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Executive function and brain development in adolescents with severe congenital heart disease (Teen Heart Study): protocol of a prospective cohort study

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ABSTRACT

Introduction Congenital heart disease (CHD) is the most frequent congenital malformation. With recent advances in medical care, the majority of patients with CHD survive into adulthood. As a result, interest has shifted towards the neurodevelopmental outcome of these patients, and particularly towards the early detection and treatment of developmental problems. A variety of mild to moderate cognitive impairments as well as emotional and behavioural problems has been observed in this population. However, a more detailed assessment of the various domains of executive function and their association with structural and functional brain development is lacking. Therefore, the current study will examine all domains of executive function and brain development in detail in a large sample of children and adolescents with CHD and healthy control children.

Methods and analysis A total of 192 children and adolescents with CHD aged 10–15 years, who participated in prospective cohort studies at the University Children's Hospital Zurich, will be eligible for this study. As a control group, approximately 100 healthy children will be enrolled. Primary outcome measures will include executive function abilities, while secondary outcomes will consist of other neurodevelopmental measures, including intelligence, processing speed, attention, fine motor abilities and brain development. An MRI will be performed to assess structural and functional brain development. Linear regression analyses will be applied to investigate group differences and associations between executive function performance and neurodevelopmental measures.

Ethics and dissemination This study is supported by the Swiss National Science Foundation (SNF 32003B_172914) and approved by the ethical committee of the Canton Zurich (KEK 2019–00035). Written informed consent will be obtained from all the parents and from children aged 14 years or older. Findings from this study will be published in peer-reviewed journals and presented at national and international conferences for widespread dissemination of the results.

Strengths and limitations of this study

► Consecutive follow-up data of cognitive performance, behaviour and quality of life are available throughout childhood (age 1–10 years) from this cohort of children with congenital heart disease.
► Executive function (EF) abilities will be assessed comprehensively using a battery of standardised neuropsychological tests in order to measure the core domains of EF: inhibition, cognitive flexibility, fluency, working memory, planning and risk taking.
► The potential risk for a recruitment bias of healthy controls with an above-average socioeconomic status exists as they are more likely to consent to serve as controls.
► Heterogeneity of types of heart defects may result in a potential variety of cognitive outcomes in the patient group.

most frequent congenital malformation. With dramatic improvements in surgical management and in neonatal and perioperative care, survival rates have significantly increased.[2,3] As cardiac outcome is often good, enabling these children to survive into adulthood, interest has mounted in the neurodevelopmental and behavioural outcomes of these children. Neurodevelopmental impairments in this at risk population can occur across all developmental domains, particularly in cognitive, language, visuoperceptual and motor abilities.[4] Further, children with CHD are at an increased risk for behavioural and emotional problems.[5,6] These problems are likely associated with lifelong individual psychological and societal financial burdens.[7]

Executive functions (EF) comprise a set of interrelated higher-order cognitive abilities that facilitate purposeful, goal-oriented behaviour. EF include domains such as inhibition, working memory and cognitive flexibility,

INTRODUCTION

Congenital heart disease (CHD) occurs in about 8/1000 live births[1] and constitutes the

verbal fluency and planning.[8] EF have a protracted developmental trajectory: they emerge in early childhood and evolve during early adolescence into young adulthood,[9] paralleling the maturation of prefrontal structures[10] and have been closely linked to academic achievement in healthy children.[11] Deficits may become apparent only during early adolescence, a time when personal autonomy develops and increasing demands are placed on various EF within both the home and school environments. While EF difficulties have been well-described in another at risk population of preterm born children,[12] information on the development of EF in CHD children is limited. Most studies have only reported individual aspects of EF (eg, working memory, planning)[13 14] or have assessed executive dysfunction in daily living by means of a questionnaire,[15] but only a few previous studies have applied more comprehensive cognitive test batteries to assess a wider spectrum of EF. Two studies in children 5–7 years old with transposition of the great arteries (TGA) reported EF difficulties in cognitive inhibition, working memory, cognitive flexibility and planning, even though IQ was in the normal range.[16 17] Another study in 10–19-year-old CHD children and adolescents reported EF impairments in flexibility and problem solving. Another study in adolescents reported worse performance on tests of EF in different types of heart defects, such as tetralogy of Fallot, TGA and hypoplastic left heart syndrome.[18–20] Another important aspect of cognitive function is processing speed. Processing speed seems to be a strong determinant of later EF and academic achievement in children with TGA[21] and has also been shown to mediate improvements in EF in very preterm born children at school-age.[22]

