathbf{r})$. Kjems et al. (1999) reviewed several methods of deformation field regularization. In the present algorithm, we use simple Gaussian low-pass filtering of the field that is obtained at the end of each iteration in the multiresolution algorithm. This method was also applied by Kosugi et al. (1993) and has worked well in our experiments.

Another very important issue that needs to be addressed when solving for the deformation field $\mathbf{w} = (u_x, u_y, u_z)$ is that the algorithm must ensure that the resulting non-linear transformation is a homeomorphism, that is, a continuous mapping between two spaces that has an inverse which is also continuous. Since at each multiresolution iteration, the deformation field is interpolated using a cubic spline fit, we can easily compute the partial derivatives of the deformation field components (u_x, u_y, u_z) with respect to the x , y , and z spatial coordinates using the cubic spline coefficients. This allows us to compute the Jacobian determinant of the field $\mathbf{r} + \mathbf{w}(\mathbf{r})$ at every voxel. We ensure that the Jacobian determinant is strictly positive at every voxel. This, together with the fact that the deformation field is kept to zero at all air voxels surrounding the head, can be shown to be a necessary and sufficient condition for the transformation to be homeomorphic (Kaplan, 1973). If the requirement of a positive Jacobian everywhere in the image is not met, we incrementally increase the width of the smoothing Gaussian kernel and repeat the procedure until the condition is met. Smoothing is guaranteed to have the desired effect because at the limit of infinite width smoothing kernel, the deformation field $\mathbf{w}(\mathbf{r})$ approaches a constant and, therefore, the Jacobian determinant of $\mathbf{r} + \mathbf{w}(\mathbf{r})$ approaches 1.

Finally, we approximate the components of the deformation fields (u_x, u_y, u_z) by a truncated Fourier-Legendre series as follows:

$$u(\mathbf{r}) = \sum_{n,m,q=0}^M c_{nmq} P_n(x) P_m(y) P_q(z) \quad (3)$$

where P_n denotes a Legendre polynomial of degree n (Kaplan, 1973). The coefficients c_{nmq} of the series are efficiently computed using the orthogonality property of Legendre polynomials. The coefficients are stored and can be used later to synthesize the deformation field. This allows efficient representation and storage of the deformation field $\mathbf{w}$ since only a few parameters corresponding to the coefficients of the Legendre basis polynomials need to be stored and can later be recalled to synthesize the deformation field.

3. Results

The algorithm implemented in C++ takes less than 1 min on a 2.4 GHz personal computer to complete a registration. The algorithm successfully registered all image sets. Fig. 2 shows the results of application of the program to images from four different object mice. The images are all matched to the same target image (not shown). The landmarks (in green) are extracted from the target image volume and superimposed on the object images before (top

row) and after (bottom row) registration. All landmarks are closely matched to their location on the target image.

In the first study, a comparison of T_2 measurements calculated from original and spatially registered T_2 maps showed a very high correlation, although these two methods of analysis were statistically different. As previously reported (Helpem et al., 2002), the transverse relaxation time (T_2) was significantly reduced in the cortex and hippocampus of 18 months old PS/APP mice but not in age matched non-transgenic (NTG) controls or PS mice. There was a systematic bias in the registered images (slightly lower T_2); nevertheless, the use of the registration algorithm improved the ability to statistically discriminate between the groups and to visually reflect intra-regional distributions of T_2 (Table 1). The image registration algorithm reduced the processing time of T_2 calculations by a factor of 27 (number of mice), and allowed the creation of color maps representative of the average distribution of T_2 , as shown in Fig. 3. These images visually demonstrate the reduction of T_2 seen on the cortex of the PS/APP mouse model ($P = 0.041$).

In the second study, the image registration algorithm improved the ability to statistically discriminate small differences between the two groups of young PS and NTG mice. A T_2 threshold to detect pixels with T_2 values between 48 and 120 showed difference in CSF T_2 pixel values between NTG and PS young (6 weeks old mice). The PS group had more pixels with T_2 values over 48 ms as showed in the histogram in Fig. 4. The comparison between mean T_2 values showed a clear T_2 difference in the CSF (56.50 ms for PS and 46.73 ms for NTG) and no difference in the cortex (39.53 ms for PS and 39.37 ms for NTG). Also, the image registration algorithm allowed us to create 3D renderings of each averaged registered group of mice, which showed that the PS young mice had cerebral ventricular volume increase compared with NTG young mice (Fig. 5).

4. Discussion

We have applied a non-linear registration algorithm that uses a multi resolution approach to match anatomical mice brain MR scans and T_2 maps from different transgenic mice genotypes. The algorithm performed well and was able to successfully register all images in our study.

