An iterative, non-linear mouse atlas for mouse brain phenotyping in a Huntington's disease model

S. J. Sawiak[1], G. B. Williams[1], N. I. Wood[2,3], A. J. Morton[3], and T. A. Carpenter[1]

[1]Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, England, United Kingdom, [2]Brain Repair Centre, University of Cambridge, England, United Kingdom, [3]Department of Pharmacology, University of Cambridge, England, United Kingdom

Introduction

With the growing use of genetically modified mouse models for human disease, techniques for fast and accurate identification of statistically significant morphological variation are of increasing importance[1]. An important part of this work is to establish the morphological structure and variation in a cohort of specimens. Variation between mouse strains is high so it is advantageous to use a specific atlas where possible. Building from similar techniques in the literature[1], we present a pipeline for atlas creation along with three mouse atlases: a wildtype atlas for the C57/Bl6 mouse based on 47 mice, an atlas for the R6/2 model of Huntington's disease based on 43 transgenic mice and a combined atlas using all 90 mice. An iterative technique is used to converge upon the minimum-deformation atlas, defined as the atlas from which the deformations to each subject are a minimum.

Methods

Brains from 90 C57/BL6 mice (43 transgenic R6/2, 47 wildtype C57/Bl×CBA-F1; 48 male) were perfused with 4% paraformaldehyde solution and excised from the skull at 20 weeks. These were soaked in a proton-free susceptibility matching fluid[2] (FluorInert-77, 3M) and imaged individually in a custom-built 13mm solenoid coil in a 1T Bruker AVANCE system. A RARE sequence (TR/TE_{eff} = 2000/50.5ms, NEX 4, ETL 4, total imaging time ~14h) was used with Bruker ParaVision 3 for reconstruction. Resolution was 70µm isotropic.

Registration software based on vtk-CISG[3] was used first to bring images manually into alignment, followed by affine registration to a previously published publicly-available digital atlas[2]. These images were averaged to create an initial target atlas. To prevent more intense images skewing the morphology seen in the average image, an automatic intensity scaling procedure was applied to each image. The scaling procedure applied a lower and upper threshold to the data and scaled the intensity distribution so the maximum intensity of each image coincided.

The same software was then used to non-linearly register each image based on a series of control points, with interstitial points deformed according to a *B*-spline between the points[3]. A control spacing of 1mm (14 voxels) was used. Registration was performed from the initial average to each of the target images, to prevent positive feedback accumulating errors in the atlas process. After each iteration, intensity scaling was repeated and the images averaged again to create a new target. This was repeated until the changes became insignificant.

Results

Figure 1a shows a horizontal slice of a single image, 1b a horizontal slice from the original affine average and 1c from the final atlas. Inset in each image is a close up of the hippocampus, where the visibility of the dentate gyrus is a guide to the accuracy of the registration achieved. In addition to the information available on the images, the morphological deviations in each class to get to the atlas on a voxel can be used to quantify the variability of each cohort. In the present data, the mean deformation value over points in the average affine image to points in the atlas is 90µm. This gives a characteristic length scale for variations between brains.

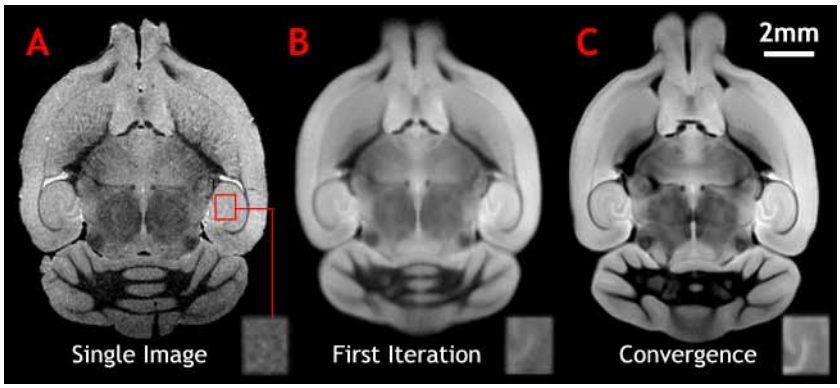

Figure 1 An original image, the first iteration and the converged atlas image

Conclusions

The efficacy of the registration scheme used is shown clearly by the sharp definition of structure in the final atlas image. Creating an atlas of multiple cohorts allows a detailed comparison to be performed without bias to a specific specimen. The information available in the deformation maps gives a point by point mapping from one cohort to the other, allowing detailed statistical comparisons to be made in finding morphological differences between the groups. Sharp details in the anatomy, unavailable with either single images or affine averages are much clearer with these techniques.

References

1. Bedell MA Genes Dev. 1997; 11(1):11-43
2. Ma Y *et al.* Neuroscience. 2005;135(4):1203-15
3. Rueckert D *et al.* Lec. Notes in Comp Sci 1998; vol 1496