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The association between cardiac physiology, acquired brain injury and postnatal brain growth in critical congenital heart disease

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Abstract

Objective—To assess the trajectory of peri-operative brain growth in relationship to cardiac diagnosis and acquired brain injuries.

Methods—This is a cohort study of term neonates with hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA). Subjects underwent brain MRIs pre- and post-operatively to determine brain injury severity and total and regional brain volumes utilizing automated morphometry. Comparisons were made by cardiac lesion and injury status.

Results—79 subjects were included (49-TGA, 30- HLHS). HLHS subjects had more post-operative brain injury (55.6% vs. 30.4%, p= 0.03) and more severe brain injury (moderate to severe white matter injury (WMI), p= 0.01). Total and regional peri-operative brain growth was not different by brain injury status (either pre- or post-operative). However, subjects with moderate to severe WMI had a slower rate of brain growth in white and gray matter as compared to those with no injury. HLHS subjects had a slower rate of growth globally and in white and deep gray matter as compared to TGA (TBV- 12 cm^3/week vs. 7 cm^3; WM- 2.1 cm^3/week vs. 0.6 cm^3; deep

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GM- 1.5cm^3/week vs. 0.7 cm^3; p<0.001), after adjusting for gestational age at scan and the presence of brain injury. This difference remained after excluding subjects with moderate to severe WMI.

Conclusions—Neonates with HLHS have a slower rate of global and regional brain growth as compared to TGA, likely related to inherent physiologic differences post-operatively. These findings demonstrate the complex interplay between cardiac lesion, brain injury and brain growth.

Introduction

Advances in surgical techniques and peri-operative care have led to improved survival of newborns with critical congenital heart disease (CHD), such as hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA)[1]. Although there has been a decline in gross neurologic insults in these children, many experience behavioral, emotional, cognitive and motor impairments, suggesting widespread brain dysfunction[2,3]. Studies assessing neonates with TGA and HLHS as a single cohort have identified delayed brain development and a similar prevalence of pre-operative brain injury despite the fact that these lesions are anatomically and physiologically distinct from one another[4–7]. Interestingly, both lesions have evidence of altered fetal cerebral oxygen delivery and smaller total brain volumes as compared to the normal fetus, although the underlying mechanisms may differ in each lesion[8–10].

Measurements of simple metrics of brain growth on MRI have identified smaller total and regional brain size at birth and infancy in CHD as compared to controls[11,12]; however the rate of brain growth was similar and did not differ by cardiac lesion[11]. Cerebral MRI volumetry is a quantitative measure of total and regional brain volume providing an accurate means to assess brain volume and growth trajectory[13–15]. Sophisticated automated volumetry techniques can model brain tissue characteristics during neonatal development and have identified decreased total and regional brain volumes in neonates with complex CHD prior to any corrective operation[16]. In particular, studies have shown associations between smaller total and regional brain volumes (white matter and cortical grey matter) with neurodevelopmental outcome in adolescents with CHD[17], as well as association between brain volume at birth and neonatal neurobehavior[18]. These studies highlight the potential usefulness of this quantitative measure in identifying the patients at highest risk for neurodevelopmental impairment.

We sought to assess the trajectory of peri-operative brain growth in relationship to cardiac diagnosis and acquired brain injuries utilizing MR morphometry in a large sample of well characterized patients with standardized imaging time-points in the neonatal period. We hypothesize that patients with HLHS exhibit slower rates of brain growth due to a palliative, staged surgical approach with persistent cyanosis and potential for on-going postoperative brain injury. In contrast, newborns with TGA undergo definitive surgical correction with restoration of normal brain oxygen delivery, providing more favorable conditions for brain growth.

Methods

Between 2001–2014, newborns with critical CHD at the University of California San Francisco Benioff Children's Hospital were consecutively invited to participate in a prospective protocol studying brain development and brain injury in CHD using magnetic resonance imaging (MRI). Brain imaging findings from earlier versions of this cohort were previously reported[4,5]. Patients who were born prior to 36 weeks gestation, had a suspected congenital infection, had clinical evidence of a congenital malformation or syndrome, and/or had a suspected or confirmed genetic or chromosomal anomaly were excluded. Once written informed consent was received, patients underwent brain MRI before and after cardiac surgery. The institutional committee on human research approved the study protocol.

Patients diagnosed as having d-TGA with or without a ventricular septal defect (VSD) or HLHS were included in this current study. HLHS was defined as the presence of 1 functioning right ventricle with varying degrees of severe left heart hypoplasia requiring a palliative surgical intervention for survival (i.e. Stage I operation) in the newborn period. All subjects had a Stage I (Norwood) operation with a RV-PA conduit (Sano) modification.

