November 2002

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Child Neuropsychology
2002, Vol. 8, No. 2, pp. 83–92

0929-7049/02/0802-083$16.00

Executive Functions in Preschool Children Born Preterm: Application of Cognitive Neuroscience Paradigms

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ABSTRACT

Although children born preterm are at risk for neuropsychological impairments at school age and adolescence, including difficulties with visual motor integration, spatial/constructional skills, attention, arithmetic, and nonverbal executive functions, specific neuropsychological outcome has not been investigated adequately in preschoolers. Application of cognitive neuroscience tasks offers the opportunity to characterize early executive functions in young children born preterm. In a preliminary sample of 29 preschool children born preterm (*M* birth gestational age = 32.4 weeks), executive function outcome was compared to that of fullterm controls by contrasting performance on two prototypic delayed-response-type paradigms, Delayed Alternation and Spatial Reversal. Preschoolers born preterm correctly retrieved the reward on fewer trials on Delayed Alternation than did matched controls. Furthermore, preschool children born preterm used problem-solving strategies that included more perseverative errors than controls. These preliminary findings highlight the utility of cognitive neuroscience paradigms to understand neuropsychological outcome in preschool children born preterm and suggest areas of developmental vulnerability that may include dorsolateral prefrontal circuits.

Approximately 10% of newborns are born at low birth weights (<2500 g) and prematurely (≤ 36 weeks gestation). Costs associated with preterm birth (e.g., initial hospital stay, early intervention, special education, and mental health services) are high. For example, infants who weigh <1500 g at birth utilize at least $26,000 more in neonatal hospital costs than their normal-weighing peers (Lewitt, Baker, Corman, & Shiono, 1995). Substantial savings could be realized if morbidity could be identified and treated early. School-aged children born preterm have characteristic neuropsychological impairments, that is, visual motor, spatial/constructional, attention, nonverbal executive function deficits, and academic arithmetic disorders (Hack, Klein, & Taylor, 1995; Taylor, Klein, & Hack, 2000). Interestingly, only about 10% of very low birth weight infants have demonstrable evidence of brain damage on perinatal ultrasound scans (Aziz et al., 1995), related to limits in the resolution and timing of ultrasound imaging. The consistency of neuropsychologic impairment, however, suggests at least some degree of shared brain dysfunction across children born prematurely. When perinatal ultrasound abnormalities are found, the genesis is most typically the highly vascularized subcortical germinal matrix that sits just beneath the floor of the lateral ventricles. Other types of brain damage occur as a result of periventricular

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Accepted for publication: September 5, 2002.

hemorrhagic infarctions or periventricular leukomalacia (Volpe, 1995).

Recently, Dammann and Leviton (1999) proposed a two-component model of indirect and direct contributors to brain damage in preterm infants that often is localized in the subcortical white matter. Developmentally, the brain of the preterm neonate is vulnerable indirectly because: (1) immature oligodendroglia do not begin myelin formation until early in the third trimester of pregnancy, concurrent with birth for many preterm neonates, and (2) many neuroprotective trophic factors are derived from maternal sources (Reuss, Paneth, & Susser, 1994), unavailable for preterm neonates. In preterm infants, white matter is damaged directly by hypoxic, ischemic, and reperfusion insults because the fetal brain is less able to autoregulate vessel pressure (Volpe, 1995). Even subclinical levels of acidosis, an index of neonatal hypoxia, affect later cognitive outcome in children born preterm (Stevens, Raz, & Sander, 1999). Although the specific mechanism of damage is not yet known, structures vulnerable to early damage in preterm infants may include both the basal ganglia and subcortical white matter tracts, including those that project to the frontal lobe. In support of this premise, Peterson et al. (2000) found that regional brain volume was smaller in the basal ganglia of 8-year-old children born preterm compared to fullterm controls. Because of the protracted course of prefrontal circuit development, including myelination (Kinney, Brody, Kloman, & Gilles, 1988), synaptogenesis (Huttenlocher & Dabholkar, 1997), and early functional/electrical organization (Thatcher, 1997), the prefrontal circuits may be vulnerable to disruption by early pre- and perinatal events.

