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## Long-term neuropsychological outcomes in children and adolescents after cardiac arrest

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**Take-home message:** Long-term neuropsychological assessment of CA survivors showed significant weaknesses, but also relatively intact functioning. As deficits in intelligence, memory and executive functioning have significant impact on the child, long-term follow-up and neuropsychological support of CA survivors is warranted.

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**Abstract Purpose:** Research into neuropsychological functioning of survivors of cardiac arrest (CA) in childhood is scarce. We sought to assess long-term neuropsychological functioning in children and adolescents surviving CA.

**Methods:** Neuropsychological follow-up study involving all consecutive children surviving CA between January 2002 and December 2011. Intelligence (IQ), language, attention, memory, visual-spatial, and executive functioning were assessed with internationally validated, neuropsychological tests and questionnaires. Scores were compared with Dutch normative data.

**Results:** Of 107 eligible children, 47 who visited the outpatient clinic (median follow-up interval: 5.6 years) were analyzed. Fifty-five percent had an in-hospital CA, 86 % a non-shockable rhythm, and 49 % a respiratory-related etiology. CA survivors scored significantly worse on full-scale IQ ( $\bar{x} = 87.3$ ), verbal IQ ( $\bar{x} = 92.7$ ), performance IQ ( $\bar{x} = 85.6$ ), verbal comprehension

index ( $\bar{x} = 93.4$ ), perceptual organization index ( $\bar{x} = 83.8$ ), and processing speed index ( $\bar{x} = 91.1$ ), than the norm population (mean IQ = 100). On neuropsychological tests, compared with norms, respectively adjusted for IQ, significantly worse scores were found on visual memory, significantly better on verbal memory (recognition), and comparable outcomes on visual-motor integration, attention, other measures of verbal memory, and executive functioning. On questionnaires, parents reported better executive functioning than the norm, but teachers reported more problems in planning/organizing skills. **Conclusions:** Long-term neuropsychological assessment of CA survivors showed significant weaknesses, but also relatively intact functioning. As deficits in IQ, memory and executive functioning have significant impact on the child, long-term follow-up and neuropsychological support of CA survivors is warranted.

**Keywords** Heart arrest · Follow-up studies · Neuropsychology · Pediatric · Cognition

## Introduction

Survival after cardiac arrest (CA) in children is low and dependent on the location of the arrest [1]. In-hospital (IH) CAs are associated with relatively high survival rates of 30–50 and 60–90 % have a generally good neurologic outcome [1, 2]. Out-of-hospital (OH) CAs generally have a low survival rate of 10 % and high morbidity rates (>90 %) [1, 3]. Long-term prognosis in survivors seems to be associated with location, age, rhythm, witnessing of the arrest and Pediatric Cerebral Performance Category (PCPC) score at discharge [4]. Until now, a detailed overview of the long-term neuropsychological consequences is lacking.

Neuropsychological functioning refers to, e.g., memory, language, attention, and executive functioning. Executive functioning refers to several higher-order and interrelated cognitive functions (e.g., cognitive flexibility, task initiation, planning, working memory, self-regulation, and response inhibition). Considering the adverse impact of a lack of oxygen to the brain, neuropsychological deficits are to be expected. Problems with attention, executive functioning and deficits in visual-motor integration have been reported in children with complex congenital heart disease and survivors of meningococcal septic shock [5, 6]. Also, in neonates with severe respiratory failure treated with ECMO, deficits in attention and behavior were found [7].

Only three small studies and one case report have investigated the neuropsychological functioning of children who survived a CA. Maryniak et al. [8] found visual and verbal memory impairments 6 months after the arrhythmic CA ( $n = 10$ ; mean age 15.7 years). Amicuzi et al. [9] reported a detailed long-term case study of a 9-year-old girl recovering from an anoxic encephalopathy after CA and reported dysfunctions in gnosis, praxis and self-regulation. Morris et al. [10] reported lower scores on tests measuring intelligence, visual-perceptual-motor, achievement, and adaptive functioning in CA survivors at least 1-year post-CA ( $n = 25$ ; mean age 67 months; median follow-up interval unknown; 80 % had a congenital heart disease). Suominen et al. [11] found impairments in intelligence, verbal and/or visual memory, and executive functions in resuscitated drowned children ( $n = 21$ ; median age 12.5 years; median follow-up interval 8.5 years). However, these studies had methodological limitations (small sample size, short follow-up interval or only subgroups of CA studied). It is therefore unknown whether these results can be generalized to all CA survivors.

We sought to systematically investigate the long-term neuropsychological outcomes and predictors of those outcomes in a relatively large cohort of consecutive survivors of CA in childhood. We used internationally

validated, well-known neuropsychological assessment instruments.

