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Executive function in early-treated phenylketonuria: Profile and underlying mechanisms ☆,☆☆

Shawn E. Christ [a,*], Stephan C.J. Huijbregts [b], Leo M.J. de Sonneville [b], Desirée A. White [c]

[a] Department of Psychological Sciences, 210 McAlester Hall, University of Missouri, Columbia, MO 65203, USA
[b] Department of Clinical Child and Adolescent Studies, P.O. Box 9555, 2300 RB Leiden, Leiden University, The Netherlands
[c] Department of Psychology, 1 Brookings Drive, Washington University, St. Louis 63130, USA

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ABSTRACT

Despite early and continuous dietary intervention, individuals with early-treated phenylketonuria (PKU) experience significant neurocognitive sequelae. An area of cognitive ability that is believed to be particularly affected is executive function (EF). This paper provides a critical review of the evidence for EF impairment in early-treated PKU within the context of recent advances in neuropsychological theory and research. The most consistent findings of PKU-related EF impairment were in executive working memory and prepotent response inhibition. Surprisingly, findings on shifting ability and other more complex aspects of EF were largely equivocal. Cohort (e.g., age, phenylalanine (Phe) levels) and task (e.g., standard clinical versus experimental tasks) related differences likely contributed to the variability in findings reported by these studies. Day-to-day EF also appears to be impaired although the precise pattern of impairment remains unclear, as does the relationship between laboratory measures of EF and questionnaires assessing day-to-day EF. Similarly, whereas several studies have found a relationship between Phe levels and EF, the best predictor variable (e.g., concurrent Phe level, lifetime Phe level, Phe level variability) of current EF performance varied from study to study. Neurologic compromise related to dopamine deficiency, white matter abnormalities, and disruptions in functional connectivity likely underlies the EF impairments described in this review. In closing, this review identifies remaining unanswered questions and future avenues for research.

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Introduction

Imbecillitas phenylpyrouvica, or phenylketonuria (PKU; OMIM 261600 and 261630) as it would later become known, was first identified in 1934 by Asbjørn Følling, a Norwegian biochemist and physician, with the assistance of Borgny Egeland, the determined mother of two affected children [1]. Subsequent work by Følling and others [2,3] demonstrated that PKU is a rare autosomal recessive condition characterized by a deficiency in the phenylalanine hydroxylase (PAH; EC 1.14.16.1) enzyme that is necessary for the metabolism of the amino acid phenylalanine (Phe) [4].

Phe is a metabolite of tyrosine, a precursor of dopamine and other important neurotransmitters. In individuals with PKU, the disruption in Phe metabolism results in elevated Phe and deficiencies in tyrosine, dopamine, and other neurotransmitters. Excess Phe also competes with the available tyrosine, tryptophan (a precursor for the neurotransmitter serotonin), and other large neutral amino acids to cross the blood–brain barrier, compounding the deficiency in dopamine and other neurotransmitters [5]. In addition, abnormalities in the white matter of the brain have been identified in individuals with PKU [6–8] and may further compromise brain function due to disruptions in the interconnectivity between brain regions.

If untreated, PKU is associated with significant delays in developmental milestones (e.g., crawling, walking, talking), and approximately 98% of individuals with untreated PKU fall in the range of global intellectual disability [9]. Since the implementation of newborn screening in the 1960s, the majority of individuals with PKU have been identified at birth and placed on a Phe-restricted diet. Although early diagnosis and dietary treatment prevent the severe impairments associated with untreated PKU, individuals with early-treated PKU nonetheless experience significant neurocognitive sequelae. Early-treated PKU is associated with a slight decrease in intelligence [10], coupled with impairments in specific aspects of cognition. In particular, individuals with early-treated PKU have difficulty with higher-order cognitive abilities such as

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* Corresponding author.
E-mail address: christse@missouri.edu (S.E. Christ).

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planning [11,12], organization [13], working memory [14,15], and inhibitory control [16,17]. As such, some researchers suggest that the cognitive deficits in early-treated PKU are best conceptualized as disorders of executive function (EF) [12].

This paper presents findings from studies of EF in individuals with early-treated PKU within the context of recent advances in neuropsychological theory and research, as well as the metabolic and neurophysiological abnormalities in PKU. It also examines results on clinical/laboratory tests of EF in comparison to indices of day-to-day functioning and highlights factors that place individuals with early-treated PKU at greater risk for EF impairments. This review of previous studies reveals unanswered questions and avenues for future research.

Executive function

EF refers to higher-order cognitive abilities that facilitate the flexible modification of thought and behavior in response to changing cognitive or environmental demands. EF encompasses abilities such as planning, organization, cognitive flexibility, inhibitory control, and working memory. These abilities are considered executive because they require the integration and processing of information across a range of cognitive domains, sensory modalities, and response modalities.

The prefrontal cortex (PFC) and associated brain regions play a crucial role in EF. Fig. 1 illustrates brain regions associated with specific executive abilities. Findings from neuroimaging studies of neurologically intact children and adults indicate that EF is associated with activity in the PFC and related brain regions [18]. Implicated regions include inferior frontal gyrus (located in PFC), ventromedial PFC, dorsolateral PFC, anterior cingulate cortex, and also non-frontal brain regions such as the posterior parietal cortex. From a developmental perspective, improvements in EF have been linked to maturational changes in the neurophysiology of these brain regions and their interconnections [19]. Studies of patients have also been informative. Children with infarcts involving the PFC show particular difficulties in EF [20,21], and damage to the white matter pathways connecting the PFC with distal brain regions has been shown to result in EF impairment [22,23].

