Neonatal frontal-limbic connectivity is associated with externalizing behaviours in toddlers with Congenital Heart Disease

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**A B S T R A C T**

Children with Congenital Heart Disease (CHD) are at increased risk of neurodevelopmental impairments. The neonatal antecedents of impaired behavioural development are unknown. 43 infants with CHD underwent presurgical brain diffusion-weighted MRI (postmenstrual age at scan median (IQR) = 39.29 (38.71–39.71) weeks) and a follow-up assessment at median age of 22.1 (IQR 22.0–22.7) months in which parents reported internalizing and externalizing problem scores on the Child Behaviour Checklist. We constructed structural brain networks from diffusion-weighted MRI and calculated edge-wise structural connectivity as well as global and local brain network features. We also calculated presurgical cerebral oxygen delivery, and extracted peripherative variables, socioeconomic status at birth and a measure of cognitively stimulating parenting. Lower degree in the right inferior frontal gyrus (partial \( \rho = -0.687, p < 0.001 \)) and reduced connectivity in a frontal-limbic sub-network including the right inferior frontal gyrus were associated with higher externalizing problem scores. Externalizing problem scores were unrelated to neonatal clinical course or home environment. However, higher internalizing problem scores were associated with earlier surgery in the neonatal period (partial \( \rho = -0.538, p = 0.014 \)). Our results highlight the importance of frontal-limbic networks to the development of externalizing behaviours and provide new insights into early antecedents of behavioural impairments in CHD.

**1. Introduction**

Congenital heart disease (CHD) occurs in up to 1 % of births (EUROCAT, 2015). Over 90 % of infants with CHD survive into adulthood (Wren and Sullivan, 2001), yet survivors are at increased risk of difficulties across several domains including executive functioning, cognition, and internalizing and externalizing behaviors (Clancy et al., 2020; Feldmann et al., 2021; Marino et al., 2012). These difficulties may persist into adolescence (Bellinger et al., 2011) and adulthood (Klouada et al., 2017) and have a prolonged impact on quality of life (Dewey and Volkovinskaia, 2018) and educational achievement (Lawley et al., 2019). As such, understanding the mechanisms underpinning impaired neurodevelopment in survivors of CHD is critical.

MRI studies have identified both acquired brain lesions (Beca et al., 2013; Kelly et al., 2019a; Miller et al., 2007; Stegeman et al., 2021) and impaired brain development in infants with CHD. In particular, brain volumes are reduced (Bouyssi-Kobar et al., 2012; Limperopoulos et al., 2010; Ng et al., 2020; von Rhein et al., 2015) and development of the

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cortex is impaired compared to healthy controls (Kelly et al., 2017; Kelly et al., 2019b). The degree of altered early brain development is associated with reductions in cerebral oxygen delivery (CDO2) (Kelly et al., 2017; Kelly et al., 2019b; Sun et al., 2015).

Recently, studies have reported neonatal neuroimaging correlates of impaired cognition in children with CHD. In early childhood, lower cognition has been associated with reduced cortical and cerebellar volumes (Meuwly et al., 2019) and dilated CSF spaces (Heye et al., 2018; Knirsch et al., 2017) after surgery. 6 year old children with CHD and IQ scores below 85 also had lower postoperative neonatal basal ganglia, thalamus and brainstem volumes compared with survivors with higher IQ scores (Claessens et al., 2018). In addition, we have previously shown that reduced CDO2 is indirectly associated with lower cognitive scores in early childhood through the mediating effect of impaired presurgical neonatal deep grey matter development (Bonthrone et al., 2021a). Diffusion MRI (dMRI) has been used to investigate both brain development in neonates (Claessens et al., 2019; Karmacharya et al., 2018; Kelly et al., 2019b; Mulkey et al., 2014) and neural correlates of cognitive abilities in adolescents and adults (Brewster et al., 2015; Ehler et al., 2020, 2021; Rollins et al., 2014) with CHD. However, the neonatal dMRI correlates of childhood outcomes and the neonatal neuroimaging correlates of internalizing and externalizing symptoms in CHD have yet to be fully characterized.

Graph theory encompasses a set of analyses designed to describe global and local organizational properties of brain networks extracted from MRI data (Bullmore and Sporns, 2009). In infants with CHD, reduced functional connectivity in a cortico-subcortical sub-network (de Asis-Cruz et al., 2018) and altered structural network topology (Schmithorst et al., 2018) have been reported before surgery as well as reduced network integration and greater network segregation pre- and postoperatively (Feldmann et al., 2020). We have previously reported intact global network topology but reduced structural brain connectivity in a sub-network encompassing the cerebellum, deep grey matter, temporal lobe and parieto-occipital regions before surgery, compared to healthy controls (Ni Bhroin et al., 2020). In a mixed cohort of infants with CHD and those with hypoxic-ischemic encephalopathy, reduced neonatal global efficiency, a measure of network integration, was associated with poorer motor abilities at 30 months (Ramirez et al., 2022). Graph theoretical approaches have been used to describe changes in global and local brain networks associated with internalizing disorders such as depression and anxiety (Ely et al., 2021), externalizing disorders such as ADHD (Bare et al., 2017; Li et al., 2021), and internalizing and externalizing behaviors in children born prematurely (Gilchrist et al., 2022). However, to our knowledge no study has characterized the relationship between neonatal brain network organization and behavioral outcomes in children with CHD.

