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Cognitive dysfunction in Adult Congenital Heart Disease with different structural complexity

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ABSTRACT

Objective

A cross-sectional study assessed cognitive function in a sample of Adult Congenital Heart Disease patients, within the Functioning in Adult Congenital Heart Disease study London. The association between cognitive functioning and disease complexity was examined.

Methods

Three hundred and ten patients participated. Patients were classified into four structural complexity groups (Tetralogy of Fallot, Transposition of the Great Arteries, Single Ventricle and Simple conditions). Each participant underwent neuropsychological assessment to evaluate cognitive function (memory, executive function) and completed questionnaires to assess depression and anxiety.

Results

Forty one percent of the sample showed impaired performance (>1.5 SD below the normative mean) on at least 3 tests of cognitive function compared to established normative data. This was higher than the 8% that would be expected in a normal population. The sample exhibited significant deficits in divided attention, motor function and executive functioning. There was a significant group difference in divided attention ($F=5.01$, $p=.002$) and mean total composite score ($F=5.19$, $p=.002$) between different structural complexity groups with the Simple group displaying better cognitive function.

Conclusion

The results indicate that many Adult Congenital Heart Disease patients display impaired cognitive function relative to a healthy population, which differs in relation to disease complexity. These findings may have implications for clinical decision making in this group of patients during childhood. Possible mechanisms underlying these deficits and how they may be

reduced or prevented are discussed; however further work is needed to draw conclusive judgments.

INTRODUCTION

Recent advances in medical and surgical techniques have significantly changed the outlook for patients with congenital heart disease, giving rise to a new group of patients: Adults with Congenital Heart Disease. Until recently, approximately 50% of these patients would not have survived through childhood but a large proportion can now be expected to survive into adulthood (85%).[1] In the UK an estimated 1,600 Congenital Heart Disease patients reaching 16 years of age are referred for follow-up care in adult services each year.[2] A similar rise has also been reported in Canada.[3]

The steady rise in the number of survivors with Congenital Heart Disease has shifted attention to the long-term impact of the condition for this new patient population. Interest is moving away from mortality to long-term psychosocial outcomes such as quality of life, social functioning and wellbeing.[4]

One potential difficultly affecting this patient group is impairment of cognitive function. Existing literature indicates a relationship between Congenital Heart Disease, its related treatments and patients' cognitive functioning. However this research has largely focused on child cohorts.[5] The impact of Congenital Heart Disease on cognition in adults is relatively understudied despite recent research suggesting cognitive impairment persists into adolescence.[6]

The primary focus of research on cognitive functioning has been on the assessment of IQ in both child and adult patients. A recent meta-analysis suggested that IQ was adversely affected in

children with complex heart defects but remained within the normal range in those with simpler forms of Congenital Heart Disease.[7] The limited adult literature suggests that IQ is relatively unaffected in Adult Congenital Heart Disease.[5] To date only one study has reported lower IQ in Adult Congenital Heart Disease patients in comparison to a normal group.[8] While informative, the assessment of IQ alone does not provide a comprehensive and clear understanding of cognitive function, as it fails to capture performance in specific domains of cognition, such as memory, executive functioning, verbal fluency and attention.

Preliminary research in child cohorts has reported cognitive deficits across a range of domains, in particular language, psychomotor functioning, visuo-spatial skills, attention and memory.[8- 11] In a review of the literature we identified only 5 studies that examined cognition in Adult Congenital Heart Disease (two on the same cohort),[5,8, 12-15] of which only one study tested cognitive domains beyond IQ. These patients exhibited significant impairment of executive function and marginal memory, attention and learning deficits suggesting that patients may have difficulty with planning, dealing with novel situations, learning and recalling new information and remaining focused on a task. However, this sample was restricted to Tetralogy of Fallot and hence does not provide an understanding of the cognitive problems in different forms of Adult Congenital Heart Disease.[9]

The literature is further limited by the inclusion of heterogeneous patient samples in many studies. The varying complexity, treatment regimens and associated complications seen across congenital heart conditions is likely to differentially impact upon cognition. Greater cognitive impairment may be expected in cyanotic conditions due to increased risk of cerebral hypoxia.[16] Similarly patients with more complex forms of Congenital Heart Disease and those requiring multiple surgical interventions may be at increased risk of cognitive impairment. Research has

suggested that micro emboli entering cerebral blood flow during cardiopulmonary bypass may cause infarcts resulting in cerebral injury and consequent cognitive impairment.[17] Grouping patients with diverse forms of Adult Congenital Heart Disease may mask the true nature of the relationship between Adult Congenital Heart Disease and cognitive impairment.

