Site Generalization: Stroke Lesion Segmentation on Magnetic Resonance Images from Unseen Sites

Weiyi Yu, Zhizhong Huang, Graduate Student Member, IEEE, Junping Zhang, Senior Member, IEEE, and Hongming Shan, Senior Member, IEEE

Abstract—There are considerable interests in automatic stroke lesion segmentation on magnetic resonance (MR) images in the medical imaging field, as strokes are the main cause of various cerebrovascular diseases. Although deep learning-based models have been proposed for this task, generalizing these models to unseen sites is difficult due to not only the large intersite discrepancy among different scanners, imaging protocols, and populations but also the variations in stroke lesion shape, size, and location. Thus, we propose a U-net–based segmentation network termed SG-Net to improve unseen site generalization for stroke lesion segmentation on MR images. Specifically, we first propose masked adaptive instance normalization (MAIN) to minimize intersite discrepancies, standardizing input image MR images from different sites into a site-unrelated style by dynamically learning affine parameters from the input. Then, we leverage a gradient reversal layer to force the U-net encoder to learn site-invariant representation, which further improves the model generalization in conjunction with MAIN. Finally, inspired by the “pseudosymmetry” of the human brain, we introduce a simple, yet effective data augmentation technique that can be embedded within SG-Net to double the sample size while halving memory consumption. As a result, stroke lesions from the whole brain can be easily identified within a hemisphere, improving the simplicity of training. Experimental results on the benchmark Anatomical Tracings of Lesions After Stroke (ATLAS) dataset, which includes MR images from 9 different sites, demonstrate that under the “leave-one-site-out” setting, the proposed SG-Net substantially outperforms recently published methods in terms of quantitative metrics and qualitative comparisons.

Index Terms—Stroke lesion segmentation, multisite learning, domain generalization, convolutional neural network.

I. INTRODUCTION

As one of the most common cerebrovascular diseases in humans, strokes are the main cause of adult disability and the second leading cause of death worldwide [1]. Neuroimaging can be used to obtain measurements of brain structures, aiding radiologists in understanding and predicting post-stroke brain changes [2]. Currently, T1-weighted magnetic resonance imaging (MRI), a noninvasive neuroimaging technology, is widely used to examine structural changes in the patient’s brain after a stroke. Manual delineation of the boundary of stroke lesions is time-consuming and cumbersome; different radiologists may delineate various boundaries for the same lesion, and the same radiologist may not be able to reproduce their previous segmentations. Therefore, automatic stroke lesion segmentation has become a popular research topic over the past decade.

Multiple studies have investigated medical image segmentation [3]–[5]. Recently, deep learning-based approaches have shown extraordinary potential in medical image segmentation tasks, especially for convolutional neural networks (CNNs) [6]–[11]. Here, we briefly survey works related to stroke lesion segmentation on the benchmark ATLAS dataset [12].

Given that a limited number of medical samples severely influence the performance of CNNs, some researchers divided MR images into 2D slices and used them as the input to 2D CNNs. X-Net, which includes a nonlocal attention module [13], and MSDF-Net, which involves a multiscale deep fusion module [14], were proposed to capture long-range dependencies. Such methods [13]–[15] provide more feature relationships for stroke lesion segmentation; nonetheless, 2D CNNs capture few interslice dependencies.

To integrate inter-slice and intra-slice dependencies, 3D CNNs are commonly employed. Some researchers fused 2D and 3D CNNs to establish methods, such as D-U-Net [16], etc. [17]–[19]. In addition to model architecture, efforts have also been made to improve the training strategy. Based on 3D residual U-net, a zoom-in&out training strategy [20] was proposed that first trains the model on images with small lesion sizes, and then fine-tunes the model on images with large lesion sizes. The input of MI-U-Net [21] is concatenated with brain parcellations as prior knowledge, which helps 3D U-net perform more accurate stroke segmentation. Nevertheless, the registration step before deep learning requires considerable time cost. Though 3D CNNs generally perform better than 2D CNNs, they typically require more training data to prevent overfitting. The situation becomes even worse when the different site presents different variations in the multisite scenario.

The shape, size, and location of the lesions can vary substantially, leading to model learning difficulties, especially when there are few training images. Fig. [1] shows some sample lesions with large variations. Many efforts mentioned above have been made to address the problem of stroke lesion variability. However, the existing methods mentioned above were established assuming that MR images from different sites have consistent distributions. Thus, their generalization to unseen sites tends to be substantially challenging. Differences

W. Yu and H. Shan are with the Institute of Science and Technology for Brain-inspired Intelligence and MOE Frontiers Center for Brain Science, Fudan University, Shanghai, 200433, China, and also with the Shanghai Center for Brain Science and Brain-inspired Technology, Shanghai 201210, China (e-mail: wyu20@fudan.edu.cn; hmshan@fudan.edu.cn).
Z. Huang and J. Zhang are with the Shanghai Key Lab of Intelligent Information Processing and the School of Computer Science, Fudan University, Shanghai 200433, China (email: zhuang19@fudan.edu.cn; jzpzhang@fudan.edu.cn).

Z. Huang and J. Zhang are with the Shanghai Key Lab of Intelligent Information Processing and the School of Computer Science, Fudan University, Shanghai 200433, China (email: zhuang19@fudan.edu.cn; jzpzhang@fudan.edu.cn).
among MR scanners, imaging protocols, and variations in the patient population, greatly affect model generalization to unseen sites.

