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Abnormal Development of Thalamic Microstructure in Premature Neonates with Congenital Heart Disease

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Abstract

Background and Purpose—Preterm birth is associated with alteration in cortico-thalamic development, which underlies poor neurodevelopmental outcomes. Our hypothesis was that *preterm* neonates with CHD would demonstrate abnormal thalamic microstructure when compared to critically ill neonates without CHD. A secondary aim was to identify any association between thalamic microstructural abnormalities and peri-operative clinical variables.

Material and Methods—We compared thalamic DTI measurements in 21 preterm neonates with CHD to two cohorts of neonates without CHD: 28 term and 27 preterm neonates, identified from the same neonatal intensive care unit. Comparison was made with three other selected white matter regions using ROI manual based measurements. Correlation was made with post-conceptional age and peri-operative clinical variables.

Results—In preterm neonates with CHD, there were age-related differences in thalamic diffusivity (axial and radial) compared to the preterm and term non-CHD group, in contrast to no differences in anisotropy. Contrary to our hypothesis, abnormal thalamic and optic radiation microstructure was most strongly associated with an elevated first arterial blood gas pO_2 and elevated pre-operative arterial blood gas pH ($p<0.05$).

Conclusion—Age-related thalamic microstructural abnormalities were observed in preterm neonates with CHD. Perinatal hyperoxemia and increased peri-operative serum pH was associated

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with abnormal thalamic microstructure in preterm neonates with CHD. This study emphasizes the vulnerability of thalamo-cortical development in the preterm neonate with CHD.

Introduction

Approximately one in every 100 babies born in the United States is affected with congenital heart disease (CHD), and more than 15% of those are born prematurely. Interestingly, CHD is twice as common in preterm infants compared to term infants [1]. These facts have a vast impact on the newly born infant, his/her family, the healthcare team, and society as it has been consistently demonstrated that such an individual is at great risk for morbidity, mortality, and prolonged neurodevelopmental challenges [1 – 17].

Preterm birth in neonates with*out* CHD has been shown to be associated with abnormal corticothalamic development, which is thought to underlie multi-domain neurocognitive deficits [18, 19]. Additionally, and perhaps not coincidentally, the peak peroid of perinatal brain injury in preterms concides with the development of the subplate, a structure that is critical to the development of thalamo-cortical connections [20 – 22]. We have previously reported on abnormal white matter findings in preterm CHD neonates using Diffusion Tensor Imaging and Tract Based Spatial Statistics [23]. Despite the large number of studies demonstrating how the thalamus and its connections are abnormal in the preterm brain, the microstructure of the thalamus in the preterm CHD patients has not been investigated.

In the present study, we used diffusion tensor imaging (DTI) to investigate the microstructural integrity of the thalamic parenchyma in preterm neonates with CHD. DTI is a quantitative MRI technique that can assess the microstructural integrity of the brain tissue based on the Brownian motion of water molecules. Our hypothesis was that preterm neonates with CHD would demonstrate thalamic microstructural abnormalities at near term-equivalent age when compared to other critically ill neonates without CHD. We included two separate comparison groups: term neonates without CHD and preterm neonates without CHD, both of which were identified from the same high risk NICU. The term neonates without CHD provided a comparison for what the images of the preterm non-CHD brains should approximate at term-equivalent age. The preterm neonates without CHD allowed us to determine whether the presence of a congenital heart defect resulted in further thalamic microstructural abnormality than would be accounted for by prematurity alone. Our secondary aim was to identify any association between thalamic microstructural abnormalities and both post-conceptional age and peri-operative clinical variables. We specifically tested the hypothesis that both age and hypoxic perinatal and peri-operative factors would be associated with abnormal thalamic microstructure in preterm CHD neonates.

Materials and Methods

Subjects

Cohort of preterm neonates with CHD—Neonates undergoing clinically-indicated brain MRIs at near term-equivalent age during the period of 2005 to 2010 were recruited as part of on-going longitudinal studies of neurodevelopment in neonates with prematurity and

CHD at Children's Hospital Los Angeles. In the preterm CHD group, we included neonates with any heart anomaly treated surgically in infancy, including: the combination of atrial septal defect (ASD) and ventricular septal defect (VSD) (requiring surgery after term-equivalency), hypoplastic left heart syndrome (HLHS), Ebstein's anomaly, coarctation of the aorta, truncus arteriosus, transposition of the great arteries (TGA), and double outlet right ventricle. CHD patients were excluded if: (1) the heart anomaly did not require surgery; (2) if they had an identified chromosomal abnormality; (3) if the brain MRI did not include DTI data which were analyzable (i.e., due to motion artifact or technical factors), or (4) if there was a congenital brain malformation or a significant brain abnormality/injury/infection, which could distort subsequent DTI measurements. Approximately 10 preterm CHD neonates were excluded.

