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ADHD, learning, and academic performance in phenylketonuria

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ABSTRACT

Despite having average intellectual abilities, academic difficulties are relatively common in children and adolescents with PKU. These academic difficulties may be a function of attention deficit hyperactivity disorder (ADHD), executive functioning deficits, and processing speed deficits, all of which are known to affect academic performance in non-PKU populations. This review focuses on what is currently known about academic performance in youth with PKU and offers suggestions for future research.

ADHD, learning, and academic performance in phenylketonuria

Over the past 40 years, newborn screening and dietary restrictions to limit phenylalanine (Phe) intake have prevented mental retardation and global cognitive delays in children, adolescents, and young adults with phenylketonuria (PKU; OMIM 261600 and 261630). In this regard, PKU treatment is one of the true success stories in modern medicine. Children who were once destined to have mental retardation and significant global developmental delays are now able to successfully navigate school and function independently.

The remarkable efficacy of the combination of newborn screening and a Phe-restricted diet remained largely unquestioned until the mid 1980s. At that point, research began to surface indicating that while children with PKU were clearly spared from mental retardation, many of these children were struggling academically despite an average intellectual quotient (IQ). Over the past 25 years, research has accumulated demonstrating that children, adolescents, and young adults with PKU are more likely than their non-PKU peers to have academic difficulties.

This article reviews what is presently known about PKU and academic performance, with a focus on attention deficit hyperactivity disorder (ADHD), executive functioning deficits, and processing speed deficits, all of which are known to affect academic performance in non-PKU populations.

ADHD in individuals with PKU

ADHD occurs in approximately 4–6% of the population [1–3] and is defined by developmentally inappropriate levels of inattention, hyperactivity, or impulsivity [1]. A highly heritable condition thought to have its basis in dopaminergic abnormalities [4], ADHD is currently categorized into three subtypes with varying rates of prevalence: ADHD-inattentive subtype (approximately 25–30%), ADHD-hyperactive/impulsive subtype (<5%), and ADHD-combined subtype (65–70%). Stimulant medications such as methylphenidate and mixed amphetamine salts, in conjunction with psychosocial treatments such as behavioral management training for parents, are the most efficacious treatments for ADHD [5,6]. In ADHD, stimulant medications work by increasing dopamine available in the synaptic cleft, either by blocking reuptake or producing more dopamine presynaptically [7].

Although better substantiated in ADHD, both individuals with ADHD and PKU are thought to have low levels of dopamine, especially in the prefrontal cortex and striatum [8,9]. This hypodopaminergic state (and the resulting noradrenergic effects) potentially links ADHD and PKU. Dopamine is organized into three pathways: the mesolimbic, nigrostriatal, and mesocortical subsystems [10,11]. Mesocortical system dysfunction has been hypothesized to link PKU and attention regulation deficits [12]. Projecting from the ventral tegmental area to the motor, premotor, and prefrontal cortices, the mesocortical system influences a variety of cognitive processes, including working memory and attention regulation [13].

Phenylalanine hydroxylase (PAH; EC 1.14.16.1) is an enzyme necessary to convert Phe to tyrosine (Tyr). In PKU, the gene that codes for PAH is absent or defective. Thus, without treatment, Phe levels rise, Tyr is limited, and available Tyr competes with

Abbreviations: PKU, phenylketonuria; Phe, phenylalanine; ADHD, attention deficit hyperactivity disorder; Tyr, tyrosine.

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Phe to cross the blood–brain barrier. The net result is lower levels of Tyr that are available to synthesize dopamine in the brain.

The prefrontal cortex is especially sensitive to low levels of dopamine, more so than other areas of the brain [14]. As such, even mild elevations of Phe create a cascade effect, which can lead to low levels of dopamine in the prefrontal cortex. ADHD and PKU are therefore theoretically linked by low levels of dopamine available in the prefrontal cortex.