With this type of brain dysfunction in children born preterm, the challenge is to utilize outcome measures that are sufficiently sensitive both to performance differences within the normal range and to prefrontal disruption. Recent evidence suggests that several developmental disorders carry unique profiles of executive dysfunction in process subcomponents (Pennington, 1997). Therefore, it is likely that only some executive processes are impaired as a result of preterm birth and accompanying neonatal complications. Children born preterm exhibit executive function and attention deficits both at school age (Taylor, Hack, Klein, & Schatschneider, 1995) and into adolescence (Taylor, Klein, Minich, & Hack, 2000) on more molar experimental and clinical measures that tap multiple abilities. Such measures have a high degree of sensitivity, but may be less able to parse the specific, underlying neuropsychological deficits that may result from perinatal insult. Using measures adapted from cognitive neuroscience that are designed to assess more discrete neuropsychological abilities, Luciana, Lindeke, Georgieff, Mills, and Nelson (1999) found that school age children with histories of prematurity made 25% more errors on a spatial working memory task compared to fullterm controls. There were no differences between groups in spatial recognition memory, suggesting that the observed working memory dysfunction observed in children born preterm was specific. Contrasting performance on other discrete cognitive neuroscience based tasks may help to identify the specific cognitive impairments that result from perinatal insults in those born preterm.

Although clinical neuropsychology has begun to use more cognitively sophisticated tasks to understand outcome, there are few such measures available for use in young children. Recently developed standardized preschool tests (e.g., DAS: Elliott, 1990; NEPSY: Kemp, Kirk, & Korkman, 1998) have well-developed normative bases; however, their ability to assess specific executive function processes is limited. One fruitful way to investigate outcome is to supplement clinically available measures with tasks adapted from the developmental cognitive neuroscience literature. Such tasks are advantageous because their relation to prefrontal cortical function has been established, at least in well-controlled studies with animals, and the minimal response requirements are well suited for preschool children.

One of the most consistently demonstrated structure-function relations is that between working memory and the dorsolateral prefrontal circuit (Goldman-Rakic, 1987b). Using the classic Delayed Response paradigm with monkeys, Goldman-Rakic (1987a) has demonstrated that working memory is affected by both cortical, as well as subcortical, experimental manipulations.

Mishkin (1964) also used a variant of the Delayed Response paradigm and identified the importance of the ventromedial and orbitofrontal circuits in the alteration of responding in light of reversals in reward contingencies. Delayed-response-type tasks are ideal for use with preschool children because of the nonverbal nature, simple manual response demands, and doling out of frequent, tangible rewards (Espy, Kaufmann, McDiarmid, & Glisky, 1999). Delayed-response-type tasks are sensitive to age-related differences in normal preschool children (Espy, Kaufmann, Glisky, & McDiarmid, 2001). These tasks have been used successfully to differentiate clinical populations of young children with presumed prefrontal dysfunction due to phenylketonuria (Diamond, Prevor, Callender, & Druin, 1997) and prenatal cocaine exposure (Espy, Kaufmann, & Glisky, 1999) from matched controls. Finally, performance on such tasks has been related to resting frontal EEG signals in normal infants (e.g., Fox & Bell, 1990).

Delayed-response-type paradigms also may be useful in understanding outcome in those born prematurely. For example, in a study with 10-month old infants, Ross, Tesman, Auld, and Nass (1992) compared performance between those born preterm (with and without intraventricular hemorrhage) and those born fullterm on the A-not-B task (Piaget, 1954). A-not-B is a developmental task that is similar in format to the Delayed Response paradigm (Diamond & Doar, 1989). Ross et al. (1992) examined performance on "reversal trials", that is, where the location of the reward on a specific trial differs from the previous trial, thus requiring the infants to keep the location of the reward on the current trial in mind, while inhibiting the prepotent motor response to search at the location that was rewarded previously. Approximately 60% of the preterm infants were unable to find the reward on two reversal trials, compared to 13% of fullterm infants. These findings demonstrate the utility of these paradigms with young children, both with and without medical disorders, and suggest that they may be useful here to understand outcome in preschool children born preterm. The purpose of the current study, then, was to examine the impact of preterm birth on executive function outcome in preschoolers by contrasting performance on two delayed-response-type tasks with differing demands. Preschool children born preterm were expected to perform more poorly on tasks considered to measure working memory in comparison to those born fullterm.