MRI studies in fetuses, neonates, children and adolescents with CHD have shown that brain alterations and delayed brain maturation already occur prenatally and that there are persistent global and local reductions in brain volume, particularly in the white matter, the hippocampus and the cortical grey matter.[23–25] However, the implications of structural changes, delayed brain maturation, reduced brain volumes and poorer connectivity, for later neurodevelopmental outcome are still unclear. Delayed brain maturation in the CHD population may lead to overall slower development until school age with consecutively delayed development of higher order brain networks and associated functions such as EF. Previous studies on healthy individuals and patients with a variety of neurological or psychiatric conditions have shown that EF performance is dependent on frontoparietal as well as the cingulo-opercular networks and the cerebellum.[26 27]

A systematic review of imaging findings in adolescents and young adults with CHD estimated the odds of brain abnormalities to be 15.6 times higher compared with healthy controls, with focal and multifocal lesions being the most frequent abnormalities.[24] There is emerging evidence that brain alterations revealed by volumetric, structural and functional analyses are associated with poorer neurocognitive performance.[24] Brain volumes in adolescents with a wide variety of CHD diagnoses are globally reduced and correlate with functional deficits.[28] With regard to brain structural connectivity, so far, only very few studies reported on the relation of diffusion tensor imaging (DTI) and neurodevelopmental outcome in adolescents with CHD. A study in patients with TGA revealed that lower fractional anisotropy in the left parietal region, right precentral region and right frontal region was associated with impaired EF performance and lower academic achievement.[29] Two studies showed that reduced fractional anisotropy in the white matter tracts was associated with impairments in various cognitive domains such as IQ, processing speed and memory.[30 31] Further, a connectomic analysis revealed a link between decreased global efficiency, increased modularity, increased small-worldness and worse EF and academic achievement.[32] However, to date there is only limited information regarding EF impairments in adolescents with CHD, risk factors for impaired EF and the association between impaired EF and brain abnormalities.

Aims and hypothesis of study

The main aim of this project is to assess the extent and spectrum of EF deficits in relation to cerebral MRI findings, brain volumes and connectivity in children and adolescents aged 10–15 years who have undergone cardiopulmonary bypass (CPB) surgery for severe CHD.

1. To evaluate a broad spectrum of EF in children with severe CHD between the age 10–15 years in comparison to healthy controls. *Hypothesis*: Children/adolescents with CHD will show impairments in overall EF and across all subdomains of EF with the strongest effects in flexibility according to Cassidy *et al*.[21]
2. To assess structural, morphometric and connectivity changes using cerebral MRI and to correlate these with EF performance in children with CHD between the ages 10 and 15 years. *Hypothesis*: Children/adolescents with CHD will show brain atrophy and small white matter lesions, reduced global and regional brain volumes. Connectivity analyses will demonstrate network alterations in the frontoparietal and/or cingulo-opercular networks, which will correlate with EF performance.
3. To evaluate and identify patient-specific and treatment-associated risk factors for poorer EF and, in a subsample of children, to evaluate neonatal cerebral MRI biomarkers for poorer EF. *Hypothesis*: We will be able to identify specific risk factors (patient-specific, treatment-associated and cerebral imaging) which will constitute early biomarkers for later EF difficulties.

METHODS AND ANALYSIS
Study participants

We will recruit the participants at the age of 10–15 years from two prospective cohort studies, the *REACHOUT (REsearch and Assessment of Child Health and OUTcome)* study and the *Heart and Brain cohort 1* study. Variables describing medical, neurological, perioperative and demographic properties have been collected prospectively.

In the *Reachout* study, children were enrolled between July 2004 and July 2009 prior to CPB surgery and underwent comprehensive and standardised neurodevelopmental and behavioural assessments at defined ages (1, 4, 6 and 10 years). Quality of life and factors associated with quality of life were assessed through questionnaires at all time points. For the 1, 4 and 6 year examination, children with a genetic comorbidity were also examined.

In the *Heart and Brain cohort 1,* children with CHD without a genetic comorbidity who were born between November 2009 and February 2012 and who had CPB surgery during the neonatal period or early infancy underwent neonatal preoperative and postoperative cerebral MRI assessment. They had neurodevelopmental assessments at the age of 1, 4 and 6 years of age.

