

## Figure Captions

**Figure 1:** Workflow illustration for the proposed pipeline. Processing of the multi-modal input MRI for a single subject, using the multi-modal symmetric template, results in the generation of the feature images. These feature images are used as input to the Stage 1 RF model producing the initial RF probability map estimates. The Stage 1 voting maps, the original feature images, and the Stage 2 RF model result in the final voting maps which includes the WMH probability estimate. Note that the RF models are constructed once from a set of training data which are processed using the same feature-construction pipeline as the single-subject input MRI.

**Figure 2:** Canonical views of the multivariate, bilaterally symmetric template constructed from the MMRR data set (only shown are the FLAIR, T1, and T2 modalities— the components relevant for this work). These images are important for asymmetry-based features.

**Figure 3:** Representation of Stage 1 feature images for subject 9. The FLAIR, T1-, and T2-weighted images are rigidly pre-aligned to the space of the T1 image. The three modality images are then preprocessed (N4 bias correction and adaptive denoising) followed by application of standard ANTs brain extraction and  $n$ -tissue segmentation protocols using the MMRR symmetric template and corresponding priors applied to the T1 image. The feature images are then generated for voxelwise input to the RF model which results in the voting maps illustrated on the right. This gives a probabilistic classification of tissue type. Not shown are the probability and voting images for the brain stem and cerebellum.

**Figure 4:** Sample FLAIR acquisition image slices showing both manual and random forest segmen-

tations for both stages obtained during the leave-one-out evaluation. Manual segmentations were performed by one of the authors and provided the ground truth WMH labels for training the random forest models.

**Figure 5:** Evaluation measures for both Stages of the leave-one-out protocol of the described protocol in the Methods section: (a) sensitivity, (b) positive predictive value, (c)  $F_1$  score, and (d) relative volume difference. These quantitative assessments are given for three quantile ranges spanning the range of the manually-derived lesion volumes. Overall improvement in all three whole lesion-based measures is seen as the second Stage RF model is applied for all three quantile ranges. The relative volume difference corresponding to the Stage 2 results tend to predict a decreased predicted volume over the Stage 1 results.

**Figure 6:** Average *MeanDecreaseAccuracy* plots generated from the creation of all 24 random forest models for Stage 1 during the leave-one-out evaluation. These plots are useful in providing a quantitative assessment of the predictive importance of each feature. Features are ranked in descending order of importance. The horizontal error bars provide the 95<sup>th</sup> percentile and illustrate the stability of the feature importance across the leave-one-out models. At this initial stage only 31 feature images are used.

**Figure 7:** Average *MeanDecreaseAccuracy* plots generated from the creation of all 24 random forest models for Stage 2 during the leave-one-out evaluation. These plots are useful in providing a quantitative assessment of the predictive importance of each feature. Features are ranked in descending order of importance. The horizontal error bars provide the 95<sup>th</sup> percentile and illustrate the stability of the feature importance across the leave-one-out models. We augment the 31 feature images from the first stage by adding an additional seven voting maps and 7 segmentation posteriors from

application of the Bayesian-based segmentation for a total of 45 images for the second stage.

**Figure 8:** (a) FLAIR image slice illustrating WMHs which have been manually delineated. The region around the WMHs is enlarged (b) in the original FLAIR and the (c) contralateral FLAIR difference image.