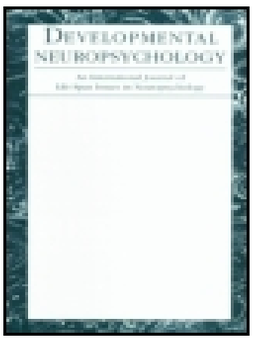

Developmental Neuropsychology

ISSN: 8756-5641 (Print) 1532-6942 (Online) Journal homepage: http://www.tandfonline.com/loi/hdvn20

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To cite this article: Marie T. Banich , Alessandra M. Passarotti , Desiree A. White , Marsha J. Nortz & Robert D. Steiner (2000) Interhemispheric Interaction During Childhood: II. Children With Early-Treated Phenylketonuria, Developmental Neuropsychology, 18:1, 53-71, DOI: 10.1207/S15326942DN1801_4

To link to this article: https://doi.org/10.1207/S15326942DN1801_4

Published online: 08 Jun 2010.

DEVELOPMENTAL NEUROPSYCHOLOGY, *18*(1), 53–71

Interhemispheric Interaction During Childhood: II. Children With Early-Treated Phenylketonuria

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This study examined whether children with early-treated phenylketonuria (ETPKU) exhibited a disruption in communication between the hemispheres as a function of computational complexity (Banich & Belger, 1990; Belger & Banich, 1992, 1998) when compared to neurologically uncompromised children who were matched in age and IQ. This investigation was motivated by findings that phenylketonuria affects myelination of neurons, including those that make up the corpus callosum, the main neural conduit for interhemispheric interaction. Children performed 2 tasks: a less

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complex physical-identity task and a more complex name-identity task. For both tasks, we compared performance on across-hemisphere trials, which require interhemispheric interaction, and on within-hemisphere trials, in which no hemispheric interaction is required. On the more complex name-identity task, children with ETPKU exhibited less of a benefit from across-hemisphere processing than did neurologically intact children. These results suggest that the interhemispheric interaction required to complete computationally complex tasks is compromised in children with ETPKU. Such an insufficiency may explain some of the attentional deficits observed in this group of children.

In this study, we examined interactions between the cerebral hemispheres in a group of children with early-treated phenylketonuria (ETPKU) as compared to children without neurological compromise. Phenylketonuria (PKU) has been demonstrated to affect myelination of neurons in both humans (e.g., Bauman & Kemper, 1982; Macombe et al., 1992) and animals (Reynolds, Burri, Mahal, & Herschkowitz, 1992). The corpus callosum, a massive white matter tract connecting the cerebral hemispheres, becomes heavily myelinated during childhood (Giedd et al., 1996; Yakovlev & Lecours, 1967). Hence, PKU may be expected to affect interhemispheric interaction.

PKU is a genetic disorder that produces an inborn error of metabolism caused by a deficiency of the enzyme phenylalanine hydroxylase (Woo, Lidsky, Güttler, Chandra, & Robson, 1983). The result is that phenylalanine (an amino acid) is not efficiently converted into tyrosine (another amino acid), which is a precursor of dopamine (a neurotransmitter). High levels of phenylalanine can lead to mental retardation (Koch, Azen, Friedman, & Williamson, 1982). Furthermore, glial cells are especially vulnerable in PKU, resulting in the noted compromise of myelination (Dyer et al., 1996).

Because of the negative effects of PKU, many countries have implemented mandatory screening for PKU at birth (e.g., Lund & Wamberg, 1970; Starfield & Holtzman, 1975). Neonates who screen positive are placed on a diet to restrict the intake of phenylalanine (Bickel, Gerrard, & Hicksman, 1954; Hudson, Mordaunt, & Leahy, 1970). Nonetheless, children with ETPKU may experience subtle deficits in cognition. For example, an overall drop in IQ relative to siblings has been observed (Dobson, Kushida, Williamson, & Friedman, 1976) and appears to be more pronounced when dietary control is poor (e.g., Smith, Beasley, & Ades, 1991). Although disruptions in myelination can be partially ameliorated through dietary control (e.g., Thompson et al., 1993), other evidence points to persisting white matter abnormalities (e.g., Bick et al., 1991).

The association between PKU and disrupted myelination led Gourovitch, Craft, Dowton, Ambrose, and Sparta (1994) to examine interhemispheric interaction in individuals with ETPKU who ranged from 6 to 23 years of age. These researchers

used the standard Poffenberger (1912) paradigm to examine the crossed–uncrossed difference (CUD) as an estimate of interhemispheric transfer time. In this paradigm, individuals must respond to a simple laterally presented visual stimulus (e.g., a light flash) by depressing a response key. In the uncrossed condition, the responding hand is controlled by the same hemisphere as that which receives the stimulus (e.g., a right-hand response is given to a stimulus presented to the right visual field [RVF]). In the crossed condition, the responding hand is controlled by the opposite hemisphere (e.g., RVF stimulus and left-hand response). In this case, information must cross the corpus callosum before a response can be initiated. The elongation of reaction time (RT) on the crossed condition relative to the uncrossed condition is taken as a measure of interhemispheric transfer time.

Gourovitch et al. (1994) found that individuals with ETPKU exhibited an exaggerated slowing in RT when the left hand was used to respond to targets presented in the RVF. They interpreted these results as indicating that interhemispheric transfer from the left to the right hemisphere was compromised in individuals with ETPKU as compared with their two other study groups (neurologically intact children and children with attention deficit hyperactivity disorder). In addition, the results revealed that a greater degree of slowing of interhemispheric transfer from the left hemisphere to the right was associated with higher phenylalanine levels at birth.

In addition to compromising the process of myelination, PKU also appears to selectively affect regions of the brain that are highly innervated by dopaminergic neurons. Studies have shown that phenylalanine levels are negatively correlated with dopamine level in individuals with PKU (e.g., Krause et al., 1985). Children with PKU exhibit deficits in contrast sensitivity, which has been suggested to be caused by abnormal functioning of retinal neurons, whose functioning is highly dependent on dopamine (Diamond & Herzberg, 1996). In addition, there are numerous reports that children with ETPKU experience dysfunction in a variety of cognitive abilities subserved by the frontal lobes (e.g., Diamond, Prevor, Callender, & Druin, 1997), a brain region that receives substantial dopaminergic innervation. For example, Smith, Klim, Mallozzi, and Hanley (1996) found that children with ETPKU showed greater deficits on tasks subserved by frontal as compared to posterior regions of the brain, and that the degree of phenylalanine elevation was significantly correlated with performance on tasks tapping frontal but not posterior brain function. Deficits on attentional tasks subserved by the frontal lobes (e.g., the Stroop task) were also revealed, and again, performance on these tasks was significantly correlated with serum phenylalanine levels (e.g., Weglage, Pietsch, Funders, Koch, & Ullrich, 1996).

