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

Alexandra F. Bonthrone [a], Andrew Chew [a], Megan Ní Bhroin [a,b], Francesca Morassutti Rech [a], Christopher J. Kelly [a], Daan Christiaens [a,c], Maximilian Pietsch [a,d], J-Donald Tournier [a], Lucilio Cordero-Grande [a,e], Anthony Price [a], Alexia Egloff [a], Joseph V. Hajnal [a,f], Kuberan Pushparajah [f,g], John Simpson [g], A. David Edwards [a], Mary A. Rutherford [a], Chiara Nosarti [a,h], Dafnis Batalle [a,d], Serena J. Counsell [a,*]

[a] Centre for the Developing Brain, School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK
[b] Trinity College Institute of Neuroscience and Cognitive Systems Group, Discipline of Psychiatry, School of Medicine, Trinity College, Dublin, Ireland
[c] Department of Electrical Engineering (ESAT/PSI), KU Leuven, Leuven, Belgium
[d] Department for Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[e] Biomedical Image Technologies, ETSI Telecomunicación, Universidad Politécnica de Madrid & CIBER-BBN, Madrid, Spain
[f] Biomedical Engineering Department, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK
[g] Paediatric Cardiology Department, Evelina London Children's Healthcare, London, UK
[h] Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

ARTICLE INFO

ABSTRACT

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 perioperative 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 (Klouda

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

* Corresponding author.
  E-mail address: serena.counsell@kcl.ac.uk (S.J. Counsell).

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 (CDO_2) (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 CDO_2 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; Ehrler 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 (Ní 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 (Beare 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.

2. Materials and methods

2.1. Ehical approval

The National Research Ethics Service West London committee provided ethical approval (07/H0707/105). In accordance with the declaration of Helsinki, informed written parental consent was obtained before neonatal MRI and neurodevelopmental follow-up at 22 months.

2.2. Recruitment

Infants with critical or serious CHD were recruited between 2016 and 2019 at St Thomas' Hospital London. Based on a previously published UK categorization (Ewer et al., 2011) critical CHD was defined as infants with hypoplastic left heart syndrome (HLHS), interrupted aortic arch,

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) 11/4.6 ms, flip angle 9°, voxel size 0.8 mm^3), T2-weighted (multislice turbo spin echo TR/TE 12000/156 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/mm^2 (n = 20), b = 400 s/mm^2 (n = 64), b = 1000 s/mm^2 (n = 88), b = 2600 s/mm^2 (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 haemorrhage 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; Veraart et al., 2016), Gibbs ringing artefact suppression (Kellner et al., 2016), and correction for motion and image distortion using Spherical Harmonics and Radial Decomposition 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 Ní Bhroin et al, see (Ní Bhroin et al., 2020) for details). ODFs were normalized to obtain quantitative measures (Dhollander 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; Batalle 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 (Batalle 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 (Ní Bhroin et al., 2020). In keeping with previously published results (Ní Bhroin 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 assess the association between internalizing and externalizing scores, clinical and environmental features: CDO$_2$, 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 CDO$_2$ and graph theory features analyses.

All p-values underwent false discovery rate correction (p$_{FDR}$) 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 (Ní 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 ρ = −0.448 p$_{FDR}$ = 0.084, covarying 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 ρ = −0.538, p$_{uncorrected}$ = 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 ρ = −0.522 p$_{FDR}$ = 0.036), and somatic complaints (partial ρ = −0.570 p$_{FDR}$ = 0.036) but not withdrawn (partial ρ = −0.447 p$_{FDR}$ = 0.064) or anxiety and depression (partial ρ = −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 ρ = −0.687 p$_{FDR}$ < 0.001; Fig. 4). Post-hoc analyses reveal both aggressive (partial ρ = −0.654 p$_{FDR}$ < 0.001) and attention problem subscales (partial ρ = −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

Table 1
Sample Demographics.

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)

Table 2
Brain injury ratings in infants with CHD.

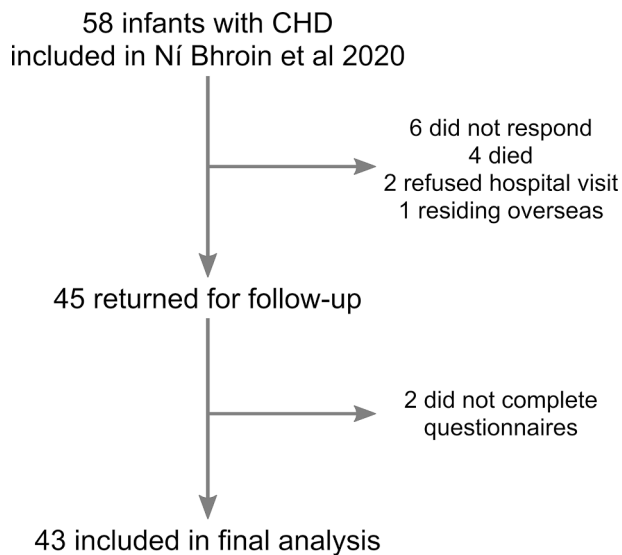|	
None/Mild, N (%)	37 (86.0)
Moderate/Severe, N (%)	6 (14.0)
Brain Injury Type	
None, N (%)	27 (62.8)
Mild WMI, N (%)	8 (18.6)
Mild cerebellar haemorrhage, N (%)	2 (4.6)
Moderate WMI with mild cerebellar haemorrhage, N (%)	1 (2.3)
Moderate WMI, N (%)	4 (9.4)
Severe WMI, N (%)	1 (2.3)

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

Table 3
Neurodevelopmental outcome scores in infants with CHD.

Internalizing raw score Median (IQR)	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; Liamlahi 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
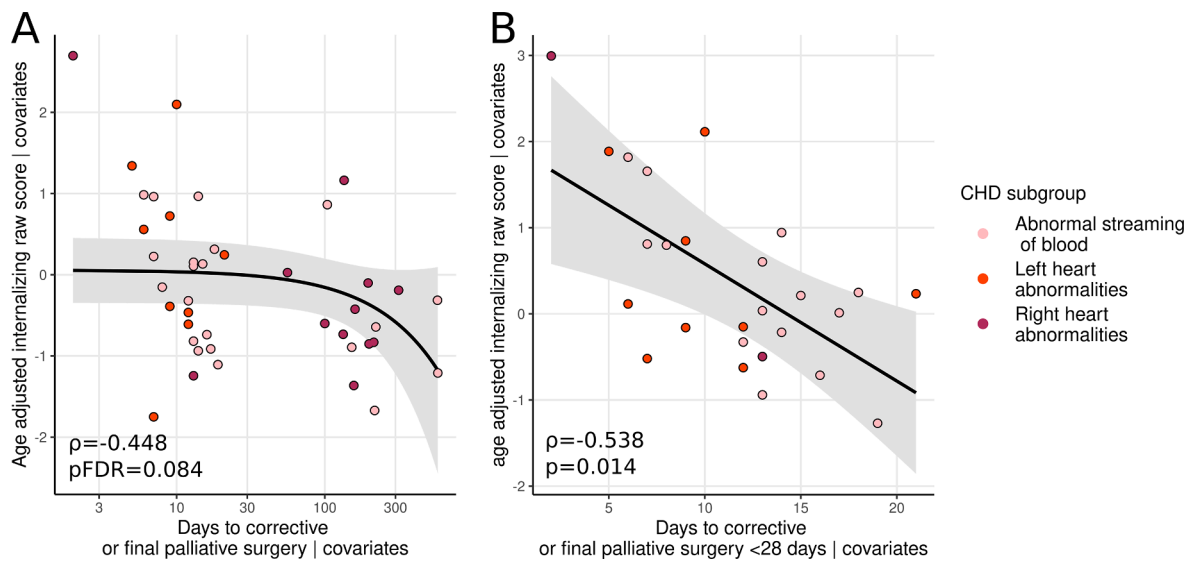
Fig. 2. Relationship between days to corrective or final palliative surgery and age adjusted internalizing raw scores in A) the whole sample, B) infants who underwent corrective or final palliative surgery at <28 days. Covarying for gestational age at birth, sex, brain injury rating, cognitive composite score and IMD.

