Deficits in Memory Strategy Use Related to Prefrontal Dysfunction During Early Development: Evidence From Children With Phenylketonuria

Desirée A. White, Marsha J. Nortz, and Tammy Mandernach
Washington University

Kathleen Huntington
Doernbecher Children's Hospital

Robert D. Steiner
Doernbecher Children’s Hospital and Oregon Health Sciences University

The prefrontal cortex has been implicated in the mediation of executive processes that facilitate learning and memory. The authors hypothesized that children with prefrontal dysfunction related to phenylketonuria (PKU) would experience deficits in learning and memory because of impaired strategy use. They evaluated 23 children with PKU and 23 controls by using the California Verbal Learning Test—Children's Version (CVLT-C). General executive abilities were tested using the Stroop Color and Word Test, the Wisconsin Card Sorting Test, and phonemic and category fluency. Children with PKU, especially older children, showed poorer learning across trials and less use of semantic clustering on the CVLT-C but intact retention of previously encoded information. With the exception of phonemic fluency, deficits were not observed in general executive control. Results are discussed within the context of abnormalities in the prefrontal cortex and white matter of the brain.

The prefrontal cortex of the brain has been implicated in the mediation of numerous cognitive abilities. From the broadest perspective, this brain region is thought to subservce an executive control system that coordinates interactions among basic cognitive processes to permit higher order cognition (Norman & Shalice, 1986; Shalice & Burgess, 1991; Stuss, 1992). At a neurochemical level, the metabolic properties of dopaminergic neurons projecting to prefrontal cortex make this region particularly sensitive to dysregulations in dopamine that do not affect other brain regions (Porrino & Goldman-Rakic, 1982; Sawaguchi & Goldman-Rakic, 1991). Adults with disorders related to dopamine dysregulation (e.g., schizophrenia and Parkinson’s disease) exhibit impairments in executive control, and these impairments have been shown to negatively affect learning and memory (Gabrieli, Singh, Stebbins, & Goetz, 1996; Pillon et al., 1998; Seidman et al., 1994; Stone, Gabrieli, Stebbins, & Sullivan, 1998; Taylor, Saint-Cyr, & Lang, 1990).

Moscovitch and a colleague (Moscovitch, 1992; Moscovitch & Umiltà, 1990, 1991) have suggested a model in which a prefrontally mediated executive control system works with memory to enhance the organization of to-be-remembered information. These investigators provided compelling arguments that processes mediated by prefrontal cortex are organizational and strategic in nature whereas processes mediated by medial temporal structures are associative. The executive control system works with information that is to be encoded or retrieved from memory, resulting in richer memory traces than would be produced using simple associative processes. A specific role for the prefrontal cortex in encoding and retrieval has been supported by findings from neuroimaging studies (Buckner & Petersen, 1996; Kapur et al., 1994; Nyberg, Cabeza, & Tulving, 1996; Petrides, 1995) and from studies of individuals with frontal lobe damage (Gershberg & Shinamuro, 1995; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994; Wheeler, Stuss, & Tulving, 1995).

Facilitation of Learning and Memory Through Executive Strategy Use

A robust finding in the cognitive and neuropsychological literature is that using executive strategies facilitates learning and memory. For example, processing verbal information at a deeper semantic level leads to better recall than processing information at a more shallow phonological or perceptual level (Craik & Lockhart, 1972; Kapur et al.,

Desirée A. White, Marsha J. Nortz, and Tammy Mandernach.
Department of Psychology, Washington University, Kathleen Huntington, Child Development and Rehabilitation Center, Doernbecher Children’s Hospital, Portland, Oregon; Robert D. Steiner, Child Development and Rehabilitation Center, Doernbecher Children’s Hospital, and Departments of Molecular and Medical Genetics, Oregon Health Sciences University.

We thank S. Bruce Dowton, Anne Hing, Carol Mantia, Keiko Ueda, and Diane Smith for their generous contributions to recruitment and medical characterization. We also thank Ryan Calong, Betsy Leritz, and Micah Rose for their contributions to data collection and data management.

