

Quantitative Longitudinal T₂ Analysis in Transgenic Mouse Models of AD Pathology

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SYNOPSIS: We have performed a longitudinal analysis of the regional differences in T₂ relaxation times in three transgenic mouse lines of Alzheimer's Disease (AD) pathology. This analysis, which was performed at 6 weeks and 9 months, demonstrated a reduction of T₂ values by age in the cortex and hippocampus of PS/APP mice. No T₂ changes were observed with age in PS or NTg mice. These results support a temporal relationship between progressive A β deposition and changes in T₂ relaxation times.

INTRODUCTION: We have been investigating non-invasive methods to detect early changes in brains of transgenic mouse models of Alzheimer's pathology (AD) using high field MRI. Our assumption is that the presence of A β plaques would have an effect on the biophysical environment of the brain water, which could be measured by MR parameters like relaxation times. We have previously shown reduced mean T₂ values in the hippocampus and cortex of 18 months old PS/APP mice *in vivo* (Helpert et al., 2004). Since the PS/APP mice begin to form plaques early in life, we investigated if changes in T₂ could also be detected at an age in which the mice do not show a so extensive amyloid deposition. In this work we studied three genotypes (PSAPP, PS and Ntg) longitudinally at two different ages (6-week and 9 months) and report a reduction of T₂ values in the cortex and hippocampus of 9 months old PS/APP mice compared with age-matched non-transgenic (NTg) littermate controls.

METHODS: MRI was performed at a 7 Tesla. Two age groups: 6-week old (n=6) and 9 months old (n=6) for each genotype and three genotypes: PS/APP, PS and NTG. Animals were anesthetized with isoflurane (1- 2%) in NO₂ (75%) and O₂ (22%). Images were acquired with a multi-slice single spin-echo sequence. Imaging parameters are: one signal average, 48 slices, FOV of 2.56 x 2.56cm², matrix size of 128 x 96, echo times (TE) of 15,20,25,35,55 and 75 ms, and repetition time (TR) of 4000 ms. T₂ parametric maps were generated using MEDx software (Sensor Systems Inc., Sterling, VA) as previously described by Helpert et al (2004). Regions of interest (ROIs) were manually drawn at the level of the dorsal (HippoD) and ventral (HippoV) portions of the hippocampus (HippoT) and cortex. An ROI in the muscle was used as an internal control. To estimate T₂ relaxation times for each ROI, a mean image intensity value was computed.

RESULTS and DISCUSSION: As seen in Figure 1, the PS/APP was the only genotype to show significantly reduced T₂ values between 6-week and 9 month old mice at the level of the cortex (p<0.005) and hippocampus (p<0.003). Shown in Table 1 are the mean T₂ values by genotype for the 9 months old age group. Significantly reduced T₂ values are apparent in the cortex and hippocampus of 9 months old PS/APP mice compared with age matched PS and Ntg mice. The mean T₂ value was indistinguishable between the three genotypes for 6-week old mice and when comparing 6-week and 9 months old PS and NTg mice. These results support a temporal relationship between progressive A β deposition and changes in T₂ relaxation time, indicating that T₂ may be a sensitive marker of A β deposition in this transgenic mouse model of AD pathology. We hypothesize that the presence of iron in the A β plaques in this model is a significant factor responsible for the reduction of T₂. We are currently investigating this aspect with histopathology and MRI co-registration techniques.

Figure1: Longitudinal T₂ Analysis

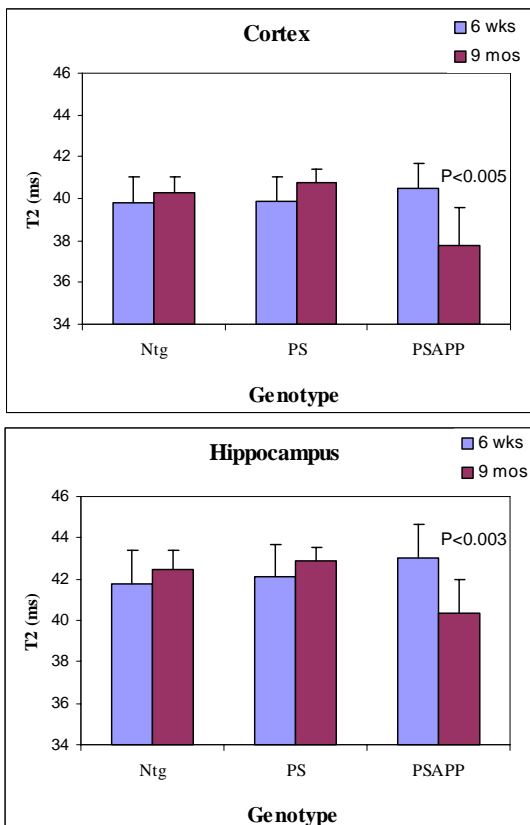


Table 1: Comparison of Regional T₂ values* in 9 Month-Old Transgenic Mice

	Cortex	HippoT	HippoD	HippoV	Muscle
PSAPP	37.79 (1.76)	40.38 (1.58)	40.90 (1.82)	39.53 (2.07)	23.13 (1.33)
PS	40.74 (0.63)	42.92 (0.58)	42.22 (0.84)	43.11 (0.64)	22.94 (0.82)
Ntg	40.28 (0.79)	42.46 (0.93)	42.30 (0.40)	42.51 (1.16)	23.31 (1.43)
p-value PS/APP vs. Ntg	0.010	0.020	0.095	0.012	0.828
PS/APP vs. PS	0.003	0.004	0.138	0.002	0.771
PS vs. Ntg	0.296	0.322	0.829	0.297	0.595

* All T₂ values are given in ms units as mean (\pm SD)

Statistically significant difference was assigned for p<0.05.

Reference: Helpert et al., 2004. In Vivo Detection of Neuropathology in an Animal Model of Alzheimer's Disease by Magnetic Resonance Imaging. M R M. 2004; 51, 794-798.

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