It has been suggested that dopaminergic innervation is especially important for left-hemisphere function (e.g., Tucker & Williamson, 1984), which raises the possibility that children with PKU may exhibit specific left-hemisphere dysfunction. Such an association is suggested by the work of Craft, Gourovitch, Dowton,

Swanson, and Bonforte (1992). They used the Posner attention-cueing paradigm and found that males with ETPKU exhibited slowed responses to RVF targets following a left visual field (LVF) cue. This pattern is similar to that observed in patients with damage to the left parietal lobe and has been interpreted as a left-hemisphere deficit in the ability to disengage attention. In this situation, attention is first engaged by the LVF cue. Then attention must be disengaged before it can be moved in a rightward direction to the RVF target. The left hemisphere would be responsible for disengaging attention so that it could be moved in a rightward direction. In contrast, the right hemisphere would be responsible for disengaging attention such that it could be moved in a leftward direction (e.g., Kinsbourne, 1993; Posner, Inhoff, Friedrich, & Cohen, 1987). These authors suggested that such left-hemisphere dysfunction was mediated by dopamine, as they found a correlation between the phenylalanine levels at the time of testing and the degree of the disengagement deficit for males (at least when the delay between the cue and target was 800 msec).

In this study we wished to address two issues. First, we wished to examine whether children with ETPKU would exhibit deficits in interhemispheric interaction for higher order information rather than for the simple visual light flashes used in the Gourovitch et al. (1994) study. To do so, we used two matching tasks, one in which children decided if letters were physically identical (physical-identity task) and one in which they decided if letters had the same name (name-identity task). We also chose these tasks because it has been shown previously that the utility of interhemispheric interaction varies as a function of computational complexity (e.g., Banich & Belger, 1990; Belger & Banich, 1992, 1998; Weissman & Banich, 1999). The name-identity task is more complex than the physical-identity task, because not only must items be encoded on the basis of their physical characteristics and a response emitted, but the letters must be transformed into some other code (e.g., a case-neutral code, a name code) before a decision can be made.

In brief, our prior studies have shown that when tasks are relatively simple, they are performed more rapidly and accurately by one hemisphere as compared with having both hemispheres cooperate to perform the task. In contrast, for more complex tasks, across-hemisphere processing provides a performance advantage. In our previous work, we have shown that these effects are observed in both adults (Banich & Belger, 1990; Belger & Banich, 1992, 1998) and school-age children (Banich, Passarotti, & Janes, this issue). We have suggested that a within-hemisphere advantage occurs under conditions of low complexity because there is no computational gain from dividing processing across the hemispheres to offset the costs entailed in the "overhead" of coordinating processing across the hemispheres. For more computationally complex tasks, however, this overhead is relatively less important compared to the computational power gained by dividing processing across the hemispheres; this results in the across-hemisphere advantage.

The issue explored in this study was whether children with ETPKU would exhibit a pattern of performance similar to that of neurologically intact children. To differentiate between various possible types of interhemispheric deficits, it was important that two tasks be used, one that yielded a within-hemisphere advantage and one that yielded an across-hemisphere advantage (for a more detailed discussion, see Banich & Shenker, 1994). One possibility is that ETPKU may impede interhemispheric interaction such that performance on all across-hemisphere trials is disrupted. In this case, children with ETPKU would exhibit performance more similar to that of patients with callosal dysfunction or callosal disconnection. On the other hand, the deficit could be more subtle and may emerge only when across-hemisphere processing is critical or beneficial to task performance, as under conditions of high complexity. In this case, we would expect to observe the deficit on the name-identity task but not on the physical-identity task.

The second issue we wished to further explore was the possibility that children with ETPKU exhibit a specific deficit in left-hemisphere function. The Banich and Belger (1990) paradigm is especially useful in this regard because it allows one to examine not only differences between within- and across-hemisphere processing, but hemispheric differences as well, both on within- and across-hemisphere trials. In our paradigm, three items are presented on every trial. A lateralized target item appears below two probes, one positioned in each visual field. On within-hemisphere trials, both matching items are presented in the same visual field, and hence we assume that the decision is subserved by the contralateral hemisphere (e.g., the left hemisphere makes the match decision when the matching items are presented in the RVF). On across-hemisphere trials, each hemisphere receives one of the matching items, which allows for the possibility that either hemisphere could make the match decision.

Our prior research has allowed us to determine which hemisphere makes the match decision on across-hemisphere trials. We have evidence that the decision is made by the hemisphere contralateral to the matching probe item. Hence, when the target is presented in the LVF and the probe is presented in the RVF (across-probe RVF trials), the decision is subserved by the left hemisphere. In contrast, when the target is presented in the RVF and the probe is presented in the LVF (across-probe LVF trials), the decision is subserved by the right hemisphere (see Figure 1).

Evidence for this assertion comes from a study in which we manipulated the mood of our participants into one of two mood states, either neutral or sad. Consistent with prior reports that a sad mood differentially affects right-hemisphere performance (e.g., Ladavas, Nicoletti, Umilta, & Rizzolatti, 1984), we found that, compared with a neutral mood state, a sad mood state reduced performance on within-hemisphere LVF trials relative to within-hemisphere RVF trials. Likewise, we found a reduction in performance on across-probe LVF trials relative to across-probe RVF trials, suggesting that the match decision is made by the right hemisphere on across-probe LVF trials (Banich, Stolar, Heller, & Goldman,