Empirical evidence suggests that at least three core abilities comprise EF: updating (working memory), inhibition (inhibitory control), and shifting (cognitive flexibility) [24]. These abilities are not necessarily orthogonal in terms of either theoretical conceptualization or neural underpinnings. In fact, it is likely that

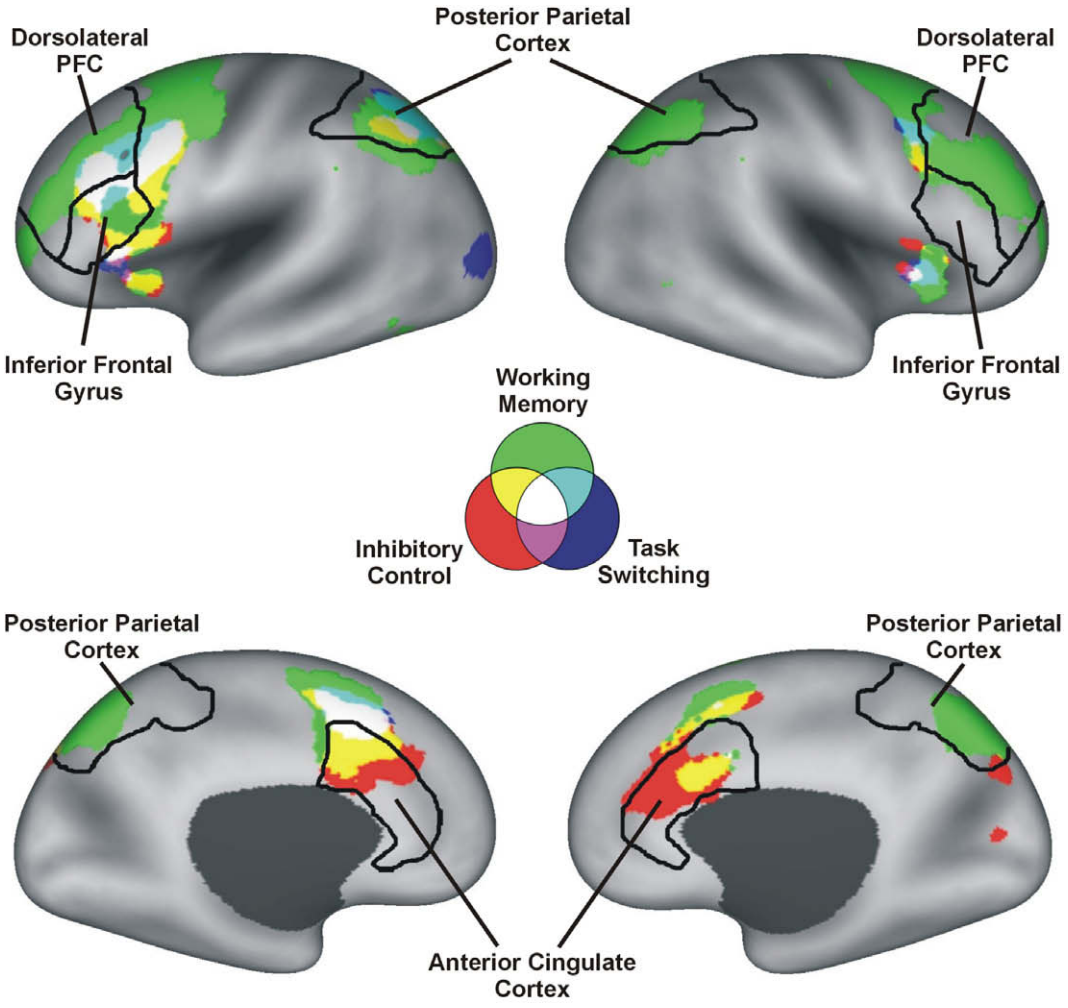

Fig. 1. The results of recent activation likelihood estimate (ALE) meta-analyses of neuroimaging findings on measures of working memory, inhibitory control, and task switching [18,25,55,121] viewed on the inflated PALS atlas surface [122]. The working memory component of the ALE map [121] was derived from studies utilizing verbal and non-verbal versions of the *n*-back task although there was a disproportionally greater contribution by verbal studies. Also, the inhibitory control component of ALE map [55] was derived from neuroimaging studies utilizing the Stroop Color-Word task; however, other meta-analyses [25] using more non-verbal inhibition tasks (e.g., go/no-go task) have shown greater involvement of the right inferior frontal gyrus/ventrolateral PFC. Figure was adapted from Christ et al. [18].

the interplay among executive abilities maximizes EF. For example, successful completion of complex tasks that involve working memory, planning, or organization (e.g., Wisconsin Card Sorting Test, Tower of Hanoi) appear to rely on a combination of executive abilities [24,25]. This review first addresses research measuring executive abilities in relative isolation. Attention is then turned to research employing tasks that place demands on multiple executive abilities.

Working memory

Overview

Working memory involves the active maintenance and manipulation of information over a brief period of time. Building upon the seminal work of Baddeley and Hitch [26], most current models of working memory include multiple components and distinguish between processes involved in storing and maintaining information versus processes involved in more effortful executive processing [26–28]. In the neuropsychological literature, the storage component of working memory has been traditionally labeled short-term memory [28]. This component comprises memory representations that are maintained in an easily accessible state, including non-attention-demanding maintenance functions such as phonemic rehearsal, chunking, and other well-practiced strategies [27]. In contrast, the executive component of working memory is involved in the manipulation and updating of information that is maintained by the storage component. This executive component supports the active maintenance of memory representations in the presence of concurrent processing demands, resistance to interference by task-irrelevant information, and implementation of attention-demanding strategies. It is important to note that there are no pure measures of the storage versus executive components, as all working memory tasks rely on both to some degree. It is possible, however, to distinguish between those tasks that primarily assess storage and those that assess both storage *and* executive processing [29].