We hypothesized that survivors of CA in childhood have significant impairments in neuropsychological outcome.

## Methods

This study was performed at the intensive care unit (ICU) of the Erasmus MC-Sophia Children's Hospital in Rotterdam, the only university specialized pediatric ICU in this region with approximately 4.2 million inhabitants, representative of the Dutch population.

The Erasmus MC Ethical Review Board approved the study protocol (NL 39084.078.12) in accordance with Dutch laws and regulations, and international conventions, such as the Declaration of Helsinki.

### Patient sample

This study concerned all consecutive surviving patients aged 0–18 years with CA between January 2002 and December 2011, admitted to the ICU of the Erasmus MC-Sophia Children's Hospital.

CA was defined as absent pulse rate or the need for cardiac compressions. Treatment of children with CA in our hospital was in line with the European Resuscitation Council guidelines for pediatric life support.

All CA data were retrospectively collected from ambulance registration forms, clinical and electronic medical records, and CA registration forms. We collected: (1) basic patient characteristics (e.g., gender, age, medical history), (2) CA characteristics [e.g., type of resuscitation (BLS/APLS), etiology of arrest, first monitored rhythm, bystander CPR, location], and (3) outcome (mortality).

Eligible for this study were children resuscitated: (1) in-hospital (e.g., emergency department, ward, ICU), (2) in a regional hospital or other university hospital, and after return of spontaneous circulation (ROSC) subsequently admitted to our ICU, and (3) out-of-hospital, and subsequently admitted to our ICU. Neonates resuscitated at the hospital's neonatal intensive care unit (NICU), or in another hospital and subsequently admitted to the NICU of our hospital, were excluded.

Procedure: informed consent was obtained from parents, and children (if  $\geq 12$  years). In May 2013, participating children (and parents) were invited for an extensive neuropsychological examination, in-hospital, by a pediatric psychologist (MM), 2–11 years after ICU-discharge.

## Neuropsychological functioning

### *Intelligence tests and neuropsychological tests*

Dutch versions of the intelligence tests and neuropsychological tests were used to assess the variables below:

1. Intellectual functioning: the age-appropriate versions of the Wechsler Scales (WPPSI-III, WISC-III, WAIS-IV) [12–14].
2. Language: Peabody picture vocabulary test—3rd edition (PPVT-III) [15].
3. (Verbal) memory: Rey’s auditory verbal learning test (RAVLT) [16, 17]; Rey–Osterrieth Complex Figure test (ROCF) [18].
4. Visual–spatial functioning: Rey–Osterrieth complex figure test (ROCF) [18]; Beery developmental test of visual motor integration—5th edition (Beery VMI-5th edition) [19].
5. Attention: test of everyday attention for children (TEA-Ch) [20].
6. Executive functions: stroop color word test (Stroop) [21]; trail-making test (TMT) [22].

Scores on neuropsychological tests were compared with normative data from representative Dutch general population samples, for corresponding age categories (see Supplementary Table 1).

### *Neuropsychological questionnaire*

Behaviour rating inventory of executive function questionnaires [BRIEF; parent version (5–18 years), teacher version (5–12 years), and self-report version (12–18 years)] [23].

### Putative predictors

The following predictors were tested: age at time of CA and follow-up, gender, type of CPR (BLS/APLS), location (in-hospital/out-of-hospital), CA-related pre-existing medical condition, participation in a standardized multidisciplinary follow-up program, and socioeconomic status (SES) at follow-up. In our hospital, a multi-disciplinary follow-up program for children with congenital anatomical malformations and children treated with ECMO was started as standard of care in 1999. SES at time of follow-up was based on parents’ occupation, and categorized as “low” (elementary occupations), “middle” (‘middle’ occupations), or “high” (‘highest’ scientific occupations) conforming to Dutch classification [24]. The highest occupation of both parents was used.

## Statistical analyses

Patient and CA characteristics of participants and non-participants were examined with independent sample *t* tests for normally distributed continuous data, and Mann–Whitney *U* tests for non-normally distributed data. Normality of all data was examined with the Kolmogorov–Smirnov test. Fisher’s exact test was used for comparison of dichotomous data.

One-sample statistical tests were performed to compare CA survivors with normative data regarding the BRIEF and intelligence. One-sample *t* test was performed for normally distributed data (*t* scores presented; means of the normative data presented in Supplementary Table 1), or one-sample Wilcoxon signed rank test for non-normally distributed data. Data of the neuropsychological assessment were compared with normative data, corrected for age, gender, or intelligence. In order to compare the performances of all children, scores were converted into *Z* scores. These *Z* scores were compared with the *Z* score of the overall performance of CA-children on full-scale intelligence, as this reflects the overall capacity of the functioning of CA survivors; children with a lower IQ will have a lower neuropsychological functioning. To compare this neuropsychological outcome of CA survivors with normative data, the one-sample *t* test was performed for normally distributed data, or the one-sample Wilcoxon signed rank test for non-normally distributed data.

