Tensor-based morphometry as a sensitive biomarker of Alzheimer's disease neuropathology in a Tau transgenic mouse

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Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder, characterized by structural brain changes and cognitive impairment. The key neuropathological hallmarks of the disease are deposits of hyperphosphorylated tau and amyloid beta. The presence of these toxic aggregates is believed to precede a clinical diagnosis of AD by up to 15 years [1]. It is crucial that sensitive biomarkers of AD pathology are developed, to aid early diagnosis of AD and facilitate drug development. In this work, we have used an optimised sequence for high resolution *in vivo* µMRI to evaluate structural changes in the TG4510 mouse model of tauopathy and age-matched wildtype controls. This study will build on previous work [2] with higher field strength, optimised scan parameters and high resolution isotropic voxels, providing a novel platform for high sensitivity to subtle change in morphometry [3]. A new tensor-based morphometry (TBM) pipeline has been employed to locate regions of significant atrophy in the transgenic population. TBM's value lies in its ability to detect change in any region of the brain without time-consuming manual intervention such as the delineation of regions of interest.

Methods

Animals. Transgenic TG4510 mice and wild-type (WT) littermates were bred as published previously [4]. 9 TG4510 and 17 WT litter matched control mice (8.5 months) were imaged *in vivo*. Prior to imaging, mice were secured in a cradle under anaesthesia with 1-2% isofluorine in 100% oxygen using a custom-built head holder to reduce motion. Body temperature was maintained at 36 – 37.5 ^{o}C using a water-heating system and warm air fan. Core body temperature and respiratory rate were monitored using a temperature probe and pressure pad (SA Instruments, NY). *Image acquisition.* All scans were performed on an Agilent 9.4 T VNMRS 20 cm horizontal-bore system (Agilent Inc. Palo Alto, CA, USA). A 72 mm birdcage radiofrequency (RF) coil was used for RF transmission and a quadrature mouse brain surface coil (RAPID, Germany) was used for signal detection. A T2 weighted, 3D fast spin-echo sequence was implemented for structural imaging with the following parameters: FOV = 19.2 mm x 16.8 mm x 12.0 mm; resolution = 150 µm x 150 µm x 150 µm; TR = 2500 ms, TE_{eff} = 43 ms, ETL = 4; NSA = 1. Total imaging time was approx. 1 h and 30 mins. *Image processing*. Images were brought into alignment via their principal axes, corrected for non-uniformity using an iterative expectation maximisation algorithm [5], and intensity-normalised. The images were masked using a STAPLE procedure which registered 10 sets of labels from the MRM NeAT mouse brain atlas to each image [6, 7]. Dilated masks and a target image from the population were used for both affine (5 iterations) and non-rigid (20 iterations) registration using the open-source NiftyReg package [8], to create an average atlas and deformation maps. Regions of significant volumetric change were found using the general linear model to apply a voxel-wise t-test on the log of the determinant of the Jacobian of these deformations, with animal weight used as a covariate.

Results

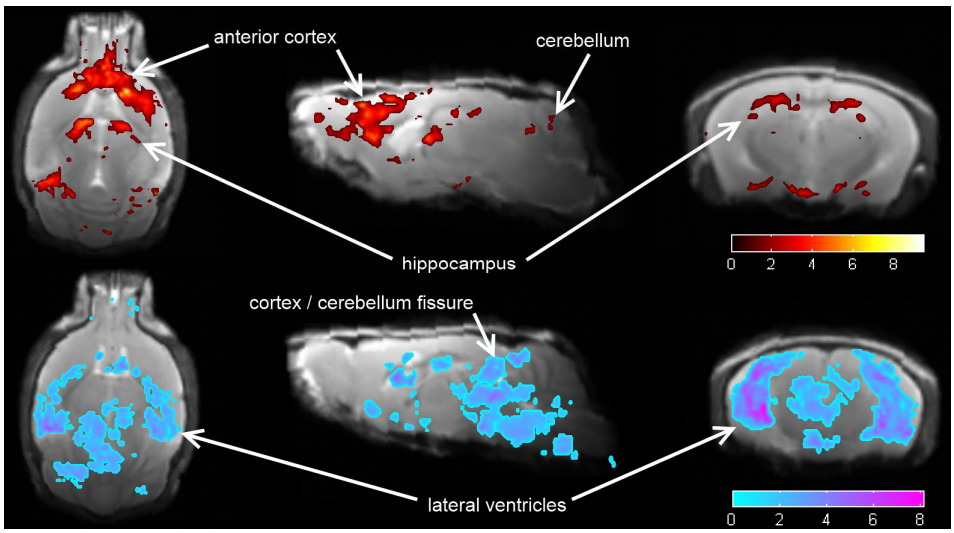

Figure 1: Representative transverse, sagittal and coronal slices showing TBM results overlaid on an average structural image after 20 iterations of non-rigid registration.

Figure 1 provides information on regions with a statistically significant ($p < 0.05$) local volume difference between groups. Regions of significant decrease (red) and increase (blue) in volume in the transgenic animals relatve to the controls are shown, along with corresponding t-value scales. We detected atrophy in both the hippocampus and the anterior cortex. These observations correlate well with the neuroanatomical regions known to be affected in both this mouse model and clinical cases of the disease [4]. In addition, TBM detected dilation in the lateral, third and fourth ventricles, as well as an enlargement of the fissure separating the cerebellum from the posterior part of the cortex. Surprisingly, we also observed some local decrease in volume in the cerebellum, a region previously not known to be affected. This warrants further evaluation to confirm a volumetric change, via histology and both manual and automatic segmentation.

Discussion

We have used an automated pipeline for morphometric analysis which has detected significant volumetric changes between a transgenic mouse model of tauopathy and a control group. The detection of changes in regions expected for this model allows us to validate the use of TBM as an unbiased automated tool for the discovery of previously unknown changes, which we have noted in the cerebellum. We illustrate the potential of TBM as a sensitive biomarker for *in vivo* assessment of AD neuropathology in the mouse. Future work will validate the sensitivity of this method in a longitudinal study at earlier time points, where pathology is less severe. We intend to publicly release our TBM pipeline in the coming months.

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