MR Image Segmentation of Patients' Brain Using Disease Specific a Priori Knowledge

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Abstract

Segmentation of high quality brain MR images using *a priori* knowledge about brain structures enables a more accurate and comprehensive interpretation. Benefits of applying *a priori* knowledge about the brain structures may also be employed for image segmentation of specific brain and neural patients. Such procedure may be performed to determine the disease stage or monitor its gradual progression over time. However segmenting brain images of patients using general *a priori* knowledge which corresponds to healthy subjects would result in inaccurate and unreliable interpretation in the regions which are affected by the disease. In this paper, a technique is proposed for extracting *a priori* knowledge about structural distribution of different brain tissues affected by a specific disease to be applied for accurate segmentation of the patients' brain images. For this purpose, extracted *a priori* knowledge is gradually represented as disease specific probability maps throughout an iterative process, and then is utilized in a statistical approach for segmentation of new patients' images. Experiments conducted on a large set of images acquired from patients with a similar neurodegenerative disease implied success of the proposed technique for representing meaningful *a priori* knowledge as disease specific probability maps. Promising results obtained also indicated an accurate segmentation of brain MR images of the new patients using the represented *a priori* knowledge, into three tissue classes of gray matter, white matter, and cerebrospinal fluid. This enables an accurate estimation of tissues' thickness and volumes and can be counted as a substantial forward step for more reliable monitoring and interpretation of progression in specific brain and neural diseases.

Keywords: Brain MR Images, Segmentation, Tissue Classification, Image Registration, A Priori Knowledge, Brain Tissue Probability Maps, Neurodegenerative Disease.

1. INTRODUCTION

Magnetic Resonance Imaging (MRI) [1] of brain is well known as a powerful technique for diagnosis which is widely used by many clinicians to detect structural abnormalities that cause neurological disorders. Until a few years ago, most of the neurologist just employed their personal expertise to inspect a number of cross sections of the patient's brain MRI to diagnosis the disorder or monitor the effects of a specific therapy. Swift progresses in medical image processing [2] have introduced automatic and semi-automatic methods to enable more precise and reliable diagnosis and treatments. Image segmentation [3] is an example for such methods which is widely used in many biomedical applications. A popular application of image segmentation in neurology is partitioning a specific brain structure into three major tissues of gray matter, white matter, and cerebrospinal fluid. Such a segmentation process makes it possible to estimate distributions of different tissue types in the brain in addition to calculate their volumes accurately. This information is very beneficial to make an accurate diagnosis or monitor the treatment progress precisely.

Either manual or automatic Interpretation of brain's high quality images can benefit from utilizing atlases as well as *a priori* knowledge represented as comprehensive probabilistic maps [4, 5]. Brain atlases are three dimensional (3D) images produced by averaging on a large number of brain images of healthy subjects. Probabilistic maps which are frequently represented as 3D images are structures which determine the probabilities by which each voxel of a typical brain image corresponds to any of the major tissue type. Developing advantageous atlases and/or *a priori* knowledge in the forms of inclusive probabilistic maps requires collecting and processing a large set of brain images [6] in addition to utilizing suitable strategies for image registration and warping [7].

Great benefits of employing atlases as well as *a priori* knowledge hidden in probabilistic maps can be extended for analyzing brain images of specific patients with a similar neurological disorder such as neurodegenerative diseases. Neurodegenerative diseases including mild cognitive impairment, Alzheimer [8], and major depression [9, 10], are disorders caused by progressive deterioration of neurons that eventually leads to their death. Clinical symptoms of neurodegenerative diseases include disabilities and dysfunctions resulting in dementia (memory dysfunctions) and/or ataxia (movement disabilities) [11]. Progressive death of neurons in neurodegenerative disease results in atrophy of the brain structures. Such gradual effects can be monitored or even quantified using MRI [12]. The quantification is performed via MR image segmentation and estimating distribution of different brain tissues. Segmentation is usually performed through parametric methods [13] and its precision can be improved using *a priori* knowledge of probabilistic maps registered on the image of patient's brain [14, 15].