Given the overlap in the neurobiological mechanisms and the clinical anecdotes reported by metabolic physicians, it is surprising that very few studies have been published in which the association between PKU and ADHD has been examined. That said, in a series of studies that empirically investigated the relationship between PKU, maternal PKU (MPKU), and ADHD, Antshel and Waisbren [15,16] studied 46 children with early- and continuously-treated classical PKU (Age $M = 10.8$ years, $SD = 2.1$ years), 15 MPKU offspring (Age $M = 11.2$ years, $SD = 2.3$ years), and 18 typically developing control children (Age $M = 10.7$ years, $SD = 1.1$ years). Using strict DSM-IV diagnostic criteria, 6 of the 46 children with PKU (13%) and 6 of the 15 MPKU offspring (40%) met full DSM-IV criteria for ADHD. No control children met criteria for ADHD. The PKU and ADHD prevalence in this study was 2.5 times greater than that of the general population, while the MPKU prevalence rate was 8 times greater. Both the PKU and MPKU groups had higher ADHD prevalence rates relative to controls ($p < 0.001$).

Most children with PKU in the Antshel and Waisbren studies [15,16] did not meet full DSM-IV diagnostic criteria for ADHD because many lacked significant functional impairments in two or more settings and/or had an age of onset after age 7 years. Nonetheless, of the 9 DSM-IV inattentive symptoms, a mean (*SD*) of 5.5 (1.1) was endorsed by both teachers and parents of children with PKU as occurring "often" or "very often." In the MPKU sample, a mean (*SD*) of 5.9 (1.5) of the 9 DSM-IV inattentive symptoms was endorsed by teachers and parents as occurring "often" or "very often." In contrast, in the control sample, the mean (*SD*) number of these symptoms endorsed by parents as occurring "often" or "very often" was only 1.3 (0.8).

The number of DSM-IV hyperactive/impulsive symptoms ($M = 1.1$, $SD = 0.4$) was rated by parents of children with PKU as being far less than the number of DSM-IV inattentive symptoms. All children with PKU who met formal diagnostic criteria for ADHD were diagnosed with ADHD-inattentive type. Conversely, DSM-IV hyperactive/impulsive symptoms ($M = 6.3$, $SD = 1.4$) were rated by parents of MPKU offspring as occurring more than DSM-IV inattentive symptoms. All MPKU offspring who met formal diagnostic criteria for ADHD were diagnosed with ADHD-combined type. The authors concluded that the developmental timing of exposure to elevated levels of Phe may affect the expression of ADHD symptoms. Although exposure at any time appears to affect attention regulation, prenatal exposure is associated with greatly increased hyperactive/impulsive symptoms. In addition, both PKU and MPKU samples demonstrated a dose-dependent relationship between ADHD symptoms and Phe levels; higher levels of Phe exposure were associated with a greater number of ADHD symptoms [15,16].

The Antshel and Waisbren series of studies is, surprisingly, the only data that have been published on the prevalence of ADHD in PKU and MPKU samples. However, Arnold and colleagues [17] examined the prevalence of stimulant medication use in a sample of 38 youths (23 males, 15 females; age range 5–20 years) with early- and continuously-treated classical PKU. Seventy-six youths with type 1 diabetes (46 males, 30 females; age range 5–20 years) comprised a control group. The mean age in both groups was approximately 11 years.

Nineteen (50%) of the parents of youths with PKU reported that their child had significant inattentive symptoms. Of those 19 children, 10 children (26% of total PKU sample; 7 boys, 3 girls) had been prescribed a stimulant medication. Eight children were prescribed methylphenidate, one mixed amphetamine salts, and one dextroamphetamine. Pediatricians were the most common prescribing physicians. In contrast, in the diabetes sample, 5 of the 76 youths (6.5%; 4 boys, 1 girl) were prescribed a stimulant medication. The prevalence of the stimulant prescriptions in the PKU sample was significantly higher ($p < 0.006$) than the stimulant prescriptions in the type 1 diabetes sample, a control group with a chronic disease given dietary treatment. In addition, stimulant prescriptions were higher than in the general population (6%).

