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Early working memory is a significant predictor of verbal and processing skills at 6–7 years in children born extremely preterm

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Abstract

Objective: The study was designed to investigate whether attainment of object permanence, a measure of early working memory used at 18–22 months corrected age, was associated with executive function at 6–7 years in a cohort of children born extremely preterm.

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JL, KW, JF, RDH, and SRH were involved with the conception and design of the study. CMB, AD, and RDH analyzed the data. JL and CMB drafted initial versions of the manuscript, which were revised critically for important intellectual content by the other authors JF, BRV, AD, SRH, KW, and RDH. JL, JF, BRV, SRH, KW, and RDH performed the primary investigation. RDH and AD provided supervision and oversight. All authors approved the final version of the manuscript.

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Study Design: Children enrolled in the Neuroimaging and Neurodevelopmental Outcome (NEURO) study, a secondary study to the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) of the NICHD NRN, were eligible for this longitudinal study. Testing completed at 18 to 22 months corrected age was compared to testing at school age with a specific focus on measures of executive function.

Results: Children who had achieved object permanence mastery at a corrected age of 18–22 months had higher mean scores on the WISC-IV tests of verbal comprehension and processing speed at age 6–7 years. Regression models indicated that object permanence scores were significant predictors of both verbal comprehension and processing speeds scores, after controlling for other factors. When analyzed by subgroup for sex, these results were significant for girls but not for boys.

Conclusions: This study found that an early mastery of object permanence was associated with higher scores in areas of verbal comprehension and processing speed in girls. These results have implications for potentially identifying young children born preterm that are at greater risk for difficulties with cognitive and working memory skills at school age.

Keywords

extremely low birth weight; development; executive function

1. INTRODUCTION

Children born preterm frequently have executive function difficulties, which have been linked to cognitive, academic, and behavioral problems [1]. Executive function is a term that encompasses three main areas of processing skills: working memory, inhibition, and cognitive flexibility [2]. Problems of executive function persist through school age in children born preterm, often resulting in poor academic performance [3]. Tests of cognitive skills have been used most frequently to identify early learning problems that result in later behavior, learning, and executive function difficulties [4].

In an earlier study of executive function in young children born preterm, Woodward et al. [5] found that 2 year-old children born preterm had difficulty encoding new information in working memory compared to term-born infants. On MRI these children had bilateral reduction in cerebral tissue volume in areas specifically related to working memory (dorsolateral prefrontal cortex, parieto-occipital, and premotor areas). In another study using a test of object permanence as a measure of early working memory, preterm children who received erythropoiesis-stimulating agents had higher object permanence scores and higher scores on the Bayley III cognitive scale [6].

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) previously reported that at 18–22 months adjusted age, scores on the Bayley-III cognitive and language scales correlated positively with a measure of object permanence [7]. The present study was designed to investigate whether the measure of object permanence used at 18–22 months in that study was associated with executive function at 6–7 years in these children [8].

Measures of fluid cognition ability at school age allow us to better identify children with difficulty in domains of executive function and related abilities, such as working memory, inhibition, perceptual reasoning, or processing skills [9]. We hypothesized that early object permanence mastery score at 18–22 months would correlate with higher scores of executive function at age 6–7 years in this group of children born extremely preterm. As girls did better on tests of object permanence at 18–22 months adjusted age, we hypothesized that they would continue to do better on tests of executive function at school age. We further hypothesized that adverse findings on cranial ultrasound and significant lesions on MRI would correlate with lower scores on early tests of object permanence and lower scores on tests of cognition and executive function at school age.

2. METHODS

2.1. Study Population

The study cohort was originally enrolled at birth in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) of the NICHD NRN and were eligible if they had also been enrolled in its secondary study, the Neuroimaging and Neurodevelopmental Outcome (NEURO) [8]. The SUPPORT study was a randomized multicenter trial of ventilation and oxygenation management strategies, and enrolled infants at 24–27 6/7 weeks gestation [10]. Children were eligible for the present study if they had been tested between June 2005 and February 2009 in one of the 15 participating centers of the NRN, had object permanence scores at 18 to 22 months adjusted age, and had completed testing at 6 to 7 years. Figure 1 provides a study selection flow chart of the children in the current study. Parent report was used to obtain information on ethnicity/race and maternal education level.

