# Neurodevelopment and Behavior after Transcatheter versus Surgical Closure of Secundum Type Atrial Septal Defect

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**Objective** To assess the neuropsychological and behavioral profiles of school-aged children treated for atrial septal defect, secundum type (ASD-II) with open-heart surgery or catheterization.

**Study design** Patients (n = 48; mean age, 9 years, 3 months) and a matched healthy group (mean age, 9 years, 2 months) were evaluated with a shortened intelligence scale (Wechsler Intelligence Scale for Children, third edition, Dutch version) and a developmental neuropsychological test battery (Developmental Neuropsychological Assessment, second edition, Dutch version). Parents completed behavioral checklists (Achenbach Child Behavior Checklist for Children aged 6-18). Hospitalization variables were retrieved from medical files for studying associations with long-term neurodevelopment.

**Results** Compared with the healthy matched controls, patients treated for ASD-II had significantly lower scores on subtasks underlying such Developmental Neuropsychological Assessment, second edition, Dutch version domains as Attention and Executive Functioning, Language, Working Memory, Sensorimotor Functioning, Social Cognition, and Visuospatial Information Processing. Only subtle differences, mainly in Visuospatial Information Processing, were found between the surgical repair and transcatheter repair groups. Socioeconomic status, longer hospital stay, and larger defect size were associated with neurocognitive outcome measures. Parents of patients reported more thought problems, posttraumatic stress problems, and lower school performance compared with parents of healthy peers.

**Conclusion** After treatment for ASD-II, children display a range of neuropsychologic difficulties that may increase their risk for learning problems and academic underachievement. Differences related to treatment were not found. Our results suggest that neurodevelopmental and behavioral follow-up at school age is warranted in this group. *(J Pediatr 2015;166:31-8)*.

Surgery and catheterization for symptomatic atrial septal defect, secundum type (ASD-II) have proven to offer excellent survival rates and functional outcome,[1] yet little emphasis has been placed on the long-term neurodevelopment of this patient cohort. Few studies have addressed the impact of cardiac intervention to treat acyanotic congenital heart disease (CHD) on later neurocognitive function. Negative mental and behavioral sequelae after intervention for acyanotic heart defects have been documented.[2-6] Studies have reported a high prevalence of low-to-average intelligence scores, attentional dysfunction, and problems with visuospatial information processing and motor function in cohorts of acyanotic patients.[2,3,5,7-9] Studies also have focused on understanding the various possible causes underlying neurobehavioral impairment, including genetics, surgical procedures, cerebral hypoperfusion, microembolization, the inflammatory response, and the general psychological and physical strain caused by surgery and hospitalization.[10-14] More recently, the influence of family factors, such as socioeconomic status (SES) and parental stress, have received more attention. These noncardiac environmental factors can counterbalance the impact of risk factors and are protective against adverse developmental outcomes.[4,5,13]

The aim of the present study was to evaluate neurocognitive and behavioral sequelae following different interventions for symptomatic ASD-II. We compared the neuropsychologic profiles of children with corrected ASD-II and matched healthy controls. In addition, we evaluated the differential influence of treatment methods by comparing patients who underwent surgical closure and those who underwent transcatheter closure for ASD-II.

| | |
|---|---|
| ASD-II | Atrial septal defect, secundum type |
| CBCL-6/18 | Achenbach Child Behavior Checklist for children aged 6-18 |
| CHD | Congenital heart disease |
| DSM | *Diagnostic and Statistical Manual of Mental Disorders* |
| PTSD | Posttraumatic stress disorder |
| SES | Socioeconomic status |

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## Methods

The study cohort included patients treated for an ASD-II in 2 Belgian specialized heart centers, Ghent University Hospital and University Hospital Gasthuisberg Leuven. The selected patients underwent neurodevelopmental screening at school age (6-12 years). Exclusion criteria were perinatal problems, preterm birth (<37 weeks gestational age), birth weight <2000 g, other cardiac malformations, genetic abnormalities, and developmental syndromes. Out of 87 invited children, the parents of 48 children with ASD-II (55%) elected to participate in the study. For the surgical repair group, 62% of the respondents were enrolled; in the transcatheter repair group, 51%. Reasons for nonparticipation included diagnosis of a developmental syndrome (4.5%), family issues (3.5%), and no response (37%).

Surgical closure of ASD-II was performed via midline sternotomy with direct suture using mild to moderate hypothermic (range, 28-37°C) cardiopulmonary bypass. There were no significant differences in surgical defect repair between the 2 centers.

Percutaneous ASD-II closure was performed using a Figulla ASD occluder (Occlutech, Jena, Germany) at Ghent University Hospital, and transcatheter repair was achieved using an Amplatzer occlusion device (AGA Medical Corporation, Plymouth, Minnesota) at University Hospital Gasthuisberg Leuven. Both devices have proven to provide effective closure of ASD-II.[15]

The patient cohort comprised 18 patients who underwent surgical repair and 30 patients who underwent transcatheter repair (mean age, 9 year, 3months ± 1 year, 9 months). All 48 patients had undergone functional ASD-II repair and were considered healthy at the time of assessment. The healthy control group was recruited through approval of primary school boards and was matched with the patients on sex, age, and parental education. Parents completed demographic surveys. SES was determined using the Hollingshead Four-Factor Index,[16] which combines parental occupational and educational level. Raw scores ranged from 24 to 66, with a higher score indicating higher social status. The 2 hospitals' Medical Ethics Committees approved the study, and written consent was obtained from the parents of all patients. The study protocol was in accordance with the Declaration of Helsinki.[17]

