NeuroImage: Clinical 32 (2021) 102885

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Microstructural alterations of the corticospinal tract are associated with poor motor function in patients with severe congenital heart disease

Melanie Ehrler [a,b,c], Michael von Rhein [a,b], Ladina Schlosser [a,c,d], Peter Brugger [e,f], Matthias Greutmann [g], Oliver Kretschmar [c,h], Beatrice Latal [a,b,c,1], Ruth Tuura O'Gorman [b,i,1,*]

[a] Child Development Center, University Children's Hospital Zurich, Switzerland
[b] Children's Research Center, University Children's Hospital Zurich, Switzerland
[c] University of Zurich, Switzerland
[d] Department of Neurology, University Hospital Zurich, Switzerland
[e] Department of Psychiatry, University Hospital Zurich, Zurich, Switzerland
[f] Rehabilitation Center Valens, Valens, Switzerland
[g] University Heart Center, Department of Cardiology, University of Zurich, Switzerland
[h] Pediatric Cardiology, Pediatric Heart Center, University Children's Hospital Zurich, Switzerland
[i] Center for MR Research, University Children's Hospital Zurich, Switzerland

ARTICLE INFO

Keywords:
Diffusion tensor imaging
Congenital heart disease
Motor function
White matter microstructure
Corticospinal tract
Neurodevelopment

ABSTRACT

Congenital heart disease (CHD) patients are at risk for neurodevelopmental impairments, including altered motor function. However, little is known about the neuroanatomical correlates of persistent motor deficits in CHD. Thus, we examined the link between corticospinal tract (CST) microstructure and motor function in adolescent and adult CHD patients compared to healthy controls.

This study investigated 89 CHD patients ($N_{(adolescents)} = 47$, $N_{(adults)} = 42$, mean age = 19.9 years) and 97 age-matched healthy controls ($N_{(adolescents)} = 44$, $N_{(adults)} = 53$, mean age = 20.6 years). Diffusion tensor imaging was conducted and fractional anisotropy (FA) of the left and right CST was extracted for each participant. Fine (pegboard) and pure motor (repeated finger, hand and foot movements) performance was evaluated with a standardized test battery. FA and motor performance were correlated and the effect of CHD complexity was tested using multivariate linear regression.

Clinically relevant motor impairments (>2SD below normative mean) were evident in 24% of patients and 9% of controls. On average, motor performance was lower in CHD patients compared to controls, particularly in those with more complex CHD (fine motor: $p = 0.023$; pure motor: $p < 0.001$). FA CST was lower in patients compared to controls, particularly in those with more complex CHD (left: $p < 0.001$, right: $p = 0.003$). There was a significant interaction between CHD complexity and FA CST (left: $p = 0.025$, right: $p = 0.025$), indicating that FA correlates significantly with pure motor in patients with severe CHD, while there is only a weak association in moderate CHD and no association in patients with simple CHD and controls.

Microstructure of the CST is altered in CHD patients, and is associated with pure motor impairments in patients with severe CHD. This indicates that persistent motor impairments may arise from atypical development of the primary motor pathway in the presence of a complex CHD. Early interventions promoting brain maturation in infancy may prevent persisting impairments across the lifetime.

1. Introduction

Congenital heart disease (CHD) is the most common birth defect, affecting about 1 in 100 live born children (Liu et al., 2019; Van Der Linde et al., 2011). Progress in surgical management and postoperative care of complex CHD has improved survival considerably, leading to a

Abbreviations: CHD, congenital heart disease; CST, corticospinal tract; FA, fractional anisotropy; TR/TE, repetition time/echo time; SES, socio-economic status; TBSS, tract based spatial statistics; ZNA, Zurich Neuromotor Assessment.

* Corresponding author at: Center for MR Research, University Children's Hospital Zurich, 75 Steinwiesstrasse, 8032 Zurich, Switzerland.
E-mail address: ruth.tuura@kispi.uzh.ch (R. Tuura O'Gorman).

[1] Shared last authorship.

https://doi.org/10.1016/j.nicl.2021.102885
Received 27 July 2021; Received in revised form 8 November 2021; Accepted 16 November 2021
Available online 19 November 2021

decrease of mortality to about 10% (Marelli et al., 2007), even for the most severe forms of CHD (Wernovsky, 2008). However, it has become evident that children with complex CHD requiring open-heart surgery are at increased risk for neurodevelopmental impairments in various developmental domains including cognitive, behavioral and motor function. Delayed motor milestones may already appear in the first year of life (Latal, 2016) and mild to moderate motor impairments often persist across childhood and adolescence (Bolduc et al., 2020).

For a better understanding of the etiology of neurodevelopmental alterations in CHD patients, neuroimaging studies have sought to find a neuroanatomical basis for these delays. One of the most common findings from neuroimaging studies in CHD is an apparent reduction in brain volume, which is evident in CHD patients from fetal life (Khalil et al., 2016; Olshaker et al., 2018), through infancy (Skotting et al., 2021; von Rhein et al., 2015), into adolescence and young adulthood (Bolduc et al., 2018). These alterations in brain volume are associated with poorer neurodevelopmental outcome in CHD patients: Studies in infants with CHD have shown that altered brain volume at infancy predicts cognitive abilities in later childhood, including intellectual function (Meuwly et al., 2019) and language development (Rollins et al., 2017). Several studies in adolescents and young adults with CHD demonstrated associations between lower local and total brain volume and intellectual function (Von Rhein et al., 2014), working memory (Fontes et al., 2019; Latal et al., 2016), and executive function (Naef et al., 2021; Semmel et al., 2018). In addition to *macroscopic* alterations in brain volume, neuroimaging studies have also revealed alterations in brain *microstructure* in infants, children and young adults with CHD, which also appear to be linked to delayed or altered cognitive development. A study in CHD neonates, who underwent brain MRI with diffusion tensor imaging (DTI) and continuous EEG-monitoring, showed that patients with delayed microstructural development had significantly stronger high-frequency connectivity and significantly weaker low-frequency connectivity, suggesting that delayed microstructural brain development has immediate functional consequences in CHD patients (Birca et al., 2016). Studies in adolescents and young adults with CHD revealed that altered white matter microstructure, measured by means of lower fractional anisotropy (FA), was associated with a range of cognitive impairments (Brewster et al., 2015; Ehrler et al., 2021, 2020; Rollins et al., 2014; Watson et al., 2018). However, while these neuroimaging studies have helped to elucidate the relationship between brain microstructural alterations and cognitive function in the CHD population, relatively little is known about the neuroanatomical correlates of persistent motor deficits, and there is a need for further investigation to better predict neurodevelopmental outcomes in CHD patients (Peyvandi et al., 2019).

In particular, the motor system could serve as a promising model to study the association of anatomical alterations and functional (i.e., motor) outcome in CHD patients, since it is a rather simple functional system, which has frequently been described to be impaired in the CHD population (Bolduc et al., 2020; Schaefer et al., 2013; Snookes et al., 2010). However, to date no study has investigated a direct association between neuroanatomic findings and neuromotor outcomes in CHD patients. Therefore, we examined the link between the microstructure of the corticospinal tract (CST), a primary motor projection pathway connecting the sensorimotor cortex and the spinal cord, which is responsible for voluntary movements especially in the distal extremities, and motor function in adolescents and adults with CHD and age-matched controls. We hypothesize that both, motor performance and mean fractional anisotropy (FA) of the CST is lower in patients with CHD compared to healthy controls, and that this reduction is more pronounced in patients with more complex CHD. Further, we hypothesize that FA CST is associated with fine and pure motor performance in patients and controls.

2. Materials and methods

2.1. Sample

Data of two different samples were pooled for this analysis. **Sample 1** includes adolescent patients with different types of CHD, who underwent full-flow cardiopulmonary bypass (CPB) surgery at the University Hospital Zurich between 1995 and 1998 (for further details see Von Rhein et al., 2012). Of 78 eligible participants, 23 opted not to participate, two could not be contacted, three patients did not undergo a DTI scan and three patients had to be excluded due to extensive movement artifacts in the MRI. Thus, in total, 47 patients with various types of CHD and 44 healthy controls with similar age and sex were included in the study. Healthy controls had participated in another study (n = 34) using the same DTI and motor test protocols or were recruited for this study (n = 10). Four of the 44 controls were excluded from analyses on motor performance because of missing data in these individuals.