Correspondence concerning this article should be addressed to Desirée A. White, Department of Psychology, Campus Box 1125, Washington University, One Brookings Drive, St. Louis, Missouri 63130. Electronic mail may be sent to dawhite@artscl.wustl.edu.

221
Knowledge of semantic category structures may also be used to develop strategies (e.g., semantic clustering of word lists) for efficiently organizing material in memory (Bousfield, 1953). In adult patients with prefrontal dysfunction related to dopamine disregulation, deficits have been observed in semantic clustering and learning, but retention of information over a delay interval, which is largely mediated by medial temporal structures, remains relatively intact (Daum et al., 1995; Massman, Delis, Butters, Levin, & Salmon, 1990; Taylor et al., 1990).

Children provide intriguing opportunities to explore the evolution of executive control processes as these unfold within the context of ongoing prefrontal maturation. Childhood represents a dynamic period with regard to both cognitive and prefrontal development, which extends into early adulthood (for a comprehensive review, see Krasnegor, Lyon, & Goldman-Rakic, 1997). It has been hypothesized that prefrontal maturation underlies an increase in the efficiency of executive control (Dempster, 1992; Gathercole & Baddeley, 1993), which in turn facilitates learning and memory. The spontaneous use of semantic clustering strategies occurs at a relatively late stage in development. This strategic approach is not effectively used by children until 10 or 11 years of age (for a review, see Bjorklund & Douglas, 1997).

Given the relationship between prefrontal function and executive control, we predicted that children with disruptions in prefrontal development would demonstrate organizational strategy deficits and subsequent impairments in learning and memory. We examined this issue in children with early treated phenylketonuria (PKU), a disorder that results in early dopamine depletion.

**Phenylketonuria**

PKU is a genetic disorder that affects approximately 1 in 10,000 children in the United States (Bickel, Bachmann, & Beckers, 1981; for a comprehensive overview of the disorder, see Scrivere, Kaufman, Einsmuth, & Woo, 1995). The disorder is characterized by a deficiency in monooaminergic neurotransmitters, including dopamine. Animal and human studies have shown that two key factors contribute to deficiencies in the availability of dopamine. First, phenylalanine is not properly metabolized into tyrosine, an essential precursor of dopamine (Curtius et al., 1981; Diamond, Caramitaro, Donner, Djali, & Robinson, 1994; Krause et al., 1985; Paans et al., 1996). This metabolic problem occurs because phenylalanine hydroxylase, the enzyme responsible for the conversion of phenylalanine into tyrosine, is deficient in individuals with PKU. Second, excess phenylalanine competes with available tyrosine for passage across the blood–brain barrier (Aragon, Gimenez, & Valdivieso, 1982). In addition to the biochemical brain changes associated with PKU, white matter abnormalities (Bick et al., 1991; Dyer et al., 1996; Hasselbalch et al., 1996; Lou et al., 1992; Thompson et al., 1993), decreased glucose metabolism (Hasselbalch et al., 1996), and electroencephalographic abnormalities (Krause, Epstein, Averbuck, Dembure, & Elsas, 1986; Pietz et al., 1993) have been identified.

The brain abnormalities associated with PKU result in mental retardation if the disorder is not properly treated by restricting the dietary intake of phenylalanine (Scrivere et al., 1995). Following the development of newborn screening techniques in the early 1960s, this profound cognitive sequela became a rarity. Because bodily protein requirements preclude the complete elimination of phenylalanine from the diet, however, children with early treated PKU sustain mild elevations in phenylalanine. In individuals with classic PKU who do not receive dietary treatment, blood phenylalanine levels are typically greater than 20 mg/dl (the levels in individuals without PKU are approximately 2 mg/dl). The ideal range of blood phenylalanine levels with dietary treatment is between 2 and 6 mg/dl (for a detailed discussion of this issue, see Scrivere et al., 1995), but because of the difficulties in maintaining strict dietary control, it is not unusual to see levels higher than the ideal.

