Investigating variability of brain anatomy using three common mouse strains

Jan Scholz[1], Matthijs van Eede[1], Jason P Lerch[1,2], and Mark Henkelman[1,3]
[1]*Mouse Imaging Centre, Hospital for Sick Children, Toronto, ON, Canada,* [2]*Medical Biophysics, University of Toronto, Toronto, ON, Canada,* [3]*Medical Biophysics, University of Toronto, ON, Canada*

Target Audience

This study is targeted at Neuroscientists interested in how brain morphology is determined by genetics.

Purpose

The way in which brain structures adopt different morphologies is not fully understood. Here we investigate variability in brain anatomy using ex vivo MRI of three common mouse strains. We use Generalised Procrustes Analysis (GPA) to estimate modes of variability for a number of brain structures. This will allow us to test for genetically-determined differences in shape and shape variability. The three common mouse models can serve as background for genetic modification in future studies, thus allowing to probe for a causal role between genetics, cell morphology [1], and brain anatomy.

Methods

Mice: Three mouse strains were used, 129 (N=25), C57 (N=25), CD-1 (N=27). *Image acquisition*: Brains were fixated and scanned within skulls on a 7 T, 40 cm diameter bore magnet (Varian Inc. Palo Alto, CA). A T2-weighted sequence was used to obtain images for deformation based morphometry (3DFSE, TR=2000 ms, echo train length=6, TEeff=42 ms, FOV=25×28×14 mm, matrix size=450×504×250, time=12 h). *Analysis*: Brains were distortion corrected and aligned to a non-linear average with its associated segmented atlas using nonlinear image registration with iterative template refinement [2,3,4]. The surfaces of the atlas segmentations of three structures (hippocampus, striatum, thalamus) were randomly seeded with 25 points per mm^2. These 'point clouds' were then back-projected to each individual using the previously obtain transformations and fed into GPA. Point clouds of specific structures were again brought into optimal alignment to remove any additional misalignment using rigid registration and scaling before principal components (PC) were calculated. *Statistics*: ANOVA was used to test for genotype differences of standardized PC scores for each individual PC.

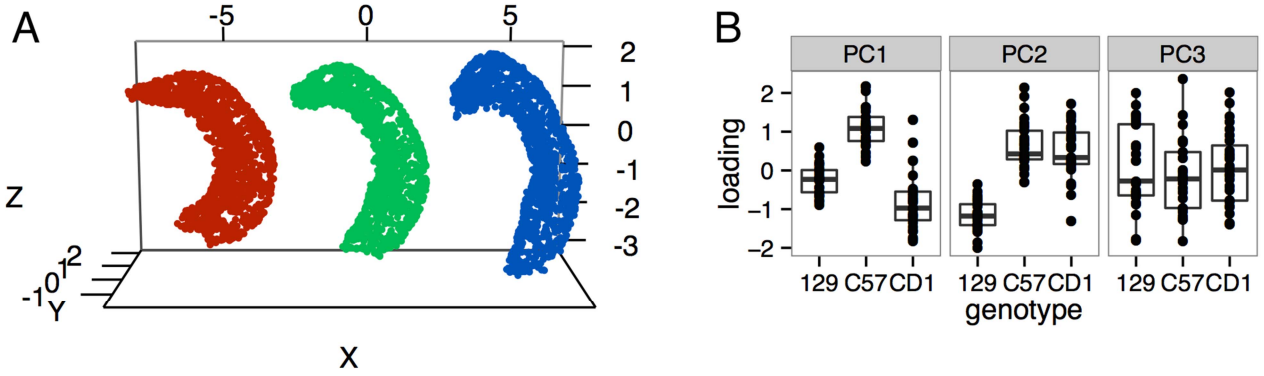

Figure 1: *(A) PC1 of the right hippocampus applied to its mean shape (green). Red and blue correspond to -5 and 5 standardized PC scores. (B) Standardized PC scores of each strain for the first three PCs.*

Results

First we calculated the modes of greatest variability in the hippocampus. The first 3 PCs explain about 60% of the variance. The first PC captured the variation between a more compact and thicker hippocampus and a dorso-ventrally elongated and thinner hippocampus (Fig 1, A). We found a clear difference in how PC1 was distributed across strains ($p<0.001$, Fig 1B). The compact shape was more typical of the CD-1 strain and the elongated shape was more typical of the C57 strain with the 129 strain closer to the mean shape. Similarly, we found strain differences for PC2 ($p<0.001$), but none for PC3 ($p=0.71$). The remaining PCs resembled PC3 in their distribution across strains. Independently estimated PC scores (PC1-3) correlated significantly across left and right hippocampi ($r^2>0.49$). GPA of the striatum produced results similar to the hippocampus. In the corpus callosum all PCs (PC1-3) showed significant strain differences.

Conclusion

Here we present the first systematic evaluation of anatomical shape differences across three common mouse strains. These results raise the question of how brain shape is genetically determined and whether shapes vary continuously or cluster around discrete modes as our results suggest.

References

[1] Yin Z et al. (2013). Nature Cell Biology, 15(7), 860–71. [2] Kovacević N et al. (2005). Cerebral Cortex, 15(5), 639-45. [3] Lerch JP et al. (2011). Neuroimage, 54(3), 2086-2095. [4] Dorr AE et al. (2008). Neuroimage, 42(1), 60–69.