The mean Phe levels over 12 months for the PKU sample were also significantly associated with inattentive symptoms ($p < 0.02$). The mean Phe level for the past year in the stimulant-using group was 13.2 mg/dL ($SD = 6.6$), whereas the non-stimulant-using group had a mean Phe level of 8.1 mg/dL ($SD = 5.6$). All parents of children with PKU who were prescribed a stimulant reported that the medication was efficacious and none discontinued the medication due to side effects. Nonetheless, the efficacy of the stimulant medication was not achieved through lowering Phe levels; the mean Phe levels in the years before and after initiating stimulant use were not significantly different.

In the Arnold et al. study [17], the association between higher Phe levels and stimulant use in the PKU group is interesting and raises the possibility that the stimulant medications are being used to manage less well-controlled dietary Phe intake. If dietary management improves and the inattentive symptoms disappear, there may be no need for the stimulant medication. However, it is also conceivable that even with improved metabolic control the inattentive symptoms may persist, because the Phe levels in individuals with well-treated PKU are still 2–10 times higher than in the general population [18]. If this is the case, and if the inattentive symptoms are affecting the ability to function, it may be prudent to consider the use of a stimulant medication. Moreover, if metabolic control improves and the impairing inattentive symptoms still persist, providers need to be aware that diagnostic overshadowing may be present [19]. Diagnostic overshadowing refers to a process by which symptoms (i.e., inattentive symptoms) are misattributed to one condition (i.e., PKU) without consideration of a second comorbid condition (i.e., ADHD).

Future research should continue to investigate the prevalence of ADHD in PKU. Prospective studies should focus on associations between ADHD symptoms, metabolic control, and use of both psychological tests administered in a controlled clinical setting and real-world functional outcomes (e.g., scholastic grades). For example, in the general population, several hundred studies have been published supporting the association of ADHD and academic underachievement and learning disabilities. A meta-analysis reported the mean difference in academic achievement between ADHD and control groups to be in the moderate to large range (Cohen's $d = 0.71$) [20]. On average, a child with ADHD attains roughly 11 points less than his or her non-ADHD peer on a standardized test of reading, math, or written expression [20]. Similarly, several hundred studies have been published demonstrating that youth with ADHD are at increased risk for grade retention and dropping out of school (see Barbaresi et al. [21] for a review and epidemiological data.) To date, no data have been reported on the association between ADHD and scholastic outcomes in the PKU population. This is a crucial area of research in PKU that needs to be addressed.

Academic performance in individuals with PKU

School performance and scholastic outcomes have been studied in the early-treated PKU population for more than 30 years. Many adolescents and young adults with PKU struggle academically, and much data have been reported demonstrating that individuals

with early-treated PKU are more likely than both siblings and unaffected peers to struggle academically [22–36].

In one of the earliest studies of cognitive and academic performance in youth with early-treated PKU, Berry et al. [25] followed 69 individuals with PKU (31 female, 38 male) ranging in age from 4 to 35 years. The majority of individuals in the Berry study had classical PKU ($n = 37$). Of those with classical PKU, 21 were early-treated and the remainder was either late-treated or untreated (because late-treated or untreated PKU is currently quite rare, in this review results from only the 21 early-treated individuals will be discussed). Parents and siblings of the PKU group comprised the control group. The IQ of the early-treated cohort with classical PKU ($M = 98$, $SD = 14$) was well within the average range. Nonetheless, as shown in Table 1, the IQ of the early-treated PKU group was significantly lower than that of the parents and non-PKU siblings of the individuals with PKU ($p < 0.001$).

In addition, academic achievement was studied using the Wide Range Achievement Test (WRAT), for which the normative sample has a mean (SD) score of 100 (15). As shown in Table 1, academic attainment in reading and spelling were average for age and not significantly different from non-PKU siblings. Academic attainment in math, however, was significantly lower ($p < 0.05$) in the early-treated classical PKU cohort than in non-PKU controls [25].