With adherence to dietary restrictions, the majority of children with early treated PKU perform within normal limits on tests of general intellectual ability (Waisbren, Mahon, Schnell, & Levy, 1987), but their test scores are often lower than those of unaffected parents and siblings or healthy control children (Dobson, Williamson, Azen, & Koch, 1977; Koch, Azen, Friedman, & Williamson, 1984; Ris, Williams, Hunt, Berry, & Leslie, 1994). Studies of specific neuropsychological abilities in individuals with early treated PKU have yielded somewhat inconsistent findings (for overviews, see Mazzocco et al., 1994; Welsh, 1996). A thorough discussion of this issue is beyond the scope of the present investigation. Briefly, our review of the literature suggests that inconsistent findings may be related to variations in the measures used to assess particular ability areas, variations in the phenylalanine levels of study participants, and differences in the ages at which dietary treatment was implemented.

With these variables in mind, impairments have been identified across a range of neuropsychological domains. The areas of deficit include academic abilities (Berry, O’Grady, Perlmutter, & Botinger, 1979; Brunner, Jordan, & Berry, 1983), response speed (Krause et al., 1985; Pietz et al., 1993), visuospatial and visuomotor abilities (Brunner, Berch, & Berry, 1987; Fishler, Azen, Henderson, Friedman, & Koch, 1987; Koff, Boyle, & Pueschel, 1977; Pennington, Van Doorninck, McCabe, & McCabe, 1985; Ris et al., 1994), attention (Craft, Gourovitch, Dowton, Swanson, & Bonforte, 1992; Lou, Güttler, Lykkelund, Bruhn, & Niederwieser, 1985; Ris et al., 1994), and interhemispheric transfer of information (Banich, Passarotti, White, Nortz, & Steiner, 2000; Gourovitch, Craft, Dowton, Ambrose, & Sparta, 1994). As in adult populations with prefrontal dysfunction, deficits in executive control have been reported in children with early treated PKU (Brunner et al., 1983; Diamond, 1994; Diamond, Prevor, Callender, & Druin, 1997; Faust, Libon, & Pueschel, 1986; Pennington et al., 1985; Weglage, Pietsch, Funder, Koch, & Ullrich, 1996; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990). Language and long-term memory, however, have generally been reported as intact (Faust et al., 1986; Pennington et al., 1985; Welsh et al., 1990).
To date, the contributions of executive control to learning and memory have not been thoroughly investigated in school-age children with early treated PKU. In most studies, memory has been assessed using measures of retention over a delay interval. Little research has been conducted to examine the strategic organization of information to be learned and retained. We hypothesized that an analysis of the executive control processes involved in learning and memory would reveal impairments in children with early treated PKU, although retention of previously encoded information over time would remain relatively intact.

Method

Participants

A total of 23 (12 female, 11 male) children with early treated PKU were recruited through the Division of Medical Genetics/Department of Pediatrics at St. Louis Children's Hospital in Missouri and through the Metabolic Clinic at the Child Development and Rehabilitation Center at Doernbecher Children's Hospital in Portland, Oregon. Only children who were diagnosed and treated prior to 6 weeks of age were included. All children were on a dietary control program to limit phenylalanine intake at the time of participation. The phenylalanine levels obtained closest to time of participation in our study ranged from 2 to 16 mg/dl (M = 8.2 mg/dl, SD = 3.8 mg/dl).

The performances of children with PKU were compared with those of 23 (12 female, 11 male) healthy control children. For both PKU and control groups, children with histories of learning disorder or major medical disorder other than PKU were excluded. Children in both groups ranged from 6 to 17 years of age. Mean (SD) years of age for control and PKU groups were 10.7 (3.4) and 11.1 (3.7), respectively. Education ranged from 0.6 to 11.3 years for the control group and from 0.7 to 11.9 years for the group with PKU. Mean (SD) years of education for the control and PKU groups were 5.1 (3.2) and 5.8 (3.7), respectively. There were no significant group differences on these variables. Basic verbal and nonverbal abilities for each group were estimated using the Picture Vocabulary and Spatial Relations subtests of the Woodcock-Johnson Psycho-Educational Battery—Revised (Woodcock & Johnson, 1989). Mean (SD) verbal standard scores for the control and PKU groups were 113 (19) and 106 (19), respectively. Mean (SD) nonverbal standard scores for the control and PKU groups were 114 (16) and 107 (15), respectively. There were no significant group differences on these variables.

