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WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological and Brain Sciences

Blood Phenylalanine Trajectory and Executive Function Outcomes

in Individuals with Phenylketonuria

by

Clarissa T. Tardiff

A thesis presented to  
the Graduate School  
of Washington University in  
partial fulfillment of the  
requirements for the degree  
of Masters of Arts

May, 2021  
St. Louis, Missouri

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Clarissa T. Tardiff

*Washington University in St. Louis*

*May 2021*

## ABSTRACT OF THE THESIS

Blood Phenylalanine Trajectory and Executive Function Outcomes

in Individuals with Phenylketonuria

by

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Master's of Arts in Psychology

Washington University in St. Louis, 2017

Professor Desirée White, Chair

Phenylketonuria (PKU) is an autosomal recessive disorder characterized by mutations in phenylalanine hydroxylase genes. As a result, phenylalanine (Phe) metabolism is disrupted, and this amino acid accumulates in blood and tissue (Pietz, 1998; Scriver et al., 2000). Although the most severe symptoms of PKU may be avoided by early detection and treatment, many individuals with early-treated PKU still experience difficulties in executive function, attention, and processing speed (Antenor-Dorsey et al., 2013; Araujo et al., 2013; Christ et al., 2020; Hawks, Strube, Johnson, Grange, & White, 2018; Hood, Grange, Christ, Steiner, & White, 2014; Janos et al., 2012; White et al., 2002). Of particular relevance to the current investigation are the executive abilities of strategic processing, working memory, and inhibition. The present study is the first to investigate the rate of blood Phe level increase as a function of increasing age and its relationship to these executive abilities, with the hypothesis that a greater rate of change is associated with poorer executive performance. Repeated blood Phe measures were collected from children ages 0-24 years of age with early- and continuously-treated PKU whose executive abilities were assessed ( $n = 73$ , males = 37, females = 36, mean age at assessment = 14.3 years). The relationships between blood Phe and semantic clustering scores (strategic processing),

recognition span scores, n-back errors (working memory), and go-no-go commission errors (inhibition), as well as their interactions with age, were examined using hierarchical linear modeling to account for longitudinal dependencies. Consistent with hypotheses, better semantic clustering and recognition span scores were associated with less increase in blood Phe as age increased, whereas more n-back and go-no-go errors were associated with greater increase in blood Phe as age increased. Continued efforts to specify the time frame during which rates of blood Phe increase and executive performance are most strongly related will aid in identifying developmental periods during which PKU treatment adherence may be especially important for mitigating executive deficits.

## Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder characterized by mutations in the phenylalanine hydroxylase gene. This mutation inhibits the metabolism of phenylalanine (Phe), which is a critical amino acid found in all proteins, into the amino acid tyrosine and results in the buildup of Phe in blood and tissue (Pietz, 1998; Scriver et al., 2000). Because tyrosine is a precursor of catecholamines, PKU is associated with deficiencies in dopamine and other catecholamines (Curtius et al., 1981; Diamond, Ciaramitaro, Donner, Djali, & Robinson, 1994; Krause, Epstein, Averbuch, Dembure, & Elsas, 1986; White, Nortz, Mandernach, Huntington, & Steiner, 2001).

If left untreated, PKU is associated with severe mental retardation (IQ<30), seizures, and severe behavioral difficulty (Jervis, 1937, 1954; Paine, 1957). The incidence of PKU varies globally, but is 1:10,000 in North America (Scriver, 2001). Fortunately, the most severe symptoms can be prevented through neonatal screening and early treatment (Holtzman, Kronmal, van Doorninck, Azen, Kochet, 1986; Michals, Azen, Acosta, Koch, Matalon, 1988; National Institutes of Health, 2001). The primary treatment for PKU is dietary restriction of Phe consumption, with significant limitations on high Phe foods such as meat, fish, dairy products, nuts, and beans (Singh et al., 2014). This diet is quite burdensome, and lapses in adherence are common (Bilginsoy, Waitzman, Leonard, & Ernst, 2005; Fisch, 2000; Gassió et al., 2003; Matalon, Michals, & Gleason, 1986; Mütze et al., 2011; Prince, McMurray, & Buist, 1997; Waisbren, Hamilton, St James, Shiloh, & Levy, 1995; Walter et al., 2002).

Even with neonatal screening and early treatment, individuals with PKU exhibit brain abnormalities (Anderson & Leuzzi, 2010; Antenor-Dorsey et al., 2013; Bodner et al., 2012; Christ et al., 2016), lower scores on intelligence tests (Ris, Williams, Hunt, Berry, & Leslie,

1994; Waisbren et al., 2007), psychosocial and psychiatric difficulties (Brumm, Bilder, & Waisbren, 2010; Gentile, Hoedt, & Bosch, 2010; Weglage et al., 2000), and executive deficits (Christ, Huijbregts, de Sonnevile, & White, 2010). Although the precise mechanisms resulting in the cognitive deficits experienced by people with PKU are unknown, it is generally accepted that they are related to elevations in blood Phe at various life stages (Hofman, Champ, Lawton, Henderson, & Dye, 2018). Cognitive outcomes have especially been associated with blood Phe levels in early childhood through adolescence, and of particular interest to this study is the demonstrated negative relationship between blood Phe and executive function (Brunner, Jordan, & Berry, 1983; Christ et al., 2020; Diamond, Prevor, Callender, & Druin, 1997; Hofman et al., 2018; Huijbregts et al., 2002; Waisbren, Mahon, Schnell, & Levy, 1987; Weglage, Pietsch, Funder, Koch, & Ullrich, 1996; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990).

Executive function is defined as a collection of higher order cognitive abilities including response monitoring, working memory, strategic processing, and inhibition (Goldstein & Naglieri, 2013). Although executive function improves as typically developing children age (Zelazo et al., 2013), deficits in executive function have been widely observed in children and adults with PKU and become increasingly pronounced as children age (Albrecht, Garbade, & Burgard, 2009; Bilder et al., 2016; DeRoche & Welsh, 2008; White et al., 2001). Prefrontal cortex dysfunction is believed to underlie the impairments in executive function among individuals with PKU (Christ, Steiner, Grange, Abrams, & White, 2006; Diamond et al., 1997; White et al., 2001; White, Nortz, Mandernach, Huntington, & Steiner, 2002).

