Multiple Sclerosis Lesion Inpainting Using Non-Local Partial Convolutions

Hao Xiongᵃ, Chaoyue Wangᶜ,*, Dacheng Taoᶜ, Michael Barnettᵃ,ᵇ, Chenyu Wangᵃ,ᵇ

ᵃBrain and Mind Centre, The University of Sydney, Sydney, Australia
ᵇSydney Neuroimaging Analysis Centre, Sydney, Australia
ᶜUBTECH Sydney Artificial Intelligence Centre and School of Information Technologies, The University of Sydney, Sydney, Australia

Abstract

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that results in focal injury to the grey and white matter. The presence of white matter lesions biases morphometric analyses such as registration, individual longitudinal measurements and tissue segmentation for brain volume measurements. Lesion-inpainting with intensities derived from surrounding healthy tissue represents one approach to alleviate such problems. However, existing methods inpaint lesions based on texture information derived from local surrounding tissue, often leading to inconsistent inpainting and the generation of artifacts such as intensity discrepancy and blurriness. Based on these observations, we propose non-local partial convolutions (NLPC) that integrates a Unet-like network with the non-local module. The non-local module is exploited to capture long range dependencies between the lesion area and remaining normal-appearing brain regions. Then, the lesion area is filled by referring to normal-appearing regions with more similar features. This method generates inpainted regions that appear more realistic and natural. Our quantitative experimental results also demonstrate superiority of this technique of existing state-of-the-art inpainting methods.

Keywords: Multiple Sclerosis, Lesions Inpainting, Non-Local Module, MRI, Partial Convolution

2010 MSC: 00-01, 99-00

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease that results in progressive damage to the central nervous system (CNS). MS is characterised by
focal inflammatory demyelinating lesions in both the grey and white matter, formation of which may be accompanied by acute episodes of neurological dysfunction or relapses. In the longer term, progressive axonal loss and gliosis, both within lesions and normal appearing white matter (NAWM), results in brain atrophy and the accumulation of physical and cognitive disability.

Accordingly, morphological measurements derived from magnetic resonance imaging (MRI) scans are extensively utilized to monitor disease progression [1, 2]. The link between brain volume loss and the evolution of motor and cognitive disability in MS is well established. Estimation of brain atrophy is therefore considered an important surrogate for, and predictor of, clinical disability.

The measurement of brain substructures, such as white matter, gray matter and cerebrospinal fluid (CSF), requires brain tissue segmentation on MRI images [3, 4, 5]. Although the T1 intensity of white matter lesions may vary according to the severity of tissue injury, similarity with grey matter intensities may result in erroneous substructure volume measurements [6, 7, 8, 9]. Misclassification of MS lesions therefore generates biased white and grey matter volume estimations, and necessitates the development of effective means to address the impact of lesions on morphological analysis.

Imaging processing methods currently use filling algorithms to inpaint lesions with normal appearing white matter-like intensities. Both local and global white matter lesion inpainting methods have been proposed [10]. Local inpainting methods base filling algorithms on surrounding tissue, whilst global methods employ an average intensity derived from the whole brain white matter. More recent models [11] utilize a normal tissue intensity distribution. By sampling the
distribution, the lesion is filled with the most probable white matter intensity. Based on this approach, Magon et al. [12] proposed slice by slice inpainting of the whole brain and Valverde et al. [13] performed lesion filling with mean intensity of two periplaque NAWM voxels.

The above approaches assume that lesions should, without exception, be filled with white matter like intensities. This hypothesis is flawed, as lesions may occur within grey matter or overlap white and adjacent grey matter. Additionally, lesion masks are generally provided by either manual labeling or automated methods. Automated lesion segmentation often results in misclassifications, and in some cases generates "lesions" that inappropriately involve the CSF. In such circumstances, the aforementioned lesion inpainting methods fail.

