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Processing Speed and Executive Abilities in Children with Phenylketonuria

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by

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Abstract

Objective: Phenylketonuria (PKU) is a hereditary metabolic disorder that often results in neuropsychological impairment, even in individuals treated early and continuously. This study was conducted to examine processing speed, variability in processing speed, and the relationship between processing speed variables and executive abilities in children with early- and continuously-treated PKU.

Method: Participants were 42 children with PKU and 81 typically-developing children ranging from 7 to 18 years of age. Children completed three computerized reaction time (RT) tasks (simple reaction time, go/no-go, stimulus-response compatibility) and seven tasks assessing various aspects of executive abilities (working memory, inhibitory control, strategic processing).

Results: The performance of children with PKU was significantly slower and more variable than that of controls across the three tasks administered. When age was considered, it was shown that processing speed improved with age to a comparable degree for both groups. Variability in processing speed, however, improved more with age for the PKU than control group, reflecting the fact that variability in younger, but not older, children with PKU was greater than that of controls. With regard to executive abilities, processing speed and variability contributed to performance on most, but not all, executive tasks and, after controlling for processing speed and variability, executive impairments were still identified in working memory and inhibitory control (not strategic processing).

Conclusions: These findings indicate that information processing is slower and less efficient in children with PKU. In addition, processing speed and variability contribute to some, but not all, of the impairments in executive abilities observed in children with PKU.

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Introduction

Phenylketonuria (PKU) is a hereditary disorder characterized by the inefficient metabolism of the amino acid phenylalanine (Phe) due to abnormalities in the phenylalanine hydroxylase enzyme. Untreated PKU results in neurological abnormalities (Moyle, Fox, Bynevelt, Arthur, & Burnett, 2007) and intellectual disability (de Groot, Hoeksma, Blau, Reijngoud, & van Spronsen, 2010; Paine, 1957). Even with early and continuous dietary treatment to limit Phe intake, PKU is associated with lower than expected intelligence (for a review, Brumm & Grant, 2010) and deficits in specific aspects of cognition such as executive abilities and processing speed (for reviews, Albrecht, Garbade, & Burgard, 2009; Christ, Huijbregts, de Sonneville, & White, 2010; DeRoche & Welsh, 2008; Janzen & Nguyen, 2010).

Two primary neural mechanisms are hypothesized to underlie brain dysfunction and subsequent neuropsychological impairment in individuals with PKU: dopamine deficiency and white matter abnormalities. Turning first to dopamine, this essential neurotransmitter is synthesized from the amino acid tyrosine (Tyr), of which Phe is a precursor (for an overview, de Groot et al., 2010). Because Phe is not properly metabolized, Tyr production is limited, which in turn limits dopamine synthesis. In addition, Tyr and Phe are among the large neutral amino acids (LNAAs) that competitively bind to the large neutral amino acid type 1 (LAT1)-transporter for passage across the blood-brain barrier. Compared with other LNAAs, Phe binds more strongly with the LAT1-transporter. As a result, high blood Phe levels impede the transport of available Tyr across the blood-brain barrier, which further limits dopamine synthesis (for an overview, de Groot et al., 2010).

Dopamine deficiency has long been viewed as the primary neural mechanism underlying brain dysfunction and impaired cognition in individuals with PKU. In recent years, however, increasing evidence has emerged suggesting that white matter abnormalities also play a role. Neuroimaging studies have identified white matter abnormalities even in individuals with early- and continuously-treated PKU (Anderson et al., 2004, 2007; Anderson & Leuzzi, 2010; White et al., 2010; Peng, Tseng, Chien, Hwu, & Liu, 2004), with the prevalence and severity of these abnormalities increasing at higher Phe levels (Anderson et al., 2004; Anderson & Leuzzi, 2010).

