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# Neurodevelopmental outcome after surgery for acyanotic congenital heart disease

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ABSTRACT

*Background:* Inconsistent results on neuropsychological outcome in patients treated for acyanotic congenital heart disease (aCHD) questioned the clinical relevance of possible neurobehavioral sequelae in this group. This study was designed to objectify the neuropsychological profile and evaluate associations with medical data.
*Methods:* Patients with a corrected atrial or ventricular septal defect, ASD-II or VSD, ($n = 46$; mean age 9 years, 2 months) and a matched control group were submitted to an intelligence test (Wechsler Intelligence Scale for Children, third edition, Dutch version) and evaluated with a neuropsychological test battery (Developmental Neuropsychological Assessment, second edition, Dutch version). Hospitalization variables were retrieved to evaluate associations with cognitive outcome. Parents completed a behavioral checklist (Achenbach Child Behavior Checklist for Children aged 6–18).
*Results:* ASD-II patients showed lower scores in domains of visuospatial processing, language, attention, and social perception. VSD patients displayed subtle problems in attention and visuospatial information processing. Only few perioperative medical factors, but also socioeconomic variables were associated with cognitive outcomes. Parents of ASD-II patients reported more school problems when compared to controls.
*Conclusions:* After treatment for aCHD, subtle cognitive difficulties can present in domains of visuospatial information processing, language, attention, and social perception. These shortcomings might hamper school performances, as is suggested by lower school competence ratings. Ongoing follow-up and cognitive screening is warranted to promote developmental progress, in which both parents and clinicians share responsibility.


## 1. Introduction

Mortality in children with congenital heart disease (CHD) decreased substantially over the past decades. Hence, long-term morbidity, such as neurodevelopmental outcome and subsequent quality of life became more important in ongoing

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research. Acyanotic congenital heart defects (aCHD) such as atrial septal defect secundum type (ASD-II) or ventricular septal defect (VSD), are the most common congenital cardiac anomalies in children (Moons et al., 2009). Although corrective procedures show excellent cardio-functional results, several studies reported on suboptimal neurobehavioral functioning for aCHD children in neuropsychological domains of attention, language, visuo-perceptual skills, motor functioning and social cognition (Brandlistuen et al., 2011a; Majnemer et al., 2009; Sarrechia, Miatton, De Wolf, Francois, & Vingerhoets, 2013; Simons, Glidden, Sheslow, & Pizarro, 2010; Visconti, Bichell, Jonas, Newburger, & Bellinger, 1999; von Rhein, Dimitropoulos, Buechel, Landolt, & Latal, 2012; Yang, Liu, & Townes, 1994), but findings in older aCHD patients show conflicting results (Quartermain et al., 2010). This late cognitive morbidity may hinder academic attainment, employability, and ultimately associated quality of life when progressing into adulthood (Zomer et al., 2012).

Nowadays, it is generally accepted that the etiology of neurocognitive sequelae after CHD repair is multifactorial with genetic, environmental, and perioperative management strategies all contributing to neurobehavioral outcome (Fuller et al., 2009; Limperopoulos et al., 2002; Wernovsky, 2006a). Moreover, neuroimaging methods such as Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) before and after surgery have been used to study atypical neurologic development caused by genetic etiology or hypoxic/ischemic events induced by the cardiac lesion (Ortinau et al., 2013). These studies in turn revealed that reduced brain volumes in CHD patients are associated with functional cognitive outcomes (von Rhein et al., 2013).

We aimed to further elucidate the influence of possible medical and socio-economic correlates in long-term neurodevelopment for surgically treated congenital acyanotic cardio-pathology. Risk factors such as presence of genetic morbidity, duration of cardiopulmonary bypass (CPB), hospitalization, and cross-clamp time have been identified and studied numerous times for children with complex forms of CHD (Fuller et al., 2009; Majnemer et al., 2009; Wernovsky, 2006a). To what extent some of these factors may influence the long-term development in school-aged children treated for mild CHD remains largely unknown. Majnemer et al. (2009) identified acyanotic CHD as a particular risk factor for poor neurobehavioral functioning in a longitudinal follow-up study.

This study's main objective was the description of the neuropsychological and behavioral outcome of children with a surgically corrected aCHD compared to matched healthy controls. Given that CPB techniques and cardioplegic arrest may have a distinct impact at different ages, we expect divergent neuropsychological profiles in these patients. Moreover, due to severe heart failure, longer procedural time, prolonged cross clamp time and hospital stay, we hypothesized that VSD patients would show more subtle cognitive difficulties as compared to matched controls than the group of surgically treated ASD-II patients. Medical parameters were retrieved from patient files to explore associations with long-term cognitive development. In particular, we aimed to investigate whether the rising concern for developmental delays in aCHD children rarely considered at risk, is warranted.

## 2. Patients and methods

### 2.1. Participants

Patients were recruited from 2 Belgian specialized pediatric heart centers, Ghent University Hospital and University Hospital Gasthuisberg Leuven. Patients with additional perinatal problems (asphyxia or infections such as toxoplasmosis, rubella or HIV), preterm gestational age (<37 weeks), birth weight of less than 2000 g, associated cardiac malformations, genetic abnormalities or developmental syndromes were excluded from the study.

Out of 83 invited patients, the parents of 46 (55%) responded positively to our call and these children were enrolled in the study. Reasons for non-participation included the presence of developmental syndromes (3%), refusal to participate (6%), and no response at all (36%). Responders and non-responders did not differ in age at intervention or total hospital stay. All patients had corrective cardiac surgery with full flow cardiopulmonary bypass and mild to deep hypothermia (25–37 °C) between 1999 and 2010. Neurodevelopmental testing was performed between the ages of 6 and 12.

