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Research Article

A comprehensive assessment of neurocognitive and psychological functioning in adults with early-treated phenylketonuria

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Abstract

Objective: Relative to youth with early-treated phenylketonuria (ETPKU), much less is known regarding the cognitive profile of adults with ETPKU. The present study aimed to address this gap by providing a comprehensive assessment of neuropsychological functioning among adults with ETPKU. **Method:** A sample of 40 adults with ETPKU (ages 18 – 36) and a demographically matched group of 32 healthy individuals without PKU participated. Participants completed a comprehensive neuropsychological battery including the NIH Toolbox, Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II), Conners' Continuous Performance Test (CPT-3), select subtests from the Weschler Adult Intelligence Scale – Fourth Edition (WAIS-IV) as well as several self-report measures of cognitive and psychoemotional functioning. Scores from these tests were combined to create cognitive composites reflecting overall task performance in the areas of verbal ability, visuospatial skills, executive functioning, motor skills, and processing speed. **Results:** No group differences were observed for full scale IQ or verbal ability. However, individuals with ETPKU demonstrated poorer performance on measures of executive functioning, processing speed, motor skills, and visuospatial skills as compared to the non-PKU group. Within the ETPKU group, recent blood phenylalanine levels (an indicator of metabolic control) were significantly correlated with performance across most cognitive domains and aspects of psychological functioning. **Conclusions:** Present findings suggest that the neuropsychological profile of adult ETPKU is characterized by circumscribed impairments in select cognitive domains. In addition, the results underscore the importance of maintaining metabolic control across the lifespan in individuals with ETPKU.

Keywords: executive function; attention; motor skills; visual spatial processing; phenylalanine; cognition

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Phenylketonuria (PKU) is an autosomal recessive condition characterized by a deficiency in the phenylalanine hydroxylase enzyme that is necessary for the metabolism of the amino acid phenylalanine (phe) to tyrosine. PKU is associated with higher-than-normal levels of phe as well reductions in tyrosine and its metabolites such as dopamine and other catecholamines, in both the central nervous system and peripheral tissues (de Groot et al., 2010). In addition, the excess phe competes with other available large neutral amino acids (e.g., tryptophan, valine, leucine) to cross the blood-brain barrier (Pardridge, 1977; Shulkin et al., 1995; de Groot et al., 2010). As such, central levels of other noncatecholaminergic neurotransmitters (e.g., serotonin) are also impacted (Smith et al., 1987; Welsh et al., 1990). Elevated brain phe may also directly impact processes such as protein synthesis and myelin formation (Pardridge, 1998; de Groot et al., 2010).

If left untreated, PKU is associated with severe neurologic and cognitive impairment (Paine, 1957; Bechar et al., 1965). Current practices encourage individuals with PKU to initiate a phe-restricted diet shortly after birth and to maintain these restrictions across one's lifetime (Vockley et al., 2014). Although individuals with early-treated PKU (ETPKU) experience much improved outcomes relative to those who do not undergo treatment, many still experience neurologic and cognitive disruptions.

The most widely reported neurologic finding among individuals with ETPKU is cortical white matter (WM) abnormalities. Indeed, a review by Anderson and Leuzzi (2010) estimated that WM abnormalities are detectable in over 90% of adults with ETPKU. These abnormalities are typically observed proximal to the posterior aspects of the lateral ventricles and extend more anteriorly with increased severity. The extent and severity of the WM abnormalities are positively correlated with age and blood phe levels (Hood et al., 2015; Wesonga et al., 2016; Clocksin et al., 2021). More recent research suggests that gray matter structures (e.g., posterior cortex, putamen, cerebellum) may be affected in PKU as well (e.g., Bodner et al., 2012; Christ et al., 2016; Aldridge et al., 2020).

The majority of past neuropsychological studies of ETPKU have focused on children and adolescents. This literature supports a neurocognitive profile characterized by slight decrease in overall intellectual ability coupled with circumscribed impairments in particular domains including executive function, attention, processing speed, and fine motor control (for review, see Canton et al., 2019). For example, Anderson et al. (2007) administered a neuropsychological battery

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Table 1. Demographic information

	ETPKU ($n = 40$)			Non-PKU ($n = 32$)	
Variable	M (SD)	Range	*n*	M (SD)	Range
Age (years)	26.4 (5.5)	18 - 36		25.9 (4.2)	18–34
Sex (M/F)	14/26			11/21	
Education (years)	14.3 (2.4)	8 - 19		14.8 (1.6)	11–19
Phenylalanine Levels (μmol/L)					
Most recent level	589 (444)	79 - 1946	38	–	–
Mean level for previous year	589 (393)	86 - 1959	38	–	–
IDC for early childhood (0–5 years)	325 (113)	139 - 590	29	–	–
IDC for middle childhood (6–11 years)	438 (213)	135 - 1021	34	–	–
IDC for adolescence (12–17 years)	578 (284)	182 - 1239	35	–	–
IDC for adulthood (18+ years)	604 (342)	229 - 1684	29	–	–
IDC for lifetime (0-present)	464 (214)	180 - 1027	26	–	–

to a sample of children with and without ETPKU. They found that the ETPKU group performed more poorly than the non-PKU group on full scale IQ as well as measures of processing speed, sustained attention, and memory. The ETPKU group also showed delays in their acquisition of achievement such as reading and arithmetic. Consistent with other studies, they found that task performance was negatively correlated with blood phe levels (an indicator of metabolic control) in many cases.