In this study we aimed to investigate the relationship between neonatal presurgical global and local structural network features extracted from multi-shell diffusion MRI, clinical and environmental measures, and behavioral outcomes at 22 months in infants with CHD, pulmonary atresia with an intact ventricular septum, transposition of the great arteries (TGA) and all infants requiring surgery within the first 28 days of life with the following conditions: aortic stenosis, coarctation of the aorta (CoA), pulmonary stenosis, pulmonary atresia with ventricular septal defect, tetralogy of Fallot (TOF) and total anomalous pulmonary venous connection. Serious CHD was defined as any cardiac lesion not defined as critical, which requires cardiac catheterization or surgery between 1 month and 1 year of age. Infants were categorized into abnormal streaming of blood, left-sided heart abnormalities and right-sided heart abnormalities according to the haemodynamic impact of their anatomy using the sequential segmental approach (Anderson et al., 1984). Exclusion criteria included suspected or confirmed chromosomal abnormality or congenital syndrome, previous neonatal surgery before recruitment (excluding cardiac catheterization procedures) or suspected congenital infection (Kelly et al., 2019a).

2.3. MRI acquisition

Brain MRI was performed during natural sleep on a Philips (Best, Netherlands) 3 Tesla system situated in the neonatal intensive care unit at St. Thomas’ Hospital using a 32-channel neonatal head coil and neonatal positioning device (Hughes et al., 2017). Earplugs moulded from silicone-based putty were placed in the external auditory meatus (President Putty, Coltene Whaledent, Mahwah, NJ), followed by neonatal earmuffs (MiniMuffs, Natus Medical Inc, San Carlos, CA) and an acoustic hood placed over the infant. Scanning was supervised by a paediatrician trained in MR procedures and pulse oximetry, temperature, electrocardiography, and respiratory rate were monitored throughout.

T1-weighted (magnetisation prepared rapid gradient echo, repetition time (TR)/echo time (TE) 11.46/6 ms, flip angle 9°, voxel size 0.8 mm3), T2-weighted (multislice turbo spin echo TR/TE 1200/156 ms, in-plane resolution 0.8 × 0.8 mm, slice thickness 1.6 mm, 0.8 mm overlap) and susceptibility-weighted imaging (TR/TE 3200/25 ms, flip angle 12°, voxel size 0.45 × 0.45 × 1.8 mm) were acquired. dMRI was acquired with a high angular resolution diffusion multi-shell protocol designed for the neonatal brain (TR/TE 3800/90 ms, multiband factor 4, sensitivity encoding in-plane acceleration factor 1.2, in-plane resolution 1.5 × 1.5 mm, slice thickness 3 mm, 1.5 mm overlap, 300 volumes, diffusion gradient encoding: b = 0 s/mm2 (n = 20), b = 400 s/mm2 (n = 64), b = 1000 s/mm2 (n = 88), b = 2600 s/mm2 (n = 128) with 4x interleaved phase encoding) (Hutter et al., 2018). Quantitative flow imaging was acquired using velocity sensitized phase contrast angiography (PCA) with a single-slice T1-weighted fast field echo sequence (TR/TE 6.4/4.3 ms, flip angle 10°, repetitions 20, velocity encoding 140 cm/s, field of view 100 × 100 mm, resolution 0.6 × 0.6 × 4.0 mm) (Varela et al., 2012). PCA was available in 37 infants (not acquired due to infant waking N = 3; unsuitable for analysis N = 3).

2.4. MR image review

All images were reviewed by two perinatal neuroradiologists and lesions were recorded as white matter injury (WMI), cerebellar hemor rhage or intraventricular haemorrhage as reported previously (Kelly et al., 2019a). WMI was classified into normal (no injury), mild (≤3 foci and all ≤2 mm), moderate (>3 and ≤10 foci or any >2 mm) or severe (>10 foci) (Kelly et al., 2019a).

Overall, each infant was categorized into two brain injury groups: normal/mild (mild: intraventricular haemorrhage, and/or cerebellar hemorrhage ≤2 mm, and/or mild WMI) and moderate/severe (moderate: cerebellar hemorrhage >2 mm and/or moderate WMI; severe: severe WMI) (Bonthrone et al., 2021b; Kelly et al., 2019a). Brain injury ratings are summarized in Table 2.
2.5. MRI pre-processing

T2-weighted images acquired in the axial and sagittal plane underwent motion correction and reconstruction to a 0.5 mm grid (Cordero-Grande et al., 2018), dMRI underwent parallel imaging reconstruction, denoising (Cordero-Grande et al., 2019; Varga et al., 2016), Gibbs ringing artefact suppression (Kellner et al., 2016), and correction for motion and image distortion using Spherical Harmonics and Radial Decimation reconstruction to a 1.5 mm grid (Christiaens et al., 2021).