The clinical population consisted of 18 ASD-II surgery patients and 28 VSD surgery patients. They were considered healthy at the moment of assessment and did not experience any physical restrictions as recorded by parental reports. Healthy controls were recruited through approval of school boards of regular primary schools. We randomly contacted over 80 regular primary schools, of which 11 agreed to participate. We consulted school lists and selected children similar to our patients in terms of age, gender and educational level of parents (if provided). Fifty families were approached and invited to participate, of which 46 responded positively (response rate 92%). These parents completed a short questionnaire on demographics and birth characteristics to affirm eligibility and after consent, these children were enrolled.

The hospital's Medical Ethics Committees approved the study and parental written consent was obtained for all participants. Study protocol was in accordance with the Helsinki Declaration (World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects, 1997).

### 2.2. Materials

A shortened version of the WISC-III-NL (3rd edition, Dutch version) was adopted to obtain a valid and reliable estimate of overall intelligence (Grégoire, 2000).

A developmental neuropsychological battery (NePsy-II-NL; a Developmental Neuropsychological Assessment—2nd edition, Dutch version) (Korkman, Kirk, & Kemp, 2007) was used to assess neurocognitive domains of Attention and

**Table 1**
Selected NePsy tasks.

| Nepsy domains and subtasks | Ability assessed |
|---|---|
| **Auditory attention and executive functioning** | |
| Auditory attention and response test | Selective auditory attention; vigilance; shifting; inhibition |
| Design fluency | Planning; problem solving skills |
| Inhibition | Shift and maintenance of new visual set; inhibition |
| **Language domain** | |
| Comprehension of instructions | Receiving, processing and executing oral instructions |
| Repetition of nonsense words | Phonological encoding and decoding |
| Speeded naming | Rapid semantic access and production of names |
| Word generation | Verbal productivity |
| **Memory and learning domain** | |
| Memory for faces | Encoding of facial features; immediate and long-term memory for faces |
| Memory for names | Name learning; short recall and long-term memory for names |
| Narrative memory | Encoding of story details; free and cued recall |
| Word list inference | Verbal working memory; repetition and recall after inference |
| **Sensorimotor domain** | |
| Imitating hand positions | Visuospatial analysis and motor programming |
| Manual motor sequences | Imitation of rhythmic manual movement sequences |
| Visuomotor precision | Graphomotor speed; accuracy |
| **Social perception domain** | |
| Affect recognition | Recognize and compare emotional affect |
| Theory of mind | Ability to understand mental functions and another's point of view |
| **Visuospatial processing domain** | |
| Block construction | Ability to reproduce 3D from 2D drawings |
| Design copying | Motor and visuo-perceptual skills in copying 2D designs |
| Geometric puzzles | Visuospatial analysis; mental rotation |
| Route finding | Visuospatial relations; directionality |

Korkman M, Kirk U, Kemp S. NEPSY-II: A Developmental Neuropsychological Assessment. 2007. *Note:* Domain scores were not included in the current version of the NEPSY-II-NL to make clear that subtests within a domain are multi-factorial, and the domain itself may cover many constructs.

Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception and Visuospatial Information Processing. The participants were assigned to 21 subtasks with 33 outcome scores targeting different aspects of the aforementioned domains. Table 1 gives an overview of the selected tasks.

Outcome scores were expressed as age-adjusted standardized scores (mean: 10, SD: 3), or percentile scores, which are considered to be process scores ($pc < 2$–$pc75$). These scores assess specific abilities or error rates that enable the clinician to evaluate a child's performance in more detail.

Total test duration was 3 h; breaks were provided during the test procedure to avoid fatigue. Parents completed demographic surveys. Meanwhile, socioeconomic status (SES) was estimated using the Hollingshead Four Factor Index, which combines parental occupational and educational level to compute a socioeconomic status score. Raw scores ranged from 27 to 66, with a higher score indicating higher social status.

All parents completed the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001). This questionnaire contains problem behavior scales and competence scales, to be rated in frequency on a three-point Likert scale. The 113 items cluster into three composite scales: Internalizing scale, Externalizing scale and grouped together, these scales constitute the Total Problem Behavior.

### 2.3. Medical factors

Medical charts were retrieved for pre-, peri-, and post-operative data of the patients, to evaluate possible associations with cognitive outcome (Table 3).

Gender, SES age and weight at intervention were categorized as non-modifiable patient-specific parameters. Factors as duration of intensive care unit (ICU) stay, total hospital stay, surgery, time on extracorporeal circulation (ECC), clamp time, intubation, degree of cooling and several postoperative hemodynamic parameters and the first arterial blood sample in the morning post-surgery were considered (post)operative management parameters.

### 2.4. Data analysis

Normally distributed data are presented as means with standard deviation, non-normal distributed data as medians with inter-quartile range, and clinical frequencies as indicated.

Nominal data were analyzed with Pearson's $\chi^2$-statistics, or with Fisher's Exact Test.

Since patients and controls were matched, paired t-tests and Wilcoxon matched-pairs signed ranks tests were rendered to explore group differences. We corrected for multiple testing by using the False Discovery Rate (Benjamini & Hochberg, 1995).