Analyzing images of patients' brain using general *a priori* knowledge extracted from brain images of healthy subjects would result in inaccurate and unreliable interpretation in the regions which are affected by the disease [16]. For example in image segmentation of patients' brain, this may result in misclassification of brain tissues and consequently inaccurate measurement of their volumes. As such presentencing a systematic method for development of *a priori* knowledge about structural distribution of brain tissues which is affected by a specific disease and maps is a paramount necessity for more reliable studies on progression of the specific neurologic disorders, and monitoring their gradual affects on different brain tissues.

In this paper a novel technique is proposed for systematically representation of *a priori* knowledge about effects of a specific neurological disease on different tissue structures of the brain. The initial application proposed for the developed knowledge in this paper is segmentation of patients' brain images into its three major tissue types. Such customized segmentation process can also accurately calculate the volumes of each tissue type accurately. Experiments conducted on a large set of images acquired from patients with a similar neurodegenerative disease implied success of the proposed technique for representing meaningful *a priori* knowledge as disease specific probability maps. Promising results obtained also indicated an accurate segmentation of brain MR images of the new patients using the represented *a priori* knowledge, into three tissue classes of gray matter, white matter, and cerebrospinal fluid. This can pave the way for a more precise disease diagnosis, mentoring its gradual growth, and following the treatment progress.

This paper is organized as follows. The required preliminaries are presented in the next section. Section 3 introduces the iterative method used in this paper for development of the disease specific *a priori* knowledge and the segmentation of the brain image of the patients. The experiments conducted and the results obtained are presented in section 4. Finally section 5 discusses the obtained results and concludes this paper.

2. PRELIMINARIES

2.1 Medical Image Registration

In image registration, a one-to-one mapping or transformation is determined between the coordinates of one image space to those in the other. In rigid registration the transformation is

limited to translation and rotation while in affine registration the transformation may also include scaling and shearing. Eq. (1) shows the general form of 3D affine transformation. In this equation T_{Shear}, T_{Scale}, and T_{Rigid} are *4×4* matrices and the a_{ij} parameters are coefficients related to rotation, scaling and shearing, while the *t* parameters determine translation [17].

$$T_{affine}(x,y,z)=\begin{bmatrix}x'\\y'\\z'\\1\end{bmatrix}=T_{shear}.T_{scale}.T_{rigid}.\begin{bmatrix}x\\y\\z\\1\end{bmatrix}=\begin{bmatrix}a_{11}&a_{12}&a_{13}&t_x\\a_{21}&a_{22}&a_{23}&t_y\\a_{31}&a_{32}&a_{33}&t_z\\0&0&0&1\end{bmatrix}.\begin{bmatrix}x\\y\\z\\1\end{bmatrix} \quad (1)$$

While rigid and affine registration are suitable for modeling global motion, they are not capable of modeling local motion which usually occurs in deformable objects such as soft tissue. To model the local motion, non-rigid or deformable registration approaches have been developed.

A Free-Form Deformation (FFD) technique was introduced by Ruckert *et al.* for registering breast MR images [18]. Later, this FFD technique and its modified versions were widely used in other applications of non-rigid image registration by several research groups [19, 20, 21, 22]. FFD models the global and local deformations within the object separately, and then combines them to form an overall smooth deformation. In practice this translates into a global transformation followed by a local transformation:

$$T(x,y,z)=T_{local}(T_{global}(x,y,z)) \quad (2)$$

where T_{global} is a rigid or affine transformation and T_{local} is a deformation model based on B-splines [23].

A modified implementation of the FFD was used in this paper as the non-rigid registration method in the algorithm proposed for generating disease specific probability maps described in Section 3-1. Following the original version of the FFD, let Φ denote an $n_x \times n_y \times n_z$ size mesh of control points ($\phi_{i,j,k}$) with a uniform spacing δ_d in direction *d*. Also suppose that $\varphi_{i,j,k}$ denotes the displacement of the corresponding control point. Hence, the local transformation can be formulated as a 3D tensor product of 1D cubic B-splines:

$$T_{local}(x,y,z)=(x,y,z)+\sum_{l=0}^{3}\sum_{m=0}^{3}\sum_{n=0}^{3}B_l(u)B_m(v)B_n(w)\,\varphi_{i+l,j+m,k+n} \quad (3)$$