Of particular relevance to the current investigation, it is probable that the white matter abnormalities associated with PKU result in slowed information processing due to disruptions in the speed with which neural signals are transmitted. Indeed, slowed information processing is a common finding in studies of individuals with PKU (Anderson et al., 2007; Channon, Mockler, & Lee, 2005; Feldmann, Denecke, Grenzebach, & Weglage, 2005; Moyle, Fox, Arthur, Bynevelt, & Burnett, 2007; Moyle et al., 2007b; for a meta-analysis, Albrecht et al., 2009), and PKU-related white matter abnormalities are associated with slowed performance across a range of cognitive tasks (Anderson et al., 2004; Anderson et al., 2007). It is also possible that white matter abnormalities and slowed information processing contribute to the impairments in executive abilities observed in individuals with PKU due to inefficiencies in the interconnections between prefrontal cortex and posterior brain regions (Anderson & Leuzzi, 2010). As pointed out by Salthouse, slowed processing may result in "impairments of higher order processes such as abstraction, elaboration, or integration,

because not all of the relevant information will be available in a usable form when it is needed" (Salthouse, 1996, p. 406).

In the current study, processing speed and variability in processing speed were examined, as well as the relationship of each with executive abilities, in children with early- and continuously-treated PKU. In typically-developing children, information processing speed increases with age (Conners, Epstein, Angold, & Klaric, 2003; Nettelbeck & Burns, 2010), and faster processing has been associated with developmental improvements in executive abilities including working memory (Salthouse & Babcock, 1991; Salthouse, 1992; Zanto, Toy, & Gazzaley, 2010), inhibitory control (Bugg, DeLosh, Davalos, & Davis, 2007), and strategic processing (Imbo & Vandierendonck, 2007). To our knowledge, however, research has not been conducted with a focus of either the relationship between processing speed and executive abilities or variability in processing speed in children with PKU.

To address these issues, RT and variability in RT were evaluated using three speeded tasks (simple reaction time, go/no-go, stimulus-response compatibility) in children with PKU and typically-developing control children. RTs from three tasks were used to ensure that processing speed findings were not due to the particularities of a single task. Executive performance on tasks assessing working memory, strategic processing, and inhibitory control was also examined in relation to RT and variability in RT. By assessing children across a broad age range (i.e., 7 to 18 years of age), it was possible to explore potential differential effects of age on RT, variability in RT, and relationships with executive abilities across our PKU and control groups.

Method

Participants

A total of 42 children (23 girls, 19 boys) with PKU were recruited through the Division of Medical Genetics at St. Louis Children's Hospital in Missouri and the Metabolic Clinic at the Child Development and Rehabilitation Center at Doernbecher Children's Hospital in Portland, Oregon. All children were diagnosed soon after birth and were treated early and continuously using dietary treatment to limit Phe intake. Blood Phe levels were not available for three children due to missing values in medical records. Blood Phe level obtained closest to the time of participation in the study (typically the same day) was available for 39 children and ranged from 121 to 1574 µmol/L (M = 546, SD = 331). Average blood Phe level obtained within the year prior to participation in the study was available for 38 children (for one child only one Phe level was obtained within the year prior to study) and ranged from 176 to 1124 µmol/L (M = 495, SD = 264).

The performance of children with PKU was compared with that of 81 typically-developing control children (42 girls, 39 boys) recruited from the St. Louis and Portland communities (the only exception was that two children in the control group failed to complete a verbal fluency task). No child in the study had a history of major medical (e.g., head injury with loss of consciousness, diabetes) or learning disorder (e.g., dyslexia) unrelated to PKU. Years of age for children in the PKU (M = 11.8, SD = 3.5) and control (M = 12.3, SD = 3.2) groups ranged from 7 to 18. Years of education ranged from 1 to 13 for the PKU group (M = 6.0, SD = 3.4) and 1 to 14 for the control group (M = 6.3, SD = 3.3). There was no significant difference in age or education between the groups ($p > .05$ in both instances). 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 the PKU group ranged from 83 to 139 (M = 106.0, SD = 10.9), whereas estimated IQ for the control group ranged from 82 to 143 (M = 114.6, SD = 13.9). The IQ of the control group was significantly higher than that of the PKU group [$t(121) = 3.51$, $p < .001$]. There were, however, no significant correlations between estimated IQ and processing speed variables for the control group (rs ranged from -.18 to .13), and as such IQ was not controlled in statistical analyses.