**Table 2**
Demographics.

| | ASD-II | ASD-II control | *p* | VSD | VSD control | *p* |
|---|---|---|---|---|---|---|
| *N* | 18 | 18 | | 28 | 28 | |
| Sex | ♂:6 ♀:12 | ♂:6♀:12 | *1.0* $\chi^2$ | ♂:13 ♀:15 | ♂:13 ♀:15 | *1.0* $\chi^2$ |
| Mean testage | 9y2m ± 2y2m | 9y3m ± 2y2m | *.967* | 8y9m ± 2y2m | 9y0m ± 2y2m | *.951* |
| Birth weight (g) | 3430 (2953–3607) | 3522 (3226–3967) | *.189* | 3205 (2888–3622) | 3320 (2902–3837) | *.384* |
| Birth length (cm) | 49.5 (48.3–51.1) | 50.0 (48.5–51) | *.724* | 50 (48–51) | 50 (48–51.5) | *.996* |
| Apgar score (1 min) (%) | <4: 0 | <4: 0 | *.492*$^E$ | <4: 0 | <4: 0 | *.436*$^E$ |
| | 4–6: 13.3 | 4–6: 0 | | 4–6: 0 | 4–6: 5.9 | |
| | 7–10: 86.7 | 7–10: 100 | | 7–10: 100 | 7–10: 94.1 | |
| Education mom (y) | 12 (12–15) | 15 (12–15.2) | *.225* | 15 (12–15) | 15 (12–15) | *.503* |
| Education dad (y) | 12 (12–13.5) | 12 (12–15) | *.134* | 12 (12–15) | 15 (12–15) | *.173* |
| SES | 37 (33.5–41.2) | 40 (36–47.5) | .091 | 40.5 (34.1–49) | 42.1 (37–48.5) | *.780* |

Data are presented as median (IQR) except for ages (mean ± SD). For ASD-II patients, SES range was [28–50], for ASD-II controls [32–53], VSD patients [27–59], VSD controls [32–66]. Birth weight, length and Apgar scores were based on demographic reports provided by parents.
$^E$ $\chi^2$ (with Exact option).

Effect sizes were calculated to quantify clinically meaningful differences between groups. Corrections and effect sizes were applied to standardized scores and percentile scores separately. For parametric data, Cohen's *d* was computed, for data that did not meet normality assumptions, effect sizes for Wilcoxon signed-rank, *r*, were calculated. Effect size was classified as small ($d = .20/r = .10$), moderate ($d = .50/r = .30$), large ($d = .80/r = .50$) and very large ($d = 1.3/r = .70$). Spearman's Rho (two-tailed) explored associations between hospitalization variables and outcome measures. The Statistical Package for the Social Sciences (SPSS) version 22 was used for statistical analyses. Statistical significance was reached at $p < .05$.

## 3. Results

### 3.1. Patient characteristics and medical factors

Patient demographic data and medical parameters are listed in Tables 2 and 3. Demographic characteristics did not differ significantly between the patient and control groups due to meticulous matching.

### 3.2. Neuropsychological assessment

Table 4 gives a comprehensive overview of the neuropsychological outcome of our study groups.

#### 3.2.1. ASD-II vs. healthy controls

Analyses show that ASD-II patients performed worse compared to matched controls for several measures of intelligence. Estimated full-scale IQ was 15 points lower in ASD-II children (97.4 vs. 112.4, $p = .010$), which in IQ-psychometric terms is comparable to 1 SD. Effect sizes of all intelligence measures were in the moderate-to-large range ($d = .45–1.08$), indicating clinically meaningful differences between groups (Table 4).

Concerning neuropsychological performance, ASD-II patients scored significantly lower on 13 of 33 subtasks assessed, after multiple testing corrections. In eleven subtasks, the difference is clinically relevant, eliciting large to very large effect sizes ($d \geq .80$). (Table 4)

ASD-II patients scored lower on a subtask of *Attention*, in Design Fluency, and they needed more time to inhibit a learned or automatic response in Inhibition-Time, the latter accompanied by a large-to-very large effect size ($d = 1.27$). In the *Language* domain, lower scores were reported on subtasks Comprehension of Instructions and Repetition of Nonsense Words, and Word Generation (Semantic). Large to very large effect sizes in this domain indicate meaningful group differences ($d \geq .08$). They scored poorer when remembering formerly learned face-name associations. Evaluating *Motor* competency, difficulties in Imitating Hand Positions and the memorizing and executing Manual Motor Sequences are clear, both evoking moderate to large effect sizes ($d \geq .50$). In the *Social domain*, Theory of Mind with Verbal and Contextual understanding of emotions yields significantly lower results in this patient group. Also in the same domain, a significant higher percentage of ASD-II patients scored in the clinical problematic range (≤pc10) on the subtask of Affect Recognition (50% vs. 16.7%, $p = .034$), adhering the particular large effect sizes for both subtasks ($d \geq .80$).

In the field of *Visuospatial* skills, children with ASD-II score lower on tasks of Block Construction and subtasks of Design Copying, the Motor component and the Local score. A higher proportion of these patients scored in the clinical range (>1 SD below mean) for the Motor score in Design Copying (27.8% vs. 0%, $p = .045$), as well as for the Local score (33.3% vs. 0%, $p = .019$). Correspondingly, large effect sizes show meaningful group differences.

