Parametric MRI simulation framework for Multiple Sclerosis: a step forward to a disease-specific analysis

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Abstract - *Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which often requires a complex diagnosis procedure. Usually, MRI images are required in clinical routine, in which the MS lesions are constantly verified according to total volume, spatial localization and progression. However, the manual verification is time consuming and also are subject of inter and intra rater variability. Recently, the scientific community have been offering several computation solutions to MS specialists, reducing the manual intervention and the total time requested for an MRI analysis. Nevertheless, there is a common struggling point regarding automatic lesion detection evaluation related to a ground-truth segmentation. A commonly adopted strategy to offer a controlled environment to test image analysis procedures is the usage of synthetic images. This study proposes an enhanced MS lesion simulation approach, intended to address the common issues present on other simulations tools. In addition, the full simulation algorithm is freely available as an open-source code, being able to be accessed and improved by all community.*
Palavras-chave: *Simulation, Multiple Sclerosis, Magnetic Resonance Imaging.*

Introduction

Multiple Sclerosis (MS) is a clinically challenging neurodegenerative disease that currently requires a multimodal MRI acquisition protocol on a complex diagnosis. Due to its high impact on social and economical development, MS has been growing attention for improved strategies to diagnosis, treatment and follow-up [1–3]. Usually, a multimodal MRI imaging set is required in clinical routine [1], where the MS lesions are constantly verified according the its total volume, spatial localization and progression. However, the manual verification is time consuming and also are subject of inter and intra rater variability [4].

Although in recent years many improvements have been proposed by the scientific community, a common struggling point regarding automatic evaluation related to a ground-truth segmentation still remains. In medical image processing, a complete validation of a method is necessary before a method can be applied in a clinical setting. It has been discussed in literature the need for a controlled and reliable simulation environment able to assist further automatic strategies for this challenging task [4].

Regarding MS, a well known simulation environment is BrainWeb [5]. Although this framework offered a considerable advance on MS studies, there are some limitations, namely the lack of lesion and anatomical variability and fewer MRI images modalities available. The lack of ground-truth datasets for automatic lesion detection evaluations adds uncertainties to the entire evaluation process [4]. Usually, manual segmentations have been adopted as baseline measures to many studies in automatic lesion detection approaches, however, the inter and intra-rater variability issues are commonly known as confounding factor to correctly infer the effectiveness of a determined lesion segmentation method [4].

In this study, an enhanced MS lesion simulation approach is proposed, intended to address the common issues present on others simulations tools. An automatic parametric simulation framework is mixed with MS manual assessments in order to artificially aggregate MS-like disturbances on MRI dataset of healthy individuals. In addition, the full simulation algorithm is freely available as an open-source code, being able to be improved and shared by all community.

Material and methods

The MS lesion simulation approach presented here is based on voxel-wise intensity distortions provided by the averaged MRI signal collected from real patients exams. Initially, the simulation procedure uses a database in order to provide a specific binary lesion map, which is reconstructed based on an user-defined lesion load. Then, a spatial normalization procedure is pursuit in order to fit the MS lesion pattern into the native space.

With both native MRI image and the binary MS lesion map on the same image space, it is possible to apply a series of parametric functions to locally distort the image signal in order to add MS-like lesions.

Lesions Database: The lesion database is basically composed of manual binary lesion masks provided by experienced specialists, which delineates the frontier between MS lesion and the Normal-Appearing White Matter (NAWM) tissues. Fluid Attenuate Inversion Recovery (FLAIR) sequence was used due to its importance in MS diagnosis and lesion identification, being routinely applied in clinical MS diagnosis and follow-up [1–3]. In order to add a representative selection of different patterns of MS lesions and signal contrast, a set of 3 image databases was used. A total of 82 MS patients were added in the MS lesion database, being 52 patients selected from our university hospital with the following image acquisition parameters: spin-echo sequence 2D with a voxel size of 0.60x0.60x1.0 mm^3, TE/TR/TI = 114/9000/2500 ms, FOV = 240x240x180 mm. The other 30 patients were obtained from publicly lesion segmentation challenges provided by the scientific community, regarding the MICCAI 2008 [6] and MICCAI 2016 [7] events. In all cases, the manual lesion segmentation was conducted by experienced radiologists and those manual assessments were adopted as the ground truth lesion delineation to construct the MS lesion database.