MRI Study

Preoperative MRI studies were performed as soon as the baby could be safely transported to the MRI scanner as determined by the clinical team. Postoperative studies were performed after completion of perioperative care and prior to discharge from the hospital. Imaging time points were separated by an average of 15 days in the entire cohort. Detailed MRI methods are listed in supplementary material. A neuroradiologist reviewed each MRI (A.J.B.). Brain injury was characterized as stroke, white matter injury (WMI), intraventricular hemorrhage (IVH), and/or global hypoxic ischemic injury as previously described[5,6]. Post-operative brain injuries are limited to newly acquired lesions not evident on the pre-operative scan. WMI was classified as mild (1–3 foci each < 2mm), moderate (>3 foci or any foci > 2mm), or severe (>5% of white matter volume)[5]. Intraventricular hemorrhage was characterized as grade I, II, III, or IV using the system of Papile et al[19]. In addition, brain injury severity (BIS) was determined for each patient as previously described[20]. The BIS was assigned as follows: 0 indicates normal (no injury); 1, minimal injury (minimal WMI and IVH grade I or II); 2, stroke (all stroke); and 3, moderate to severe injury (moderate and severe WMI, IVH grade III or global hypoxic-ischemic injury).

Morphometry

Using an automated approach, segmentation of the gray matter (GM), white matter (WM) and deep gray matter structure (combining the thalamus, the basal ganglia and the periventricular germinal zone) was performed, as previously described[21] (Figure 1). Detailed methods are listed in supplemental material.

Clinical Variables

Clinical data were prospectively collected from the medical records by a team of trained neonatal research nurses and reviewed by a pediatric intensivist (P.M.) blinded to all neuroimaging findings.

Statistical Analysis

Demographic characteristics, descriptors of brain injury and clinical variables were compared between patients with HLHS and d-TGA using standard descriptive statistics. To analyze brain structural volumes, we used general linear models that included gestational age (GA) at scan, type of cardiac lesion (TGA or HLHS), BIS and sex as dependent variables while TBV, GM, WM, or deep GM volumes were set as the independent variables. As most subjects were scanned twice (one before and one after the surgery), mixed-effect linear models were used to take into account multiple measurements per subject. To assess whether pre-operative or post-operative brain injury influenced brain volumes, all subjects were first dichotomized into those with a cumulative BIS score > 0 and those with a BIS score = 0 based on the maximum value between pre-op and post-op BIS scores. In a separate analysis, an interaction term was included as BIS x GA at scan into the linear model in order to assess differences in brain growth rate depending on the presence of brain injury.

Finally, to assess difference by cardiac lesion, a linear model that contained a group term of cardiac lesion type (TGA or HLHS) and GA at scan as the main effect term was performed, including an interaction term (cardiac lesion x GA at scan). Adjustments were made for the presence of brain injury. The Bonferroni adjustment for multiple comparisons was used to obtain corrected p-values, which after adjusting for 8 comparisons was p= 0.006.

Results

A total of 79 infants were included in this study, 49 with d-TGA and 30 with HLHS. There were a total of 79 pre-operative brain MRI's and 73 post-operative brain MRI's. The post-operative MRI was not analyzed in 5 subjects due to motion degradation. One subject did not have a post-operative MRI due to pacemaker placement. Demographics and clinical variables are listed in Tables 1 and 2. Both groups were similar in pre-operative clinical characteristics including birth weight and birth head circumference. Post-operatively, HLHS subjects had more frequent cardiac arrest events and a longer length of hospital stay as compared to TGA subjects. In addition, the post-operative MRI was performed on average 6.5 days later in the HLHS group (DOL MRI: median 24 days, IQR: 20–30) as compared to the TGA group (DOL MRI median 17.5 days, IQR: 15–25, p= 0.001). The average time between scans was 15 days (IQR 10–21) in the entire cohort, 12.5 days in TGA (IQR 9–17) and 19 days in HLHS (IQR 15–25). Weight at the time of the second MRI was similar in both groups (TGA: 3492.9g, 95% CI: 3364.6–3621.4; HLHS: 3308.5g, 95% CI: 3183.1–3433.8); p= 0.06) with a similar increase in weight from birth to the time of the second MRI in both groups (TGA: 96.1 grams; HLHS: 96.6 grams) (Table 1).

The frequency of pre-operative brain injury was highest in HLHS, but not statistically significant (TGA= 14.3%, HLHS= 30%, p= 0.09). In contrast, HLHS subjects had a higher prevalence of new post-operative injury (TGA= 30.4%, HLHS= 55.6%, p= 0.03), mostly in the form of stroke (Table 3). The cumulative BIS score, which represents the highest score on either MRI, is represented in Figure 2. HLHS subjects had higher cumulative BIS scores than TGA subjects (BIS = 2 and 3) (p= 0.01).

Morphometry

Total and regional brain volumes increased significantly with increasing age in the entire cohort, even when accounting for the presence of brain injury, sex and the type of cardiac lesion ($p < 0.0001$ for all regions).

