

## Original Research Article

# Automatic Segmentation and Quantitative Assessment of Stroke Lesions on MR images

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**Abstract:** Lesion studies are crucial in establishing brain-behavior relationships, and accurately segmenting the lesion represents the first step in achieving this. Manual lesion segmentation is the gold standard for chronic strokes. However, it is labor-intensive, subject to bias, and limits sample size. Therefore, our objective is to develop an automatic segmentation algorithm for chronic stroke lesions on T1-weighted MR images. **Methods:** To train our model, we utilized an open-source dataset: ATLAS v2.0 (Anatomical Tracings of Lesions After Stroke). We partitioned the dataset of 655 T1 images with manual segmentation labels into five subsets and performed a 5-fold cross-validation to avoid overfitting of the model. We used a deep neural network (DNN) architecture for model training. **Results:** To evaluate the model performance, we used three metrics that pertain to diverse aspects of volumetric segmentation including shape, location, and size. The Dice similarity coefficient (DSC) compares the spatial overlap between manual and machine segmentation. The average DSC was 0.65 (0.61- 0.67; 95% bootstrapped CI). Average symmetric surface distance (ASSD) measures contour distances between the two segmentations. ASSD between manual and automatic segmentation was 12mm. Finally, we compared the total lesion volumes and the Pearson correlation coefficient ( $\rho$ ) between the manual and automatically segmented lesion volumes, which was 0.97 ( $p$ -value < 0.001). **Conclusions:** We present the first automated segmentation model trained on a large multicentric dataset. This model will enable automated on-demand processing of MRI scans and quantitative chronic stroke lesion assessment.

**Keywords:** Stroke; automatic segmentation, stroke, deep neural networks, 3D-UNet, lesion studies, vascular neurology, precision medicine

## Highlights:

1. Overall, we found that DNN enabled objective and automated assessment of chronic lesions secondary to stroke in vascular neurology at high throughput and could ultimately serve to improve clinical decision-making.
2. Our model in conjunction with voxel-based lesion-symptom mapping will facilitate the study of brain-behavior relationships in chronic stroke

## 1. Introduction

Over the past century, human lesion studies have provided key insights into the relationship of brain areas to behavior. Lesion studies are highly valuable in cognitive neuroscience as lesions such as stroke create a dissociation of function. This dissociation provides causal evidence of a brain area for the function [1].

In this quest, automatic lesion segmentation has emerged as a crucial tool [2]. Automatic image segmentation refers to the assignment of non-overlapping boundaries in an image to regions that are dissimilar in core features such as intensity or texture [3]. There are numerous automatic segmentation algorithms for acute stroke, however, in comparison, there is a paucity of algorithms for chronic stroke lesions [2]. The reasons for this are multifold. First, acute stroke requires time-sensitive and precise clinical decision-making. Neuroimaging plays a pivotal role in this decision-making, therefore there are concerted efforts to develop automatic segmentation models for acute stroke [4–6]. Second, the lesions in acute and chronic stroke are assessed with distinct MR imaging sequences, and segmentation methods developed for acute stroke imaging are not directly applicable to chronic stroke imaging [7]. In acute stroke, diffusion, perfusion, and susceptibility-weighted images offer the most clinically relevant information [8]. In contrast, in chronic stroke, T1-weighted are preferred as they offer high spatial resolution which makes them suitable to study the structure-function relationship [7]. Third, imaging in acute stroke is mandatory, therefore large neuroimaging datasets exist, which enable automatic model training and testing [9]. In comparison, large chronic stroke imaging datasets are rare [10].

Due to all these reasons, currently, manual segmentation is the gold standard for chronic stroke lesions. However, it is labor-intensive, time-consuming, subject to bias and prone to inter-observer variability [9]. All these factors ultimately limit the sample size. To overcome these limitations, chronic stroke automatic segmentation models are required.

In this study, we aim to develop a fully automatic algorithm to segment chronic stroke lesions on T1-weighted MR images. To develop our model, we used a deep neural network architecture (DNN). Among the machine learning algorithms, DNN is a class that has become well-established in computer vision tasks such as automatic segmentation [11]. Therefore, we applied 3D-UNet as it is suitable for volumetric segmentation of medical imaging [12].

## 2. Materials and Methods

### 2.1 Dataset

We employed an open-source dataset: ATLASv2.0 (Anatomical Tracings of Lesions After Stroke, version 2). This dataset has 655 T1-weighted MR images in training set assembled from worldwide multicentric cohort sites as a part of the ENIGMA Stroke Recovery Group [10]. Each site obtained ethical approval, and the studies were conducted in accordance with Declaration of Helsinki, 1964. In addition, the central image receiving site obtained ethical approval for the reception and dissemination of the deidentified MR images.

### 2.2 Manual tracing

Manual tracers followed standard operation protocol to trace lesion labels on the raw T1-weighted images. This was done using of software ITK-SNAP (version 3.8.0) [13,14]. The lesion masks were assessed by two raters separately and edited based on a standardized protocol. The link to standardized protocol is provided in the supplementary materials.

### 2.3 Preprocessing and dataset partitioning

Automated brain extraction using HD-BET algorithm was performed on all the MR images [15]. Preprocessing included intensity normalization, registration to a standardized template (MNI-152), and defacing. The training dataset contained both the preprocessed images without labels and with labels as separate files, to enable training and testing models.

