Journal of the International Neuropsychological Society (2019), **25**, 624–643

doi:10.1017/S1355617719000146

CRITICAL REVIEW

Neuropsychological Profile of Children with Early and Continuously Treated Phenylketonuria: Systematic Review and Future Approaches

Marie Canton[1,2,3], Didier Le Gall[2,4], François Feillet[1], Chrystele Bonnemains[1] and Arnaud Roy[2,5]

[1]Reference Center for Inborn Errors of Metabolism, INSERM U954, Nancy University Children's Hospital, 54000 Nancy, France
[2]Laboratory of Psychology, UBL, EA4638, University of Angers, 49000 Angers, France
[3]Reference Center for Learning Disabilities, Pediatric Neurology Department, Nancy University Children's Hospital, 54000 Nancy, France
[4]Neuropsychology unit, Department of Neurology, Angers University Hospital, 49000 Angers, France
[5]Neurofibromatosis Clinic and Reference Center for Learning Disabilities, Nantes University Hospital, 44000 Nantes, France

(Received November 15, 2017; Final revision December 22, 2018; Accepted January 20, 2019; First Published Online April 29, 2019)

Abstract

Objective: To provide a comprehensive systematic review of the literature by examining studies published on all cognitive aspects of children with early and continuously treated phenylketonuria (ECT-PKU) included in the databases Medline, PsycINFO, and PsycARTICLE. **Method:** In addition to a classical approach, we summarized methodology and results of each study in order to discuss current theoretical and methodological issues. We also examined recent advances in biochemical markers and treatments of PKU, with implications for future research on metabolic control and its role as a determinant of neuropsychological outcome. **Results:** Consistent with previous reviews, the hypothesis of a specific and central executive impairment in children with ECT-PKU was suggested. However, findings are inconclusive regarding the nature of executive impairments as well as their specificity, impact on everyday life, persistence over time, and etiology. **Conclusion:** Given the current state of the science, we suggest future directions for research that utilizes a developmental and integrative approach to examine the effects of recent advances in biochemical markers and treatment of PKU. (*JINS*, 2019, *25*, 624–643)

Keywords: Phenylketonuria, children, neuropsychological profile, executive function, review

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine metabolism caused by deficiency of phenylalanine hydroxylase (PAH). This enzyme converts phenylalanine into tyrosine, a precursor of dopamine and other catecholamines (Scriver & Kaufman, 2001). Tetrahydrobiopterin, also known as sapropterin, is a necessary cofactor of PAH (Erlandsen & Stevens, 2001). The PAH gene is located on chromosome 12q23.1 (Scriver & Kaufman, 2001). Systematic newborn screening programs are conducted in several countries since the 1970s. Usual classification scheme of PKU severity is based on pretreatment blood phenylalanine levels. The normal range of blood phenylalanine concentrations is 50–110 µmol/L. Patients with classical PKU (phenylalanine level > 1200 µmol/L) and mild PKU (phenylalanine level between 600 and 1200 µmol/L) require treatment. Patients with phenylalanine levels lower than 600 µmol/L are classified in the group of mild hyperphenylalaninemia. Prevalence rate of PKU varies between countries, from approximatively 1/3500 newborns in Turkey, to 1/15,000 newborns in the United States (Scriver & Kaufman, 2001).

The mutation of the PAH gene leads to PAH deficiency, which increases serum levels of phenylalanine and decreases tyrosine levels, impairing cerebral protein synthesis (de Groot et al., 2013). High blood and brain phenylalanine concentrations are toxic and can cause severe and irreversible neurological damage, such as seizures, microcephaly, and intellectual disability. The aim of treatment is to decrease the blood phenylalanine concentration. The dietary phenylalanine restriction is the mainstay of treatment, but some patients with PKU, especially with a higher residual PAH activity, respond to tetrahydrobiopterin administration. PKU is treated as soon as possible after birth with a low phenylalanine diet and consumption of medical food substitutes containing the

Correspondence and reprint requests to: Marie Canton, CLAP, Hôpital d'enfants, CHRU Nancy-Brabois, Rue du Morvan, 54511 Vandoeuvre-Les-Nancy, France. E-mail: m.canton@chru-nancy.fr. Phone: + 33 (0) 3 83 15 48 84

appropriate mix of essential amino acids, vitamins, minerals, and trace nutrients (Acosta & Matalon, 2010). The primary goal of treatment is to achieve an optimal neuropsychological outcome by preventing phenylalanine toxicity. The effectiveness of treatment depends on its early introduction, its quality, and its duration (for a review, see Brumm & Grant, 2010). Currently, there is no international consensus on the upper targets of phenylalanine level at the different periods of life (for American guidelines, see Camp et al., 2014; for European guidelines, see van Spronsen et al., 2017).