A larger scale study of academic achievement in PKU has also been conducted. The United States PKU Collaborative Study (PKUCS) was a prospective, longitudinal study of the impact of a Phe-restricted diet on PKU outcomes. Conducted at 19 treatment centers across the United States, the PKUCS followed 120 youths with early-treated PKU between the years of 1967 and 1983. In late childhood or early adolescence, mean IQ scores were in the average range and mean WRAT scores were in the average range for all academic subjects [37]. Nonetheless, compared to non-PKU siblings, the PKU cohort had lower WRAT scores (on average about 4–6 points lower) across all academic subjects, and WRAT reading and arithmetic were statistically lower in the PKU group ($p < 0.01$). Those who continued diet throughout the PKUCS had significantly higher scores in late childhood or early adolescence on all WRAT subjects than those who did not continue diet [37].

Rather than using psychological test performance in the clinic as an outcome variable, other data have been obtained from the teacher's report of the child's classroom functioning. This possibly enhances the ecological validity of the data. The teacher's report of a child with PKU on academic functioning is generally more concerning than the child's performance on a psychological test. For example, most of the academic attainment data that have been published using standardized tests such as the WRAT or Wechsler Individual Achievement Test suggest that youths with PKU are academically attaining scores in the average (reading, spelling) to low average (math) ranges for their age [22–36]. Nonetheless, a teacher's report on the day-to-day classroom performance of a child with PKU is often below average for age.

Table 1
Means of IQ and academic achievement data.

Sample	IQ	Reading	Spelling	Math
Berry et al. [25]				
PKU	98[a]	103	100	92[a]
Siblings	104	107	96	97
Parents	113	—	—	—
PKUCS [37]				
PKU	101[a]	101[a]	100[a]	96[a]
Siblings	107	107	104	100

Note. PKUCS: PKU Collaborative Study. IQ measured by WISC-R (Berry et al.) or WISC-III (PKUCS). All academic achievement measured by WRAT.
[a] Significant between-group difference.

For example, Stemerdink et al. [27] compared 37 youths with early- and continuously-treated classical PKU with 37 non-PKU control participants matched for age, sex, and education. The average age in both groups was roughly 13 years ($SD = 2$). Parents and teachers completed rating scales assessing behavior and school performance. Results indicated that teachers rated the average academic performance of children with PKU to be significantly lower than that of control participants. Teachers rated over half (58%) of the early- and continuously-treated children and adolescents with PKU as below grade level compared to 17% of control participants, ($p = 0.005$). Teachers rated the amount of effort that the PKU cohort put into their school work as significantly less than that of controls ($p = 0.03$) Nonetheless, even when statistically controlling for the lower level of effort, the school performance difference between the two groups was maintained ($p = 0.008$).

In addition, in the Stemerdink et al. study [27], a teacher's report on academic performance correlated negatively with average Phe levels in the 2 years prior to the study ($r = -0.45$). Higher levels of Phe were associated with poorer academic performance ($p < 0.05$). However, no significant relationship was found between Phe levels during the first 2 years of life and any of the teachers' reports of current academic functioning, possibly due to the restricted range of Phe levels during the first 2 years of life.

Gassio et al. [34] similarly relied on real-world functional outcomes rather than psychological tests conducted in a clinic. The study looked at 26 youths (14 males, 12 females) with early- and continuously-treated PKU (Age $M = 12.3$ years, $SD = 3.7$). Twenty-one age- and sex-matched control participants consisted of classmates of the youths with PKU or volunteers from the same school. The mean IQ of the PKU cohort was 102 ($SD = 9$), indicating average intellectual abilities.

Results regarding academic functioning indicated that 13 of the 26 (50%) individuals with PKU had school difficulties: 10 youths (38.5%) required special tutoring and 3 (11.5%) had to repeat a year of school. Both percentages were higher than those of the control participants (19% and 4.8%, respectively; $p < 0.03$). The 10 individuals with PKU all required tutoring in multiple subjects, whereas of the four control subjects who did require tutoring only one required tutoring in more than one subject. Older children with PKU tended to have more difficulty in school than younger children, although this difference did not reach statistical significance [34].