METHOD

Participants

Participants were 29 preschool children between the ages of 2 and 3 years ($M = 3.25$ years) who were born preterm and of low birth weight at a local, regional Neonatal Intensive Care Unit (M gestational age at birth = 32.4 weeks; $SD = 2.2$ weeks; range 28–36.5 weeks). Preterm infants ranged in birth weight from 739 g to 2475 g ($M = 1774$ g; $SD = 484$). The sample was restricted to low-risk preterm infants ($\geq$28 weeks gestational age, with no evidence of IVH > grade II, periventricular leukomalacia, seizures, chronic lung disease, or bronchopulmonary dysplasia) in order to investigate executive function outcome in those children who are not at obvious risk for the development of severe sequelae (Hack et al., 1995). There were 17 girls and 12 boys, with 4 children of non-White minority ethnicity. Mean sample maternal education was 13.9 years ($SD = 2.23$).

Fullterm controls ($n = 29$) were culled from a larger normative, cross-sectional study of executive function development in preschool children (e.g., Espy et al., 2001). Preterm and fullterm children were matched with respect to age, sex, and maternal education, and to race where possible. There were 17 girls and 12 boys in the Fullterm group, with 7 children of non-White minority ethnicity. Mean age of the fullterm participants was 3.12 years. Mean maternal education level of the Fullterm group was 14.9 years ($SD = 1.92$), with no differences between Preterm and Fullterm groups in age or maternal education level (both $ps > .05$).

Procedure

Between the ages of 2 and 3 years, children were administered a battery of executive function tests that included two delayed-response-type tasks, Delayed Alternation (Espy, Kaufmann, McDiarmid, et al., 1999) and Spatial Reversal (Kaufmann, Leckman, & Ort, 1989). A trained child clinical graduate student administered all tasks in a single session. Children were assessed individually in a quiet room with the parent or guardian present. Breaks were used when necessary to maintain cooperation and interest. Test sessions were videotaped for the purpose of later scoring.

Measures

For both delayed-response-type tasks, a gray testing board with two drilled lateral wells was used. The wells were covered with two beige coffee cups because they were displaced easily and "neutral" in color and shape. On both tasks, rewards consisted of stickers, M & M's®, or different cereal bits. Different rewards were used at the beginning of each task. In addition, because young preschoolers are more active and distractible than older children, different rewards also were used when motivation or interest lagged to maximize persistence and facilitate task completion.

Delayed Alternation

Delayed Alternation (DA; Espy et al., 2001) was adapted from studies with primates (e.g., Goldman, Rosvold, Vest, & Galkin, 1971). DA is considered a measure of working memory, consistent with results from studies of animals with lesions to dorsolateral prefrontal circuits (Goldman et al., 1971; Watanabe, Kodama, & Hikosaka, 1997) and work in our laboratory with normally developing preschoolers (Espy, Kaufmann, McDiarmid, et al., 1999). In DA, the reward was hidden out of the child's sight. On the pretrial, neither well was baited with a reward, in order to lead the child to alternate among locations from the outset. After the pretrial, the reward was hidden in the location opposite from the child's last correct response after a 10-s delay. Therefore, to achieve the maximal correct, the child had to alternate retrieval between right and left wells on each successive trial. A total of 16 trials were administered. When the child disrupted the alternation by erroneously searching on the same side, the examiner hid the reward at the same location until correct retrieval occurred, thereby resuming the alternating sequence. The number of correct retrievals was scored and expressed as a percentage of the total trials administered for the purposes of cross-task comparisons.

Spatial Reversal

Spatial Reversal (SR: Espy, Kaufmann, McDiarmid, et al., 1999; Kaufmann et al., 1989) was chosen as a measure of shifting or flexibility, as studies with animals (Mishkin, 1964; Meunier, Bachevalier, & Mishkin, 1997) have shown that such tasks are dependent upon the ventromedial/orbital frontal circuits in monkeys. Findings from our laboratory indicate that performance on reversal tasks is distinct from that on measures of working memory such as DA (Espy, Kaufmann, McDiarmid, et al., 1999). In SR, as in DA, the child did not observe the hiding of the reward and a spatial hiding rule was used. Unlike DA, the child had to retrieve the reward from a given location until a criterion of consecutive correct retrievals at the same location was met. First, the child was administered a pretrial where both wells were baited to encourage the child to persist in searching at the given location from the outset. On the first trial, the well that the child had chosen in the pretrial was baited. After a 10-s delay, the child was allowed to retrieve the reward by displacing the cup. After the child successfully retrieved the reward at the given lateral well for four consecutive trials, the reward then was hidden in the opposite lateral well. If a second set of consecutive four correct responses was obtained, the reward then was hidden in the opposite well, and so forth. A total of 16 trials was administered. Therefore, the child potentially could shift sets three times among four consecutive trial sets. The number of correct responses was scored and expressed as a percentage of the total trials administered.