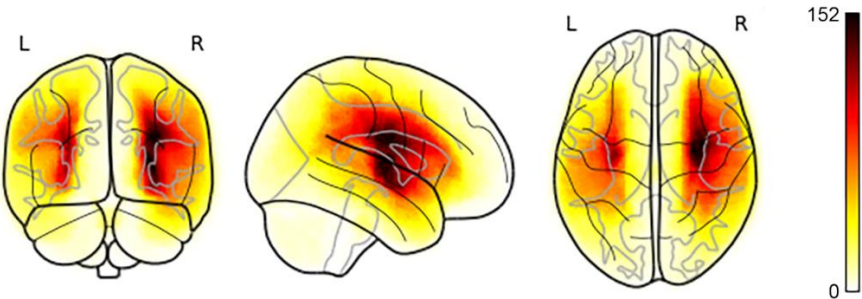
### 2.4 Lesion characteristics

Lesion characteristics are depicted in table 1. 59.9% subjects had single lesion, and 38.1% had multiple lesions. Of the subjects with multiple lesions, 7.2% had unilateral lesions, 18.5% had bilateral lesions, and 12.4% had lesions in either brainstem or cerebellum. Lesion location was considered unilateral if the lesions were present in only the left or the right hemisphere. Lesion location in brainstem or cerebellum was indicated as other. Additionally, lesions were classified as cortical, subcortical, and other.

**Table 1.** Data characteristics for training dataset.

Subjects (n = 655)	Location
Cortical lesions	Left 12%; Right 13.5 %
Subcortical lesions	Left 30.2%, Right 29.4%
Other lesions	14.8%

Figure 1 is a visualization of the lesion overlap maps across all subjects (n = 655) in the MNI space. 57.1% subjects had at least one left hemisphere lesion, and 58.8% had at least one right hemisphere lesion [2].

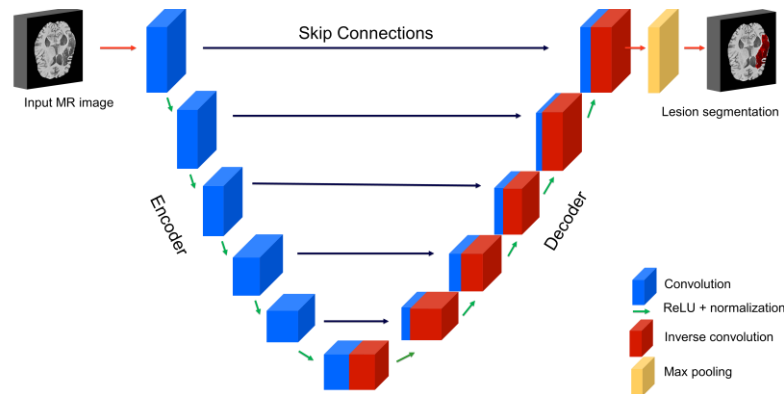


**Figure 1.** Lesion map across all subjects (n= 655) visualized in the standard MNI template. Darker colors indicate a higher frequency of lesions at a given voxel.

2.5 Model architecture

We applied 3D-UNet, a deep neural network (DNN) architecture to segment the volumetric imaging data. Our implementation of the 3D-UNet on the ATLAS v2.0 dataset is similar to that of Isensee et al. in the nnUnet framework [15]. Previously, we adapted this architecture to successfully train an automatic segmentation model on ATLAS v.1.2 data set [16].

An overview of the 3D-UNet model and its components is shown in Figure 2. The 3D-UNet architecture consists of a symmetrical encoder and decoder structure. During the analysis phase (encoding), convolutions and down sampling operations combine and create a bottleneck at the center of the structure. During the synthesis phase (decoding) a series of convolutions and up sampling (inverse convolutions) reconstruct the image. The addition of skip connections improves training by assisting backward gradient flow [17]. A skip connection allows access to low- and mid-level visual representations of the input to the decoder component, which is similar to the bypass connections in the primate visual system [18].



**Figure 2.** Schematic representation of 3D-UNet architecture

### 2.6 Model training

We optimized the hyperparameters for the training using a grid search and cross-validation on a validation set. Model performance on the validation set determined the hyperparameters. The model was trained for 1000 epochs (where an epoch is defined as 250 batches). Adaptive learning rates were used during the training. For the first 500 epochs, a cosine-annealing learning rate schedule of  $1e-2$  to  $1e-4$  was used; for epochs 500–1000, a cosine-annealing learning rate schedule of  $1e-5$  to  $1e-9$  was utilized. A weight decay ( $3e-5$ ) method was used for regularization. To augment the 3D data, scaling, rotation, gamma adjustments, mirror transformations, and additive brightness were randomly performed at probabilities of 0.2, 0.2, 0.3, 0.5, and 0.15, respectively.

