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Beyond executive function: Non-executive cognitive abilities in individuals with PKU ☆

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ABSTRACT

Individuals with early-treated phenylketonuria (ETPKU) most often present with impairment in executive function (EF) and average intelligence compared to the general population. The topic of this review, which is less often discussed, is non-EF impairments that may be associated with ETPKU. Studies that have included assessment of non-EF cognitive functions such as information processing speed, fine motor skills, and perception and visual–spatial abilities suggest that individuals with ETPKU are compromised in these areas. Those assessing non-EF cognitive functions of language skills, long-term memory, and learning skills have yielded mixed results, with some suggesting impairment and others suggesting intact abilities. Although more studies are required, research to date suggests that mechanisms for non-EF deficits may include prefrontal cortex dopamine deficiency and/or white matter abnormalities related to elevated blood phenylalanine levels. For individuals with ETPKU to reach their full potential in life, it is vital to address the challenges associated with EF and non-EF deficits by identifying impairments and appropriate treatment strategies.

Background

Individuals with phenylketonuria (PKU; OMIM 261600 and 261630) are deficient in the enzyme phenylalanine hydroxylase (PAH; EC 1.14.16.1), which is necessary for the conversion of phenylalanine (Phe) into tyrosine [1]. If untreated, PKU typically results in mental retardation [1,2]. With dietary treatment to restrict Phe intake, intelligence is usually in the average range, although it remains somewhat lower than that of peers and siblings without PKU [1]. In addition to the slight decrease in intelligence, impairment in executive function (EF) is one of the most consistent findings across studies of cognition in individuals with PKU [3]. A meta-analysis of 33 studies [4] concluded that individuals with early-treated PKU (ETPKU) have relatively small decrements in intelligence compared with demographically matched controls, whereas they have larger decrements in executive abilities such as planning, working memory, inhibition, and cognitive flexibility.

A comprehensive review of executive abilities in individuals with PKU, as well as an examination of attention-deficit/hyperactivity disorder and learning disabilities, is presented elsewhere in this journal supplement. As such, the balance of this review will focus on impairments in other areas of cognition. These non-executive impairments include slowed information processing speed, motor skill problems, perception and visual–spatial difficulties, language deficits, and memory and learning impairments. Because there are almost certainly variations in symptom expression among individuals with PKU, it is important to consider the possibility of impairments in cognitive function beyond intelligence and executive abilities so that treatment, recommendations, and outcomes are optimized. In the discussion that follows, the impairments in non-executive abilities associated with PKU will be discussed.

Neuropathological underpinnings of cognitive impairment in PKU

Before discussing the impairments in cognition that are associated with PKU, it is important to comment on the neuropathological mechanisms that likely underlie such impairments. Further research is needed to clearly delineate these mechanisms and their specific contributions to impairments in specific cognitive abilities.

Abbreviations: Phe, phenylalanine; PKU, phenylketonuria; PAH, phenylalanine hydroxylase; ETPKU, early-treated PKU; EF, executive function.

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That said, dopamine deficiency and white matter abnormalities undoubtedly play major roles.

As noted earlier, individuals with PKU are deficient in the PAH enzyme that is necessary for the conversion of Phe into tyrosine [1]. Because tyrosine is a precursor of dopamine, this essential neurotransmitter, which is particularly crucial to function of the prefrontal cortex, is also deficient. Given that the prefrontal cortex subserves executive abilities, it is not surprising that dopamine deficiency has been widely hypothesized as the neural mechanism underlying executive impairment in individuals with PKU [4]. As noted later in this review, dopamine deficiency likely contributes to other cognitive impairments as well. In addition to neurotransmitter dysregulation, gross structural white matter abnormalities have been identified in individuals with PKU using MRI [5–8]. There are also studies demonstrating that more subtle abnormalities occur in the microstructure of the white matter [9–12] even when gross structural abnormalities are not present. As will be demonstrated later, it is very likely that these abnormalities contribute significantly to the cognitive impairments associated with PKU.

