Characterization of Transgenic Mouse Models of Alzheimer's Disease by Fully Automated Analysis of Brain MRI

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Introduction

Transgenic mouse models of human Alzheimer's disease (AD) with mutations to human amyloid precursor protein (APP), presenilin 2 (PS2) and Tau_{P301L} have been shown to recapitulate the hallmarks of the disease pathology: amyloid-β (Aβ) accumulation due to excess cleavage of APP and neurofibrillary tangles containing hyperphosphorylated Tau. As these models become more widely used in drug development it is important to create robust biomarkers to quantify potential treatment effects. MRI has been used to characterize various aspects of brain pathology: e.g. volumetric MRI for brain atrophy, diffusion anisotropy for white matter degradation, and T_2 imaging for detection of amyloid plaque deposits. Our goal was to develop and validate a fully automated method of evaluating subtle regional and local differences in the brain structure by diffeomorphic coregistration of in-vivo mouse brain MRI data and a multi-object in-vivo brain atlas. We have applied this method to further characterize the brain morphology and T_2 properties of PS2/APP, Tau_{P301L}, and PS2/APP/Tau_{P301L} transgenic mice.

Methods

Animal procedures were approved by the institutional AAALAC-accredited review board. Four genotype groups of 15-19 mo. aged female mice were imaged: Thy1.PrP.hAPP.hPS2 dual transgenic (PS2APP, n=12), Thy1.hTau_{P301L} transgenic (Tau, n=12), triple transgenic (PS2APPTau, n=9), and wild type (WT, n=9). MRI was performed on a 9.4T MRI system with a 30 mm quadrature volume coil (Agilent). A T_2-weighted anatomical reference image was acquired with a 3D fast spin-echo (3DFSE) sequence (TR=350ms, TE=10.2ms, ETL 8, kzero 4 (TEeff 40.8ms), 19.2^3 mm^3 FOV, 96x96x96 matrix, zero-filled to 150 μm voxel dimensions, 4 averages, scan time 28 minutes). T_2 maps were generated from a multi-echo multi-slice sequence (TR=4000 ms, TE ranged 10.4 – 83.2ms for 8 echoes, slice thickness 0.5mm, FOV 25.6 x 25.6 mm^2, 128x64 matrix zero-filled to 128x128, 4 averages, scan time 18 min). The 3DFSE images were preprocessed using an adaptive restoration filter (AnalyzeDirect), which lowpass filters using a voxel-wise adaptive method based on local neighborhood statistics, to reduce image artifacts and noise, and then coregistered using the DARTEL method in SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, UK), which was also used for voxel based morphometry (VBM) [2]. Volumetric and T_2 ROI analyses were based on a 20-region in-vivo mouse atlas [3] that was coregistered to the study template. The ROI volumes were normalized to whole brain volumes. Dunnett's test was used for group comparisons against the WT with p-value threshold p<0.0025 (corrected for multiple ROI comparisons). The accuracy of the registration technique was validated by comparing the automated atlas-based whole brain and hippocampal volumes with manual segmentation by a trained reader. The Aβ plaque burden and phosphorylated Tau levels will be confirmed by histological evaluation.

Results and Discussion

The atlas-based whole brain volumes showed strong correlation with volumes from manual segmentation (R^2=0.88, p<0.0001, Fig. 1A). For hippocampal volumes, the correlation was lower but significant (R^2=0.55, p<0.0001, Fig. 1B). Significant volume differences were observed in a number of ROI's for the transgenic groups when compared to the WT (p<0.0025): the PS2APP group had lower volumes in external capsule, thalamus, and the rest of midbrain, and higher volumes in ventricles, neocortex, and basal forebrain and septum. The Tau group had lower volumes in hippocampus (Fig. 2) and superior colliculi. The PS2APPTau group had lower volumes in hippocampus (Fig. 2) and higher volumes in neocortex. T_2 was lower in neocortex and external capsule for the PS2APP group (p<0.0025). VBM detected areas of significantly lower gray matter volume in the hippocampus for the Tau group compared to the WT (FWE corrected p<0.05, Fig. 3). The hippocampal atrophy observed in the Tau_{P301L} positive groups recapitulates a feature of human AD. Expansion of the neocortex in the PS2/APP positive groups may be due to the high Aβ load and inflammation observed in this model at this time point. This is the first application of automated registration-based analysis of in-vivo volumetric brain MRI data for the PS2/APP and PS2/APP/Tau_{P301L} transgenic mouse models. This analysis identified significant regional volume differences in these mouse models that are consistent with known pathologies of AD. The presented method provides a valuable tool for preclinical research of neurodegenerative diseases, and allows non-invasive serial monitoring of disease progression in treatment efficacy studies.

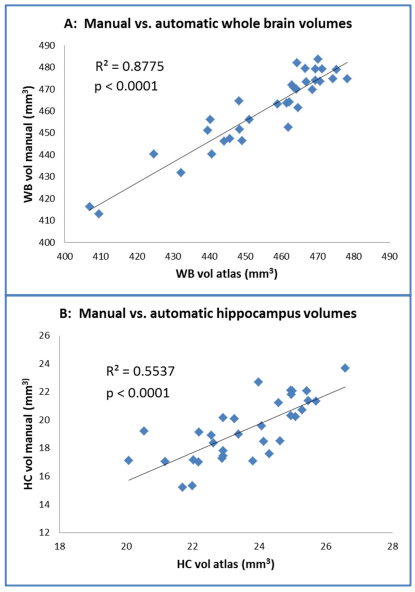

Figure 1: Comparison of manual vs. automatic segmentation.

References:

[1] Grueninger et al., Neurobiol Dis, 2010

[2] Ashburner and Friston, Neuroimage, 2000

[3] MRM NeAt, http://brainatlas.mbi.ufl.edu/

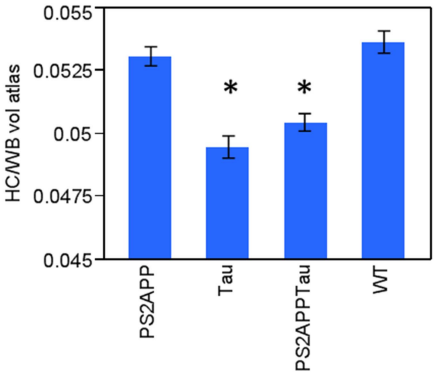

Figure 2: Relative hippocampal volumes by group (Mean +/- SEM, * p<0.0001, compared to WT, Dunnett's test).

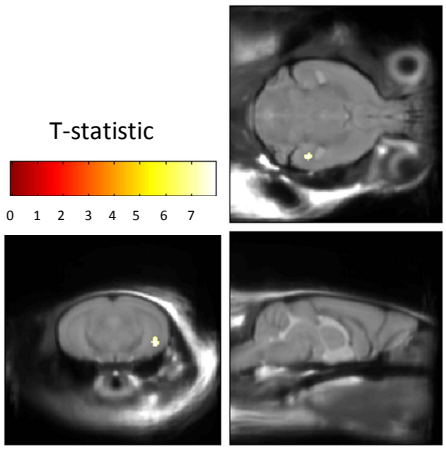

Figure 3: Voxels of significantly lower gray matter volume in Tau mice compared to wild type were located in the hippocampus by VBM.