where $i=\left\lfloor\frac{x}{\delta_x}\right\rfloor-1,\ j=\left\lfloor\frac{y}{\delta_y}\right\rfloor-1,\ k=\left\lfloor\frac{z}{\delta_z}\right\rfloor-1,\quad u=\frac{x}{\delta_x}-\left\lfloor\frac{x}{\delta_x}\right\rfloor,\ v=\frac{y}{\delta_y}-\left\lfloor\frac{y}{\delta_y}\right\rfloor,\ w=\frac{z}{\delta_z}-\left\lfloor\frac{z}{\delta_z}\right\rfloor,$ and *B(.)*'s represent the basis functions of B-spline:

$$\begin{aligned}B_0(u)&=\frac{(1-u)^3}{6}\\B_1(u)&=\frac{(3u^3+6u^2+4)}{6}\\B_2(u)&=\frac{(-3u^3+3u^2+3\mathrm{u}+1)}{6}\\B_3(u)&=\frac{u^3}{6}\end{aligned} \quad (4)$$

As such, the algorithm uses an optimization technique to find the optimum displacements of the control points that yield the best registration in some sense (e.g. maximum similarity).

Considering Eq. 3, the derivative of the deformation field with respect to the B-spline coefficients can be given by:

$$\frac{\partial T_{local}(x,y,z)}{\partial \varphi_{i,j,k}} = B_l(u)B_m(v)B_n(w) \quad (5)$$

where $l = i - \left\lfloor \frac{x}{\delta_x} \right\rfloor + 1,\ m = j - \left\lfloor \frac{y}{\delta_y} \right\rfloor + 1,\ n = k - \left\lfloor \frac{z}{\delta_z} \right\rfloor + 1$ and $B_l(u) = 0$ for $l < 0$ and $l > 3$. This implies that the derivative term is nonzero only in the neighbourhood of the corresponding control point. Having such a derivative equation for the transformation, the optimization part of the registration process can be implemented efficiently using an iterative gradient descent or other derivative-based optimization techniques.

2.2 Medical Image Segmentation

Image segmentation is the process of partitioning an image into a number of regions or classes with similar properties based on pre-defined criteria. For example a brain image may be segmented into three soft tissue regions of gray matter, white matter, and cerebrospinal fluid where a more precise qualitative and/or quantitative analysis is made possible. According to [13] segmentation methods are categorized into four major classes:

1) Thresholding methods
2) Deformable models
3) Fuzzy connectivity methods
4) Statistical techniques

The segmentation technique applied in this paper is a statistical method known as expectation maximization [24, 25]. It is an iterative method through which the maximum likelihood parameters are estimated for segmentation. In summary, the expectation maximization is consists of two iterative steps of calculating the expectation and maximizing it. In the first step, the expectation of the complete data log-likelihood is calculated. In the next step maximum likelihood parameters which maximize the expectation are estimated. These parameters are then applied in the first step of the next iteration. As such, parameters which result in a segmentation with maximum likelihood are progressively obtained via this iterative loop. More details on this method can be found in [24, 25, 26].

3. METHOD

The method proposed in this paper dynamically segment brain MR images of a group of patients with a similar neurological disorder in an iterative process where the disease specific *a priori* knowledge is also extracted concurrently. The extracted *a priori* knowledge corresponds to the distribution of different brain tissues affected by the disease. It would be represented in the form of separate probability maps for gray matter, white matter, and cerebrospinal fluid. The conventional approach for generating brain atlases and probability maps usually perform this task in one single step and by averaging on a number of brain images segmented previously. In the technique proposed in this paper, current simple methods are substituted with an iterative image segmentation process which aims for both enhancing the quality of newly generated probability maps in each iteration a well as improving the precision of input images segmentation simultaneously. The technique applies deformable image registration for adjusting the input images in a reference coordinate, and employs expectation maximization technique for segmenting the patient's brain images. The new probability maps in each iteration are generated by averaging on intensity distribution of images for each specific tissue type. More details on the proposed technique have been provided in the following section.