In comparison to the aforementioned childhood literature, much less is known regarding the neurocognitive and psychological profile of adults with ETPKU. Relatively recent changes in treatment guidelines (e.g., consensus support for treatment and maintenance of metabolic control throughout life – not just until person reaches young adulthood), a preliminary focus within the literature on the effects of phe level exposure in childhood, and the large number of adults lost to follow-up have contributed to a discrepancy in the number of studies focused on adult neurocognitive outcomes relative to those focused on pediatric outcomes (for further discussion, see Berry et al., 2013; Vockley et al., 2014). In addition, research suggests potential developmental changes in the neurocognitive profile as children with ETPKU age. For example, White et al., (2002) found that impairments in working memory performance were more evident in older as compared to younger children with ETPKU. Many other past studies (e.g., Moyle et al., 2007; Nardecchia et al., 2015) have included small sample sizes coupled with wide age ranges, encompassing both adolescents and adults, thus making it difficult to disentangle potential developmental contributions to the observed neurocognitive profile. In terms of the available studies on adults with ETPKU, most have focused on a few select cognitive functions rather than representing a comprehensive evaluation across domains (e.g., Dawson et al., 2011; Weglage et al., 2013). Taken together, these factors have contributed to a lack of consensus regarding the neurocognitive profile of adults with ETPKU and the impact of historic and concurrent metabolic control on cognitive functioning (for additional discussion of these issues, see Hofman et al., 2018). For example, based on data from nine studies, a meta-analysis by Bilder et al. (2016) found that working memory was not significantly affected in adults with ETPKU. In contrast, a systematic review by Hofman et al. (2018) covering data from sixteen studies concluded that working memory represented one of the most consistent deficits in adults with ETPKU.

In light of these challenges, more recent work with adults has endeavored to include more comprehensive neuropsychological batteries. For example, Palermo et al. (2017) included 28 tasks spanning several cognitive domains including executive function, sustained attention, visuomotor coordination, language, and memory in a study of 37 adults with ETPKU. Similarly to the aforementioned childhood literature, the adult ETPKU group had significantly lower FSIQ than the non-PKU comparison group, suggesting that differences in overall intellectual ability may persist across development. In addition, adults with ETPKU performed worse on measures of sustained attention, processing speed, visuomotor skills, and higher-order executive function requiring flexibility and planning.

The researchers conducted additional analyses to examine the relationship between the cognitive data and phe levels during different developmental epochs (Romani et al., 2017). Although several cognitive areas (e.g., sustained attention) showed the strongest correlation with recent phe levels, others revealed vulnerability across multiple developmental epochs. For example, visual-motor coordination was correlated with recent, lifetime, adolescent, and adult phe levels. Yet still other domains such as complex executive function were most strongly related to phe levels during adolescence. These findings are consistent with the notion that the impact of phe levels on neuropsychological outcome varies based on developmental timing and cognitive domain.

The present study

The present study was designed to further this line of research and advance our understanding of the neurocognitive and psychological profile of adults with ETPKU. Within this context, we utilized a relatively new measure with emerging popularity in the cognitive assessment community, namely the NIH Toolbox (for full description, see Heaton et al., 2014). Briefly, the NIH Toolbox is a compilation of computerized assessments that can be flexibly administered either singly or as part of a larger battery to evaluate functional domains such as overall cognition or motor functions. Specific areas of cognition assessed by the NIH Toolbox include attention, episodic memory, processing speed, inhibitory control, and working memory. The NIH Toolbox has been used to successfully evaluate neurocognitive functioning among individuals with a diverse array of acute and chronic conditions (e.g., stroke, Carlozzi et al., 2017; sickle cell disease, Hood et al., 2019; alcohol use disorder, Meredith et al., 2020; among others). The present study represents one of the first to utilize the NIH Toolbox with individuals with ETPKU.

So as to provide a full comprehensive picture of neurocognitive functioning, we coupled the NIH toolbox with additional standardized measures designed to further assess overall intellectual

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Table 2. Tasks administered and neurocognitive domains assessed

Cognitive Domain	Measure/Task
Overall functioning	
	Fluid Cognition Composite Score (NIH Toolbox)
	Full Scale Intelligence Quotient (WASI – II)
Verbal ability composite	
	Similarities (WASI-II)
	Vocabulary (WASI-II)
Visuospatial skills composite	
	Block Design (WASI-II)
	Visual Puzzles (WAIS-IV)
Executive function composite	
	Matrix Reasoning (WASI-II)
	Flanker Inhibitory Control and Attention (NIH Toolbox)
	Dimensional Change Card Sort (NIH Toolbox)
	Commissions (CPT-3)
	Omissions (CPT-3)
	List Sorting Working Memory (NIH Toolbox)
Motor skills composite	
	9-hole Pegboard (NIH Toolbox)
	Grip Strength (NIH Toolbox)
	Grooved Pegboard
	Standing Balance (NIH Toolbox)
	Walk Endurance Test (NIH Toolbox)
	Walk Gait (NIH Toolbox)
Processing speed composite	
	Coding (WAIS-IV)
	Hit Reaction Time (CPT-3)
	Oral Symbol Digit (NIH Toolbox)
	Pattern Comparison (NIH Toolbox)
	Symbol Search (WAIS-IV)
Self-report measures	
	Social Responsiveness Scale – Second Edition
Internalizing symptoms	
	Beck Anxiety Inventory
	Beck Depression Inventory – Second Edition
Executive abilities	
	Behavior Rating Inventory of Executive Function – Adult Version
	Connors' Adult ADHD Rating Scales