**Table 3**
Patient characteristics.

| | ASD-II | VSD | *p* |
|---|---|---|---|
| *Medical parameters* | | | |
| Mean age at intervention | 2y8m ± 1y8m | 0y6m ± 1y3m | **.000**** |
| Weight intervention (pc) (%) | 3–10: 72.2<br>25–50: 16.7<br>75–90: 11.1 | 1–10: 87.5<br>25–50: 12.5<br>75–90: 0 | *.261*$^{E}$ |
| Defect size (mm) | 19 (14.25–21) | 8 (7–10) | **.000**** |
| ICU stay (days) | 1 (1–2.25) | 3 (2–4) | **.001**** |
| Hospital stay (days) | 7 (6–7) | 8.5 (7–11.75) | **.000**** |
| Duration operation (min) | 112.5 (95–131.2) | 145 (110–175) | **.046*** |
| Duration intubation (min) | 350 (277–551) | 1420 (705–1650) | **.000**** |
| *Preop* | | | |
| Creatinine (mg/dL) | .51 (.40–.58) | .49 (.45–.56) | *.916* |
| Hb (mg/dL) | 12.3 (11.7–13.1) | 11.2 (9.8–12.2) | **.001**** |
| *Periop* | | | |
| Aorta cross clamp (min) | 24 (15–36) | 36 (29.5–57.5) | **.003**** |
| Cooling (°C) | 32 (31.5–36.25) | 30 (28–32) | **.000**** |
| Mean arterial blood pressure (mmHg) | 44.6 (39.9–49.7) | 43.1 (39.1–50.4) | *.845* |
| Hb (g/dL) | 8.25 (7.58–9.7) | 8.6 (7.9–9.5) | *.543* |
| pH | 7.34 (7.31–7.38) | 7.34 (7.32–7.38) | *.676* |
| *Postop* | | | |
| $SaO_2$ (%) | 98.9 (97.1–99) | 98.8 (97.5–99.5) | *.355* |
| Creatinine (mg/dL) | .48 (.38–.57) | .54 (.47–.58) | *.053* |
| pH | 7.39 (7.36–7.41) | 7.39 (7.35–7.41) | *.803* |
| Glycemia high (mg/dL) | 178 (138–224.5) | 192 (166–262) | *.206* |
| Glycemia low (mg/dL) | 100 (91–109.5) | 105 (85–130) | *.734* |
| Median mean lactate concentrations (mg/dL) | 12.8 (9.7–18.3) | 11 (9–13.2) | *.212* |
| CRP (mg/dL) | 3.65 (2.32–5.04) | 2.45 (1.6–4.42) | *.206* |
| Inotropic medication (%) | Yes: 5.6<br>No: 94.4 | Yes: 67.9<br>No: 32.1 | **.000****$^{E}$ |

Data are presented as median (IQR), except for age (mean ± SD).
$^{E}$ $\chi^2$ (with Exact option).
* $p < .05$.
** $p < .01$.

### 3.2.2. VSD vs. healthy controls

Children surgically treated for VSD displayed similar intelligence scores compared to their matched healthy peers (105 vs. 105.5, ns), but scored lower on 4 of 33 selected NePsy tasks, of which 2 considered clinically meaningful as indicated by large effect sizes ($d \geq .80$). Paired analysis showed that patients needed significantly more time to complete an Inhibition task and scored poorer on a subtest for expressive language. Children treated for VSD obtained significantly lower scores for *Visuospatial Skills* Design Copying, on Motor and -Local assessment, with the latter resulting in a clinical meaningful difference ($d \geq .80$). Moreover, a higher proportion of VSD patients scored in the clinical problematic range (≤pc10) on the Total score of Design Copying as compared to the matched controls (71.4% vs. 39.3%, $p = .016$).

## 3.3. Behavior

Analysis showed no significant difference between patients and controls on the subscales of the CBCL (Table 5). However, a statistically significant higher proportion of parent of ASD-II children reported school problems as compared to controls (33% vs. 0%).

## 3.4. Correlations

### 3.4.1. ASD-II

Several *patient-specific factors* disclosed associations with long-term cognitive outcomes.

A positive relation existed between SES and performance on the Vocabulary scale ($r_s = .468$, $N = 18$, $p = .05$). Scores on Manual Motor Sequences were positively associated with age at intervention ($r_s = .492$, $N = 18$, $p = .038$) and weight at intervention ($r_s = .571$, $N = 18$, $p = .013$).

Gender and defect size were not related to any of the outcome measures.

Correlation analysis with *operative management parameters* revealed that hospitalization duration showed an inverse relation with performance of Manual Motor Sequences ($r_s = -.524$, $N = 18$, $p = .026$). Degree of cooling was negatively associated with language competence in Vocabulary ($r_s = -.553$, $N = 18$, $p = .017$) and Comprehension of Instructions ($r_s = -.492$, $N = 18$, $p = .038$). Operative pH levels were inversely related to Repetition of Nonsense Words ($r_s = -.546$, $N = 18$,

