Automatic Segmentation of Gray Matter Multiple Sclerosis Lesions on DIR Images

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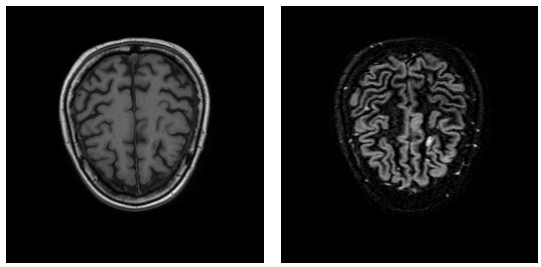
Abstract—**Multiple Sclerosis (MS) is a chronic inflammatory-demyelinating disease that affects both white and gray matter (GM). GM lesions have been demonstrated to play a major role in the physical and cognitive disability and in the disease progression. The diagnosis and monitoring of the disease is mainly based on magnetic resonance imaging (MRI). Lesions identification needs visual detection performed by experienced graders, a process that is always time consuming, error prone and operator dependent. We present a technique to automatically estimate GM lesion load from double inversion recovery (DIR) MRI sequences. We tested the proposed algorithm on DIR sequences acquired from 50 MS patients. Regions corresponding to probable GM lesions were manually labeled to provide a reference. The resulting automatic lesion load estimate provides a correlation of 98.5% with manual lesion number, and of 99.3% with manual lesion volume.**

Keywords—**Multiple sclerosis, Double inversion recovery, Lesion segmentation.**

I. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system with a usual onset on young adults, causing morphological and structural changes to the brain and leading to physical disability and cognitive impairment. Its diagnosis and patient follow-up can be helped by an evaluation of the lesions load, which can be studied thanks to MRI sequences. Although since the '60s there have been evidences of cortical demyelinated lesions (CLs) in autopsied brains in more than 90% of patients with chronic MS ([1]), traditionally lesions in the white matter (WM) have been regarded as the most important pathologic feature in MS. Only over the last few years, the role of CLs in the pathophysiology of MS has gained increasing attention ([2, 3, 4, 5]), despite the higher difficulty to detect them with conventional imaging techniques.

In order to accurately detect the anatomic border between the cortex and subcortical white matter the use of double inversion-recovery (DIR) MR sequence has been proposed. This sequence, proposed in ([6]) and subsequently used by ([7]), consists of two inversion pulses preceding a conventional spin-echo sequence; suitable choice of inversion times allows the suppression of either CSF and WM, so to image the cortex alone, proving useful in providing a better gray-white matter differentiation than other sequences [8, 9] Still, CLs identification is based on visual detection, a process that is both time consuming and strongly operator dependent. Besides, given that DIR is not a conventional MR sequence, it would take time for the human rater to gain the experience to easily and confidently evaluate the acquired images. As pointed out in Geurts et al. ([10]) where a consensus has been established for the identification of GM lesions on DIR sequence, readers should become acquainted with this sequence and with its artifacts, which are typically present in the insula and in the correspondence of cortical vessels. In this paper we present a new method to automatically segment gray matter multiple sclerosis lesions, based on the use of DIR sequence. It provides an extremely good capability of detecting actual CLs, together with repeatability short computational time.



(a) (b)

Fig. 1 Different acquisition modalities and appearance of MR data from the same patient and approximately the same brain position. In the leftmost panel a T1 MR slice (a), in the rightmost panel a DIR slice (c).

II. Materials

Fifty patients (37 women and 13 men overall mean age 34.0 $\pm$ 10.7 years, range 18-65 years) affected by Relapsing Remitting Multiple Sclerosis (RRMS) who consecutively presented to the Multiple Sclerosis Centre of Veneto Region from June to October 2009 were included in the study. The

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mean disease duration was 11 $\pm$ 7.5 years, range 2-31 years. The study was approved by the local Ethic Committee and written informed consent was obtained from all subjects.

Examinations were performed at the Euganea Medica Medical Center (Albignasego (Padova), Italy) with a 1.5T MR imager (Achieva, Philips Medical Systems, Best, The Netherlands) with 33 mT/m power gradient, using a 16 channel head coil. MRI examination protocol included a DIR sequence (TR = 15631 ms, TE = 25 ms, TI = 3400 ms, 50 contiguous axial slices, images with a field of viwe of 250x250, a matrix of 256x256, in-plane resolution of 1 mm^2, with a thickness = 3 mm). An example of a typical DIR slice along with its corresponding T1-weighted slice is shown in Fig. 1.

In our study, MS lesions were manually identified and outlined by two experienced neurologists (M.C. and A.F.) who were not aware of the results of our automatic method. They were asked to manually highlight MS cortical lesions in DIR images with possible visual inspection of the corresponding FLAIR and T1-weighted images. The voxels corresponding to a cortical lesion as defined in [10] were manually identified. When the two human raters provided different evaluation of a cortical region, they were asked to reach a consensus.The final results were used as gold standard for the evaluation of the performance of our algorithm.