Subjects were dichotomized by cumulative BIS score (BIS =0 vs. BIS>0). Overall, mean global and regional brain volumes (all pre- and post-operative data points combined) were higher in subjects without brain injury as compared to those with brain injury, except in WM (TBV: 385 cm^3 v. 359 cm^3, $p< 0.0001$; GM: 147 cm^3 vs. 139 cm^3, $p<0.0001$; Deep GM: 48 cm^3 vs. 46 cm^3, $p< 0.004$; WM: 121 cm^3 vs. 116 cm^3, $p=0.007$). Although pre-operative brain injury did not predict pre-operative brain volumes, it was associated with significantly lower GM volumes on the post-operative MRI (147 cm^3 vs. 157 cm^3, $p = 0.0001$). Similarly, post-operative brain injury was associated with lower GM volumes on the post-operative MRI (149 cm^3 vs. 159 cm^3, $p = 0.0001$). In contrast, pre-operative brain volumes were not associated with new post-operative brain injury ($p =0.2$). Despite the difference in brain volumes at single points in time, the rate of global and regional brain growth did not correlate with the presence of brain injury noted on the pre- or post-operative MRI (Rate of growth in those with no brain injury (cumulative BIS=0) vs. those with brain injury (cumulative BIS>0)- TBV: 12.3 cm^3 vs. 12.4 cm^3, $p>0.3$; GM: 8.15 cm^3 vs. 8.14 cm^3, $p>0.5$; WM: 5.52 cm^3 vs. 5.46 cm^3, $p>0.4$; Deep GM: 1.21 cm^3 vs. 1.18 cm^3, $p>0.3$) (Figure 3A, Supplementary Figure 1A). However, when only evaluating patients with the most severe form of brain injury (moderate to severe WMI, cumulative BIS= 3), the rate of growth in WM and GM was significantly slower as compared to those with no brain injury (GM: 6.7 cm^3/week vs. 8.1 cm^3/week, $p= 0.001$; WM: 1.2 cm^3/week vs. 1.8 cm^3/week, $p < 0.001$) (Figure 3B, supplementary Figure 1B).

When assessing differences by cardiac lesion, there was no difference in overall mean total and regional measures of brain volume (all pre- and post-operative data points combined and when assessing each time point separately) in subjects with TGA compared to HLHS (TBV: 375 cm^3 vs. 372 cm^3, $p >0.2$; GM: 142 cm^3 vs. 145 cm^3, $p>0.1$; WM: 120 cm^3 vs. 117 cm^3, $p=0.1$; Deep GM: 47 cm^3 vs. 46 cm^3, $p>0.1$). However, D-TGA subjects had a faster rate of increase in global and regional brain growth as compared to HLHS subjects, even when adjusting for gestational age at scan and the presence of any injury (TBV- 12 cm^3/week vs. 7 cm^3/week; WM volume- 2.1 cm^3/week vs. 0.6 cm^3/week; deep GM volume-1.5 cm^3/week vs. 0.7 cm^3/week; $p<0.001$; Figure 4, supplementary Figure 2). GM did not show a significant difference in growth by cardiac lesion ($p=0.2$). Even when excluding subjects with moderate to severe WMI (BIS =3), those with D-TGA had a faster rate of increase in global and regional brain growth as compared to HLHS subjects ($p < 0.001$ for TBV, deep GM and WM).

Discussion

Our results demonstrate better perioperative brain growth in patients with d-TGA as compared to HLHS. Specifically, there was a 40% increase in the rate of brain growth in WM, GM and TBV in d-TGA subjects in this short period from preoperative to postoperative imaging. Interestingly, although subjects with brain injury had overall smaller

brain volumes at individual points in time as compared to those without injury, the strongest predictor of brain growth trajectory was cardiac lesion. This is the first report, to our knowledge, directly comparing the peri-operative patterns of brain growth between two infant groups with common, yet physiologically distinct critical congenital cardiac defects utilizing advanced MR morphometry.

In the fetal time period, both d-TGA and HLHS fetuses have evidence of delayed brain development (TBV and metabolic brain development)[9], although the underlying mechanisms likely differ by cardiac physiology and anatomy. In particular, based on fetal lamb models, those with HLHS have abnormalities in both perfusion (due to retrograde flow from the ductus arteriosus) and oxygenation of cerebral blood flow. In contrast, those with d-TGA are more likely to have abnormalities in oxygenation of cerebral blood flow[10]. Ultimately, both lesions result in decreased cerebral oxygen delivery and consumption[8]. Recently Rudolph suggested that decreased substrate delivery to the brain such as glucose may be the primary cause for the abnormalities in brain development[22]. Most studies find no differences by cardiac lesion in the degree of fetal or neonatal pre-operative brain development[4,7]. Some evidence suggests that within a particular group, specific anatomic features such as aortic atresia in HLHS leads to the greatest degree of delayed microstructural brain development[23]. Our study did not demonstrate significant differences pre-operatively in measures of brain volumes when comparing HLHS to d-TGA. This demonstrates that although these lesions are physiologically different, brain growth is similar during fetal and up to the pre-operative time period.

