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Neurocognitive and executive functioning in adult survivors of congenital heart disease

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Abstract

Objective: Congenital heart disease (CHD) can affect the developing central nervous system, resulting in neurocognitive and behavioral deficits. Preoperative neurological abnormalities as well as sequelae of the open heart operations required to correct structural abnormalities of the heart contribute to these deficits. There are few studies examining the neurocognitive functioning of adults with CHD. This study sought to investigate multiple domains of neurocognitive functioning in adult survivors of CHD who had childhood cardiac surgery with either moderate or severe disease complexity.

Design: A total of 48 adults (18–49 years of age) who had undergone cardiac surgery for CHD prior to five years of age participated in the study. CHD severity was classified as moderate or severe according to the 32nd Bethesda Guidelines. A computerized battery of standardized neurocognitive tests (CNS-Vital Signs), a validated rating scale of executive functioning, and demographic questionnaires were administered.

Results: There were no significant differences between the moderate CHD group and normative data on any cognitive measure. In contrast, the severe CHD group differed from norms in multiple domains: psychomotor speed, processing speed, complex attention, reaction time, and on the overall neurocognitive index. Number of surgeries was strongly related to worse executive functioning. There was no association between age at first surgery or time since last surgery and neuropsychological functioning. Number of surgeries was also unrelated to neurocognitive test performance.

Conclusions: Patients with severe CHD performed significantly worse on measures of processing speed, attention, and executive functioning. These findings may be useful in the long-term care of adults with congenital heart disease.

KEYWORDS

congenital cardiac surgery, congenital heart defect, executive function, neurocognitive outcomes

1 | INTRODUCTION

Almost 1% of newborns are born with congenital heart disease (CHD),[1] and with recent advances in medicine, a large majority of these children will now survive into adulthood.[2] Congenital heart disease includes a wide array of anatomic and structural cardiac defects. Some defects do not need any treatment and these patients need only lifelong observation, while other defects are severe and need several cardiac operations throughout life, sometimes starting in the newborn period. Unfortunately, CHD commonly results in injury to the developing central nervous system, resulting in a higher incidence of neurocognitive,[3] academic,[4] and behavioral deficits.[5] This brain injury results from multiple factors, including preoperative neurological abnormalities[6] believed

Abbreviations: CHD, congenital heart disease; NCI, neurocognitive index; PVL, periventricular leukomalacia; SES, socioeconomic status.

TABLE 1 Neurocognitive domains on the CNS-VS

CNS-VS domain	Neurocognitive functions assessed
Verbal memory	Verbal learning and recognition memory (immediate and delayed)
Visual memory	Visual learning and recognition memory (immediate and delayed)
Composite memory	Combined index of verbal and visual memory
Processing speed	Symbol/digit coding speed and accuracy
Executive functioning	Attention shifting (correct responses minus errors)
Cognitive flexibility	Attention shifting plus inhibitory control
Psychomotor speed	Bilateral finger tapping speed + coding speed
Reaction time	Response speed on a test of verbal inhibition (Stroop)
Complex attention	A combined index of performance errors on tests of continuous performance (sustained attention and vigilance), attention shifting, and verbal inhibition
Neurocognitive Index (NCI)	Combined index comprising: composite memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility

to be associated with cyanosis and hypoperfusion in utero and/or with postnatal hemodynamic instability,[7] as well as with sequelae of the open heart surgeries required to correct structural abnormalities of the heart and associated procedures such as cardiopulmonary bypass.[8] Identified mechanisms of neurocognitive pathology in CHD include altered cerebral blood flow, reduced brain oxygenation, and hypoxic-ischemic events, all of which affect brain development and in particular myelination.[9]

One of the most common neuropathological outcomes of CHD is periventricular leukomalacia (PVL), damage to cerebral white matter tracts that connect diverse cortical and subcortical regions. PVL occurs in up to 50% of infants with complex CHD postsurgery.[10] A characteristic pattern of deficits in neurocognitive functioning has been identified in children with complex CHD, involving cognitive processing speed, executive functioning, attention, and visual-motor skills,[9,11] functions that rely on white matter integrity.[12] Deficits in information processing can, in turn, have downstream effects on intellectual development. A meta-analysis[13] showed that children with complex CHD exhibit lower overall intellectual functioning, verbal IQ and performance IQ compared to controls, whereas children with moderate CHD have lower performance IQ only, and children with mild CHD do not differ from controls. Studies with adolescent survivors of CHD have reported cognitive and executive impairment suggesting that these neurodevelopmental deficits persist into adolescence.[14,15]