Because the spontaneous use of executive strategies develops relatively late, we wished to examine possible differences in performance on our study measures across developmental epochs. This was accomplished by subgrouping children into those who were less than 11 years of age (younger) and those who were greater than or equal to 11 years of age (older). Although the subgrouping procedure yielded small sample sizes, we believed that this approach was worthwhile for exploratory purposes. The resulting younger subgroups included 11 control children and 11 children with PKU. For both of these subgroups, mean age and education were 7.7 and 2.4 years, respectively; there were no significant group differences on these variables. The resulting older subgroups included 12 control children and 12 children with PKU. For the older control group, mean age and education were 13.4 and 7.7 years, respectively. For the older PKU group, mean age and education were 14.1 and 8.9 years, respectively.

Although this PKU subgroup was somewhat older and better educated than the control group, there were no significant group differences on these variables.

Procedure

Learning, memory, and executive control measures were administered using standard clinical procedures as components of a larger neuropsychological test battery.

Learning and memory. Learning and memory were evaluated using the California Verbal Learning Test—Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994). This measure was used to assess recall of a 15-item word list (List A) over five trials. Words comprising the list represented three semantic categories (things to play with, things to wear, and fruits). Subscores reflecting the following variables were examined: free recall of List A following a single presentation (Trial 1), free recall of List A following five presentations (Trial 5), free recall of a novel 15-word interference list (List B), recall of List A following short and long delay intervals, recognition discriminability, total intrusion errors, and total perseverative errors. Some of the scores that were generated using standard scoring procedures did not account for the effects of previous learning on subsequent recall. In these instances, we statistically controlled for such effects by including variables reflecting earlier recall as covariates in our analyses (see the Results section for further details). In addition, we evaluated the use of semantic clustering on Trials 1 and 5 by using the ratio of raw semantic cluster scores to the number of words correctly recalled on a given trial.

General executive control. Several standard clinical measures of executive control were administered. Category fluency was assessed by asking children to orally generate animal names, whereas phonemic fluency was assessed by asking children to orally generate words beginning with the “sh” sound (McCarthy, 1972). The number of correct responses, perseverative errors, and intrusion errors produced during a 1-min interval were recorded for each type of fluency.

The Stroop Color and Word Test (Golden, 1978) was used to assess processing speed and susceptibility to interference. Three conditions were administered. In the first condition, children were asked to read color names ("red," "green," "blue") that were printed in black ink. In the second condition, children were asked to name the color of ink (red, green, blue) in which Xs were printed. Finally, in the interference condition, children were asked to name the color of ink in which the words were printed while disregarding the written word. The number of correct responses produced during a 45-s interval was recorded for each condition. Because of inadequate reading skill, one 6-year-old child in each of the control and PKU groups did not complete this task.

Mental flexibility and abstraction were assessed using the Wisconsin Card Sorting Test (Heaton, 1981). Children were presented with a set of stimulus cards varying along the dimensions of color, form, and number. They were required to abstract sorting principles based on the examiner's feedback. At designated intervals, the correct sorting principle was switched, and children were required to detect and conform to a new principle. The number of correct responses and perseverative errors were recorded.

Results

Study variables were subjected to analysis of variance with group (control and PKU) as a between-subjects variable. Although age and education were not significantly different between the study groups and subgroups, the chil-
dren with PKU tended to be older and better educated. Because relatively small differences in these variables can affect performance during early development, we used age and education as covariates in all analyses. Means and standard deviations for raw group scores are presented in Table 1. In addition, Table 1 includes z scores for the PKU group as a whole, as well as for the younger and older PKU subgroups. The z scores are based on the means and standard deviations of the control group or control subgroups and are included to provide a context for interpreting the clinical significance of identified deficits in performance. As in our other analyses, age and education were statistically controlled when calculating the z scores. For the findings reported below, insignificant results reflect analyses for which p values were greater than .10.