Therefore, there is an urgent need for stroke lesion segmentation methods that would allow a trained model to generalize well to a new, unseen site. In practice, it would also be desirable to obtain a trained model that can work well with data from a new hospital or site without further collecting extra data to perform fine-tuning. This is essentially related to multisite or multidomain learning in the medical image field, such as domain adaptation [22], [23]. Although being widely used in biomedical tasks [24], [25], domain adaptation aims to maximize the performance on a given target domain while domain generalization aims to maximize the generalization to an unseen domain, which is the problem we are tackling for stroke lesion segmentation.

On the one hand, among different strategies for multisite data harmonization, histogram matching and z-score normalization are the most commonly used preprocessings [27] to achieve multisite learning. Histogram matching generally matches the histogram distribution of training data to that of the testing data; however, it requires the latter to be known before training, a problem applicable to domain adaptation but not to domain generalization. Z-score normalization consists of subtracting the mean intensity of the region of interest (covered by brain mask) from each voxel value and dividing it by the corresponding standard deviation. Our experimental results also show that z-score normalization is helpful. However, its effectiveness remains limited and is inconsistent across data from different sites.

On the other hand, learning domain-invariant representation through adversarial training gains increasing attention. One simple, popular way is the gradient reversal layer (GRL) [28], [29]. It treats domain invariance as a classification problem and directly maximizes the loss function of the domain classifier by reversing its gradients, which matches the marginal distributions across domains. It has been used widely in various comparative studies [30]–[33] and domain adaptation [34], [35]. However, there is little attention being paid on the site generalization for stroke lesion segmentation.

In summary, for the stroke lesion segmentation, when processing the ATLAS dataset, which is composed of MR images from 9 sites, the existing methods do not consider the generalization of the trained model to a new, unseen site. And the 9 sites involved also present challenging for multisite learning.

Therefore, aiming to overcome the challenges mentioned above, we propose SG-Net, a U-net-based stroke lesion segmentation network for improving unseen site generalization [36] on MR images. SG-Net integrates data harmonization and domain-invariant representation learning to boost the model generalization to unseen sites. Specifically, we propose a masked adaptive instance normalization (MAIN) method prior to feeding the input images to U-net. This method dynamically standardizes the input MR images into a site-unrelated style. We implement MAIN as a linear transformation here because although the overall intensity values of MR images between different sites are significantly different, the intensity values of T1-weighted MR images are, by nature, relatively consistent. For instance, the intensity values of white matter are always higher than those of gray matter and lower than those of the cerebrospinal fluid in the brain. Compared with conventional z-score normalization, MAIN learns better affine parameters from input images to dynamically standardize them for better generalization. Moreover, we leverage the gradient reversal layer to enforce the encoder of U-net to learn site-invariant representation, further improving model generalization to unseen sites in conjunction with MAIN.

Inspired by the “pseudosymmetry” structure of the human brain, we also introduce a simple, yet effective data augmentation technique that can be embedded within SG-Net to double the number of samples while halving memory consumption. As a result, stroke lesions from the whole brain can simply be identified within single cerebral hemispheres, making it much easier to locate the lesions during training. Finally, it is worth noting that, to date, no studies have yet to perform leave-one-site-out validation [37] on the ATLAS dataset.

The contributions of this paper are summarized as follows.

1) We propose SG-Net, a U-net-based stroke lesion segmentation to improve model generalization to unseen sites. To the best of our knowledge, this is the first attempt at site generalization for stroke lesion segmentation.

2) We propose a masked adaptive instance normalization (MAIN) method, which dynamically standardizes the input MR images into a site-unrelated style by learning adaptive affine parameters to minimize the intersite discrepancy among different sites. The learning of MAIN is coupled with a gradient reversal layer to enforce the encoder of U-net to learn a site-invariant representation.

3) We present a simple, yet effective data augmentation technique that leverages the “pseudosymmetry” structure of the human brain. As a result, the number of samples is doubled, and the memory consumption is halved, making the training much easier for locating the lesions.

4) Through extensive experiments on the benchmark Anatomical Tracings of Lesions After Stroke (ATLAS) dataset that includes MR images from nine different sites, the results show that under the “leave-one-site-out” setting, the proposed SG-Net considerably outperforms recently published methods for stroke lesion segmentation in terms of quantitative metrics and qualitative comparisons. Moreover, the trained models generalize well to unseen external sites.

Fig. 1. Example T1-weighted MR images of stroke lesion. Stroke lesions present with large variations in terms of shape, size, location and number.
II. METHODOLOGY

We present SG-Net, as illustrated in Fig. 2, to improve stroke lesion segmentation model generalization to unseen sites. To that end, we use U-net as the backbone and propose MAIN to dynamically standardize the input MR images into a site-unrelated style, minimizing the large intersite discrepancy. We leverage the site classifier with a gradient reversal layer to guide the learning of the encoder of the U-net and MAIN for site-invariant representation. In addition, we also introduce a simple, yet effective data augmentation technique inspired by the “pseudosymmetry” structure of the human brain, which can be embedded within SG-Net to double the number of samples while halving memory consumption and making training much easier for locating lesions.

We now describe the key components in detail, followed by the detailed network architecture and the loss function.