Of particular relevance to the current investigation are the executive abilities of strategic processing, working memory, and inhibition. First, strategic processing, which is the ability to evaluate and alter plans to perform cognitive and behavioral tasks efficiently, has been found to

be poorer in children with PKU, especially older children (De Felice, Romani, Geberhiwot, MacDonald, Palermo, 2018; Nardecchia et al., 2015; White et al., 2001). There is evidence that higher blood Phe during childhood is associated with poorer strategic processing in adulthood (Bartus et al., 2018; Jahja et al., 2017).

Secondly, working memory involves the maintenance and manipulation of information for brief periods of time during cognitive task performance (Baddeley 1986). This ability has also been found to be poorer among individuals with PKU (Bartus et al., 2018; Brumm et al., 2004; Channon, German, & Lee, 2004; Christ et al., 2020; Jahja et al., 2017; Palermo et al., 2017). Furthermore, the age-related improvements in working memory that are observed in typically developing children has not been found in children with PKU (White et al., 2001). As for the relationship between blood Phe and working memory, high blood Phe has been associated with poorer working memory (Channon et al., 2004; Channon, Goodman, Zlotowitz, Mockler, & Lee, 2007).

Finally, inhibition is the ability to suppress thought processes, actions, or expressions that would interfere with attainment of a cognitive or behavioral goal (Carlson, Moses, & Breton, 2002). Individuals with PKU have deficits in inhibition, as demonstrated by more commission errors (i.e., false alarms) on tests of inhibition compared with typically developing controls (Araujo et al., 2009, 2013). Relatedly, Wiersema, van der Meere, and Roeyers (2005) showed that children with PKU have a higher rate of attention deficit hyperactivity disorder than the general population. In terms of Phe, higher blood Phe has been associated with poorer inhibition (Jahja et al., 2017; Romani, Palermo, MacDonald, Limback, & Hall, 2017).

In the present study we wished to move beyond the simple relationships between blood Phe and executive function by examining the relationships among the rate of blood Phe change

over time and executive function. To do so, we collected blood Phe measurements over time for each study participant from their medical record. In conjunction, executive function was assessed using a battery that included measures of strategic processing, working memory, and inhibition.

## **Methods**

### *Participants*

Children and adolescents ages 0-24 years with early- and continuously-treated PKU (n = 73, males = 37, females = 36, mean age at assessment = 14.3 years) were recruited through metabolic clinics at St. Louis Children's Hospital, University of Missouri, University of Florida, St. Louis University, Washington University, New York Medical College, and University of Nebraska. All were assessed at Washington University in St. Louis (n = 35), University of Missouri Columbia (n = 10), or Oregon Health and Science University (n = 28). Demographic information is presented in Table 1.

### *Procedure*

As a measure of long-term memory and strategic processing, a word list task (see Figure 1) was administered (n = 65, mean age at assessment = 13.9 years). During this task, participants listened as an examiner read a list of 18 words at a pace of 1 word per second and then recalled the list over 5 learning trials. Each list comprised items from different semantic categories (e.g., fruit, clothing, toys) such that there were 6 words from each category. Following presentation of the list, participants were asked to recall the words in any order. Memory of the items after a 20-minute delay was also assessed. The strategic processing variable of interest was semantic clustering, which indicates words that were sequentially reported from the same semantic category when individuals recalled words from the list. For example, “banana, watermelon,

strawberries, hat, belt, shorts” counted as two clusters (one fruit cluster, one clothing cluster). The average number of semantic clusters across all trials was used in analyses.

To assess working memory, a recognition span task ( $n = 27$ , mean age at assessment = 16.8 years) and an n-back task ( $n = 25$ , mean age at assessment = 16.7 years) were administered. During the recognition span task (see Figure 2), series of two to nine stimuli were presented within a grid on a computer monitor. There were two conditions, with one focusing on stimuli location and the other focusing on stimuli shape. Series comprising each condition were administered as a block. Stimuli within a series were presented one at a time, with each stimulus remaining on the monitor for 1250 ms. The interstimulus interval was 500 ms. Following the presentation of the last stimulus in a series, an array appeared that included all stimuli presented in that series. In the location condition, participants were asked to point to the locations in which stimuli appeared in the order in which they were presented. In the shape condition, participants were asked to point to the shapes that appeared in the order presented. The examiner depressed a right or left computer mouse button to record correct or incorrect responses, respectively. For each condition, 12 discrimination, 2 practice, and 18 experimental trials were administered. The average recognition span score across both conditions was used in analyses.

During the n-back task (see Figure 3), individuals watched a computer monitor as one of nine letters (A, C, F, H, J, N, P, Q, and S) appeared in one of nine locations along an imaginary circle eccentric to central fixation. There were two conditions, with one focusing on stimuli identity (i.e., letter) and the other focusing on stimuli location. In the letter condition, participants were asked to press a target button when the letter was the same as that which was presented two trials ago (regardless of location). For the location condition, participants were asked to press a target button when the location was the same as that which was presented two trials ago

(regardless of letter identity). Individuals heard a “beep” following correct responses and a “buzz” following incorrect responses. For each condition, participants completed a practice block of 24 trials and then 98 experimental trials. The average number of errors across both conditions, including both false alarms (commission errors) and missed targets (omission errors), was used in analyses.

As a measure of inhibition, participants completed a go-no-go task (see Figure 4) ( $n = 73$ , mean age at assessment = 14.3 years). There were two types of trials, with one focusing on go responses and the other focusing on no-go responses. On each trial, one of four stimuli (square, triangle, diamond, circle) was presented centrally on a computer monitor. One stimulus shape was designated as a non-target at the beginning of the task. Participants were asked to press a response button as quickly as possible when any stimulus appeared except the non-target. Go and no-go trials were randomly intermixed. If a participant failed to respond within 1500 ms on a go trial (omission error), a tone was presented. If an individual responded to a non-target (commission error), a tone was also presented. Participant completed 20 practice trials followed by 200 experimental trials. The number of responses to the non-target (i.e., number of commission errors) was used in analyses.

