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A white matter lesion-filling approach to improve brain tissue volume measurements

Sergi Valverde[a,*], Arnau Oliver[a], Xavier Lladó[a]

[a]Computer Vision and Robotics Group, University of Girona, Campus Montilivi, Ed. P-IV, Girona 17071, Spain

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ABSTRACT

Multiple sclerosis white matter (WM) lesions can affect brain tissue volume measurements of voxel-wise segmentation methods if these lesions are included in the segmentation process. Several authors have presented different techniques to improve brain tissue volume estimations by filling WM lesions before segmentation with intensities similar to those of WM. Here, we propose a new method to refill WM lesions, where contrary to similar approaches, lesion voxel intensities are replaced by random values of a normal distribution generated from the mean WM signal intensity of each two-dimensional slice. We test the performance of our method by estimating the deviation in tissue volume between a set of 30 T1-w 1.5 T and 30 T1-w 3 T images of healthy subjects and the same images where: WM lesions have been previously registered and afterwards replaced their voxel intensities to those between gray matter (GM) and WM tissue. Tissue volume is computed independently using FAST and SPM8. When compared with the state-of-the-art methods, on 1.5 T data our method yields the lowest deviation in WM between original and filled images, independently of the segmentation method used. It also performs the lowest differences in GM when FAST is used and equals to the best method when SPM8 is employed. On 3 T data, our method also outperforms the state-of-the-art methods when FAST is used while performs similar to the best method when SPM8 is used. The proposed technique is currently available to researchers as a stand-alone program and as an SPM extension.

1. Introduction

Magnetic resonance imaging (MRI) permits to assess tissue abnormalities in vivo and approximate histopathological changes of the multiple sclerosis (MS) disease (Ganiler et al., 2014; Kearney et al., 2014). Several studies have shown that the percentage of change in brain atrophy tends to correlate with the progression of the disease (Pérez-Miralles et al., 2013; Sormani et al., 2014). Moreover, changes in gray matter (GM) atrophy are observed independently from white matter (WM), and hence atrophy measures based on segmentation-based methods are nowadays employed as they allow classifying brain tissues separately (Pérez-Miralles et al., 2013). The performance of different segmentation methods used to quantify brain atrophy or volume estimation has been evaluated deeply in the last 5 years (Klauschen et al., 2009; Derakhshan et al., 2010). However, it is well known that the presence of WM lesions can induce errors on brain tissue volume measurements (Chard et al., 2010; Battaglini et al., 2012; Gelineau-Morel et al., 2012) and non-rigid registration (Sdika and Pelletier, 2009; Diez et al., 2014), if lesions are processed within the images. For instance, if WM lesion voxels are classified as WM, lesion voxels with hypointense signal intensities are added into the WM tissue distribution, increasing the probability of GM voxels with similar intensity to be misclassified also as WM (Chard et al., 2010).

In the last years, some authors have proposed different techniques to overcome these issues in MS patients by filling WM lesions with intensities similar to those of WM before performing tissue segmentation and image registration. These methods can be divided into two groups: methods which use *local* intensities from the surrounding neighboring voxels of lesions (Sdika and Pelletier, 2009; Battaglini et al., 2012; Magon et al., 2013) and methods which use *global* WM intensities from the whole brain (Chard et al., 2010). In all cases, the performance of these methods is directly related with their ability to minimize the impact of refilled voxels on original tissue distribution, not only due to the addition of these voxels into the tissue distribution, but also due to the effect on the global tissue distributions of filled images.

Within *local* methods, Sdika and Pelletier (2009) have proposed to refill each WM lesion voxel with the mean of its three-dimensional neighboring normal appearance white matter (NAWM) voxels. Battaglini et al. (2012) have suggested refilling each WM lesion voxel with intensities derived from a histogram of NAWM voxels surrounding the two-dimensional lesions. In a recent study, Magon et al. (2013) have proposed to refill each two-dimensional lesion with the intensity from the mean of the surrounding area of the lesion. Regarding *global*

* Corresponding author.
E-mail address: svalverde@eia.udg.edu (S. Valverde).

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methods, Chard et al. (2010) have proposed a different approach by using intensities re-sampled from a global WM distribution to refill WM lesion voxels, based on the mean and standard deviation of the total NAWM of the whole image. Both Chard et al. (2010) and Battaglini et al. (2012) methods are available for the community. FSL-L (Battaglini et al., 2012) runs from a computer command-line and does not provide any graphical interface that aids the process. This technique has been integrated into the latest FSL package, and therefore it depends on the whole FSL installation. In the case of LEAP (Chard et al., 2010), the method runs as a stand-alone script also from the command-line and requires the installation and configuration of several external dependencies, which may be difficult to install for non-computer experts.

In this paper we propose a new technique to refill WM lesions which is a compromise between *global* and *local* methods. Hence, for each slice composing the three-dimensional image, we compute the mean and standard deviation of the signal intensity of NAWM tissue. On the one hand, compared to local methods (Battaglini et al., 2012; Magon et al., 2013) which only make use of a limited range of voxel intensities, the fact of using global information from the whole image slice reduces the bias caused by refilled voxels on GM and WM tissue distributions, especially on images with high lesion load. On the other hand, compared to other global methods (Chard et al., 2010), which are based on the mean signal intensity of the NAWM of the three-dimensional image, our method re-computes the mean signal intensity of the NAWM at each two-dimensional slice with the aim of reproducing more precisely the signal variability between MRI slices, especially in low resolution images. In order to easily integrate it into current platforms, the proposed method called SLF is currently available as a stand-alone program and as SPM[1] extension at the SALEM group site (http://atc.udg.edu/salem/slfToolbox).