With regard to the neural substrates of working memory, activated memory representations appear to be stored in the same brain regions that are involved in the initial perceptual processing of the information [30]. For example, in functional magnetic resonance imaging (fMRI) studies, modality-specific patterns of brain activation were identified when information had to be maintained but not manipulated in working memory. Specifically, parietal cortex and dorsal premotor cortex were activated during the maintenance of spatial information (i.e., remembering *where* something is), whereas extrastriate cortex and ventral temporal cortex were activated during the maintenance of object identity (i.e., remembering *what* something is) [31,32].

In contrast, the network of brain regions underlying the executive component of working memory appears to be less modality-specific and is subserved by more anterior regions of the cortex [33]. Neuroimaging [34] and neurophysiological [35] studies have documented increased activation in PFC during tasks requiring the manipulation of information in working memory. In addition, disruption of PFC function via transcranial magnetic stimulation adversely affects performance on working memory tasks requiring that information be maintained *and* manipulated, although similar disruption of PFC function does not adversely affect performance on tasks requiring that information be maintained but not manipulated [36].

Although a number of PFC sub-regions appear to play a role in working memory, most research has focused on dorsolateral PFC. This region, along with posterior parietal cortex, may be responsible for the integration of information across modalities and for the creation and maintenance of supramodal representations in working memory (these representations are more abstract than their counterpart representations maintained in unimodal association and sensory areas) [33]. The dorsolateral PFC has also been implicated in the strategic reorganization of information in working memory as well as the suppression of distracting sensory information during maintenance activities.

Early-treated PKU and the storage component of working memory

A widely-used paradigm for assessing the storage of information in working memory is the simple span task. In this task, participants are usually presented with consecutive stimuli (e.g., digits, words, spatial locations) that comprise a series. The number of stimuli presented in a series typically increases across trials. For example, a trial on which 2–8–5 is presented might be followed by a trial on which 9–5–7–3 is presented. After the presentation of each series, participants are asked to recall the stimuli, most often in the order presented.

Findings from studies using simple verbal (e.g., digit span) [37–40] and spatial [41] span tasks suggest that working memory storage is intact in individuals with early-treated PKU. In contrast, evidence for a PKU-related impairment in working memory storage comes from studies by Luciana et al. [41] and White et al. [15]. In each of these studies, working memory measures were administered that were non-standardized yet well-established in the cognitive neuroscience literature. In the White et al. study [15], children were shown series of stimuli ranging from 2 to 9 stimuli in length. After each series, children were presented with all stimuli and were asked to point to them in the order in which they had been presented. This procedure was repeated using digits, abstract objects, and spatial locations. Children with early-treated PKU correctly recalled significantly fewer stimuli than demographically-matched controls across all three types of stimuli. In addition, the degree of impairment was greater in older than younger children with early-treated PKU. Luciana et al. [41] also found a PKU-related impairment in young adults on a spatial delayed response task requiring that participants recall the location of a visual stimulus. (Of note, these same patients failed to show impairments on simple digit or spatial span tasks.)

The reason for the discrepancy among studies of working memory storage is unclear; however, one possibility is that the tasks used by White et al. [15] and Luciana et al. [41] may engage additional processes beyond working memory storage. For example, the longer spans (i.e., 7–9 items) in the White et al. study [15] may exceed the typical capacity of working memory storage and, as such, may lead to the engagement of non-automatic, more sophisticated methods of manipulating working memory content (e.g., forming semantic connections between the items). For the Luciana et al. study [41], precise localization of the stimulus likely requires substantial cognitive control of visual search (more so than with a simple spatial span task). Within this context, it can be argued that working memory storage, when assessed in relative isolation, is largely intact in individuals with early-treated PKU.

Early-treated PKU and the executive component of working memory

Administration of simple span tasks is often accompanied by administration of an analogous complex span task measuring the executive component of working memory. In these tasks, participants are again shown a series of stimuli, but successful performance requires manipulation of the information prior to recall (e.g., recall in reverse order). As was the case for working memory storage, findings from studies of executive working memory are mixed.

Anderson et al. [37] reported intact performance for school-aged children with early-treated PKU on a digit span backward task (a commonly used standard clinical measure), as did Luciana et al. [41] using the task with adults. Brumm et al. [39], however, reported impaired performance on this task in adults with early-treated PKU. It is notable that, in comparison with the study by Luciana et al. [41], participants in the Brumm et al. study [39] were older (mean age = 21 years versus 29 years, respectively), had slightly higher concurrent Phe levels ($M \approx 15$ mg/dL versus 17 mg/dL, respectively), and had presumably been off diet longer.

Turning to more experimental tasks, Diamond et al. [42] evaluated executive working memory in toddlers and young children using a task requiring that a group of boxes (3 or 6 boxes) be searched for rewards. The number of reaches needed to complete the search of all boxes was recorded. Efficient performance required that participants remember which boxes had already been searched. In some conditions, boxes were scrambled after each reach, requiring that participants rely solely on the appearance of the box rather than the spatial location. Children with early-treated PKU performed comparably to healthy control children on this task. Using a task which is conceptually similar to that used by Diamond et al. [42], Smith et al. [43] also failed to find evidence of executive working memory impairment in school-aged children with early-treated PKU on a self-ordered pointing task. In contrast with the findings of Diamond et al. [42] and Smith et al. [43] in children, Channon et al. [14] reported that adults with early-treated PKU performed more poorly than healthy controls on a self-ordered pointing task.

A task that is now widely used in neuroscience research is the *n*-back task. Participants are shown a series of letters and are asked to press a button when the current stimulus is the same as that which was presented *n* items before. For example, in a 2-back task, a button press should occur upon the appearance of the second Q in the series F–Q–L–Q. Using this type of task, Channon et al. [44] found that individuals with early-treated PKU were generally slower to respond than controls, but they did not perform disproportionally worse in the working memory demanding 2-back condition. In contrast, data from a recent fMRI study found poorer working memory performance and atypical PFC activity in an early-treated PKU sample compared with a control group during a digit *n*-back task [45].