### *Statistical Approach*

Analyses were conducted in R (R Core Team, 2019 using ggplot2 (Wickham, 2016), lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017), dplyr (Wickham, François, Henry, & Müller, 2020), foreign (R Core Team, 2018), and interactions (Long, 2019). Hierarchical linear modeling was used to account for longitudinal dependencies (i.e., multiple blood Phe measurements nested within individuals) in the data. Since blood Phe commonly increases in a non-linear fashion over early development (Walter & White, 2004), first, second, and third-order

polynomials models were tested. The second-order (quadratic) model was determined to be the best fit because it minimized AIC and BIC without overfitting. Blood Phe was a dependent variable, Age<sup>2</sup> and Age were Level 1 variables, and executive function (EF) was a Level 2 variable. Cross-level interactions (Age<sup>2</sup> x EF, Age x EF) were modeled, and continuous variables were grand mean centered. Intercept and slope were modeled as random effects. Results were considered statistically significant at  $p < 0.05$ .

## **Results**

The results of all hierarchical linear models are reported in Tables 1-6 and illustrated in Figures 5-9. As noted previously, age and executive scores were grand mean centered. Only the significant effects in the quadratic model will be discussed below.

### *Age*

When using age as a predictor in a fully random hierarchical linear model, the quadratic age term was significant ( $p < 0.001$ ), indicating a quadratic increase of blood Phe as age increased. These results are reported in Table 2 and Figure 5.

### *Strategic Processing*

With regard to strategic processing as measured by the semantic clustering score, two results were of interest. The quadratic age term was significant ( $p < .001$ ), indicating a quadratic increase in blood Phe as age increased, at mean levels of age and semantic clustering. Furthermore, the quadratic interaction term between blood Phe and semantic clustering was significant ( $p < .001$ ), signifying that higher semantic clustering scores were associated with a shallower slope in blood Phe increase over age as age increased. These results are reported in Table 3 and Figure 6.

### *Working Memory*

Two results related to working memory were also notable. The quadratic age term was significant ( $p = .020$ ), indicating a quadratic increase in blood Phe as age increased, at mean levels of age and recognition span. The quadratic interaction term between blood Phe and recognition span score was also significant ( $p < .001$ ). This indicated that higher recognition span scores were associated with a shallower slope in blood Phe increase over age as age increased. These results are reported in Table 4 and Figure 7.

Regarding the n-back task model, the quadratic interaction term between blood Phe and n-back errors was also significant ( $p = .004$ ). This indicated that higher numbers of n-back errors were associated with a steeper slope in blood Phe increase over age as age increases. These results are reported in Table 5 and Figure 8.

### *Inhibition*

With regard to go-no-go performance, the quadratic age term was significant ( $p < .001$ ), indicating a quadratic increase of blood Phe as age increased. The quadratic interaction term between blood Phe and go-no-go commission errors was also significant ( $p < .001$ ). This indicated that higher go-no-go commission errors were associated with a steeper slope in blood Phe increase over age as age increased. These results are reported in Table 6 and Figure 9.

## **Discussion**

The present study investigated the trajectory of blood Phe levels over time and its relationship with executive function by modeling blood Phe over age and incorporating executive abilities, specifically strategic processing, working memory, and inhibition, as predictors. The average raw number of semantic clusters on a word list learning task was used as a measure of strategic processing. The average raw number of stimuli remembered on a

recognition span task, as well as the average raw number of errors on an n-back task, were used as measures of working memory. Finally, the average raw number of commission errors on a go-no-go task was used as a measure of inhibition. Data were analyzed using hierarchical linear modeling to account for longitudinal dependencies in the data and it was determined that the quadratic model best fit the slope of blood Phe over time.

Although the effect of age and executive function interaction was of greatest interest, we first address the effect of age alone. The quadratic age term was significant in the quadratic model with age alone as a predictor, and also across all the executive function conditions except in the n-back task, demonstrating that when age was grand mean centered, blood Phe increased quadratically up to age 24 years. It is likely that this effect was not found in the n-back task due to the fact that a smaller number of participants completed that task. The quadratic models are consistent with and contribute to the current understanding of increases in blood Phe with age due to decreasing dietary limitations on Phe intake. As individuals with PKU grow older, they tend to take more control over their diet, which would have previously been managed by their parents. As they take control, there is also a tendency to relax their diet (Waisbren et al., 2007). With this in mind, it follows that blood Phe would increase quadratically.

Next, we draw attention to the interaction of the quadratic age and executive function terms. Across all executive tasks, the interaction of age and executive abilities scores was significant at mean centered levels of age and executive scores. This indicated that, for participants who performed better on the strategic processing, working memory, and inhibition tasks, the relationship between age and blood Phe increased at a slower rate. More simply put, participants whose blood Phe increased more rapidly over time had poorer executive function outcomes.

Previous research has examined the impact of blood Phe on executive function and has highlighted the need for individuals with PKU to limit their Phe intake for adequate executive function. In no research to date, however, has the impact of the rate of blood Phe increase over time on executive function been examined. As our results indicate, the rate of blood Phe increase is an important predictor of executive function. Individuals with PKU, their families, and their healthcare providers should take this into consideration when planning dietary management and adherence to dietary prescriptions over time, especially during childhood and adolescence.

In terms of limitations, the age of our participants was restricted to 0-24 years because that is when blood Phe is known to change most significantly. It is likely that, after age 24 years, blood Phe plateaus and the present quadratic model will not be sufficient. Furthermore, the present study only examined the relationship between blood Phe trajectory and executive function when age was grand mean centered (age = 5.0395). It would be informative to center age at different points to determine the age range at which the rate of blood Phe increase is most strongly predicted by executive function. Practically, determining a specific age period during which rate of blood Phe increase is most negatively related to executive function could point to periods during which dietary management is most important for executive function.

### **Conclusion**

Our results indicated that children and adolescents with PKU exhibited a quadratic increase in blood Phe up to age 24 years when age was mean centered at 5. More importantly, the interaction of age and executive function, at mean centered levels of age and executive function score, indicated that the rate of increase in blood Phe predicted later executive function. This finding has practical implications for dietary restriction during childhood. Although strict

adherence to diet has always been recommended to manage PKU, its importance is emphasized by the knowledge of the predictive importance of rates of blood Phe increase over time.

