Axonal degeneration in the APP/PS1 mouse model of Alzheimer's disease

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Introduction: At autopsy, the hallmark pathological signs of Alzheimer's disease (AD) are β-amyloid plaques and neurofibrillary tangles, which then confirm the clinical diagnosis. However progressive neuronal loss through axonal atrophy and neuronal death are also part of the disease process. The cholinergic hypothesis states that dysfunction of acetylcholine containing neurons causes the cognitive decline in Alzheimer's disease patients [1]. Targeted degeneration of cholinergic fore brain tracts has been shown using tractography in a surgical mouse model of Alzheimer's disease [2].

The aim of this study is to determine if there is a change in diffusion parameters in the double transgenic APPSwe/PS1 mouse model (Jackson Laboratories, Bar Harbor, Maine). These mice have the Swedish mutation of the amyloid precursor protein (APPSwe), as well as the mutant form of human presenilin 1 (PS1), which produces a substantial Amyloid-β plaque burden [3].

Methods: Spatial memory was assessed using a Morris water maze for 7-month (7m) old APP/PS1 mice (six transgenic positive animals (7m-TgP), five wildtype animals (7m-TgM)). Additionally, 22-month old mice (five 22m-TgP and three 22m-TgM), were perfused transcardially with 4%PFA in PBS. The 22m old mice were deemed unfit to swim. The extracted brains were then washed in PBS for 4 days, prior to imaging.

MRI data was acquired on a 16.4 Tesla vertical bore small animal imaging system using a micro 2.5 gradient system and 15 mm SAW volume coil, running Paravision 5.1. Brains were imaged in Fomblin oil. Diffusion weighted (DW) images were acquired according to [4] using a 3D DW spin-echo sequences (TR/TE = 400ms/22.3ms, b=5000s/mm^2, 30 non-collinear directions, resolution=100µm isotropic, 1.5 zero-fill acceleration factor on the phase and slice directions, with the total imaging time=15h 40min). ß-Amyloid plaque load was also assessed using high-resolution 3D spin echo sequences, as well as with histology, to confirm the disease status.

Whole-brain deterministic fibre-tracking was performed using DiffusionToolkit/Trackvis (www.trackvis.org). Target regions was the basal forebrain (VDB, MS, HDB, 1.34-0.86mm anterior to Bregma), as well as the hippocampus and hippocampal commissure (2.06mm posterior to Bregma) [5]. Filter volumes, fractional anisotropy, ADC, λ1, λ2, λ3 were assessed within streamlines. Streamline length and volume was also assessed. Statistical evaluation of tractography was done using unpaired, one tailed t-tests.

Results. Morris water maze: Statistical significance between 7m-TgP and 7m-TgM was determined for escape latencies using the Mann-Whitney test, showing spatial memory deficits in the TgP. Tractography: A significantly decreased axial diffusivity (λ1) was observed in the 22m TgP animals compared to 7m TgP animals, as well as between 22m TgM animals compared to 7m TgM animals, indicating significant axonal degeneration with increasing age. While axial diffusivity appeared similar between the 7 month old TgM and TgP animals, significant differences were observed between the 22m old TgM and TgP animals ($p<0.05$). This suggests that axonal degeneration is more prominent in the TgP animals at 22m.

Radial diffusivity [$(\lambda_2+\lambda_3)/2$] was slightly increased in TgP animals compared to TgM, however these differences were not statistically significant, with the comparison between 7m-TgP and 22m-TgP animals showing the largest trend of $p=0.08$. This suggests that myelin degeneration may not be a significant process in TgP animals.

Fractional anisotropy in controls showed a trend towards increase over time ($p=0.054$), and a statistically significant increase in TgP animals (7m and 22m), but no significant differences between TgP and TgM animals of the same age group.

Conclusion. This study found significant changes due to axonal degeneration of cholinergic fibres, that have their origin in the basal forebrain. While APP/PS1 mice don't experience the neuronal degeneration described in humans and the brains of 6–12 month old mice are still growing [6], degenerations of forebrain fibres is occurring secondarily to Amyloid-β plaque formation.

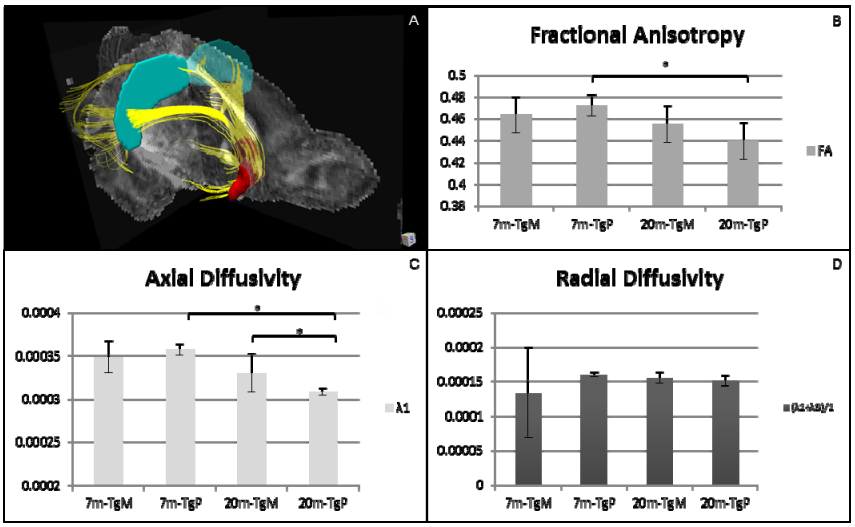

Figure 1. (A) Brain tractography showing the streamlines (yellow) filtered through the forebrain basal forebrain (red) and passing through the hippocampus or the hippocampal commissure (blue). (B) Average and Std Dev (bar) of the fractional anisotropy, statistical significance * ($p<0.05$) (C) Axial diffusivity (average and Std dev). Statistical significance denoted by * ($p<0.05$) (D) Radial Diffusivity (average and Std dev).

References

[1] Terry AV, *Journal of Pharmacology and Experimental Therapeutics* 2003:306:821-827 [2] Keller MD *et al*., World Molecular Imaging Conference, Kyoto, 2010 [3] Thiessen JD, *et al*., *Physics in Canada*. 2007:63:134–7.[4] Moldrich RX *et al*., *NeuroImage*, 2010:51:1027.[5]Frannklin *et al*. *The Mouse Brain in Stereotaxic Coordinates*, Academic Press 2007. [6] Maheswaran S *et al*., *Brain Research*, 2009:1270: 19-32