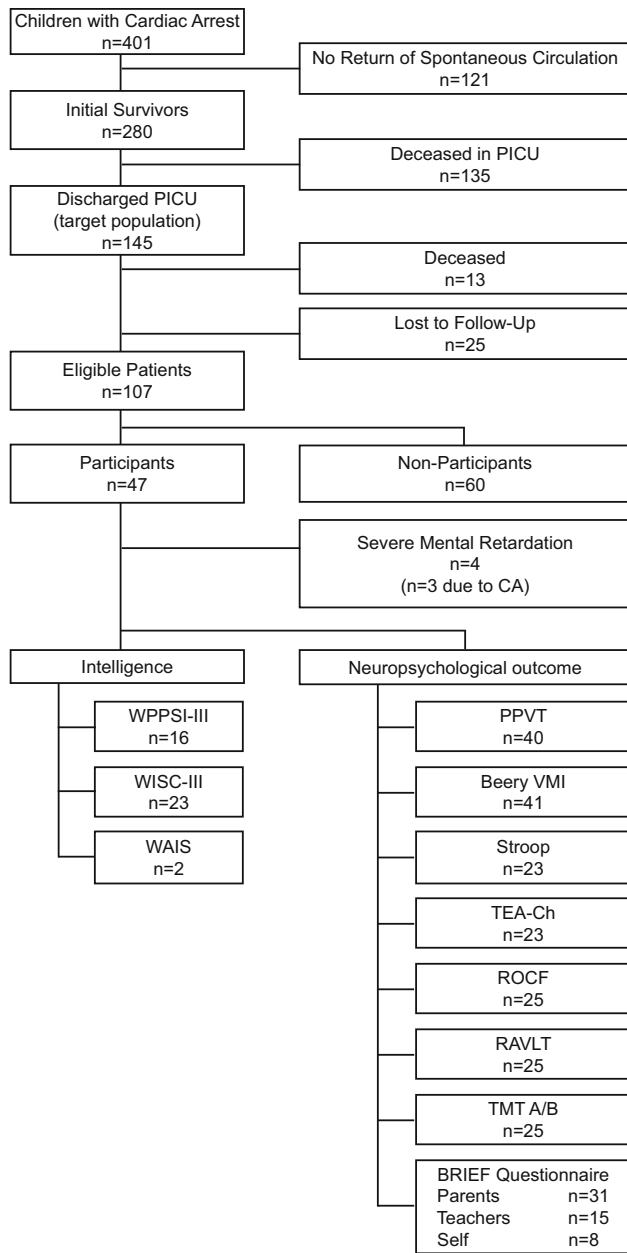
Predictors of neuropsychological outcomes were examined with Spearman correlations for continuous variables (age at time of CA, age at follow-up), Mann–Whitney *U* test for dichotomous variables (gender, location, BLS/APLS, CA-related pre-existing condition, participation in a follow-up program), and the Kruskal–Wallis test for ordinal variables (SES).

All analyses were performed with SPSS 21.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance was considered with 2-tailed *p* values of <0.05.

## Results

Our target population consisted of 145 surviving patients, 38 of whom were deceased or lost to follow-up (Fig. 1). Causes of death after hospital discharge were another CA without ROSC (*n* = 3), underlying disease (*n* = 2), severe cerebral damage (*n* = 1), or unknown (*n* = 7).

Of 107 eligible patients, 47 (44 %) participated. Median follow-up interval was 5.6 years (range 1.8–11.9). Intellectual functioning of one patient was recently tested (<1 year) and therefore not repeated at our hospital. His test results were used in this study. Twelve of 47 patients participated in the multidisciplinary follow-up program.



**Fig. 1** Flowchart of patient inclusion. Lost to follow-up: moved abroad  $n = 7$ , untraceable  $n = 18$ .  $n$  is the actual number of children tested, or the number of respondents to the questionnaire (BRIEF). Numbers of patients may differ for neuropsychological tests due to different age ranges covered by the different tests (and availability of norm data). *Beery VMI* Beery developmental test of visual motor integration, *BRIEF* Behaviour rating inventory of executive function questionnaires, *PICU* pediatric intensive care unit, *PPVT* peabody picture vocabulary test, *RAVLT* Rey's auditory verbal learning test, *ROCF* Rey–Osterrieth complex figure test, *Stroop* stroop color word test, *TEA-Ch* test of everyday attention for children, *TMT* trail making test, *WAIS* Wechsler adult intelligence scale, *WISC* Wechsler intelligence scale for children, *WPPSI* Wechsler preschool and primary scale of intelligence

Four participants could not be tested due to severe mental retardation ( $n = 3$  due to CA).

