Inpainting Multiple Sclerosis Lesions for Improving Registration Performance with Brain Atlas

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***Abstract*—Multiple sclerosis (MS) is a inflammatory autoimmune disease of the central nervous system which damage the myelin layer of White Matter (WM) and Grey Matter (GM). The loss of myelin layer (demyelination) exposes the WM and GM, which is viewed as lesions in the MRI brain scans. To treat and monitor the progression of MS in standardized way, patient MRI brain scans are registered with brain atlas. However, in this registration step, the MS lesions create a strong distortion in the output transformation which creates a bias in registered image. In this paper, we propose a novel image inpainting technique to reduce such bias. Image inpainting is used to reconstruct the lost or deteriorated parts of image data. We inpaint the MS lesions to make it appear like healthy tissue and register this inpainted MS brain with the brain atlas, and add the masked lesions afterwards. To evaluate the performance of our proposed inpainting algorithm, we employ a two step evaluation process. Firstly, we inpaint distorted 2D images and artificial MS lesions in 3D MRI image data with our proposed and state-of-the-art methods. Secondly, we register the inpainted brain with an atlas and compare its performance with the ground truth. This two step evaluation indicates that the proposed inpainted algorithm performs comparatively better than other state-of-the-art methods and it also increases the registration performance and significantly reduces the bias previously created by the MS lesions.**

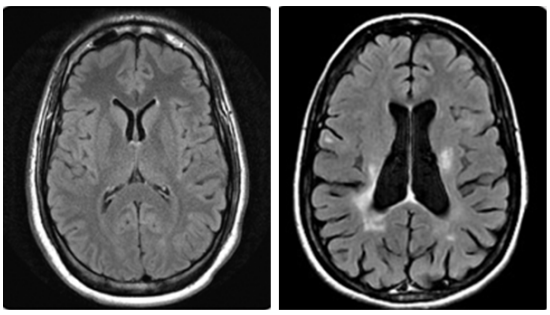
***Keyword*-Inpainting Algorithm; Multiple Sclerosis(MS); Brain Atlas; Artificial lesion; MRI; BET**

I. Introduction

MULTIPLE Sclerosis (MS) is a chronic inflammatory disease of the central nervous system causing axonal demyelination in brain and spinal cord, and neuronal degeneration [1]. The Multiple Sclerosis Foundation (MSF) estimates that more than 400,000 people in the USA and about 2.5 million people around the world have MS. The effect of demyelination are comprehended as lesions in the conventional MRI brain scans;White Matter (WM) lesions are more common than the Grey Matter (GM) lesions. Figure 1 shows the comparison between a healthy brain and an MS affected brain. The white plaques near the Cerebrospinal Fluid (CSF) are the MS lesions. Registration of the MS brain to a brain atlas is an essential step for analyzing brain structures. This is because the human brain has significant variation in its morphometry where any standardized diagnosis on the basis of morphometry can be erroneous.

Use of brain atlases enable us to segment images using a prelabeled atlas [2], to follow the evolution of brain structures in longitudinal studies [3] or for morphometry [4]. For treatment, diagnosis and evaluating the progression of MS, such registration to brain atlas is very common. However, losing the myelin layer, the MS lesions appears different than rest of the surrounding anatomy in MRI image. This creates a bias in registration performance. All the inpainting algorithms that works on intensity driven nonrigid distribution follows rudimentary structures. Hence comes the distortion with the reference image and the patient image [5]. This distortion of the transformation will be an important problem to solve. According to some studies, the main cause is change in GM volume with increasing WM damages. These WM lesions affects the WM intensity values which leads to erroneous GM segmentation [6], [7], [8]. Higher white matter lesions artificially reduced the total GM volumes [9] which further add to the registration bias.

Image inpainting is one of the most used image processing technique used by the professional restorers. In this paper, we propose an inpainting algorithm to fill out the MS lesions for delineating the effects of lesions on registration bias. The inpainted MS brain is morphometrically more feasible in terms of registration accuracy and reduction of bias when calculating the output transformation matrix. Once the transformation matrix is calculated it can be used to add the masked MS lesions into the registered brain atlas. In this paper, we also investigate if such preprocessing step (i.e. inpainting) contributes to the registration accuracy.



a b

Fig. 1. (a) Healthy Brain (b) MS affected brain

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This paper is organised as follows. Section II discusses about the recent development in inpainting algorithms, its application in brain imaging. In Section III we develop an inpainting algorithm and apply this technique as a preprocessing tool in the registration step. In Section IV, we compare the performance of our proposed algorithm with other state-of-the-art inpainting methods, and also investigate the improvement contributed by using the proposed inpainting algorithm in the registration step. We discuss the results and formulate our future direction in Section V.