2.2. Test Measures

The object permanence measure consisted of 3 items from the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [11] Cognitive Scale. These object permanence items sequentially increase in difficulty and are scored as pass or fail. First, the child is asked to find a toy hidden under one of two washcloths (Finds Hidden Object), then the cloths are reversed after the toy is hidden (Finds Hidden Object – Reversed), and finally the toy is hidden under one cloth, removed and hidden a second time under the second cloth (Finds Hidden Object – Visual Displacement). Object permanency score ranged from 0 to 3 and object permanence mastery (categorical) was scored when the child had correctly answered two or 3 items.

Testing at 6 to7 years included the Wechsler Intelligence Scale for Children – 4th edition (WISC-IV) [12], which was administered individually. Examiners were certified to ensure consistency of administration for all centers. The composite scores used in the analysis included verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index. The standard score had a mean of 100 and standard deviation of 15. Full scale IQ is the summation of the above scales and was therefore not used in the analyses.

Selected subtests of the Developmental NEuroPSYchological Assessment −2nd edition (NEPSY-II) [13], were used as measures of executive function and other domains of fluid intelligence. The Memory for Names scale included an immediate recall and 30-minute delayed recall scale. The Inhibition scale combined scores for speed and accuracy of responses into a total score, which was converted into a standardized scaled score for analyses. Standardized scaled scores were calculated with a mean of 10 and standard deviation of 3.

2.3. Cranial ultrasound and MRI

A conventional, qualitative brain MRI was obtained at 35–42 weeks postmenstrual age, and a cranial ultrasound within 2 weeks of the MRI. Central reader interpretations were used for study analyses, and a masked central reader reviewed all brain MRIs utilizing white matter abnormality scoring according to a widely used classification system [14]. Inter-rater agreement for moderate or severe white matter abnormalities was reported to be 96% to 98%, using this classification system [14]. Adverse findings on brain MRI were defined as significant cerebellar lesions (defined as lesions that were bilateral, cystic, and/or ≥4 mm in size) or moderate or severe white matter abnormalities.

2.4. Statistical Methods

First, we computed bivariate analyses to examine the relationship between object permanence at 18–22 months adjusted age and cognitive outcomes at 6–7 years of age. T-tests were conducted to compare mean scores on the WISC-IV and NEPSY-II subscales based on object permanence mastery. Then we fit linear mixed effect regression models of the WISC-IV and NEPSY-II subscales by object permanence mastery, including center as a random effect and controlling for the following background variables: moderate/severe white matter abnormality on MRI, significant cerebellar lesions on MRI, late cranial ultrasound (CUS) adverse finding, early CUS adverse finding, gestational age, sex, severe retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), age at assessment, maternal education, and race/ethnicity. We then tested for a sex by object permanence mastery interaction within the regression models to determine whether the relationship between object permanence and executive functioning differs between boys and girls.

We also examined the relationship between neonatal neuroimaging findings and object permanence at 18–22 months corrected age. We fit mixed effect regression models predicting object permanence by each type of neuroimaging finding, including center as a random effect and controlling for variables collected during the newborn period (i.e., gestational age, sex, severe ROP, BPD, maternal education, and race/ethnicity). A linear model was used for object permanence scores and a generalized linear model for object permanence mastery.

3. RESULTS

Among our sample, birth weights ranged from 370 to 1410 grams with a mean of 844 grams. The mean gestational age was 26 weeks with a range of 24 to 27 weeks. A total of 247 (64%) of the 383 children exhibited object permanence mastery at 18–22 months corrected age. Significantly more girls (124/175 = 71%) than boys (123/208 = 59%) had object permanence mastery ($\chi^2(1) = 5.70$, p = 0.017). Table 1 displays demographic characteristics and scale scores.