Non-participants refused participation due to practical reasons ( $n = 23$ , e.g., distance to hospital/work of parents), or emotional reasons ( $n = 16$ , e.g., too anxious/confronting). For 21 non-participants, the reasons were unknown.

Medical characteristics of participants and non-participants were compared, and differed significantly on high SES (Table 1).

## Neuropsychological functioning

### Intelligence tests

CA survivors scored significantly worse on full-scale IQ (87.3,  $t = -6.01$ ), verbal IQ (92.7,  $t = -3.32$ ), performance IQ (85.6,  $t = -7.07$ ), verbal comprehension index (93.4,  $t = -2.26$ ), perceptual organization index (83.8,  $t = -5.81$ ), and processing speed index (91.1,  $t = -3.16$ ), than the normal population (Table 2).

### Neuropsychological tests

After adjustment for (taking into account) their intellectual functioning (mean IQ Z score:  $-0.84$ ), CA survivors performed significantly better on receptive vocabulary (PPVT), attentional switching (TEA-Ch attentional switching), and verbal memory recognition (RAVLT recognition) (Figs. 2, 3; Table 2). Significantly worse scores were found on short- and long-term visual–spatial memory (Rey immediate and delayed recall). No significant differences were found on visual–motor integration, attention, verbal memory (RAVLT 1-5, delayed recall), and executive functions.

### Questionnaire

Parents reported significantly better functioning on the executive composite score and behavior regulation index, and subtests organization of materials, and monitoring (Table 3; Supplementary Table 3). Teachers reported better scores on subtest inhibition, but worse on subtest planning/organizing compared to normative data. On self-reports, no significant differences were found.

### Predictors of outcome

Males scored significantly worse than females on performance IQ ( $Z = -2.522$ ,  $p = 0.012$ ), visual–motor integration ( $Z = -1.999$ ,  $p = 0.046$ ), selective attention

**Table 1** Characteristics of participants and non-participants

	Participants ( <i>n</i> = 47)		Non-participants ( <i>n</i> = 60)		<i>P</i> value
	<i>n</i> <sup>a</sup>		<i>n</i> <sup>a</sup>		
Age at cardiac arrest (years)	47	0.4 (0–16.1)	60	0.6 (0–17.0)	0.220
Male gender	47	25 (53 %)	60	39 (65 %)	0.238
Advanced pediatric life support (APLS)	47	25 (53 %)	60	43 (72 %)	0.068
Out-of-hospital arrest	47	21 (47 %)	60	18 (30 %)	0.157
Bystander CPR	47	46 (98 %)	57	56 (98 %)	1.00
Initial rhythm non-shockable	36	31 (86 %)	56	48 (86 %)	1.00
Etiology					
Cardiac	47	16 (34 %)	60	22 (37 %)	0.840
Respiratory	47	23 (49 %)	60	35 (58 %)	0.434
Other	47	8 (17 %)	60	3 (5 %)	0.056
Pre-existing medical condition <sup>b</sup>	47	26 (55 %)	60	29 (48 %)	0.560
Cardiac	26	13 (50 %)	29	17 (59 %)	0.840
Respiratory	26	10 (39 %)	29	10 (35 %)	0.434
Other	26	3 (12 %)	29	2 (7 %)	0.056
Mild therapeutic hypothermia <sup>c</sup>	47	7 (15 %)	60	15 (25 %)	0.235
Socioeconomic status at follow-up <sup>d</sup>					
Level 1: “Low”	47	4 (9 %)	60	14 (23 %)	0.066
Level 2: “Middle”	47	21 (45 %)	60	31 (52 %)	0.560
Level 3: “High”	47	22 (47 %)	60	15 (25 %)	<b>0.024</b>
Age at follow-up (years)	47	8.7 (2.4–18.3)	–	–	–

All data are presented as “number of subject (%)”, except age which is presented as “median (range)”. Significant value ( $p < 0.05$ ) in bold

CPR cardiopulmonary resuscitation, ICU intensive care unit, *n* number, – not available

<sup>a</sup> Number of subjects from which the variable was obtained

<sup>b</sup> Children with a pre-existing medical history which was the cause of the CA

<sup>c</sup> Children treated with mild therapeutic hypothermia

<sup>d</sup> SES for non-participants at time of follow-up was calculated on the basis of a combined status score of the Netherlands Institute for Social Research based on home address [24]. This score consisted of four variables: average income in neighborhood, percentage of people with low income, percentage of less educated people, and percentage of people not working. A status score of 0 ( $\pm 1.16$  SD) was classified as middle SES, a status score of  $< -1.16$  was classified as low SES, and a status score of  $> +1.16$  was classified as high SES

