



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Logistic Regression-Based Model Is More Efficient Than U-Net Model for Reliable Whole Brain Magnetic Resonance Imaging Segmentation

Citation for published version:

Dieckhaus, H, Meijboom, R, Okar, S, Wu, T, Parvathaneni, P, Mina, Y, Chandran, S, Waldman, AD, Reich, DS & Nair, G 2022, 'Logistic Regression-Based Model Is More Efficient Than U-Net Model for Reliable Whole Brain Magnetic Resonance Imaging Segmentation', *Topics in magnetic resonance imaging : TMRI*, vol. 31, no. 3, pp. 31-39. <https://doi.org/10.1097/RMR.0000000000000296>

Digital Object Identifier (DOI):

[10.1097/RMR.0000000000000296](https://doi.org/10.1097/RMR.0000000000000296)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Topics in magnetic resonance imaging : TMRI

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Logistic Regression–Based Model Is More Efficient Than U-Net Model for Reliable Whole Brain Magnetic Resonance Imaging Segmentation

Henry Dieckhaus, BS,* Rozanna Meijboom, PhD,† Serhat Okar, MD,‡ Tianxia Wu, PhD,§
Prasanna Parvathaneni, PhD,‡ Yair Mina, MD,¶|| Siddharthan Chandran, PhD,† Adam D. Waldman, PhD,†
Daniel S. Reich, MD, PhD,‡ and Govind Nair, PhD*

Abstract: Objectives: Automated whole brain segmentation from magnetic resonance images is of great interest for the development of clinically relevant volumetric markers for various neurological diseases. Although deep learning methods have demonstrated remarkable potential in this area, they may perform poorly in nonoptimal conditions, such as limited training data availability. Manual whole brain segmentation is an incredibly tedious process, so minimizing the data set size required for training segmentation algorithms may be of wide interest. The purpose of this study was to compare the performance of the prototypical deep learning segmentation architecture (U-Net) with a previously published atlas-free traditional machine learning method, Classification using Derivative-based Features (C-DEF) for whole brain segmentation, in the setting of limited training data. **Materials and Methods:** C-DEF and U-Net models were evaluated after training on manually curated data from 5, 10, and 15 participants in 2 research cohorts: (1) people living with clinically diagnosed HIV infection and (2) relapsing–remitting multiple sclerosis, each acquired at separate institutions, and between 5 and 295 participants' data using a large, publicly available, and annotated data set of glioblastoma and lower grade glioma (brain tumor segmentation). Statistics was performed on the Dice similarity coefficient using repeated-measures analysis of variance and Dunnett–Hsu pairwise comparison. **Results:** C-DEF produced better segmentation than U-Net in lesion (29.2%–38.9%) and cerebrospinal fluid (5.3%–11.9%) classes when trained with data from 15 or fewer participants. Unlike C-DEF, U-Net showed significant improvement when increasing the size of the training data (24%–30% higher than baseline). In the brain tumor segmentation data set, C-DEF produced equivalent or better segmentations than U-Net for enhancing tumor and peritumoral edema regions across all training data sizes explored. However, U-Net was more effective than C-DEF for segmentation of

necrotic/non-enhancing tumor when trained on 10 or more participants, probably because of the inconsistent signal intensity of the tissue class.

Conclusions: These results demonstrate that classical machine learning methods can produce more accurate brain segmentation than the far more complex deep learning methods when only small or moderate amounts of training data are available ($n \leq 15$). The magnitude of this advantage varies by tissue and cohort, while U-Net may be preferable for deep gray matter and necrotic/non-enhancing tumor segmentation, particularly with larger training data sets ($n \geq 20$). Given that segmentation models often need to be retrained for application to novel imaging protocols or pathology, the bottleneck associated with large-scale manual annotation could be avoided with classical machine learning algorithms, such as C-DEF.

Key Words: brain segmentation, deep learning, machine learning, MRI

(*Top Magn Reson Imaging* 2022;31:31–39)

In recent years, imaging markers of atrophy and inflammation derived from brain segmentation have been widely used to inform disease status and progression in neurological disorders.^{1–3} These volumetric markers, particularly regarding white matter lesions,^{4,5} are of great interest as potential end points for clinical trials. Although labels manually drawn by an expert rater remain the gold standard for segmentation accuracy, this is prohibitively tedious and costly to do on a large scale. Whole brain segmentation is particularly time-consuming because of the large number of detailed contours that must be delineated across many individual slices. Automation of brain segmentation can therefore help by delivering fast and reproducible imaging markers.⁶

Among automated brain segmentation algorithms, supervised learning methods have demonstrated strong capability to model the signal intensity profiles and spatial context of brain tissues to produce robust brain segmentations. Atlas-free methods offer ability to segment the brain in a disease-independent manner using signal intensity signatures of various tissue types from multiple contrasts and derived image filters.⁷ Recently, deep learning has risen to the forefront by demonstrating state-of-the-art results on a range of medical image segmentation benchmarks, including the MICCAI Brain Tumor Segmentation (BraTS) Challenge, Medical Segmentation Decathlon, and others.^{8–11} The U-Net framework, introduced in 2015 by Ronneberger et al,¹² used a convolutional neural network with skip connections to capture complex spatial information at multiple scales. Since then, much research has focused on improvement of this framework using various strategies for multiscale feature aggregation^{9,13,14} and localization.^{15,16} Despite the proliferation of U-Net-style architectures, many of the same challenges still persist regarding model development and deployment. Model training requires specialized graphics processing

From the *qMRI Core Facility, NINDS, National Institutes of Health, Bethesda, MD; †Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom; ‡Translational Neuroradiology Section, NINDS, National Institutes of Health, Bethesda, MD; §Clinical Trials Unit, NINDS, National Institutes of Health, Bethesda, MD; ¶Viral Immunology Section, NINDS, National Institutes of Health, Bethesda, MD; and ||Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Received for publication April 26, 2022; accepted May 24, 2022.

Address correspondence to Govind Nair, PhD, qMRI Core Facility, NINDS, National Institutes of Health, Room 5C440, 10 Center Drive, Bethesda, MD 20892 (e-mail: bhagavatheeshg@mail.nih.gov).

Supported by the Intramural Research Program at the NINDS. Some images used in this study were sourced from FutureMS study, funded by a grant from the Chief Scientist Office, Scotland, to Precision Medicine Scotland Innovation Centre (PMS-IC) and by Biogen Idec Ltd Insurance (combined funding under reference Exemplar SMS-IC010) to the University of Edinburgh. Further funding for some of the authors included a grant from MS Society Edinburgh Centre for MS Research (R.M.; grant reference 133).

Written work prepared by employees of the Federal Government as part of their official duties is, under the U.S. Copyright Act, a “work of the United States Government” for which copyright protection under Title 17 of the United States Code is not available. As such, copyright does not extend to the contributions of employees of the Federal Government.