Few studies have evaluated the neurocognitive functioning of adults with CHD. A recent review[16] identified only five studies of adult CHD survivors. Reported findings were mixed, although a consistent outcome was that patients with more complex disease and cyanosis had lower IQ. In a study that examined specific cognitive domains in patients with tetralogy of Fallot, Daliento et al.[17] found impairment in executive functioning (planning and problem-solving) in over half of participants (despite normal intellectual functioning). A history of cyanosis in infancy was associated with greater deficits in executive functioning and complex processing speed. Overall, findings from the adult literature suggest a continuation of patterns observed in children with CHD, although conclusions are limited by the small number of studies to date.

In this study, we sought to investigate multiple domains of neurocognitive functioning in adult survivors of CHD who either had moderate or severe CHD. We hypothesized (1) that adult survivors show a pattern of deficits in attention, executive functioning, and processing speed similar to the deficits seen in children with CHD and (2) that deficits are greater in survivors with more severe disease.

2 | METHODS

2.1 | Patient population

This was a cross-sectional study. Study participants were English-speaking adults (age 18-49 years) with moderate and severe congenital heart disease. The level of severity was determined by the guidelines set in the 32nd Bethesda Conference.[18] In order to be eligible for the study, participants must have received their first cardiac surgery prior to 5 years of age. Patients were excluded from participation if they had a comorbid condition that could potentially affect performance on the neurocognitive measures, including a genetic syndrome, severe psychiatric disorder (e.g., schizophrenia and bipolar disorder), autism, neurological conditions such as epilepsy, history of substance abuse, and known history of stroke. The study was approved through Baylor College of Medicine's Institutional Review Board, and written consent was obtained from all study participants.

2.2 | Standardized neurocognitive tests

CNS Vital Signs (CNS-VS): The CNS-VS[19] is a computerized battery of seven widely used neurocognitive tests that assess a range of cognitive functions (Table 1). It has been normed on a large battery of participants (n = 1069) ages 7-90 years, and used with different clinical groups. It has acceptable test–retest reliability, and the tasks correlate with standard neuropsychological versions of these tests.[19] It takes approximately 30 min to complete. The directions are written at a fourth grade reading level.

2.3 | Validated behavioral rating scales

BRIEF-A: Daily executive functioning was assessed using the self-report version of the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A). The BRIEF-A is a standardized 75-item scale that captures views of an adult's executive functions or self-regulation in his or her everyday environment. It has acceptable internal consistency (alpha range =0.73-0.90 for clinical scales and 0.93-0.96 for indices), good test-retest reliability (alpha range =0.80-0.94 for clinical scales and 0.96-0.98 for indices), and shows significant correlations in the expected direction with other self-report measures of executive functioning. BRIEF scores are not normally distributed but are positively skewed, that is, most scores cluster at the lower (nonclinical) end of the range. As a result, percentiles for different scales vary somewhat.

2.4 | Demographics questionnaires

Demographic information was obtained via a brief questionnaire developed by the investigators. Information obtained included: gender, self-identified race/ethnicity, highest educational level attained, and occupational history. Socioeconomic status (SES) was computed using modified Hollingshead criteria (Hollingshead, unpublished manuscript), based on the educational attainment and occupational status of the participant.

2.5 | Numerical indices related to cardiac function

2.5.1 | Oxygen saturation

Standard pulse oximetry was obtained via an index finger using a Nell-Cor™ device (Covidien; Mansfield, MA, USA). All patients were on room air. For this study, oxygen saturation designation was coded as follows: 1, ≥95%; 2, 90-95%; 3, 80-90%; 4, <80% (Table 3).

2.5.2 | Ventricular function

Ventricular systolic function was assessed with echocardiography. In cases where cardiac magnetic resonance images were available, these data were used. When possible, echocardiographic ejection fraction was calculated via the Simpson's method. However, in other cases where ejection fraction calculation was not possible or in cases of a systemic right or indeterminate ventricle, qualitative measurements were used. By convention, ventricular function was categorized as follows: 1, normal; 2, mildly depressed; 3, moderately depressed; 4, severely depressed (Table 3).

