

Executive and Memory Function in Adolescents Born Very Preterm

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KEY WORDS

very low birth weight, prematurity, executive function, memory

ABBREVIATIONS

D-KEFS—Delis-Kaplan Executive Function Scale
WISC-III—Wechsler Intelligence Scale for Children, 3rd edition
PPVT-R—Peabody Picture Vocabulary Test, Revised
FSIQ—full-scale IQ
NSI—neurosensory impairment
CI—confidence interval
MD—mean difference
OR—odds ratio

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1421

doi:10.1542/peds.2010-1421

Accepted for publication Nov 24, 2010

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Funded by the National Institutes of Health (NIH).



WHAT'S KNOWN ON THIS SUBJECT: Very preterm children display significant school problems that persist into adolescence. Executive functioning and memory play important roles in learning and school attainment.



WHAT THIS STUDY ADDS: This study confirms that adolescents born very preterm exhibit deficits in executive functioning and memory in a large contemporary sample. Severe brain injury and maternal education are strong predictors of performance on executive function and memory tasks.

abstract



BACKGROUND: Many preterm children display school difficulties, which may be mediated by impairment in executive function and memory.

OBJECTIVE: To evaluate executive and memory function among adolescents born preterm compared with term controls at 16 years.

METHODS: A total of 337 of 437 (77%) adolescents born in 1989 to 1992 with a birth weight < 1250 g and 102 term controls were assessed with a battery of executive function and memory tasks. Multiple regression analyses were used to compare groups and to identify associations between selected factors and outcomes among preterm subjects.

RESULTS: Adolescents born preterm, compared with term controls, showed deficits in executive function in the order of 0.4 to 0.6 SD on tasks of verbal fluency, inhibition, cognitive flexibility, planning/organization, and working memory as well as verbal and visuospatial memory. After exclusion of adolescents with neurosensory disabilities and full-scale IQ < 70, significant group differences persisted on most tests. Preterm subjects, compared with term controls, were at increased risk of exhibiting problems related to executive dysfunction, as measured with the Behavior Rating Inventory of Executive Function, on the Metacognition Index (odds ratio [OR]: 2.5 [95% confidence interval (CI): 1.2–5.1]) and the Global Executive Composite (OR: 4.2 [95% CI: 1.6–10.9]), but not on the Behavioral Regulation index (OR: 1.5 [95% CI: 0.7–3.5]). Among adolescents born preterm, severe brain injury on neonatal ultrasound and lower maternal education were the most consistent factors associated with poor outcomes.

CONCLUSIONS: Even after exclusion of preterm subjects with significant disabilities, adolescents born preterm in the early 1990s were at increased risk of deficits in executive function and memory. *Pediatrics* 2011;127:e639–e646

The adverse effects of preterm birth on cognitive function and academic achievement have been documented in adolescents born in the 1970s and '80s.^{1–12} During teenage years, deficits in IQ scores for preterm children compared with term controls vary between 8 and 13 points.¹³ However, preterm children with normal intelligence still face significant school difficulties.⁴

Executive functions, which refer to a set of high-level mental processes necessary to regulate behavior and cognition for goal-directed actions, are thought to play an important role in school attainment.¹⁴ They include abilities such as working memory, inhibition, planning and organization, verbal fluency, and cognitive flexibility. Deficits in these domains have been observed in adolescents and young adults born preterm before the era of modern neonatology.^{3,15–18} These abilities depend on the integrity of the neural network that connects the prefrontal cortex to the brainstem, the cerebral lobes, and the limbic and subcortical regions.¹⁹ Neuroimaging studies in preterm children have shown decreased white matter volumes and impaired white matter gains compared with term controls, which indicates their increased vulnerability for executive dysfunction.^{20,21}

Moreover, memory deficits, including verbal and visual memory, have been reported in very low birth weight children, especially among those with neonatal cerebral injury, which suggests the residual sequelae of brain insults on memory function.^{3, 22} However, few studies have expanded on this important finding.

The current study encompasses a systematic assessment of executive function and memory skills of a more contemporaneous group of adolescents born preterm. The objective is to compare executive and memory functions of adolescents born preterm to term

controls and to determine the effect of selected neonatal and sociodemographic factors on these outcomes. We hypothesize that the preterm group will perform less well on tasks of executive functioning and memory than term peers, even after exclusion of those with severe disabilities, and that selective deficits in executive and memory functions will be uncovered among preterm subjects after controlling for receptive vocabulary.