Note. WASI-II = Wechsler Abbreviated Scale of Intelligence – Second Edition; WAIS-IV = Wechsler Adult Intelligence Scale – Fourth Edition; CPT-3 = Conners Continuous Performance Test – Third Edition.

ability, sustained attention, processing speed, verbal ability, executive functioning, visuospatial skills, and fine motor control. In order to capture psychological and day-to-day aspects of functioning, we also included report measures of executive function, attention, anxiety, depression, and social communication symptomatology.

Given the prior success with other clinical populations, we expect that the NIH Toolbox will provide a valid assessment of neurocognitive functioning among individuals with ETPKU, with findings in line with the more established measures included in our test battery. Specifically, based on past work (e.g., Palermo et al., 2017; Hofman et al., 2018), we hypothesize that adults with ETPKU will demonstrate particular difficulties in executive function and attention, motor skills, and processing speed. Conversely, we anticipate that verbal ability will be relatively intact/spared. We also anticipate that the magnitude of cognitive and psychological disruption will be correlated with blood phe levels (a marker of metabolic control).

Methods

Participants

A sample of 40 adults with ETPKU (18–36 years of age) and a demographically matched comparison group of 32 adults without PKU participated in the study. Demographic information for the participant sample is included in Table 1.

All participants with ETPKU were diagnosed at birth (33 classic PKU, 1 moderate PKU, 3 mild PKU; 2 hyperphenylalaninemia; 1 unspecified). [Note that PKU categorization is based on blood phe levels at the time of diagnosis (Classic: > 1200 μmol/L; Moderate: 900–1200 μmol/L; Mild: 600–900 μmol/L; Hyperphenylalaninemia: 120–600 μmol/L).] All ETPKU participants began a phe-restricted diet shortly after birth as indicated by medical records and/or patient report. Individuals with major medical conditions unrelated to PKU (e.g., diabetes) were excluded. Participants in the non-PKU group were recruited from the local community.

For participants with ETPKU, data on historic and recent plasma phe levels was compiled from available medical records and is included in Table 1. Lifetime phe level data was unavailable for three participants, so these individuals were only included in the recent and past year phe level analyses. Most recent phe level on record as well as mean phe level for the year preceding study participation were calculated. As described previously (Christ et al., 2021), the index of dietary control (the mean of all half-year median phe levels) was computed for early childhood (0–5 years), middle childhood (6–11 years), adolescence (12–17 years), adulthood (18+ years), and lifetime (0-present). See Supplementary materials for more details.

Materials and procedure

The present study was approved by the University of Missouri Internal Review Board (Review ID# 2011602) and was carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. Informed consent was obtained for all individuals prior to participation. Participants completed all tasks in a small, quiet room with adequate overhead lighting. Participants were given opportunities to take breaks in between tests.

A full list of administered measures and associated cognitive domains are included in Table 2 and more detailed task descriptions are included in the online Supplementary materials. In brief, the test battery consisted of both performance-based measures including the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2; Wechsler, 1999), cognitive and motor batteries from the NIH Toolbox, select subtests from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008), Connors' Continuous Performance Test – Third Edition (CPT-3), as well as self-report measures, including Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A), Connors' Adult ADHD Rating Scales (CAARS), Social Responsiveness Scale – Second Edition (SRS-II), Beck Anxiety Inventory (BAI), and Beck Depression Inventory – Second Edition (BDI-2).

Data processing & analysis

Performance-based measures

Each of the performance-based measures (see Table 2 for full list) yielded age-normed standard scores. [Note that normative scores are not generated automatically for the Oral Symbol Digit and Walk Gait subtests of the NIH Toolbox. For these, scores were

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Table 3. Means and standard deviations for composite neurocognitive and psychological measures

	ETPKU		Non-PKU		Group Difference		
Composite measure	M	SD	M	SD	t*	*p*	g
Cognitive composite measures							
Full scale intelligence quotient	101	11.2	104	9.0	1.16	.250	.27
Fluid cognition composite	98	14.9	108	15.5	2.64	.010	.62
Verbal ability	99	11.4	98	9.3	0.27	.789	.06
Visuospatial skills	101	11.5	110	10.2	3.44	.001	.82
Executive function	98	8.7	102	6.4	2.38	.020	.56
Motor skills	96	7.6	100	6.4	2.42	.018	.58
Processing speed	106	10.6	111	9.0	2.23	.029	.52
Self-report composite measures							
SRS-II total score	53	9.0	50	7.2	1.55	.125	.36
Internalizing symptoms	52	11.9	51	6.3	0.74	.461	.17
Executive abilities composite	49	9.1	43	7.6	3.15	.002	.74

Note. SRS-II = Social Responsiveness Scale – Second Edition.
*Degrees of Freedom: Visuospatial Skills and Motor Skills = 67; all others = 70.