A. Preprocessing

First of all, the released ATLAS dataset has been defaced, intensity normalized, and normalized to standard (MNI-152) space (for more details please refer to the normalization steps in [12]). Before the MR images are fed into the networks, we use z-score normalization to normalize the MR images based on 2D brain slices following the conventional preprocessing step. Specifically, given brain mask $B$ of input MR image $I$ of size $w \times h$, we first calculate the mean $\mu_{zs}$ and the standard deviation $\sigma_{zs}$ of the intensities within $B$. The resulting z-score–normalized image $I_{zs}$ is defined as:

$$I_{zs}^{ij} = \frac{(I^{ij} - \mu_{zs})}{\sigma_{zs}},$$

(1)

where $ij$ represents the position of the pixel in the MR image.

B. Masked Adaptive Instance Normalization

Although the z-score–normalized image serves as standard input for many tasks, the same tissue of the human brain may still present with different values at different sites, leading to poor generalization to a new unseen site. The limited generalization of traditional z-score normalization techniques motivates us to propose MAIN, a dynamic neural network [38] that can dynamically learn how to normalize different input images. MAIN leverages two affine transformation parameters $\gamma$ and $\beta$ that can be embedded within SG-Net to double the number of samples while halving memory consumption and making training much easier for locating lesions.

We assume the affine transformation parameters $\gamma$ and $\beta$ are learned from the masked z-score–normalized image $B \odot I_{zs}$, where we only care about the brain region. The output of MAIN can be represented as:

$$I_{zs}^{main} = (\gamma \times I_{zs}^{ij} + \beta) \odot B,$$

(2)

Fig. 2. Illustration of the proposed SG-Net for brain stroke lesion segmentation. (a) Masked adaptive instance normalization standardizes the MR images into a site-unrelated style. (b) The proposed data augmentation method simplifies the training for locating the lesions. (c) U-net is used as the backbone. (d) Site classifier with gradient reversal layer (−Δ) performs site-invariant learning.
Fig. 2(a) illustrates the basic structure of the proposed MAIN: a lightweight network with two heads is designed to learn the two affine transformation parameters from the masked brain region. More specifically, using a 256-dimensional vector that supposedly contains the statistical information about the intensity distribution from the brain, the two heads learn how to normalize the MR images into a site-unrelated style by making the tissues of the outputs have similar values. The detailed network architecture of MAIN is shown in Section II-E.

Relation with instance normalization. Compared with traditional instance normalization, MAIN is more suitable for brain MR images. The mean and the standard deviation are computed in the region of interest formed by the brain mask. Moreover, our MAIN is a simple, lightweight neural network module and does not impose an excessive computational burden.

Relation with adaptive instance normalization (AdaIN). In contrast to AdaIN [39], which aligns the mean and the variance of the content features with those of the style features [39], our affine transformation approach is more generalized. AdaIN can be seen as a special case of our method that involves setting the weight and bias from the images of the target style, which requires accessing the images from the target site during training. Our method is a generalized and adaptive framework for dynamically normalizing MR images, allowing for arbitrary and unseen sites’ images, more widely used in clinical applications.

C. Data Augmentation

Although the training of MAIN can ensure that the model learns a site-unrelated style of MR images for better generalization, the small size of the training samples in this study limits the generalizability, particularly in cases when strong variations in the shape, size, and location of the stroke lesions are present.

Inspired by the “pseudosymmetry” of the human brain, it is possible to make learning much easier for locating stroke lesions. Instead of locating the lesion from the whole brain image, we propose a simple, yet effective data augmentation method that can be embedded within the SG-Net and that enables SG-Net to quickly locate the stroke lesion on brain hemispheres through repetition. Specifically, the brain consists of a left and right hemisphere, forming a “pseudosymmetry” structure. To leverage this structure to simplify the training, we split each brain slice into left and right halves; these two parts are essentially mirrored. We then flip the right side horizontally to obtain a similar image on the left side. Thus, the network only needs to locate stroke lesions in a brain hemisphere instead of the whole brain. This technique works well when MR images are converted to a standard space. In addition, this technique easily doubles the number of samples without changing the brain’s tissue structure while halving GPU memory consumption. After segmentation, we can flip the right-brain segmentation mask back and concatenate the mask for the left side to form the final segmentation mask. The above operations are shown in Fig. 2(b).

This technique works for the stroke lesion segmentation task because, according to some studies [40], most stroke lesions are generally located in the gray matter and the white matter; the gray matter has a high cerebral blood flow level due to its high metabolic demand, and the white matter has a low blood supply, which is more susceptible to ischemia than other brain regions.

Relation with patch-based splitting methods. In a sense, the proposed augmentation strategy is a special kind of patch-based splitting method with anatomical motivation. However, we highlight that the patch-based splitting mainly boosts the size of the training dataset. In contrast, the proposed augmentation strategy leverage the high level of symmetry of the human brain [41], [42]. Most importantly, patch-based splitting methods can still be used after our data augmentation.