2.6. Structural network construction

Reconstructed T2-weighted images were bias field corrected (Tustison et al., 2010), brain extracted (Smith, 2002), and segmented into tissue classes [grey matter, white matter, extracerebral cerebral spinal fluid (CSF), ventricles, deep grey matter, brainstem, hippocampus and amygdala, and cerebellum] using an automatic neonatal-specific segmentation algorithm that employs expectation maximization (Makropoulos et al., 2014, Makropoulos et al., 2018).

A neonatal adaptation (Shi et al., 2011) of the automated anatomical labelling (AAL) parcellation (Tzourio-Mazoyer et al., 2002) consisting of 93 cortical, subcortical and cerebellar regions was registered to each infant’s T2-weighted image using the diffeomorphic symmetric image normalization method in Advanced Normalization Tools (Avants et al., 2011). Each infant’s tissue maps and parcellations were registered to their dMRI (average B = 0 vol as the target) using rigid registration in the Image Registration Toolkit (Studholme et al., 1999).

Orientation distribution functions (ODFs) for tissue and free water were estimated using multi-shell multi-tissue constrained spherical deconvolution in MRtrix3 (Jeurissen et al., 2014; Tournier et al., 2019), with fixed tissue response functions for white matter and CSF (Pietsch et al., 2019) averaged from control infants imaged using the same protocol (used in Ni Bhrion et al, see (Ni Bhrion et al., 2020) for details). ODFs were normalized to obtain quantitative measures (Dohllander et al., 2021; Raffelt et al., 2017; Tournier et al., 2019). Probabilistic tractography was used to generate 10 million streamlines from the tissue ODFs with anatomically constrained probabilistic tractography (Smith et al., 2012) and biologically accurate weights (SIFT2) (Smith et al., 2015; Tournier et al., 2019). Structural connectivity networks were constructed for each infant with regions of the AAL parcellation as nodes and sum of SIFT2-weighted streamlines connecting each region as edges.

2.7. Graph theory feature extraction

Graph theory features were calculated using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) in Matlab R2020b. Network infrastructure was assessed with network density defined as the proportion of observed edges out of all possible edges (Kaiser, 2011) and nodal strength defined as the sum of edge weights connected to a node. Average nodal strength was also calculated. Network integration was assessed with global efficiency defined as the inverse of the average shortest path length between nodes (Achard et al., 2007) and nodal degree defined as the number of connections linking each node to the rest of the network. Network segregation was assessed with nodal efficiency, defined for each node as the inverse of the average shortest path length connecting all neighbours of that node; and local efficiency, defined as the average nodal efficiency across all nodes of the network (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

Variance in network features may be confounded by differences in network density between infants. In order to adjust for this effect, we employed a cost-correction approach (Achard et al., 2007; Bataille et al., 2017). For each infant, a series of networks were created by thresholding original reconstructed networks to set densities from 0.05 to 0.5 increasing in 0.01 steps (proportional thresholding). Nodal strength, nodal degree as well as global, local and nodal efficiency were extracted at each network density and averaged across the range of cost corrections, resulting in a “cost-corrected” measure of each feature (Bataille et al., 2017; Ginestet et al., 2011).

We partitioned nodes in structural networks into two distinct groups corresponding to a core and periphery structure using an adapted version of the Kernighan-Lin algorithm for graph partitioning (Borgatti and Everett, 2000; Newman, 2006) as we have previously in a larger group of infants with CHD and controls (Ni Bhrion et al., 2020). In keeping with previously published results (Ni Bhrion et al., 2020), nodes partitioned into 34 core and 59 peripheral regions (Supplementary Table 1). Edges were characterized as core (connecting core nodes), peripheral (connecting peripheral nodes) or feeder (connecting a core and a peripheral node).

2.8. Cerebral oxygen delivery

Cerebral blood flow was quantified from phase-contrast angiography using previously published methods (Kelly et al., 2017; Kelly et al., 2019b).

2.8.1. Neurodevelopmental assessment

All infants attended a follow-up assessment at a median (IQR) age of 22.10 (21.95–22.36) months. Infants completed the Bayley Scales of Infant and Toddler Development–Third Edition (Bayley, 2006) administered by a developmental paediatrician to obtain cognitive composite scores [test mean (SD) = 100 (15)]. In addition, parents completed the Child Behavior Checklist (CBCL) 1.5–5 questionnaire (Achenbach and Rescorla, 2000) and internalizing (comprised of emotionally reactive, anxious/depressed, somatic complaints and withdrawn subscales) and externalizing (comprised of attention problems and aggression subscales) raw problem scores and T-scores [test mean (SD) = 50 (10)] were calculated (higher scores indicate increased symptomatology). Internalizing and externalizing problem scores were also categorised into normal (T-score < 60), borderline (T-score 60–63) and clinical (indicating a score that is within the same range as scores obtained from children referred for internalizing/externalising problems; T-score > 63) (Achenbach and Rescorla, 2000).