(TEA-Ch:  $Z = -1.999$ ,  $p = 0.046$ ), cognitive shifting and inhibition (Stroop:  $Z = -2.050$ ,  $p = 0.040$ ) (Supplementary Table 2). Older age at time of CA and follow-up were associated with worse outcomes on language ( $\rho = -0.414$ ,  $p = 0.008$ ;  $\rho = -0.408$ ,  $p = 0.009$ ). Older age at follow-up was also associated with worse outcomes on visual–motor integration ( $\rho = -0.312$ ,  $p = 0.047$ ). Children with a CA-related pre-existing medical condition scored worse on attentional switching than children without ( $Z = -2.716$ ,  $p = 0.007$ ). Children with BLS scored worse than children with APLS on the TMT part A ( $Z = -2.522$ ,  $p = 0.012$ ). Children without follow-up scored significantly worse on divided attention ( $Z = -2.116$ ,  $p = 0.034$ ) and TMT part B ( $Z = -2.000$ ,  $p = 0.046$ ) than children participating in the follow-up program. Predictors of outcome on the BRIEF questionnaires are shown in Supplementary Table 4.

## Discussion

This is one of the first studies that has systematically examined the long-term neuropsychological outcomes in

children surviving cardiac arrest (CA). As a result of the CA, 6 % sustained such serious brain damage that they could not be tested. CA survivors scored significantly worse on intelligence. On neuropsychological tests, significantly worse scores were found on visual memory, significant better scores on verbal memory (recognition), and no differences on visual–motor integration, attention, verbal memory (RAVLT 1-5, delayed recall), and executive functioning. On questionnaires, parents reported better executive functioning, but teachers reported more problems in planning/organizing skills.

### Neuropsychological functioning

#### Intelligence tests

Conform former research, lower scores were found on all intelligence scales [10, 11]. In general, intellectual outcome is highly dependent on the age at which brain injury was acquired. Acquired brain injury (ABI) at a young age results in more diffuse deficits in cognitive functioning, rather than specific deficits [25]. This can



**Table 2** Overview of intelligence and neuropsychological outcome adjusted for participants' IQ

	Cardiac arrest patients			Normative data			<i>P</i> value	<i>P</i> value adjusted for IQ <sup>e</sup>
	<i>n</i>	Mean	SD	Mean	SD	<i>P</i> value		
<b>Intelligence</b>								
Full scale IQ <sup>a</sup>	41	87.3	13.4	100	15		<b>0.002</b>	
Verbal IQ <sup>b</sup>	39	92.7	13.7	100	15		<b>&lt;0.001</b>	
Performance IQ <sup>b</sup>	39	85.6	12.7	100	15		<b>&lt;0.001</b>	
Processing speed index <sup>a,c</sup>	31	91.1	15.6	100	15		<b>0.004</b>	
Verbal comprehension index <sup>d</sup>	25	93.4	14.7	100	15		<b>0.033</b>	
Perceptual organization index <sup>d</sup>	25	83.8	13.9	100	15		<b>&lt;0.001</b>	
Intelligence subtest: digit span	25	8.0	3.1	10	3		<b>0.009</b>	
<b>Neuropsychological tests<sup>e</sup></b>								
	<i>n</i> <sup>f</sup>	Mean	SD	Mean	SD	<i>P</i> value		
Peabody picture vocabulary test (PPVT)	40	-0.12	1.2	0	1	0.451	<b>0.002</b>	
Beery visual-motor Integration (Beery VMI)	41	-0.85	0.9	0	1	<b>&lt;0.001</b>	0.841	
Stroop color word test	23	-1.14	2.4	0	1	0.059	0.692	
<b>Test of everyday attention for children (TEA-Ch)</b>								
Sky search time per target	22	-0.76	1.1	0	1	<b>0.004</b>	0.235	
Sky search attention score (selective attention)	23	-0.96	1.3	0	1	<b>0.003</b>	0.646	
Score! (sustained attention)	23	-0.59	1.3	0	1	0.052	0.502	
Creature counting accuracy (attentional switching)	23	-0.29	1.0	0	1	0.173	<b>0.010</b>	
Creature counting timing score	23	-0.68	1.2	0	1	<b>0.017</b>	0.204	
Sky search double task decrement (divided attention)	23	-1.51	1.3	0	1	<b>&lt;0.001</b>	0.059	
<b>Rey complex figure test (ROCF)</b>								
ROCF copy	23	-0.42	1.3	0	1	0.338	0.181	
ROCF immediate recall	25	-1.89	1.0	0	1	<b>&lt;0.001</b>	<b>&lt;0.001</b>	
ROCF delayed recall	25	-1.87	1.0	0	1	<b>&lt;0.001</b>	<b>&lt;0.001</b>	
ROCF recognition	25	-0.66	1.0	0	1	<b>0.022</b>	0.510	
<b>Rey's auditory verbal learning test (RAVLT)</b>								
RAVLT 1-5	25	-0.66	1.0	0	1	<b>0.005</b>	0.339	
RAVLT delayed recall	25	-0.79	1.2	0	1	<b>0.003</b>	0.716	
RAVLT recognition	24	-0.27	1.1	0	1	0.373	<b>0.010</b>	
<b>Trail-making test part A and B (TMT A/B)</b>								
TMT A	25	-0.43	1.0	0	1	<b>0.042</b>	0.109	
TMT B	25	-0.65	1.0	0	1	<b>0.003</b>	0.158	

