

AUTOMATIC SEGMENTATION OF WHITE MATTER LESIONS IN T1-WEIGHTED BRAIN MR IMAGES

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ABSTRACT

White matter lesions are common brain abnormalities. In this paper, an automatic method for segmentation of white matter lesions in T1-weighted brain magnetic resonance (MR) images is presented. A patient's T1-weighted MR image is first segmented into the three major tissue types, white matter (WM), gray matter (GM) and cerebral spinal fluid (CSF) solely based on each voxel's intensity. Since WM lesions are typically classified as GM based on their intensity characteristics, the GM class is then separated into normal GM and WM lesions. This is accomplished using a statistical model of tissue distribution of healthy brains in a stereotaxic space. The proposed method is tested on 10 MR images with WM lesions and the results of the method are visually compared with WM lesions manually labeled by an experienced radiologist.

1. INTRODUCTION

WM lesions are common abnormalities of the brain, which may be the result of different brain diseases, such as multiple sclerosis (MS) [1], Alzheimer's disease [2], stroke and head injury [3]. They also appear in normal elderly subjects [4]. MR imaging is sensitive to these WM changes and thus widely used as a non-invasive method for diagnosing such diseases clinically. This generates a large number of MR images to be analyzed. Manual lesion segmentation by trained experts, a commonly used method, is extremely time consuming, labor intensive, and suffers from high intra-observer and inter-observer variability. This raises the demand for automatic lesion segmentation methods which can reduce both the observers' burden and the intra-observer and inter-observer variability.

WM lesions are imaged in T1-weighted MR images as hypointensities with respect to surrounding healthy WM tissues. However, their intensity range also overlaps with normal GM tissues, as there is often no unambiguous lesion intensity range. This intensity overlap causes the failure of segmentation methods based solely on image intensity and is the major difficulty in accurately

segmenting WM lesions. Many different techniques have been explored to tackle this problem. Kamber *et al.* [5] investigated a probability model in a standard Talairach space for the detection of MS lesions. Udupa *et al.* [6] used the concepts of fuzzy connectedness and fuzzy objects for segmenting MS lesions. Warfield *et al.* [7] proposed an adaptive, template moderate, spatially varying statistical classification method, which combines the strength of both statistical classification methods and nonlinear registration techniques, for the segmentation of abnormal anatomy in brain MR images.

Motivated by the observation that a well trained observer can easily recognize these lesions as they have similar intensity as GM and appear in the region of normal WM, where no GM is expected, the proposed method follows a similar approach. By using a training set of normal brains in a stereotaxic space to identify normal WM regions, the WM lesions in a patient's scan are segmented via region-wise principal component analysis (PCA) method.

2. METHOD

To segment out WM lesions in a patient's T1-weighted MR image, we first automatically segment the image into the three major tissue types, WM, GM and CSF. This segmentation only uses the intensity information of each voxel, thus called intensity segmentation. Because of the intensity overlap between GM and WM lesions, the segmented GM contains both true GM and WM lesions. In order to separate them, a technique is developed to estimate what a particular subject's segmentation should look like, if the subject did not have any WM lesions. We call this the reconstructed segmentation. The core of this technique is a statistical tissue distribution model for healthy subjects in the stereotaxic space. The patient's intensity segmentation is then registered to the stereotaxic space via a high dimensional deformable registration method, and the result is called the registered intensity segmentation. The segmented GM in the registered intensity segmentation is then separated into true GM and WM lesions based on the tissue labels in its reconstructed segmentation.

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2.1. Statistical Tissue Distribution Model

A set of M labeled MR images of healthy subjects is used as training set to build the statistical tissue distribution model. In order to generate statistics from MR images of different subjects, the training images must first be aligned to a stereotaxic space so that inter-individual morphological variability is accounted for. Thus one of the M labeled healthy MR images is chosen randomly as the template for the stereotaxic space, in which each voxel is isotropic. The other $M - 1$ labeled MR images are registered to the template using a deformable registration method called HAMMER [8]. All the MR images used for building the statistical tissue distribution model are the registered versions of the labeled images.