2.8.2. Cognitively stimulating parenting

At follow-up assessment parents completed the cognitively stimulating parenting scale (CSPS) (Wolke et al., 2013), a 21-item questionnaire adapted from the Home Observation for Measurement of the Environment (HOME) Inventory (Bradley and Caldwell, 1984) designed to assess the level of cognitive stimulation at home (CSPS score range 0–46). Details of this questionnaire have been published previously (Bonthrone et al., 2021b).

2.8.3. Socioeconomic status

Index of multiple deprivation (IMD) was obtained from maternal postcode recorded at birth. IMD is a composite measure of socioeconomic status in England encompassing factors related to income, employment, education, health, and crime (https://imd-by-postcode.opendatacommunities.org/). IMD was obtained from the 2015 data release and reported as scores and quintiles (most to least deprived). It was not possible to obtain IMD for one infant.

2.9. Clinical information

Hospital records were reviewed to calculate days on the intensive care unit (ICU) post-surgery, time on bypass during surgery, and days to corrective or final palliative surgery. In children who underwent more than one surgery, days on ICU and time on bypass were summed across procedures (Bonthrone et al., 2021b).

2.9.1. Statistical analysis

Standardized residuals were calculated for raw internalizing and
externalizing scores adjusting for corrected age at follow-up assessment. Age adjusted raw scores were used for all subsequent analyses. A Kruskal-Wallis H test was used to assess the relationship between CHD subgroup and internalizing and externalizing scores. Kruskal-Wallis was used due to uneven group sizes (Abnormal streaming of blood n = 22; Right heart abnormalities n = 12; Left heart abnormalities n = 9).

Partial Spearman’s rank correlations were used to test the association between internalizing and externalizing scores, clinical and environmental features: CDO₂, days in intensive care, time on bypass and days to surgery, CSPS and IMD; and graph theory features: total network density, cost-corrected average nodal strength, global efficiency and local efficiency, cost-corrected nodal efficiency, strength and degree for each node.

All analyses covaried for gestational age at birth (GA), sex, brain injury severity, cognitive composite score and IMD (except in the correlation between IMD and internalizing/externalizing problem scores). Postmenstrual age at MRI (PMA) was also included as a covariate in the CDO₂ and graph theory features analyses.

All p-values underwent false discovery rate correction (p<0.05) to correct for multiple comparisons (Benjamini and Hochberg, 1995).

2.9.2. Network based statistics

Edge-wise structural connectivity was assessed with the network-based statistics (NBS) toolbox, which implements permutation testing to detect edge-wise associations with brain connectivity (Zalesky et al., 2010). A general linear model with 10,000 permutations and cluster-based family-wise error rate correction for multiple comparisons was used to test for associations between network extent (i.e., total number of connections) and internalizing and externalizing symptoms. The critical p-value was set at 0.025. A test-statistic threshold (t = 3.1) was set, where connections exceeding this threshold were considered significant. NBS results are highly dependent on the primary test-statistic threshold, therefore we additionally tested a range of values (t = 2.5–3.5, in 0.1 steps). Brain injury rating, cognitive composite score, sex, GA, PMA and IMD were entered as covariates. Significant networks were visualized with BrainNet Viewer (Xia et al., 2013).

2.10. Data availability

The anonymised processed data analysed during this study is available from the corresponding author upon reasonable request.

3. Results

3.1. Sample characteristics

A prospective cohort of 43 infants with critical or serious CHD was recruited between 2016 and 2019 at St Thomas’ Hospital London (Table 1). The infants were part of a larger group (N = 58) included in our previous publication investigating differences in graph theoretical measures in infants with CHD and controls (Ni Bhroin et al., 2020), details of inclusion are given in Fig. 1.

3.2. Neurodevelopmental outcome scores

Internalizing and externalizing problem scores, as well as cognitive composite, cognitively stimulating parenting scale (CSPS) scores and index of multiple deprivation (IMD) scores in toddlers with CHD are summarized in Table 3. Internalizing behaviors were categorised as clinical in 7 % of infants (Left heart abnormalities n = 2, right heart abnormalities n = 1). 10 % of infants were categorised as clinical on the externalizing scale (Abnormal Streaming of Blood n = 2, Left heart abnormalities n = 1, right heart abnormalities n = 4). 28 % of infants (n = 12; Abnormal Streaming of Blood n = 4, Left heart abnormalities n = 3, right heart abnormalities n = 4) scored in the borderline or clinical ranges for internalizing or externalizing problem scores.