D. Site-Invariant Learning

Due to the differences in the type of MR scanner, the imaging protocol, or population variation, intersite heterogeneity seriously influences model generalizability to a new, unseen site. To guide MAIN to convert multisite images into a site-unrelated style and the encoder of U-net to learn site-invariant representations, we further introduce a site classifier to identify the discrepancies among sites. In this paper, we use the gradient reversal layer in the site classifier to encourage MAIN and the encoder of U-net to minimize the intersite discrepancy. The network architecture of the site classifier, including its gradient reversal layer, is shown in Fig. 2(d); this kind of classifier has previously been known to be effective in domain adaptation fields [28], [34].

The gradient reversal layer acts as an identity transformation during the forward propagation. However, during the back-propagation, it takes the gradient from the subsequent level and changes its sign (i.e., multiplies it by -1) before passing it to the preceding layer [29]. Therefore, the gradient reversal layer can help the encoder extract site-invariant features and the classifier predict sites simultaneously. We note that although adversarial training is widely used in domain adaptation, for our stroke lesion segmentation task with a small amount of
data, the gradient reversal layer within the site classifier can be more easily trained than iteration optimization in the GAN framework. We also find that the gradient reversal layer is robust to the site-imbalanced data.

The overall forward and backward propagation during training is shown in Fig. 2. The overall training process includes MAIN (orange) and the encoder (pink) and decoder (blue) of U-net, which together form a standard feed-forward architecture. Considering that representations related to different sites influence the segmentation results, domain (site) generalization is achieved by adding a site classifier (green) to MAIN and the encoder via a gradient reversal layer [28], that multiplies the gradient by a certain negative constant (−1 in this paper) during backpropagation-based training. Moreover, the training proceeds in a standard way and minimizes the segmentation Dice loss and the classification site loss.

In this case, the model parameters are optimized with backpropagation:

\[
\theta_M \leftarrow \theta_M - \mu \left( \frac{\partial L_d}{\partial \theta_M} - \frac{\partial L_s}{\partial \theta_M} \right),
\]

(3)

\[
\theta_E \leftarrow \theta_E - \mu \left( \frac{\partial L_d}{\partial \theta_E} - \frac{\partial L_s}{\partial \theta_E} \right),
\]

(4)

\[
\theta_D \leftarrow \theta_D - \mu \frac{\partial L_d}{\partial \theta_D},
\]

(5)

\[
\theta_S \leftarrow \theta_S - \mu \frac{\partial L_s}{\partial \theta_S}
\]

(6)

where \( \mu \) is the learning rate; \( \theta_M, \theta_E, \theta_D, \) and \( \theta_S \) represent the model parameters of MAIN, encoder, decoder, and site classifier, respectively; and \( L_d \) and \( L_s \) denote Dice loss and site loss, respectively.

Consequently, the gradient reversal layer ensures that the feature distributions among the multiple sites are similar (as indistinguishable as possible for the site classifier). This layer also helps MAIN to compute dynamic affine parameters adaptively for each input image. In addition, the proposed MAIN and site-invariant learning can help the encoder of U-net to extract site-invariant features. Therefore, the skip connections reuse the features from the encoder of U-net, which are supposed to contain little site information.

E. Network Architecture

1) MAIN: As shown in Fig. 2(a), the branch structures for computing \( \gamma \) and \( \beta \) are the same. Every convolutional block consists of a 3x3 convolution, batch normalization, and ReLU activation, with one filter. Each max-pooling layer divides the resolution of the feature map by 2x2. Moreover, the fully connected layer has 2,688 input features and 256 output features, and can summarise the statistics of the input MR images. After the fully connected layer, the feature maps are then reshaped to size 16x16. The average pooling layer compresses the resolution to 1x1, allowing us to obtain the adaptive affine parameters \( \gamma \) and \( \beta \) for each input image.

2) U-net: As shown in Fig. 2(c), the backbone of the model is U-net [43]. In our experiment, one convolutional block consists of a 3x3 convolution, batch normalization, and ReLU activation. Specifically, the structural details of U-net are shown in Table I.

| Feature size | Parameters |
|--------------|------------|
| Input        | 1 x 224 x 96 |
| Conv 1       | 64 x 224 x 96 | [3 x 3, 64 conv] x 2<sup>a</sup> |
| Pooling 1    | 64 x 112 x 48 | [2 x 2, max pooling]<sup>b</sup> |
| Conv 2       | 128 x 112 x 48 | [3 x 3, 128 conv] x 2 |
| Pooling 2    | 128 x 56 x 24 | [2 x 2, max pooling] |
| Conv 3       | 256 x 56 x 24 | [3 x 3, 256 conv] x 2 |
| Pooling 3    | 256 x 28 x 12 | [2 x 2, max pooling] |
| Conv 4       | 512 x 28 x 12 | [3 x 3, 512 conv] x 2 |
| Pooling 4    | 512 x 14 x 6 | [2 x 2, max pooling] |
| Conv 5       | 1024 x 14 x 6 | [3 x 3, 1024 conv] x 2 |
| Upsampling 1 | 1024 x 28 x 12 | [2 x 2, upsampling]-[Conv 4]<sup>c</sup> |
| Conv 6       | 512 x 28 x 12 | [3 x 3, 512 conv] x 2 |
| Conv 7       | 256 x 56 x 24 | [2 x 2, upsampling]-[Conv 3] |
| Conv 8       | 256 x 112 x 48 | [3 x 3, 256 conv] x 2 |
| Conv 9       | 128 x 112 x 48 | [2 x 2, upsampling]-[Conv 2] |
| Conv 10      | 128 x 224 x 96 | [3 x 3, 64 conv] x 2 |
| Conv 11      | 64 x 224 x 96 | [3 x 3, 64 conv] x 2 |
| Output       | 1 x 224 x 96 | [1 x 1, 1 conv]+Sigmoid |

<sup>a</sup>[3 x 3, 64 conv] corresponds to a convolution with a kernel size of 3 x 3 and 64 feature maps.