Learning and Memory

On the CVLT-C, there was no significant group difference for Trial 1 recall, indicating that the PKU and control groups recalled approximately the same number of words following the initial presentation of List A. For Trial 5 recall, however, a significant group difference was observed, F(3, 42) = 5.18, p < .05. This finding remained significant after we statistically controlled for the contribution of initial learning as measured by Trial 1 recall, F(4, 41) = 4.84, p < .05. Thus, although initial learning and recall were equivalent, the children with PKU failed to learn and recall as many words as the control children by the fifth presentation of the word list.

To further explore the findings of equivalent recall on Trial 1 but differences in recall on Trial 5, we examined the use of semantic clustering. There was no significant group difference in semantic clustering for Trial 1; for Trial 5, however, a significant group difference was observed both before, F(3, 42) = 4.34, p < .05, and after, F(4, 41) = 4.45, p < .05, we controlled for semantic clustering on Trial 1. This finding reflects the fact that the control children made increasing use of semantic clustering across learning trials, whereas the children with PKU used this strategy less effectively. These findings suggest that children with PKU may have recalled fewer words than controls on the last learning trial because of their deficit in the use of semantic clustering. The notion that semantic clustering resulted in poorer recall for the PKU group is supported by the finding that the significant group difference in Trial 5 recall was no longer observed after we statistically controlled for differences in semantic clustering on Trial 5.

No significant group difference was observed for List B recall, again indicating that initial learning of a novel word list was equivalent between our study groups. In addition, no significant group differences were observed for short- or long-delay recall after we statistically controlled for differences on previous recall trials (i.e., Trial 5 recall and short-delay recall, respectively). These results suggest that previously encoded information was adequately maintained and retrieved by children with PKU. In a similar manner, no significant difference was observed between groups in recognition discriminability, intrusion errors, or perseverative errors.

With regard to our younger and older subgroupings, there were no statistically significant findings on any of the CVLT-C variables when we compared the performances of the younger control and younger PKU subgroups. A different picture emerged when we compared the performances of the older control and older PKU subgroups. Trial 5 recall was significantly poorer for this PKU subgroup after we

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California Verbal Learning Test—Children’s Version</td>
<td>6.87</td>
<td>1.46</td>
</tr>
<tr>
<td>Trial 1 (words correct)</td>
<td>11.35</td>
<td>3.17</td>
</tr>
<tr>
<td>Trial 5 (words correct)</td>
<td>6.04</td>
<td>2.40</td>
</tr>
<tr>
<td>List B (words correct)</td>
<td>0.27</td>
<td>0.19</td>
</tr>
<tr>
<td>Trial 1 semantic cluster ratio</td>
<td>0.41</td>
<td>0.21</td>
</tr>
<tr>
<td>Trial 5 semantic cluster ratio</td>
<td>10.35</td>
<td>3.39</td>
</tr>
<tr>
<td>Short-delay free recall (words correct)</td>
<td>10.43</td>
<td>2.94</td>
</tr>
<tr>
<td>Long-delay free recall (words correct)</td>
<td>6.43</td>
<td>3.45</td>
</tr>
<tr>
<td>Phonemic (words correct)</td>
<td>16.57</td>
<td>6.92</td>
</tr>
<tr>
<td>Category (words correct)</td>
<td>71.09</td>
<td>9.81</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>17.91</td>
<td>13.44</td>
</tr>
<tr>
<td>Correct responses</td>
<td>107.49</td>
<td>30.92</td>
</tr>
<tr>
<td>Perseverative errors</td>
<td>80.95</td>
<td>22.62</td>
</tr>
<tr>
<td>Stroop Color and Word Test</td>
<td>48.72</td>
<td>15.62</td>
</tr>
</tbody>
</table>