Sample 2 includes adult patients with different types of CHD, who were treated at the outpatient clinic of the University Hospital Zurich, Switzerland (for details see (Ehrler et al., 2021)). Sixty-six patients agreed to participate in the study, of whom 46 patients underwent an MRI scan. One patient was excluded due to movement artifacts in the DTI scan. Three patients had previously participated in sample 1 and were thus excluded from sample 2 to guarantee a set of independent data. Therefore, sample 2 includes 42 patients. Of the 55 age- and sex-matched controls enrolled in this sample, 54 underwent a DTI scan with adequate quality. One control subject also participated in sample 1 and was thus excluded. Therefore 53 healthy controls were included in this analysis.

Inclusion criteria for all participants of both samples were: no further congenital malformation, no genetic or neurological disorder (e.g., clinical stroke requiring hospitalization, multiple sclerosis), age at assessment between 9 1/12 and 16 11/12 years (study 1), respectively 18 and 32 years (study 2) and fluency in the German language.

Both studies were approved by the ethics committee of the Canton of Zurich. All participants and primary care givers of minors respectively, gave written informed consent prior to the study participation in accordance with the Declaration of Helsinki. STROBE guidelines for reporting observational studies have been followed.

2.2. Outcome assessment

Motor function was measured with the Zurich Neuromotor Assessment (Largo et al., 2001), a standardized test battery assessing fine and pure motor function, and static and dynamic balance. Since in study 2 only fine and pure motor performance was assessed, the current analyses were restricted to those domains. Fine motor function was tested by means of the pegboard test (timed performance) conducted with both dominant and non-dominant hand separately. Pure motor function was assessed as timed performance of repetitive and sequential finger movements, and repetitive and alternating movements of feet and hands with the dominant and the non-dominant side separately. Two composite scores were built for fine and pure motor performance, combining both dominant and non-dominant performances of the respective subtests. Using normative data (N = 662), composite scores were z-transformed, corrected for age and sex. Impaired motor function was defined as having a z-score below −2 (i.e., >2SD below normative mean) in the fine and/or pure motor function composite scores. Participants were examined by an experienced pediatric neurologist (sample 1, MvR) or psychologist (sample 2, LS), who were aware of the participant's medical condition but not of the imaging results.

Socio-economic status (SES) was estimated by means of a six-point scale of maternal and paternal education with a range from 2 to 12 (Largo et al., 1989). Cardiac variables were obtained from patient's charts.

2.3. DTI acquisition and processing

Brain MRI was performed with a 3.0 Tesla whole-body system (GE TwinSpeed HD.xt [sample 1] and GE MR750 [sample 2], GE Healthcare, Milwaukee, WI). A diffusion tensor imaging sequence was acquired, oriented parallel to the anterior commissure—posterior commissure plane, with parameters: repetition time/echo time (TR/TE) = 7500/89 msec; acquisition matrix = 96 × 96; field of view = 280 mm, slice thickness 3.6 mm. For sample 1, a total of 21 diffusion-weighted gradient directions were acquired with b = 1000 s/mm^2 and five interleaved non-diffusion weighted images with b = 1000 s/mm^2, while for sample 2, a gradient scheme with 35 gradient directions and four non-diffusion weighted images was used.

DTI data was processed using FSL Software on Linux (Smith et al., 2004). Distortion and movement artifacts were corrected with eddy current correction (Andersson and Sotiropoulos, 2016) followed by brain extraction using BET (Brain Extraction Tool, Smith, 2002). Diffusion tensors were fitted at each intracerebral voxel and fractional anisotropy (FA) maps were calculated for each participant. FA maps were aligned into (1x1x1mm^3) MNI152 standard space using tract-based spatial statistics (TBSS; (Smith et al., 2006), and the group mean FA map was generated. The same transformation into standard space was applied to the mean diffusivity (MD) and radial diffusivity (RD) data in order to create mean MD and RD maps respectively. FA, MD and RD values range from 0 to 1. Altered white matter microstructure is linked to lower FA and higher MD and RD, respectively.

The left and right corticospinal tracts (CST) were extracted for both hemispheres separately with fslmaths using the JHU White Matter Tractography atlas. For each participant, two mean FA, MD and RD values were then generated with fslstats, one for each left and right CST.

2.4. Statistical analyses

The population characteristics age, sex, and SES were reported for both samples separately, were subsequently pooled and compared between patients and controls. Two-tailed Mann-Whitney U tests were conducted to examine differences in age and SES and Fisher's exact test were used to test differences in sex. For patients, the CHD diagnoses stratified by CHD complexity (according to Warnes et al., 2001) and number of CPB surgeries are reported.

For hypothesis testing, multivariable linear regression models with the pooled data of sample 1 and sample 2 were calculated. For group comparisons, subjects were divided into four groups: 1 = healthy controls, patients with 2 = simple, 3 = moderate, and 4 = severe CHD complexity (ordinal variable, Warnes et al., 2001). Group differences in motor performance (i.e., fine motor and pure motor) were tested with two separate models adjusting for sample. Group differences in mean FA of the left and right CST were tested with two separate models adjusting for age, sex, handedness and sample. For visual reference, a TBSS analysis restricted to within the left and right CST was conducted to demonstrate clusters with significantly lower or higher FA in patients compared to controls. Subsequently, the association between motor performance and FA in the CST was investigated. Therefore, models were tested including either fine or pure motor performance as outcome and FA of the CST as predictor (left and right hemisphere, separately), resulting in four separate models (1. fine motor, left CST; 2. fine motor, right CST; 3. pure motor, left CST; 4. pure motor, right CST). Models further included the predictors CHD complexity and SES and controlled for age, sex, handedness and sample. In an additional step, an interaction term between group and FA was added. Standardized β and unstandardized B (including 95%-CI) were reported as estimates and adjusted R^2 were reported as effect size measures. The distribution of residuals was examined to evaluate normality. FA was considered as the primary DTI measure of interest as previous DTI studies have used this measure to investigate microstructural alterations in CHD patients and their neurodevelopmental correlates (Brewster et al., 2015; Ehrler et al., 2021, 2020; Rollins et al., 2014; Watson et al., 2018). However, post hoc, the above-described analyses were performed for secondary DTI measures, namely MD and RD.

Lastly, a mediation analysis was conducted to investigate whether the effect of CHD complexity (X) on motor function (Y) is mediated by FA of the CST (M). The R package 'lavaan' was used and standardized beta coefficients were reported for the direct paths (a, b, c), the indirect effect (a*b) and the total effect of the model (c + indirect effect = c + a*b). The model was controlled for sample. See Fig. 1 for model visualization.

All the statistical analyses were performed using the computing environment R version 4.0.3 (R Core Team, 2020). P values below α = 0.05 were considered as statistically significant. Analyses were hypothesis driven and were thus not corrected for multiple comparison.

3. Results

3.1. Participant characteristics and outcomes

Participant characteristics, motor outcome and patient's cardiac characteristics are given in Table 1. Patients (*mean* age = 19.88; 55% females) and controls (*mean* age = 20.56; 50% females) did not differ in regard to age (W = 4594, p = 0.45, *CI-95* = -0.86 to 1.99) or sex (OR = 0.80, p = 0.49, *CI-95* = 0.43 to 1.48). SES was significantly higher in controls (*median* SES = 9.0) compared to patients (*median* SES = 8.0) (W = 4208, p = 0.01, *CI-95* = 0.00 to 1.00). Fine motor performance was lower in CHD patients (*mean* = -0.47) compared to controls (*mean* = 0.06) with a small to moderate effect size ($t(df)$ = 3.21(180), p = 0.002, *CI-95* = 0.20 to 0.85, Cohen's d = 0.48). Pure motor performance was lower in CHD patients (*mean* = -0.53) compared to controls (*mean* = 0.13) with a moderate effect size ($t(df)$ = 3.478(180), $p < 0.001$, *CI-95* = 0.29 to 1.04, Cohen's d = 0.52). Clinically relevant motor impairments (z-score < -2) were identified in 24% patients with CHD and in 9% healthy controls. Patients had significantly more motor impairments compared to controls (X^2 = 6.554, p = 0.010).

