Age-related changes in regional brain T1 and T2 relaxation times in the healthy mouse at 17.6 T

Firat Kara[1], Fu Chen[1], Itamar Ronen[2], Huub J. M. de Groot[1], Jorg Matysik[1,3], and A Alia[1,2]

[1]*Leiden Institute of Chemistry, Leiden University, Leiden, Netherlands,* [2]*Department of Radiology, Leiden University Medical Center, Leiden, Netherlands,* [3]*Institut fuer Analytische Chemie, Universitaet Leipzig, Leipzig, Germany*

Introduction: The changes in T_1 and T_2 values of the brain tissue are widely used as a surrogate marker in the evaluation of various brain disorders [1] and to observe changes in the healthy brain during aging [2]. Ultra-high magnetic field systems, such as 17.6 T, which provides greater signal to noise ratio (S/N), increased resolution, sensitivity and specificity, can serve as a powerful tool to detect more subtle abnormalities in anatomical and functional characteristics of emerging mouse models of neurodegenerative diseases [3]. Knowledge of age-related T_1 and T_2 changes in the healthy mouse brain is mandatory if disease-related deviations in T_1 and T_2 have to be studied in longitudinal studies. To our knowledge age-dependent regional brain T_1 *and* T_2 changes in C57BL/6J mice have not been analysed at 17.6 T. This mouse is generally used as a background strain for the generation of transgenic models of various brain diseases such as AD [3]. In this study age-related regional brain T_1 *and* T_2 changes in the healthy mouse were observed at 17.6 T, which can provide a useful reference for comparison with disease-related deviations in T_1 *and* T_2 relaxation for future studies.

Methods: Total 10 female C57BL/6J mice were used. The experiments were performed on 17.6T vertical 89-mm bore magnets equipped with a 1 Tm^{-1} actively shielded imaging gradient insert (Bruker, Germany). RF transmission and reception was performed with a volume coil (20 mm). Bruker ParaVision 5.0 was used for scan control and image acquisition. In vivo T_1 *and* T_2 values in the C57BL/6J mouse brain were followed with age using MSME sequence and RAREVTR, respectively. MSME experiments were performed longitudinally by using same mice as described previously [4] with following modifications: number of echoes = 16 with echo spacing 8.5; TR= 3 s; voxel resolution = 0.078 x 0.078 x 1 mm^3. RAREVTR experiments were performed as described previously [5] with following modifications: TE = 5.5 ms; TR-array = 0.1, 0.18, 0.36, 0.6, 0.8, 1.0, 1.5, 2.0, 4.0, 6.0, 10.0 and 15.0 s; Matrix size= 128 x 128; FOV = 1.7 x 1.7 cm; Slice number =1; Slice thickness = 0.9 mm. To study the dependence of T_2 on the refocusing inter-pulse interval (τ), the measurements were performed using the MSME sequence with 16 echo and 4 different refocusing inter-pulse intervals, namely 5.6, 8.5,10, and 18 ms. While inside the probe, respiration rate and body temperature of the mouse was constantly monitored. To calculate relaxation times, following fit functions were used: T_2vtr fit function ($y= A+C*\exp(-t/T_2)$ for T_2 evaluation (A= Absolute bias, C= signal intensity) and $M(t) = A+M_0 *(1 - \exp(t/T_1)$ for T_1 evaluation where M_0 is the equilibrium magnetization. ROIs were manually defined. Statistical significance was assigned for values of $P < 0.05$.

Results and Discussion: Age-dependent changes in T_2 values over different brain areas were evaluated at 17.6T (Fig. 1). T_2 values typically increased with age in multiple brain regions except in the HT and the Cpu, where a slight decrease was observed (Fig. 2) (Table 1). No dependence of T_2 on τ was observed. This result suggests that the changes observed in T_2 values with age depend more on changes in tissue properties in the individual brain structures rather than magnetic field disturbances. Comparison of the T_1 values in multiple brain regions did not show any significant differences in young and old mice (Fig. 3) (Table 2). Except, a slightly lower T_1 was observed in the CC and the Cpu regions in old mice as compared to young mice. These age-dependent T_1 changes are in agreement with measurements in humans (at 1.5 T) and rats (at 16.4 T) [6,7,8]. In addition, we also observed a slightly higher T_1 values in TH region of old mice as compared to young mice. An increase in TH T_1 values with age has also been reported in human at 1.5 T [8]. The age-related changes in T_1 *and* T_2 might reflect various physiological processes. For example an increase in iron content of brain tissue can lead to a decrease in T_1 *and* T_2, while a decline in the number of myelinated fibers can cause an increase in T_1 and T_2 [9,10]. These estimates of *in vivo* T_1 *and* T_2, relaxation of mouse brain will be useful to optimize sequence for optimal image contrast and sensitivity in mouse brain at 17.6 T. In addition, establishment of age-related relaxation time changes over different brain regions offers baseline values against which aging and/or disease related changes can be assessed.