Summary of working memory in early-treated PKU

The storage component of working memory in individuals with early-treated PKU appears to be largely intact in individuals with early-treated PKU. With regard to the executive component of working memory, findings were more equivocal. A general pattern, however, was evident, in that most studies reporting impairment in the executive component of working memory included adults with early-treated PKU, whereas studies reporting intact executive working memory focused on children. Importantly, White et al. [13] identified this pattern within a single study in which adolescents with early-treated PKU showed greater impairment than children with early-treated PKU. Taken together, these findings suggest that working memory impairments may emerge as individuals with early-treated PKU age, but longitudinal research is needed to thoroughly address this issue.

Inhibitory control

Overview

Inhibitory control is the ability to suppress the activation, processing, or expression of information that would otherwise interfere with the efficient attainment of a cognitive or behavioral goal [46]. A number of models of inhibitory control have been proposed [47–49]. Of particular relevance to this review, Friedman and Miyake [50] used a latent variable approach to analyze data from young adults on nine inhibitory tasks and found that inhibitory control is best conceptualized as comprising at least three subtypes: (1) Prepotent Response Inhibition – withholding a prepotent or dominant response [51], (2) Resistance to Distractor Interference – ignoring irrelevant visual information while processing target stimuli [52], and (3) Resistance to Proactive Interference – ignoring competing information while performing a working memory task [53].

The brain regions implicated in inhibitory control include dorsolateral PFC, inferior frontal gyrus, medial PFC (encompassing aspects of the anterior cingulate cortex and dorsal premotor cortex), and the basal ganglia [54]. Performance of verbal and non-verbal inhibitory tasks is associated with increased activity in the left and right dorsolateral PFC, respectively [25,55]. In terms of verbal response inhibition, the left inferior frontal gyrus also appears critical, as reflected by increased activation during tasks such as the Stroop Color-Word Test (see task description below and Fig. 1) and disrupted suppression of interference during transcranial magnetic stimulation [56]. In terms of non-verbal response inhibition, the right inferior frontal gyrus and medial PFC are also important. Non-verbal response inhibition is associated with increased activation in these regions in healthy individuals [25] and is impaired following either damage to these regions [57,58] or temporary disruption by transcranial magnetic stimulation [59].

Early-treated PKU and prepotent response inhibition

A number of paradigms have been used to study prepotent response inhibition in individuals with early-treated PKU, but perhaps the most widely used is the Stroop Color-Word Test. In a classic Stroop task, color words are presented in conflicting hues (e.g., the word *blue* printed in red ink). Participants must inhibit the prepotent tendency to read the word and instead name the color of the stimulus. Performance in this inhibitory condition is often compared with that in one or more control conditions (e.g., reading color words printed in black ink).

A number of studies have shown that both school-age children [13,16,60–63] and adults [64] with early-treated PKU perform comparably to healthy controls on Stroop tasks. Indeed, in a study of adults with early-treated PKU who had been off diet since early childhood, Brumm et al. [39] found intact Stroop performance despite the presence of significant impairments on a number of other cognitive tasks. A possible exception comes from a study by Weglage et al. [65], in which impaired performance was reported for individuals with early-treated PKU across three conditions (color word reading, color naming, and color–word interference) of a Stroop task. It is likely, however, that these results reflect poorer general processing speed rather than a specific impairment in inhibitory control because the decrease in performance between the color naming condition and the inhibitory control condition was comparable for the early-treated PKU and comparison groups (84% in both instances).

Findings from other tasks requiring the inhibition of a prepotent verbal response are mixed. Diamond et al. [42] and Griffith et al. [66] found that children with early-treated PKU were impaired on the Day/Night interference task and the Opposite Worlds Different subtest of the Test of Everyday Attention for Children, respectively. Both tasks required that children inhibit a previously learned word association (e.g., say night when shown a picture of the sun). In contrast, Channon et al. [14] reported intact performance in adults with early-treated PKU on the Hayling Sentence Completion Test [67]. In this task, participants must complete

sentences as quickly as possible, first using words that are appropriate given the context of the sentence (the control condition) then using words that are not appropriate (the inhibitory condition).

Continuous performance tests represent another category of tasks that have been used to evaluate inhibitory control in individuals with early-treated PKU. In a typical task, participants are shown a lengthy series of stimuli. Some stimuli (e.g., the letter A) appear with high frequency (e.g., 80%) and require a specific response (e.g., press a button with the right hand), whereas other stimuli (e.g., the letter X) appear with low frequency (e.g., 20%) and require that either a different response be made (e.g., press a button with the left hand) or that a response be withheld altogether. After a short time, a strong bias towards the high frequency response emerges, resulting in a need to inhibit this response when a low frequency stimulus occurs. Impairments in inhibitory control, reflected by an increase in errors for low frequency stimuli, have been identified in both children [68] and adults with early-treated PKU [69]. Additional studies using go/no-go tasks (i.e., continuous performance tasks in which a response to a low frequency stimulus must be withheld) provide converging evidence of PKU-related impairment [16,39,63,66]. In each study, researchers found increased rates of commission errors on no-go trials in individuals with early-treated PKU compared with healthy controls. Moyle et al. [70] identified a similar (albeit non-significant) pattern of performance on a go/no-go task in individuals with early-treated PKU. In addition, they found that PKU performance on the task was associated with atypical neurophysiological activity as measured by electroencephalography (EEG).

