Updated MRI Methods

Removal of Non-brain tissues: The skull is removed using an atlas-based method[1] followed by human quality control to provide generally minor cleanup if needed. Structural MRI brain images are then nonlinearly registered performed by a cubic B-spline deformation [2] to a minimal deformation template (MDT) synthetic brain image[3] adapted for age range of 60 and above.

Image Intensity Inhomogeneity Correction: B1 field inhomogeneity is a common problem that limits the precision of image segmentation. We utilize a template-based iterative method for correcting field inhomogeneity bias[4]. At each algorithm iteration, the update of a B-spline deformation between an unbiased template image and the subject image is interleaved with estimation of a bias field based on the current template-to-image alignment. The bias field is modeled using a spatially smooth thin-plate spline interpolation based on ratios of local image patch intensity means between the deformed template and subject images. This is used to iteratively correct subject image intensities which are then used to improve the template-to-image deformation.

Gray, White and CSF Measurement: Our segmentation algorithm is based on an Expectation-Maximization (EM) algorithm that iteratively refines its segmentation estimates to produce outputs that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness [5, 6]. Like all EM algorithms, the system must be initialized with a reasonable estimate. We produce this initial estimate from the template-space warps of previously segmented images; because locations of WM/GM/CSF tissues are known in the template space, transforming these masks back to the each image's native space produces rough estimate 3-tissue segmentations. We then calculate the mean and standard deviation of the image intensities in locations labeled as each tissue type. These values then form the initial parameters for a Gaussian model of image intensity for each class. At each iteration, the algorithm uses a Gaussian model of T1-weighted image intensity for each tissue class, in order to produce a segmentation. In the first iteration, these models are estimated as described above. The segmentation yielded by these appearance models alone is then refined using a Markov Random Field (MRF) model, a computational statistical method that efficiently produces a label map consistent with both the input intensities and image smoothness statistics. Inference in the MRF is computed using an adaptive priors model[6]. This refined segmentation from the MRF is then used to compute new Gaussian intensity models for each tissue class, and the algorithm repeats, iteratively switching between calculating Gaussian appearance models and MRF-based segmentation, until convergence. The MRF-based segmentation at the final iteration is used as the final output segmentation.

White Matter Hyperintensity: WMH is performed on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure based on a previously published method of histogram fitting [7]. Prior probability maps for WMH were created from more than 700 individuals with semi-automatic detection of WMH followed by manual editing. Likelihood estimates of the native image are calculated through histogram segmentation and thresholding. All segmentation is initially performed in standard space resulting in probability likelihood values of WMH at each voxel in the white matter. These probabilities are then thresholded at 3.5 sd above the mean to create a binary WMH mask. Further segmentation is based on a modified Bayesian approach that combines image likelihood estimates, spatial priors and tissue class constraints. The segmented WMH masks are then back-transformed on to native space for tissue volume calculation. Volumes are log-transformed to normalize population variance.

Automatic Hippocampal Segmentation: MRI-derived hippocampal volumetry has been a widely used biomarker in AD to improve early diagnosis[8], enrich subject selection[9], and monitor

treatment efficacy[10, 11]. To address this need, the EADC-ADNI Working Group established a Delphi panel to determine the optimum protocol[12], selected orientation parameters[13] and developed the final, rigorously tested protocol along with making publically available labels from over 100 ADNI subjects[14]. Our hippocampal segmentation method employs a standard atlas based diffeomorphic approach[15] with the minor modification of label refinement. We further modified this approach to include the EADC-ADNI harmonized hippocampal masks to assure standardization across cohorts. Therefore we have adopted the following approach: 1) Subject image pre-processing with extraction of intracranial cavity, non-uniformity correction, tissue classification as discussed above; 2) Atlas Registration of all EADC-ADNI hippocampal masks[8, 12, 14, 16, 17] to each subject; 3) Atlas Fusion utilizing MALF [18, 19]; and 4) Intensity-based label refinement.

ROI-based Analysis: Software developed by the IDeA laboratory allows the creation of any set of user-defined ROIs or utilization of published ROIs. The lab provides multiple sets of predefined regions of interest including lobar volumes, the Desikan-Killiany Atlas from Freesurfer[20] and Brodmann areas defined by an expert anatomist [21]. Regional measures are calculated by back transformation of the atlas into segmented image native space. A voting scheme is used to assure precise labelling of each region after interpolation of the atlas into native space.

Cortical Thickness: We utilize a registration based method based on Das et al.[22] which consists of the following steps: an initial probabilistic segmentation of GM, WM and CSF after intensity inhomogeneity correction[4] using our segmentation methods [6]. From the three probability maps, a three label image is formed by picking the tissue type with the highest probability at each voxel. A greedy diffeomorphic registration algorithm is then used to expand the WM segment, to match the GM + WM segment or until a maximum of 6 mm displacement is reached. For each boundary voxel on the GM/WM boundary, the thickness is calculated as the distance moved under the registration transformation, and this thickness value is then propagated across the GM mask.

Infarcts: The presence of MRI infarction was determined from the size, location and imaging characteristics of the lesion. The image analysis system allowed for superimposition of the subtraction image, the proton density image and the T2 weighted image at three times magnified view to assist in interpretation of lesion characteristics. Signal void, best seen on the T2 weighted image was interpreted to indicate a vessel. Only lesions 3mm or larger qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included: 1) CSF density on the subtraction image and 2) If the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels. Kappa values for agreement amongst the three raters are generally good and range from 0.73 to 0.90.

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