Although image registration algorithms have been extensively applied in human MRI analysis, such warping techniques have not been commonly applied in animal studies. The objective of this work was to validate the application of a non-linear registration algorithm on a quantitative analysis of MRI parameters between different groups of transgenic mouse models of AD pathology. We assumed that we could obtain additional information by registering and averaging mice brain scans for each group. Indeed, by using the algorithm we not only corroborated, but also improved the statistical power to distinguish regional T_2 differences in transgenic mice models of Alzheimer pathology. Moreover, the image registration algorithm provided the ability to generate average T_2 maps for different groups allowing the visualization of intra-regional distributions of T_2 .

It should be noted that the image registration algorithm reduced the processing time of T_2 calculations. Rather than spending time drawing several ROIs for each animal, the ROIs needed to be drawn only once on the target mouse brain. By using this type of algorithm in longitudinal studies with a large number of animals, the data analysis processing time will be reduced by the number of animals in the study and much of the inter-rater subjectivity will be eliminated, which is another important concern for these types of studies.

Additionally, the algorithm provided the ability to detect slight differences and changes between groups not previously detected by individual mouse brain analysis. This was

evident in the T_2 difference in the cerebrospinal fluid found between PS and NTG mice and the increase of ventricular volume in the young PS mouse group. PS mice have small-elevated levels of endogenous A β -42 (Duff et al., 1996), and do not form amyloid deposits. They are considered not to have any evident pathology, especially at young age. Even though old PS mice do not show changes in MRI parameters when compared with PS/APP mice (Helpert et al., 2004), we have recently detected a shift to shorter T_2 in the hippocampus (Falangola et al., 2003) and cortex (data not published) of old (18 months) PS compared with young PS (6 weeks) mice. Although the reason for this CSF T_2 difference is unknown at this time, this difference could reflect early changes in CSF composition related to A β soluble levels or an indication of changes in protease activity due to the effects of mutant pre-senilin. There are no reports about CSF changes in transgenic PS mice, and due to difficulty in collecting sufficiently large samples of CSF from mouse, only few studies have been published showing CSF changes in other mouse models of AD (DeMattos et al., 2002; Kawarabayashi et al., 2001; Liu et al., 2003). Even though no morphological changes have been previously described for this genotype, we believe that the ventricular structural difference could reflect an adverse developmental effect that the human PS1 mutation could cause in these mice. The image resolution resultant from the MRI protocol used in this study was not enough to detect the small changes when we analyzed each animal individually. Only the averaged T_2 maps resulting from the warping process showed the increase of ventricular volume in the young PS mice. At present, further work is necessary to confirm this morphological change over time, and to determine the factors causing both the volume increase and the CSF T_2 changes in the PS mice.

In conclusion, the significance of this study was to validate the application of a non-linear registration algorithm as part of the data analysis methodology in quantitative MRI longitudinal studies to improve the ability to statistically discriminate between the groups and to effectively characterize and detect small or unexpected changes in the phenotype of genetically manipulated mice.

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Fig. 1.

A single mouse brain MRI slice at four different levels of resolution: (a) $1.6 \text{ mm} \times 1.6 \text{ mm}$; (b) $0.8 \text{ mm} \times 0.8 \text{ mm}$; (c) $0.4 \text{ mm} \times 0.4 \text{ mm}$; and (d) the original image slice with a resolution of $0.2 \text{ mm} \times 0.2 \text{ mm}$.

Fig. 2.
Landmarks derived from the target image are superimposed on the original object images (top row) and the transformed object images (bottom row).

Fig. 3.

T_2 average color maps showing regional T_2 distribution between 18 months old PS/APP and NTG mice. The reduction of T_2 ($P = 0.041$) can be seen on the cortex of the PS/APP mouse model (green color).

Fig. 4. Histogram (64 bins; range of 30–120 ms) showing the T_2 distribution for a group of six PS and NTG mice after registration.

Fig. 5.
3D images of mean brain T_2 maps for NTG and PS mice with threshold between 48 and 120 ms.

Comparison of mean T_2 values and standard deviation for PS/APP and NTG using non-warped and warped T_2 maps

Table 1

	Cortex		Hippo	
	Original	Warped	Original	Warped
PS/APP	37.23 (2.48)	36.63 (2.68)	39.17 (3.02)	38.45 (3.17)
NTG	39.34 (1.73)	38.97 (1.66)	41.70 (1.92)	41.06 (1.73)
PS/APP vs. NTG P -values	0.053	0.041	0.05	0.045