Additional evidence of an impairment in inhibitory control comes from a study by Christ et al. [16] in which individuals with early-treated PKU had more difficulty than healthy controls inhibiting reflexive eye movements to visual stimuli that were presented peripherally (i.e., a brightening box). Huijbregts et al. [17] found similar PKU-related impairments on an analogous paradigm requiring directional button presses in response to lateralized (left/right) visual stimuli.

Early-treated PKU and resistance to distractor interference

The flanker task [52] is the most frequently used paradigm for assessing the ability to resist interference from visual distractors. In a typical flanker task, participants respond to the identity of centrally presented target stimuli. For example, participants may be required to press a left button in response to the letter *S* and press a right button in response to the letter *H*. Centrally presented target stimuli are flanked by distractor stimuli that are either compatible (mapped to the target response; e.g., *SSS*), neutral (mapped to no response; e.g., *XSX*), or incompatible (mapped to a different response; e.g., *HSH*). Of the four past flanker studies involving individuals with early-treated PKU [16,40,44,71], none found inhibitory control to be impaired.

Early-treated PKU and resistance to proactive interference

Past studies have not directly assessed resistance to proactive interference in individuals with early-treated PKU. The most relevant available findings come from studies that utilized the California Verbal Learning Tests [72,73]. In these list-learning tasks, participants complete five successive trials in which the same list of semantically-related words is presented and then recalled. Following the fifth trial, participants are presented with a new list and are asked to recall the words from this interference list. Importantly, some words from the interference list are from the same semantic category as words from the original list. This results in proactive interference, which may impair recall on the interference list. Unfortunately, of the three studies that used the California Verbal Learning Tests [13,39,60], only one [13] reported findings from the interference list. In this study by White et al. [13], the mean number of words recalled from the interference list was comparable for children with early-treated PKU and healthy controls (5.9 and 6.0 words, respectively).

Summary of inhibitory control in early-treated PKU

The pattern of findings regarding inhibitory control is fairly clear. With regard to prepotent response inhibition, the performance of individuals with early-treated PKU was impaired on most tasks requiring the inhibition of prepotent responses [16,17,39,42,63,66,68,69]. An exception was the Stroop task, on which individuals with early-treated PKU exhibited intact performance [13,16,39,60–64]. Further research will be required to resolve this discrepancy. With regard to resistance to distractor interference, the performance of individuals with early-treated PKU appears to be intact [16,40,44,71]. Finally, evidence from one study [13] suggests that the third subtype of inhibitory control, resistance to proactive interference, may also be intact.

Shifting

Overview

Shifting, also called cognitive flexibility or rule shifting, refers to switching between tasks or mental sets in response to changing task demands. Shifting involves disengagement from one set of goals followed by engagement in another set of goals. Successful shifting results in behaviors that are consistent with new rules or new stimulus–response mappings. For example, a child completing math homework might be expected to alternate between addition and subtraction problems. Failing to shift from addition when a subtraction problem is presented would result in an incorrect response.

The dorsolateral PFC and posterior parietal cortex have been consistently implicated in neuroimaging studies of shifting in healthy young adults [25]. In addition, impaired shifting has been documented in patients with PFC infarcts [74] and in individuals with neurodevelopmental disorders (e.g., autism) associated with PFC dysfunction [75].

As noted previously, there is significant conceptual and neuroanatomical overlap between shifting and other executive abilities. Proficient shifting likely requires suppression of proactive interference from a previous task set (i.e., inhibitory control) as well as active maintenance and monitoring of multiple sets of goals (i.e., working memory). Within this context, tests of shifting may be conceptualized as necessarily involving other executive abilities [24,25,76].

Early-treated PKU and shifting

A test commonly used to assess shifting is the Wisconsin Card Sorting Test. During this test, through trial and error, participants must deduce the rule (e.g., based on color, shape, or number) by which a set of stimulus cards is sorted. As the task progresses, the correct sorting rule periodically changes without warning, requiring that the participant shift sets and re-determine the correct sorting rule. Difficulties in shifting often manifest as perseveration, or a tendency to continue sorting based on a previous rule despite feedback indicating that this rule is no longer the correct basis for sorting. Findings from Wisconsin Card Sorting Test in individuals with early-treated PKU are mixed. Although some researchers have identified impaired shifting (i.e., a higher rate of perseverative errors) in children and adults with early-treated

PKU [39,77,78], others have reported intact performance in similar samples [13,79,80]. In yet other studies [43,61], participants with early-treated PKU have performed more poorly than healthy controls on non-shifting aspects of the task (e.g., time to first category, percentage of conceptual responses).

Results are also mixed for the Trail Making Test, which relies on shifting and working memory [81]. In the shifting condition of the test (i.e., Trails B), participants are shown a page of small circles containing digit and letter stimuli. Participants must draw lines connecting the stimuli in alternating numerical and alphabetic order (e.g., *1–A–2–B–3*, etc.). Gassió et al. [63] and Brumm et al. [39] found intact performance on Trails B in children and adults with early-treated PKU, respectively. In contrast, Moyle et al. [82] found a trend (albeit non-significant) for poorer performance on Trails B in adults with early-treated PKU. In addition, VanZutphen et al. [62] reported impairments in children and young adults with early-treated PKU on the Number–Letter Switching component of a Trails subtest from the Delis–Kaplan Executive Function System, which is analogous to Trails B of the Trail Making Test.

Other studies have utilized tasks that assess primarily shifting and inhibitory control. For example, Griffiths et al. [66] found that school-aged children with early-treated PKU were impaired on the Creature Counting subtest of the Test of Everyday Attention for Children, which requires that participants switch between counting forward and backward based on visually presented stimuli. Huijbregts et al. [17] found that the inhibitory difficulties experienced by individuals with early-treated PKU on a stimulus–response compatibility task were exaggerated when compatible trials were intermixed with incompatible trials, thus placing demands on both inhibitory control and shifting when incompatible trials followed compatible trials. Huijbregts et al. [17] also noted that this exaggerated difficulty during intermixed trials was driven primarily by the disproportionally poorer performance of PKU patients with higher Phe levels.

