Review Article on Pediatric Heart

Biological and structural phenotypes associated with neurodevelopmental outcomes in congenital heart disease

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Abstract: Neurodevelopmental disability (NDD) is recognised as one of the most common comorbidities in children with congenital heart disease (CHD) and is associated with altered brain structure and growth throughout the life course. Causes and contributors underpinning the CHD and NDD paradigm are not fully understood, and likely include innate patient factors, such as genetic and epigenetic factors, prenatal haemodynamic consequences as a result of the heart defect, and factors affecting the fetal-placental-maternal environment, such as placental pathology, maternal diet, psychological stress and autoimmune disease. Additional postnatal factors, including the type and complexity of disease and other clinical factors such as prematurity, peri-operative factors and socioeconomic factors are also expected to play a role in determining the final presentation of the NDD. Despite significant advances in knowledge and strategies to optimise outcomes, the extent to which adverse neurodevelopment can be modified remains unknown. Understanding biological and structural phenotypes associated with NDD in CHD are vital for understanding disease mechanisms, which in turn will advance the development of effective intervention strategies for those at risk. This review article summarises our current knowledge surrounding biological, structural, and genetic contributors to NDD in CHD and describes avenues for future research; highlighting the need for translational studies that bridge the gap between basic science and clinical practice.

Keywords: Neurodevelopment; congenital heart disease (CHD); genetics; fetal; brain

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Introduction

Congenital heart disease (CHD) is the most common birth defect, affecting 0.6–1.3% of babies born each year (1). It is associated with significant mortality and morbidity (2) with many individuals with CHD requiring lifelong medical care and treatment (3). The cause of most CHD is unknown and attributed to a combination of genetic, epigenetic and environmental factors (4). Following advances in treatment and care, >90% of affected children now survive to adulthood (5), resulting in greater appreciation and interest in longer-term health outcomes, such as neurodevelopment and quality of life (6).

Overview of neurodevelopmental disability in CHD and relevance at all ages

Neurodevelopmental delay and/or disability (NDD) is now recognised as a lifespan issue for many children born with CHD (7). Those with more complex forms of CHD, such as those with single ventricles pathologies or transposition of the great arteries who typically experience more severe disease requiring neonatal bypass operations and on-going monitoring and care, are at a greater risk of worse prognosis (8,9). However, risk factors contributing to more severe or persisting disability are not fully understood and appear multifactorial and synergistic (10). A spectrum of outcomes is observed, and many individuals with CHD demonstrate no impairment and their level of functioning may exceed population norms. However, as many as 50% demonstrate mild to moderate NDD and later cognitive impairment, and a small number demonstrate global cognitive or intellectual disability (7,8,11-15). These challenges have important implications throughout the life course, including on academic achievement, employment opportunities, psychological and social functioning, and overall quality of life (16-19). Established guidelines document the need for routine neurodevelopmental follow-up throughout childhood (7), however, this has not yet translated to standard clinical care in most paediatric centres. Importantly, neuropsychological services for children and adults with CHD are under-resourced in comparison to other clinical paediatric populations, such as those born very preterm, despite similar risk factors and adverse outcomes (11). Understanding biological and structural phenotypes associated with NDD in CHD are necessary to advance clinical care and the development of effective intervention strategies for those at risk. Interventions targeting the earliest stages of development will be vital for optimising developmental outcomes. An overview of the risk factors contributing to NDD in CHD is outlined in *Figure 1*.

Early manifestations of NDD typically include poor feeding, speech and language delay, challenges with gross and fine motor movement, and early cognitive concerns (20-22). Early speech and language delays more commonly resolve over time (23), whereas motor impairments are a persisting concern throughout childhood (24,25), and the extent of cognitive challenges typically worsen over time (14,21). In infants with more complex CHD, such as those undergoing the single ventricle pathway, the early developmental years are impacted by the need for multiple cardiac surgeries and prolonged exposure to the restrictive and artificial hospital environment. Length of inpatient stay is usually a surrogate marker of more complex diagnoses and post-operative complications and is a strong predictor of long-term neurodevelopmental outcomes (7).

