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Response Monitoring in Children With Phenylketonuria

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Abstract

Phenylketonuria (PKU) is characterized by a disruption in the metabolism of phenylalanine and is associated with dopamine deficiency (Diamond, Prevor, Callender, & Druin, 1997) and cerebral white matter abnormalities (e.g., Anderson et al., 2007). From a neuropsychological perspective, prefrontal dysfunction is thought to underlie the deficits in executive abilities observed in individuals with PKU (Christ, Steiner, Grange, Abrams, & White, 2006; Diamond et al., 1997; White, Nortz, Mandernach, Huntington, & Steiner, 2001, 2002). The purpose of our study was to examine a specific aspect of executive ability, response monitoring, as measured by posterror slowing. The authors examined posterror reaction time (RT) in 24 children with well-controlled, early treated PKU and 25 typically developing control children using a go/no-go task. Results showed that RTs of both controls and children with PKU slowed significantly following the commission of errors. The magnitude of posterror slowing, however, was significantly less for children with PKU. These findings indicate deficient response monitoring in children with PKU.

Keywords

response monitoring; phenylketonuria; children; executive abilities; development

Response monitoring refers to the detection of errors or conflict during the performance of cognitive tasks and the subsequent adjustments in performance that are made following their detection. A robust finding in the response monitoring literature is that, during speeded tasks, reaction time (RT) slows on trials immediately following errors (Rabbitt, 1966). This posterror slowing is thought to reflect compensatory behavior that increases the probability of correct responding after the commission of errors.

Evidence from studies with adults using ERP (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; van Veen & Carter, 2002) and fMRI (Carter et al., 1998) indicate that response monitoring is subserved by a neuroanatomical network in which frontal brain regions, specifically anterior cingulate and dorsolateral prefrontal cortices, play major roles. As such, we examined posterror slowing in children with phenylketonuria (PKU), a disorder in which frontal brain function is compromised (Diamond, Prevor, Callender, & Druin, 1997). We hypothesized that children with treated PKU would exhibit poorer response monitoring as demonstrated by less posterror slowing in comparison with typically developing children.

The literature regarding response monitoring in children is limited but consistent with findings from adults in terms of the importance of anterior cingulate and prefrontal cortices. In addition, studies conducted with children and adolescents have shown that, similar to adults, responses are slower following the commission of errors on tasks such as go/no-go (Wiersma, van der Meere, & Roeyers, 2007) and flanker (Ladouceur, Dahl, & Carter, 2007). Findings from these studies also suggest that the magnitude of posterror slowing is constant from childhood through early adulthood.

Although there is a paucity of research regarding response monitoring in populations with developmental disorders, several studies have been conducted with children with Attention Deficit/Hyperactivity Disorder (ADHD) and Attention Deficit Disorder (ADD) using stop signal (Schachar et al., 2004), go/no-go (Wiersma, van der Meere, & Roeyers, 2005a), choice RT (Wiersma et al., 2005a), and Sternberg search (Krusch et al., 1996; Sergeant & van der Meere, 1988) tasks. In each instance, posterror slowing in children with ADHD/ADD was less pronounced than in control children or was not observed at all. This research is of particular relevance to the current investigation because, similar to children with PKU, it is hypothesized that disruptions in dopamine regulation may compromise frontal brain function in children with ADHD (for a review, see Swanson et al., 2007).

In children with PKU, a deficiency in dopamine synthesis results from a disruption in the metabolism of phenylalanine (Diamond et al., 1997). Neuroimaging studies have also identified white matter abnormalities in individuals with PKU, even in treated cases (Anderson et al., 2007; Vermathen et al., 2007). Because of the high degree of interconnectivity with other brain regions, it is likely that white matter abnormalities further compromise the function of frontal brain regions in individuals with PKU.