This study assessed cognitive function in a group of Adult Congenital Heart Disease patients from different structural complexity groups with varying levels of morphological complexity, on a wide range of domains of cognitive function. The study aimed to (a) assess the level of cognitive functioning in Adult Congenital Heart Disease patients in comparison to age-matched norms and (b) investigate differences in cognitive function between different Adult Congenital Heart Disease structural complexity groups.

METHODS

Participants

Participants were recruited from the Grown Up Congenital Heart Unit at the Heart Hospital, University College Hospital, London, UK. Inclusion criteria were: (a) age 16 years or over, (b) diagnosis of Congenital Heart Disease, (c) fluent in English. Exclusion criteria included (a) presence of chromosomal anomalies: Trisomy-21 (Downs Syndrome), 22q11deletion (Di George syndrome), (b) history of stroke, (c) presence of mental retardation and learning difficulties, (d) Patent Foramen Ovale without any other structural anomaly, (e) physically disabled (unable to undergo exercise testing and/or neuropsychological assessment) and (f) presence of sensory loss or communication difficulty sufficient to interfere with the assessment.

Patient classification

Patients were classified into four groups based on the morphological complexity of the congenital heart condition: i) Tetralogy of Fallot diagnosis, pulmonary atresia, major aortopulmonary collateral arteries, pulmonary valve replacement), ii) Transposition of the Great Arteries diagnosis, atrial switch operation), iii) Single Ventricle (Single Ventricle physiology, Fontan repair operation) and iv) Simple (atrial septal defect, ventricular septal defect, coarctation of the aorta (including re-coarctation). Groups i-iii represent cyanotic, and group iv acyanotic, conditions. A sample size calculation indicated that for a four-group study to detect significant group difference on cognitive functioning, 280 participants were required to attain 80% power to detect a small-medium effect size, at the 0.05 significance level.

Procedure

A purposive sample of patients was recruited into the four structural complexity groups from patient databases and outpatient clinic lists. From an estimated 5000 patients 1199 were assessed for eligibility, 708 patients who met the inclusion criteria were invited. Eligible patients were invited by letter. Two-hundred and seventy three (38.6%) patients declined the invitation, 81 (11.4%) did not respond and 29 (4.1%) withdrew. The final sample included 310 patients (43.8% of those invited). Written informed consent was obtained from all patients following the provision of information sheets and the opportunity to ask questions (Ethics ref: 08/H0715/105). All the assessments were conducted in a suitable private room by a trained researcher.

MEASURES

Neuropsychological assessments

A comprehensive range of neuropsychological tests were utilized to assess several cognitive domains; including memory, attention, executive function and verbal fluency (*See Table 1*). The 3-subtests short-form measure of IQ (Wechsler Adult Intelligence Scale- WAIS-III) was scored

to produce an estimated full scale IQ (FSIQ-EST) which was derived using a formula by Tellegen and Briggs (1967).[18]

Measures of Mood

Mood was assessed to examine whether it influenced cognitive performance.

The Positive and Negative Affect Scale (PANAS)

PANAS is a 20-item self-report measure of positive (e.g. proud, alert, and inspired) and negative affect (e.g. upset, guilty, scared). Both subscales have shown good reliability: PA (alpha=0.89) and NA (alpha=0.85). Higher scores on each subscale indicate stronger affect.[27]

Centre for Epidemiological studies Short Depression Scale (CESD-10)

The CESD-10 is a self-report measure of depressive symptomology over the previous week. Ten items are rated on a 4 point scale ranging from "0= rarely/none of the time" to "3= All of the time". Higher scores indicate greater depression. The CESD-10 has demonstrated satisfactory internal consistency(r= 0.84) and test-retest reliability(r=0.71).[28]

State Trait Anxiety Inventory (STAI)

The 6-item version of STAI was used to assess state anxiety associated with a medical condition. Higher scores indicate greater anxiety. The scale has shown good internal consistency (0.82).[29]

Statistical analysis Data analysis was conducted using IBM SPSS, (version 21). Data was tested for the assumptions of normality; preliminary analysis indicated a non-normal distribution of the neuropsychological data. Square root and logarithmic transformations did not improve the data distribution. The overall level of missing data was <5%; to address this and obtain a complete

data set, a single imputation model was conducted using predictive mean matching (PMM)- further details of missing levels and imputation available from authors.