Children will be eligible for the current study if they were born between 2004 and 2012 and underwent their first CPB surgery before the age of 6 years, are currently living in Switzerland and have not been diagnosed with a genetic comorbidity or dysmorphic syndrome. There are 192 children (125 male) eligible (*REACHOUT* study n=160, *Heart and Brain cohort 1* n=32). The majority are diagnosed with a TGA (n=68). Other diagnoses include univentricular CHD (n=36) and other severe CHD requiring CPB surgery in the neonatal period or during early infancy. If necessary, to ensure the required power by means of a sufficient sample size, additional patients with CHD meeting our inclusion criteria can be recruited from the paediatric cardiology clinic of the University Children's Hospital Zurich and from collaborating paediatric cardiology centres.

Recruitment of all of the patients with CHD will be done with an invitation letter sent by post to their parents, followed by contact via telephone. Healthy, term-born children will be recruited as a control group. Children from the control group will be recruited from peers of the participating patients with CHD and through advertisements in schools. Controls will be excluded if they are diagnosed with a significant developmental disorder (specific learning disorder or attention deficit hyperactivity disorder) or any neurological diagnoses.

This research will be done without direct patient involvement in regard to commenting on the study design, developing patient relevant outcomes or interpreting the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Outcome measures

Primary outcome measures will include EF abilities, while secondary outcomes will consist of other neurodevelopmental measures, including intelligence, processing speed, attention, fine motor abilities and brain development. An MRI will be performed to assess structural and functional brain development. Questionnaires, filled out by the parents and the children, will be used to gather information on behavioural problems, quality of

Table 1 Study specific test battery to assess executive function ability

Assessed domains	Applied assessment tool
Inhibition	Go/NoGo (TAP) Colour Word Interference Task (D-KEFS)
Working Memory	Digit Span forward & backward (WISC-IV) Letter-number Sequencing (WISC-IV) Corsi Block Tapping Test
Cognitive Flexibility	Trail Making Task (D-KEFS) Flexibility (TAP)
Planning	Tower Task (D-KEFS)
Fluency	Verbal Fluency (RWT) Design Fluency (D-KEFS)
Risk taking	Balloon Analogue Risk Task For Youth (BART-Y)

life, personality and the quality of the family and social environment.

Primary outcome measures: executive functions

An extensive neuropsychological test battery consisting of well established, standardised tests will be used to assess EF performance with regard to inhibition, working memory, cognitive flexibility, planning, fluency and risk-taking behaviour (table 1).

The *Delis-Kaplan Executive Function System*[33] encompasses a set of key tasks to assess EF in a standardised manner. In this study, we will use the *Trail Making Test* (flexibility), the *Color-Word Inference Task* (inhibition), the *Tower Task* (visual-spatial planning) and the *Design Fluency Test* (visual-spatial fluency). The *Test of Attentional Performance* (TAP)[34] is a validated set of computer-based tests to selectively assess specific aspects of attention processes. In our study, the subtests *Flexibility* and *Go/NoGo* (inhibition) will be conducted. The *Regensburger Verbal Fluency Test*[35] has been validated in German speaking populations and assesses phonetic and semantic verbal fluency. Verbal working memory will be assessed with the two subtests *Digit span* and *Letter-number sequencing* from the WISC-IV. Visual-spatial working memory will be assessed using the *Corsi Block Tapping-Test*[36] with a forward and backward condition.

Risk taking behaviour, a form of emotion-charged EF,[37] will be measured by the youth-version of the *Balloon analogue risk task*.[38] For this study, the task will be implemented in PsychoPy.[39] All settings will be adopted from the original study by Lejuez.[38]

A global composite score for EF as well as composite scores for each subtype of EF will be calculated using z-transformed scores of the tests measuring inhibition, working memory, cognitive flexibility, planning and fluency.

To assess EF skills in daily life, parents will complete the validated questionnaire *Behaviour Rating Inventory of Executive Functions*[40].

Secondary outcome measures
Neurodevelopmental measures: intelligence, processing speed, attention and fine motor abilities

The IQ will be estimated by means of a well-established four-subtest short version of the WISC-IV that correlates highly (r>0.90) with the full version.[41 42] A combination of the subtests *Matrices, Similarities, Letter Number Sequencing* and *Symbol Search* will be assessed. Processing speed will be assessed with the subtest *Coding* and *Symbol Search* from the WISC-IV and a global score for processing speed will be estimated according to the manual of the WISC-IV. Attention will be measured using the subtest *Alertness* of the Test of Attentional Performance (TAP). To measure fine motor abilities, the subtest *Pegboard* of the Zurich Neuromotor Assessment, Second edition[43] will be used.