Information processing speed

Because myelinated white matter increases the speed of neural transmission along axons, it is reasonable to hypothesize that slowed processing speed is associated with the white matter abnormalities that occur in individuals with PKU [13,14]. This appears to be the case, as studies by Anderson et al. [5,6] revealed that structural white matter abnormalities observed on MRI in children with ETPKU were related to impaired processing speed on Symbol Search, Coding, Continuous Naming, and Rapid Name Retrieval tests. In addition, a study by Brumm et al. [15] revealed that processing speed in adults, as measured by the Trail-Making Test Part A, were associated with white matter abnormalities but not current Phe levels.

Findings from a number of behavioral studies verify that processing speed is impaired in individuals with PKU. For example, Feldmann et al. [16,17] compared the performance of adolescents with PKU and type 1 diabetes on the Culture Fair Intelligence Test, Wisconsin Card Sorting Test, Trail-Making Test, and Stroop Test. Patients with diabetes were thought to represent a better control group than healthy individuals because they have a chronic metabolic illness [16]. The performance of adolescents with PKU was poorer than that of adolescents with diabetes, but all differences were due to reduced processing speed rather than deficits in specific cognitive abilities (e.g., executive abilities) [16,17]. Impaired processing speed was also correlated with blood Phe levels. Studies in adults with ETPKU [15,18,19] have revealed processing speed deficits in comparison with healthy adults as well, and this was the case even when Phe levels were controlled continuously via a Phe-restricted diet.

Meta-analytic studies have also been informative. Moyle et al. [13] found evidence of processing speed impairments in a meta-analysis that included 218 patients with PKU. In terms of the measures used to assess processing speed, a number of tasks have been used, including simple and choice reaction time (RT) tasks, continuous performance tests, and executive tests with speeded components (e.g., the Trail-Making Test) [13,16]. Of these types of tests, a meta-analysis by Albrecht et al. [20] suggested that choice RT tests may be the most sensitive to elevated Phe levels.

With regard to day-to-day function, it is important to note that the performance of individuals with PKU who have processing speed deficits may be affected across multiple settings, including home, school, and work environments. Parents may find that their children struggle to manage multistep directions and require more time to complete complex tasks. Teachers may observe that, in comparison with their peers, students with PKU take longer to begin tasks, work less efficiently under time constraints, and struggle to take notes rapidly. Coworkers may notice that adults with PKU are less productive and require extra time to complete projects, especially those that are novel. To enhance performance across these settings, practice and rehearsal to make tasks more automatic is beneficial, as is the support and understanding of parents, teachers, peers, and coworkers.

Motor skills

Gross motor problems rarely occur when PKU is diagnosed and treated early [21], but impairments in fine motor control have been widely reported [13]. For example, Pietz et al. [22] found that adults with ETPKU, in comparison with healthy controls, had significant reductions in hand–wrist steadiness, finger–hand dexterity, and hand–wrist speed. Similarly, Weglage et al. [23] reported poorer performance for children with ETPKU than control children on measures of arm–hand–finger precision and speed using a motor performance battery (Motorische Leistungsserie), and these deficits were significantly correlated with blood Phe levels [23]. Other tests have also been used to identify impairments in fine motor control. Gassio et al. [24] found that individuals with PKU obtained significantly poorer fine motor scores than controls on the Purdue test, whereas Arnold et al. [25] found that children with PKU obtained significantly impaired fine motor scores on the Peabody Developmental Motor Scales. In both studies negative correlations were reported between Phe levels and fine motor scores [24,25], and fine motor scores have also been associated with the early implementation of dietary Phe restrictions in children with PKU [26].

Higher order motor control has also been examined in individuals with PKU. In a study of children with ETPKU, Huijbregts et al. [14] administered a pursuit task requiring planning and execution of unpredictable movements and a tracking task requiring predictable circular movements. Although children with ETPKU showed significantly poorer motor control on both tasks in comparison with control children, the impairment was more pronounced on the pursuit task and in children younger than 11 years of age. Because the impairment was most notable on the pursuit task, the researchers concluded that motor deficits are more severe when higher order controlled processing is required [14]. The researchers also concluded that their findings support the hypothesis that motor control in the unpredictable pursuit task required dorsolateral prefrontal cortex (which mediates executive abilities) involvement in addition to the involvement of brain regions primarily subserving motor abilities, which is supported by findings from other studies of motor learning and controlled motor processing [27,28].