The statistical tissue distribution model tries to capture the local residual spatial variations of the three major tissue types after registration. Since it is computationally prohibitive to generate a model on a voxel by voxel basis, we partition the images into non-overlapping cubic sub-volumes. Thus, the m th labeled MR image of size $Row \times Col \times Slice$ is divided into sub-volumes $V_{i,j,k}^m$ of size w , where $1 \leq i \leq Row/w$, $1 \leq j \leq Col/w$, $1 \leq k \leq Slice/w$. The pixel values in $V_{i,j,k}^m$ are the respective tissue labels (0: background, 1: CSF, 2: GM, 3: WM). $V_{i,j,k}^m$ is then mapped to a row vector $\mathbf{X}_{i,j,k}^m$ using the lexicographic ordering. The mapped sub-volumes $\mathbf{X}_{i,j,k}^m$ ($1 \leq m \leq M$) with the same subscript (i, j, k) from all the M healthy MR images form a sample of healthy tissue distribution for sub-volume (i, j, k) . We want to model this distribution using a parameterised model. Such a model can be used to examine whether a sub-volume of a new image for the same location is healthy or not.

To build the model, the mean and covariance of tissue distribution for sub-volume (i, j, k) are first computed as :

$$\overline{\mathbf{X}}_{i,j,k} = \frac{1}{M} \sum_{m=1}^M \mathbf{X}_{i,j,k}^m \quad (1)$$

$$\mathbf{S}_{i,j,k} = \frac{1}{M-1} \sum_{m=1}^M (\mathbf{X}_{i,j,k}^m - \overline{\mathbf{X}}_{i,j,k}) (\mathbf{X}_{i,j,k}^m - \overline{\mathbf{X}}_{i,j,k})^T \quad (2)$$

Then the eigenvectors $\phi_{i,j,k}^l$ ($l = 1, 2, \dots, M-1$) and corresponding eigenvalues $\lambda_{i,j,k}^l$ ($l = 1, 2, \dots, M-1$) of $\mathbf{S}_{i,j,k}$ are determined. The statistical tissue distribution model consists of the mean $\overline{\mathbf{X}}_{i,j,k}$, and eigenvector matrix $\Phi_{i,j,k}$ and eigenvalue matrix $\lambda_{i,j,k}$ for every (i, j, k) , where $\Phi_{i,j,k}$ and $\lambda_{i,j,k}$ are defined in Equation (3) and Equation (4) respectively:

$$\Phi_{i,j,k} = [\phi_{i,j,k}^1 | \phi_{i,j,k}^2 | \dots | \phi_{i,j,k}^{M-1}] \quad (3)$$

$$\lambda_{i,j,k} = \begin{pmatrix} \lambda_{i,j,k}^1 & 0 & \dots & 0 \\ 0 & \lambda_{i,j,k}^2 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \lambda_{i,j,k}^{M-1} \end{pmatrix} \quad (4)$$

Thus any mapped sub-volume $\widehat{\mathbf{X}}_{i,j,k}$ can be expressed as:

$$\widehat{\mathbf{X}}_{i,j,k} \approx \overline{\mathbf{X}}_{i,j,k} + \Phi_{i,j,k} \hat{\mathbf{b}}_{i,j,k} \quad (5)$$

where $\hat{\mathbf{b}}_{i,j,k}$ is a $M - 1$ dimensional vector given by

$$\hat{\mathbf{b}}_{i,j,k} = \Phi_{i,j,k}^T (\widehat{\mathbf{X}}_{i,j,k} - \overline{\mathbf{X}}_{i,j,k}) \quad (6)$$

If we assume that the elements of $\hat{\mathbf{b}}_{i,j,k}$, $\hat{b}_{i,j,k}^l$, are independent and Gaussian, then the logarithm of the probability of the occurrence of a particular $\hat{\mathbf{b}}_{i,j,k}$ is given by:

$$\log p(\hat{\mathbf{b}}_{i,j,k}) = -0.5 \sum_{l=1}^{M-1} \frac{(\hat{b}_{i,j,k}^l)^2}{\lambda_{i,j,k}^l} + const \quad (7)$$

