Correlating Learning and Memory Deficits to Changes in Perforant-Path Microstructure in the Aged Rat

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Introduction

While alterations to hippocampal structure and function are assumed responsible for most age-related memory deficits[1], variations within hippocampal subregions in response to aging [2-4] has complicated the identification of therapeutic targets. Most notably, it is still unclear how synaptic changes alter local circuit function and how such local changes manifest in cognitive deficits. In the current study, we have examined whether changes in learning proficiency correlate with alterations in microstructural anatomy as measured by magnetic resonance microscopy (MRM) in both young and aged, behaviorally characterized rats.

Experimental

Young (4-6 mo.) and aged (23-25 mo.) male Fisher 344 x Brown Norway hybrid rats (n = 6) were trained in an operant working memory task[5] to quantify their learning and memory proficiency. Next, rats were trained in an object-place paired associate (OPPA) task requiring them to choose between two different objects located at the ends of both arms of a y-maze for a food reward (**Fig.1**). Rats train until they can select the correct object in 26 or more of 32 trial attempts for two consecutive days. Afterwards, two identical objects which are dissimilar to those used during training are placed over the wells and the rat is tasked with selecting the well containing food. After behavioral testing, rats were euthanized, and their perfusion-fixed brains imaged in the AMRIS facility at UF using the 750MHz spectrometer (DTI-Standard: TE/TR = 20/1000ms, δ = 1.2ms, Δ = 10ms, b = 1200 s/mm^2, 21 direction, res = 47μm^2 in-plane, slice = 250μm thick, avg = 4, temp = 23^{o}C, time = 12.5h). Fractional anisotropy (FA) maps were generated (**Fig.2**), and the mean FA of the left hemisphere's perforant path was quantified.

Results and Discussion

Mean FA values for perforant-path ROIs were calculated in the aged (0.278) and young (0.332) rat brains. These data were compiled from preliminary experiments collected in two matched pairs of rats (n = 2). The difference in means (5.4%) suggests an age-associated loss of microstructural integrity in the perforant path.

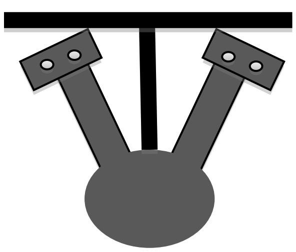

Fig.1 Schematic illustrating the y-maze used for the object-place paired associate (OPPA) task. Rats traverse bilaterally oriented arms between the starting platform (large grey circle) and the choice platforms (gray boxes). Food rewards are placed in wells (small, light gray circles) concealed by training objects.

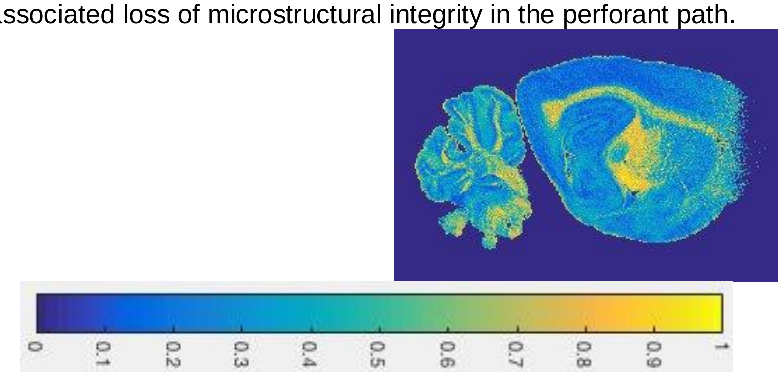

Fig.2 Representative fractional anisotropy (FA) maps—transverse, 1 of 4, sagittal, 1 of 9—displaying the directional dependence of water diffusion across the brain. Voxel color corresponds to the local FA value represented on the accompanying colorbar.

Acknowledgements

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