Strategies

In response to the differing reward contingencies on DA and SR, a child can make one of two types of errors on these tasks: (1) Win-stay errors are incorrect searches for the reward at the previously rewarded location, and (2) Lose-stay errors are incorrect searches for the reward at a location that was not previously rewarded. Videotapes were reviewed in order to tabulate win-stay and lose-stay errors for both tasks. Win-stay and lose-stay errors were expressed as a percentage of total trials completed for comparison across tasks.

RESULTS

Repeated measures, multivariate analyses of variance were conducted to compare group performance on the number of correct retrievals on the two delayed-response-type tasks, with task type (DA vs. SR) as the within-subject factor and preterm status group (Preterm vs. Fullterm) as the between-subject factor. For statistical comparisons, α was set at .05, with marginal trends ($p < .10$) noted. Mean performance as a function of task type and preterm status group is depicted graphically in Figure 1. Performance differed jointly as a function of the interaction of task type and preterm status, Wilk's $\Lambda = .91$; $F(1, 51) = 4.91$, $p < .05$, indicating that that pattern of performance on the two delayed-response-type tasks differed between Preterm and Fullterm groups. There also was a main effect of task type, Wilk's $\Lambda = .40$; $F(1, 51) = 75.71$, $p < .001$, with more correct reaches on the SR task, regardless of

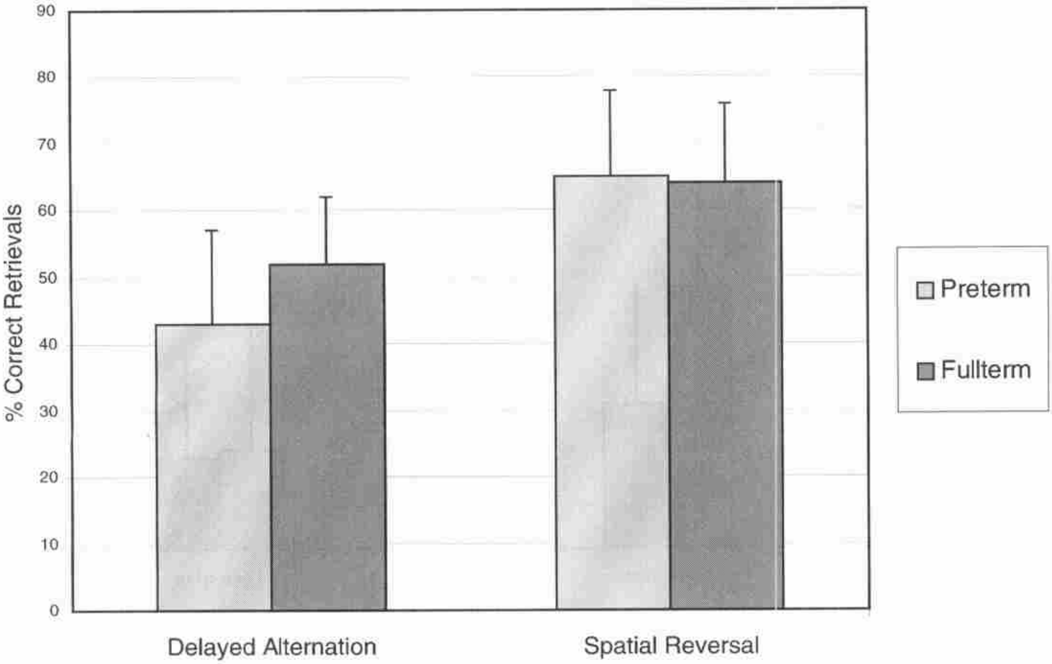

Fig. 1. Mean percentage of correct responses as a function of task type and group.

group. Across the DA and SR tasks, performance differed marginally as function of preterm status, $F(1, 51) = 2.90$, $p < .10$, with children born preterm correctly retrieving the reward on fewer trials.