The data (raw scores) were transformed into standardized scores (z-scores). The z-scores were derived using the Standard Deviation (SD) from age-matched normative data for each test, according to the scoring recommendations for each test (e.g. scoring manuals) (See supplementary file), which was then used to compare the performance of the patient group with that of a healthy population. Taking account of the direction of poorer performance (lower number correct in memory tests, slower performance in timed tests) patient performance of 1.5 Standard Deviations (1.5 SD) or greater in the direction of poorer functioning than that of the normative group was used as an indicator of the presence of cognitive difficulty in the particular test. 1 SD, 1.5 SD and 2 SD are commonly used cut-off criteria in the neuropsychological literature[30]. Use of 1 SD is likely to identify false-positives whilst the stringent 2 SD criteria may increase the number of false negatives. The 1.5 SD criterion was selected as an attempt to balance the Type I and Type II errors[31]. Furthermore, this criterion is utilized in the diagnosis of Mild Cognitive Impairment[32]. For ease of interpretation poor performance will be described as 1.5 SD below the mean irrespective of the actual direction of scoring.

Ingraham and Aiken[30] provide useful data on determining criteria for impairment in multiple test batteries. On a single test 7% of a population would be expected to score 1.5 SD below the mean by chance[30]. In a battery of 15 tests (the present study yielded 15 scores from 8 neuropsychological tests) 66% of a normal population would be expected to score 1.5 SD below the mean score on one test and 8% of a normal population would be expected to score 1.5 SD below the mean score on three tests.

A total mean composite z score was computed from all neuropsychological test z-scores to provide a single measure of neuropsychological function. Group differences were tested on demographic and clinical variables using Chi-square tests, Man-Whitney U or Kruskal-Wallis tests where appropriate (two-tailed significance levels reported). Analysis of Covariance was used to assess differences in cognitive test scores (z scores) between the structural complexity groups, while controlling for covariates educational attainment and mood as these are factors known to influence cognition.

RESULTS

Sample characteristics

Of the 314 participants 4 did not provide complete neuropsychological data and were excluded from further analysis. Participants had a mean age of 33.3 years (SD 10.7) and 56% were male. Demographic and clinical characteristics of the sample are presented in *Table 2*. The Single Ventricle group was significantly younger than all other structural complexity groups (Transposition of the Great Arteries $U=1845$, $p=.003$ Tetralogy of Fallot $U=1770$, $p<.001$, Simple $U=1714$, $p<.001$).

As expected clinical variables differed between patient groups. The Transposition of the Great Arteries group were significantly younger at age of first repair than the Tetralogy of Fallot, Single Ventricle and Simple groups ($U=1066.0$, $p<.001$, $U=157.5$, $p<.001$, $U=1423.5$, $p<.001$ respectively). Tetralogy of Fallot patients were significantly younger at age of first repair than Single Ventricle patients ($U=1142.5$, $p<.001$). In addition Simple patients had significantly fewer interventions than Tetralogy of Fallot ($U=1768.0$, $p<.001$), Transposition of the Great Arteries

(U=1311.0, p<.001) and Single Ventricle patients (U=907.0, p<.001). Single Ventricle patients had a greater number of interventions than Tetralogy of Fallot (U=1944.0, p=.005) and Transposition of the Great Arteries patients (U=2101.5, p=.036). Time since last operation was significantly longer in Transposition of the Great Arteries patients than Single Ventricle patients (U=1577.5, p<.001).

Cognitive function in Adult Congenital Heart Disease compared to general population norms

Cognitive performance of the Adult Congenital Heart Disease sample in comparison to age-matched normative populations was assessed using z-scores calculated using the mean and the standard deviations of the normative data. Nearly three quarters (71.3%) of the sample performed 1.5 SD below the mean of the normative data on at least one test, higher than the 66% expected in a normal population using a battery of 15 tests; i.e. only 5.3% greater than expected. 41% of the sample scored at least 1.5 SD below the normative mean on 3 or more tests, which was significantly greater than the 8% expected in the normal population[30] The number of domains affected ranged from 1-13.

Compared to normative data, The the greatest proportion majority of patients showed deficits in executive function (problem solving) (21.3% to 25.2%), divided attention (20.3%-23.9%), verbal fluency (22.3%) and fine motor function (20.6% -27.4%). Deficits were seen in WCST scores, which primarily assess executive function, with the exception of the WCST failure to maintain score which is dependent on working memory and attention rather than problem solving skills. This result is consistent with the lack of memory deficits seen on the Rey Auditory Verbal

Learning Test. Twenty four percent of the sample had an IQ score at least 1 SD below the normative mean of 100 (i.e. scored <85).

