A novel method for automatic determination of different stages of multiple sclerosis lesions in brain MR FLAIR images

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Abstract

It is very important to detect stages of multiple sclerosis (MS) lesions in order to exactly quantify involved voxels. In this paper, a novel method is proposed for automatic detection of different stages of MS lesions in the brain magnetic resonance (MR) images, in fluid attenuated inversion recovery (FLAIR) studies.

In the proposed method, firstly, MS lesion voxels are segmented in FLAIR images based on adaptive mixtures method (AMM) and Markov Random Field (MRF) model. Then, signal intensity of each lesion voxel is modeled as a linear combination of signals related to the normal and also abnormal parts, in the voxel. By applying an optimal threshold, voxels with new intensities are primarily classified into two stages: previously destructed (chronic) and on going destruction (acute) lesions. Finally, the acute lesions, according to their activities, are classified, by another optimal threshold, into two new stages, early and recent acute.

Evaluation of the proposed method was performed by manual segmentation of chronic and enhanced (early) acute lesions in gadolinium enhanced T1-weighted (Gad-E-T1-w) images by studying T1-weighted (T1-w) and T2-weighted (T2-w) images, using similarity criteria. The results showed a good correlation between the lesions segmented by the proposed method and by experts manually. Thus, the suggested method is useful to reduce the need for paramagnetic materials in contrast enhanced MR imaging which is a routine procedure for separation of acute and chronic lesions.

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1. Introduction

MS is one of the progressive central nervous system diseases, which causes morphological and structural changes to the brain. Quantitative assessment of the changes in the brain MR images in association with clinical judgment can provide more accurate assessment of the disease progress. Also, it can provide important information in order to find out the most effective therapeutic method for patients. Due to high resolution and good differentiation between soft tissues and other structures, MRI has superiority to the other imaging techniques for the studies of nervous system diseases. MRI has been known as the best paraclinical examination for MS which can reveal abnormalities in 95% of the patients [1]. Because of inflammation and destruction of myelin in central nervous and subsequent pathological changes, MR images of MS patients show scattered singular or collective plaques with small or big sizes in different shapes. The appearances of the lesions in different MRI images including, T1-w, T2-w and FLAIR are not the same (see Fig. 1).

There are many proposed approaches for segmentation of the brain tissues as well as automatic and semi-automatic detection methods of MS lesions according to different degrees of automation or user interference [2–10]. Recently, Anbeek et al. [11] have proposed a novel automatic approach for segmentation of white matter lesions in the MR images of brain. The introduced algorithm uses different information, including voxel intensity and the spatial information, to classify voxels by a K-Nearest Neighbor (KNN) classifier. This technique assigns a probability to each voxel for being part of white matter lesion. Similarity Index (SI), then, is used for determination of the optimal threshold on the probability map, to segment the images. They have showed the high accuracy of their approach, in comparison with the other methods for similar task. These methods have been
focused on the segmentation of MS lesions in MR images and less attention has been paid to the detection of stages of lesion in FLAIR images. Three main stages of lesions are: acute or enhanced lesions on Gad-E-T1-w images, chronic lesions in T1-w images, and other lesions specified on FLAIR (T2-w) images. Because of more inflammation, edema, and little demyelination, acute plaques appear with less signal changes in T1-w images. Consequently, these plaques, in T1-w images, compared with white matter, will be signal isointense or hypointense (less darkness). In addition, their borders are vague and cannot be marginated well. With progress in demyelination process and also chronicity of the disease, the plaques gradually become darker in T1-w images. More demyelination and gliosis (replacement of fibrous tissue instead of myelin and neuron) lead to sharpness of the lesions borders. This process results in the formation of some chronic plaques known as black holes. These plaques will appear as hyperintense areas in T2-w images and their signal intensity will not change in enhanced T1-w images (by injection of the paramagnet contrast materials) [12]. It is important to mention that acute lesions can be classified into several stages according to their rate of the activity. It means that, there is a spectrum of lesions, some lesions are new with higher activity which are enhanced on Gad-E-T1-w images (we call these lesions as early acute), and some others are going to become chronic with lower or minimal activity (we call these lesions as recent acute). Routinely, the differentiation of acute and chronic lesions is possible by comparing the T1-w, T2-w, and Gad-E-T1-w images in different times. Because of transient destruction and inflammation in blood brain barrier, acute and active lesions can be enhanced and magnified by Gad-E-T1-w imaging, at least for 8–12 weeks after the beginning of the destruction [13]. Some new or acute plaques may not be enhanced because of low value of blood brain barrier destruction or relative inactivity of the lesion that leads the lesion toward to chronicity.