The children's intelligence was assessed using a shortened version of the Wechsler Intelligence Scale for Children, third edition, Dutch version. In the Wechsler Intelligence Scale for Children, third edition, Dutch version, 2 verbal subtests (similarities and vocabulary) and 2 performance tasks (picture arrangement and block design) constitute a reliable measure of overall intelligence.[18]

The Developmental Neuropsychological Assessment, second edition, Dutch version is a reliable test battery for assessing an extensive range of neurocognitive skills in children.[19] The Developmental Neuropsychological Assessment, second edition, Dutch version domains of Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception, and Visuospatial Processing were assessed through 21 subtasks with 37 outcome scores. **Table I** (available at www.jpeds.com) summarizes the selected tasks. Outcome scores are expressed as age-adjusted standardized scores (mean ± SD, 10 ± 3), or percentile scores, which are considered process scores (<2nd to 75th percentile). These scores assess specific abilities or error rates that allow the clinician to evaluate a child's performance in more detail. Total test duration was 3 hours; breaks were provided during the test procedure when necessary to avoid fatigue.

The Achenbach Child Behavior Checklist for children aged 6-18 (CBCL-6/18)[20] was used to obtain standardized measures of various aspects of behavioral, social, and emotional functioning of the children as rated by their parents. The CBCL-6/18 contains problem behavior scales and competence scales, rated in terms of frequency on a 3-point Likert scale. The 113 items cluster into 8 syndrome scales. Three composite scales are computed—internalizing, externalizing, and combined—which constitute the total problem behavior. Specific classifications of behavioral questions represent clinical *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-oriented scales. Outcome scores are expressed as t-scores.

Medical charts were retrieved for patient hospitalization data potentially associated with cognitive outcome measures (**Table II**). Correlations with outcome measures and SES, age and weight at intervention, total hospital stay, and defect size were explored. Additional analyses were performed in the surgical repair group to study associations between outcome scores and time on extracorporeal circulation and level of hypothermia during the procedure.

### Statistical Analyses

Normally distributed data are presented as mean ± SD; data that do not meet normality assumptions, as median (IQR). Demographic characteristics and cognitive outcome measures were compared between the patient group and matched controls. Nominal data were compared using the Fisher exact test. For data derived from the medical charts, median and IQR were calculated.

For evaluating Developmental Neuropsychological Assessment, second edition, Dutch version outcomes, ANOVA was used to analyze group contrasts. Percentile scores were analyzed by the nonparametric Mann-Whitney *U* test with the exact option for nonrelated samples. In comparisons of different treatment outcomes, SES was added as a covariate in the analyses. To control for multiple testing, *P* values were adjusted according to the Benjamini-Hochman false discovery rate.[21] Effect sizes were calculated to quantify the difference between groups. Corrections and effect sizes were applied to standardized scores and percentile scores separately. For parametric data, the Cohen *d* was computed, which determines effect size based on difference between 2 means divided by the pooled SD. For data that did not meet normality assumptions, the Mann-Whitney *r* was calculated. Effect size was classified as small (*d*= .20/*r*=.10), moderate (*d*= .50/*r*= .30), large (*d*= .80/*r*=.50) and very large (*d* =

**Table II. Demographic data**

| Variables | Patients | Controls | *P* value | Surgical repair group | Transcatheter repair group | *P* value |
|---|---|---|---|---|---|---|
| Number | 48 | 48 | | 18 | 30 | |
| Sex | 19 males, 29 females | 19 males, 29 females | 1.0, $\chi^2$ | 6 males, 12 females | 13 males, 17 females | .493, $\chi^2$ |
| Age at testing, mean ± SD | 9 y, 3mo ± 1 y, 9 mo | 9 y, 2mo ± 1 y, 9 mo | .845 | 9 y, 2mo ± 2 y, 2 mo | 9 y, 3mo ± 1 y, 7 mo | .952 |
| Birth weight, g, mean ± SD | 3228 ± 491 | 3497 ± 570 | **.015*** | 3316 ± 387 | 3175 ± 543 | .341 |
| Birth length, cm, mean ± SD | 49.5 ± 2 | 50.8 ± 2.6 | **.008**† | 49.8 ± 2 | 49.3 ± 2 | .478 |
| 5-min Apgar score, % | <4: 0<br>4-6: 0<br>7-10: 100 | <4: 0<br>4-6: 0<br>7-10: 100 | NS | <4: 0<br>4-6: 0<br>7-10:100 | <4: 0<br>4-6: 0<br>7-10: 100 | NS |
| SES, mean ± SD | 40.1 ± 8 | 43.2 ± 7.1 | .055 | 37.2 ± 6.6 | 41.9 ± 8.4 | **.045*** |
| Age at intervention, mean ± SD<br>Range | - | - | | 2 y,9mo ± 1 y, 8 mo<br>4.8 m to 6 y, 7 mo | 4 y, 2mo ± 1 y, 7 mo<br>6.4 m to 7 y, 6 mo | **.014*** |
| Weight percentile at intervention, % | - | - | | 3-10: 72.2<br>25-50: 16.7<br>75-90: 11.1 | 3-10: 31<br>25-50: 31<br>75-90: 38 | .054[E] |
| Hospital stay, d, median (IQR) | - | - | | 7 (6-7) | 2 (2-2) | **.000**† |
| Defect size, mm, median (IQR) | - | - | | 19 (14-21) | 11 (10-13) | **.000**† |
| Extracorporeal circulation time, min, median (IQR) | - | - | | 38.5 (32-49) | - | |
| Level of hypothermia, °C, median (IQR) | - | - | | 32 (31.5-36.2) | - | |

*NS*, not significant.
Nominal data: $\chi^2$ with the Fisher exact test[(E)].
**P* < .05.
†*P* < .01.

