



INFLUENCE OF WHITE MATTER LESION FILLING ON VOLUMETRIC ASSESSMENT IN MULTIPLE SCLEROSIS

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ABSTRACT

Background: The continuous progress of information technology has made possible the creation of tools for post processing of magnetic resonance and other imaging modalities, including software programmes aimed at volumetric studies of the brain. They have the potential to enrich visual data with precise numeric values but have to be used with caution because of their possible susceptibility to errors if scans with specific pathology are fed in.

Objective: The purpose of the present study is to assess whether filling white matter lesions on magnetic resonance scans of multiple sclerosis patients would influence volumetric values.

Methods: MS lesions were filled on T1 3D images of 49 patients by the lesion-filling algorithm of FSL, using previously created lesion masks. Volumes of brain grey and white matter, peripheral grey matter and ventricle CSF were calculated using SIENAX for the filled and non-filled series, which were then compared.

Results: There were statistically significant differences for white matter volume before and after lesion filling ($p < 0.05$). No other volumes were significantly different.

Conclusion: Filling of white matter lesions may be time-consuming, but can improve the accuracy of SIENAX by reducing bias due to misidentification of tissue intensity. Sometimes though, improvement of specific values may not reach statistical significance.

Keywords: lesion filling, multiple sclerosis, SIENAX, volumetric study

INTRODUCTION

Magnetic resonance imaging (MRI) machines and techniques are subject to constant development. Modern scanners with higher magnetic fields, better resolution and image quality have been introduced into practice. The method has thus proved itself essential for imaging the brain in neurological diseases. Information technology is also in constant devel-

opment. More powerful hardware and software products come out on a regular basis. Ideas for joining the forces of both sectors have resulted in the creation of software tools and packages for post processing of MRI and other imaging modalities. These programs allow various measurements, calculations, and graphical editing to be performed. With their help, the data provided by neuroimaging studies can be enriched substantially with precise numeric values which can be of great importance in basic and clinical research. Moreover, many of these programs can be downloaded for free, but their use requires specific skills, knowledge and experience, in order to obtain reliable results.

Brain volumetric studies are a good example of the symbiosis between neuroimaging and information technologies. One of the widely used software modules for calculation of brain volumes in cross-sectional studies is SIENAX, part of FSL [1, 2]. It is able to calculate the total brain volume, grey and white matter volumes, peripheral grey matter and ventricle CSF volumes, all these in raw form and normalized according to the subject's head. SIENAX, as a segmentation-based method, may be more susceptible to errors when there are unexpected areas of different density throughout the brain's white or grey matter, such as lesions from a pathologic process. Such pitfalls can be encountered in the assessment of disorders which present with both cerebral atrophy and lesions, a typical example being multiple sclerosis (MS).

A considerable amount of facts has been accumulated about the neurodegenerative nature of MS. The number of studies assessing brain volumes of affected patients in order to obtain evidence of brain atrophy as a sign of neurodegeneration is increasing. Together with this, data has been acquired that hypointense T1 white matter lesions may be misinterpreted by the software which would bias the final results [3]. To overcome this problem, researchers have proposed and implemented different algorithms for "filling" the lesions with the correct density, so that the software can identify these regions correctly as belonging to the white matter [4]. It should be noted though that the presence of

white matter lesions may itself contribute to grey matter atrophy in MS [5].

Chard et al. have developed an automated lesion-filling technique (LEAP) and have tested it with simulated lesions with different volumes and intensities. Their conclusions were in favor of using the technique, which enables more accurate measurements, and is applicable to structural scans independently of the volumetric software which is going to be used [6].

A similar method of introducing artificial white matter lesions into T1 weighted images of healthy subjects, and then using segmentation and registration-based methods for white and grey matter volume calculation, was used by Battaglini et al. They found that refilling the lesions with intensities matching the surrounding normal appearing white matter improved the accuracy of tissue-class measurements [7]. Based on this research is the lesion-filling routine, part of FSL. It uses previously generated lesion masks, registered to the image that is to be filled, to fill the lesions with the density of the neighboring white matter. Lesion-filling is a feasible method for reducing lesion based bias in measuring brain atrophy in multiple sclerosis [8].

Creating lesion masks can be a time-consuming process, given the fact that in most cases this is done manually or semi automatically. Although software programs for fully automatic (or with minimal operator intervention) delineation of lesions as regions of interest also exist, they usually require multispectral (T1, T2, PD, etc.) MRI [9-11]. Measuring the volume of lesions on the other hand is important in MS, as it represents a key parameter for analysis. To save time and efforts, the regions of interest created for the lesions can be used as masks at a later time when filling the lesions on the T1 weighted image of the same patient. Masking lesions of the white matter may lead to more precise volumetric results for other structures of the brain as well. Magon et al. investigated the effect of WM lesions bias on the estimation of cortical thickness. They applied a lesion filling approach which significantly improved the accuracy of their results [12].

An automated brain tissue segmentation method was developed by de Boer et al. They incorporated a white matter lesion segmentation routine, also requiring no user intervention and found no errors in the majority of their cases, concluding that automatic segmentation accuracy can be close to the interobserver variability of manual segmentations [13].

According to Valverde et al., their novel method of refilling white matter lesions by replacing lesion voxel intensities by random values of a normal distribution generated from the mean white matter signal intensity of each two-dimensional slice is superior to other state-of-the-art methods [4].

Another new method is reported by Prados et al. [14]. It fills the lesions with the most plausible texture, rather than with normal appearing white matter. According to the authors the technique has some advantages, including better performance with lesions neighboring the grey matter and cerebrospinal fluid.