In daily life, individuals with fine motor deficits often appear clumsy or uncoordinated. Children may struggle to button clothes, fasten jackets, or tie shoes. Adults may find it difficult to use tools with precision or complete household chores requiring finer motor control. There is no single treatment that results in the best outcome, but interventions such as occupational therapy, physical therapy, or a combination of both are quite helpful, as is support from significant others.

Perception and visual–spatial abilities

Impaired perception and visual–spatial abilities have been identified in a number of studies of individuals with PKU. For example, Gassio et al. [24] found that performance on the Rey–Osterreith Complex Figure Test was poorer for individuals with ETPKU than

a healthy control group, and Moyle et al. [18] found that adults with ETPKU (but currently off diet) received lower scores on the Perceptual Organization Index of the Wechsler Adult Intelligence Scale-III than a healthy control group. Diamond and Herzberg [24,29] also showed that sensitivity to visual contrast was significantly poorer in children with ETPKU than healthy controls, even after controlling for between-group differences in IQ and visual acuity [29].

In terms of the neural underpinnings of the visual–spatial difficulties associated with PKU, there are two major hypotheses. The first argues that increased Phe levels lead to increased turnover of myelin and associated myelin defects [30]. Myelin abnormalities have been noted in the visual pathways of the brain in adults and children with PKU [31]. In addition, visual evoked potentials are often abnormal in both untreated and treated patients with PKU, which could reflect a central myelin defect causing slowed neural conduction along the fibers of the optic nerves or sensory radiations [32]. The second hypothesis suggests that dopaminergic transmission in neurons of the retina and the lateral geniculate nuclei is compromised due to low dopamine levels [30]. Diamond and Herzberg [29] hypothesized that even mild elevations in Phe relative to tyrosine could result in less tyrosine reaching projecting dopaminergic neurons and dopamine neurons in the retina.

Turning to the effects on daily life, perceptual and visual–spatial impairments may result in difficulty navigating through the environment or using navigation tools such as maps or directions. Decoding and understanding charts and diagrams may be difficult as well, which may affect success at school and work. Visual tracking and contrast sensitivity are of particular concern in terms of completing timed tests, with lower scores resulting from impairment in these abilities. With regard to specific academic abilities, mathematics may be particularly affected given the significant correlation between mathematical ability and visual–spatial ability [33]. Reading is another area of considerable concern, as impaired contrast sensitivity increases the difficulty of reading printed material under conditions of low contrast. As a result, a child or adult student may experience reading difficulties and fall behind in school, which in turn may be misattributed to lower intelligence or a reading disability. Early recognition of impaired perception and visual–spatial abilities will lead to implementation of better strategies to circumvent these problems, as strategies such as verbal mediation of visual–spatial tasks may be implemented.

Language

Findings from studies of language skills in individuals with PKU are mixed. In a study of 12 children with ETPKU, Melnick et al. [34] reported that six had delays in language development, with performance below average for chronologic age on tests of short-term auditory memory. In contrast, Zartler and Sassaman [35] found that none of their sample of children aged 2–6 years had deficiencies in short-term auditory memory, syntax, morphology, phonology, or semantics. Findings from a number of other studies also suggest that language is intact in individuals with PKU [36–39].

With regard to the relationship between language and control of Phe levels, findings are relatively clear. In a large scale study (the United States Collaborative Study), 120 children with PKU were followed longitudinally [40]. Children were grouped on the basis of whether they had continued to follow a Phe-restricted diet or had discontinued Phe restrictions after the sixth year of life. Results revealed that children who continued Phe restrictions and maintained better control of blood Phe levels had better language scores than those who discontinued diet, but the scores of both groups declined over time [40]. Similarly, Fishler et al. [41] found that language scores declined over time in children who had and had not discontinued dietary Phe restrictions after 6 years of age. Taken together, these findings suggest that language should be assessed over time rather than at a single point in time to capture age-related changes that may occur.

