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Aberrant brain functional connectivity in newborns with congenital heart disease before cardiac surgery

Josepheen De Asis-Cruz[a], Mary T. Donofrio[b], Gilbert Vezina[a], Catherine Limperopoulos[a,*]

[a] Division of Diagnostic Imaging and Radiology, Children's National Health System, Washington, D.C. 20010, USA
[b] Division of Cardiology, Children's National Health System, Washington, D.C. 20010, USA

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ABSTRACT

Newborns with congenital heart disease (CHD) requiring open heart surgery are at increased risk for neurodevelopmental disabilities. Recent quantitative MRI studies have reported disrupted growth, microstructure, and metabolism in fetuses and newborns with complex CHD. To date, no study has examined whether functional brain connectivity is altered in this high-risk population after birth, before surgery. Our objective was to compare whole-brain functional connectivity of resting state networks in healthy, term newborns (n = 82) and in term neonates with CHD before surgery (n = 30) using graph theory and network-based statistics. We report for the first time intact global network topology – efficient and economic small world networks – but reduced regional functional connectivity involving critical brain regions (i.e. network hubs and/or rich club nodes) in newborns with CHD before surgery. These findings suggest the presence of early-life brain dysfunction in CHD which may be associated with neurodevelopmental impairments in the years following cardiac surgery. Additional studies are needed to evaluate the prognostic, diagnostic and surveillance potential of these findings.

1. Introduction

Congenital heart disease (CHD) affects brain development across the lifespan. While long-term survival after neonatal cardiac surgery has dramatically improved, the risk for neurodevelopmental impairments remain largely unchanged (Gaynor et al., 2015). Neurodevelopmental disabilities affect over 50% (McQuillen et al., 2007) of surviving infants with CHD and involve multiple domains, including motor function, learning, social behavior, and executive function (Donofrio and Massaro, 2010; Marelli et al., 2016). Early studies proposed intraoperative procedures, such as prolonged cardiopulmonary arrest time (Bellinger et al., 1995; Hövels-Gürich et al., 2002) and the cardiac bypass procedure itself (Newman et al., 2001), as major risk factors for brain injury in CHD. While these factors may contribute to future neurologic impairment, neurobehavioral evaluation in newborns with CHD before open heart surgery have demonstrated neurologic dysfunction in more than half of infants (Limperopoulos et al., 1999, 2002). Notably, these pre-operative findings have been found to be important independent baseline predictors for later neurodevelopmental dysfunction. Recently, advanced neuroimaging studies have provided further evidence for delayed brain growth and structural brain injury in CHD infants before surgery (Clouchoux et al., 2013; Limperopoulos et al., 2010; Miller et al., 2007) providing accruing evidence for the origin and evolution of brain dysfunction in this high-risk group.

Magnetic resonance imaging (MRI) has played a pivotal role in advancing our understanding of the onset, progression and mechanisms of brain injury in CHD. Conventional MRI studies have reported clinically-silent white matter lesions in newborns CHD before surgery, akin to those observed in premature brains (Miller et al., 2004). More importantly, advanced, quantitative MRI approaches such as magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) have revealed alterations in biochemistry and microstructure in CHD when there are none evident on conventional MRI. Specifically, MRS has revealed decreased *N*-acetylaspartate (NAA) and the presence of lactate, suggesting neuronal loss and increased anaerobic metabolism, respectively (Miller et al., 2007). In contrast to focal white matter injury detected on conventional MRI, DTI has revealed diffuse white matter injury (reduced fractional anisotropy, FA), a finding consistent with the wide spectrum of neurodevelopmental abnormalities seen in surviving infants with CHD. More recently, in utero quantitative MRI studies in CHD fetuses provides further support for third trimester disturbances in brain growth, alterations in cortical gyrification and sulcation, as well as impaired cerebral metabolism (Clouchoux et al., 2013; Limperopoulos et al., 2010).

However, the extent to which alterations in brain structure and

* Corresponding author at: Children's National Health System, 111 Michigan Ave. N.W., Washington, D.C. 20010, USA.
E-mail address: climpero@childrensnational.org (C. Limperopoulos).

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metabolism in CHD are accompanied by brain circuitry dysfunction has yet to be explored. In this study, we used resting state functional connectivity MRI (rs-fcMRI) to compare brain connectivity in neonates with CHD before open heart surgery to full-term healthy control newborns. Resting state functional connectivity MRI provides critical insights into brain function by detecting temporal correlations between intrinsic, low frequency fluctuations of blood oxygen level dependent (BOLD) signals from different areas of the brain (Biswal et al., 1995). Neuropsychiatric disorders (i.e. autism spectrum disorder, attention deficit hyperactivity disorder, and schizophrenia), have been linked with disrupted large-scale network organization defined by rs-fcMRI and clinical measures of disease severity (Itahashi et al., 2014; Lynall et al., 2010) or presence/absence of disease (Moseley et al., 2015). In addition, we and others have described the organization of resting state networks in healthy, term newborns (De Asis-Cruz et al., 2015; Fransson et al., 2011; Gao et al., 2011). In this study, we used rs-fcMRI to characterize functional network organization in the developing CHD brain. To the best of our knowledge, this is the first rs-fcMRI study to examine the effects of CHD on brain function after birth, before open heart surgery. We hypothesized that newborns with CHD with no evidence of structural brain injury on conventional MRI would demonstrate connectivity disturbances involving multiple brain regions, akin to the diffuse white matter changes observed with DTI. To test this hypothesis, we used two complementary approaches. First, we characterized global, intermediate and local network organization in CHD compared to control networks using graph theoretic techniques. Second, we used network-based statistics (NBS) to delineate whole-brain simple functional connectivity, evaluating temporal correlations between BOLD signals from regions of interest (ROIs).