II. Related Work

A. Image inpainting techniques

Image inpainting is mathematically highly ill posed process because once something is lost completely, we could never retrieve original but make the best assumption of what was lost. There are many image inpainting algorithm available such as Harmonic inpainting, Transport inpainting, Mumford Shah inpainting [10] etc. All of these algorithms are part of structural image inpainting. Structural inpainting fills out the empty parts in the image by using local structural information only. Harmonic inpainting uses second order diffusion technique for inpainting. Its evaluation describes a multi scale analysis of an image, that is a family of transformation, which when applied to a given image produces, a sequence of new images just like solving the heat equation [11]. It constitutes a smooth and linear interpolation process that roughly fills in missing gray values by averaging the given gray values on the boundary of inpainting domain. But it does not show good results on the edges of lost data. Transport inpainting works on third or higher order inpainting process. Its mainly a curvature driven diffusion [12]. But it lacks of simplicity. Mumford and Shah imposes a segmentation model which is based on the idea of decomposing an image into piecewise smooth parts that are separated by an edge set [13]. It is the higher order extension of the approach by an Euler elastic regularization. Though Mumford and Shah models reduces complexity but it needs fine tuning to get superior performance. In this research, we extend these methods to propose a new inpainting algorithm that can be used to fill out the MS lesions in the brain as well as distortions in the 2D images.

B. MRI image inpainting

Registration of one brain image to a brain atlas or a healthy brain is done so that the common features overlap and deviations from the healthy brain are apparent. In any given case the goal of registration is to find similarities between the reference image with the floating image

For registration of a brain with an abnormal structure e.g. tumor or lesions, the invertibility of the transformation is not possible as these structures are not present in atlas. To solve the problem of registering a brain with tumors to a healthy brain, biomechanical model of the tumor growth was planted in the reference image before and after the registration [14], [15] to mimic the effect that a tumor would have if it was on the healthy brain. The biomechanical model of the tumor or the "tumor seed" would push the surrounding tissues of the brain and would account for the distortion in the transformation that was to be caused by the "real" tumor. But a "tumor seed" cannot model the WM lesions as the lesions replace healthy tissues rather than pushing them like tumors. Another approach is to ameliorate the effect of the abnormal growths e.g. tumors [16], focal lesions [5] in registration by masking the regions of interest. The voxels that contain the lesions are removed from the similarity metric of the registration which means the cost function will only be applied on the voxels which are "healthy". Furthermore, in [17], different brain structures are segmented and parameterized to find the optimum transformation to match these structures. This takes care of the MS lesions bias as the lesions do not appear in these structures.

Three approaches are given below.

- Removing the lesions from the patient image.
- Adding the lesions to the atlas and aligning.
- Removing the influence of the lesions during the registration.

In this work, the MS lesions are inpainted created before performing registration to make the lesions look like healthy brain tissue. This is a fully automated process as the mask used to create the lesions are known apriori. Thus, it is an easy preprocessing step before registration.

III. Methods

In this paper a method is proposed that applies to the registration of MS brains.In our paper Figure 2 shows proposed framework MS creates lesions in WM and GM but the lesions in the cortical or deep GM are difficult to understand in traditional T1 images. In this paper only WM lesions will be appreciated and this method can easily be extended to GM lesions.

A. Data

We used commonly available 2D images to test and compare our proposed inpainting method. We report the results using the Matlab® default image "pout.tif".

To get raw brain data, we used Human Connectome Project (HCP) [18] open source data of healthy brains. The dataset was provided by HCP database which was composed of 5 set of patients data. After qualitatively anlaysing, we chose the suitable one to work with. Every set was composed of a 3D acquired T1w, a T2w and a PDw image and a lesion mask created from the image. The data is acquired by MRI scanning. The image dimensions for 3D acquired T1w was 256 x 320 x 320 voxels with voxel size 1.171 x 1.171 x 1 mm.

