When is a young rat brain adult? Volume and myelination changes in cortex and striatum

Luam Mengler[1], Artem Khmelinskii[2], Michael Diedenhofen[1], Chrystelle Po[1], Marius Staring[2], Boudewijn P. F. Lelieveldt[2, 3], and Mathias Hoehn[1]

[1]Max Planck Institute for Neurological Research, In-vivo-NMR Lab - Cologne, Germany
[2]LUMC, Dept. of Radiology, Division of Image Processing - Leiden, the Netherlands
[3]Delft University of Technology, Dept. of Intelligent Systems - Delft, the Netherlands

Introduction

Longitudinal studies on brain pathology rely on a steady state adult brain to exclude confounds of brain development changes. Thus, knowledge when adulthood is reached is indispensable to discriminate developmental phase and adulthood.

We are conducting a lifespan study on rats, imaging juvenile development as well as ageing processes of the brain with noninvasive techniques including functional and anatomical MRI and different PET-tracers. Here we present a high-resolution longitudinal MRI study at 11.7T of male Wistar rats between 21 days and six months of age, characterizing cerebral volume changes and tissue-specific myelination as a function of age.

Methods

Twelve Wistar rats, housed pairwise in cages, were used in MRI experiments from the age of three weeks up to three or six months, respectively.

MR experiments were conducted on an 11.7T Bruker BioSpec scanner (Bruker Biospin, Germany). Animals were anaesthetized using 2% Isoflurane in 70:30 N_2O:O_2 and vital functions were monitored continuously.

T2 maps were chosen for their anatomical detail and quantitative reproducibility; diffusion tensor imaging for information on tissue anisotropy and myelination. Maps were calculated from a multislice multiecho sequence (10 echoes) with TE=10ms, TR=5000ms, inplane resolution of 0.146x0.146mm and 0.5mm slice thickness (no gaps).

For all individuals, T2 maps from the different ages were coregistered non-rigidly using a B-spline transform (1), and the corresponding deformation fields were calculated. Volumetric changes of brain regions were derived from the deformation fields.

At three weeks, three and six months, a subset of four rats was sacrificed for histological evaluation using *Cresyl Violet* and *Black and Gold II* staining for myelin.

Results

Cortical thickness reaches final value at 1 month, but volume increases of cortex, of striatum and the whole brain end only after two months. Myelin accretion is pronounced till the end of the third month. Continuing myelination increases in the cortex are seen on histological analysis, but are no longer reliably detectable with diffusion-weighted MRI due to parallel tissue restructuring processes.

A combination of reduced T2 and decreased cortical volume is implying an increasing tissue density (myelination and cell number) during development, lowering the relative amount of free water, and thus reducing the cortical volume. This was confirmed by histological evaluation.

Conclusions

In conclusion, cerebral development continues over the first three months of age. This is of relevance for future studies on brain disease models, which should not start before end of month 3 to exclude serious confound of continuing tissue development.

Acknowledgement / References

This work was financially supported by grants from BMBF (0314104) and the EU-FP7 program TargetBraIn (HEALTH-F2-2012-279017).

(1) Klein & Staring et al. "elastix: a toolbox for intensity based medical image registration", 2010, IEEE-TMI