Lateral ventricle segmentation based on fusion of expert priors in AD.

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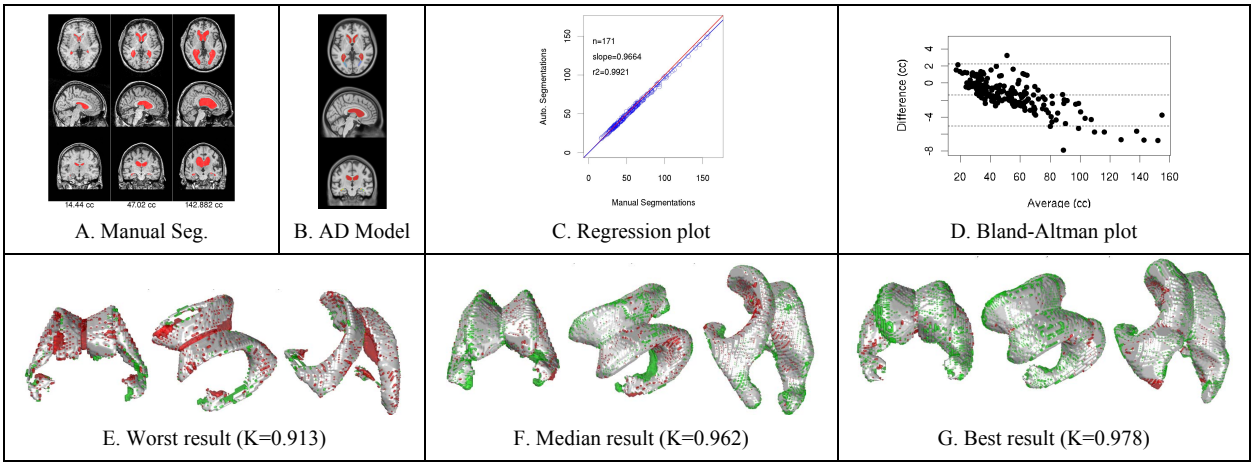
INTRODUCTION: Volume measurements of the lateral ventricles are often used as surrogate markers of atrophy and disease progression in studies of neurodegenerative brain disorders (Schnack et al., NeuroImage, 2001), (Xia et al., NeuroImage, 2004), (Nestor et al., Brain, 2008). Manual segmentation can be time-consuming and has the drawbacks of inter- and intra-observer variability. Even though there is high contrast between tissue and cerebrospinal fluid (CSF) in MRI, segmentation of the lateral ventricles can be difficult. For example, partial volume effects make it difficult for region-growing algorithms to accurately segment the temporal horns and occipital poles of the ventricles. Choroid plexus has image intensity similar to grey matter (GM) on T1 weighted (T1w) images which can confound threshold-based techniques. As subjects age, the ventricles can increase in size significantly, and this can be amplified by disease and presents a challenge for warping-based techniques. We present a precise and accurate technique to automatically segment the lateral ventricles (LV) and validate the method on a large cohort of patients with Alzheimer's Disease (AD).