<sup>b</sup>[2 x 2, max pooling] denotes max pooling with a kernel size of 2 x 2.

<sup>c</sup>[2 x 2, upsampling] indicates that the height and width of the feature map are twice as large as the original via upsampling, following a convolution with a kernel size of 1 x 1 and a half as many feature maps; [ ]-[ ] denotes the concatenation of two feature maps.

3) Site Classifier: As shown in Fig. 2(d), the structure of the site classifier is simple: there are two convolutional blocks, one max-pooling layer, one average-pooling layer, one fully connected layer with 1,024 input features, and 8 output features. One convolutional block consists of a 3x3 convolution, batch normalization, and ReLU activation, and both convolutional blocks contain 1,024 filters. The output of the site classifier has 8 classes, corresponding to the 8 sites in the training set.

F. Loss Functions

1) Dice Loss: Dice loss to train the segmentation capacity can be formally defined for one sample as follows:

\[
L_d = 1 - \frac{2 \sum_i \sum_j \hat{p}_{ij} p_{ij} + \epsilon}{\sum_i \sum_j \hat{p}_{ij}^2 + \sum_i \sum_j \hat{p}_{ij}^2 + \epsilon},
\]

(7)

where \( p_{ij} \) represents the ground truth at the pixel; and \( \hat{p}_{ij} \) represents the model prediction probability; \( \epsilon = 10^{-5} \) is a smoothing term.
2) Site Loss: Cross-entropy loss is used to train the site classifier with a gradient reversal layer in our experiment. Site loss can be formally defined for one sample as follows:

$$\mathcal{L}_s = -\sum_{k=1}^{K} y_k \log \hat{y}_k,$$  \hspace{1cm}  (8)

where $K$ denotes the number of sites; $y_k$ represents whether the sample comes from the $k$-th site; and $\hat{y}_k$ represents the site classifier prediction probability value for the $i$-th site.

3) Total Loss: Our goal is to train a segmentation model that can not only perform very well but can also generalize well to an unseen site. Therefore, our total loss function for optimizing SG-Net is defined for one sample as follows:

$$\mathcal{L} = \mathcal{L}_d + \mathcal{L}_s.$$  \hspace{1cm}  (9)

III. EXPERIMENT

We empirically evaluate SG-Net on the benchmark stroke lesion dataset ATLAS, which includes T1-weighted MR images from 9 different sites. We start by describing the benchmark ATLAS in Section III-A and the implementation details in Section III-B, followed by details of an ablation study in Section III-C and a comparison with recently published methods under the “leave-one-site-out” setting in Section III-D.

Finally, the generalization to unseen external sites is presented in Section III-E.

A. ATLAS Dataset

ATLAS v1.2 \cite{12} is an open-source dataset consisting of the T1-weighted MR images of 229 defaced patients with normalized intensity localized in the standard space (MNI-152 template). We note that the size of the original dataset is 309. However, due to technical difficulties and differences in scanner image quality, following \cite{13}, \cite{18}, we excluded the images of lower resolution or failed registration, which were done by the original authors of ATLAS v1.2 \cite{12}. Each patient has 189 T1-weighted normalized image slices of size $233 \times 197$.

This dataset was collected from 9 sites worldwide. Table II presents the site information, location, scanner, and the number of patients for each site. There is no test-retest scan within-site or between-sites, except Site 8 that includes 9 test-retest scans (regarded as 18 patients). Thus, it should not affect the “leave-one-site-out” validation, as the test-retest scans only exist on one site. The large intersite discrepancy can be described as follows. First, this dataset covers diverse regions, involving four countries and eight cities, which leads to substantial challenges in generalizing across sites.

According to \cite{12}, the lesions, ranging in size from 10 to $2.838 \times 10^5$ mm$^3$, in the dataset were manually segmented by two specialists collaboratively, meaning that quality control was performed on each lesion mask by a second tracer. Consequently, there is no individual labeling difference among these lesion masks. In terms of location, most lesions are roughly equally distributed between the left and right hemispheres (48% left hemisphere vs 44% right hemisphere); only 8% are found in other locations, such as the brainstem and the cerebellum, which supports the rationale of our proposed data augmentation method. Overall, slightly more than half of the subjects have only one lesion (58%), while the remaining have multiple lesions (42%).

Unlike existing works that partition the ATLAS dataset via patient indexes to form diverse training and testing sets, we directly use site information to form the two sets, following the “leave-one-site-out” principle \cite{37} in this work, i.e., taking images obtained at one site as the testing set and those at the other eight sites as the training set. By repeating this process 9 times, we evaluate our SG-Net in terms of quantitative metrics and visual analysis.