The purpose of the present study is to assess whether the filling of white matter lesions on T1 weighted 3-D MRI scans of MS patients would influence the values of total brain volume, grey and white matter volumes, peripheral grey matter and ventricle CSF volumes.

MATERIAL AND METHODS

Forty-nine relapsing-remitting MS patients, 13 males (26.5%) and 36 females (73.5%), aged 39.7 ± 9.8 years, ranging from 20 to 59, with mean EDSS score of 2.8 ± 1.3 , ranging between 1.0 and 6.0, were included in the study. All subjects signed an informed consent approved by the local ethics committee. Subjects were recruited among the inpatients of First clinic of neurology, St. Marina university hospital in Varna, Bulgaria. MRI scans were obtained using a 1.5 T Signa HDxt machine (General Electric, Milwaukee, WI, USA). DICOM series were converted to an appropriate format for further processing. White matter lesions were delineated on T2 FLAIR images using MRICron software (Chris Rorden, McCausland Center for Brain Imaging, Columbia SC, USA) and a graphical tablet. Lesion masks were saved as volumes of interest and their volume was calculated automatically. Brain extraction parameters (bet, part of FSL) were adjusted for each case. Lesions were filled on 3D T1-weighted images using FSL-lesion-filling and filled images were saved as separate files. Total brain volume, white and grey matter volumes, peripheral grey matter and ventricular CSF volumes were calculated for filled and non-filled images using SIENAX. Statistical analysis was performed: Descriptive analysis (minimum and maximum values, mean and standard deviation for each volume) and Student's paired samples t-test (to check for statistically significant differences before and after application of the lesion-filling procedure) were performed.

RESULTS

The routines completed without errors in all 49 cases, providing images with filled lesions (Fig.1). Descriptive statistics for the different volumes before lesion filling are shown on Table 1, and after the procedure, on Table 2.

Fig. 1. Example of MRI images before (left) and after (right) lesion filling

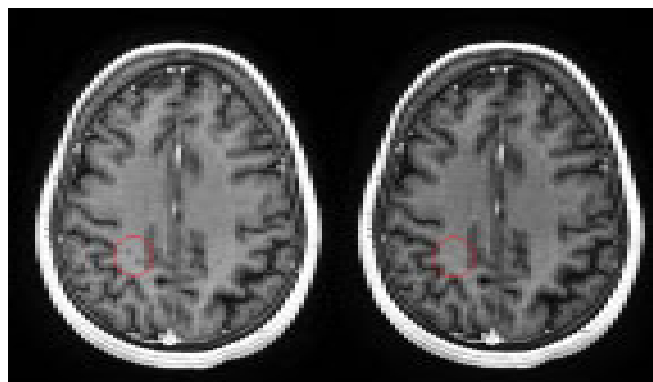


Table 1. Descriptive analysis of total brain volume (Total), white (WM), and grey matter (GM) volumes, peripheral grey matter (PGM) and ventricular CSF volumes *before* lesion filling (mm³)

	Minimum	Maximum	Mean	SD (±)
Total	1326493.33	1708254.46	1520221.22	104939.33
WM	593143.64	813468.64	688774.03	48184.48
GM	684484.45	956208.85	831447.19	71159.80
PGM	516201.34	762898.83	645388.81	57277.96
CSF	14648.20	101481.51	43832.42	21402.95

Table 2. Descriptive analysis of total brain volume (Total), white (WM), and grey matter (GM) volumes, peripheral grey matter (PGM) and ventricular CSF volumes *after* lesion filling (mm³)

	Minimum	Maximum	Mean	SD (±)
Total	1329622.70	1706965.60	1524514.40	102461.77
WM	584427.34	802129.46	691753.15	47253.74
GM	684801.88	954501.10	832761.25	69734.44
PGM	516470.09	762571.43	646617.56	56167.63
CSF	14543.40	118803.05	43858.61	22433.80

The mean calculated volumes of each structure were compared before and after lesion filling using paired samples t-test. There were statistically significant differences for white matter volume before and after lesion filling ($p < 0.05$). No other volumes were significantly different (Table 3).

Table 3. Comparison of total brain volume (Total), white (WM), and grey matter (GM) volumes, peripheral grey matter (PGM) and ventricular CSF volumes before and after lesion filling using paired samples t-test.

Paired Samples t-Test	t	p
Total	1.558	0.126
WM	2.269	0.028
GM	0.867	0.390
PGM	1.002	0.321
CSF	0.063	0.950

DISCUSSION

In our study we applied lesion filling, which is generally recommended in segmentation-based volumetric assessments. We used the lesion filling algorithm included in the FSL package, because the main volumetric tool that we had chosen, SIENAX, is also part of FSL. We thus aimed at achieving maximal straightforwardness, often solicited by

users, especially when they are competent in the medical, but not in the technical field. In our patients we found statistically significant differences between white matter volumes before and after lesion filling. This is an expected result, bearing in mind not only the data from the literature, but also the fact that white matter properties are directly affected by the lesions that reside in it. Neither the total volume of the brain, nor the grey matter volume were affected significantly by the procedure in our sample, though other authors report such dependencies. There were some trends for decrease in grey matter, but they did not reach statistical significance.

CONCLUSION

Filling of white matter lesions on T1-weighted scans is a widely applied procedure in brain volumetric studies of patients with MS. It may be time-consuming, but can improve the accuracy of the assessment by reducing bias due to misidentification of intensity, that is why it is generally recommended. Sometimes though, lesion filling may not lead to a significant improvement of specific values, such as total brain volume and grey matter volume, as was the case in our study. Further research in larger populations would hopefully clarify the problem in detail and lead to the elaboration of algorithms and criteria for the application of lesion filling in volumetric studies in MS.

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