3.3. Clinical and environmental correlates of internalizing and externalizing problem scores

Although the relationship between internalizing scores and time to surgery was not significant (partial $\rho = -0.448 p_{FDR} = 0.084$, for gestational age at birth (GA), sex, brain injury severity, cognitive composite score and IMD; Fig. 2A), post-hoc tests revealed this relationship was significant (partial $\rho = -0.538$, $p_{corrected} = 0.014$; Fig. 2B) in infants who underwent final corrective or palliative surgery when they were younger than 28 days (n = 27).

A post-hoc analysis of age adjusted raw items that are used to obtain internalizing problem scores, revealed days to surgery was correlated with emotionally reactive (partial $\rho = -0.522 p_{FDR} = 0.036$), and somatic complaints (partial $\rho = -0.570 p_{FDR} = 0.036$) but not withdrawn (partial $\rho = -0.447 p_{FDR} = 0.064$) or anxiety and depression (partial $\rho = -0.289 p_{FDR} = 0.217$) subscales.

There were no additional significant relationships between clinical or environmental variables and age adjusted raw internalizing or externalizing problem scores (Table 4).

3.4. Nodal brain network correlates of internalizing and externalizing problem scores

Partial Spearman’s rank correlations between nodal characteristics and internalizing and externalizing problem scores covarying for GA, postmenstrual age at scan (PMA), sex, brain injury severity, cognitive composite score and IMD are summarized in Fig. 3. Cost-corrected degree in the right inferior frontal gyrus (pars opercularis), a peripheral node, was significantly associated with externalizing scores (partial $\rho = -0.687 p_{FDR} < 0.001$; Fig. 4). Post-hoc analyses reveal both aggressive (partial $\rho = -0.654 p_{FDR} < 0.001$) and attention problem subscales (partial $\rho = -0.588 p_{FDR} < 0.001$) were associated with cost-corrected nodal degree in the right inferior frontal gyrus (pars opercularis).

There were no other significant associations between cost-corrected

| Measure | n = 43 |
|---|---|
| Gestational Age at Birth, Median (IQR) | 38.57 (38.21–38.86) |
| Postmenstrual Age at Scan, Median (IQR) | 39.29 (38.71–39.25) |
| Male, N (%) | 21 (49.8) |
| Primary Cardiac Lesion |  |
| Abnormal Streaming of Blood |  |
| Transposition of the Great Arteries, N (%) | 22 (51.2) |
| Left-sided heart abnormalities |  |
| Coarctation of the Aorta, N (%) | 8 (18.6) |
| Hypoplastic Left Heart Syndrome, N (%) | 1 (2.3) |
| Right-sided heart abnormalities |  |
| Tetralogy of Fallot, N (%) | 4 (9.3) |
| Pulmonary Stenosis, N (%) | 4 (9.3) |
| Pulmonary Atresia, N (%) | 3 (7) |
| Tricuspid Atresia, N (%) | 1 (2.3) |
| Minutes on bypass median (IQR) | 143 (72–189) |
| Days to corrective or final palliative surgery median (IQR) | 15 (10–144) |
| Days on Intensive Care Unit post-surgery median (IQR) | 5 (3–7) |

| Brain injury ratings in infants with CHD. |
|---|---|
| None/Mild, N (%) | 37 (86.0) |
| Moderate/Severe, N (%) | 6 (14.0) |
| Brain Injury Type |  |
| None, N (%) | 27 (62.8) |
| Mild WMI, N (%) | 8 (18.6) |
| Mild cerebellar haemorrhage, N (%) | 2 (4.6) |
| Moderate WMI with mild cerebellar haemorrhage, N (%) | 1 (2.3) |
| Moderate WMI, N (%) | 4 (9.4) |
| Severe WMI, N (%) | 1 (2.3) |
58 infants with CHD included in Ni Bhroin et al 2020
6 did not respond
4 died
2 refused hospital visit
1 residing overseas
45 returned for follow-up
2 did not complete questionnaires
43 included in final analysis

Fig. 1. Flow diagram of inclusion of infants from Ni Bhroin and colleagues (Ni Bhroin et al., 2020) in the current study.