Summary of shifting in early-treated PKU

The integrity of shifting in individuals with early-treated PKU is unclear. Disparate findings have been reported across studies, even among those utilizing the same measure. Although some studies have reported intact performance [13,39,63,79,80], other studies have reported evidence of PKU-related impairment in shifting [39,62,77,78]. In addition, the majority of shifting tasks place secondary demands on working memory and inhibitory control. As such, when an impairment is evident, it is unclear whether it is attributable to difficulties with one specific executive ability (shifting, working memory, or inhibitory control) or is evident only when demands are placed on multiple executive abilities simultaneously.

Early-treated PKU and multiple executive abilities

In one of the first large studies of EF in young children with early-treated PKU, Diamond et al. [42] reported an interesting pattern of results. Infants and children with early-treated PKU performed comparably to healthy control children on tests purported to assess working memory alone (e.g., the scrambled box test). In contrast, participants with early-treated PKU experienced difficulties on tests (e.g., the A/not-B task) believed to require both working memory and inhibitory control. Based on these findings, Diamond et al. [42] postulated that PKU-related problems in EF may be subtle and that impairment is evident only when concurrent demands are placed on multiple executive abilities. This section explores evidence related to this hypothesis and reviews findings from studies of early-treated PKU that focused on more complex tests of EF.

Early-treated PKU and planning/organization

A number of studies have used a tower task (e.g., Towers of Hanoi, Towers of London) to study planning and goal management in individuals with early-treated PKU. In a typical tower task, participants are presented with a board with several beads/disks positioned on three pegs. They are instructed to rearrange the beads as efficiently (i.e., in as few moves and as quickly) as possible to match a visual model. The task is made more difficult by the imposition of rules governing the movement of the beads (e.g., only one bead may be moved at a time; a bead cannot be moved if another bead is located on top of it). Neuroimaging and behavioral research indicate that multiple executive abilities contribute to performance on tower tasks [24,25]. In fMRI studies of healthy individuals, performance on tower tasks resulted in increased activation in frontal and parietal regions of the brain [83,84]. Also, impaired tower performance has been reported in individuals with PFC damage [85]. In the first study using a tower task in individuals with early-treated PKU, Welsh et al. [12] found impaired performance in preschool-age children with early-treated PKU compared with healthy controls. With the exception of two studies reporting non-significant trends towards PKU-related impairment [37,86], however, subsequent studies have failed to find evidence of impairment in older samples of individuals with early-treated PKU [62,78,80].

The copy component of the Rey–Osterreith Complex Figure test [87] is also commonly used to assess planning and organization. For this test, participants are asked to copy a complex geometric figure. In addition to requiring non-EF skills such as processing speed and visuomotor coordination, accurate reproduction of this figure requires planning and ongoing monitoring of performance. Impairments on the Rey–Osterreith Complex Figure test have been documented in both children [60,63,77] and adults [39,79] with early-treated PKU. The one exception is a study by Channon et al. [14] in which performance was intact in adults with early-treated PKU who had remained on a Phe-restricted diet (albeit relaxed) throughout their lives. Concurrent Phe levels for participants in the Channon et al. study were below those of the adult participants in the other two published adult studies [39,79], both of which found PKU-related impairments.

Early-treated PKU and strategic processing

List learning has been used to examine strategic processing in individuals with early-treated PKU. As described earlier, in a typical list-learning task, participants are presented with a set of stimuli (usually words) one at a time and are then asked to recall as many stimuli as possible in any order. Presentation of the same list is repeated, with recall occurring following each presentation. On some list-learning tasks, the words within the list are semantically related, which allows participants to enhance their performance through the use of a semantic clustering strategy. As such, poorer performance on list-learning tasks may reflect the use of a suboptimal strategy (e.g., serial clustering) rather than a learning and memory problem per se. Consistent with this notion, White et al. [13] and Antshel and Waisbren [60] reported both poorer list learning and decreased semantic clustering for children with early-treated PKU in comparison with controls.

In addition, White et al. [13] reported that the observed impairment in learning on the children's version of the California Verbal Learning Test was driven primarily by the performance of older rather than younger children with early-treated PKU. Because more sophisticated strategies such as semantic clustering are used

minimally by young children, it is not surprising that a strategy-related impairment in learning was not identified in younger children. As children age, however, the use of such strategies increases. Thus, from a developmental perspective, a strategy-related impairment in learning would be expected to manifest as emerging with age in children with early-treated PKU, as was the case in the White et al. [13] study.

Early-treated PKU and EF in the real world

The extent to which performance on EF measures administered in the laboratory correspond with EF in day-to-day life remains unclear. Indeed, numerous studies involving individuals with and without brain dysfunction have reported only modest correlations between performance on laboratory tests of EF and the extent of EF problems in the real world [88,89].

A major factor that likely contributes to the tenuous link between the laboratory and the real world is the inherent difference between the two environments. In the laboratory, researchers endeavor to structure and control as many variables as possible. The result is structured tests with specified rules and predefined goals that are administered in a quiet testing room devoid of distractions. In addition, in designing laboratory tests it is usually a goal that the executive ability of interest be measured in relative isolation from other executive abilities.

In contrast, as individuals navigate complex day-to-day environments, they are continually bombarded with potentially distracting stimuli. EF within this context represents a dynamic and ongoing process that simultaneously draws upon multiple executive abilities. Information must be integrated from multiple sources; primary and ancillary goals must be formulated; plans must be devised; behaviors must be initiated; and goals, plans, and behaviors must be monitored and altered based on feedback. It is difficult, if not impossible, to emulate these parameters within the laboratory.