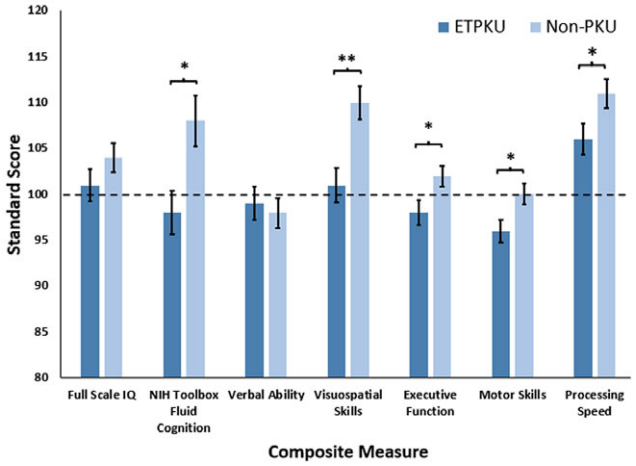

Figure 1. Mean composite scores shown separately for cognitive domain and group (ETPKU and non-PKU). Higher composite scores are indicative of better performance. A dashed line is included at a standard score of 100 for reference. *$p < .05$; **$p < .005$.

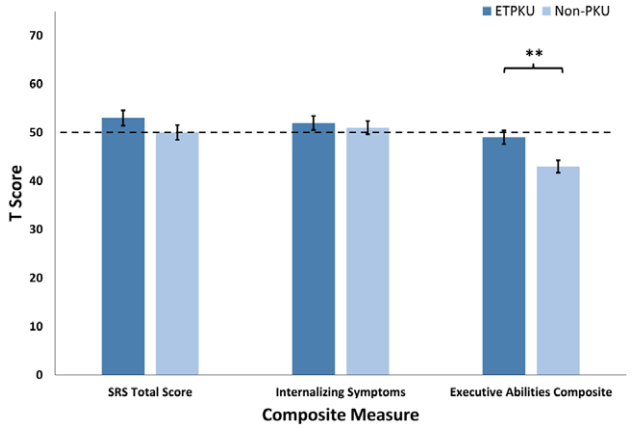

Figure 2. Mean t scores shown separately for each self-report measure and group (ETPKU and non-PKU). Higher t scores are indicative of increased difficulties and symptomatology. A dashed line is included at a T score of 50 for reference. *$p < .05$; **$p < .00$.

calculated manually using the normative data reported in the NIH Toolbox Technical Manual.] So as to allow for easy comparison as well as calculation of composite domain scores (see below), normed scores for all performance-based measures were converted to a standard score scale with a mean of 100 and a standard deviation of 15. Also, where applicable, the performance-based scores were adjusted such that a higher score reflected better performance.

In a procedure similar to Romani et al. (2017), the standard scores of contributing measures were averaged to generate composite scores in the areas of verbal ability, visuospatial skills, executive functioning, motor skills, and processing speed. Table 2 includes a list of measures included in each composite. For both the performance-based and self-report measures, to protect against an increase in the likelihood of a Type I error related to multiple comparisons, we confirmed a statistically significant finding on one of the broader composite scores before proceeding to analyze the contributing individual subtest scores.

Self-report measures

All of the self-report measures generated normed t scores ($M = 50$, $SD = 10$) in which a higher score reflected worse/more symptomatology (Beck & Steer, 1993; Beck et al., 1996; Roth et al., 2005; Constantino, 2012). Scores generated from self-report measures were not modified due to their common scale. Similar to the approach taken with the performance-based measures, a composite score reflecting everyday difficulties with executive function and attention was computed based on overall scores from the BRIEF-A (Global Executive Composite; GEC) and CAARS (Overall ADHD Index). Scores from the BAI and BDI-2 were averaged to create a composite score representing symptomatology related to internalizing problems. Given that the SRS-2 captures a unique aspect of everyday functioning relative to the other measures, it was analyzed separately.

For both the performance-based and self-report measures, to protect against an increase in the likelihood of a Type I error related to multiple comparisons, we confirmed a statistically significant finding on one of the broader composite scores before proceeding to analyze the contributing individual subtest scores. A false discovery rate (FDR; $q < .05$) approach was used to correct for multiple comparisons associated with the correlation analyses between scores and phe levels.

Statistical approach

The primary statistical approach was an independent samples *t*-test with Hedges *g* as a measure of effect size. The normative scores for the reported measures were already corrected for age, and the majority corrected for sex as well. (Scores from the WASI-II and WAIS-IV were corrected for age only.) As such, these factors were not included as covariates. Correlations between scores and phe level measurements were also calculated.

Results

Mean composite scores are listed in Table 3 and illustrated in Figures 1 and 2. Two participants (one from each group) did not complete the CPT-3 due to technical problems. NIH Toolbox motor data were unavailable for three ETPKU participants. As such, they were excluded from analysis of the associated composite score.