The effect of CHD complexity was investigated using linear regression models: Both, fine and pure motor performance were significantly associated with CHD complexity (Fine motor: β = -0.170, p = 0.023; Pure motor: β = -0.272, $p < 0.001$; see Supplementary Table 1 and Fig. 2). For fine motor performance, the post-hoc contrast effect was only significant between healthy controls and simple CHD. For moderate and severe CHD, there was only a trend with a small effect size (moderate: β = -0.127, p = 0.099; severe: β = -0.143, p = 0.063) potentially due to rather small variance in fine motor performance within patients with moderate and severe CHD compared to larger variance in controls and simple CHD.

Mean FA of both left and right CST was significantly lower in CHD patients compared to controls (left CST: β = -0.195, p = 0.008; right CST: β = -0.167, p = 0.014). Supplementary Fig. 1 shows all clusters within the CST with significantly lower FA in patients compared to controls.

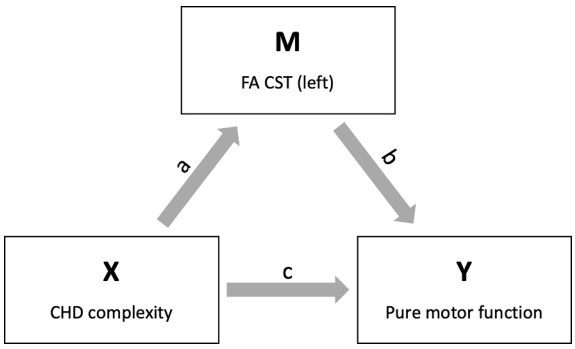

Fig. 1. Mediation model.

Table 1
Participant characteristics stratified by group.

Characteristics	Sample 1 *adolescents*		Sample 2 *adults*	
Sample	Patient	Control	Patient	Control
N	47	44	42	53
Demographics				
Age [a]	13.7 (1.6)	13.9 (1.8)	26.8 (3.5)	26.1 (3.2)
Male sex [b]	23(49%)	20 (45%)	26(62%)	28(53%)
SES [a]	7.7(2.1)	8.5(1.5)	8.4(2.0)	8.8(1.7)
Right handedness [b]	39 (83%)	43 (98%)	39(93%)	46(87%)
Motor performance				
Fine motor (z-score) [a]	−0.6 (1.3)	0.5(1.1)	−0.3 (0.9)	−0.2 (1.0)
Pure motor (z-score) [a]	−0.0 (1.1)	0.5(1.2)	−1.1 (1.2)	−0.2 (1.2)
Cardiac factors				
Simple CHD [b]	16(34%)		15(36%)	
Aortic valve disease	0		6	
Arterial/ventricular septal defect	16		2	
Mild pulmonic stenosis	0		1	
Mitral valve disease	0		3	
Small patent ductus arteriosus	0		1	
Other simple	0		2	
Moderate CHD [b]	14(30%)		18(43%)	
Aortic coarctation	1		8	
Aortic stenosis	3		0	
Ebstein	0		2	
Pulmonary stenosis	2		0	
Shone complex	1		0	
Supravalvular aortic stenosis	0		1	
Tetralogy of Fallot	5		2	
Tot. anomalous pulmonary venous return	2		0	
Ventricular septal defect with residuals	2		4	
Other moderate	0		1	
Severe CHD [b]	17(36%)		9(21%)	
Fontan procedure	3		2	
Pulmonary atresia	2		0	
Transposition of the great arteries	10		7	
Tricuspid atresia	1		0	
Truncus arteriosus	1		0	
Number of CPB surgeries [c]	1 (1–3)		1 (0–3)	

[a] Mean (SD).
[b] Number of individuals (%).
[c] median (range).

There were no significant clusters with higher FA in patients compared to controls. Furthermore, lower FA was associated with CHD complexity (left CST: β = -0.003, p = <0.001; right CST: β = -0.003, p = 0.003; see Fig. 3 and Supplementary Table 2). Post hoc analyses revealed that MD and RD were also significantly associated with CHD complexity (Supplementary Table 3).

3.2. Association between motor outcome and FA in CST

Separate linear regression models with fine and pure motor performance were tested with FA of either the left or the right CST, CHD complexity and SES as predictors. Age, sex, handedness and sample were included as covariates. Models for fine motor performance were not significant (Model including FA of the left CST: p = 0.262; Model including FA of right CST p = 0.328) and are thus not reported in detail. For pure motor performance, FA of the left and right CST, as well as CHD complexity were significant predictors for pure motor performance (see Table 2). The models explained 15%, respectively 16% variance, indicating a small to moderate effect size. When adding an interaction term between FA and CHD complexity, there was a significant interaction (left: β = 4.850, *B(CI-95)* = 12.957(1.665 to 24.249), p = 0.0248, adjusted R^2 = 0.180; right: β = 4.1744, *B(CI-95)* = 11.18671(1.401 to 20.972), p = 0.0253, adjusted R^2 = 0.176). Post hoc contrast analyses within the complexity subgroups revealed that FA was associated with pure motor performance in patients with severe CHD (left CST: β = 0.494, p = 0.011; right CST: β = 0.556, p = 0.021). In moderate CHD, there was a weaker association trending toward significance (left CST: β = 0.340, p = 0.069; right CST: β = 0.376, p = 0.055). In patients with simple CHD and healthy controls, there was no association between FA and pure motor function (left CST: β = 0.042, p = 0.836; right CST: β = 0.008, p = 0.967) and healthy controls (left CST: β = 0.066, p = 0.572; right CST: β = 0.084, p = 0.513). See Fig. 4 for visualization. As for FA, model fits of models investigating the association between fine motor function and MD or RD were not significant (MD: Model including MD of the left CST, p = 0.376 or the right CST: p = 0.295; RD: Model including RD of the left CST, p = 0.215 or the right CST: p = 0.262). Model fits of models predicting pure motor function were significant but there was no association with MD (left CST: p = 0.333, right CST: p = 0.122) or RD (left CST: p = 0.093, right CST: p = 0.076).

Mediation analyses is displayed in Fig. 5 and Supplementary Table 4. The model revealed that the indirect effect (i.e., mediation effect) was very small (left CST: β = -0.043, p = 0.040; right CST: β = -0.037, p = 0.058). Interestingly, the indirect effect was substantially smaller than the direct effect from CHD complexity to pure motor function (β = -0.229). This indicates that FA CST as mediating factor cannot sufficiently explain differences in motor function between the complexity types.

4. Discussion

CHD entails a risk for mild to moderate cognitive and motor impairments across the lifespan and is, thus, considered as a chronic condition. Our findings demonstrate poorer fine and pure motor performance, as well as lower fractional anisotropy of the corticospinal tract (FA CST) in adolescent and adult patients with CHD compared to age and sex-matched healthy controls. Importantly, both lower motor performance and lower FA CST are associated with more complex CHD. Further, the association between pure motor function, assessed as timed performance of repeating finger, hand and foot movements, and FA CST was only evident in patients with more complex CHD. We therefore conclude that the CST is specifically vulnerable in the context of complex forms of CHD and that these alterations have a clinical correlate in pure motor performance.

Previous studies have reported that motor impairments occur in approximately one-third of all patients with CHD across infancy, childhood and adolescence (see systematic review: (Bolduc et al., 2020). Infants with CHD undergoing heart surgery before the age of 6 months show noticeably delayed motor development at the age of one year with an average Psychomotor Development Index of 78 measured with the Bayley Scales of Infant Development II (Snookes et al., 2010). It has been suggested that motor function is more strongly impaired in early infancy and may improve to a milder form during childhood (Naef et al., 2019). However, our current study shows that motor impairments may persist into adolescence and young adulthood: CHD patients, especially those with more complex CHD, had significantly lower fine and pure motor functions in comparison to matched healthy controls. Further, clinically relevant motor impairments (either fine or pure motor z-score < -2) were still evident in 24% of adolescents and young adults with CHD compared to 9% in the controls.