At school age, intelligence quotients are generally within population norms, although typically fall within the low average range (26,27). In contrast, early NDD typically manifests as specific cognitive challenges that have important implications for academic performance and achievement, often requiring additional school provisions and support (19,28). Key challenges include deficits in attention, processing speed, visuospatial skills, memory, social cognition, and executive functioning—that encompasses a range of higher order cognitive skills including working memory, mental flexibility, problem-solving, and inhibitory control (27,29-32). Many children show challenges across multiple domains of functioning, requiring greater intervention and support (21). Behavioural and psychological disorders (e.g., anxiety, depression, and poor behavioural or emotional regulation) are also an important concern (33,34). The extent to which these difficulties are associated with NDD has not yet been established but are anticipated to be linked. In addition, children with CHD are at an increased risk of developing disorders of social functioning, including autism spectrum disorder (35).

Higher-order executive skills continue to develop throughout childhood in conjunction with the maturation of key brain structures, notably the pre-frontal cortex (36), and the full extent of these challenges may not be observed until adolescence or early adulthood. Indeed, studies have shown that executive functioning deficits are among the most prevalent and severe impairments observed in older children and young adults with CHD (8,28,37), which

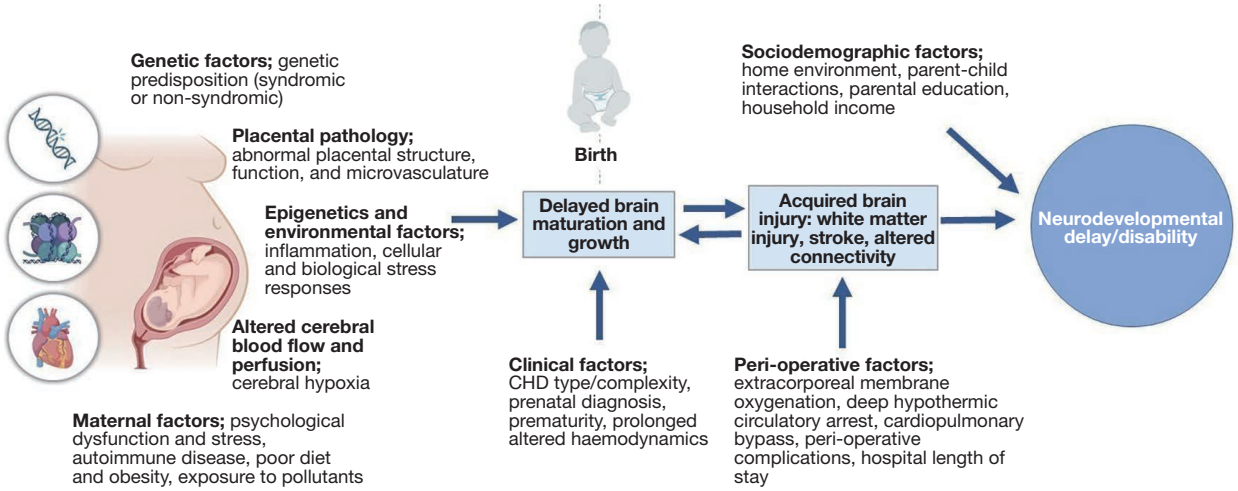

Figure 1 Contributors to neurodevelopmental delay and disability in CHD. CHD, congenital heart disease.

become an increasingly significant challenge alongside greater cognitive demands and the need for increased functional independence that occurs with maturation into adulthood. Cognitive dysfunction persists throughout adulthood (8,38-40), although longer-term outcomes have been less extensively studied. Older adults with a Fontan circulation (up to 50 years old) have been found to have worse neurocognitive dysfunction compared to Fontan adolescents after controlling for age (8), that may suggest a possible worsening of cognitive challenges throughout adulthood in those with highly complex forms of CHD. Although the extent to which these outcomes may reflect an era effect relating to previous surgical strategies and medical care are currently undetermined. Concerningly, adults with all forms of CHD are at a significantly increased risk of dementia, including early onset dementia (41). As the adult CHD population continues to grow, so does the need for a better understanding of the accumulating risk factors that compound early NDD and contribute to worse long-term cognitive outcomes.

Brain structure and function: insights from neuroimaging

In individuals with CHD, NDD is paralleled by abnormalities in brain structure and function across the lifespan (42-44). Neuroimaging studies of the fetal CHD brain have demonstrated that abnormal brain development begins *in utero*. Altered cortical development and reduced brain size are observed as early as the second trimester of gestation in fetuses with complex cardiac lesions (45-47) and precede anomalous growth patterns and reduced brain volumes, that become progressively more pronounced throughout the third trimester (45,48-51). Fetal brain volume has been shown to predict neurodevelopmental outcomes at 2 years of age in children with CHD (52), suggesting prenatal brain parameters may have prognostic value in identifying infants at risk of early NDD; however, further studies are needed to replicate these findings, and associations with longer-term neurodevelopmental outcomes are yet to be determined.