METHODS

Study Population

Between September 1989 and August 1992, 505 very preterm infants with birth weight \leq 1250 g admitted to 3 hospital centers in Providence, Rhode Island; Portland, Maine; and New Haven, Connecticut, were enrolled in the Multicenter Randomized Indomethacin Intraventricular Hemorrhage Prevention Trial and prospectively followed.^{23,24} At age 16 years, 337 of 437 survivors were available for assessment (77%). Participants were representative of the eligible preterm subjects with respect to gestational age, birth weight, gender, antenatal steroids exposure, prophylactic indomethacin, severe brain injury, and bronchopulmonary dysplasia. However, participants were more likely to be multiples (participants: 21%; nonparticipants: 9%) and have white non-Hispanic mothers (participants: 73%; nonparticipants: 61%).

The term cohort was selected from the local community or from a telemarketing list of 10 000 families at 8 years. They were frequency-matched to the preterm group on zip code, age, gender and race. Of the 124 eligible controls, 102 were evaluated at 16 years (82%).

Written assent/consent was obtained from all families. The institutional boards of all participating universities approved the protocols.

Procedures

Subjects were seen for a half-day session by assessors trained to 90% interrater reliability. The assessors were unaware of the preterm children's neonatal course.

Outcome Measures

Cognitive aspects of executive function were assessed with subtests of the Delis-Kaplan Executive Function Scale (D-KEFS).²⁵ In the Verbal Fluency subtest, subjects were asked to generate as many words as possible starting with a given letter (phonological fluency) or belonging in a specific category (semantic fluency) in 1 minute, to examine language skills, initiation, and speed of processing. The Color-Word Interference subtest tapped into verbal inhibition and cognitive flexibility: subjects had to read aloud color names printed in a different color ink or name the ink color of a different printed word. The Tower subtest, in which subjects had to displace disks from a starting to an ending position by following a set of rules, assessed spatial planning, rule learning, and inhibition. All D-KEFS subtests yield a scaled score with a mean of 10 ± 3 . The Backward Spatial Span of the Wechsler Memory Scale, 3rd edition²⁶ appraised visual working memory by having the examinee touch a sequence of blocks as demonstrated by the examiner, but in the reverse order. Scaled scores are calculated with means of 10 ± 3 .

To assess behavioral manifestation of executive function in daily life, parents filled the Behavior Rating Inventory of Executive Function,²⁷ which measures 8 different domains: inhibit (to resist impulse); shift (to make transitions between tasks and mindsets); emotional control (to regulate emotional response); initiate (to start an activity independently); working memory (to hold information to complete a task);

plan/organize (to plan and organize ahead for future events); organization of materials (to order and organize things); and monitor (to check own performance for proper goal attainment). These 8 scales form 2 indices, the Behavioral Regulation Index and the Metacognition Index. One general summary score, the General Executive Composite, also is derived from the 8 scales. A higher score reflects more problematic behavior. Scores ≥ 65 are considered clinically significant.

Verbal memory was evaluated with the California Verbal Learning Test, Children's Version.²⁸ Subjects were presented with a list of words throughout 5 trials and had to recall as many words as possible after each trial (trials 1–5 total score measures immediate recall) and after a 20-minute period (long-delay free recall). The trial 1 to 5 total score is a T-score (mean: 50 ± 10), whereas the long-delay free recall is a z score (mean: 0.0 ± 1.0). The Rey-Osterrieth Complex Figure Test required subjects to copy a complex design and draw it again after 30 seconds (immediate recall) and after 35 minutes (delayed recall). The test examined visuospatial memory. Raw scores were obtained.

Other Variables

General intellectual ability was measured using the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III).²⁹ Receptive vocabulary was assessed with the Peabody Picture Vocabulary Test, Revised (PPVT-R).³⁰ PPVT-R scores have been shown to be highly correlated with measures of intelligence.³⁰ The Pearson correlation coefficient (ρ) in our own data ($n = 410$) for PPVT-R standard score and full-scale IQ (FSIQ) was 0.84 at 16 years.

Data on neonatal characteristics and neurologic status were retrieved from the study database. Parents and adolescents provided updated sociodemographic information.

