High Resolution MRI of Enriched Environment Induced Structural Brain Changes

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Introduction

Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder which causes dementia. Its two most distinct physiological features at the cell and tissue level are extra cellular amyloid plaques and intraneuronal neurofibrillary tau tangles (NFT). The pathologies associated with the disease sums up to a consistent loss of white matter during the course of the disease. Therapeutic approaches to AD try to address the formation of the plaques and tangles. Other approaches target the cell death accompanying the disease; such approaches can also target the promotion and induction of neurogenesis as a counter balance to the loss of white matter. The dementia might be caused due to a decrease below a threshold in the number of connections between neurons; the enhanced neurogenesis in earlier stages of life can help establishing higher starting point as regard to the number of neurons and synapses, "brain reserve". Beside biochemical or surgical approaches to neurogenesis induction, an important research approach tries to explore the induction of neurogenesis in mice (and synaptogenesis) by means of environmental enrichment. The enrichment is implemented by keeping the animals in larger cages which enables more complex social interaction, exploratory behavior, physical activity and sometimes more variable food supply. Indeed, currently studies have shown that enriched environment can cause neuroanatomical changes in the brain, increased dendritic arborization, increased hippocampal thickness, neurogenesis, gliogenesis, synaptogenesis, and improves learning and spatial memory. The aim of this research was to use MRI, specifically diffusion tenser imaging, DTI, in order to get new insights regarding the brain changes following the use of the enriched environment paradigm.

Materials and methods

Twelve male C57BL/6J mice at the age of weaning (3 weeks old) were randomly divided into two groups, six mice per group. The groups were: four months environmental enrichment (n=6, EN) and four months non environmental enrichment (n=6, REG). The control mice were housed in regular shoebox cages (30x20x18) and for the enriched environment we used 50cm × 40cm × 40cm cages. The enriched cages were divided into two floors with a plastic ladder between them and included also: one plastic house, plastic ladders, wooden toys, several hollow plastic tunnels linked between them and a running wheel. After 4 months in the enrichment cages the enrichment period was ended and animals were transferred to a regular shoebox cage. After an additional one month all animals were scanned in the MRI following which they were sacrificed and brains were preserved for further study.

Mice of the two groups were scanned in a 7T/30 spectrometer (Bruker, Rheinstetten, Germany). The MRI protocol included diffusion-weighted echo planar images (Dti-Epi, TR/ TE=4000/25 ms, 4 EPI segments, Δ/δ=10/4.5 ms, b value of 1000 s/mm2 acquired at 16 gradient directions). The field of view was 1.8cm^2, the original resolution was 128x96 pixels for a total of 12 coronal slices with a thickness of 0.75cm with no gap between them). The DTI-EPI data were analyzed using the DTI analysis framework to produce the FA, ADC, $\lambda_{//}$ and $\lambda_{\perp}$. Following DTI analysis, the brains were extracted from the surrounding skull and fat tissue by an in-house software. Then, all images were coregistered and normalized to a digitized template brain from a printed atlas using the SPM software (version 2, UCL, London, UK). Following successful co-registration and normalization, statistic parametric maps of the voxel-based t-test between the EN and REG group for the the FA, ADC, $\lambda_{//}$ and $\lambda_{\perp}$ were computed

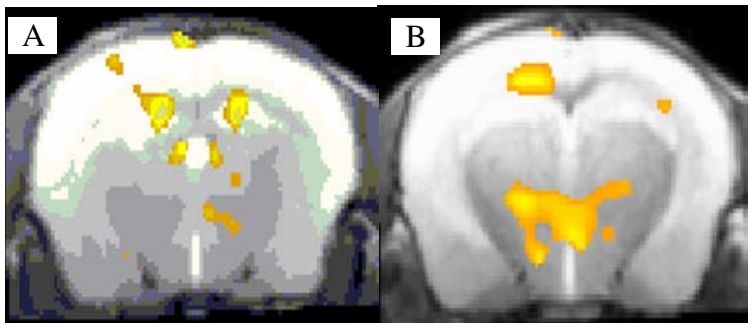

Fig. 1. Coronal MRI section showing areas of the frontal hippocampus (A) and of the paraventricular thalamic nucleus(B). In Color the Areas with significant ADC difference.

Results

For the ADC we found significant differences in the frontal hippocampus area ($p<0.005$) and in the paraventricular thalamic nucleus ($p<0.001$). For the FA we found significant differences in the frontal corpus callosum ($p<0.001$). For the $\lambda//$ we found significant differences in the corpus callosum ($p<0.001$) and in the paraventricular thalamic nucleus ($P<0.001$). For the $\lambda_{\perp}$ we found significant differences in the right dorsal hippocampal commissure ($p<0.001$) and in the molecular layer of the dentate gyrus in the hippocampus ($P<0.001$).

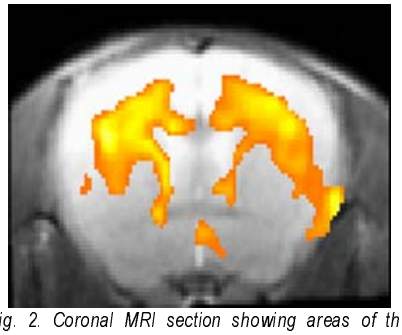

Fig. 2. Coronal MRI section showing areas of the frontal corpus callosum. In Color the Areas with significant FA difference.

Discussion

In this study we investigated the brain differences induced by enriched environment as reflected with DTI, and the usability of the DTI as a tool to monitor brain changes *in-vivo* in the enriched environment paradigm allowing longer research paradigms. ADC showed significant differences in the frontal hippocampus. Previous researches showed the hippocampus as the main area of difference after environmental enrichment and thus the differences in the hippocampus were expected from previous research. In addition to the hippocampus the ADC showed significant differences in the paraventricular thalamic nucleus, an area connected with cognitive arousal. The FA shows significant differences in the frontal corpus callosum. These observations were not marked before (by histological procedures) as affected after environmental enrichment. The $\lambda//$, showed significant differences in the paraventricular thalamic nucleus and in the corpus callosum. Both the paraventricular thalamic nucleus and the corpus callosum are areas responsible for, or having important role in the connectivity between different areas in the brain. The $\lambda_{\perp}$ showed significant difference in the right dorsal hippocampal commisure and in the molecular layer of the dentate gyrus in the hippocampus. These findings are in accordance with previous research showing the hippocampus as the main area of difference between mice going through environmental enrichment and control group. Following this study it is suggested to further examine white matter in the specific areas marked with the use of DTI (the corpus callosum and the paraventricular thalamic nucleus) after the induction of the environmental enrichment paradigm. It can be concluded that the environmental enrichment contributes to alteration in neuronal circuitry involving both hemispheres (the corpus callosum) and involving the thalamus (innervations to the paraventricular thalamic nucleus). It is also suggested that MRI and specifically DTI can be used as an important tool to study brain differences following environmental enrichment and other paradigms and that the MRI and DTI can contribute to isolate phenomena which might be overlooked if not specifically being searched for, such as the differences showed here in white matter properties.