Comparison cohorts of critically ill term and preterm neonates without CHD— For comparison, we included data from two cohorts of neonates without CHD identified from the same high-risk NICU--the first obtained as part of an IRB-approved retrospective review of neonatal MRIs conducted at the same institution as above between 2005–2010 and the second obtained as part of an ongoing longitudinal research program focused on prematurity. All near term-7 equivalent MRIs were completed under clinical-indications. The clinical indication for these studies included suspected abnormal brain morphology (not confirmed), suspected brain injury or infection (not confirmed by imaging or relevant laboratory studies); assessment of possible seizure activity, and assessment of a non-intracranial abnormality, including a facial or orbital lesion. For all neonates, medical records were reviewed, including pertinent outpatient follow-up, by a neonatologist (LP) and a pediatric neuropsychologist (JW). By choosing crtically ill term controls with normal conventional MRI, we hoped to learn more about the potential paths of aberrent brain development in high-risk neonates, term and preterms.

MR Imaging Protocol

All imaging was obtained in a 1.5T General Electric System (GE-Medical Systems, Milwaukee, WI) with a neonatal head coil and neonatal incubator (if clinically necessary). The following imaging sequences were acquired: T2-weighted FSE in axial and coronal plane (TE/TR = 85/5000 msec, FOV = 20 cm, matrix = 320×160 or 256×128; slice thickness 3 mm, spacing=0); Coronal T1 3D SPGR (TE/TR=6/25 msec, FOV=18 cm, matrix= 256 × 160; slice thickness=1mm, spacing=0). The DTI protocol included an Echo-planar imaging (EPI) sequence with the following parameters: TE/TR = 80/10000 msec, FOV = 22 cm, matrix = 128×128, slice thickness = 4.5 mm, spacing = 0, with an in-plane resolution of 1.7 mm applied along 25 non-colinear directions with a b-value of 700 s/mm^2.

ROI analysis

DTI analysis was performed off-line using DTI Studio (Johns Hopkins University, Baltimore, MD). Diffusivity and anisotropy metrics were measured in a total of 4 standardized ROI's [24]. Specifically, the manually-delineated regions included the thalamus (drawn on a single axial slice at the level of the thalamus and genu/splenium of the callosum); and three other white matter structures: optic radiations, parietal periventricular cross-roads (a region known to be commonly affected by pWML or PVL involving

intersections between longitudinal cortico-cortical tracts in anterior-posterior and left-right orientation and thalamocortical tracts radiating centrally toward the peripheral cortex), and the splenium of the corpus callosum These specific white matter regions were chosen as these involved projections from the thalamus and abnormalities of these areas have been demonstrated previously in CHD populations [9,23]. Standardized axial slices were used for all regions of interest. In cases of head tilt, ROIs were delineated at multiple slice levels and then averaged. For structures such as the thalamus, ROIs were drawn so as to outline the structure. For other ROIs, a standardized circular ROI of a given diameter was used. The senior neuroradiologist (AP) ensured consistency of positioning for all regions. In all regions, standard measurements were obtained: fractional anisotropy (FA), eigenvalue 1 (λ_1), eigenvalue 2 (λ_2), eigenvalue 3 (λ_3) and mean diffusivity (MD) were calculated. Eigenvalue 1 was also considered as axial diffusivity (λ_{11})(AD). Radial diffusivity ($\lambda_{\perp}$)(RD) was calculated as the average of eigenvalues 2 & 3. Definition of these diffusion tensor metrics have been previously described [23].

Clinical Variables

The first arterial blood gas was the first documented blood gas for the neonate. The admission blood gas was the first blood gas at our facility upon arrival. The pre-operative blood gas done on the day of surgery immediately prior to surgery and the post-operative blood gas was the first blood gas obtained after surgery. Necrotizing enterocolitis was defined by the clinical team caring for the infant.

Statistical Analyses

Continous clinical variables were compared using a three-way ANOVA. Pairwise comparisons were then made using Tukey's analysis. Categortical clinical variables were compared using Kruskal-Wallis or chi-square tests, as appropriate. Differences in peri-operative variables were determined by non-parametric tests. R Developmental Core Team and SPSS (Version 19, IBM Corporation) were used for all statistical analyses.