Continued efforts to specify the time frame during which rates of blood Phe have the strongest effect on executive function outcomes will provide individuals with PKU, their families, and their healthcare providers with guidance as to when dietary adherence may be most important.

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## Tables and Figures

*Table 1.* Demographic information, grouped by participants in overall pool and for each executive abilities task.

<i>Subjects</i>	<i>n</i>	<i>Male</i>	<i>Female</i>	<i>Mean Lifetime Phe (mg/dL)</i>	<i>SD Lifetime Phe (mg/dL)</i>	<i>Mean Age at Blood Phe Measurements (yrs)</i>	<i>Mean Age at Executive Assessment (yrs)</i>
All	73	37	36	7.09	3.42	5.04	14.29
Semantic Clustering	65	31	34	6.85	3.22	5.13	13.90
Recognition Span	27	17	10	8.03	3.65	4.87	16.81
N-Back	25	15	10	7.88	3.61	4.87	16.72
Go-No-Go	73	37	36	7.09	3.42	5.04	14.29

Table 2. Hierarchical Linear Model for Age Effect on Blood Phe, Data Nested within Subject ID Number

<b>Age Effect on Blood Phe</b>			
	<b>Blood Phe, mg/dL</b>		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Intercept	6.59	5.81 – 7.38	<0.001
Age	1.72	0.56 – 2.87	0.003
Age <sup>2</sup>	8.09	4.28 – 11.90	<0.001
<b>Random Effects</b>			
$\sigma^2$	14.00		
$\tau_{00}$ IDNUMBER	10.55		
$\tau_{11}$ IDNUMBER.I(Age.c/10)	19.96		
$\tau_{11}$ IDNUMBER.I((Age.c/15) <sup>2</sup> )	201.56		
$\rho_{01}$	0.26		
	-0.35		
ICC	0.51		
N IDNUMBER	73		
Observations	12085		
Marginal R <sup>2</sup> / Conditional R <sup>2</sup>	0.099 / 0.562		

Table 3. Hierarchical Linear Model for Age and Semantic Clustering Effect on Blood Phe, Data Nested within Subject ID Number

<b>Age and Semantic Clustering Score Effect on Blood Phe</b>			
	<b>Blood Phe, mg/dL</b>		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Intercept	6.30	5.50 – 7.10	<0.001
Age	1.48	0.42 – 2.54	<b>0.006</b>
Semantic Clustering	0.16	-0.02 – 0.34	0.073
Age <sup>2</sup>	7.83	6.80 – 8.86	<0.001
Age:Semantic Clustering	0.22	-0.01 – 0.46	0.064
Age <sup>2</sup> :Semantic Clustering	-1.29	-1.58 – -1.00	<0.001
<b>Random Effects</b>			
$\sigma^2$	14.03		
$\tau_{00}$ IDNUMBER	9.45		
$\tau_{11}$ IDNUMBER.I(Age.c/10)	14.87		
$\rho_{01}$ IDNUMBER	0.06		
ICC	0.47		
N IDNUMBER	65		
Observations	11336		
Marginal R <sup>2</sup> / Conditional R <sup>2</sup>	0.071 / 0.504		

Table 4. Hierarchical Linear Model for Age and Recognition Span Effect on Blood Phe, Data Nested within Subject ID Number

<b>Age and Recognition Span Score Effect on Blood Phe</b>			
	<b>Blood Phe, mg/dL</b>		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Intercept	7.56	6.29 – 8.83	<0.001
Age	2.45	0.66 – 4.23	0.007
Recognition Span	2.16	0.33 – 3.99	0.021
Age <sup>2</sup>	3.24	0.51 – 5.97	0.020
Age:Recognition Span	1.75	-0.72 – 4.22	0.165
Age <sup>2</sup> :Recognition Span	-9.72	-14.61 – -4.83	<0.001
<b>Random Effects</b>			
$\sigma^2$	17.58		
$\tau_{00}$ IDNUMBER	9.04		
$\tau_{11}$ IDNUMBER.I(Age.c/10)	15.62		
$\rho_{01}$ IDNUMBER	0.38		
ICC	0.42		
N IDNUMBER	27		
Observations	2803		
Marginal R <sup>2</sup> / Conditional R <sup>2</sup>	0.108 / 0.485		

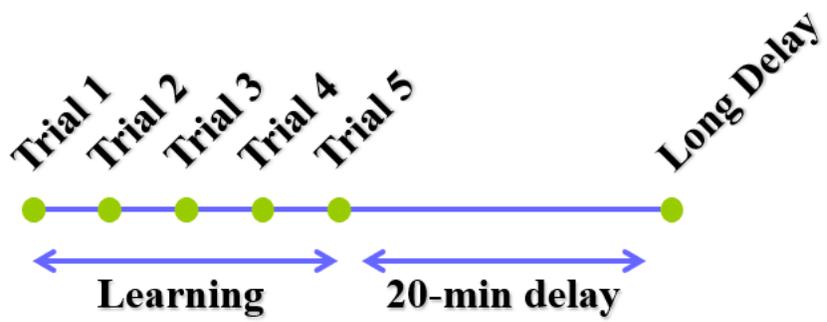
Table 5. Hierarchical Linear Model for Age and N-Back Effect on Blood Phe, Data Nested within Subject ID Number

<b>Age and N-Back Errors Effect on Blood Phe</b>			
	<b>Blood Phe, mg/dL</b>		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Intercept	7.70	6.38 – 9.02	<0.001
Age	2.34	0.55 – 4.12	<b>0.010</b>
N-Back	-0.15	-0.40 – 0.10	0.247
Age <sup>2</sup>	1.57	-0.79 – 3.93	0.193
Age:N-Back	-0.04	-0.40 – 0.32	0.812
Age <sup>2</sup> :N-Back	0.83	0.26 – 1.39	<b>0.004</b>
<b>Random Effects</b>			
$\sigma^2$	17.40		
$\tau_{00}$ IDNUMBER	9.77		
$\tau_{11}$ IDNUMBER.I(Age.c/10)	16.22		
$\rho_{01}$ IDNUMBER	0.52		
ICC	0.44		
N IDNUMBER	25		
Observations	2710		
Marginal R <sup>2</sup> / Conditional R <sup>2</sup>	0.049 / 0.464		

