# Abstract

White matter hyperintensities (WMHs) are foci of abnormal signal intensity in white matter regions seen with magnetic resonance imaging (MRI). WMHs are associated with normal aging and have shown prognostic value in neurological conditions such as traumatic brain injury (TBI). The impracticality of manually quantifying these lesions limits their clinical utility and motivates the utilization of machine learning techniques for automated segmentation workflows. Herein, we develop a concatenated random forest framework with tailored features for segmenting WMHs in a TBI cohort. The framework is provided publicly through the Advanced Normalization Tools (ANTs) and ANTsR toolkits. MR (3D FLAIR, T2-, and T1-weighted) images from 24 service members and veterans scanned in the Chronic Effects of Neurotrauma Consortium’s (CENC) observational study were acquired. Manual annotations were employed for both training and evaluation using a leave-one-out strategy. Lesion load and overlap evaluative comparisons are complimented by feature rankings which showcase the utility of the concatenated approach. Our findings suggest supervised learning methods may be applied to quantify WMHs on routine brain imaging. Paired with correlative outcome data, supervised learning methods may allow for identification of imaging features predictive of diagnosis and prognosis in individual TBI patients.

# Introduction

## White matter hyperintensities in TBI

White matter hyperintensities (WMHs) are foci of abnormally increased signal intensity seen within white matter regions within the cerebrum and brainstem on fluid attenuation inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences. These lesions are distinguished from prominent perivascular spaces seen on T2-weighted imaging by the lack of fluid suppression of signal on FLAIR sequences. WMHs in the periventricular and deep brain regions are associated with normal aging and neurological conditions including hypertension and stroke. WMHs are also a frequent finding following traumatic brain injury (TBI) and have been correlated with functional outcome and injury severity in both pediatric [1,2] and adult [3–6]. Further, the regional distribution and volume of WMHs have been shown to possess prognostic value in the TBI patient [2,6–8]. Specifically, lesion volume in corpus callosum correlates with functional scores in the acute phase following injury, while lesion volume in frontal lobes correlates with scores at 1 year following injury [6]. Further, volume of FLAIR lesions within the corpus callosum, brainstem, and thalamus in patients with severe TBI correlates with Glasgow Outcome-Extended (GOS-E) scores [4]. Additionally, in patients who are comatose following severe TBI the regional distribution of FLAIR lesions within the pons, midbrain, hypothalamus, basal forebrain, parietal, temporal, occipital lobes, and insula along with the observation of grasping or chewing behavior are associated with poor outcome [7].

Despite the above findings, outside of multiple sclerosis, WMHs are not routinely employed as a diagnostic measure in clinical practice. Their presence within asymptomatic patients or in association with a variety of conditions, such as stroke, dementia, neuroinflammatory conditions, and TBI challenge their utility in narrowing a radiological differential diagnosis. Further, performing a comprehensive manual counting of number and distribution of lesions in the clinical setting is simply not practical. Despite the limited inclusion of WMH observations in routine radiological reports, two large meta-analyses demonstrated an association between WMHs, cognitive function, increased risk of stroke, dementia, and death [9,10]. As such, the development of automated methods for the rapid identification and quantification of WMHs within individual patients may allow for identification of correlative patterns between WMH number, volume, distribution, and disease state. Further, the development of such lesion quantification approaches may allow for the practical inclusion of this type of information within routine radiological practice.

## Random forests for WMH segmentation

Machine learning and pattern recognition techniques have seen increased application for various medical image analysis workflows (see, for example, the annual Workshop on Machine Learning in Medical Imaging held in conjunction with the Medical Image Computing and Computer-Aided Intervention (MICCAI) international meeting). Popular techniques such as support vector machines and neural networks have been applied successfully to clinically relevant imaging tasks such as supervised image segmentation (e.g., [11]) and diagnostic prediction (e.g., [12,13]). Facilitating the current employment of such techniques are the number of available imaging data sets [14] and the public availability of data science packages such as SciPy [15] and the R project for statistical computing [16] and their associated extensions.

The random forests framework [17] is a popular machine learning technique that has demonstrated significant utility for supervised segmentation tasks (e.g., normal human brain segmentation [18]) and other computer vision applications (e.g., human gait detection [19]). In the context of neuropathology, random forest-based paradigms have been employed in the delineation of multiple sclerosis lesions [20], stroke lesions [21], and brain tumors [22–25] for both single and multi-modal acquisition protocols. Of note, these latter random forest approaches for brain tumor segmentation have performed well in recent international competitions established in response to the lack of objective comparisons between segmentation algorithms (i.e., the Multimodal Brain Tumor Segmentation (BRATS) challenge was initiated in 2012 [26].