Results

Characterization of the Clinical Population and Clinical Variable Data

There were 76 cases that met the inclusion criteria for this study: 21 preterm neonates with CHD, 28 neonates born at term (≥ 37 weeks; term non-CHD comparison group) and 27 neonates born between 23 and 36 weeks gestational age (preterm non-CHD comparison group). There were no significant differences in post-conceptional age (PCA; defined as gestational age at birth plus post-natal age) at time of MRI among the three groups, including the subset of preterm CHD cases identified with pWMLs (p=0.58 ANOVA) (Table 1. Diagnoses, clinical course, MRI and surgical variables for preterm CHD cases are summarized in Table 1–2. Of note, 8/21 (38%) of the preterm CHD MRIs were obtained (clinically) prior to undergoing cardiac surgery.

Assessment of Thalamic Parenchyma

Using ROI technique, there was no significant difference between the preterm CHD group and the two non-CHD groups (term and preterm) in the thalamic anisotropy measurements

(Table 3). In contrast, there was increased axial diffusivity (AD) in the thalamus of the preterm CHD group compared to the term non-CHD group (p value = 0.042). There was also a trend towards increased radial diffusivity (RD) and ADC of both preterm groups compared to the term non-CHD group (Table 3).

Comparative Assessment of Adjacent Central Cerebral White Matter

To compare the thalamic findings with adjacent central white matter regions, we also performed similar ROI measurements in three central white matter structures: parietal white matter, optic radiations, and splenium of the corpus callosum. The parietal white matter showed no differences across the three study groups. In contrast, there were significant differences seen in the optic radiations including reduced FA (p value =0.045). There was also reduced FA seen in the splenium (p-value < 0.0001) with increased radial diffusivity (p value < 0.0001) between the preterm CHD group compared to the term and preterm comparison groups (Table 3).

Developmental Trajectories of Thalamic Microstructure Across Groups

In order to investigate how development of microstructure in the thalamus might be differentially impacted across groups, we computed the correlation between age and each metric for the neonates in our preterm CHD and term/preterm non-CHD comparison groups. In the thalamus and optic radiations, there were increases in FA with post conceptional age in all three groups, without a significant age interaction. Significant age-related changes in radial diffusivity were also observed in the thalamus and optic radiations, and although these appeared to be associated with different correlations in preterms with CHD compared to other critically ill neonates, the interaction terms were not significant (Table 5). In the thalamus, radial diffusivity decreased with age in the preterm CHD group (r=−0.486, p=0.026), but not in the preterm neonates without CHD (r=−0.129, p=0.520) or the term neonates without CHD (r=−0.307, p=0.111). In the optic radiation, radial diffusivity decreased with age in the preterm CHD group (r=−0.587, p=0.007) and the term neonates without CHD (r=−0.423, p=0.025) but not in the preterm neonates without CHD (r=−0.269, p=0.175) (see Figure 2).

Correlations among Preterm CHD DTI metrics and clinical-perioperative variables

Clinical variables (NEC, 1st ABG [arterial blood gas] pH, 1st ABG pO2, admission ABG pH, admission ABG pO2, pre-op ABG pH, pre-op ABG pO2, post-op ABG pH, post-op ABG pO2) and DTI measurements (FA, AD, RD, MD) of the thalamus and associated cerebral white matter structures (optic radiation parietal white matter and splenium) were correlated within the preterm CHD group. Our results indicated that the DTI metrics obtained in the thalamus were most strongly associated (0.60 or better) with an elevated first arterial blood gas pO_2 (pO_2 range 23–232) and elevated pre-operative arterial blood gas pH (pH range 7.13–7.59) (Table 4). Additionally, there were a number of strong correlations between DTI metrics in the vicinity of the optic radiations and the first arterial blood gas pO_2 and the post-operative arterial blood gas pH (Table 4).

Discussion

This is the first study to describe selective microstructural imaging abnormalities in the thalamus and central white matter matter regions in premature babies born with CHD. When correlated with clinical variables, hyperoxemia at birth was predictive of abnormal diffusivity in the thalamus, splenium, parietal white matter, and optic radiations at term-equivalent age in the preterm CHD group. Additionally, a greater pre-operative pH was associated with a lower FA at term-equivalent in the preterm CHD group. Our data of the non-CHD diffusivity measurements is corroborated by measurements previously reported in the literature [24, 25]. Additionally, the white matter findings are consistent with Tract Based Spatial Statistics results recently reported [23].

In regards to the thalamus, the diffusivity of the preterm groups (CHD and non-CHD) were similarly greater than the term group, suggesting a difference in degree of myelination. Interestingly, the lag in myelination is demonstrating a trend toward being more pronounced in the CHD group (as illustrated by the greater slope of the line on Figure 2); and neither preterm group approximates the diffusivity of the term neonates even by 60 weeks post-conceptional age. It is difficult to know the exact reason for such delay as the mechanism and pathophysiology may be different between these two prematurely born populations. Delayed maturation has been demonstrated in the premature brain [19], as well as the term infant with CHD [26 – 28]. However, arrested development versus disarrayed development may appear grossly equivalent but in fact have a profound impact on future potential.