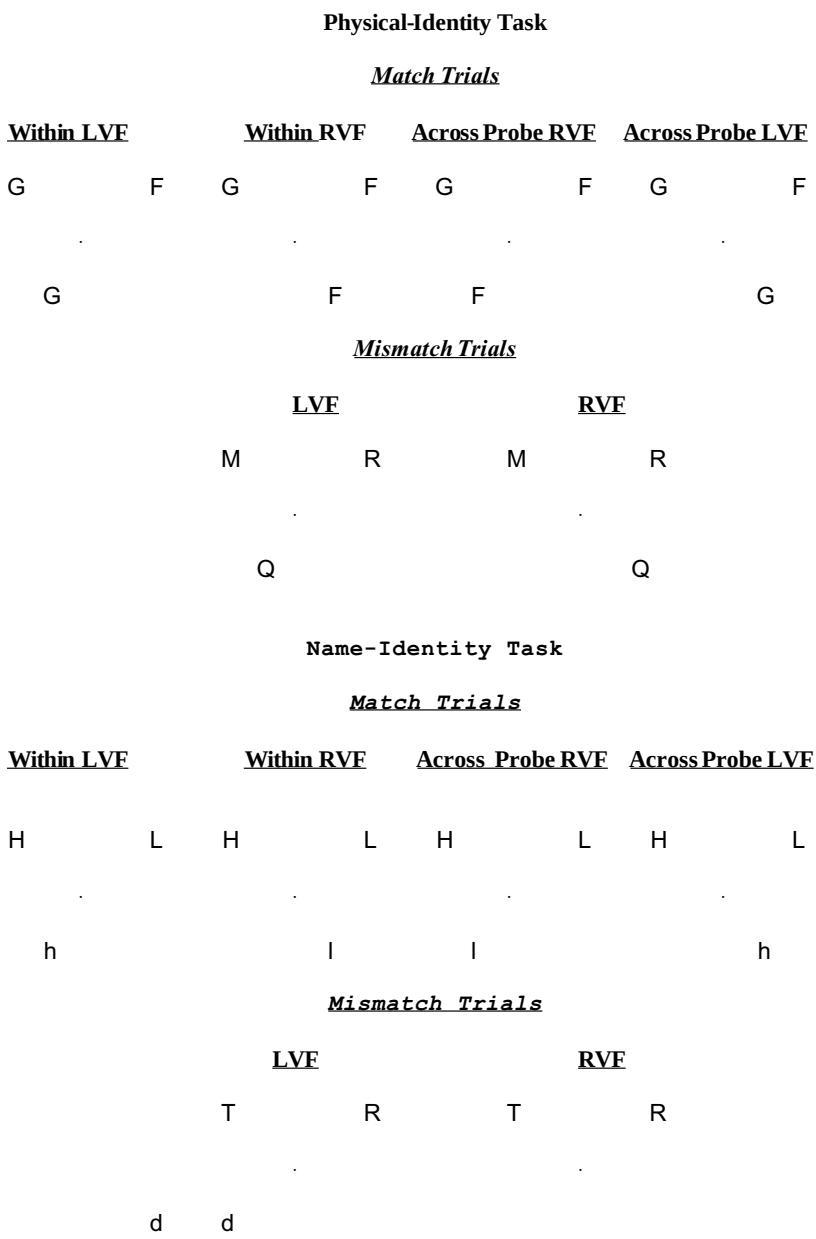

FIGURE 1 Sample trials for the physical-identity and name-identity tasks. Note. LVF = left visual field; RVF = right visual field.

1992). Thus, if children with ETPKU have specific left-hemisphere dysfunction, their performance should be compromised on within-RVF trials and on across-probe RVF trials.

In sum, we had two main objectives in our study. First, we wished to determine if children with ETPKU exhibit a disruption in interhemispheric processing. If such a disruption were observed, we wished to more carefully characterize it, determining whether it was exhibited under all conditions or only under situations with high computational demands. Second, we wished to examine whether there is any evidence that either hemispheric or interhemispheric processing is asymmetrically disrupted in children with ETPKU. More specifically, we wished to examine whether children with ETPKU exhibited left-hemisphere dysfunction or disruption in the transfer of information from the left hemisphere to the right.

METHOD

Participants

Participants were 9 children with ETPKU and 12 neurologically intact children. Children with ETPKU were recruited through the Phenylketonuria Clinic in the Division of Medical Genetics/Department of Pediatrics at St. Louis Children's Hospital, Washington University School of Medicine. All of the children had been diagnosed with PKU prior to 6 weeks of age and were on a diet to restrict phenlyalanine intake at the time of participation. The phenylalanine levels obtained closest to time of participation in our study ranged from 5.9 mg/dl to 13.7 mg/dl (M = 9.67 mg/dl, SD = 3.0 mg/dl). The neurologically intact children were from the St. Louis community.

None of the children in either the ETPKU or the neurologically intact groups had histories of learning disabilities or major medical disorders other than PKU. Children in the ETPKU group ranged from 6 to 15 years of age, whereas children in the neurologically intact group ranged from 7 to 14 years of age. Mean ages for the ETPKU and for the neurologically intact groups were 10.6 (SD = 2.8) and 10.7 (SD = 2.2) years, respectively. General intellectual abilities (i.e., IQ) as estimated by the Picture Vocabulary subtest from the Woodcock–Johnson Psychoeducational Battery–Revised (Woodcock & Johnson, 1989) ranged from 96 to 125 for the ETPKU group and from 90 to 138 for the neurologically intact group. Mean estimated IQs for the ETPKU and for the neurologically intact groups were 114 (SD = 11.9) and 116 (SD = 16.1), respectively. There were no significant between-group differences on any of these variables (see Table 1).

The sample of ETPKU children consisted of two right-handed boys, two left-handed boys, four right-handed girls, and one left-handed girl. The sample of neurologically intact children consisted of two right-handed boys, two

TABLE 1
Characteristics of Phenylketonuria and Neurologically Intact Participants

Group	*Sex*	*Handedness*	*Age at Testing*[a]	*PPVT (Standardized)*[b]
Phenylketonuria intact individuals				
1	Male	Right	12.25	124
2	Female	Right	7.50	110
3	Female	Right	9.00	122
4	Female	Left	9.25	120
5	Female	Right	6.75	125
6	Male	Right	13.75	100
7	Male	Left	11.00	124
8	Female	Right	15.00	96
9	Male	Left	10.75	101
Neurologically intact individuals				
1	Female	Right	11.00	115
2	Male	Right	12.75	94
3	Female	Left	12.50	90
4	Female	Right	8.75	128
5	Male	Left	13.75	118
6	Female	Right	9.75	104
7	Female	Right	14.00	135
8	Male	Right	11.50	120
9	Female	Right	9.00	132
10	Female	Right	8.75	138
11	Female	Right	7.75	112
12	Male	Left	8.50	100

Note. PPVT = Peabody Picture Vocabulary Test.

[a]For the phenylketonuria-intact group, mean age at testing was 10.58 years (*SD* = 2.76). For the neurologically-intact group, mean age was 10.67 years (*SD* = 2.20).

[b]For the phenylketonuria-intact group, mean PPVT was 113.56 (*SD* = 11.85). For the neurologically-intact group, mean PPVT was 115.50 (*SD* = 16.07).

left-handed boys, seven right-handed girls, and one left-handed girl. Previously, we have found no difference between right- and left-handed adults in the interhemispheric processing measures employed in this study (Belger & Banich, 1998).