Early and continuously treated PKU (ECT-PKU) prevents intellectual disability and the most severe neurodevelopmental consequences of PKU (Mitchell et al., 2011). However, there is a higher risk of a slight decrease in intelligence (for a meta-analysis, see DeRoche & Welsh, 2008) and neuropsychological problems (for a meta-analysis, see Moyle et al., 2007). These outcomes are due to a complex array of factors, including phenylalanine toxicity. Phenylalanine-level targets in children with ECT-PKU are supposed to prevent neuropsychological problems, but they're still higher in comparison with the normal level of non-PKU children. Diamond et al. (1997) and Blau et al. (2010) hypothesized that neuropsychological impairments may be caused by reduced dopamine and serotonin synthesis. In addition to neurotransmitter dysregulation, Dyer (1999) and Anderson and Leuzzi (2010) related the extent and severity of cognitive deficits to impairment in the maintenance and production of myelin. The prefrontal cortex and dopaminergic activity play a crucial role in higher-order cognitive abilities conceptualized as executive functions (EFs) (Jurado & Rosselli, 2007; Welsh et al., 1990). In this context, many studies were devoted to EFs (for a review, see Christ et al., 2010a). Less often discussed, impairments have been identified in nonexecutive abilities as well (for a review, see Janzen & Nguyen, 2010).

Earlier qualitative and critical reviews have pointed to a number of neuropsychological problems in children with ECT-PKU. However, the neuropsychological risks associated with ECT-PKU are not fully elucidated. Neuropsychological sequelae have an influence on treatment adjustment and care in PKU; therefore, it is particularly important to understand the nature of those risks. Previous reviews (Christ et al., 2010a; Janzen & Nguyen, 2010) suggested the need for a more comprehensive approach to the neuropsychology of ECT-PKU. These reviews discussed neural underpinnings (i.e., dopamine dysfunction hypothesis/white matter hypothesis), but did not discuss recent advances in biochemical aspects and treatments of PKU.

The first aim of this study was to present a systematic and integrative review of studies of the neuropsychological profile of children and adolescents with ECT-PKU to inform future directions for research. The second aim was to present recent advances in biochemical markers and treatments of PKU, and focus on the role of metabolic control as a determinant of neuropsychological outcome. An argumentative synthesis, as well as clinical and research prospects, is presented in the final section.

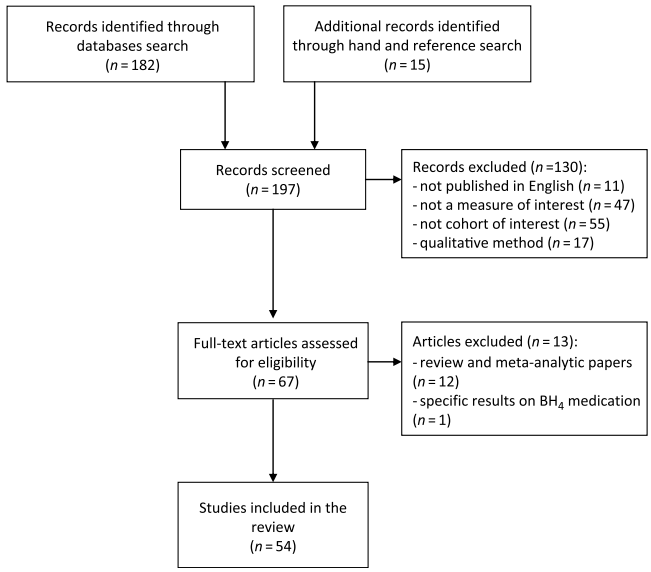


Fig. 1. PRISMA flowchart from search results.

METHODS

For the first section of this review, neuropsychological studies of children and adolescents with ECT-PKU were identified through computerized searches of Medline via the PubMed interface, PsycINFO, and PsycARTICLE. Search terms were (phenylketonuria) AND (children) AND (neuropsychology OR cognitive OR cognition OR executive function). This systematic review was based on the PRISMA statements (Moher et al., 2015). The flow of studies through the screening process is presented in the PRISMA flowchart (see Figure 1). Abstracts were screened and the inclusion criteria applied.