In spite of constant magnetic field and pulse sequence parameters, the study of the FLAIR images shows that the MS lesions appear with diverse signal intensity which can be classified in separate classes, such as chronic and acute (see Fig. 1(e) and (f)).

In this paper, we present a novel approach for automatic differentiation between stages of lesions based on the signal intensity of the voxels in FLAIR images. In the next section, first, an overall perspective of the proposed approach is presented. Then, the applied methods including: patients and MR imaging procedure, manual segmentation of chronic and enhanced acute lesions, brain segmentation in a head image, and MS lesion segmentation are discussed. Later on, the proposed approach is explained in more details and the evaluation method is presented.

2. Methods

The general overview of the procedure for detection of lesion stages is shown in Fig. 2.

In the first step, the lesions are extracted from normal tissue and cerebrospinal fluid (CSF) in the FLAIR images [14]. In the second step, a binary mask is generated from the lesions class, resulted from previous step and applied to the original FLAIR slices to extract the lesions. In the third step, by using a mapping, voxel chronicity and voxel activity for each voxel are computed. In the fourth step, the voxels resulted from this mapping are classified into chronic and acute lesions, by two different meth-
Fig. 2. Block diagram for detecting stages of lesions.

The proposed approach is evaluated by comparing the results with manual segmentation of chronic and enhanced (early) acute lesions in Gad-E-T1-w images.

2.1. Patients and MR imaging

Twenty definite MS patients, including 16 females and 4 males with average age of 29 ± 8 years old, were selected in this study according to the revised McDonald criteria 2005 (Polman et al. [15]). Mean disease duration of the patients was 5 years. For all patients the same MR images were obtained via a Siemens 1.5 Tesla scanner. All images were acquired according to full field MRI criteria of MS [15] in T2-w, T1-w, Gad-E-T1-w, and FLAIR in axial, sagittal and coronal surfaces.

We selected the FLAIR images especially axial slices with lesions in deep, priventricular, subcortical, and cortical white matters (supratentorial lesions). More lesion load and higher accuracy of FLAIR in revealing these MS lesions were the reason for this selection [13].

Scan parameters of, repetition time (TR)/echo time (TE)/inversion time (TI), for FLAIR were 9000/144/2500 ms; TR/TE, for T1-w were 424/10 ms; TR/TE, for T2-w were 3820/105 ms. Each image volume (patient data) consisted of averagely 40 slices with a 256 × 256 scan matrix, scaled linearly from the original 12-bit data to 8 bits. The pixel size was 1 mm², and the slice thickness was 3 mm without any gap.

For a better evaluation of the proposed method, different FLAIR images were selected from all patient images (data set). These images included slices which their T1-w and Gad-E-T1-w images had black holes with clear anatomical borders. Also, some of these selected slices had enhanced (early) acute lesions in their Gad-E-T1-w images. We divided them into two groups: learning set (i.e., 70% of all selected slices) and test set (i.e., 30% of the all selected slices).

2.2. Manual segmentation of chronic and enhanced acute lesions

There are two complimentary methods to separate acute and chronic (black holes) lesions: the first is the observation of GD-enhanced lesions for acute ones and the second is the observation of serial T1-w, T2-w, and Gad-E-T1-w slices in different times (imaging follow-up study) for chronic ones. In the second method, lesions which have not been enhanced and repeated in serial T1-w images are recognized as black holes.

In this study, a neurologist and a radiologist, who were not aware of the results of the computerized methods in this research, were asked to perform manual segmentation of MS lesions in FLAIR images and also, chronic and enhanced (early) acute lesions in corresponding Gad-E-T1-w slices. The results of this step for all the selected slices (learning and test) provided binary segmented images, considered as gold standard, for usage in evaluation step [11].

Also, the results of manual segmentation of chronic and enhanced (early) lesions, in the learning slices, were used to find two optimal threshold values, one needed for classification of chronic and acute lesions and the other needed for classification of early and recent acute lesions. Further discussion about finding these optimal thresholds will be presented in Sections 2.5 and 2.7.