Table 3
Neurodevelopmental outcome scores in infants with CHD.

| Score Type | Median (IQR) |
|------------|-------------|
| Internalizing raw score | 7 (3.11.5) |
| Internalizing T-score Mean (SD) | 48.2 (10.6) |
| Normal (<60) N (%) | 34 (79) |
| Borderline (60–63) N (%) | 6 (14) |
| Clinical (≥63) N (%) | 3 (7) |
| Abnormal Streaming of Blood Internalizing T-score Median (IQR) | 48 (38–54.5) |
| Left heart abnormalities Internalizing T-score Median (IQR) | 49 (41–62) |
| Right heart abnormalities Internalizing T-score Median (IQR) | 49 (40–57) |
| Externalizing raw score median (IQR) | 12 (8–18) |
| Externalizing T-score mean (SD) | 50.3 (9.5) |
| Normal (<60) N (%) | 38 (88) |
| Borderline (60–63) N (%) | 1 (2) |
| Clinical (≥63) N (%) | 4 (10) |
| Abnormal Streaming of Blood Externalizing T-score Median (IQR) | 50 (46–56.75) |
| Left heart abnormalities Externalizing T-score Median (IQR) | 50 (40–57) |
| Right heart abnormalities Externalizing T-score Median (IQR) | 47.5 (43.75–55.75) |
| Cognitive Composite Score Mean (SD) | 93.6 (10.2) |
| Cognitively Stimulating Parenting Scale Mean (SD) | 32.0 (6.6) |
| Index of Multiple Deprivation Median (IQR) | 18.66 |
| (13.18–30.27) |
| Index of Multiple Deprivation Quintile |
| 1st (Most deprived) | 8 |
| 2 | 11 |
| 3 | 9 |
| 4 | 9 |
| 5 | 5 |

Nodal degree, strength or efficiency and internalizing or externalizing problem scores.

3.5. Network based statistics

Network based statistics revealed a frontal-limbic sub-network (p = 0.013) of 20 nodes (6 core, 14 peripheral), including the right inferior frontal gyrus (pars opercularis), sharing 25 edges (2 core, 10 feeder and 13 peripheral) where reduced connectivity was associated with higher age adjusted externalizing raw scores in toddlers with CHD covarying for GA, PMA, sex, brain injury severity, cognitive composite score and IMD (Fig. 5). Table 5 lists edges negatively associated with externalizing scores and the associated t-statistic at a threshold of $t = 3.1$. Sensitivity analysis revealed no significant edges at t-statistic thresholds of 2.5, 2.6 and 2.9. Significant edges were identified in at t-statistic thresholds of 2.7, 2.8 and 3.0–3.5 (Supplementary Table 2).

Post-hoc partial correlations revealed total connectivity in the sub-network was significantly associated with aggressive ($\rho = -0.779$ $p_{FDR} < 0.001$) and attention problems ($\rho = -0.607$ $p_{FDR} < 0.001$) subscales.

3.6. Global brain network correlates of internalizing and externalizing problem scores

There were no significant relationships between global brain network features and internalizing or externalizing problem scores (Table 6).

4. Discussion

This study investigated the association between neonatal structural brain network organization, clinical variables and internalizing and externalizing symptoms in toddlers with CHD. 28 % of toddlers with CHD had elevated internalizing or externalizing problem scores. Using graph theoretical analyses, we identified associations between reduced frontal-limbic structural connectivity and integration of the right inferior frontal gyrus (pars opercularis) before surgery and higher externalizing symptoms at 22 months. In contrast, increased internalizing symptoms were associated with earlier corrective or final palliative surgery but not brain connectivity.

While mean internalizing and externalizing problem T-scores were within the normal range, 28 % of toddlers with CHD had internalizing or externalizing problem scores within the borderline or clinical ranges. This is in keeping with a systematic review which found that while, overall, preschool children with CHD score within the normal ranges, a large subset show increased internalizing or externalizing behaviors compared to healthy peers (Clancy et al., 2020). In addition, children and adolescents with CHD are at increased risk of internalizing disorders such as depression and anxiety (Landolt et al., 2014; Pradhan et al., 1998) and externalizing difficulties such as ADHD, inattention and hyperactivity (Gonzalez et al., 2021; Latham et al., 2014; Shillingford et al., 2008). These findings suggest that from early childhood, children with CHD are at increased risk of emotional and behavioral regulation impairments.

Several studies have implicated altered frontal-limbic networks in externalizing behaviors in both healthy children and clinical populations. In the healthy population, lower neonatal clustering coefficient of the right amygdala was associated with higher externalizing scores at 22 and 48 months, while higher clustering coefficient of the right inferior frontal cortex has been reported to predict higher externalizing symptoms at 48 months (Wee et al., 2017). Higher externalizing behaviors have also been linked to thinner right orbitofrontal cortex (Tanzer et al., 2021), left orbitofrontal cortex and right retrosplenial cortex and reduced structural covariance between the left amygdala and orbitofrontal cortex (Ameis et al., 2014). Lower fractional anisotropy in the left cingulum bundle and uncinate fasciculus (Andre et al., 2020) and increased functional connectivity between the amygdala and orbitofrontal cortex (Thijssen et al., 2021) have been associated with higher externalizing symptoms in healthy children and adolescents. In children with autism, reduced functional connectivity between the amygdala and ventrolateral prefrontal cortex bilaterally was associated with higher externalizing behaviors (Ibrahim et al., 2019). Taken together with our results, this evidence demonstrates the importance of frontal-limbic circuitry for the development of externalizing behaviors in childhood.

