Voxel-based Morphometry in the Mouse Brain: the R6/2 Huntington's disease model

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Introduction

Morphological phenotyping of normal and transgenic mouse models is of increasing importance. Thus fast methods for the accurate, objective analysis of these data are needed to deal with the large amounts of data that can be rapidly acquired using volumetric MRI. This modality allows *in-vivo* investigation, requires fewer animals and can be much faster than traditional histological surveys. Voxel-based morphometry (VBM) is well established in the human brain for detecting morphological differences. We have extended these techniques to the mouse brain using the SPM5 package[1] with the R6/2 mouse model of Huntington's disease (HD), a neurodegenerative disorder characterised by brain atrophy.

Image Acquisition

Forty five transgenic R6/2 brains and 42 brains from wildtype (WT) C57/Bl6J × CBA F1 littermate controls were imaged *ex-vivo* at 1T with a RARE sequence on a Bruker console (TR/TE_{eff} 2000/50.5ms, NEX 4, ETL 4, matrix 256×192×128, FOV 17.9×13.4×9.0mm^3, to give a final isotropic resolution of 70µm in 13.5 hours).

Image Processing

Datasets were aligned with a publicly-available digital C57 mouse brain atlas[2] by an affine transformation and an iterative scheme[3] was used to generate a dataset specific average atlas. The atlas was segmented into nominal grey matter (GM), white matter (WM) and residual fixative fluid. These images were smoothed by an isotropic 250µm Gaussian kernel to serve as tissue probability maps (figure 1). Each brain was then simultaneously non-linearly registered to these maps and segmented using the unified segmentation model with correcting factors for bias correction. The Jacobian determinants from the transformation were used to modulate the resulting maps for each tissue class to preserve original class concentrations.

Results

The GM maps for R6/2 and WT groups were compared using a two-tailed *t*-test with false-discovery rate (FDR) applied to correct for multiple comparisons. To control for the effect of overall brain volume, we included the total brain volume as a covariate in the analysis. Figures 2 and 3 show the results, we found significant differences (corrected $p < 0.05$) throughout the basal ganglia, thalamus and cortex, in agreement with other studies in both the R6/2 mouse and human patients[4]. In the figures clusters less than 50 voxels are not shown.

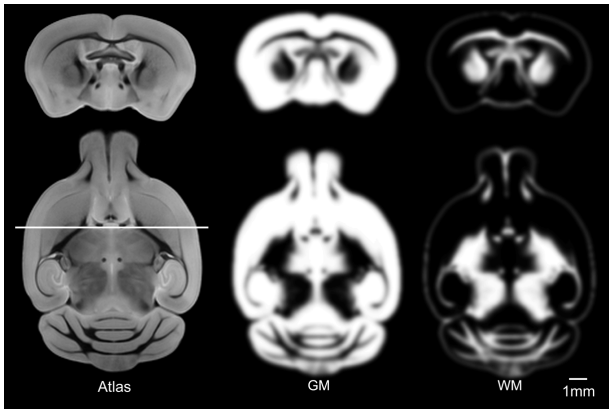

Figure 1 The atlas from 87 datasets and segmentations into nominal grey and white matter groups.

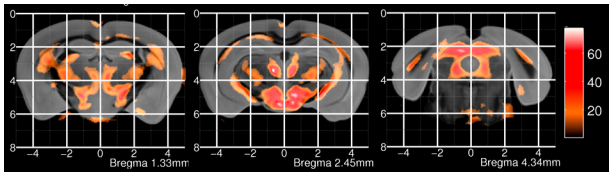

Figure 2 Slices indicating regions of significant difference ($p < 0.05$, FDR corrected) between R6/2 and WT brains. Horizontal and vertical grid gives standard Bregma coordinates, colour bar indicates $F_{1,84}$ score.

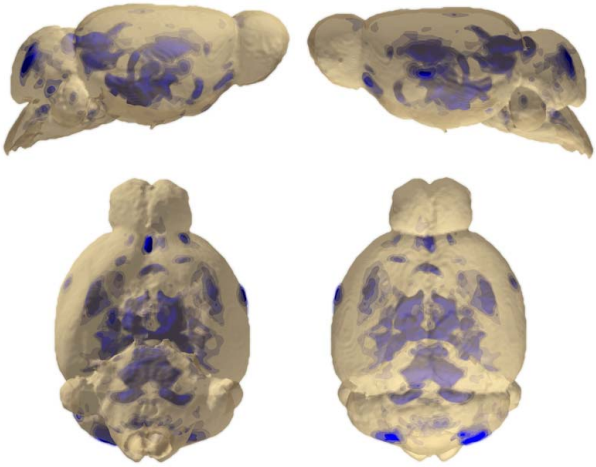

Figure 3 3D reconstructions of clusters found to be significantly different between R6/2 and WT brains.

Conclusion

We have extended SPM5 to implement voxel-based morphometry in the mouse brain and used it to map the morphological phenotype of Huntington's disease. We are still analysing these data to assess the importance of our findings in the context of this disease model, but we expect our methods will be of use in, for example, phenotyping and comparative drug treatment studies.

References

[1] Ashburner *et al.* NeuroImage (2005) 26:839-851

[2] Ma *et al.* Neuroscience 2005;135(4):1203-15

[3] Sawiak *et al.* Proc. Intl. Soc. Mag. Res. Med. 2006 Berlin

[4] Stack *et al.* J Comp Neurol. 2005 Oct 3;490(4):354-70.