After birth and prior to their neonatal operation, patients with both d-TGA and HLHS are at risk for brain injury in the form of WMI and stroke[5,24,25]. Indeed, both groups have a similar risk of brain injury, likely secondary to shared risk factors such as hypoxia, length of time to surgery, embolism and preoperative cardiac arrest[26–29]. New, post-operative brain injury is common and tends to be more prevalent in subjects with single ventricle physiology[5]. Similarly, we found that post-operative brain injury was more common in the HLHS group with a higher number of small focal strokes, consistent with embolism. As opposed to TGA patients, HLHS patients after a Norwood procedure are vulnerable to embolic injury, which may be modifiable based on post-operative management and hospital length of stay. The relationship between brain development and injury is complex and dependent on methods used to measure brain development. Several studies agree that brain immaturity, measured utilizing semi-quantitative methods, is a risk factor for pre-operative brain injury[20,28,30]. However, our measures of total and regional brain volumes pre-operatively did not seem to predict the presence of new post-operative brain injury. The impact of brain injury on measures of *ongoing* brain development is less clear. For example, our group has shown that pre-operative brain injury predicts delayed post-operative metabolic and microstructural brain development[20]. We found that pre-operative brain injury is associated with smaller post-operative gray matter volumes and that overall brain volumes were smaller in those with injury as compared to those without injury. However, we found that rate of brain growth did not differ by the presence of brain injury globally or regionally. Thus, although brain injury is associated with brain volume loss, there appears to be minimal influence on continued brain growth at least in the peri-operative time period. On the most severe end of the spectrum, subjects with moderate to severe WMI exhibit a slower rate of growth in white

and gray matter. We believe this result is driven by the complex interplay between cardiac lesion, brain injury and brain growth. In our cohort, a larger percentage of subjects with HLHS had moderate to severe WMI, suggesting that cardiac lesion is the initial risk factor that influences both injury and brain growth. In fact, when subjects with moderate to severe WMI were removed from the analysis, those with d-TGA continued to have an even faster rate of global and regional brain growth as compared to HLHS.

Studies analyzing pyramidal tract maturation in newborns with CHD have demonstrated less rapid changes in fractional anisotropy over the peri-operative time period in subjects with pre-operative brain injury[31], similar to what is seen in premature infants with brain injury[32]. This suggests that the effects of brain injury on brain development may differ at macroscopic and microscopic scales. The techniques utilized to measure these different aspects of brain development are unique and offer different perspectives on brain maturity. More sensitive measures of brain growth in regions corresponding to the location of acquired focal lesions may lead to a deeper understanding of the longer term effects of milder forms of brain injury on brain growth.

The relationship between brain volumes in particular and injury is inherently complicated. Brain injury may lead to swelling and increased volume acutely, followed by tissue loss, potential repair and finally, in the immature brain, variable subsequent growth. Brain growth is one component of several factors that may impact long term neurologic outcomes in patients with complex CHD. The experience with preterm infants has demonstrated the close interplay between injury and continued brain growth and their collective influence on outcomes. Specifically, studies in premature infants have demonstrated long term effects of WMI or periventricular leukomalacia (PVL) on brain growth and function[33]. Although PVL is localized to the white matter, it can lead to disruption of cortical activity [34] and gray matter hypoplasia [35], with important consequences for developing cortical circuits[36–39]. Neuropathologic studies in non-survivors of critical CHD have shown abnormalities in the thalamus with thalamic neuronal loss and gliosis[40], regions critical for working memory and attention, a common deficit noted in survivors of critical CHD. Our data demonstrates that moderate to severe WMI does appear to slow the rate of brain growth in white and gray matter. Although this is likely largely driven by cardiac lesion, the impact of injury on brain growth and long term neurodevelopmental outcomes warrants further study.

Our findings demonstrate a clear link between cardiac sub-group and ongoing peri-operative brain growth. Given the high burden of acquired injury and delayed brain development early in life, the potential for repair and optimal brain growth is critical. Although HLHS and TGA patients appear to share similar fetal and pre-operative risk factors, they differ significantly post-operatively. D-TGA subjects undergo a corrective operation (arterial switch operation) restoring normal cardiovascular physiology, while those with HLHS undergo a series of palliative operations never achieving normal circulation, with ongoing hypoxia and risk for diminished systemic perfusion. Patients with single ventricle physiology rely upon circulation in series that may result in diminished systemic perfusion with compromised overall cerebral blood flow. There are several other differences between these groups including operative strategies (low or full flow bypass only vs. circulatory arrest or regional cerebral perfusion) and post-operative management (length of stay,

duration of mechanical ventilation) that influence our findings. Finally, somatic growth likely plays a role in brain development, particularly for those with single ventricle physiology. However, in the short time period evaluated in our study, both groups had a similar rate of weight gain in the peri-operative time period. In line with the cardiac physiology influences on brain development in CHD, we recently reported a relationship between the benefits of prenatal diagnosis and a healthier pre-operative state with perioperative brain development[41].