3.1 Developing Disease Specific *A Priori* Knowledge for Brain Image Segmentation

Expectation Maximization as a parametric approach for image segmentation estimates the intensity distribution for each tissue type in a MR image. Such estimation is performed using *a priori* knowledge represented as probability maps. As such gradual enhancement of probability

maps' quality would progressively results in improving the accuracy of image segmentation as well.

Figure 1 demonstrates schematic structure of the proposed technique for generating disease specific probability maps for each tissue type. As can be seen in this figure the method receives a set of brain MR images of patients with a similar neurological disorder along with a reference brain atlas and its corresponding probability maps as the inputs and consequently goes through the following processing steps:

1) Loading input data including brain MR images of patients as well as reference atlas and probability maps.
2) Initial segmentation for each input image:
   2.1) Registering the reference atlas into the patient's image space.
   2.2) Mapping the probability maps for gray matter, white matter, and cerebrospinal fluid into patient's image space using the transformation function obtained in the previous step.
   2.3) Soft segmentation of the patient's image via expectation maximization method which outputs a patient specific probability map for each tissue type.
3) Entering to the iterative loop for disease specific probability maps generation:
   3.1) Registering each patient's image into the reference atlas space.
   3.2) Mapping each set of patient specific probability maps (obtained in step 2.3 or 3.5) to the reference atlas space using the corresponding transformation function obtained in step 3.1.
   3.3) Averaging patient specific probability maps for each tissue type in the reference space to generate/update the disease specific probability map for the corresponding brain tissue.
   3.4) Transferring new probability maps into each patient's image space using inverse of the transformation function obtained in step 3.1.
   3.5) Soft segmentation of patients' images via expectation maximization method using the new probability maps transformed in step 3.4. The output is a specific set of probability maps for each patient.
   3.5) Return step to 3.2.

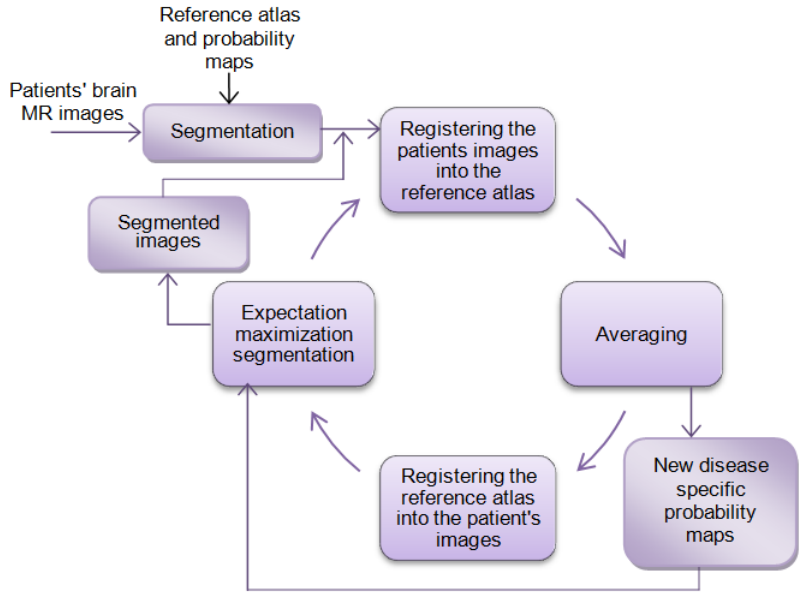

FIGURE 1: Schematic structure of the proposed technique for generating disease specific probability maps as well as segmenting the patients' images.

As mentioned earlier, the processes of generating/updating new disease specific probability maps and improving the precision of patients' image segmentation have been tied together. In other words, for generating/updating disease specific probability maps segmentation of patients' images is a prerequisite, and on the other hand, for a more accurate segmentation of patients' images high quality disease specific probability maps are required. As such, the proposed algorithm employs an iterative loop for generating/updating the disease specific probability maps and in the same loop, applies these new maps for improving the accuracy of segmentation of the patients' brain images. Eventually and after a number of iteration, high quality and precise disease specific probability maps are obtained. Such maps can then be applied for segmenting brain images of new patients accurately where it enables more reliable qualitative and/or quantitative analysis for diagnosis and/or monitoring the disease progress.