Bivariate comparisons of the executive functioning scales by object permanence mastery are shown in Table 2. Children with object permanence mastery exhibited significantly greater mean WISC-IV verbal comprehension scores than those with no mastery (89.1 vs. 84.6, p = 0.006). Similarly, those with object permanence mastery had significantly higher mean WISC-IV processing speed scores (90.4 vs. 86.8, p = 0.032). No significant differences were found for the WISC-IV perceptual reasoning or working memory indices or for any of the NEPSY-II measures. These findings remained when controlling for other factors using regression models. Children with object permanence mastery continued to have significantly higher adjusted mean scores for the verbal comprehension (p = 0.039) and processing speed (p = 0.034) indices than those without mastery (Table 2). Using Cohen's d (i.e., standardized mean difference) as a measure of effect size, the size of the difference in mean scores between those with vs. without object permanence mastery was a d value of −0.24 which is equivalent to 0.24 SDs lower for verbal comprehension and a d value of −0.30 equivalent to 0.30 SDs lower for processing speed.

A sex by object permanence interaction was then tested for each model to determine whether the relationship between object permanence and executive functioning differs for boys vs. girls. This interaction was statistically significant for the WISC-IV working memory ($F(1,318) = 9.06$, p = 0.003) and processing speed ($F(1,313) = 7.92$, p = 0.005) indices. Figure 2 shows the differences in mean scores on NEPSY-II and WISC-IV for children with vs. without object permanence mastery, after controlling for other factors. Higher values indicate that those with mastery scored higher on the assessments than those without mastery. As shown in the figure, girls with object permanence mastery had significantly higher working memory scores (p = 0.009) and higher processing speed (p < 0.001) than girls without object permanence mastery; however, these differences were not observed among boys (p = 0.159; p = 0.924). While the sex by object permanence mastery interaction was not statistically significant for verbal comprehension ($F(1,318) = 2.83$, p = 0.094), a similar pattern was evident in examining the sex differences in the associations of object permanence mastery with other cognitive outcomes. Object permanence mastery was significantly associated with higher scores among girls (p = 0.010), but not boys (p = 0.587). Among boys, the effect sizes for the differences in scores on these two scales between those with vs. without object permanence mastery were: verbal comprehension (d=0.13) and processing speed (d=0.07). Data were substantially more robust for girls with effect sizes for those with and without object permanence mastery of (d=0.49) for verbal comprehension and (d=0.63) for processing speed, respectively. No significant sex by object permanence mastery interactions were found for the NEPSY-II scales.

There was no significant relationship between object permanence scores and either early or late CUS findings (Table 3). In contrast, on univariate analysis, lower object permanence scores were significantly associated with cerebellar lesions, (p = 0.016) and moderate/severe white matter abnormality on MRI scans (p = 0.048) (Table 3). When controlling for other neonatal factors, only the association with cerebellar lesions remained significant (p = 0.029).

4. DISCUSSION

In this study, we found that girls who had achieved object permanence mastery at a corrected age of 18–22 months had higher mean scores on the WISC-IV tests of verbal comprehension and processing speed at age 6, after controlling for other factors. In our previous study at 18–22 months, we found that boys had significantly lower object permanence scores and Bayley-III language scale scores than girls [7].

Although we had hypothesized that the object permanence scores also would be associated with tests of executive function, we found no relationship of object permanence score with NEPSY-II scores. Few studies have looked at measures of early executive function, although several studies have assessed the relationship of early tests of overall cognitive function with later behavioral and executive function outcomes. Gould and associates [4] found that in a cohort of Australian children born preterm and tested at 18–22 months, lower Bayley-II mental developmental index scores were associated with difficulties in measures of behavior and executive function at 7 years. In another longitudinal study, a group of Swedish children born preterm were assessed at 10 months, 5 ½ years, and 18 years. Those authors also found Bayley-II mental developmental index scores, together with parental education level, were related to scores of cognitive flexibility and working memory at 5 ½ years. Further findings in this study indicated that working memory scores at 5 ½ years were related to working memory scores at 18 years [15]. Many studies continue to confirm that behavior problems and difficulty with executive function are greater in preterm children compared to those born full term [9], and that these problems persist overtime [16].

Studies of preterm children have consistently shown that boys do less well on developmental tests at young ages [17]. Although some studies have indicated that they catch up at later school age [18], others have found that boys born preterm continue to have more problems in areas of cognition, behavior, and neurologic status when tested at 10 years of age [19].