Rather than filling lesions with white matter like intensity only, Battaglini et al. [14] inpainted lesions with either white matter or grey matter using a histogram derived from peri-lesional white and grey matter, resulting in improved blending with neighbourhood normal appearing tissues. In the method described by Guizard et al. [15], lesions are first pre-filled with the median of intensity from surrounding normal-appearing tissues, and the most similar patches calculated using only the nearby regions. The same group subsequently proposed an iterative, concentric patch-based filling approach to preserve local anatomical information [16]. Similarly, Prados et al. [17] use neighbourhood patches to fill lesions with the most appropriate intensity; and exploit a minimal kernel-based convolution to achieve better inpainting effects.

In the general (non-medical) computer vision community, various inpainting techniques have been proposed to remove objects, texts or scratches from images using the remaining information in the image. Examples include (1) an "onion-peel" strategy that fills regions of interest (ROI) from an outermost to innermost concentric ring with reference to available patches [18]; (2) an exemplar-based method [19] that fills specific regions by directly copying similar patches extracted from the whole image; and (3) synthesis of ROI intensities with textures from matched patches by applying a Non-Local Means algorithm [20, 21]. Advances in deep learning have significantly enhanced inpainting effects. Initial deep learning based inpainting frameworks, in which networks are trained to fill ROI contents based on its surroundings, have been described by a number of groups [22, 23, 24, 25]. These techniques suffer from both pixel-wise reconstruction loss and adversarial loss, and tend to generate artifacts between inpainted and neighbourhood areas. The addition of more convolutions, which integrates distant areas into inpainting algorithms, has been applied [22, 26] to mitigate the appearance discrepancies introduced by deep learning; and further optimization undertaken [27] to minimize the difference between filled regions and their neighbourhood. However, increasing convolutional layers and applying optimization are computationally intensive and are substantially more time consuming.

Liu et al. [28] have recently described a model that uses so-called partial convolutions. Unlike traditional convolutional layers, which mask the convolution and thus perform convolution operations only on non-missing pixels, this method achieves remarkable inpainting effects by incorporating VGG-16 [29]
Figure 2: Network architecture. The network takes both the T1 brain image and associated lesion mask as inputs, and then outputs inpainted results. In the training stage, the lesion areas are randomly synthesized to generate training masks. Two non-local blocks are inserted after PConv13 and PConv14, respectively.

Based on the superiority of deep learning based techniques for inpainting of non-medical color images, we explore MS lesion inpainting under this framework (Fig. 1). Unlike arbitrary objects, which are morphologically heterogeneous, the human brain consists of defined, reproducible structures such as WM, GM and CSF. More specifically, ordinary images may contain arbitrary object types, such as scenery, faces, furniture that do not necessarily have uniform structure or properties. Therefore, when designing deep learning frameworks for image ROI inpainting, very few assumptions can be made. By contrast, the relative uniformity of brain structure and appearance among individuals permits the integration of a deep learning framework with a non-local module to facilitate brain lesion inpainting.

The non-local module links one brain voxel with spatially long range brain voxels. Hence, the response of one voxel is a weighted sum of the features from all relevant local (neighbourhood) and distant (beyond neighbourhood) voxels. By modeling long range dependencies, the algorithm is able to inpaint lesion areas with reference to the whole brain area rather than only the local neighbourhood. Therefore, we propose a model with the following distinguishing features: 1) the model does not make any assumption that the lesion area is/should be filled with white matter like intensity; 2) the model integrates global brain information based on the consistency of brain structure, rather than using neighbourhood texture as the key factor to determine the filled intensity; 3) when a lesion mask that erroneously overlaps with normal tissues (such as CSF) is supplied as an input, our algorithm is able to inpaint the lesion ROI with appropriately disposed normal tissue intensities. In other words, the algorithm is able to maintain normal tissue architecture rather than simply filling lesion masks ROIs with white matter like intensity. Synthetic lesions can be generated by non-linear co-registration of real FLAIR image derived MS lesion masks with healthy subject MRI T1 images to validate the technique and provide a ready-made ground truth for comparative experiments. Herein, we demonstrate the effectiveness and efficiency of MS lesion inpainting using these methods.
2. Material and methods

Our proposed inpainting model is stacked by partial convolutions and simultaneously integrates several non-local blocks. We first explain concepts of partial convolution and non-local block, and then introduce network architecture and implementation.