**Table 4**
Neuropsychological performance in matched comparison.

| | ASD-II | ASD-II-control | $p^a$ | Effect size, $d/r$ | VSD | VSD-control | $p^a$ | Effect size, $d/r$ |
|---|---|---|---|---|---|---|---|---|
| *N* | *18* | 18 | | | 28 | 28 | | |
| **WISC-III-NL** | | | | | | | | |
| *Estimated full scale IQ* | 97.4 ± 14.8 | 112.4 ± 12.8 | **.010*** | 1.08 | 105 ± 12.1 | 105.5 ± 8.1 | *.954* | .04 |
| Similarities | 11.8 ± 3.4 | 13.1 ± 2.2 | *.212* | .45 | 12.3 ± 2.3 | 11.6 ± 2 | *.785* | .32 |
| Picture arrangement | 8.3 ± 3.4 | 11.6 ± 2.5 | **.010*** | 1.10 | 10.1 ± 2.5 | 10.7 ± 2.8 | *.785* | .22 |
| Block design | 8.9 ± 2.7 | 11.3 ± 3.1 | **.027*** | .82 | 10.5 ± 2.8 | 11 ± 2 | *.785* | .20 |
| Vocabulary | 9.4 ± 2 | 11.8 ± 2.7 | **.015*** | 1.01 | 10.2 ± 2.5 | 10.2 ± 1.9 | *.954* | 0 |
| **NEPSY** | | | | | | | | |
| *Auditory attention and executive functioning* | | | | | | | | |
| Auditory attention (pc) | 62.5 (25–75) | 75 (75–75) | *.075* | .41 | 75 (56.25–75) | 75 (50–75) | *1.0* | 0 |
| Response test (pc) | 25 (25–50) | 50 (43.75–50) | *.245* | .26 | 50 (25–50) | 50 (50–50) | *.682* | .17 |
| Response test inhibition error (pc) | 25 (21.25–75) | 50 (25–75) | *.387* | .17 | 25 (10–75) | 25 (10–75) | *.898* | .08 |
| Design fluency | 8.7 ± 1.7 | 10.3 ± 2.3 | **.018*** | .79 | 9.8 ± 2.2 | 10.7 ± 2.3 | *.348* | .40 |
| Inhibition (pc) | 50 (50–62.5) | 50 (50–75) | *.181* | .31 | 50 (50–75) | 50 (50–75) | *.573* | .21 |
| Inhibition time | 9.4 ± 2 | 11.7 ± 1.6 | **.004**** | 1.27 | 9.7 ± 1.8 | 11.3 ± 1.9 | **.000**** | .86 |
| *Language domain* | | | | | | | | |
| Comprehension of instructions | 9.8 ± 2.7 | 13 ± 1.8 | **.007**** | 1.39 | 11.3 ± 2.8 | 11.1 ± 2.1 | *.904* | *.08* |
| Repetition of nonsense words | 9.2 ± 2.3 | 12.7 ± 1.7 | **.000**** | 1.73 | 10 ± 2.3 | 11.7 ± 2 | **.045*** | .78 |
| Speeded naming | | | | | | | | |
| Total (pc) | 25 (25–50) | 50 (25–75) | *.086* | .37 | 50 (25–50) | 50 (25–50) | *1.0* | .01 |
| Speeded naming time (pc) | 75 (75–75) | 75 (75–75) | *.312* | .27 | 75 (75–75) | 75 (75–75) | *1.0* | .13 |
| Word generation | | | | | | | | |
| Semantic | 9 ± 2.1 | 11.1 ± 2.6 | **.026*** | .88 | 9.5 ± 2.5 | 9.8 ± 2.1 | *.834* | .13 |
| Linguistic (pc) | 25 (7.5–62.5) | 50 (25–56.25) | *.393* | .15 | 50 (25–50) | 50 (10–50) | *.845* | .10 |
| *Memory and learning domain* | | | | | | | | |
| Memory for faces | 9.6 ± 3.3 | 10.1 ± 2.6 | *.908* | .16 | 10 ± 2.2 | 9.3 ± 2.8 | *.762* | .27 |
| Delayed | 9.1 ± 3.4 | 11.9 ± 2.9 | *.147* | .88 | 11.4 ± 3.5 | 11.4 ± 2.7 | *1.0* | 0 |
| Memory for names | 8.6 ± 2.4 | 10.2 ± 1.8 | **.037*** | .75 | 9.3 ± 2.6 | 9 ± 2.6 | *1.0* | .11 |
| Narrative memory | 10.4 ± 2.3 | 11.4 ± 1.8 | *.241* | .48 | 11.3 ± 1.9 | 10.7 ± 1.8 | *.309* | .32 |
| Cued recall (pc) | 50 (25–50) | 62.5 (50–75) | *.075* | .41 | 50 (50–75) | 50 (50–75) | *.780* | .13 |
| Word list inference | | | | | | | | |
| Working memory | 10.4 ± 2 | 11.9 ± 1.8 | *.084* | .78 | 10.1 ± 1.8 | 10.3 ± 1.9 | *.904* | .10 |
| Word recall | 11.1 ± 2.5 | 12 ± 2.4 | *.186* | .36 | 11.4 ± 2.3 | 11 ± 2.3 | *.762* | .17 |
| *Sensorimotor domain* | | | | | | | | |
| Imitating hand positions | 8.8 ± 2.4 | 10.4 ± 2 | **.018*** | .72 | 9.4 ± 2.6 | 10.2 ± 1.8 | *.355* | .35 |
| Manual motor sequences | 10.7 ± 3.8 | 13.3 ± 2.3 | **.044*** | .82 | 11.8 ± 2.8 | 12.8 ± 1.9 | *.349* | .41 |
| Visuomotor precision (pc) | | | | | | | | |
| Time (pc) | 50 (25–56.25) | 50 (50–75) | *.181* | .30 | 50 (25–75) | 50 (50–75) | *.898* | .06 |
| Error (pc) | 50 (19.25–75) | 25 (10–75) | *.531* | .11 | 25 (10–50) | 25 (13.7–75) | *.573* | .17 |
| *Social perception domain* | | | | | | | | |
| Affect recognition (pc) | 17.5 (4.25–56.25) | 37.5 (25–56.25) | *.235* | .24 | 17.5 (2.75–50) | 17.5 (5–50) | *.573* | .20 |
| Theory of mind | | | | | | | | |
| Verbal task | 10 ± 2.6 | 12.2 ± 2.2 | **.019*** | .91 | 10.9 ± 2.7 | 11.1 ± 2.1 | *.904* | .08 |
| Contextual task | 9.1 ± 2.4 | 11.3 ± 1.6 | **.015*** | 1.07 | 10.4 ± 2.5 | 10.5 ± 1.9 | *.904* | .04 |
| *Visuospatial processing domain* | | | | | | | | |
| Block construction | 9.3 ± 1.9 | 12.8 ± 2.4 | **.000**** | 1.61 | 11 ± 2.2 | 11.6 ± 2.4 | *.762* | .26 |
| Design copying (pc) | 5 (2–13.75) | 10 (10–25) | *.075* | .40 | 10 (5–25) | 25 (10–25) | *.105* | .35 |
| Motor | 7.9 ± 3.2 | 11.7 ± 2.4 | **.004**** | 1.34 | 10 ± 2.5 | 11.8 ± 2.3 | **.006**** | .74 |
| Global (pc) | 25 (10–50) | 25 (21.2–50) | *.181* | .28 | 25 (10–50) | 25 (25–50) | *.898* | .07 |
| Local | 7.5 ± 2.4 | 9.7 ± 2 | **.019*** | .99 | 8 ± 2 | 9.7 ± 1.8 | **.006**** | .89 |
| Geometric puzzles (pc) | 25 (21.5–50) | 50 (25–56.2) | *.181* | .30 | 50 (25–50) | 50 (25–50) | *1.0* | 0 |
| Route finding (pc) | 25 (10–25) | 25 (25–50) | *.117* | .36 | 25 (25–43.7) | 25 (25–50) | *.127* | .31 |

Standardized scores (mean ± SD): paired samples *t*-test. Pc scores (median (IQR), Wilcoxon matched-pairs signed-ranks test. *p* Value reached statistical significance is indicated in bold type. $p^a$ adjusted *p*-value according to the Benjamini- and Hochberg False Discovery Rate (1995).
Level of significance * $p < .05$, ** $p < .01$.