Procedure

Processing Speed. Processing speed was assessed using variables selected from three speeded tasks: simple RT, go/no-go, and stimulus-response compatibility. Data from the go/no-go task have been reported elsewhere (Araujo et al., 2009; Christ et al., 2006), but response monitoring and inhibitory control were the foci of previous studies. In the current study, we focused on basic processing speed by examining data from the control conditions of each speeded task. All tasks were presented on a computer monitor, and responses to stimuli were made via manual key press. For each task, intra-individual RT mean and RT standard deviation (SD) served as dependent variables to permit examination of average processing speed and variability in processing speed, respectively.

Simple RT Task. For the simple RT task, children were instructed to respond to a centrally-positioned cross by pressing a response key as rapidly as possible using their dominant hand. To discourage anticipatory responding, the inter-trial interval varied

randomly from 700 to 2500 ms. If children responded in less than 100 ms after stimulus presentation (anticipatory error), a brief tone followed by the message "Too quick" were presented. If children failed to respond within 1500 ms (omission error), a brief tone followed by the message "Too slow" were presented. Following 10 practice trials, children completed 40 experimental trials. Response speed and accuracy were recorded for each trial. RT mean and RT SD for correct trials were included in processing speed analyses.

Go/No-Go Task. On each trial of this task, one of four shapes (square, triangle, diamond, circle) appeared at the center of the monitor, with an inter-trial interval of 2,000 ms. At the beginning of the task, one shape was designated as the non-target, with the designated shape counterbalanced across children. Children were instructed to press a centrally-positioned response key as quickly as possible when any shape other than the non-target shape appeared (go trials; processing speed condition) and to withhold their response when the non-target shape appeared (no-go trials; inhibitory control condition). Non-targets were randomly presented on 25% of the trials. If children responded in less than 100 ms after presentation of a target or non-target (anticipatory error), a brief tone and the message "Early response" were presented. If children failed to respond within 1,500 ms of presentation of a target (omission error), a tone and the message "Too slow" were presented. If children responded to a non-target (commission error), a brief tone and the message "No response needed" were presented. Children completed 20 practice trials followed by 200 experimental trials. Response speed and accuracy were recorded for each trial. RT mean and RT SD for correct go trials were included in processing speed analyses.

Stimulus-Response Compatibility Task. At the beginning of each trial of this task, an array of three horizontally-aligned circles appeared on the monitor. After 300 ms, the middle circle brightened (i.e., filled with color) for 500 ms. After 300 ms, one of the peripheral circles brightened. Two experimental conditions were administered: response compatible (processing speed condition) and response incompatible (inhibitory control condition). In the compatible condition, children were instructed to press a left response key when the left circle brightened and a right response key when the right circle brightened. In the incompatible condition, children were instructed to press the left response key when the right circle brightened and the right response key when the left circle brightened. The circles remained on the screen for 3,000 ms or until children completed a response. After a response was made, or following 3,000 ms, the circles disappeared and there was a blank inter-trial interval of 2,000 ms. Children completed practice blocks of 10 compatible trials followed by 10 incompatible trials and were given feedback regarding the accuracy of each response ("Correct" or "Wrong Response" appeared on the monitor). Following practice, children completed 96 experimental trials (with no feedback regarding accuracy) during which the two conditions were presented in alternating blocks of 16 trials each. At the beginning of each block, children were instructed to press a key on either the same or opposite side as the peripheral circle that brightened. On each trial, left and right circles were equally likely to brighten. Response speed and accuracy were recorded for each trial. RT mean and RT SD for correct compatible trials were included in processing speed analyses.

Executive Abilities. Tasks assessing working memory, inhibitory control, and strategic processing were administered to evaluate the relationship between processing speed and executive abilities.

Working Memory.

Digit span task. The digit span subtest from the Children's Memory Scale (Cohen, 1997) was administered to assess simple storage and manipulation in working memory. In the digit span forward condition, children repeated series of orally-presented digits in the order of presentation (e.g., 8-2-6-9). In the digit span backward condition, children repeated series of digits in reverse order (e.g., 9-6-2-8). Raw scores for digit span forward and backward were included in analyses.