Table 4
Relationship between age adjusted internalizing and externalizing raw scores and clinical variables.

	Internalizing	Externalizing
CHD subgroup	H = 0.394, p_{FDR} = 0.958	H = 0.152, p_{FDR} = 0.958
CDO_2	Partial ρ = −0.073, p_{FDR} = 0.958	Partial ρ = −0.106, p_{FDR} = 0.958
Minutes on bypass	Partial ρ = −0.119, p_{FDR} = 0.958	Partial ρ = 0.211, p_{FDR} = 0.958
Days on ICU post-surgery	Partial ρ = −0.105, p_{FDR} = 0.958	Partial ρ = 0.037, p_{FDR} = 0.958
Days to corrective or final palliative surgery	Partial ρ = −0.448, p_{FDR} = 0.084	Partial ρ = −0.170, p_{FDR} = 0.958
IMD	Partial ρ = 0.086, p_{FDR} = 0.958	Partial ρ = −0.009, p_{FDR} = 0.958
CSPS	Partial ρ = −0.021, p_{FDR} = 0.958	Partial ρ = −0.296, p_{FDR} = 0.553

striatum and right frontal pole at term/term-equivalent age mediated the relationship between low socioeconomic status and increased externalizing symptoms at age two (Ramphal et al., 2020). In healthy-four-year-old boys, lower fractional anisotropy in fibres connecting the right amygdala and prefrontal cortex mediated the relationship between maternal prenatal depression and increased externalizing behaviors (Hay et al., 2020). CHD may act as an early life stressor, altering frontal-limbic connectivity in the developing brain leading to increased externalizing behaviors in childhood, however this hypothesis requires further investigation.

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 TGA (Lim et al., 2019) and better clinical outcomes 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 (Montirosso et al., 2016a; Montirosso 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
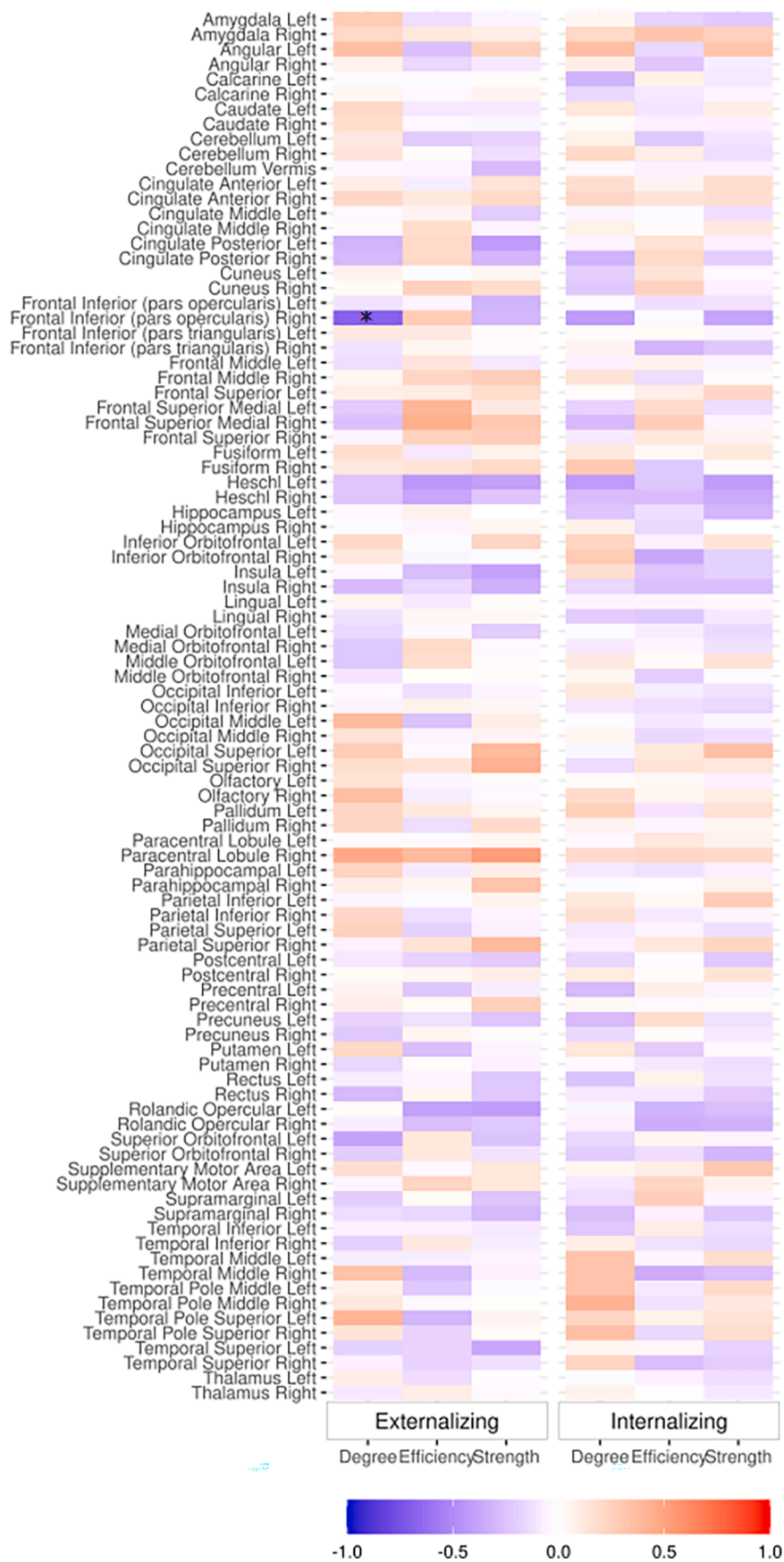
Fig. 3. Partial Spearman's rank correlation coefficients between nodal characteristics and age adjusted internalizing and externalizing raw scores adjusted for covariates.
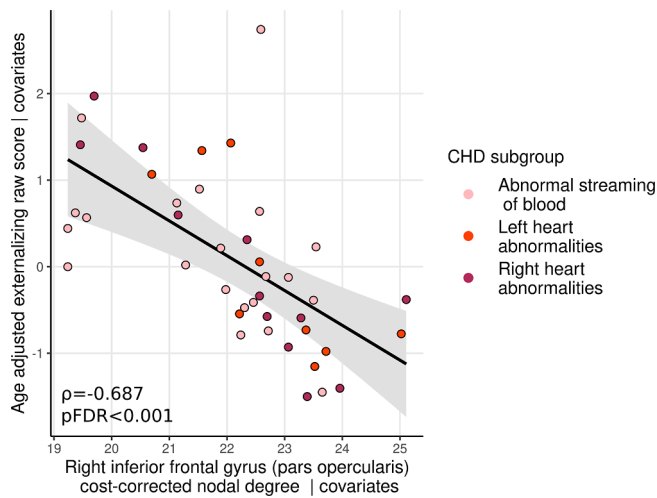
Fig. 4. Relationship between cost-corrected nodal degree in the right inferior frontal gyrus (pars opercularis) and age adjusted internalizing raw scores adjusted for covariates.
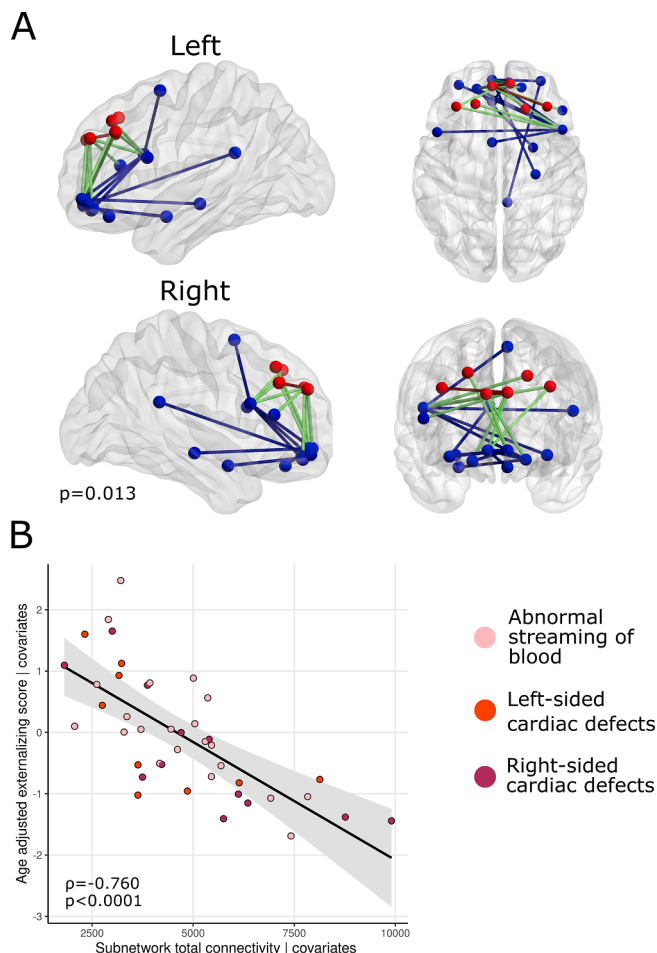