Performance-based neurocognitive measures

Overall intellectual functioning

No group differences were observed in overall intellectual ability as estimated using the WASI-2 [$M_{PKU} = 101$; $M_{non\text{-}PKU} = 104$;

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$t(70) = 1.16$, $p = .250$, $g = .27$], although individuals with ETPKU obtained a significantly lower Fluid Cognition Composite score on the NIH Toolbox than individuals without PKU [$M_{PKU} = 98$; $M_{non\text{-}PKU} = 108$; $t(70) = 2.64$, $p = .010$, $g = .62$].

Verbal ability

The groups performed similarly on the verbal ability composite [$M_{PKU} = 99$; $M_{non\text{-}PKU} = 98$; $t(70) = .27$, $p = .789$, $g = .06$].

Visuospatial skills

Individuals with ETPKU demonstrated worse performance on the visuospatial composite as compared to individuals without PKU [$M_{PKU} = 101$; $M_{non\text{-}PKU} = 110$; $t(67) = 3.44$, $p = .001$, $g = .82$]. Further analysis confirmed that both tests (Block Design and Visual Puzzles) contributed to this finding [$t(67) > 2.35$, $p < .022$, $g > .56$, in both instances].

In order to rule out that the finding was driven by secondary task demands related to processing speed and executive function, a post hoc hierarchical linear regression was conducted. Scores on the visuospatial skills composite served as the dependent variable. Scores on the executive function and processing speed composites were entered in the first step of the model, followed by group (PKU and non-PKU) in the second step. Importantly, after accounting for variance related to executive function and processing speed, there continued to be a significant effect of group [$F(1,65) = 5.49$, $p = .022$, $pr^2 = .08$].

Executive function

The ETPKU group scored significantly lower on the executive function composite as compared to the non-PKU group [$M_{PKU} = 98$; $M_{non\text{-}PKU} = 102$; $t(70) = 2.38$, $p = .020$, $g = .56$]. Subsequent analysis of contributing tests revealed that the finding was primarily driven by group differences on measures of working memory [List Sort Working Memory; $t(70) = 3.47$, $p = .001$, $g = .82$] and sustained attention [CPT Omissions; $t(39) = 2.09$, $p = .043$, $g = .46$]. No statistically significant group differences were found on the remaining tests [$t(66) < 1.23$, $p > .22$, $g < .29$, in all instances].

Motor skills

Individuals with ETPKU performed worse on the motor skills composite than individuals without PKU [$M_{PKU} = 96$; $M_{non\text{-}PKU} = 100$; $t(67) = 2.42$, $p = .018$, $g = .58$]. Further analysis of contributing subtests showed that this difference was driven primarily by the grooved pegboard task with participant's dominant hand as well as the simple pegboard task with participant's nondominant hand [$t(70) > 2.52$, $p < .014$, $g > .59$, in both instances]. A trend toward significance was found on the grooved pegboard task with participant's nondominant hand [$t(60) = 1.89$, $p = 0.06$, $g = .42$]. Group differences for the simple pegboard task with participant's dominant hand did not reach significance [$t(70) < 1$, $p = 0.49$, $g = .16$]. A trend toward significance was also observed on a few measures of gross motor skills, including walk endurance and walk gait, with individuals with ETPKU performing worse than individuals without PKU [$t(67) > 1.76$, $p < 0.082$, $g > .42$, in both instances]. No statistically significant group differences were found for any of the other contributing tests [$t(67) < 1.01$, $p > .31$, $g < .24$, in all instances].

Processing speed

The ETPKU group demonstrated significantly lower scores on the processing speed composite as compared to the non-PKU group [$M_{PKU} = 106$; $M_{non\text{-}PKU} = 111$; $t(70) = 2.23$, $p = .029$, $g = .52$]. Group differences were most apparent on the WAIS-IV Symbol Search subtest that contributed to this composite [$t(70) = 3.21$, $p = .002$, $g = .75$]. Participants with ETPKU also demonstrated lower scores on the NIH Toolbox Pattern Comparison subtest, although this difference did not reach significance [$t(70) = 1.81$, $p = .074$, $g = .43$]. No other significant findings were observed for contributing tests [$t(66) < 1.46$, $p > .14$, $g < .35$, in all instances].

Self-report measures

The ETPKU group scored significantly higher (poorer) on the executive function and attention composite measure as compared to the non-PKU group [$M_{PKU} = 49$; $M_{non\text{-}PKU} = 43$; $t(70) = 3.15$, $p = .002$, $g = .74$]. Subsequent analysis confirmed that scores from both the BRIEF-A and CAARS contributed to this finding. The ETPKU group demonstrated significantly elevated GEC, MI, and BRI composite scores on the BRIEF as compared to the non-PKU group [$t(69) > 3.03$, $p < .003$, $g > .71$, in all instances]. With regards to contributing BRIEF clinical scales, group differences were most apparent on the Working Memory clinical scale [$M_{PKU} = 56$; $M_{non\text{-}PKU} = 47$; $t(67) = 4.10$, $p < .001$, $g = .92$]. Significant group differences were also observed on the Inhibition, Shifting, Emotional Control, and Organization of Materials clinical scales [$t(65) > 2.45$, $p < .017$, $g > .57$ in all instances]. A trend toward significance was observed on the remaining clinical scales [$t(70) > 1.76$, $p < .083$, $g > .41$, in all instances].