*1.3/r = .70*). Effect sizes were calculated for equal samples (patients vs controls) and unequal sample sizes (surgical repair group vs transcatheter repair group), respectively.

Pearson and Spearman correlations (2-tailed) were used to explore associations between neuropsychologic outcomes and medical variables for standardized and percentile scores, respectively.

## Results

Table II provides an overview of birth characteristics, demographic data, and hospitalization data, retrieved from medical charts. Birth weight and birth length differed significantly between patients and controls. No other differences were found, owing to the careful matching of the 2 groups.

Performance on intelligence assessment and neuropsychologic screening is summarized in Table III. Intelligence outcome scores showed no significant between-group differences. Overall estimated intelligence and associated verbal and performance subtasks were within normal ranges and reflected small effect sizes (*d* 0.07-0.39).

In terms of the neuropsychological profile, between-group differences were evident in all domains assessed. Although standard scores were close to normal population means, moderate to large effect sizes ($d \geq 0.50$ / $r \geq 0.30$) were evident in the majority of the scores, where significant differences between groups were observed.

In the Attention and Executive Functioning domain, patients scored lower than controls on almost every outcome. On the subtest level, auditory attention, inhibition, design fluency, and sustained attention as measured by inhibition time yielded significantly lower results in the patient group. In the Language domain, performance on subtasks of comprehension of instructions and repetition of nonsense words was lower for patients compared with controls. Memory scores differed in terms of the recall of previously familiarized faces and the working memory aspect in word list interference. The patients scored significantly lower on the subtasks of the Sensorimotor Function domain, where imitation of hand positions, manual motor sequences, and visuomotor precision assessed refined motor skills. Theory of mind tasks in the Social Cognition domain elicited group differences. The significant value for the affect recognition subtask showed a trend after correction for multiple testing. Visuospatial competency was lower in the patient group for block construction and design copying.

Among the patient cohort, the surgical repair and transcatheter repair groups differed significantly in terms of SES, age at intervention, length of hospital stay, and defect size. SES was entered as a covariate in the analyses. Patients in the surgical repair group scored lower in the subtasks cued recall of a narrative and, more explicitly, visuospatial skills, assessment of motor and visual perceptual skills, and visuospatial analysis. However, following correction for multiple testing with the Benjamini-Hochmann method, none of these differences remained significant, and the 2 treatment groups showed no differences in long-term neurocognitive outcomes. Splitting the patient cohort reduced the power of our analysis; for example, according to power calculations, we would need 45 subjects in each group to reach 80% power to find a significant difference ($P < .05$) in full estimated IQ.

Of note is the pattern of the scores, with the surgical repair group scoring lower on the majority of the subtests, although the differences do not achieve statistical significance. The false discovery rate multiple testing correction discarded some of the significant *P* values; however, in terms of clinical relevance, we can discern particular moderate to large effect sizes ($d \geq 0.50$ / $r \geq 0.30$) in the Intelligence Inhibition

