In vivo detection of Alzheimer disease in APP transgenic mice with T2-Mapping

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Hypothesis:
Alzheimer disease can be detected by MRI in APP transgenic mice by T2-Mapping without the need for contrast agent or high resolution imaging.

Methods:
We used six 20-week old TgCRND8 mice and five age- and gender- matched wildtype mice for MRI. TgCRND8 mice encode a double mutant form of amyloid precursor protein under the control of the PrP gene promoter. Thioflavine S-positive Aβ amyloid deposits are present at 3 month, with dense-cored plaques and neuritic pathology evident from 5 month of age [1].
Imaging was performed on a small animal scanner (Clinscan, Bruker, Ettlingen, Germany). A Bruker mouse head phased array coil (2x2) was used for imaging. The protocol consisted of a high resolution (100µm isotropic) T2-weighted TSE- sequence (TR: 1250ms, TE: 43ms) and a T2*-weighted GRE- sequence (TR: 50ms, TE: 11ms, FA: 18°) with the same resolution for plaque imaging. A multiecho- sequence (TR: 2500ms, 12x TE: 8 - 97 ms, 156 x 156 x 700µm) was used for T2-calculation. T2-Maps of the mouse brain were calculated with internal software discarding the first echo (due to signal loss to achieve steady state) and subtracting background noise. For comparison of groups 12 regions of interest (ROI) in 2 slices were defined and analyzed (Fig. 1). As a measure of effect size Cohan's d was calculated.
During the whole imaging protocol (3h duration) mice were anaesthetised with isoflurane. Breathing and body temperature were monitored and carefully adjusted.

Results:
The biggest differences of the T2-values from the ROIs between the groups are in ROI 2(anterior ventral insular cortex), ROI 3 (perirhinal and posterior insular cortex), ROI 10(hippocampus) and ROI 12(lateral septal nucleus). The mean T2-shortening due to plaque load is between 0.8 and 1.2 ms or of about 1.5% in these ROIs (Fig. 2). Cohan's d gives the strongest effect size of plaques in ROI 2 with 1.3 corresponding to the ventral insular cortex. ROIs with strong effect (Cohan's d>0.8) are 2, 3, 7, 10 and 12 (Fig. 1 + 2).

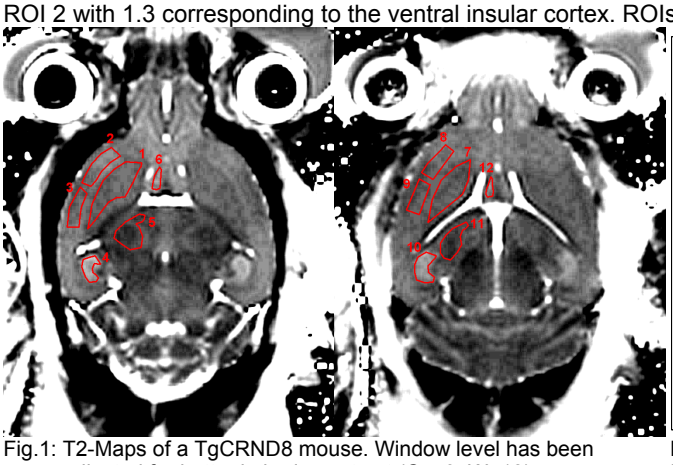

Fig.1: T2-Maps of a TgCRND8 mouse. Window level has been adjusted for better in brain contrast (C: 53, W: 18).
ROIs were defined in 2 slices as follows:
1 + 6: Caudate Putamen; 2 + 7 ventral insular cortex (IC)
3 + 8 posterior IC + somato-sensory cortex
4 + 9 hippocampus; 5 + 10 thalamic nuclei
6 + 12 lateral septal nucleus

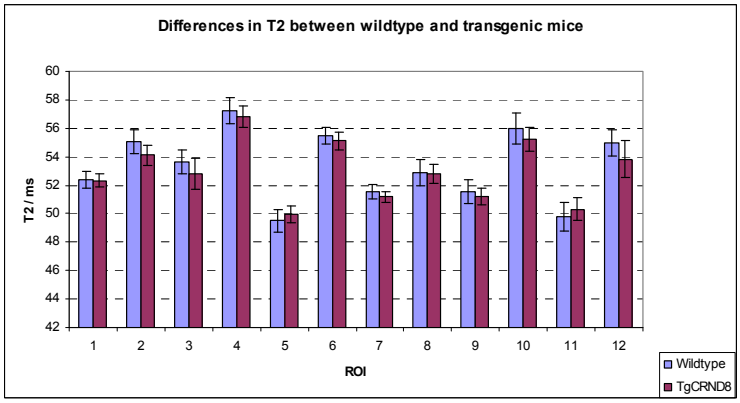

Fig.2: T2- Comparison of transgenic and wildtype mice.
Mean values and standard deviation are shown. The strongest effects of T2 shortening can be measured in ROIs 2, 3, 7, 10 and 12

Discussion:
It has been shown by various groups that Alzheimer plaques (mean size 20µm at 3 month) can be imaged in mice with MRI with very high resolution (<100µm) due to their enhanced iron load in T2 and T2*-contrast using specially designed contrast agents or very long imaging times (>6h) [2]. The aim of this study was to show the potential of T2-mapping as a very simple and robust technique for in vivo imaging of transgenic mice. For the 20-week old TgCRND8 mice strong effects on T2 can be measured. In this age plaque load of TgCRND8 mice is very small [1, 2], but can already be measured with T2-Mapping. This shows the potential of T2-Mapping for control of pathogenesis and possible treatment (for example with plaque breakers). Teipel et al. [3] measured a similar setup on 20-week old APP/PS1-mice and got a T2- reduction of about 5% in ROIs where we measured a strong effect on T2 (1.5% reduction). This supports our results because of stronger and earlier plague load of AβPP/PS1- mice compared with TgCRND8-mice [1, 2, 3]. For better statistical power more animals and older mice with higher plaque accumulation should be examined. In addition therapy monitoring should be considered.

References:
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