Procedure

Children were administered the Banich and Belger (1990) interhemispheric task as part of a larger neuropsychological test battery. Results from this battery will be reported elsewhere. It should be noted that the procedure used in this study (and described later) was identical to that of Banich, Passarotti, and Janes (this issue), except that, because of time constraints, there were fewer experimental trials.

Stimuli. Stimuli were the uppercase and lowercase versions of the letters *A, B, D, E, F, G, H, L, M, Q, R,* and *T* presented in Chicago font. Each display contained three black letters on a white background. Each letter subtended no more than .95° horizontally and 1.3° vertically. The two probe items were centered 1.6° above fixation and 2.68° laterally from midline, with one in each visual field. The target item was centered 1.6° below fixation and 1.6° laterally from midline. For the physical-identity task, all items were uppercase letters. For the name-identity task, the two probes were presented in uppercase and the target was presented in lowercase.

One half of all trials were match trials, in which one of the probes matched the target item, and half were mismatch trials, in which all three letters were different. For match trials, half were within-hemisphere trials, in which the target and the matching probe were presented in the same visual field, and half were across-hemisphere trials, in which the target and matching probe were presented in opposite visual fields. For all conditions in both match and mismatch trials, the target appeared equally often in the LVF and RVF (see Figure 1).

Experimental presentation. Children received 8 practice trials and 80 test trials. At the beginning of a trial, a black square appeared for 300 msec, drawing attention to this fixation point. Next, the three letters (along with a smaller fixation square) were displayed for 200 msec. After the stimulus display, a blank white screen appeared for 3,000 msec, during which time children were asked to press the space bar if there were a match and to refrain from responding if there were no match (go–no-go responses). RT was recorded for each matching trial. The task required approximately 45 min to complete.

Equipment

The task was run on a Macintosh Plus with SuperLab 1.55 software.

RESULTS

Accuracy

To obtain a measure of accuracy that was free from the response biases of individual children (e.g., responding impulsively or overly conservatively), we utilized *d′*. We performed a repeated measures analysis of variance (ANOVA) on *d′* with the between-subject factor of *group* (ETPKU, neurologically intact) and the within-subjects factors of *task* (physical identity, name identity), *trial type* (within hemisphere, across hemisphere), and *visual field of the matching probe*

(LVF, RVF). We included this last factor (visual field of the matching probe) in our analysis because our prior work suggested that the match decision is made by the hemisphere contralateral to this probe on both within-hemisphere and across-hemisphere trials (see Banich, 1995, for a longer explanation).

The analysis revealed a main effect of task, $F(1, 18) = 23.54$, $p < .0003$, because accuracy was higher for the physical-identity task ($d' = 3.65$) than for the name-identity task ($d' = 2.96$). A main effect of trial type was also observed, $F(1, 18) = 8.74$, $p < .01$, as responses were more accurate on across-hemisphere trials ($d' = 3.41$) than on within-hemisphere trials ($d' = 3.20$). Both of these effects were modified by a significant four-way Group × Task × Trial Type × Visual Field of the Matching Probe interaction, $F(1, 18) = 9.98$, $p < .005$ (see Figures 2 and 3).

Decomposition of this interaction indicated that the Group × Trial Type × Visual Field of the Matching Probe interaction was not significant for the physical-identity task. On this task, neither group exhibited either a within- or an across-hemisphere advantage ($p > .10$). In contrast, the Group × Trial Type × Visual Field of the Matching Probe interaction was significant for the name-identity task, $F(1, 18) = 11.06$, $p < .005$. Decomposition of this interaction revealed that the patterns did not differ for the ETPKU and neurologically intact groups for LVF-probe name-identity trials because neither group exhibited a within- or an across-hemisphere advantage. However, the pattern for the two groups differed on

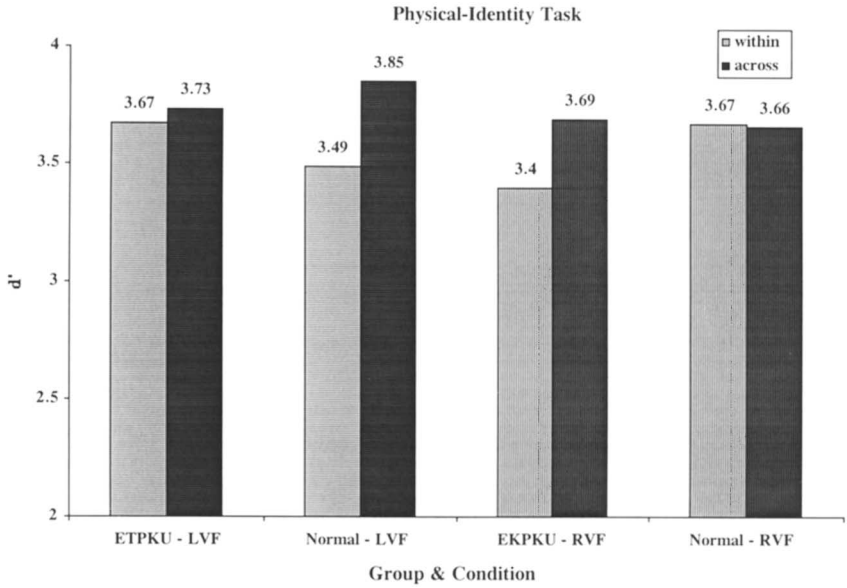

FIGURE 2 Mean accuracy (d') for the physical-identity task. *Note.* ETPKU = early-treated phenylketonuria; LVF = left visual field matching probe; RVF = right visual field matching probe.

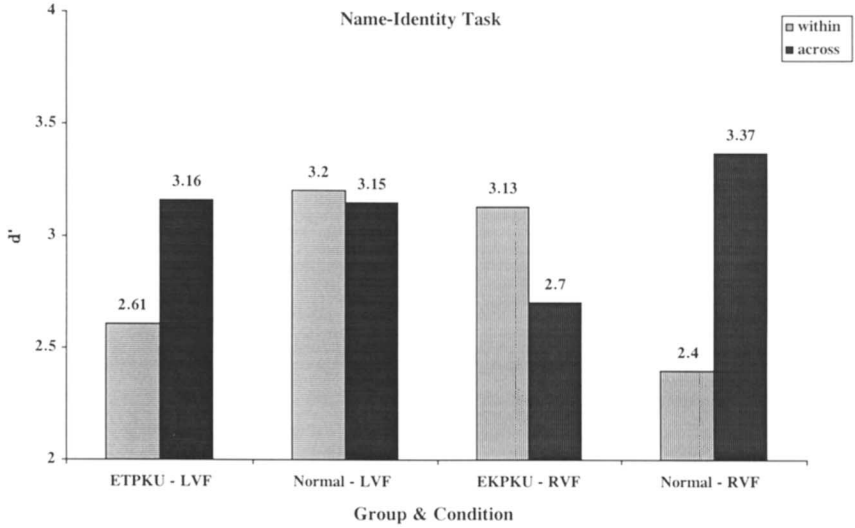

FIGURE 3 Mean accuracy (d') for the name-identity task. *Note.* ETPKU = early-treated phenylketonuria; LVF = left visual field matching probe; RVF = right visual field matching probe.