B. Implementation Details

The proposed SG-Net is implemented in PyTorch, and trained on a single NVIDIA V100 Tensor Core GPU. In our model, we use stochastic gradient descent to optimize the trainable parameters, with an initial learning of 0.001 and a 4% weight decay after each epoch for a total of 50 epochs. The mini-batch size is set to 16 for training. We initially validate the performance of the model on Site 5, and use the same configuration for all sites. Following \cite{13}, \cite{18}, we preprocess the ATLAS dataset by cropping all slices to a size of $224 \times 192$. After MAIN, the size of the input becomes
The p-values confirm that each combination of the components has the same performance across different sites. We adopted Wilcoxon test [44] to examine if each combination of the components has the same performance as the baseline. 

| DA | SL | MAIN | Dice   | Recall  | F1-score |
|----|----|------|--------|---------|----------|
|    |    |      | 0.5295 ± 0.2407 | 0.4416 ± 0.2015 | 0.4565 ± 0.2406 |
| ✓  | ✓  |      | 0.5436 ± 0.2134 | 0.4560 ± 0.2141 | 0.4827 ± 0.2134 |
| ✓  | ✓  |      | 0.5626 ± 0.2018 | 0.4907 ± 0.2242 | 0.5335 ± 0.2018 |
| ✓  | ✓  |      | 0.5866 ± 0.2274 | 0.6048 ± 0.2315 | 0.6077 ± 0.2072 |
| ✓  | ✓  | ✓    | 0.5930 ± 0.2292 | 0.5729 ± 0.2429 | 0.6154 ± 0.2292 |
| ✓  | ✓  | ✓    | 0.6018 ± 0.2344 | 0.6570 ± 0.2354 | 0.6246 ± 0.2276 |

| Site 4 / Siemens Trio / 12 Subjects | Dice   | Recall  | F1-score |
|------------------------------------|--------|---------|----------|
|                                      | 0.2928 ± 0.2846 | 0.3658 ± 0.3186 | 0.4437 ± 0.3182 |
| ✓                                  | 0.3130 ± 0.2906 | 0.3576 ± 0.3186 | 0.4529 ± 0.3259 |
| ✓                                  | 0.3011 ± 0.2796 | 0.3714 ± 0.3063 | 0.4577 ± 0.3017 |
| ✓                                  | 0.3322 ± 0.2916 | 0.3783 ± 0.3259 | 0.4691 ± 0.3172 |
| ✓                                  | 0.3529 ± 0.2865 | 0.4128 ± 0.3182 | 0.4706 ± 0.3276 |
| ✓                                  | 0.3625 ± 0.2893 | 0.4439 ± 0.3042 | 0.4883 ± 0.3126 |

| Site 5 / Phillips Achieva / 27 Subjects | Dice   | Recall  | F1-score |
|------------------------------------------|--------|---------|----------|
|                                        | 0.4396 ± 0.2273 | 0.4044 ± 0.2631 | 0.4565 ± 0.2263 |
| ✓                                       | 0.4659 ± 0.2605 | 0.4365 ± 0.2870 | 0.4831 ± 0.2605 |
| ✓                                       | 0.4766 ± 0.2199 | 0.5138 ± 0.2615 | 0.4966 ± 0.2201 |
| ✓                                       | 0.4946 ± 0.2472 | 0.5268 ± 0.2814 | 0.5335 ± 0.2472 |
| ✓                                       | 0.5123 ± 0.2108 | 0.5069 ± 0.2530 | 0.5123 ± 0.2108 |
| ✓                                       | 0.5322 ± 0.2474 | 0.5294 ± 0.2794 | 0.6040 ± 0.2474 |

Table II presents the segmentation results for various component combinations. We select three sites with different types of scanners as the testing sets (Sites 1, 4 and 5) for the ablation study. Notably, each component consistently contributes to an increasing segmentation performance across different sites. We adopted Wilcoxon test [44] to examine if each combination of the components has the same performance as the baseline. The p-values confirm that each combination of the components is significantly better than the baseline method. Since all p-values are less than 5%, we do not show them in the table.

Before analyzing the contribution of each component, we note that z-score normalization is also helpful for site generalization. Taking Site 5 as an example, if we feed the U-net with unnormalized MR images, the segmentation performance drops substantially (Dice: 0.3794, Recall: 0.3408, F1-score: 0.3746). In other words, z-score normalization increases the Dice coefficient by 0.06. However, the effect of z-score normalization remains limited when the MR images from different sites demonstrate different means and standard deviations for z-score normalization.

### 1) Effect of Site-Invariant Learning

Taking Site 5 as an example, Table II shows that the combination of the gradient reversal layer and the site classifier increases the Dice coefficient from 0.4396 to 0.4766 for the baseline U-net and from 0.4695 to 0.4946 for the baseline U-net with data augmentation, demonstrating that the gradient reversal layer contributes to learning site-invariant representations for improving generalization to unseen sites. We repeat the same training process five times and display the averaged training curves with a standard deviation as error bound in Fig. 4, which shows that the model converges well. More importantly, the accuracy of the site classifier reaches approximately 0.14—very close to an ideal random guess ($\frac{1}{5} = 0.20$)—which
highlights that the site classifier cannot identify which site the sample comes from, leading to site-invariant learning.