There was a positive correlation between the first measured arterial pO2 and the thalamic diffusivity, as well as the diffusivity of the associated central cerebral white matter regions. This is potentially very interesting as it was consistently a strong association and suggestive of seeing the end-result imaging measurements at term-equivalent of the effects of perinatal hyperoxemia in the preterm baby. As only approximately 30% of the premature CHD group was prenatally diagnosed as having complex congenital heart disease, it is possible that the clinical course involved the premature infant being given progressively more supplemental oxygen to achieve acceptable oxygenation. Once on significant amounts of oxygen and the preterm neonate was not responding as expected, an echocardiogram was obtained that revealed the heart lesion; then, oxygen goals were revised and the supplemental oxygen likely weaned. But, exposure to hyperoxic conditions had already occurred and possibly affected the developing brain. It is known that the developing brain is vulnerable to hyperoxemia effects which causes apoptosis, increased inflammation, and cell death [29]. Specifically in the preterm neonate, the cells necessary for myelin production are forming and at risk. Oligodendroglial precursors and premyelinating oligodendroglia are susceptible to injury by free radicals, reactive oxygen and nitrogen species, and inflammatory cytokines [29 – 31]. The microglia defense network of the brain has also been demonstrated to become activated by an increase in cerebral gene expression of inflammatory mediators (IL-1beta, IL-12p40, TLR-2, and TRL-4) [29]. And, neurotrophic factor production is suppressed by hyperoxemia [32]. Such oxidative stress effects have been demonstrated to have a predilection for the deep and central white matter [29, 30]. The association of abnormal diffusivity in the associated central cerebral white matter regions in our study is supported by such previous findings. It has been demonstrated in the rat that exposure to hyperoxia

(80% oxygen) over a two-hour duration lead to significant cell death in the brain 24 hours later [32]. Such timing is consistent with the timing of hyperoxemia exposure being seen in this study's patients. As well, a critical time period of vulnerability seems to exist for such oxidative damage to the developing brain. Again, in the rat hyperoxemic population, the largest numbers of cell death within cortical white matter tracts occurred within the first seven days. In humans, this time period is thought to begin with the third trimester of gestation [32]. The suggestion of increased risk of cell death in the developing preterm brain is important as it has been demonstrated that decreased volume of grey matter structures correlates with cognitive deficits [32]. As well, following such ideas it is tempting to speculate that hyperoxemia-therapy in undiagnosed complex congenital heart disease neonates may exacerbate the delayed regional development and/or volumetric brain growth [28].

Additionally, there was an inverse correlation between the pre-operative arterial pH and the thalamic FA and a trend of the same in the optic radiations, which was unexpected. This may be a function of a sicker premature neonate who is being over-ventilated, perhaps acutely due to vigorous resuscitation. Or, it may be due to more chronic management attempting to maintain stability while trying to delay cardiac repair in a small baby such as aggressive diuretic therapy or over-ventilating in making an effort to achieve a normal pH in the face of evolving metabolic acidosis due to hypoperfusion resulting from the cardiac lesion. Due to cerebral vasoregulation, low carbon dioxide levels lead to vasoconstriction in the brain. In the premature brain, there is not much vasculature extending to the white matter, which may explain why the greatest effect of elevated pH was seen in the thalamus. Or, perhaps it is because the thalamus is a very active region of development during this time period as thalamocortical projections are extending through this region and are affected.

Perhaps the critical structure that deserves more attention in the preterm CHD individual's brain development is the subplate. The subplate is the origin of many cortical synapses and is critical for the development of cortical thalamic development [30]. By the late preterm period, most corticothalamic connections have been made and corticocortical pathways are still being established [30]. Subplate neurons have been demonstrated to result in cortical visual impairment and they are known to be vulnerable to hypoxia/ischemia [20]. It is generally accepted that these neurons are helpful for working around areas of damage and they typically involute by 34 weeks of gestation [30]. It is plausible that in preterm CHD neonates who have likely delayed brain maturation by an average four weeks [27], a significant insult to their developing brain that affects the subplate could disrupt/delay crucial thalamocortical connections from being established. Such deficits could explain, in part, the neurodevelopmental challenges faced by children with CHD [33].

