Mean Diffusivity as a non-invasive biomarker of the amount of amyloid plaques in Alzheimer's disease: a preliminary evaluation in a mouse model.

Matteo Figini[1], Alessandro Scotti[1], Ileana Zucca[1], Emanuela Maderna[2], Margherita Ruggerone[2], Marcella Catania[2], Giuseppe Di Fede[2], Fabio Moda[2], Fabrizio Tagliavini[2], and Maria Grazia Bruzzone[3]

[1]Scientific Direction, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Milan, Italy, [2]Neuropathology Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy, [3]Neuroradiology Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

TARGET AUDIENCE: Pre-clinical MRI researchers, Neurologists, Researchers in the field of neurodegenerative diseases.

PURPOSE. One of the fundamental neuropathological features of Alzheimer's Disease is Aβ-amyloid deposition in the brain[1]. Diffusion MRI (dMRI[2]) is a non-invasive technique for the microstructural characterization of brain tissue in healthy and pathological conditions. The purpose of this work is to investigate the potential of dMRI-derived parameters for the early detection of amyloid plaques and for monitoring changes in amyloid burden and area fraction that can be associated to disease progression or therapeutic effect.

METHODS. dMRI experiments were carried out on a 7T MRI scanner (Bruker BioSpec 70/30) in 16 mice divided in 4 groups: APPswe/PS1(dE9) mice treated with a saline solution (TrS, n = 4), APPswe/PS1(dE9) mice treated with a synthetic peptide every week (Tr1, n = 4), APPswe/PS1(dE9) mice treated with the same synthetic peptide every 2 weeks (Tr2, n = 4) and wild type mice (WT, n = 4).

MRI scans were performed at 7, 8 and 9 months of age.

Two dMRI sequences were performed in each experiment. The first has 3 directions of the diffusion-sensitizing gradients, 7 b-values (b = 400, 600, 800, 1000, 1500, 2000 and 2500 s/mm^2), a spatial resolution of 80 x 80 x 400 μm^3 and an acquisition time of 69 minutes. The second one has 15 directions of the diffusion-sensitizing gradients, 1 b-value (b = 1000 s/mm^2), a spatial resolution of 100 x 100 x 400 μm^3 and an acquisition time of 34 minutes. The images were corrected for motion and distortions using FLIRT[3].

The Mean Diffusivity (MD) was estimated from the images acquired with the first protocol and the Fractional Anisotropy (FA) was estimated from the images acquired with the second protocol by a homemade MatLab code. MD was extracted from Regions of Interest (ROIs) manually delineated in the olfactory bulb, hippocampus, frontal cortex, entorhinal cortex and thalamus as shown in Figure 1. FA was evaluated in ROIs manually delineated in the corpus callosum and fimbria.

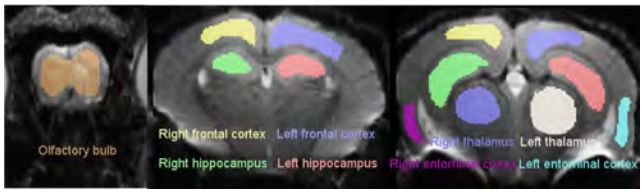

Figure 1. ROIs for MD analysis overlaid on a representative MD map

Immunohistochemical staining for Aβ amyloid was performed and the total number of plaques and the area fraction quantified using NIS elements software.

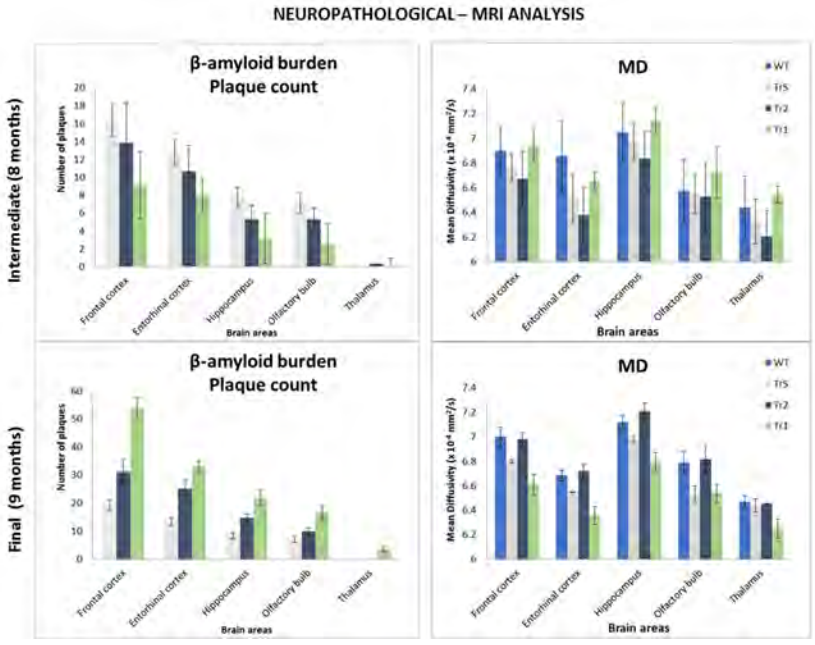

Figure 2. Left: Number of amyloid plaques resulting from the immunohistochemical analysis at the intermediate (top) and final (bottom) time point in TrS, Tr1 and Tr2 mice. Right: MD values found in WT, TrS, Tr1 and Tr2 groups at 8 (top) and 9 (bottom) months of age.

RESULTS. At 7 months, MD was reduced in TrS, Tr1 and Tr2 mice compared to WT in all the ROIs. At 8 months TrS mice still had lower MD than WT; Tr2 mice showed even lower MD values, while Tr1 mice had higher MD than TrS and Tr2, comparable to WT. At 9 months WT and TrS mice had similar values to the previous time point, while MD decreased in Tr1 mice and increased in Tr2 mice (Figure 2).

Immunohistochemistry at the intermediate time point in Tr2 and Tr1 mice highlighted a reduction of the number of plaques and area fraction with respect to the saline-treated group, approximately proportional to the frequency of treatment. On the contrary, at 9 months the number of plaques and area fraction was higher in Tr1 and Tr2 mice than in TrS (Figure 2).

FA in the corpus callosum and fimbria did not provide differences among the groups. The histological analysis did not find evident alterations in white matter.

DISCUSSION AND CONCLUSION. The dMRI analysis of a murine model of Alzheimer's disease showed an inverse relationship between MD and the amount of amyloid plaques. In particular, MD reflects the different number of plaques found in mice treated with different doses of a synthetic peptide. Instead, the MD ratios between treated and control animals do not correspond to the respective amounts of plaques; probably MD is sensitive to additional factors such as the microglial activation found in Tr1 and Tr2 animals. FA values were similar in all the groups, in accordance with histology, which did not show fiber alterations in this mouse model.

In conclusion, our preliminary results, to be confirmed on larger populations, showed the potential of MD as a non-invasive biomarker of the amount of amyloid plaques in Alzheimer's disease, with important possible applications for diagnosis and therapy assessment of Alzheimer's patients.

REFERENCES: **1.** Duyckaerts C et al., Acta Neuropathol 2009, 118: 5–36. **2.** Le Bihan D et al., Radiology 1986, 161(2):401-407. **3.** Jenkinson M et al., Neuroimage 2002, 17(2): 825-841.