Tensor based morphometry on the Tc1 mouse model of Down syndrome highlights previously undetected phenotypes

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Introduction: The Tc1 model is an aneuploid mouse line that stably transmits a human chromosome 21 (Hsa21). Trisomy of this chromosome is the genetic cause of Down syndrome. The Tc1 model has previously been shown to exhibit many of the features found in human Down syndrome, including deficits in synaptic plasticity, congenital heart defects and reduced cerebellar neuron density[1]. Here we undertake the first volumetric study of the Tc1 mouse brain, in order to observe regions affected by the additional chromosome and determine the correspondence to the human condition. Human Down syndrome individuals exhibit marked neurological deficits, the most pronounced being reduction in total brain volume, and a further reduction in the size of the cerebellum as a proportion of total brain volume, here we show that some features are replicated in the Tc1 model, and others not.

Methodology:
Image acquisition: 14 Tc1 mice and 14 wild-type (WT) littermate controls, age 18-21 weeks, were perfuse-fixed and decapitated. Excess tissue and bone structures were removed and the intact skulls post-fixed in a solution of 4% formal-saline and 8mM Gd-DTPA for 9 weeks. Skulls were then imaged on a Varian 9.4T VNMRS system with a 26mm quadrature volume coil using a 3D spoiled gradient echo sequence. Parameters: TE=4.03ms, TR=17ms, FA=52^o, FOV=20.48x13.04x13.04mm^3, Matrix=512x326x326, Averages=6, Scan time=3 hours[2].
Image processing: The 28 brains were group-wise registered, and their average taken to produce a high SNR atlas. The group-wise registration consisted of two iterations of a block-matching affine registration algorithm[3], followed by 10 iterations of a free-form deformation(FFD) algorithm[4]. The FFD registration was constrained as to heavily penalise any biologically inconsistent folding, resulting in registered images with positive Jacobian determinants at all voxels. At each voxel of the atlas, and for each subject, the determinant of the Jacobian (a direct measure of volume change between atlas and source image) was calculated using the transformation models determined by the registration. Statistical parametric mapping software (SPM8, http//www.fil.ion.ucl.ac.uk/spm) was used to compare the determinant of the Jacobian between groups at each voxel of the atlas, thus producing a map of regional volume differences between Tc1 and control groups. Such analysis is referred to as tensor-based morphometry (TBM). In addition to TBM, the volume of brain substructures were measured by registration of a pre-segmented atlas[5] to each raw image and subsequent resampling of these segmentations in the space of the raw images.

Results: Brain volume differences have been calculated with and without normalisation to total brain volume. *Unnormalised volume:* The TBM study indicates that the majority of the brain was larger in the Tc1 mice than the controls. Figure 1 demonstrates that regions in the medula, pons, superior colliculus, hypothalamus, cortex, hippocampus and caudate putamen all show statistically significant increases in volume. No statistically significant regions of volume decrease (compared with WT) were found within the brain. *Normalised volume:* We have also considered local volume as a proportion of total brain volume. Figure 2 shows significant differences in the proportional size of structures. We see that regions of the cerebellum are proportionally smaller for the Tc1s, likewise the olfactory bulbs and the posterior part of the corpus callosum. The results of segmentation propagation are similar to those of the TBM. We find that most substructures are increased in size, and that the size of the whole of the cerebellum reduces as a proportion of brain volume by 6.6% ($p<0.002$).

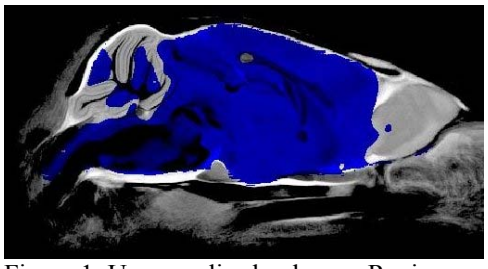

Figure 1: Unnormalised volume - Regions where Hsa21+ mice show a significant ($p<0.05$, corrected by false discovery rate of 0.05) increase in volume are blue.

Figure 2: Proportional volume – Regions where Tc1 mice show statistically significant increases are blue, and decrease are red.

Discussion: This is the first time that the Tc1 mouse model of Down syndrome has been analysed by MR and image processing methods. These data highlight previously undetected changes in brain volumetrics which may have important consequences for the role of the Tc1 model of Down syndrome. The increase in size of the majority of regions in the Tc1 group is contrary to that seen in the human condition, but this feature is potentially very interesting, as further investigation may uncover genetic factors affecting brain growth. The large difference in mean total brain size between Tc1 and wild-type mice obscures group differences in the relative size of structures. In order to determine the difference in relative sizes, we normalise the Jacobian determinants and substructure volumes to the total brain volume. In doing so we find that the human DS characteristic of reduction in proportional size of the cerebellum is replicated in the Tc1 model. The results presented here do not negate previous studies indicating strong DS phenotypes in the Tc1 model, but they do however call for a re-examination of the effect of key genes in chromosome 21 which may feature in the large brain volume increase we observe.

References: [1] O'Doherty et al. Science (2005), vol 309, p2033-2037, [2] Cleary JO et al. 2010 Proc ISMRM #1044, [3] Ourselin et al. Image and Vision Computing (2000), vol 19 , p25-31, [4] Modat et al. Comput Meth Prog Bio (2010), vol. 98 (3), p278-84, [5] Dorr et al. Neuroimage (2008) , vol 42, issue 1, p60-69