Follow-up univariate ANOVA's examining the effect of preterm status on performance then were conducted within each task. For DA, performance differed as a function of preterm status, $F(1, 51) = 7.19$, $p < .01$. That is, preschoolers born preterm correctly retrieved the reward on fewer DA trials than did control children born fullterm. In contrast, Preterm and Fullterm groups performed comparably on SR, $F(1, 56) = 0.02$, $p > .05$. The number of SR trials where the reward was retrieved correctly was similar between groups.

Repeated measures, multivariate analyses of variance also were conducted to determine whether errors differed as a function of task type and preterm status group. Error type by task and group are depicted graphically in Figure 2. Performance differed marginally as a function of the interactive effect of task and preterm status, Wilk's $\Lambda = .88$, $F(3, 49) = 2.32$, $p < .10$. Error patterns differed among tasks, Wilk's $\Lambda = .35$; $F(3, 49) = 30.66$, $p < .001$, where all preschoolers made more errors on DA. Error patterns also differed by preterm status group, $F(1, 51) = 5.57$, $p < .05$, with Preterm group children making more errors across the two delayed-response-type tasks than those in the Fullterm group. Therefore, follow-up analyses were conducted within each task to determine the effect of preterm status on delayed-response-type task error patterns.

For DA, errors differed as a function of the joint effect of the interaction between error type (win-stay vs. lose-stay) and preterm status, Wilk's $\Lambda = .90$; $F(1, 51) = 5.84$, $p < .05$. DA errors also differed as a function of the main effect of preterm status, $F(1, 51) = 6.77$, $p < .05$. Finally for DA, errors differed marginally by type, Wilk's $\Lambda = .94$; $F(1, 51) = 3.23$, $p < .10$. Univariate ANOVA's revealed that Preterm group children made more lose-stay errors on DA, $F(1, 51) = 6.60$, $p < .05$, than did Fullterm controls. In addition, children born preterm made marginally

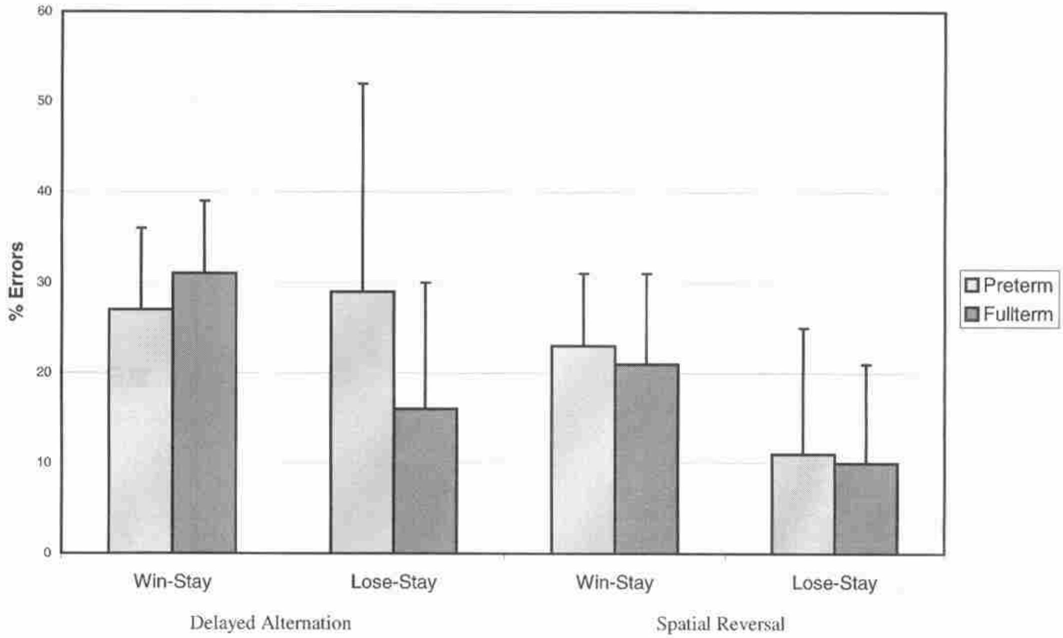

Fig. 2. Mean percentage of errors by error type, task type, and group.

fewer win-stay errors on DA, $F(1, 51) = 3.14$, $p < .10$, than did fullterm controls.