Limitations

It could be suggested that we should have focused on the complex cyanotic heart lesions and excluded infants with other lesions such as ASD and VSD due to marked differences in the hemodynamics in these neonates both in utero and postnatally [34]. However, the incidence of complex CHD among preterm infants is relatively rare and we did not have sufficient

sample size to study individual lesions. A second limitation in this study is the inclusion of cases with MRI scans performed preoperatively and postoperatively, with the majority of the scans being performed postoperatively. Because the post-operative status cannot tease out the innate effects of brain microstructural maldevelopment versus those therapeutically influenced (bypass, timing of surgery, etc), the demonstrates microstructural changes may be the beginning or the evolution of aberrant development. Third, there is the potential for sampling bias as we relied on clinical scans to identify our neonates prior to study inclusion. Additionally, it would have been interesting to look at the correlation of initial blood gas findings in the non-CHD premature group in relation to their microstructural findings. However, these data were not available as these babies were not inborn. Lastly, our comparison groups were also critically ill neonates and not truly normal controls, who were found to have structurally normal brains on screening studies.

Conclusion

Our study provides evidence that preterm neonates with CHD demonstrate DTI-metric age-related microstructural abnormalities in the thalamus when compared to other critically ill neonates without CHD. In addition, perinatal hyperoxemia and elevated preoperative pH appear to be predictive of abnormal thalamic microstructure in preterm neonates with CHD. This study emphasizes the vulnerability of thalamo-cortical development in the preterm neonate with CHD.

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Abbreviation List

CHD	congenital heart disease
NICU	neonatal intensive care unit
ASD	atrial septal defect
VSD	ventricular septal defect
HLHS	hypoplastic left heart syndrome
TGA	transposition of the great arteries
DORV	double outlet right ventricle
FA	fractional anisotropy
RD	radial diffusivity
AD	axial diffusivity

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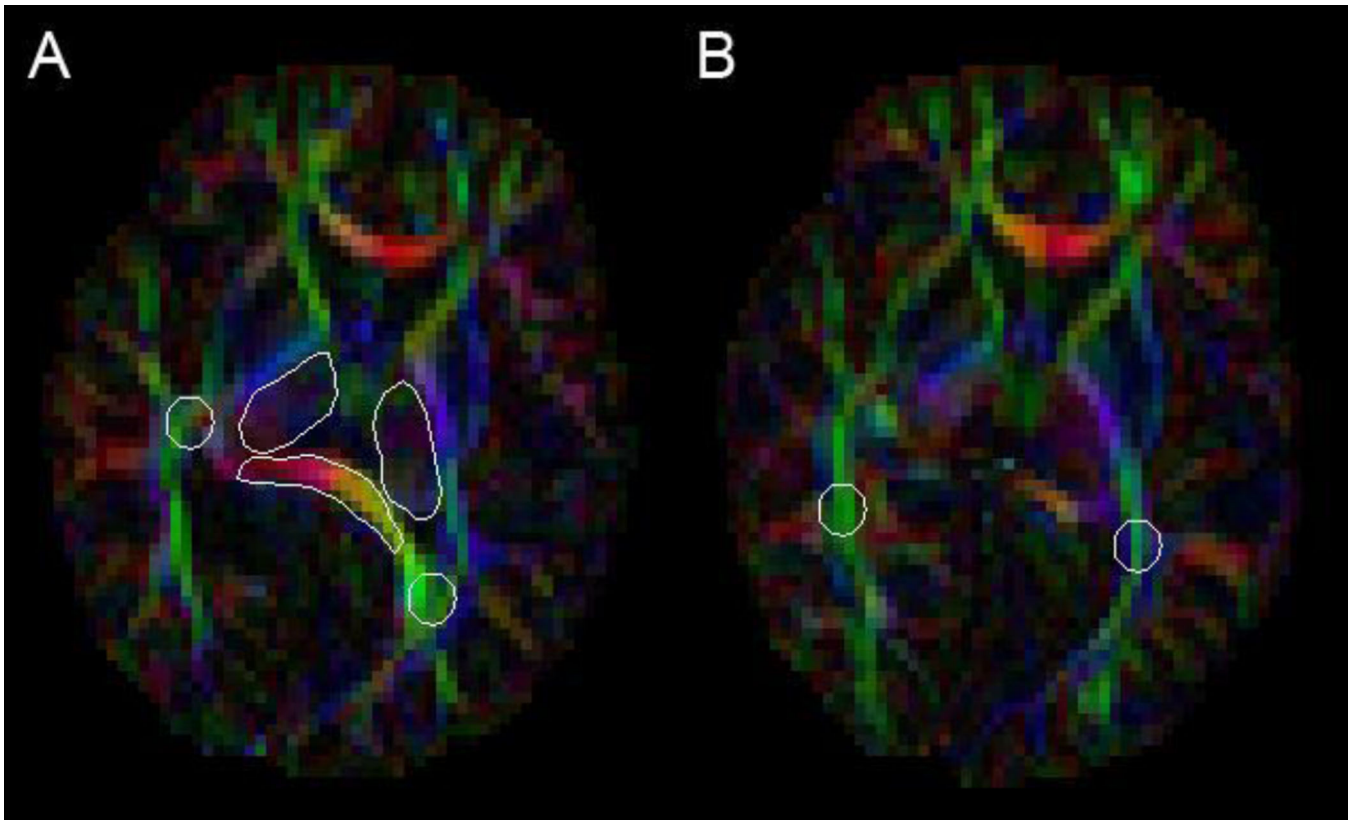