Newborn screening for early detection and persistent treatment with dietary restriction of phenylalanine intake have for the most part eliminated the profound cognitive deficits (e.g., mental retardation) once associated with PKU. Nonetheless, even children with treated PKU experience subtle decreases in IQ in comparison with typically developing children (Waisbren et al., 2007). Of greater relevance to the current investigation, impairments in executive abilities subserved by frontal brain regions have been identified in children with PKU (Christ, Steiner, Grange, Abrams, & White, 2006; Diamond et al., 1997; Huijbregts, de Sonnevile, Licht, Sergeant, & van Spronsen, 2002; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990; White, Nortz, Mandernach, Huntington, & Steiner, 2001, 2002), as has an increased incidence of ADHD (Antshel & Waisbren, 2003; Arnold, Vladutiu, Orlowski, Blakely, & DeLuca, 2004).

In a number of studies it has also been established that children with PKU make more errors than typically developing children during speeded tasks (Christ et al., 2006; Huijbregts, de Sonnevile, Licht, van Spronsen, et al., 2002). To date, however, no research has been conducted to examine response monitoring in this population. In the current study, we reexamined previously reported data from an inhibitory control task (go/no-go; Christ et al., 2006) to evaluate response monitoring. We hypothesized that posterror slowing would be exhibited by both children with PKU and typically developing control children. We also hypothesized, however, that the magnitude of posterror slowing would be less for children with PKU in comparison with controls.

Method

Participants

A total of 24 children (13 girls, 11 boys) with PKU were recruited through the Division of Medical Genetics and Genomic Medicine/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. All children were diagnosed shortly after birth and were treated early and continuously through dietary management to limit phenylalanine intake. Blood phenylalanine level obtained closest to the time of participation in the study (typically within 1 week) for children with PKU ranged from 0.2 to 20.2 mg/dL ($M = 7.6$ mg/dL; $SD = 5.6$ mg/dL). The average phenylalanine level obtained 3 months before testing ranged from 2.3 to 20.9 mg/dL ($M = 8.4$ mg/dL; $SD = 4.6$ mg/dL) and the highest phenylalanine level on record, a measure of severity, ranged from 8.0 to 40.2 mg/dL ($M = 16.4$ mg/dL; $SD = 7.6$ mg/dL).

The performance of children with PKU was compared with that of 25 typically developing control children (14 girls, 11 boys) recruited from the St. Louis and Portland communities. Children in the PKU group ranged from 6 to 17 years of age ($M = 10.7$, $SD = 2.5$), whereas children in the control group ranged from 7 to 18 years of age ($M = 11.3$, $SD = 3.4$). Household income ranged from \$13,000 to \$145,000 ($M = \$83,308$, $SD = \$35,484$) for the PKU group and \$35,000 to \$145,000 ($M = \$98,652$, $SD = \$31,439$) for the control group. There was no significant difference in age or household income between the groups ($p > .05$ in both instances). Consistent with the fact that PKU is a hereditary disorder primarily affecting individuals of European descent, all children in the study were Caucasian. No child

in the study had a history of mental retardation, learning disorder, or major medical disorder unrelated to PKU.

General intellectual ability was estimated using the Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999). Estimated IQ for children in the PKU group ranged from 74 to 119 ($M = 102.1$, $SD = 10.3$), whereas estimated IQ for children in the control group ranged from 83 to 129 ($M = 107.7$, $SD = 10.6$). There was no significant difference in IQ between the groups ($p > .05$). In addition, preliminary analyses revealed no significant correlations between IQ and the primary variables of interest (go RT and posterror RT) in the study; this was the case when correlations were examined using combined data from both groups and each group separately (the highest correlation between IQ and either RT variable was $r = .27$). As such, IQ was not controlled in statistical analyses.

Because response monitoring was examined using posterror RT, all children included in the study had to have responded correctly on at least two go trials that immediately followed the commission of errors on the go/no-go task (described below).

Procedure

Go/no-go task—This task comprised two conditions: go and no-go. Children were seated in front of a computer monitor. On each trial of the task, one of four shapes (square, triangle, diamond, circle) subtending approximately 6° vertically and horizontally appeared at the center of the monitor. At the beginning of the task, one shape was designated as the nontarget (the designated shape was counterbalanced across children). Children were instructed to press a response button as quickly as possible when any shape other than the nontarget shape appeared (go trials). They were instructed to withhold responses when the nontarget shape appeared (no-go trials; inhibitory condition). The intertrial interval was 2,000 milliseconds.