2.6 | Statistical analysis

We had complete data for all subjects. However, three subjects (two with moderate CHD, and one with severe CHD) had invalid administrations of the continuous performance test, due to interrupted performance in two cases, and indiscriminate responding (for an unknown reason) in the third. The Complex Attention Index could therefore not be calculated for these three subjects, who were omitted from analyses of Complex Attention. Their data were included in all other analyses. There were no other missing data on any measure.

Descriptive statistics were generated for each CHD group. One-sample *t* tests were computed to compare standard scores (M = 100, SD = 15) against expected values (EVs) for each neuropsychological test and to compare the percentage of participants showing impairment on each measure based on prevalence of impairment within the normal distribution curve (moderate impairment, standard score ≤85, EV = 16%; severe impairment, standard score ≤70, EV = 2.2%). Likelihood of overall cognitive impairment based on CHD group was determined using logistic regression. CHD group differences in neurocognitive functioning were examined using a series of univariate analyses of variance with significant between-group differences in demographic variables entered as covariates. To control for relative effects of age within each CHD group, age-normed standard scores were used instead of raw scores in all analyses.

All analyses were conducted using PASW Statistics version 21 for Windows (IBM SPSS Inc., Chicago, IL, USA). Alpha was set at .05, and *p* values were adjusted using the Bonferroni-Holm method[20] to correct for multiple comparisons.

3 | RESULTS

3.1 | Demographic information

Six hundred ninety-one consecutive clinic patients with congenital heart disease were seen between April and November 2013. Two hundred fifteen of those patients did not have their first cardiac surgery by five years of age. Additionally, 145 patients did not fulfill the age criteria (18–49 years of age). Further patients were excluded based on comorbid genetic syndromes (67 patients), neurologic conditions or known history of stroke (30 patients), severe psychiatric disorders (11 patients). Nine patients did not speak English and were not able to participate. From the 214 patients who fulfilled inclusion criteria, 48 patients (22%) enrolled in the study and were grouped based on severity of cardiac diagnosis (summarized in Table 2). The 166 patients who declined to participate in the study most commonly cited time constraints. The moderate CHD group consisted of 24 participants (11 females, mean age 26.3 years, range 19-43 years) and the severe group consisted of 24 patients (12 females, mean age 32.8 years, range 20-48 years) (Table 3). The two groups were comparable based on gender, race/ethnicity, level of education, and occupational attainment. The severe CHD group was older on average than the moderate CHD group (M = 32.8 years vs. 26.3 years, $F(46, 1) = 9.509$, $P = .003$). As would be expected, the severe CHD group had worse current cardiac function, both in terms of systemic ventricular function, $F(46, 1) = 14.23$, $P = .0005$, and mean O_2 saturation, $F(46, 1) = 8.065$, $P = .007$. Current cardiac function and age were therefore entered as covariates in subsequent between-group comparisons.

3.2 | Demographic differences in cognitive functioning

Men had marginally better visual memory than women (M = 107.5 ± 15.6 vs. 96.6 ± 22.1, $P = .054$). There were no

TABLE 2 Diagnoses in moderate and severe CHD groups

	n
Moderate CHD (*n* = 24)	
Tetralogy of Fallot (TOF)	11
Coarctation of the aorta	4
Atrioventricular canal	3
Pulmonary valve repair	3
Aortic valve repair	2
Partial anomalous pulmonary venous connection	1
Severe CHD (*n* = 24)	
Transposition of great arteries (repaired)	9
Single ventricle, status-post Fontan	9
TOF, status-post Blalock-Taussig shunt	5
Double-inlet LV, status-post Blalock-Taussig shunt	1

significant cognitive differences based on patient SES, race/ethnicity, or other demographic variables.

3.3 | Effect of clinical factors on cognitive functioning

There was no association between age at first surgery or time since last surgery and neuropsychological functioning on the CNS-VS battery. Number of surgeries was also unrelated to neurocognitive test performance. In contrast, number of surgeries was strongly related to self-reported executive functioning as measured on the BRIEF-A-SR Global Executive Composite, $F(43, 4) = 5.445$, $P = .001$, $\eta^2 = 0.336$ (Figure 1). Two-thirds of the BRIEF subscales (monitor, plan/organize, working memory, inhibit, task monitor, and initiate) were significantly related to number of surgeries at a corrected P value $<.05$.

