A Longitudinal Study of Brain Morphometrics Using Serial Magnetic Resonance Imaging Analysis in a Canine Model of Aging

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Purpose
Longitudinal monitoring of human aging is relatively difficult due to the long time needed to follow patients. Beagle dogs have a lifespan of approximately 15 years, thus could be followed easily to cover the critical decline phase of aging. In this study, a group of old beagle dogs were studied over a 3-year period. Annual magnetic resonance imaging (MRI) was performed to acquire images from the whole brain, and the longitudinal changes in cortical atrophy, ventricular enlargement, and development of brain lesions were investigated. Lesions (lacunar infarcts or cysts) in various brain regions were assessed by visual inspection. Quantitative volumetric measurement using manual ROI planimetry and qualitative visual examination were performed to assess developments of cortical atrophy and ventricular enlargement with aging. The changes in different chronological age groups were also compared.

Methods
A group of 47 healthy beagle dogs (24 males, 23 females) were studied. The age at the start of the study was 8-11 years, with N=11, 18, 9, and 9 in each chronological age group. Four MRI studies were performed, annually from 1999 to 2002. The study was performed using the 1.5 Tesla GE mobile scanner. The animal was anesthetized by inhalation of Isoflurane (1.5-2%). A set of 3D images across the whole brain were acquired using a SPGR pulse sequence, with 16 cm FOV, 256 x 256 matrix, 2 NEX; TR/TE = 40/9 msec; flip angle = 40°; slice thickness = 1.2 -1.5 mm. A total of 60 images were acquired. Manual region of interest (ROI) planimetry was applied to measure total cerebral volume (TCV), total intracranial volume, and lateral ventricular volume (LVV). The MR images of each dog obtained in 4 studies were co-registered using SPM. The shape and size of lateral ventricles and the shape and size of cortical sulci and gyri were compared to determine whether there were substantial changes indicating ventricular enlargement and cortical atrophy. For each dog, images collected in 2002 were carefully examined to detect lesions, and recorded into five brain regions: caudate, frontal cortex, cerebral cortex (i.e. regions other than frontal cortex), olfactory bulbs, and thalamus. Based on the aligned images a lesion would be determined as previously existing or an interval lesion that occurred between 2 examinations.

Results
The lateral ventricular volume (LVV) steadily increased from 1999 to 2002 (p < .001). The increased % LVV/TCV over the baseline (in 1999) was calculated, shown in Figure 1, which clearly demonstrated a significance increase every year. The increase in 2002 over the baseline value in 1999 was also calculated in each chronological age group. The mean ± standard deviation was 1.1 ± 0.5% for 8-years-old, 1.2 ± 0.7% for 9-years-old, 1.6 ± 0.7% for 10-years-old, and 2.8 ± 0.9% for 11-years-old. All age groups showed increased LVV/TCV, and the highest change was seen in the oldest group, significantly higher compared to other age groups. In contrast, the total cerebral volume did not show significant decrease over the 3-year period. Cortical atrophy may present as deepened or widened gyri and sulci, not brain shrinkage, and as such visual examination assessing cortical thickness may be more sensitive. Co-registered images were visually inspected slice-by-slice, and the shape and size of gyri and sulci remained unchanged over the 3 years. Figure 2 shows images from 4 different levels acquired in 1999 to 2002. Larger ventricles over time can be appreciated, but not cortical atrophy. This dog had many small lacunes and one large infarct in 2002 (bottom row). Of all 47 dogs in 2001, 12 (25 %) had visible lesions, and one year later 22 of 41 dogs (54 %) had visible lesions. Table 1 shows the number of lesion-bearing dogs in each chronological age group in 2001 and 2002 studies. It can be seen that dogs started to show lesions at age of 11, and by age of 14 most dogs (6/7) had aging lesions. In regional analysis, lesions in the frontal cortex and caudate were more numerous compared to other brain regions. More than 76% of the total lesions were located in these two regions.

Table 1: The number of lesion-bearing dogs in each chronological age group in 2001 and 2002

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Discussion
The canine model is well suited for assessment of brain aging from various aspects. Dogs share many of the cognitive, behavioral, and pathological hallmarks of aging observed in humans [1], and have been shown as a good model for studying the effect of diet and environmental enrichment interventions on cognitive decline [2-3]. In this study we investigated the changes in brain structures by MRI. As in humans the dog brain shows ventricular enlargement with aging, assessed using quantitative volumetric measurements and qualitative visual examination. The enlargement rate was significantly increased after age of 12. However, cortical atrophy was not noted, even in the oldest group. One finding which was less common in humans was the development of spontaneous aging lesions, primarily in the frontal cortex and caudate nucleus. The incidence and number of lesions increased with age. A better characterization of the canine aging model may facilitate its future applications.

References

Acknowledgement
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Figure 1: The increased % LVV/TCV over the baseline value measured in 1999. The lateral ventricular volume steadily increased from 1999 to 2002 (p < .001). The increase in 2001 was significantly higher than in 2000, and the increase in 2002 was also significantly higher than in 2000 and 2001.

Figure 2: Serial images from 1999 to 2002 from one dog. LARGER ventricles can be appreciated, especially in 2002. No apparent cortical atrophy was noted. This dog had many lacunes and one large infarct in 2002 (bottom row, marked). It can be seen that the pre-frontal lesion was also present in 2001 but not others.