2-back task. Two conditions were presented: letter and location. In both conditions, children observed one of eight letters (C, F, H, J, N, P, Q, S) positioned at one of eight locations along an imaginary circle that was eccentric to central fixation (+). In the location condition, children were asked to press a target button when any letter appeared in the same location as two trials ago (regardless of letter identity) and to press a non-target button otherwise. In the letter condition, children were asked to press a target button when a letter appeared that was identical to the letter presented two trials ago (regardless of location) and to press a non-target button otherwise. In both conditions, stimuli remained on the screen for 2,500 ms, with an inter-trial interval of 1,000 ms. Children heard a "beep" following correct responses and a "bloop" following incorrect responses. Children completed a practice block of 24 trials followed by 96 experimental trials. The condition presented first was counterbalanced across children. Response speed and accuracy were recorded for each trial. For purposes of the current study, number of

commission errors (i.e., incorrect responses for non-target trials) for each condition was included in analyses.

Recognition span task. Two conditions were presented: shape and location. Children observed as a series of 12 shapes (e.g., star, oval, cross) appeared one at a time in one of 12 locations on a 3 X 4 grid. Depending on the condition, children were asked to remember either the shapes or the grid locations in the order presented. After each series was presented, children observed a screen with all possible shapes and locations presented and were asked to point to the items in the order of presentation. The maximum number of items recalled in correct serial order for each condition was included in analyses to assess working memory.

Inhibitory Control.

Go/no-go task. This task was described in detail earlier. To assess inhibitory control, the number of incorrect responses occurring during the no-go condition (i.e., commission errors) was included in analyses.

Strategic Processing.

California Verbal Learning Test – Children's Version (CVLT-C). During the CVLT-C (Delis, Kramer, Kaplan, & Ober, 1994), children were instructed to recall a list of 15 words from three semantic categories (i.e., toys, clothing, fruits) that were presented orally over five repeated learning trials. To assess strategic processing, the number of words reported within semantic clusters on the fifth learning trial was included in analyses.

Verbal fluency. We also examined performance on the food/drink condition of Verbal Fluency subtest of the NEPSY (Korkman, Kirk, & Kemp, 1998) to assess

strategic processing. An in-depth description of results from this task in children with PKU is presented elsewhere (Banerjee, Grange, Steiner, & White, 2010). Briefly, children were instructed to name as many words that fall into the category of food or drink as quickly as possible for 60 seconds. For purposes of the current study, the total number of words correctly reported was included in analyses.

Results

Effects of Group on Processing Speed

To examine the effects of group on processing speed and variability in processing speed (see Table 1), we conducted two repeated measures analyses of variance (ANOVA), with RT mean and RT SD serving as dependent variables in separate analyses. In both analyses, task (simple RT, go/no-go, stimulus-response compatibility) served as the within-subjects factor, and group (PKU, control) served as the between-subjects factor.

For RT mean, results revealed a significant main effect of task [$F(2, 242) = 157.05$, $p < .001$, $\eta_p^2 = .57$]. Paired sample t-tests revealed faster performance on the simple RT task than either the go/no-go [$t(122) = -23.21$, $p < .001$] or stimulus-response compatibility [$t(122) = -8.96$, $p < .001$] tasks and faster performance on the stimulus-response compatibility task than the go/no-go task [$t(122) = -8.14$, $p < .001$]. There was also a significant main effect of group [$F(1, 121) = 8.52$, $p < .005$, $\eta_p^2 = .07$], with slower performance for the PKU than control group. The interaction between task and group was not significant, indicating that processing speed was generally slower for the PKU than control group across the tasks administered.

For RT SD, results again revealed a significant main effect of task [$F(2, 242) = 27.09$, $p < .001$, $\eta_p^2 = .18$]. Paired sample t-tests revealed less variable performance on the simple RT task than either the stimulus-response compatibility [$t(122) = -6.20$, $p < .001$] or go/no-go [$t(122) = -9.56$, $p < .001$] tasks. There was also a significant main effect of group [$F(1, 121) = 9.06$, $p < .005$, $\eta_p^2 = .07$], with more variable performance for the PKU than control group. The interaction between task and group was not significant, indicating that variability in processing speed was generally greater for the PKU than control group across the tasks administered.

Clinical Significance of Group Differences in Processing Speed

The clinical significance of differences in processing speed and variability in processing speed was also examined. Because there was no interaction between task and group, composite z scores were computed for RT mean and RT SD across the three tasks administered. The mean and SD of the RT mean and RT SD of the control group were first calculated for each task. Next, z scores based on these values were computed for each child on each task. Finally, z scores for each child on each task were averaged to obtain RT mean and RT SD composite z scores.