Ibuki et al demonstrated normalization of total and frontal brain volumes at three years of age in d-TGA subjects but not in single ventricle patients[42]. Their data suggested an association between hypoxia (SpO2) and measures of neurodevelopmental outcome (psychomotor development index on the Bayley's scale of infant development-II) in the single ventricle group. Their study was limited due to a small sample size, considerable variability and long time intervals between imaging studies. In our study, the larger sample size, standardized imaging timepoints in the neonatal peri-operative period, and the short interval between MRI studies strengthens our conclusions and suggests that the differences in brain growth by cardiac lesion begin soon after the neonatal operation.

Our findings suggest improved peri-operative brain growth in TGA subjects, however; evidence suggests that these patients continue to have structural and functional neurologic abnormalities later in life. TGA adolescents have altered grey matter volume and thickness[43] as well as diminished white matter microstructure[17,44,45] as compared to healthy controls. Neurodevelopmental assessments have revealed ongoing impairments in executive skills, visual-spatial skills and the need for remedial services[46], suggesting that abnormal fetal and pre-operative physiology and acquired brain injury may have lasting effects. Indeed, patients with HLHS demonstrate the greatest deficits and neurodevelopmental morbidity[2,47–49].

Our findings are limited by not knowing the exact timing of acquired brain injury despite two imaging time points in the peri-operative time period. Although we are invoking developmental etiologies (lack of oxygen and substrate delivery) as the primary influence on neonatal brain growth, the impact of injury as a destructive etiology on brain growth requires a larger sample size and more imaging timepoints, particularly in the transitional period after birth.

In conclusion, brain growth in the peri-operative time period is influenced more by cardiac sub-group than by brain injury. HLHS subjects have a slower rate of peri-operative brain growth globally and regionally in WM and deep GM. Further studies are needed to determine the predictive abilities of this measure of brain development on long term neurodevelopmental outcomes, with a goal of identifying specific impairments as targets for early intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary of Abbreviations

CHD	congenital heart disease
HLHS	hypoplastic left heart syndrome
TGA	d-transposition of the great arteries
MRI	magnetic resonance imaging
WMI	white matter injury
IVH	intraventricular hemorrhage
BIS	brain injury severity
GM	gray matter
WM	white matter
TBV	total brain volume
GA	gestational age
DOL	day of life

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Central Message

Neonates with hypoplastic left heart syndrome have a slower rate of peri-operative brain growth than d- transposition of the great arteries. Brain injury has less influence on neonatal brain growth.

Perspective Statement

Brain injury and delayed brain development are common in neonates with hypoplastic left heart syndrome (HLHS) and d-Transposition of the great arteries (TGA). Despite similarities in brain health pre-operatively, neonates with HLHS have a slower rate of on-going brain growth in the peri-operative time period, a reflection of the post-operative physiologic differences between these two cardiac lesions.

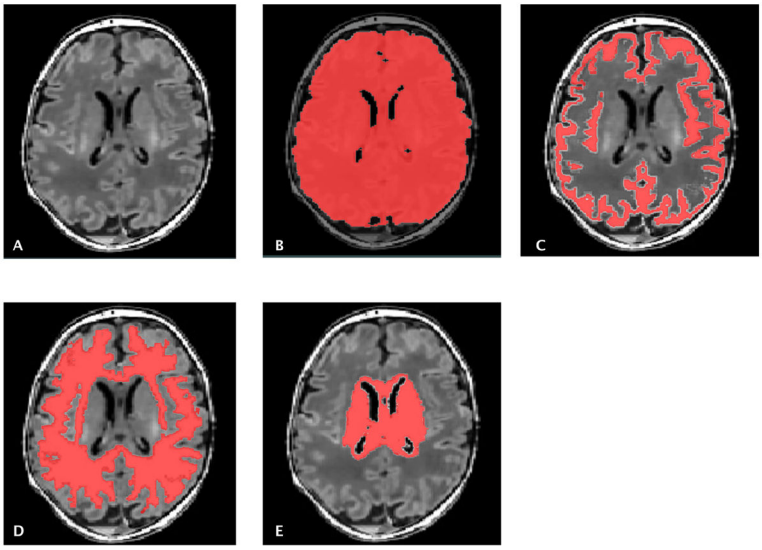


Figure 1.