The average number of annotated lesions was 8.48 per subject, with a range going from a minimum of 0 (no lesion) to a maximum of 43.

III. METHODS

The algorithm performs at first a pre-processing step, in order to provide a skull-stripped version of the brain. Then, exploiting the relatively high contrast of DIR images between gray and white matter, we obtain a segmentation of the GM. Then, candidate lesions are identified by finding locally hyperintense regions, which are finally classified as true lesions by a supervised classifier using texture features, similarly to what has been proposed to segment brain tissues in healthy subjects. It is worth noting that both the extraction of the contour of the brain and the segmentation of the GM do not make use of any anatomical *a priori* information, i.e., we do not exploit image registration on brain atlases. Moreover, we do not use commonly available brain tissue segmentation tools, such as FSL ([11]), SPM8 ([12]) or Freesurfer ([13]), because they have been designed for general use, so they might not be optimized for application to images from patients with MS disease ([14, 15, 16]): in particular the segmentation of MR images of MS patients executed with such tools causes the misclassification of the voxels belonging to MS lesions, either as WM or as GM or as partial volume effect ([14]).

The proposed algorithm can be used on the whole 3D data, or separately slice by slice. In our implementation, the preprocessing step (skull stripping and GM segmentation) is used in 3D modality in order to exploit the z-connectivity of the brain structures, whereas we chose to detect the lesions in 2D modality, separately on each slice. We used a 2D inspection since the slice thickness of DIR images increases the risk of linking together hyperintense regions belonging to different structures.

A. Data Preprocessing

The DIR sequence is specifically designed to enhance gray matter tissue while attenuating both white matter and cerebro-spinal fluid ([6]), so that the highest intensities in the data are given by gray matter, bones and lesions. By evaluating the Otsu's threshold th ([17]) on the voxels' intensities, considering only the voxels brighter than th identifies the skull and the gray matter as disconnected regions, plus a number of noisy voxels. After the application of a morphological closing obtained with a ball-shaped structuring element of radius $R = 1$ voxels, the largest connected region is identified as gray matter. The binary skull stripped image is then used to mask the original data, in order to take into account only voxels belonging to GM.

Furthermore, in order to enhance the contrast of the DIR sequence and to smooth the noise, we apply the algorithm proposed in [18] using as structuring element for the dilation and the erosion a disk of radius $R = 3$ voxels.

B. Candidate Lesion Segmentation

Given the enhanced slice F_k, we estimate the local mean $I_{\mu,k}(x,y)$ and standard deviation $I_{\sigma,k}(x,y)$ of the gray matter around each voxel, considering a neighborhood of NxM voxels. Then, the locally hyperintense voxels are identified as those fulfilling the inequality:

$$F_k(x,y) - I_{\mu,k}(x,y) \geq \theta_{glob} I_{\sigma,k}(x,y) \quad (1)$$

where θ_{glob} is a parameter with which it is possible to balance the sensitivity and the specificity of the detection phase. Then, and all regions smaller than 4 voxels are discarded in accordance with the recommendations in [10].

In order to detect only the regions that show a real lesion-like appearance, a further classification at the region-level is

needed. First of all, the mean intensity of the gray matter in each slice is computed:

$$\mu_{gm,k} = E[F_k(x-y) - I_{\mu,k}(x,y)] \quad (2)$$

Then, for each candidate region $L_{cand,kj}$, the mean $\mu_{kj,int}$, the maximum value $\max_{kj,int}$ and standard deviation $\sigma_{kj,int}$ of its intensities, and the mean $\mu_{kj,ext}$ and standard deviation $\sigma_{kj,ext}$ on the intensities of the cortical voxels belonging to its contour are evaluated. The external surrounding is obtained with a dilation of $L_{cand,kj}$ with a structuring element of radius 1 voxel, paying attention not to include in the external neighborhood voxels that might belong to other candidate lesions.

In order to discard all candidates whose region-wide statistics mark them clearly as non-lesion, we will consider as candidate lesions those regions that are brighter with respect to the mean cortical gray level, and, as further condition, that are brighter than the gray matter in their immediate surrounding, and finally that show a sufficiently high maximum intensity:

$$\text{Cond. 1} \quad \frac{\mu_{kj,int}}{\mu_{gm,k}} > \theta_1 \quad (3)$$

$$\text{Cond. 2} \quad \frac{\mu_{kj,ext} - \mu_{kj,int}}{\sigma_{kj,ext}} > \theta_2 \quad (4)$$

$$\text{Cond. 3} \quad \max_{kj,int} > \theta_3 \quad (5)$$

where the θ_i are user-defined parameters.