T-tests revealed significant between-group differences in RT mean [$t(121) = -3.00$, $p < .005$] and RT SD [$t(121) = -3.46$, $p < .001$] composite z scores. Scores for the PKU group [RT mean = .52; RT SD = .63] were significantly higher than those of the control group, indicating slower and more variable performance. Thus, processing speed and variability in processing speed were at least one-half SD poorer for the PKU than control group.

Relationships between Age and Processing Speed

In previous studies, we identified differential effects of age on strategic processing (White et al., 2001) and working memory (White et al., 2002) across PKU and control groups, suggesting greater impairment as a function of increasing age in children with PKU. To examine the relationships between age and processing speed in the current study, separate linear regression analyses were conducted using the composite z scores for RT mean and RT SD noted earlier. In both regressions, age was entered in the first step, group was entered in the second step, and the interaction between age and group was entered in the final step. Analyses were also conducted to examine possible quadratic effects of age, but in no analysis did age^2 account for significant variance beyond that attributable to age; as such, age^2 was removed from the results reported here.

For RT mean, age accounted for a significant proportion of the variance in the composite z score [$R^2 = .37$, $F(1, 121) = 70.11$, $p < .001$], with faster performance as a function of increasing age. As expected based on findings from the ANOVA examining group effects, group accounted for additional variance beyond that attributable to age [$\Delta R^2 = .05$, $\Delta F(1, 120) = 9.82$, $p < .005$], with slower performance for the PKU than control group. The interaction between age and group did not account for a significant proportion of the variance beyond that attributable to age and group.

For RT SD, age again accounted for a significant proportion of the variance in the composite z score [$R^2 = .32$, $F(1, 121) = 56.40$, $p < .001$], with less variable performance as a function of increasing age. As expected based on findings from the ANOVA examining group effects, group accounted for additional variance beyond that attributable to age [$\Delta R^2 = .07$, $\Delta F(1, 120) = 13.08$, $p < .001$], with more variable performance for the

PKU than control group. The interaction between age and group was also significant [ΔR^2 = .03, $\Delta F(1, 119) = 5.26$, $p < .05$]. As shown in Figure 1, although variability decreased as age increased for both the PKU [$R^2 = .46$, $F(1, 40) = 33.61$, $p < .001$] and control [R^2 = .24, $F(1, 79) = 25.43$, $p < .001$] groups, at younger ages variability in performance was greater for the PKU than control group. In terms of clinical significance, variability in processing speed was approximately 1 SD poorer for the PKU than control group at the youngest ages, although variability was comparable at the oldest ages.

Relationships between Phe Levels and Processing Speed

We next examined the relationships between Phe levels and processing speed and variability in processing speed in children with PKU. Four separate linear regression analyses were conducted using the composite z scores for RT mean and RT SD as dependent variables and Phe closest to time of testing and average Phe over the past year as independent variables. Phe levels tend to increase with age in children with PKU, and in our study both Phe closest to time of testing [$r = .52$, $p < .001$] and average Phe over the past year [$r = .63$, $p < .001$] increased significantly with age. As such, age was entered in the first step of all analyses. Phe level was entered in the second step, and the interaction between age and Phe level was entered in the final step.

For RT mean in the analysis examining the possible contribution of Phe closest to time of testing, as expected, age accounted for a significant proportion of the variance in the composite z score [$R^2 = .57$, $F(1, 37) = 49.25$, $p < .001$], with faster performance as a function of increasing age. Neither Phe closest to time of testing nor the interaction between age and Phe closest to time of testing accounted for additional variance. Similarly, in the analysis examining the possible contribution of average Phe over the

past year, age accounted for a significant proportion of the variance in the composite z score [$R^2 = .55$, $F(1, 36) = 43.97$, $p < .001$], but neither average Phe over the past year nor the interaction between age and average Phe over the past year accounted for additional variance.