T1 weighted MRI image (A). Automatic segmentation of brain structures to measure total brain (B), gray matter (C), white matter (D) and deep gray matter volumes (E).

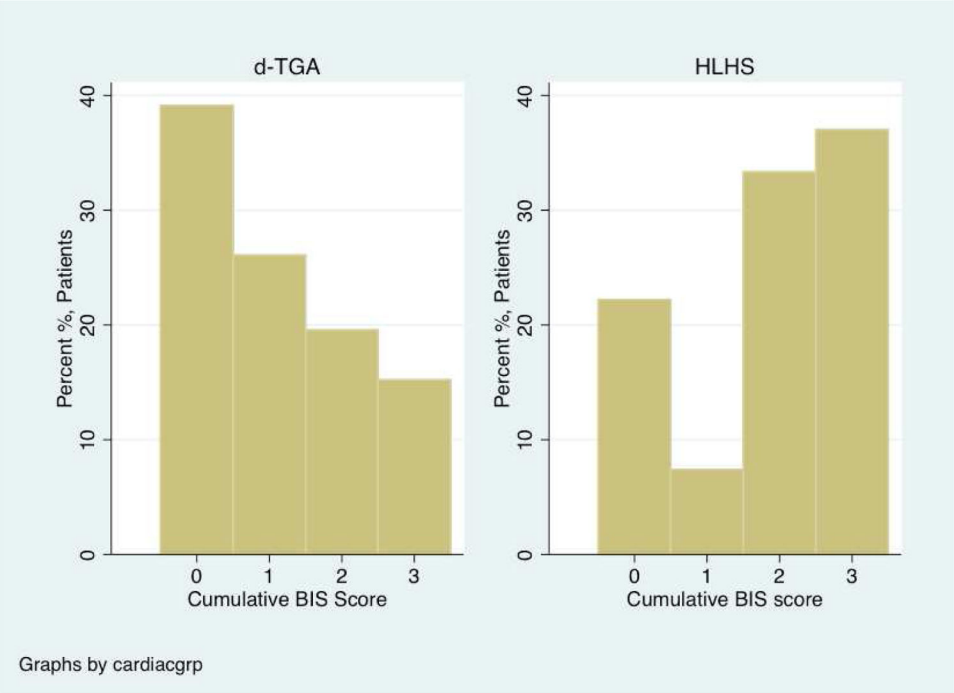


Figure 2.

Distribution of the cumulative Brain Injury Severity (BIS) score by cardiac lesion. The cumulative BIS score is the worst score when combining the pre- and post-operative MRI. A test for trends demonstrates less severe cumulative BIS scores in the TGA group (p = 0.01).