Neurodevelopmental impairments in patients with CHD, including motor difficulties, show many similarities to those of very premature children (Easson et al., 2018). The similarities between CHD patients and former premature born babies are particularly interesting, because numerous neuroimaging studies have shown that children with CHD are at risk of congenital and acquired brain lesions particularly affecting the white matter (Claessens et al., 2017; Guo et al., 2019; Mebius et al.,

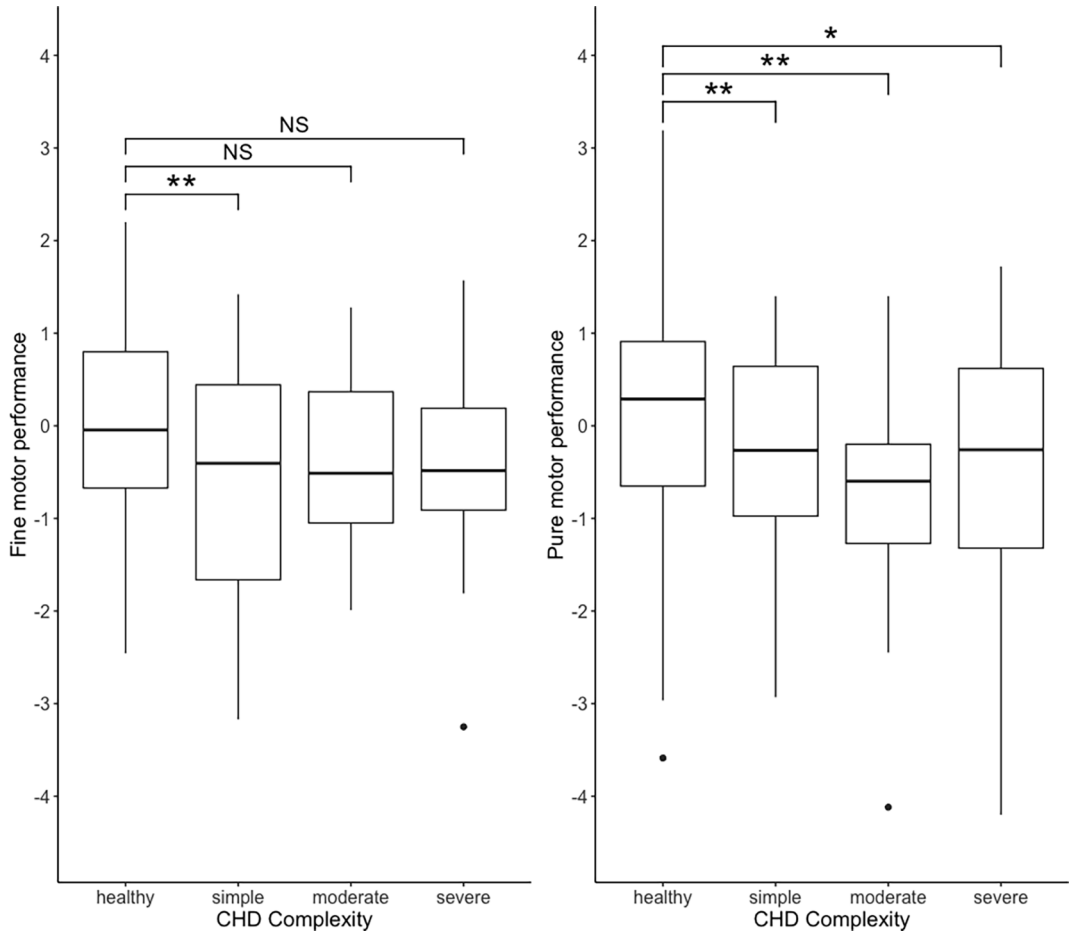

Fig. 2. Group comparison motor function Note. CHD = congenital heart disease. The lower/upper border of the box represent the first/third quartile. The line within the box corresponds to the median. Dots represent outliers (>1.5 IQR below/above the first/third quartile). Motor performance is represented by age-corrected z-scores. Significance level NS $p > 0.05$, * $p < 0.05$, ** $p < 0.01$ represents the contrast effects within the regression model (see Supplementary Table 1 for details). To estimate contrast effects, the predictor CHD complexity was considered as categorical variable with healthy controls as reference group. The overall effect of CHD complexity (factor included as ordinal variable) was significant (fine motor: $p = 0.023$; pure motor: $p < 0.001$).

2017). These neuroimaging findings in CHD infants show to some extent similarities with the ones described in premature birth (Beca et al., 2013; Guo et al., 2019; Limperopoulos et al., 2010). Furthermore, term born CHD patients display signs of delayed brain maturation at birth (Lauridsen et al., 2019; Licht et al., 2009; Miller et al., 2007), which suggest the possibility to transfer insights linking neuroimaging findings to neuro-functional outcome from former preterm born babies to the CHD population. In adults born very preterm and/or with very low birth weight (VLBW), white matter alterations of the CST were previously described - even in the absence of visible white matter lesions (Jurcoane et al., 2016). Furthermore, probabilistic tractography of the CST in a group of adults with former VLBW, showed lower FA in non-crossing fiber regions and higher FA in crossing fiber regions of the CST compared to controls. Within the VLBW group, poorer fine motor function was associated with higher FA in crossing fiber regions of the CST, most likely due to lower FA of the crossing fibers in VLBW compared to controls, reducing the axial diffusivity of VLBW to a lower extent than in controls and thus leading to higher regional FA (Hollund et al., 2018). The current study in patients with CHD demonstrated lower mean FA across the full CST in patients with severe CHD compared to controls. A TBSS analysis restricted to the CST showed that there were no clusters with significantly higher FA in CHD patients compared to controls. Further, clusters with lower FA in patients were evident in single and crossing fiber (i.e., centrum semiovale) regions.

Interestingly, our study demonstrates lower FA in CHD patients compared to controls indicating that CST microstructure is altered in CHD. Higher FA is associated with more myelination and increased/denser axonal packing in white matter tracts. However, FA can also decrease artefactually if crossing fibers are present (Goddings et al., 2021; Soares et al., 2013), particularly if non-isotropic voxels with larger slice thickness are used (Oouchi et al., 2007). Thus, lower FA in CHD patients may provide evidence for alterations in the white matter microstructure but not for specific properties underlying these alterations. Previous studies have demonstrated that altered white matter microstructure in CHD is not restricted to the CST but is a rather global trait evident across the whole brain (Brewster et al., 2015; Ehrler et al., 2021, 2020; Rollins et al., 2014; Watson et al., 2018), which can already be detected postnatally and is associated with decreased oxygen delivery (Karmacharya et al., 2018; Kelly et al., 2019). Of note is that two previously conducted studies in adolescents with CHD did not find any significant difference in FA of the CST compared to controls, while there was significantly lower FA in other major tracts (Easson et al., 2020; Watson et al., 2018). Different methodological approaches may partly explain these contradicting results (Ressel et al., 2018). However, to our knowledge, the present study is the first to demonstrate an association between FA and pure motor function in patients with severe CHD. In contrast, there was only a weak association in patients with moderate CHD and no association between FA and pure motor function in patients with simple CHD and healthy controls. This lack of an association in simple CHD and controls may indicate that FA CST values in these subjects represent the normal spectrum of variability, while the FA CST in severe CHD patients reflects a structural impairment with associated