2.3. Brain and MS lesions segmentation

Brain segmentation in head images is performed using a fully automatic object-oriented approach [16]. Also, for segmentation of the MS lesions, a fully automatic segmentation approach based on adaptive mixtures method (AMM) and Markov Random Field (MRF) model is utilized. In this method, distribution function of a FLAIR image is estimated with a mixture of a large number of normal terms by AMM. Then, these mixed terms, according to the class conditional probability density functions (CCPDFs) and the a priori probabilities, are categorized into three classes, normal tissue, CSF, and lesions. The MS lesions are classified based on Bayesian classification. In the next steps, a priori probabilities of the classes as well as the mean and variance of CCPDF for each class are attained and updated utilizing the MRF model and the AMM, respectively [14]. In this method, to estimate the CCPDFs and a priori probabilities, no initially training samples and initial values are needed. Using this method, the FLAIR images are classified into three classes: normal tissue, CSF, and lesions.
2.4. Determination of different stages of MS lesions

After segmentation of MS lesions, each lesion voxel, based on amount of demyelination, is classified into different stages. The procedure for this step is as follows.

The signal intensity, $G_i(k, l)$, of the lesion voxel $v_i(k, l)$ (located at $(k,l)$ in $i$th slice) is modeled as:

$$G_i(k, l) = a \times k_n(k, l) + b \times k_d(k, l)$$ (1)

where $a$, $b$, $k_n$, and $k_d$ stand for the mean value of signal intensity of normal tissues, the maximum signal intensity of the lesions, normal fraction and involved fraction of voxel $v_i(k, l)$, respectively. It is obvious that:

$$k_n(k, l) + k_d(k, l) = 1$$ (2)

It can be concluded from (1) and (2):

$$k_d(k, l) = \frac{G_i(k, l) - a}{b - a}. \quad (3)$$

This equation represents a mapping.

With achievement of $k_d$ for all voxels of the $i$th slice, an image is produced where each voxel intensity value is defined by the amount of chronicity of that voxel. The result of this mapping is classified into different lesions classes, according to the fraction of the involvement. Fig. 3 displays three possible classes such as: acute (early acute), acute toward chronic (recent acute) and chronic (black hole).

Since only manual segmentation of lesions, by neurologist and radiologist, into a limited number of stages, such as chronic and early acute is feasible (as mentioned in Section 2.2), the result of mapping, in this study, firstly, is classified into two classes, chronic and acute. Then, in turn, the acute lesions are classified into two new stages: early and recent acute lesions. This classification result, now, can be validated by experts.

2.5. Classification of chronic and acute lesions based on the OTS method

In this method, classification of chronic and acute lesions is performed by applying a threshold to the result of mapping. The selection of the threshold value in this classification is very important. In order to find the optimal value, first, the Mean of Similarity Index (MSI) for the learning slices is calculated and represented in a graph as a function of threshold, running from 0 to 1. Then, the optimal threshold is selected corresponding to the maximum of the MSI. Further discussion about SI criterion will be presented in the evaluation step.

2.6. Classification of chronic and acute lesions based on the ATS method

In order to compare the OTS method with the other methods, we made use of the ATS method. However, the images resulted from mapping, instead of FLAIR images, are given to this algorithm. Then, the lesions are classified into two classes: chronic and acute. This algorithm was already introduced in Section 2.3 [14]. In this algorithm a threshold is required for grouping the normal terms of the estimated distribution of the input image into two classes as the CCPDFs and a priori probabilities of classes. For the best result, this threshold is set automatically, equal to the mean of the signal intensities in the result of the mapping.

2.7. Classification of early and recent acute lesions

In this step, after classification of the chronic and acute lesions, the acute lesions are classified into two new stages: recent and early acute according to their activities. In this classification, an acute lesion will be classified as early acute if the difference between its signal intensities in the T1-w and Gad-E-T1-w images is more than a threshold value. Similar to the determination of the optimal threshold, explained in Section 2.5, the optimal threshold value in this step, also, is selected corresponding to the maximum of the MSI calculated for the learning slices. These learning slices are chosen from the selected images including the enhanced (early) acute lesions in Gad-E-T1-w images.