Within the context of daily function, individuals with language deficits generally form two groups, those with receptive language impairment and those with expressive language impairment. Individuals with difficulties in receptive language struggle to comprehend oral and written materials, with particular difficulty following multistep instructions or complex syntax. In such cases, clarification, repetition, and breaking instructions into single steps are helpful. In individuals with expressive language problems, vocabulary may be limited and simple errors in communication (e.g., using incorrect tense) often occur. Sentence structure may also be simplistic, making it difficult to convey thoughts in conversations and presentations. For individuals who also have problems in articulation, communication is further limited by mispronunciations. Early identification and prompt implementation of therapeutic interventions with speech and language professionals will facilitate the best outcomes for individuals with language deficits.

Memory and learning

Word-list-learning tasks (e.g., California Verbal Learning Test or Rey Auditory Verbal Learning Test) are commonly used to assess verbal learning and memory, and findings from studies of PKU using such tasks are mixed. The discrepancy across studies appears to be related to whether tasks are administered in which it is possible to organize the words to be recalled into semantic categories. Studies that have used tasks comprising unrelated words which are not categorizable have largely found learning and memory to be intact in individuals with PKU [39,42,43] (for an exception, see Anderson et al. [6]). In contrast, studies that have used tasks comprising related words that are categorizable have identified impaired learning and memory [15,44,45].

When words to be recalled are categorizable it is possible to implement an executive strategy (i.e., semantic clustering) to enhance recall. Given that impaired executive abilities is such a common finding among individuals with PKU, it is not surprising that learning and memory scores are poorer when strategic processing is required for optimal performance. Consistent with this notion, Antshel and Waisbren [44] and White et al. [45] found that semantic clustering was decreased in children with PKU compared with healthy controls. Thus, learning and memory may be largely intact in individuals with PKU, whereas the use of executive strategies to enhance learning and memory are impaired. In addition, in their study, White et al. [45] found that older children with ETPKU performed more poorly than younger children with ETPKU in comparison with age-matched peers, possibly because older children are expected to make more use of sophisticated strategies such as semantic clustering.

Turning to the learning and memory of nonverbal materials, for the most part these abilities appear to be impaired in individuals with PKU (for an exception, see Gassio et al. [24]). Using the memory components of the Rey–Osterreith Complex Figure Test, both children [44] and adults [15] with PKU exhibited impaired performance. Using the Rey Visual Design Learning Test (which assesses the recall of designs across five learning trials), Anderson et al. [6] also identified impaired memory for nonverbal information in children with PKU. As was the case for verbal learning and memory, production of the complex visual designs used to assess nonverbal learning and memory require the use of organizational strategies for optimal performance. As such, it is possible that impaired executive abilities underlie the findings of poorer performance on nonverbal learning and memory tests.

Because individuals with PKU may be at risk for learning and memory learning difficulties, particularly when higher order cognitive strategies are necessary, it is important that they be assisted in developing strategies to facilitate everyday learning. One such strategy is to divide complex information into more manageable units. Another strategy is to develop mnemonic devices, such as that used by young children when they learn the color spectrum (i.e., Roy G. Biv). Other strategies include making lists, using a memory notebook or daily planner, and practicing new information so that it becomes over-learned.

Conclusions

In addition to the consistently reported deficits in general intelligence and executive abilities that are associated with PKU, impairments have been identified in other areas of cognition as well. A number of studies have shown that information processing speed, fine motor control, and perception and visual–spatial abilities are compromised. Results of studies assessing language are mixed, with some suggesting intact abilities and others suggesting impairment. Mixed findings also come from studies of learning and memory, and it is possible that compromised performance on tasks assessing these abilities may be related more to difficulties in implementing executive strategies than to actual deficits in learning and memory.

It is important to remember that individuals with PKU are just that—individuals. As such, there is considerable variability in the cognitive abilities that are intact and impaired across individuals. Many individuals with ETPKU can be successful in their daily lives in spite of cognitive challenges, particularly if ongoing monitoring occurs and appropriate therapeutic interventions are implemented to address their challenges. In this regard, early identification and treatment of cognitive impairments is especially important in facilitating optimal outcomes for individuals with PKU.

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