As can be seen in Table 3, when examining current cardiac functioning, there were too few subjects with abnormal function to make meaningful comparisons. We therefore compared patients with normal function ($n = 31$) versus abnormal function of any severity ($n = 17$). Patients with abnormal cardiac function at the time of testing had slightly slower processing speed, but this difference did not remain significant when correcting for multiple comparisons ($P = .073$). No other group differences related to current cardiac functioning emerged.

3.4 | CHD group differences in neurocognitive functioning

3.4.1 | CHD versus normative sample

There were no significant differences between the moderate CHD group and normative data on any cognitive measure. In contrast, the severe CHD group differed from norms in multiple domains: psychomotor speed, $t(23) = -4.907$, $P = .0006$, $d = 2.046$; processing speed, $t(23) = -3.824$, $P = .007$, $d = 1.594$; complex attention, $t(23) = -2.973$, $P = .049$, $d = 1.239$; reaction time, $t(23) = -2.894$, $P = .049$, $d = 1.206$; and on the overall neurocognitive index (NCI), $t(23) = -4.174$, $P = .0036$, $d = 1.741$. Differences from normative data (in *z*-scores) are depicted in Figure 2.

3.4.2 | Moderate versus severe CHD

As can be seen in Figure 3, the severe CHD group performed worse than the moderate group in all domains. Differences were significant in psychomotor speed ($P = .004$), complex attention ($P = .009$), and the overall NCI ($P = .002$), and marginal in processing speed ($P = .055$). When controlling for age, current cardiac function, and multiple comparisons, significant differences remained evident in complex attention, $F(41, 1) = 11.558$, $P = .015$, $d = 1.037$, and on the overall NCI, $F(41, 1) = 8.945$, $P = .042$, $d = 0.912$, with a marginal difference evident in psychomotor speed, $F(47, 1) = 3.253$, $P = .078$, $d = 0.532$.

3.4.3 | Neurocognitive impairment

The NCI was used as a summary measure to examine incidence of neurocognitive impairment. We defined moderate impairment as performance $\geq$1 SD below the normative mean (i.e., standard score $\leq$85), and severe impairment as performance $\geq$2 SDs below the normative mean (i.e., standard score $\leq$70). The severe CHD group had a significantly higher incidence of moderate neurocognitive impairment compared to normative expectations, $t(23) = 2.130$, $P = .044$, $d = 0.888$. Moreover, compared to the moderate CHD group, the severe group had an almost sixfold increase in odds of having moderate neurocognitive impairment, a finding that was marginally significant ($P = .052$) (Figure 4). On average, subjects in the severe CHD group showed impairment in twice as many domains as moderate CHD subjects, M = 2.17 versus 0.96, $F(46, 1) = 5.664$, $P = .022$, $d = 0.702$. The two groups did not differ from each other, or from normative expectations, in incidence of severe neurocognitive impairment (Figure 4).

3.5 | Daily executive functioning

3.5.1 | CHD versus normative sample

The groups with CHD did not differ significantly from normative data on the BRIEF-A self-report when controlling for multiple comparisons. However, within-CHD group differences were again evident, as discussed below.

3.5.2 | Moderate versus severe CHD

The moderate and severe CHD groups differed in emotional control, $F(46, 1) = 8.798$, $P = .046$, $d = 0.875$; self-monitoring, $F(46, 1) = 8.874$, $P = .046$, $d = 0.878$; overall behavioral regulation, $F(46, 1) = 9.724$, $P = .038$, $d = 0.920$; and overall executive functioning (i.e., on the Global Executive Composite), $F(46, 1) = 9.218$, $P = .043$, $d = 0.895$. A marginal difference was also evident in working memory, $F(46, 1) = 7.992$, $P = .055$, $d = 0.834$.