To evaluate the performance of our method, we estimate the deviation in GM and WM tissue volume between a set of healthy images and the same images where artificial WM lesions have been refilled with the proposed technique. To do so, we register WM lesion masks from diagnosed MS patients into two sets of 30 1.5 and 3 T T1-weighted (T1-w) images of healthy subjects, respectively. Afterwards, we simulate realistic lesions on healthy images by replacing the signal intensities of registered lesion voxels with values similar to those of the mean GM/WM interface. Brain tissue volume is computed using both FAST (Zhang et al., 2001) and SPM8 (Ashburner and Friston, 2005) segmentation methods, in order to avoid possible correlations between the filling and segmentation processes. Furthermore, we compare our results with the same images where artificial WM lesions have been segmented as normal tissue, masked-out before tissue segmentation, and refilled using also the methods proposed by Chard et al. (2010); Battaglini et al. (2012), and Magon et al. (2013).

2. Materials and methods

2.1. Image data

The first set of images is composed of 30 images of healthy subjects (matrix size: $176 \times 208 \times 176$, voxel size: $1 \times 1 \times 1.25$ mm), acquired on a 1.5 T Vision scanner (Siemens, Erlangen, Germany) and obtained from the Open Access Series of Imaging Studies (OASIS) repository[2] (Marcus et al., 2007). Only images from young and middle-aged subjects are selected (age < 50) as they have not been diagnosed with any related pathology. Image references included in the study are as follows: 2, 4, 5, 6, 7, 9, 11, 12, 14, 17, 18, 20, 25, 26, 27, 29, 34, 37, 38, 40, 43, 44, 45, 47, 49, 50, 51, 54, 55, and 57.

The second set of images is composed of 30 images of healthy subjects (matrix size: $256 \times 150 \times 256$, voxel size: $0.92 \times 0.92 \times 1.20$ mm) acquired on a Philips 3 T scanner (Philips Healthcare, Best, NL) and obtained from the Information eXtraction from Images (IXI) repository maintained by the Imperial College London in London, UK.[3] We selected 30 images acquired from the Hammersmith Hospital. Image references included in the study are as follows: 12, 13, 14, 15, 33, 34, 39, 48, 49, 51, 52, 57, 59, 72, 80, 83, 92, 95, 96, 97, 104, 105, 126, 127, 128, 131, 136, 137, 146, and 159.

2.2. Preprocessing

All images are manually reoriented to match the standard MNI space. Skull-stripping is performed using the Brain Extraction Tool (BET) (Smith, 2002), following the optimization workflow suggested by Popescu et al. (2012), with the exception that cerebrospinal fluid tissue has been refilled on skull-stripped images again. This procedure is preferred over other alternatives as it provides the best performance on some lesion-filling methods such as Chard et al. (2010), being also the choice in other recent studies (Popescu et al., 2014). IXI images are corrected from possible intensity non-uniformities and acquisition artifacts using N4, the ITK (Ibáñez et al., 2003) implementation of the N3 package (Sled et al., 1997). N4 is applied on IXI images with default options. Images from the OASIS repository are provided already with N4 applied.

2.3. Lesion generation

We use a set of 37 patients with clinically confirmed MS, provided with *initial* and *follow-up* studies (Diez et al., 2014). In these patients, lesions have been annotated semi-automatically on Proton Density-weighted (PD-w) images by a trained technician using JIM software[4] and afterwards co-registered with T1-w images. In order to maintain the independence between the 1.5 and 3 T sets of images, we match randomly 30 patients from the *initial* study into the OASIS images, and we repeat the same procedure with the follow-up study and the IXI image set.

MS lesion masks are registered into healthy images by a non-rigid transformation (Rueckert et al., 1999). To ensure that resulting lesion masks are placed on WM, we remove registered lesion voxels that have not been segmented as WM by both FAST and SPM8 on the healthy image. We computed a Wilcoxon rank sum test to analyze the difference in lesion volumes generated between OASIS and IXI datasets, obtaining that differences were not statistically significant ($p = 0.162$). The obtained mean lesion volume on OASIS images was 21.1 ± 20.8 ml (range from 0.5 to 65 ml), while 15.4 ± 16.2 ml (range from 0.8 to 62 ml) on IXI 3 T images. Note that due to the existing anatomical differences between 1.5 and 3 T image subjects and the enforced WM tissue constraint, the effect of registering the same MS lesion mask into a 1.5 and 3 T image results in two different lesion masks. For instance, the effect of registering lesions from the initial study into the 3 T dataset provided different lesion volumes (10.30 ± 12.10 ml) and reported statistically significantly differences ($p = 0.007$) on the Wilcoxon rank sum tests.

Artificial lesions are simulated by replacing registered lesion voxel intensities with ones between the GM and WM interface, following the same strategy shown in Battaglini et al. (2012). For each original image, GM and WM tissue distributions are computed using only voxels in agreement between FAST and SPM8. WM lesion voxels are filled with random intensities coming from a newly generated normal distribution, with mean equal to the average of the GM and WM mean values and standard deviation equal to the difference between mean WM and GM, divided by 4 (Battaglini et al., 2012). Artificial lesions are refilled with the aim of simulating a profile which clearly separates their signal intensity with healthy tissue. This intensity profile chosen does not

[1] http://www.fil.ion.ucl.ac.uk/spm/software/spm8/.
[2] Publicly available at: http://www.oasis-brain.org.
[3] Publicly available at http://biomedic.doc.ic.ac.uk/brain-development/index.php?n=Main.Datasets.
[4] Xinapse Systems, JIM software webpage, http://www.xinapse.com/home.php.