C. Lesion Classification

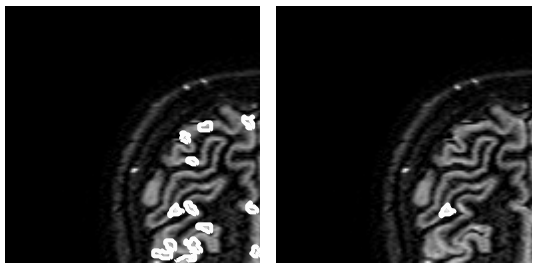
Due to the natural variability of gray matter tissue, method described in Sec. Bprovides a number of candidate lesions that can be high. To improve the specificity of the identification, a support vector machine (SVM) classifier ([19]), with radial basis function is trained. Each candidate lesion is represented by means of a set of features, composed by statistics on the intensities in the region or on its surroundings (mean intensity, standard deviation, kurtosis, skewness, maximum value, minimum value), by morphological measures (area, perimeter, solidity), and by the normalized histograms of local binary patterns ([20]) of the candidate's voxels.

The performance of the SVM classification is assessed on the 46 volumes of the test set by means of a leave-one-out procedure, so that at each round the classifier is trained on the candidate lesions identified in 45 subjects, and tested on the candidates segmented in the remaining subject.

A representative result of the identified lesions is shown in Fig. 2.

D. Performance Metrics

To test the capability of our algorithm in finding correct CLs, and to assess the performance of the whole identification pipeline (candidates identification and lesions classification). We computed the number of true positive (TP), false positive (FP) and false negative (FN). From these, we evaluated the sensitivity index $TP/(TP+FN)$ and fraction of false positives $(FP/(TP+FN))$ on the 46 subjects of the test set using the leave-one-out procedure.



(a) (b)

Fig. 2 Representative results of the candidate lesion identification (a) in a DIR image, and the final lesion identification (b).

IV. Results

A. Parameters Setup

On four subjects out of the 50 available, the parameters for the identification of the candidate lesions were chosen as to guarantee a high sensitivity and a reduced number of false positives are $N = M = 51$, $\theta_{glob} = 1.8$, $\theta_1 = 0.15$, $\theta_2 = 0.4$ and $\theta_3 = 0.05$. The Support Vector Machine (SVM) lesion classifier was evaluated using a leave-one-out procedure, using one volume as test set and the remaining as training at each round.the Paper.

B. Experimental Results

On the remaining 46 volumes of the validation set, a total number of 397 lesions were manually detected by the raters, who were blind to the result of our algorithm. Of the 397 true, 389 were correctly recognized by the candidate detection stage, providing a percentage of sensitivity of 98.0%. When the candidate lesions were classified with the SVM, the mean sensitivity using the leave-one-out validation decreased to 94.2%. However, the number of false positives was reduced from 12 times the number of true lesions to thrice the number of true lesions. Interestingly, the number of false positives has a Pearson correlation coefficient of 0.92 ($p < 10^{-10}$) with the number of real lesions as can be seen in Fig. 3, suggesting a correlation between the number of true lesions and the appearance of gray matter in terms of intensity variability.

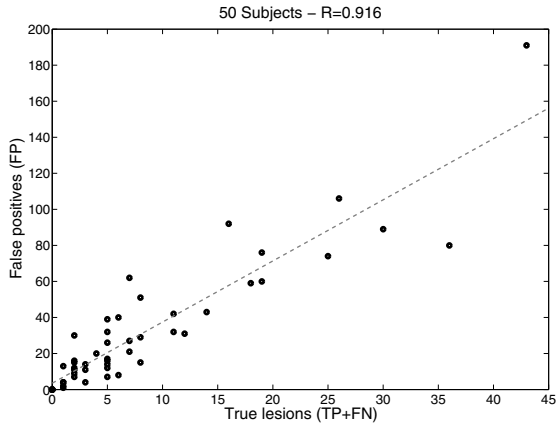


Fig. 3 Correlation between the true lesions present in a volume (true positives and false negatives) and those erroneously identified (false positives).

V. Conclusion

To the best of our knowledge the diagnosis and monitoring of the disease is mainly based on visual detection of MRI lesions ([21]), a process that is always time consuming, error prone and operator dependent. Moreover the identification of CLs requires an accurate training of the operator in order to avoid any lesion misclassification, even for the detection of WM lesions, that are usually much more prominent and easily recognizable than cortical lesions. Here we have developed an algorithm that provides an automatic segmentation of cortical MS lesions on double inversion recovery (DIR) MRI sequences. It provides a great sensitivity, thus speeding up the usual procedure of lesions segmentation, which is developed manually by experienced rater.

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