After adjusting for other variables, white matter injury on MRI scans in the newborn period was not significantly associated with object permanence scores at 18 – 22 months; however, cerebellar lesions remained significantly associated with lower object permanence scores at age 18 – 22 months. In the same cohort of children, Hintz et al. found that significant cerebellar lesions were also associated with severe disability at school age [8]. Others have reported that cerebral white matter abnormalities on newborn MRI scan were related to lower scores on tests of cognition and working memory in 4 and 6 year olds born preterm [20]. In a group of preterm-born 7 year-old children, cerebral white matter and deep gray matter injury on neonatal MRI scan were associated with lower cognitive scores, while cerebellar injury was associated with math and motor function problems [21].

Our study did not find an association between either early or late CUS and object permanence scores. It is important to note that very few children had significant early or late CUS abnormalities (9% and 6% respectively), defined as grade III or IV intracranial hemorrhage or cystic periventricular leukomalacia. Ongoing controversy exists regarding the value of either MRI or CUS in the newborn period in identifying later disability, due to the variable positive predictive value of these tests [22].

Identifying early markers of future learning difficulty would be beneficial, allowing early intervention services to target the most vulnerable children. The lack of inclusion of measures other than cognition or intelligence has been noted as a weakness in many studies of both preterm and term children [23]. Though measures of early executive function are limited [24], more test measures are being used that can assess these constructs in young children [25]. Including a measure such as object permanence in a test battery could potentially assist in both research and early intervention as a means of identifying young children at greater risk for later learning problems. More intervention programs are being developed to target methods of enhancing cognitive skills that may best benefit preterm children [21,26].

This study has both limitations and strengths. Testing of young children is difficult and only represents their behaviors at one point in time. In addition, tests can be racially and ethnically biased, although we did include both ethnicity and maternal education as factors in our statistical analyses. Strengths of this research included that our sample size was robust, we used a longitudinal design, and all examiners were certified in the test measures.

5. CONCLUSION

In conclusion, our study found that early attainment of object permanence was associated with higher scores at school age in areas of cognition in girls, but not boys. These results have implications for potentially identifying young children born preterm who are at greater risk for difficulties with cognitive and working memory skills at school age. In comparison to more cumbersome and expensive tools, such as MRI or CUS, a simple test of object permanence could possibly help identify children as young as 18 months who may have greater risk for learning difficulties.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, RTI International had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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REFERENCES

1. van Houdt CA, van Wassenaer-Leemhuis AG, Oosterlaan J, van Kaam AH, Aarnoudse-Moens A. Developmental outcomes of very preterm children with high parental education level. Early Hum Dev 2019;133:11–7. [PubMed: 31035105]
2. Kraybill JH, Kim-Spoon J, Bell MA. Infant attention and age 3 executive function. Yale J Biol Med 2019;92(1):3–11. [PubMed: 30923468]
3. Costa DS, Miranda DM, Burnett AC, Doyle LW, Cheong JL, Anderson PJ. Executive function and academic outcomes in children who were extremely preterm. Pediatrics 2017;140(3):1–10.
4. Gould JF, Hunt E, Roberts RM, Louise J, Collins CT, Makrides M. Can the Bayley Scales of Infant Development at 18 months predict child behavior at 7 years? J Paediatr Child Health 2019;55:74–81. [PubMed: 30101998]
5. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355(7):685–94. [PubMed: 16914704]
6. Ohls RK, Kamath-Rayne BD, Christensen RD, Wiedmeier SE, Rosenberg A, Fuller J, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. Pediatrics 2014;133:1023–30. [PubMed: 24819566]

7. Lowe JR, Duncan AF, Bann CM, Fuller J, Hintz SR, Das A, et al. Early Hum Dev 2013; 89:1055–61. [PubMed: 23993309]

8. Hintz SR, Vohr BR, Bann CM, Taylor G, Das A, Gustafson KE, et al. Preterm neuroimaging and school age cognitive outcomes. Pediatrics 2019;142:1–13.

9. Loe IM, Heller NA, Chatav M. Behavior problems and executive function impairment in preterm compared to full term preschoolers. Early Hum Dev 2019;130:87–95. [PubMed: 30708271]

10. Carlo WA, Finer NN, Walsh MC, et al. Target oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959–69. [PubMed: 20472937]

11. Bayley N Bayley scales of infant and toddler development. 3rd edition (Bayley-III). San Antonio (TX): Harcourt Assessment 2006.