For SR, errors differed as a function of the main effect of type, Wilk's $\Lambda = .64$; $F(1, 56) = 31.64$, $p < .001$. However, errors did not differ as a function of the interaction of type with preterm status, Wilk's $\Lambda = .99$; $F(1, 56) = 0.00$, $p > .05$, nor as a function of the main effect of preterm status, $F(1, 56) = 0.63$, $p > .05$. Therefore, preschool children made more win-stay errors on SR than lose-stay errors, independent of preterm status.

DISCUSSION

Preschool children born preterm evidenced a unique pattern of performance on the delayed-response-type tasks. Specifically, 2- and 3-year-old preterm children obtained fewer correct on Delayed Alternation compared to demographically matched, fullterm controls. Furthermore, preschoolers born preterm made more lose-stay errors on Delayed Alternation. Delayed Alternation is considered a measure of working memory, in that the child has to maintain information from the previous trial in order to guide subsequent responding on the next trial. In contrast, there were no group-related performance differences on Spatial Reversal. Spatial Reversal can be viewed as a measure of shifting or flexibility, as the child has to determine the response rule, persist in responding to that rule, and then alter responding when the contingency rule is changed. The specific deficits in Delayed Alternation performance, but not in Spatial Reversal performance, that were observed in preschoolers born preterm point to unique difficulties in working memory. These findings are consistent with those of Luciana et al. (1999) who noted reduced performance on a spatial working memory task in school age children who were born preterm. Interestingly, the magnitude of the group differences in working memory performance was large (Cohen, 1987), a *d* of approximately .75 *SD*, and similar to that observed by Luciana et al. (1999) in school age children. These observed performance differences on Delayed Alternation might represent earlier manifestations of working memory deficits observed at school age, signifying that emergent executive dysfunction can be quantified in the 2- and 3-year-old age range. In addition, these findings build upon Ross et al. (1992) who reported that fewer preterm infants correctly retrieved the reward on two of three reversal trials on A-not-B. Taken together, there appears to be a consistency in vulnerability to working memory impairments across age when developmentally appropriate tasks are used to assess neuropsychological performance.

Interestingly, groups did not differ in performance on Spatial Reversal. These findings are similar to those reported by Luciana et al. (1999) where those born preterm did not differ in shifting between dimensional rules. Similar to the study by Espy, Kaufmann, McDiarmid, et al. (1999) with normally developing preschoolers, working memory and shifting abilities appear to be distinct in those born preterm. Reversal task performance discriminated children diagnosed with Autism from matched comparison children with mental retardation in some (McEvoy, Rogers, & Pennington, 1993), but not in all studies (e.g., Griffith, Pennington, Wehner, & Rogers, 1999). Reversal tasks may be sensitive only to severe disturbances in mental flexibility. Spatial Reversal and Delayed Alternation performance also differ in developmental trajectory (Espy et al., 2001), which may have influenced the observation of differences in this age range. Although Spatial Reversal was chosen as a shifting or flexibility task, alternatively, others have viewed the task as a developmentally appropriate analogue of the Wisconsin Card Sorting Test (Kaufmann et al., 1989). Studies comparing Spatial Reversal performance to other measures of preschool shifting behavior, such as the Shape School (Espy, 1997) and other more recently developed instruments such as the Object Classification test (Smidts & Anderson, 2002), or the Concept Formation subtest from the Woodcock-Johnson-III Assessment of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001) would be useful to understand the measurement characteristics of this task and the impact of prematurity on performance.

Further examination of the errors committed by preschool children born preterm revealed substantive discrepancies, where errors were specific in type and task. Preschool children born preterm made more lose-stay errors, that is, they choose the previously un-rewarded well more often then fullterm controls. Moreover, this maladaptive strategy was apparent only on Delayed Alternation, an executive function task that requires online processing trial by trial and has been linked solidly to the function of the dorsolateral prefrontal circuit in animals. Because the preschoolers born preterm also made marginally fewer win-stay errors relative to fullterm controls, it does not appear that preterm children indiscriminately make more errors. Rather, a specific response bias, that is, persisting at choosing a maladaptive and unrewarding strategy, was evident in preschool children born preterm. Such a response style is consistent with perseverative responding, a hallmark of executive dysfunction that has been described extensively in adults with damage to the prefrontal system (e.g., Eslinger & Damasio, 1985).