To extract the brain matter from the whole brain scan, we used Brain Extraction Tool (BET) [19]. BET deletes non-brain tissues like skull, tongue from an MRI image and extracts the brain matters from it . After BET, reduction of noise from our data has been done with Structure preserving noise reduction method named SUSAN [20]. For carrying out these operations,

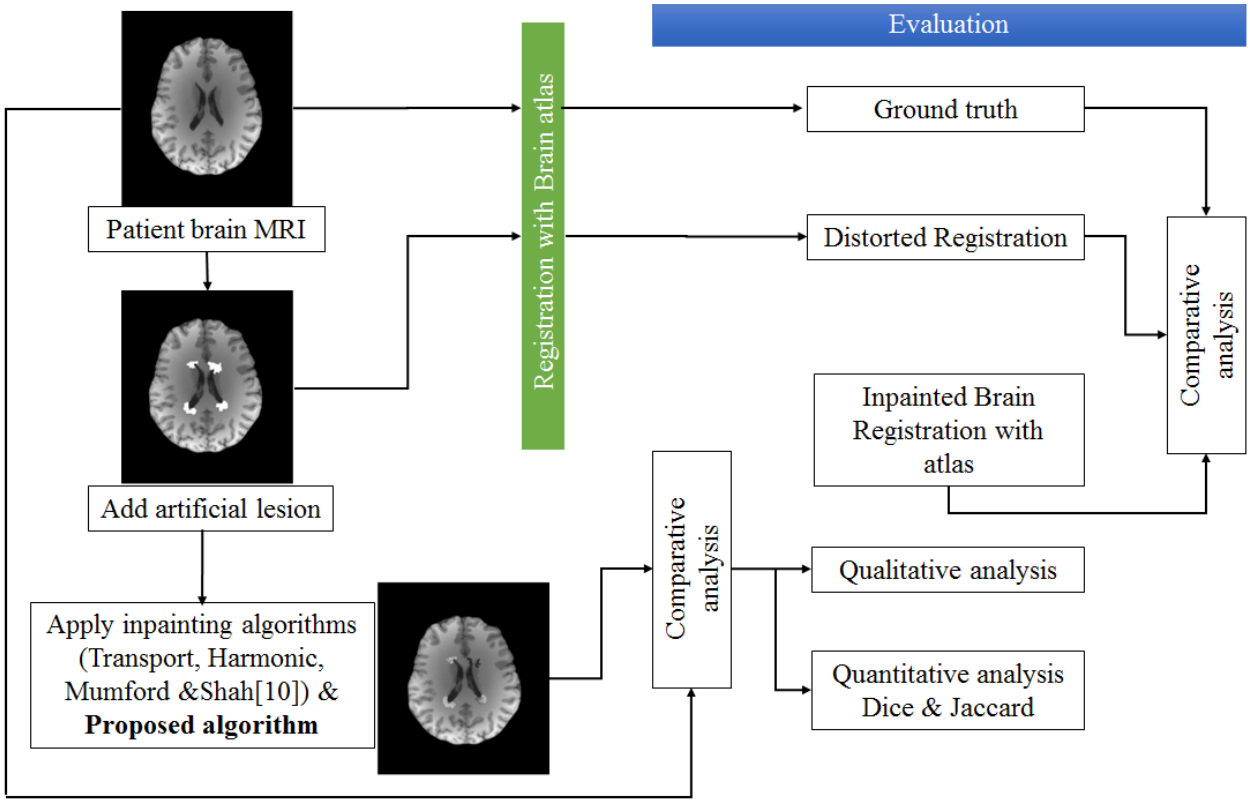

Fig. 2. Overview of our proposed framework

we used FMRIB Software Library (FSL) is utilized which is an open source software [21].

As at the scope of this work, we did not have MS patient data so created artificial lesions in the healthy brain and performed our analysis to test the feasibily of our proposed algorithm.

B. Preprocessing

Presumptuously considering about the inherent noise in our image we decided to apply a nonlinear digital filtering technique, in our case we considered the median filter. We did not thoroughly look about the conditions in which it preserves edges as edge preservation is not our primary focus.

C. Inpainting algorithm

We implemented the state-of-the-art inpainting algorithms like harmonic, Mumford-Shah, transport. Our proposed algorithm has low complexity and it does not solely depend on neighbourhood points for inpainting process. During the analysis of previous proposed methods we speculated the possibility of improvement by the exploitation of Total Variation (TV) model proposed in [22].

