Decreased mean diffusivity and changes in proton spectra in the brain of aged rats with learning deficits

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Introduction: Aging, as well as many neurodegenerative diseases, is accompanied by serious cognitive deficits, particularly impaired learning and memory loss. Cognitive decline in old age has been linked to changes in brain anatomy, morphology, volume, and functional deficits [1]. Nervous tissue, particularly in the hippocampus and cortex, is subject to various degenerative processes, including a decrease in the number and efficacy of synapses, neuronal loss, astrogliosis, and changes in extracellular matrix proteins. These and other changes not only affect the efficacy of signal transmission at synapses, but could also affect extrasynaptic (volume) transmission, mediated by the diffusion of transmitters as well as other substances through the volume of the extracellular space [2]. Therefore, we studied the diffusion of water in the brain tissue of aged rats with and without a learning deficit. These data were correlated with metabolite concentrations assessed by proton spectroscopy.

Subjects and methods: Experiments were performed in vivo on 4- (adult) and 22-month-old (aged) Wistar male rats. Diffusion-weighted (DW) MRI was used to determine the mean diffusivity <D> and fractional anisotropy FA [3] in different brain regions of behaviorally characterized rats. Seven non-collinear directions were used for FA evaluations. Proton spectra were measured using a modified single voxel STEAM sequence in both hipocampi, and the spectra were evaluated using the LC-Model [4]. Prior to MR measurements, the ability to cognitively process spatial information was tested in a Morris water maze [5], and superior and inferior learners were selected according to their escape latencies [6].

Results: The aged superior learners did not show significantly longer escape latencies (28±2 s) than adult rats (29±1 s), but the latencies were significantly different in inferior learners (45±2 s). We evaluated mean diffusivity and fractional anisotropy in the primary somatosensory cortex, corpus callosum, CA1 region of the hippocampus, dentate gyrus and striatum (Figure 1). In all these regions, the mean diffusivity was significantly lower in inferior learners when compared either to adult rats or superior learners. There were no such differences between adult rats and aged superior learners except in the corpus callosum. The values are summarized in Table 1. We have not found any change in fractional anisotropy related to learning abilities. However, an age-related decrese in FA in the somatosensory cortex was observed (from 0.179±0.007, N=8 in adult to 0.153±0.005, N=16 in aged rats). The concentration of creatine metabolites (Cr) and glutamate (Glu) showed a significant decrease in inferior learners (6.8±0.9 mM and 6.8±0.5 mM, respectively) when compared to both superior learners (8.5±0.4 mM and 9.0±0.8 mM, respectively) and controls (N=6). The N-acetyl aspartate (NAA) concentration in aged rats showed a significant difference between aged inferior (7.3±0.4 mM) and superior (8.5±0.4 mM) learners. Inositol concentration increased from 3.0±0.1 mM to 4.3±0.4 mM in aged animals regardless of their learning abilities.

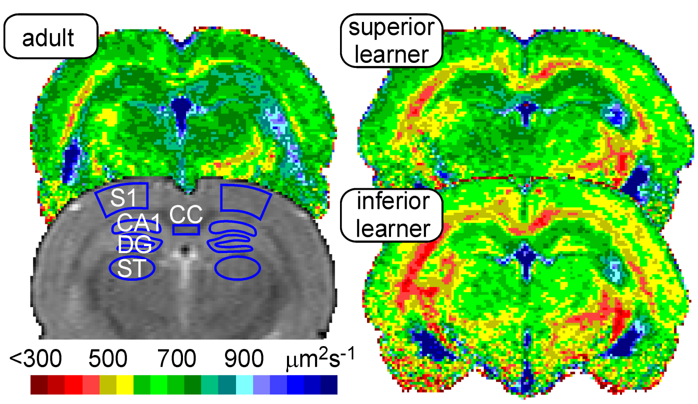

Figure 1: Diffusivity maps acquired in the brain of aged superior and inferior learners and in an adult control. Note the decrease of diffusivity in the inferior learner's brain. The mean values of <D> were calculated in the delineated areas: primary somatosensory cortex (S1), corpus callosum (CC), CA1 region of the hippocampus, dentate gyrus (DG) and striatum (ST).

	adult <D> $\mu m^2 s^{-1}$	superior learners <D> $\mu m^2 s^{-1}$	inferior learners <D> $\mu m^2 s^{-1}$
cortex	654 ± 8	637 ± 7	613 ± 4*†
corpus callosum	602 ± 15	546 ± 5*	516 ± 10*†
CA1	705 ± 10	719 ± 4	685 ± 6*†
dentate gyrus	645 ± 10	649 ± 5	605 ± 5*†
striatum	670 ± 13	658 ± 5	611 ± 8*†

Table 1: Mean diffusivity in aged rats, divided into two subgroups according to their learning abilities, and in adult rats (controls). All groups of animals shown in the table consisted of 8 rats; data are expressed as mean ± S.E.M. Significant differences (two-tailed Student's t-test, $p<0.05$) compared to adult rats or superior learners are marked with asterisks or crosses, respectively.

Discussion and conclusion: Fractional anisotropy is not a sensitive measure of the structural changes found previously in the hippocampus of aged inferior learners [6]. Decreased mean diffusivity was found in aged inferior learners but not in aged superior learners, whose mean diffusivity and performance in the Morris water maze were essentially indistinguishable from those of much younger adult animals. Similarly, changes in NAA, Cr and Glu concentrations were found only in aged inferior learners. Thus, our data suggest that learning deficits are not only an inevitable result of the aging process, but that decreases in mean diffusivity such as those observed in inferior learners can significantly influence extrasynaptic transmission and thereby contribute to age-related learning deficits.

References and acknowledgement:

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