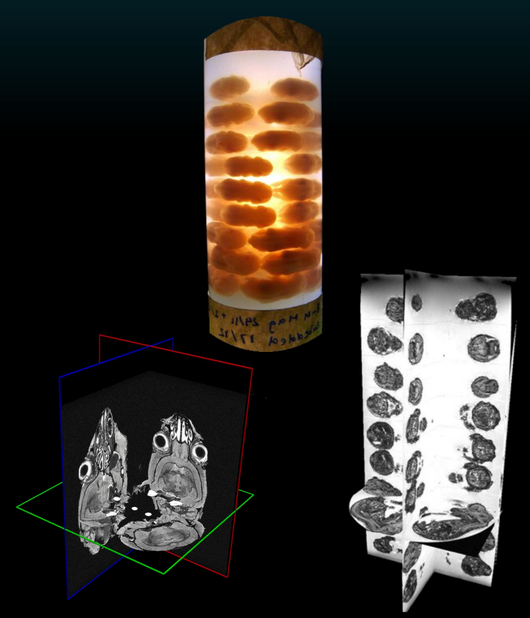
MouseMorph:
Automated high-throughput morphometric phenotyping of mouse brains and embryos with µMRI

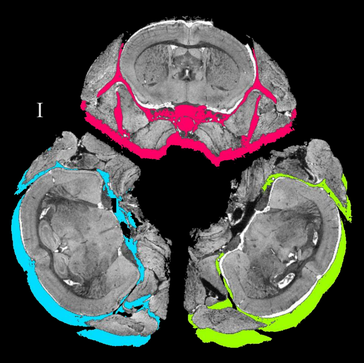
[1] cmic Centre for Medical Image Computing [2] CABI centre for advanced biomedical imaging

Nick Powell*[1,2], M. Modat[1], M.J. Cardoso[1], D. Ma[1,2], F. Norris[2], H. Holmes[2], M.F. Lythgoe[2], S. Ourselin[1]

UCL

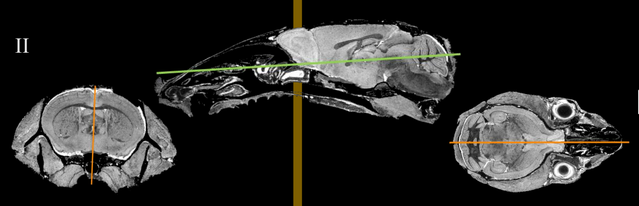
Physical and behavioural traits – determined both by genetics and environment – define an organism's *phenotype*. µMRI preclinical phenotyping of mice allows us to identify the physical effects both of individual genes – a goal of the International Knock-Out Mouse Consortium – and correlates of human disease, such as Alzheimer's – a key stage in the development of novel drugs. We show the stages of a complete, automatic pipeline for large-cohort mouse brain and embryonic phenotyping, from scanner to statistical parametric map. Such maps are the result of tensor and voxel-based morphometry (T/VBM), [1,2] which enable the detection of morphological differences between groups of wild-type and genetically altered – or diseased – mice, without the laborious delineation of regions of interest or isolation of specific structures. The pipeline also enables automated segmentation propagation for volume measurement, with an appropriate atlas. Although software exists for clinical morphometry (e.g. SPM), it omits the pre-processing steps necessary for high-throughput pre-clinical studies, wherein dozens of subjects may be scanned at once (left: brains and embryos). Our pipeline fills this gap. It is fully open-source, automatic, and suitable for use with both *in-* and *ex-vivo* data.





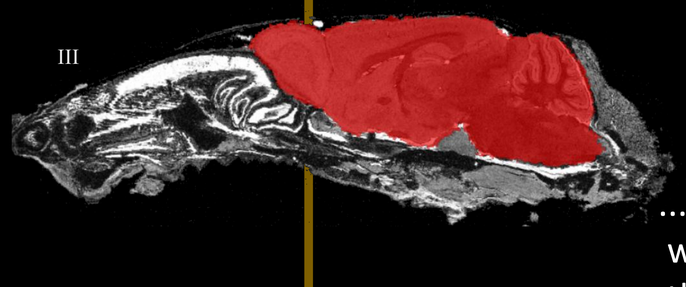
I. Subject separation

Subjects are automatically identified and separated from a multi-subject µMRI image by thresholding, largest-connected-component labelling, and volume range windowing



II. Orientation to standard space

We use the 3D images' inherent principal (green) and symmetry (orange) axes to automatically align subjects with a standard space (e.g. RAS)



III. Brain Extraction

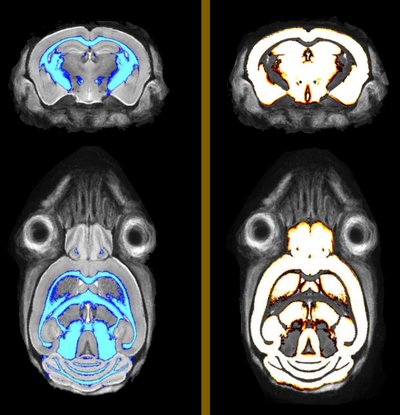
Multiple parcellated atlases are registered to our data and their labels combined using a STAPLE algorithm [3] to generate a complete, highly accurate brain mask (left), improved iteratively with registration, used to separate brain from skull