RVF-probe name-identity trials, $F(1, 18) = 18.16$, $p < .0005$. The ETPKU group exhibited neither a within- nor an across-hemisphere advantage ($p > .09$), whereas the neurologically intact group exhibited a highly significant across-hemisphere advantage, $F(1, 18) = 19.42$, $p < .0005$, a pattern also observed in a separate sample of neurologically intact children (Banich, Passarotti, & Janes, this issue).

To examine whether there was any evidence of a specific left-hemisphere deficit in children with ETPKU, we performed tests of simple effects to compare their responses on RVF-probe name-identity trials to those of the neurologically intact group. There were no significant differences in performance between the groups for either within-hemisphere or across-hemisphere trials.

RT

We performed a repeated measures ANOVA on median RT using the same between- and within-subjects factors as noted previously. As in the d' analysis, this analysis revealed a main effect of Task, $F(1, 18) = 80.73$, $p < .0001$, as RT for physical-identity trials (520 msec) was faster than that for name-identity trials (728 msec). A main effect of trial type was also observed, $F(1, 18) = 5.55$, $p < .05$, as RT for within-hemisphere trials (605 msec) was faster than that for across-hemisphere trials (643 msec). The main effect of trial type was opposite to that found for d'. Be-

cause there were several higher order significant interactions that modified this main effect, we discuss the possibility of a speed–accuracy trade-off when we consider these higher order effects. These included significant interactions of Trial Type × Visual Field of the Matching Probe, $F(1, 18) = 8.09$, $p < .03$, and of Task × Trial Type × Visual Field of the Matching Probe, $F(1, 18) = 9.60$, $p < .01$.

Although the four-way interaction of Group × Task × Trial Type × Visual Field of the Matching Probe did not reach conventional levels of significance ($p < .20$), we performed a decomposition similar to that performed on the *d´* data to look for correspondence between the two measures of performance (i.e., *d´* and median RT.

As with the *d´* data, there was no Group × Trial Type × Visual Field of the Matching Probe interaction for the physical-identity task ($p > .40$) because both groups demonstrated a significant within-hemisphere advantage, $F(1, 18) = 14.38$, $p < .003$. For the name-identity task, the Group × Trial Type × Visual Field of the Matching Probe interaction approached significance ($p < .10$). Similar to the *d´* data, there was no group difference in the processing of LVF-probe trials for the name-identity task ($p > .35$). Surprisingly, both groups showed a significant within-hemisphere advantage, $F(1, 18) = 5.89$, $p < .05$. Although we may have expected a within-hemisphere advantage for the ETPKU group, we would not have expected such a pattern for the neurologically intact children. Previous results with

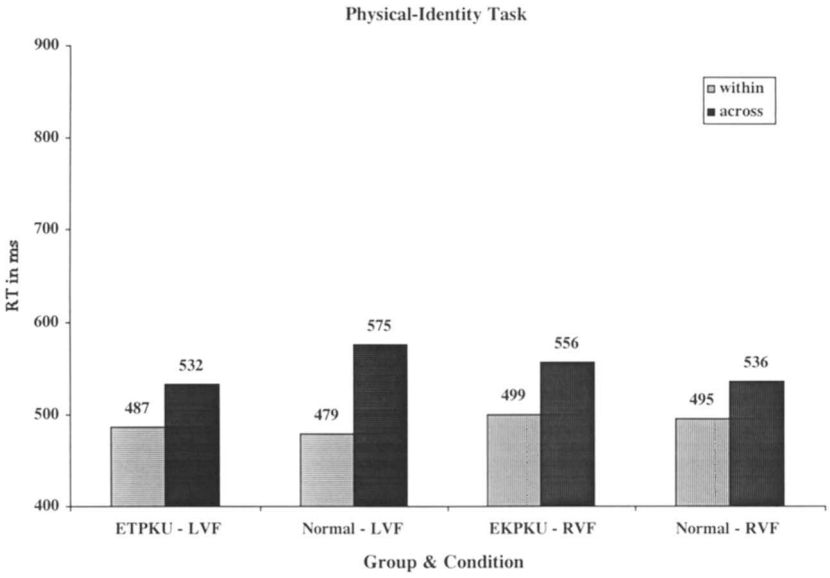

FIGURE 4 Median reaction time (RT) for the physical-identity task. *Note.* ETPKU = early-treated phenylketonuria; LVF = left visual field matching probe; RVF = right visual field matching probe.

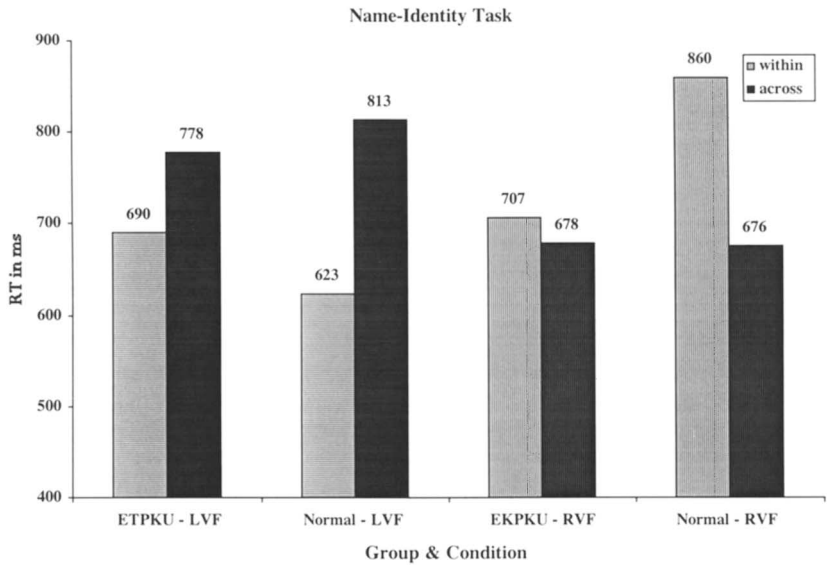

FIGURE 5 Median reaction time (RT) for the name-identity task. *Note.* ETPKU = early-treated phenylketonuria; LVF = left visual field matching probe; RVF = right visual field matching probe.

neurologically intact children (Banich, Passarotti, & Janes, this issue) and adults (Banich & Belger, 1990; Belger & Banich, 1992, 1998) suggest that the name-identity task typically yields an across-hemisphere advantage. Hence, the results in this study may represent a speed–accuracy trade-off for this group because the *d´* measure yielded neither a within- nor an across-hemisphere advantage.