**Table III. Neuropsychological performance**

| Variables | Patients | Controls | *P* value | Adjusted *P* value* | Effect size, *d*/*r* | Surgical repair group | Transcatheter repair group | *P* value | Adjusted *P* value* | Effect size, *d*/*r* |
|---|---|---|---|---|---|---|---|---|---|---|
| Number | 48 | 48 | | | | 18 | 30 | | | |
| **WISC-III-NL** | | | | | | | | | | |
| Estimated full-scale IQ | 102.9 ± 15.7 | 107.9 ± 10.6 | .075 | .176 | 0.37 | 97.4 ± 14.8 | 106.3 ± 15.6 | .310 | .516 | 0.58 |
| Similarities | 12.2 ± 3.1 | 12.4 ± 2.3 | .738 | .738 | 0.07 | 11.8 ± 3.4 | 12.5 ± 2.9 | .860 | .860 | 0.22 |
| Picture arrangement | 9.5 ± 3.4 | 10.7 ± 2.6 | .052 | .176 | 0.39 | 8.3 ± 3.4 | 10.3 ± 3.2 | .228 | .516 | 0.61 |
| Block design | 9.9 ± 2.8 | 10.8 ± 2.9 | .141 | .176 | 0.31 | 8.9 ± 2.7 | 10.6 ± 2.8 | .297 | .516 | 0.61 |
| Vocabulary | 10.2 ± 2.6 | 11 ± 2.2 | .107 | .176 | 0.33 | 9.4 ± 2.0 | 10.7 ± 2.9 | .477 | .596 | 0.49 |
| **NEPSY-II-NL** | | | | | | | | | | |
| Auditory Attention and Executive Functioning domain | | | | | | | | | | |
| Auditory attention | 50 (25-75) | 75 (75-75) | .000† | **.000†** | 0.38 | 62.5 (25-75) | 50 (25-75) | .989 | 1.0 | 0 |
| Comission errors | 75 (10-75) | 75 (75-75) | .012‡ | **.029‡** | 0.25 | 50 (10-75) | 75 (10-75) | .209 | .496 | 0.19 |
| Omission errors | 37.4 (25-75) | 75 (50-75) | .014‡ | **.029‡** | 0.24 | 75 (25-75) | 25 (25-75) | .331 | .571 | 0.14 |
| Response test | 50 (25-50) | 50 (50-68.7) | .009† | **.029‡** | 0.29 | 25 (25-50) | 50 (21.2-50) | .361 | .571 | 0.14 |
| Comission errors | 25 (10-25) | 75 (56.25-75) | .000† | **.000†** | 0.64 | 17.5 (10-31.2) | 25 (10-25) | .452 | .660 | 0.11 |
| Omission errors | 25 (25-68.7) | 75 (50-75) | .002† | **.009†** | 0.35 | 25 (25-50) | 50 (25-75) | .293 | .556 | 0.17 |
| Inhibition errors | 25 (10-75) | 25 (25-75) | .169 | .251 | 0.15 | 25 (21.2-75) | 25 (10-75) | .735 | .821 | 0.05 |
| Design fluency | 9.2 ± 1.8 | 10.5 ± 2.4 | .004† | **.010†** | 0.61 | 8.7 ± 1.7 | 9.5 ± 1.9 | .336 | .617 | 0.43 |
| Inhibition | 50 (50-50) | 50 (50-75) | .013‡ | **.029‡** | 0.25 | 50 (50-62.5) | 50 (50-50) | 1.0 | 1.0 | 0 |
| Inhibition time | 10 ± 2.4 | 11.1 ± 1.9 | .022‡ | **.033‡** | 0.50 | 9.4 ± 2.0 | 10.5 ± 2.5 | .375 | .617 | 0.47 |
| Language domain | | | | | | | | | | |
| Comprehension of instructions | 10.6 ± 2.9 | 11.9 ± 2.4 | .015‡ | **.024‡** | 0.48 | 9.8 ± 2.7 | 11.1 ± 2.9 | .419 | .617 | 0.46 |
| Repetition of nonsense words | 9.9 ± 2.6 | 12.1 ± 1.8 | .000† | **.000†** | 0.98 | 9.2 ± 2.3 | 10.4 ± 2.7 | .480 | .617 | 0.46 |
| Speeded naming | | | | | | | | | | |
| Total | 50 (25-50) | 50 (25-50) | .185 | .251 | 0.13 | 25 (25-50) | 50 (25-50) | .171 | .464 | 0.20 |
| Speeded naming time | 75 (75-75) | 75 (75-75) | .174 | .251 | 0.11 | 75 (75-75) | 75 (75-75) | .577 | .688 | 0.09 |
| Word generation | | | | | | | | | | |
| Semantic | 9.8 ± 2.7 | 10.2 ± 2.4 | .475 | .534 | 0.15 | 9.0 ± 2.1 | 10.3 ± 2.9 | .448 | .617 | 0.49 |
| Linguistic | 50 (10-75) | 50 (25-50) | .938 | .938 | 0 | 25 (7.5-62.5) | 62.5 (21.2-75) | .139 | .440 | 0.23 |
| Memory and Learning domain | | | | | | | | | | |
| Memory for faces | 9.8 ± 3.2 | 9.8 ± 2.7 | .977 | .977 | 0 | 9.6 ± 3.3 | 9.9 ± 3.2 | .997 | .997 | 0.09 |
| Delayed | 10.3 ± 2.9 | 11.8 ± 2.7 | .009† | **.029‡** | 0.53 | 9.2 ± 3.4 | 10.8 ± 2.6 | .157 | .617 | 0.54 |
| Memory for names | 9.6 ± 2.9 | 9.3 ± 2 | .540 | .571 | 0.12 | 8.6 ± 2.4 | 10.2 ± 3.0 | .228 | .617 | 0.57 |
| Narrative memory | 10.1 ± 2.3 | 10.8 ± 1.7 | .109 | .140 | 0.34 | 10.4 ± 2.3 | 10.0 ± 2.3 | .237 | .617 | 0.17 |
| Cued recall | 50 (25-75) | 50 (50-75) | .459 | .513 | 0.07 | 50 (25-50) | 62.5 (50-75) | .026‡ | .123 | 0.32 |
| Word list inference | | | | | | | | | | |
| Working memory | 10.4 ± 2 | 11.5 ± 1.9 | .011‡ | **.019‡** | 0.56 | 10.4 ± 2.0 | 10.4 ± 2.0 | .913 | .997 | 0 |
| Word recall | 11.6 ± 2.6 | 11.1 ± 2.4 | .399 | .478 | 0.19 | 11.1 ± 2.5 | 11.9 ± 2.7 | .478 | .617 | 0.30 |
| Sensorimotor domain | | | | | | | | | | |
| Imitating hand positions | 8.9 ± 2.4 | 10.5 ± 1.6 | .000† | **.000†** | 0.78 | 8.8 ± 2.4 | 9.1 ± 2.4 | .988 | .997 | 0.12 |
| Manual motor sequences | 11.6 ± 3 | 13.4 ± 1.9 | .000† | **.003†** | 0.71 | 10.7 ± 3.8 | 12.2 ± 2.4 | .285 | .617 | 0.50 |
| Visuomotor precision | | | | | | | | | | |
| Time | 50 (25-50) | 50 (50-75) | .000† | **.000†** | 0.36 | 50 (25-56.25) | 25 (25-50) | .280 | .556 | 0.15 |
| Error | 25 (10-68.7) | 25 (10-50) | .707 | .746 | 0.03 | 50 (19.25-75) | 25 (10-56.2) | .547 | .688 | 0.08 |
| Social Perception domain | | | | | | | | | | |
| Affect recognition | 25 (5-50) | 50 (25-50) | .030‡ | .057 | 0.22 | 17.5 (4.25-56.25) | 25 (8.75-50) | .580 | .688 | 0.08 |
| Theory of mind | | | | | | | | | | |
| Verbal task | 10.6 ± 2.8 | 12 ± 2.2 | .007† | **.015‡** | 0.55 | 10 ± 2.6 | 10.9 ± 3.0 | .686 | .823 | 0.31 |
| Contextual task | 9.8 ± 2.6 | 11.3 ± 1.9 | .001† | **.003†** | 0.65 | 9.1 ± 2.4 | 10.2 ± 2.6 | .322 | .617 | 0.43 |
| Visuospatial Processing domain | | | | | | | | | | |
| Block construction | 10.4 ± 2.4 | 12.3 ± 2.2 | .000† | **.000†** | 0.82 | 9.3 ± 1.9 | 11.1 ± 2.5 | .069 | .414 | 0.78 |
| Design copying | 10 (5-25) | 10 (10-25) | .012‡ | **.029‡** | 0.25 | 5 (2-13.75) | 10 (7.5-25) | .013‡ | .101 | 0.35 |
| Motor | 9.7 ± 3.1 | 11.9 ± 2.4 | .000† | **.000‡** | 0.79 | 7.9 ± 3.2 | 10.8 ± 2.5 | .004† | .072 | 1.04 |
| Global | 25 (25-50) | 25 (25-50) | .271 | .343 | 0.11 | 25 (10-31.25) | 25 (10-50) | .106 | .402 | 0.23 |
| Local | 8.5 ± 2.2 | 9.5 ± 2 | .024‡ | **.033‡** | 0.47 | 7.5 ± 2.4 | 9.1 ± 1.9 | .028‡ | .252 | 0.76 |
| Geometric puzzles | 50 (25-50) | 50 (25-75) | .344 | .408 | 0.09 | 25 (21.5-50) | 50 (43.7-75) | .009† | .101 | 0.37 |
| Route finding | 25 (10-43.7) | 25 (25-50) | .164 | .251 | 0.14 | 25 (10-25) | 25 (25-50) | .016‡ | .101 | 0.34 |