2.1. Partial convolution

In general, the partial convolution operation proposed by Liu et al. \cite{28} consists of two parts: a partial convolutional layer and mask updating. Suppose $X$ refers to the feature values or intensity of the MRI slice, $M$ is the binary mask representing zero and one as lesion and normal brain tissue areas, respectively. The partial convolution is defined as:

$$
x = \begin{cases} 
W^T (X \odot M) \frac{\text{sum}(1)}{\text{sum}(M)} + b, & \text{if } \text{sum}(M) > 0 \\
0, & \text{otherwise}
\end{cases},
$$

where $W$ and $b$ are convolutional weights and bias respectively. Meanwhile, $1$ has the same size as $M$ and are filled with all ones. By taking mask $M$ into account, the output of the partial convolution only relies on unmasked values.

Concurrently, mask $M$ is updated as follows:

$$
m = \begin{cases} 
1, & \text{if } \text{sum}(M) > 0 \\
0, & \text{otherwise}
\end{cases}.
$$

Here, $x$ and $m$ are the updated feature map and updated mask from the partial convolution layer, respectively.

2.2. Non-Local block

Traditional convolution operations focus on the cues within the ROI neighbourhood and thus ignore global information. Even with a large receptive field, convolution operations are still based on local information. In contrast, the non-local module aims to perform inpainting by taking long distance cues into consideration. More specifically, given a specific location within brain slice, the non-local module will compute the responses between this location and its counterparts within the whole image, exploiting the relative homogeneity and internal correlation of brain structure.

Given feature maps $x \in \mathbb{R}^{C \times N}$ from a partial convolution layer, the non-local block then transforms $x$ into three feature spaces $f$, $g$ and $h$, where $f(x) = W_f x, g(x) = W_g x$ and $h(x) = W_h x$. Here, $W_f, W_g$ and $W_h$ are weight matrices to be learned and such linear operations can be implemented as $1 \times 1$ convolutions.

The self-attention module subsequently requires $f(x)$ and $g(x)$ for attention map calculation. More specifically, the attention map can be obtained by:

$$
a_{ji} = \text{softmax}(f(x_i)g(x_j)),
$$

5
Figure 3: The attention maps of color coded queries. **Top Row:** Brain slices with query locations **Bottom Row:** attention maps of red, green and blue dot queries are shown from left to right for each image. **Red Dot:** query on white matter or thalamus **Green Dot:** query on grey matter **Blue Dot:** query on background (regions outside brain area). Here, the size of attention map is 64×64, while the size of testing slice is 256×256. Note that the whitest regions in the grayscale attention map are best correlated to the queries and vice versa. Despite differing resolution between the attention map and testing slice, the whitest regions within attention maps are appropriately located in regions that correspond to the respective queries. The attended areas all are within the global domain rather than a local region.

Here, \( a_{ji} \) is namely the softmax operation along the dimension \( j \). Evidently, the softmax operation here measures the similarity between \( i^{th} \) and \( j^{th} \) locations in \( x \). The self-attention form is finally expressed as:

\[
    s = a h(x),
\]

(4)

This is to say that the self-attention module computes a response at a location by attending all positions and taking their weighted average in an embedding space. Subsequently, the self-attention module is incorporated into the non-local block as:

\[
    y = W_s s + x,
\]