Post-natal brain development continues to follow an altered growth trajectory, with progressive growth of both regional and global brain volumes occurring at a slower rate compared to typically developing infants (53,54). Consistently, widespread reductions in global and regional brain volumes have been demonstrated pre-operatively in various heterogenous CHD cohorts (54-59). In infants with transposition of the great arteries, the rate of brain growth has been found to significantly increase after surgical correction and normalisation of the cardiac circulation and there may be some 'catch-up' growth by 3 years of age (60). In contrast, reduced brain growth and smaller brain volumes persist in infants with hypoplastic left heart syndrome post-operatively (60,61), suggesting that continued haemodynamic instability may have an important contributory role in pervasive post-natal brain development.

In infants requiring cardiac surgery, peri-natal brain immaturity is associated with a greater risk of pre- and post-operative brain injury (62-65), that occurs in as many as 40% and 26–44%, respectively (53,65-68). Predominant lesions include patterns of white matter injury and stroke;

the prevalence and severity of which are typically worse in infants with univentricular lesions (65,68). Recently, Peyvandi and colleagues found that moderate to severe peri-operative injury is associated with subsequent reduced brain growth (68), demonstrating a complex interplay between brain development and acquired injury and a possible "two-hit phenomena" (69).

Associations between peri-operative brain injury and early neurodevelopmental outcomes are variable (65,66,68,70,71). The current understanding is that altered brain maturation may be more closely linked to NDD (52,55,72-74). Consistently, significant associations between smaller brain volumes and worse cognitive outcomes are observed throughout childhood and adulthood in various CHD cohorts (8,56,75-79). Alterations in white matter microstructure, that may reflect aberrant white matter maturation, have also shown significant associations with cognitive dysfunction in older children and adults with CHD (80-84), with some variation reported in recent findings (85). In contrast, associations with structural brain injury continue to be broadly inconsistent, despite adolescents and adults demonstrating an alarming rate of injury in some studies (8,42).

Current research has advanced into the field of "connectomics" in an effort to better understand the impact of CHD on structural brain connectivity, which may provide clearer insight into direct structure-function relationships. Emerging studies have demonstrated reduced maturation in the whole brain connectome (i.e., neural connections or networks) and specific brain networks in infants with CHD that is associated with peri-operative white matter injury burden (86-88); however, studies investigating associations with NDD are limited. Ramirez and colleagues have demonstrated that global and regional structural connectivity in infants with CHD predicts early motor development and language outcomes (89). Similarly, Panigraphy and colleagues have found that network topology mediates the differences observed in cognitive functioning in adolescents with CHD compared to healthy controls (90).

While major advances have been made in our understanding of brain development in CHD, much remains unknown and longitudinal brain magnetic resonance imaging (MRI) studies evaluating the developmental trajectory and timing of injury in the CHD brain from gestation onwards are needed to fully elucidate the impact of perinatal brain abnormalities on NDD and longer-term cognitive dysfunction.

Weighing causes and contributors including placental insufficiency

Distinguishing the causes and consequences of acute brain injury, such as stroke, from altered neurodevelopment, which appears to be pre-programmed, will have important implications for the development of targeted NDD interventions. This is made difficult given the considerable overlap between these two entities, particularly in neonates undergoing cardiac surgery, and notably in those on the single ventricle pathway (68). The need for cardio-pulmonary resuscitation (CPR) or extracorporeal membrane oxygenation (ECMO) via the heart-lung machine, more common in the neonatal cardiac surgery population, may be associated with acute brain injury.

Early assumptions that NDD was due to perinatal neurological compromise or perioperative brain injury are not correct (10,91). The use of deep hypothermic circulatory arrest, a common operative strategy in complex heart operations during which the body is cooled to temperatures ranging from 20–25 ℃ thereby ceasing blood circulation and brain function, was also for a long time, implicated as a cause or contributor to NDD. However, it is likely that deep hypothermic circulatory arrest is just one of many contributors with small effect sizes, including the generation of cerebral microemboli or blood clots by the heart-lung machine and the consequences of the systemic inflammatory response that occurs during surgery. These may contribute to acute brain injury, and may worsen neurodevelopmental trajectory but are not thought of as the primary causes of NDD and best estimates indicate that peri-operative factors explain only 5–8% of the variability in neurodevelopmental outcomes (91-93). Importantly, NDD may occur despite an optimal clinical course of cardiac care, where no complications are observed.