$p = .023$), and with Theory of Mind subtask, the Verbal ($r_s = -.504$, $N = 18$, $p = .033$) and Contextual item ($r_s = -.532$, $N = 18$, $p = .023$).

Evaluation of *postoperative parameters* disclosed a positive association between highest glycemia levels and Total estimated IQ ($r_s = .668$, $N = 17$, $p = .003$) and Vocabulary ($r_s = .810$, $N = 17$, $p = .000$), whereas lowest reported values of glycemia appeared associated with Total estimated IQ ($r_s = .594$, $N = 17$, $p = .012$), Vocabulary ($r_s = .618$, $N = 17$, $p = .008$), and Block Design ($r_s = .605$, $N = 17$, $p = .010$). Finally, postoperative mean lactate values were found to be inversely correlated with visuomotor and -spatial skills in Manual Motor Sequences ($r_s = -.494$, $N = 18$, $p = .037$) and Block Construction ($r_s = -.479$, $N = 18$, $p = .044$).

**Table 5**
Child behavior checklist.

| **CBCL** | ASD-II | ASD-II-control | *p* | | VSD | VSD-control | *p* | |
|---|---|---|---|---|---|---|---|---|
| Internalizing | 49.5 ± 9.8 | 49.2 ± 7.7 | *.909* | .03 | 55 ± 9 | 50 ± 10.6 | *.184* | .50 |
| Externalizing | 46.1 ± 10.3 | 48.2 ± 10.2 | *.459* | .20 | 50.9 ± 8.9 | 48.2 ± 10.7 | *.503* | .27 |
| Total problem score | 48.8 ± 10 | 47.3 ± 7.6 | *.614* | .16 | 53.8 ± 8 | 49.7 ± 10.3 | *.238* | .44 |
| Total competence | 42.5 ± 8.4 | 44.8 ± 8.8 | *.453* | .26 | 42.2 ± 8.5 | 41.7 ± 7.7 | *.531* | .06 |
| Special education (%) | Yes: 5.6 | Yes:0 | *1.0*[E] | | Yes: 10.7 | Yes: 0 | *.238*[E] | |
| Repeating a school year (%) | Yes: 22.2 | Yes: 0 | *.104*[E] | | Yes: 7.1 | Yes: 4 | *1.0*[E] | |
| School problems (%) | Yes: 33.3 | Yes: 0 | **.019**[E*] | | Yes: 32.1 | Yes: 20 | *.317* $\chi^2$ | |

*p* Value reached statistical significance is indicated in bold type.
* $p < .05$.
E $\chi^2$ (with Exact option).

### 3.4.2. VSD

Examining relations with *patient specific parameters* of the VSD group revealed that scores on the visuospatial task of Design Copying-Local was inversely correlated with age at intervention ($r_s = -.400$ $N = 28$, $p = .035$) and weight at time of intervention ($r_s = -.427$, $N = 28$, $p = .024$).

Evaluation of *medical factors* revealed that preoperative creatinine was negatively associated with the subcomponents of Design Copying, the Motor score ($r_s = -.436$, $N = 28$, $p = .020$), and the Local score ($r_s = -.477$, $N = 28$, $p = .010$). Postoperative creatinine was also inversely related to the former mentioned outcome score ($r_s = -.477$, $N = 28$, $p = .048$).

Other perioperative parameters such as duration of surgery or total clamp time were not associated with cognitive outcomes. Postoperative hemodynamic markers such as or $SaO_2$, hematocrit, hemoglobin or C-reactive protein levels did not reveal associations with long-term developmental outcome.

## 4. Discussion

Few studies have characterized the neuropsychological profile of children treated surgically for aCHD across all cognitive domains with a single standardized test battery. Our data provide a comprehensive outline of neuropsychological performance in ASD-II and VSD patients. Neurocognitive functions were assessed at school-age and compared with matched samples of healthy peers. Furthermore, outcomes were correlated with retrospectively collected hospitalization, together with perioperative variables and socioeconomic factors.

### 4.1. Neuropsychological profile

Overall, we see a fair performance of our clinical groups with mean scores within normal average population-based ranges. Remarkably, and contrary to our assumptions, the ASD-II patients (and not the surgical VSD patients) displayed lower scores in several domains as compared to the controls. Children treated surgically for ASD-II displayed a 15-point difference in estimated full scale IQ. These results are in line with previous studies in children with various forms CHD where lower intelligence scores in acyanotic cohorts were evident (Majnemer et al., 2009; Visconti et al., 1999; Yang et al., 1994).

Neuropsychologically, ASD-II and VSD patients needed more time to complete a naming task, measuring inhibition skills as compared to their matched controls, suggesting difficulty with inhibiting a former learned or automatic response. The presence of attention difficulties have been demonstrated in similar cohorts of surgically treated aCHD patients (Sarrechia et al., 2013; Yang et al., 1994). This may place children at risk for learning difficulties, considering that attention and vigilance is essential for higher neurocognitive tasks these children face in everyday school life, similar to previous findings from our institution with a different patient sample (Sarrechia et al., 2013), language difficulties were evident in our aCHD cohort, confirming poor skills in both expressive and receptive language. The ASD-II patients showed more difficulties in receiving, processing and executing oral instructions with increasing complexity. They also performed worse on word productivity, phonological encoding and decoding during non-sense word repetition. In accordance with the published results of Hövels-Gürich et al. (2008) on the high incidence of speech therapy and articulation problems in children with corrected VSD, VSD patients in the current cohort demonstrated poor performance on repeating non-sense words. This finding reflects inadequate en- and decoding of words, but also lower orofacial praxis and articulation abilities. Linguistic skills have been found to be suboptimal in children with CHD, placing them at risk for learning difficulties and delays in school functioning. Miatton, De Wolf, Francois, Thiery, and Vingerhoets (2007) documented problems in language scores in a school-aged cyanotic and acyanotic patient cohort.