This propensity to persist in a response that had been rewarded in the past but not on the most recent trial may have important implications for these at-risk children in the longer term. The magnitude of the group differences was moderate, where d was approximately .7 *SD*. Note that there was wider variability in lose-Stay errors among preterm children, suggesting that there may be important individual differences in strategies. As children born preterm are at risk for the development of learning, attention, and behavioral disorders, these early executive function strategy impairments likely contribute to later adverse academic and behavioral outcome.

The consistency in findings across ages suggests protracted vulnerability to prefrontal cortical circuits. Given that other studies have noted reduced basal ganglia volumes (Peterson et al., 2000), the observed behavioral differences may not be due to differences in cortical structure or function, but rather in differences in subcortical regions that link the cortex with other action sites. Without direct measurement of brain structure and concurrent behavioral assessment in this age range, the specific areas that contributed to the performance differences observed here is unknown. These findings point out that it may be feasible to relate findings from neuroimaging studies to specific neuropsychological measures in young children born preterm.

The neuropsychological ability structure in young children, however, likely is not as differentiated as that in older children. For example, there is a spatial component to performance on Delayed Alternation that has been described, as lesions to the parietal cortex also reduce performance in animal studies. It is possible that the group-related differences observed here are a consequence of known differences in spatial/constructional abilities between children born preterm and fullterm controls (e.g., Olsen et al., 1998). In the current study, primary visual-spatial abilities were not assessed; therefore, this possibility cannot be ruled out entirely. However, both Spatial Reversal and Delayed Alternation share a spatial component, that is, the reward location depends upon spatial location. If the findings were solely a product of impaired visual-spatial skills, group differences should be observed on both Delayed Alternation and Spatial Reversal. These relations among specific tasks in preschool children need to be better studied to understand the cognitive underpinnings and how these abilities are disturbed by preterm birth.

These performance differences were apparent in preschool children born preterm who are at low biologic risk for adverse outcome. All children were born at 28 weeks gestation or more, with a much lower risk of cerebral palsy, mental retardation, academic disorders, or school failure (Hack et al., 1995) than those born earlier in gestation at lower birth weights. Children born earlier in gestation may have shown more dramatic performance differences on the delayed-response-type tasks. Furthermore, those with frank brain damage and significant neonatal complications (e.g., bronchopulmonary dysplasia, periventricular leukomalacia, intraventricular hemorrhage > grade II) also were excluded from this sample, thereby reducing the ability to detect more severe sequelae. Future investigations that include children who were born earlier in gestation at greater risk for neonatal complications is the next step to determine whether the observed relations are consistent across a range of neurobiologic risk.

It is striking, however, that specific differences in executive abilities were apparent in this low-risk sample. It is precisely these children who often puzzle school personnel, as lower risk children born preterm typically do not show early developmental delays and thus escape detection by early intervention programs. At school age, approximately 25% of preterm children fail a grade or receive special education placement (Allen, 1998; Resnick et al., 1998) or are identified as having learning or behavioral problems (Hack et al., 1995). This rate of school-related disturbance is higher than that of the general population (with rates of 5–15%; US Office of Special Education, 2001). These findings suggest that there are detectable differences in early executive functions, particularly in emergent working memory skills. Additional investigations are planned to determine whether these early sequelae are related to later academic and behavioral functioning. Then, putative interventions could be developed to address weaknesses in working memory skills prior to school entry.

More generally, the application of cognitive neuroscience paradigms, such as the delayed-response-type tasks, offers the prospective to tap more discrete skills, with potentially stronger relations to specific brain areas in comparison to widely available clinical measures, such as measures of intelligence. Although the neuropsychological ability structure in preschool children may be less differentiated, these findings demonstrate that these paradigms are useful in highlighting performance discrepancies, similar to what is observed in older children and adults. Contrasting patterns of performance on delayed-response-type tasks with differing demands may lead to specific profiles of neuropsychological strengths and weaknesses among children of varying neuropathology. If these profiles are related to subsequent academic proficiency and behavior, in turn, such measures could be used to identify at-risk children earlier for intervention.

ACKNOWLEDGEMENTS

This research was supported in part by the Pediatric Neuropsychology/Developmental Cognitive Neuroscience Award of the Rita Rudel Foundation and the Special Research Program Award from the Southern

Illinois University Office of Research Development and Administration to the first author. The authors thank the participating families, undergraduates who assisted in various laboratory tasks associated with this study, and Diana Mitchell for her assistance with data collection.

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