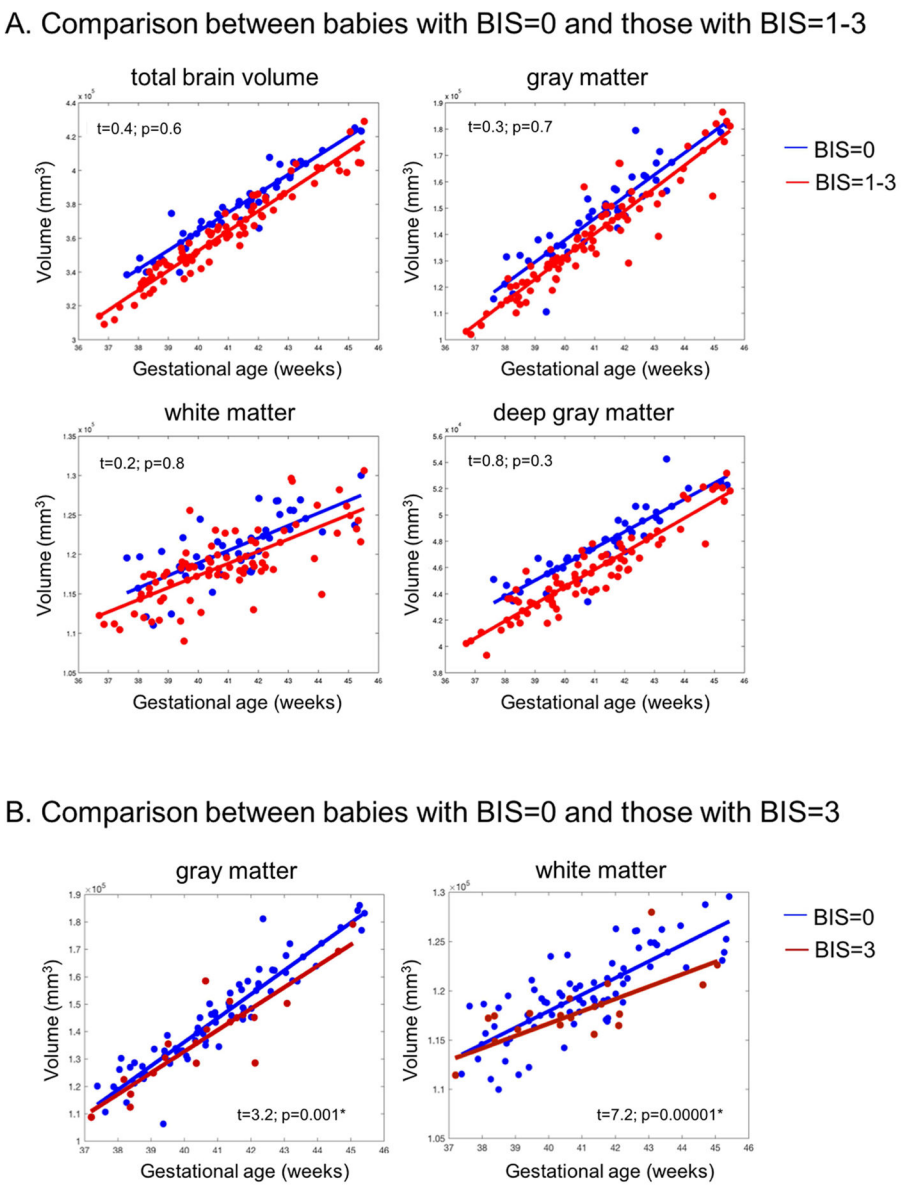


Figure 3.

A) Brain global/regional volume changes in the presence of brain injury (red line- cumulative BIS > 0) and without brain injury (blue line- cumulative BIS = 0). The x-axis represents the gestational age at the time of MRI and the y-axis represents the volume in mm^3. The plot includes pre- and post-operative brain MRI measures for each subject with a best-fitted line. Plots with paired observations for each subject are included in supplementary Figure 1. Overall, mean global and regional (gray matter and deep gray matter) brain volumes were lower in subjects with brain injury as compared to those without brain injury. However, the rate of global and regional volume change over time was not associated with brain injury (all p-values > 0.1). B) Brain regional volume changes in gray and white matter in the presence of no brain injury (blue line- cumulative BIS= 0) and in those with moderate to severe white matter injury (dark red line- cumulative BIS= 3). Those

with moderate to severe WMI have significantly slower growth in gray matter and white matter as compared to those without injury ($p= 0.001$ and $p< 0.0001$ respectively).

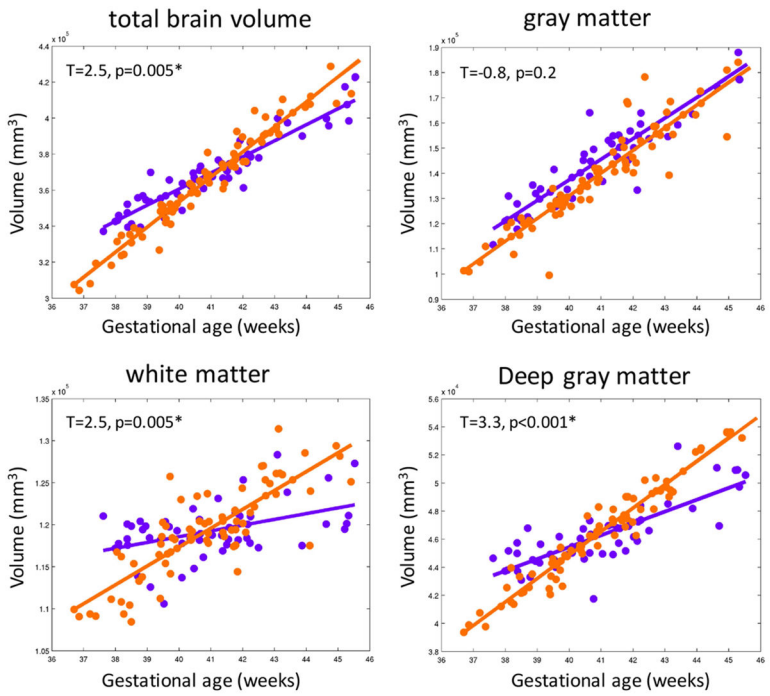
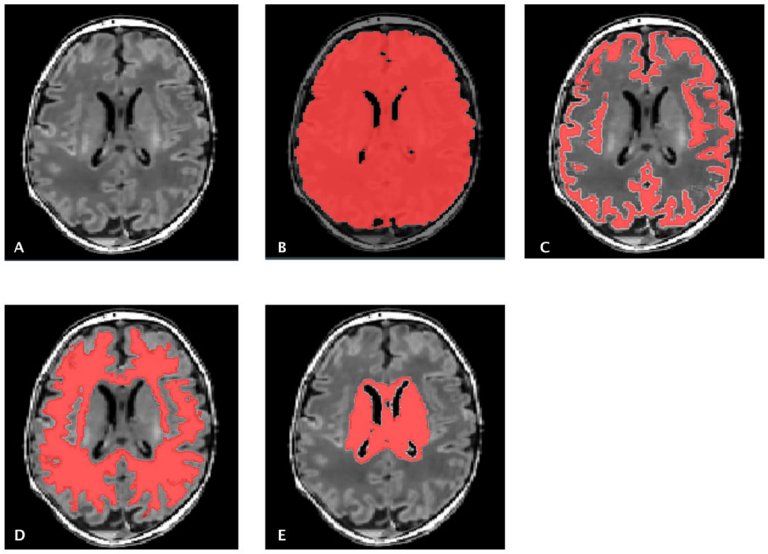


Figure 4.