IV. Non-Uniformity Correction

N3 [4] is used to correct variation in the MRI signal intensity

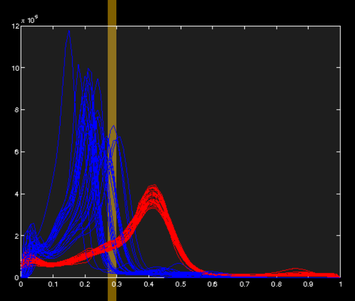
V. Brain Tissue Class Segmentation

...into Grey, White Matter & CSF, using an Expectation Maximisation algorithm, with NiftySeg [3]. We initialise with tissue priors generated from a parcellated atlas (left: probabilistic WM and GM results after segmenting an average image)



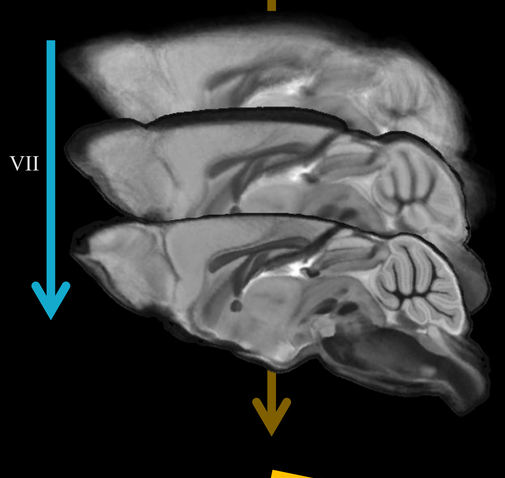
VI. Intensity Standardisation

Histograms are transformed [5] (red, right) using median intensities from tissue class segmentation (brain) and percentile histogram landmarks



VII. Registration

We perform a group-wise registration using NiftyReg [6] beginning with rigid alignment (topmost, left and right), followed by iterations of 12-dof affine and high-dof fast Free-Form Deformation to produce a sharp final result. To reduce bias, our first target is a randomly-chosen member of the population; subsequent iterations use the previous iteration's average

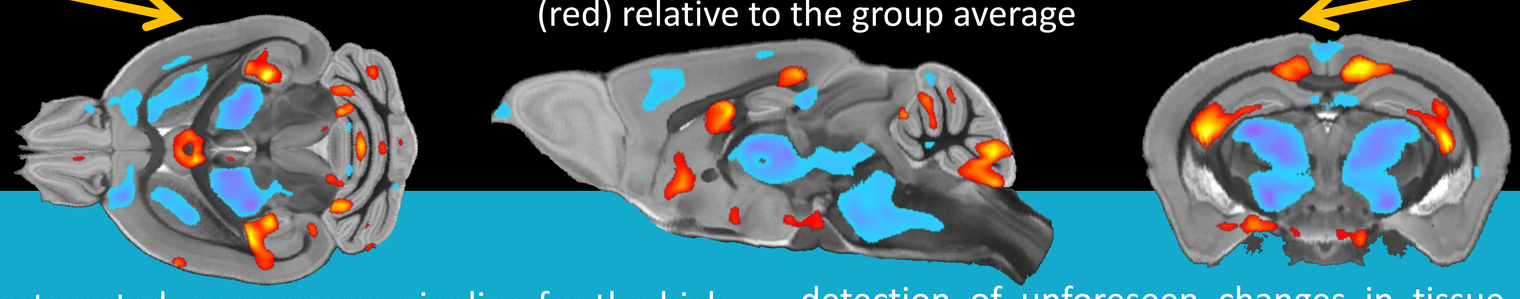


VIII. Modulation / Deformation Field Transformation

For TBM, the log of the Jacobian determinant is taken of the individual deformation fields; for VBM, the transformations from registration are applied to the tissue maps; these are modulated to maintain consistent volume

IX. Statistics with General Linear Model

Maps of significant between-group differences are generated from the transformed deformation fields (TBM) and tissue classes (VBM), covariating for (e.g.) brain size; age; sex. These show local expansion (blue) and contraction (red) relative to the group average



Discussion

We have developed a fully-automated, open-source pipeline for the high-throughput phenotyping of mouse brains and embryos, both *in-* and *ex-vivo*, enabling the verification of mouse models, the longitudinal observation of disease progression and drug therapy, as well as the detection of unforeseen changes in tissue structure caused by genetic abnormalities or behavioural adaptation. The pipeline has been applied to over 15 phenotyping datasets of brains and embryos, and we aim to develop further capabilities for longitudinal data in the near future.

Software available from **cmic.cs.ucl.ac.uk**

∗ Corresponding: nicholas.powell.11@ucl.ac.uk

References

[1] Ashburner, J., et al. (2000). NeuroImage, 11(6 Pt 1), 805–21. [2] Ashburner, J., et al. (2000). NeuroImage, 11(5), S465. [3] Cardoso, M.J., et al. (2011). NeuroImage, 56(3), 1386–97. [4] Sled, J. G., et al. (1998). Medical Imaging, IEEE, 17(1), 87–97. [5] Nyul, L., et al. (2000). Medical Imaging, IEEE, 19(2), 143–150. [6] Modat, M., et al. (2010). Comp. methods and programs in biomed., 98(3), 278–84.

NiftyReg

NiftySeg

MRC Medical Research Council