Structural complexity group differences in cognitive functioning

The percentage of patients in each group scoring 1.5 SD below the normative mean on at least one or three neuropsychological test scores is shown in Table 3. The Simple group showed the lowest levels of impairment with only 26.2% demonstrating impairment on three or more tests. The Simple group showed significantly less deficits compared to TGA on three or more tests ($P<0.05$). All other comparisons were non-significant. All groups showed greater frequency of impairment than would be expected to occur in a normal population.[30] Overall mean neuropsychological performance using a composite z score (norm adjusted standardised scores) indicated the highest performance (-1.004) occurred in the Simple group while the Transposition of the Great Arteries group had the poorest performance (-6.15) (see Figure 1).

Analysis of covariance was used to investigate between group differences in overall neuropsychological performance with years of education and mood as covariates. Age was controlled for using age corrected normative scores. A significance level of $p<0.01$ was used to allow for multiple comparisons.

Analysis of covariance revealed a group difference in composite neuropsychological test scores (Group: F (1,303)= 3.992, p=.002, partial η^2p =.038, Education: F= (1,303)= 33.29, p=.000, partial η^2p =.099, Positive affect: F (1,303)= 8.68, p=.003, partial η^2p =.028). Post hoc (Sidak) tests indicated a significant difference between the Simple and Transposition of the Great Arteries group (Adj Mean: -5.9694, SE= 1.305 , p=.008).

Table 4 shows the proportion of patients within each structural complexity group showing impaired performance on the neuropsychological tests (>1.5 SD below the mean). See table 5 for 2 SD cut-off indicating more extreme deficiencies. Both are higher than expected by chance compared to normative data.

Analysis of covariance was used to explore between group differences in cognitive performance on each neuropsychological test. One neuropsychological function significantly differed between groups: divided attention (Trail Making Test -B) (Group: F=5.01, p=.002, η^2 =.047, Education: F=5.54, p=.019, η^2 =.018, Positive affect: F=9.97, p=.002, η^2 =.032). Post-hoc tests (Sidak) revealed that the Simple group performed significantly better than the Tetralogy of Fallot (Adj Mean =.958, SE=.180, p=.009) and Single Ventricle (Adj Mean =.147, SE=.177, p=.007).

Borderline significant differences were found in response inhibition (Stroop-Word test) (Group: F=3.56, p=.015, η^2 =.034), executive functioning (WCST-No of categories) (Group: F = 3.49, P =.016, η^2 =.033) and motor function and dexterity (Grooved Pegboard) (Group: F=3.30, p = .021, η^2 =.032).

IQ scores

Results indicated that the mean scores for all four groups were within the 'average' IQ category as classified by Wechsler (IQ= 90-109). No significant difference was seen between group IQ scores after controlling for education and mood (Group: F=1.04, p=.375). Visual inspection of the data suggested the Simple group attained the highest IQ (mean=100.4), followed by Single

Ventricle (mean =96.6), Transposition of the Great Arteries (mean =95.2) and lastly Tetralogy of Fallot (mean =95.04). Group: $F=(3,299)=1.04$, $p = .375$, $\eta^2 = .001$.

DISCUSSION

The persistence of cognitive deficits into adulthood as a result of Congenital Heart Disease and its associated treatments was examined in this study. The cognitive function of Adult Congenital Heart Disease patients was compared to age-matched population norms, and differences in cognitive function between structural complexity groups assessed.

The results indicated that a considerable proportion of Adult Congenital Heart Disease patients had cognitive abilities below that of age-matched healthy adults in a range of domains of cognitive functioning including executive function, divided attention and fine motor function. These findings suggest Adult Congenital Heart Disease patients may have difficulty attending to multiple tasks, dealing with novel and complex situations and performing fine motor tasks. A considerable number of patients displayed deficits in multiple domains. Almost a quarter of the sample showed deficits in IQ suggesting a generalized effect of congenital heart disease on cognition. However, in line with previous research, memory was found to be largely unaffected.[9]