The ASD-II patients in our study performed worse on tasks measuring ability to imitate gestural positions and had difficulty to repeat a sequence of hand movements with varying complexity, suggesting poor tactile-kinesthetic feedback and poor eye-hand coordination. Reduced fine and gross motor skills are a robust finding in outcome studies in children with CHD (Brandlistuen et al., 2011a; Fuller et al., 2009; McCusker et al., 2007; von Rhein et al., 2012) and may impact overall physical and psychosocial well-being. Poor motor skills have also been identified in cohorts treated for aCHD (Brandlistuen

et al., 2011a; Majnemer et al., 2009; Miatton et al., 2007), suggesting that these children, may cope with an underlying neurological vulnerability before, during or after surgical repair.

Another possibility is that parents adopt an overprotective parenting style following diagnosis and treatment whereupon they are less inclined to allow their children to engage in sports activities or other social activities requiring significant physical effort. The exact origin of these persisting shortcomings in motor functioning has yet to be determined.

Our results show that children with corrected ASD-II obtained poor results on the Theory of Mind contextual subtask, suggesting difficulties with perspective taking and with understanding contextual emotions. In addition, a significant proportion of these children scored in clinical problematic ranges on the subtask of Affect Recognition. Social cognition is an infrequent studied domain in children with CHD, aside from parental reports (Brandlistuen et al., 2011b; Spijkerboer, Utens, Bogers, Verhulst, & Helbing, 2008). Communication impairments in 3-year-old children with mild to moderate CHD have been found (Brandlistuen et al., 2011b), and social cognition problems seem to persist into adolescence in cyanotic CHD cohorts (Chiavarino et al., 2013).

Recently, direct evidence has been found for poor emotion comprehension in patients with corrected transpositions of the great arteries (TGA) (Calderon, Angeard, Pinabiaux, Bonnet, & Jambaque, 2014). Although aforementioned studies show that children, as well as adults with cyanotic CHD are at higher risk for deficits in social cognition, the results from the current study suggest that this domain deserves further attention in aCHD populations too. Results show that the ASD-II patients score lower on visuospatial skills, specifically in converting and building 3D constructions, but also tend to score lower than controls in visuo-perceptual analysis and understanding directionality.

Significant higher percentages of ASD and VSD patients obtained results in clinical problematic ranges on subtasks of Design Copying as compared to healthy peers. Persisting poor hand–eye coordination and poor visuospatial information processing have been consistently found in cyanotic as well as acyanotic patient populations (Miatton et al., 2007; Visconti et al., 1999). Simons and colleagues demonstrated visual-motor integration to be poorer in patients operated for VSD when assessed with the drawing test of the Wide Range Assessment of Visual-Motor abilities at a mean age of ~9 years (Simons et al., 2010). The authors hypothesized that age at intervention may play an important role, as surgery at younger age may have detrimental effects on visual, non-verbal abilities. This is in contrast with the results of the current study since age at intervention was inversely related to visuo-spatial information processing. Another study suggested that the deficient integration and coordination in visuospatial skills is likely to be caused by impaired visuo-perceptual organization abilities in TGA patients, rather than problems in motor control or deficient meta-cognitive abilities (Bellinger, Bernstein, Kirkwood, Rappaport, & Newburger, 2003), and might serve as an explanation for this clinical cohort too. Longitudinal follow-up studies should provide more information that could affect optimal timing for surgical intervention, assess determinants of these adverse outcomes in this domain, and study temporal trends.

When reaching adulthood, these children will have to face different challenges next to academic attainment, such as employability. To what extent adverse neurodevelopmental outcomes at school age will affect career opportunities, remains to be clarified by prospective longitudinal study designs. Previous research showed that grown-ups with congenital heart disease (GUCH), are disadvantaged on the job market when compared to peers (Kamphuis, Vliegen, Verloove-Vanhorick, Ottenkamp, & Vogels, 2005). Loup et al.'s results showed that disability pensions were more frequent in a group of patients treated for VSD (Loup et al., 2009). These findings suggest that continuous follow-up, care and career coaching is warranted from childhood throughout adolescence, and adulthood in this cohort with seemingly normal outcome.

### 4.2. Behavior

A significant proportion of parents reported that their child treated surgically for ASD-II experienced school problems as compared to parental ratings of controls. This is in line with the neuropsychological performances they displayed. Further, VSD patients did not differ from matched controls in terms of behavioral outcome.

### 4.3. Associations with clinical and demographic variables for aCHD

Higher levels of postoperative glycemia and high SES were associated with better outcomes in the Intelligence domain for the ASD-II group. Linguistic scores were also found to be associated with SES and degree of cooling, underscoring the neuroprotective nature of cooling strategies. Visuospatial proficiency was associated with postoperative lactate levels, a marker for tissue hypoxia.

It seems important to note that some intra-operative management factors classically associated with lower cognitive performance, such as duration of ECC, cross clamp time, metabolic acidosis ($pH < 7.15$), and long postoperative intubation period (Wernovsky, 2006b) did not result in significant correlations in this study.