Fig. 5. A) Network of reduced connectivity associated with increased externalizing behaviors, red nodes are core, blue nodes are peripheral; red edges are core connections, blue edges are peripheral connections and green edges are peripheral to core connections. B) Association between age adjusted externalizing 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		Edges		
Location	Type	Location	Type	t-stat
Superior frontal gyrus (medial) left	Core	Inferior frontal gyrus (pars opercularis) right - Superior frontal gyrus (medial) left	Feeder	5.02
Superior frontal gyrus (medial) right	Core	Inferior frontal gyrus (pars opercularis) right - Superior frontal gyrus (dorsal) left	Feeder	4.08
Superior frontal gyrus (dorsal) left	Core	Orbitofrontal cortex (medial) left - Orbitofrontal cortex (medial) right	Peripheral	3.7
Superior frontal gyrus (dorsal) right	Core	Inferior frontal gyrus (pars opercularis) right - Inferior frontal gyrus (pars opercularis) left	Peripheral	3.69
Middle frontal gyrus left	Core	Superior frontal gyrus (medial) right - Orbitofrontal cortex (medial) left	Feeder	3.65
Middle frontal gyrus right	Core	Inferior frontal gyrus (pars opercularis) right - Supplementary motor area left	Peripheral	3.65
Rectus gyrus left	Peripheral	Orbitofrontal cortex (medial) right - Rectus gyrus left	Peripheral	3.64
Orbitofrontal cortex (medial) left	Peripheral	Inferior frontal gyrus (pars triangularis) right - Superior frontal gyrus (medial) left	Feeder	3.55
Orbitofrontal cortex (medial) right	Peripheral	Middle frontal gyrus right - Superior frontal gyrus (medial) left	Core	3.52
Orbitofrontal cortex (middle) left	Peripheral	Superior frontal gyrus (medial) left - Orbitofrontal cortex (medial) right	Feeder	3.47
Orbitofrontal cortex (middle) right	Peripheral	Orbitofrontal cortex (middle) right - Posterior cingulate gyrus right	Peripheral	3.36
Orbitofrontal cortex (superior) left	Peripheral	Orbitofrontal cortex (middle) right - Orbitofrontal cortex (medial) left	Peripheral	3.34
Orbitofrontal cortex (superior) right	Peripheral	Superior frontal gyrus (medial) left - Superior frontal gyrus (medial) right	Core	3.32
Inferior frontal gyrus (Opercular) left	Peripheral	Inferior frontal gyrus (pars opercularis) right - Middle frontal gyrus left	Feeder	3.3
Inferior frontal gyrus (Opercular) right	Peripheral	Inferior frontal gyrus (pars opercularis) right - Orbitofrontal cortex (middle) left	Peripheral	3.26
Inferior frontal gyrus (pars triangularis) right	Peripheral	Orbitofrontal cortex (superior) left - Orbitofrontal cortex (medial) right	Peripheral	3.23
Supplementary motor area left	Peripheral	Orbitofrontal cortex (medial) left - Hippocampus right	Peripheral	3.23
Posterior cingulate gyrus right	Peripheral	Inferior frontal gyrus (pars opercularis) right - Orbitofrontal cortex (medial) left	Peripheral	3.2
Hippocampus right	Peripheral	Orbitofrontal cortex (superior) right -	Feeder	3.19

Table 5 (*continued*)

Nodes		Edges		
Location	Type	Location	Type	*t*-stat
Amygdala Right	Peripheral	Superior frontal gyrus (medial) left Orbitofrontal cortex (superior) left - Amygdala right	Peripheral	3.16
		Orbitofrontal cortex (superior) left - Superior frontal gyrus (medial) right	Feeder	3.16
		Superior frontal gyrus (dorsal) right - Orbitofrontal cortex (medial) left	Feeder	3.15
		Orbitofrontal cortex (superior) right - Orbitofrontal cortex (medial) left	Peripheral	3.13
		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 ρ	p_{FDR}	Partial ρ	p_{FDR}
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.

CRediT authorship contribution statement

Alexandra F. Bonthrone: Formal analysis, Investigation, Visualization, Methodology, Resources, Data curation, Writing – original draft. **Andrew Chew:** Investigation, Resources, Writing – review & editing.

Megan Ní Bhroin: Formal analysis, Investigation, Methodology, Writing – review & editing. **Francesca Morassutti Rech:** Investigation, Writing – review & editing. **Christopher J. Kelly:** Methodology, Resources, Data curation, Writing – review & editing. **Daan Christiaens:** Methodology, Software, Writing – review & editing. **Maximilian Pietsch:** Methodology, Software, Writing – review & editing. **J-Donald Tournier:** Methodology, Software, Writing – review & editing. **Lucilio Cordero-Grande:** Methodology, Software, Writing – review & editing. **Anthony Price:** Methodology, Resources, Writing – review & editing. **Alexia Egloff:** Investigation, Writing – review & editing. **Joseph V. Hajnal:** Methodology, Software, Writing – review & editing. **Kuberan Pushparajah:** Validation, Writing – review & editing. **John Simpson:** Validation, Writing – review & editing. **A. David Edwards:** Validation, Writing – review & editing. **Mary A. Rutherford:** Validation, Writing – review & editing. **Chiara Nosarti:** Conceptualization, Methodology, Writing – review & editing. **Dafnis Batalle:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Serena J. Counsell:** Supervision, Conceptualization, Methodology, Visualization, Funding acquisition, Project administration, Writing – original draft.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103153.

References

Achard, S., Bullmore, E., 2007. Efficiency and cost of economical brain functional networks. *PLoS Comput. Biol.*, *3*(2), e17. 10.1371/journal.pcbi.0030017.