### 2.7 Model performance evaluation

We assessed model performance both qualitatively and quantitatively. For quantitative evaluation, we employed a multitude of evaluation metrics. To compare the spatial overlap of the manual and automatic segmentation labels, we utilized Sørensen-Dice similarity coefficient (DSC) [19]. It is calculated as:

$$DSC = \frac{2|R \cap M|}{|R| + |M|} * 100$$

where  $R$  is the ground truth reference brain mask (manual segmentation), and  $M$  is the predicted mask (automatic segmentation). The output values for DSC range between 0 (no overlap), and 1 (perfect agreement). We complemented DSC with average symmetric surface distance (ASSD). ASSD is the average of all distances between the predicted mask and the ground truth boundary [20]. In addition, we compared lesion volumes across cross-validation folds.

### 2.8 Statistical analysis

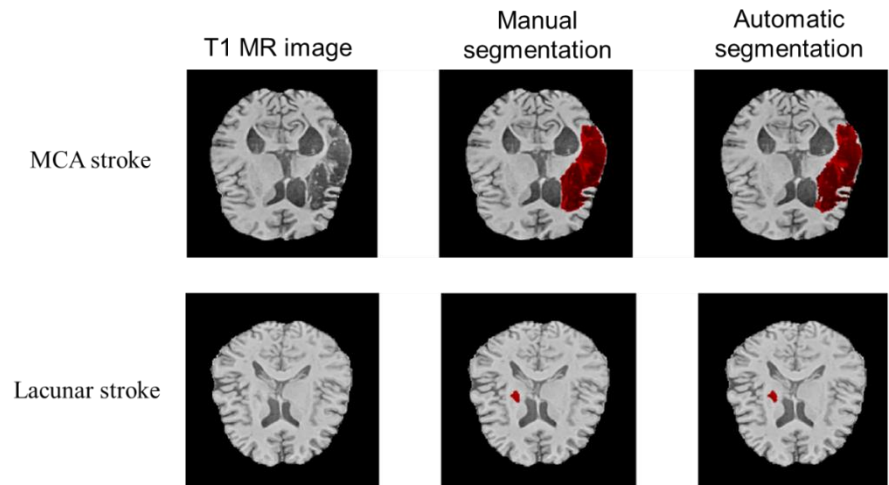
Bootstrap resampling ( $n = 1000$ ) was used to estimate 95% confidence intervals for the evaluation metrics (DSC and ASSD). We report descriptive statistics (median, 95% CI) for DSC and ASSD across all cross-validation folds. A two-tailed Wilcoxon matched-pairs signed-rank test was done to test the statistical significance of the differences between the manual and automatic segmentation volumes. For quantification of the relationship between manual and automatic segmentation volumes, Pearson correlation coefficient was utilized. We employed a randomization test to estimate the p-value of the correlation coefficient ( $n = 1000$ ).

3. Results

We evaluated the performance of our model by comparing manual and automatic segmentation masks across 5-fold cross-validation.

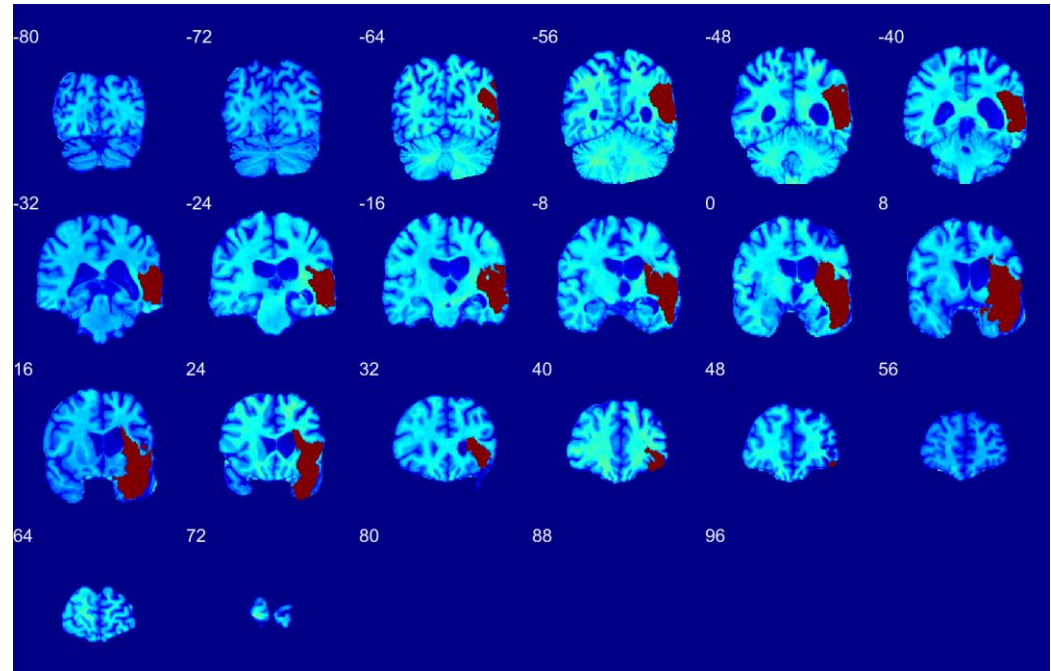
3.1 Qualitative performance

Visual evaluation of performance was done across multiple lesion locations and sizes. To illustrate model’s optimal performance on both large and small lesions, refer to figure 3.