Alterations in frontal-limbic circuitry have also been associated with exposure to stressors in early life. Early adverse childhood experiences are associated with altered functional connectivity of the inferior frontal gyrus in childhood (Barch et al., 2018). The degree of altered connectivity predicted the severity of externalizing symptoms over childhood and early adolescence (Barch et al., 2018). In both premature and full-term toddlers, increased functional connectivity between the left
and clinical variables.

It has been proposed that the development of attentional control, self-regulation and inhibition in early childhood scaffold the development of more complex executive functions related to cognitive flexibility, goal setting and problem solving (Anderson, 2002; Diamond, 2013). In preschool children with externalizing disorders, impaired executive functions are associated with externalizing behaviors and the strength of association increases with age (Schoemaker et al., 2013). A recent meta-analysis reported children with CHD have impaired executive functions (Feldmann et al., 2021). It is possible that impaired development of the frontal network identified in our study is associated with early externalizing behaviors and subsequent executive function impairments in children with CHD.

To our knowledge, this is the first study to identify an association between younger age at surgery and higher internalizing symptoms in infants who undergo corrective or final palliative surgery in the neonatal period. This contrasts with previously published work reporting improved brain growth and early language abilities in infants with hypoplastic left heart syndrome (Anderson et al., 2015) who underwent earlier cardiac surgery. However, these publications included a different range of cardiac defects compared to this study and investigated different outcome measures; it is therefore not possible to draw direct conclusions. It is also important to note that earlier surgery in the neonatal period may reflect more severe illness which may, in turn, be associated with increased internalizing behaviors in early childhood.

Childhood internalizing symptoms have been linked to changes in DNA methylation (Cimino et al., 2021). In particular, accelerated epigenetic aging has been implicated in internalizing behaviors in healthy children (Tollenaar et al., 2021) and those exposed to maltreatment (Dammering et al., 2021). Early adverse life events alter epigenetic modulation of DNA transcriptional activity (Hyman, 2009). This has been studied in premature infants with high pain exposure, neonatal morbidity and adverse NICU experiences implicated in changes to epigenetic mechanisms such as DNA methylation (Everson et al., 2020; Giarraputo et al., 2017; Provenzi et al., 2015, Provenzi et al., 2018). Altered methylation of serotonin transporter genes at NICU discharge has been associated with temperament changes and poor stress regulation at 3 months in this population (Montiroso et al., 2016a; Montiroso et al., 2016b). In critically ill children, early treatment with parenteral nutrition is associated with increased methylation and subsequent behavioral impairments 4 years post treatment (Jacobs et al., 2021). Altered DNA methylation has been reported in neonates with CHD (Cao et al., 2021; Chang et al., 2021) although to our knowledge the effect of cardiac surgery has yet to be investigated. Earlier cardiac surgery or more severe neonatal illness may induce epigenetic changes associated with increased risk of internalizing symptoms in early childhood, however this hypothesis requires further investigation.

5. Limitations

It is important to acknowledge that this work has some limitations. We did not include a control group and therefore cannot determine whether the results are specific to CHD or may also be identified in healthy children. We did not acquire postsurgical imaging in these infants and therefore it was not possible to determine if postsurgical
Fig. 3. Partial Spearman’s rank correlation coefficients between nodal characteristics and age adjusted internalizing and externalizing raw scores adjusted for covariates.
Fig. 4. Relationship between cost-corrected nodal degree in the right inferior frontal gyrus (pars opercularis) and age adjusted internalizing raw scores adjusted for covariates.

Fig. 5. A) Network of reduced connectivity associated with increased externalizing behaviors, red nodes are core, blue nodes are peripheral; red edges are core connections, blue edges are peripheral connections and green edges are peripheral to core connections. B) Association between age adjusted externalizing raw scores and sub-network connectivity from sub-network adjusted for covariates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Nodes and edges where reduced connectivity was significantly associated with higher age adjusted externalizing scores.