Note. Asterisks indicate significantly (p < .05) poorer performance for the group or subgroups with phenylketonuria (PKU).
controlled for Trial 1 recall, \( F(4, 19) = 7.04, p < .05 \). Although there was a trend toward less use of semantic clustering by the older PKU subgroup on Trial 5, \( F(4, 19) = 3.16, p = .09 \), statistical significance was not reached. Nonetheless, the significant subgroup difference in Trial 5 recall was no longer observed after we statistically controlled for differences in semantic clustering, again suggesting that reductions in semantic clustering may have contributed to poorer recall on the last learning trial. Examination of z scores indicated that reductions in Trial 5 recall and Trial 5 semantic clustering were more pronounced in older than younger children with PKU. In fact, the lowest z score for the older PKU group was on Trial 5 recall. It should be kept in mind, however, that this score was within one standard deviation of that of the older control group, which points to a fairly subtle deficit.

**General Executive Abilities**

A significant group difference was observed for phonemic fluency, \( F(3, 42) = 10.25, p < .005 \), with the PKU group generating fewer words than the control group. Category fluency was not significantly different between groups, nor were there significant group differences in intrusion or perseverative errors for either form of fluency. There were no significant group differences on scores from the Wisconsin Card Sorting Test. On the Stroop Color and Word Test, significant differences were observed in word reading, \( F(3, 40) = 6.52, p < .05 \), and color naming, \( F(3, 40) = 9.65, p < .005 \), with slower performances for children with PKU. There was also a significant difference in the color–word condition, \( F(3, 40) = 10.61, p < .005 \), but this finding was no longer significant after we statistically controlled for speed of word reading and color naming. This pattern reflects slowed information processing but intact resistance to interference in children with PKU.

An almost identical pattern emerged in comparisons between our younger and older control and PKU subgroups. Phonemic fluency was significantly reduced for both younger, \( F(3, 18) = 5.56, p < .05 \), and older, \( F(3, 20) = 4.76, p < .05 \), PKU subgroups as compared with their respective control subgroups; category fluency, however, was not significantly different. None of the subgroup comparisons of scores from the Wisconsin Card Sorting Test were significant. On the Stroop Color and Word Test, the younger PKU subgroup was significantly slower than the younger control subgroup on both word reading, \( F(3, 16) = 9.56, p < .05 \), and color naming, \( F(3, 16) = 9.90, p < .05 \), but there was no significant difference in the color–word condition after we statistically controlled for performance in the other two conditions. Examination of z scores suggested that processing speed was the area of most pronounced difficulty for the younger PKU subgroup. A similar pattern was observed in comparisons between the older control and PKU subgroups on the Stroop Color and Word Test. The older PKU subgroup was significantly slower than the older control subgroup on color naming, \( F(3, 20) = 7.68, p < .05 \), but there was only a trend toward slower performance on word reading, \( F(3, 20) = 3.14, p = .09 \). As was the case in the younger subgroup comparison, there was no significant group difference in the color–word condition after we statistically controlled for speed of word reading and color naming.

**Discussion**

In this study, we examined the hypothesis that children with prefrontal dysfunction related to developmental dopamine depletion would exhibit deficits in the use of organizational strategies that facilitate learning and memory. We further hypothesized that such deficits would occur within the context of relatively intact retention abilities. Our findings provided support for both hypotheses.

We found that immediate recall after one presentation of a word list was equivalent for children with early treated PKU and control children. Retention, recall, and recognition of previously learned information over a delay interval were also intact. The amount of verbal information learned over repeated trials, however, was an area of impairment and appeared to be related to a reduction in the spontaneous use of a semantic organizational strategy. This pattern of results suggests a deficit in the use of prefrontally mediated executive control processes to efficiently learn and organize long-term memory material, although basic memory abilities that are largely mediated by medial temporal structures were uncompromised. In addition, basic verbal and nonverbal skills were intact in children with PKU, indicating that impairments in learning and memory are related to higher order executive control deficits rather than to deficits in the more fundamental cognitive abilities that are necessary to complete learning and memory tasks.