3.5.3 | Impairment

The severe CHD group showed an elevated incidence of clinically-significant problems (i.e., *t*-scores $\geq$65) with emotional control compared to the expected normative mean of 50, $t(23) = 3.021$, $P = .006$, $d = 1.259$. Compared to the moderate CHD group, the severe group had a significantly greater incidence of problems in emotional control (37.5% vs. 4.3%), $F(46) = 9.316$, $P = .004$, $d = 0.9$, and working memory (20.8% vs. 0%), $F(46) = 6.053$, $P = .18$, $d = .725$, as well as on all

TABLE 3 Participant characteristics

		Moderate CHD (n = 24)	Severe CHD (n = 24)
Age (years)		26.3 ± 7.2	32.8 ± 7.6 ($P < .05$)
Female (%)		45	50
Race/ethnicity (%)			
White		92	100
Asian		8	0
Marital status (%)			
Single/never married		67	50
Married		29	42
Divorced		4	8
Hollingshead SES score, M ± SD		38.3 ± 20.3	35.5 ± 17.9
Employed (%)		75	63
Education (%)			
Some high school		0	4
High school		13	4
Some college		29	33
College		42	54
Graduate school		17	4
BMI		26.01 ± 6.49	28.01 ± 6.19
NYHA class, n			
I		24	16
II		0	8
O_2 saturation, n			
>95%	Normal	24	17
90%-95%	Mild hypoxia	0	5
80%-90%	Moderate hypoxia	0	2
<80%	Severe hypoxia	0	0
Systemic ventricular function, n			
1	Normal	23	12
2	Mildly depressed	1	7
3	Moderately depressed	0	4
4	Severely depressed	0	1
Age at first operation[a]		8 mo (1 wk to 5 y)	4 mo (1 wk to 3 y)
Number of operations		1.5 (1-3)	2 (1-5)
Time since last operation		18.5 mo (6-39 mo)	24 mo (2-42 mo)

[a]Additional data: median (range).

three overall indices: the Behavioral Regulation Index (20.8% vs. 0%), $F(46) = 6.053$, $P = .018$, $d = 0.725$; Metacognitive Index (16.7% vs. 0%), $F(46) = 4.60$, $P = .037$, $d = 0.632$; and the Global Executive Composite (16.7% vs. 0%), $F(46) = 6.053$, $P = .037$, $d = 0.725$.

4 | DISCUSSION

In this study, adult survivors of moderate CHD showed no significant differences in neurocognitive functioning from normative samples. In contrast, severe CHD in early childhood was associated with an array of cognitive deficits in adulthood. Compared to the normative sample, survivors of severe CHD showed significantly slower psychomotor speed, information processing speed, and reaction time, and worse overall attention. They were also twice as likely as the normative sample to have impairment in one or more cognitive domains. Compared to survivors with moderate CHD, the severe group had worse attention and executive functioning, worse overall neurocognitive function, and a marginally higher incidence of moderate neurocognitive impairment. Moreover, the size of these effects was generally in the large range, according to current convention.[21] Taken together, the observed pattern of deficits on neurocognitive tests indicates a general slowing of cognitive function in the severe CHD group.

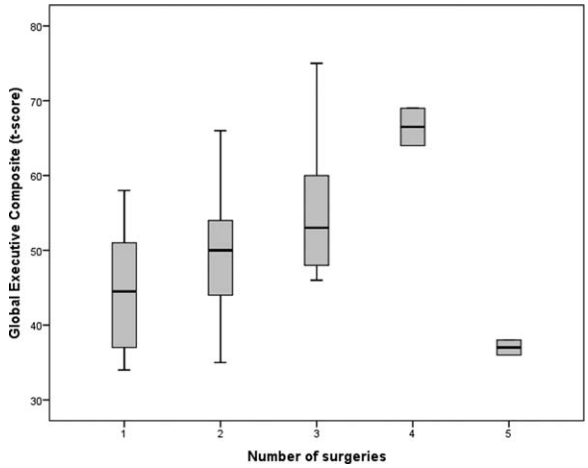

FIGURE 1 Box plot showing relation between global executive functioning on the BRIEF-A-SR and number of cardiac surgeries. Higher *t* scores indicate worse functioning