DOI: 10.1097/RMR.000000000000296

unit (GPU) resources that are of little use in other aspects of clinical informatics workflows. Owing to the high number of parameters (often greater than a million) involved in training for large 3D or 4D (if multicontrast) volumes, GPU memory limitations often dictate that input size be reduced, with patch extraction being the most common approach.^{17,18} With this in mind, the relative performance of these highly complex deep learning algorithms as opposed to less resource-intensive machine learning algorithms needs to be investigated.

Perhaps more importantly, deep learning models still frequently rely on extensive training data sets and demonstrate inconsistent generalizability across imaging protocols and pathologies. This is significant because a model trained on hundreds of well-labeled public data sets may still find itself to be of limited use while segmenting naive images. Bias introduced by factors such as scanner type and imaging parameters can be great enough to significantly confound segmentation tasks.¹⁹ These factors can make transfer learning or domain adaptation with few labeled examples challenging, particularly if the disease or scanner protocol of interest is rare or novel, making previously learned features less relevant. Therefore, real-world applications of automated segmentation often rely on training models from scratch with manually curated labels from each data set. Such manual annotation requires expert knowledge and therefore places a substantial time demand on qualified experts. Manual annotation is also prone to significant interoperator and intraoperator variability requiring consensus readings,²⁰ further adding to the cost of curation. This can create a significant bottleneck for model development in many cases,²¹ so reducing the size of training data set that is needed may be of wide interest. Therefore, there is a need for algorithms that are robust to training on limited data and a greater understanding of the behavior of supervised segmentation methods under limited training conditions. Several previous studies have observed the effect of training data set size on the performance of deep learning models for medical segmentation tasks, including head-and-neck computed tomography²² and carotid ultrasound.²³ However, this line of inquiry remains underexplored in the domain of whole brain segmentation. In addition, these studies typically do not consider alternative segmentation methods such as classical machine learning for comparison.

This study aims to address these gaps in knowledge by comparison of a deep learning method (U-Net) and a classical machine learning method (Classification using Derivative-based Features [C-DEF]) for segmentation on several clinical data sets under limited training conditions. Each model was evaluated in parallel on 2 moderately sized cohorts ($n = 20$ for each cohort) composed of patients diagnosed with human immunodeficiency virus (HIV) infection and relapsing–remitting multiple sclerosis (MS), respectively. Algorithms were assessed solely for tissue segmentation performance within each cohort to assess the reliability of each method. The amount of training data provided for training was varied to assess the relationship between training data abundance and segmentation performance. This comparison was then extended to a publicly available segmentation benchmark, the MICCAI BraTS 2020 Training data set, modified to classify only the manually delineated pathological tissue subtypes, to validate the observed trends over a larger range of training data set sizes.

MATERIALS AND METHODS

Data Sets and Preprocessing

Multimodal brain magnetic resonance imaging scans were obtained at 3T from study participants clinically diagnosed with relapsing–remitting MS using the 2010 revised McDonald Criteria²⁴ (MS cohort) and people living with human immunodeficiency virus (HIV) infection

(HIV cohort). MS cohort participants were recruited as part of the FutureMS study (<https://future-ms.org>). Study protocols were approved by the institutional review board of the National Institute of Neurological Disorders and Stroke (reference number NCT01875588) for the HIV cohort and the National Health Service South East Scotland Research Ethics Committee 02 (reference number 15/SS/0233) for the MS cohort, and all participants provided written informed consent. Images used in this analysis included MPRAGE (repetition time [TR]/echo time [TE]/inversion time [TI] = 2500/2.26/1100 ms, 1-mm isotropic resolution), 3D FLAIR (TR/TE/TI = 5000/393/1800 ms, 1-mm isotropic resolution), and proton density/T2 (2D fast spin echo, TR/TE = 3630/9.6 and 96 ms, $0.7 \times 0.7 \times 3$ mm resolution) acquired on a Siemens Prisma 3T for the MS cohort and MPRAGE (TR/TE/TI = 6.9/3.2/900 ms, 1-mm isotropic resolution), FLAIR (TR/TE/TI = 4800/350/1650 ms, 1-mm isotropic resolution), and proton density/T2 (2D turbo spin echo, TR/TE = 3418/15 and 100 ms, $0.9 \times 0.9 \times 3$ mm resolution) acquired on the Philips Achieva 3T (Philips Healthcare, Andover, MA) for the HIV cohort. All magnetic resonance images were coregistered to the corresponding MPRAGE image and were skull stripped, bias field corrected, and normalized using AFNI tools,²⁵ as described in the study by Selvagesan et al.⁷ Whole brain segmentations were obtained using FreeSurfer²⁶ on the MPRAGE and FLAIR images and then converted into the following labels: cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM). These labels were then manually edited for errors, and lesions were manually drawn by either a trained neurologist (Y.M., S.O.) or a clinical neuroscientist (R.M.), each with more than 5 years of experience.

The multi-institutional MICCAI BraTS 2020 Training data set (BraTS cohort, <https://www.med.upenn.edu/cbica/brats2020/data.html>) was used to check the applicability of our findings to a much larger data set with widely accepted gold standard masks.¹¹ This data set contains preprocessed multimodal input data and expert-drawn glioma region segmentations for 369 participants. The images were individually z-score normalized before modeling. For these experiments, the healthy tissue labels were omitted because it contained a mixture of signal intensity profiles from WM, GM, and CSF and therefore was not relevant to the techniques being tested herein. The 3 remaining labels of the tumor regions were used for training and testing: enhancing tumor (ET), peritumoral edema (PE), and necrotic/non-enhancing tumor (NCR/NET).

Brain Segmentation Methods

Figure 1 shows the inference pipeline for our parallel evaluation of C-DEF and U-Net. All models were trained from scratch on each cohort. In the C-DEF pathway (blue shading), image features were derived and used as inputs for a logistic regression classifier following the previously published method.⁷ Gaussian blur and Gaussian gradient filters with kernel sizes of 3^3 , 5^3 , 7^3 , 9^3 , 17^3 , 33^3 , and 65^3 were calculated for each contrast and concatenated with the unfiltered images.²⁷ These features were z-score normalized based on the mean and standard deviation of the entire training data set and were then used to train a multinomial logistic regression classifier with a maximum of 200 iterations and L2 regularization ($C = 0.05$) to prevent overfitting. For detailed methods, refer to the study by Selvagesan et al.⁷ C-DEF models were implemented on a computing cluster with 64× Intel Xeon central processing units (CPUs) (Intel Corporation, Santa Clara, CA) with 256 GB RAM running CentOS 7.7.