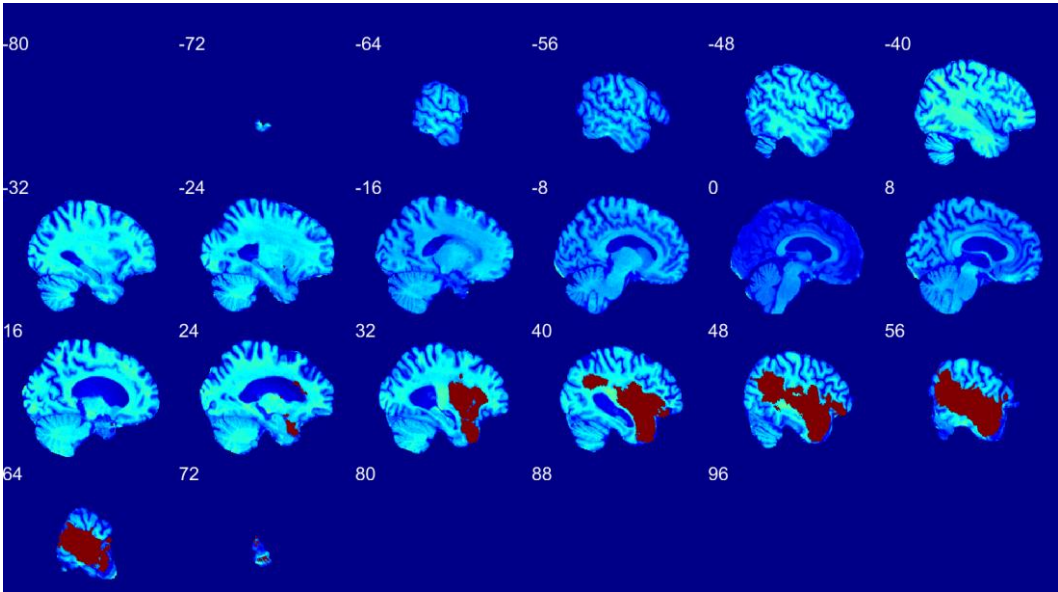
**Figure 3.** Axial sections showing examples of manual and automatic segmentation. Top row depicts the segmentation performance for a Middle Cerebral Artery (MCA) stroke and the bottom panel demonstrates performance for a lacunar stroke.

Figures 4, 5 and 6 illustrate the model’s performance across the full extent of the lesion volume on the coronal, axial, and sagittal sections respectively.

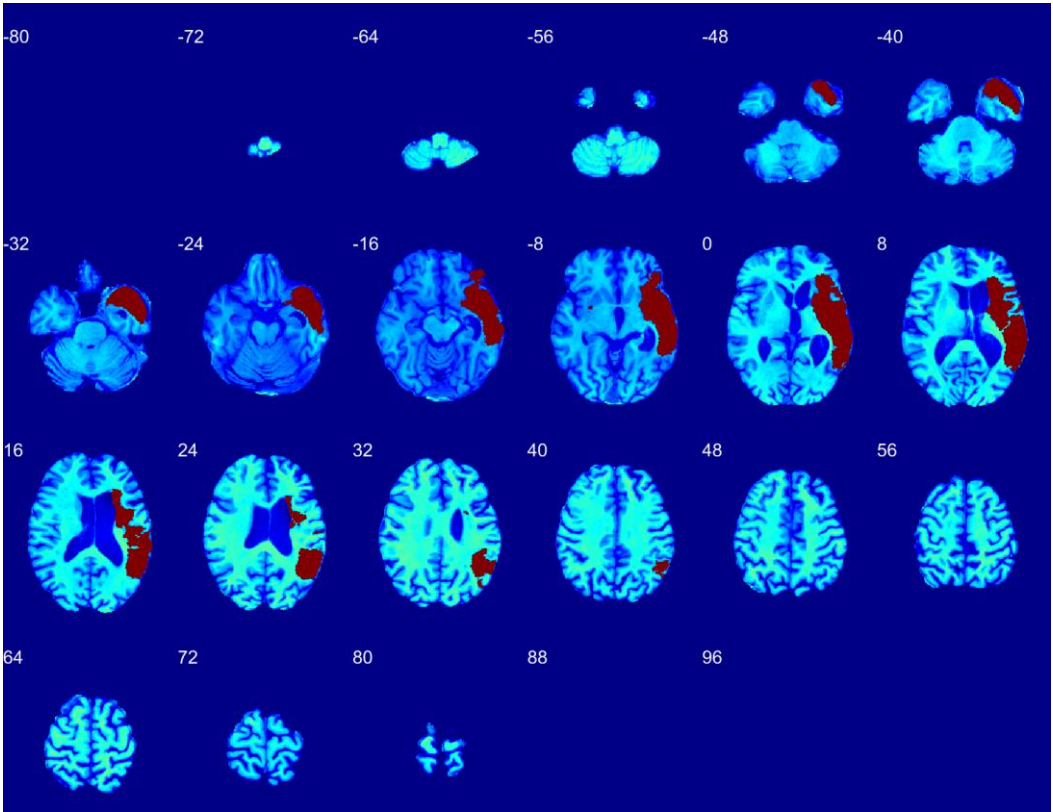


**Figure 4.** Coronal sections showing automatic segmentation of left MCA stroke as mapped on MNI152 template. The brain slices are sampled at the intervals of 8 mm.