Statistical Analyses

Results on tests of executive and memory function were compared between preterm and term subjects with adjustment for potential confounders (male gender, maternal education, minority status, and single-parent household) using linear (for continuous variables) or logistic (for categorical variables) regression. To identify selective deficits in executive function or memory not because of differential intelligence between the 2 groups, the above analyses were repeated on the entire cohort controlling for PPVT-R score. The PPVT-R score was used as a proxy measure of intelligence instead of FSIQ because of the high correlation between FSIQ and executive and memory function ($\rho = 0.57$ – 0.70 on the different executive function and memory measures). High correlation between FSIQ and scores on executive function tests was expected because some WISC-III subtests (similarities, digit span, block design, picture arrangement) tap at specific aspects of executive function.³¹ To determine whether adolescents born preterm without severe disabilities also presented with deficits in executive function or memory, comparative analyses between preterm and term controls were repeated after exclusion of children with neurosensory impairment (NSI; hearing aids, services for the blind, cerebral palsy, seizure, ventriculoperitoneal shunt) and FSIQ < 70 . Multiple regression analysis was used to identify perinatal and social factors that predicted scores on executive and memory tests at 16 years among all preterm subjects. Independent variables were selected on the basis of the most common risk factors of adverse outcomes identified in the literature. The effect of prophylactic indomethacin on outcomes also was explored. Analyses were conducted with SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Sociodemographic and medical characteristics of the preterm and term cohorts are outlined in Table 1.

Mean FSIQ between the 2 cohorts differed by 16 points (95% confidence interval [CI]: 12–20) in favor of the term group, with 15% of adolescents born preterm scoring in the significantly impaired range (< 70), compared with 2% of term controls. Among adolescents with NSI ($n = 50$), some were either untestable or obtained the lowest possible score on all subtests of the WISC-III ($n = 2$), the D-KEFS ($n = 15$), or on all memory tasks ($n = 4$). Their FSIQ ranged from 40 to 107.

Executive Functioning

Although adolescents born preterm scored within the normal ranges on tests of executive function (Table 2), they performed 0.4 to 0.6 SD below their term counterparts in all domains including phonological and semantic fluency, verbal inhibition (Color/Word Inhibition), cognitive flexibility (Color/Word Inhibition Switching), spatial planning and rule learning (Tower), and visual working memory (Spatial Span). Among very preterm subjects, 6% to 18% exhibited significant impairment (score < 2 SD) in executive function, compared with only 1% to 3% of adolescents born at term. Controlling for PPVT-R revealed selective deficits among adolescents born preterm compared with term controls in all domains of executive function.

Memory

Table 3 displays results on memory tasks and between-group comparisons. Compared with controls, the very preterm cohort scored more poorly on measures of verbal memory (California Verbal Learning Test, Children's Version) and visuospatial memory (Rey-Osterrieth Complex Figure Test). Again, significant verbal memory im-

TABLE 1 Baseline Characteristics of the 16-Year-Old Cohort

	Preterm	Term
No. subjects at inception	505	—
Proportion surviving to NICU discharge, <i>n</i> (%)	446 (88%)	—
Proportion surviving to 16 y, <i>n</i> (%)	437 (87%)	—
Follow-up at 16 y (%)	337 (77%)	102
Child characteristics		
Gestational age, mean (SD)	28 (2)	—
Birth weight, mean (SD)	961 (173)	—
Small for gestational age, <i>n</i> (%)	79 (23%)	—
Male gender, <i>n</i> (%)	178 (53%)	49 (48%)
Multiple births, <i>n</i> (%)	71 (21%)	—
Antenatal steroids, <i>n</i> (%)	113 (34%)	—
Prophylactic indomethacin, <i>n</i> (%) ^a	162/329 (49%)	—
Severe brain injury, ^b <i>n</i> (%)	31/334 (9%)	—
Grade 3–4 intraventricular hemorrhage	11 (3%)	—
Periventricular leucomalacia	17 (5%)	—
Grade 2 and higher ventriculomegaly	17 (5%)	—
O ₂ at 28 d, <i>n</i> (%)	155/336 (46%)	—
Neurosensory impairment, <i>n</i> (%)	50 (15%)	0
Cerebral palsy ^c	30 (9%)	—
Hearing aids	8 (2%)	—
Services for the blind	10 (3%)	—
Seizure disorder	9 (3%)	—
Ventriculoperitoneal shunt	8 (2%)	—
Social factors		
Maternal age at birth, mean (SD), y	28 (6)	30 (6)
Maternal education, mean (SD), y	14 (2)	15 (3)
Maternal education < high school, <i>n</i> (%)	41 (12%)	5 (5%)
Single-parent household, <i>n</i> (%)	111 (33%)	25 (25%)
Minority status of child by caregiver report (race and ethnicity), <i>n</i> (%)	107 (32%)	30 (29%)
Mean age at assessment, mean (SD), y	16.1 (0.3)	16.2 (0.3)
WISC-III FSIQ, mean (SD)	88 (19)	104 (16)
PPVT-R, mean (SD)	95 (24)	106 (21)

