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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