2.8. Evaluation

The results of the chronic lesions classification based on the OTS and ATS methods are compared with the gold standard. The similarity criteria, SI [17], overlap fraction (OF) and extra fraction (EF) [18], are calculated for the all selected (learning and test) slices. The SI is a criterion for the correctly classified chronic lesions area relative to the total area of chronic lesions in both the gold standard and the area of the segmented image. The OF and EF specify, respectively, the areas which have been correctly and falsely classified as chronic lesions areas relative to the chronic lesions area in the gold standard. The similarity
Fig. 4. Comparison of a binary segmented image (Seg) with the reference image (Ref). TP, TN, FP, and FN represent true positive, true negatives, false positives, and false negatives voxels, respectively [11].

criteria are defined by the Eq. (4)(4.1–4.3) (see Fig. 4).

\[
SI = \frac{2 \times TP}{2 \times TP + FP + FN} \quad (4.1)
\]

\[
OF = \frac{TP}{TP + FN} \quad (4.2)
\]

\[
EF = \frac{FP}{TP + FN} \quad (4.3)
\]

In these equations, TP stands for true positive voxels, FP for false positive voxels, and FN for false negative voxels. In binary segmentation, it is desired to achieve \((SI, OF) \in \{0,1\}\) with regard to the amount of overlap between the segmentation outputs resulted from manual (gold standard) and the proposed segmentation approach. Theoretically, an optimized segmentation SI and OF should be close to 1 and EF should be close to 0. Practically, a value for SI more than 0.7 represents an excellent agreement [19].

For evaluation of the segmentation of *early* acute lesions, a similar procedure has been used and the results have been compared with the gold standard.

3. Results

The proposed algorithm was implemented on different FLAIR images using a Pentium 4 processor 2.66 GHz, 512 MB RAM. In Fig. 5(a–c) a typical original image as a sample slice in FLAIR and its corresponding T1-w, and Gad-E-T1-w images have been shown, respectively.

Fig. 5(d) displays the result of gray level slice of the segmented MS lesions. Means and standard deviations of SI, OF, and EF are equal to 0.75 ± 0.03, 0.74 ± 0.05, and 0.23 ± 0.06, respectively. These values show a better performance of MS

Fig. 5. Steps of the proposed method: (a) original FLAIR image of a sample slice, (b) T1-w image of the same slice, (c) Gad-E-T1-w image of the same slice, (d) gray level slice of the segmented MS lesions, (e) result of the mapping (f) segmentation of chronic lesions (blue) and acute lesions (red) with a manually-selected threshold. The chronic lesions in all images are indicated with blue arrows (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.).
more than 0.7 is considered as an excellent segmentation [19]. It is recalled, that the value of SI of the similarity criteria were computed for the learning slices the effects of the optimal and manually-selected thresholds proposed algorithm is acceptable[19]. A comparison between slices, as this value is still higher than 0.7, the performance of the EF criterion. In spite of a decrease in the SI value for the test slices compared to the learning slices decreased about 6% and Table 1.

<table>
<thead>
<tr>
<th>Slices</th>
<th>Similarity Index (SI)</th>
<th>Overlap fraction (OF)</th>
<th>Extra fraction (EF)</th>
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<tbody>
<tr>
<td>Learning</td>
<td>0.84 ± 0.07</td>
<td>0.9 ± 0.03</td>
<td>0.23 ± 0.05</td>
</tr>
<tr>
<td>Test</td>
<td>0.74 ± 0.05</td>
<td>0.85 ± 0.05</td>
<td>0.28 ± 0.06</td>
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</table>

is shown in Fig. 7. In this figure (a–c) represent the Gad-E-T1-w image of the sample slice, segmentation of the chronic lesions for manually-selected threshold, and the OTS method, respectively.

The chronic lesions in the all images are indicated with blue arrows. As it is seen, for the optimal threshold value, all of the chronic lesions have been detected properly. The computed total volume of the chronic lesions (i.e., 0.37 cc) is very close to that of the true volume (i.e., 0.37 cc). As it was mentioned before, these acute lesions have not been enhanced because of low value of blood brain barrier destruction or relative inactivity of the lesion that leads the lesion toward to chronicity.