The MNI152 brain template with 1 mm of spatial resolution [8] was adopted as standard space for the creation of the MS lesion database. A conjugated strategy with a global Affine and elastic B-Spline registration procedures was used to fit the native image of each patient to the MNI space. This registration process was achieved using the tools FLIRT and FNIRT, available in the FSL software package [9]. After all lesion label were transformed to a common space, an individualized splitting procedure was applied. Each single lesion was defined as a spatially disconnected volume, as illustrated in Figure 1, and then grouped in different categories depending on the lesion volume. The 5 volume categories were defined as: 0.05 to 0.1 mL, 0.1 to 0.5 mL, 0.5 to 1.0 mL, 1.0 to 5.0 mL, and 5.0 mL or more. In total, there were obtained 2.229 individual lesions.

Simulation Evaluation: In order to show the applicability of the simulation pipeline proposed in this study, a set of MRI images from healthy individuals was used. The image simulation quality was evaluated empirically by two technical specialists and one experienced radiologist, responsible for visually inspecting each image modality and providing their assessments regarding simulation fidelity to MS lesion patterns. Until this moment, a simple evaluation step was conducted, which was intended to offer a visual comparison between real and simulations cases.

Results

As noticed by the specialists, general lesion signal distortion showed a consistent contrast between MS lesion and NAWM, which is widely similar from the real situation. Furthermore, the lesion shape seems well defined, with the signal distortion properly simulated using the right set of simulation parameters.

It is also worth comparing the proposed method with usual MS lesion simulation methods used by scientific community. There are several brain simulations softwares, which offer a wide variety of methods to simulate different MR imaging techniques. One of the most known and used softwares for MS lesion simulation is BrainWeb [5]. The simulation approach offered in BrainWeb is based on signal parametrization of relaxation characteristic constants on a probabilistic brain model, where the signal changes are modulated by the effective relaxation modulation at each voxel of the image [5]. Even though this approach is well presented as a anatomically preserving technique, the major drawback is the lack of variability in lesion patterns, which is a current problem in MS. A discussion about the problem was already presented by other authors [4], reinforcing the importance of a more broad image simulation procedure to MS. Our approach overcome this issue by proposing different lesion load to the simulation task, showing a visually promising results as noticed in Figure 2.

Discussion

In summary, the proposed MS lesion simulation have demonstrated several improvements regarding other simulation already published in the literature. Some achievements could be highlighted such as the wide lesion patterns provided from a large set of manual segmentations, an innovative strategy offering different brain anatomies to the lesion detection procedures using healthy individual MRI dataset, and a open-source project

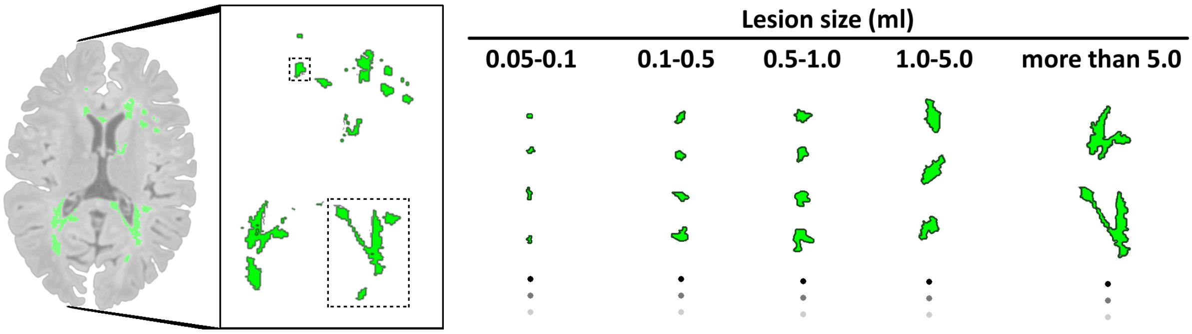

Figure 1 – An diagram illustrating the MS lesion database construction, where the manual binary lesion masks are splitted into individual lesions volumes and then organized in different categories. This strategy is useful to recreate similar lesion spatial patterns for distinct lesion loads, showing different shapes regarding the lesion load. A total of 2.229 individual lesions were collected, offering a large possibility of lesion simulations.