(5)

where \( y \) refers to the non-local block and \( W_s \) is the weight matrix of the 1×1 convolution to be learned. Initially, \( W_s \) is set as zero and thus \( y \) is exactly \( x \), which means that the inpainting task only relies on neighbourhood cues initially. After gradually updating \( W_s \), more non-local evidence is considered in the training and future inpainting. In our model, the non-local block is integrated with a partial convolution layer. As shown in the first row of Fig. 3, the red, green, blue dots represent query locations within the white matter, grey matter and background (regions outside brain area) respectively. In the second row, the corresponding attention maps of the color coded query dots are displayed. Note that the size of each attention map here is 64×64 (see section 2.3 for further details), while the size of input MRI slice is 256×256. Meanwhile, the most-attended regions are the whitest areas in the attention map and vice versa. Though the size of the attention map and input slice are discrepant, the attended area approximates its expected anatomic counterpart. For example,
attended regions for grey matter queries are generally located at the periphery of the brain in areas that approximate the location of the cortex; and attended regions for background queries are consistently located outside the brain area in attention maps. Moreover, Fig. 4 illustrates the inpainting effects with and without the non-local module.

2.3. Network design and implementation

Our network is based on the architecture described by Liu et al. [28] (Table 1), and exploits partial convolutional layers to stack the network rather than traditional convolutional layers. Both the encoder and decoder in the network has 8 layers. The feature maps and binary masks from the encoder stage are concatenated by skip links into the decoder stage. Furthermore, the size of the binary mask is exactly matched with the respective input brain slice and will be updated in the following encoder and decoder stages. The values of weight
matrix and bias for the binary mask are initially set as 1 and 0 respectively, and kept fixed during training. Likewise, the values of weight matrices and bias for \( f \), \( g \) and \( h \) are initially set as 1 and 0, respectively, but only bias is fixed during training.

However, the integration of a non-local module into the network is computationally intensive. In order to facilitate computational efficiency, the number of channels with feature spaces \( f \), \( g \) and \( h \) is therefore reduced to half of the number of channels of \( x \) in our method. Meanwhile, in Eq.\( \ref{eq:wv} \) the number of channels of \( s \) can be increased with \( W_s \) so as to match the number of channels of \( x \). Additionally, a max pooling layer is applied after \( g \) and \( h \) to speed computation. In our case, the stride of max pooling layer is 2.

In the experimental work presented, the following principals are applied with respect to the integration of non-local blocks:

1. Non-local blocks should be inserted in the decoder stage, where they are closer to the output of the network.
2. The more non-local blocks embedded within the network, the more accurate the inpainting effects are.

Based on Eq.\( \ref{eq:nonlocal} \) it is optimal to insert two non-local blocks directly after PConv13 and PConv14, respectively. Though some techniques are applied to speed up computation, the maximum number of added non-local blocks is 2. PConv15 is physically the closest layer to the output layer but this layer’s feature maps are relatively larger than those relating to PConv13 and PConv14.

Therefore, computational efficiency is improved by not inserting a non-local block after PConv15, while not sacrificing model accuracy at same time. The training set contains approximately 50800 slices; the initial learning rate is set as 0.00005 and the batch size as 10. The learning rate for fine-tuning is set as 0.00001. There are approximately 125 and 10 epochs for training and fine-tuning respectively.

### 2.4. Loss function

The output of the above network \( I_{\text{output}} \) is fed into the following loss function for more accurate per-pixel reconstruction, where the loss function is defined according to Liu et al. \[28\]:

\[
L_{\text{total}} = L_{\text{valid}} + 6L_{\text{hole}} + 0.05L_{\text{perceptual}} + 120L_{\text{style}} + 0.1L_{\text{tv}},
\]

where \( L_{\text{valid}} \) and \( L_{\text{hole}} \) are the loss terms aiming to enhance per-pixel reconstruction accuracy of the whole brain slice including any inpainted region.

The terms \( L_{\text{valid}} \) and \( L_{\text{hole}} \) are defined as follows:

\[
L_{\text{hole}} = \frac{1}{N_{I_{\text{gt}}}} \| (1 - M) \odot (I_{\text{out}} - I_{\text{gt}}) \|_1,
\]

\[
L_{\text{valid}} = \frac{1}{N_{I_{\text{gt}}}} \| M \odot (I_{\text{out}} - I_{\text{gt}}) \|_1,
\]

where \( I_{\text{gt}}, M \) and \( N_{I_{\text{gt}}} \) respectively represent ground truth slice, binary lesion mask (0 represents lesion area) and the number of voxels in the slice.
Partial Convolution based Network