**Figure 5:** Sagittal sections showing automatic segmentation of left MCA stroke.



**Figure 6:** Axial sections showing automatic segmentation of left MCA stroke.

3.2 Quantitative performance

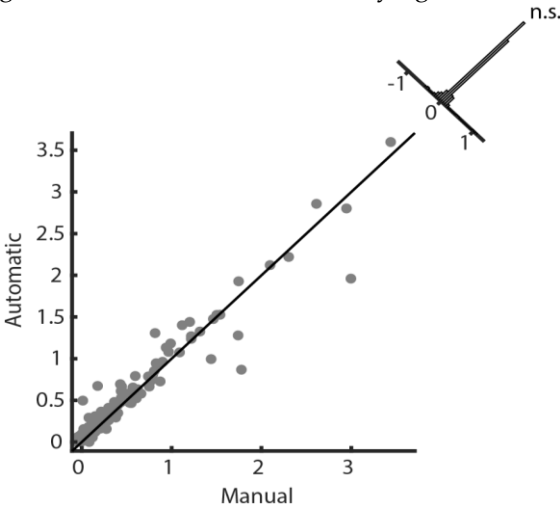
Quantitative performance was evaluated by using DSC, ASSD and total volume comparisons. These discrepancy metrics assess the similarity and dissimilarity of

automatically segmented lesions as compared to the ground truth, that is the manually segmented label [21]. A summary of descriptive statistics for DSC and ASSD is presented in Table 2.

**Table 2:** Segmentation performance of the trained model across cross-validated folds.

Performance Metric	Mean (bootstrap 95% CI)
Sørensen–Dice coefficient	0.65 (0.61 – 0.67), median: 0.73
Average symmetric surface distance (ASSD) on MNI152 template (in mm)	12.04 (8.44 – 19.53), median: 2.23

To demonstrate accurate volume prediction, a scatter plot with histogram of differences was constructed which showed no significant difference (p-value = 0.84) between the manual and automatic segmentation volumes. The Pearson correlation coefficient ( $\rho$ ) between the two volumes was 0.97(p-value < 0.001, randomization test (n = 1000)). The results establish the state-of-the-art performance of 3D-UNet both qualitatively (Figures 3-6) and quantitatively (Table 2 and Figure 7). In addition, Figure 7 also shows the stability of segmentation across lesions of varying sizes.



**Figure 7.** A scatter plot with a histogram of differences shows no significant difference (Wilcoxon rank-sum test, p-value = 0.84) between the manual and automatic lesion volumes across cross-validation folds. Segmented lesion volumes ( $\times 10^5 \text{ mm}^3$ ).

4. Discussion

Understanding the brain structure-function relationship remains the fundamental challenge for both clinical and basic neurosciences. Brain lesions such as stroke offer a unique insight into brain function [1]. Although stroke lesions tend to be focal in nature, they usually follow vascular territories, and involve concomitant brain areas [22]. Furthermore, the immense variations in stroke lesions, and the subsequent functional recovery adds to the challenge of delineating the structure-function relationship [10]. Therefore, to study this relationship, one needs large neuroimaging dataset [23] in combination with the ability to accurately localization lesions.

In this study, we developed an automatic segmentation model using state-of-the-art deep learning techniques and a novel combination of regularization methods.

4.1 Regularization methods to overcome overfitting

The ultimate test of a prediction model is its generalizability to novel datasets [24]. It is therefore essential to avoid overfitting the model on the data it is trained on. Overfitting refers to the model's high performance on the data it is trained on, and a discordant performance on novel data [11]. It is hypothesized that overfitting occurs when the model learns irrelevant aspects of data [11].To address this issue, we used two regularization

measures. The first measure was k-fold cross-validation. In k-fold cross-validation the data is randomly partitioned into k number of subsets, then the model is trained on k-1 subsets (termed as training sets); and tested on the left-out subset (termed as testing set). Another regularization method we utilized is data augmentation [26]. Like k-fold cross validation, this method does not require a novel dataset to test, rather it capitalizes on the available data. In this method, synthetic distortions such as geometric transformation, rotation, cropping, luminance variation, and magnification are introduced to the images [26]. The goal is to augment the available dataset with the generation of synthetic images [26].

#### 4.2 A combination approach for quantitative analysis

Individual metrics are sensitive to specific aspects of segmentation performance, hence, they are sensitive to different kinds of errors. Therefore, if used singly they risk ranking an algorithm high that only performs well on a particular aspect. As no single metric is considered gold standard, a combination approach is recommended. The various kinds of errors that can occur in segmentation tasks include errors in lesion shape, location, and size [20]. Therefore, we utilized a metric targeting each of these errors, and reported these under the section quantitative assessment of model performance.

As the name suggests overlap metrics are best at capturing the degree of overlapping voxels in the 2 segmentations, however they are not as sensitive in detecting discrepancies in the overall spatial distribution of the segmentation [20]. The overlap metric that we used is the Sørensen-Dice similarity coefficient (DSC). This index was originally described by Dice for ecological studies[19], but it has been commonly used in medical image segmentation [27].