The review included (1) English language studies; (2) prospective and retrospective studies; (3) longitudinal and cross-sectional studies; (4) studies with an experimental group of children and/or adolescent with ECT-PKU; (5) studies that compared the performances of children with ECT-PKU to a control group or test norms using quantitative methods; and (6) studies on intellectual functioning, nonverbal abilities (visual perception, visual–spatial abilities, visual construction, and motor skills), language and academic achievement, memory, EFs, and information processing speed. Based on the current understanding of executive dysfunction in attention-deficit hyperactivity disorder (ADHD) (Barkley, 1997; Sonuga-Barke et al., 2008), we included a review of ADHD symptoms in the review of EFs.

The review did not include (1) case studies; (2) review and meta-analytic papers; (3) studies of adults with PKU; (4) studies of children/adolescents with PKU who were treated after 60 days of life or had stopped their treatment early; (5) studies of participants with mild hyperphenylalaninemia; and (6) studies of children with ECT-PKU who used tetrahydrobiopterin medication.

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

Table 1. Neuropsychological findings before 2000

Article	Participants with ECT-PKU *n* Age (years)	Comparison group *n*	Intellectual efficiency	Oral language and learning abilities	Visual perception, visual–spatial abilities and motor skills	Memory	Executive functions, ADHD, and information processing speed
Williamson et al. (1981)	132 6	Not specified	STB*				
Koch et al. (1984)	23 8	23	WISC$^{(FSIQ)}$	WRAT$^{(R, A, S)}$			
Holtzman et al. (1986)	38 8	Not specified	WISC$^{(FSIQ)}$	WRAT$^{(R, A, S)}$			
De Sonneville et al. (1990)	32 8.7	20^{a,b}	HAWIK-R$^{(FSIQ*, PIQ*, VIQ)}$				SVAT$^{(CAE, DPE)}$ [PKU(l)] SVAT$^{(CAE*, DPE*)}$ [PKU(h)]
Michel et al. (1990)	132 <5; 5; 6 (longitudinal)	Not specified	<5 years : CMM 5 years : HAWIVA$^{(PIQ*, VIQ)}$ 6 years : HAWIVA$^{(PIQ, VIQ)}$	5 + 6 years. : HAWIVA$^{(MT*)}$, PET	5 years : DTVP*, LOSKF18 6 years : DTVP, LOSKF18		
Ozanne et al. (1990)	29 7–16	29$^{a–c}$		TOLD-P, TOLD-I, TOAL-2, SICD, FLTAC			
Welsh et al. (1990)	11 4,64	11$^{a–d}$					EF composite score, *FLV$^{(S*)}$, TOH*, VST*, FT
Mazzocco et al. (1994)	17 6–13	17^{a,b,d}			VMI, GC	CVLT$^{(5, DR)}$	TOH, VST, MFFT, RFFT, CNT$^{(E, T)}$, WCST
Stemerdink et al. (1995)	33 11.8 (2.9)	33$^{a–c}$	WISC-R$^{(FSIQ, PIQ, VIQ*)}$				SRT, FLANK$^{(RT, E)}$
Burgard et al. (1996)	89 3 ; 6 ; 9 (longitudinal)	200^{a}	3 years. : CMM 6 + 9 years. : WPPSI + WISC-R$^{(FSIQ*, VIQ*, PIQ*)}$				
Diamond and Herzberg (1996)	12 7,82 (1,1)	29			Vistech*		
Weglage et al. (1996)	20 10,1 (1,3)	20^{a,b}	CFT-20		MLS$^{(FT*, LP*, S, FL, A, R)}$		STROOP$^{(I*, L*)}$, d2$^{(E*, RT*)}$
Burgard et al. (1997)	23 7–15 (cross-sectional)	21^{a,b,d}					SVAT$^{(FMSE, DPE, LPE)}$ [PKU(c)] SVAT $^{(FMSE*, DPE*, LPE*)}$ [PKU(a)]
Diamond et al. (1997)	37 <1–7 (longitudinal)	25^{siblings} 36$^{a–c}$ 25	STB		NVT [PKU(h), PKU(l)]		AB, OR, DN, TAP, 3P [PKU(l)] AB*, OR*, DN*, TAP*, 3P* [PKU(h)] 3-6B, CORSI [PKU(h), PKU(l)] WLAB
Griffiths et al. (1997)	15 12,1 (1,2)	None (test norms)					
Griffiths et al. (1998)	11 8,8	11^{a}					CPT$^{(C, RT)}$

(*Continued*)

Table 1. (*Continued*)

