Deformation-based morphometry in the R6/2 Huntington's disease mouse brain

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Introduction

Mouse models of disease are of increasing importance due to the relative ease of creating genetic knock-in and knock-outs representative of human pathologies, which can be used to assess pathology in a controlled environment or the efficacy of potential treatments. The enormous amounts of data generated by such trials make whole brain histological assessments prohibitively labour-intensive. Automated morphometry based on MRI is widely used to assess morphological changes in both healthy and pathological human populations with established techniques such as voxel- and deformation-based morphometry (VBM and DBM [1]). We have previously implemented VBM for the mouse brain [2] in the popular SPM package [3] applied to the R6/2 Huntington's disease model and wildtype (WT) controls, here we present methods and results for applying DBM to the same model, comparing both techniques and providing further insight into the R6/2 phenotype.

Methods

116 mouse brain datasets (age range: 10.5-18 weeks, 57 WT/59 R6/2, resolution $(70\mu m)^3$ acquired at 1T *ex-vivo,* see [2] for full acquisition details) were initially linearly registered to a previously published target atlas based on both R6/2 and WT brains [4] shown in figure 1, the transformed brains were averaged to form a new template which seeded an iterative non-linear registration scheme where the average of transformed images at each iteration was used as the target for the next. Registrations were performed with algorithms from vtkCISG [5], using *b*-splines with a final control point spacing of 3 voxels. The Jacobian determinant was found from the transformation giving the local volume change at each voxel. A two-group Student's *t*-test was performed in a general linear model with overall brain volume and age as covariates. Correction for multiple comparisons was performed with the false-discovery rate (FDR) technique using $p < 0.05$ for the corrected threshold. This means that on average, one would expect 5% of results reported as significant to in fact be false positives.

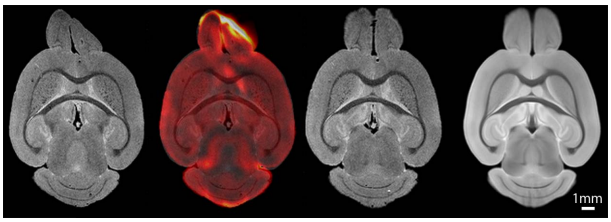


Figure 1 (from left to right) a linearly registered R6/2 image, image overlay with the Jacobian map of local volume change superposed, the transformed image, and the target atlas.

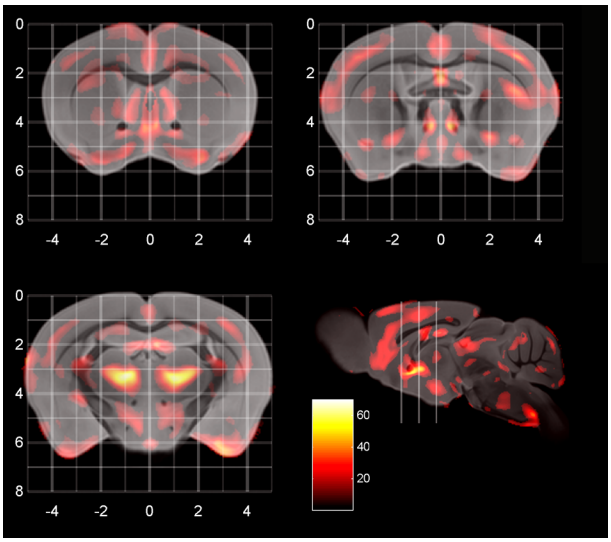
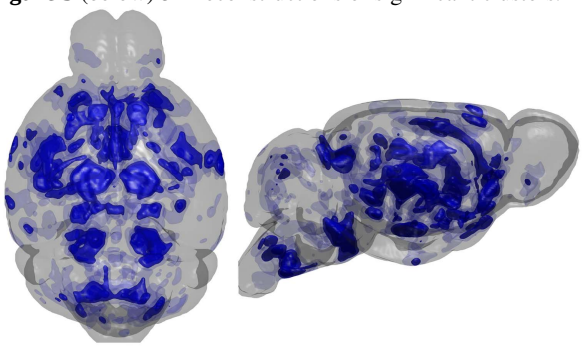


Figure 2 (above) Slices showing significant differences. Scale is *F*-statistic, thresholded above $p_{FDR} < 0.05$. Grid lines indicate bregma (mm)

Figure 3 (below) 3D reconstructions of significant clusters.



Results

The results are shown in figures 2 and 3. As expected in this model, differences are seen in the cortex and in particular the basal ganglia. In comparison with the VBM results reported previously, more differences are visible in structures of similar tissue type, which is not unexpected as VBM uses the probability of grey matter as its statistic, where DBM as used here uses the local volume change independent of tissue type. This is particularly clear in the hippocampal formation, substantia nigra and hypothalamus.

Conclusions

DBM finds more significant changes than VBM and is more sensitive to changes in regions of similar tissue class that VBM can miss. In contrast to the human brain, the mouse brain has less white matter and it is less widely distributed which can be challenging for tissue class-based methods. As DBM does not make these assumptions, those problems are avoided here. The detailed deformation maps required, however, require extensive computer processing time which may not always be available. In conclusion, DBM finds all of the results seen by VBM with more significant regions seen within regions of the same broad tissue classes.

References

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