For RT SD, in the analysis examining the possible contribution of Phe closest to time of testing, again as expected, age accounted for a significant proportion of the variance in the composite z score [$R^2 = .49$, $F(1, 37) = 35.33$, $p < .001$], with faster performance as a function of increasing age. Neither Phe closest to time of testing nor the interaction between age and Phe closest to time of testing accounted for additional variance. Similarly, in the analysis examining the possible contribution of average Phe over the past year, age accounted for a significant proportion of the variance in the composite z score [$R^2 = .48$, $F(1, 36) = 32.98$, $p < .001$]. In contrast with findings from other analyses, however, average Phe over the past year accounted for additional variance beyond that attributable to age [$\Delta R^2 = .09$, $\Delta F(1, 35) = 7.43$, $p < .01$]. It should be noted, however, that these results suggest that higher Phe levels are associated with less rather than more variability in processing speed. The reason for this finding is unclear, but may be related to the complex relationships between age, Phe levels, and performance. The interaction between age and average Phe over the past year did not account for additional variance.

Relationships between Processing Speed and Executive Abilities

We examined the relationship between processing speed and four measures of working memory (i.e., digit span forward, digit span backward, the averaged number of commission errors in the spatial and letter conditions of the 2-back task, and the averaged

maximum number of items recalled in correct serial order in the shape and location conditions of the recognition span task). Conditions of the 2-back and recognition span tasks were combined because there was no significant interaction between group and condition for either task in repeated measures ANOVAs for each task. We also examined the relationship between processing speed and one measure of inhibitory control (i.e., number of commission errors in the no-go condition of the go/no-go task) and two measures of strategic processing (i.e., number of semantically clustered words on the fifth learning trial of the CVLT-C and number of words correctly reported on the food/drink verbal fluency task).

Separate linear regression analyses were conducted for each measure. In all analyses, age was entered in the first step, composite z score for either RT mean or RT SD was entered in the second step (separate analyses were conducted for each of these processing speed variables), group was entered in the third step, the interaction between age and composite z score for either RT mean or RT SD was entered in the fourth step, the interaction between age and group was entered in the fifth step, the interaction between composite z score for either RT mean or RT SD and group was entered in the sixth step, and the interaction between age, composite z score for either RT mean or RT SD, and group was entered in the seventh step. In no analysis did interactions between age and group, between composite z score for either RT mean or RT SD and group, or between age, composite z score for either RT mean or RT SD, and group account for significant variance beyond that attributable to other variables entered in the models. As such, results from these interactions are not discussed further.

Working Memory.

Digit span task. Age accounted for a significant proportion of the variance in digit span forward [$R^2 = .21$, $F(1, 121) = 32.35$, $p < .001$] and backward [$R^2 = .32$, $F(1, 121) = 56.33$, $p < .001$], with improved performance as a function of increasing age in both instances. For digit span forward, other variables in the models did not account for additional variance. For digit span backward, however, additional variance was explained by composite z score for both RT mean [$\Delta R^2 = .04$, $\Delta F(1, 120) = 6.80$, $p < .01$] and RT SD [$\Delta R^2 = .05$, $\Delta F(1, 120) = 9.18$, $p < .01$], indicating that working memory was poorer as processing speed slowed and variability in processing speed increased. There was also a trend [$\Delta R^2 = .02$, $\Delta F(1, 119) = 3.60$, $p < .06$] suggesting that variance in digit span backward was also attributable to group, with poorer performance for the PKU than control group. No other variables in the models explained additional variance. These findings show that processing speed plays a role in digit span backward but not forward, and that the PKU group's performance on simple working memory tasks was similar to that of controls after taking differences in processing speed into account.

2-back task. Age accounted for a significant proportion of the variance in the averaged number of commission errors in the spatial and letter conditions of the 2-back task [$R^2 = .21$, $F(1, 121) = 32.50$, $p < .001$], with fewer errors as age increased. Composite z score for RT mean [$\Delta R^2 = .04$, $\Delta F(1, 120) = 7.00$, $p < .01$] and RT SD [$\Delta R^2 = .10$, $\Delta F(1, 120) = 16.52$, $p < .001$] accounted for additional variance; similar to findings from digit span backward, working memory was poorer as processing speed slowed and variability in processing speed increased. Group accounted for additional variance beyond that attributable to age and composite z score for RT mean [$\Delta R^2 = .03$, $\Delta F(1, 119)$

= 4.11, $p < .05$], with more errors for the PKU than control group. The interaction between age and composite z score for RT mean [$\Delta R^2 = .04$, $\Delta F(1, 118) = 7.35$, $p < .01$] also explained additional variance, indicating that there was a significant differential effect of processing speed on number of incorrect responses depending upon age. No other variables in the models explained additional variance. These findings again demonstrate that processing speed plays a role in working memory. In addition, performance on this more complex working memory task was compromised in children with PKU, even after accounting for between-group differences in processing speed.