Instead, current thinking implicates impaired fetal brain development (94), placental dysfunction (95,96) and genetic factors (4,97), both fetal and maternal, as predominant causes of NDD. Two important 'environmental' stressors affect human fetuses in the context of CHD. The first is a form of placental insufficiency; the placenta may be smaller and structurally abnormal leading to relative substrate deficiency, slower than normal fetal growth, smaller brain volumes, preterm birth, and lower birthweight (96,98) The second is the relative hypoxia encountered by the fetal brain in circumstances where the normal highly oxygenated blood cannot reach the brain because of aortic atresia (99,100), a fundamental component in many single

ventricle patients. In this context, blood with a lower-than-normal oxygenation reaches the brain retrograde via the ductus arteriosus and possibly at a lower pressure. These factors may explain lactate accumulation within the brain of CHD fetuses (101), and the relative brain immaturity of neonates with CHD (102). Other environmental factors including maternal obesity, stress, autoimmune disease are also associated with NDD in offspring (103). As well as being implicated in the cause of the CHD (4,97), genetic variants are likely implicated in the adaptive responses to these environmental stresses.

These environmental factors may contribute to the abnormal brain development observed throughout gestation and we lack an understanding of which factors are important at which specific time-points. We also do not know the extent to which amelioration of these factors—including maternal oxygen therapy (104)—might improve developmental trajectories in the child, or whether any of these pathways might be amenable to post-natal intervention.

Genetic contributions and unknowns

NDD in syndromic CHD

That genetics may underpin both heart and brain development is evidenced in the many established genetic syndromes incorporating both heart defects and neurodevelopmental issues as part of the disease spectrum. While the exact cause and/or genetic contribution of the neurodevelopmental phenotype in most established syndromes remains unknown, several candidate genes have been identified in some established syndromes. In syndromes associated with chromosomal alterations and copy number variations, where multiple genes may be implicated, significant headway has been made to understand which genes contribute towards specific phenotypic components, including neurodevelopment. For example, in 22q11.2 deletion syndrome, which encompasses 32 genes all of which are candidates for CHD and NDD, genes contributing towards both heart and brain development [*TBX1* (100) and *HIRA* (105) among others] or solely towards the neurodevelopmental/neurological phenotype (*COMT* and *PRODH* (106)), have been identified. Similarly, in Williams syndrome, which typically involves 25–27 genes, the *ELN* gene is thought to primarily contribute towards the characteristic cardiovascular phenotype, supravalvular aortic stenosis, and the *GTF2I* and *GTF2IRD1* genes towards the neurodevelopmental phenotype (107).

In syndromes caused by variations in single genes, the mechanism by which these genes likely affect two or more organ systems such as the heart and brain among others, is due to their ability to regulate or interact with multiple genes and/or gene pathways. Indeed, chromatin modifying genes *KMT2D*, *CHD7* and *CDK13* which cause Kabuki and CHARGE syndrome (108) and CDK13-related disorder (109) respectively, modulate gene expression by altering access to the DNA and thereby disrupting multiple developmental processes, including in the heart and brain. Similarly, transcriptional regulators, including *FOXP1* (110), *ZEB2* (111) among others, have been implicated in both CHD and NDD.

While NDD is the most common co-morbidity associated with CHD, other extra-cardiac anomalies, such as those affecting the urogenital system (112), are often seen in conjunction with CHD and/or NDD, suggesting that genetic risk may extend beyond heart and brain development to other organ systems.

NDD in non-syndromic CHD

With the exact cause and/or genetic contribution of the neurodevelopmental phenotype in many established syndromes unknown, it is not surprising that understanding the genetic contribution of NDD in non-syndromic CHD poses a significant challenge, not helped by the fact that these represent most presenting cases. Over the last decade; however, advances in genomic technologies combined with large cohorts and sophisticated statistical analyses, have provided important clues to the genetic architecture underlying this patient group. Specifically, these studies identified a 2-fold enrichment in damaging *de novo* variants in genes highly expressed in the heart in patients with CHD and NDD and a 4.7-fold enrichment in patients with CHD, NDD and other congenital anomalies, suggestive of an additive effect in heart-expressing genes with increasing non-cardiac phenotypic complexity (97). Further, 69 genes harbouring damaging *de novo* variants, were shared between CHD patients and cohorts comprising patients with isolated NDD, providing additional support for shared genetic aetiologies to heart and brain development. Not surprisingly many of these genes are chromatin modifying genes and transcriptional regulators, likely exerting wide-reaching phenotypic effects. Importantly, CHD patients with damaging *de novo* variants in these 69 genes, were

at significantly increased risk of NDD, providing a basis for future downstream applications of precision medicine approaches.