Achenbach, T., Rescorla, L., 2000. *Manual for the ASEBA Preschool Forms & Profiles.* University of Vermont Research Center for Children, Youth, & Families.

Ameis, S.H., Ducharme, S., Albaugh, M.D., Hudziak, J.J., Botteron, K.N., Lepage, C., Zhao, L., Khundrakpam, B., Collins, D.L., Lerch, J.P., Wheeler, A., Schachar, R., Evans, A.C., Karama, S., 2014. Cortical thickness, cortico-amygdalar networks, and externalizing behaviors in healthy children. Biol. Psychiatry 75 (1), 65–72. https://doi.org/10.1016/j.biopsych.2013.06.008.

Anderson, P., 2002. Assessment and development of executive function (EF) during childhood. Child Neuropsychol. 8 (2), 71–82. https://doi.org/10.1076/chin.8.2.71.8724.

Anderson, R.H., Becker, A.E., Freedom, R.M., Macartney, F.J., Quero-Jimenez, M., Shinebourne, E.A., Wilkinson, J.L., Tynan, M., 1984. Sequential segmental analysis of congenital heart disease. Pediatr. Cardiol. 5 (4), 281–287. https://doi.org/10.1007/BF02424973.

Anderson, B.R., Ciarleglio, A.J., Salavitabar, A., Torres, A., Bacha, E.A., 2015. Earlier stage 1 palliation is associated with better clinical outcomes and lower costs for neonates with hypoplastic left heart syndrome. J. Thoracic Cardiovasc. Surgery 149 (1), 205–210.e1. https://doi.org/10.1016/j.jtcvs.2014.07.094.

Andre, Q.R., Geeraert, B.L., Lebel, C., 2020. Brain structure and internalizing and externalizing behavior in typically developing children and adolescents. Brain Struct. Funct. 225 (4), 1369–1378. https://doi.org/10.1007/s00429-019-01973-y.

Avants, B. B., Tustison, N., & Song, G. (2011). *Advanced Normalization Tools (ANTS)*. 1–35.

Barch, D.M., Belden, A.C., Tillman, R., Whalen, D., Luby, J.L., 2018. Early childhood adverse experiences, inferior frontal gyrus connectivity, and the trajectory of externalizing psychopathology. J. Am. Acad. Child Adolesc. Psychiatry 57 (3), 183–190. https://doi.org/10.1016/j.jaac.2017.12.011.

Batalle, D., Hughes, E.J., Zhang, H., Tournier, J.-D., Tusor, N., Aljabar, P., Wali, L., Alexander, D.C., Hajnal, J.V., Nosarti, C., Edwards, A.D., Counsell, S.J., 2017. Early development of structural networks and the impact of prematurity on brain connectivity. NeuroImage 149, 379–392. https://doi.org/10.1016/j.neuroimage.2017.01.065.

Bayley, N., 2006. Bayley Scales of Infant and Toddler Development, 3rd ed. PsychCorp, Pearson.

Beare, R., Adamson, C., Bellgrove, M.A., Vilgis, V., Vance, A., Seal, M.L., Silk, T.J., 2017. Altered structural connectivity in ADHD: a network based analysis. Brain Imag. Behav. 11 (3), 846–858. https://doi.org/10.1007/s11682-016-9559-9.

Beca, J., Gunn, J.K., Coleman, L., Hope, A., Reed, P.W., Hunt, R.W., Finucane, K., Brizard, C., Dance, B., Shekerdemian, L.S., 2013. New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. Circulation 127 (9), 971–979. https://doi.org/10.1161/CIRCULATIONAHA.112.001089.

Bellinger, D.C., Wypij, D., Rivkin, M.J., DeMaso, D.R., Robertson, R.L.J., Dunbar-Masterson, C., Rappaport, L.A., Wernovsky, G., Jonas, R.A., Newburger, J.W., 2011. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. Circulation 124 (12), 1361–1369. https://doi.org/10.1161/CIRCULATIONAHA.111.026963.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc.: Ser. B (Methodol.) 57 (1), 289–300. http://www.jstor.org/stable/2346101.

Bonthrone, A.F., Chew, A., Kelly, C.J., Almedom, L., Simpson, J., Victor, S., Edwards, A. D., Rutherford, M.A., Nosarti, C., Counsell, S.J., 2021a. Cognitive function in toddlers with congenital heart disease: the impact of a stimulating home environment. Infancy 26 (1), 184–199. https://doi.org/10.1111/infa.12376.

Bonthrone, A.F., Dimitrova, R., Chew, A., Kelly, C.J., Cordero-Grande, L., Carney, O., Egloff, A., Hughes, E., Vecchiato, K., Simpson, J., Hajnal, J.V., Pushparajah, K., Victor, S., Nosarti, C., Rutherford, M.A., Edwards, A.D., O'Muircheartaigh, J., Counsell, S.J., 2021b. Individualized brain development and cognitive outcome in infants with congenital heart disease. Brain Commun. 3 (2), fcab046. https://doi.org/10.1093/braincomms/fcab046.

Borgatti, S.P., Everett, M.G., 2000. Models of core/periphery structures. Social Networks 21 (4), 375–395.

Bouyssi-Kobar, M., Limperopoulos, C., Clouchoux, C., du Plessis, A.J., McElhinney, D.B., Brown, D.W., Newburger, J.W., Robertson Jr., R.L., Tworetzky, W., Gholipour, A., Warfield, S.K., Kudelski, D., McCarter, R.J., Evans, A.C., 2012. Delayed cortical development in fetuses with complex congenital heart disease. Cereb. Cortex 23 (12), 2932–2943. https://doi.org/10.1093/cercor/bhs281.

Bradley, R., Caldwell, B., 1984. *Home Observation for Measurement of the Environment*.

Brewster, R.C., King, T.Z., Burns, T.G., Drossner, D.M., Mahle, W.T., 2015. White matter integrity dissociates verbal memory and auditory attention span in emerging adults with congenital heart disease. J. Int. Neuropsychol. Soc.: JINS 21 (1), 22–33. https://doi.org/10.1017/S135561771400109X.

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 (3), 186–198. https://doi.org/10.1038/nrn2575.

Cao, J., Wu, Q., Huang, Y., Wang, L., Su, Z., Ye, H., 2021. The role of DNA methylation in syndromic and non-syndromic congenital heart disease. Clin. Epigenetics 13 (1), 93. https://doi.org/10.1186/s13148-021-01077-7.

Chang, S., Wang, Y., Xin, Y., Wang, S., Luo, Y., Wang, L., Zhang, H., Li, J., 2021. DNA methylation abnormalities of imprinted genes in congenital heart disease: a pilot study. BMC Med. Genomics 14 (1), 4. https://doi.org/10.1186/s12920-020-00848-0.

Christiaens, D., Cordero-Grande, L., Pietsch, M., Hutter, J., Price, A.N., Hughes, E.J., Vecchiato, K., Deprez, M., Edwards, A.D., Hajnal, J.V., Tournier, J.-D., 2021. Scattered slice SHARD reconstruction for motion correction in multi-shell diffusion MRI. NeuroImage 225, 117437. https://doi.org/10.1016/j.neuroimage.2020.117437.

Cimino, S., Cerniglia, L., De Carli, P., Simonelli, A., 2021. DNA methylation and allelic polymorphism at the dopamine transporter promoter affect internalizing and externalizing symptoms in preschoolers. Child Psychiatry Hum. Dev. 52 (2), 281–290. https://doi.org/10.1007/s10578-020-01009-1.