The measures for processing speed, attention and fine motor abilities will be used to ensure that differences in EF performance are not caused by differences in these domains.

The neurodevelopmental test battery, including the tests for EF performance, intelligence, processing speed, attention and fine motor abilities will take approximately 2 ½ hours. The tests will be conducted in a randomised order to avoid effects of fatigue and motivation loss. Trained psychologists and paediatricians from the Child Development Center at the University Children's Hospital Zurich will administer and interpret the tests. The radiologist reviewing the MR scans will be blinded.

Magnetic resonance imaging

Cerebral MRI will be performed on a 3T GE MR750 scanner. Suitability for MRI acquisition will be assessed prior to the study participation using a safety-screening questionnaire, which will be filled out by the parents. All surgery reports will be screened for magnetic implants to confirm MR safety. For the MRI scan, hearing protection will be provided with earplugs and headsets. The heart rate and respiratory rate as well as the specific absorption rate will be monitored.

High-resolution three-dimensional T1 weighted images will be acquired using a three dimensional spoiled gradient echo pulse sequence (SPGR) to assess brain volumes, cortical thickness and the presence of white matter lesions or other abnormalities. SPGR images will be acquired using the following parameters: repetition time/echo time (TR/TE)=11/5 ms; inversion time=600 ms; flip angle=8°; reconstructed matrix=256 × 256; field of view (FOV)=26 cm; 176 contiguous axial slices, 1 mm slice thickness.

For the investigation of global network connectivity and maturation of white matter microstructure, DTI will be performed. The imaging slices will be oriented parallel to the anterior commissure—posterior commissure plane, with parameters: TR/TE=7500/89 ms; acquisition matrix=96×96; FOV=28 cm; slice thickness 3.6 mm. A total of 35 diffusion-weighted gradient directions will be acquired with four interleaved non-diffusion weighted images with b=0 s/mm^2.

Table 2 List of applied questionnaires

Assessed domains and subdomains	Questionnaire	Completed by
Information on child		
Quality of life	Kidscreen-27[49] Kidscreen-10	Parent Child
Resilience (Personality trait)	Resilience Scale 13[50]	Child
Executive functions in daily living	Behaviour Rating Inventory for Executive Function	Parent
Behavioural difficulties	Strength and Difficulties Questionnaire[51]	Parent
Family situation		
Family environment	Family Relationship Index[52]	Parent
Parenting style and bonding	Parenting Style inventory[53] Zurich Brief Questionnaire for the Assessment of Parental Behavior[54]	Parent Child
Parental mental health	Brief Symptom Inventory 18[55]	Parent
Parental resilience (Personality trait)	Resilience Scale 13	Parent
Parental quality of life Aversive life events	36-Item Short Form Survey[56] Life Event Scale*	Parent Parent
Social situation		
Social support	Social Support Questionnaire[57]	Parent
Socioeconomic status	Information on maternal education and parental occupation	Parent

*Landolt MA, Vollrath M. Life event scale. University Children's Hospital Zurich, Zurich, Switzerland, 1998.

Functional resting state MRI will be conducted to analyse functional connectivity and to map connectome networks in combination with structural DTI data. Patients will be asked to close their eyes during this sequence. The following parameters will be applied: TR/TRE=1925/17 ms; flip angle=74°, FOV=24 cm; acquisition matrix=64×64; slice thickness 3.6 mm.

In a subset of 32 participants, preoperative and postoperative neonatal brain imaging (MRI) will be investigated in relation to adolescent MRI.[44]

Questionnaires

In order to evaluate behaviour, quality of life, resilience and the family and social situation, participants and their parents will be asked to complete a set of questionnaires.

Participants will fill out three questionnaires on quality of life, resilience and the parenting style of their parents.

Parents of the participating children/adolescents will be asked to complete questionnaires about their child's behaviour and quality of life, as well as on their own well-being (physical and mental health) and various aspect of their family and social situation (see table 2 for detailed

information on the applied questionnaires). Socioeconomic status (SES) will be estimated by means of two six-point scales of maternal education and paternal occupation with a range from 2 to 12.[45]

Patient and public involvement

Patients were neither involved in developing the research questions nor the study design. However, patients were involved in the recruitment of healthy controls, as they were encouraged to bring a friend to best possible balance demographic variables (eg, age, sex and SES) between groups.