Table 6. Hierarchical Linear Model for Age and Go-No-Go Effect on Blood Phe, Data Nested within Subject ID Number

<b>Age and Go-No-Go Commission Errors Effect on Blood Phe</b>			
	<b>Blood Phe, mg/dL</b>		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Intercept	6.56	5.75 – 7.37	<0.001
Age	1.07	0.03 – 2.11	<b>0.044</b>
Go-No-Go	-0.03	-0.23 – 0.17	0.767
Age <sup>2</sup>	7.71	6.62 – 8.80	<0.001
Age:Go-No-Go	0.11	-0.15 – 0.37	0.404
Age <sup>2</sup> :Go-No-Go	0.70	0.41 – 1.00	<0.001
<b>Random Effects</b>			
$\sigma^2$	14.44		
$\tau_{00}$ IDNUMBER	11.23		
$\tau_{11}$ IDNUMBER.I(Age.c/10)	17.22		
$\rho_{01}$ IDNUMBER	-0.11		
ICC	0.50		
N IDNUMBER	73		
Observations	12085		
Marginal R <sup>2</sup> / Conditional R <sup>2</sup>	0.058 / 0.530		

Figure 1. Semantic Clustering Task



<b>bananas</b>	<b>sweater</b>	<b>puzzle</b>
<b>jacket</b>	<b>grapes</b>	<b>blocks</b>
<b>watermelon</b>	<b>shorts</b>	<b>crayons</b>
<b>peaches</b>	<b>balloons</b>	<b>hat</b>
<b>strawberries</b>	<b>t-shirt</b>	<b>ball</b>
<b>apple</b>	<b>belt</b>	<b>marbles</b>