On the CAARS, the ETPKU group reported significantly more attention-related symptomatology in general as evidenced by group differences on the Overall ADHD Index [$M_{PKU} = 47$; $M_{non\text{-}PKU} = 42$; $t(70) = 2.46$, $p = .016$, $g = .58$]. Group differences were also observed on Total DSM-IV ADHD Symptoms, DSM-IV Inattentive Symptoms, DSM-IV Hyperactive/Impulsive Symptoms, Inattention/Memory Problems, Impulsivity/Emotional Lability, and the Hyperactivity/Restlessness subscales [$t(65) > 2.13$, $p < .037$, $g > .48$, in all instances]. Group differences approached significance on the Problems with Self-Concept subscale [$t(70) = 1.92$, $p = .059$, $g = .45$].

No evidence of group differences were observed for the internalizing symptom composite based on the BAI and BDI-2 [$M_{PKU} = 52$; $M_{non\text{-}PKU} = 51$; $t(70) < 1$, $p = .46$, $g = .17$]. The ETPKU group also did not report significantly more symptoms of social communication problems as compared to the non-PKU group on the SRS-2 [$M_{PKU} = 53$; $M_{non\text{-}PKU} = 50$; $t(70) = 1.55$, $p = .13$, $g = .36$].

Clinical significance

Despite statistically significant groups differences across multiple performance-based and self-report measures, the associated mean scores for the ETPKU group were only modestly elevated relative to the available normative data. To investigate this issue further, we conducted additional analyses to examine the potential clinical significance of the observed elevations. Using the established criteria of 1.5 standard deviations above the normative mean as an indication of a "clinically elevated" score, we conducted chi-squared tests to compare the observed frequency of individuals with and without ETPKU who demonstrated a clinically elevated score on one or more of the performance-based composite scores. The frequency of individuals with elevated scores was significantly greater for the ETPKU group (18%) as compared to the non-PKU group (6%) [$\chi^2(1, 40) = 8.64$, $p = .003$]. Analysis of the self-report data from the executive function (ETPKU = 10%; non-PKU = 3%) and internalizing symptom composite scores (ETPKU = 15%;

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Table 4. Correlations between metabolic markers and task performance

	Neurocognitive Composite Scores						
Phenylalanine Levels (μmol/L)	Full Scale IQ	Fluid Cognition	Verbal Ability	Visuospatial Skills	Executive Function	Motor Skills	Processing Speed
IDC for early childhood (0–5 years)	−.14	−.20	−.05	−.21	−.21	−.24	−.25
IDC for middle childhood (6–11 years)	−.27	−.30	−.02	−.30	−.28	−.20	−.24
IDC for adolescence (12–17 years)	−.52**	−.49*	−.19	−.48*	−.54**	−.19	−.39*
IDC for adulthood (18+ years)	−.61**	−.52*	−.42*	−.47*	−.61**	−.41*	−.57**
IDC for lifetime (0-present)	−.62**	−.56*	−.31	−.55*	−.53*	−.27	−.46*
Mean level for previous year	−.53**	−.50**	**−.34**	−.53**	−.60**	−.48*	−.47*
Most recent level	−.53**	−.57**	−.37*	−.41*	−.64**	−.47*	−.55**

Note: IDC = Index of Dietary Control (mean of all half-year median phe levels).
*$p < .05$ FDR corrected; **$p < .005$ FDR corrected; $p < .05$ uncorrected indicated in bold.

Table 5. Correlations between metabolic markers and self-report measures

	Self-Report Composite Scores		
Phenylalanine Levels (μmol/L)	SRS Total Score	Internalizing Symptoms	Executive Abilities Composite
IDC for early childhood (0–5 years)	.03	.32	.15
IDC for middle childhood (6–11 years)	.32	.42*	.26
IDC for adolescence (12–17 years)	.54**	.46*	.57**
IDC for adulthood (18+ years)	.50*	.34	.55*
IDC for lifetime (0-present)	.49*	.32	.39
Mean level for previous year	.57**	.51**	.51**
Most recent level	.60**	.48*	.49*

Note: IDC = Index of Dietary Control (mean of all half-year median phe levels).
*$p < .05$ FDR corrected; **$p < .005$ FDR corrected; $p < .05$ uncorrected indicated in bold.

non-PKU = 3%) yielded similar results [$\chi^2(1, 40) > 6.41$, $p < .011$ in both instances].

Relationship with blood phe levels

Correlations between composite scores and phe level measurements are listed in Tables 4 and 5 and illustrated in supplemental Figures S1 and S2. Scatter plots of the data are also included in supplemental Figures S3 and S4. All p values noted below have been corrected for multiple comparisons using a FDR approach ($q < .05$).

Performance-based neurocognitive measures

As can be seen in Table 4 and supplemental Figure S1, in general, task performance was strongly correlated with recent and adulthood phe levels [$r = .37$–73, $p < .05$, in all instances] but less so for earlier levels [0–5 years old: $r = .14$-$.25$, $p > .200$; 6–11 years old: $r = .20$–30, $p > .131$]. This was true across all of the cognitive domains assessed. Within this context, executive function had the most robust relationship to recent phe levels [$r = .64$, $p < .001$] whereas verbal ability had the least significant [$r = .37$, $p = .037$].