Significant values ( $p < 0.05$ ) in bold

<sup>a</sup> Intelligence scores of different age-groups were combined for the total sample by combining scores on, respectively: (1) Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III;  $n = 16$ ), (2) Wechsler Intelligence Scale for Children (WISC-III;  $n = 23$ ), and (3) Wechsler Adult Intelligence Scale (WAIS-IV;  $n = 2$ ). One child was too young to be tested with the WPPSI-III (<2.6 years), and for one child the testing of intellectual functioning had to be stopped prematurely due to substantial attentional problem behavior, which made accurate testing of the intellectual functioning impossible

<sup>b</sup> Intelligence scores combined for the total group of (1) Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), and (2) Wechsler Intelligence Scale for Children (WISC-III). WAIS-IV does not include the PIQ and VIQ

<sup>c</sup> Processing Speed Index is not available for children <4,5 years ( $n = 10$ ), on the WPPSI-III

<sup>d</sup> Perceptual organization index and verbal comprehension index are not available on the WPPSI-III ( $n = 16$ )

<sup>e</sup> All neuropsychological test were converted into Z scores and compared with the Z score (-0.84) of the mean IQ of CA survivors, as significant difference in intelligence were found and developmental delay (lower IQ) worsens their abilities on neuropsychological tests

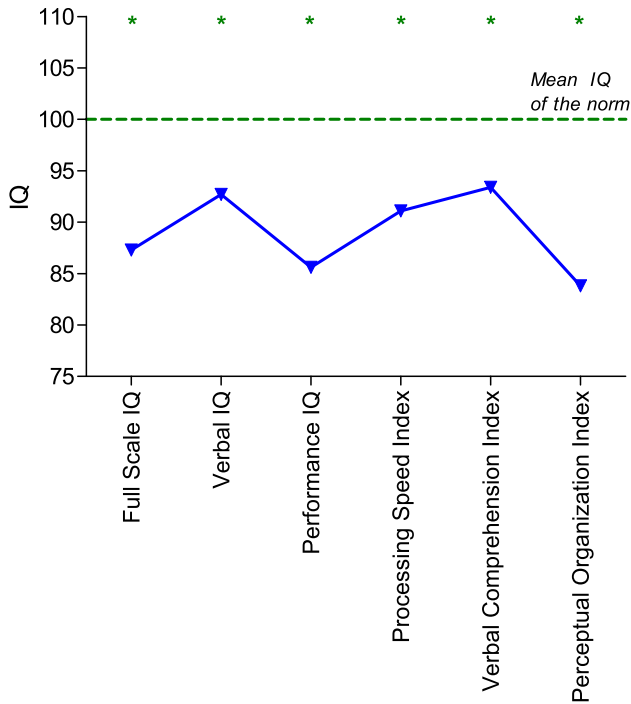
<sup>f</sup> Numbers of patients differ for neuropsychological tests due to different age ranges and diversity in availability of normative data. The  $n$  is the actual number of patients tested

be explained by the vulnerability theory, since children with ABI at young age have to learn new skills with impaired basal functions [26]. The most susceptible areas to ischemic injury within the brain are vascular end zones, hippocampus, insular cortex, and basal ganglia [27]. With an increasing severity of hypoxic ischemia, more extensive and global neocortical injury will occur and could lead to global cerebral atrophy, as shown in adults [27, 28]. Moreover, ABI at young age has long-lasting effects on intelligence [29].