For RVF-probe name-identity trials, the Group × Trial Type interaction approached but failed to reach significance ($p < .08$). Tests of simple effects revealed that for the ETPKU group there was neither a within- nor an across-hemisphere advantage ($p > .60$), whereas for the neurologically intact group there was a significant across-hemisphere advantage, $F(1, 18) = 12.68$, $p < .003$, which was consistent with the pattern we observed in a separate sample of neurologically intact children (Banich, Passarotti, & Janes, this issue). Hence, across both measures of performance, the groups appear to differ on RVF-probe name-identity trials, with the neurologically intact children showing a pattern similar to that obtained previously in adults (i.e., an across-hemisphere advantage) and the children with ETPKU not manifesting this pattern.

Once again, we performed tests of simple effects in an attempt to determine whether there were group differences in performance on RVF-probe name-identity trials. Contrary to what would be expected if there were left-hemisphere dysfunction in the ETPKU group, their RT was actually marginally significantly faster than that

of the neurologically intact group, $F(1, 18) = 4.127$, $p < .06$, for within-hemisphere trials. No group differences were noted for across-hemisphere trials ($p > .98$).

DISCUSSION

The results of this study indicate that interhemispheric processing is less advantageous to children with ETPKU than to children who have no neurological compromise. Our results suggest that ETPKU has an additional effect on interhemispheric interaction beyond those reported in prior studies. Previously, Gourovitch et al. (1994) found deficits in the speed of interhemispheric transmission from the left to right hemisphere in children with ETPKU, as inferred from a Poffenberger (1912) paradigm, which requires simple integration of sensorimotor information. Our task, in contrast, was more cognitively demanding than the Poffenberger paradigm, but children with ETPKU also exhibited an atypical pattern of interhemispheric interaction.

However, this effect was not ubiquitous, and it is instructive to examine the conditions under which it occurred. First, the patterns of performance of children with ETPKU and of neurologically intact children did not differ for a computationally simple physical-identity task that typically yields a within-hemisphere advantage. Hence, no disruption in interhemispheric interaction was noted when such interaction was not particularly beneficial to task performance. However, when interhemispheric interaction would aid task performance, as was the case for the name-identity task, children with ETPKU did not exhibit the typical across-hemisphere interaction. Thus, it does not seem that their callosal functioning was affected under all conditions, but only when callosal channels were taxed and required for more efficient and accurate performance than was observed when all critical information was directed to a single hemisphere.

Second, the differences between neurologically intact children and those with ETPKU were most apparent for trials in which the left hemisphere made the match decision. Consistently across both the d' and RT measures for the RVF-probe trials, the children with ETPKU did not exhibit a significant across-hemisphere advantage, whereas the neurologically intact children did. This pattern may lead one to conclude that the deficit in interhemispheric interaction is asymmetric, a conclusion consistent with that of Gourovitch et al. (1994). However, there are reasons not to jump to such a conclusion. The data of the neurologically intact children on LVF-probe name-identity trials appear to be contaminated by a speed–accuracy trade-off, which means that these data do not provide a good baseline against which to evaluate whether the children with ETPKU have atypical interhemispheric interaction. Hence, as an exploratory analysis we compared performance on the name-identity task of children with ETPKU to that of a larger sample of neurologically intact children (Banich, Passarotti, & Janes, this issue) who were not matched for age and IQ. In this

comparison, a difference between the children with ETPKU and the neurologically intact children was observed for LVF-probe name-identity trials, and once again the children with ETPKU failed to manifest an across-hemisphere advantage. Thus, rather than having specific left-hemisphere dysfunction, it may be that the deficit in children with ETPKU is apparent only under conditions in which an across-hemisphere advantage is obtained in neurologically intact children.

There are other reasons to believe that the performance of children with ETPKU may not be limited to left-hemisphere trials. The pattern we observed does not map well onto the results of Gourovitch et al. (1994). In their study, children with ETPKU exhibited a specific deficit when the left hemisphere received the stimulus and the right hemisphere generated the response. In contrast, in our study the most consistent evidence for atypical interhemispheric processing in children with ETPKU was observed on RVF-probe trials in which the decision was subserved by the left hemisphere. For our results to accord well with those of Gourovitch et al., deficits would have had to be observed not on RVF-probe trials but rather on across-hemisphere LVF-probe trials in which the decision was subserved by the right hemisphere. Therefore, rather than positing an asymmetric effect, we believe that children with ETPKU are likely to exhibit deficits whenever across-hemisphere processing is particularly beneficial to task performance.

Another issue we wished to address was whether there was a specific deficit in left-hemisphere functioning in children with ETPKU. Our data do not provide support for this notion. Our method allowed us to address this question in two separate manners. First, we were able to compare performance for the two groups of children on only those items in which all the critical sensory information was directed to the left hemisphere and in which the left hemisphere subserved a response (within RVF probe trials). Second, we were able to compare performance for the two groups of children on across-hemisphere RVF-probe items in which the critical sensory information was divided across the hemispheres, and in which the left hemisphere subserved a response. Neither of these comparisons provided any hint of a specific deficit in left-hemisphere processing for children with ETPKU, because their level of performance was not inferior to that of the neurologically intact children.

It is unclear which portion of the callosum is critical for performance of the Banich and Belger (1990) task. Copeland & Zaidel (1997) found that our interhemispheric tasks could not be performed by a split-brain patient with anterior section of the corpus callosum. Their findings suggest that the task is supported by callosal transfer of information between frontal regions. Hence, the deficits observed in the children with PKU may be related to frontal lobe function, which has a high degree of dopaminergic innervation. Although there is some recent evidence that the bilateral comparison of letters can be supported by the anterior commissure in acallosal individuals (Brown, Jeeves, Dietrich, & Burnison, 1999), we think it unlikely that this structure is playing the main role in our task in neurologically intact individuals. The anterior commissure appears to be able to

support the transfer only of information that is relatively simple. For example, although a letter-matching task containing two sets of items can be performed in individuals without a corpus callosum but with an intact anterior commissure, a more complex pattern task cannot. We think that the complexity of our name-identity task exceeds that which can be supported by the anterior commissure.