In order to solve the Total Variation inpainting problem which is unconstrained variational methodology can facilitate to a great extent.Let D be the inpainting domain E is a fixed domain in the complement of D.

$$P[u] = \int_{EUD} |\nabla u| dxdy + \frac{Ł}{2} \int_{E} |u - u^0|^2 dxdy \quad (1)$$

Where L is the lagrange multiplier for the constrained variational problem. Euler-lagrange equation for the minimization of energy functional P is

$$-\nabla \cdot \left(\frac{\nabla u}{|\nabla u|} \right) + \lambda_e (u - u^0) = 0 \quad (2)$$

For all $z = (x, y) \epsilon E \cup D$. The extended lagrange multiplier L_c contains two different value for two different regions

$$L_c = \begin{cases} L, & \text{for } z \epsilon E \\ 0, & \text{for } z \epsilon D \end{cases} \quad (3)$$

The most steep descent equation for $P[u]$ is following

$$\frac{\partial u}{\partial t} = L \cdot \left(\frac{\nabla u}{|\nabla u|} \right) + L_c (u - u^o) \quad (4)$$

Our approach initiates with a image having artificial lesion placed where we artificially inserted some region to imitate MS lesion in practical cases. Details of insertion of region is included in the inpainting the lesion part. In the original image a gradient analysis of the whole image is operated.

Necessary filtering, rotation and conversion of image for the ease of usage and denoising gives a clear view of the

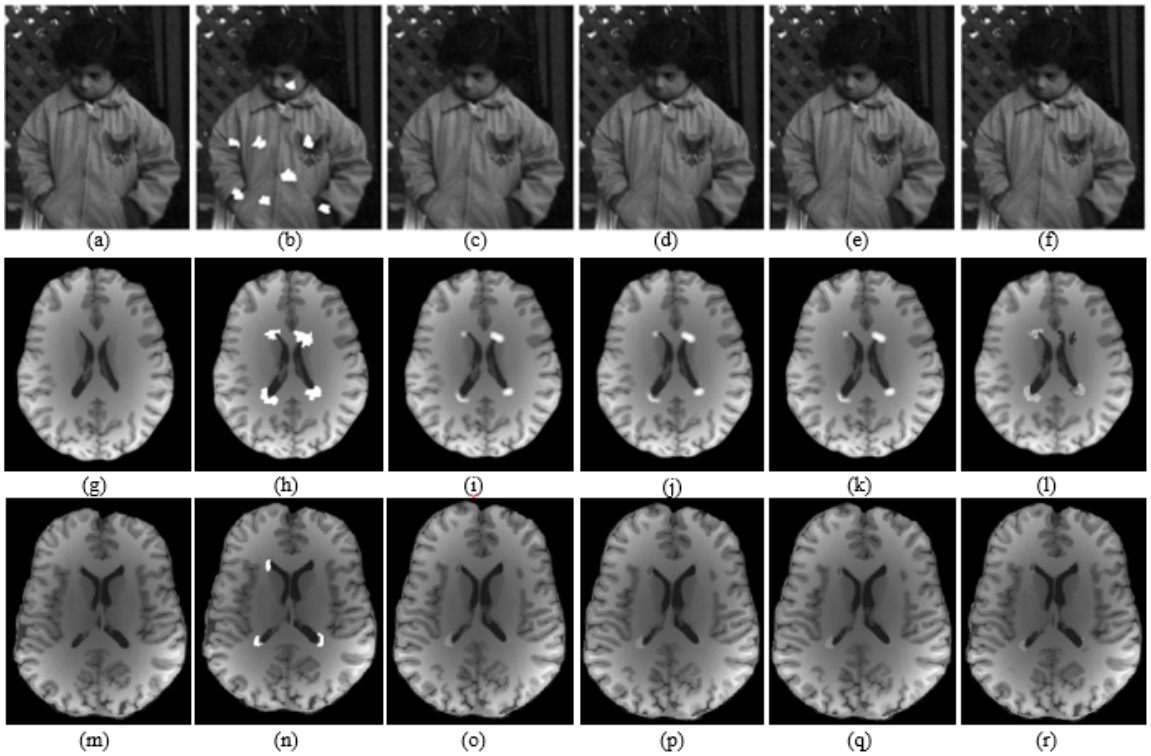

Fig. 3. From left to right (for each row) original image, some distortion is artificially added to the image, inpainting with harmonic, transport, Mumford & shah and proposed method. For 2D Image (a-f), For patient 1 MRI (g-l) and For patient 2 MRI (m-r)

respective image. TV inpainting approach the inpainted value of the target pixel has been found out with the help of adjacent neighborhood originally while our approach is concentrated on finding a neighborhood which has almost same gradient as our targeted region by optical evaluation of the gradient of whole image.