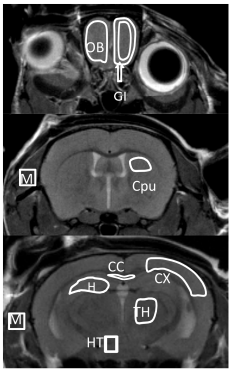

Fig. 1. Regions of interests depicted on images acquired with RARE sequence (TR: 6000 ms; TE:15 ms). Three representative MRI coronal slices showing different ROIs in brain regions: hippocampus (HC), cortex (CX), thalamus (TH), hypothalamus (HT), corpus callosum (CC), caudate putamen (Cpu), olfactory bulb (OB), glomerular layer of OB (GI) and muscle (M).

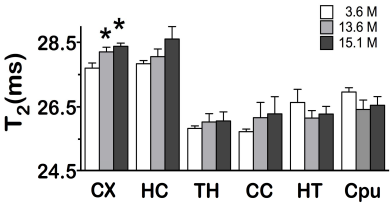

Fig. 2. In vivo T_2 relaxation times of the mouse brain with age measured at 17.6 T. Values are expressed as mean T_2 in ms ± SEM (error bars); n=5. Paired t test, *P < 0.05, significant from T_2 at 3.6 month (M). Same mice were scanned at the age of 3.6, 13.6 and 15.1 months.

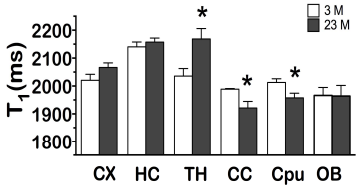

Fig. 3. In vivo T_1 relaxation times changes for a variety of brain regions in young (3 months of age) and old (23 months of age) mice. Values are expressed as mean T_1 in ms ± SEM (error bars); n=5. Two-tailed t-test: *$P < 0.05$ compared to young mice

Table 1: In Vivo T_2 Values of the Mouse Brain at 17.6 T

Age (Month)	HC	CX	TH	HT	CC	Cpu
3.6	27.84 ± 0.10	27.70 ± 0.16	25.83 ± 0.08	26.64 ± 0.41	25.73 ± 0.08	26.96 ± 0.13
13.6	28.06 ± 0.24	28.20 ± 0.15	26.03 ± 0.26	26.15 ± 0.23	26.17 ± 0.48	26.42 ± 0.29
15.1	28.60 ± 0.38	28.38 ± 0.10	26.06 ± 0.28	26.28 ± 0.23	26.28 ± 0.53	26.55 ± 0.27

Table 2: In Vivo T_1 Values of the Young (3 months) and Old (23 months) Mouse Brain at 17.6 T

Tissue	Young	Old
HC	2.14 ± 0.02	2.16 ± 0.01
CX	2.02 ± 0.02	2.07 ± 0.02
TH	2.05 ± 0.02	2.17 ± 0.02*
CC	1.99 ± 0.00	1.92 ± 0.02*
Cpu	2.01 ± 0.01	1.96 ± 0.02*
OB	1.97 ± 0.01	1.96 ± 0.02

References: [1] Damadian R., Science 1971, 171:1151; [2] Kumar et al., J Magn Reson Imaging 2012, 35: 300; [3] Kara et al., Neuroimage 2012, 60: 958 [4] Braakman et al, J Magn Reson Imaging 2006, 24:530 [5] van de Ven et al., Magn Reson Med 2007, 58:390; [6] Pohmann et al., Magn Reson Med 2011, 66:1572 ; [7] Saito et al., Magn Reson Imaging 2009, 27:895; [8] Cho et al., Magn Reson Imaging 1997, 15: 1133 ; [9] Vymazal et al., Magn Reson Med 1996, 35:56; [10] Lacomis et al., Magn Reson Med 1986, 3:194.

Acknowledgement*: This work was supported by grants from Internationale Stichting Alzheimer Onderzoek (ISAO) and Centre for Medical Systems Biology*