In sum, our results provide evidence of atypical interhemispheric processing in children with ETPKU. However, this effect is not ubiquitous and only appears to emerge under conditions in which across-hemisphere processing is beneficial to performance. Thus, although basic interhemispheric processing mechanisms appear to be intact, children with ETPKU cannot accrue a performance advantage by dividing processing across the hemispheres under conditions of high computational complexity. It is possible that this inability may help to explain some of the other cognitive deficits observed in ETPKU. As reviewed by Banich (1998), interaction between the hemispheres appears to modulate and enhance a wide variety of attentional functions. It is noteworthy that attentional functioning is often compromised in individuals with PKU. For example, it has been reported that individuals with ETPKU have difficulties in sustained attention (e.g., Schmidt, Burgard, & Rupp, 1996; Schmidt et al., 1994). It is interesting to note that poorer callosal functioning in normal children has been linked to poor performance on sustained attention tasks (Rueckert & Levy, 1996; Rueckert, Sorenson, & Levy, 1994). Attentional deficits in ETPKU are not limited to sustained attention and have been found for other attentional tasks, such as the Stroop task (e.g., Weglage et al., 1996). Both lesion studies (e.g., Vendrell et al., 1995) and neuroimaging studies (e.g., Banich et al., 2000; Bench et al., 1993; Carter, Mintun, & Cohen, 1995) suggest that attentional selection in the Stroop task relies in part on the prefrontal cortex. Disruptions in interhemispheric interaction may also explain some of these effects in children with ETPKU, as we have found that interhemispheric interaction can modulate Stroop performance (Shenker & Banich, 2000). Future studies may fruitfully explore the relation between deficits in attentional functioning and interhemispheric interaction on tasks such as these.

ACKNOWLEDGMENTS

Portions of this research project were supported by Grant R01 MH 54217 from the National Institute of Mental Health to the Marie T. Banich.

We thank S. Bruce Dowton, Anne Hing, Carol Mantia, and Keiko Ueda for their generous contributions to recruitment and medical characterization of children with early-treated phenylketonuria. We also thank Ryan Calong, Betsy, Leritz, Tammy Mandernach, and Micah Rose for their contributions to data collection and data management. Finally, we thank Warren S. Brown for many helpful comments on previous versions of the article.

REFERENCES

Banich, M. T. (1995). Interhemispheric interaction: Mechanisms of unified processing. In F. L. Kitterle (Ed.), *Hemispheric communication: Mechanisms and models* (pp. 271–300). Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Banich, M. T. (1998). The missing link: The role of interhemispheric interaction in attentional processing. *Brain and Cognition, 36,* 128–157.

Banich, M. T., & Belger, A. (1990). Interhemispheric interaction: How do the hemispheres divide and conquer a task? *Cortex, 26,* 77–94.

Banich, M. T., Milham, M. P., Atchley, R. A., Cohen, N. J., Webb, A., Wszalek, T., Kramer, A. F., Liang, Z.-P., Wright, A., Shenker, J., Magin, R., Barad, V., Gullett, D., Shah, C., & Brown, C. (2000). fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. *Journal of Cognitive Neuroscience, 12,* 1–13.

Banich, M. T., & Shenker, J. I. (1994). Investigations of interhemispheric processing: Methodological considerations. *Neuropsychology, 8,* 263–277.

Banich, M. T., Stolar, N., Heller, W., & Goldman, R. (1992). A deficit in right-hemisphere performance after induction of a depressed mood. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 5,* 20–27.

Banich, M. T., Passarotti, A. M., & Janes, D. (2000/this issue). Interhemispheric interaction during childhood: I. Neurologically intact children. *Developmental Neuropsychology, 18,* 33–51.

Bauman, M. L., & Kemper, T. L. (1982). Morphologic and histo-anatomic observations of the brain in untreated human phenylketonuria. *Acta Neuropathologica, 58,* 55–63.

Belger, A., & Banich, M. T. (1992). Interhemispheric interaction affected by computational complexity. *Neuropsychologia, 30,* 923–931.

Belger, A., & Banich, M. T. (1998). Costs and benefits of integrating information between the cerebral hemispheres: A computational perspective. *Neuropsychology, 12,* 380–398.

Bench, C. J., Frith, C. D., Grasby, P. M., Friston, K. J., Paulesu, E., Frackowiak, R. S. J., & Dolan, R. J. (1993). Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia, 31,* 907–922.

Bick, U., Fahrendorf, G., Ludolph, A. C., Vassallo, P., Weglage, J., & Ullrich, K. (1991). Disturbed myelination in patients with treated hyperphenylalaninaemia: Evaluation with magnetic resonance imaging. *European Journal of Pediatrics, 150,* 185–189.

Bickel, H., Gerrard, J., & Hicksman, E. M. (1954). The influence of phenylalanine intake on the chemistry and behavior of a phenylketonuric child. *Acta Paediatrica, 43,* 64–77.

Brown, W. S., Jeeves, M. A., Dietrich, R., & Burnison, D. S. (1999). Bilateral field advantage and evoked potential interhemispheric transmission in commissurotomy and callosal agenesis. *Neuropsychologia, 37,* 1165–1180.

Carter, C., Mintun, M., & Cohen, J. D. (1995). Interference and facilitation effects during selection attention: An $H_2{}^{15}O$ PET study of Stroop task performance. *Neuroimage, 2,* 264–272.

Copeland, S. A., & Zaidel, E. (1997). Callosal channels and the bilateral distribution advantage: Patterns in agenesis and partial section of the corpus callosum [Abstract]. *Journal of the International Neuropsychological Society, 3,* 50.

Craft, S., Gourovitch, M. L., Dowton, S. B., Swanson, J. M., & Bonforte, S. (1992). Lateralized deficits in visual attention in males with developmental dopamine depletion. *Neuropsychologia, 30,* 341–351.

Diamond, A., & Herzberg, C. (1996). Impaired sensitivity to visual contrast in children treated early and continuously for phenylketonuria. *Brain, 119,* 523–538.

Diamond, A., Prevor, M. B., Callender, G., & Druin, D. P. (1997). Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. *Monographs of the Society for Research in Child Development, 62,* 1–205.

Dobson, J. C., Kushida, E., Williamson, M., Friedman, E. G. (1976). Intellectual performance of 36 phenylketonuria patients and their nonaffected siblings. *Pediatrics, 58,* 53–58.