Our findings across two early developmental epochs suggest that the aforementioned pattern of findings was driven primarily by the poorer performance of older children with PKU. Given that the use of higher order organizational learning and memory strategies does not typically develop until 10 or 11 years of age (Bjorklund & Douglas, 1997), this result was not surprising. Deficits cannot be identified until a child reaches the age at which particular skills are expected to emerge. Therefore, deficits in some aspects of learning and memory related to prefrontal dysfunction may not be identifiable until children reach the earliest stages of puberty.

It is interesting to note that, for the most part, performance decrements were not identified by using traditional measures of executive control for either younger or older children with PKU. Previous investigations of school-age children with PKU revealed executive impairments using the Stroop Color and Word Test (Weglage et al., 1996) and the Wisconsin Card Sorting Test (Pennington et al., 1985). On the Stroop Color and Word Test in our study, younger and older children with PKU processed information more slowly than controls, but performance on the executive component of this task (i.e., susceptibility to interference) was spared. In a similar manner, we identified no deficits in executive control using the Wisconsin Card Sorting Test. Mazzocco et al. (1994) also failed to find deficits in children with PKU when using this measure.
The inconsistencies across studies may be related to differences in the dietary control of phenylalanine. In both Pennington et al.’s (1985) and Weglage et al.’s (1996) studies, it was noted that only some children were on phenylalanine restricted diets at the time of neuropsychological evaluation; in our study, all children were on restricted diets. In addition, the upper limit of the phenylalanine range for children in Pennington et al.’s and Weglage et al.’s studies was considerably higher than that in our study (i.e., approximately 29 mg/dl in these studies vs. 16 mg/dl in our study). It is possible that the higher phenylalanine levels for some children in the two noted studies resulted in more pervasive prefrontal dysfunction and deficits in general executive control.

The only general executive control task on which deficits emerged in our study was phonemic fluency, and this was the case for both younger and older children with PKU. Category fluency was intact. Previous studies have indicated that temporal structures play a greater role in mediating category fluency whereas prefrontal structures play a greater role in mediating phonemic fluency (Martin, Wiggins, Lalonde, & Mack, 1994; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). Thus, the disparity between category and phonemic fluency lends support to our supposition that deficits in learning and memory in children with PKU are related to prefrontal dysfunction.

In combination with our results from the CVLT-C, these findings also suggest the possibility that children with PKU have particular difficulty on tasks requiring integrative processing between the prefrontal cortex and distal regions of the brain. In the case of the CVLT-C, the use of prefrontally mediated executive control seems to play a role in the efficient learning and recall of information in episodic memory. In the case of phonemic fluency, prefrontally mediated executive control seems to play a role in the efficient recall of information in semantic memory. Thus, deficits for children with PKU were identified only when the integration of processes subserved by prefrontal and posterior cortices was required for optimal performance, suggesting possible disruption in the interconnections between these regions.

Findings from cognitive studies of healthy children have suggested that such interconnections play a crucial role in the developmental improvements that occur in higher order cognitive skills. For example, in a study of working memory in children between the ages of 4 and 8 years, Luciana and Nelson (1998) found that the performance of younger and older children was comparable on tasks with minimal working memory demands. As working memory demands increased, however, age-associated differences were observed, with better performance by older children. The authors hypothesized that developmental improvements on working memory-demanding tasks were likely related to the increasing efficiency of prefrontal cortex function. They also hypothesized that improvements on such tasks were associated with age-related increases in the functional connectivity between prefrontal cortex and distal brain regions that play a role in performing complex tasks (e.g., posterior brain regions subserving sensory and perceptual abilities).