Article	Participants with ECT-PKU *n* Age (years)	Comparison group *n*	Intellectual efficiency	Oral language and learning abilities	Visual perception, visual–spatial abilities and motor skills	Memory	Executive functions, ADHD, and information processing speed
Stemerdink et al. (1999)	36 13.3 (3)	36[a–d]	WISC-R*(Matrix, Vocabulary)		Vistech		EF composite score*
Weglage et al. (1999)	Assessment 3 years after 1996				MLS(FT, LP*, S, FL, A, R)		STROOP(I*, L*), d2(E, RT*)

PKU(h) = subgroup of patients with high phenylalanine levels; PKU(l) = subgroup of patients with low phenylalanine levels; PKU(c) = subgroup of children with ECT-PKU; PKU(a) = subgroup of adolescents with ECT-PKU.
See Supplementary Material for the list of abbreviations used for the tools.
[a]Age-controlled; [b]Genre-controlled; [c]Socioeconomic status-controlled; [d]Intelligence Quotient-controlled; *Impairments.

Of the 197 studies retrieved from the search, we considered 54 eligible for analysis. Overall, the studies ranged in publication date from 1981 to the end of 2016. We summarized the methodology and results of each article in three tables (before 2000, Table 1; from 2000 to 2009, Table 2; from 2010 to 2017, Table 3).

The second part of this paper presents findings from studies of neuropsychological profiles within the context of recent advances in biochemical markers and treatments of PKU.

Table 4 and Figure 2 summarize results and key recommendations from the extensive review.

RESULTS

Neuropsychological Profile of Children and Adolescents with ECT-PKU

Intellectual functioning

Intellectual functioning was assessed in 63% of the articles in the literature. In 41% of these studies, intellectual level was measured as a control variable. In all studies on intellectual functioning, the mean Full Scale Intelligence Quotient (FSIQ) score of children with ECT-PKU group was within the normal range. The mean FSIQ of the group with ECT-PKU was compared with a control group or test norms in most studies (73% *vs.* 6%, respectively). In 52% of these studies, children with ECT-PKU performed significantly lower than controls or test norms. Approximately half of the studies on intellectual functioning used complete intelligence tests (e.g., WISC—Weschler Intelligence Scale for Children). The other half used abbreviated versions of these scales or *g* factor tests (e.g., WASI—Wechsler Abbreviated Scale of Intelligence). A majority of studies that identified lower intellect used entire rather than abbreviated tests (62% *vs.* 36%, respectively).

Aside from the slight downward shift in FSIQ, only five studies have compared verbal and perceptual reasoning in children with ECT-PKU to controls or normative samples. And results were mixed. To our knowledge, only two studies have compared Verbal Intelligence Quotient (VIQ) to Performance Intelligence Quotient (PIQ) within group, again with mixed results. Cappelletti et al. (2013) found no significant discrepancy between VIQ and PIQ, whereas Griffiths et al. (2000) found lower PIQ than VIQ.

Visual perception, visual–spatial and visual construction abilities, and motor skills

Visual perception was assessed in seven studies (13% of the literature). Findings suggested that visual perception was intact. Mixed results were found concerning sensitivity to visual contrast (Diamond & Herzberg, 1996; Stemerdink et al., 1999).

Seven studies examined visual–spatial and visual construction abilities (13% of the literature). Only two studies used simple spatial tasks (spatial subtests of British Abilities Scales and Beery-Developmental Test of Visual

