Characterization of age induced brain changes using MRI in rats

T. Blumenfeld-Katzir[1], O. Pasternak[2], and Y. Assaf[1]

[1]Neurobiochemistry Department, Faculty of Life Sciences,Tel-Aviv University, Tel-Aviv, Israel, [2]School of Computer Science, Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv, Israel

Introduction

Aging is a heterogeneous process with wide-spread manifestations among humans. Age Related Cognitive Decline (ARCD) is typically characterized by reduced memory, learning, attention, concentration and use of language. The neurodegenerative pathological processes that underlie age related behavioral changes are affected by genetic factors as well as by life-time experience (e.g. education, nutrition). Histological and imaging studies have pointed to regional degeneration of specific brain systems (hippocampus, frontal lobe). However, the relative contribution of white and gray matter pathologies to aging is under debate. In order to test the different pathological mechanisms in aging we established a non interventional rodent model of aging. With this model we have combined behavioral, histological and imaging procedure to follow up on the regional neurodegenerative processes in aging.

Methods

Twenty eight Wistar male rats were scanned in a 7T MRI system (Bruker, Germany) divided into three age groups (3 months, n=11; 9 months, n=8; 19 months, n=9). The rats were grown in the animal facility from the age of 4 weeks without any interventional conditions until MRI and behavioral test were acquired. Following the MRI the rats were sacrificed and prepared for ex-vivo MRI and histological analysis.

The MRI protocol included diffusion weighted echo-planar imaging (DWI-EPI) with the following parameters: TR/TE=4000/25 ms, Δ/δ =10/4.5ms, 16 non-collinear gradient directions, 12 slices of 1.2 mm thickness and in-plane resolution of 0.2x0.2mm^2.

Image analysis included diffusion tensor imaging analysis of the DWI-EPIs to produce for each rat fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps[1]. For statistical comparison between rats (voxel based morphometry) each rat brain volume was co-registered with template rat atlas. The registration and statistical analysis were performed using SPM2 (FIL, UCL, London, UK).

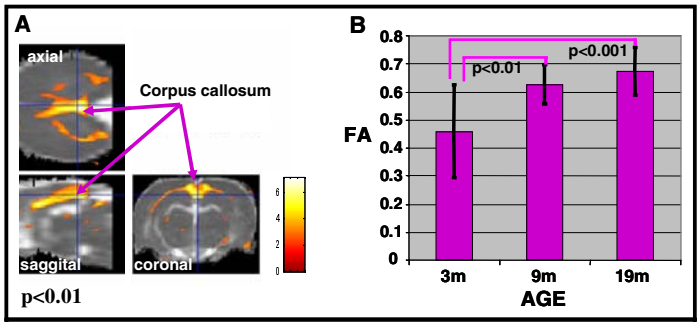

Figure 1: Positive Correlation of FA and Age

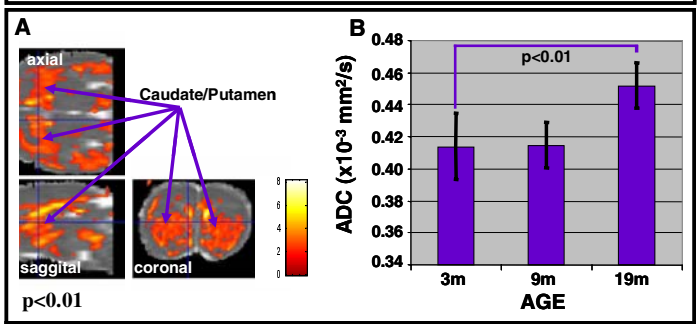

Figure 2: Positive Correlation of ADC and Age

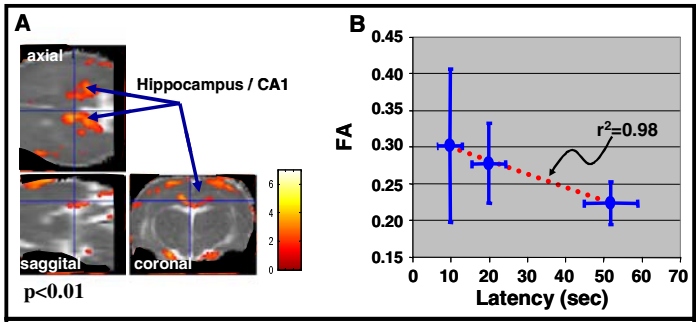

Figure 3: Negative Correlation of FA and latency in Morris water maze

Results and discussion

Both FA and ADC showed positive correlation with age but in different regions. FA showed strong positive correlation with age (Figure 1) especially in white matter regions implying that in mature and aged rats, FA is increased with age. The increase in FA was most significant in the corpus callosum ($p<0.001$, Figure 1B). Those changes are mostly due to FA increase between 3 months and 9 months with only minor further increase afterwards (Figure 1B). This result is opposite than what frequently found in human where FA reduces with age (above 20 years). By contrast, ADC shows major changes in cortical regions (Figure 2A). For example, in the caudate/putamen area a strong positive correlation is observed indicating increase of ADC with age (Figure 2B). This correlation was characterized by small ADC increase between 3 and 9 months and a more pronounced ADC increase between 9 and 19 months. This result is in-line with ADC changes found in the aging human brain. Figure 3 shows the negative correlation of FA with rat's performance (latency) in the Morris water behavioral task. Better memory and learning performance of the rat is manifested by shorter latency times. Only in the hippocampus, a negative correlation was found (Figure 3B) indicating that reduction in FA might be associated with memory and learning decline, especially in the CA1 area.

Another interesting result was of the ex-vivo, formalin fixated, MRI brain experiments. Here it was found that completely different pattern of brain changes occurs with age. For example, the ADC of the 3 months old rats was much higher than that of the 19 months old rats in most brain areas (data not shown). In addition, FA analysis of the ex-vivo brain revealed opposite trend than the in-vivo pattern. In the ex-vivo experiment FA reduced with age only in some white matter areas (internal capsule but not corpus callosum). These results imply that study of aging using formalin fixated tissue bias the MRI results and might also affect histological measures (cell counting and staining intensity per area).

Conclusions

The data presented in this work support the use of rodents as a model for aging. Although the DTI characteristics of aging are different between human and rat, as shown in this work, the ADC pattern is similar indicating some similarity between the aging process of the two species. It is reasonable to assume that in rodents biological aging is the sole factor affecting tissue degeneration while in human multiple factors can contribute to progressed tissue degeneration (stress, nutrition and environmental factors). Thus, this model can be used to assess the efficiency of neuro-protective drugs to biological aging.

Reference: 1. Basser PJ, Pierpaoli C. Magn Reson Med 1998;39(6):928-934.