METHODS: ***Subjects and Image Acquisition***: Baseline MRI data from 271 elderly patients with mild to moderate AD, ages 50-85, participating in a clinical trial. MR data were acquired from 62 study sites using the following protocol: T1-Weighted RF-spoiled, gradient-recalled echo with TR = 22 ms, TE = 10 ms, flip angle = 30°, 250 mm field-of-view, 256 x 256 matrix and 110-120 sagittal partitions of 1.5 mm thickness. The resulting voxel size was 0.98 x 0.98 x 1.5 mm3. All patients (or their designated caregivers) gave informed consent and the local REB at each site approved the study. ***Manual LV Segmentations***: Manual segmentations were performed on the native MRI data by three raters at the clinical trial MRI reading center (NeuroRx Research, Montreal, Canada). The manual labels were generated independently of any automatic segmentation method (unlike Schnack 2001 who corrected automatically generated labels). The segmentation protocol consisted of the following steps: (i) manual selection of two regions of interest: one within a lateral ventricle, clear of the walls and choroid plexus (ROIv), and the second within the caudate nucleus (ROIc); (ii) calculation of the upper threshold for ventricular CSF: Threshold=(M(ROIv)+M(ROIc)/2); (iii) manual painting of the voxels within the CSF using the calculated threshold to define the ventricular border; (iv) manual correction of voxels containing choroid plexus, which might not have been selected in the previous step. The raters ensured that the full lateral ventricle was identified on each subject (i.e., the raters labeled the temporal and occipital horns). Examples of these segmentations are shown in **Fig-A**. ***Automatic LV Segmentations***: Data from these same scans were used to generate fully-automated LV segmentations using the following novel technique that combines population-specific atlas warping (Grabner *et al.* MICCAI 9 (Pt 2) 2006;58-66) and label-fusion (Heckemann *et al*., NeuroImage. 2006;33:115-26). A population-specific anatomical average model (i.e., an AD model) was constructed using the MRI data from the *training* subset, using a Minimal Deformation Template (MDT) method similar to (Grabner, 2006) with 2mm non-linear registration resolution. The T1w anatomical scans and the manual labels from the *training* set were then warped using non-linear deformation fields obtained during the model creation to produce a Anatomical Library of 100 subjects in the non-linear space. We also averaged the warped T1w MRI scans to produces a mean T1w intensity target image with high anatomical detail (**Fig-B).** For segmentation, each subject from the *test* set was nonlinearly registered to this model using the ANIMAL algorithm (Collins, Human Brain Mapping, 1995) with 2mm resolution, and its anatomical scan was then resampled using the recovered non-linear transformation. The subject's resampled MRI was then compared against all the anatomical scans in the Anatomical Library using mutual information. The best N (=20) matching datasets from the library were averaged to produce a subject-specific probabilistic ventricle segmentation in the non-linear space of the population-specific model. This segmentation was then warped back into the native space of the MRI scan and thresholded at 50% probability to produce a discrete segmentation map for the subject in question. This procedure takes 15-20 minutes per scan on modern PC hardware.

RESULTS: As shown in **Fig-C**, a very strong linear relationship was found between the 171 testing-set LV volumes generated by the expert readers (*i.e.*, the manual segmentations that had not been used to train the model used by the automated segmentation technique) and by our automated segmentation technique ($r = 0.99$, $p < 0.00001$). The Bland-Altman plot (**Fig-D)** shows that there is a slight underestimation overall (slope=0.9664) and a slightly larger underestimation of the largest ventricles. Furthermore, the overlaps between the manual and automatic labels are very high as measured by Dice Kappa: median , range = 0.962 , 0.913 – 0.977, supporting the accuracy of this automated approach. **Figs-E-G** show 3D rendering of the segmentation result on three subjects using the proposed technique. White indicates agreement with manual segmentation, red - false positives and green - false negatives. **Fig-E** shows the worst segmentation result, **Fig-F**, the median result and **Fig-G** shows the best result as measured by Kappa.



A. Manual Seg. | B. AD Model | C. Regression plot | D. Bland-Altman plot

E. Worst result (K=0.913) | F. Median result (K=0.962) | G. Best result (K=0.978)

DISCUSSION: In the present study, we have provided evidence for the accuracy of a novel, fully-automated, MRI-based technique for the segmentation of the lateral ventricles in patients with AD. The combination of population-specific atlas warping with label fusion offers two main advantages. 1) non-linear registration of a subject to the population-specific atlas should help to reduce the inter-subject anatomical variability when comparing to subjects in the Anatomical Library, and *(ii)* the label-fusion technique helps compensate for the residual variability and imperfectness of the registration technique.

The authors are grateful to Elan Pharmaceuticals for allowing us the use of their data, and to Dr. Josefina Maranzano and Dr. Tao Li for their manual segmentations.