The model can be used to determine whether the sub-volumes of a patient's scan contain abnormal tissue or not. If the $p(\hat{\mathbf{b}}_{i,j,k})$ of a patient's sub-volume is smaller than a predefined threshold $p_{i,j,k}^t$, then it is considered to contain abnormal tissue (lesions). The threshold levels are estimated from the probability distribution of healthy subjects. This is normally achieved by using another set of healthy MR images as a test set. But since we only have M healthy MR images altogether, we used the leave-one-out method to approximate the threshold levels. $M - 1$ healthy MR images are used as training images to build the statistical distribution model, the $\hat{\mathbf{b}}_{i,j,k}$ for each sub-volume in the one left healthy MR image is computed using Equation (6) and its probability $p(\hat{\mathbf{b}}_{i,j,k})$ is calculated using Equation (7). The process is repeated M times until each of the healthy MR images has been used to estimate the probability distribution for $\hat{\mathbf{b}}_{i,j,k}$. Thus for each sub-volume (i, j, k) , there will be M probability values. These probability values are then used as threshold levels.

2.2. White Matter Lesions Detection

To segment WM lesions out of a patient's scan, the intensity segmentation of its T1-weighted MR image is first obtained using an adaptive fuzzy segmentation method [9]. The intensity segmentation is then registered to the stereotaxic space using HAMMER.

The patient's registered intensity segmentation is then divided into non-overlapping cubic sub-volumes, $\widehat{V}_{i,j,k}$, of the same size w as in the model and mapped into vector $\widehat{\mathbf{X}}_{i,j,k}$. The $\hat{\mathbf{b}}_{i,j,k}$ and $p(\hat{\mathbf{b}}_{i,j,k})$ for each $\widehat{\mathbf{X}}_{i,j,k}$ are obtained using Equation (6) and Equation (7) respectively. The reconstructed $\widehat{\mathbf{X}}_{i,j,k}^r$ represents an estimate of what an individual's image should look like in the respective sub-volume, if the individual's image were normal, according to the training set. It is calculated as the following:

1) if $p(\hat{\mathbf{b}}_{i,j,k}) \geq p_{i,j,k}^t$, then $\widehat{\mathbf{X}}_{i,j,k}^r = \widehat{\mathbf{X}}_{i,j,k}$;

2) if $p(\hat{\mathbf{b}}_{i,j,k}) < p_{i,j,k}^t$, then scale each element of $\hat{\mathbf{b}}_{i,j,k}$ using

Equation (8) to get $\check{\mathbf{b}}_{i,j,k}$ for $1 \leq l \leq M - 1$,

$$\check{b}_{i,j,k}^l = \frac{M-1}{2} (const - \log p_{i,j,k}^t) |\lambda_{i,j,k}^l| \text{sign}(\hat{b}_{i,j,k}^l) \quad (8)$$

and set $\mathbf{X}_{i,j,k}^r = \overline{\mathbf{X}}_{i,j,k} + \Phi_{i,j,k} \check{\mathbf{b}}_{i,j,k}$.

After the patient's reconstructed segmentation in the stereotaxic space is obtained, it is compared to the registered intensity segmentation result to separate the segmented GM into true GM and WM lesions and generate the initial lesion segmentation result. For each voxel that is segmented as GM in the registered intensity segmentation, if it is labeled as WM in the reconstructed segmentation, then it is a WM lesion voxel.

In order to remove the false positive detections in the initial segmentation results, a binary mask that indicates where false positive detections might occur by using the model is generated. The leave-one-out method is again used to generate the mask from the M healthy MR images. $M - 1$ healthy MR images are used as training images to build the statistical tissue distribution model. The model is then used to segment WM lesions in the one left

healthy MR image. The procedure is repeated M times until each one of the M healthy MR images has been used for segmenting WM lesions. Since all the M images are from healthy subjects, any WM lesions segmented out from them are false positive detections and contribute to the mask.