Random forests are conceptually straightforward [17]. They consist of ensembles of decision trees that are built from training data. Once constructed, data to be classified is "pushed" through each decision tree resulting in a single classification "vote" per tree. These votes are then used for regression or classification of the data. Although decision trees had been extensively studied, the success of employing collections of such weak learners for boosting machine learning performance (e.g., AdaBoost [27,28]) influenced the similarly sytled conglomeration of decision trees into "forests" with randomized node optimization [29,30]. Finally, Breiman17 improved accuracy by random sampling of training data (i.e., "bagging") resulting in the current random forest technique applied here.

In this work, we develop a concatenated random forest framework with a tailored contextual feature image set (both spatial and intensity-based) for segmenting WMHs in a large TBI cohort. Additionally, the entire framework is provided publicly through the well-known open-source Advanced Normalization Tools (ANTs)[[1]](#footnote-1) and ANTsR[[2]](#footnote-2) toolkits. Further motivating this research is the availability of several large publicly available imaging data sets that permits testing reproducibility of this automated routine for WMH segmentation and quantification.

# Materials and Methods

## Imaging

MR images utilized for this initial report were acquired from a single scanner involved in the Chronic Effects of Neurotrauma Consortium’s (CENC) observational study (see Walker et al., this issue). Briefly, participants were Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) era Service Members and Veterans between the ages of 18-60 years with prior combat exposure and deployment(s). The feature images consisted of 26 subjects aged 39.6 ± 8.1 years (range 28 – 58 years). Within this cohort, 24 (92%) were considered positive for TBI based upon the potential concussive events (PCE) interview process described in detail in Walker et al., this issue). Each of the participants that were selected from the larger cohort of participants in this study demonstrated at least one white matter hyperintensity (but as many as 20) on FLAIR imaging.

Images were acquired on a Philips 3.0T Ingenia system with an 8-channel SENSE head coil (Philips Medical Systems, Best, Netherlands). 3D FLAIR sequences were acquired with a turbo spin echo inversion recovery sequence with the following parameters: repetition time (TR) = 4800 ms, echo time (TE) = 325 ms, inversion time (TI) = 1650 ms; 170 sagittal slices with a 1.2 mm slice thickness, 256 x 256 acquisition matrix, and 256 x 256 mm FOV. 3D T1-weighted sequences were acquired with a fast field echo (FFE) sequence with the following parameters: TR = 6.8 ms, TE = 3.2 ms, echo train length (ETL) = 240; Flip angle = 9°, 170 sagittal slices with a 1.2 mm slice thickness, 256x240 acquisition matrix, and 256 x 256 mm FOV. In addition, 3D T2-weighted images were acquired with a turbo spin echo sequence with the following parameters: TR = 2500 ms, TE = 245 ms, ET: = 133; 170 sagittal slices with a 1.2 mm slice thickness, 256 x 256 acquisition matrix, and 256 x 256 mm FOV.

## Quantitative analysis

Crucial to these supervised segmentation approaches are the creation and selection of "features" as input in conjunction with expertly identified structures of interest for model construction. For the targeted application in this work (i.e., WMHs), tissue classification is performed at the voxelwise level. In other words, each voxel within the region of interest is sent through the ensemble of decision trees and receives a set of classification votes from each tree thus permitting a regression or classification solution. Since this procedure is performed at the voxelwise level, intensity information alone is insufficient for good segmentation performance due to the lack of spatial context. For example, as pointed out in [31], higher intensities can be found at the periventricular caps in normal subjects which often confounds automated lesion detection algorithms. Other potential confounds include MR signal inhomogeneity and noise. Therefore, even though machine learning and pattern recognition techniques are extremely powerful and have significant potential, just as crucial to outcome is the creative construction and deployment of salient feature images which we detail below.