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

Table 2. Neuropsychological findings from 2000 to 2009

Article	Participants with ECT-PKU *n* Age (years)	Comparison group *n*	Intellectual efficiency	Oral language and learning abilities	Visual perception, visual–spatial abilities and motor skills	Memory	Executive functions, ADHD, and information processing speed
Chang et al. (2000)	32 11,9	None (test norms)		WJR(D*, WS*, MC*, AP, LWI, PC)			
Griffiths et al. (2000)	57 8,1 (0,3)	None (test norms)	WISC-R + WISC-III(FSIQ*, VIQ*, PIQ*) PIQ < VIQ				
Smith et al. (2000)	19 9,4 (2,9)	19[a,b,d]				VLT* [PKU(h)] VLT [PKU(l)]	WCST, FAS, SOPT [PKU(l)] WCST*, FAS, SOPT [PKU(h)]
Stemerdink et al. (2000)	30 12,3 (2,5)	*n* = 23[a–d]		ACH*			
Luciana et al. (2001)	18 17,88 (2,74)	16[a–c] 17[e]					EF composite score
White et al. (2001)	23 10,7 (3,4) (cross-sectional)	23[a]				CVLT(1, 5*,DR , Clu*, P, I) CVLT(1, 5, DR,Clu, P, I) [PKU(c)] CVLT(1, 5*, DR,Clu, P, I) [PKU(a)]	STROOP(L*, I), FLV(P*, S), WCST [PKU(c), PKU(a)]
Anderson et al. (2002)	44 5–18	80					BRIEF(GEC, MI, BRI, Inhibit, Emotional Control, Initiate,Working Memory, Plan/Organize, Organizationof materials, Shift*, Monitor*)
Feldmann et al. (2002)	42 14,7 (2,9)	42[a–c,e]	CFT-20				WCST, d2(E, RT*), STROOP(L*, I*), TMTB(RT*)
Huijbregts et al. (2002a)	58 10,9 (cross-sectional)	69					ANT(SASV «Inhibitionofprepotent responding»*) [PKU(l,c), PKU(l,a), PKU(h,c), PKU(h,a)] ANT(SASV «attentional flexibility» *) [PKU(h,c)] ANT(SASV «attentional flexibility») [PKU(h,a), PKU(l,c), PKU(l,a)]
Huijbregts et al. (2002c)	57 7–14 (cross-sectional)	65					ANT(SA) [PKU(l,c), PKU(l,a)] ANT(SA*) [PKU(h,c), PKU(h,a)] ANT(BS*) [PKU(h,c), PKU(h,a), PKU(l,c), PKU(l,a)]

(*Continued*)

Table 2. (*Continued*)

Article	Participants with ECT-PKU *n* Age (years)	Comparison group *n*	Intellectual efficiency	Oral language and learning abilities	Visual perception, visual–spatial abilities and motor skills	Memory	Executive functions, ADHD, and information processing speed
Huijbregts et al. (2002d)	67 7–14	73[a]					ANT[(MS)] [PKU(h), PKU(,l)] ANT[(FA, FL, FI)] [PKU(l)] ANT[(FA*, FL*, FI*)] [PKU(h)]
White et al. (2002)	20 11,4 (3,5) (cross-sectional)	20[a]		WJR[(PV)]	WJR[(SR)]		WMT [PKU(c)] WMT* [PKU(a)]
Antshel and Waisbren (2003a)	46 10,9 (2,1)	18[a,b]	WISC-III[(Block Design, Vocabulary)]		ROCF[(C*)]	CVLT[(Clu*, 5*)], ROCF[(M*)]	WCode*, WSymb*, STROOP[(I, L*)], ROCF[(C*)], BRIEF[(MI*, BRI)]
Antshel and Waisbren (2003b)	46 10,9 (2,1)	18[a,b,d]					ADHD Rating Scales IV[(NumberofInattention Symptoms*, Numberof impulsive/hyperactive symptoms)]
Huijbregts et al. (2003)	61 7–14 (cross-sectional)	69[d]	WISC-R[(FSIQ*)]		ANT[(T*, P*)] [PKU(h,c), PKU(l,c)] ANT[(T, P)] [PKU (h,a), PKU (l,a)]		ANT[(BS*)] [PKU(h,c), PKU(h,a), PKU(l,c), PKU(l,a)] ANT[(T*, P*)] [PKU(h,c), PKU(l,c)] ANT[(T, P)] [PKU(h,a), PKU(l,a)]
Anderson et al. (2004)	32 11,2 (3,6)	34[a,c]	WISC-III + WAIS[(FSIQ*)]	WRAT3[(R*, A*, s)] [PKU(wma)] WRAT3[(R, A, S)] [PKU(wwma)]	ROCFT[(C)] [PKU(wma), PKU(wwma)]	RAVLT + RVDLT[(1, Tot*)] [PKU(wma)] RAVLT, RVDLT[(1, Tot)] [PKU(wwma)]	WCode*, WSymb, TEACh[(DT*, Sky, Digit, CT)], CNT[(E*, T*)], TOL, ROCFT[(C)] [PKU(wma)] WCode, WSymb, TEACh[(DT, Sky, Digit, CT)], CNT[(E, T)], TOL, ROCFT[(C)] [PKU(wwma)]
Leuzzi et al. (2004b)	14 10,8	14[a–d]			ROCF[(C*)]	ROCF[(M*)] [PKU(h)] ROCF[(M)] [PKU(l)]	TOL*, ELAB*, ROCF[(C*)], WCST*, VST, WST, MML [PKU(h)] TOL, ELAB*, ROCF[(C)], WCST, VST, WST, MML [PKU(l)]
Gassió et al. (2005)	37 9,9 (5,3)	29[a,b]	KABC + WISC-R + WAIS[(FSIQ*)]		ROCF[(C*)], PPT*, FT	CVLT + RAVLT[(1, 5, DR)], ROCF[(M)]	ROCF[(C*)], CPT[(C*, O, RT)], TMTA[(RT*)], TMTB[(RT)], STROOP[(L*, I)], WCST