4. EXPERIMENTS AND RESULTS

The proposed technique was evaluated on a large set of brain MR images of patients with a similar neurodegenerative disease. The dataset consisted of 108 T1 weighted images of different patients where it was randomly partitioned into two sets of training (98 images) and testing (10 images). The images of training set were used for generating a set of disease specific probability maps for different tissue type, while the never seen images of the testing set were applied for evaluating the performance and accuracy of the generated maps for segmenting brain images of new patients.

Quality of generated probability maps at each iteration of the proposed algorithm was examined by a medical imaging expert. After 6 iterations no major improvement was observed on the quality of generated maps. As such the algorithm's loop was stopped at the end of this iteration and its output was used as the disease specific probability maps for segmentation of new patients' images.

Figure 2 shows the probability maps obtained for the gray matter. The Figure 2(a) demonstrate the initial probability map used as the input of the algorithm in coronal and sagittal planes. Figure 2(b)-(g) present the disease specific probability maps obtained in successive iterations, respectively. As it can be observed, the process of disease specific probability maps generation implies a progressive sharpening of the edges and clarification of the maps. More details may be detected in the probability map images after passing each iteration of the proposed algorithm. Such enhancement may be more appreciated for the images of rows three and four (outputs of second and third iterations). These observations confirm that the generated probability maps enriched with disease specific *a priori* knowledge have rapidly converged toward a similar structure which conforms the disease progress.

In the next stage, the generated disease specific probability maps were applied in the process of image segmentation for new patients' images of the testing set. These never seen brain images had not been presented to the algorithm before. Figure 3 illustrates the typical results obtained for segmentation of gray matter, white matter, and cerebrospinal fluid in one patient's brain image. The figure shows those results obtained by applying the initial probability maps (obtained from healthy subjects' brain images) in the expectation maximization segmentation methods, as well as those obtained through the same segmentation technique by applying the generated disease specific probability maps. Qualitative evaluation performed on the results obtained using the two sets of probability maps suggests that a more precise segmentation has been done using the generated disease specific probability maps. In this case brain tissue structures have been revealed with more meaningful details as well as with less undesirable artifacts via the segmentation process. This can be more appreciated by comparing the two rows of images in Figure 3, and specially in Figure 3(C).

The accuracy of the results obtained for testing set images segmentation using the two sets of initial and generated probability maps was then analyzed quantitatively. For this purpose, the segmentation results obtained using the initial set of probability maps are first corrected manually

in a time consuming process and by a medical imaging expert. The manually corrected segmentation was then used as the reference for evaluating the precision of the segmentation processes performed using the initial and generated probability maps. Two criteria of True Positive Volume Fraction (TPVF) and False Positive Volume Fraction (FPVF) were utilized for the quantitative analysis and evaluations. The average results obtained for gray matter, white matter and cerebrospinal fluid have been reported in Tables 1. The results given in this table imply a considerable increase in the segmentation accuracy of the gray matter, white matter and cerebrospinal fluid by applying the disease specific probability maps generated using the proposed algorithm. In the case of gray matter segmentation, the disease specific *a priori* knowledge could increase TPVF while decreasing the FPVF. Similar results obtained in the case of white matter segmentation as well. In the case of cerebrospinal fluid segmentation, the TPVF has been increase substantially. However it also resulted in a slight increase in FPVF simultaneously. Such increase seems negligible considering the excellent performance of the probability maps in all other cases.