In the U-Net pathway (green shading), a 3D U-Net model was used to train and predict on 3D image patches, and then, the output patches were concatenated to produce the final segmentation. U-Net architecture was adapted from the original 3D U-Net method²⁸ with 32 filters in the first convolution layer, but with

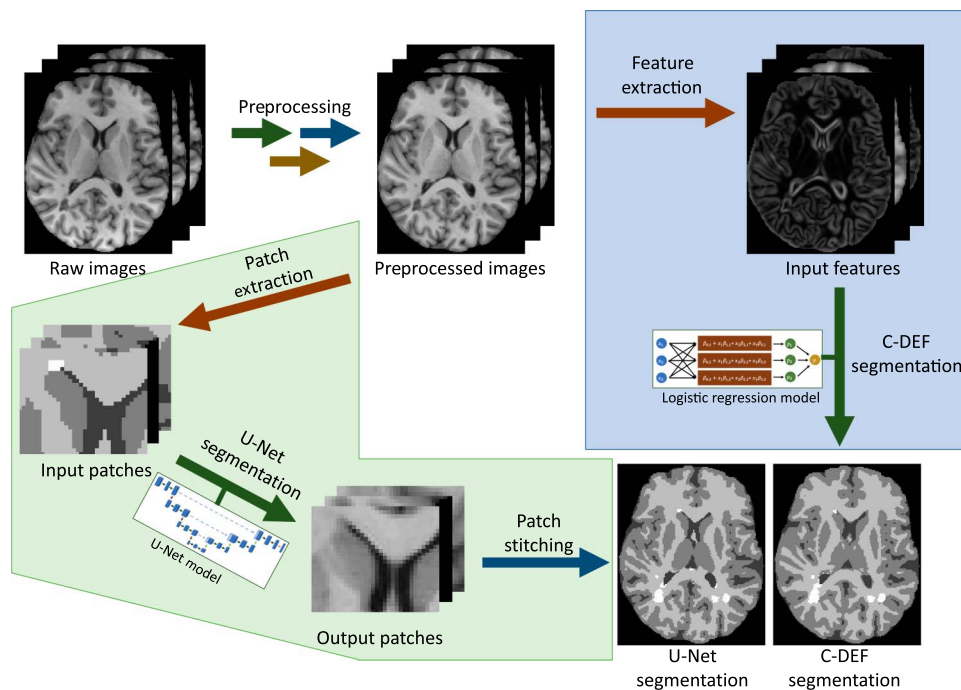


FIGURE 1. Analysis workflow. C-DEF (shaded in blue) and U-Net (shaded in green) algorithms for brain segmentation. Preprocessing consisted of coregistration, bias correction, and intensity normalization. C-DEF, Classification using Derivative-based Features.

the use of padded convolution layers and randomly sampled input patches for training.¹⁸ Key hyperparameters, including patch size, batch size, learning rate, and number of epochs, were tuned by 5-fold cross-validation grid search on the MS cohort (data not shown), and the configuration with the highest average Dice similarity coefficient (DSC) was chosen. Based on this, the Adam optimizer with categorical cross-entropy loss and a learning rate of 1×10^{-3} was trained for a maximum of 50 epochs with a batch size of 60, and early stopping was conditioned on validation loss to prevent overfitting. For each participant, 1000 random nonzero voxels were selected and patches of size 32^3 were extracted centered at each voxel. Data augmentation consisted of random patch-wise reflections, rotations, and elastic deformations during training. The U-Net model was implemented in Keras with TensorFlow backend on an NVIDIA v100-SXM2 GPU (NVIDIA, Santa Clara, CA) with 32 GB VRAM and 8 Intel Xeon Gold 6410 CPUs (Intel Corporation, Santa Clara, CA) with 64 GB RAM.

C-DEF Versus U-Net Comparison

The optimized C-DEF and U-Net methods were then applied to the full MS and HIV cohorts. Models were evaluated by 5-fold cross-validation using an 80/20 training/testing split for C-DEF and U-Net, with 25% of the training data used for validation in the latter case. For each cross-validation fold, the training (including validation in the case of U-Net) data set was then subsampled to include 5, 10, or 15 participants for model fitting to simulate limited training data availability. This subsampling was randomly generated but kept consistent between corresponding C-DEF and U-Net runs (eg, C-DEF-5 and U-Net-5) to provide a fair comparison. The same comparison was also applied to the BraTS cohort with additional models trained with data from 20, 40, 80, 160, and 295 (maximum available) participants. Mean computational cost statistics were calculated from 3-fold repeated measurements.

Qualitative Evaluation

Output segmentations for the HIV and MS cohorts were first visually inspected and then qualitatively scored by an experienced neurologist (S.O.) or trained clinical neuroscientist (R.M.), respectively, while blinded to the method and model used to generate each segmentation. A 5-point rating scale was used ranging from 1 = “very bad” to 5 = “very good” for each tissue class. Net score for each segmentation was calculated as the mean of the ratings for all tissue classes, with lesion segmentations weighted double because of their importance as a potential marker for neurological disease progression.

Quantitative Evaluation and Statistical Analysis

DSC scores were calculated according to the following formula:

$$DSC = \frac{2 TP}{2 TP + FP + FN}$$

where TP, FP, and FN are the number of true positive, false positive, and false negative voxels, respectively, when segmentation results were compared with labels manually drawn by an expert neurologist. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). Box-Cox data transformation was applied to the 2 data sets with minimum observations <0.1 . The Shapiro-Wilk test (sample size <50) or the Kolmogorov-Smirnov test was used to check the normality assumption. For each tissue class, repeated-measures analysis of variance was conducted to evaluate the effect of the scoring method on mean DSC. Intraclass correlation coefficient (ICC) and 95% confidence intervals (CIs) were calculated to examine the correlation and

agreement of the different scoring methods (treated as raters). The Bland–Altman agreement analysis was performed using segmentation tissue volumes of model pairs to examine potential biases between C-DEF and U-Net models trained on the same data. The Bonferroni-corrected P -value <0.05 was considered to be statistically significant.

Code and Data Availability

BraTS is a publicly available data set. Code and data for C-DEF and prototypical U-Net models used herein will be made available through GitHub on acceptance of manuscript. The MS and HIV data in this project are confidential and obtained through a natural history study but may be obtained with Material Transfer Agreements, subject to NIH's policy on data sharing.

RESULTS

Participant Cohorts

The Institutional Review Board approved the study protocols, and all participants provided written informed consent. Images acquired from participants diagnosed with relapsing–remitting MS (MS cohort, $n = 20$, 13 women, age 36 ± 8 years, time from diagnosis 0.2 ± 0.1 years, and Expanded Disability Status Scale 2.5 ± 1.8) and people living with HIV (HIV cohort, $n = 18$, 10 women, age 56 ± 4 years, time from diagnosis 20 ± 8 years) were used in this study (mean \pm standard deviation). Label masks were

derived from FreeSurfer segmentations,²⁶ which were converted to WM, GM, and CSF. These were carefully edited by 1 of 3 neurologists and/or clinical neuroscientists (R.M., Y.M., S.O.), who then manually added the lesion class. In addition, a collection of multimodal magnetic resonance imaging scans of patients with glioblastoma ($n = 293$) and patients with lower-grade glioma ($n = 76$) with manually drawn tumor segmentation masks were downloaded from the MICCAI BraTS 2020 online portal and modified to exclude normal brain regions^{11,29} (<https://www.med.upenn.edu/cbica/brats2020/data.html>).