3. EXPERIMENTS AND RESULTS

In this study, twelve T1-weighted MR images of healthy subjects were selected as training images for building the statistical tissue distribution model from the Baltimore Longitudinal Study of Aging (BLSA) [10]. The size of these MR images was $256 \times 256 \times 124$, and the voxel size was $0.9375 \text{mm} \times 0.9375 \text{mm} \times 1.5 \text{mm}$. These MR images were labeled using the method in [11] which was validated in [12]. One of the 12 labeled MR images was selected as the template whose middle slice of axial section is shown in Fig. 1(a). The corresponding mask used to remove false positive detections is shown in Fig. 1(b).

The proposed method has been tested on 10 MR images from BLSA with WM lesions. To visually evaluate the performance of our method, the WM lesions in these 10 MR images have been manually labeled by an experienced radiologist whose labels were used as ground truth. Fig. 2(a) shows the middle slice of axial section of one of 10 MR images in the stereotaxic space with WM lesions. The WM lesions labeled by the radiologist overlaid on the MR image is shown in Fig. 2(b).

An example of the segmentation results corresponding to the MR images in Fig. 2(a) at different stages of our method is shown from Fig. 3 to Fig. 4. These results are obtained using $w = 16$ voxels to build the statistical distribution model, and the threshold level are the largest value for each location respectively. The registered intensity segmentation result is shown in Fig. 3(a). The initial WM lesion segmentation result is shown in Fig. 3(b). The result after applying the mask is shown in Fig. 4(a). From Fig. 4(a), it is observed that the segmentation result is still very noisy. Thus to smooth the segmentation result, two simple post processing steps are applied. First, a binary morphological dilation is performed with disk like structure element of radius 1. This procedure will remove the holes in the segmented white matter lesions. Then the segmented white matter lesion voxels are grouped into objects based on their 3D spatial connectivity. Any object with less than 100 voxels is considered to be noise and removed. The final segmentation result is shown in Fig. 4(b). Two more examples of WM lesion segmentation results of our method and corresponding ground truth are shown in Fig. 5 and Fig. 6 respectively. These results show that our WM lesions segmentation results has a great extent of agreement to the manually labeled ground truth.

4. CONCLUSIONS

We have demonstrated a method for automatic segmentation of WM lesions in T1-weighted MR images in a stereotaxic space. The method follows the basic idea of how a human observer detects WM lesions in MR images. The proposed method used a fuzzy segmentation method to automatically segment a patient's MR image into the 3 major tissue types. The intensity segmentation result is then registered to a stereotaxic space using HAMMER. A statistical tissue distribution model is then used to reconstruct a segmentation out of the intensity segmentation result in the stereotaxic space which estimates what the patient's brain should

look like if the lesions were removed. With the help of the reconstructed segmentation, the segmented GM are separated into true GM and WM lesions. The proposed method has been tested on 10 T1-weighted MR images with WM lesions. The WM lesions segmented by our method show a great extent of agreement with the WM lesions manually labeled by an experience radiologist by visually comparison.

5. REFERENCES

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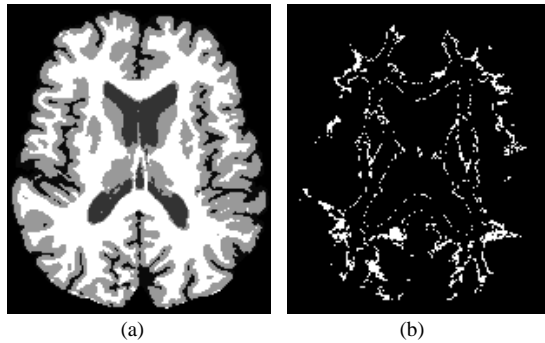


Fig. 1. (a) The middle slice of axial section of the segmented image used as template in this study. (b) The corresponding mask used to remove the false positive segmentations.