Our intended approach was to estimate the value of our target pixel with the help of all the neighbour pixel of a region having almost same gradient as our target region. u_{NW},u_N, u_{NE}, u_E, u_{SE}, u_S, u_{SW}, u_W, u_{NW} denotes neighbour points pixel value of that region. Symbolically u_e, u_w, u_n, u_e depicts midpoints value which is not available from specified image. h signifies grid size which is always 1 in image processing.Analogous region corresponding target point pixel value depicted by u_0^0

$$|\nabla u_e| = \frac{1}{h}\sqrt{(u_E - u_0^0)^2 + \frac{u_{NE} + u_N - u_S - u_{SE}}{4}^2} \quad (5)$$

Some variations on this formula may render better and improved performances. Due to concentrated focus on a working algorithm it was not viable for us to explore them. The weights, w_p of this midway points are necessary to implement our proposed algorithm.

$$w_p = \frac{1}{|u_p|} \quad (6)$$

Actually we want to approximate the value of our inpainted point with the help of an equation which in nature signifies a low pass filter. According to our guideline paper [22] a Jacobi iteration scheme is used. In our this specialized scenario this iteration is somewhat observed ancillary.

$$u_0 = \sum h_{OP} u_p + h_{00} u_0^0 \quad (7)$$

Illustrated equation more or less represents a low pass filter. Smoothing of the image by decreasing the disparity among the value of pixels was our intended purpose. Low pass filter was assumed to give an upper hand on this requisite.

Second part of this equation, $h_{00}u_0^0$ deals with the original value of our intended pixel to be inpainted. Original value multiplied with an appropriate filter coefficient abided by a specified equation should assist us. First part deals with all the values of neighbourhood points of that pixel to be inpainted. Cumulative value of them multiplied with a necessary filter coefficient is our prior need.

$$h_{OP} = \frac{w_p}{\sum_{Q \epsilon \lambda_0} w_Q + \lambda_e} \quad (8)$$

λ_0 signifies the set of four corner neighbour pixel value.

$$h_{00} = \frac{\lambda_e}{\sum_{Q \epsilon \lambda_0} w_Q + \lambda_e} \quad (9)$$

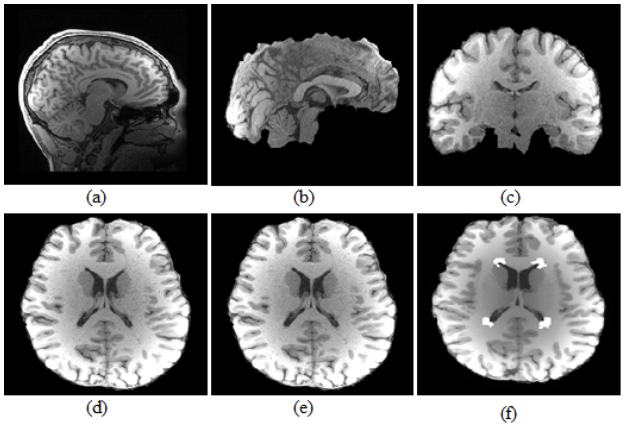

Fig. 4. Different stage of preprocessing (a) Raw image of the whole head, (b) brain extracted, (c) Orientation changed (coronal view), (d) Orientation corrected (axial view), (e) SUSAN filtered & (f) applied lesioned mask.

Our specified filter coefficients must coincide with a given constraint to align with the attributes of a low pass filter for smoothing purpose.

$$\sum_{P \epsilon \lambda_0} h_{OP} + h_{00} = 1 \tag{10}$$

Since we are not including any iteration in our approach, it must abides by the maximum principle.

D. Inpainting the lesions

After adding mask over the healthy brain, we will use the conventional inpainting algorithms to remove the artificial lesions. Then our proposed inpainting method will be utilized to inpaint the lesions in the brain.

E. Registration to brain atlas

Registration are of two kinds named functional and structural. Here in our paper we work with the structural registration or voxel based registration. Predominantly, to detect the transformation that delineates the voxels from one image (the target) to the voxels of the other (the source image) is the main goal of registration.

After inpainting , we perform registration to brain atlas using the inpainted image. We use FLIRT (FMRIBs Linear Image Registration Tool) which is a fully automated robust and accurate tool for linear (affine) intra- and inter-modal brain image registration in case of 2D or 3D images. It can be run with a number of different transformation models (degrees of freedom) as well as it implements a general cost function weighting scheme according to necessity. For affine, traditional, global rescale or rigid body tranformations in 3D scenario, DOF is set to be 12, 9, 7 and 6 respectively. In 2D to 2D mode only rigid body transformations are allowed involving 3 DOF. For each registration, we used trilinear interpolation technique and affine registration (12 DOF). For FLIRT, an input and a reference volume is to be taken primarily, the calculated affine transformation is to be saved as an affine matrix which is responsible for registration and secondarily, output volume where the transform is applied to the input volume to align it with the reference volume.

