Deformation-based morphometry in a mouse model of intrauterine growth restriction

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Background

- *Intrauterine growth restriction* (IUGR) refers to the failure of a fetus to reach its growth potential. Maternal malnutrition and placental insufficiency are among the most frequent causes of IUGR (Fig. 1). Approximately 5-10% of all pregnancies are afflicted with IUGR.[1]
- The "*brain sparing*" hypothesis posits that fetal brain and head size are preserved at the expense of the trunk in IUGR pregnancies.[2] Yet this adaptive response does not ensure normal brain development.[3]
- *Registration* involves mapping one image into the space of another. The analysis of these transformations is known as *deformation-based morphometry*.

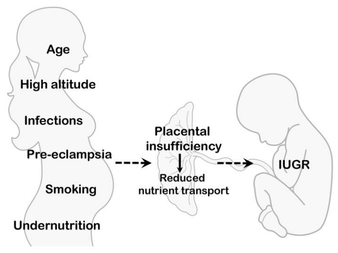

Fig. 1 Intrauterine growth restriction schematic.

Objectives

- We tested the brain sparing hypothesis by experimentally inducing IUGR in a sample of E18 mouse embryos (N=277) through heterozygous knockout (KO) of all 22 placenta-specific prolactin (PRL)-related genes and chronic protein malnourishment (20% vs. 6%) of dams. The project has three specific aims:

1. Generate a series (E13, E16, E18) of brain and whole skeleton atlases using a study-specific volumetric registration pipeline;
2. Apply deformation-based morphometry and automated landmarking to fetal heads and whole skeletons to quantify variation in shape and form;
3. Automatically segment and compute whole and regional brain volumes, as well as key growth parameters (biparietal diameter, head circumference, femoral length, abdominal circumference)

Materials and methods

- A subset of embryos (n=110) were stained overnight with Lugol's iodine (3.75% w/v), then embedded in 1% agarose and prepared for 3D X-ray microscopy (Zeiss Xradia 510 Versa) (Voltage, power: 50 kV, 4W; exp. time = 2 sec; scan time = 1.75 hrs; voxel size = 10 µm; binning = 2).
- Medical Imaging NetCDF libraries and high-performance computing were deployed to create a study-specific registration algorithm for deformation-based morphometry and tissue segmentation.[4]
- Source and target volumes were subjected to a series of linear and iterative non-linear transformations.
- Simplex optimization and cross-correlation were used to estimate the best transformation parameters.