To capture location-based errors, boundary-based-distance method is utilized. These methods assess dissimilarity of the automatic segmentation with ground truth based on the contour distances of the 2 lesion masks. The boundary-based-distance metric we used is the average symmetric surface distance (ASSD). ASSD focuses on location errors, but it is not as sensitive in identifying errors in the absolute size [20]. To capture errors in size, we compared the 2 segmentation volumes. Total volume comparison is best for comparing the total sizes, but it does not consider the shape and location of the 2 lesion masks. Therefore, by employing a combination approach we ensured a rigorous and comprehensive performance evaluation.

#### 4.3 Limitations

With any machine learning algorithm, one of the limitations is that it can learn biases from the training dataset. Our algorithm was optimized to be sensitive to manual segmentation labels, therefore it was prone to learn any biases associated with the manual segmentation process [28]. Although the dataset was derived from multiple sites, yet the manual segmentation was done by a common group of tracers, which can introduce subjectivity and confounds [29]. To overcome this, the model will need to be tested on independent datasets. This, however, represents another challenge as there are limited publicly available datasets for chronic stroke with manual segmentation labels [9]. Moreover, since the testing is done on a subset of data, it provides evidence for adequate internal validity, however, provides little information regarding external validity. As this issue is common for automatic segmentation of chronic lesions, the authors of ATLASv2.0 have created a subset of test data (n =300), which has only preprocessed images available to request. The research groups who develop models are encouraged to request access to this dataset, run the model and submit the automatic labels. In this manner, an objective and unbiased test of generalization can be done [29].

#### 4.4 Future directions

Automatic segmentation models have the potential to serve as an aid in clinical decision-making pertaining to neurorehabilitation [30]. This is a prospective area of personalized medicine wherein more accurate predictions regarding patient's recovery and relevant rehabilitation programs for individual patients will be made [30]. Furthermore, as strokes tend to reoccur in the same patient, even in cases of acute stroke, the chronic lesion segmentation models can aid in foreseeing the prognosis. Chronic stroke segmentation can



predict the pre-stroke modified rankin score (pre-mRS) [30], which is an independent predictor of poststroke prognosis [31]. This highlights the role of chronic stroke segmentation models in both acute and chronic stroke settings.

From the research standpoint, the combination of this technique with voxel-based lesion-symptom mapping (VLSM) will enable the establishment of new relationships between brain structure and function. VLSM is a lesion-defined method in which the patients are grouped on the basis of similar lesions and then comparison regarding behavioral deficit is made on voxel-by-voxel basis[32,33]. In terms of cognitive function localization, VLSM studies in stroke patients have presented localization data pertaining to deficits in cognition[34], language[35], memory[36], and executive functions.[37]

Lastly, we shared our code, detailed model architecture, and trained models in the supplementary materials. Data sharing is of special value when it comes to neuroimaging segmentation modeling [38]. In addition to potential future use by other authors, sharing this data enables independent verification, and reproduction of the results, thereby adding to the credibility of our scientific enquiry and method [39].

## 5. Conclusions

For the first time, we report an automated lesion segmentation model on the ATLAS v2.0 dataset. This model facilitates a high-throughput, objective, and automated assessment of chronic stroke lesions. We utilized a novel combination of regularization methods to avoid overfitting. To verify the robustness of our model we utilized a combination of quantitative metrics. This model, in combination with the latest image analysis techniques such as voxel-based lesion-symptom mapping will enable the study of structure-function relationships. Ultimately, this work will facilitate large scale neuroimaging analyses for stroke rehabilitation research.

**Supplementary Materials:** Standard operating protocols for manual lesion segmentation by ATLASv2.0 authors can be found here: <https://github.com/npn/ATLAS/> [2]. The complete code, detailed model architecture, and pre-trained models can be found at the following link: <https://github.com/SatwantKumar/3D-unet>.

**Author Contributions:** Conceptualization, K.V., and S.K.; Data curation K.V., and S.K.; Formal analysis, K.V., and S.K.; Methodology, K.V, D.P., and S.K.; Software, S.K.; Validation, K.V., and S.K., Visualization, K.V., and S.K.; Writing - original draft, K.V., and S.K.; Writing- review and editing, K.V., S.K., and D.P. All authors have read and agreed to the final version of the manuscript.

