Using Structural MRI to Compare Frontal Lobe Volume with Beta-Amyloid and Executive Dysfunction in a Canine Model of Aging

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Purpose

The human frontal lobes are particularly vulnerable to aging [1]. Rates of age-related frontal atrophy are twice as high as rates for the entire brain, hippocampus, and amygdala [2]. Accordingly, the frontal theory of aging suggests frontal lobe atrophy is largely responsible for cognitive aging. Like humans, beagle dogs exhibit cognitive dysfunction with age. Age-related frontal lobe atrophy in the canine and its relationship to beta-amyloid deposition and cognitive dysfunction however, are unknown. In the present study, changes in regional brain volume in young and old beagle dogs were examined with MRI. In a subset of animals, total frontal lobe volume was compared to beta-amyloid deposition and complex cognitive function (executive function) to determine the effects of age on frontal lobe structure, function, and pathology.

Methods

A GE-LX 1.5T mobile MRI scanner and quad-knee coil was used to collect structural scans for 66 beagle dogs (aged 3 months – 15 years). 60 T_1-weighted images in the coronal plane were acquired using: spoiled gradient (SPGR) pulse sequence; NEX = 2; 256 x 256 matrix; 12 cm field of view; repetition time [TR] = 40 msec; echo time [TE] = 9.0 msec; flip angle = 40^0; slice thickness = 1.2 – 1.4 mm; pixel size = 0.47 mm. After correcting for variations in head tilt, pitch, and rotation using standard neuroanatomical landmarks, regions of interest (ROIs) were traced manually in the coronal plane using Analyze® version 5.0. ROIs included: total brain volume (TBV), total frontal lobe volume (FLV), frontoventricular volume (FVV), hippocampal volume (HCV), and occipital volume (OCCV). TBV was calculated as a proportion of total intracranial volume (TBV/TICV), and all regional measures were calculated as a proportion of TBV (e.g. FLV/TBV). ROIs were compared to cognitive [3] and neuropathology [4] measures in a subset of animals.

Results

Frontal lobe slices from a young (A) and old (B) beagle dog are shown in figure 1. TBV, FLV, and HCV decreased with age and FVV increased with age (figure 2). TBV was significantly smaller in senior dogs compared to puppies, young, middle aged, and old dogs ($p < .001$). FLV decreased early beginning around 8 years and was smaller in old and senior dogs compared to young and middle-aged dogs ($p < .001$). HCV was also smaller in puppies compared to young, middle-aged, and old dogs ($p < .001$) and in senior dogs compared to middle-aged and young dogs ($p < .05$). OCCV did not significantly vary with age. FVV was largest in the senior dogs compared to puppies, young, middle-aged, and old dogs ($p < .05$). HCV only correlated with discrimination learning [$r(35) = -0.572$, $p = .008$]; decreased FLV was related to increased errors on several measures of executive function including inhibitory control [$r(46) = -0.325$, $p = .02$], concept learning [$r(10) = -0.516$, $p = .05$], and complex working memory [$r(10) = -0.677$, $p = .01$]. Decreased FLV was also associated with a significant increase in beta-amyloid in the frontal cortex [$r(23) = -0.504$, $p = .007$].

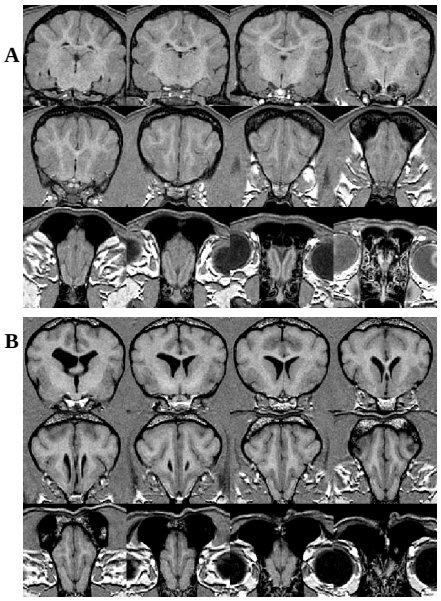

Figure 1. Examples of slices through the frontal lobes of a young (A) and old (B) beagle dog.

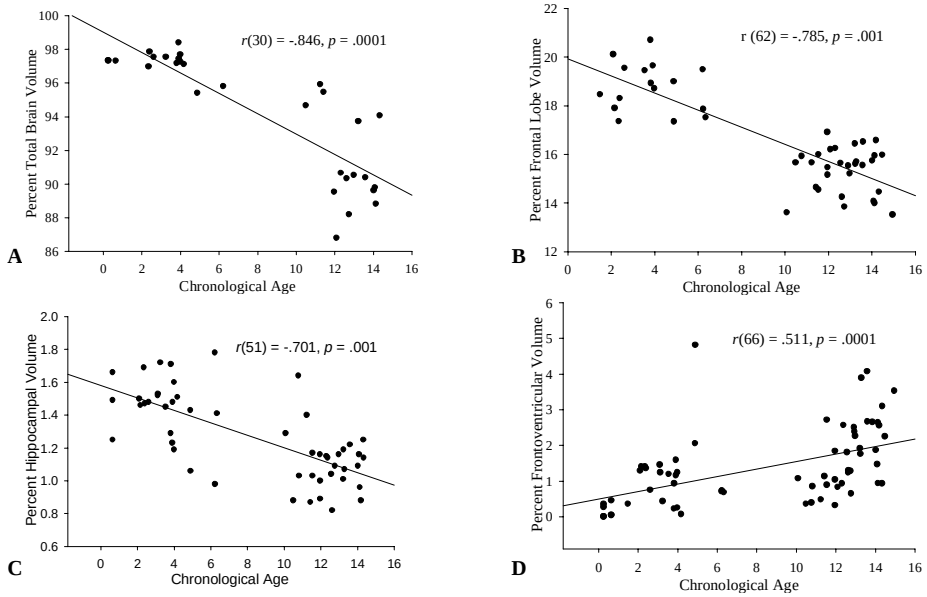

Figure 2. Changes in TBV (A), FLV (B), HCV (C), and FVV (D) as a function of chronological age in the beagle dog.

Discussion

Age-related changes in brain volume of the beagle dog were examined with MRI. Compared to TBV and HCV which remained relatively stable from 3 months to 11 years of age, FLV decreased early beginning around 8 years of age. Decreases in FLV were related to increased executive dysfunction and beta-amyloid deposition in the frontal lobes. These findings are consistent with human brain aging and the frontal lobe hypothesis which suggests that the frontal lobes are particularly sensitive to aging. This the first study to examine changes in frontal lobe volume in dogs and correlate these changes with behavioral and neuropathological markers in the dog. The present results further validate the use of the canine as a useful model to study functional and neuropathological aspects of aging.

References

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