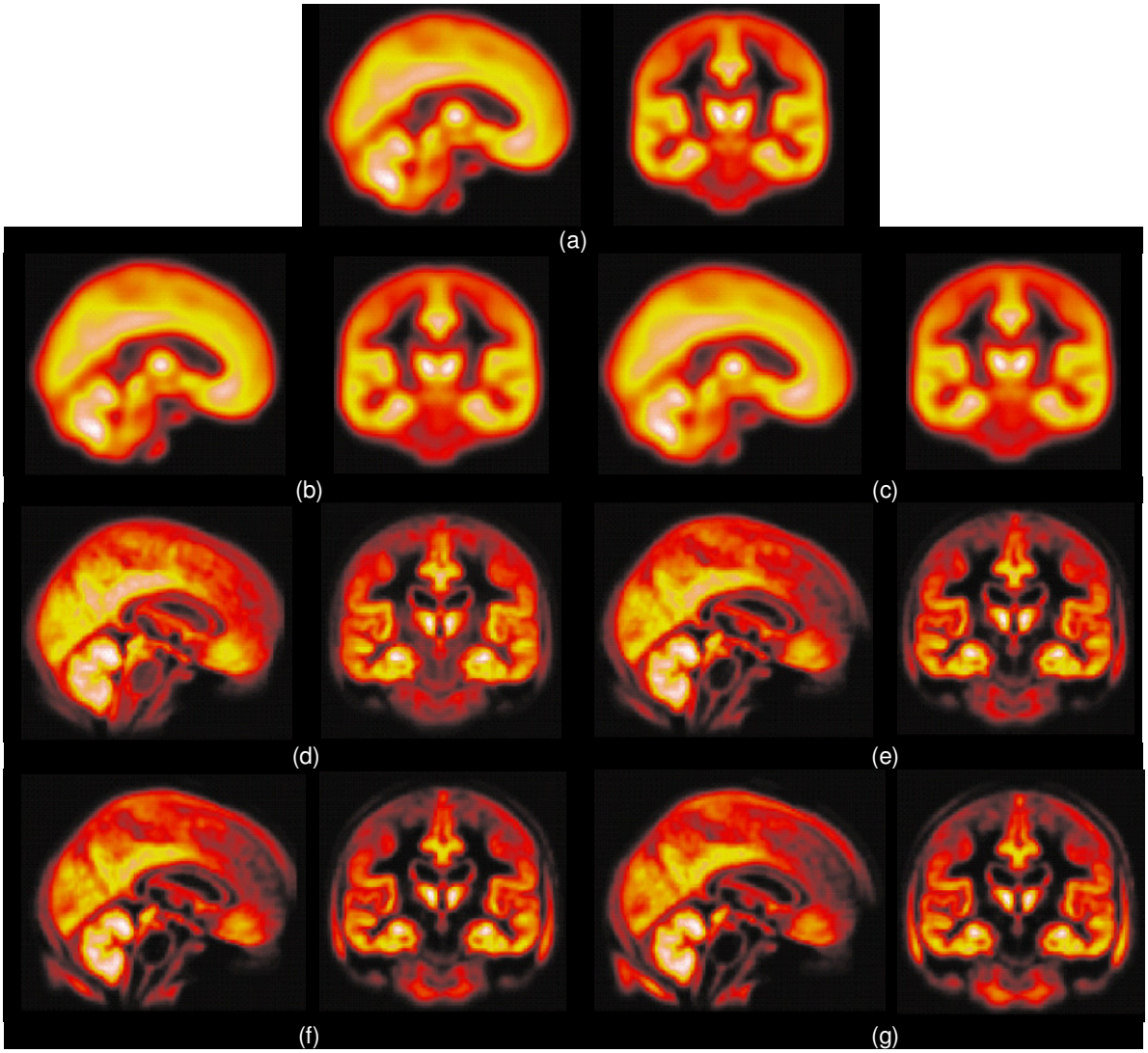

FIGURE 2: Sagittal (left) and Coronal (right) planes of the gray matter probability map. (a): initial probability map, (b)-(g): the neurodegenerative disease specific probability maps, generated in first to sixth iterations of the proposed algorithm, respectively.

5. DISCUSSION AND CONCLUSION

A technique was proposed and evaluated in this paper to extract *a priori* knowledge about structural distribution of different brain tissues affected by a specific neurological disorder from a set of brain MR images of the suffering patients and consequently represented as disease specific probability maps. The disease specific a priori knowledge was then applied in brain image segmentation process of new patients in order to increase the process precision. The processes of generating/updating new disease specific probability maps and improving the precision of patients' image segmentation are mutually contingent on each other. As such, the proposed algorithm utilizes an iterative loop for generating/updating the disease specific probability maps and in the same loop, employs these new maps for improving the accuracy of segmentation of the patients' brain images. Eventually and after a number of iteration, high quality and precise disease specific probability maps are obtained. The obtained maps can then be applied for segmenting brain images of new patients precisely where a more meaningful qualitative/quantitative analysis for diagnosis/monitoring the disease progress is made possible. In addition and utilizing the proposed algorithm, the disease specific probability maps may be made more enriched with further *a priori* knowledge extracted from new sets of patients' images whenever such data is available.