Figure 1.
ROI placement: Image A: Thalamus (darker outilined region), Splenium (yellow and red outlined region), Parietal WM (green outlined region); Image B: Optic Radiations

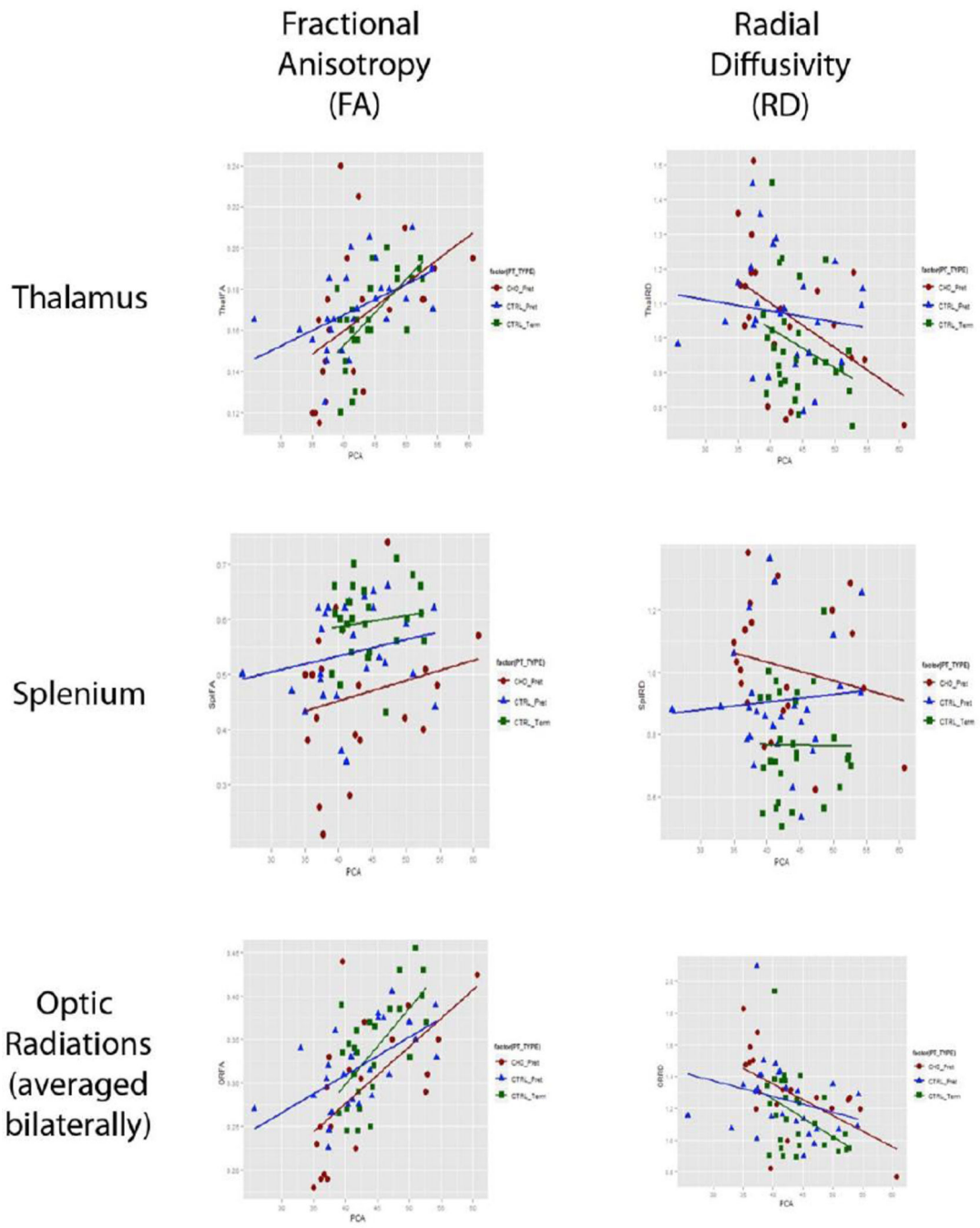

Figure 2.