^a Not all children were randomly assigned to receive prophylactic indomethacin.

^b Numbers do not add up to 31 because some children had more than 1 injury.

^c Among children with cerebral palsy, 9 had spastic diplegia, 4 had spastic hemiplegia, and 17 had spastic quadriplegia.

pairment was observed in a higher proportion of very preterm subjects compared with term controls. Secondary analysis adjusting for PPVT-R

score did not alter findings thus highlighting selective deficits in memory function among adolescents born preterm.

Outcomes in Adolescents Born Preterm Without Significant Disabilities

Analyses were repeated with exclusion of subjects with NSI and FSIQ < 70. After adjusting for PPVT-R scores, group differences were detected on phonological fluency (mean difference [MD]: -1.0 [95% CI: -1.7 to -0.2] *P* = .01), verbal inhibition (MD: -1.1 [95% CI: -1.8 to -0.4] *P* < .005), immediate verbal memory (MD: -4.2 [95% CI: -6.5 to -1.9] *P* < .005), and delayed verbal memory (MD: -0.5 [95% CI: -0.7 to -0.3] *P* < .005), and on immediate visuospatial memory (MD: -2.8 [95% CI: -4.6 to -1.0] *P* < .005) and delayed visuospatial memory (MD: -2.9 [95% CI: -4.7 to -1.1] *P* < .005). However, analyses did not reveal significant differences in semantic fluency, cognitive flexibility, spatial planning/rule learning, and visual working memory.

Behavioral Manifestations of Executive Dysfunction

As shown in Table 4, parents reported on the Behavior Rating Inventory of Executive Function that adolescents born preterm were more likely to exhibit clinically significant behavioral problems as a result of executive dysfunction in the Initiate and Working Mem-

TABLE 2 Results of Comparisons in Executive Function Between Very Preterm and Term Adolescents at 16 Years

	Preterm			Term			Adjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI), Controlling for PPVT-R Score
	<i>n</i>	Mean (SD)	Impairment (<2 SD)	<i>n</i>	Mean (SD)	Impairment (<2 SD)		
D-KEFS verbal fluency								
Letters scaled score	307	8.7 (3.6)	8.1%	100	10.8 (3.3)	0	-1.5 (-2.3--0.7) ^a	-1.0 (-1.7--0.3) ^b
Category scaled score	301	9.7 (3.7)	6.3%	99	11.3 (3.1)	1.0%	-1.3 (-2.1--0.5) ^a	-0.8 (-1.5--0.0) ^b
D-KEFS color/word								
Inhibition scaled score	302	7.9 (3.8)	17.6%	99	10.2 (2.6)	3.0%	-2.0 (-2.8--1.2) ^a	-1.5 (-2.2--0.8) ^a
Inhibition switching scaled score	302	8.4 (3.8)	15.6%	98	10.3 (2.9)	3.0%	-1.5 (-2.4--0.7) ^a	-1.0 (-1.8--0.3) ^b
D-KEFS Tower								
Total achievement scaled score	301	8.5 (3.1)	9.3%	99	10.3 (2.2)	0	-1.6 (-2.2--0.9) ^a	-1.1 (-1.7--0.5) ^a
WMS spatial span								
Backward span scaled score	300	8.8 (3.9)	11%	95	11.0 (2.7)	0	-1.7 (-2.5--0.8) ^a	-1.0 (-1.8--0.3) ^b

Impairment was defined as a score that fell 2 SDs below the standard mean. Gender, maternal education, minority status, and single-parent household were adjusted for. Mean differences were adjusted for PPVT-R scores to take into account the effect of differential intelligence between the 2 groups.