| Encoder          | Decoder |
|------------------|---------|
| PConv1           | Concat1(NearestUpSample1/ PConv7) |
|                  | PConv9  |
| PConv2           | Concat2(NearestUpSample2/ PConv6) |
|                  | PConv10 |
| PConv3           | Concat3(NearestUpSample3/ PConv5) |
|                  | PConv11 |
| PConv4           | Concat4(NearestUpSample4/ PConv4) |
|                  | PConv12 |
| PConv5           | Concat5(NearestUpSample5/ PConv3) |
|                  | PConv13 |
| PConv6           | Concat6(NearestUpSample6/ PConv2) |
|                  | PConv14 |
| PConv7           | Concat7(NearestUpSample7/ PConv1) |
|                  | PConv15 |
| PConv8           | Concat8(NearestUpSample8/ Input) |
|                  | PConv16(Output Layer) |

Table 1: **Partial Convolution based Network**. PConv: Partial Convolution Layer Concat: concatenate the previous nearest neighbour upsampled results with feature maps from corresponding PConv in encoder stage. Two non-local blocks are inserted directly after PConv13 and PConv14, respectively.

In addition to the direct output ($I_{out}$) for pixel wise reconstruction, $L_{perceptual}$ and $L_{style}$ are defined to ensure that the inpainted areas have a more realistic and natural texture and structure.

The definition of $L_{perceptual}$ is as follows:

$$L_{perceptual} = \sum_{p=0}^{P-1} \frac{\|\psi_{p}^{I_{out}} - \psi_{p}^{I_{gt}}\|_1}{N_{p}^{I_{gt}}} + \sum_{p=0}^{P-1} \frac{\|\psi_{p}^{I_{comp}} - \psi_{p}^{I_{gt}}\|_1}{N_{p}^{I_{gt}}}.$$  

(8)

Here, $I_{comp}$ is actually $I_{out}$ but with non-lesion area set to ground truth. $N_{p}^{I_{gt}}$ is the number of elements in $\psi_{p}^{I_{gt}}$. The inclusion of $L_{perceptual}$ accepts feature vectors by projecting $I_{out}$, $I_{gt}$ and $I_{comp}$ into a high level feature space $\psi_{p}^{I_{gt}}$ with a pretrained VGG-16 network. The layers pool1, pool2, pool3 in VGG-16 are utilized for feature extraction in our work. Furthermore, since the VGG-16 network requires an image of at least $236 \times 236$, all brain slices in our model are padded to size $256 \times 256$ for training and testing. The 3D median filter is applied to alleviate minor inconsistency between slices.

Similarly, the loss term $L_{style}$ is defined as:

$$L_{styleout} = \sum_{p=0}^{P-1} \frac{1}{C_{p}C_{p}} \|K_p((\psi_{p}^{I_{out}})^T(\psi_{p}^{I_{out}}) - (\psi_{p}^{I_{gt}})^T(\psi_{p}^{I_{gt}})))\|_1.$$  

(9)
where the high level features $\psi_{I_p}^{\text{comp}}$ is of shape $(H_p W_p) \times C_p$ ($H_p, W_p, C_p$ are height, width and channel number of slice $I_p$), resulting in a $C_p \times C_p$ Gram matrix, and $K_p$ is the normalization factor $1/C_p H_p W_p$.

Lastly, $L_{tv}$ represents the total variation term for smoothing penalty.

\[
L_{tv} = \sum_{(i,j) \in R, (i,j+1) \in R} \frac{\|I_{comp}^{i+1,j} - I_{comp}^{i,j}\|_1}{N_{I_{comp}}} + \sum_{(i,j) \in R, (i,j+1) \in R} \frac{\|I_{comp}^{i+1,j} - I_{comp}^{i,j}\|_1}{N_{I_{comp}}},
\]

where $R$ denotes the region of 1 pixel dilation of the lesion area. $N_{I_{comp}}$ is the number of voxels in $I_{comp}$. We adopt the same hyperparameter values of loss term weights as described by Liu et al. [28].