Age-interaction graphs: Fractional Anisotropy and Radial Diffusivity measurements in Thalamus, Splenium, and Optic Radiations correlating to Gestational Age (weeks) at time of MRI on x-axis. Preterm CHD—Red, Preterm Non-CHD—Blue, Term Non-CHD—Green.

Table 1

Comparison of Clinical Variables Among Preterm CHD cases and High Risk Term Non-CHD and Preterm Non-CHD Groups

		Preterm CHD group (n=21)	**Term Comparison Group (n=28)**	**Preterm Comparison Group (n=27)**	***p* value (all groups)**
GA (weeks)	mean (SD)	32.2(3)	39.8 (0.9)	30.7 (4.6)	0.000
PNA at MRI (weeks)	mean (SD)	11.5 (9)	4.7 (3.9)	11.1 (8.4)	0.009
PCA at MRI (weeks)	mean (SD)	43.7 (8)	44.4 (4.2)	42.6 (6.5)	0.585
Apgar 1 min	median (n)	7 (19)	8 (9)	6 (21)	0.037
Apgar 5 mins	median (n)	8 (19)	9 (9)	8 (21)	0.086
Apgar 10 mins	median (n)	7 (3)	− (0)	7 (3)	0.406
Size for GA	Small: %	35	14	8	0.0001
	Appropriate: %	59	81	84	
	Large:%	6	5	8	
ISAM	% (n)	0 (10)	0 (18)	8.3 (24)	0.08
Postnatal Sepsis	% (n)	67 (42)	14.8 (27)	62.5 (24)	0.001
Hydrocortisone	% (n)	28 (18)	10.7 (28)	18.5 (27)	0.188
Days on Hydrocortisone	mean (SD)	1.33 (4.68)	0.6 (1.9)	1.7 (6.1)	0.770
Inotropes	% (n)	72 (18)	17.9 (28)	46.2 (26)	0.000
Days on Dopamine	mean (SD)	3.78 (4.4)	1.3 (3.2)	3.8 (6)	0.073
NEC	% (n)	28 (18)	3.6 (28)	19.2 (26)	0.061

CHD= Congenital heart disease; GA= gestational age at birth; PNA=Postnatal age; PCA=post-conceptional age (calculated as GA plus PNA); ISAM=Infant of Substance-Abusing Mother NEC=Necrotizing Enterocolitis

Exposure to hydrocortisone and/or inotropes includes immediately pre- and post-operatively
Sepsis and NEC includes the entire hospitalization from birth until first discharge

Table 2

Preterm CHD Cases: Frequency of Diagnoses

Heart Defects	**n=21**
Hypoplastic Left Heart Syndrome	5
Ebstein's Anomaly	2
Coarctation of the aorta	3
Transposition of the Great Arteries	2
Atrial Septal Defect and Ventricular Septal Defect, and/or Patent Ductus Arteriosus requiring surgery	8
Double Outlet Right Ventricle	1

TABLE 3

DTI-Manual ROI-based results comparing Preterm CHDs with High Risk Term Non-CHD and Preterm Non-CHD Comparison Groups

		Preterm	Term	Preterm CHD	
		n=27 mean (SD)	n=28 mean (SD)	n=21 mean (SD)	p *
Peripheral White Matter					
Parietal**	FA	.17 (.06)	.18 (.05)	.17 (.06)	.948
	RA	.14 (.05)	.15 (.04)	.14 (.06)	.953
	Axial	1.95 (.33)	1.80 (.35)	1.91 (.40)	.378
	Radial	1.52 (.33)	1.39 (.31)	1.49 (.38)	.492
	ADC	1.67 (.33)	1.53 (.32)	1.63 (.38)	.475
Optic	FA	.32 (.05)	.34 (.06)	.29 (.08)	# .045
Radiation**	RA	.27 (.04)	.29 (.05)	.25 (.07)	# .032
	Axial	2.07 (.32)	1.95 (.34)	2.05 (.32)	.387
	Radial	1.26 (.24)	1.15 (.24)	1.30 (.26)	.162
	ADC	1.53 (.26)	1.41 (.26)	1.54 (.26)	.243
Deep White Matter					
Splenium	FA	.54 (.09)	.59 (.07)	.46 (.12)	## .00001
	RA	.50 (.10)	.57 (.08)	.42 (.13)	## .00003
	Axial	2.32 (.34)	2.20 (.34)	2.23 (.35)	.615
	Radial	.91 (.20)	.77 (.17)	1.02 (.22)	## .00008
	ADC	1.38 (.22)	1.24 (.21)	1.42 (.21)	# .012
Gray Matter					
Thalamus**	FA	.17 (.02)	.17 (.02)	.16 (.03)	.716
	RA	.14 (.02)	.14 (.02)	.14 (.02)	.624
	Axial	1.36 (.20)	1.23 (.19)	1.34 (.21)	# .042