^a *P* < .005.

^b *P* < .05.

TABLE 3 Results of Comparisons in Memory Abilities Between Very Preterm and Term Adolescents at 16 Years

	Preterm			Term			Adjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI), Controlling for PPVT-R Score
	<i>n</i>	Mean (SD)	Impairment (<2 SD)	<i>n</i>	Mean (SD)	Impairment (<2 SD)		
California Verbal Learning Test								
Trials 1–5 total T-score	307	42.0 (12.2)	19.5%	99	50.1 (9.9)	4.0%	−7.1 (−9.7–−4.5) ^a	−5.2 (−7.5–−2.9) ^a
Long Delay Free Recall z score	308	−0.7 (1.4)	10.7%	99	0.3 (0.9)	1.0%	−0.8 (−1.1–−0.5) ^a	−0.6 (−0.8–−0.3) ^a
Rey-Osterrieth Complex Figure Test								
Immediate recall raw score	302	15.9 (9.2)	—	101	22.4 (8.1)	—	−5.6 (−7.6–−3.6) ^a	−3.9 (−5.7–−2.2) ^a
Delayed recall raw score	298	15.6 (9.1)	—	101	22.2 (8.2)	—	−5.7 (−7.6–−3.7) ^a	−4.0 (−5.7–−2.3) ^a

Impairment was defined as a score that fell 2 SDs below the standard mean. Gender, maternal education, minority status, and single-parent household were adjusted for. Mean differences were adjusted for PPVT-R scores to take into account the effect of differential intelligence between the 2 groups.

^a $P < .005$.

TABLE 4 Proportion of Very Preterm and Term Adolescents That Scored In the Clinical Range on the BRIEF

	Preterm	Term	Adjusted OR (95% CI)
Behavioral regulation >64, <i>n/N</i> (%)	45/311 (14)	8/100 (8)	1.5 (0.7–3.5)
Inhibit	45/312 (14)	7/100 (7)	1.8 (0.7–4.2)
Shift	51/311 (16)	7/100 (7)	2.2 (1.0–5.2)
Emotional control	36/312 (12)	6/100 (6)	1.6 (0.6–3.9)
Metacognition >64, <i>n/N</i> (%)	69/311 (22)	10/100 (10)	2.5 (1.2–5.1) ^a
Initiate	59/311 (19)	8/100 (9)	2.5 (1.1–5.6) ^a
Working memory	88/311 (28)	16/100 (16)	1.9 (1.1–3.5) ^a
Planning/organization	72/310 (23)	13/100 (13)	1.8 (0.9–3.5)
Organization of materials	42/311 (14)	16/100 (16)	0.9 (0.5–1.7)
Monitoring	47/311 (15)	11/100 (11)	1.3 (0.6–2.6)
Global executive composite >64, <i>n/N</i> (%)	60/311 (19)	5/100 (5)	4.2 (1.6–10.9) ^a

Gender, maternal education, minority status, and single-parent household were adjusted for. BRIEF indicates Behavior Rating Inventory of Executive Function.

^a $P < .05$.

ory domains than were term peers. A higher proportion of very preterm subjects scored in the significant range on the Metacognition Index (odds ratio [OR]: 2.5 [95% CI: 1.2–5.1]), but not on the Behavioral Regulation Index (OR: 1.5 [95% CI: 0.7–3.5]). Overall, 19% of the very preterm cohort displayed

problems on the Global Executive Composite, compared with 5% of the term group, representing a fourfold increase in risk. After exclusion of children with NSI and FSIQ < 70, preterm birth remained associated with increased risk of displaying problems in the initiate domain on the Metacogni-

tion Index and the Global Executive Composite.

Predictors of Poor Performance Among Adolescents Born Preterm

Severe brain injury on neonatal ultrasound was the most significant factor associated with lower scores on all measures of executive and memory function (Table 5). The second most consistent finding was the relationship between higher level of maternal education and better results on all executive functions, except for semantic fluency, and on delayed visual recall. Male gender, antenatal steroids exposure, being small for gestational age, birth weight, and oxygen requirement at 28 days were not related to any of the outcomes. Effects of indomethacin were explored separately with gender stratification and were not significant for any of the study outcomes (results available on request).