12. Wechsler D, Kaplan E, Fein D, Kramer J, Morris R, Delis D, et al. Wechsler Intelligence Scale for Children: Fourth Edition (WISC-IV). San Antonio, TX: Pearson 2003.

13. Korkman M, Kirk U, Kemp S. NEPSY-II. Developmental NEuroPSYchological Assessment - 2nd edition. San Antonio (TX): Pearson Assessments 2007.

14. Horsch S, Skiold B, Hallberg B, Nordell B, Nordell A, Mosskin M, et al. Cranial ultrasound and MRI at term age in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed 2010;95:F310–4. [PubMed: 19843500]

15. Stalnacke J, Lundequist A, Bohm B, Forssberg H, Smedler AC. A longitudinal model of executive function development from birth through adolescence in children born very or extremely preterm. Child Neuropsy 2019;25:318–35.

16. Everts R, Schone CG, Murner-Lavanchy I, Steinlin M. Development of executive functions from childhood to adolescence in very preterm-born individuals – A longitudinal study. Early Hum Dev 2019;129:145–51.

17. Mansson J, Fellman V, Stjernqvist K. Extremely preterm birth affects boys more and socio-economic and neonatal variables pose sex-specific risks. Acta Paediatr 2015;104:514–21. [PubMed: 25620552]

18. Linsell L, Malouf R, Morris J, Kurinczuk J, Marlow N. Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight – A systematic review. JAMA Pediatr 2015;169(12):1162–72. [PubMed: 26457641]

19. Kuban KC, Joseph RM, O'Shea TM, Allred EN, Heeren T, Douglass L, et al. Girls and boys born before 28 weeks gestation: risks of cognitive, behavioral, and neurologic outcomes at age 10 years. J Pediatr 2016;173:69–75. [PubMed: 27004675]

20. Woodward LJ, Clark CA, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. PLoS One 2012;7(12):e51879. [PubMed: 23284800]

21. Anderson PJ, Lee KJ, Roberts G, Spencer-Smith MM, Thompson DK, Seal ML, et al. Long-term academic functioning following Cogmed working memory training for children born extremely preterm: a randomized controlled trial. J Pediatr 2018;202:e94.

22. Nongena P, Ederies A, Azzopardi DV, Edwards AD. Confidence in prediction of neurodevelopmental outcome by cranial ultrasound and MRI in preterm infants. Arch Dis Child Fetal Neonatal Ed 2010;95(6):F388–390. [PubMed: 20870903]

23. Aylward G Neurodevelopmental outcomes of infants born prematurely. J of Dev Behav Pediatr 2005;26:427–550. [PubMed: 16344661]

24. Kilbride HW, Aylward GP, Carter B. What are we measuring as outcome? Looking beyond neurodevelopmental impairment. Clin Perinatol 2018;45:467–84. [PubMed: 30144850]

25. Carlson SM, Koenig MA, Harms MB. Theory of mind. WIREs Cogn Sci 2013;4:391–402.

26. Diamond S Executive functions. Annu Rev Psychol 2013;64:135–168. [PubMed: 23020641]

Highlights

- Object permanence at 18 months was associated with testing of preterm 7-year olds
- Object permanence score was associated with cerebellar lesions on MRI at birth
- Object permanence score was associated with WISC-IV verbal comprehension score
- Object permanence was associated with working memory scores in girls born preterm