Claessens, N.H.P., Algra, S.O., Ouwehand, T.L., Jansen, N.J.G., Schappin, R., Haas, F., Eijsermans, M.J.C., Vries, L.S., Benders, M.J.N.L., Moeskops, P., Išgum, I., Haastert, I. C., Groenendaal, F., Breur, J.M.P.J., 2018. Perioperative neonatal brain injury is associated with worse school-age neurodevelopment in children with critical congenital heart disease. Dev. Med. Child Neurol. 60 (10), 1052–1058.

Claessens, N.H.P., Breur, J.M.P.J., Groenendaal, F., Wösten-van Asperen, R.M., Stegeman, R., Haas, F., Dudink, J., de Vries, L.S., Jansen, N.J.G., Benders, M.J.N.L., 2019. Brain microstructural development in neonates with critical congenital heart disease: An atlas-based diffusion tensor imaging study. NeuroImage. Clinical 21, 101672. https://doi.org/10.1016/j.nicl.2019.101672.

Clancy, T., Jordan, B., de Weerth, C., Muscara, F., 2020. Early emotional, behavioural and social development of infants and young children with congenital heart disease: a systematic review. J. Clin. Psychol. Med. Settings 27 (4), 686–703. https://doi.org/10.1007/s10880-019-09651-1.

Cordero-Grande, L., Hughes, E.J., Hutter, J., Price, A.N., Hajnal, J.V., 2018. Three-dimensional motion corrected sensitivity encoding reconstruction for multi-shot multi-slice MRI: application to neonatal brain imaging. Magn. Reson. Med. 79 (3), 1365–1376. https://doi.org/10.1002/mrm.26796.

Cordero-Grande, L., Christiaens, D., Hutter, J., Price, A.N., Hajnal, J.V., 2019. Complex diffusion-weighted image estimation via matrix recovery under general noise models. NeuroImage 200, 391–404. https://doi.org/10.1016/j.neuroimage.2019.06.039.

Dammering, F., Martins, J., Dittrich, K., Czamara, D., Rex-Haffner, M., Overfeld, J., de Punder, K., Buss, C., Entringer, S., Winter, S.M., Binder, E.B., Heim, C., 2021. The pediatric buccal epigenetic clock identifies significant ageing acceleration in children with internalizing disorder and maltreatment exposure. Neurobiol. Stress 15, 100394. https://doi.org/10.1016/j.ynstr.2021.100394.

De Asis-Cruz, J., Donofrio, M.T., Vezina, G., Limperopoulos, C., 2018. Aberrant brain functional connectivity in newborns with congenital heart disease before cardiac surgery. NeuroImage. Clinical 17, 31–42. https://doi.org/10.1016/j.nicl.2017.09.020.

Dewey, D., Volkovinskaia, A., 2018. Health-related quality of life and peer relationships in adolescents with developmental coordination disorder and attention-deficit-hyperactivity disorder. Dev. Med. Child Neurol. 60 (7), 711–717. https://doi.org/10.1111/dmcn.13753.

Dhollander, T., Tabbara, R., Rosnarho-Tornstrand, J., Tournier, J.-D., Raffelt, D., Connelly, A., 2021. Multi-tissue log-domain intensity and inhomogeneity normalisation for quantitative apparent fibre density. ISMRM 29, 2472.

Diamond, A., 2013. Executive functions. Annu. Rev. Psychol. 64, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750.

Ehrler, M., Latal, B., Kretschmar, O., von Rhein, M., O'Gorman Tuura, R., 2020. Altered frontal white matter microstructure is associated with working memory impairments in adolescents with congenital heart disease: A diffusion tensor imaging study. NeuroImage. Clinical 25, 102123. https://doi.org/10.1016/j.nicl.2019.102123.

Ehrler, M., Schlosser, L., Brugger, P., Greutmann, M., Oxenius, A., Kottke, R., O'Gorman Tuura, R., Latal, B., 2021. Altered white matter microstructure is related to cognition in adults with congenital heart disease. Brain Commun. 3 (1), fcaa224. https://doi.org/10.1093/braincomms/fcaa224.

Ely, B.A., Liu, Q., DeWitt, S.J., Mehra, L.M., Alonso, C.M., Gabbay, V., 2021. Data-driven parcellation and graph theory analyses to study adolescent mood and anxiety symptoms. Transl. Psychiatry 11 (1), 266. https://doi.org/10.1038/s41398-021-01321-x.

EUROCAT. (2015). *Eurocat Prevalence Tables*. http://www.eurocat-network.eu/accessprevalencedata/prevalencetables.

Everson, T.M., O'Shea, T.M., Burt, A., Hermetz, K., Carter, B.S., Helderman, J., Hofheimer, J.A., McGowan, E.C., Neal, C.R., Pastyrnak, S.L., Smith, L.M., Soliman, A., DellaGrotta, S.A., Dansereau, L.M., Padbury, J.F., Lester, B.M., Marsit, C.J., 2020. Serious neonatal morbidities are associated with differences in DNA methylation among very preterm infants. Clin. Epigenetics 12 (1), 151. https://doi.org/10.1186/s13148-020-00942-1.

Ewer, A.K., Middleton, L.J., Furmston, A.T., Bhoyar, A., Daniels, J.P., Thangaratinam, S., Deeks, J.J., Khan, K.S., 2011. Pulse oximetry screening for congenital heart defects in newborn infants (PulseOx): a test accuracy study. Lancet 378 (9793), 785–794. https://doi.org/10.1016/S0140-6736(11)60753-8.

Feldmann, M., Bataillard, C., Ehrler, M., Ullrich, C., Knirsch, W., Gosteli-Peter, M. A., Held, U., Latal, B., 2021. Cognitive and executive function in congenital heart disease: a meta-analysis. *Pediatrics*, *148*(4), e2021050875. 10.1542/peds.2021-050875.

Feldmann, M., Guo, T., Miller, S.P., Knirsch, W., Kottke, R., Hagmann, C., Latal, B., Jakab, A., 2020. Delayed maturation of the structural brain connectome in neonates with congenital heart disease. Brain Commun. 2 (2), fcaa209. https://doi.org/10.1093/braincomms/fcaa209.

Giarraputo, J., DeLoach, J., Padbury, J., Uzun, A., Marsit, C., Hawes, K., Lester, B., 2017. Medical morbidities and DNA methylation of NR3C1 in preterm infants. Pediatr. Res. 81 (1–1), 68–74. https://doi.org/10.1038/pr.2016.185.

Gilchrist, C.P., Thompson, D.K., Kelly, C.E., Beare, R., Adamson, C., Dhollander, T., Lee, K., Treyvaud, K., Matthews, L.G., Tolcos, M., Cheong, J.L.Y., Inder, T.E., Doyle, L.W., Cumberland, A., Anderson, P.J., 2022. The structural connectome and internalizing and externalizing symptoms at 7 and 13 years in individuals born very preterm and full term. Biol. Psychiatry: Cognitive Neurosci. Neuroimag. 7 (4), 424–434. https://doi.org/10.1016/j.bpsc.2021.10.003.

Ginestet, C. E., Nichols, T. E., Bullmore, E. T., & Simmons, A. (2011). Brain network analysis: separating cost from topology using cost-integration. *PloS One*, 6(7), e21570. 10.1371/journal.pone.0021570.

Gonzalez, V.J., Kimbro, R.T., Cutitta, K.E., Shabosky, J.C., Bilal, M.F., Penny, D.J., Lopez, K.N., 2021. Mental health disorders in children with congenital heart disease. Pediatrics 147 (2). https://doi.org/10.1542/peds.2020-1693.

Hay, R.E., Reynolds, J.E., Grohs, M.N., Paniukov, D., Giesbrecht, G.F., Letourneau, N., Dewey, D., Lebel, C., 2020. Amygdala-prefrontal structural connectivity mediates the relationship between prenatal depression and behavior in preschool boys. J. Neurosci. 40 (36), 6969–6977. https://doi.org/10.1523/JNEUROSCI.0481-20.2020.