Whole Brain Segmentation

Qualitative examination of segmentation results from C-DEF trained on data from 5, 10, and 15 MS cohort participants revealed no obviously visible improvement (Fig. 2A, top row; mean ratings: 3.77, 3.79, and 3.79, respectively), whereas significant improvements (yellow arrows) were seen, especially for lesion segmentation, by increasing the training data supplied to U-Net (Fig. 2A, middle row; mean ratings: 3.55, 3.90, and 3.93, respectively). U-Net-5 had low lesion sensitivity, especially for small punctate lesions (red arrows), and higher occurrence of false positives from artifactual hyperintensities (not shown). These results were mostly replicated in the HIV cohort (Fig. 2B), with the exception that U-Net-15 (4.12) rated worse than U-Net-10 (4.58) because of errors in the brainstem.

The quantitative results found that, for both cohorts, DSC from C-DEF segmentations was unchanged with additional training data, but DSC from U-Net segmentation improved significantly with more training data ($P < 0.05$, slice test applied to DSC from each tissue

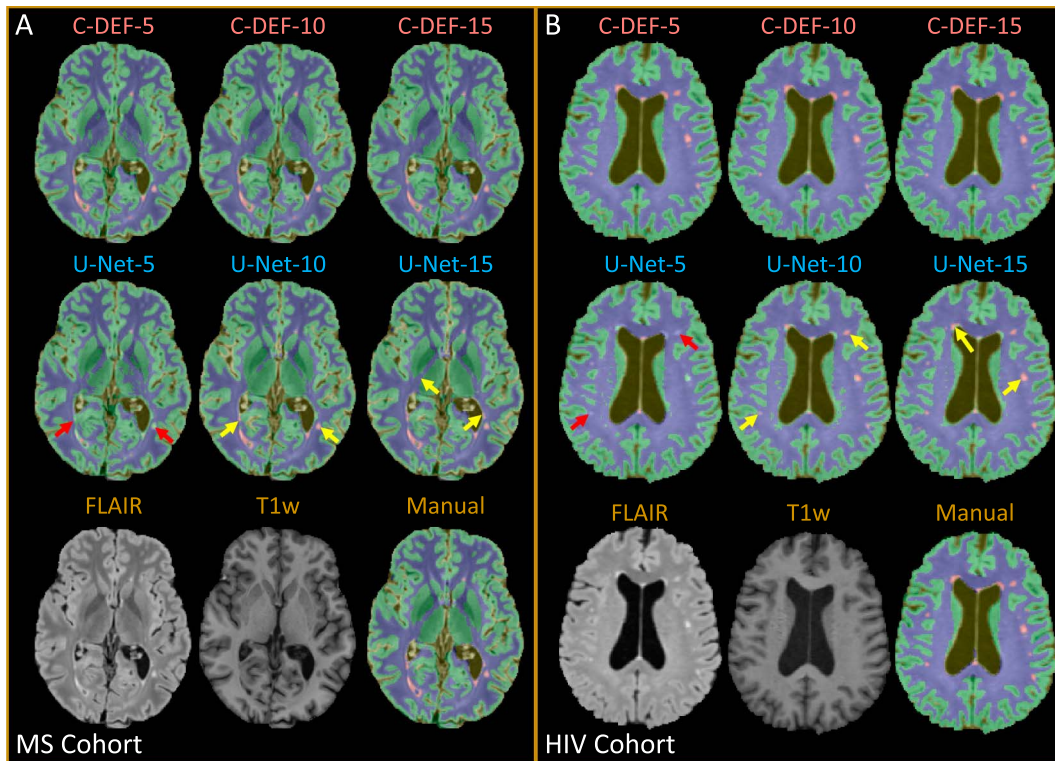


FIGURE 2. Qualitative assessment of segmentation at various training data set sizes. Output of segmentation performed with varied numbers of training data (5, 10, and 15) using C-DEF and U-Net algorithms shown on a representative slice from a participant in (A) (male participant, 34 years) the MS cohort and (B) (female participant, 56 years) the HIV cohort. The bottom row shows preprocessed input scans and the manually drawn mask for reference. Red arrows indicate segmentation errors, while yellow arrows indicate areas of improved segmentation with more training data. C-DEF, Classification using Derivative-based Features; HIV, human immunodeficiency virus; MS, multiple sclerosis.

