Does the brain fit the skull? Fitting mouse skulls for size with combined MRI and x-ray CT

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Introduction

The mammalian brain and skull develop in a coordinated and concurrent fashion that proceeds with remarkable precision. Large variations in one of these structures are frequently accompanied by morphological changes in the other. However, the complex morphology of the brain and skull makes quantitative analysis of any relationship between phenotypes in these structures complex. In this work, we investigate the combined use of micro-computed tomography (CT) and MRI for deformation-based analysis of the brain and skull in the mouse. We apply the methods in a mouse model of Dandy-Walker Syndrome (DWS), a malformation affecting the hindbrain and skull that occurs in approximately 1 of every 25,000 live human births.

Methods

Wildtype (N=10) and DWS mice (N=9) were perfusion fixed by intracardial perfusion of paraformaldehyde and 2 mM Prohance. Samples were prepared for imaging by removing the extracranial tissue around the skull, leaving the skull and brain intact. High-resolution MRI images were acquired in overnight scan sessions (fast spin-echo, TR=325 ms, TEeff=30 ms, 6 echoes, 25x14x14 mm field-of-view, 780x432x432 field-of-view, 32 um isotropic resolution, 4 averages, 11h14min scan time). Following MRI, specimens were scanned with CT at 78 um isotropic resolution. The MRI and CT data sets were then independently registered nonlinearly in an unbiased fashion to produce a consensus average image for each modality. Statistically significant alterations in brain and skull shape were computed with reference to the consensus average and corrected for multiple comparisons using the false discovery rate (FDR). In the case of the brain, the volumes of 62 segmented neuroanatomical structures were also compared between WT and DWS groups.

Comparison of the brain and skull phenotypes observed in the separate MRI and CT data sets were made after registration of the MRI data to the CT skull data. For this purpose, a twelve parameter linear registration was performed to match the consensus MR and CT average images, aligning the hyperintense bone of the CT image with the hypointense bone observed on MRI. The resulting linear transform was used to transform all individual MRI deformations to place them within the context of the CT consensus average of the skull. The magnitudes of deformations on the brain surface and on the internal surface of the skull were then both mapped for comparison.

Results

MR and CT analyses independently revealed several DWS phenotypes in the brain and skull respectively. In the brain, 37 of the 62 structures tested were altered in volume (FDR<5%), including an ~25% decrease in the overall size of the cerebellum. The skull also showed changes, primarily in the vicinity of the interparietal bone. Co-registration of the MRI and CT data sets mapped the MRI data into the CT space. Visualization of the deformations of the MR and skull are shown after co-registration of the MRI and CT data sets (Figure 1). The magnitude, normal and in-plane displacements detected by MRI on the surface of the brain corresponded closely with equivalent CT measures on the inside surface of the skull. Intracranial volume and brain volume were also highly correlated. However, nowhere did bulk measurements (such as brain or cerebellum volume) provide an improved statistical explanation of skull deformation than did genotype.

Discussion and Conclusion

Our results indicate that the brain fits very tightly within the skull, and that changes in brain shape are consistent with changes in the shape of the inside of the skull. Nonetheless, in the WT and DWS mice, genotype remains a stronger predictor of skull shape than the underlying brain deformations on the brain surface. Combined analysis of the brain and skull surface provides an important tool for assessing genetic or other alterations that might disrupt the tightly regulated concurrent development observed in mammals.

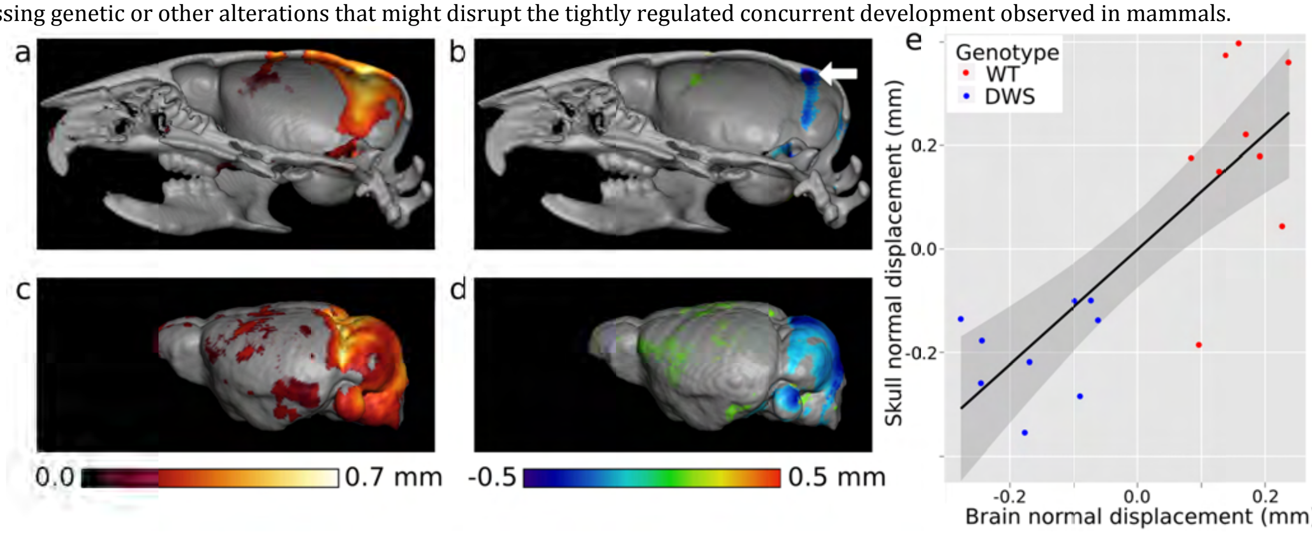

Figure 1: Changes in the brain and skull shape in WT and DWS mice. The average deformations between genotypes on the inside skull surface from CT images (a, b) compare closely with those observed on the surface of the brain with MR (c, d). The magnitude of deformations (a, b) and the component of the deformation normal to the skull surface (c, d) are mapped onto the surface renderings in regions where FDR<5%. A plot of the normal displacements at a mid-sagittal voxel of the interparietal bone (white arrow, b) is also provided (e).