Heye, K. N., Knirsch, W., Latal, B., Scheer, I., Wetterling, K., Hahn, A., Akinturk, H., Schranz, D., Beck, I., O Gorman Tuura, R., Reich, B., 2018. Reduction of brain volumes after neonatal cardiopulmonary bypass surgery in single-ventricle congenital heart disease before Fontan completion. *Pediatric Res.*, 83(1–1), 63–70. 10.1038/pr.2017.203.

Hughes, E.J., Winchman, T., Padormo, F., Teixeira, R., Wurie, J., Sharma, M., Fox, M., Hutter, J., Cordero-Grande, L., Price, A.N., Allsop, J., Bueno-Conde, J., Tusor, N., Arichi, T., Edwards, A.D., Rutherford, M.A., Counsell, S.J., Hajnal, J.V., 2017. A dedicated neonatal brain imaging system. Magn. Reson. Med. 78 (2), 794–804. https://doi.org/10.1002/mrm.26462.

Hutter, J., Tournier, J.D., Price, A.N., Cordero-Grande, L., Hughes, E.J., Malik, S., Steinweg, J., Bastiani, M., Sotiropoulos, S.N., Jbabdi, S., Andersson, J., Edwards, A. D., Hajnal, J.V., 2018. Time-efficient and flexible design of optimized multishell HARDI diffusion. Magn. Reson. Med. 79 (3), 1276–1292. https://doi.org/10.1002/mrm.26765.

Hyman, S.E., 2009. How adversity gets under the skin. Nat. Neurosci. 12 (3), 241–243.

Ibrahim, K., Eilbott, J.A., Ventola, P., He, G., Pelphrey, K.A., McCarthy, G., Sukhodolsky, D.G., 2019. Reduced amygdala-prefrontal functional connectivity in children with autism spectrum disorder and co-occurring disruptive behavior. Biol. Psychiatry 4 (12), 1031–1041. https://doi.org/10.1016/j.bpsc.2019.01.009.

Jacobs, A., Güiza, F., Verlinden, I., Dulfer, K., Garcia Guerra, G., Joosten, K., Verbruggen, S.C., Vanhorebeek, I., Van den Berghe, G., 2021. Differential DNA methylation by early versus late parenteral nutrition in the PICU: a biological basis for its impact on emotional and behavioral problems documented 4 years later. Clin. Epigenetics 13 (1), 146. https://doi.org/10.1186/s13148-021-01124-3.

Jeurissen, B., Tournier, J.-D., Dhollander, T., Connelly, A., Sijbers, J., 2014. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. NeuroImage 103, 411–426. https://doi.org/10.1016/j.neuroimage.2014.07.061.

Kaiser, M., 2011. A tutorial in connectome analysis: topological and spatial features of brain networks. NeuroImage 57 (3), 892–907. https://doi.org/10.1016/j.neuroimage.2011.05.025.

Karmacharya, S., Gagoski, B., Ning, L., Vyas, R., Cheng, H.H., Soul, J., Newberger, J.W., Shenton, M.E., Rathi, Y., Grant, P.E., 2018. Advanced diffusion imaging for assessing normal white matter development in neonates and characterizing aberrant development in congenital heart disease. NeuroImage. Clinical 19, 360–373. https://doi.org/10.1016/j.nicl.2018.04.032.

Kellner, E., Dhital, B., Kiselev, V.G., Reisert, M., 2016. Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn. Reson. Med. 76 (5), 1574–1581. https://doi.org/10.1002/mrm.26054.

Kelly, C.J., Makropoulos, A., Cordero-Grande, L., Hutter, J., Price, A., Hughes, E., Murgasova, M., Teixeira, R.P.A.G., Steinweg, J.K., Kulkarni, S., Rahman, L., Zhang, H., Alexander, D.C., Rueckert, D., Hajnal, J.V., Simpson, J., Edwards, A.D., Rutherford, M.A., Counsell, S.J., 2017. Impaired development of the cerebral cortex in infants with congenital heart disease is correlated to reduced cerebral oxygen delivery. Sci. Rep. 7 (1), 15088. https://doi.org/10.1038/s41598-017-14939-z.

Kelly, C.J., Arulkumaran, S., Tristão Pereira, C., Cordero-Grande, L., Hughes, E.J., Teixeira, R.P.A.G., Steinweg, J.K., Victor, S., Pushparajah, K., Hajnal, J.V., Simpson, J., Edwards, A.D., Rutherford, M.A., Counsell, S.J., 2019a. Neuroimaging findings in newborns with congenital heart disease prior to surgery: an observational study. Arch Dis Child 104 (11), 1042–1048.

Kelly, C.J., Christiaens, D., Batalle, D., Makropoulos, A., Cordero-Grande, L., Steinweg, J. K., O'Muircheartaigh, J., Khan, H., Lee, G., Victor, S., Alexander, D.C., Zhang, H., Simpson, J., Hajnal, J.V., Edwards, A.D., Rutherford, M.A., Counsell, S.J., 2019b. Abnormal microstructural development of the cerebral cortex in neonates with congenital heart disease is associated with impaired cerebral oxygen delivery. J. Am. Heart Assoc. 8 (5), e009893.

Klouda, L., Franklin, W.J., Saraf, A., Parekh, D.R., Schwartz, D.D., 2017. Neurocognitive and executive functioning in adult survivors of congenital heart disease. Congenital Heart Disease 12 (1), 91–98. https://doi.org/10.1111/chd.12409.

Knirsch, W., Mayer, K.N., Scheer, I., Tuura, R., Schranz, D., Hahn, A., Wetterling, K., Beck, I., Latal, B., Reich, B., 2017. Structural cerebral abnormalities and neurodevelopmental status in single ventricle congenital heart disease before Fontan procedure. Eur. J. Cardio-Thoracic Surgery 51 (4), 740–746. https://doi.org/10.1093/ejcts/ezw399.

Landolt, M.A., Ystrom, E., Stene-Larsen, K., Holmstrøm, H., Vollrath, M.E., 2014. Exploring causal pathways of child behavior and maternal mental health in families with a child with congenital heart disease: a longitudinal study. Psychol. Med. 44 (16), 3421–3433. https://doi.org/10.1017/S0033291713002894.

Lawley, C.M., Winlaw, D.S., Sholler, G.F., Martin, A., Badawi, N., Walker, K., Nassar, N., Lain, S.J., 2019. School-age developmental and educational outcomes following cardiac procedures in the first year of life: a population-based record linkage study. Pediatr. Cardiol. 40 (3), 570–579. https://doi.org/10.1007/s00246-018-2029-y.

Li, D., Cui, X., Yan, T., Liu, B., Zhang, H., Xiang, J., Wang, B., 2021. Abnormal rich club organization in hemispheric white matter networks of ADHD. J. Attent. Dis. 25 (9), 1215–1229. https://doi.org/10.1177/1087054719892887.

Liamlahi, R., von Rhein, M., Bührer, S., Valsangiacomo Buechel, E.R., Knirsch, W., Landolt, M.A., Latal, B., 2014. Motor dysfunction and behavioural problems frequently coexist with congenital heart disease in school-age children. Acta Paediatr. n/a–n/a.

Lim, J.M., Porayette, P., Marini, D., Chau, V., Au-Young, S.H., Saini, A., Ly, L.G., Blaser, S., Shroff, M., Branson, H.M., Sananes, R., Hickey, E.J., Gaynor, J.W., Van Arsdell, G., Miller, S.P., Seed, M., Mei, L.J., Prashob, P., Davide, M., Mike, S., 2019. Associations between age at arterial switch operation, brain growth, and development in infants with transposition of the great arteries. Circulation 139 (24), 2728–2738. https://doi.org/10.1161/CIRCULATIONAHA.118.037495.

