T1 and T2 relaxation time modifications in a mouse model of Alzheimer's disease

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Introduction: Cerebral amyloid deposits are one of the hallmarks of Alzheimer's disease. Understanding the effect of these microscopic lesions on relaxation times (T1, T2) and proton density (PD) within the brain might help developing new methods for early diagnosis of the disease by MRI. Previous studies [1] comparing APP/PS1 animals, modeling massive cerebral amyloid deposition, with PS1, amyloid-free animals, did not show any difference neither in T2 or T1 values nor in PD in different brain areas. In our study, we evaluated in vivo cerebral modification of these parameters in young and old animals from another APP/PS1 model.

Materials and methods: Transgenic APP/PS1 mice (Thy1 APP751 SL (Swedish and London mutations) x HMG PS1 M146L) were compared to control PS1 animals. Forty-five transgenic mice divided into two age groups, "young adults" (27 to 45 weeks, 10 APP/PS1, 9 PS1) and "old" animals (60 to 83 weeks, 13 APP/PS1, 13 PS1) were evaluated.
In vivo images were recorded on a 4.7T Bruker Biospec system using a surface coil actively decoupled from the transmitting birdcage probe. For **T2 measurements**, a multislice multiechos sequence was used: TE=12.2 to 73.2 ms, TR=2000 ms, FOV=1.5x1.5 cm^2, matrix 128x128, slice thickness=1mm. Five slices equally separated by 2 mm were acquired, the second one was positioned on the interventricular foramen. For **T1 and PD measurements**, an inversion recovery sequence was performed: TE=10 ms, TR=5000 ms, TI=13.5, 100, 300, 500, 700, 800, 900, 1000, 1500, 2000, 3000 ms; FOV=1.5x1.5 cm^2, matrix 128x128, slice thickness=1mm. Three slices equally separated by 2 mm were acquired, the first one was located on the interventricular foramen.
Parametric T1, T2 and PD images were generated by fitting the data to exponential curves. MR characterization of various brain structures (thalamus, hippocampus, amygdala, subiculum, striatum, corpus callosum, parietal cortex and visual cortex) was done by manually drawing regions of interest (ROIs) on T1, T2 and PD maps. On T2 maps, two additional ROIs were drawn in the frontal cortex. An ROI in the muscle was used as internal control. For each ROI, PD was calculated from parametric images after eliminating T2 dependence using previously calculated T2 values. Means and standard deviations for T2, T1 and PD for each ROI were calculated. Mann Whitney's tests were used and statistical significance was assigned for $P<0.05$. After completion of MRI studies, mice were sacrificed and their brain processed for histological analysis (amyloid and iron loads).

Results: Comparison of **T2 values** in young animals revealed a shorter T2 in the subiculum of APP/PS1 animals (Mann Whitney's test, U=8.5; $p<0.01$; figure a). With aging, both genotypes showed significant decreases of T2 values in most of the evaluated areas (example of the thalamus on figure b), except for the hippocampus and the visual cortex for PS1 animals; the amygdala, the parietal cortex (figure c), the hippocampus, the subiculum and the muscle for APP/PS1 animals. T2 values in aged animals did not show any significant difference between the two genotypes. **T1 values** of young animals were shorter in the amygdala of APP/PS1 animals (Mann Whitney's test, U=17, $p<0.05$) with respect to PS1 mice. Aged PS1 animals had lower striatal T1 than young PS1 mice (Mann Whitney's test, U=14, $p<0.05$, figure d). The comparison of young and old APP/PS1 mice showed T1 decrease in additional areas such as the corpus callosum, the thalamus, and the parietal cortex (Mann Whitney's test, $p<0.05$, figure e and f). Old APP/PS1 and PS1 animals showed a significant difference in T1 values in the corpus callosum and the parietal cortex (Mann Whitney's test, $p<0.01$, figure e and f). **PD** did not show any significant difference neither between the young and old group of both genotypes nor between the age-matched groups. Correlative analysis between in vivo MRI and postmortem histological measures (amyloid and iron loads) is in process.

Discussion/Conclusion: Age-related T1 decrease was observed only in the striatum in PS1 animals. APP/PS1 mice showed T1 decrease in additional areas. Amyloid burden might contribute to this decrease in APP/PS1 animals, as suggested by (1) the significant difference of T1 values between old APP/PS1 and age-matched PS1 mice in the parietal cortex and in the corpus callosum, (2) the significant difference in T1 values in these same regions between young and old APP/PS1 animals.
The significant difference between T2 values in the subiculum of young APP/PS1 and PS1 animals might be related to the high amyloid load in the subiculum, which is one of the first regions to display amyloid deposits in young double transgenic mice. However other, yet to be determined factors, are obviously responsible for the age-related T2 decrease noted in the two genotypes.

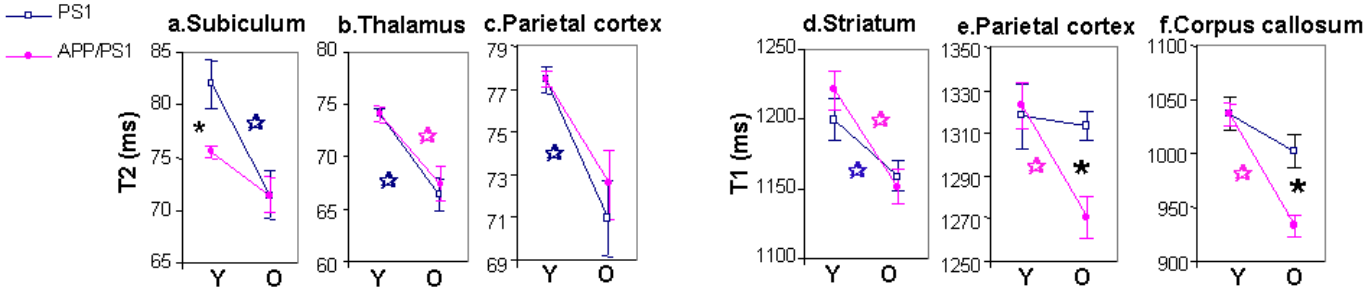

Figure: T1 and T2 values (mean±SEM) in different brain areas in young (Y) and old (O) APP/PS1 and PS1 animals (☆: significant differences between animals of the same genotype; *: Significant differences between age-matched APP/PS1 and PS1 animals).

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Reference: Helpern JA et al., Magnetic Resonance in Medecine. 51(4):794-8; 2004.