Self-report measures

Results for the self-report executive function composite was generally consistent with findings for the performance-based cognitive measures. Self-reported symptoms were robustly correlated with adolescent and adult phe levels [$r > .55$, $p < .005$, in both instances] but less so for levels from early and middle childhood [$r < .26$, $p > .161$, in both instances]. A different pattern was found for measures of psychoemotional functioning. Self-reported symptoms of internalizing symptoms showed robust correlations with recent phe levels as well as those from middle childhood and adolescence [$r > .42$, $p < .023$, in all instances] with no significant relationship with early childhood or adult phe levels [$r < .34$, $p > .110$, in both instances]. The self-report measure of social communication correlated robustly with adolescent and most recent phe levels [$r > .54$, $p < .004$, in all instances] and less so with earlier levels [$r < .32$, $p > .082$, in both instances].

Discussion

The majority of past studies on neuropsychological functioning and ETPKU have focused on children and adolescents. Much less is known regarding the neurocognitive and psychological profile of adults with ETPKU. The present study aimed to provide a comprehensive evaluation of neurocognitive and psychoemotional functioning among adults with ETPKU using the NIH Toolbox and other standardized measures. In addition, we examined the relationship between task performance and historic blood phe levels (i.e., a marker of metabolic control) during different developmental epochs.

In the present study, ETPKU-related impairments in executive function were apparent on both performance and self-report measures. Subsequent analysis confirmed that the areas of working memory and sustained attention appeared to be particularly affected, with group-related differences on the executive function composite being driven primarily by performance on the NIH

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Toolbox's List Sort Working Memory subtest and the Connors' Continuous Performance Test (i.e., a test of sustained attention). Whereas the broader literature on working memory in adults with ETPKU has yielded somewhat mixed findings (for review, see Bilder et al., 2016), the present results are consistent with findings on the Cambridge Neuropsychological Test Automated Battery (CANTAB), another computerized assessment tool. For example, Bik-Multanowski et al., (2011) reported that adults with ETPKU performed below expectations (based on normative data) on tests of spatial working memory and sustained attention from CANTAB.

The present ETPKU group also scored significantly worse than the non-PKU group on self-report measures of executive dysfunction and attentional symptomatology (i.e., the BRIEF and CAARS, respectively). Group differences on the BRIEF were most apparent on the Working Memory clinical scale. This finding is in line with the results of a recent study of BRIEF performance in a large sample (n = 286) of children and adults with ETPKU, which found that the Working Memory scale showed the largest effect size, with 19% of children and 29% of adults scoring in the "abnormally elevated" range (Christ et al., 2020). In terms of the present CAARS data, scores for the ETPKU group were elevated relative to the non-PKU group in terms of both inattentive and hyperactive symptomatology. Antshel & Waisbren, (2003) also reported elevated ADHD-related symptomatology in a sample of children with ETPKU. Interestingly, in contrast to the present findings, the aforementioned study found that children with ETPKU were more likely to demonstrate inattentive symptoms (as opposed to hyperactive/impulsive symptoms). Additional research is needed to better understand potential age-related changes in the manifestation of ADHD-related symptomatology in individuals with ETPKU.

ETPKU-related impairments were also observed on the motor skills composite. This finding was driven primarily by group differences on measures of fine motor skills (e.g., grooved pegboard and simple pegboard) more so than those assessing gross motor ability (e.g., grip strength, walk endurance). The presence of disruptions in fine motor control has been widely reported in past studies of both children and adults with ETPKU (for reviews, see Moyle et al., 2007; Christ et al., 2021). Recent research from Christ et al., (2021) suggests that disruptions in motor learning likely contribute to the observed fine motor difficulties. In addition, neurological studies in ETPKU have identified structural and/or functional disruptions in several brain regions (e.g., prefrontal cortex, parietal cortex, basal ganglia, cerebellum) known to play an important role in fine motor control and learning (Bodner et al., 2012; Christ et al., 2016, 2021; Aldridge et al., 2020). Taken together, these findings reinforce the need for future research to evaluate the relationship between neurological sequelae and observed disruptions in motor skills among individuals with ETPKU.

We also found that the ETPKU group performed more poorly on measures of processing speed as compared to the non-PKU group, a finding that is also consistent with the existing literature (Janzen & Nguyen, 2010; Palermo et al., 2017; Aitkenhead et al., 2021). From a theoretical perspective, it is hypothesized that disruptions in structural and functional brain connectivity likely contribute to the processing speed deficits frequently observed in individuals with ETPKU (e.g., Anderson & Leuzzi, 2010; Christ et al., 2012; Clocksin et al., 2021) although research directly confirming this link is still needed.