TABLE 5 Multiple Regression Analyses to Identify Neonatal and Social Factors Associated With Executive and Memory Function Scores Among Very Preterm Adolescents

	Executive Function, β (SE)						Memory, β (SE)			
	Phonological Fluency	Semantic Fluency	Verbal Inhibition	Cognitive Flexibility	Spatial Planning	Working Memory	Verbal Immediate Recall	Verbal Delayed Recall	Visuospatial Immediate Recall	Visuospatial Delayed Recall
Birth weight, 100 g	0.03 (0.12)	0.03 (0.14)	0.3 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.5)	0.04 (0.05)	0.6 (0.3)	0.5 (0.3)
SGA	−1.1 (0.5)	−0.9 (0.5)	−0.4 (0.5)	−0.2 (0.5)	−0.2 (0.4)	−0.5 (0.5)	−0.5 (1.7)	−0.00 (0.19)	0.7 (1.2)	0.6 (1.2)
Male gender	−0.6 (0.4)	−0.2 (0.4)	−0.9 (0.4)	−0.6 (0.4)	−0.3 (0.3)	−0.4 (0.4)	−3.5 (1.4)	−0.36 (0.15)	−2.3 (1.0)	−2.3 (1.0)
Antenatal steroids	0.1 (0.4)	0.4 (0.4)	1.0 (0.4)	0.6 (0.4)	0.5 (0.4)	0.4 (0.4)	3.5 (1.5)	0.39 (0.16)	1.2 (1.1)	1.1 (1.1)
O ₂ at 28 d	−0.5 (0.4)	−0.5 (0.5)	−0.4 (0.5)	−0.7 (0.5)	0.3 (0.4)	−0.2 (0.5)	0.8 (1.6)	0.22 (0.17)	0.9 (1.1)	1.0 (1.2)
Severe brain injury	−3.6 (0.7) ^a	−3.9 (0.7) ^a	−3.6 (0.7) ^a	−4.2 (0.7) ^a	−4.0 (0.6) ^a	−3.9 (0.7) ^a	−9.2 (2.4) ^a	−1.44 (0.26) ^a	−9.6 (1.7) ^a	−9.6 (1.8) ^a
Maternal education, y	0.4 (0.1) ^a	0.2 (0.1)	0.3 (0.1) ^a	0.3 (0.1) ^a	0.2 (0.1) ^a	0.5 (0.1) ^a	0.5 (0.3)	0.06 (0.03)	0.5 (0.2)	0.6 (0.2) ^a

β coefficients represent the amount of increase or decrease in test scores for a 1-unit change in the predictor variable. SGA indicates small for gestational age.

^a $P < .005$.

DISCUSSION

This study reveals that adolescents born preterm in the early 1990s, compared with term peers, display deficits across all measures of executive function and memory. Selective deficits persist on tests of phonological fluency, verbal inhibition and memory after exclusion of adolescents with significant neurosensory and cognitive disabilities. Not surprisingly, severe brain injury and lower level of maternal education are strong predictors of adverse cognitive sequelae.

Our assessment of executive function reveals significant impairment among very preterm subjects in abilities such as verbal fluency, verbal inhibition, cognitive flexibility, spatial planning, and spatial working memory. In addition, problems with executive function translate into behavioral manifestations at home as reported by parents: adolescents born preterm have more difficulties with initiation of activities or generation of new ideas and with working memory. A higher proportion of adolescents born preterm compared with term controls score in the clinical range on the Global Executive Composite, thus highlighting their higher propensity for overall executive dysfunction. Our findings indicate that deficits in a wide range of executive processes that have been documented in previous studies on a population of very preterm children at early and middle school age^{18,31–35} persist in adolescence. We used the D-KEFS, in which certain subtests also tapped at cognitive processes other than executive function (language skills for the verbal fluency subtests and processing speed for the Tower subtest). Therefore, it is possible that the observed impairments were not solely because of deficits in executive function.³⁵ However, our findings parallel that of other studies in which different tasks were used to assess similar domains. Lower per-

formance in phonological and semantic verbal fluency has been observed among adolescents born at < 33 weeks' gestation.³⁶ Taylor et al³ also have reported on a cohort with birth weight < 750 g assessed at 16 years that displayed significant impairment in spatial planning, spatial and verbal working memory, vigilance, and set shifting. The authors controlled for verbal-semantic ability to identify areas of relative executive dysfunction and found almost identical results, except for verbal working memory and vigilance, for which group differences were no longer significant. Similarly, our analyses included adjustment for receptive vocabulary and revealed relative deficits that were mostly significant for verbal inhibition and spatial planning. Nosarti et al¹⁵ have documented persisting executive dysfunction in areas such as verbal fluency, response initiation and inhibition, and cognitive flexibility in young adults. In our study there also is evidence for deficits in verbal and visuospatial memory in adolescents born preterm compared with term controls, which corroborates the work of Taylor et al.^{3,22}