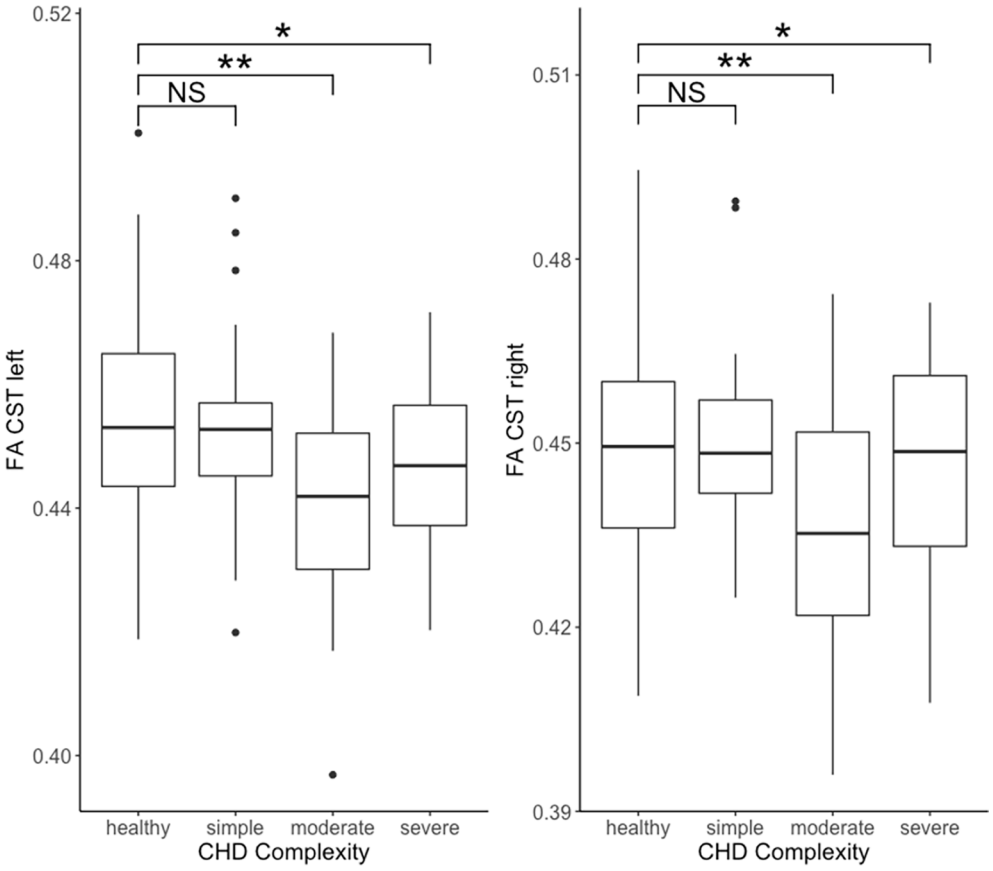

Fig. 3. Group comparison FA of the left and right CST Note. FA CST = fractional anisotropy of the corticospinal tract. CHD = congenital heart disease. The lower/upper border of the box represent the first/third quartile. The line within the box corresponds to the median. Dots represent outliers (>1.5 IQR below/above the first/third quartile). Significance level NS $p > 0.05$, * $p < 0.05$, ** $p < 0.01$ represents the contrast effects within the regression model (see Supplementary Table 2 for details). To estimate contrast effects, the predictor CHD complexity was considered as categorical variable with healthy controls as reference group. Within the severe CHD subgroup, patients with transposition of the great arteries did not differ from patients with univentricular CHD (left: $t(df) = 0.26(23)$, $p = 0.799$; right: $t(df) = 0.37(23)$, $p = 0.717$). The overall effect of CHD complexity (factor included as ordinal variable) was significant (left: $p < 0.001$, right: $p = 0.003$).

Table 2
Linear regression models predicting motor function.

Outcome	Predictors	$\beta_{standardized}$	$B(CI\text{-}95)_{unstandardized}$	p-value	$R^2_{adjusted}$	p-value$_{Model\ fit}$
Pure motor	**FA CST left**	**0.192**	**16.400(3.882 to 28.922)**	**0.011**	0.158	<0.001
	Complexity	**−0.234**	**−0.278(-0.457 to −0.100)**	**0.002**		
	SES	−0.032	−0.023(-0.130 to 0.084)	0.671		
	Age	−0.162	−0.032(-0.106 to 0.042)	0.397		
	Sex	0.139	0.369(-0.017 to 0.754)	0.061		
	Handedness	0.033	0.148(-0.493 to 0.788)	0.650		
	Sample	0.109	0.290(-0.714 to 1.294)	0.570		
Pure motor	**FA CST right**	**0.195**	**15.470(2.976 to 27.972)**	**0.016**	0.155	<0.001
	Complexity	**−0.241**	**−0.286(-0.464 to −0.108)**	**0.002**		
	SES	−0.033	−0.023(-0.130 to 0.084)	0.668		
	Age	−0.189	−0.037(-0.110 to 0.037)	0.323		
	Sex	0.134	0.357(-0.029 to 0.743)	0.070		
	Handedness	0.041	0.182(-0.461 to 0.826)	0.576		
	Sample	0.016	0.043(-0.961 to 1.047)	0.933		

Note. FA CST = Fractional anisotropy of the corticospinal tract. Significant effects are represented in bold.

functional consequences. Due to the rather small differences and overlapping variability between CHD complexity groups, FA of the CST does, most likely, not serve as a reliable biomarker for motor outcome in CHD patients. However, significant alterations in CST FA in the patients with more complex CHD highlight that persisting neurological pathology of motor tracts may occur during brain development in this population. With regard to developmental effects, the CST shows a relatively flat maturation trajectory across adolescence and early adulthood in the healthy population, following an intense maturation process in the CST in early childhood (Lebel et al., 2008). Usually, the CST is at almost full maturity during adolescence. Therefore, only strong alterations in FA, as it is evident in patients with severe CHD, may have direct consequences for motor function at this age, while minor differences in FA appear not to show any functional consequence. Previous studies in other neurological patient populations reported similar findings as seen in the more complex forms of CHD: In pediatric patients with traumatic brain injury, FA of the CST was lower compared to controls and was associated with lower balance skills (Caeyenberghs et al., 2011). In adult stroke patients, CST injury identified with DTI (i.e., fiber number ratio of affected and unaffected CST) correlated with motor impairments during both, acute and chronic phase (Maraka et al., 2014). In a group of children with acquired brain injuries (from stroke or traumatic brain injury), lower FA of the ipsilesional CST was related to worse motor function, assessed from the motor sub scores of a functional independence measure for children (Ressel et al., 2017). Some studies even suggest that FA CST may be used as a prognostic biomarker for motor recovery in patients with stroke (Puig et al., 2013) or other forms of acquired brain injury (Ressel et al., 2017). While this may be the case for