2) Effect of MAIN: We note that MAIN should be used with site-invariant learning to learn site-unrelated style for different sites so that we do not list the results of MAIN only. Table III shows that MAIN can also consistently improve all metrics. To investigate how MAIN changes the distribution of input MR images from different sites, we take the 94th slice among 189 slices for every patient at each site and plot the distributions of their grayscale values before and after the application of MAIN, as shown in Fig. 5. According to Fig. 5(a), without MAIN, traditional z-score normalization is incapable of managing the misalignment among different sites for low grayscale value regions. In contrast, Fig. 5(b) shows that with MAIN, the resulting distributions from different sites are quite similar to each other, potentially eliminating the discrepancies in image appearance. Because of the use of a brain mask $B$ in (2), there is a peak at a grayscale value of zero after applying MAIN, which increases the normality of the distribution. As a result, MAIN leads to better generalization to unseen sites by dynamically standardizing the input MR images.

3) Effect of Data Augmentation: As shown in Table III, the proposed data augmentation method consistently improves all metrics by large margins. Take Site 5 for example, the Dice coefficient is increased by approximately 0.03, demonstrating the effectiveness of the proposed data augmentation approach. Table IV shows that the proposed data augmentation method also can halve the memory consumption of the model and doubles the computational speed in terms of multiply-accumulate operations (MACC). We note that the SG-Net with data augmentation has the same floating-point operations (FLOPs) as the one without it since SG-Net requires performing segmentation on two cerebral hemispheres. Therefore, the proposed data augmentation method can improve the memory usage and computational efficiency of the model and make it much easier for locating stroke lesions.

D. Comparison to Prior Work

We compare our SG-Net to prior work with the ATLAS dataset under the “leave-one-site-out” [37] setting; that is, we regard one site as the testing set and the other eight sites as the training set, and then report the average performance. We emphasize that the testing set is not used to tune the hyperparameters, as this could lead to overfitting. The prior work we compared includes U-net [43], ResUNet [45], PSP-Net [46], DeepLabv3+ [47], X-Net [13], U-Net3+ [48], nnU-
TABLE V
Comparison with other methods under the leave-one-site-out setting in terms of various evaluation metrics (the standard deviation behind ± is across sites). Each of the other methods takes z-score–normalized MR images as input. Each metric is represented as the mean and the standard deviation of nine experiments. #Par.: the number of model parameters; Mem.: total GPU memory of the model; MACC: multiply-accumulate operations; and FLOPs: floating-point operations.

| Method       | Dice (±) | Recall (±) | F1-score (±) | #Par. [M] | Mem. [MB] | MACC [G] | FLOPs [G] |
|--------------|----------|------------|--------------|-----------|-----------|----------|-----------|
| U-net [43]   | 0.4712 ± 0.1952 | 0.4315 ± 0.1931 | 0.4864 ± 0.2161 | 28.94 | 260.20 | 63.21 | 31.63 |
| ResUNet [45] | 0.4780 ± 0.1952 | 0.4693 ± 0.1931 | 0.5322 ± 0.1846 | 28.94 | 260.20 | 63.20 | 31.63 |
| PSPNet [46]  | 0.4318 ± 0.2054 | 0.3813 ± 0.1792 | 0.3921 ± 0.1948 | 38.28 | 261.91 | 65.07 | 32.56 |
| Deeplabv3+  | 0.4639 ± 0.2077 | 0.4594 ± 0.2118 | 0.4714 ± 0.1840 | 59.33 | 171.63 | 28.98 | 14.50 |
| X-Net [47]   | 0.5083 ± 0.1926 | 0.4954 ± 0.1844 | 0.5179 ± 0.1896 | 15.05 | 915.67 | 40.49 | 20.33 |
| U-Net3+ [48] | 0.5210 ± 0.2077 | 0.4851 ± 0.1849 | 0.4972 ± 0.1930 | 26.97 | 261.91 | 65.07 | 32.56 |
| nnU-Net [25] | 0.5047 ± 0.2002 | 0.4916 ± 0.1990 | 0.5268 ± 0.2026 | 18.67 | 155.01 | 21.22 | 10.18 |
| Unlearning [49] | 0.5415 ± 0.1881 | 0.5632 ± 0.1721 | 0.5365 ± 0.1881 | 27.90 | 205.73 | 50.50 | 23.86 |
| SG-Net (ours) | 0.5711 ± 0.1957 | 0.5977 ± 0.1587 | 0.5623 ± 0.1926 | 29.64 | 130.79 | 31.60 | 33.63 |

Fig. 7. Examples of segmentation results on ATLAS dataset. The rows show the performance for cases involving different lesion locations, sizes or numbers. The first and second columns represent the input images and ground-truth segmentation masks, and the remaining columns represent different segmentation methods: (a): Input MR image; (b): Ground-truth segmentation mask; (c) SG-Net (Ours); (d) U-net; (e) ResUNet; (f) PSPNet; (g) DeepLabv3+; (h) X-Net; (i) U-Net3+; (j) nnU-Net; and (k) Unlearning. Note that the other methods all use z-score–normalized images as input.
has a consistently better performance than other methods in all the metrics.

IV. DISCUSSION

A. Discussion on the Preprocessing Techniques

The z-score-normalized preprocessing and our MAIN rely on the brain mask. Although the quality of the brain mask may affect the results, we emphasize that the brain mask can be easily obtained and is of robust quality. The proposed data augmentation leverages the pseudo-symmetric brain, which relies on the spatial normalization preprocessing. In the released dataset, the MR images have been spatially normalized

E. Generalization to Unseen External Sites

To further evaluate the generalization to unseen sites, we use data from Sites 38, 40, and 48 from ATLAS v2.0 [51]. The new version contains more new unseen sites that could serve as external datasets for further evaluation of generalisability. In addition, the types of MR scanners for Sites 38, 40, and 48 are Siemens Allegra, Siemens Vision, and Philips Achieva, respectively.

