MR studies of aging in the hippocampus of the FBNF1 rat show correlations with behavioral and structural degeneration

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INTRODUCTION

We undertook a multi-modality investigation of the hippocampus to identify age-related changes that might be specifically linked to hippocampus-dependent memory deficits. Our secondary goal was to add to the development of a rat model of hippocampal aging that has shown similarities to the changes in elderly humans. We used Fisher 344 X Brown Norway hybrid (FBNF1) rats, purpose-bred by the National Institute on Aging for aging research.

METHODS

Thirty FBNF1 female rats (NIA/Harlan) were divided into 3 groups: Young adult (3 months), Middle-aged (12 months), and Old (24 months), 10 rats in each group. Rats were behaviorally characterized with the Morris water task[1] and transverse-patterning discrimination task[2] to investigate hippocampus-dependent spatial and nonspatial memory respectively. MRI was done at 9.4 T with a Bruker Avance console. T_2-weighted spin echo (SE) coronal MRI was obtained (TR/TE =2/40ms, 1mm slice/ 20 slices, no gap, FOV = 2.5cm, matrix 256x256, NA=4). Volumetric analysis of the MRI data was performed using in-house software (Marevisi). The hippocampus was traced on 6 consecutive slices in each animal[3]. Intracranial volume (ICV) was measured by tracing all images. Localized ^{1}H MR Spectroscopy (MRS) was performed with a STEAM pulse sequence (TR/TE=2000ms/20ms, TM=26ms, SW=10000 Hz, NA= 1024). Two identical voxels (2x2x3mm), centred within the hippocampus were collected. Spectra were quantified with jMRUI (AMARES) [4] and ratios of NAA and choline to creatine were analyzed. All animals were sacrificed, brains extracted, post-fixed, sectioned, and stained. Neuronal density (light microscopy) and synaptic and mitochondrial density (electron microscopy) using unbiased stereological counting techniques were measured.

RESULTS

Aging was associated with functional deficits on hippocampus-dependent memory tasks. These deficits were accompanied by structural alterations observed both *in vivo* (MRI- decreased hippocampal volume) and *post-mortem* (lower neuronal density) (Fig. 2). There was a significant correlation between hippocampus-dependent memory, measured with the Morris water task and transverse-patterning discrimination task, and hippocampal volume (p=0.047 and p=0.008 respectively). Neuronal metabolic integrity, assessed by levels of N-acetylaspartate showed no changes.

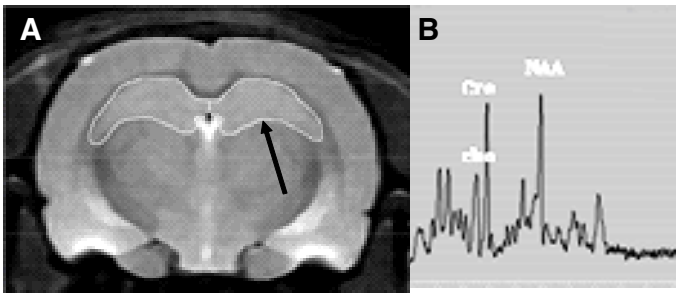

Figure 1. Example data. A) T_2-weighted MRI of the hippocampi outlined in white (black arrow). B) A representative MR spectrum from the hippocampus with Choline, Creatine and NAA labeled.

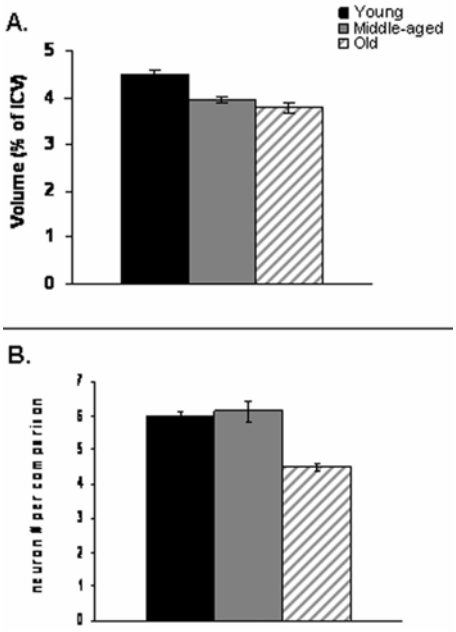

Figure 2. Morphological changes with age. A) Differences in hippocampal volume (F (2,27) =7.274, p = .003). Middle-aged and Old rats have significantly smaller hippocampal volumes. **B)** Changes in neuronal density (F (2,14) = 5.603, p = .019). Neuronal density is significantly reduced in the Old rats.

CONCLUSION. The results suggest that while the neurons residing in the aged hippocampus retain their ability for normal metabolic functioning, the loss in the structure is such that the hippocampus as a whole is unable to sustain normal mnemonic processes. Moreover, the FBNF1 rats seem to be useful as a model of normal hippocampal aging in humans, given that the observed age-related changes that occur in the rat hippocampus are remarkably similar to those previously reported in humans.

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