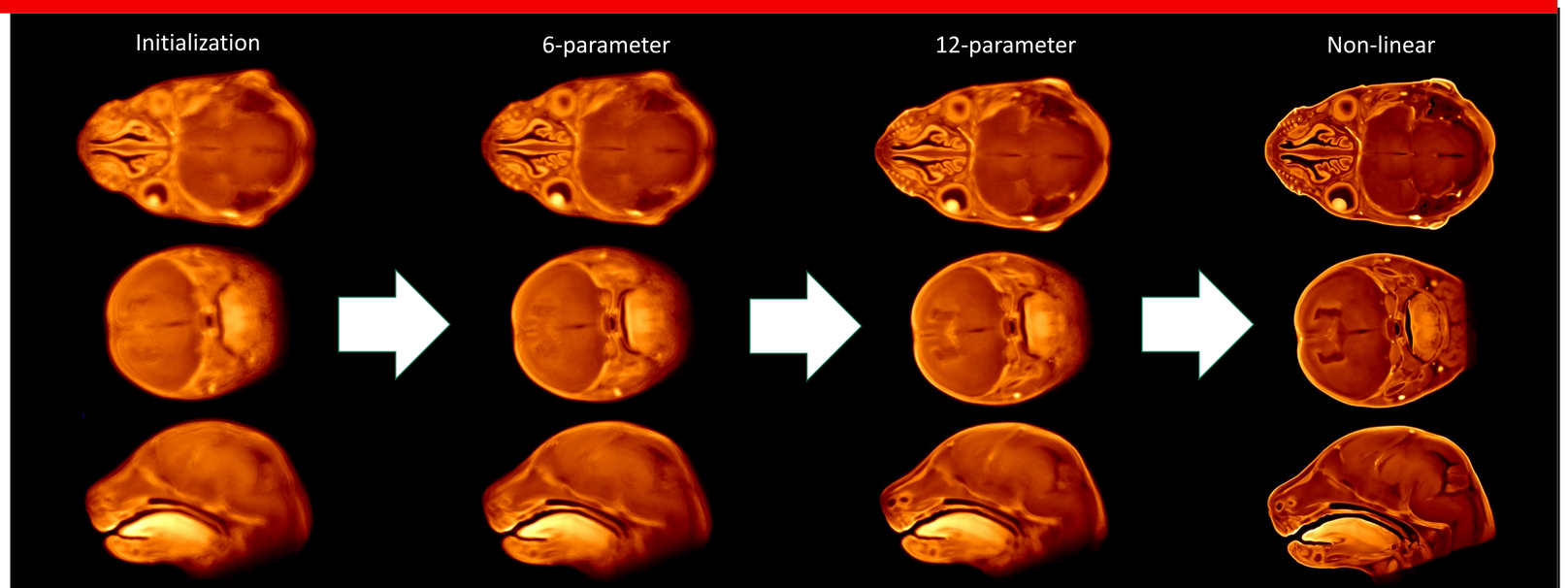

Fig 3. Transverse (left), coronal (middle) and sagittal (right) slices through a stained E18 average head. Specimens are subjected to a series of linear and non-linear optimization procedures so as to sequester variation and produce an average head in standardized 3-D space.

Preliminary findings

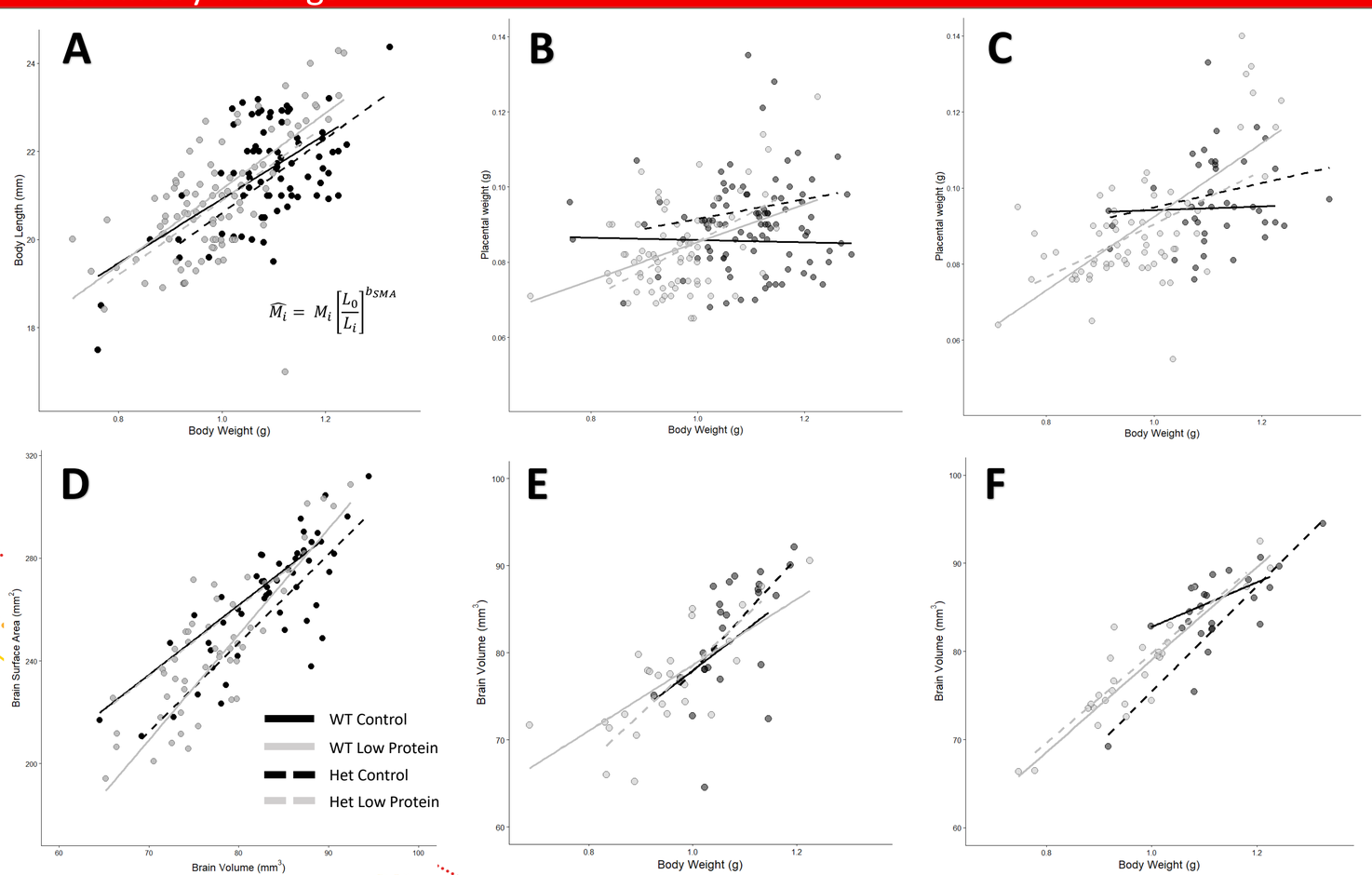

Fig 4. A: Scaled mass index, where M is body mass, L_0 is the mean length, and b_{SMA} is the scaling exponent estimated by dividing the OLS slope by the Pearson's correlation coefficient (r=0.71), is significantly predicted by diet (p<0.0001, β=-0.12), genotype (p<0.05, β=0.04), and marginally so by sex (p=0.079, β=0.03). **B/C:** Diet*Placental weight significantly predict fetal weight (females left, males right) (p<0.0001, β=0.04), as do Sex*Placental weight to a lesser extent (p=0.078). **D:** Brain SA-V ratio is significantly influenced by Diet*Genotype (p<0.0001, R^2=0.27). **E/F:** Brain-body ratio is significantly predicted by Diet*Genotype*Sex (p<0.01, R^2=0.11).

