# Quantitative MRI Measures of Infant Brain Size: Prematurity as a Risk Factor in the Setting of Surgery and Critical Care with Prolonged Sedation

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## Introduction

Both prematurity[1] and critical illness in early infancy[2] are known to be associated with long-term neurobehavioral sequelae. However, it is not known what impact gestational age has on patient outcome in the setting of gastrointestinal congenital anomalies requiring life-saving surgery. *We hypothesized that brain size of full-term infants who underwent gastrointestinal surgery requiring prolonged sedation as part of their life-saving critical care will differ from that of premature infants but not of naïve controls (comparative baseline).*

## Patient Cohort & Methods

***Full-term*** **(n=13)** and ***preterm*** patients **(n=12)** with *long-gap esophageal atresia*, and comparative **healthy controls (n=14)** less than 1 year of age underwent non-sedated structural MRI using a 3T Siemens scanner, as per IRB approval at Boston Children's Hospital. Patients were scanned following completion of surgery and critical care treatment. **T1-weighted images** were acquired using a 32-channel head coil (TR 2520ms; TE 1.75ms; FOV 180x180; slice thickness 1mm; voxel size 1.0x1.0x0.99mm$^3$). Freeview was used for manual orientation of structural images (**Fig. 1**). Two blinded researchers measured 7 diameters and 2 surface areas using ITK-SNAP[3] (**Fig. 2**). Both absolute (mm or cm$^2$) and normalized (ratio %) values were checked for normality and tested for correlation with age and group. Differences of mean data values were assessed using one-way ANOVA.

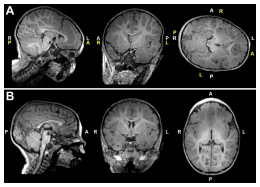

**Figure 1. MRI Alignment.** Figure illustrates an example of full-term infant brain MRI before (**Panel A**) and after alignment (**Panel B**). White labels represent header information stored with the T1 image, as visualized in FSLView. Correct labels are in yellow. Correct alignment is illustrated in 3 views: sagittal, coronal, and axial (left to right; **Panel B**).

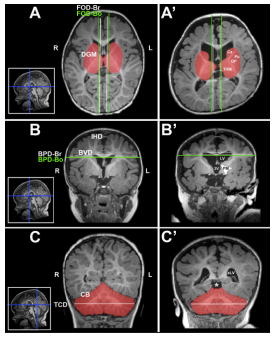

**Figure 2. Outline of Linear and 2D Brain Metrics.** ITK-SNAP was used for measurement of 7 diameters and 2 surface areas on selected axial (**A** and **A'**), and coronal sections (**B, B', C,** and **C'**). *Abbreviations*: **3V**, third ventricle; **BVD**, biventricular distance; **BPD-Br** and **BPD-Bo**, biparietal diameters of the *brain* and *bone*; **Ca**, caudate; **CB**, cerebellum; **DGM**, deep gray matter; **FM**, foramen of Monroe; **FOD-Br** and **FOD-Bo**, fronto-occipital diameters of the *brain* and *bone*; **GP**, globus pallidus; **IHD**, interhemispheric distance; **LV**, lateral ventricle; **Pu**, putamen; **TCD**, transcerebellar distance; **THM**, thalamus; **xLV**, atrium of the lateral ventricle.

## Qualitative Analysis

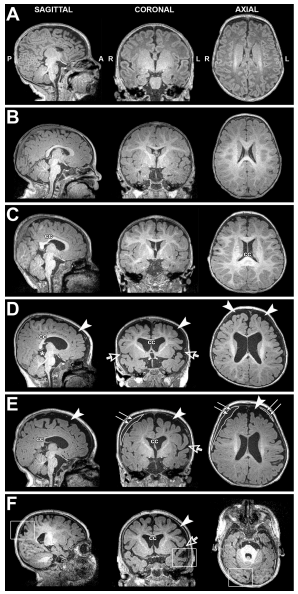


**Figure 3. Qualitative Findings.** T1-weighted MRI images from *full-term* healthy infant controls (**A** and **B**) and patients with history of long-gap esophageal atresia repair (**C-F**). **Panels A** and **B** show examples of normal brain structure in two different *full-term* infants at 0.7 and 7.1 months of age, respectively. Note gray/white matter contrast reversal between two control subjects, with the older one (**B**) displaying tissue characteristics found in adult brain MRI: cortical gray matter is darker in comparison to white matter tracts.