More recently, a significant overlap of genetic burden has been identified in patients with CHD and patients with autism (113). Enrichments in *de novo* variants in genes involved in the connectome, have also recently been implicated in patients with CHD (114).

While these studies have provided important insight into disease mechanisms of NDD in CHD, specifically in terms of shared genetic aetiologies, the findings are not readily applicable to the individual patient. Studies assessing the clinical relevance of this information have identified important genetic burden associated with 'neurotransmitters', 'axon guidance' and 'RASopathy' pathways in patients with CHD and NDD; however, no clinically actionable cause for the NDD could be identified (115).

The contribution of common variants in both heart and brain development is becoming increasingly relevant (116,117) and will likely inform the development of polygenic risk scores used to identify those CHD patients most at risk of NDD.

So, while significant headway has been made to unravel the genetic component of NDD in CHD, specifically the contribution of rare and damaging *de novo* genetic variant burden, which is often in chromatin modifying and connectome genes; additional factors such as common genetic variants, morphology, epigenetics and the environment, are increasingly highlighted as important contributors in the final phenotypic presentation.

Inherited and epigenetic associations in other forms of NDD

Increasing evidence suggests that inflammation, cellular stress, and epigenetic factors at the gene-environment interface play a key role in the pathogenesis of NDDs (118-120). Neurodevelopment begins in-utero and continues to 21 years of age, through a constant process of synaptic pruning and re-wiring (121). Gestation is a particularly sensitive time, as key brain networks are being established in the developing fetus (122). The maternal immune activation hypothesis posits that fetal exposure to inflammation and dysregulated immune milieu adversely affects neurodevelopment (122,123). Many environmental factors, such as poor diet, low exercise, sleep, infection, stress, and pollutants can cause maternal immune activation and have all been associated with increased risk of NDDs in offspring (103,124). Environmental risk factors experienced by the mother during pregnancy are hypothesized to be 'biologically embedded' in the cellular and epigenetic architecture of the offspring (125). These inherited vulnerabilities can then be modulated by post-natal risk factors, such as neonatal infections, childhood trauma, or other early life stress (126).

Environmental insults can influence the transcription of susceptibility genes via key inflammatory and cellular stress signalling pathways, including the Toll-like receptor pathway (103), and the integrated stress response (127). These signalling cascades may then modulate the expression of NDDs through finely tuned epigenetic, gene regulation, and post-transcriptional processes (128-130). Epigenetic modifications are chemical or physical changes to chromatin which can either increase or repress gene transcription (130). The four main epigenetic modifying factors are DNA methylation, histone modifications, chromatin modelling, and microRNA. Controlled, yet dynamic, epigenetic patterns are crucial for brain development and are highly sensitive to environmental changes (130).

Preclinical evidence indicates that maternal inflammation during pregnancy can induce long-lasting changes in DNA methylation, histone modifications, and microRNA expression in the offspring brain (131-133). Importantly, animal models have shown that prenatal environmental insults can lead to epigenetic alterations and associated behavioural abnormalities in second—and third-generation offspring, suggesting transferability of epigenetic programming (134,135). Human studies have linked inflammatory risk factors affecting pregnancy, including depression, anxiety, and smoking, to epigenetic changes in the placenta, offspring umbilical cord blood, peripheral blood, and buccal cells (128,136). Furthermore, maternal obesity, gestational diabetes, depression, and asthma, have been associated with epigenetic changes in immune, metabolic, and oxidative stress pathways in offspring umbilical cord blood (137-140). These findings highlight the transgenerational effects and widespread, long-term consequences of disturbances in prenatal programming.

At the post-transcriptional stage, maternal immune activation has been shown to disrupt mRNA translation, ribosome biogenesis, and protein synthesis in rodent brains (127,141,142). These processes are tightly regulated and fundamental to brain development and neural function. Activation of the integrated stress response has been implicated as one mechanism through which these disturbances occur (127); however, this field is very much in its infancy. Therefore, by increasing attention

to environmental effects and their epigenetic or cellular consequences, there may be significant opportunities for prevention (e.g., public health measures in pregnancy) or individualised treatments for people with neurodevelopmental disorders.