As expected, investigation of structural complexity group differences indicated that patients in the 'Simple' group had better cognitive function than other groups. This indicates that the more morphologically complex the disease is, the greater the possibility of experiencing cognitive deficits. A possible explanation of this pattern is the inherent risk involved with having a severe form of congenital heart disease, including an increased risk for congenital brain anomalies.[33] Patients with severe heart conditions also have an increased risk of cognitive deficits due to

frequent surgery, particularly high-risk surgical interventions such as cardio-pulmonary bypass,[34] pre- and postoperative poor cerebral perfusion, and seizures.[35] The findings of the present study are consistent with a meta-analysis reporting patients with more severe forms of congenital heart disease having poorer levels of cognitive functioning than those with less severe forms.[7]

The general cognitive assessment of IQ did not show statistically significant differences between patient groups. This finding, in contrast to the assessment of specific domains of cognition, emphasizes the limitations of generalized measures of cognitive function such as IQ.

Executive function and other so called 'higher-order' cognitive skills were the most impaired domain within our sample. Deficits of this nature have the potential to impact on educational attainment and employment prospects.[36] Furthermore they may cause difficulties for patients during their daily lives when conducting instrumental activities of daily living such as managing finances and problem solving.

LIMITATIONS

While the current study is one of the largest and first of its kind to explore cognitive functioning in Adult Congenital Heart Disease patients across a range of cognitive domains and levels of disease complexity several limitations must be considered. The sample included the major Adult Congenital Heart Disease structural complexity groupings however it does not encompass all forms of Adult Congenital Heart Disease, and generalizability is restricted to the conditions included in the study. Although a broad range of cognitive domains were assessed in the study practicalities, including participant fatigue and time constraints, limited inclusion of a greater range of assessments. A broader range of memory abilities and visuo-spatial skills could be explored in future studies. Cognitive performance within the sample was compared against

normative data corrected for age. While this gives a good indication of the sample's performance against a healthy population the inclusion of an age matched health control group may have further strengthened the study design.

The present study highlights the significant extent of cognitive dysfunction present in patients with Adult Congenital Heart Disease compared to established normative data. Further work is now needed to identify the underlying mechanisms that can explain the specific causes of these deficits, and inform tools and interventions to evaluate and address potential deficits within clinical practice. Investigations into the long-term stability of these deficits will further inform clinicians and health care practitioners to be able to identify vulnerable groups and offer appropriate ongoing support and care.

IMPLICATIONS

This paper reports one of the first studies to include a large sample of Adult Congenital Heart Disease patients and assesses a wide range of cognitive domains as opposed to a composite measure of cognitive functioning. It is hoped that this may enable clinicians to identify and intervene with patients at an increased risk of cognitive deficits, and enable provision of additional developmental support where appropriate.

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CONTRIBUTORSHIP STATEMENT

Professor Stanton Newman is the guarantor and the principal investigator of the study. Manavi Tyagi drafted the paper and was involved in the design and execution of the study. Catherine Hurt and Lorna Rixon made significant contributions to the drafting of the paper. Theodora Fteropoulli, Nathalie Picaut and Fiona Kennedy were involved with the execution of the study. Dr Shay Cullen, Professor John Deanfield, and Professor Stanton Newman were involved with the design and management of the study. All authors contributed to the writing and review of the paper.

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CONFLICT OF INTEREST

None declared

References

1. Gatzoulis M, Webb G, Daubeney P. Diagnosis and management of Adult Congenital Heart Disease. 2nd ed Churchill Livingstone: 2011.
2. Wren C, O'Sullivan J. Survival with congenital heart disease and need for follow up in adult life. Heart 2001;85:438-443.
3. Gatzoulis M, Hechter S, Siu S, et al. Outpatient clinics for adults with congenital heart disease: increasing workload and evolving patterns of referral. Heart 1999;81:57-61.
4. Fteropoulli T, Stygall J, Cullen S, et al. Quality of life of adult congenital heart disease patients: a systematic review of the literature. Cardiol Young 2013;23:473-485.
5. Tyagi M, Austin K, Stygall J, et al. What do we know about cognitive functioning in adult congenital heart disease? Cardiol Young 2014;24:13-19.
6. Schaefer C, Rhein MV, Knirsch W, et al. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. Dev Med Child Neurol 2013;55:1143-1149.
7. Karsdorp PA, Everaerd W, Kindt M, et al. Psychological and cognitive functioning in children and adolescents with congenital heart disease: A meta-analysis. *J Pediatr Psychol* 2007;32:527-541.
8. Eide MG, Skjaerven R, Irgens LM. Associations of birth defects with adult intellectual performance, disability and mortality: population-based cohort study. Pediatr Res 2006;59:848-53.
9. Daliento L, Mapelli D, Russo G, et al. Health related quality of life in adults with repaired tetralogy of fallot: psychosocial and cognitive outcomes. Heart 2005;91:213-218.
10. Bellinger DC, Newburger JW. Neuropsychological, psychosocial, and quality-of-life outcomes in children and adolescents with congenital heart disease. Prog Pediatr Cardiol 2010;29:87-92.

