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

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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.

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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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

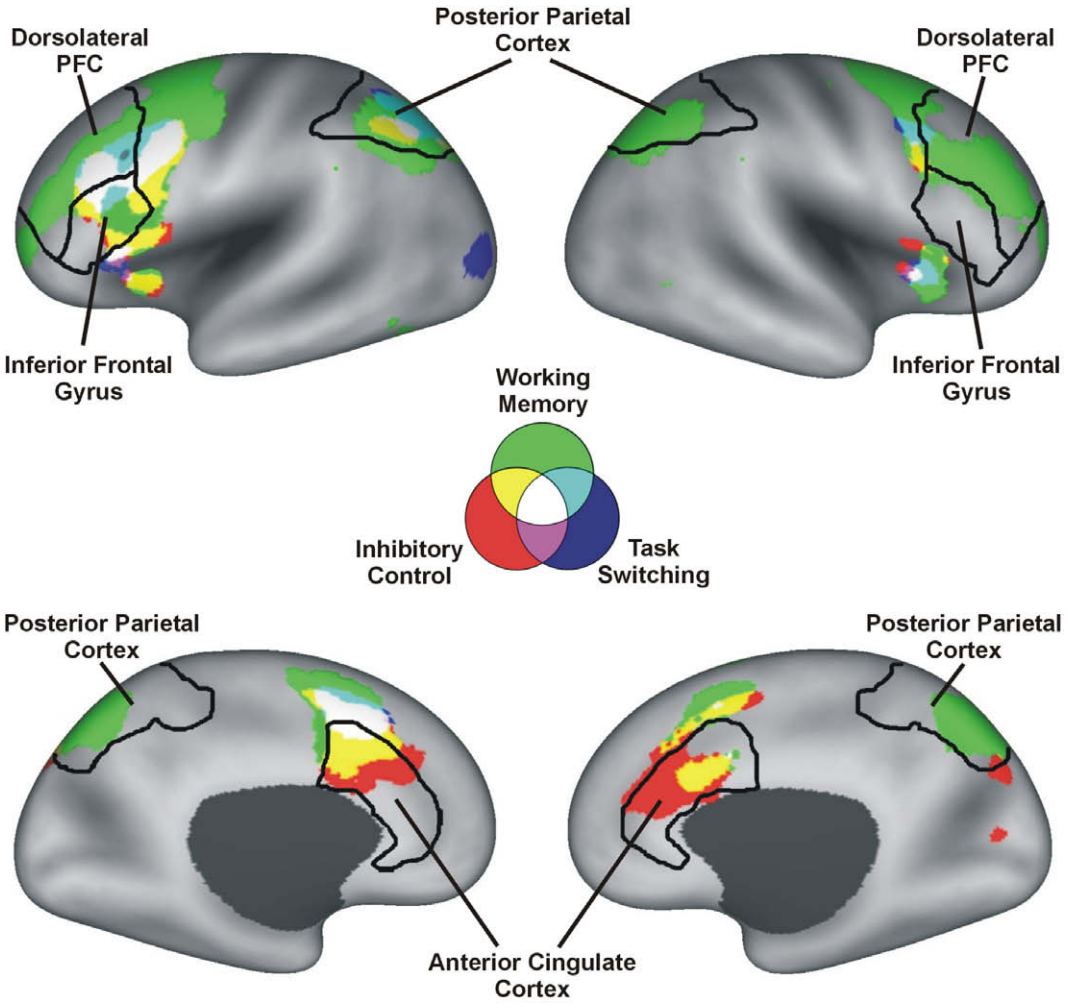

Fig. 1. The results of recent activation likelihood estimate (ALE) meta-analyses of neuroimaging findings on measures of working memory, inhibitory control, and task switching [18,25,55,121] viewed on the inflated PALS atlas surface [122]. The working memory component of the ALE map [121] was derived 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].