We compared our method with the baseline U-net [43] and the most competing Unlearning [49], and the results are presented in Table VI. The results can further validate more effectiveness and the generalization of our method overall on new sites regardless of the scanner types. Although the difficulty of segmentation varies in different sites, our method

Table VI

| Method       | Dice     | Recall    | F1-score  |
|--------------|----------|-----------|-----------|
| Site 38 / Siemens Allegra / 49 Subjects | U-net [43] | 0.1098 ± 0.0398 | 0.0783 ± 0.0258 | 0.0968 ± 0.0265 |
|              | Unlearning [49] | 0.1778 ± 0.0236 | 0.1690 ± 0.0366 | 0.2022 ± 0.0246 |
|              | SG-Net (ours) | 0.2251 ± 0.0263 | 0.3048 ± 0.0462 | 0.2251 ± 0.0263 |
| Site 40 / Siemens Vision / 45 Subjects | U-net [43] | 0.2470 ± 0.0332 | 0.1923 ± 0.0431 | 0.2064 ± 0.0326 |
|              | Unlearning [49] | 0.3993 ± 0.0141 | 0.3546 ± 0.0350 | 0.3762 ± 0.0346 |
|              | SG-Net (ours) | 0.4301 ± 0.0243 | 0.4316 ± 0.0475 | 0.4301 ± 0.0243 |
| Site 48 / Philips Achieva / 23 Subjects | U-net [43] | 0.1272 ± 0.0352 | 0.0762 ± 0.0124 | 0.1325 ± 0.0376 |
|              | Unlearning [49] | 0.3642 ± 0.0252 | 0.3793 ± 0.0331 | 0.3672 ± 0.0346 |
|              | SG-Net (ours) | 0.3894 ± 0.0225 | 0.4259 ± 0.1792 | 0.3921 ± 0.0148 |

Table VII

| Sampling     | Dice     | Recall    | F1-score  |
|--------------|----------|-----------|-----------|
| Non-balanced | 0.5711 ± 0.1957 | 0.5977 ± 0.1580 | 0.5623 ± 0.1926 |
| Balanced     | 0.5690 ± 0.1925 | 0.5851 ± 0.1793 | 0.5568 ± 0.1824 |
| p-value      | 0.7793 | 0.3120 | 0.6879 |
through the MINC-toolkit [52]. When the MR images failed to be spatially normalized, the proposed data augmentation could reduce a general splitting-based data augmentation.

B. Discussion on the Data Imbalance Across Sites

Table [11] shows that the number of patients in each site is not balanced. We performed experiments with balanced sampling according to the inverse ratio of the number of patients from each site. The balanced sampling could make each site equally be sampled for training. The results of balanced sampling, as well as our non-balances sampling, are shown in Table VII. Regarding the p-values for different evaluation metrics in the Wilcoxon tests, there are also no statistically significant differences between with and without balanced sampling. This may be due to the gradient reversal layer for backpropagation: when the model initially has a bias towards a special site, the gradient reversal layer overcomes this bias and makes all sites indistinguishable.

C. Discussion on the Performance of Individual Sites

Different sites have different difficulties. We provide the boxplot of each metric for individual sites in Fig. [8]. Combined with Table [11] the scanner types seem to not directly influence segmentation performance. For instance, the type of MR scanners in Site 1 is the same as Site 8 (GE 750 Discovery), however, there is a significant difference between their segmentation performances. We further analyzed the performance of our model in relation to the lesion size. Fig. [9] shows the distribution of the lesion size for each site. It shows that the worst performance of the model on Site 8 mainly results from a large proportion of patients with a small lesion. On the other hand, it is easier for the model to achieve a high Dice score for a large lesion; a similar phenomenon was also demonstrated in [20], [21]. For example, Sites 6, 7, and 9 include a large proportion of patients with a large lesion. More importantly, the great variance of lesion size resulted in the large standard deviation cross subjects in the metrics.

D. Limitations

We acknowledge the following limitations about this work. First, the proposed data augmentation is only suitable for symmetric body parts, such as the human brain. For non-symmetric body parts, the proposed data augmentation reduces to trivial splitting-based data augmentation. Second, the current SG-Net requires the data from all sites to be on the same server.

However, in some scenarios, the data from sites may not be allowed to share due to strict legal and ethical requirements to protect patient privacy. One possible solution is federated learning [53]–[55]. Finally, since the ATLAS v1.2 dataset is relatively small, further experiments on ATLAS v2.0 dataset are suggested. We plan to investigate the generalizability using larger multisite datasets to further improve site generalization.

V. Conclusion

In this paper, we proposed SG-Net for site generalization, including MAIN, data augmentation, and site-invariant learning. The experimental results on the ATLAS dataset demonstrate that our SG-Net shows increased model generalization to unseen sites. The ablation study also validates the effectiveness of each component.

In conclusion, the proposed SG-Net substantially enhances the stroke lesion segmentation performance on MR images from unseen sites, which suggests its potential applicability in clinical practice.

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