The PKUCS mentioned earlier also included real-world academic functional outcomes. Of the 112 children with early-treated PKU who had school records, 32% were having difficulties by the first grade, and by the fourth grade 34% were deemed to be at least 1 year below grade level in one or more academic subjects [37].

Possible explanations for math difficulties

Math has consistently been reported as an area of vulnerability for individuals with PKU [22,28,30,35,36], but no studies have been conducted that explain why math is particularly vulnerable. Hypotheses can be formed, however, based upon existing knowledge of PKU neuroanatomy and physiology. Potential influences of PKU-associated math difficulties include visuospatial or perceptual deficits [34,38–45], executive functioning deficits [12,16,30,46–57], and myelin anomalies [58–64] (especially within the parietal lobes) [65–67]. All of these potential influences on math performance have been reported in PKU.

From a cognitive perspective, positive associations between visuospatial/perceptual abilities and math performance have been demonstrated in typically developing populations [68–70] and clinical populations such as neurofibromatosis type 1 [71], Turner syndrome [72], and velocardiofacial syndrome [73]. Visuospatial/perceptual deficits may be associated with impaired non-symbolic

magnitude judgments, mental number-line skills, alignment errors, place value confusion, fractions, geometry, and reading graphs, all of which are elements of mathematical problem solving. In addition, executive functions, especially working memory, play a central role in math skills [74–79].

From an anatomical perspective, the parietal lobes are central to visuospatial/perceptual task completion. Not surprisingly, much data have been reported demonstrating the functional activity of parietal regions and various aspects of math performance, including numerosity [80,81] and symbolic representations of quantity [82–84]. In the PKU population, white matter anomalies are associated with poorer performance in arithmetic but not reading or spelling [85]. In addition, frontal regions are particularly active during math calculation tasks [86], and these regions are especially vulnerable in individuals with PKU due to elevated Phe and associated dopamine disregulation.

It is therefore plausible that math difficulties arise in individuals with PKU due to concomitant deficits in visuospatial/perceptual or executive/working memory abilities, parietal myelin anomalies, frontal neurotransmitter abnormalities, or some combination of these variables. Future research should investigate math attainment in PKU using both functional neuroimaging and biochemical measures to explain the particular vulnerability of math abilities in the PKU population.

Learning disabilities in individuals with PKU

Although much data have been published suggesting that individuals with PKU struggle academically, far fewer data have been reported which suggest the presence of learning disabilities. This may be a function of how learning disabilities are operationalized or it may be that academic outcomes have been examined far less than other cognitive variables such as IQ, processing speed, and executive functions.

The DSM-IV diagnosis of a learning disability is made when an individual's achievement on standardized measures of academic attainment are substantially below expectation for age, schooling, and level of intelligence [1]. Substantially below expectation is usually defined as a discrepancy of >1.5 standard deviations between achievement and IQ. The academic disturbance must interfere significantly with academic achievement or activities of daily living that require the academic skill. Merely having an IQ or academic achievement discrepancy is not sufficient; the academic disturbance must interfere significantly with the individual's performance in the academic setting or in activities of daily living [1].

As noted above, mean IQs and academic attainment scores are both generally reported to be in the average range (math excluded) in PKU research studies. Psycho-educational assessments given by the school districts generally consist of intellectual and academic measures. Although there are exceptions, most children with PKU score in the average range on formal tests of academic attainment or fail to show a substantial discrepancy between IQ and academic attainment. Thus, a learning disability may not be diagnosed and the academic accommodations and interventions that accompany such a diagnosis may not be granted by schools [87].

Nonetheless, despite having average IQs and academic attainment scores, many youths with PKU struggle academically, especially in middle and high school. This may be a function of the slow processing speed and executive dysfunction which often occur in PKU. For example, there are ample research data suggesting that executive functions account for large portions of the variance in day-to-day academic functioning in non-PKU populations [88,89]. In other words, although children with PKU may perform capably on many of the formal academic tests administered in the context of a one-to-one testing environment, the child's day-to-day functioning in the real-world classroom may be quite different. Overall, although very little data have been reported on the prevalence of learning disabilities in the PKU population, many children with PKU struggle academically.