### Feature images for WMH segmentation

Supervised methodologies are uniquely characterized, in part, by the feature images that are used to identify the regions of interest. In Table 1, we provide a list and basic categorization of the feature images used for the initial (i.e., Stage 1---more on the use of multiple random forest stages below) segmentation of the WMHs. In addition Figure 1 provides a representation of a set of feature images for a single subject analyzed in this work. Note that in this work we categorize the brain parenchyma with seven labels:

* cerebrospinal fluid (label 1),
* gray matter (label 2),
* white matter (label 3),
* deep gray matter (label 4),
* brain stem (label 5),
* cerebellum (label 6), and
* white matter hyperintensities (label 7).

As mentioned previously, input for each subject comprises FLAIR, T1-, and T2-weighted acquisitions. The FLAIR and T2 images are rigidly registered to the T1 image using the open-source Advanced Normalization Tools (ANTs) [32]. The aligned images are then preprocessed using the denoising algorithm of [33] followed by N4 bias correction [34] which are then normalized to the intensity range . Although we could have used an alternative intensity standardization algorithm (e.g., [35]), we found that a simple linear rescaling produced better results similar to previous work [25].

The T1 image is then processed via the ANTs brain extraction and normal tissue segmentation pipelines [36]. Any effect of pathology is minimal because WMHs are not commonly seen in T1-weighted MRI. This protocol involves preprocessing using N4 bias correction followed by a template-based strategy for brain extraction. Once the brain has been extracted, we apply a Bayesian-based segmentation algorithm with a template-based prior probability strategy to segment the parenchymal tissue types. The result is a mask delineating the brain parenchyma and probabilistic estimates of the CSF, gray matter, white matter, deep gray matter, brain stem, and cerebellum. These provide the expertly annotated labels for the first six tissue labels given above. The WMHs were manually identified by one of the authors (J. R. S.) using the ITK-SNAP tool37. Segmentation is performed using the ANTs Atropos tool [38] and multi-model optimal symmetric shape/intensity templates [25] created from the public MMRR data set [39] (cf Figure 3).

To model the intensity information the first set of images simply includes the preprocessed and normalized intensity FLAIR, T1, and T2 image voxel values. We also calculate a set of neighborhood statistics (mean, standard deviation, and skewness) feature images using a Manhattan radius of one voxel given the typical size of individual WMHs. For each of the normalized images, we calculate the difference in intensities with the corresponding warped template component. Previous success in the international brain tumor segmentation competition [26] was based on an important set of intensity features that were created from multi-modal templates mentioned previously [25] and listed in Table 1. We employ the same strategy here. For example, the template difference feature image for the FLAIR image, is calculated as:

where is the transform which maps from the individual subject space to the template space and is the FLAIR template component. Also, to take advantage of the gross bilateral symmetry of the normal brain (in terms of both shape and intensity), and the fact that WMHs do not generally manifest symmetrically across hemispheres, we use the symmetric templates to compute the contralateral intensity differences as an additional intensity feature. For the FLAIR component, this contralateral difference image is calculated from

where denotes a horizontal reflection perpendicular to the mid-sagittal plane of the symmetric template.

The segmentation probability images described above are used as feature images to provide a spatial context for the random forest model prediction step. Additional spatial contextual feature images include the distance maps40 based on the csf, gray matter, and deep gray matter images. These latter images are intended to help distinguish white matter hyperintensities from false positives induced by the partial voluming at the gray/white matter interface. A third set of images are based on the voxel location within the space of the template. The T1 image of the subject is registered to the T1 template component using a B-spline variant [41] of the well-known ANTs Symmetric Normalization (SyN) algorithm [42]. Since the inverse transform is also derived as part of the registration process, we can warp the voxel index locations back to the space of the individual subject which motivates similar work by others [43]. However, this previous work lacks the normalization to the standard coordinate system provided by the template to dramatically improve spatial specificity across all subjects.

### Stacked (concatenated) random forests for improved segmentation performance

In previous brain tumor segmentation work [25], it was demonstrated that a concatenated supervised approach, whereby the prediction output from the first random forest model serves as partial input for a second random forest model, can significantly improve segmentation performance. We do the same thing for the work described here where we employ two stacked random forests (or two "stages"). The Stage 1 feature images of the training data (as described previously) are used to construct the Stage 1 model. The training data Stage 1 features are then used to produce the voxelwise "voting maps" (i.e., the classification count of each decision tree for each tissue label) via the Stage 1 random forest model. All the Stage 1 features plus the Stage 1 voting maps are used as input to the Stage 2 model. In addition, we use the Stage 1 voting maps as tissue priors (i.e., probabilistic estimates of the tissue spatial locations) for a second application of the Atropos maximum aposteriori algorithm with an additional Markov Random Field spatial prior (MAP-MRF) [38]. However, for the second stage we use all three aligned preprocessed images for a multivariate segmentation. The resulting seven posterior probability images constitute a third additional feature image set for Stage 2.