Parental psychological stress, anxiety, and depression

Many complex CHD diagnoses, such as those with single ventricles or transposition of the great arteries, now occur prenatally and coincide with the critical *in utero* period of neurodevelopment. Severe maternal stress and anxiety surrounding fetal CHD diagnosis is well-established (143-146). Until recently, however, we have had little understanding of the consequences of these maternal symptoms for brain development in CHD.

Threats to the health of the fetus have long been recognized as an important risk factor for maternal psychological disturbance in the perinatal period (147). Parents' experiences of CHD diagnosis are often associated with enduring psychological distress (2,148,149). Up to 80% of parents report severe psychological distress at some point in their child's medical trajectory and as many as 50% report anxiety or depressive symptoms indicative of a need for clinical intervention (2,143). These rates far exceed norms for perinatal anxiety and depression in the general population (149); yet the severity and consequences of these symptoms are often under-recognized and under-treated by healthcare professionals. Without timely intervention, parents with higher distress also report poorer physical health (150), greater parenting burden (151), higher health service use (152), more suicidal ideation (153), and poorer quality of life for both themselves and their child with CHD (154,155) compared with parents of sick children with lower distress.

Decades of research demonstrate an association between parent mental health and child neurodevelopment (156-158). Studies of children with CHD and their caregivers suggest that parent psychological distress is one of the strongest predictors of child emotional, behavioural, and developmental outcomes (154,159-161). For example, parent post-traumatic stress, referring to specific psychological and physiological symptoms (e.g., flashbacks, avoidance, hyperarousal) following exposure to a traumatic event (e.g., witnessing their child go into cardiac arrest), is associated with lower psychosocial functioning (160) and quality of life (155) for children and adolescents with CHD. While the mechanisms underlying these associations are not fully understood, family environment and parent-child interactions likely play an important role (148,162). There is also evidence that high and persistent maternal psychological stress and anxiety during pregnancy can alter fetal brain development in both healthy fetuses and fetuses with CHD (147).

Animal studies have shown that stress-elicited perturbations in maternal prenatal biology (e.g., hypothalamic-pituitary-adrenal axis function) affect offspring development, including stress reactivity (163). Studies of psychological stress in pregnant women largely mirror these findings, showing links to long-term cognitive, behavioral, and emotional dysfunction in children across development (164-168). High maternal stress during the middle-second and third trimesters - a time when the fetal brain is highly susceptible to modification by environmental factors and when CHD diagnosis is also most common—may be associated with the greatest neurodevelopmental impact (169). These effects persist after controlling for family socioeconomic status and maternal postnatal mental health, indicating a window of opportunity during fetal development when we may be able to intervene to prevent or minimize adverse child neurodevelopmental outcomes (170).

Maternal prenatal stress is linked to altered fetal brain development

Maternal prenatal stress, anxiety or depression has been linked with cortical thinning (171), altered brain microstructure (172,173), altered amygdala (174) and hippocampal (175) growth, and alterations in functional neural networks (i.e., the connectome) (176-178) in offspring with (179) and without CHD. Altered placental function (180,181), including decreased perfusion (182) and placental expression of neurotropic precursors, such as 11-beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2), are potential mechanisms (183). Decreased 11β-HSD2 expression may increase fetal cortisol exposure (184,185), affecting gene expression in fetal brain cells (186), such that small changes to early developmental trajectories may have life-altering consequences for neurodevelopment (55) and mental health outcomes (174,181,187-189). These findings underscore the importance of targeted therapies aimed at reducing prenatal stress to optimize both maternal and fetal wellbeing.

If maternal distress elicited by prenatal cardiac diagnosis negatively impacts fetal brain development, we are obliged to understand these 'off-target' effects and initiate prenatal

neuroprotective therapies to improve long-term outcomes. Expectant mothers are especially motivated for self-care (190), and studies in other populations show prenatal interventions, including interpersonal psychotherapy (191-193), effectively prevent or reduce maternal anxiety and depression (191,192,194-197). In CHD, one postnatally-delivered psychological intervention targeting mothers demonstrated efficacy in improving infant mental development at age 6 months (198), but this benefit was not sustained (159). Neurocognitive interventions delivered later in life, for children or adolescents with CHD, have had only limited success (199-201).