Academic performance and executive abilities

Multiple studies have reported that academic outcomes worsen with age in early-treated PKU [32,34,35,37,90]. Although this may simply be a function of the difficulty in adhering to the PKU diet [91] and the negative consequences which accompany elevated Phe levels, this negative association may also be explained by the increased demand for executive functions in the middle- and high-school years relative to elementary school. Beyond elementary school, children and adolescents are required to manage and comprehend larger amounts of more complex information, to perform tasks more rapidly, to flexibly shift between activities, and to link sequences of cognitive operations in an on-line fashion. Most, if not all, of these requirements are dependent upon executive functions [92,93]. Therefore, as a result of executive functioning deficits (which are associated with poor dietary adherence), youths with PKU may be at risk for increasingly poorer academic performance as they age.

Cross-sectional data by White et al. [47,94] provide support for this notion. In a series of studies, White and colleagues performed a cross-sectional investigation of working memory and strategic processing in long-term memory, both aspects of executive function, in children with early- and continuously-treated PKU. In the 2001 study [47], 23 youths (12 female, 11 male) with PKU completed a series of cognitive tests. Mean concurrent Phe level at the time of testing was 8 mg/dL ($SD = 4$). Results were contrasted with those of an age- and gender-matched control group of typically developing children. Mean age for both groups was roughly 11 years.

As a component of the cognitive battery, the California Verbal Learning Test—Children's Version (CVLT-C), a commonly used test of long-term learning and memory, was administered [47]. In the CVLT-C, a 15-item word list is presented over five trials, with free recall occurring after each presentation of the list. Words in the list comprise three semantic categories (fruits, clothing, and toys). A semantic clustering ratio is computed that reflects the degree to which words are spontaneously clustered on the basis of semantic categories during recall, which is thought to reflect the use of an executive strategy that enhances recall [95].

In this study, no differences between PKU and control participants emerged in terms of the number of words recalled on Trial 1; both groups had a mean recall of just less than seven words. On Trial 5, however, control participants recalled a mean of over 11 words, which was one more word recalled than PKU participants ($p < 0.05$). Although initial list recall was similar, the control participants appeared to benefit more than the PKU participants from continued presentation of the list. This finding could be explained by the fact that control participants were more likely to use semantic clustering than individuals with PKU ($p < 0.05$). White et al. also divided the PKU group into younger (10 years and below) and older (11 years and above) subgroups. Older individuals with PKU performed comparatively poorer than older control participants on Trial 5, but younger individuals with PKU performed comparably to control participants on Trial 5, indicating that performance was poorer as a function of increasing age for the PKU group [47].

In the 2002 study [94], 20 youths (11 female, 9 male) with early- and continuously-treated PKU completed a computerized task assessing working memory for different types of materials:

letters, objects, and spatial locations. Mean concurrent Phe level at the time of testing was 8 mg/dL (*SD* = 4). Working memory results were contrasted with those of an age- and gender-matched control group. Mean age for both groups was roughly 11 years (*SD* = 4). Results indicated that control participants performed better on the working memory tasks ($p < 0.01$), with no significant effect of stimulus type, indicating that controls outperformed individuals with PKU across all three tasks. Of greater interest, however, were the linear regression analyses which assessed the developmental trajectory of working memory. The slope of the regression line for the control group (0.29) was more positive than that of the PKU group (0.08). These findings indicate that age-related improvements in working memory were occurring for the control group but not for the PKU group.

The younger cohort (10 years and under) of individuals with PKU had lower mean Phe levels (7 mg/dL) than the older cohort (9.3 mg/dL). Thus, to assess the impact of concurrent Phe levels on working memory, White et al. [94] recomputed analyses using Phe level as a covariate. After statistically controlling for concurrent Phe levels between subgroups (younger PKU vs. older PKU), differences in working memory between the lower (younger) and higher (older) Phe groups remained significant. Thus, the poorer performance for older than younger children was not driven by differences in Phe levels but by differences in age (which may, however, reflect exposure to elevated Phe over a longer period of the life-time).