Figure 2. Recognition Span Task

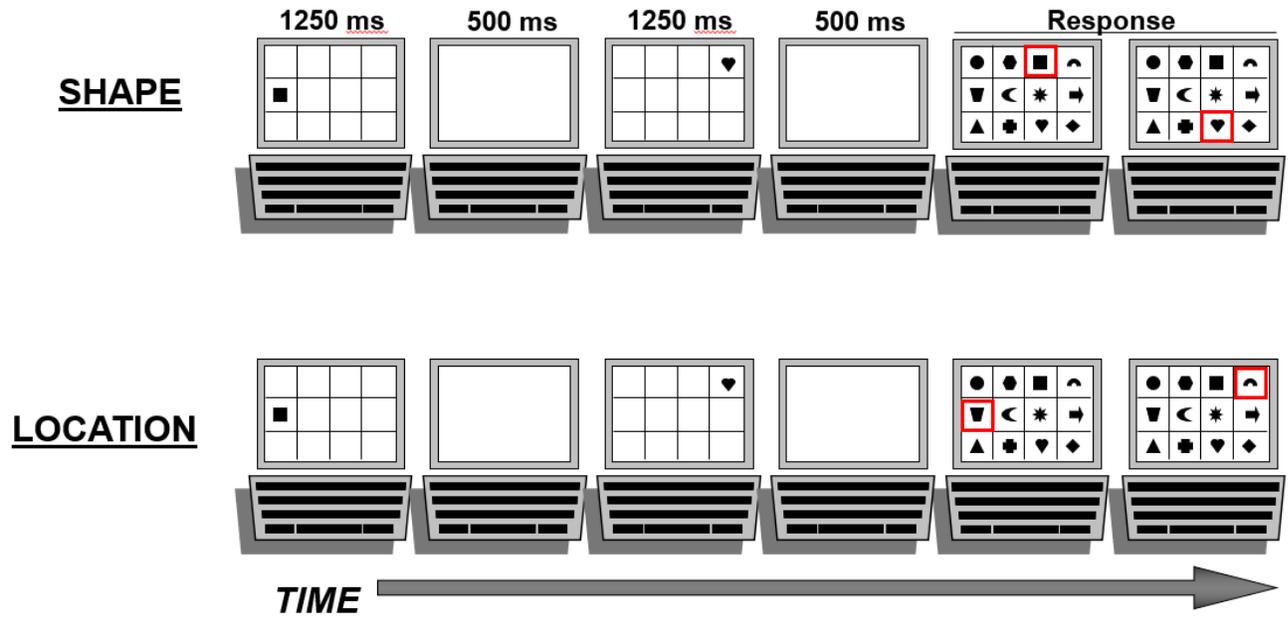


Figure 3. N-Back Task

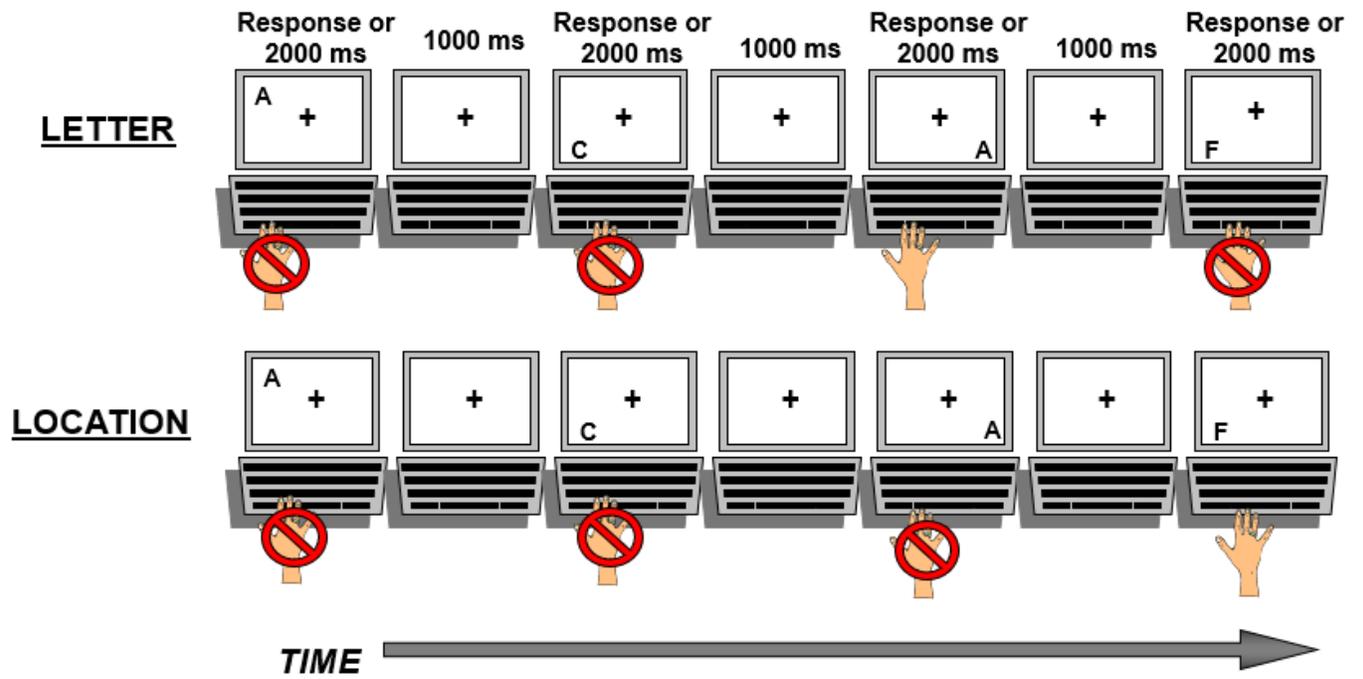


Figure 4. Go-No-Go Task

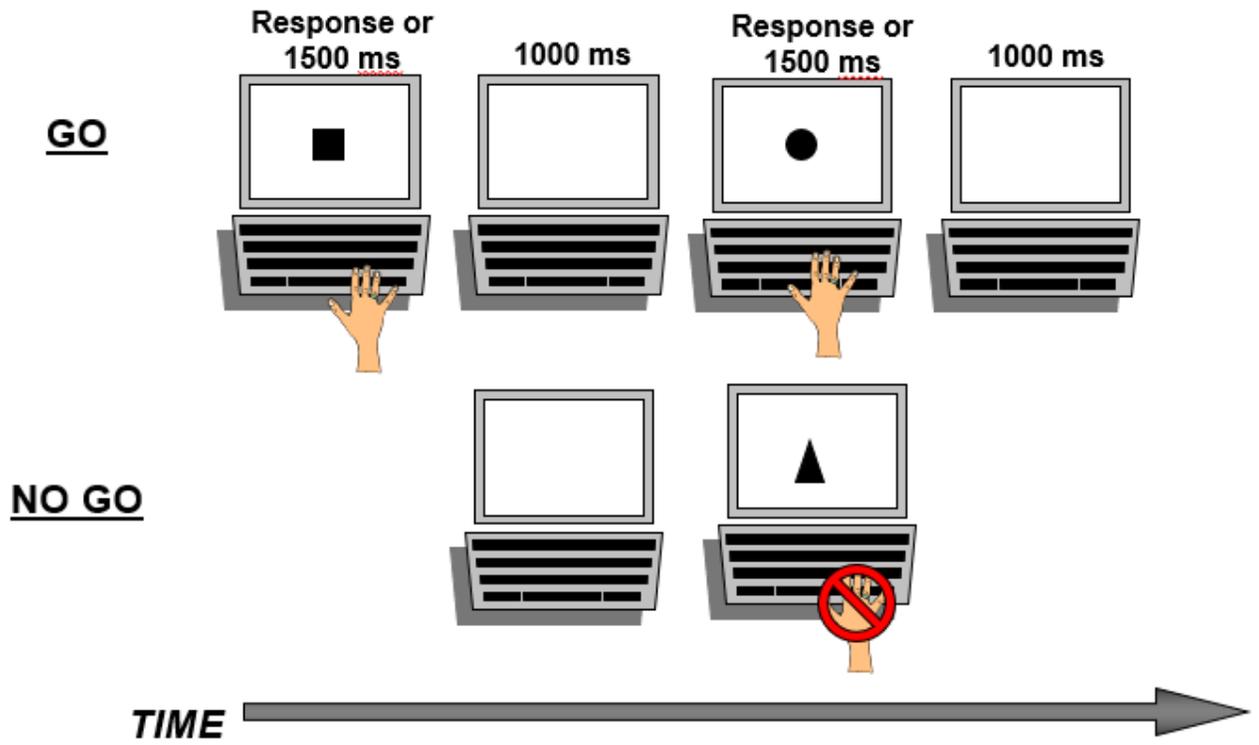


Figure 5. Effect of Age on Blood Phe

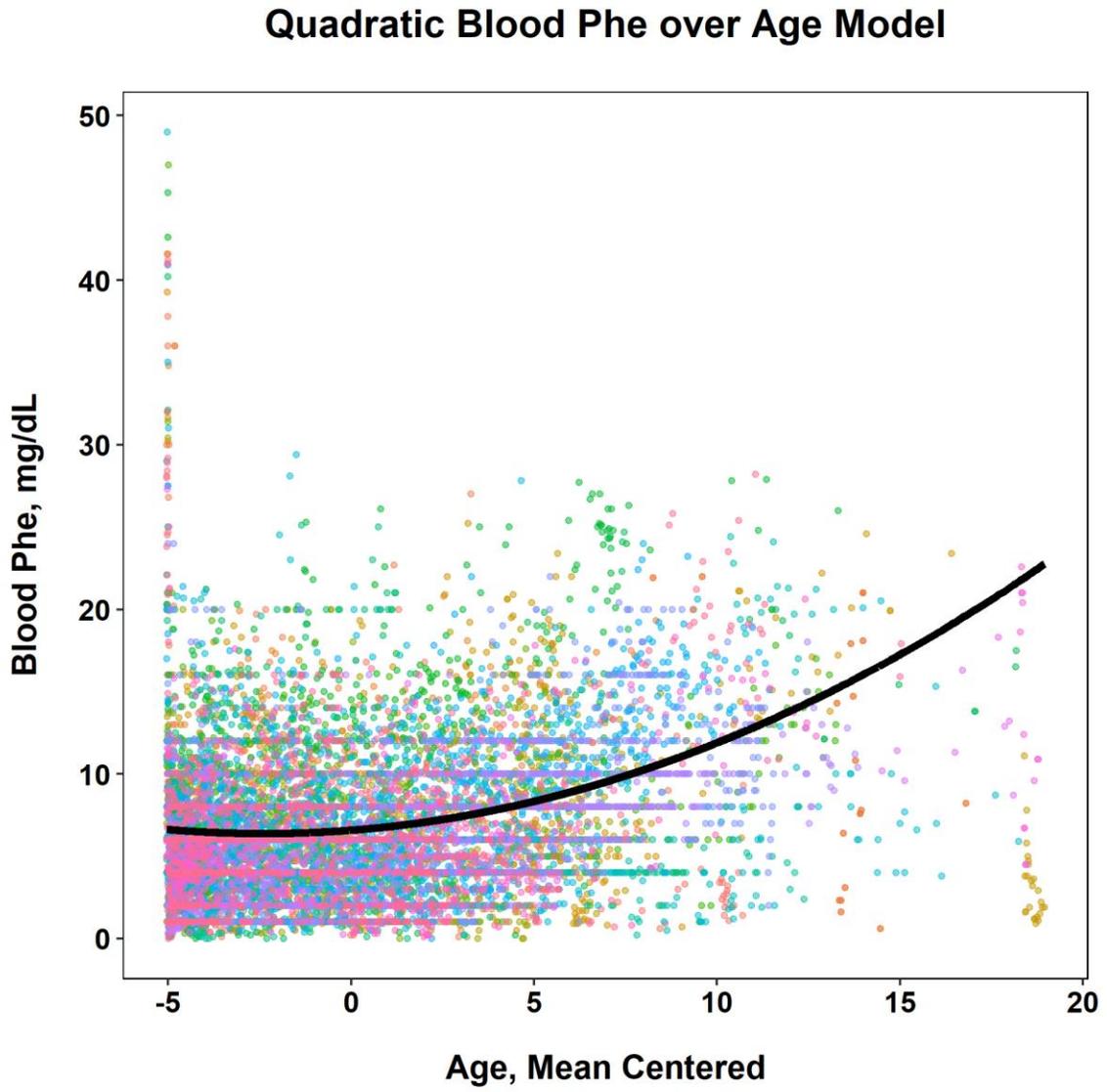