If children responded in less than 100 milliseconds after presentation of a target or nontarget (anticipatory error), a tone and the visual message “Early response” were presented. If children failed to respond within 1,500 milliseconds of presentation of a target (omission error), a tone and the visual message “Too slow” were presented. Finally, if children responded to a nontarget (commission error), a tone and “No response needed” were presented; number of commission errors is typically used to evaluate inhibitory control.

Children completed 20 practice trials followed by 200 experimental trials. Any of the four shapes was equally likely to appear on a given trial. Nontargets were randomly presented on 25% of the trials. At intervals of 40 trials, children were offered the opportunity to take a break. RT on each trial and number of errors were recorded.

Results

The t test was the primary method of analysis. Given our a priori hypotheses, one-tailed tests were used, with a statistical significance threshold of $p < .05$.

Inhibitory Control

As a first step, we conducted a traditional analysis to evaluate inhibitory control by examining the number of commission errors made during the go/no-go task. As was the case in our earlier report using largely the same samples (Christ et al., 2006; see Figure 1), the PKU group made significantly more errors of commission than the control group, $t(47) = -2.23$, $p < .02$, $\omega^2 = .08$. In contrast, there was no significant between-groups difference in either number of anticipatory errors or omission errors ($p > .05$ in both instances). These findings indicate that inhibitory control is compromised in children with PKU.

Processing Speed

Because posterror RT was used as our indicator of response monitoring, we first examined possible between-groups differences in general processing speed by comparing the RT of the two groups on correct trials of the go condition after eliminating RT for correct go trials that immediately followed error trials (i.e., posterror RT was eliminated). As depicted in Figure 2 (see Go RT), there was no significant between-groups difference in processing speed ($p > .05$). There was, however, a significant correlation between go RT and posterror RT (combined PKU and control groups, $r = .52$, $p < .001$; PKU group, $r = .52$, $p < .009$; control group, $r = .55$, $p < .004$), such that faster RT on posterror trials was associated with faster RT on go trials. Thus, go RT was controlled before conducting the between-groups comparison of posterror RT.

Response Monitoring

To evaluate posterror slowing, we examined RT from the go/no-go task on correct go trials that immediately followed trials on which commission errors were made (posterror RT). The number of correct posterror go trials was greater for the PKU group ($M = 12.8$, $SD = 5.8$) than the control group ($M = 9.7$, $SD = 5.5$), $t(47) = -1.90$, $p < .04$, $\omega^2 = .05$; this was expected because number of posterror trials is directly related to number of errors, which was greater for the PKU group. Of greater importance, as shown in Figure 2 (see Posterror RT), we found that posterror RT was significantly slower than go RT for both the PKU, $t(23) = 9.42$, $p < .001$, $\omega^2 = .65$, and control, $t(24) = 7.93$, $p < .001$, $\omega^2 = .55$, groups. That is, significant posterror slowing occurred for both groups of children.

Next we conducted analyses to determine if the magnitude of posterror slowing differed for the PKU and control groups. As noted earlier, preliminary analyses revealed a significant correlation between posterror RT and go RT. As such, we used regression analysis to remove the variance in posterror RT that was attributable to go RT to ensure that general processing speed was adequately controlled. The resulting unstandardized residual of posterror RT was then used in between-groups analysis. Our findings revealed that the magnitude of posterror slowing was significantly greater for the control group than the PKU group, $t(47) = 1.86$, $p < .03$, $\omega^2 = .05$. In other words, consistent with our hypothesis, the magnitude of posterror slowing was decreased for children with PKU and suggested poorer response monitoring.

Relationship With Phenylalanine Levels

There were no significant correlations between any of the phenylalanine levels obtained (i.e., closest to time of participation, average across three months preceding participation, and highest on record) and number of commission errors (reflecting inhibitory control) or RT on either go trials or posterror trials of the go/no-go task. The failure to find significant correlations may be related to the fact that the range of phenylalanine levels in our study was more restricted than in some past studies because dietary control has become increasingly stringent over the years.

