Longitudinal whole-brain atrophy measurement in a mouse model of tauopathy using the Generalised Boundary Shift Integral

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Introduction Imaging biomarkers are increasingly used to detect, diagnose and stage neurodegenerative disease[1]. The Boundary Shift Integral (BSI) has been shown to sensitively and robustly measure the rate of atrophy[2] of cerebral structures in human Alzheimer's disease (AD), by measuring the volume through which their boundaries shift in structural MRI scans, over 6-12 months[2,3].

We demonstrate the first application of the BSI to a non-human animal, the rTG4510 mouse model of tauopathy, which develops neurofibrillary tangles coinciding with the exhibition of profound structural atrophy of the cortex, entorhinal cortex and hippocampus, and ventricular enlargement, after 3 months of age (Fig 1)[4], reflecting the progressive neurodegeneration seen in AD.

Early signs of neurodegeneration may fall within the normal range of ageing-related tissue loss, or natural volume differences between subjects[5]. Errors in segmentation-based methods of volume measurement may be of the same order as these natural differences. Such errors are likely to be compounded in the mouse brain, where structures are much smaller and partial volume is more significant. An objective, repeatable measure of tissue change over time within a single subject is therefore likely to be advantageous for the early detection of pathology, and to quantify the efficacy of disease-modifying drugs over short timescales, particularly in preclinical trials[1].

To investigate, we used the generalised BSI (gBSI)[1], a fully-automated pipeline, to measure the volume and rate of whole-brain atrophy between a baseline (timepoint 1, TP1) and two serial follow-up *in vivo* structural scans (TP2, TP3) of untreated (UT) rTG4510 mice and wild-type (WT) littermates. This is the first demonstration of the BSI's viability in an animal study and the first objective measure of atrophy in the rTG4510 model at short timescales.

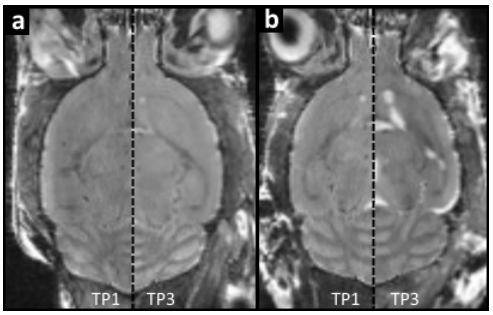

***Figure 1**: Baseline (TP1, left of dashed lines) and the same slice at a second follow-up scan (TP3, right) of (a) a WT brain, relatively preserved; and (b) an untreated rTG4510 showing severe ventricular enlargement and cortical atrophy.*

Methods *Animals & image acquisition.* Female transgenic rTG4510 mice and wild-type (WT) littermates were bred and imaged *in-vivo* at three time points, TP1, TP2, TP3 (mean ages at first scan, WT: 134 days; UT 155 days; mean 43 days from TP1 to TP2; mean 74 days TP2 to TP3) using a 9.4T Agilent scanner, 72mm volume coil and 4-channel receiver coil (Rapid Biomedical), as previously described[6]. Animals were distinguished between scans using ear notches, and genotypes were confirmed via PCR and histology. Structural images were generated using a T2 weighted, 3D FSE sequence with parameters: FOV=19.2x16.8x12.0mm; resolution 150μm^3 (isotropic); TR=2500ms, TE_{eff}=43ms, ETL=4; NSA=1, imaging time approx. 1h30m.

Image preprocessing. 6 Images (3 UT, 3 WT) were oriented to standard space[7] and non-uniformity corrected (N4ITK[8]). Whole-brain masks were generated using STEPS label fusion, based upon an atlas database[9,10]. Ventricles were removed from the masks via thresholding.

Brain BSI. For each animal, image pairs were registered to a half-way space between time points: TP1-TP2; TP2-TP3, using 12-degree-of-freedom symmetric affine registration, with *NiftyReg*[11], such that the "direction" of registration did not bias the result. The masks were resampled following the resulting affine transformation, using linear interpolation. Differential bias correction was applied to minimise global intensity diffrences between scans. A non-binary XOR (exclusive or) region of interest, defining the brain boundary region, (Fig. 2a) was adaptively estimated from the probabilistic brain masks of each scan, in order to better localise and capture the brain atrophy. Voxel-wise clipped intensity differences between images, weighted by the pXOR, within this region are interpreted as atrophy or growth. The clipping intensity window is determined automatically based on the intensity properties of each tissue, using a k-means classification.

The gBSI pipeline returns the BSI (in ml) and the overall percentage brain volume change (PBVC) between time-points. We standardised this to 30 days.

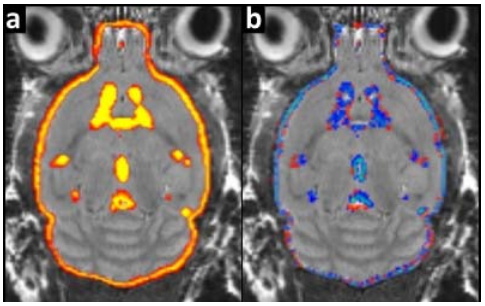

***Figure 2**: Transverse views of a UT rTG4510 mouse brain in the half-way space, overlaid with (a) the probabilistic XOR mask and (b) the BSI result for the same animal (UT; TP1-TP3).*

Results A sample XOR region is shown in Fig. 2a. Fig. 2b illustrates localised BSI results, highlighting the primary regions of atrophy: the ventricles, cortical surface, and the entorhinal cortex. A summary of results from the 3 WT and 3 UT rTG4510 brains is shown in Table 1.

	PBVC (30 days), mean (std)	
	TP1 - TP2	**TP2 - TP3**
WT	-0.1927 (0.356)	-0.2116 (0.166)
UT	-1.3841 (0.972)	-0.5982 (0.738)

***Table 1**: Mean and standard deviation percentage brain volume change (PBVC) for each group and time point pair, standardised to 30 days.*

Discussion We have for the first time demonstrated the use of the Boundary Shift Integral, a sensitive, quantitative and objective measure of longitudinal tissue volume change, in a mouse brain. While the WT brain is relatively preserved, exhibiting around 0.2% volume reduction between each time point, initial findings suggest that the rTG4510 model exhibits gross atrophy after approximately 3 months of age. This is in line with prior brain weight loss previously observed over longer timescales[4]. The rate appears more severe, at over 1% brain volume loss in 30 days, between TP1-TP2. The atrophy continues, though its rate reduces, throughout the animal's life when left untreated. In human AD, the PBVC has been estimated using the gBSI at around 1.34% per year[1].

Conclusions This small cohort indicates the viability of BSI in the mouse brain. The technique shows promise as a sensitive measure of brain atrophy in mouse disease models – it may be used as an outcome measure in preclinical drug trials, and to detect early signs of neurodegeneration. The rTG4510 model is well-suited to this paradigm. Future work will focus on expanding the measurement to more animals (over 200 serial MRI scans have been completed, of nearly 100 animals), and structures (the ventrices and hippocampus), as well as drug treatment tests (including doxycycline, a known tau suppressor in this model, and epothilone D, a microtubule stabiliser). We will also investigate the effect of the animal's age on the rate of atrophy. Finally, the BSI will be compard with other measures of volume change, such as segmentation via atlases, and tensor-based morphometry[7,9].

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