Figure 6. Effect of Age and Semantic Clustering Score on Blood Phe

### Quadratic Interaction of Semantic Clustering Score and Age

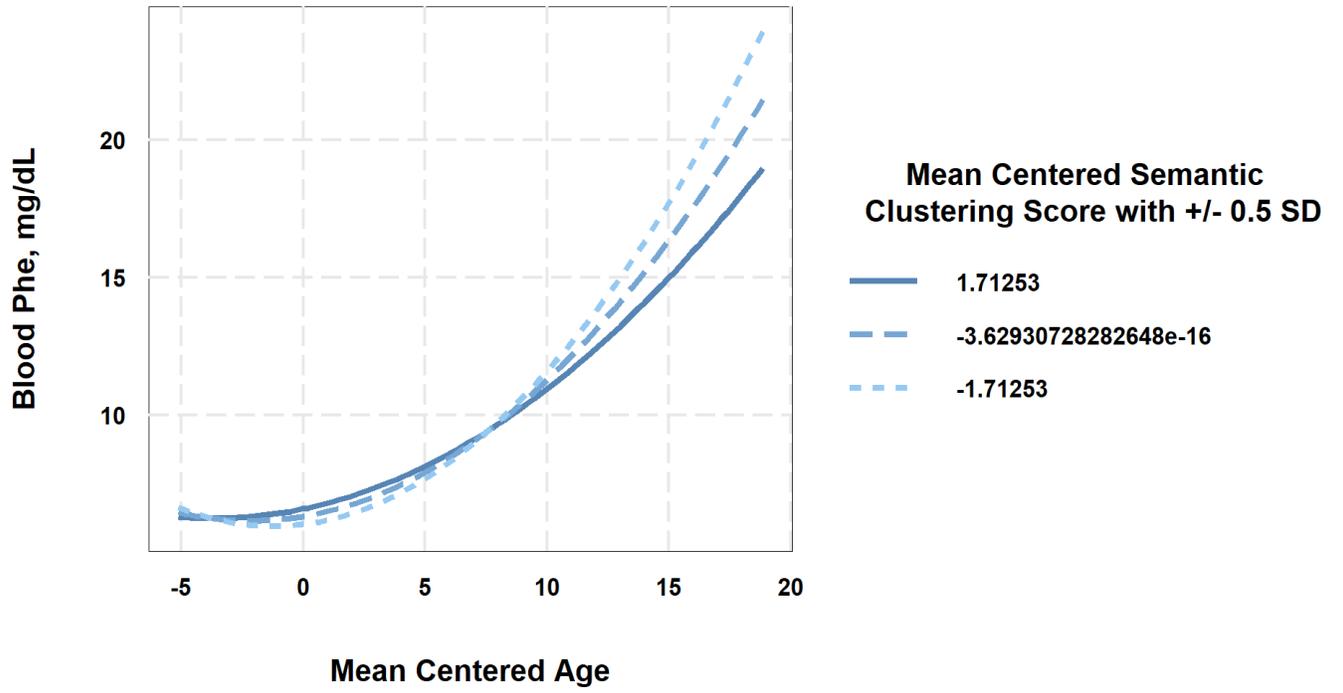


Figure 7. Effect of Age and Recognition Span Score on Blood Phe

### Quadratic Interaction of Recognition Span and Age

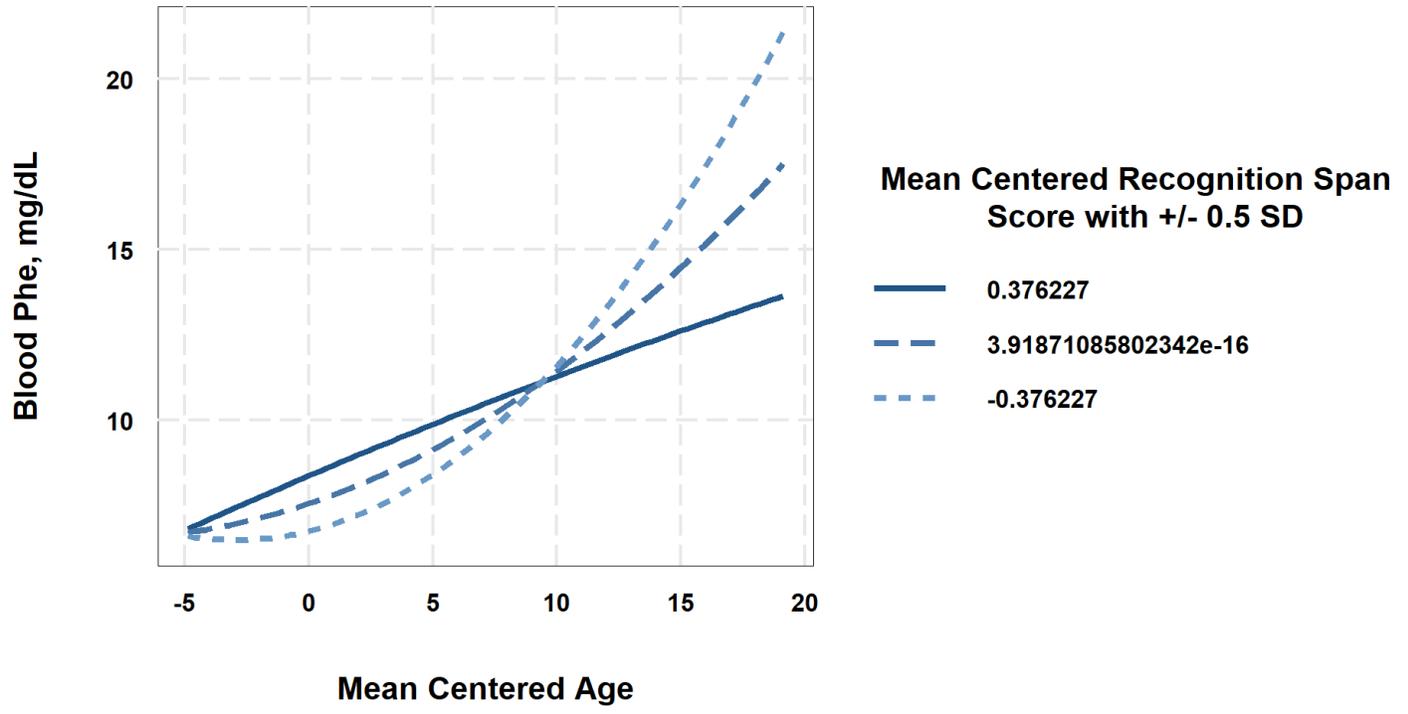