*NEPSY-II-NL*, Developmental Neuropsychological Assessment, second edition, Dutch version; *WISC-III-NL*, Wechsler Intelligence Scale for Children, third edition, Dutch version.
Between-group differences were explored using AN(C)OVA for standardized scores (mean ± SD) and the Mann-Whitney *U* test for process scores, expressed as percentile (median and IQR).
d: Cohen d effect size, r: Mann-Whitney effect size.
*P* value reached statistical significance after correction for multiple testing is indicated in bold type.
*Adjusted *P* value according to the Benjamini-Hochberg false discovery rate.
†$P < .01$.
‡$P < .05$.

Memory and Learning, and Visuospatial Information Processing domains, suggesting meaningful differences between treatment groups.

Table IV presents CBCL-6/18 data for patients vs controls and for the surgical repair group vs the transcatheter repair group. Compared with healthy peers, parents of patients reported more thought problems and posttraumatic stress disorder (PTSD) symptoms in the DSM-oriented scales. The parents of patients also rated their child's school performance significantly lower than the parents of controls, leading to a higher percentage of patients repeating a grade. No significant differences were found between the surgical repair and transcatheter repair groups. Both comparisons generated relatively small effect sizes.

SES was positively associated with a number of outcomes, including full-scale estimated IQ ($r = 0.536$; n = 48; $P < .000$), inhibition time ($r = 0.377$; n = 48; $P < .01$), comprehension of instructions ($r = 0.353$; n = 48; $P < .05$), repetition of nonsense words ($r = 0.417$; n = 46; $P < .01$), manual motor sequences ($r = 0.303$; n = 48; $P < .05$), theory of mind–verbal ($r = 0.349$; n = 48; $P < .05$), and block construction ($r = 0.378$; n = 48; $P < .01$). This demographic factor also was associated with significant differences on the CBCL-6/18 for PTSD symptoms ($r = -0.279$; n = 48; $P < .05$), need for special education ($r = 0.285$; n = 48; $P < .05$), and repeating a grade ($r = 0.426$; n = 48; $P < .01$).