Recognition span task. Age accounted for a significant proportion of the variance in the averaged maximum number of items correctly recalled in the shape and location conditions of the recognition span task [$R^2 = .24$, $F(1, 121) = 38.18$, $p < .001$], with improved performance as age increased. Composite z score for RT mean [$\Delta R^2 = .14$, $\Delta F(1, 120) = 26.73$, $p < .001$] and RT SD [$\Delta R^2 = .11$, $\Delta F(1, 120) = 20.65$, $p < .001$] accounted for additional variance, again demonstrating that working memory was poorer as processing speed slowed and variability in processing speed increased. Group accounted for additional variance beyond that attributable to age and composite z score for RT mean [$\Delta R^2 = .04$, $\Delta F(1, 119) = 8.59$, $p < .01$] and RT SD [$\Delta R^2 = .04$, $\Delta F(1, 119) = 8.21$, $p < .01$], with poorer performance for the PKU than control group. No other variables in the models explained additional variance. Again, these findings indicate that processing speed plays a role in working memory. In addition, performance on this complex working memory task was compromised in children with PKU, even after accounting for between-group differences in processing speed.

Inhibitory Control.

Go/no-go task. Age accounted for a significant proportion of the variance in number of commission errors in the no-go condition of the go/no-go task [$R^2 = .05$, $F(1, 121) = 6.47$, $p < .02$], with fewer errors as age increased. Composite z score for RT mean and RT SD did not account for additional variance beyond that attributable to age. Group, however, accounted for additional variance beyond that attributable to age and RT mean [$\Delta R^2 = .07$, $\Delta F(1, 119) = 9.40$, $p < .01$] and RT SD [$\Delta R^2 = .03$, $\Delta F(1, 119) = 4.40$, $p < .04$], with more errors for the PKU than control group. No other variables in the models explained additional variance. These findings show that inhibitory control was compromised in children with PKU.

Strategic Processing.

CVLT-C. Age accounted for a significant proportion of the variance in the number of semantically clustered words on the fifth learning trial of the CVLT-C [$R^2 = .24$, $F(1, 121) = 37.17$, $p < .001$], with more words clustered as age increased. Composite z score for RT mean [$\Delta R^2 = .03$, $\Delta F(1, 120) = 4.03$, $p < .05$] and RT SD [$\Delta R^2 = .05$, $\Delta F(1, 120) = 8.78$, $p < .01$] accounted for additional variance, indicating that strategic processing was poorer as processing speed slowed and variability in processing speed increased. No other variables in the models explained additional variance. These findings demonstrate that processing speed plays a role in strategic processing, and that the PKU group's strategic processing was similar to that of controls after taking differences in processing speed into account.

Verbal fluency task. Age accounted for a significant proportion of the variance in number of words correctly reported on the food/drink verbal fluency task [$R^2 = .37$, $F(1,$

119) = 71.21, $p < .001$], with more words generated as age increased. Composite z scores for RT mean [$\Delta R^2 = .04$, $\Delta F(1, 118) = 7.74$, $p < .01$] and RT SD [$\Delta R^2 = .03$, $\Delta F(1, 118) = 4.88$, $p < .03$] accounted for additional variance, again indicating that strategic processing was poorer as processing speed slowed and variability in processing speed increased. No other variables in the models explained additional variance. Similar to findings from the CVLT-C, these results show that processing speed plays a role in strategic processing, and that the PKU group's strategic processing was similar to that of controls after taking differences in processing speed into account.