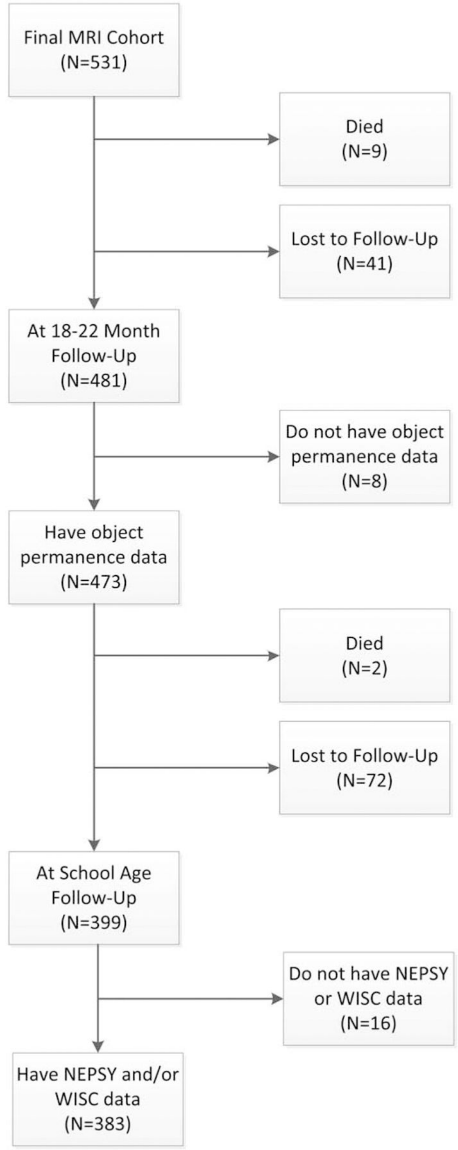

Figure 1.
Sample Selection Flowchart

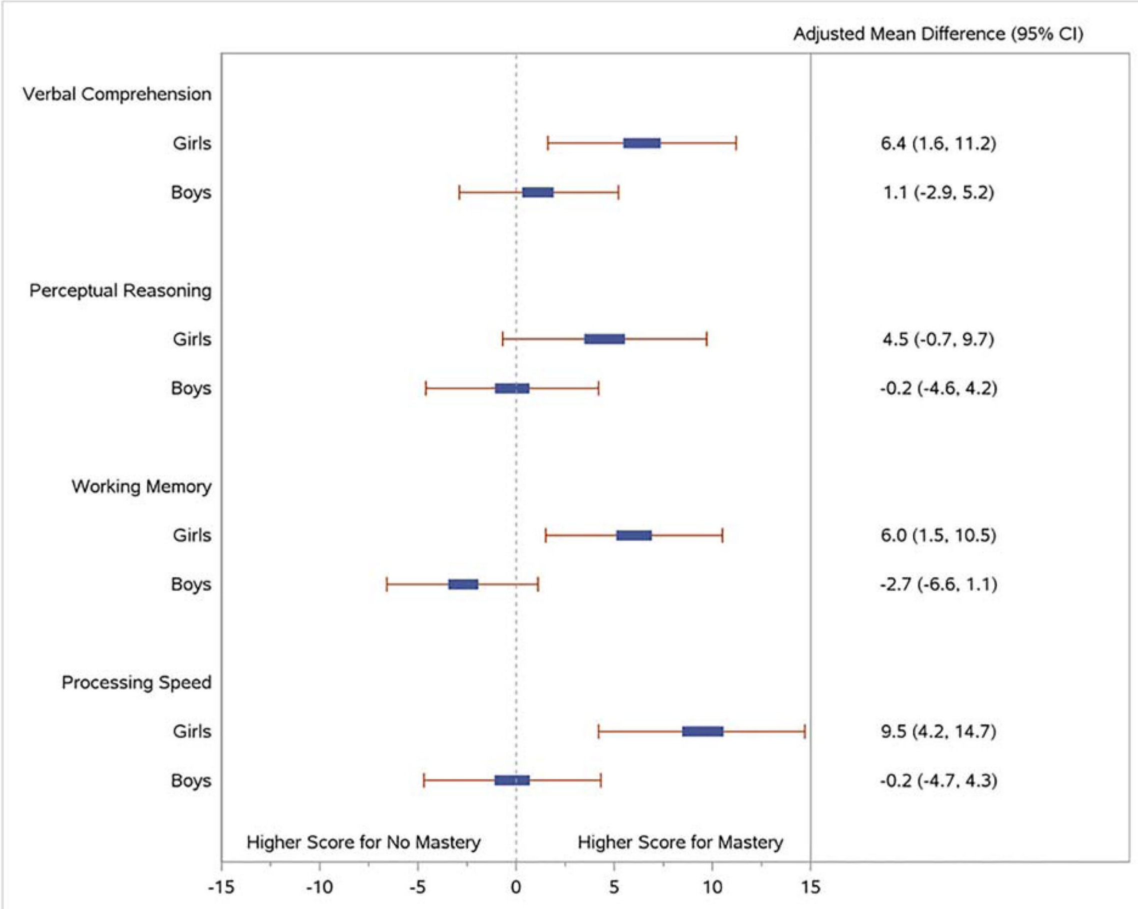

Figure 2.
Adjusted Mean Differences of WISC-IV and NEPSY-II Scores for Object Permanence Mastery vs. No Object Permanence Mastery by Sex
Note: Adjusted mean differences control for object permanence mastery, sex, object permanence mastery x sex interaction, center, moderate/severe white matter abnormality on MRI, significant cerebellar lesions on MRI, late cranial ultrasound adverse finding, gestational age, severe ROP, BPD, age at assessment, maternal education, and white race.

Table 1.

Demographic and Medical Characteristics and Scale Scores (N=383)

Characteristic	All (N=383)	Boys (N=208)	Girls (N=175)	Boys vs. Girls
	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	p-value
Birth weight	863.7 ± 191.8	887.6 ± 196.1	835.4 ± 182.9	0.008
Gestational age	25.9 ± 1.0	25.9 ± 1.0	26.0 ± 1.0	0.269
Multiple gestation	87 (23)	50 (24)	37 (21)	0.501
Antenatal steroids	365 (95)	198 (95)	167 (95)	0.913
Late sepsis	119 (31)	65 (31)	54 (31)	0.934
NEC				
No NEC	352 (93)	191 (92)	161 (92)	0.242
Medical NEC	17 (4)	7 (3)	10 (6)	
Surgical NEC	14 (4)	10 (5)	4 (2)	
Severe ROP *	37 (10)	18 (9)	19 (12)	0.477
Surgery for PDA, NEC or ROP *	65 (18)	32 (17)	33 (20)	0.400