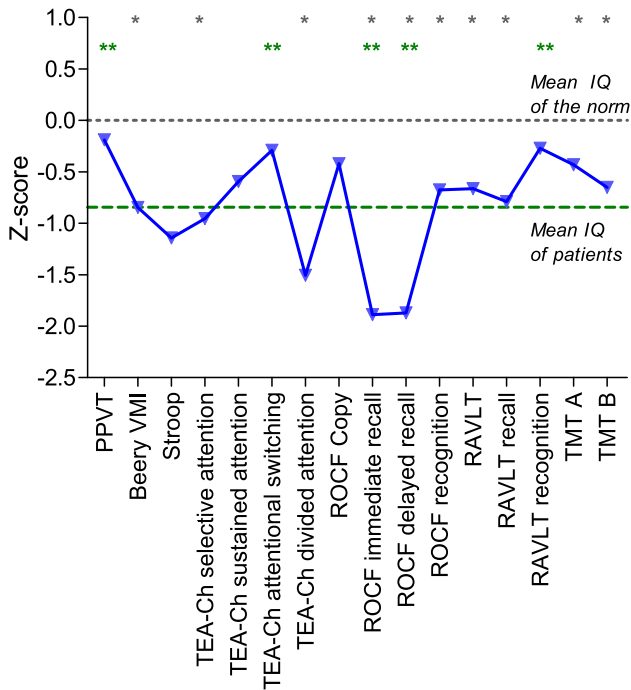
### Neuropsychological tests

Long-term neuropsychological functioning has mainly been assessed in subgroups of CA patients, i.e. congenital heart disease or drowned children [10, 11]. Besides impairments in intelligence, impairments in verbal and/or visual memory, visual-perceptual-motor functioning, and executive functions were also found [10, 11].

A discrepancy between visual and verbal information processing is not only found on our results on the



**Fig. 2** Results on intelligent tests compared with normative data. \*Significantly different from the norm



**Fig. 3** Results on neuropsychological tests, adjusted for mean full-scale IQ of CA survivors. \*Significantly different from the norm. \*\*Significantly different from what would be expected based on the mean full-scale IQ of CA survivors

intelligence profile but also on our memory results, as only visual memory problems (Rey) were found, not verbal memory problems (RAVLT). In addition, the PPVT and TEA-Ch attentional switching are both verbal tasks. Since the children’s verbal functions are relatively good, this may result in an overestimation and better reported executive functioning by parents, as instructions by parents are mainly verbal. Academic achievement tasks at school are both visual–spatial and verbal orientated, which is reflected by the lower executive functioning reported by teachers. As these children have visual weaknesses and relatively intact verbal functioning, the visual–spatial deficits could be supported by verbal instructions at school, to improve their academic achievements.

Various pathological mechanisms may explain our findings on the neuropsychological tests. The hippocampus, playing an important role in memory, is sensitive to cerebral hypoperfusion. While neuronal injury is mostly observed within 3 h after ROSC, delayed neuronal death, especially in the hippocampus, can be present up to 48–72 h after ROSC [30].

Furthermore, the watershed areas in the brain are particularly vulnerable to effects of hypoperfusion and hypoxia resulting in cognitive deficits and prefrontal lesions [31]. Cognitive deficits could be explained by periventricular leukomalacia (white matter injury), which is believed to arise from several factors including ischemia to the watershed areas [5]. As the integrity of the white matter is correlated with full-scale IQ and performance IQ, and not with verbal IQ, white matter injury could be an important explanation for our findings in CA survivors [32]. Damage to the prefrontal region could result in various types of frontal syndromes, which manifest themselves in deficits in executive functions, information processing and attention. The relatively high scores on the BRIEF do not necessarily mean better functioning, but could be an expression of a dorsolateral prefrontal syndrome. This syndrome is characterized by lack of initiative, personality changes, blunted affect, or problems with executive functions such as working memory and planning. Children with a lack of initiative are more dependent on external stimulation; rapid emotional changes and high distractibility are less common. This would also explain the positive results on the teacher-reported inhibition scale. Unfortunately, no imaging was performed, which could have provided valuable information on the neuropsychological outcome and CA-related brain damage [33].

*Questionnaire*

Parents reported significantly better executive functions, particularly in behavior regulation, as compared to par-