		Preterm	Term	Preterm CHD	
		n=27 mean (SD)	n=28 mean (SD)	n=21 mean (SD)	p *
	Radial	1.07 (.16)	.98 (.16)	1.07 (.18)	.066
	ADC	1.17 (.17)	1.07 (.18)	1.16 (.19)	.063

* ANOVA

** Measurements are average of L and R readings

p-value ≤ 0.05 significant

Tukey's Pairwise Comparisons:

Term controls significantly different from CHD's. 2 other pairwise comparisons (term controls vs. preterm controls, preterm controls vs. CHD's) non-significant

CHD's significantly different from both preterm and term controls. Pairwise comparison of preterm and term controls non-significant

Table 4

Correlations between DTI metrics and Preterm CHD Clinical Variables

		FA	AD	RD	ADC
NEC	Splenium	0.08	−0.142	−0.157	−0.226
	Parietal WM	−0.106	−0.269	−0.189	−0.223
	Thalamus	0.172	−0.329	−0.347	−0.349
	Optic Rad	0.149	−0.089	−0.152	−0.128
Ist ABG pH	Splenium	0.285	−0.020	−0.428	−0.333
	Parietal WM	−0.002	0.015	0.013	0.011
	Thalamus	0.025	0.001	−0.007	−0.007
	Optic Rad	0.203	0.181	0.105	0.169
1st ABG pO2	Splenium	0.296	0.883	0.374	0.740
	Parietal WM	−0.22	0.810	0.831	0.824
	Thalamus	−0.035	0.846	0.746	0.783
	Optic Rad	0.453	0.936	0.935	0.944
Adm ABG pH	Splenium	−0.017	0.075	−0.009	−0.054
	Parietal WM	0.398	0.047	−0.129	−0.068
	Thalamus	−0.055	0.298	0.279	0.275
	Optic Rad	0.194	0.209	0.028	0.102
Adm ABG pO2	Splenium	−0.16	−0.141	−0.006	−0.107
	Parietal WM	0.416	−0.173	−0.323	−0.275
	Thalamus	0.143	−0.104	−0.125	−0.113
	Optic Rad	0.187	0.172	0.022	0.072
Pre-op ABG pH	Splenium	−0.114	0.084	0.211	0.225
	Parietal WM	0.034	0.336	0.258	0.287
	Thalamus	−0.600	0.249	0.315	0.328
	Optic Rad	−0.429	−0.112	0.149	0.041
Pre-OP ABG pO2	Splenium	0.121	0.331	0.241	0.248
	Parietal WM	0.436	0.314	0.14	0.208
	Thalamus	0.012	0.348	0.315	0.328

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		FA	AD	RD	ADC
	Optic Rad	0.166	0.418	0.323	0.385
Post-OP ABG pH	Splenium	0.107	−0.060	−0.262	−0.241
	Parietal WM	−0.103	0.104	0.079	0.085
	Thalamus	−0.140	0.153	0.166	0.164
	Optic Rad	0.138	0.225	0.600	0.134
Post-OP ABG pO2	Splenium	0.013	0.225	0.090	0.216
	Parietal WM	0.208	0.161	0.063	0.098
	Thalamus	−0.021	0.324	0.300	0.300
	Optic Rad	0.156	0.302	0.107	0.183

Table 5

Study Group Comparisons of DTI Metric Correlations with Gestational Age

		Fractional Anisotropy			Radial Diffusivity		
		Correlation	***p*−value**	**Interaction by group**	**Correlation**	***p*−value**	**Interaction by group**
Thal	**Preterm CHD**	**0.482**	**0.027**	p< 0.68	−0.486	0.026	p<0.49
	Preterm	**0.488**	**0.0097**		−0.129	0.520	
	Term	**0.644**	**.0002**		−0.307	0.111	
Splen	**Preterm CHD**	0.220	0.338	p<0.62	−0.213	0.352	p<0.80
	Preterm	0.212	0.288		0.082	0.686	
	Term	0.133	0.500		0.010	0.959	
Optic Rad	**Preterm CHD**	**0.628**	**0.003**	p<0.63	**−0.587**	**0.007**	p<0.32
	Preterm	**0.587**	**0.001**		−0.269	0.175	
	Term	**0.643**	**0.0002**		**−0.423**	**0.025**	

Correlations significantly different from 0 are in BOLD. Thal=thalamus; Splen=Splenium; Optic Rad=Optic Radiations