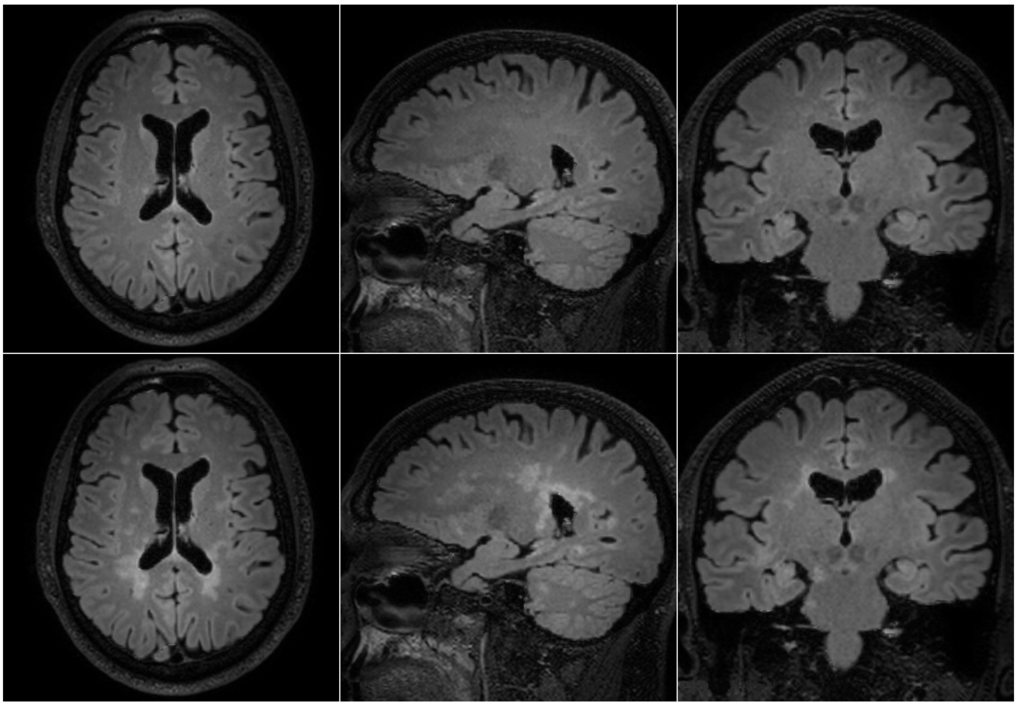

Figure 2 – Example of FLAIR image with simulated lesion load of 15 mL. The axial, sagittal and coronal orientation are illustrated, which is clear to see the hyperintense lesions with different locations and shapes. A global lesion patterns shows a close relationship with real MS patients, being useful to ground-truth lesion detection evaluations.

that is available to the community. However, even though our simulation approach showed promising results, there are some minor issues that were not able to be added in this context. Firstly, it is important saying that the entire simulation procedure is based on a specific subtype of MS, i.e. SPMS. Although this is a limiting factor to our simulation method, SPMS represents a large portion of clinical cases in etiological studies [1–3]. In theory, the effort to add more MS subtypes, e.g. PPMS and RRMS, in future updates is relatively easy, since all the method requires is the manual lesion segmentation from experts in the field. Secondly, in recent years there was a growing attention to another MRI imaging technique that offer more insights to MS progression, known as Double-Inversion Recovery (DIR) images [3]. This new imaging modality have been presented as a highly sensible technique to find MS lesion in the brain cortex [3]. Although DIR images have been showing promising results to MS, it still presents practical limitation to add this type of image in our simulation approach, e.g. lack of manual lesion assessments and few standardization for MS lesion definition. However, as previously discussed, as DIR images mature in the context of MS, it could be added in the scope of our simulator tool.

In fact, the MS lesion delineation requires a long experience in the field and it is not an easy task. In certain way, our simulation method aggregates both arguments, i.e. the use of manual segmentation and a precise location of MS lesion in the brain. Hence, a realistic lesion mask is guaranteed by the manual segmentations and the image voxel-wise distortion follows the exact delineation offered by real MS lesions. As an extend of previous issue, our simulation method can be also applied to specific MS training, offering a framework to evaluate beginners specialists to the challenging MS lesion detection task. As a general matter, MRI image simulations provides an extend opportunity to assist many health professionals to a initial contact to MS, showing a controlled environment to lesion detection training. There is no doubt that many efforts have been made to the brain simulation area, however, specific solution to MS lesion simulation needed further improvements. We hope that our framework can be helpful to many professionals in healthy and neuroscience knowledge areas, providing a stable and reliable solution to MS analysis.

Conclusion

In this study, an enhanced MS lesion simulation tool is provided, offering available solutions to MRI strategy. The growing necessity to more imaging techniques and analysis procedures turned MS into a complex and challenging disease. Due to its social and economical impact, MS claimed a special attention in past decades, where the scientific community contribute with several ideas. However, a controlled simulation environment was still lacking to improve the evaluations metrics on further MS studies. It worth commenting that the entire computational framework will be freely offered as a 3DSlicer module to the scientific community.

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