A population-based template for high-dimensional normalization of postmortem human brains from elderly subjects

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Introduction: In Alzheimer's disease (AD) research, postmortem MRI of the human brain offers several advantages over in vivo imaging. For example, histological analysis can be performed following the MR scan, allowing for verification of the imaging findings and testing of new MRI diagnostic techniques[1]. Spatial transformation of individual postmortem brain MRI volumes to a common reference frame would be of great benefit to research in this area, since it would facilitate voxel-based investigations, which would provide information throughout the brain in a timely manner and without user bias, in contrast to regions of interest (ROI) analyses. However, a suitable template does not exist for MRI data from postmortem human brains, whose morphology and contrast tend to be substantially different from those of data acquired in living subjects, due to the effects of cell death, fixation in formaldehyde solution, and lack of supporting bone structure[2]. Therefore, the purpose of this work was to create and evaluate a population-based anatomical MRI template to be used for high-dimensional spatial normalization of postmortem human cerebral hemispheres.

Methods: During life, 86 elderly subjects were divided into the following three groups, based on a comprehensive neuropsychological evaluation: Alzheimer's disease (AD), mild cognitive impairment (MCI), and no cognitive impairment (NCI). Following death, one cerebral hemisphere from each subject was immersed in 4% formaldehyde solution and stored at 4° C. Approximately two months postmortem, each hemisphere was removed from refrigeration and scanned at room temperature using a 3.0-T GE MR imager (General Electric, Waukesha, WI). A 2D fast spin echo sequence with two echo-times was used to acquire proton density (PD) weighted and T_2-weighted images, in sagittal slices through the hemispheres, with TE_1 = 13.0 ms, TE_2 = 52.0 ms, and true resolution of 0.625 mm × 0.625 mm × 1.5 mm. From each of the three groups, 12 subjects were selected to be used in the creation of the template. The resulting 36 total subjects were exactly balanced in terms of both sex and laterality (left vs. right hemisphere), and were also age-matched between males and females, between left and right hemispheres, and among the three diagnosis groups (average age at death = 87.1 years). After intensity normalization, the 36 masked PD-weighted volumes were aligned using affine registration (left hemispheres were mirrored to appear as right hemispheres) and averaged to obtain a starting template. Then, by the method of Joshi, et al.[3], the individual volumes were iteratively warped to the most recent version of the template and averaged to generate the updated version. The Automated Registration Toolbox[4] (ART) was used to accomplish the high-dimensional warping necessary for this process, since it is one of the most accurate nonlinear registration algorithms[5]. The iterative procedure was terminated when the template did not significantly change between consecutive steps. To test the degree to which the iterative warping reduced anatomical variability among the 36 template hemispheres, seven landmarks were manually placed in each hemisphere prior to registration, and the root-mean-square (RMS) dispersion of the landmarks was measured post-registration. The same landmarking procedure was employed for the remaining 50 hemispheres used in this study, in order to evaluate how well hemispheres from outside the template pool become normalized to the template.

Results: The final template was obtained after 55 iterations of warping, with most of the improvements coming within approximately the first 10 iterations (Fig.1). Among the 36 hemispheres that were used to form the template, the post-registration RMS dispersion of the landmarks placed manually prior to registration, was 2.7 mm. Among the 50 additional hemispheres that were not used to form the template, the RMS dispersion of the landmarks after registration to the template was 3.0 mm.

Discussion: The postmortem human cerebral hemisphere template was generated using a population-based technique and avoids bias toward any single subject. The iterative warping approach succeeded in maintaining local anatomical features in the final template by reducing anatomical variability among the template subjects, as evidenced by the small post-registration dispersion of the landmarks among the 36 template hemispheres. The blurred appearance of the initial template was replaced by sharp borders around the lateral ventricle and between white and gray matter in the final template (Fig.1). These features have made the final template a good target for high-dimensional spatial normalization of postmortem cerebral hemispheres (Fig.2), as confirmed by the small post-registration dispersion of landmarks in the 50 non-template hemispheres. Therefore, this template could be used for voxel-based investigations in postmortem cerebral hemispheres, eliminating the need for time-consuming manual selection of ROIs.

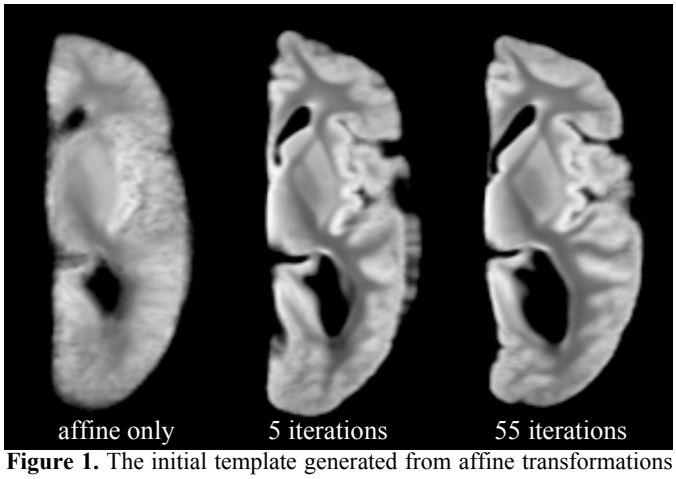

Figure 1. The initial template generated from affine transformations of 36 subjects, an intermediate version after 5 iterations of homeomorphic warping, and the final version after 55 iterations.

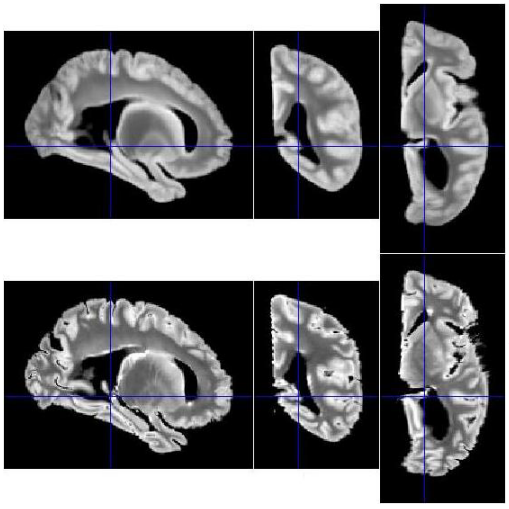

Figure 2. Images of the final postmortem brain template (top) and one individual hemisphere after normalization to the template using ART (bottom). The blue crosshairs are placed on the same location in the tail of the hippocampus in both volumes.

References: [1] Bobinski M, et al., Neuroscience, 2000;95:721-725. [2] Dawe R, et al., MRM, 2009;61:810-818. [3] Joshi S, et al., NeuroImage, 2004;23:S151-S160. [4] Ardekani B, et al., J Neurosci Methods 2005;142:67-76. [5] Klein A., et al., NeuroImage, 2009;46:786-802.