The global deficits in executive and memory function observed in adolescent born preterm are congruent with neuroimaging findings reported in this population. The neural circuitry that connects the prefrontal cortex to other areas of the brain, notably the posterior cortical and subcortical regions, is thought to be central in ensuring normal executive processes.^{19, 37} Therefore, damage to any of these components may lead to deficits in executive function. Longitudinal studies on brain volume changes in our cohort have demonstrated that white matter volumes increased by 26% to 27% between 8 and 12 years in term controls, compared with only 10% in preterm subjects.²¹ Differential decreases in

gray matter volumes also were noticed between preterm and term subjects in the frontal and deep gray regions.²¹ In addition, significant volume reduction in areas subserving executive processes, such as the prefrontal gyri, the cingulate gyrus, and the frontostriatal and frontal-parietal white matter pathways, have been observed in preterm children at 12 years.²⁰ Edgin et al³⁸ provided evidence for a relationship between early white matter pathology and later difficulties on tasks of executive function in very preterm children. In addition, alterations in gray and white matter distribution have been shown to be related to performance on tests of executive function, accounting for up to 29% of the variance.³⁶ Correlations between changes in brain microstructures and executive function have also been noted by Gimenez et al,^{39,40} who found that decreased volumes of the thalamic gray matter and the genu of the corpus callosum were associated with poorer verbal fluency in very preterm subjects at 14 years. As for memory function, the neural substrate has been ascribed to the frontal and medial temporal (hippocampal) areas of the brain.⁴¹ Reduced volume for the hippocampus has been documented,^{20,42} and correlations have been found between reduced left hippocampal volume and poorer verbal memory skills among preterm subjects.⁴³ Thus, perturbations in preterm brain development may explain the increased vulnerability of adolescents born preterm for impairment in executive function and memory.

In our study we identified an association between severe neonatal brain injury and maternal education and most outcomes. It was expected that adolescents who suffered early brain insults would perform more poorly on neuropsychological testing, as previously documented in this cohort at 12

years.⁴⁴ Higher maternal education also was associated with increasing scores on tasks of executive function and visuospatial memory. Likewise, Aarnoudse-Moens et al⁵² found that maternal education accounted for 12% of the variance in a task of response inhibition. Because better executive functioning is correlated to higher school attainment,¹⁴ mothers with higher maternal education probably had strong abilities related to executive function, thus laying a genetic ground for better performance in their offspring.

This study draws its strength from the comprehensive evaluation of executive function, which tapped at several distinct cognitive abilities and explored behavioral consequences as viewed by the parents. Neuropsychological measures were based on well standard-

ized, objective, and validated tools to reduce the potential for observer bias, because examiners, although unaware of neonatal course, were not completely blind to preterm versus term status as they had been involved in previous assessment of the same cohort. Despite an attrition rate of 23% with the known selection bias that may result (ie, underestimation of impairment),⁴⁵ this rate is comparable to other long-term follow-up studies.^{3,8,9,12} The study large sample size has allowed assessment of the impact of multiple relevant neonatal and demographic factors on outcomes.

CONCLUSION

The neuropsychological sequelae of preterm birth extend into adolescence and involve higher-level cognitive processes such as executive function and memory. Even after correction for re-

ceptive vocabulary, relative deficits still remain, which may explain in part the lower scholastic attainment observed in the preterm population. With advances in neuroimaging techniques, correlational studies will allow additional identification of the neural circuitry underlying executive and memory processes in preterm subjects. Thus, intervention strategies to either prevent injury to vulnerable cerebral regions or to stimulate development of compensatory circuitry can be explored.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grant NS 27116.

We thank Victoria Watson, Susan Delancy, Jill Maller-Kessleman, Marje Ainley, and June Gagnon for neurodevelopmental testing; and Karol Katz for data management.

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