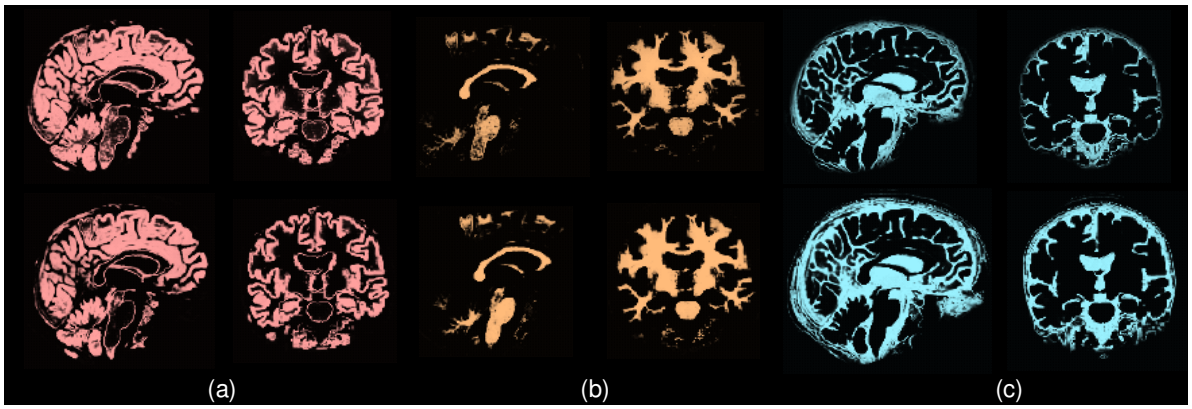

FIGURE 3: Typical results obtained for segmentation of a patient's brain MR image using *a priori* knowledge of the initial probability maps (top row), and the generated disease specific probability maps (bottom row). (a): Gray matter segmentation, (b): White matter segmentation, (c): cerebrospinal fluid segmentation

Brain Tissue	***TPVF (Initial probability maps)***	***TPVF (Disease specific probability maps)***	***FPVF (Initial probability maps)***	***FPVF (Disease specific probability maps)***
Gray matter	93.9%	97.1%	15.7%	5.4%
White matter	86.8%	92.0%	5.6%	1.9%
Cerebrospinal fluid	70.6%	89.2%	1.9%	2.7%

TABLE 1: Accuracy of different brain tissues segmentation by applying *a priori* knowledge involved in initial (general) and generated (disease specific) probability maps in expectation maximization segmentation algorithm.

The experiments conducted on a large set of MR brain images of patients suffering from a similar neurological disorder confirmed a desirable performance of the proposed method for representing disease specific *a priori* knowledge as well as in employing it for brain image segmentation of new patients. Qualitative evaluation of the generated probability maps implied their high quality conformance with the disease structural progress. The qualitative examinations carried out on the performance of the brain image segmentation of new patients using the generated disease specific probability maps showed a more accurate classification in comparison to the case where a general set of probability maps was used. In the former case, brain tissue structures were

revealed with more meaningful details as well as with less undesirable artifacts throughout the segmentation process. The quantitative evaluations performed on brain image segmentation of new patients also verified a considerable increase in the segmentation precision in the case where the generated disease specific probability maps were applied. Here a favorable increase in TPVF was achieved concurrently with an encouraging decrease in FPVF, in most case.

As mentioned earlier, the immediate goal aimed in this paper for generation and representation of disease specific *a priori* knowledge was brain image segmentation for diagnosing the disease and monitoring/measuring its gradual effects on different brain tissue structures. As such and considering the substantial increase accomplished in the accuracy of the brain image segmentation of new patients using the generated disease specific probability maps, a substantial step has been taken forward towards this goal. This will pave the way for a more reliable disease diagnosis, measuring its progress, and monitoring the treatment response.

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