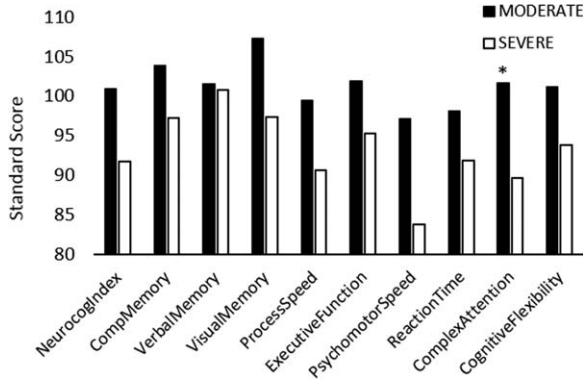

FIGURE 3 CHD group differences in neurocognitive functioning across domains, controlling for group differences in age, current cardiac function, and multiple analyses. Higher scores indicate better performance. $^{*}P < .05$

These findings are consistent with the pediatric literature.[13] Neurocognitive deficits associated with childhood CHD are therefore likely to be a life-long issue for survivors. Our results are also consistent with and expand upon the findings of Daliento et al.[17] Like their patients, our subjects with severe CHD had a high incidence of deficits in psychomotor speed and executive skills, with intact memory functioning. While we reported on pulse oximetry around the time of testing, we did not have historical data on chronic cyanosis in our subjects. Cyanosis may have been more prevalent in the severe CHD group and may have contributed to their worse performance. Future studies are needed to evaluate the influence of cyanosis on performance. Our findings are also consistent with Cassidy who found significant self-reported difficulties in emotional regulation, suggesting that this may be an especially salient area of concern for individuals with CHD.[22]

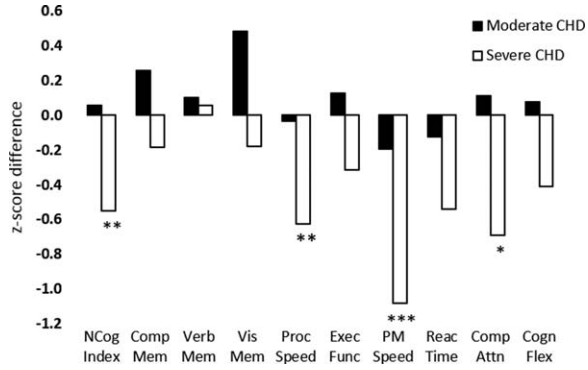

FIGURE 2 Standardized differences in neuropsychological functioning between CHD groups and normative samples. NCog Index, Neurocognitive Index. Comp Mem, Composite Memory. Verb Mem, Verbal Memory. Vis Mem, Visual Memory. Proc Speed, Processing Speed. Exec Func, Executive Functioning. PM Speed, Psychomotor Speed. Reac Time, Reaction Time. Comp Attn, Complex Attention. Cogn Flex, Cognitive Flexibility. *P* values reflect differences from normative sample. $^{*}P < .05$. $^{**}P < .01$. $^{***}P < .001$

Group differences were not observed on the executive functioning measures of the CNS-VS, but it is generally accepted that performance-based measures of EF are only weakly correlated with EF questionnaires.[23]

In our study, self-reported executive functioning was strongly related to number of cardiac operations, suggesting that repeated cardiovascular procedures over time may take their toll on these executive skills and the frontal networks that underlie their development. As many of these repeat operations occurred in adolescence and young adulthood, this finding is consistent with the idea that adolescence may be a sensitive period of neurodevelopmental vulnerability to insult, particularly with regards to executive functioning, which is known to develop rapidly in this period.[26,27] Moreover, neurocognitive deficits arising in childhood may be associated with reduced personal achievement in adulthood. Consistent with this observation, we found that neurocognitive deficits were associated with subjects' level of education and employment status. Deficits in executive functioning can also negatively impact self-care and medical adherence,[28] making it more challenging for patients to adhere to recommendations for surveillance and long-term management of CHD. Our findings can be considered a conservative measure of CHD group differences in neurocognitive functioning, as we controlled for multiple analyses, group differences in ventricular function. The observed deficits were not attributable to hypoxia or depressed ventricular function during testing, although these factors can have an effect on cognitive performance.