Neurophysiological evidence also indicates that the functional connectivity between frontal cortex and distal brain regions improves across early development. Using electroencephalography, Thatcher and colleagues (Thatcher, 1991; Thatcher, Walker, & Guidice, 1987) identified developmental spurs that correspond with the elaboration of interconnections between frontal cortex and distal brain regions (e.g., temporal, occipital, and parietal cortices). Thatcher (1991) likened the frontal cortex to the conductor of an orchestra and likened nonfrontal regions to the various sections of an orchestra. He suggested that the ongoing development of interconnections with the conductor permits increasing coordination among disparate musical sections, “resulting in the evolution of richer and deeper music at each step . . . until at adulthood the full cerebral ensemble is in orchestration” (Thatcher, 1991, p. 417).

Thatcher and colleagues (Thatcher, 1991; Thatcher et al., 1987) suggested that alterations in synaptic connectivity underlie the increased efficiency of interactions among frontal and distal brain regions. It is possible that this process is disrupted in children with PKU, particularly given the neurotransmitter abnormalities associated with this disorder. In addition, one might speculate that difficulty integrating cognitive processes subserved by different brain regions could be the result of white matter dysfunction. That is, the white matter abnormalities associated with PKU could result in disruption of the interplay between executive control and learning and memory abilities that are subserved by prefrontal and posterior cortex. Although future research is needed to investigate this issue, both neuroanatomical and neuropsychological findings lend support to this preliminary hypothesis.

Hasselbalch et al. (1996) identified structural and metabolic white matter changes in adults with PKU. Specifically, magnetic resonance imaging revealed white matter hyperintensities in the frontal and occipital lobes, whereas positron emission tomography revealed a reduction in glucose metabolism in anterior periventricular brain regions. From a neuropsychological perspective, deficits in the interhemispheric transfer of information, which is largely subserved by the corpus callosum, have been identified in two studies of children with early treated PKU (Banich et al., 2000; Gourouvitch et al., 1994). In addition, in the present study, we found reductions in processing speed in children with early treated PKU, which could be related to white matter dysfunction. Thus, although most investigators have framed their findings of neuropsychological deficits in children with PKU almost entirely in terms of prefrontal dysfunction, it is possible that some deficits result from the combined effects of prefrontal and white matter dysfunction.

In conclusion, further investigation is required to more precisely define the neuroanatomical interplay that underlies executive, learning, and memory impairments in children with early treated PKU. In addition, we cannot speak to the generalizability of our findings to the nonverbal domain. Should future research suggest that executive, learning, and memory abilities are spared when nonverbal materials are presented, a reanalysis of our hypotheses regarding the
neuroanatomical underpinnings of verbal impairments may be required. Nonetheless, to use the terminology of Moscovitch and a colleague (Moscovitch, 1992; Moscovitch & Umiltà, 1990, 1991), it appears that children with PKU experience deficits in the “organizational” and “strategic” aspects of verbal learning and memory but not in the “associative” aspects of verbal memory. In other words, these children experience difficulty working with memory rather than simply remembering.

References


Received April 13, 1999
Revision received October 5, 2000
Accepted October 6, 2000

---

**Low Publication Prices for APA Members and Affiliates**

**Keeping you up-to-date.** All APA Fellows, Members, Associates, and Student Affiliates receive—as part of their annual dues—subscriptions to the *American Psychologist* and *APA Monitor*. High School Teacher and International Affiliates receive subscriptions to the *APA Monitor*, and they may subscribe to the *American Psychologist* at a significantly reduced rate. In addition, all Members and Student Affiliates are eligible for savings of up to 60% (plus a journal credit) on all other APA journals, as well as significant discounts on subscriptions from cooperating societies and publishers (e.g., the American Association for Counseling and Development, Academic Press, and Human Sciences Press).

**Essential resources.** APA members and affiliates receive special rates for purchases of APA books, including the *Publication Manual of the American Psychological Association*, and on dozens of new topical books each year.

**Other benefits of membership.** Membership in APA also provides eligibility for competitive insurance plans, continuing education programs, reduced APA convention fees, and specialty divisions.

**More information.** Write to American Psychological Association, Membership Services, 750 First Street, NE, Washington, DC 20002-4242.