(*Continued*)

Table 2. (*Continued*)

Article	Participants with ECT-PKU *n* Age (years)	Comparison group *n*	Intellectual efficiency	Oral language and learning abilities	Visual perception, visual–spatial abilities and motor skills	Memory	Executive functions, ADHD, and information processing speed
Griffiths et al. (2005)	22 11,2 (2,9)	22[a–c]		BAS-2[(VS, WD)]	BAS-2[(PC*, RD)]		TEACh[(Sky*, OW*, CC*, WW*, CT, MM, S, SDT, DT)]
Wiersema et al. (2005)	9 9,2 (1,9)	9[a,d] 9[f]	WAIS-III [(FSIQ)]				GNG [(C*, RT)]
Christ et al. (2006)	26 11.2 (3.1)	25[a,c]	WASI*[(Matrix, Vocabulary)]				GNG[(C*, RT)] + ANTIS[(RT*, E)], FLANK[(RT, E)], STROOP[(I)]
Anderson et al. (2007)	33 11,2 (3,6)	34[a–c]	WISC-III + WAIS[(FSIQ*)]	WRAT3[(R*, A*, S)]	ROCFT[(C)]	RAVLT+RVDLT[(1, Tot*)]	WCode*, WSymb*, TEACh[(DT*, Sky, Digit*, CT)], CNT[(E, T*)], TOL, ROCF[(C)], COWAT
VanZutphen et al. (2007)	15 8–20	None (test norms)	WASI[(Matrix, Vocabulary)]				DKEFS[(S*, TMT*,FLG*, FLV, TOW, CWI)]
Gassió et al. (2008)	36 9,7	29[a–c]					CPT*
Araujo et al. (2009)	24 10.7 (2.5)	25[a]	WASI[(Matrix, Vocabulary)]				GNG[(C*, O, RT)]
Sharman et al. (2009a)	10 8–17	6[a]					BRIEF[(GEC, MI, BRI, Shift, Monitor, Emotional Control, Plan/ Organize, Organizationof materials, Initiate*, Working Memory*)]

PKU(h) = subgroup of patients with high phenylalanine levels; PKU(l) = subgroup of patients with low phenylalanine levels; PKU(c) = subgroup of children with ECT-PKU; PKU(a) = subgroup of adolescents with ECT-PKU; PKU(wma) = subgroup of patients with white matter abnormalities; PKU(wwma) = subgroup of patients without white matter abnormalities.
See Supplementary Material for the list of abbreviations used for the tools.
[a]Age-controlled; [b]Genre-controlled; [c]Socioeconomic status-controlled; [d]Intelligence Quotient-controlled; [e]Diabetic patients controls; [f]ADHD patients controls; [*]Impairments.

Table 3. Neuropsychological findings from 2010 to 2017

Article	Participants with ECT-PKU *n* Age (years)	Comparison group *n*	Intellectual efficiency	Oral language and learning abilities	Visual perception, visual–spatial abilities and motor skills	Memory	Executive functions, ADHD, and information processing speed
Christ et al. (2010b)	6 18,3 (4,9)	6[a,b]	WASI[(Matrix, Vocabulary)]				NBACK[(RT*, E)]
Da Silva and Lamônica (2010)	10 3–6	10[a–c]		DDSTII[(LGG*)]	DDSTII[(MFA, MG)]		
Banerjee et al. (2011)	32 12,2 (3,9)	41[a–d]	WASI				PKU < FLV[(PTot*, PSwi*, PClu, SClu, STot +SSwi "Food/Drink"*, STot +SSwi "Animal")]
Janos et al. (2012)	42 11,8 (3,5)	81[a,c]	WASI*[(Matrix, Vocabulary)]			CVLT	SRT*, NBACK*, GNG[(C*, RT*)], DS, FLV[(S Food/Drink)]
Araujo et al. (2013)	61 7–17	80[a–d]					GNG[(C*, O, RT)]
Cappelletti et al. (2013)	35 11,5 (6,2) (cross-sectional)	None (test norms)	WPPSI + WISC-III + WAIS[(FSIQ)] VIQ = PIQ				TOL* [PKU(c) < PKU(a)]
Jahja et al. (2014)	63 10,8 (2,3)	73[a]					ANT[(SASV, P, FL, SA)] [PKU(l)] ANT[(SASV*, P*, FL*, SA*)] [PKU(h)]
Sharman et al. (2015)	13 13,9 (1,8)	9					PKU = BRIEF[(GEC, Working Memory)]
Soleymani et al. (2015)	*n* = 30 4–6,5	42[a–c]	WPPSI[(FSIQ*, VIQ*)]	TOLD-P[(SE*, SL*, LI*, OR*, SP*, SY*)]			
Jahja et al. (2016)	39 7–17	42[a–d]	WISC-III*[(Block design, Vocabulary)]				SCST, SSRS, FR, IFE [PKU(c)] RME*, FPT*, SSRS, FR, IFE [PKU(a)]