This study has a number of limitations. Given the cross-sectional design and lack of baseline data, we are unable to make strong inferences about the relative effect of early surgery on cognitive development. While we were able to rule out effects of later operations and current cardiac function on neurocognitive performance, it is possible that some of the patients in this study had neurologic abnormalities that predated their first surgery,[6] even though we excluded patients with known genetic syndromes or brain injuries. More longitudinal studies, ideally following patients from the neonatal period into adulthood, are needed. A second limitation is the fact that we used a sample of patients in active follow-up at our clinic. Almost all (42/44) of the

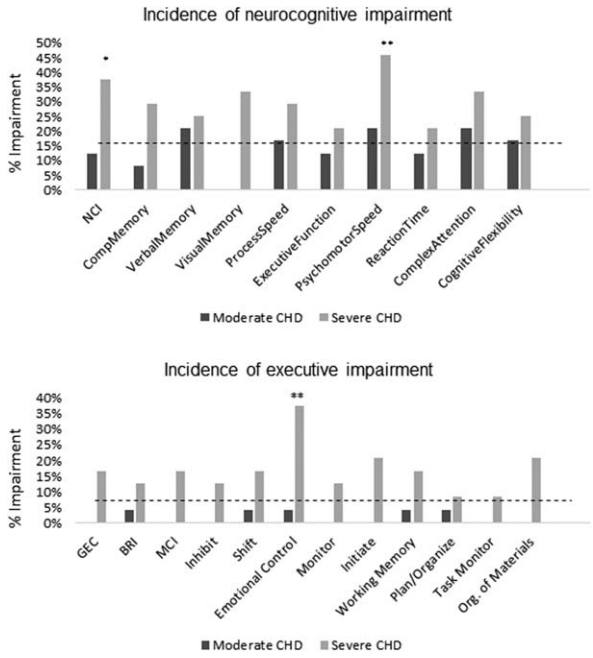

FIGURE 4 Incidence of neurocognitive impairment on the CNS-VS and executive function impairment on the BRIEF-A-SR by CHD group. NCI, Neurocognitive Index; CompMemory, Composite Memory; GEC, Global Executive Composite; BRI, Behavioral Regulation Index; MCI, Metacognition Index; Org. of Materials, Organization of Materials. Moderate neurocognitive impairment is defined as standard score $\leq$85. Executive function impairment is defined as *T*-score $\geq$65. The dotted line represents the expected value based on the area under the normal curve. $^{*}P < .05$. $^{**}P < .01$. *P* values represent differences from normative expectations

patients were white, and they were relatively well-educated, as 98% had completed high school and over half (58%) had college degrees. Thus, our subjects are socioeconomically different than the diverse American population. However, the fact that neurocognitive deficits were apparent in such a high-functioning sample suggests that neurocognitive sequelae are likely quite widespread in all socioeconomic classes of adults with severe CHD. The fact that ventricular ejection fraction was utilized as a measure of cardiac function could be also regarded as a further limitation. Even though there were some patients with single ventricles, some with systemic right ventricles, and some with systemic left ventricles, ejection fraction and assessment of ventricular systolic function via echocardiography is the standard of care and widely used, even when comparing different congenital heart defects. However, since there is heterogeneity in the cardiac anatomic diagnoses, ventricular function (normally an indicator of cardiac function, cardiac output, and contractility) may not be expressly comparable between the two groups. The relatively small sample size (48 subjects) also limits some conclusions. A larger sample would have allowed us to examine possible mediators and moderators more closely, and may also have allowed us to detect more subtle deficits in the moderate CHD group. Lastly, since the final sample size represented small fraction (22%) of the eligible patients, this may lead to bias towards the type of patients who were actually enrolled.

5 | CONCLUSION

This study provides one of the few investigations of neurocognitive and executive functions in adult survivors of CHD. Severe congenital heart disease is associated with cognitive deficits in adulthood that implicate involvement of frontal system networks and their diverse connections throughout the brain. Prospective research that combines neurocognitive testing with repeat neuroimaging and tracks functional outcomes is necessary to determine the course and causes of disease- and treatment-related injury to different brain regions in individuals with CHD.

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CONFLICT OF INTERESTS

The authors do not have any disclosures or conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors contributed to study design, critical revision, and final approval of the article.

Contributed to drafting the article: Klouda, Saraf, Franklin, and David Schwartz.

Contributed to data collection, analysis, and interpretation: Klouda, Franklin, and Schwartz.

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