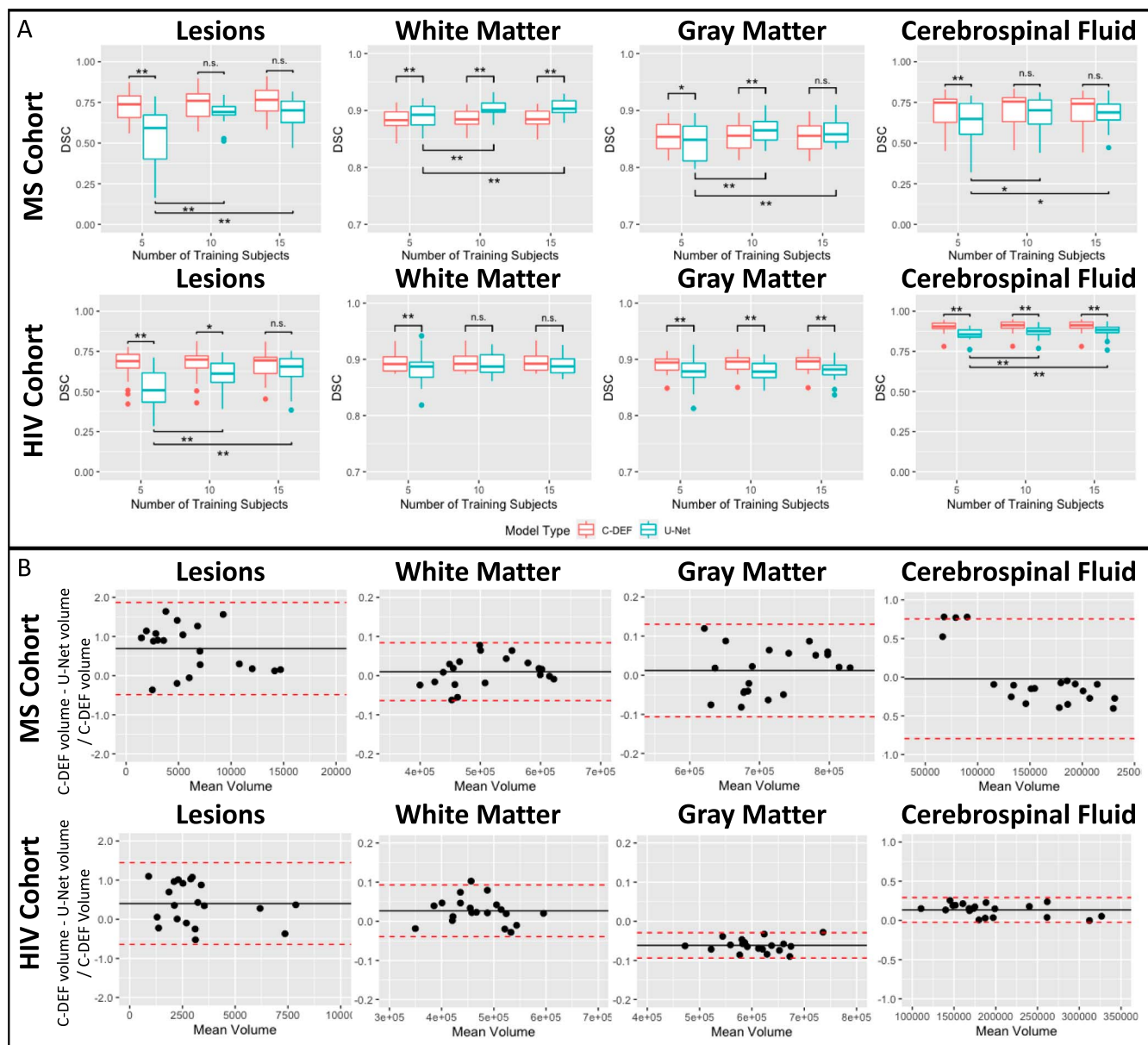


FIGURE 3. Comparison of U-Net and C-DEF segmentation. (A) DSC of the output of the C-DEF and U-Net models with manually annotated mask, when trained with varied numbers of training data (5, 10, and 15). Asterisks indicate statistically significant differences ($*P < 0.05$, $**P < 0.005$). Note that DSC (y axis) for white and gray matter is scaled 0.7–1.0 for better visualization. (B) Bland–Altman analysis of tissue volumes of C-DEF and U-Net trained on data from 5 participants from the MS (top) and HIV (bottom) cohort. Bias (black line) and 95% CI (red dotted line) are indicated. C-DEF, Classification using Derivative-based Features; CI, confidence interval; DSC, Dice similarity coefficient; HIV, human immunodeficiency virus; MS, multiple sclerosis.

class; Fig. 3A). In the MS cohort, DSC from the U-Net segmentation improved, on average, by 30% in the lesion class ($P < 0.001$), 8% in the CSF class ($P < 0.01$), 2% in the GM class ($P < 0.001$), and 1% in WM class ($P < 0.001$) when using training data from 15 participants compared with the data from 5 participants. U-Net segmentation in the HIV cohort showed similar DSC increases with a 24% improvement in the lesion class ($P < 0.001$) and 2% improvement in the CSF class ($P < 0.01$). It should be noted that the DSC from WM and GM segmentation was not significantly changed in the HIV cohort. Consistent with qualitative examination, the quantitative results from U-Net-5 segmentation had worse DSC across all tissues

than C-DEF-5 for both cohorts, except for WM in the MS cohort. Meanwhile, U-Net-15 segmentation had similar lesion, GM, and CSF DSC as C-DEF-15 segmentation in the MS cohort and similar lesion and WM DSC in the HIV cohort.

ICC between C-DEF models trained with data from 5, 10, and 15 participants were >0.92 and >0.96 in all tissue classes in the MS cohort and the HIV cohort, respectively. Between U-Net models, it varied from 0.72 (CI: 0.52–0.87) in the WM class to less than 0.1 (CI: -0.15 to 0.39) in the lesion class in the MS cohort and from 0.60 (CI: 0.35–0.81) in the CSF class to less than 0.4 (CI: 0.07–0.65) in the lesion class in the HIV cohort. Furthermore, the Bland–Altman

analysis (Fig. 3B) found that U-Net-5 consistently gave much smaller lesion volumes compared with C-DEF-5 segmentation in both cohorts (MS cohort mean bias: 0.69, CI: -0.49 to 1.87 ; HIV cohort mean bias: 0.40, CI: -0.64 to 1.45). The same comparison with models trained on 15 data points (not shown) found a 67%–70% reduction in lesion volume bias (MS: 0.20, CI: -0.35 to 0.75 ; HIV: 0.13, CI: -0.47 to 0.73) compared with the 5 participant models. In the MS cohort, C-DEF-5 produced smaller CSF volumes compared with U-Net-5 for most participants, with a few exceptions. Visual inspection of the 4 U-Net segmentations that deviated from this trend (not shown) revealed abnormally low sulcal CSF sensitivity. For each tissue class, the MS cohort had a greater range of relative volume differences, which is consistent with qualitative observations of greater similarity between C-DEF and U-Net segmentations in the HIV cohort. In addition, the Bland–Altman analysis of C-DEF compared with the manually edited masks (not shown) confirmed that MS cohort CSF volumes for C-DEF were consistently lower than those present in the manual labels, regardless of the amount of training data used.

Difference map calculations of MS cohort segmentations revealed that C-DEF was better able to detect fine details of the cerebellar GM/WM folds, whereas U-Net typically failed to do so (Fig. 4A). C-DEF also produced more plausible cortical GM boundaries than U-Net in many cases (Fig. 4B). Qualitative inspection of the FreeSurfer-derived manually edited training labels found that these 2 areas were particularly prone to labeling noise and subtle errors, which were more readily replicated by U-Net than by C-DEF. Finally, C-DEF more often misclassified parts of subcortical GM structures, including the globus pallidus and thalamus, as WM, whereas U-Net generally labeled them correctly (Fig. 4C).

Tumor Segmentation of Glioma Data Set

To validate and extrapolate these findings, we downloaded a large publicly available data set and modified it to simulate tissue

segmentation using signal intensity profiles. Table 1 summarizes the performance of C-DEF and U-Net models on the modified BraTS cohort. C-DEF outperformed U-Net by mean DSC on the ET and PE classes when trained on the data from 5 participants ($P < 0.001$, Dunnett–Hsu test), while the NCT/NET DSC was not significantly different between C-DEF-5 and U-Net-5. Although no difference in mean DSC for any class was seen between C-DEF-5 and C-DEF-10, it did increase significantly for all classes between U-Net-5 and U-Net-10. When trained on much more data (>20 participants), C-DEF mean DSC did eventually increase significantly, with an average improvement of 12% (ET), 7.6% (PE), and 190% (NCR/NET) from minimum to maximum amount of training data. Over the same range, U-Net scores increased: 43% (ET), 62% (PE), and 200% (NCR/NET). C-DEF was better or statistically equivalent to U-Net by DSC for PE and ET tissue classes for every training regime tested, except for PE with 160 training data. However, U-Net did demonstrate a significant advantage on the NCR/NET tissue class for all except 5 and 15 training data models. Although C-DEF models collectively produced ICCs of 0.81 (0.78–0.83) and 0.89 (0.88–0.91) for ET and PE DSC, indicating highly similar segmentation results, it had a far lower ICC of 0.62 (0.58–0.66) for NCR/NET DSC, indicating only mild consistency in segmentation results for C-DEF models trained on different amounts of data.