The Behavior Rating Inventory of Executive Function (BRIEF) is purported to be a measure of EF that is more ecologically valid than most other laboratory tasks. This inventory is a standardized informant report designed to assess EF within the context of an individual's day-to-day environment [90,91]. It yields nine non-overlapping clinical scale scores reflecting different aspects of EF, including inhibitory control, self-monitoring, planning and organization, emotional control, and working memory. In addition, two broad indices (Behavioral Regulation Index and Metacognition Index) and an overall index reflecting EF in general (Global Executive Composite) are computed.

In the three studies using the BRIEF in children with early-treated PKU, problems in day-to-day EF were reported. However, there was little consistency across the studies in terms of the specific EF domains that were impaired. Anderson et al. [86] identified impairment on subscales assessing shifting and monitoring. Antshel and Waisbren [60] reported that children with early-treated PKU had significantly lower Metacognition Index scores than healthy controls (unfortunately, subscale scores were not reported). Sharman et al. [92] documented impairment on several subscale scores including initiation, working memory, planning, organization, and monitoring. In contrast, using another standardized informant report, the DysExecutive Questionnaire, Channon et al. [44] found no differences between individuals with early-treated PKU and controls.

Only a modest relationship has been shown between performance on the BRIEF and other laboratory measures of EF in early-treated PKU. Anderson et al. [86] reported that correlations between scores on the BRIEF and other laboratory tests ranged from 0.01 to 0.48, whereas Channon et al. [44] failed to find any significant correlations between their experimental EF measures (i.e., flanker and *n*-back tasks) and scores on the DysExecutive Questionnaire.

Additional research is necessary to fully appreciate the extent to which individuals with early-treated PKU have difficulties implementing EF in everyday situations, as well as the relationship between such difficulties and performance on laboratory measures of EF. The inclusion of both laboratory tests and day-to-day measures of EF in future studies of PKU will be critical to advance our knowledge in this area, and this endeavor will be easier given the growing number of ecologically valid EF tests [93]. Observational techniques (e.g., classroom observations from teachers or researchers) might also be incorporated into studies assessing EF in daily life, as well as techniques permitting examination of the relationships among EF in the laboratory, EF in daily life, and related issues such as behavioral management and emotional regulation.

EF, Phe, and development

Findings regarding relationships between EF and Phe levels are mixed. Some studies have identified correlations between EF assessment performance and concurrent Phe levels [12,60,62,65,79,94], whereas others have not [8,38,44,66,95]. Even within single studies in which multiple measures of EF were administered, there are findings of associations between concurrent Phe levels and performance on some but not all tasks [16,62,65]. In yet other studies, it has been found that concurrent Phe levels within a given sample of individuals with PKU do not correlate with EF. However, when the PKU sample is divided into subgroups with higher versus lower Phe levels, differences in EF are observed, with the higher Phe subgroup performing more poorly than the lower Phe subgroup [17,43,77].

Results have also been mixed for studies employing within-subject designs where Phe levels are manipulated through dietary changes. Whereas Huijbregts et al. [96] found strong effects of Phe manipulation on neuropsychological outcomes (i.e., improved task performance in children whose Phe levels went down), Griffith et al. [97] did not. Importantly, however, Griffiths et al. [97] focused on verbal and spatial memory, attention, and fine motor coordination; whereas Huijbregts et al. [96] focused more on EF. In addition, participants in the Griffiths et al. [97] study were generally older (10–16 years of age), whereas those in the Huijbregts et al. [96] study were 7–14 years of age, and the greatest differences were found among younger participants (<11 years of age).

With regard to development, several studies have shown that the correlations between EF and Phe levels during particular periods of childhood are stronger than those between EF and Phe levels obtained during other periods of development [17,98]. This type of age-related analysis, however, is uncommon, and further research is needed to assess the generalizability of such findings across various executive abilities. It may also be the case that lifetime Phe levels are more predictive of EF than Phe levels that are concurrent with EF assessment. For example, Anderson et al. [8] found that lifetime Phe levels in children with early-treated PKU were correlated with performance on EF tasks whereas concurrent Phe levels were not, and VanZutphen et al. [62] found a larger number of significant correlations between EF and lifetime Phe levels than between EF and concurrent Phe levels.

Another issue that requires further consideration is exactly which variable related to Phe is most predictive of EF. It is possible that the Phe-to-tyrosine ratio may be more predictive of EF than Phe levels alone [42,92,98]. Another important issue is variability in Phe levels over time, as it has been suggested that Phe variability

may be a more powerful predictor of EF than mean Phe levels at discrete points in development or across the lifetime [42].

Overall, there is little consensus regarding the contribution of Phe levels to EF. A number of factors likely contribute to discrepancies across studies. Because PKU is a relatively rare disorder, sample sizes tend to be small thus limiting statistical power to detect significant correlations between Phe levels and EF. Cohort differences in age, age of diagnosis and treatment implementation, and length of dietary restriction of Phe also likely contribute to discrepancies across studies. Additional research with larger samples will be needed to reach more definitive conclusions regarding the role of Phe in the development and integrity of EF.

Neural underpinnings of EF impairment in early-treated PKU

Dopamine dysfunction hypothesis

The dopamine dysfunction hypothesis of EF problems in early-treated PKU is based on the premise that EF is associated with PFC activity, which is in turn dependent on sufficient dopaminergic activity [12]. High Phe levels in PKU interfere with the normal transport ratios of neurotransmitter precursors at the blood–brain barrier, which results in a shortage of tyrosine, the metabolic precursor of dopamine and noradrenaline, and tryptophan, the metabolic precursor of serotonin. Whereas this deficiency could result in widespread cognitive and behavioral difficulties, Phe-restricted diets and other treatments have mitigated the most severe consequences in individuals with early-treated PKU. Nonetheless, the PFC is sensitive to the mild deficiencies in dopamine that are associated with early-treated PKU, because the dopaminergic neurons innervating the PFC have a faster firing rate and more rapid dopamine turnover than neurons innervating other brain regions [99,100].