White et al. [45,94] concluded that their working and long-term memory findings in PKU represent a developmental deficit rather than a developmental delay. In other words, youths with PKU appeared to grow into, rather than out of, their memory difficulties. Given that much of middle and high-school academic performance relies on test grades, these difficulties in executive aspects of memory may negatively affect academic outcomes in adolescents with PKU more than younger children with PKU.

In summary, very few data have been reported that suggest learning disabilities are over-represented in the PKU population. However, large amounts of data have been reported which suggest that many (but not all) children, adolescents, and young adults with PKU struggle academically. In addition, it is possible that age-related deficits in executive and/or other cognitive abilities may result in worsening academic attainment over time, and research is needed to address this issue directly.

Academic performance and processing speed

Processing speed deficits are reliable cognitive vulnerabilities in the adolescent and adult early- and continuously-treated PKU population [96]. A 2007 meta-analysis of 11 PKU studies (>200 PKU participants, >200 control participants) suggested that, on average, effect sizes between PKU and control participants were the largest for processing speed measures (e.g., reaction time on continuous performance tests). The average effect size indicated that adolescents and adults with early- and continuously-treated PKU performed nearly one standard deviation below control participants on processing speed measures. These processing speed differences emerged regardless of the type of psychological test (e.g., visual, auditory) or the type of processing speed measure (e.g., simple reaction time, completion time, etc.). All of the other cognitive domains had average effect size differences close to one-half standard deviation [96]; across all cognitive domains, with controls outperforming early- and continuously-treated PKU adolescents and adults.

Given the centrality of processing speed deficits in adolescents and adults with PKU, it is surprising that few studies have investigated the relationship between processing speed and academic outcomes. However, data which have been published in the non-PKU population provide insight into possible associations between processing speed and school performance. For example, in ADHD literature, a sizeable subset of individuals with ADHD-inattentive type (about 30–50%) has been described as having a "sluggish cognitive tempo" (SCT) [97–100]. Processing speed deficits are common in ADHD-inattentive type [101,102], and they are a defining feature of individuals with SCT.

In the ADHD literature, a moderately positive relationship also has been demonstrated between processing speed and academic outcomes [103,104]. Moderate relationships between processing speed and academic performance have been demonstrated in other populations as well, such as learning disability [105], survivors of acute lymphoblastic leukemia [106], and people with autism [107]. Although further research is clearly warranted, by extension one might predict that the processing speed deficits associated with PKU contribute to the difficulties in academic performance observed in individuals with PKU.

Conclusion

Prior to the 1960s, individuals with PKU were destined to have serious delays in general cognition and academic skills due to elevations in Phe. In this regard, the treatment of PKU is one of the more remarkable successes of modern medicine. Although dietary restrictions to limit Phe intake has unquestionably improved the academic functioning of individuals with PKU, more subtle but significant difficulties remain. On standard psycho-educational testing assessing only IQ and academic attainment, individuals with PKU may perform adequately. Nonetheless, children (and especially adolescents and young adults) with PKU struggle academically, especially in math. These academic difficulties may be a function of ADHD, executive functioning deficits, processing speed deficits, and/or neuroanatomical abnormalities.

In addition to controlling Phe levels, future efforts should focus on further understanding the academic vulnerabilities in the PKU population. Promising research avenues to consider include: (a) using real-world academic outcomes (e.g., grades, teacher's reports, SAT scores, etc.) in conjunction with psychological tests completed in a controlled clinical setting; (b) incorporating neuroimaging tools such MRS or fMRI with longitudinal research focused on academic functioning; (c) further investigating the predictive power of executive functioning, processing speed, and other cognitive variables as predictors to academic functioning; and (d) investigating behavioral and pharmacological treatment outcomes aimed at improving academic performance. Research ventures such as these will enable individuals with PKU to academically perform at their potentials.

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