PKU(h) = subgroup of patients with high phenylalanine levels; PKU(l) = subgroup of patients with low phenylalanine levels; PKU(c) = subgroup of children with ECT-PKU; PKU(a) = subgroup of adolescents with ECT-PKU.
See Supplementary Material for the list of abbreviations used for the tools.
[a]Age-controlled; [b]Genre-controlled; [c]Socioeconomic status-controlled; [d]Intelligence Quotient-controlled; [*]Impairments.

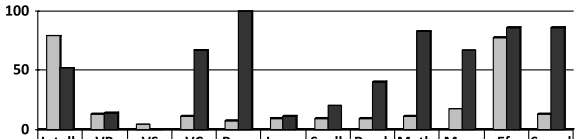
Table 4. Synthesis of findings and key recommendations

A systematic analysis of intellectual functioning	A more comprehensive evaluation of other cognitive domains
Intellectual functioning was widely studied. Intelligence is usually in the average range, somewhat lower than matched controls. A majority of studies identifying this slight intellectual downward shift in FSIQ used intelligence scales. Verbal/nonverbal discrepancy was suggested. Unknown is whether cognitive impairments are associated with this discrepancy → Analyze the verbal/nonverbal discrepancy at intelligence scales and its links with cognitive impairments → Unjustified to control for FSIQ differences by matching procedure or by using FSIQ scores as covariates	Other cognitive domains were poorly studied. However, children present an increased risk of developing problems in many cognitive and academic domains (learning, praxis, processing speed, and mathematics). The implication of EFs on cognitive performances is unknown → Adopt a comprehensive and systematic approach to the different components of each cognitive domain with specific tasks and various measures: 1. Memory: verbal and nonverbal tasks + encoding, storage, and retrieval scores 2. Nonverbal abilities: visual perception, visual–spatial, constructive, and fine motor tasks 3. Language: oral language (expressive and receptive), spelling, and reading tasks 4. Mathematics: calculations and word problems tasks. → Understand the potential links between these cognitive domains and executive functioning
A comprehensive and integrative approach of executive functioning	**A study of biochemical markers and treatments, within a developmental perspective**
EFs were widely studied and areas of weakness. The hypothesis of a potentially specific and central executive impairment is suggested. However, general consensus has yet to be reached with regards to the nature, the severity, and the specificity of these impairments, as well as their pathogenesis or their impacts on everyday life → Simultaneously use different measures of "cool EFs" (planning, inhibition, shifting, and working memory), within a developmental and conceptual framework of EFs → More systematic research on "hot EFs" and on the EFs on everyday life → Analyze EFs both with and without processing speed and nonverbal abilities as covariates → Compare EFs of ECT-PKU children (with and without ADHD phenotype) with children with ADHD (without PKU) within a conceptual framework of ADHD → Understand the links between mathematics performances and EFs	While a causal relationship between metabolic control and brain dysfunction is unquestionable, disease-independent individual factors contribute to an individual vulnerability to phenylalanine and interindividual variability in neuropsychological outcome of ECT-PKU patients. These individual factors are not recognized. The hypothesis of an individual resilience or vulnerability to phenylalanine with age has been a scarcely studied topic. Currently, studies remain too sporadic to determine an international consensus about the phenylalanine-level upper target in relation with developmental milestones → Study the advantages of phenylalanine-tyrosine ratio, fluctuation in phenylalanine, and nutritional components, in relation to neuropsychological outcome → Determine the factors that contribute to an individual vulnerability to phenylalanine and interindividual variability in neuropsychological outcome → Confirm safety and efficacy on neuropsychological outcomes of new treatments such as sapropterin (for responsive patients) and LNAA (without phenylalanine) → Design systematic cross-sectional studies and longitudinal studies in relation with different upper of phenylalanine levels (e.g., ≤240, 240–360, and ≥360 μmol/L)

Motor Integration scales). Impairments were not revealed in such tasks. Deficits were mainly demonstrated on tasks with more complex demands. Six studies used visual constructive tasks, including five that used the copy component Rey–Osterrieth Complex Figure Test (ROCF). Deficits were identified in four of these studies.