Postnatal steroids	26 (7)	17 (8)	9 (5)	0.247
BPD	139 (36)	87 (42)	52 (30)	0.014
Maternal Education				
Less than high school	96 (25)	51 (25)	45 (26)	0.706
High school graduate	108 (29)	56 (27)	52 (30)	
Some college or more	173 (46)	98 (48)	75 (44)	
Maternal race/ethnicity				
Black	122 (32)	62 (30)	60 (34)	0.754
White	161 (42)	92 (44)	69 (39)	
Hispanic	90 (24)	49 (24)	41 (23)	
Other/unknown	10 (3)	5 (2)	5 (3)	
Neonatal neuroimaging				
Early CUS adverse finding (Grade III/IV ICH or cPVL)	34 (9)	19 (9)	15 (9)	0.847
Late CUS adverse finding (Moderate/severe VE, cPVL, Porencephalic cyst, shunt)	22 (6)	13 (6)	9 (5)	0.643
Moderate/severe white matter abnormality on MRI	72 (19)	44 (21)	28 (16)	0.198
Any cerebellar lesion on MRI	53 (14)	34 (16)	19 (11)	0.121
Significant cerebellar lesion on MRI	36 (9)	22 (11)	14 (8)	0.389
Adjusted age at 18–22 month assessment (months)	19.7 ± 2.1	19.9 ± 2.3	19.5 ± 1.8	0.101
Object Permanence at 18 – 22 months				
Score	1.9 ± 1.1	1.8 ± 1.1	2.0 ± 1.1	0.035
Mastery (number (%))	247 (64)	123 (59)	124 (71)	0.017
Age at school age follow-up (years)	6.3 ± 0.5	6.3 ± 0.5	6.3 ± 0.5	0.881
WISC-IV				
Verbal Comprehension Index (VCI)	87.5 ± 15.3	86.0 ± 15.6	89.3 ± 14.8	0.040
Perceptual Reasoning Index (PRI)	91.7 ± 16.4	90.6 ± 16.7	92.9 ± 15.9	0.180