For comparison of the results of the OTS method for segmentation of the chronic and the acute lesions, the ATS method was reapplied to the result of the mapping with the threshold preset automatically to 0.58. Then, the means and standard deviations of the similarity criteria were computed again for the all selected slices (learning and test) (see Table 2).

As it is seen in this table, the means of the calculated similarity criteria for the test slices compared to learning slices decreased about 10% and 5% for SI and OF, respectively, and increased about 5% for EF. Like, the OTS method, there are trivial differences between learning and test slices. In Fig. 7(d), the result of the chronic lesion segmentation performed by the ATS method has been shown. As it is seen, all chronic lesions have been detected correctly. The computed total volume of the chronic lesions (i.e., 0.345 cc) is very close to that of the true volume (i.e., 0.37 cc).

We selected the OTS method as the reference method for segmentation of the chronic and acute lesions due to good accuracy according to Tables 1 and 2 and low computational complexity.

For classification of early and recent acute lesions by the introduced method, the optimal value of the threshold was computed using MSI of the learning slices which had the enhanced MSI of the learning slices that had the enhanced acute lesions in Gad-E-T1-w images. The MSI has been presented in Fig. 8 as a function of the threshold, running from 0 to 1.

Using the maximum of MSI (equals to 0.834), the optimum threshold value can be selected as 0.74 (the red spot in Fig. 6). Using the optimal threshold value and Eq. (4) (4.1–4.3), means of the similarity criteria were computed for the learning slices (see the first row in Table 1). It is recalled, that the value of SI more than 0.7 is considered as an excellent segmentation [19].

In the evaluation step, the determined optimal threshold value was set to 0.74 and the classification was performed for the test slices, then, the means and standard deviations of the similarity criteria were computed and showed in the second row of Table 1.

The means of the calculated similarity criteria for the test slices compared to the learning slices decreased about 6% and 4% for SI and OF, respectively, and increased about 3% for EF criterion. In spite of a decrease in the SI value for the test slices, as this value is still higher than 0.7, the performance of the proposed algorithm is acceptable [19]. A comparison between the effects of the optimal and manually-selected thresholds

![Fig. 6. Mean Similarity Index of chronic lesion segmentation in the learning slices, as a function of threshold.](image-url)
In the evaluation step, the determined optimal threshold value was set to 22 and the classification was performed for the test slices, then the means and standard deviations of the similarity criteria were computed and showed in the second row of Table 3. The means of the calculated similarity criteria for the test slices, compared to the learning slices, showed decreases of about 10% and 10% for SI and OF, respectively, and an increase of about 4% for EF. Fig. 9(a–c) indicate the FLAIR, T1-w and Gad-E-T1-w images of the sample slice, respectively. Also, the result of the mapping, segmentation of the chronic and acute lesions, and segmentation of the enhanced (early) acute lesion have been shown in Fig. 9(d–f), respectively.

As it is seen, although, the early acute lesion has a little volume, it has been detected properly. The computed total volume of the acute lesion (i.e., 0.033 cc) is very close to that of the true volume (i.e., 0.03 cc).

Finally, the proposed methods based on optimal thresholds showed a high degree of similarity to the manual segmentation of stages of lesions according to Tables 1 and 3.

4. Discussion

A novel method for detecting stages of lesion voxels according to their signal intensity in FLAIR images was presented in this paper. Indeed, the proposed algorithm has three steps. In the first step, The MS lesions were segmented in FLAIR images. The numerical results of the similarity criteria obtained in this step were compared to the results previously reported by the researchers such as Johnston et al. [3], Boudraa et al. [8], Leem-
Fig. 9. Procedure of segmentation of chronic, recent and early acute lesions in FLAIR images: (a) original FLAIR image of a sample slice, (b) T1-w image of the same slice, (c) Gad-E-T1-w image of the same slice, (d) result of the mapping, (e) segmentation of the chronic and acute lesions, (f) segmentation of the enhanced (early) acute lesions in the sample slice. The chronic, recent acute and early acute lesions in all images are indicated with blue, red, and yellow arrows, respectively (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.).

put et al. [9], and Zijdenbos et al. [20], who used similar methods for their evaluation (i.e., SI). It is reminded that these researchers have used manual segmentation for evaluation of their methods. We, too, used manual segmentation for evaluation. Therefore, comparison of our method with these methods is reasonable. This comparison is done in Table 4.