The rate of change in global and regional brain volumes by cardiac lesion after adjusting for the presence of brain injury. The x-axis represents the gestational age at the time of MRI and the y-axis represents the volume in mm^3. The plots include pre- and post-operative brain MRI measures for each subject with a best-fitted line. Plots with paired observations for each subject are included in supplementary Figure 2. Subjects with HLHS (purple line) have a slower rate of growth in total brain volume, white matter and deep gray matter as compared to those with d-TGA (orange line). *Significant after Bonferroni correction, $p<0.006$.



Central Picture.

Legend: T1 weighted MRI image (A). Automatic segmentation of brain structures to measure total brain (B), gray matter (C), white matter (D) and deep gray matter volumes (E).

Table 1

Demographics by Cardiac Lesion

	TGA (n= 49)	HLHS (n= 30)	p-value
EGA Delivery, wk (mean, 95% CI)	39.2 (38.8–39.6)	38.9 (38.4–39.3)	0.35
Birth weight, g (mean, 95% CI)	3396.8 (3228.0–3565.6)	3211.9 (3030.6–3393.3)	0.16
Male, N(%)	39 (79.6%)	16 (53.3%)	0.02
Birth Head Circumference, cm (mean, 95% CI)	34.0 (33.7–34.3)	34.1 (33.6–34.6)	0.78
Weight at MR2, g (mean, 95% CI)	3492.9 (3364.6–3621.4)	3308.5 (3183.1–3433.8)	0.06

TGA= d- transposition of the great arteries; HLHS= hypoplastic left heart syndrome; EGA= estimated gestational age; CI= confidence interval

Table 2

Pre- and post-operative Clinical Variables by cardiac lesion

	TGA (n= 49)	HLHS (n= 30)	p-value
Balloon atrial septostomy N (%)	30 (61.2%)	1 (3.3%)	< 0.001
Lowest pre-op O2 sat Mean (95%CI)	56.9 (52.0–61.7)	80.1 (76.2–84.0)	< 0.001
Pre-op pH (1st ABG) Mean (95% CI)	7.27 (7.23–7.31)	7.29 (7.24–7.35)	0.43
Pre-op Base excess (1st ABG) Mean (95% CI)	−6.2 (−8.5 to −3.9)	−4.1 (−6.7 to −1.4)	0.23
Pre-op Cardiac Arrest N (%)	1 (2.0%)	2 (6.7%)	0.55
Day of life operation Median (IQR)	8 (5.5–11)	8 (6–11)	0.99
Day of life MRI 1 Median (IQR)	5 (3–6)	5 (3–6)	0.96
Post-op Cardiac Arrest N (%)	0	5 (16.7%)	0.006
Post-op ECLS N (%)	2 (4.1%)	4 (13.3%)	0.19
Post-op duration of mechanical ventilation Median (IQR)	5 (3–7)	8 (6–10)	0.0002
Day of life MRI2 Median (IQR)	17.5 (15–25)	24 (20–30)	0.001
Hospital LOS Mean (95% CI)	23.8 (19.2–28.3)	40 (30.0–50.0)	0.001

TGA= d-transposition of the great arteries; HLHS= hypoplastic left heart syndrome; ABG= arterial blood gas; IQR= inter-quartile range; ECLS= extra-corporeal life support; LOS= length of stay

Table 3

Pre- and post-operative brain injury by cardiac lesion

	TGA (n= 49)	HLHS (n= 30)	P-value
Pre-operative			
Any Injury	17/49 (34.7%)	13/30 (43.3%)	0.44
WMI	7/49 (14.3%)	9/30 (30.0%)	0.09
Stroke	12/49 (24.5%)	6/30 (20.0%)	0.64
New Post-operative *			
Any Injury	14/46 (30.4%)	15/27 (55.6%)	0.03
WMI	13/46 (28.3%)	9/27 (33.3%)	0.65
Stroke	1/46 (2.2%)	7/27 (25.9%)	0.003

WMI= white matter injury; TGA= transposition of the great arteries; HLHS= hypoplastic left heart syndrome

* Post-op MRI missing in 3 subjects with TGA and 3 subjects with HLHS due to death of subject