Characteristic	All (N=383)	Boys (N=208)	Girls (N=175)	Boys vs. Girls
	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	p-value
Working Memory Index (WMI)	88.9 ± 13.7	88.1 ± 13.1	89.9 ± 14.4	0.214
Processing Speed Index (PSI)	89.2 ± 15.5	86.8 ± 16.2	91.9 ± 14.2	0.001
NEPSY-II				
Memory for Names				
MN and MND	8.3 ± 3.3	8.1 ± 3.3	8.5 ± 3.4	0.286
Inhibition				
INN combined	7.2 ± 3.6	7.1 ± 3.7	7.4 ± 3.5	0.369
INI combined	7.1 ± 3.3	6.7 ± 3.3	7.4 ± 3.3	0.065

*Number of participants with missing data: ROP (N=23), surgery for ROP, NEC, or PDA (N=27), postnatal steroids (N=3), and education (N=6). Percentages are computed out of those with data for the corresponding variable.

Table 2.

WISC-IV and NEPSY-II Scores at 6–7 Years by Object Permanence Mastery (OPM) at 18–22 Months

Scale	Unadjusted			Adjusted		
	OP* Mastery Mean (95% CI)	No Mastery Mean (95% CI)	p	OP Mastery Mean (95% CI)	No Mastery Mean (95% CI)	p
WISC-IV						
Verbal Comprehension	89.1 (87.2, 91.0)	84.6 (81.9, 87.3)	0.006	88.1 (86.1, 90.2)	84.8 (82.1, 87.5)	0.039
Perceptual Reasoning	92.6 (90.8, 94.5)	89.9 (86.7, 93.2)	0.127	93.1 (89.9, 96.2)	91.3 (87.5, 95.0)	0.311
Working Memory	89.5 (87.7, 91.2)	88.0 (85.6, 90.3)	0.312	89.3 (86.9, 91.7)	88.3 (85.3, 91.2)	0.507
Processing Speed	90.4 (88.5, 92.3)	86.8 (84.0, 89.6)	0.032	90.2 (87.6, 92.7)	86.3 (83.0, 89.6)	0.034
NEPSY-II#						
Memory for Names						
MN and MND	8.3 (7.9, 8.7)	8.3 (7.7, 8.8)	0.909	8.2 (7.6, 8.8)	8.1 (7.4, 8.9)	0.781
Inhibition						
INN combined	7.4 (6.9, 7.8)	7.0 (6.3, 7.7)	0.382	7.5 (6.9, 8.2)	7.0 (6.2, 7.9)	0.267
INI combined	7.1 (6.6, 7.5)	7.1 (6.4, 7.7)	0.928	7.1 (6.6, 7.6)	7.0 (6.2, 7.7)	0.769

Note: Adjusted means control for center, moderate/severe white matter abnormality on MRI, significant cerebellar lesions on MRI, late cranial ultrasound adverse finding, gestational age, sex, severe ROP, BPD, age at assessment, maternal education, and white race.

*OP = object permanence

#scale means 10, SD 3

Table 3.

Object Permanence Scores at 18–22 Months by Neonatal Neuroimaging Findings

Neuroimaging Finding	Unadjusted		Adjusted	
	Mean (95% CI)	p	Mean (95% CI)	p
Early CUS adverse finding (Grade III/IV ICH or cPVL)				
Yes	1.6 (1.2, 2.0)	0.166	1.8 (1.3, 2.2)	0.214
No	1.9 (1.8, 2.1)		2.0 (1.8, 2.3)	
Late CUS adverse finding (Moderate/severe VE, cPVL, porencephalic cyst, shunt)				
Yes	1.5 (0.9, 2.0)	0.056	1.7 (1.1, 2.2)	0.184
No	1.9 (1.8, 2.1)		2.0 (1.7, 2.3)	
Significant cerebellar lesions on MRI				
Yes	1.5 (1.1, 1.9)	0.016	1.6 (1.1, 2.0)	0.029
No	2.0 (1.8, 2.1)		2.0 (1.8, 2.3)	
Moderate/severe white matter abnormality on MRI				
Yes	1.7 (1.4, 2.0)	0.048	1.8 (1.5, 2.2)	0.130
No	2.0 (1.8, 2.1)		2.0 (1.8, 2.3)	

Note: Adjusted means control for center, gestational age, sex, severe ROP, BPD, maternal education, and white race.