Additional insight into the nature of the relationship between EF and dopamine regulation may come from molecular genetics studies. For example, the catechol-*O*-methyltransferase (COMT[1]) gene regulates an enzyme that accounts for more than 60% of dopamine degradation in the PFC [101]. When the methionine polymorphism of the COMT gene is present, dopamine in the PFC is degraded more slowly. This variant has been associated with better performance on cognitive tasks requiring multiple executive abilities (viz., working memory, and inhibition) [102–104]. By the same token, dopamine depletion in PFC (such as that associated with early-treated PKU) might be expected to result in *poorer* performance on such tasks. Indeed, studies by Diamond et al. [42] and Huijbregts et al. [17,71] found that PKU-related impairments were most readily evident on tasks/conditions requiring working memory plus inhibition as compared to conditions requiring only working memory or inhibition, respectively. Research examining the COMT gene in individuals with early-treated PKU may offer new insights into the molecular basis of EF impairment in this population.

Early-treated PKU is also associated with a considerable number of cognitive problems that cannot easily be attributed to prefrontal/dopamine dysfunction. Examples include perceptual and visuospatial difficulties [105,106], difficulties in sustaining attention [107], and slower information processing speed [61,107]. Within this context, additional neurological effects such as disruption of white matter development may also contribute to the neurocognitive profile of early-treated PKU.

[1] *Abbreviations used:* COMT gene, catechol-*O*-methyltransferase gene; DTI, diffusion tensor imaging; EEG, electroencephalography; EF, executive function; fMRI, functional magnetic resonance imaging; Phe, phenylalanine; PKU, phenylketonuria; ALE, activation likelihood estimate; PFC, prefrontal cortex; PAH, phenylalanine hydroxylase.

White matter/demyelination hypothesis

In addition to resulting in deficient dopamine, excess Phe damages myelin, possibly due to the sensitivity of oligodendrocytes to high Phe levels [108]. Structural MRI studies have identified white matter hyperintensities in individuals with early-treated PKU [108–110] that typically occur in periventricular brain regions, but in more severe cases the hyperintensities extended to frontal and subcortical regions [108]. In one of the few studies investigating the relationship between cognition and white matter abnormalities in early-treated PKU, Anderson et al. [8] found that moderate white matter hyperintensity was associated with EF impairment. This is counter to the view held by some researchers that the impact of white matter abnormalities on EF in PKU is minimal [111,112].

In recent years researchers have made increasing use of sophisticated imaging techniques such as diffusion tensor imaging (DTI) and functional connectivity (fMRI and EEG) to examine the microstructural and functional integrity of the brain's interconnections in individuals with early-treated PKU. DTI studies have consistently demonstrated abnormalities in the microstructural integrity of the white matter, even when white matter hyperintensities are not present (i.e., in normal-appearing white matter) [113–119]. In addition, fMRI [45] and EEG [120] studies have shown that the functional interactivity between brain regions is disrupted in individuals with early-treated PKU.

At present it is not possible to determine the degree to which dopamine deficiency, white matter abnormalities, and disruptions in functional connectivity between brain regions are isolated versus interrelated neural mechanisms in early-treated PKU. In addition, it is not yet known which of these mechanisms or combinations of these mechanisms make the greatest contribution to EF impairment. Research examining EF within the context of findings from various neurophysiological and imaging techniques within single samples of individuals with early-treated PKU will be helpful in addressing these issues.

Conclusions

It is a commonly held belief that, along with general intelligence, EF represents the most consistent area of cognitive impairment in individuals with early-treated PKU. This review does not necessarily discount that view. It does, however, point to a surprising number of discrepancies across studies of EF in early-treated PKU, with some but not all studies finding evidence of EF impairment.

PKU-related impairments were most consistently associated with the executive component of working memory and the prepotent response inhibition component of inhibitory control. The storage component of working memory as well as the distractor interference and proactive interference components of inhibitory control appear to be largely intact in early-treated PKU. Mixed findings across studies of shifting ability and other more complex aspects of EF (e.g., planning and organization) may be related to a number of factors, including cohort differences (e.g., age, Phe levels), variability in the extent to which tasks placed demands on executive working memory and/or prepotent response inhibition, and variability in the sensitivity of the tasks to detect subtle performance differences (e.g., standard clinical versus experimental tasks).

Findings also point towards problems in day-to-day aspects of EF; however, there was little consistency across studies in terms of the specific EF domains that were impaired. Further, scores on questionnaires assessing day-to-day EF were only weakly related to performance on laboratory EF measures [60,86,92]. Within this

context, future development of a systematic approach to measuring EF in specific day-to-day life situations (e.g., classroom, work environment) is critical. Viable approaches include the supplementation of questionnaires with observational data to obtain an accurate impression of day-to-day EF.

In terms of additional directions for future research, there is a clear need for larger scale studies that track individuals with early-treated PKU over the life-span. Because PKU is relatively rare, collaborative research across institutions will be essential. Cross-institutional efforts that examine EF within the context of neuroimaging and neurophysiological findings will be particularly informative. Also, in future research greater attention should be given to possible confounds that exist within the tasks used to assess EF. For example, many standard clinical measures of EF do not adequately take into account the contributions of non-executive abilities such as processing speed and vigilance/sustained attention that may also be affected in early-treated PKU [44,105,107,120]. As noted previously, the relationship between performance on laboratory EF measures and EF in daily life is also a very important avenue for ongoing research, as the ultimate goal of our research and clinical care is to improve the lives of individuals with PKU by helping them to reach their full potentials.

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