The results from this study will be disseminated to participants and their families by means of newsletters, patient organisation platforms and public informative meetings.

Statistical analyses
Study design and power calculation

Based on a previous study on EF performance in adolescents with CHD,[21] we expect a minimum effect size of 0.55 for differences in the different domains of EF, with a range in effect size from 0.55 (planning) to 0.81 (flexibility) when comparing patients with CHD and healthy controls. Considering the smallest effect size of 0.55, a minimum sample size of 70 participants per group is needed, assuming an alpha level of 0.05 and a power of 0.9. Considering that we plan to investigate global EF and its six domains (see table 1), a Bonferroni correction for these additional variables would result in an alpha level of 0.007 (alpha corrected=0.05/7=0.007). Under this assumption, the minimum sample size per group would then be 104. Based on the high follow-up rates from the previous neurodevelopmental assessments of the *REACHOUT* cohort,[46] this sample size is assumed to be achievable.

As often seen when recruiting healthy controls, there might be a sampling bias for higher functioning individuals[47] which may be evident with regard to IQ and SES. These imbalances will be taken into account in the statistical analysis.

Statistics

Descriptive statistics will include mean and SD for continuous variables and number and percentage for categorical variables. T-tests will be conducted for continuous variables and χ^2 tests for categorical variables.

Linear regression models will be used in order to investigate differences between the patients with CHD and healthy controls in EF abilities. The independent variable will be group status (patients with CHD, healthy controls) and other potential cofounders, such as socioeconomic status, age and sex will be considered. Posthoc analyses will be conducted to investigate whether the type of CHD has an effect on outcome. We will aim for balanced groups when categories are selected for posthoc analyses.

Further associations between secondary variables, such as MR parameters for brain development, will be investigated using linear regression analyses. For these models, group and potential cofounders will be included in the models.

Regarding brain network analysis, structural DTI and functional resting-state MRI data will be combined using graph theory measures, such as topological organisation (modularity, small-world and rich-club indices), integration and segregation.

All analyses will be conducted with an alpha level of 0.05. Bonferroni or false discovery rate correction will be applied if needed. The statistical programming language R[48] will be used for all analyses. In the case that the data do not meet the linearity and normality assumptions, non-parametric tests will be used to ensure the interpretability of the results.

Ethics and dissemination

The protocol was approved by the ethical committee of the Canton of Zurich in Switzerland (BASEC-Nr: 2019–00035). Written informed consent will be obtained from the parents and children aged 14 years or older. Data handling, record keeping and archiving will be done according to the guidelines given by the ethical committee. For widespread dissemination, the results of this study will be presented at national and international conferences, published in peer-reviewed journals and presented to parent organisations and healthcare stakeholders.

REFERENCES

1. van der Linde D, Konings EEM, Slager MA, *et al*. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;58:2241–7.
2. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. *Cardiol Young* 2006;16:92–104.
3. Oster ME, Lee KA, Honein MA, *et al*. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics* 2013;131:e1502–8.
4. Latal B. Neurodevelopmental outcomes of the child with congenital heart disease. *Clin Perinatol* 2016;43:173–85.
5. Latal B, Helfricht S, Fischer JE, *et al*. Psychological adjustment and quality of life in children and adolescents following open-heart surgery for congenital heart disease: a systematic review. *BMC Pediatr* 2009;9:6.
6. Shillingford AJ, Glanzman MM, Ittenbach RF, *et al*. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics* 2008;121:e759–67.
7. Marino BS. New concepts in predicting, evaluating, and managing neurodevelopmental outcomes in children with congenital heart disease. *Curr Opin Pediatr* 2013;25:574–84.

8   Anderson P. Assessment and development of executive function (EF) during childhood. *Child Neuropsychology* 2002;8:71–82.

9   Sousa SS, Amaro E, Crego A, *et al*. Developmental trajectory of the prefrontal cortex: a systematic review of diffusion tensor imaging studies. *Brain Imaging Behav* 2018;12:1197–210.

10 Moriguchi Y, Hiraki K. Longitudinal development of prefrontal function during early childhood. *Dev Cogn Neurosci* 2011;1:153–62.