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## References

1. Adolphs, R. Human Lesion Studies in the 21st Century. *Neuron* **2016**, *90*, 1151–1153, doi:10.1016/j.neuron.2016.05.014.
2. Liew, S.-L.; Lo, B.P.; Donnelly, M.R.; Zavaliangos-Petropulu, A.; Jeong, J.N.; Barisano, G.; Hut-ton, A.; Simon, J.P.; Juliano, J.M.; Suri, A.; et al. A Large, Curated, Open-Source Stroke Neuroimag-ing Dataset to Improve Lesion Segmentation Algorithms. *Sci. data* **2022**, *9*, 320, doi:10.1038/s41597-022-01401-7.
3. Haralick, R.M.; Shapiro, L.G. Image Segmentation Techniques. *Comput. Vision, Graph. Image Process.* **1985**, *29*, 100–132, doi:https://doi.org/10.1016/S0734-189X(85)90153-7.
4. Nazari-Farsani, S.; Nyman, M.; Karjalainen, T.; Bucci, M.; Isojärvi, J.; Nummenmaa, L. Auto-mated Segmentation of Acute Stroke Lesions Using a Data-Driven Anomaly Detection on Diffu-sion Weighted MRI. *J. Neurosci. Methods* **2020**, *333*, 108575, doi:10.1016/j.jneumeth.2019.108575.
5. Chen, L.; Bentley, P.; Rueckert, D. Fully Automatic Acute Ischemic Lesion Segmentation in DWI Using Convolutional Neural Networks. *NeuroImage. Clin.* **2017**, *15*, 633–643, doi:10.1016/j.nicl.2017.06.016.
6. Clèrigues, A.; Valverde, S.; Bernal, J.; Freixenet, J.; Oliver, A.; Lladó, X. Acute Ischemic Stroke Lesion Core Segmentation in CT Perfusion Images Using Fully Convolutional Neural Networks. *Comput. Biol. Med.* **2019**, *115*, 103487, doi:10.1016/j.compbio.2019.103487.
7. Tomita, N.; Jiang, S.; Maeder, M.E.; Hassanpour, S. Automatic Post-Stroke Lesion Segmenta-tion on MR Images Using 3D Residual Convolutional Neural Network. *NeuroImage Clin.* **2020**, *27*, 102276, doi:https://doi.org/10.1016/j.nicl.2020.102276.
8. Schellinger, P.D.; Fiebach, J.B.; Hacke, W. Imaging-Based Decision Making in Thrombolytic Therapy for Ischemic Stroke. *Stroke* **2003**, *34*, 575–583, doi:10.1161/01.STR.0000051504.10095.9C.
9. Liew, S.-L.; Anglin, J.M.; Banks, N.W.; Sondag, M.; Ito, K.L.; Kim, H.; Chan, J.; Ito, J.; Jung, C.; Khoshab, N.; et al. A Large, Open Source Dataset of Stroke Anatomical Brain Images and Manual Lesion Segmentations. *Sci. Data* **2018**, *5*, 180011, doi:10.1038/sdata.2018.11.
10. Liew, S.-L.; Zavaliangos-Petropulu, A.; Jahanshad, N.; Lang, C.E.; Hayward, K.S.; Lohse, K.R.; Juliano, J.M.; Assogna, F.; Baugh, L.A.; Bhattacharya, A.K.; et al. The ENIGMA Stroke Recovery Working Group: Big Data Neuroimaging to Study Brain–Behavior Relationships after Stroke. *Hum. Brain Mapp.* **2022**, *43*, 129–148, doi:https://doi.org/10.1002/hbm.25015.
11. Yamashita, R.; Nishio, M.; Do, R.K.G.; Togashi, K. Convolutional Neural Networks: An Over-view and Application in Radiology. *Insights Imaging* **2018**, *9*, 611–629, doi:10.1007/s13244-018-0639-9.
12. Zhou, Y.; Huang, W.; Dong, P.; Xia, Y.; Wang, S. D-UNet: A Dimension-Fusion U Shape Net-work for Chronic Stroke Lesion Segmentation. *IEEE/ACM Trans. Comput. Biol. Bioinforma.* **2021**, *18*, 940–950, doi:10.1109/TCBB.2019.2939522.
13. Yushkevich, P.A.; Gerig, G. ITK-SNAP: An Intractive Medical Image Segmentation Tool to Meet the Need for Expert-Guided Segmentation of Complex Medical Images. *IEEE Pulse* **2017**, *8*, 54–57, doi:10.1109/MPUL.2017.2701493.
14. Yushkevich, P.A.; Piven, J.; Hazlett, H.C.; Smith, R.G.; Ho, S.; Gee, J.C.; Gerig, G. User-Guided 3D Active Contour Segmentation of Anatomical Structures: Significantly Improved Efficiency and Reliability. *Neuroimage* **2006**, *31*, 1116–1128, doi:10.1016/j.neuroimage.2006.01.015.
15. Isensee, F.; Schell, M.; Pflueger, I.; Brugnara, G.; Bonekamp, D.; Neuberger, U.; Wick, A.; Schlemmer, H.-P.; Heiland, S.; Wick, W.; et al. Automated Brain Extraction of Multisequence MRI Using Artificial Neural Networks. *Hum. Brain Mapp.* **2019**, *40*, 4952–4964, doi:https://doi.org/10.1002/hbm.24750.
16. Verma, K (Department of Neurology/Dell Medical School at UT Austin), Kumar, S. (Centre of P.S.A. Society for Neuroscience, 2021. In Proceedings of the Automatic segmentation of stroke le-sions on MR images for voxel based lesion symptom mapping; 2021.
17. Annotation“ozgün, A.; Içek, C.; Abdulkadir, A.; Lienkamp, S.S.; Brox, T.; Ronneberger, O. 3D U-Net: Learning Dense Volumetric Segmentation from Sparse Annotation“Ozgün.
18. DiCarlo, J.J.; Zoccolan, D.; Rust, N.C. How Does the Brain Solve Visual Object Recognition? *Neuron* **2012**, *73*, 415–434, doi:10.1016/j.neuron.2012.01.010.
19. Dice, L.R. Measures of the Amount of Ecologic Association between Species. *Ecology* **1945**, *26*, 297–302.
20. Yeghiazaryan, V.; Voiculescu, I. Family of Boundary Overlap Metrics for the Evaluation of Medical Image Segmentation. *J. Med. imaging (Bellingham, Wash.)* **2018**, *5*, 15006, doi:10.1117/1.JMI.5.1.015006.
21. Zhang, Y.J. A Survey on Evaluation Methods for Image Segmentation. *Pattern Recognit.* **1996**, *29*, 1335–1346.