| Nodes          | Location                        | Type       | Edges          | Location                        | Type       | t-stat |
|----------------|---------------------------------|------------|----------------|---------------------------------|------------|--------|
| Superior frontal gyrus (medial) left | Core                  | Inferior frontal gyrus (pars opercularis) right | Feeder   | 5.02 |
| Superior frontal gyrus (medial) right | Core                  | Inferior frontal gyrus (pars opercularis) right | Feeder   | 4.08 |
| Superior frontal gyrus (dorsal) left | Core                  | Orbitofrontal cortex (medial) left | Peripheral | 3.7 |
| Superior frontal gyrus (dorsal) right | Core                  | Orbitofrontal cortex (medial) right | Peripheral | 3.69 |
| Middle frontal gyrus left | Core                  | Superior frontal gyrus (medial) right | Feeder   | 3.65 |
| Middle frontal gyrus right | Core                  | Superior frontal gyrus (pars opercularis) right | Supplementary motor area left | Peripheral | 3.65 |
| Rectus gyrus left | Peripheral | Orbitofrontal cortex (medial) right | Peripheral | 3.64 |
| Orbitofrontal cortex (medial) left | Peripheral | Inferior frontal gyrus (pars triangularis) right | Feeder   | 3.55 |
| Orbitofrontal cortex (medial) right | Peripheral | Middle frontal gyrus right | Core     | 3.52 |
| Orbitofrontal cortex (middle) left | Peripheral | Superior frontal gyrus (medial) left | Feeder   | 3.47 |
| Orbitofrontal cortex (middle) right | Peripheral | Orbitofrontal cortex (middle) right | Peripheral | 3.36 |
| Orbitofrontal cortex (superior) left | Peripheral | Orbitofrontal cortex (superior) left | Peripheral | 3.34 |
| Orbitofrontal cortex (superior) right | Peripheral | Superior frontal gyrus (medial) left | Core     | 3.32 |
| Inferior frontal gyrus (Opercular) left | Peripheral | Inferior frontal gyrus (pars opercularis) right | Feeder   | 3.3  |
| Inferior frontal gyrus (Opercular) right | Peripheral | Orbitofrontal cortex (middle) left | Peripheral | 3.26 |
| Inferior frontal gyrus (pars triangularis) right | Peripheral | Orbitofrontal cortex (superior) left | Peripheral | 3.23 |
| Supplementary motor area left | Peripheral | Orbitofrontal cortex (medial) right | Peripheral | 3.23 |
| Posterior cingulate gyrus right | Peripheral | Hippocampus right | Peripheral | 3.2  |
| Hippocampus right | Peripheral | Orbitofrontal cortex (superior) right | Feeder   | 3.19 |
6. Conclusions

Toddlers with CHD are at risk of elevated internalizing and externalizing symptoms in early childhood. We provide the first evidence that reduced neonatal structural connectivity of a frontal-limbic network and integration of the right inferior frontal gyrus (pars opercularis) before surgery are associated with increased externalizing symptoms at 22 months in toddlers with CHD. These results complement previous studies in healthy children which have implicated frontal-limbic networks in externalizing behaviours. On the other hand, earlier corrective or final palliative surgery in the neonatal period was associated with higher internalizing symptoms. Frontal-limbic network development and age at surgery may represent important neonatal antecedents of behavioral impairments in CHD in childhood.

Table 5 (continued)

| Nodes | Edges |
|-------|-------|
| Location | Type | Location | Type | t-stat |
| Superior frontal gyrus (medial) left | Orbitofrontal cortex (superior) left - Amygdala right | Peripheral | 3.16 |
| Orbitofrontal cortex (superior) left - Superior frontal gyrus (medial) right | Superior frontal gyrus (dorsal) right - Orbitofrontal cortex (medial) left | Feeder | 3.16 |
| Orbitofrontal cortex (superior) right - Orbitofrontal cortex (medial) left | Inferior frontal gyrus (pars opercularis) right - Orbitofrontal cortex (superior) left | Peripheral | 3.13 |
| Middle frontal gyrus left - Orbitofrontal cortex (medial) right | | Feeder | 3.11 |

Table 6
Partial Spearman’s rank correlations between global network features and internalizing and externalizing scores.

| Network Feature | Age adjusted internalizing raw scores | Age adjusted externalizing raw scores |
|-----------------|--------------------------------------|--------------------------------------|
|                 | Partial p | p corr | Partial p | p corr |
| Total Network Density | –0.178 | 0.575 | –0.374 | 0.208 |
| Cost-corrected average nodal strength | –0.235 | 0.544 | –0.066 | 0.801 |
| Cost-corrected global efficiency | –0.144 | 0.575 | 0.016 | 0.925 |
| Cost-corrected local efficiency | –0.217 | 0.544 | –0.135 | 0.575 |

changes in brain connectivity were related to internalizing symptoms at 22 months. Finally, it is possible that in early childhood externalizing symptoms, which manifest in outward behaviors, may be easier to detect than internalizing symptoms (Papachristou and Flouri, 2020). However, externalizing T-scores were not significantly higher than internalizing T-scores in this cohort (t(42) = 1.43, p = 0.16).

6. Conclusions

Toddlers with CHD are at risk of elevated internalizing and externalizing symptoms in early childhood. We provide the first evidence that reduced neonatal structural connectivity of a frontal-limbic network and integration of the right inferior frontal gyrus (pars opercularis) before surgery are associated with increased externalizing symptoms at 22 months in toddlers with CHD. These results complement previous studies in healthy children which have implicated frontal-limbic networks in externalizing behaviours. On the other hand, earlier corrective or final palliative surgery in the neonatal period was associated with higher internalizing symptoms. Frontal-limbic network development and age at surgery may represent important neonatal antecedents of behavioral impairments in CHD in childhood.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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