2. Materials and methods

2.1. Subjects

We acquired T2-weighted and resting state EPI data from 138 term neonates – 43 with CHD before open-heart surgery and 95 healthy controls – as part of an ongoing prospective observational study examining brain growth and development in fetuses and newborns with complex CHD. See Supplementary Table 1 for exclusion criteria. Resting state data from 23 newborns, 10 CHD and 13 controls, were excluded from further analysis for failing initial quality checks (see Preprocessing of functional images). Conventional MRI scans of the remaining 115 infants, were reviewed by an expert pediatric neuroradiologist (G.V.) who was blinded to group (CHD vs control) and clinical course of CHD infant. Data from three subjects were excluded. Two CHD newborns had parenchymal brain injury before cardiac surgery, specifically cerebellar punctate hemorrhage (1) and a small infarct in the left striatum and posterior limb of the internal capsule (1); one had cerebellar hypoplasia. The remaining 30 CHD and 82 control newborns had structurally normal brain MRI scans and underwent rs-fcMRI analyses. Neonates with CHD were delivered and scanned earlier compared to controls, had lower birth weights and lower APGAR scores at 1 and 5 min ($p < 0.05$ for all). The APGAR score is a means for rapidly assessing a newborn's health; it stands for **A**ppearance (skin color), **P**ulse (heart rate), **G**rimace (reflex irritability), **A**ctivity (muscle tone), and **R**espiration. Table 1 details characteristics of cohorts.

Parental informed consent was obtained for all newborns prior to the study. This study was approved by the Institutional Review Board (IRB) of the Children's National Health System. All experiments were performed in accordance with the regulations and guidelines of the Children's National Health System IRB.

2.2. Data acquisition

All MRI data were acquired using a 3 T GE scanner (Discovery MR750, GE Healthcare, Milwaukee, WI) using an 8-channel infant head coil. Prior to scanning, infants were fed, swaddled in a warm blanket, immobilized using an infant vacuum pillow, and provided ear protection using silicone ear plugs and adhesive ear muffs. Their physiologic state (i.e. heart rate and oxygen saturation) was monitored by a nurse throughout the scan. All control newborns were scanned unsedated while three CHD neonates were sedated during their preoperative scan. All infants (controls and CHD) underwent the exact same MRI protocol. Specifically, anatomical T2-weighted fast spin echo images were collected with the following parameters: TR = 2000 ms, TE = 64.49 ms, and voxel size = 0.625 × 1 × 0.625 mm. Resting state data were obtained using a T2-weighted gradient-echo planar imaging (EPI) sequence with parameters TR = 2000 ms, TE = 35 ms, voxel size = 3.125 × 3.125 × 3 mm, flip angle = 60°, field of view = 100 mm, and matrix size = 64 × 64. A total of 200 volumes - 6 min and 40 s of data - were collected. To achieve whole brain coverage, around 34 slices (range = 31–36), without slice gap, were obtained per subject.

Table 1
Demographic and clinical characteristics of cohorts.

	Control n = 82	CHD n = 30	*p* value[a]
Male sex (n)	44	17	0.8
GA at birth (wk)			0.002
Median	39.6	39	
Interquartile range	38.9–40.3	38.3–39.4	
PMA at preoperative MRI (wk)			8.9×10^{-12}
Median	41.5	39.4	
Interquartile range	40.7–42.1	38.9–39.7	
Birth weight (g)[b]			0.0502
Median	3337	3119	
Interquartile range	3070–3620	2940–3463	
APGAR score at 1 min[c]			0.003
Median	8	8	
Interquartile range	8–9	8–8	
APGAR score at 5 min (n)[c]			2.2×10^{-6}
Median	9	9	
Interquartile range	9–9	8–9	
Cardiac lesion			
Single-ventricle defects (n)			
Hypoplastic left heart syndrome	–	10	–
Two-ventricle physiology (n)			
Transposition of the great vessels	–	7	–
Double outlet right ventricle	–	4	–
Atrioventricular septal defect	–	3	–
Coarctation of the aorta	–	2	–
Tetralogy of Fallot	–	1	–
Ventricular septal defect	–	1	–
Pulmonary atresia	–	1	–
Ebstein's anomaly	–	1	–
Preoperative mechanical ventilation	–	15	–
Lowest pH prior to MRI[d]			
Median	–	7.32	–
Interquartile range	–	7.29–7.35	–
Lowest pO_2 prior to MRI (mm Hg)[d]			
Median	–	34.1	–
Interquartile range	–	28.1–42.4	–
Highest pCO_2 prior to MRI (mm Hg)[d]			
Median	–	38.9	–
Interquartile range	–	35–46	–
Lowest O_2 saturation prior to MRI (%)[d]			
Median	–	62.5	–
Interquartile range	–	51.3–70	–

[a] All Between-group comparisons, except for gender done using Mann-Whitney *U* Test; sex comparison performed using (Fisher's exact test).
[b] Birthweight not available for 1 control newborn; missing data replaced with median birth weight for the control cohort.
[c] Apgar scores not available for 5 controls; Apgar at 5 min not available for 1 CHD neonate.
[d] Pre-operative lowest pH, pO_2, pCO_2 and O_2 saturation levels not available for 5 CHD neonates; pO and O_2 saturation levels not available for two subjects.