### Code and data availability

As pointed out in a recent comprehensive multiple sclerosis lesion segmentation review [44], although the number of algorithms reported in the literature is quite extensive, there were only four publicly available segmentation algorithms at the time of writing this article. In contrast to the current work, none are based on supervised learning. As we did for our brain tumor segmentation algorithm [25], all of the code described in this work is publicly available through the open-source ANTs/ANTsR toolkits. Through ANTsR (an add-on toolkit which, in part, bridges ANTs and the R statistical project) we use the *randomForest* package [45] using the default settings with 2000 trees per model and 500 randomly selected samples per label per image. Note that we saw little variation in performance when these parameters were changed (i.e. up to 1000 random samples and as little as 1000 trees) which is consistent with our previous experience.

In addition, similar to our previous offering,[[3]](#footnote-3) we plan on creating a self-encapsulated example to showcase the proposed methodology. The fact that the data will also be made available through the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository along with the manual labelings will facilitate reproducibility on the part of the reader as well as any interest in extending the proposed framework to other data sets.

### Evaluation protocol overview

In order to evaluate the protocol described, we performed a leave-one-out evaluation using the data acquired from the 24 subjects described above. Initial processing included the creation of all Stage 1 feature images for all subjects. The initial brain segmentation of each T1 image and the manual white matter hyperintensity tracings were combined to provide the truth labels for the training data. The "truth" labels are the seven anatomical regions given above.

The leave-one-out procedure is as follows:

* Create Stage 1 feature images for all 24 subjects.
* For each of the 24 subjects:
  + sequester the current subject and corresponding feature images.
  + construct the Stage 1 random forest model from the remaining 23 subjects.
  + apply the Stage 1 random forest model to the feature images of the 23 training subjects.
  + the previous step produces the Stage 1 voting maps for all seven labels.
  + for each of the 23 subjects, perform a Bayesian-based segmentation with an MRF spatial prior using the seven voting maps as additional tissue priors.
  + construct the Stage 2 random forest model from all the Stage 1 feature images, seven voting maps, and seven posterior probability maps from the previous step.
  + send the sequestered subject through the random forest models for both stages.
  + compare the final results with the manually-defined white matter hyperintensity regions.

# Results

## Ranking feature importance

After performing the leave-one-out evaluation, we calculated the *MeanDecreaseAccuracy* feature values for each of the 24 subjects 2 models per subject total models. This measure (per feature, per model) is calculated during the out-of-bag phase of the random forest model construction and quantifies the decrease in prediction accuracy from omitting the specified feature. In other words, this quantity helps determine the importance of a particular feature and, although we save such efforts for future work, this information provides us with guidance for future feature pruning and/or additions.

The resulting rankings for both Stages are given in Figures 4 and 5 where the values for the separate stages are averaged over the entire corresponding model set. In addition, we track the variance for each feature over all models to illustrate the stability of the chosen features during the evaluation. This latter information is illustrated as horizontal errors bars providing the percentile. Note that the reader can cross reference Table 1 for identifying corresponding feature types and names.

One can also use these measurements as a type of sanity check. For example, from the Stage 1 plot, one can see that the *MeanDecreaseAccuracy* values for the location indices in the anterior-posterior direction (i.e., *TemplateIndicesWarped1*) are greater than those for either the inferior-superior (i.e., *TemplateIndicesWarped2*) or the left-right (i.e., *TemplateIndicesWarped0*) directions in the space of the symmetric template.

Additionally, it is interesting to note some of the other top performing features for Stage 1. The contralateral difference FLAIR image is highly discriminative over the set of evaluation random forest models (see Figure 6). This accords with the known clinical relevance of FLAIR images for identifying white matter hyperintensities and the fact that such pathology does not typically manifest symmetrically in both hemispheres. Interestingly, the posterior maps for the deep gray matter are extremely important for accurate white matter hyperintensity segmentation. Perhaps the spatial specification of deep gray matter aids in the removal of false positives. Inspection of the bottom of the plots demonstrates the lack of discriminating features associated with the T1 image which is also well-known in the clinical literature.