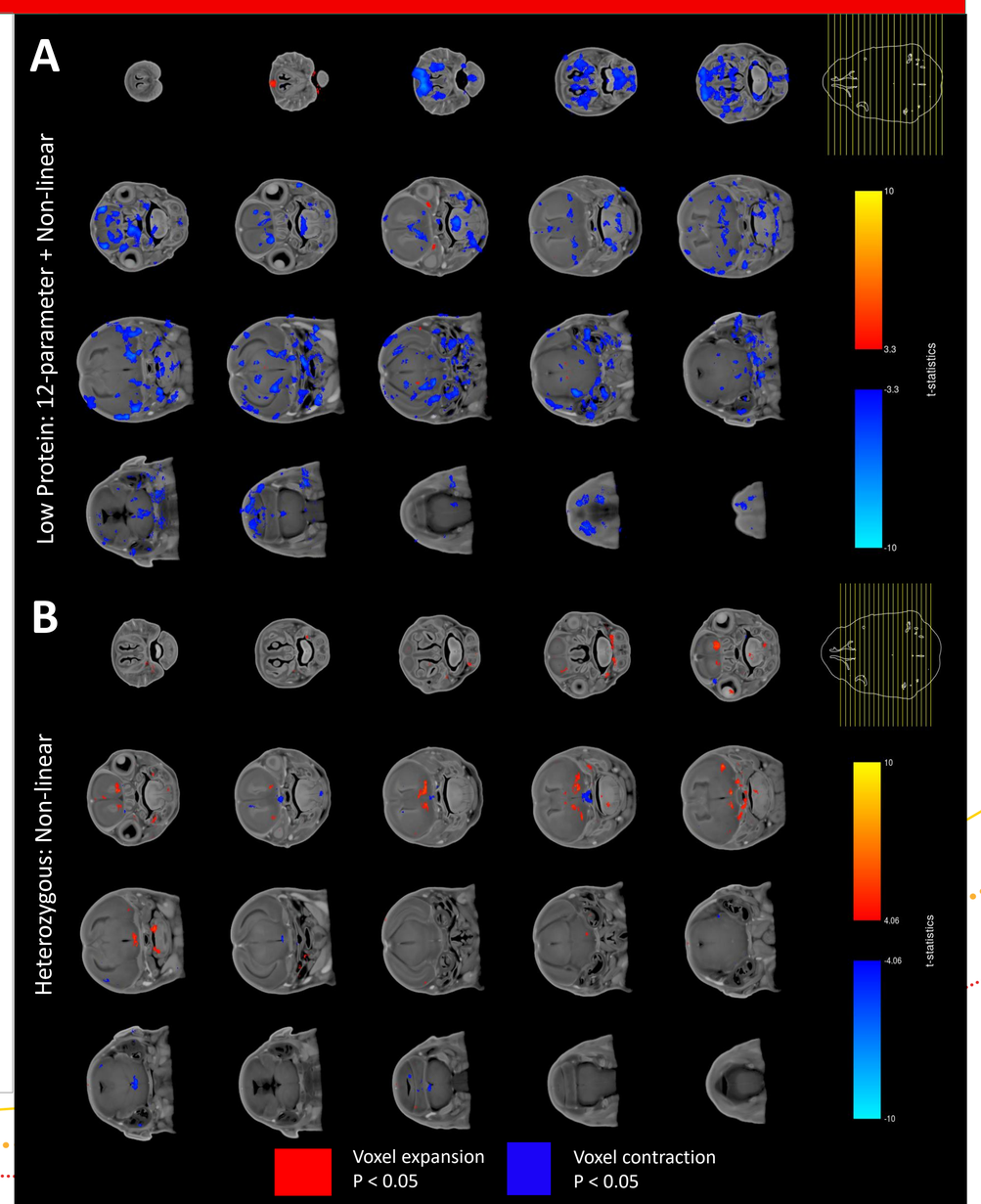

Fig 5. Jacobian determinants were computed from linear and non-linear transformations, then subjected to a false discovery rate test for significance. **A:** Average differences in head *form* between control and low protein embryos. **B:** Average differences in head *shape* between wild type and heterozygous embryos.

References

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