11 Bull R, Espy KA, Wiebe SA. Short-Term memory, working memory, and executive functioning in preschoolers: longitudinal predictors of mathematical achievement at age 7 years. *Dev Neuropsychol* 2008;33:205–28.

12 van Houdt CA, Oosterlaan J, van Wassenaer-Leemhuis AG, *et al*. Executive function deficits in children born preterm or at low birthweight: a meta-analysis. *Dev Med Child Neurol* 2019;61:1015–24.

13 Bellinger DC, Wypij D, duPlessis AJ, *et al*. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston circulatory arrest trial. *J Thorac Cardiovasc Surg* 2003;126:1385–96.

14 Schaefer C, von Rhein M, Knirsch W, *et al*. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. *Dev Med Child Neurol* 2013;55:1143–9.

15 Gerstle M, Beebe DW, Drotar D, *et al*. Executive functioning and school performance among pediatric survivors of complex congenital heart disease. *J Pediatr* 2016;173:154–9.

16 Calderon J, Bonnet D, Courtin C, *et al*. Executive function and theory of mind in school-aged children after neonatal corrective cardiac surgery for transposition of the great arteries. *Dev Med Child Neurol* 2010;52:1139–44.

17 Calderon J, Jambaqué I, Bonnet D, *et al*. Executive functions development in 5- to 7-year-old children with transposition of the great arteries: a longitudinal study. *Dev Neuropsychol* 2014;39:365–84.

18 Bellinger DC, Rivkin MJ, DeMaso D, *et al*. Adolescents with tetralogy of Fallot: neuropsychological assessment and structural brain imaging. *Cardiol Young* 2015;25:338–47.

19 Bellinger DC, Wypij D, Rivkin MJ, *et al*. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation* 2011;124:1361–9.

20 Bellinger DC, Watson CG, Rivkin MJ, *et al*. Neuropsychological status and structural brain imaging in adolescents with single ventricle who underwent the Fontan procedure. *J Am Heart Assoc* 2015;4.

21 Cassidy AR, White MT, DeMaso DR, *et al*. Executive function in children and adolescents with critical cyanotic congenital heart disease. *J Int Neuropsychol Soc* 2015;21:34–49.

22 Mulder H, Pitchford NJ, Marlow N. Processing speed mediates executive function difficulties in very preterm children in middle childhood. *J Int Neuropsychol Soc* 2011;17:445–54.

23 von Rhein M, Buchmann A, Hagmann C, *et al*. Severe congenital heart defects are associated with global reduction of neonatal brain volumes. *J Pediatr* 2015;167:1259–63.

24 Bolduc M-E, Lambert H, Ganeshamoorthy S, *et al*. Structural brain abnormalities in adolescents and young adults with congenital heart defect: a systematic review. *Dev Med Child Neurol* 2018;60:1209–24.

25 Limperopoulos C, Tworetzky W, McElhinney DB, *et al*. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation* 2010;121:26–33.

26 Nowrangi MA, Lyketsos C, Rao V, *et al*. Systematic review of neuroimaging correlates of executive functioning: converging evidence from different clinical populations. *J Neuropsychiatry Clin Neurosci* 2014;26:114–25.

27 Schmidt EL, Burge W, Visscher KM, *et al*. Cortical thickness in frontoparietal and cingulo-opercular networks predicts executive function performance in older adults. *Neuropsychology* 2016;30:322–31.

28 von Rhein M, Buchmann A, Hagmann C, *et al*. Brain volumes predict neurodevelopment in adolescents after surgery for congenital heart disease. *Brain* 2014;137:268–76.

29 Rollins CK, Watson CG, Asaro LA, *et al*. White matter microstructure and cognition in adolescents with congenital heart disease. *J Pediatr* 2014;165:936–44.

30 Watson CG, Stopp C, Wypij D, *et al*. Altered white matter microstructure correlates with IQ and processing speed in children and adolescents Post-Fontan. *J Pediatr* 2018;200:140–9.

31 Brewster RC, King TZ, Burns TG, *et al*. White matter integrity dissociates verbal memory and auditory attention span in emerging

32 Panigrahy A, Schmithorst VJ, Wisnowski JL, *et al*. Relationship of white matter network topology and cognitive outcome in adolescents with d-transposition of the great arteries. *Neuroimage* 2015;7:438–48.