22. Rorden, C.; Karnath, H.O. Using Human Brain Lesions to Infer Function: A Relic from a Past Era in the fMRI Age? *Nat. Rev. Neurosci.* **2004**, *5*, 812–819, doi:10.1038/NRN1521.
23. Kimberg, D.Y.; Coslett, H.B.; Schwartz, M.F. Power in Voxel-Based Lesion-Symptom Mapping. *J. Cogn. Neurosci.* **2007**, *19*, 1067–1080, doi:10.1162/jocn.2007.19.7.1067.
24. Poldrack, R.A.; Huckins, G.; Varoquaux, G. Establishment of Best Practices for Evidence for Prediction: A Review. *JAMA psychiatry* **2020**, *77*, 534–540, doi:10.1001/jamapsychiatry.2019.3671.
25. Hastie, T.; Tibshirani, R.; Friedman, J.H.; Friedman, J.H. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*; Springer, 2009; Vol. 2;.
26. Shorten, C.; Khoshgoftaar, T.M. A Survey on Image Data Augmentation for Deep Learning. *J. Big Data* **2019**, *6*, 60, doi:10.1186/s40537-019-0197-0.
27. Crum, W.R.; Camara, O.; Hill, D.L.G. Generalized Overlap Measures for Evaluation and Validation in Medical Image Analysis. *IEEE Trans. Med. Imaging* **2006**, *25*, 1451–1461, doi:10.1109/TMI.2006.880587.
28. Ito, K.L.; Kim, H.; Liew, S.-L. A Comparison of Automated Lesion Segmentation Approaches for Chronic Stroke T1-Weighted MRI Data. *Hum. Brain Mapp.* **2019**, *40*, 4669–4685, doi:https://doi.org/10.1002/hbm.24729.
29. Liew, S.-L. The Anatomical Tracings of Lesions after Stroke (ATLAS) Dataset - Release 2.0, 2021 2021.
30. Mah, Y.-H.; Nachev, P.; MacKinnon, A.D. Quantifying the Impact of Chronic Ischemic Injury on Clinical Outcomes in Acute Stroke With Machine Learning. *Front. Neurol.* **2020**, *11*, 15, doi:10.3389/fneur.2020.00015.
31. Han, T.S.; Fry, C.H.; Gulli, G.; Affley, B.; Robin, J.; Irvin-Sellers, M.; Fluck, D.; Kakar, P.; Sharma, S.; Sharma, P. Prestroke Disability Predicts Adverse Poststroke Outcome. *Stroke* **2020**, *51*, 594–600, doi:10.1161/STROKEAHA.119.027740.
32. Chao, L.L.; Knight, R.T. Contribution of Human Prefrontal Cortex to Delay Performance. *J. Cogn. Neurosci.* **1998**, *10*, 167–177.
33. Bates, E.; Wilson, S.M.; Saygin, A.P.; Dick, F.; Sereno, M.I.; Knight, R.T.; Dronkers, N.F. Voxel-Based Lesion-Symptom Mapping. *Nat. Neurosci.* **2003**, *6*, 448–450, doi:10.1038/nn1050.
34. Munsch, F.; Sagnier, S.; Asselineau, J.; Bigourdan, A.; Guttmann, C.R.; Debruxelles, S.; Poli, M.; Renou, P.; Perez, P.; Dousset, V. Stroke Location Is an Independent Predictor of Cognitive Outcome. *Stroke* **2016**, *47*, 66–73.
35. Biesbroek, J.M.; van Zandvoort, M.J.E.; Kappelle, L.J.; Velthuis, B.K.; Biessels, G.J.; Postma, A. Shared and Distinct Anatomical Correlates of Semantic and Phonemic Fluency Revealed by Lesion-Symptom Mapping in Patients with Ischemic Stroke. *Brain Struct. Funct.* **2016**, *221*, 2123–2134.
36. Biesbroek, J.M.; van Zandvoort, M.J.E.; Kappelle, L.J.; Schoo, L.; Kuijf, H.J.; Velthuis, B.K.; Biessels, G.J.; Postma, A.; group, U.V.C.I. study Distinct Anatomical Correlates of Discriminability and Criterion Setting in Verbal Recognition Memory Revealed by Lesion-symptom Mapping. *Hum. Brain Mapp.* **2015**, *36*, 1292–1303.
37. Kalénine, S.; Shapiro, A.D.; Buxbaum, L.J. Dissociations of Action Means and Outcome Processing in Left-Hemisphere Stroke. *Neuropsychologia* **2013**, *51*, 1224–1233, doi:10.1016/j.neuropsychologia.2013.03.017.
38. Jwa, A.S.; Poldrack, R.A. The Spectrum of Data Sharing Policies in Neuroimaging Data Repositories. *Hum. Brain Mapp.* **2022**, *43*, 2707–2721, doi:https://doi.org/10.1002/hbm.25803.
39. Alter, G.; Gonzalez, R. Responsible Practices for Data Sharing. *Am. Psychol.* **2018**, *73*, 146–156, doi:10.1037/amp0000258.