Development of a VBM Protocol for Assessing Regional Gray and White Matter Brain Changes in a Canine Model of Aging

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Purpose Application of manual region of interest (ROI) planimetry has shown that brain aging varies regionally and differs in males and females [1]. Despite improved sensitivity in measuring local cortical atrophy, manual ROI is labor intensive, has poor reproducibility, and is prohibitive for measuring multiple brain regions in large data sets. These problems can be overcome with automated voxel-based morphometry (VBM) which permits rapid voxel by voxel comparisons of gray and white matter concentrations between subject cohorts [2]. Several VBM studies have reported regional differences in gray (GM) and white matter (WM) atrophy in aging humans but few studies have used VBM to examine brain aging in nonhuman models. The purpose of the present study was to develop a VBM protocol in a canine model of human brain aging. Development of a VBM protocol in the canine will permit analysis of data from longitudinal studies that are typically harder to perform in humans and will be valuable for assessing the efficacy and safety of new interventions developed to promote brain health in aging.

Method Beagle dogs (31 males, 31 females) aged 6 months to 15 years were scanned. For each dog, 60 3D SPGR images were acquired on a GE-LX 1.5T mobile MRI scanner [NEX = 2; 256 x 256; FOV = 12 cm; [TR] = 40 msec; echo time [TE] = 9.0 msec; flip angle = 40^0; slice thickness = 1.2 – 1.4 mm]. Standardized dog-brain templates and probability maps were first created from 192 scans acquired from dogs between 2000-2002. All scans were AC-PC aligned and co-registered to produce a mean image. The 192 scans were then spatially normalized to the mean image and a second mean image was made resulting in a standard dog brain template. The 192 scans were skull stripped and segmented into GM, WM, and CSF. A smoothed-mean image was created for each GM, WM, and CSF segment to yield an initial probability map. This process was repeated resulting in secondary probability maps used to segment the standard dog brain template into GM, WM, and CSF. In the final step, study-specific dog brain templates were created for the 62 dogs in this study using an iterative process. Scans were co-registered, normalized, smoothed, and a mean image created at each iterative step. After four iterations, the resultant template was segmented into GM, WM, and CSF using the standard a priori probability maps. Scans from the 62 animals were then segmented using the study-specific template. Segmentations from this step were averaged and smoothed to produce final study-specific probability maps (fig 1). Optimized-modulated VBM procedures in SPM2 were performed on the 62 original scans using study-specific templates and final probability maps. Global and regional changes in GM and WM were assessed using a general linear model and Gaussian random field theory. Statistical inferences were made at each voxel using chronological age and sex as independent variables. Effects of interest were examined using linear contrasts of parameter estimates at a threshold of $p<0.01$.

Fig 1. Study-specific probability maps for 62 animals presented in coronal plane for GM (A), WM (B), and CSF (C).

Results Increasing age was associated with a decrease in global GM [$r(62)=0.214$, $p=.051$] but not WM [$r(62)=0.063$, $p=.313$]. GM atrophy varied as a function of age and sex in several regions. As shown in figure 2, age-related GM atrophy was greater for males in the frontal lobes compared to females ($p<0.005$). Conversely, old females exhibited greater age-related GM atrophy in temporal lobe brain areas ($p<0.005$). WM atrophy also varied with age and sex (fig 3). Atrophy of the internal capsula was significant and common to both males and females ($p<0.005$), but females exhibited greater atrophy of the alveus of the hippocampus relative to males ($p<0.005$). By contrast, WM atrophy of the optic nerve bundle was predominant in old male dogs ($p<0.005$).

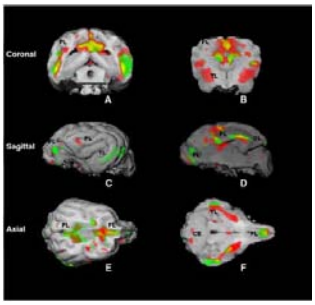

Fig 2. 3D surface renderings of significant age-related atrophy in GM for males (green) and females (red). Regions of overlap where age-related GM atrophy is similar among males and females are shown in yellow (FL = frontal lobe, PL = parietal lobe, TL = temporal lobe, OL = occipital lobe, CB = cerebellum).

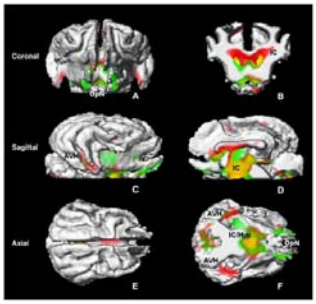

Fig 3. 3D surface renderings of significant age-related atrophy in WM for males (green) and females (red). Regions of overlap where age-related WM atrophy is similar among males and females are shown in yellow (IC = internal capsula, AVH = alveus of the hippocampus, OpN = optic nerve bundle, IC/Hyp = internal capsula/hypophysis).

Discussion The present study is the first successful application of VBM techniques for assessing changes in brain morphometry in a canine model of aging. Consistent with earlier manual-based ROI analyses [3], significant frontal lobe atrophy was observed in aging dogs. Moreover, the VBM analysis indicated that age-related cortical atrophy is more widespread than initially reported and varies among males and females. Although VBM techniques are more common in human brain aging, there are several advantages to VBM techniques in the canine. First, VBM provides a more reliable and rapid technique for evaluating longitudinal or time-dependent changes in brain morphometry due to aging or disease characteristics in the canine model. Second, development of a VBM method in the canine facilitates rapid comparisons between in vivo analysis of GM and WM atrophy and in vitro studies to identify mechanisms involved in aging and disease. Finally, VBM can be valuable for rapidly assessing the efficacy and safety of new interventions to promote brain health on brain structure before new chemical entities move to clinical testing in human subjects.

References [1] Coffey et al. Arch. Neurol. 1998, 55:169-179. [2] Ashburner & Friston. NeuroImage. 2001, 14:1238-1243. [3] Tapp et al. J. Neurosci. 2004, 24:8205-8213.

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