As it is seen in Table 4, the MS lesion segmentation algorithm used in this paper improves the results reported by others: 10% (compared to Johnston et al. [3]), 13% (compared to Boudraa et al. [8]), 24% (compared to Leemput et al. [9]), and 7% (compared to Zijdenbos et al. [20]).

In the second step, for segmentation of chronic and acute lesions, a method based on optimal thresholding was proposed (i.e., the OTS method). Using manual segmentation of the chronic lesions in Gad-E-T1-w images, evaluation of the OTS method was performed by calculation of similarity criteria for all selected slices (learning and test). Then, the results were compared with the results obtained by applying the ATS method. The results of the OTS method, compared with the results of ATS method, for segmentation of the chronic lesions in the learning slices showed a decrease of about 1% for SI and increases of about 2% and 7% for OF and EF criteria, respectively.

For the test slices, the results of the OTS method, compared to the ATS method, showed increases of about 3%, 3% and 5% for SI, OF and EF values, respectively. Therefore, the OTS method shows positive effects on SI and OF values and a negative effect on the EF value. Moreover, the computational complexity of the OTS method is much less than the complexity of the ATS method. Thus, we selected the OTS method as the reference method for segmentation of the chronic and acute lesions.

In the third step, an algorithm, which uses information of T1-w and Gad-E-T1-w images, for segmentation of early acute lesions, was suggested. Using manual segmentation of the early acute lesions in Gad-E-T1-w images, evaluation of the proposed method was performed by calculation of similarity criteria for the learning and test slices including obviously enhanced acute lesions. Because of good values for the similarity criteria, related to the segmented early acute lesions of the test slices, the introduced method is considered to have a high performance.

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<tr>
<td>Similarity Index</td>
<td>≥0.65</td>
<td>≥0.62</td>
<td>0.51</td>
<td>0.68</td>
<td>&gt;0.75</td>
</tr>
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</table>
Conventionally, Gad-E-T1-w images are used for segmentation of chronic and acute lesions. However, our proposed algorithm performs this task via FLAIR images, and only, for finding the optimal threshold, needs to Gad-enhanced images. It means a substantial decrease in need to utilization of paramagnet materials. This algorithm presents a more cost effective and less time consuming method and lends itself for a better treatment follow-up. As a future direction for extension of the proposed algorithm and in order to obtain a more accurate quantification of the stages of the lesions, the lesions can be classified into several subsets. This classification may be performed according to characteristic of the lesion in a volumetric neighborhood. This idea is under investigation by the authors.

Currently, the exact differentiation of acute and chronic lesions can be performed via microscopic pathological examination. However, such proposed computational methods create a new way for cost effective differentiation between stages of the lesions and it will probably be evolved and developed in the future.

5. Summary

Multiple sclerosis (MS) is one of the inflammatory, demyelinating, and progressive central nervous system diseases. To select the most proper treatment and its follow-up method, it is very important to detect the stages of the MS lesions. In this paper, a novel method is proposed for detecting different stages of MS lesions based on their signal intensities in the brain FLAIR-MR images.

The proposed algorithm has three steps, in the first of which, the MS lesions were segmented in FLAIR images. The numerical results of the similarity criteria obtained in this step showed an improvement, compared with the results reported by the others.

In the second step, for segmentation of chronic and acute lesions a method based on the optimal threshold (called OTS method) was proposed. For comparison of the results of the OTS method, an algorithm (called ATS method) was utilized. Because of better efficiency and lower complexity, the OTS method was selected as the reference method for the next step.

In the third step, an algorithm for segmentation of early acute lesions was introduced. The means of similarity criteria for segmented early acute lesions in the early test group slices showed a higher performance for the introduced method.

Conventionally, Gad-E-T1-w images are used for segmentation of chronic and acute lesions. However, our proposed algorithm performs this task via FLAIR images, and only, for finding the optimal threshold, needs to Gad-enhanced images. It means a substantial decrease in need to utilization of paramagnet materials. This algorithm presents a more cost effective and less time consuming method useful for a better treatment follow-up.

Currently, the exact differentiation, between acute and chronic lesions, is performed via microscopic pathological examination. However, such proposed computational methods create a new way for cost effective differentiation between stages of the lesions and it will probably be evolved and developed in the future.

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References


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