11. Newburger JW, Jonas RA, Wernovsky G, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med 1993;329:1057-1064.
12. Daliento L, Mapelli D, Volpe B, et al. Measurement of cognitive outcome and quality of life in congenital heart disease. Heart 2006: 569–574
13. Wernovsky G, Stiles K, Gauvreau K, et al. Cognitive development after the Fontan operation. Circulation 2000: 883–889
14. Utens EM, Verhulst FC, Erdman RA, et al. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res 1994: 745–758.
15. Utens EM, Versluis D, Verhulst FC, et al. Psychopathology in young adults with congenital heart disease. Follow-up results. Eur Heart J 1998: 647–651.
16. Newburger JW, Silbert AR, Buckley LP, et al. Cognitive function and age at repair of transposition of the great arteries in children. N Egl J Med 1984;301:1495-1499.
17. Pugsley W, Klinger L, Paschalis C, et al. Microemboli and cerebral impairment during cardiac surgery. Vasc Surg 1990;24:34-43.
18. Tellegen A, Briggs PF. Old wine in new skins: grouping Wechsler subtests into new scales. J Consult Psychol 1967;31:499-506.
19. Ruff RM, Light RH, Parker SB, et al. Benton controlled oral word association test: Reliability and updated norms. Arch. Clin. Neuropsychol1996;11:329-338.
20. Matthew CG, Klove K. Instruction manual for the Adult Neuropsychological Test Battery Madison Wisc: University of Wisconsin Medical School 1964.
21. Michael S. Rey auditory verbal learning test: a handbook. Los Angeles: Western Psychological Services 1996.
22. Trenerry MR, Crosson B, DeBoe J, Leber WR. Stroop Neuropsychological Screening

Test. Odessa. FL: Psychological Assessment Resources 1989.

23. Smith A. The Symbol Digit Modalities Test Manual Western Psychological Services: Los Angeles 1982.
24. Reitan RM. Trail Making Test: Manual for administration and scoring: Reitan Neuropsychology Laboratory 1986.
25. Kongs SK, Thompson LL, Iverson GL, Heaton RK. Wisconsin card sorting test-64 card version (WCST-64). Odessa FL: Psychological Assessment Resources; 2000.
26. Wechsler D. Wechsler Adult Intelligence Scale, 3rd ed. The Psychological Corporation: New York 1997.
27. Watson D, Lee AC, and Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063-1070.
28. Andresen EM, Malmgren JA, Carter WB, et al. Screening for depression in well older adults: evaluation of a short form of the CES-D. Am J Prev Med 1994;10:77-84.
29. Marteau TM, Bekker H. The development of a six- item short- form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992;31:301-306.
30. Ingraham LJ, Aiken CB. An empirical approach to determining criteria for abnormality in test batteries with multiple measures. Neuropsychology 1996;10:120-124.
31. Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). Neuropsychological assessment (5th ed.). New York: Oxford University Press.
32. Petersen, R. C. (2004). "Mild cognitive impairment as a diagnostic entity." Journal of Internal Medicine 256(3): 183-94.
33. Glauser TA, Rorke LB, Weinberg PM, et al. Congenital brain anomalies associated with the hypoplastic left heart syndrome. Pediatrics 1990;85:984-990.

34. Stavinoha PL, Fixler DE, Mahony L. Cardiopulmonary bypass to repair an atrial septal defect does not affect cognitive function in children. Circulation 2003;107:2722-2725.
35. Goldberg CS, Schwartz EM, Brunberg JA, et al. Neurodevelopmental outcome of patients after the Fontan operation: a comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. J Pediatr 2000;137:646-652.
36. Marino B, Lipkin P, Newburger J, et al. On behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation 2012;126:1143-72.