Remaining representative images show incidental MRI findings in 4 different patient subjects characterized by an abnormality (**C**) or thinning (**D-F**) of the corpus callosum (cc), widened Sylvian Fissures (open arrows; **D-F**), enlarged extra-axial space (white arrowheads) with ventriculomegaly (**D-F**). Incidental findings were also unique for the presence of a cyst (asterisk) in a 8.9 month-old infant (**D**), bilateral subdural hematoma (outlined in white line and indicated by double arrows) in 4.5 month-old infant (**E**), as well as areas of old venous hemorrhagic strokes (square boxes) in 5.8 month-old infant (**F**). Infant in **Panel C** was 10 months-old. Left side of coronal and axial images corresponds to right side of the brain. *Abbreviations:* **A**, anterior; **L**, left; **P**, posterior; **R**, right.

## Quantitative Analysis

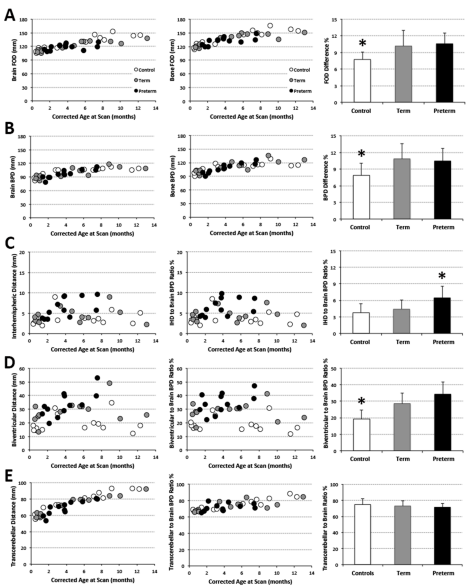


**Figure 4. Linear Brain Metrics Results.** Graphs summarize different metrics results in three groups: comparative healthy controls (white), full-term (gray) and preterm (black) patients. Fronto-occipital diameter (FOD; **A**), biparietal diameter (BPD; **B**), and transcerebellar distance (**E**) increase with age for all subjects, suggestive of head and brain growth with age. Normalized values implicate increase in extra-axial space (**A, B**) and ventricular size (**D**) in patients in comparison to controls. Significantly increased normalized interhemispheric distance (IHD) in preterm group implicates potentially smaller forebrain in comparison to other groups (**C**). Absolute and normalized transcerebellar distance shows no difference between groups, suggesting no change in cerebellar size following patients' treatment (**E**).

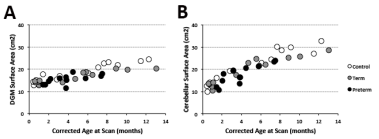


**Figure 5. 2D Brain Metrics Results.** Graphs summarize surface area results for deep gray matter (DGM; **A**) and cerebellum (**B**) in three groups: comparative healthy controls (white), full-term (gray) and preterm (black) patients. Both DGM (F=131.04, p<0.01) and cerebellar (F=219.72, p<0.01) surface areas increase with age, indicating growth with age irrespective of group status. Difference between groups is only significant for DGM (F=9.1, p<0.01; **A**), but not cerebellum (F=2.62, p=0.09; **B**).

## Results

- According to the intraclass correlation coefficient, inter-observer reliabilities were high (>0.8).
- We report significant qualitative incidental brain MRI findings in full-term infants without any previously known neurological concerns (**Fig. 3**).
- Selected MRI brain metrics implicate a significant *increase in extra-axial space volume* between patients (irrespective of gestational age at birth) and comparative healthy infants (**Fig. 4A-C**).
- Data also suggest that both full-term and premature patients are at increased risk for *ventriculomegaly* in comparison to healthy controls (**Fig. 4D**).
- Absolute deep gray matter surface area was significantly different among groups (**Fig. 5A**). No such findings were observed for cerebellar diameters and surface area (**Figs. 4E** and **5B**).

## Conclusion

- Data suggest full-term patients in the context of long-gap esophageal atresia treatment are as vulnerable to changes in cerebrospinal fluid and forebrain tissue as premature patients.
- Data also suggest that cerebellar size is not affected in patients.
- Presented data warrant future volumetric studies of brain size and growth in critically-ill infants in the presence and absence of surgery.

## References

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**3.** Woodward, L.J. et al. *Neonatal MRI to predict neurodevelopmental outcomes in preterm infants*. New Engl J Med, **2006**. 355: p. 685-94.

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