Limperopoulos, C., Tworetzky, W., McElhinney, D.B., Newburger, J.W., Brown, D.W., Robertson, R.L.J., Guizard, N., McGrath, E., Geva, J., Annese, D., Dunbar-Masterson, C., Trainor, B., Laussen, P.C., du Plessis, A.J., 2010. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation 121 (1), 26–33. https://doi.org/10.1161/CIRCULATIONAHA.109.865568.

Makropoulos, A., Gousias, I.S., Ledig, C., Aljabar, P., Serag, A., Hajnal, J.V., Edwards, A. D., Counsell, S.J., Rueckert, D., 2014. Automatic whole brain MRI segmentation of the developing neonatal brain. IEEE Trans. Med. Imaging 33 (9), 1818–1831. https://doi.org/10.1109/TMI.2014.2322280.

Makropoulos, A., Robinson, E.C., Schuh, A., Wright, R., Fitzgibbon, S., Bozek, J., Counsell, S.J., Steinweg, J., Vecchiato, K., Passerat-Palmbach, J., Lenz, G., Mortari, F., Tenev, T., Duff, E.P., Bastiani, M., Cordero-Grande, L., Hughes, E., Tusor, N., Tournier, J.-D., Hutter, J., Price, A.N., Teixeira, R.P.A.G., Murgasova, M., Victor, S., Kelly, C., Rutherford, M.A., Smith, S.M., Edwards, A.D., Hajnal, J.V., Jenkinson, M., Rueckert, D., 2018. The developing human connectome project: A minimal processing pipeline for neonatal cortical surface reconstruction. NeuroImage 173, 88–112.

Marino, B.S., Lipkin, P.H., Newburger, J.W., Peacock, G., Gerdes, M., Gaynor, J.W., Mussatto, K.A., Uzark, K., Goldberg, C.S., Johnson, W.H.J., Li, J., Smith, S.E., Bellinger, D.C., Mahle, W.T., 2012. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation 126 (9), 1143–1172. https://doi.org/10.1161/CIR.0b013e318265ee8a.

Meuwly, E., Feldmann, M., Knirsch, W., von Rhein, M., Payette, K., Dave, H., Tuura, R. O. G., Kottke, R., Hagmann, C., Latal, B., Jakab, A., Brain, R. G. H., 2019. Postoperative brain volumes are associated with one-year neurodevelopmental outcome in children with severe congenital heart disease. *Sci. Rep.*, 9(1), 10885. 10.1038/s41598-019-47328-9.

Miller, S.P., McQuillen, P.S., Hamrick, S., Xu, D., Glidden, D.V., Charlton, N., Karl, T., Azakie, A., Ferriero, D.M., Barkovich, A.J., Vigneron, D.B., 2007. Abnormal brain development in newborns with congenital heart disease. New England J. Med. 357 (19), 1928–1938. https://doi.org/10.1056/NEJMoa067393.

Montirosso, R., Provenzi, L., Fumagalli, M., Sirgiovanni, I., Giorda, R., Pozzoli, U., Beri, S., Menozzi, G., Tronick, E., Morandi, F., 2016a. Serotonin transporter gene (SLC6A4) methylation associates with neonatal intensive care unit stay and 3-month-old temperament in preterm infants. Child Dev. 87 (1), 38–48.

Montirosso, R., Provenzi, L., Giorda, R., Fumagalli, M., Morandi, F., Sirgiovanni, I., Pozzoli, U., Grunau, R., Oberlander, T.F., Mosca, F., Borgatti, R., 2016b. SLC6A4 promoter region methylation and socio-emotional stress response in very preterm and full-term infants. Epigenomics 8 (7), 895–907.

Mulkey, S.B., Ou, X., Ramakrishnaiah, R.H., Glasier, C.M., Swearingen, C.J., Melguizo, M.S., Yap, V.L., Schmitz, M.L., Bhutta, A.T., 2014. White matter injury in newborns with congenital heart disease: a diffusion tensor imaging study. Pediatr. Neurol. 51 (3), 377–383. https://doi.org/10.1016/j.pediatrneurol.2014.04.008.

Newman, M.E.J., 2006. Modularity and community structure in networks. Proc. Natl. Acad. Sci. U.S.A. 103 (23), 8577–8582.

Ng, I.H.X., Bonthrone, A.F., Kelly, C.J., Cordero-Grande, L., Hughes, E.J., Price, A.N., Hutter, J., Victor, S., Schuh, A., Rueckert, D., Hajnal, J.V., Simpson, J., Edwards, A. D., Rutherford, M.A., Batalle, D., Counsell, S.J., 2020. Investigating altered brain development in infants with congenital heart disease using tensor-based morphometry. Sci. Rep. 10 (1), 14909. https://doi.org/10.1038/s41598-020-72009-3.

Ní Bhroin, M., Abo Seada, S., Bonthrone, A.F., Kelly, C.J., Christiaens, D., Schuh, A., Pietsch, M., Hutter, J., Tournier, J.-D., Cordero-Grande, L., Rueckert, D., Hajnal, J. V., Pushparajah, K., Simpson, J., Edwards, A.D., Rutherford, M.A., Counsell, S.J., Batalle, D., 2020. Reduced structural connectivity in cortico-striatal-thalamic network in neonates with congenital heart disease. NeuroImage. Clinical 28, 102423. https://doi.org/10.1016/j.nicl.2020.102423.

Papachristou, E., Flouri, E., 2020. The codevelopment of internalizing symptoms, externalizing symptoms, and cognitive ability across childhood and adolescence. Dev. Psychopathol. 32 (4), 1375–1389. https://doi.org/10.1017/S0954579419001330.

Pietsch, M., Christiaens, D., Hutter, J., Cordero-Grande, L., Price, A.N., Hughes, E., Edwards, A.D., Hajnal, J.V., Counsell, S.J., Tournier, J.-D., 2019. A framework for multi-component analysis of diffusion MRI data over the neonatal period. NeuroImage 186, 321–337. https://doi.org/10.1016/j.neuroimage.2018.10.060.

Pradhan, S., Gupta, R.K., Kapoor, R., Shashank, S., Kathuria, M.K., 1998. Parainfectious conus myelitis. J. Neurol. Sci. 161 (2), 156–162.

Provenzi, L., Fumagalli, M., Sirgiovanni, I., Giorda, R., Pozzoli, U., Morandi, F., Beri, S., Menozzi, G., Mosca, F., Borgatti, R., Montirosso, R., 2015. Pain-related stress during the Neonatal Intensive Care Unit stay and SLC6A4 methylation in very preterm infants. Front. Behav. Neurosci. 9, 99. https://doi.org/10.3389/fnbeh.2015.00099.

Provenzi, L., Guida, E., Montirosso, R., 2018. Preterm behavioral epigenetics: A systematic review. Neurosci. Biobehav. Rev. 84, 262–271. https://doi.org/10.1016/j.neubiorev.2017.08.020.

Raffelt, D., Dhollander, T., Tournier, J.-D., Tabbara, R., Smith, R.E., Pierre, E., Connelly, A., 2017. Bias field correction and intensity normalisation for quantitative analysis of apparent fibre density. ISMRM 26, 3541.

Ramirez, A., Peyvandi, S., Cox, S., Gano, D., Xu, D., Tymofiyeva, O., McQuillen, P.S., 2022. Neonatal brain injury influences structural connectivity and childhood functional outcomes. PLoS ONE 17 (1), e0262310–e. https://doi.org/10.1371/journal.pone.0262310.