Dyer, C. A., Kendler, A., Philibotte, T., Gardiner, P., Cruz, J., & Levy, H. L. (1996). Evidence for central nervous system glial cell plasticity in phenylketonuria. *Journal of Neuropathology and Experimental Neurology, 55,* 795–814.

Giedd, J. N., Rumsey, J. M., Castellanos, F. X., Rajapakse, J. C., Kaysen, D., Vaituzis, A. C., Vauss, Y. C., Hamburger, S. D., & Rapoport, J. L. (1996). A quantitative MRI study of the corpus callosum in children and adolescents. *Developmental Brain Research, 91,* 274–280.

Gourovitch, M. L., Craft, S., Dowton, S. B., Ambrose, P., & Sparta, S. (1994). Interhemispheric transfer in children with early-treated phenylketonuria. *Journal of Clinical and Experimental Neuropsychology, 16,* 393–404.

Hudson, F. P., Mordaunt, V. L., & Leahy, I. (1970). Evaluation of treatment begun in the first three months of life in 184 cases of phenylketonuria. *Archives of Disease in Childhood, 45,* 5–12.

Kinsbourne, M. (1993). Orientation bias model of unilateral neglect: Evidence from attentional gradients within hemispace. In I. H. Roberson & J. C. Marshall (Eds.), *Unilateral neglect: Clinical and experimental studies* (pp. 63–86). Hove, England: Erlbaum.

Koch, R., Azen, C., Friedman, E. G., & Williamson, M. L. (1982). Preliminary report on the effects of diet discontinuation in PKU. *Pediatrics, 100,* 870–875.

Krause, W. L., Halmanaki, M., McDonald, L., Dembure, P., Salvo, R., Freides, D., & Elsas, L. J. (1985). Biochemical and neuropsychological effects of elevated plasma phenylalanine levels in patients with treated phenylketonuria. *Journal of Clinical Investigations, 75,* 40–48.

Ladavas, E., Nicoletti, R., Umilta, C., & Rizzolatti, G. (1984). Right hemisphere interference during negative affect: A reaction time study. *Neuropsychologia, 22,* 479–485.

Lund, E., & Wamberg, E. (1970). Phenylketonuria in Denmark. A screening programme 1962–1968. *Danish Medical Bulletin, 17,* 13–18.

Macombe, P. A., McLaughlin, D. B., Chalk, J. B., Brown, N. N., McGill, J. J., & Pender, M. P. (1992). Spasticity and white matter abnormalities in adult phenylketonuria. *Journal of Neuropathology and Experimental Neurology, 25,* 254–268.

Poffenberger, A. T. (1912). Reaction time to retinal stimulation with special reference to time lost in conducation through nerve centers. *Archives of Psychology (NY), 23,* 1–73.

Posner, M. I., Inhoff, A. W., Friedrich, F. J., & Cohen, A. (1987). Isolating attentional systems: A cognitive-anatomical analysis. *Psychobiology, 15,* 107–121.

Reynolds, R., Burri, R., Mahal, S., & Herschkowitz, N. (1992). Disturbed myelognsis and recovery in hyperphenylalaninemia in rats: An immunohistochemical study. *Experimental Neurology, 115,* 347–367.

Rueckert, L., & Levy, J. (1996). Further evidence that the callosum is involved in sustaining attention. *Neuropsychologia, 34,* 927–935.

Rueckert, L., Sorensen, L., & Levy, J. (1994). Callosal efficiency is related to sustained attention. *Neuropsychologia, 32,* 159–173.

Schmidt, E., Burgard, P., & Rupp, A. (1996). Effects of concurrent phenylalanine levels on sustained attention and calculation speed in patients treated early for phenylketonuria. *European Journal of Pediatrics, 155*(Suppl. 1), S82–S86.

Schmidt, E., Rupp, A., Burgard, P., Pietz, J., Weglage, J., & de Sonneville, L. (1994). Sustained attention in adult phenylketonuria: The influence of the concurrent phenylalanine-blood-level. *Journal of Clinical and Experimental Neuropsychology, 16,* 681–688.

Shenker, J. I., & Banich, M. T. (2000). *The modulation of attentional capacity in the Stroop task by communication between the cerebral hemispheres.* Manuscript submitted for publication.

Smith, I., Beasley, M. G., & Ades, A. E. (1991). Effect on intelligence of relaxing the low phenylalanine diet in phenylketonuria. *Archives of Disease in Childhood, 66,* 311–316.

Smith, M. L., Klim, P., Mallozzi, E., & Hanley, W. B. (1996). A test of the frontal-specificity hypothesis in the cognitive performance of adults with phenylketonuria. *Developmental Neuropsychology, 12,* 327–341.

Starfield, B., & Holtzman, N. A. (1975). A comparison of effectiveness of screening for phenylketonuria in the United States, United Kingdom and Ireland. *New England Journal of Medicine, 293,* 118–121.

Thompson, A. J., Tillotson, S., Smith, I., Kendall, B., Moore, S. G., Brenton, D. P. (1993). Brain MRI changes in phenylketonuria. Associations with dietary status. *Brain, 116,* 811–821.

Tucker, D. M., & Williamson, P. A. (1984). Asymmetric neural control systems in human self-regulation. *Psychological Review, 91,* 185–215.

Vendrell, P., Junqué, C., Pujol, J., Jurado, M. A., Molet, J., & Grafman, J. (1995). The role of prefrontal regions in the Stroop task. *Neuropsychologia, 33,* 341–352.

Weglage, J., Pietsch, M., Funders, B., Koch, H. G., & Ullrich, K. (1996). Deficits in selective and sustained attention processes in early treated children with phenylketonuria—Result of impaired frontal lobe functions? *European Journal of Pediatrics, 155,* 200–204.

Weissman, D. H., & Banich, M. T. (1999). Global–local interference modulated by communication between the hemispheres. *Journal of Experimental Psychology: General, 128,* 283–308.

Woo, S. L. C., Lidsky, A. S., Güttler, F., Chandra, T., & Robson, K. J. H. (1983). Cloned human phenylalanine hydroxylase gene allows prenatal diagnosis and carrier detection of classical phenylketonuria. *Nature, 306,* 151–155.

Woodcock, R. W., & Johnson, M. B. (1989). *Woodcock–Johnson Psychoeducational Battery–Revised.* Itasca, IL: Riverside.

Yakovlev, P. I., & Lecours, A. R. (1967). The myelogenetic cycles of regional maturation of the brain. In A. Minkowski (Ed.), *Regional development of the brain in early life* (pp. 3–70). Oxford, England: Blackwell.