Relationship With Age

In previous studies, we identified differential effects of age on working memory (White et al., 2002) and strategic processing (White et al., 2001) in PKU and control groups, suggesting the emergence of greater impairment as children with PKU age. Using regression analysis in the current study, we identified significant correlations between age and number of commission errors ($r = -.64, p < .001$), go RT ($r = -.56, p < .001$), and the unstandardized residual of posterror RT after statistically controlling for the variance attributable to go RT ($r = .34, p < .02$). These correlations indicated that fewer errors were made and RT was faster as age increased. We did not, however, identify age by group interactions for any variable. Thus, unlike our previous findings regarding working memory and strategic processing, age does not appear to differentially affect inhibitory control, processing speed, or response monitoring in children with PKU and control children.

Discussion

The current study was conducted to examine response monitoring in children with treated PKU. We predicted that, during a go/no-go task, RT on trials following the commission of errors (i.e., posterror RT) would be slower than RT on trials following correct responses for both children with PKU and typically developing control children. We further predicted, however, that the magnitude of posterror slowing would be less for children with PKU compared with controls.

Our findings provided support for both hypotheses. First, the RTs of children in both groups slowed significantly on trials immediately following error trials, reflecting posterror slowing. Second, children with PKU exhibited significantly less posterror slowing than controls, indicating impaired response monitoring. It is important to note that the impairment in children with PKU was specific to posterror RT, as we carefully controlled for general processing speed. Overall, these results point to a difficulty in modulating performance following errors and extend previous findings of impairment to another aspect of executive abilities in children with PKU.

The impairment in response monitoring in children with PKU appears similar to that of children with ADHD/ADD (Krusch et al., 1996; Schachar et al., 2004; Sergeant & van der Meere, 1988; Wiersma et al., 2005a), and it is possible that dopamine dysregulation underlies the impairment in both groups. It should be noted, however, that performance is not always equivalent for these groups. For example, during a go/no-go task, Wiersma, van

der Meere, and Roeyers (2005b) found that children with PKU tended to make more errors of commission than either children with ADHD or controls. In contrast, the RT of children with ADHD on the go/no-go task was more variable than that of either children with PKU or controls. In the current study, no direct comparison was made between children with PKU and ADHD. As such, we cannot state with certainty that response monitoring is comparable in these populations.

In addition to the lack of direct comparison with ADHD, there are other limitations to the study. The sample sizes were relatively small, which limited power to detect between-groups differences. That said, we found significant differences between the PKU and control groups on our primary variable of interest (i.e., posterror RT). Statistical effect sizes were, however, quite small, which is consistent with the notion that the cognitive impairments associated with treated PKU are subtle (Christ et al., 2006). The broad age range of children in the study might also be viewed as a limitation but allowed us to determine that there was no differential effect of age on posterror slowing in children with PKU and controls. Finally, because neither neurophysiological nor neuroimaging data were collected, it is not possible to definitively comment on the neuroanatomical underpinnings of the impairment in response monitoring we identified in children with PKU.

Future research is needed to more thoroughly explore response monitoring and the neural mechanisms underlying response monitoring in individuals with PKU. The contributions of dopamine dysregulation and white matter abnormalities will be of particular interest, as will the roles of the anterior cingulate and prefrontal cortex. In combination with behavioral approaches, especially fruitful avenues of research may include ERP, fMRI, diffusion tensor imaging, spectroscopy, and comparisons with other populations of children with disorders affecting frontal brain function.

More generally, further research is needed to enhance our understanding of the real-world implications of posterror slowing. For example, although it seems reasonable to assume that poorer response monitoring may have a negative impact on academic achievement, this issue has not been examined. This will be an important area of research if we are to understand the implications of impaired response monitoring in children with PKU and other developmental disorders.

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Figure 1.
Mean number of errors for PKU and control groups.

Figure 2.
Mean RT for PKU and control groups.