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Evaluating Age-Related Brain Changes in the Female Ferret

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Synopsis

Keywords: Biomarkers, Aging, Ferret, Morphology

Motivation: An open-ended question in normal aging is how the brain changes over time and which regions are most susceptible to age-related changes.

Goal(s): Using bias-free voxel-wise approach and evaluating warp fields using the logarithm of the determinant of the Jacobian (LogJ), we investigated age-related changes in the female ferret.

Approach: We imaged four female ferrets at 1-2 years of age and later at 3-4 years of age using diffusion tensor imaging.

Results: Average LogJ maps revealed 24.8% reduction in the superior colliculus.

Impact: Voxel-wise morphology in the ferret allows us to track age-related changes in a longitudinal fashion.

Introduction

An open-ended question in normal aging is how the brain changes over time and which regions are most susceptible to age-related changes. Longitudinal imaging allows for individual evaluation of age-related changes, however, there are limitations to human clinical studies in which environmental and underlying conditions add confounds to aging interpretations[1,9]. Additionally, many studies focus on volumetric changes in generalized regions such as grey matter volume, white matter volume, and cortical volume[1], but may not capture trends in all anatomical regions (e.g. such as hippocampus and thalamus). Using bias-free voxel-wise approach and evaluating warp fields using the logarithm of the determinant of the Jacobian (LogJ), we investigated age-related changes in the female ferret. Pre-clinical imaging offers the benefit of controlled environment, socialization, and diet, while not sacrificing inter-individual differences[7]. The ferret is the smallest gyrencephalic animal and has more white matter to grey matter ratio, making it suitable for high strength field pre-clinical MRI[3,6]. Additionally, ferrets are considered "senior" around the age of 3-4 years old, showing increased cancer risk 4 years of age[2]. The ferret's unique brain structural attributes and their early observed phenotypical changes with respect to age, make them a suitable candidate for longitudinal imaging to study aging.

Methods

Eight female co-housed ferrets were imaged at 1-2 years of age (Summer 2022) and four of these were again imaged at a later timepoint (Summer 2024) at 3-4 years of age on a Pre-Clinical Bruker 7T scanner using Paravision v3.2-v3.5 software. A Quadrature RF coil (86mm) and a rodent cardiac coil (60mm) was used for transmit and receive, respectively. Induction ranged from 2-5% and maintenance was 1-3% delivered with 100% oxygen. Each ferret also received subcutaneous fluids and 1mg/kg cerenia prior to MRI. Multiple MRI scans were obtained including high resolution anatomical (T1 FLASH; 0.3x0.3x0.3mm,TE/TR=7 ms, 5000 ms), T1 weighted (0.4x0.4x0.6mm,TE/TR=3.1 ms,4000 ms), T2 weighted (0.4x0.4x0.6xmm,TE/TR=6 ms,30 ms), and Diffusion Tensor imaging (DTI) (0.5x0.5x1mm; TE/TR=58 ms, 4500 ms,b=400,800,1600,dir=6,6,32) at both timepoints. DTI scans were processed using TORTOISE[3,4,5,7], to obtain Fractional Anisotropy (FA) and Trace (TR) maps. For the 4 ferrets imaged longitudinally, individual 2nd timepoint diffusion tensors (DTs) were tensor aligned to 1st timepoint DTs using DTIREG. All eight young adult ferret scans were used to create a DT template and we tensor aligned the 1st and 2nd timepoints DTs to this space for group-level analysis.

Results

Average LogJ maps revealed 24.8% reduction in the superior colliculus. Other regions of shrinkage included the inferior colliculus, cingulate gyrus, posterior sigmoid gyrus, and cingulate (22.6%, 22.6%, 20.2%, and 17%, respectively).

Discussion and Conclusions

Given ferret's visual and auditory acuity, shrinking in the inferior and superior colliculus may be related to sensitivity in sensory integration[10]. In addition to MRI metrics, we have also collected behavioral data on this cohort, and plan to evaluate these with respect to age to better understand the functional relationship of our observed brain structure differences.

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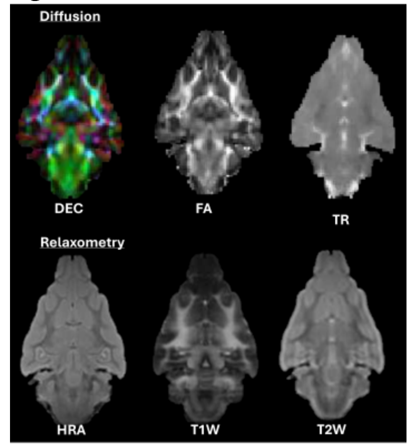
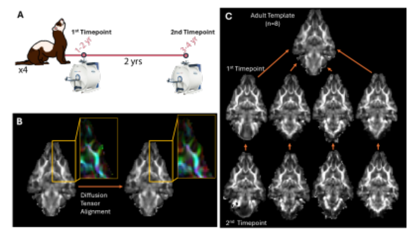
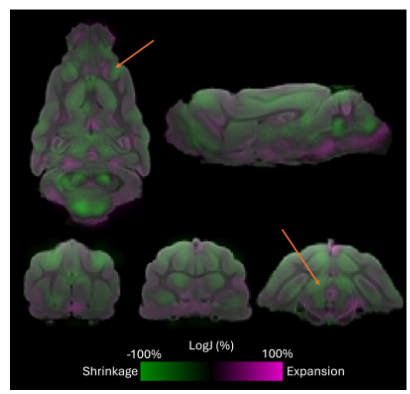
Figures



Overview of MRI Metrics Collected such as Diffusion Metrics: DEC, FA, and TR; and Relaxometry: High Resolution Anatomical, T1 weighted, and T2 weighted



A) Longitudinal Study Design B) Group-Level Analysis Diffusion Tensor Registration – showing close-up of diffusion tensor alignment performed between timepoints and template on DEC map C) Individual timepoint registration scheme to young template for group-level analysis



LogJ Average Subtraction Map Between 2nd and 1st Timepoint (bright green indicates -100% shrinkage while bright purple represents 100% expansion)

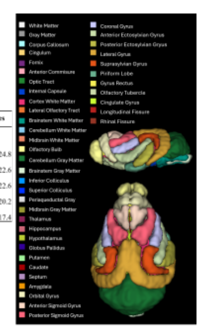


Table : Highest Ranking Brain Regions with Volume Changes

Brain Region	Shrinkage (% change)
Superior Colliculus	-24.8
Inferior Colliculus	-22.6
Cingulate Gyrus	-22.6
Posterior Sigmoid Gyrus	-20.2
Cingulum	-17.4

Atlas registered to young template with

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legend of corresponding anatomical labels - Sagittal and Axial view of volume render; Table 1 - Highest Ranking Brain Regions with Volume % Change