**Table 3** Parent, teacher, and self-reported executive functioning

BRIEF parents-report	Patients Mean (SD) <i>n</i> = 31 <sup>a</sup>	Norm Mean (SD) <i>n</i> = 770	<i>P</i> value
Behavioral regulation index	39.52 (12.0)	45.22 (11.3)	<b>0.003</b>
Inhibit	13.81 (4.3)	15.78 (4.5)	<b>0.003</b>
Shift	10.97 (3.5)	12.62 (3.5)	<b>0.004</b>
Emotional control	14.74 (5.2)	16.79 (5.0)	<b>0.016</b>
Metacognition index	72.52 (21.6)	78.60 (17.5)	0.108
Organization of materials	10.68 (3.9)	12.14 (3.3)	<b>0.031</b>
Monitor	12.77 (4.3)	14.81 (3.7)	<b>0.017</b>
Global executive composite	112.03 (31.4)	124.13 (26.0)	<b>0.024</b>
BRIEF teacher-report	<i>n</i> = 15 <sup>a</sup>	<i>n</i> = 778	<i>P</i> value
Behavioral regulation index	39.73 (12.9)	42.89 (13.3)	0.099
Inhibit	13.33 (3.9)	15.54 (6.0)	<b>0.020</b>
Metacognition index	75.27 (23.8)	70.00 (21.0)	0.589
Plan/organize	16.73 (4.7)	13.84 (4.2)	<b>0.041</b>
Global executive composite	115.00 (34.7)	112.88 (31.6)	0.910
BRIEF self-report	<i>n</i> = 8 <sup>a</sup>	<i>n</i> = 379	<i>P</i> -value
Behavioral regulation index	48.25 (8.9)	52.02 (11.2)	0.207
Metacognition index	52.75 (15.7)	56.60 (12.8)	0.574
Global executive composite	101.00 (22.5)	108.62 (21.8)	0.327

Only the index scores and composite scores, and subscales on which significant differences were found when compared with normative data, are presented. A complete overview of all results on the BRIEF is presented in Supplementary Table 3. Higher scores implicate worse executive functioning. Significant values ( $p < 0.05$ ) in bold

*BRIEF* Behaviour rating inventory of executive function

<sup>a</sup> The actual number of respondents to the questionnaire

ents of healthy children. These results are in contrast to the negative outcomes in, e.g., patients with TBI or neonatal encephalopathy [34, 35]. Teachers reported deficits in planning/organizing skills and only favorable scores on inhibition.

Parental results on questionnaires are not supported by test results on executive functioning; on the TMT and STROOP lower outcomes found compared to normative data. Possibly, the favorable scores were influenced by “response shift” [36]. Due to the CPR, and the often traumatic and emotional experiences related to the critical illness of their child, parents have expected a worse outcome and may be happy with their child’s present functioning [37]. They therefore may overestimate the capacities of their child. Favorable outcome may also be explained by social desirability, or denial.

Furthermore, the BRIEF questionnaire may not measure executive functions to the extent that is commonly believed [38]. A recent study in critical cyanotic congenital heart disease also showed significant impairments on neuropsychological testing, but remarkably the scores on the BRIEF were average [39].

Noteworthy, executive functions are part of the higher cognitive functions. Increasing deficits may emerge later in childhood when these functions are expected to mature; this phenomenon is called “growing into deficits” [40].

#### Predictors of outcome

Univariable analyses were limited by the small number of patients, and therefore no strong conclusions can be drawn. However, there are some hypothesis-generating findings.

Overall, it is to be expected that males have a higher chance on worse neuropsychological functioning as to anatomical differences between the male and female brain. The right hemisphere of males is larger and contains more white matter than the right hemisphere of females. The impairments are found on visual-orientated tasks, which are functions more related to the right hemisphere. These results support the hypothesis of white matter injury.

In addition, older age at time of CA leads to more specific deficits, rather than global deficits, which could be explained by the vulnerability theory. Also, increasing deficits may emerge later in childhood when functions are expected to mature (growing into deficits phenomenon).

Further, our findings that children with a CA-related pre-existing medical condition scored worse on attentional switching than those without indicated that neuropsychological impairments can be related to the pre-existing condition. For example, children with a congenital heart disease and children treated with ECMO, both without CA, also have attentional problems [5, 7].



Lastly, significantly better scores were found on divided attention and TMT part B in children participating in the follow-up program. Due to the multidisciplinary follow-up, children may have been referred to a professional (mental) healthcare provider in a more timely manner.

### Limitation

First, this is a single center cohort study in a heterogeneous population. Second, since participants with a high SES are relatively overrepresented, our results may be too positive, since SES is an important predictor of outcome. Third, correction for multiple testing was not applied since this is an explorative and descriptive study. We did not want to miss any influences on long-term neuropsychological outcomes. Fourth, although we assessed the executive functions with the BRIEF questionnaire, the executive functions were not extensively tested with neuropsychological tests. Finally, some important variables are lacking, such as time to ROSC, severity of underlying illness, and treatment/course after ROSC during ICU admission.

### Conclusion

Long-term neuropsychological testing of CA survivors showed significant weaknesses, but also relatively intact functioning. A structural neuropsychological follow-up screening is warranted, since cognitive deficits can be expected later in life (“grown into deficit”). Considering academic achievement, verbal support could improve these children’s visual-spatial tasks.

**Conflicts of interest** The authors declare that they have no conflict of interest.

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