Discussion

The current study was conducted to explore both processing speed (i.e., RT mean) and variability in processing speed (i.e., RT SD) in children with early- and continuously-treated PKU. It was hypothesized that, in comparison with typically-developing control children, processing speed would be both slower and more variable in children with PKU. To test these hypotheses, the basic processing speed components of three cognitive tasks were examined: simple reaction time, go/no-go, and stimulus-response compatibility.

Results supported the hypotheses. Specifically, compared with controls, the performance of children with PKU was slower and more variable across the three speeded tasks. The processing speed finding is consistent with previous research (e.g., Albrecht et al., 2009; Anderson et al., 2007; Channon et al., 2004), whereas identification of greater variability in processing speed adds a new dimension to PKU research. Because variability in processing speed is considered a measure of efficiency (Simmonds

et al., 2007), together these findings indicate that performance on cognitive tasks in children with PKU is compromised in terms of both speed and efficiency.

With regard to clinical significance, processing speed and variability in processing speed were approximately one-half standard deviation slower for children with PKU than controls. When age was considered, however, it became clear that variability in processing speed was compromised in younger children with PKU but approximated that of controls by late adolescence. Although longitudinal study is necessary to reach definitive conclusions, these results suggest that consistency in performance on cognitive tasks may improve as children with PKU age, although their responses continue to be slower than those of typically-developing children.

Because processing speed is associated with performance on executive tasks (Salthouse, 1996) and executive abilities are compromised in children with PKU (for a review, Christ et al., 2010), the relationship between speed and executive abilities was also explored. To do so, variables from four working memory tasks, one inhibitory control task, and two strategic processing tasks were considered. Not surprisingly, performance improved with age for children with PKU and controls across all executive tasks. After taking the maturational effects of age into account, processing speed and variability in processing speed contributed to performance on five of the seven tasks; the only exceptions were digit span forward and go/no-go (number of commission errors), which are arguably less demanding and complex than the other tasks administered. Overall, these findings support the notion that processing speed plays a significant role in executive abilities.

Of particular relevance to the current investigation, after controlling for age and processing speed, it was apparent that children with PKU performed more poorly than controls on the two most demanding working memory tasks (with a trend for poorer performance on a third) and on the inhibitory control task. In terms of variability in processing speed, children with PKU performed more poorly than controls on one of the four working memory tasks and on the inhibitory control task. In other words, a primary impairment in working memory and inhibitory control was evident even after carefully controlling for processing speed and variability in processing speed. As such, compromised executive abilities in children with PKU cannot be attributed solely to impairments in processing speed. That said, strategic processing in children with PKU appeared comparable to that of controls after taking age and speed into account.

In a previous study of children with PKU using principal components analyses, Anderson et al. (2007) reported that processing speed and executive factors were unrelated. These findings suggest that impairment in executive abilities is independent of impairment in processing speed. Findings from the current study, however, indicate that this is not always the case. It should be noted that the tasks administered in the current study were different from the executive (Tower of London, Rey Complex Figure Test, Contingency Naming Test, Controlled Oral Word Association Test) and processing speed (Symbol Search, Coding, Contingency Naming Test) tasks administered in the Anderson et al. study, which may account for discrepant findings. For example, the computerized tasks employed in the current study may have been more sensitive measures of processing speed, permitting detection of relationships with executive abilities.

In closing, findings from the current study clearly indicate that processing speed and variability in processing speed are compromised in children with PKU. In addition, although primary impairments in executive abilities are present in children with PKU, the contribution of processing speed to such impairments requires ongoing investigation. Neuroimaging and biochemical studies will also be of great interest to further elucidate the neural underpinnings of both processing speed and executive impairments. Ongoing investigation of these issues will enhance our understanding of PKU and guide the development of interventions to prevent and/or treat neuropsychological impairment in individuals with PKU.

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Tables and Figures

Table 1

Means and standard deviations for processing speed variables (ms)

Variable	Control				PKU			
	Mean		Standard Deviation		Mean		Standard Deviation	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Simple Reaction Time	383	80	94	48	435*	103	138*	81
Go condition of Go/No-Go	587	134	145	57	642*	138	183*	77
Compatible condition of Stimulus-Response Compatibility	479	175	155	127	565*	162	199	130

Note: * indicates significantly slower or more variable performance for the PKU than control group.

Figure 1. Effect of age on RT SD z-score composite for PKU and control groups