2.5. Data

Three different MRI datasets were used in training and testing stages.

1. IXI dataset: a publicly available collection of 665 MR images from normal, healthy subjects (https://brain-development.org/ixi-dataset/). The IXI data was acquired on three different MRI scanners (Philips 3T system, Philips 1.5T system, GE 1.5T system). The acquisition protocol for each subject includes the following sequences: T1, T2, proton density (PD), and diffusion-weighted images (15 directions). Here, we use only T1 images, but our method can be applied to other MRI sequences. Brain volumes were randomly selected for training (n=300) and testing (n=50). All brain volumes were intensity normalized with mean and variance before training and testing. Synthetic lesions, generated by non-linear co-registration with MS lesion masks (see below), were applied to the 50 selected testing volumes and regarded as ground truth for subsequent evaluation.

2. The second dataset consists of MRI scans from 20 patients with relapsing-remitting multiple sclerosis (RRMS). T1-weighted sequences were acquired on a 3T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) with the following parameters: FOV 256mm, slice thickness 1mm, TE 2.7ms, TR 7.2ms, Flip angle 12, Pixel spacing 1mm. Acquisition Matrix (Freq. Phase) is 256 x 256, which results in 1mm isotropic acquisition voxel size. The reconstruction matrix is 256 x 256. This data, which has no ground truth, was utilized for demonstration in Fig. 1, Fig. 3 and Fig. 4.

3. The third dataset contains MRI scans from 50 patients with RRMS and is primarily exploited for deriving lesions masks for subsequent generation of synthetic lesions on T1 images from the IXI healthy control testing dataset. Sagittal FLAIR CUBE (pre-contrast) sequences were acquired on a 3T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) with the following parameters: FOV 256mm, slice thickness 1.2mm, TE 163ms, TR 8000ms,
TI 2180ms. Acquisition Matrix (Freq. Phase) is $256 \times 244$. Additionally, pre-contrast axial T1-weighted (IR-FSPGR) sequences were acquired with the following parameters: FOV 256mm, slice thickness 1mm, TE 3.2ms, TR 8.1ms, TI 900ms, pixel spacing 1mm. Acquisition Matrix (Freq. Phase) is $256 \times 256$, which results in 1mm isotropic acquisition voxel size. The reconstruction matrix is $256 \times 256$. All lesion ROIs for MS cases were performed semiautomatically on FLAIR images using JIM6.0 (https://www.xinapse.com) by an experienced MS neuroimaging analyst.

All datasets were acquired cross-sectionally and included both female and male subjects.

2.6. Data and code availability statement

Code developed in the course of this work and aggregated data are available on direct request to the corresponding author and may be re-used with the authors permission and acknowledgement.

3. Results

We compared four lesion inpainting algorithms on T1 images, including 1) the lesion filling tool included in FSL v6.0 [30]. FSL is a comprehensive library of analysis tools for FMRI, MRI and DTI brain imaging data; 2) multi-time-point modality-agnostic lesion filling method (MMLF). To the best of our knowledge, MMLF is the most recently described lesion filling method in the medical image field. It is publically available (niftyweb.cs.ucl.ac.uk/); and 3) partial convolutions (PC) based inpainting method (PC). PC based inpainting method is considered state-of-the-art in the computer vision community. Its code is not released and was implemented by ourselves; and 4) our proposed non-local partial convolutions (NLPC) inpainting method. None of these methods rely on lesion area information to generate inpainted voxels. Therefore, given synthetic lesion masks, the values of synthetic lesion area were set as zeros before inpainting.