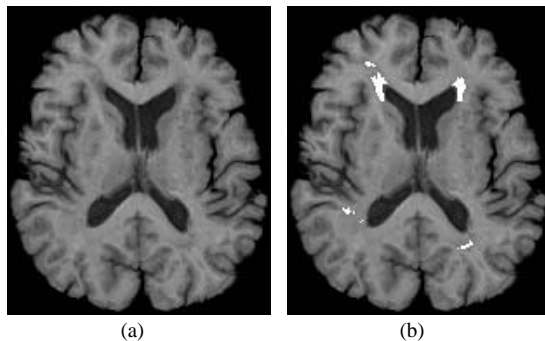


Fig. 2. (a) The trans-axial view of a patient's MR image with white matter lesions. (b) The manually labeled white matter lesions (shown in white) overlaid on Fig. 2(a).

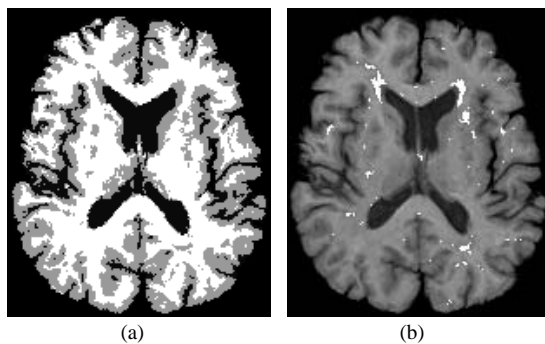


Fig. 3. (a) Registered intensity segmentation result for Fig. 2(a). (b) Initial white matter lesions (shown in white) segmentation result overlaid on Fig. 2(a).

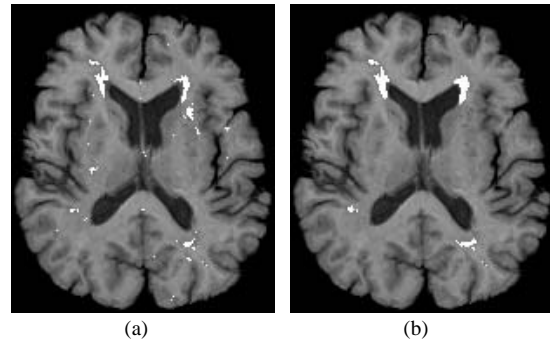


Fig. 4. (a) The result after applying the mask to the initial lesion segmentation result in Fig. 3(b). (b) Final white matter lesions (shown in white) segmentation result by the proposed method overlaid on Fig. 2(a).

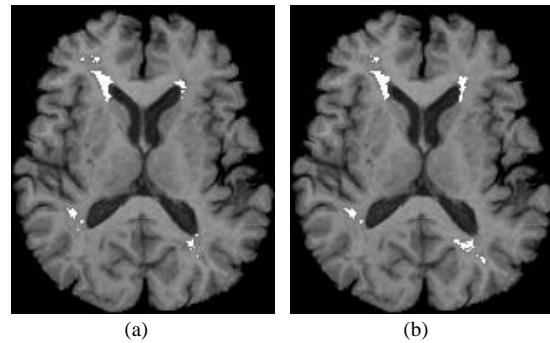


Fig. 5. (a) The patient's MR image with the manually labeled WM lesions (shown in white) overlaid on it. (b) Final white matter lesions (shown in white) segmentation result by the proposed method overlaid on the image.

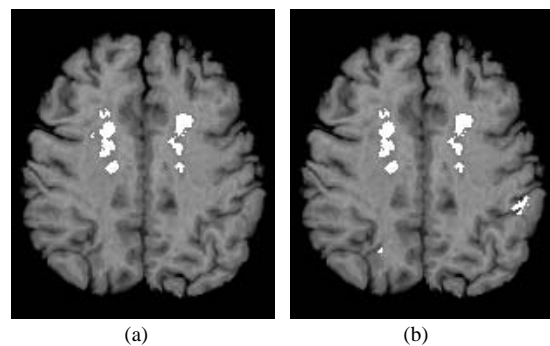


Fig. 6. (a) The patient's MR image with the manually labeled WM lesions (shown in white) overlaid on it. (b) Final white matter lesions (shown in white) segmentation result by the proposed method overlaid on the image. A false positive can be seen on the post central sulcus