'Brain in a dish' and insights from related and unrelated neurological disease

The ability to deconstruct the biological and molecular complexities of human neurodevelopmental disease and translate findings into the clinic is only made possible through the multidisciplinary approach between basic science researchers and clinicians. While animal models have been instrumental in advancing our understanding of the molecular mechanisms of several genetic or extrinsic factors, extrapolating these findings to human disease are largely ineffective (202-204). This underscores a critical need for models that can leverage the disparities between the human and non-human brain with specific regard to early developmental processes that can broadly impact NDD. Human pluripotent stem cells (hPSCs), including both embryonic- and patient-derived induced pluripotent stem cells, have been a widely utilized model to satisfy the necessity for analysing human cells and methods to direct hPSCs towards specific cell fates *in-vitro* has demonstrated to be an excellent tool for studying human development programs and disease etiology (205-209).

Several strategies for differentiation of hPSCs into specific neuronal subtypes include transcriptional programming, small molecule and growth factor directed differentiation in both monolayer, and three-dimensional mini-brain organoids. While all methods will generate the neuronal cell types of interest, factors related to the speed and efficiency of cell generation, developmental accuracy, and reproducibility need to be considered for downstream applications. Advantages of transcriptional programming include the rapid differentiation (~5–10 days) from hPSCs resulting in a near homogenous population of cells that represent the final product for analysis such as excitatory neurons and astrocytes (209). However, questions regarding how development of the neuron or astrocyte differentiate are limited as well as the study of specific subtypes of neurons or astrocytes may be limited due to a largely generic cell identity. The directed differentiation of hPSCs recapitulates aspects of brain development such as corticogenesis and spinal cord development which can illuminate the process of differentiation which provides an additional layer of analysis for neurodevelopmental disorders. Recently, hPSCs have been differentiated as three-dimensional neural spheroids or cerebral organoids to highlight the remarkable self-organizing properties of cortical development (210,211). Importantly, cerebral organoids are similar to traditional monolayer differentiation where one can analyze cortical differentiation; however, they can also recreate the cortical architecture of the human brain, providing additional insight into human development, albeit with increased cellular heterogeneity and variability (205).

Brain models derived from hPSCs have been extensively used for various disease modelling, including neurodevelopmental disorders including autism and schizophrenia (212) assessing early stages of neurogenesis (213-216). In the CHD field, this approach has been used to define molecular mechanisms of functional alterations evident in two-dimensional (2D) cultures and organoids derived from patients with 22q11.2 deletion syndrome (217). This deletion is associated with cardiac outflow tract malformations. Transcriptional profiling over 100 days demonstrated predictable differentiation and alterations in neuronal excitability genes, emulating cortical brain regions. These changes were evident in both 2D and organoid cultures and correction of haploinsufficient gene dosage was able to correct the disease phenotype. It is reassuring that a disease phenotype was evident and correctable in patient iPSC cells, highlighting the value of this approach in assessing mechanisms of disease. The impact of a chromosomal deletion may exceed the impact of one or several single nucleotide variants expected in NDD, and the cellular phenotype may also be more subtle. Nevertheless, expression profiling, functional testing and correlation of cell phenotype with patient phenotype is likely to discriminate and allow prioritization of individual genes and gene pathways that can be related back to the genomic sequence of the patients involved to corroborate individual variants and burden testing in gene set pathways.

Using a hPSC model to study NDD is advantageous as it accounts for the complexity of human brain development and eliminates confounding differences between human and rodent brain development (218). As a model to study NDD,

the use of organoids permits the characterization of fetal brain development *in-vitro* using patient derived hPSC in an environment that is similar to what would be encountered *in-vivo*. With advancement of existing technologies, patient derived hPSC can be corrected using CRISPR-Cas9 system, allowing for reversion of disease-causing gene mutations (219). However, manipulating the progenitor populations may prove to be a more effective strategy to obtain clinical relevance. As autologous transplantation becomes more widely studied, novel therapies based on replacement of genetically corrected cell populations may be utilized to treat genetic brain disease (220).

Conclusions

Clinical applications and future directions

While research into improving current diagnostic, prognostic and treatment options for NDD in CHD is on-going, there are a number of practical ways in which neurodevelopmental outcomes can be maximised for the CHD patient (69).