Affine transformation is a generalization, in other words, simplified version of linear transformation:

$$\begin{bmatrix} p' \\ q' \\ 1 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ 1 & 1 & 1 \end{bmatrix} \cdot \begin{bmatrix} p \\ q \\ 1 \end{bmatrix} \tag{11}$$

where, A is the affine transformation matrix. Affine transformation (1) has 6 parameters by and large entailing 3 pairs of corresponding points. But, more than 3 pairs are required to obtain best fitting affine parameters. This transformation includes scaling, rotation, translation, and shearing. In addition, FLIRT can also be used to apply a saved transformation to a volume. Firstly we do the registration with the healthy brain and reference MNI152 template [23]. The result is to be used as ground truth. Then we register the lesioned image as well as inpainted image with the reference one. So, we finally got registered healthy, lesioned and inpainted image. For quantitative analysis with the lesioned and inpainted ones,dice and jaccard scores has been calculated. Finally we can come to a conclusion that our proposed inpainting method has an improved effect to remove the bias in case of registration with brain atlas.

IV. Results

To evaluate our results we at first apply some image pre processing using BET(Brain Extraction Tool) in our data. Then after this pre processing we use (logical) mask to create artificial lesions and then apply our algorithm to test its feasibility.

TABLE I
DICE AND JACCARD COEFFICIENT USING DIFFERENT INPAINTING ALGORITHMS IN 2D IMAGE AND MRI BRAIN SCAN OF ONE SUBJECT.

	2D Image		MRI data	
Method	Jaccard	Dice	Jaccard	Dice
Harmonic	.8911	.9424	.9811	.9905
Mumford n Shah	.9970	.9985	.9547	.9978
Transport	.8468	.9171	.9687	.9841
Proposed (For patient 1)	.9989	.9987	.9791	.9854
Proposed (For Patient 2)	.9976	.9982	.9799	.9874

For comparing our results, we use standard comparison method Jaccard and Dice with the other inpainting algorithm (Transport, Mumford Shah, Harmonic etc) (shown in Table I). For our justification we also applied the same procedure in a normal image to see how it works on the real image. Both the cases the results were satisfactory as seen in Figure 3 and 4.

Further, we investigated the effect of inpainting the MS lesion in the registration step. To do that, we created the ground truth by registering the healthy brain to the brain atlas. We compared the distorted registration output generated by registering an MS brain with the brain atlas with the ground truth, and found that the Dice and Jaccard value are 0.8486 and

0.8086 respectively. This proves that, lesions create distortion in registration by deviating from the ground truth, and by inpainting this effect can be ameliorated.

V. Conclusion

Inpainting the white matter lesion is an easy preprocessing step and it can be used before any registration especially when one is working with MS patients. Furthermore, if one is creating an atlas of any patient population, WM lesions can create further bias as there is no standard template to register with. The different intensities in the same part of the brain will cause the floating image to deform in some unwanted way. The advantage of inpainting is that any brain with MS lesions or artificially added lesions can be used as the floating image or the registration. This is not the case with the Cost Function Masking method. In fact, if a mask is used to remove the influence of the lesions from the floating image, the voxels of the reference image is mapped to that masked region having a null cost.

Further, the improvement in Dice and Jaccard may seem very little, but this is proportional to the resolution of the floating image, template and largely on the size of the lesions. As the WM lesions are smaller compared to the total WM mask the change in Dice and Jaccard are ought to be small. But this plays a vital role when one tries to create an atlas of MS patient brains. As the lesion location change longitudinally they will have a cumulative error effect on the created atlas which may deform the whole atlas in an unwanted way and it will be very hard to trace back the root of the problem. So small change in the performance can have significant impact.

Furthermore, in this work a lower resolution template was selected i.e. MNI152 2mm template to make the calculations faster (by an order of 2) in an ordinary machine. Some previous discrete results using higher resolution template i.e. MNI152 1mm template resulted in superior improvement of Jaccard and Dice coefficient. But for the scope of this project the lower resolution template was selected to evaluate the relative performance of different inpainting methods using different transformation matrix. If better performance is of essence then the same process can be repeated for the entire test subjects ensuing higher precision.

Future work may be extending the inpainting approach to different contrast modalities e.g. T2w. PDw and use our proposed algorithm in real MS patient data.

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