Computational Cost Comparison

Benchmark computational cost data for C-DEF and U-Net models were gathered during comparison on the MS cohort. When trained on the minimum 5 participants in the same CPU environment, U-Net (8400 ± 76 min) was more than 2 orders of magnitude slower than C-DEF (38.8 ± 0.7 min) for overall training time per training participant. When deployed optimally on a v100 GPU, U-Net training time (33 ± 2 min) was comparable with C-DEF

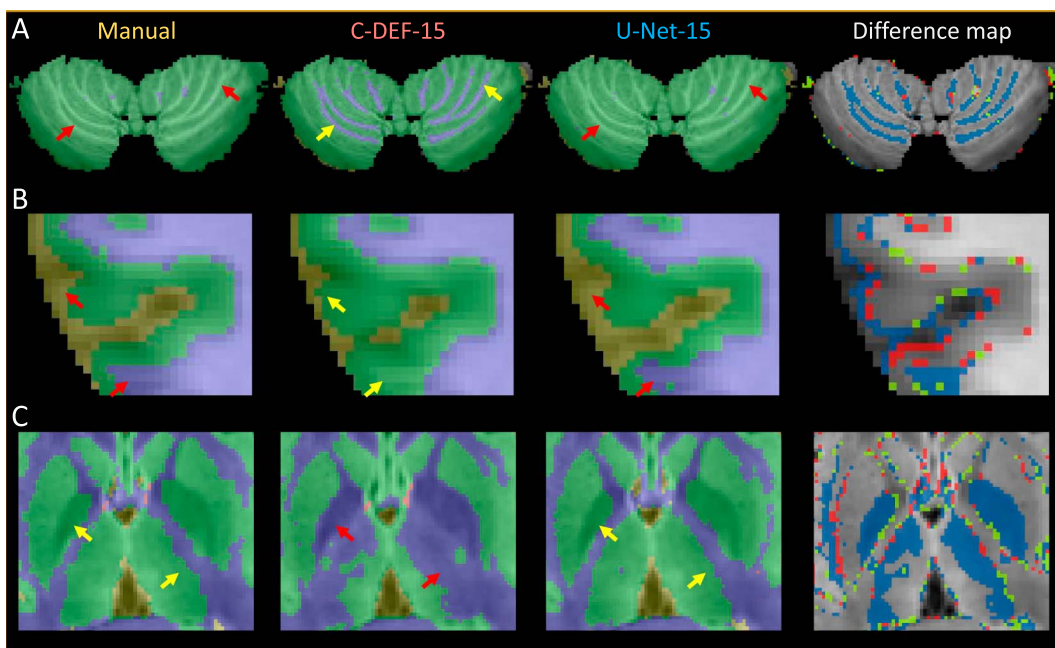


FIGURE 4. Effect of errors in training labels. Zoomed-in details of segmentation outputs from a representative MS cohort participant (male participant, 30 years) using C-DEF-15, U-Net-15, and their difference maps compared with the manually annotated mask (blue: mismatched segmentation by C-DEF-15; red: mismatched segmentation by U-Net-15; green: mismatched segmentation by both C-DEF-15 and U-Net-15) for (A) cerebellum, (B) cortical GM boundary, and (C) subcortical GM structures. Red arrows indicate segmentation errors, while yellow arrows indicate correctly labeled segmentation. C-DEF, Classification using Derivative-based Features; GM, gray matter; MS, multiple sclerosis.

TABLE 1. Performance of C-DEF and U-Net Models on BraTS Cohort Using Limited Training Data

Model	Mean DSC (95% CI)		
	ET	PE	NCR/NET
C-DEF-5	0.74 (0.72–0.76)	0.81 (0.80–0.83)	0.15 (0.13–0.18)
U-Net-5	0.58 (0.56–0.60)	0.55 (0.52–0.57)	0.17 (0.15–0.20)
C-DEF-10	0.72 (0.70–0.74)	0.83 (0.81–0.84)	0.17 (0.15–0.20)
U-Net-10	0.70 (0.68–0.72)	0.83 (0.82–0.85)	0.28 (0.25–0.31)
C-DEF-15	0.76 (0.74–0.77)	0.85 (0.83–0.86)	0.24 (0.22–0.27)
U-Net-15	0.73 (0.71–0.75)	0.82 (0.81–0.84)	0.27 (0.24–0.30)
C-DEF-20	0.76 (0.74–0.78)	0.84 (0.82–0.85)	0.21 (0.19–0.24)
U-Net-20	0.77 (0.75–0.79)	0.80 (0.79–0.82)	0.28 (0.25–0.31)
C-DEF-40	0.80 (0.78–0.81)	0.85 (0.84–0.87)	0.28 (0.25–0.31)
U-Net-40	0.78 (0.77–0.80)	0.85 (0.84–0.87)	0.34 (0.31–0.38)
C-DEF-80	0.81 (0.80–0.83)	0.86 (0.85–0.88)	0.32 (0.29–0.36)
U-Net-80	0.81 (0.80–0.83)	0.88 (0.86–0.89)	0.48 (0.44–0.52)
C-DEF-160	0.83 (0.82–0.85)	0.87 (0.86–0.89)	0.39 (0.36–0.43)
U-Net-160	0.82 (0.81–0.84)	0.89 (0.88–0.91)	0.51 (0.47–0.55)
C-DEF-All*	0.83 (0.81–0.84)	0.88 (0.86–0.89)	0.43 (0.39–0.46)
U-Net-All*	0.83 (0.81–0.84)	0.89 (0.88–0.91)	0.51 (0.47–0.55)

*Trained on data from 295 participants per fold.

BraTS indicates brain tumor segmentation; C-DEF, Classification using Derivative-based Features; CI, confidence interval; DSC, Dice similarity coefficient; ET, enhancing tumor; NCR/NET, necrotic/non-enhancing tumor; PE, peritumoral edema.

deployed on CPU, and inference was nearly 3 times faster (0.20 ± 0.01 min/participant compared with 0.55 ± 0.02 min/participant for C-DEF). It should be noted that C-DEF is currently only implemented on CPU. Overall training time of both U-Net and C-DEF increased approximately linearly with the number of training participants in both the MS and HIV cohorts.

DISCUSSION

A logistic regression model using derived image textures (C-DEF) for brain segmentation performed equivalent or better by several key metrics than a prevalent deep learning algorithm (U-Net) when trained on manually edited masks from a small to moderate number of participants ($n \leq 15$). In particular, C-DEF produced good lesion and CSF segmentations even when trained on the minimum 5 training participants, whereas U-Net did not. The performance of U-Net models for whole brain segmentation improved significantly with increasing amounts of training data; however, no significant improvements were seen in C-DEF models with increasing size of training data. U-Net produced better segmentation of certain structures, such as the thalamus and globus pallidus, with more subtle tissue intensity signatures. However, C-DEF was more robust to minor annotation errors in the training data, leading to better segmentation of certain structures, such as cerebellar folds and cortical GM boundaries. Moreover, deep learning algorithms, such as U-Net, require more compute resources than a classical machine learning method, such as C-DEF, to perform model training in a reasonable amount of time. Taken together, we have demonstrated that a classical machine learning algorithm, such as C-DEF, can produce equivalent or better whole brain segmentation based on signal intensity profiles than a much more resource-intensive deep learning algorithm, such as U-Net, in the case of limited training data. Furthermore, the accuracy of C-DEF segmentation is high even with limited ($n = 5$) training data and comparable with the accuracy of U-Net trained with larger ($n = 15$) training data, making it a less labor-intensive and more cost-effective option.