As described earlier, for Stage 2, we used the output random forest voting maps from Stage 1 as both features themselves and as priors for input to a Bayesian-based segmentation with an additional MRF spatial prior. In Figure 5, the voting maps are labeled as "*RFStage1VotingMaps*" where the final numeral is associated with the brain parenchymal labeling given previously. Similarly, the additional RF prior segmentation feature probability maps are labeled as "*RFBrainSegmentationPosteriors*". The Stage 2 feature importance plot follows similar trends as that for Stage 1 with the T1 images not contributing much to the identification of white matter hyperintensity voxels. The initial voting maps from Stage 1 are extremely important with the top 3 being the estimated locations of the 1) gray matter, 2) white matter, and 3) white matter hyperintensities. Since these tissue type can be conflated based on intensity alone it is intuitive that such features would be important.

## White matter hyperintensity segmentation evaluation

In Figure 7 are the segmentation comparisons derived from manual segmentations of the same data. Despite the large variability characteristic with manual labelings in related fields [44,46,47], such labelings are characteristic of current clinical practices and the methodology proposed herein is readily adapted to refinements in training data. On the left of Figure 7 are the improvement in Dice values [48], i.e.,

over all white matter hyperintensities when comparing the segmentations between the two stages where the sum is taken over all individually labeled manual, , and automated, , lesions and represents the intersection between the manual/automated lesion pair. Performing the second round of supervised learning improves these Dice values. One can also note from the right side of Figure 6 that the total lesion load volume illustrates a few subjects that are severe outliers in terms of the number of false positives. The second round helps to correct this issue.

# Discussion

The current communications describes a supervised statistical learning methodology for identifying WHMs within multimodal MR brain imaging. This effort utilized information acquired from the manual segmentation of WMHs from FLAIR images to help build two-stage ensembles of decision trees for the automated identification of these lesions. Although only a single expert was used to produce the manual labelings, our intent is to further refine the proposed paradigm by crowdsourcing with feedback from other experts who interact with both the data and methodology. Also, we recognize that only a single site was used for evaluating the proposed framework. However, we are currently processing other site data with the models developed for this work and the results look promising since the developed features are site-agnostic.

As far as we know, this is the first report utilizing a novel random forest approach to identify WMHs in a cohort of TBI patients. TBI WMHs tend to be more difficult to segment than MS lesions as the former tend to be smaller with an overall smaller lesion load. Also, enhancement protocols with the former tend to be less successful than with the latter. As mentioned previously, the work in MS lesion segmentation is extensive with a handful of techniques being publicly available. Our framework is also available as open-source as part of well-known neuroimaging tools which easily allows for additions/extensions but is also, as far as we know, the first random forest-based technique available for such application.

Two major meta-analyses of WMHs have been published covering the periods prior to [9] and after 2010 [10]. Debette & Markus9 found that the presence of WMHs was related to subsequent cognitive decline, a higher risk of developing dementia, stroke, and of mortality. Lesion volume at baseline was also predictive of cognitive decline. Kloppenborg et al. [10] of 23 cross-sectional studies reporting MRI and concurrent neuropsychological results in patients with heterogeneous diagnoses but without previously diagnosed cognitive impairment, found that WMHs were associated with cognitive deficit (effect size of -0.10, 95% CI: -0.13 to -0.08) after controlling for age.

Despite the potential clinical significance of WMHs these lesions receive little attention in current clinical workflows. When reported in a standard neuroradiologist interpretation, they are typically handled as incidental findings and are assigned little clinical significance. This likely reflects the impracticality of performing a detailed assessment of number, volume, and distribution within a qualitative neuroradiologist interpretation as well as the lack of correlative information on how the presence and distribution of these lesions may inform a diagnosis and prognosis in the appropriate clinical setting. To date, automated or semi-automated tools for the detection of WMHs have lacked the specificity and efficiency for the mining of large-scale datasets to generate highly granular data on whether these lesions possess any true diagnostic or prognostic value in the setting of a specific disease process. The present communication describes a supervised statistical learning tool that is appropriate for the application to such large-scale datasets.

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## Declaration of Interest/Disclaimer

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1. <https://github.com/stnava/ANTs> [↑](#footnote-ref-1)
2. <https://github.com/stnava/ANTsR> [↑](#footnote-ref-2)
3. <https://github.com/ntustison/ANTsAndArboles> [↑](#footnote-ref-3)