Correlational analysis identified only 2 medical factors as associated with suboptimal outcome measures in patients compared with controls. Longer length of hospital stay and larger defect size were correlated with lower performance in at least 4 neuropsychologic scores. The former was significantly associated with memory for faces delayed ($r = -0.328$; n = 42; $P < .05$), manual motor sequences ($r = -0.286$; n = 48; $P < .05$), block construction ($r = -0.303$; n = 48; $P < .05$), and the total score of design Copying ($r_s = -0.335$; n = 47; $P < .05$), and its subtasks motor score ($r = -0.400$; n = 47; $P < .01$) and local score ($r = -0.331$; n = 47; $P < .05$). Defect size was negatively correlated with memory for faces delayed ($r = -0.331$; n = 42; $P < .05$), the contextual part of the theory of mind task ($r = -0.381$; n = 48; $P < .01$), design copying total score ($r_s = -0.498$; n = 47; $P < .001$), and its motor score ($r = -0.431$; n = 47; $P < .01$). In the surgical repair group, duration of extracorporeal circulation and level of hypothermia did not demonstrate any relevant associations with neurocognition at follow-up.

## Discussion

Given the diverse nature of the neurocognitive impairments in children with ASD-II, affected children are at risk for learning problems and subsequent academic underachievement.

**Table IV. Behavioral functioning as measured by parental CBCL-6/18 responses**

| Variables | Patients, mean ± SD | Controls, mean ± SD | *P* value | Effect size, *d*/*r* | Surgical repair group, mean ± SD | Transcatheter repair group, mean ± SD | *P* value | Effect size, *d*/*r* |
|---|---|---|---|---|---|---|---|---|
| Problem behavior scales | | | | | | | | |
| Withdrawn/depressed | 54.4 ± 5.7 | 53.6 ± 5.4 | .525 | .06 | 53.9 ± 6.4 | 54.7 ± 5.4 | .469 | .10 |
| Somatic complaints | 55.3 ± 5.7 | 53.9 ± 5.1 | .234 | .12 | 53.7 ± 6 | 56.3 ± 5.3 | .053 | .28 |
| Anxious/depressed | 54.3 ± 5.3 | 53.8 ± 5.4 | .505 | .06 | 54 ± 5.9 | 54.4 ± 5 | .384 | .12 |
| Social problems | 54 ± 4.8 | 52.3 ± 3 | .068 | .18 | 54.1 ± 5 | 54 ± 4.7 | .962 | 0 |
| Thought problems | 56.3 ± 7.4 | 52.6 ± 3.8 | **.020*** | .23 | 53.6 ± 6.4 | 58 ± 7.5 | .083 | .25 |
| Attention problems | 55.6 ± 7.6 | 52.4 ± 2.6 | .078 | .18 | 56.5 ± 9.2 | 55 ± 6.6 | .526 | .09 |
| Rule-breaking behavior | 52.7 ± 3.7 | 52 ± 3.7 | .519 | .06 | 52 ± 2.9 | 53.1 ± 4.1 | .311 | .14 |
| Aggressive behavior | 53.6 ± 5.1 | 52.1 ± 3.9 | .125 | .15 | 53.1 ± 5.9 | 53.8 ± 4.6 | .497 | .10 |
| Internalizing | 51.5 ± 9 | 49.5 ± 8.7 | .291 | .22 | 49.5 ± 9.8 | 52.6 ± 8.4 | .191 | .33 |
| Externalizing | 47.5 ± 10.1 | 45.9 ± 8.4 | .413 | .17 | 46.1 ± 10.3 | 48.3 ± 10.1 | .272 | .21 |
| Total problem score | 50 ± 10.1 | 46.6 ± 7.7 | .067 | .37 | 48.8 ± 10 | 50.7 ± 10.3 | .222 | .18 |
| DSM clinical scales | | | | | | | | |
| Affective problems | 55.2 ± 5.8 | 53.8 ± 5.1 | .209 | .12 | 54 ± 5 | 56 ± 6.2 | .251 | .16 |
| Anxiety problems | 55.8 ± 6.4 | 53.7 ± 5 | .087 | .17 | 53.8 ± 5.4 | 57 ± 6.7 | .130 | .22 |
| Somatic problems | 55.2 ± 6.3 | 54.4 ± 5.8 | .466 | .07 | 53.8 ± 7.3 | 56.1 ± 5.6 | .074 | .25 |
| Attention/hyperactivity problems | 54.5 ± 6.1 | 52.4 ± 3.7 | .137 | .15 | 54.5 ± 6.1 | 54.4 ± 6.1 | .918 | .01 |
| Oppositional defiant problems | 53.5 ± 4.9 | 52.1 ± 3.2 | .445 | .07 | 52.9 ± 4.5 | 53.9 ± 5.2 | .567 | .08 |
| Conduct problems | 52.7 ± 4.5 | 52 ± 4 | .694 | .04 | 52.4 ± 5 | 52.9 ± 4.3 | .378 | .12 |
| Sluggish cognitive tempo | 54.8 ± 4.5 | 52.5 ± 3.2 | .224 | .12 | 54.8 ± 7.1 | 54.8 ± 6.3 | .838 | .03 |
| Obsessive/compulsive problems | 55.8 ± 7.6 | 53.5 ± 5.1 | .366 | .09 | 56.1 ± 8.2 | 55.6 ± 7.4 | .858 | .02 |
| Posttraumatic stress problems | 56.4 ± 6.5 | 53 ± 4.6 | **.019*** | .23 | 55.5 ± 7 | 56.9 ± 6.2 | .385 | .12 |
| Competence scales | | | | | | | | |
| Activity | 40.8 ± 8.8 | 38.9 ± 8.6 | .280 | .11 | 37.9 ± 7.2 | 42.6 ± 9.2 | .114 | .22 |
| Social | 50 ± 7.9 | 49.9 ± 6.7 | .681 | .04 | 48.7 ± 6.6 | 50.8 ± 8.7 | .220 | .17 |
| School | 46.8 ± 9.2 | 50.8 ± 5.3 | .057 | .19 | 45.2 ± 10.7 | 47.7 ± 8.4 | .473 | .10 |
| Special education, % | Yes: 4.2; no: 95.8 | Yes: 0; no: 100 | $.495^{E}$ | | Yes: 5.6; no: 94.4 | Yes: 3.3; no: 96.7 | $1.0^{E}$ | |
| Repeating a school year, % | Yes: 16.7; no: 83.3 | Yes: 0; no: 100 | $\mathbf{.006}^{E,\dagger}$ | | Yes: 22.2; no: 77.8 | Yes: 13.3; no: 86.7 | $.692^{E}$ | |
| School problems, % | Yes: 31.3; no: 68.8 | Yes: 8.3; no: 91.7 | $\mathbf{.005}^{\chi^2,\dagger}$ | | Yes: 33.3; no: 66.7 | Yes: 30; no: 70 | $.809^{\chi^2}$ | |
| Total competence | 44.8 ± 9.4 | 44.2 ± 9.3 | .747 | .06 | 42.5 ± 8.4 | 46.1 ± 9.8 | .452 | .39 |