Figure 8. Effect of Age and N-Back Errors on Blood Phe

### Quadratic Interaction N-Back Errors and Age

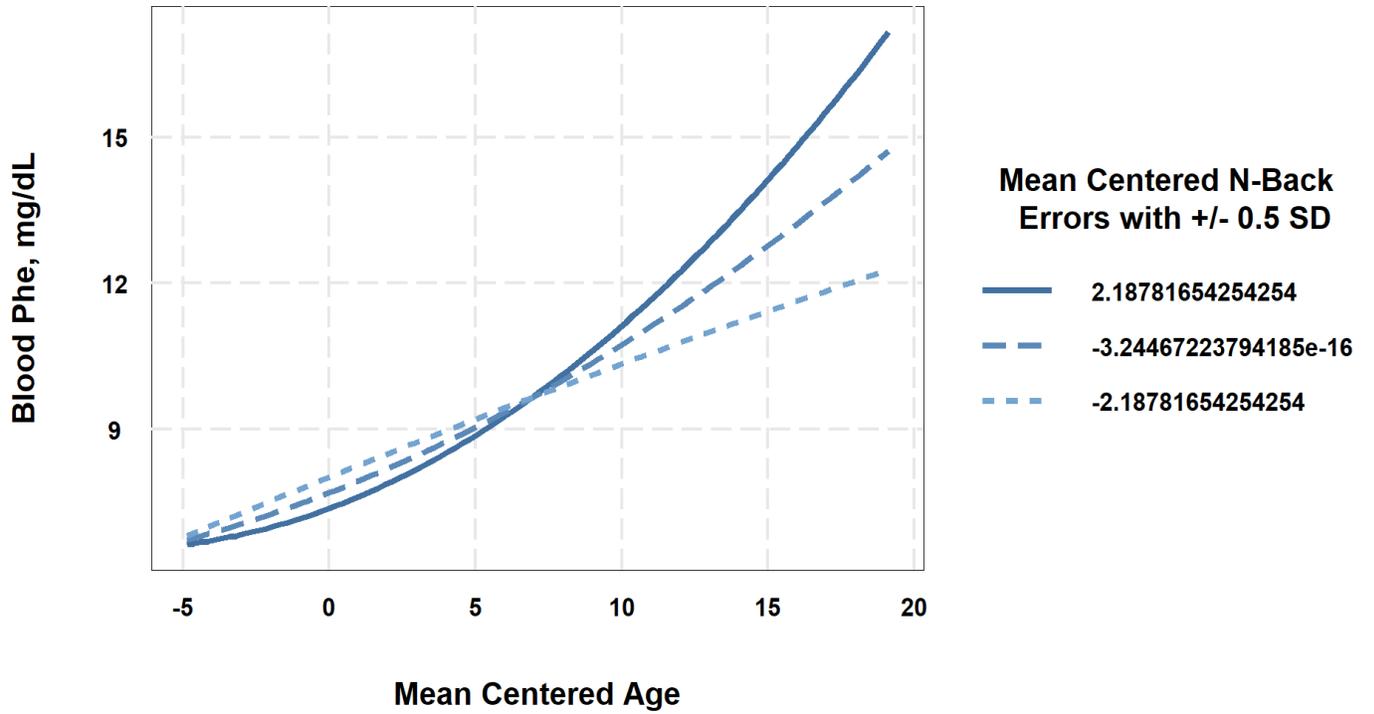


Figure 9. Effect of Age and Go-No-Go Commission Errors on Blood Phe

### Quadratic Interaction of Go-No-Go Commission Errors and Age

