Deformation based morphometry in a rodent model of Parkinson’s disease

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Introduction
Combining imaging technology with in vivo disease models provides unique tools for the study of disease processes, compensatory brain changes and testing of potential therapeutics. Rodent models of Parkinson’s disease (PD) show great promise in this respect. Longitudinal imaging studies, which track individual neuroanatomical change have proven value but have not been extensively evaluated in such models of PD. Therefore, we used quantitative high field (7 T) serial T2-weighted (T2W) structural MRI in combination with advanced image analysis techniques to investigate the underlying nigrostriatal degeneration that produces a severe behavioural deficit in a proteasome-inhibitor based rat model of PD.

Methods
Lactacystin lesion: Nigrostriatal system lesions were induced in male Sprague-Dawley rats (270±10g) by unilateral stereotactic injection of the proteasome inhibitor lactacystin (10 µg in 2.5 µl) into the left medial forebrain bundle (AP: -4.4, ML: +1.5, DV: -7.8 mm). Control animals (n=5) received an injection of saline. Behaviour: Performance on the accelerating rotarod and apomorphine-induced rotational asymmetry were assessed in all animals at baseline (BL), except apomorphine (0.1 mg/kg s.c., P<0.001; Fig.2B). In the rotarod test, performance was measured as the time taken by the animals to complete 10 revolutions. MRI: Concomitant T2-weighted MR images (MEMS sequence: TR=4200 ms, TE=10,20,30,40,50,60,70,80 ms, slice thickness 0.5 mm, isotropic in-plane resolution 189 x 189 µm) were acquired using a small horizontal bore 7.0 T MRI scanner (Varian, Oxford, UK) and resampled to isotropic voxels. Image analysis: Whole brain, striatum, globus pallidus and lateral ventricle (LV) volumes were manually segmented in JIM v5.0, software (Xinapse systems, UK). An unbiased Deformation-Based-Morphometry (DBM) approach was also used to analyze differences in volumetric change between control and lesion groups. A canonical reference was selected from the BL scans and all other BL scans were affinely registered to it using FLIRT3 and corrected for intensity-inhomogeneity effects using N33. Then W1, W3 and W5 scans were fluidly registered to their respective BL scan in reference space to obtain voxel-wise estimates (Jacobian determinants) of volume-change over time in each animal. Group differences were determined using voxel-wise unpaired t-tests of smoothed Jacobian maps with permutation-testing for significance.

Conclusions
These data suggest that serial T2W MRI in conjunction with DBM may be applied to monitor and identify pathological changes that may represent serial biomarkers of disease progression in this in vivo rodent PD model.