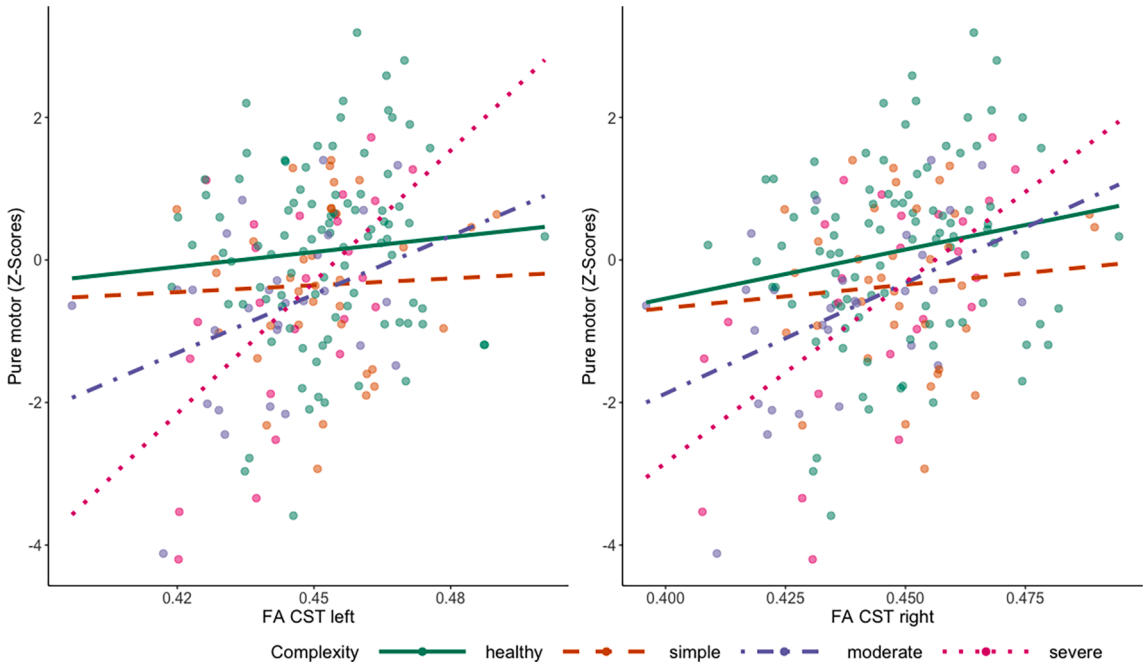

Fig. 4. Association of FA and pure motor function stratified by CHD complexity Note. FA CST = fractional anisotropy of the corticospinal tract. CHD = congenital heart disease. Post hoc analyses between pure motor function and FA CST left within the complexity subgroups: healthy ($\beta = 0.066$, $p = 0.572$), simple ($\beta = 0.042$, $p = 0.836$), moderate ($\beta = 0.340$, $p = 0.069$), severe ($\beta = 0.494$, $p = 0.011$); Pure motor and FA CST right healthy ($\beta = 0.084$, $p = 0.513$), simple ($\beta = 0.008$, $p = 0.967$), moderate ($\beta = 0.376$, $p = 0.055$), severe ($\beta = 0.556$, $p = 0.021$).

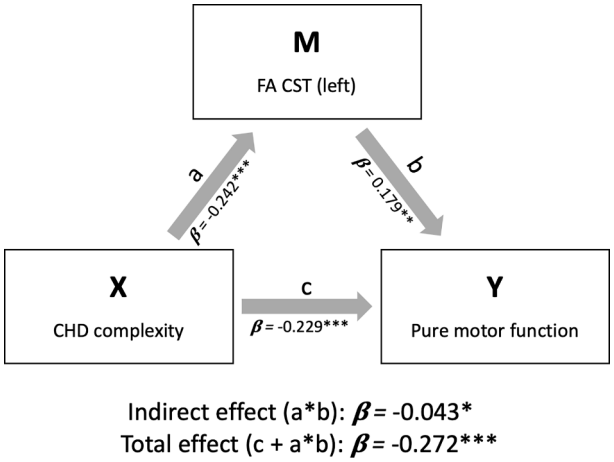

Fig. 5. Mediation model with effect sizes for each path *Note*. Model is corrected for sample. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

patient populations with acute and acquired brain injuries, our results do not provide evidence that the FA CST could be used as a biomarker for motor function in the CHD population due to overlapping variability.

4.1. Limitations

The data, which were pooled for the present analyses, were originally collected from two independent study populations. Pooling the data increased the sample size and thus the statistical power, enabling contrast analyses of CHD complexity, which has been limited in previous research. However, the studies show some methodological discrepancies, especially regarding assessment period, age range and extent of the neurodevelopmental assessment. Furthermore, white matter injury, a marker of interest with regard to white matter microstructural alterations, was only quantified in one study while in the other study brain injury was rated more unspecifically. In addition, the two studies used different imaging sequences to investigate brain injury. Therefore, the extent to which a risk factor analysis for white matter injury can be performed is limited and future studies are needed to investigate this in more detail. Nevertheless, both studies include patients with similar CHD diagnoses and complexities, as well as overlapping demographic variables and fine and pure motor assessment (see Table 1), which enabled combined analyses with sufficiently increased power. Multivariate analysis further allowed for the control of confounding variables related to methodological differences between the studies.

The patient sample includes a variety of heart defects with different complexity. Thus, conclusions cannot be drawn for specific heart defects. However, multivariate analyses including CHD complexity as predictor revealed that there are differences between heart defect complexities regarding both, white matter microstructural alterations as well as motor outcome. Further studies investigating associated perioperative (e.g., number and timing of CPB surgeries, length of hospitalization and the associated risk of a low-stimulated motor environment) and cardiac risk factors (e.g., cyanosis) explaining differences across heart defects are needed.

The fit of the model predicting fine motor performance was not sufficient and thus further reporting was omitted. As the fine motor task used in this study (i.e., pegboard) requires not only simple motor function but also visuo-motor coordination, FA of the CST, connecting the primary motor cortex with the spinal cord, may not be the foremost predictor for this outcome. Previous studies of fine motor function in other populations report inconsistent findings: While Cremers and colleagues found a positive but weak association between FA of the CST and fine motor performance in elderly adults (Cremers et al., 2016), Hollund and colleagues reported a negative association in adults born with very low birth weight (Hollund et al., 2018). Different methodological approaches (i.e., whole tract vs. regional analysis, atlas based vs. Tractography) may partly explain these inconsistencies.

5. Conclusion

Microstructural alterations in the corticospinal tract (CST) as well as fine and pure motor impairments were associated with CHD complexity, indicating that patients with more complex CHD are more likely to have lower FA of the CST and motor impairments. Furthermore, altered CST microstructure was significantly associated with pure motor function in patients with severe CHD, while there was only a weak association in patients with moderate CHD and no association in patients with simple CHD and controls. The fact that both, motor and white matter microstructural impairments are already present in early life of CHD patients and remain evident in young adults underlines the importance of future research investigating neuroprotective interventions (e.g., optimal nutrition during the neonatal period and perioperative neuroprotection) and early motor therapy promoting the maturation of motor pathways in infants with CHD. This, in turn, may prevent long lasting impairments across the lifetime.

CRediT authorship contribution statement

Melanie Ehrler: Methodology, Formal analysis, Visualization, Writing – original draft. **Michael von Rhein:** Conceptualization, Investigation, Data curation, Funding acquisition, Methodology, Writing – original draft. **Ladina Schlosser:** Investigation, Writing – review & editing. **Peter Brugger:** Conceptualization, Data curation, Funding acquisition, Methodology, Writing – review & editing. **Matthias Greutmann:** Methodology, Writing – review & editing. **Oliver Kretschmar:** Methodology, Writing – review & editing. **Beatrice Latal:** Conceptualization, Data curation, Funding acquisition, Writing – review & editing. **Ruth Tuura O'Gorman:** Methodology, Supervision, Writing – review & editing.

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.

Acknowledgements

We thank all the participants and their families. Further, thanks to Thorsten Weirauch and the MRI team for their valuable support in performing the MRI scans and Sarah Rometsch for recruiting the initial cohort of adults with CHD.

Funding

This work was supported by the Swiss Heart Foundation, Else Kröner-Fresenius Foundation, the Mäxi Foundation and the Olga-Mayenfisch Foundation. The sponsors had no influence on study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102885.

References

Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 125, 1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019.

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.

Birca, A., Vakorin, V.A., Porayette, P., Madathil, S., Chau, V., Seed, M., Doesburg, S.M., Blaser, S., Nita, D.A., Sharma, R., Duerden, E.G., Hickey, E.J., Miller, S.P., Hahn, C. D., 2016. Interplay of brain structure and function in neonatal congenital heart disease. Ann. Clin. Transl. Neurol. 3 (9), 708–722. https://doi.org/10.1002/acn3.336.

Bolduc, M.-E., Dionne, E., Gagnon, I., Rennick, J.E., Majnemer, A., Brossard-Racine, M., 2020. Motor Impairment in Children With Congenital Heart Defects: A Systematic Review. Pediatrics 146 (6), e20200083. https://doi.org/10.1542/peds.2020-0083.

Bolduc, M.-E., Lambert, H., Ganeshamoorthy, S., Brossard-Racine, M., 2018. Structural brain abnormalities in adolescents and young adults with congenital heart defect: a systematic review. Developmental Medicine and Child Neurology 60 (12), 1209–1224. https://doi.org/10.1111/dmcn.13975.

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. Journal of the International Neuropsychological Society 21 (1), 22–33. https://doi.org/10.1017/S135561771400109X.

Caeyenberghs, K., Leemans, A., Geurts, M., Linden, C.V., Smits-Engelsman, B.C.M., Sunaert, S., Swinnen, S.P., 2011. Correlations between white matter integrity and motor function in traumatic brain injury patients. Neurorehabilitation and Neural Repair 25 (6), 492–502. https://doi.org/10.1177/1545968310394870.