33 Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan executive function system: examiners manual*. Psychological Corporation, 2001.

34 Zimmermann P, Fimm B. *Testbatterie Zur Erfassung von Aufmerksamkeitsstörungen (TAP 2.3)*. Psytest, 2012.

35 Aschenbrenner S, Tucha O, Lange K. *Regensburger Wortflüssigkeitstest Hogrefe Göttingen*. Germany, 2000.

36 Corsi PM. Human memory and the medial temporal region of the brain. *Dissertation Abstracts International* 1972;819B.

37 Poon K. Hot and cool executive functions in adolescence: development and contributions to important developmental outcomes. *Front Psychol* 2017;8:2311.

38 Lejuez CW, Aklin W, Daughters S, *et al*. Reliability and validity of the youth version of the balloon analogue risk task (BART-Y) in the assessment of risk-taking behavior among inner-city adolescents. *J Clin Child Adolesc Psychol* 2007;36:106–11.

39 Peirce J, Gray JR, Simpson S, *et al*. PsychoPy2: experiments in behavior made easy. *Behav Res Methods* 2019;51:195–203.

40 Drechsler R, Steinhausen H-C. Verhaltensinventar Zur Beurteilung exekutiver Funktionen (brief): deutschsprachige adaptation des behavior rating inventory of executive function (brief) von Gerard a Gioia, peter K. Isquith, Stephen C. Guy und Der self-report version (BRIEF-SR) von Stephen C. Guy, peter K. Isquith und Gerard A. Gioia: Huber 2013.

41 Petermann F, Petermann U. HAWIK-IV. *Kindheit und Entwicklung* 2008;17:71–5.

42 Waldmann H-C. Kurzformen des HAWIK-IV: Statistische Bewertung in verschiedenen Anwendungsszenarien. *Diagnostica* 2008;54:202–10.

43 Kakebeeke TH, Knaier E, Chaouch A, *et al*. Neuromotor development in children. Part 4: new norms from 3 to 18 years. *Dev Med Child Neurol* 2018;60:810–9.

44 Bertholdt S, Latal B, Liamlahi R, *et al*. Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery. *Eur J Cardiothorac Surg* 2014;45:625–32.

45 Largo RH, Pfister D, Molinari L, *et al*. Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. *Dev Med Child Neurol* 1989;31:440–56.

46 Naef N, Liamlahi R, Beck I, *et al*. Neurodevelopmental profiles of children with congenital heart disease at school age. *J Pediatr* 2017;188:75–81.

47 Russell EW, Florida M. Norming subjects for the Halstead Reitan battery. *Arch Clin Neuropsychol* 2005;20:479–84.

48 Team RC. *R: A language and environment for statistical computing*, 2019.

49 Ravens-Sieberer U, Auquier P, Erhart M, *et al*. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. *Quality of Life Research* 2007;16:1347–56.

50 Leppert K, Koch B, Brähler E, *et al*. Die Resilienzskala (RS)– Überprüfung der Langform RS-25 und einer Kurzform RS-13. *Klinische Diagnostik und Evaluation* 2008;1:226–43.

51 Lohbeck A, Schultheiß J, Petermann F, *et al*. Die Deutsche selbstbeurteilungsversion des strengths and difficulties questionnaire (SDQ-Deu-S). *Diagnostica* 2015;61:222–35.

52 Hoge RD, Andrews DA, Faulkner P, *et al*. The family relationship index: validity data. *J Clin Psychol* 1989;45:897–903.

53 Satow L. *Eltern-Erziehungsstil-Inventar (EEI)*. Leibniz-Zentrum für Psychologische Information und Dokumentation (ZPID), 2013.

54 Reitzle M, Metzke CW, Steinhausen H. Parents and children: the Zurich brief questionnaire for the assessment of parental behaviors. *Diagnostica* 2001;47:196–207.

55 Derogatis L. *Brief Symptom Inventory (BSI)-18. Administration, scoring and procedures manual*, 2000.

56 Bullinger M, Kirchberger I, Ware J. Der Deutsche SF-36 health survey Übersetzung und psychometrische Testung eines krankheitsübergreifenden instruments Zur Erfassung Der gesundheitsbezogenen Lebensqualität. *J Public Health* 1995;3:21–36.

57 Fydrich T, Sommer G, Tydecks S, *et al*. Social support questionnaire (F-SozU): standardization of short form (K-14). *Z Med Psychol* 2009;18.