Ramphal, B., Whalen, D.J., Kenley, J.K., Yu, Q., Smyser, C.D., Rogers, C.E., Sylvester, C. M., 2020. Brain connectivity and socioeconomic status at birth and externalizing symptoms at age 2 years. Developm. Cognitive Neurosci. 45, 100811 https://doi.org/10.1016/j.dcn.2020.100811.

Rollins, C.K., Watson, C.G., Asaro, L.A., Wypij, D., Vajapeyam, S., Bellinger, D.C., DeMaso, D.R., Robertson, R.L.J., Newburger, J.W., Rivkin, M.J., 2014. White matter microstructure and cognition in adolescents with congenital heart disease. J. Pediatrics 165 (5), 932–936. https://doi.org/10.1016/j.jpeds.2014.07.028.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. NeuroImage 52 (3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003.

Schmithorst, V.J., Votava-Smith, J.K., Tran, N., Kim, R., Lee, V., Ceschin, R., Lai, H., Johnson, J.A., De Toledo, J.S., Blüml, S., Paquette, L., Panigrahy, A., 2018. Structural network topology correlates of microstructural brain dysmaturation in term infants with congenital heart disease. Hum. Brain Mapp. 39 (11), 4593–4610. https://doi.org/10.1002/hbm.24308.

Schoemaker, K., Mulder, H., Deković, M., Matthys, W., 2013. Executive functions in preschool children with externalizing behavior problems: a meta-analysis. J. Abnorm. Child Psychol. 41 (3), 457–471. https://doi.org/10.1007/s10802-012-9684-x.

Shi, F., Yap, P.-T., Wu, G., Jia, H., Gilmore, J. H., Lin, W., Shen, D., 2011. Infant brain atlases from neonates to 1- and 2-year-olds. *PloS One*, *6*(4), e18746. 10.1371/journal.pone.0018746.

Shillingford, A. J., Glanzman, M. M., Ittenbach, R. F., Clancy, R. R., Gaynor, J. W., Wernovsky, G., 2008. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics*, *121*(4), e759–e767. 10.1542/peds.2007-1066.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155. https://doi.org/10.1002/hbm.10062.

Smith, R.E., Tournier, J.-D., Calamante, F., Connelly, A., 2012. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. NeuroImage 62 (3), 1924–1938. https://doi.org/10.1016/j.neuroimage.2012.06.005.

Smith, R.E., Tournier, J.-D., Calamante, F., Connelly, A., 2015. SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. NeuroImage 119, 338–351. https://doi.org/10.1016/j.neuroimage.2015.06.092.

Stegeman, R., Feldmann, M., Claessens, N.H.P., Jansen, N.J.G., Breur, J.M.P.J., de Vries, L.S., Logeswaran, T., Reich, B., Knirsch, W., Kottke, R., Hagmann, C., Latal, B., Simpson, J., Pushparajah, K., Bonthrone, A.F., Kelly, C.J., Arulkumaran, S., Rutherford, M.A., Counsell, S.J., Benders, M.J.N.L., 2021. A uniform description of perioperative brain MRI findings in infants with severe congenital heart disease: results of a european collaboration. Am. J. Neuroradiol. 42 (11), 2034–2039.

Studholme, C., Hill, D.L.G., Hawkes, D.J., 1999. An overlap invariant entropy measure of 3D medical image alignment. Pattern Recogn. 32 (1), 71–86.

Sun, L., Macgowan, C.K., Sled, J.G., Yoo, S.-J., Manlhiot, C., Porayette, P., Grosse-Wortmann, L., Jaeggi, E., McCrindle, B.W., Kingdom, J., Hickey, E., Miller, S., Seed, M., 2015. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation 131 (15), 1313–1323. https://doi.org/10.1161/CIRCULATIONAHA.114.013051.

Tanzer, M., Derome, M., Morosan, L., Salaminios, G., Debbané, M., 2021. Cortical thickness of the insula and prefrontal cortex relates to externalizing behavior: Cross-sectional and prospective findings. Dev. Psychopathol. 33 (4), 1437–1447. https://doi.org/10.1017/S0954579420000619.

Thijssen, S., Collins, P.F., Weiss, H., Luciana, M., 2021. The longitudinal association between externalizing behavior and frontoamygdalar resting-state functional connectivity in late adolescence and young adulthood. J. Child Psychol. Psychiatry 62 (7), 857–867. https://doi.org/10.1111/jcpp.13330.

Tollenaar, M.S., Beijers, R., Garg, E., Nguyen, T.T.T., Lin, D.T.S., MacIsaac, J.L., Shalev, I., Kobor, M.S., Meaney, M.J., O'Donnell, K.J., 2021. Internalizing symptoms associate with the pace of epigenetic aging in childhood. Biol. Psychol. 159, 108021 https://doi.org/10.1016/j.biopsycho.2021.108021.

Tournier, J.-D., Smith, R.E., Raffelt, D.A., Tabbara, R., Dhollander, T., Pietsch, M., Christiaens, D., Jeurissen, B., Yeh, C.-H., Connelly, A., 2019. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. Neuroimage 202, 116137. https://doi.org/10.1101/551739.

Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., Gee, J.C., 2010. N4ITK: improved N3 bias correction. IEEE Trans. Med. Imaging 29 (6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289. https://doi.org/10.1006/nimg.2001.0978.

Varela, M., Groves, A.M., Arichi, T., Hajnal, J.V., 2012. Mean cerebral blood flow measurements using phase contrast MRI in the first year of life. NMR Biomed. 25 (9), 1063–1072. https://doi.org/10.1002/nbm.2771.

Veraart, J., Novikov, D.S., Christiaens, D., Ades-aron, B., Sijbers, J., Fieremans, E., 2016. Denoising of diffusion MRI using random matrix theory. NeuroImage 142, 394–406. https://doi.org/10.1016/j.neuroimage.2016.08.016.

von Rhein, M., Buchmann, A., Hagmann, C., Dave, H., Bernet, V., Scheer, I., Knirsch, W., Latal, B., 2015. Severe congenital heart defects are associated with global reduction of neonatal brain volumes. *J. Pediatrics*, *167*(6), 1259-63.e1. 10.1016/j.jpeds.2015.07.006.

Wee, C.-Y., Tuan, T.A., Broekman, B.F.P., Ong, M.Y., Chong, Y.-S., Kwek, K., Shek, L.-P.-C., Saw, S.-M., Gluckman, P.D., Fortier, M.V., Meaney, M.J., Qiu, A., 2017. Neonatal neural networks predict children behavioral profiles later in life. Hum. Brain Mapp. 38 (3), 1362–1373. https://doi.org/10.1002/hbm.23459.

Wolke, D., Jaekel, J., Hall, J., Baumann, N., 2013. Effects of sensitive parenting on the academic resilience of very preterm and very low birth weight adolescents. J. Adolesc. Health 53 (5), 642–647. https://doi.org/10.1016/j.jadohealth.2013.06.014.

Wren, C., Sullivan, J. J., 2001. Survival with congenital heart disease and need for follow up in adult life. *Heart*, *85*(4), 438 LP – 443. 10.1136/heart.85.4.438.

Xia, M., Wang, J., He, Y., 2013. BrainNet Viewer: a network visualization tool for human brain connectomics. *PloS One*, *8*(7), e68910. 10.1371/journal.pone.0068910.

Zalesky, A., Fornito, A., Bullmore, E.T., 2010. Network-based statistic: identifying differences in brain networks. NeuroImage 53 (4), 1197–1207. https://doi.org/10.1016/j.neuroimage.2010.06.041.