Subscales: Mann-Whitney *U* test (with exact option); composite scales: AN(C)OVA. $\chi^2$ test (Fisher exact test $^{E}$).
*P* value reached statistical significance after correction for multiple testing is indicated in bold type.
*$P < .05$.
†$P < .01$.

Although patients with more complex cyanotic cardiopathologies often deal with unstable hemodynamics and metabolic acidosis and require advanced surgical repair, studies frequently report similar adverse neurodevelopmental outcomes in acyanotic cohorts.[4,22] Attentional shortcomings, working memory problems, language deficits, adverse socialization behavior, and especially impaired motor functioning and weak visuospatial skills have been identified in the exploration of cognitive sequelae after (acyanotic) CHD repair.[2,3,7,9,23] Larger defect size and longer hospital stay were associated with poor neuropsychological outcome measures, particularly in the visuomotor and visuospatial domain. The former may reflect the progressive nature of the left-to-right shunt on the central nervous system, extending until cardiac repair. The latter factor has been associated with lower functional and developmental outcomes in other CHD cohorts.[8,24] It should be noted that normal hospital stay for children treated surgically for an ASD-II is 4-5 days. It is possible that the children in our cohort had to cope with more postoperative problems, prolonging their hospital stay.

Even though transcatheter closure of ASD-II is favored over surgical closure because of the shorter hospital stay and lower postprocedural complication rates,[25] we found almost no differences in neuropsychologic outcomes related to treatment method.

Studies exploring the possible detrimental effects of surgical closure of ASD-II on neurodevelopment have yet to provide complete answers. Visconti et al[3] showed that, after adjusting for parental IQ, surgical closure of ASD-II was associated with a 9.5-point deficit in full-scale IQ and visuospatial problems, whereas a group that underwent transcatheter repair had more attentional problems and impulsivity. Our surgical repair group's performance on visuospatial information processing tasks is comparable with those findings, although we found no significant difference in attention scores between our 2 treatment groups. Stavinoha et al[26] evaluated the neuropsychological outcomes of 18 children undergoing surgical repair of ASD. They compared preoperative and postoperative cognitive outcomes, but failed to demonstrate a clear effect of the duration of cardipulmonary bypass on neuropsychologic status within 6 months after corrective surgical repair. Outcome scores were within normal ranges but clearly below expected norms for all cognitive functions evaluated.

Quatermain et al[27] prospectively assessed neuropsychologic domains in children with acyanotic CHD before and after surgical repair. Outcome scores were within normal ranges, although individual variability in scores was common. The authors concluded that a mild cognitive decline seen after intervention for acyanotic CHD is not necessarily attributable to the use of cardiopulmonary bypass. The population in this study underwent corrective repair at older ages and thus possibly had less urgent conditions compared with our cohort. It is possible that the subtle cognitive effects of corrective repair at a young age may become apparent many years after medical interventions for acyanotic CHD.

The correlations between SES and numerous cognitive outcomes in our patient cohort is in line with those reported in previous studies,[4,5,13] indicating that the environment in which these children are raised can serve as a protective factor against adverse neuropsychologic development.

Compared with parents of healthy controls, parents of patients reported more thought problems and higher scores on the PTSD DSM scale. The thought problems scale encompasses such items as compulsions and obsessions, as well as fears and psychotic behavior. The DSM-derived PTSD scale reflects symptomatology that adheres to the clinical classification of PTSD in individuals with acyanotic CHD. These findings apparently agree with those of previous studies in children with CHD,[3-5] confirming the prevalence of internalizing behavior problems. Internalizing behavior problems can lead to increased risk for depression, anxiety, and social withdrawal. Behavioral problems can put additional strain in the lives of children treated for ASD-II that may persist and affect peer relationships and ultimately the quality of adult life.[28]