On the other hand, this study contributes to the growing evidence that non-modifiable patient-specific factors such as SES are important determinants for later neurodevelopmental functioning (Gaynor et al., 2007; McCusker et al., 2007). In a former study with aCHD patients, Quartermain and colleagues (Quartermain et al., 2010) assessed various neuropsychological skills pre- and postoperatively and explored associations with CPB procedures. No cognitive decline or independent effects of CPB and surgery could be identified except for one test of executive function, and this finding was considered a statistical artifact. The surgical CPB patients in the aforementioned study were treated at a mean age of 11.8 years (range 5 to 18 years); their condition can be considered less urgent than that of our patient cohort. Moreover, brain

development and the response of the brain to CPB and cardioplegic arrest can have a varying impact at different ages. To what extent patient-specific and modifiable factors contribute to these specific adverse neuropsychological outcomes for this clinical group remains to be determined. Compared to normally developing children, many factors may affect the brain development and subsequent later higher cognitive functions of young children with aCHD.

Possibly, the adverse hemodynamic burden that patients with significant ASD-II suffer is underestimated in the current treatment protocol. Persistent hemodynamic instability in left-to-right shunts in utero and the early newborn period leads to diminished systemic cardiac output, cardiovascular insufficiency and cause subtle cerebral ischemic damage. As a possible consequence, newborns with aCHD have been described to display high rates of neurologic abnormalities prior to surgery (Majnemer et al., 2009). This might increase neurological vulnerability for intraoperative events.

Medical management of congenital heart defects often necessitates open heart surgery with the risk of air entrainment and emboli through manipulation of the heart or aorta. Evidence exists that microemboli in the carotid artery during pediatric cardiac surgery are particular prevalent after release of aortic crossclamp, even in 'low risk' ASD repair and independent of CPB duration (OBrien et al., 1997).

Potentially, these microemboli may cause subtle hypoxic ischemic events and result in mild cognitive impairments at school age. Intensified multimodal neurological monitoring with techniques as near-infrared cerebral oximetry, transcranial Doppler ultrasound, and electroencephalographic monitors may improve neurological outcomes and prevent adverse neurologic sequelae (Andropoulos, Stayer, Diaz, & Ramamoorthy, 2004), even in 'low risk' pediatric populations.

Postoperative complications in ASD-II patients are common and include mostly pericardial effusion and cardiac arrhythmias (Du et al., 2002), prolonging their total hospital stay, a known risk factor associated with adverse neurodevelopment (Majnemer et al., 2009; von Rhein et al., 2012).

In addition, knowledge on the relation between cognition, brain development and CHD is accumulating. The coexistence of CHD and abnormal brain maturation has been described in patients treated for aCHD without overt neurologic problem and imply reduced cortical grey matter volume, cerebellum, basal ganglia and hippocampus. These regions are related to intellectual functioning, perceptual reasoning and motor abilities (von Rhein et al., 2013), and may help to clarify the results in this study together with the socioeconomic effects.

### 4.4. Limitations

Typically in this type of research, we are faced with the possibility of selection bias. Only parents of children who indeed noticed neurocognitive difficulties might have responded to our appeal. This could be an alternative explanation for the lower performances in our ASD-II surgery group.

Although we did not receive any socio-demographic data from non-responders, the SES-score range is considered representative for the general population. It should be noted that mean neurodevelopmental scores for the ASD control group fell in the average/high-average range, whereas the mean scores for the ASD-II patient group fell mostly within one standard deviation from the population-based mean and reflect mild weaknesses rather than significant impairments.

Preoperative screening in our patients was not conducted, so mild cognitive deficits might have been present before surgery. Although children with known genetic syndromes were excluded from our study sample, formal genetic screening was not always performed if there was no clinical indication. Statistical analyses and multivariate regression techniques were restricted and underpowered by the small sample size. Enrolling more control subjects (3:1 patient) to enhance statistical power might have enhanced the generalizability of the findings in this study.

We acknowledge that the medical variables studied are likely interrelated and therefore, we cannot proceed to evaluate the unique contribution of specific medical aspects in the management of aCHD. The retrospective nature of the study did not allow us to control for confounding variables that might have been present before surgery or neurodevelopmental testing. Nevertheless, our data suggest that, despite excellent functional septal defect repair, ASD-II and VSD patients are at risk for suboptimal neuropsychological outcomes which may hamper long-term school competence.

### 4.5. Conclusion

Limited up-to-date literature exists on the long-term neurodevelopment of children with corrected aCHD. Results in the current study suggest that patients treated for aCHD perform relatively well as a group when compared to healthy controls, but there remain some areas of concern, especially for patients treated for ASD-II. Neuropsychological problems emerge in domains of visuospatial information processing, language, attention, and social perception. Some hospitalization parameters, but also patient-specific factors were associated with these suboptimal outcomes.

We conclude that this study documents subtle neuropsychological impairments in school-aged children operated for aCHD with an uncomplicated clinical course. It seems advisable for clinicians to survey parents on the child's school functioning during follow-up visits to identify and refer those patients at risk. Recommendations relating to medical and developmental surveillance, screening and periodic reevaluation for children treated for CHD at risk for developmental delay have been outlined by the American Heart Association (AHA) and American Academy of Pediatrics (AAP) (Marino et al., 2012). Neonates or newborns requiring open heart surgery are considered to be at risk for diffuse global developmental delay that has time phased variations and implications. The provided guidelines help to identify and treat those patients at risk and coordinate the multifaceted treatment process consisting of special education, behavioral counseling, speech/language,

occupational and physical therapies to improve consistency in developmental follow-up across time. Taken together, this will guide cardiologists and health practitioners toward increased awareness and better understanding of neuropsychological sequelae after treatment for aCHD. Disentangling the multifactorial etiology that places some patient groups particularly at risk for adverse cognitive outcomes is very challenging. Prospective, multidisciplinary studies will yield more insight into the contributing factors concerning cognitive outcome and will allow improved prognosis in these children.

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## Conflict of interest statement

We hereby state that there is no conflict of interest regarding the study design, data collection, analysis, interpretation of data, the writing of the manuscript, and the decision to submit the paper for publication.

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