Visuospatial skills represent a relatively understudied cognitive construct in individuals with ETPKU, with the few studies examining visuospatial skills reporting discrepant results (Brumm et al., 2004; Channon et al., 2004; Janzen & Nguyen, 2010). The present study found that the ETPKU group performed significantly worse on the visuospatial skills composite than the non-PKU group. It can be difficult with many visuospatial tests to disentangle the potential contribution of secondary demands (e.g., executive function, fine motor control, processing speed) to task performance. Within this context, significant group differences remained even after statistically accounting for the potential contribution of such secondary demands. Also, it is noteworthy that we observed group differences on the WAIS-IV Visual Puzzles subtest, a motor-free visuospatial test with minimal speed demands (i.e., participants just had to respond within 30 s to each item) that requires participants to view a completed puzzle and select three pieces that together would reconstruct the puzzle. Neuroimaging studies of ETPKU have documented irregularities in parietal and occipital regions and related WM tracts (i.e., superior longitudinal fasciculus) known to play an important role in visuospatial processing (Christ et al., 2016; Clocksin et al., 2021).

The present study also examined the relationship between task performance and historic blood phe levels (i.e., a marker of treatment adherence) during different developmental epochs (e.g., early childhood, middle childhood, adolescence, adulthood, lifetime, and recent). The results point to a similar finding across multiple cognitive domains: task performance was strongly correlated with adolescent, adulthood, and recent phe levels but less so for levels from early and middle childhood. A similar pattern was observed for the self-report measures of executive function and attention. These findings are generally in line with those of previous studies on adults with ETPKU (e.g., Channon et al., 2004; Jahja et al., 2017; Romani et al., 2017; Christ et al., 2020; Aitkenhead et al., 2021). Of note, upon initial glance, the lack of a strong correlation between task performance and early childhood phe levels may seem surprising given the substantial literature linking early treatment and cognitive outcome (e.g., Anderson et al., 2007; Waisbren et al., 2007; Canton et al., 2019). We postulate that this finding (or lack thereof) is likely a consequence of insufficient variability in our sample's early phe levels necessary for significant correlations to emerge.

In addition to cognitive difficulties, there is growing evidence that individuals with ETPKU may also experience a higher prevalence of mental health concerns including anxiety and depression (Pietz et al., 1997; Manti et al., 2016; Bilder et al., 2017). Consistent with past research (e.g., ten Hoedt et al., 2011; Clacy et al., 2014; Jahja et al., 2017), we found significant positive correlations between phe levels and internalizing symptom levels. The finding of robust correlations with phe levels across middle childhood and adolescence (6–17 years) underscores the importance of this epoch in the development of emotional processing and regulation (Weir et al., 2012). Additional work is needed to better understand not only the nature of the mental health concerns associated with ETPKU but also the potential interaction between psychological and cognitive difficulties in this population. Indeed, past research with other clinical populations (e.g., generalized anxiety disorder) suggests that the two phenomena may be linked, with increased anxiety contributing to poorer cognitive performance (Balderston et al., 2017).

Lastly, elevated phe levels (particularly during adolescence and later ages) were also associated with increased difficulties with social communication. This is not surprising given that several of the previously discussed cognitive and psychological abilities (e.g., executive function, processing speed, emotional processing) that are adversely affected by high phe levels contribute to proficient social communication. The result is also generally consistent with past findings of poorer social-cognitive functioning and

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perspective taking in individuals with higher phe levels as compared to those with lower phe levels (Jahja et al., 2016; Palermo et al., 2020).

Limitations and future directions

The present study represents one of the few comprehensive studies of neuropsychological and psychological functioning in adults with ETPKU. Looking forward, it will be important for future studies to include larger sample sizes with a broader/older age range. State-sponsored early screening programs for PKU began in the mid-to-late 1960s, which means that the oldest cohort of ETPKU patients are currently approaching their early to mid-50s. (The oldest participants in the present study were in their mid-30s.) Within this context, critical questions for the field moving forward include "What does it mean to grow older with PKU in terms of physical, neurologic, and psychological health? Also, what role does metabolic control (both historic and current) play in moderating health risks in this older cohort?"

Consistent with previous studies, we found a significant relationship between current phe levels and task performance, with particularly robust correlations with the executive functioning composite. To the extent that effective treatment management and adherence is associated with cognitive/executive demands, there is a potential cyclical relationship between worsening treatment adherence and poorer executive function. Future research incorporating treatment intervention and longitudinal data collection will be critical for understanding the cause/effect nature of this relationship.

As noted earlier, the present study represents one of the first to incorporate the NIH Toolbox for the study of ETPKU. Our results are promising and support the potential utility of the NIH Toolbox as a relatively quick assessment tool for individuals with ETPKU. This represents only the first step, however, towards fully validating the NIH Toolbox for use with individuals with ETPKU. It will be important for future studies to include larger sample sizes with a broader age range (i.e., including children), to directly compare performance on the NIH Toolbox with that on more established neuropsychological tests assessing the same cognitive constructs, and to also evaluate test-retest reliability.

Summary and conclusions

The present study provides a comprehensive view of neuropsychological functioning in adults with ETPKU and its relationship to historic and recent phe levels. Between-group comparisons revealed ETPKU-related weaknesses in visuospatial skills, executive function, motor skills, and processing speed. Within the ETPKU group, phe levels (particularly recent levels) were significantly correlated with performance across most cognitive domains and aspects of psychological functioning (e.g., anxiety & depression symptoms; attentional difficulties). Taken together, these findings support the presence of a circumscribed pattern of cognitive difficulties in adults with ETPKU and reinforce the importance for continued metabolic control throughout the lifespan.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617722000686

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