3.1. Qualitative evaluation

In this experiment, white matter lesions masks derived from MS FLAIR images were used to create and inpaint synthetic lesions generated on non-linearly coregistered T1 images from healthy controls. Since visible T1 hypointensities are usually a subset of T2 (FLAIR) hyperintensities, the FLAIR-derived manually labelled lesion mask may involve isointense regions on matching MS T1 images. Non-linear co-registration of MS lesion masks and healthy control T1 images is also likely to produce synthetic lesions that erroneously overlap with tissues other than white matter. Synthetic lesions were generated on T1 brain images from 50 healthy controls and inpainted with FSL, MMLF, PC and NLPC, respectively. Inpainted images from all 4 methods were visually inspected and blindly rated by a neuroimaging expert (MB) based on similarity to the ground truth (original) images. The NLPC method best approximated the ground truth in the majority (28/50) of cases reviewed. In the remaining 22/50
cases, MMLF was chosen as the method that best approximated the ground truth. Fig. 5, Fig. 6 and Fig. 7 provides examples of visual comparison of our inpainting method with existing methods.

3.2. Quantitative evaluation

Since MRI scans acquired from patients with MS have no lesion-region ground truth, most methods [13, 16, 17] have employed quantitative analysis using synthetically generated lesions in MRI slices. In our case, the original, pre-lesional tissue ROI intensities from 50 healthy subjects were regarded as the ground truth for artificial lesion generation and comparison. We employed several quantitative approaches to facilitate comparison of the MMLF, FSL, PC inpainting techniques, and our own method. The mean square error (MSE) was adopted to measure the difference between the inpainted and ground truth intensities; a smaller MSE value signifies more realistic filled intensities. As a primary goal of lesion inpainting is improve the accuracy of brain substructure volume measurement, we also evaluated WM, GM, and CSF volumes using SNIAX on the native healthy control T1 images (ground truth) and images with synthetic lesions inpainted with each technique. Closer approximation to
the ground truth volumes therefore denotes a more accurate inpainting technique. The results of quantitative assessment are shown in Table 2.

3.2.1. Synthetic lesion generation

The process of lesion generation is as follows:

1. Whole brain tissue was extracted from all images with the Brain Extraction Tool (BET). Note that the tool BET is part of FSL.

2. MS brain volumes were firstly affine and then non-rigidly registered to healthy brain volumes.

3. Binary lesion masks derived from MS FLAIR images were registered to the healthy T1 images with estimated non rigid transformations. (the CSF mask from SIENAX was used to avoid overlap of the lesion mask with CSF)

4. Synthetic lesion masks generated on healthy subject T1 images were constrained within the relevant whole brain mask derived in Step 1.
Lesion ROI FSL PC MMLF NLPC

Figure 7: The axial and zoomed views of the T1 slice with embedded synthetic lesions. Note the noisy samples generated by FSL and PC methods, and blurred boundaries obtained by MMLF method.

Lesion inpainting is not dependent on the intensities of lesion area to be filled; therefore, none of the techniques generate noise of any kind within the region of lesion mask.

3.2.2. Synthesisation error

The mean square error is defined as:

\[ \text{MSE} = \frac{1}{N} \sum_{i} (I_T - I_0)^2, \]  

where \( n \) is the number of testing volumes and \( N \) is the number of lesion voxels. \( I_T \) and \( I_0 \) refer to the intensities of ground truth volume and inpainted volume, respectively.

3.2.3. WM, GM, CSF Volume Error

SIENAX-based [31] segmentation was performed on healthy control T1 brain volumes, yielding ground truth WM, GM and CSF volumes respectively. Following insertion of synthetic lesions into T1 brain slices and lesion inpainting by each method, SIENAX-derived WM, GM and CSF volumes were re-estimated. To measure the impact of lesion inpainting using each method, we measured
the similarity of substructure volumes derived from T1-inpainted slices to those derived from native (ground truth) images by calculating both the mean error (ME) and mean absolute error (MAE). The mean error is defined as:

\[
ME = 100 \frac{V_T - V_0}{V_0},
\]

where \(V_0\) and \(V_T\) are ground truth volume and the volume estimated after inpainting with different methods respectively.