Claessens, N.H.P., Kelly, C.J., Counsell, S.J., Benders, M.J.N.L., 2017. Neuroimaging, cardiovascular physiology, and functional outcomes in infants with congenital heart disease. Dev. Med. Child Neurol. 59 (9), 894–902. https://doi.org/10.1111/dmcn.13461.

Cremers, L.G.M., Groot, M.D., Hofman, A., Krestin, G.P., Lugt, A., Van Der, W.J., Niessen, Vernooij, M.W., Ikram, M.A., 2016. Neurobiology of Aging Altered tract-speci fi c white matter microstructure is related to poorer cognitive performance : The Rotterdam Study. Neurobiol. Aging 39, 108–117. https://doi.org/10.1016/j.neurobiolaging.2015.11.021.

Easson, K., Dahan-Oliel, N., Rohlicek, C., Sahakian, S., Brossard-Racine, M., Mazer, B., Riley, P., Maltais, Désirée.B., Nadeau, L., Hatzigeorgiou, S., Schmitz, N., Majnemer, A., 2019. A Comparison of Developmental Outcomes of Adolescent Neonatal Intensive Care Unit Survivors Born with a Congenital Heart Defect or Born Preterm. J. Pediatr. 207, 34–41.e2. https://doi.org/10.1016/j.jpeds.2018.11.002.

Easson, K., Rohlicek, C.V., Houde, J.-C., Gilbert, G., Saint-Martin, C., Fontes, K., Majnemer, A., Marelli, A., Wintermark, P., Descoteaux, M., Brossard-Racine, M., 2020. Quantification of apparent axon density and orientation dispersion in the white matter of youth born with congenital heart disease. NeuroImage 205, 116255. https://doi.org/10.1016/j.neuroimage.2019.116255.

Ehrler, M., Latal, B., Kretschmar, O., Rhein, M.V., Gorman, R.O., 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, 1–8. 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 Communications 3. https://doi.org/10.1093/braincomms/fcaa224.

Fontes, K., Rohlicek, C.V., Saint-Martin, C., Gilbert, G., Easson, K., Majnemer, A., Marelli, A., Chakravarty, M.M., Brossard-Racine, M., 2019. Hippocampal alterations and functional correlates in adolescents and young adults with congenital heart disease. Hum. Brain Mapp. 40, 3548–3560. https://doi.org/10.1002/hbm.24615.

Goddings, A.-L., Roalf, D., Lebel, C., Tamnes, C.K., 2021. Development of white matter microstructure and executive functions during childhood and adolescence: a review of diffusion MRI studies. Developmental Cognitive Neuroscience 51, 101008. https://doi.org/10.1016/j.dcn.2021.101008.

Guo, T., Chau, V., Peyvandi, S., Latal, B., Mcquillen, P.S., Knirsch, W., Synnes, A., Feldmann, M., Naef, N., Chakravarty, M.M., de Petrillo, A., Duerden, E.G., Barkovich, A.J., Miller, S.P., 2019. White matter injury in term neonates with congenital heart diseases : Topology & comparison with preterm newborns. NeuroImage 185, 742–749. https://doi.org/10.1016/j.neuroimage.2018.06.004.

Hollund, I.M.H., Olsen, A., Skranes, J., Brubakk, A.M., Håberg, A.K., Eikenes, L., Evensen, K.A.I., 2018. White matter alterations and their associations with motor function in young adults born preterm with very low birth weight. NeuroImage: Clinical 17, 241–250. https://doi.org/10.1016/j.nicl.2017.10.006.

Jurcoane, A., Daamen, M., Scheef, L., G. Bäuml, J., Meng, C., M. Wohlschläger, A., Sorg, C., Busch, B., Baumann, N., Wolke, D., Bartmann, P., Hattingen, E., Boecker, H., 2016. White matter alterations of the corticospinal tract in adults born very preterm and/or with very low birth weight. Hum. Brain Mapp. 37 (1), 289–299. https://doi.org/10.1002/hbm.23031.

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.

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., 2019. Abnormal Microstructural Development of the Cerebral Cortex in Neonates With Congenital Heart Disease Is Associated With Impaired Cerebral Oxygen Delivery. Journal of the American Heart Association 8 (5). https://doi.org/10.1161/JAHA.118.009893.

Khalil, A., Bennet, S., Thilaganathan, B., Paladini, D., Griffiths, P., Carvalho, J.S., 2016. Prevalence of prenatal brain abnormalities in fetuses with congenital heart disease: a