Table 1 Summary of neuropsychological assessments

Tests utilized	Major cognitive function assessed	Definition of cognitive function assessed
Controlled Oral Word Association test (COWA-FAS)[19]	Verbal fluency	Speed and ease of verbal production
Grooved Pegboard (GPB)[20]	Manual and motor dexterity and functioning	Speed and accuracy of manipulation of fine objects with the hands
Rey Auditory Verbal Learning Test (RAVLT)[21]	Verbal learning and memory, delayed and immediate recall	Ability to learn new information and to store and retrieve information
Stroop Neuropsychological Screening test (SNST)[22]	Executive function: response inhibition	Ability to respond appropriately in novel situations; ability to perform an action when faced with a competing and more familiar action
Symbol Digit Modalities Test (SDMT)[23]	Complex visual scanning	The ability to visually locate a target within a range of complex figures
Trail making test (TMT) A and B[24]	Divided attention	The ability to respond to multiple tasks simultaneously
Wisconsin Card Sorting Test -64 (WCST)[25]	Executive function: problem solving	Ability to respond appropriately in novel situations; ability to plan and use initiative
Wechsler Adult Intelligence Scale (WAIS-III)[26]	IQ – general intelligence	General cognitive ability

Table 2 Sample demographic and clinical characteristics (by disease classification)

		TOF N=81 (26.1%)	TGA N=80 (25.8%)	SV N=65 (21.0%)	SIMPLE N=84 (27.1%)	Test statistic (p)
Age (years)	Mean (SD)	34.6 (11.0) 19-66	31.6 (6.5) 19-50	28.6 (7.7) 18-58	37.1 (13.7) 19-76	**H=** 19.734 **(<.001)**
Education (years)	Mean (SD)	13.0 (2.8)	13.4 (2.7)	13.8 (2.7)	13.6 (3.2)	H=3.08 (.370)
Gender (Male)	N (%)	43 (53.1)	51 (63.8)	43 (66.2)	37 (44.0)	χ^2=8.814 (.032)
White British	N (%)	72 (88.9)	71 (88.8)	51 (78.5)	68 (81.0)	χ^2=4.575 (.206)
Married/partner	N (%)	44 (54.3)	36 (45.0)	33 (50.7)	45(53.6)	χ^2=1.983 (.576)
Employed	N (%)	56 (69.1)	59 (73.8)	44 (67.7)	53 (63.1)	χ^2=2.678 (.444)
Depression	Mean (SD)	6.2 (4.7)	5.9 (4.3)	8.3 (6.2)	8.0 (6.6)	H=7.682 (.053)
Anxiety	Mean (SD)	9.9 (3.7)	9.9 (3.4)	11.0 (3.8)	10.2 (3.6)	H=4.666 (.198)
Positive affect	Mean (SD)	33.7 (8.2)	34.4 (8.0)	32.8 (8.0)	32.5 (8.3)	H=2.371 (.499)
Negative affect	Mean (SD)	17.8 (7.1)	16.4 (6.1)	18.6 (6.6)	17.8 (6.7)	H=4.487 (.213)
Age at first repair (months)	Mean (SD)	71.8 (115.0)	14.7(23.4)	98.9 (61.9)	136.8 (193.5)	**H=84.055 (<.001)**
Total No. interventions*	Mean (SD)	2.4 (1.2)	2.6 (1.3)	3.1 (1.6)	1.5 (0.8)	**H=74.02 (<.001)**
Years since last intervention*	Mean (SD)	15.9 (13.8)	20.0 (12.0)	13.1 (8.5)	15.2 (12.9)	**H=** 12.729 **(.012)**
NYHA	Median (Interquartile range)	1 (0)	1 (0)	1 (0)	1 (0)	χ^2=12.134 (.107)**

NYHA= New York Health Association functional classification

H= Kruskal-Wallis test, χ^2= Chi-square test

*Interventions include catheter interventioncather lab, palliative or reparative surgery

** Fisher's Fisher's exact value reported

Table 3 Percentage of patients scoring 1.5 SD below the normative mean score by structural complexity group

Group	Percentage >1.5 SD below the normative mean on at least 1 test	Percentage >1.5 SD below the normative mean on at least 3 tests	Tests 0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)	8 N (%)	9 N (%)	10 N (%)	11 N (%)	12 N (%)	13 N (%)
TOF	72.8 n=59	44.4 n=36	22 (27.2)	9 (11.1)	14 (17.3)	8 (9.9)	8 (9.9)	9 (11.1)	3 (3.7)	3 (3.7)	1 (1.2)	2 (2.5)	0	2 (2.5)	0	0
TGA	77.5 n=62	48.8 n= 39	18 (22.5)	13 (16.3)	10 (12.5)	15 (18.8)	4 (5.0)	3 (3.8)	9 (11.3)	3 (3.8)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)
SV	72.3 n=47	44.6 n= 29	18 (27.7)	11 (16.9)	7 (10.8)	8 (12.3)	5 (7.7)	2 (3.1)	6 (9.2)	3 (4.6)	2 (3.1)	1 (1.5)	0	0	2 (3.1)	0
Simple	63.1 n= 53	26.2 n= 22	31 (36.9)	19 (22.6)	12 (14.3)	8 (9.5)	5 (6.0)	2 (2.4)	4 (4.8)	1 (1.2)	1 (1.2)	0	0	1 (1.2)	0	0