Minimizing the amount of manual label annotation required to obtain a reasonable model is an important goal often overlooked during model development. This step can have a large impact on the time needed to implement a segmentation pipeline for a given

application³⁰ because it is extremely tedious and requires expert knowledge of neuroanatomy and/or neuroradiology. This is particularly true for a task such as whole brain segmentation, as opposed to targeted quantification of a single structure, such as glioma segmentation. Given that the efficacy of any supervised learning model is highly dependent on the quality of the training data, the threshold for acceptable annotations is generally quite high. It may therefore be advantageous to be able to obtain robust segmentations from only a few very carefully edited training data, rather than relying on a much larger pool of training data that may be more susceptible to large annotation errors because of its size. C-DEF achieves semantic segmentation by modeling individual voxels (along with their derived features), which means that a single annotated subject could be considered a source of millions of individual training data points. Meanwhile, U-Net dictates training on large image patches, which reduces the number of discrete training examples that can be obtained from each subject, even after data augmentation. Therefore, it is intuitive that C-DEF may be far less susceptible to overfitting and other penalties of insufficient training data.

The advantages of C-DEF were more pronounced when training was performed on a smaller number of training data. C-DEF produced reasonably good segmentations after training on data from only 5 participants, while U-Net segmentations were significantly degraded when trained with very few data points. The latter are evidenced not only by raw DSC scores (Fig. 3A) but also by the subpar CSF volumes produced in a single fold of U-Net-5 (Fig. 3B, top rightmost plot), which are sufficiently aberrant as to indicate model instability. C-DEF was also more effective in segmentation of certain structures, such as cerebellar folds and sulcal GM boundaries, particularly in the MS cohort (Figs. 4A, B). These regions were observed to be susceptible to labeling errors, which may indicate that C-DEF effectively lowers the quality threshold for training annotations by avoiding overfitting, provided that texture-enriched tissue intensity signatures are reasonably well-resolved. Indeed, we refrained from using the term gold standard masks for manually annotated masks because of the presence of such errors. This capability presents a trade-off because C-DEF was largely ineffective for segmentation of certain regions where tissue intensity signatures were not well-resolved, such as the thalamus and globus pallidus. As a result, U-Net demonstrated slightly better overall WM

and GM DSC for some training regimes, but only on the MS cohort. Our training annotations were derived from FreeSurfer subcortical segmentation, which uses an atlas of annotated examples as priors.²⁶ This mitigates the issue of overlapping tissue intensity signatures by using a combination of local and global factors and their correlations to determine the most likely label for a given voxel. U-Net was given no such priors, but it was able to identify subcortical GM structures more reliably than C-DEF using only patch-wise spatial features. This difference could be due to a number of factors but is likely related to the fact that the number and complexity of features captured by U-Net far surpass the small (<50) number of localized image textures incorporated into a single-layer logistic regression model by C-DEF. It may also indicate that deep GM structures are not linearly distributed and therefore not easily separable by the linear decision boundaries defined by C-DEF, as opposed to the more complex boundaries available to a deep network, such as U-Net.

To further explore the dependence of each algorithm on training data size, the MICCAI BraTS 2020 Training data set was used as a supplementary comparison. This data set was chosen based on its large, expert-curated set of gold standard labels and its widespread acceptance as a public benchmark in the medical image segmentation community. Unfortunately, whole brain segmentation labels are not provided for this data set, so the “healthy tissue” label encompasses regions of WM, GM, and CSF, leading to an indeterminate tissue intensity signature. To adapt the tumor segmentation task to be more comparable with whole brain segmentation, we chose to omit the healthy tissue label from training and quantify segmentation of the 3 tumor regions (ET, NCR/NET, and PE) directly rather than using the nested anatomical labels (ET, tumor core, whole tumor) of the official BraTS challenge. When evaluated on the ET and PE regions, C-DEF was better or equivalent to U-Net, regardless of the number of participants used for training (up to 295). However, we observed that both C-DEF and U-Net struggled with segmentation of NCR/NET regions, with U-Net producing significantly better results in this region with moderate ($n = 10$) and large ($n \geq 20$) training data sizes. The ET and NCR/NET labels were both modest minority classes, representing 19.8% and 22.2% of the data compared with 58.0% belonging to the PE class. The NCR/NET label also had significant overlap with the PE class for tissue intensity signatures (data not shown), which may have been exacerbated by the significant variation in intensity profiles in this multi-institutional data set. These factors may have been at least in part responsible for the larger relative increase in NCR/NET DSC with more training.

Magnetic resonance images, especially at high fields, are prone to bias fields from radiofrequency excitation and receive profiles, which can confound segmentation using only local voxel intensities.^{20,31} In addition, spatial context plays a critical role in tissue segmentation.^{7,20} To address these issues, derived image textures offer a viable alternative to atlas-based strategies. Exhaustive optimization by searching all potential texture sets remains an intractably large task, which is one limitation of the C-DEF approach. U-Net offers one solution to this problem by effectively optimizing its own filters albeit at great computational expense. The effects of changing the number of U-Net filters and spatial factors, such as patch size and overall architecture depth, are complicated, and exhaustive exploration of this space is beyond the scope of this work. Prior work has found evidence that deeper networks are not always better, depending on the complexity of the modeled data set.¹⁴ For the comparison herein, we tried to match the maximum receptive field in the U-Net architecture (which depends on the size of the filters and depth of the architecture) to the maximum filter kernel used in the C-DEF model.

The scope of this inquiry was limited to comparison of 1 representative deep learning method and 1 classical machine learning algorithm as “off-the-shelf” tools for whole brain segmentation. As such, we chose not to perform exhaustive hyperparameter optimization for either method. It is likely that such optimization could provide performance gains for the chosen data sets, but this remains difficult to predict a priori. Moreover, it is yet unclear whether or when U-Net may definitively exceed overall C-DEF performance given additional training data or whether a different network architecture is required. Studies in recent years have produced numerous derivations of U-Net intended to boost the performance in a variety of segmentation tasks.^{32–34} However, these methods remain largely developed and validated on large data sets, making it difficult to evaluate whether proposed modifications will enhance performance in a limited training context. Moreover, it is important to first establish the baseline performance characteristics of the U-Net model used herein in this context before investigation of more complicated approaches derived from this framework. For these reasons, we chose a 3D patch-based U-Net as our representative deep learning method. In the future, we plan to expand this line of inquiry by benchmarking some of these recent modifications to probe the impact of model architecture changes on training data dependence. Of particular interest for future examination is the recently proposed nnU-Net, which has shown impressive results on a wide range of medical image segmentation tasks.⁸

CONCLUSION

This study demonstrates that there is an important niche for classical machine learning methods such as C-DEF to fill by providing robust models trained on only a few labeled examples. Avenues for future study include improvement of C-DEF segmentation of subcortical GM and comparison of recent U-Net-style methods in a larger whole brain segmentation data set.