systematic review. Ultrasound Obstet Gynecol 48 (3), 296–307. https://doi.org/10.1002/uog.2016.48.issue-310.1002/uog.15932.
Largo, R., Pfister, D., Molinari, L., Kundu, S., Lipp, A., Duc, G., 1989. Significance of prenatal, perinatal and postnatal factors in the development of aga preterm infants at five to seven years. Dev. Med. Child Neurol. 31, 440–456.
Largo, R.H., Caflisch, J.A., Hug, F., Muggli, K., Molnar, A.A., Molinari, L., Sheehy, A., Gasser, T., 2001. Neuromotor development from 5 to 18 years. Part 1: timed performance. Dev. Med. Child Neurol. 43 (07), 436. https://doi.org/10.1017/S0012162201000810.
Latal, B., 2016. Neurodevelopmental Outcomes of the Child with Congenital Heart Disease. Clin. Perinatol. 43 (1), 173–185. https://doi.org/10.1016/j.clp.2015.11.012.
Latal, B., Patel, P., Liamlahi, R., Knirsch, W., O'Gorman Tuura, R., von Rhein, M., 2016. Hippocampal volume reduction is associated with intellectual functions in adolescents with congenital heart disease. Pediatr. Res. 80 (4), 531–537. https://doi.org/10.1038/pr.2016.122.
Lauridsen, M.H., Uldbjerg, N., Petersen, O.B., Vestergaard, E.M., Matthiesen, N.B., Henriksen, T.B., Østergaard, J.R., Hjortdal, V.E., 2019. Fetal Heart Defects and Measures of Cerebral Size. J. Pediatr. 210, 146–153. https://doi.org/10.1016/j.jpeds.2019.02.042.
Lebel, C., Walker, L., Leemans, A., Phillips, L., Beaulieu, C., 2008. Microstructural maturation of the human brain from childhood to adulthood. NeuroImage 40 (3), 1044–1055. https://doi.org/10.1016/j.neuroimage.2007.12.053.
Licht, D.J., Shera, D.M., Clancy, R.R., Wernovsky, G., Montenegro, L.M., Nicolson, S.C., Zimmerman, R.A., Spray, T.L., Gaynor, J.W., Vossough, A., 2009. Brain maturation is delayed in infants with complex congenital heart defects. J. Thorac. Cardiovasc. Surg. 137 (3), 529–537. https://doi.org/10.1016/j.jtcvs.2008.10.025.
Limperopoulos, C., Tworetzky, W., McElhinney, D.B., Newburger, J.W., Brown, D.W., Robertson, R.L., Guizard, N., McGrath, E., Geva, J., Annese, D., Dunbar-Masterson, C., Trainor, B., Laussen, P.C., du Plessis, Adré.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.
Liu, Y., Chen, S., Zühlke, L., Black, G.C., Choy, M.K., Li, N., Keavney, B.D., 2019. Global birth prevalence of congenital heart defects 1970–2017: Updated systematic review and meta-analysis of 260 studies. Int. J. Epidemiol. 48, 455–463. https://doi.org/10.1093/ije/dyz009.
Maraka, S., Jiang, Q., Jafari-Khouzani, K., Li, L., Malik, S., Hamidian, H., Zhang, T., Lu, M., Soltanian-Zadeh, H., Chopp, M., Mitsias, P.D., 2014. Degree of corticospinal tract damage correlates with motor function after stroke. Ann. Clin. Transl. Neurol. 1 (11), 891–899. https://doi.org/10.1002/acn3.132.
Marelli, A.J., Mackie, A.S., Ionescu-Ittu, R., Rahme, E., Pilote, L., 2007. Congenital Heart Disease in the General Population Changing Prevalence and Age Distribution. Circulation 115 (2), 163–172. https://doi.org/10.1161/CIRCULATIONAHA.106.627224.
Mebius, M.J., Kooi, E.M.W., Bilardo, C.M., Bos, A.F., 2017. Brain injury and neurodevelopmental outcome in congenital heart disease: A systematic review. Pediatrics 140, 1–21. https://doi.org/10.1542/peds.2016-4055.
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., Liamlahi, R., Hackenberg, A., Kretschmar, O., Kellenberger, C., Bürki, C., Weiss, M., 2019. Postoperative brain volumes are associated with one-year neurodevelopmental outcome in children with severe congenital heart disease. Sci. Rep. 9, 1–11. https://doi.org/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. N. Engl. J. Med. 357, 1928–1938. https://doi.org/10.1097/01.sa.0000307878.52543.ba.
Naef, N., Schlosser, L., Brugger, P., Greutmann, M., Oxenius, A., Wehrle, F., Kottke, R., Latal, B., O'Gorman, R.T., 2021. Brain volumes in adults with congenital heart disease correlate with executive function abilities. Brain Imaging and Behavior 15 (5), 2308–2316. https://doi.org/10.1007/s11682-020-00424-1.
Naef, N., Wehrle, F., Rousson, V., Latal, B., 2019. Cohort and Individual Neurodevelopmental Stability between 1 and 6 Years of Age in Children with Congenital Heart Disease. J. Pediatr. 215, 83–89. https://doi.org/10.1016/j.jpeds.2019.08.036.
Olshaker, H., Ber, R., Hoffman, D., Derazne, E., Achiron, R., Katorza, E., 2018. Volumetric brain MRI study in fetuses with congenital heart disease. American Journal of Neuroradiology 39 (6), 1164–1169. https://doi.org/10.3174/ajnr.A5628.
Oouchi, H., Yamada, K., Sakai, K., Kizu, O., Kubota, T., Ito, H., Nishimura, T., 2007. Diffusion anisotropy measurement of brain white matter is affected by voxel size: Underestimation occurs in areas with crossing fibers. American Journal of Neuroradiology 28 (6), 1102–1106. https://doi.org/10.3174/ajnr.A0488.
Peyvandi, S., Latal, B., Miller, S.P., McQuillen, P.S., 2019. The neonatal brain in critical congenital heart disease: Insights and future directions. NeuroImage 185, 776–782. https://doi.org/10.1016/j.neuroimage.2018.05.045.
Puig, J., Blasco, G., Daunis-I-Estadella, J., Thomalla, Götz, Castellanos, M., Figueras, J., Remollo, S., van Eendenburg, C., Sánchez-González, J., Serena, J., Pedraza, S., 2013. Decreased corticospinal tract fractional anisotropy predicts long-term motor outcome after stroke. Stroke 44 (7), 2016–2018. https://doi.org/10.1161/STROKEAHA.111.000382.
R Core Team, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.
Ressel, V., O'Gorman Tuura, R., Scheer, I., van Hedel, H.J.A., 2017. Diffusion tensor imaging predicts motor outcome in children with acquired brain injury. Brain Imaging and Behavior 11 (5), 1373–1384. https://doi.org/10.1007/s11682-016-9637-z.
Ressel, V., van Hedel, H.J.A., Scheer, I., O'Gorman Tuura, R., 2018. Comparison of DTI analysis methods for clinical research: influence of pre-processing and tract selection methods. European Radiology Experimental 2, 1–12. https://doi.org/10.1186/s41747-018-0066-1.
Rollins, C.K., Asaro, L.A., Akhondi-Asl, A., Kussman, B.D., Rivkin, M.J., Bellinger, D.C., Warfield, S.K., Wypij, D., Newburger, J.W., Soul, J.S., 2017. White Matter Volume Predicts Language Development in Congenital Heart Disease. J. Pediatr. 181, 42–48.e2. https://doi.org/10.1016/j.jpeds.2016.09.070.
Rollins, C.K., Watson, C.G., Asaro, L.A., Wypij, D., Vajapeyam, S., Bellinger, D.C., Demaso, D.R., Robertson, R.L., Newburger, J.W., Rivkin, M.J., 2014. White matter microstructure and cognition in adolescents with congenital heart disease. J. Pediatr. 165, 936–944.e2. https://doi.org/10.1016/j.jpeds.2014.07.028.
Schaefer, Christina, von Rhein, Michael, Knirsch, Walter, Huber, Reto, Natalucci, Giancarlo, Caflisch, Jon, Landolt, Markus, Latal, Beatrice, 2013. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. Dev. Med. Child Neurol. 55 (12), 1143–1149. https://doi.org/10.1111/dmcn.12242.
Semmel, E.S., Dotson, V.M., Burns, T.G., Mahle, W.T., King, T.Z., 2018. Posterior Cerebellar Volume and Executive Function in Young Adults With Congenital Heart Disease. Journal of the International Neuropsychological Society 24 (9), 939–948. https://doi.org/10.1017/S1355617718000310.
Skotting, M.B., Eskildsen, S.F., Ovesen, A.S., Fonov, V.S., Ringgaard, S., Hjortdal, V.E., Lauridsen, M.H., 2021. Infants with congenital heart defects have reduced brain volumes. Sci. Rep. 11, 1–8. https://doi.org/10.1038/s41598-021-83690-3.
Smith, Stephen, 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155. https://doi.org/10.1002/hbm.10062.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. NeuroImage 31 (4), 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23, 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051.
Snookes, S.H., Gunn, J.K., Eldridge, B.J., Donath, S.M., Hunt, R.W., Galea, M.P., Shekerdemian, L., 2010. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. Pediatrics 125 (4), e818–e827. https://doi.org/10.1542/peds.2009-1959.
Soares, J.M., Marques, P., Alves, V., Sousa, N., 2013. A hitchhiker's guide to diffusion tensor imaging. Front. Neurosci. https://doi.org/10.3389/fnins.2013.00031.
van der Linde, D., Konings, E.E.M., Slager, M.A., Witsenburg, M., Helbing, W.A., Takkenberg, J.J.M., Roos-Hesselink, J.W., 2011. Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. J. Am. Coll. Cardiol. 58 (21), 2241–2247. https://doi.org/10.1016/j.jacc.2011.08.025.
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. The Journal of Pediatrics 167, 1259–1264. https://doi.org/10.1016/j.jpeds.2015.07.006.
Von Rhein, M., Buchmann, A., Hagmann, C., Huber, R., Klaver, P., Knirsch, W., Latal, B., 2014. Brain volumes predict neurodevelopment in adolescents after surgery for congenital heart disease. Brain 137, 268–276. https://doi.org/10.1093/brain/awt322.
von Rhein, M., Dimitropoulos, A., Valsangiacomo Buechel, E.R., Landolt, M.A., Latal, B., 2012. Risk factors for neurodevelopmental impairments in school-age children after cardiac surgery with full-flow cardiopulmonary bypass. J. Thorac. Cardiovasc. Surg. 144 (3), 577–583. https://doi.org/10.1016/j.jtcvs.2012.02.005.
Warnes, C.A., Liberthson, R., Danielson, G.K., Dore, A., Harris, L., Hoffman, J.I.E., Somerville, J., Williams, R.G., Webb, G.D., 2001. Task force 1: the changing profile of congenital heart disease in adult life. J. Am. Coll. Cardiol. 37 (5), 1170–1175. https://doi.org/10.1016/S0735-1097(01)01272-4.
Watson, C.G., Stopp, C., Wypij, D., Bellinger, D.C., Newburger, J.W., Rivkin, M.J., 2018. Altered White Matter Microstructure Correlates with IQ and Processing Speed in Children and Adolescents Post-Fontan. J. Pediatr. 200, 140–149.e4. https://doi.org/10.1016/j.jpeds.2018.04.022.
Wernovsky, G., 2008. Improving neurologic and quality-of-life outcomes in children with congenital heart disease: Past, present, and future. J. Thorac. Cardiovasc. Surg. 135 (2), 240–242.e2. https://doi.org/10.1016/j.jtcvs.2007.07.057.