Amyloid plaque detection in two Alzheimer's disease mice models using magnetization transfer contrast imaging.

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Purpose. The detection of amyloid plaques is clinically relevant for diagnosis and therapeutic monitoring of Alzheimer's disease (AD). In this study, we used magnetization transfer contrast (MTC) imaging as a technique to non-invasively detect the presence of amyloid plaques. In brain tissue, macromolecular protons, e.g. from amyloid plaques, are characterized by a broader absorption line shape than liquid protons, which makes them sensitive to off-resonance irradiation. A pre-saturation pulse at an appropriate offset frequency followed by excitation at the center frequency will induce an energy exchange process in which the spin state of liquid protons is influenced by the spin state of macromolecular protons [1, 2]. We used APP/PS1 and BRI mice as models for AD, which are both characterized by deposition of amyloid plaques without the occurrence of tau pathology and significant neuronal loss [3]. The models differ however in their amyloid plaque composition with a higher diffuse/compact amyloid plaque ratio in BRI mice [4]. Since amyloid plaques consist of a thick network of macromolecules, we hypothesized that amyloid plaques can be saturated with a certain frequency, resulting in local higher magnetization transfer ratio (MTR) values and that the difference in amyloid plaque composition between the two models would render different results. Our results support our hypothesis.

Material and Methods. MTC was conducted on a 9,4T MR system (Bruker Biospec, Ettlingen) on 18 months old $APP_{(swe)\text{-}PS1(L166p)}$ and BRI $_{(Prnp\text{-}ITM2B/APP695*42)}$ mice of either sex and age-matched control littermates (APP/PS1: nTg/nWT = 10/11; BRI: nTg/nWT = 9/9). At 18 months of age, amyloid pathology has fully developed in the entire forebrain of both APP/PS1 and BRI mice. Images were acquired with a pre-saturation pulse (pulse strength = 12μT, number of pulses = 36, pulse length = 40ms, saturation time = 1440ms) at different offset frequencies ranging from 5000 to 22500Hz, with a spin-echo sequence (TE/TR = 5.36/1767 ms, matrix size = 256x256, field of view = 2.51x2.51 cm^2, slice thickness = 1mm, NA = 1). MTR's were obtained from acquisitions with and without off-resonance irradiation using Amira (Mercury Computer systems, San Diego). Within Amira, regions of interest (cortex, hippocampus, thalamus) were delineated and their mean MTR values were extracted for the different applied frequency offsets. Differences of parameters between genotypes were computed by means of a non-parametric Kruskal Wallis test. To validate our study, mice were sacrificed for histology of which data will soon be available.

Results. We observed significantly higher MTR- values (p-value < 0.05) in cortex, hippocampus, and thalamus of APP/PS1 mice as compared to control (fig. 1A and table 1). No significant changes between BRI mice and control littermates were observed (fig. 1B). Figure 2 demonstrates MTR maps of an individual APP/PS1 and WT mouse at offset frequency 22500Hz.

Discussion. Our results indicate that MTC is able to differ APP/PS1 from WT mice. Since amyloidosis is the principal event in this model, we assume that the differences in MTR-values in cortex, hippocampus and thalamus between APP/PS1 and control are due to the presence of amyloid plaques. We believe that different plaque composition might be the main reason why significantly higher MTR values were observed in APP/PS1 and not in BRI mice. While more diffuse and smaller compact amyloid plaques are present in BRI mice, APP/PS1 mice have large compact amyloid plaques, suggesting that thick macromolecular deposits such as large amyloid plaques elicit a larger MT effect. Further upcoming histological data of each subject might explain this and give a closer correlation between higher local MTR values and amyloid plaque load.

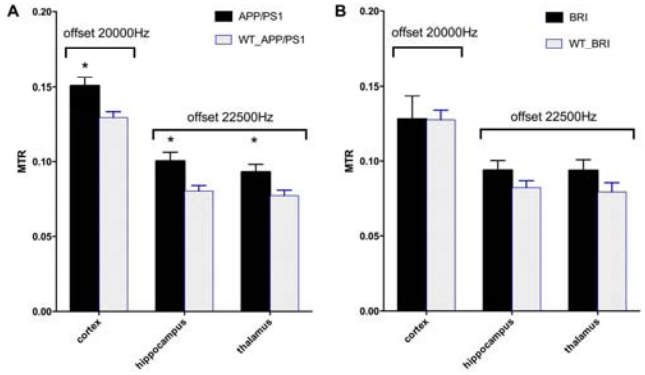

Figure 1. Averaged MTR values of cortex at offset frequency 20000Hz, and of hippocampus and thalamus at offset frequency 22500Hz, shown for APP/PS1 as compared to control (**A**) and for BRI as compared to control (**B**). Significant differences between genotypes are indicated with an (*) (p-value < 0.05)

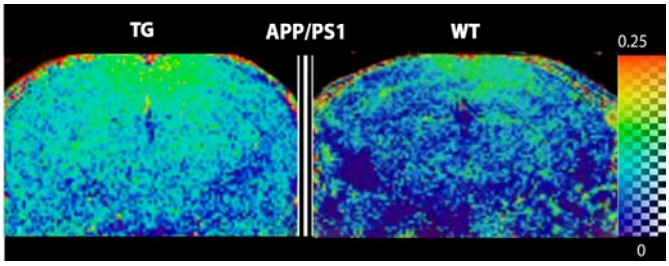

Figure 2. MTR maps of an individual APP/PS1 and WT mouse obtained with an offset frequency of 22500Hz. MTR-values are represented by the color bar on the right.

Freq (Hz)	5000	7500	10000	12500	15000	17500	20000	22500
cortex	↑	↑	↑				↑	
hippocampus			↑					↑
thalamus								↑

Table 1. Arrows indicate significant higher MTR values at different offset frequencies and in different regions for APP/PS1 mice as compared to control

References.
[1] Henkelman R.M. et al., 2001, NMR Biomed; 14: 57-64
[2] Pérez-Torres C.J. et al., 2010, NeuroImage; 50: 375-382
[3] Radde R. et al., 2006, EMBO reports; 7: 940-946
[4] McGowan E. et al., 2005, Neuron 47(2): 191-199

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