SD, Standard Deviation; TOF, Tetralogy of Fallot; TGA, Transposition of the Great Arteries; SV, Single Ventricle

Table 4: Proportion of participants scoring >1.5 SD below the mean for each of the neuropsychological assessments in each of the four structural complexity groups

	ToF N (%)	TGA N (%)	SV N (%)	Simple N (%)
TMT-A	15 (18.5)	21 (26.3)	14 (21.5)	13 (15.5)
TMT-B	22 (27.2)	16 (20.0)	23 (35.4)	13 (15.5)
COWA	17 (21.0)	24 (30.0)	12 (18.5)	16 (19.0)
GP-Dominant	24 (29.6)	29 (36.3)	19 (29.2)	13 (15.5)
GP-Non Dominant	18 (22.2)	20 (25.0)	15 (23.1)	11 (13.1)
Stroop- Colour	7 (8.6)*	10 (12.5)	8 (12.3)	8 (9.5)
Stroop-Colour word	12 (14.8)	16 (20.0)	18 (27.7)	10 (11.9)
WCST-No Categories	24 (29.6)	25 (31.3)	16 (24.6)	13 (15.5)
WCST-Failure to maintain set	9 (11.1)	6 (7.5)*	4 (6.2)*	4 (4.8)*
WCST-Trials 1st Category	5 (6.2)*	4 (5)*	6 (9.2)	3 (3.6)*
WCST-Errors	23 (28.4)	18 (22.5)	12 (18.5)	16 (19)
WCST-Conceptual Level	21 (25.9)	18 (22.5)	17 (26.2)	14 (16.7)
Rey- Total Acquisition	8 (9.9)	9 (11.3)	5 (7.7)*	5 (6.0)*
Symbol digit Written	11 (13.6)	11 (13.8)	11 (16.9)	3 (3.6)*
Symbol digit Oral	9 (11.1)	11 (13.8)	5 (7.7)*	5 (6.0)*

*<8% which would be expected in the normal population Ingraham and Aiken[30]

Table 5: Proportion of participants scoring >2 SD below the mean for each of the neuropsychological assessments in each of the four structural complexity groups

	ToF N (%)	TGA N (%)	SV N (%)	Simple N (%)
TMT-A	10 (12.3)	15 (18.8)	12 (18.5)	9 (10.7)
TMT-B	17 (21.0)	12 (15.0)	15 (23.1)	9 (10.7)
COWA	8 (9.9)	9 (11.3)	4 (6.2)	6 (7.1)
GP-Dominant	17 (21.0)	21 (26.3)	16 (24.6)	12 (14.3)
GP-Non Dominant	11 (13.6)	12 (15.0)	9 (13.8)	5 (6.0)
Stroop- Colour	7 (8.6)	10 (12.5)	8 (12.3)	8 (9.5)
Stroop-Colour word	7 (8.6)	10 (12.5)	8 (12.3)	8 (9.5)
WCST-No Categories	14 (17.3)	11 (13.8)	7 (10.8)	5 (6.0)
WCST-Failure to maintain set	9 (11.1)	6 (7.5)	4 (6.2)	4 (4.8)*

WCST-Trials 1st Category	5 (6.2)	4 (5.0)	6 (9.2)	3 (3.6) *
WCST-Errors	13 (16.0)	12 (15.0)	9 (13.8)	8 (9.5)
WCST-Conceptual Level	11 (13.6)	13 (16.3)	10 (15.4)	8 (9.5)
Rey- Total Acquisition	1 (1.2) *	2 (2.5) *	1 (1.5) *	3 (3.6) *
Symbol digit Written	8 (9.9)	7 (8.8)	7 (10.8)	2 (2.4) *
Symbol digit Oral	5 (6.2)	5 (6.3)	5 (7.7)	2 (2.4)*

*<5% which would be expected in the normal population Ingraham and Aiken[30]