| FSL | PC | MMLF | NLPC |
|-----|----|------|------|
| MSE | 0.000915 (0.00389) | 0.001647 (0.00602) | 0.000520 (0.00180) | **0.000482 (0.00119)** |
| ME(GM) | -0.0526 (0.0734) | -0.0638 (0.0928) | -0.0658 (0.0721) | **-0.0503 (0.0791)** |
| ME(WM) | -0.0526 (0.0734) | -0.0638 (0.0928) | -0.0658 (0.0721) | **-0.0503 (0.0791)** |
| MAE(GM) | 189.023 (232.728) | 227.735 (274.173) | 171.854 (191.598) | **150.383 (189.463)** |
| MAE(WM) | 230.260 (287.786) | 281.297 (368.709) | 270.596 (290.473) | **217.103 (308.794)** |
| MAE(CSF) | 58.5919 (88.608) | 60.615 (76.809) | 73.296 (85.930) | **130.388 (195.675)** |

4. Discussion

The proposed non-local partial convolutions (NLPC) lesion inpainting method, which exploits a non-local module under the framework of deep learning, demonstrated quantitative and qualitative superiority over the FSL inpainting tool, based on local intensity histogram information; MMLF, a state-of-the-art method in neuroimaging that fills lesions with the most plausible texture within a larger neighbourhood; and PC, the most recent deep learning based inpainting approach in the computer vision field.

Blinded qualitative assessment confirmed the superiority of our method (NLPC) for inpainting synthetic lesions embedded in healthy control data (examples shown in Figs. 5 - 7). The proposed method is therefore not affected by neighbouring structures; rather, it learns to fill local lesions by referring to global structures and texture information. As illustrated in Figs. 5 - 7, the inpainted results of other methods are more or less affected by neighbourhood, especially when the white matter lesion is close to either the ventricle or grey matter. Quantitative analysis (Table 2) showed that the proposed method generated the smallest MSE and therefore the most realistic inpainting result of all four techniques. Moreover, ME and MAE values show that the estimation of
GM and WM volumes using SIENAX analysis of T1 brain volumes inpainted by our method are most accurate.

During training, our method is inclined to focus on learning the feature characteristics of WM and GM. This is because CSF takes up much smaller portion of brain compared to WM and GM. As a result, synthetic lesions that overlap CSF may have a greater likelihood of being filled with white matter-like tissue intensities/texture, rather than CSF. It is unlikely that grey matter tissue-like intensities will be generated by our model, since the non-local module will judge that CSF regions to more closely approximate white matter than grey matter. As shown in figures 5 and 6, FSL and PC tend to generate noisy samples. In terms of their texture, the noisy samples were potentially more likely to be classified as CSF by comparison with the other methods. Therefore, FSL and PC performed best in terms of CSF volume estimation. However, the portion of the synthetic lesion mask that presents within the CSF is extremely small and unlikely to influence the GM, WM evaluation. The use of our model in real MS images, where the lesion mask will never overlap CSF, also ameliorates this concern.

Our training data comprised brain images derived from healthy controls. Brain atrophy rates in untreated patients with MS are significantly higher than age-matched healthy controls. However, for the purpose of lesion inpainting in MS cases, the trained non-local attention globally searches within non-lesion areas by measuring feature and structural similarity between non-lesion and lesion areas. Referencing the global non-lesion areas, our model subsequently fills lesion areas with healthy tissue-like textures. Lesion inpainting using this method is therefore unaffected by the presence or absence of brain volume loss.

5. Conclusion

We propose a new deep learning model for realistic lesion inpainting in MRI slices by exploiting the non-local module. Rather than considering the neighbourhood texture for lesion filling, our method inpaints lesion areas with the most plausible intensities by observing the structure and texture information contained within the whole image. To achieve this, the non-local module compares similarities between the features within lesion regions and remaining brain areas. Although some existing methods take into account non-local information, they are limited by algorithms that search for similar patches within a constrained bounding box, rather than the whole domain. As such, these methods prove inferior to those described in this work. Moreover, integrating the non-local module under the framework of deep learning generates an effective algorithm that outperforms traditional non-local based methods and can be incorporated into image analysis pipelines for more accurate quantitative assessment of brain substructure volumes.
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