The importance of prenatal diagnosis of CHD in reducing the risk of NDD through optimisation of perinatal care has been demonstrated (221) and presents an important modifiable factor in improving long-term neurodevelopmental outcomes for CHD patients (222). Individualised inpatient developmental care implemented in the intensive care unit have been associated with better neurodevelopmental outcomes, family functioning, and greater school attendance (223). The inclusion of parent-focused psychoeducation in such programs have demonstrated a positive impact on psychological, emotional and social development in the child with CHD (223) and extends to improved maternal psychological functioning and coping (198).

Similarly, genetic testing may identify patients at high risk of NDD, and enable early interventions aimed at optimising NDD outcomes for patients—which may be particularly important in centres where neurodevelopmental follow-up for infants with CHD is not part of standardised care. The distinction between syndromic and non-syndromic forms of CHD can be subtle and may be viewed as a continuum or spectrum of disease. The importance of a genetic assessment to identify subtle extracardiac features and possible genetic contributors to guide clinical management should be considered by physicians involved in the care of CHD patients. The European Society of Cardiology and American Heart Associations have released recommendations for genetic testing in patients with CHD (224,225). Notably, they recommend that patients with CHD and extracardiac anomalies, including significant neurodevelopmental abnormalities, should have chromosomal microarray testing, followed by trio exome or genome sequencing due to the reported high diagnostic yield of 25–40% in this patient group (226,227).

Further, they recommend that a prenatal diagnosis of CHD, should be accompanied by fetal chromosomal microarray testing and trio fetal exome and genome sequencing should be considered in any patients with complex CHD and/or extracardiac anomalies (224,225) Early diagnosis of a genetic syndrome provides important information in terms of managing associated NDD which is present in up to 75% of children with a diagnosed genetic syndrome (228).

It is important to note; however, that the absence of a genetic diagnosis or an uninformative genetic test result does not minimise the risk of NDD or preclude its development; and regular neurodevelopmental follow-up throughout childhood should be part of best care practice for all patients with CHD (7) Not all children will develop NDD; however, without regular neurodevelopmental assessments, those with issues, particularly those with minor issues, will be overlooked and opportunities for intervention and/or additional support, missed (229).

Similarly, there is growing support for increased monitoring for brain injury pre- and post-cardiac surgery that may serve as a prognostic indicator for new or worsening NDD (68). A high proportion of peri-operative brain injury is 'silent', evidenced by the disparity between the rate of brain injury identified in clinical practice (230), whereby brain imaging typically occurs in response to a clinical event, compared to studies that have included neuroimaging in an entire cohort of CHD patients (53,65-68). Routine pre- and post-operative neuroimaging may be warranted in infants with severe CHD (231). However, is generally limited by available resources and typically includes head ultrasound—that may miss up to 80% of lesions detected by MRI, particularly white matter injury (232). Better understanding of the sensitive interplay between brain injury and NDD trajectories in CHD, may inform future clinical practice in this regard.

Additional factors, including peri-operative course and socio-economic status may be stronger predictors of long-term NDD compared to conventional brain MRI (233) and these data should also be considered when determining a patient's risk profile.

Longer-term neurodevelopmental and cognitive follow-up extending beyond the early childhood years are recommended (7); however poor accessibility to neuropsychological services for older children and adults with CHD remains an important issue. Interventions to minimise new and accumulating risk factors occurring throughout the CHD life course are required to mitigate the persisting impact of NDD beyond the early childhood years.

In summary, current understanding and treatment options for NDD in CHD are still in their infancy and the coming years will likely see significant advances in the field. Clinical trials, prospective clinical studies using novel and sophisticated imaging technologies, as well as large genomic analyses and functional experiments will provide important insight into disease mechanisms, development, and progression as well as possible interventions and treatment. Indeed, examples of how genetic information can inform personalised therapies already exist in syndromes with neurodevelopmental phenotypes such as Kabuki syndrome (234). Simple dietary modifications, inducing epigenetic changes, have been shown to significantly improve cognitive function through more effective neuronal development in these patients (235).

Further, networks such as the Cardiac Neurodevelopmental Outcome Collaborative (cardiacneuro.org) are enabling large multinational, multicentre collaborations to inform future research efforts and provide important longitudinal data.

Clinically, the rapidly evolving field of fetal cardiac interventions, may be an important avenue to optimise neurodevelopmental outcomes, especially in fetuses with single ventricle pathologies (236).

Finally, polygenic risk scores, may in time provide important information to determine which CHD patients are at increased risk of developing NDD. Using prenatal genetic testing to determine individual polygenic risk scores, would enable early and on-going interventions to maximise neurodevelopmental outcomes in at risk patients.

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