Hospitalization can be a great stressor for both children[12] and their parents.[29] Parental style and family dynamics are nonnegligible factors in long-term cognitive and social development. High levels of stress in the parent–child relationship have been found to affect cognitive skills and socialization behavior in children,[5] in line with our present findings. Whether these results reflect actual PTSD problems in the child rather than parent-induced stress and anxiety after diagnosis, intervention, and hospitalization is unclear. In our patient cohort, lower SES was correlated with high rates of the need for special education, repeating a grade, and PTSD symptoms. These families' coping strategies may be less well developed, also affecting the child's neurobehavioral development. Consequently, parents may be less inclined to notice cognitive or behavioral difficulties in their children and to seek professional help. Schreier et al[29] described the interaction of family dynamics after pediatric hospitalization, with parents displaying PTSD symptoms correlating with child-reported symptoms. Family expressiveness was identified as an efficient coping strategy.[29]

A large body of literature addresses the neuropsychological outcomes of children with CHD at a very young age, when myelination of neurologic structures is incomplete and higher neurocognitive functions have yet to mature. The subtle effects of hospitalization-, anesthesia-, and procedure-related factors may become apparent only many years after surgery and are difficult to detect and quantify during early childhood. In addition, the idea that induction of anesthesia at a young age to improve the tolerance of surgical procedures is detrimental to neurodevelopment is under consideration. Information on the neurotoxicity of anesthetic agents and their influence on the young brain is accumulating. Neurologic structures mature at different rates, and it can be assumed that the vulnerable period of the young brain extends well past

the first 2 years of life.[30] This may eventually affect the plasticity of the developing brain and contribute to adverse long-term cognitive outcomes in children with CHD.

The growing into deficit hypothesis[31] can serve to clarify the chain of events. Children at risk for central nervous system injury due to a medical condition can function adequately at young school age but are hindered when academic demands begin to tap cognitive functions that were neurologically susceptible to injury and thus suboptimal from the start. This also implies that assessment of neurocognitive functions in very young children may have limited predictive value for later cognitive performance and academic achievement. The effects of the heart lesion, hospitalization, and interventional procedures on the developing brain all likely contribute to the course of events producing adverse neurodevelopmental outcomes at school age.

Limitations of the present study include possible selection bias and the lack of preoperative screening. We cannot ascertain whether the children in the patients group had neurocognitive difficulties before treatment, recognizing that the reliability and validity of assessment increase with age. Before age 6 years, it is particularly difficult to accurately evaluate a child's cognitive abilities. In addition, obtaining a uniform perspective on the neuropsychologic profiles of children with CHD has proven difficult. Numerous studies focus on different diagnoses and specific interventions, study divergent age ranges, and use various screening instruments that may measure different aspects of neurocognitive domains. This limits the comparability and generalizability of results and is the main factor in the conflicting findings obtained from this type of research. Marino et al[32] published formal guidelines for screening children with CHD at risk for developmental disorders, taking protective factors, such as family and environment, into account. In this way, consistency in developmental follow-up across time can be improved. Moreover, it remains a challenge to find a suitable control group for children with CHD that is comparable in the most important aspects related to this condition, from the psychological and physical distress of hospitalization and surgery to central nervous system risk factors that put these children at risk for hypoperfusion of vital organs, including the developing brain. Our use of 2 clinical groups in this study partially addresses this issue, given that these children were diagnosed with the same cardiac pathology but underwent different treatments depending on defect size and location. Despite the small sample size and restricted generalizability owing to the study's retrospective nature, our results are in line with previous findings in this clinical group.

It is important to enhance knowledge and awareness among clinicians concerning long-term neurocognitive consequences following a diagnosis of CHD, and also to consider parental reports of the child's neurobehavioral functioning in school during the follow-up visits after intervention. Appropriate referral to a neuropsychologist and guidance for parents then can be realized when applicable. Future research should address the differential influence of patient-specific and medical factors that put these children at risk and include pretreatment neurologic examinations. ■

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## 50 Years Ago in *THE JOURNAL OF PEDIATRICS*

### A Nasal Mask for Premature Infants

Buck JB, McCormack WC. J Pediatr 1965;66:123-125

The 1970s were challenging but exciting times for the relatively new specialty of neonatology, and for those of us trying to figure out how to do a better job of caring for preterm babies with immature lungs. Effective surfactant therapy was still more than a decade away, the infant ventilators that were available left much to be desired, there were no pulse oximeters, and arterial blood gas analysis required large volumes of blood, usually from an umbilical arterial catheter. But then came the most exciting report of the decade, from Gregory et al, presented at the Society of Pediatric Research meetings in 1970, describing the technique of continuous positive airway pressure. The follow-up publication in New England Journal of Medicine[1] was a landmark paper and has resulted in saving thousands of infant lives. But the technique described required establishing an interface with the baby's airway, either by an endotracheal tube or by placing the baby in a negative pressure chamber below the head and sealed at the neck with an iris diaphragm—both of which were associated with significant morbidity.[2]

Several of us developed a variety of devices to deliver Gregory's system for generating continuous positive airway pressure, but by the nasal route, thus taking advantage of the obligate airway of the infant, and the "safety pop-off" of the unrestricted mouth. Our device[3] was modeled after a nosepiece developed by Agostino et al,[4] but those developed by others involved a single nasopharyngeal tube, nasal oxygen prongs, or a nasal mask. We apparently missed the publication by Buck and McCormack from nearly 10 years previous in *The Journal*—clearly an invention before its time. Now, if they had just added some continuous positive pressure…

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**Table I.** Selected NEPSY-II-NL tasks[23]

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

*NEPSY-II-NL*, Developmental Neuropsychological Assessment, second edition, Dutch version.