ACKNOWLEDGMENTS

Thanks to Avindra Nath and Bryan Smith for providing the allHANDS (HIV cohort) data set. This work used the computational resources of the NIH HPC Biowulf cluster (<http://hpc.nih.gov>).

REFERENCES

1. Marquez F, Yassa MA. Neuroimaging biomarkers for Alzheimer's disease. *Mol Neurodegener.* 2019;14:21.
2. Tur C, Moccia M, Barkhof F, et al. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. *Nat Rev Neurol.* 2018;14:75–93.
3. Cortese R, Collorone S, Ciccarelli O, et al. Advances in brain imaging in multiple sclerosis. *Ther Adv Neurol Disord.* 2019;12:1756286419859722.
4. Jansen JFA, Vlooswijk MCG, Majoie HM, et al. White matter lesions in patients with localization-related epilepsy. *Invest Radiol.* 2008;43:552–558.
5. Sicotte NL, Voskuhl RR, Bouvier S, et al. Comparison of multiple sclerosis lesions at 1.5 and 3.0 Tesla. *Invest Radiol.* 2003;38:423–427.
6. Hagiwara A, Fujita S, Ohno Y, et al. Variability and standardization of quantitative imaging: monoparametric to multiparametric quantification, radiomics, and artificial intelligence. *Invest Radiol.* 2020;55:601–616.
7. Selvagesan K, Whitehead E, DeAlwis PM, et al. Robust, atlas-free, automatic segmentation of brain MRI in health and disease. *Heliyon.* 2019;5:e01226.
8. Isensee F, Jaeger PF, Kohl SAA, et al. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. *Nat Methods.* 2021;18:203–211.

9. Ji Y, Zhang R, Li Z, et al. *UXNet: Searching Multi-level Feature Aggregation for 3D Medical Image Segmentation*. Cham, Switzerland: Springer International Publishing; 2020:346–356.
10. Akkus Z, Galimzianova A, Hoogi A, et al. Deep learning for brain MRI segmentation: state of the art and future directions. *J Digit Imaging*. 2017; 30:449–459.
11. Menze BH, Jakab A, Bauer S, et al. The Multimodal Brain Tumor Image Segmentation Benchmark (BRATS). *IEEE Trans Med Imaging*. 2015;34: 1993–2024.
12. Ronneberger O, Fischer P, Brox T. U-Net: convolutional networks for biomedical image segmentation. In: Navab N, Hornegger J, Wells WM, et al, eds. *Medical Image Computing and Computer-Assisted Intervention—MICCAI 2015*. Cham, Switzerland: Springer International Publishing; 234–241.
13. Ibtehaz N, Rahman MS. MultiResUNet: rethinking the U-Net architecture for multimodal biomedical image segmentation. *Neural Netw*. 2020;121:74–87.
14. Zhou Z, Siddiquee MMR, Tajbakhsh N, et al. UNet++: redesigning skip connections to exploit multiscale features in image segmentation. *IEEE Trans Med Imaging*. 2020;39:1856–1867.
15. Schlemper J, Oktay O, Schaap M, et al. Attention gated networks: learning to leverage salient regions in medical images. *Med Image Anal*. 2019;53:197–207.
16. Yuan Y. *Automatic Brain Tumor Segmentation with Scale Attention Network*. Cham, Switzerland: Springer International Publishing; 2021:285–294.
17. Huo Y, Xu Z, Xiong Y, et al. 3D whole brain segmentation using spatially localized atlas network tiles. *NeuroImage*. 2019;194:105–119.
18. Zhao L, Feng X, Meyer CH, et al. Choroid plexus segmentation using optimized 3D U-Net. In: *Proceedings of IEEE International Symposium on Biomedical Imaging*, April 3-7, 2020. IEEE:381-384.
19. Yan W, Huang L, Xia L, et al. MRI manufacturer shift and adaptation: increasing the generalizability of deep learning segmentation for MR images acquired with different scanners. *Radiol Artif Intell*. 2020;2:e190195.
20. Despotović I, Goossens B, Philips W. MRI segmentation of the human brain: challenges, methods, and applications. *Comput Math Methods Med*. 2015; 2015:450341.
21. Wichmann JL, Willeminck MJ, De Cecco CN. Artificial intelligence and machine learning in radiology: current state and considerations for routine clinical implementation. *Invest Radiol*. 2020;55:619–627.
22. Fang Y, Wang J, Ou X, et al. The impact of training sample size on deep learning-based organ auto-segmentation for head-and-neck patients. *Phys Med Biol*. 2021;66:185012.
23. Lekadir K, Galimzianova A, Betriu A, et al. A convolutional neural network for automatic characterization of plaque composition in carotid ultrasound. *IEEE J Biomed Health Inform*. 2017;21:48–55.
24. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69:292–302.
25. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996;29:162–173.
26. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33:341–355.
27. Dieckhaus H, Meijboom R, Mina Y, et al. Expanding the texture toolkit for atlas-free segmentation of brain MRI [Conference Abstract]. Organization for Human Brain Mapping (OHBM) 2021 Annual Meeting, Seoul, South Korea (Virtual). https://www.humanbrainmapping.org/files/ohbm2021_abstracts_v2.pdf
28. Çiçek Ö, Abdulkadir A, Lienkamp SS, et al. *3D U-Net: Learning Dense Volumetric Segmentation from Sparse Annotation*. Cham, Switzerland: Springer International Publishing; 2016:424–432.
29. Bakas S, Akbari H, Sotiras A, et al. Advancing The Cancer Genome Atlas glioma MRI collections with expert segmentation labels and radiomic features. *Sci Data*. 2017;4:170117.
30. Weikert T, Cyriac J, Yang S, et al. A practical guide to artificial intelligence-based image analysis in radiology. *Invest Radiol*. 2020;55:1–7.
31. Vrenken H, Jenkinson M, Horsfield MA, et al. Recommendations to improve imaging and analysis of brain lesion load and atrophy in longitudinal studies of multiple sclerosis. *J Neurol*. 2013;260:2458–2471.
32. Henry T, Carré A, Lerosseau M, et al. *Brain Tumor Segmentation with Self-ensembed, Deeply-Supervised 3D U-Net Neural Networks: A BraTS 2020 Challenge Solution*. Cham, Switzerland: Springer International Publishing; 2021:327–339.
33. Rehman MU, Cho S, Kim J, et al. BrainSeg-Net: brain tumor MR image segmentation via enhanced encoder-decoder Network. *Diagnostics (Basel)*. 2021;11:169.
34. Al-masni MA, Kim D-H. CMM-Net: contextual multi-scale multi-level network for efficient biomedical image segmentation. *Sci Rep*. 2021;11:10191.