Four studies examined praxis (7% of the literature). Only fine motor skills and higher-order motor control were explored.

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press



	Intell.	VP	VS	VC	Prax.	Lang.	Spell.	Read.	Math.	Mem	Efs	Speed
% of studies on domain	79	13	4	11	7	9	9	9	11	17	78	13
% of studies finding an impairment	52	14	0	67	100	11	20	40	83	67	86	86

Fig. 2. Synthesis of results of review on neuropsychological profile in ECT-PKU children. *Note*. Intell., Intelligence; VP, Visual perception; VS, Visual–spatial abilities; VC, Visual construction; Prax., Praxis; Lang., Oral language; Spell., Spelling; Read., Reading; Math., Mathematics; Mem, Explicit memory; Efs, Executive functions; Speed, Processing speed.

Simple motor tasks (e.g., Purdue Pegboard or Tapping) and complex motor tasks requiring coordination and planning (e.g., target tracking) were used. Impairment was consistently reported for both simple and complex motor tasks.

Language and academic achievement

Language can be subdivided into subdomains such as receptive and expressive language, as well as specific areas of functioning that include phonology, syntax, semantics, and pragmatics. There are no studies that have systematically examined all these aspects of language in children with ECT-PKU. In particular, no studies have examined phonology and pragmatic abilities. Five studies (9% of the literature) used oral language tests. Impairments were identified in only one of those studies (Soleymani et al., 2015). The ECT-PKU group performed significantly lower than controls in both receptive and expressive language, as well as syntax and semantics. This group with ECT-PKU displayed a lower FSIQ and VIQ. Intellectual level was not specified in the other four studies on oral language.

Academic difficulties have been described in children with ECT-PKU (Stemerdink et al., 2000). Reading and spelling were examined in five studies (9% of the literature) and mathematics in six studies (11% of the literature). All these studies used composite scores from achievement tests (e.g., Wide Range Achievement Test). Two of five studies have shown a deficit in reading and only one study has shown a deficit in spelling. To our knowledge, no study systematically examined basic reading and writing skills, as well as reading comprehension. Four out of six studies have shown a deficit in mathematics. Only one work examined both calculations and applied word problems (Chang et al., 2000). Children with ECT-PKU performed significantly lower than test norms for calculations, not for applied word problems.

Memory

Explicit memory was examined in nine studies (17% of the literature). Five studies assessed visual memory with the delayed recall condition of the ROCF or the Rey Visual Design Learning Test, and eight studies used verbal memory tasks (only with word-list-learning tasks). Six out of nine memory studies (67%) reported impairment in visual (4/5 studies) as well as verbal memory (5/8 studies).

Although memory functions can be subdivided into specific processes (i.e., encoding, storage, and retrieval), no study systematically examined all these aspects. Learning was consistently measured in word-list- or design-learning tasks (eight studies). Impaired learning was found in five of these studies. In word-list-learning tasks, it is possible to implement executive strategies to enhance learning (e.g., semantic clustering). In the only two studies that have measured "cluster scores," children with ECT-PKU consistently had a lower use of this strategy. No word-recognition scores were used in the literature. The storage component of memory in children with ECT-PKU was assessed with delay-recall scores in only three studies and was consistently preserved.

EFs and attention-deficit hyperactivity disorder

EFs were widely investigated by 78% of the studies in the literature, with impairments identified in 86% of these studies. Forty-two different executive tasks were listed. In 88% of the studies on this topic, various tasks implying "cool" EFs (see "cool/hot" executive taxonomy, Zelazo & Müller, 2002) were used. Cool EFs are elicited by more purely cognitive aspects of EFs, which are characterized by relatively abstract and decontextualized problems. Cool EFs in these studies encompassed abilities such as planning, inhibition, shifting, and working memory (Lehto et al., 2003; Levin et al., 1991). Hot EFs are required for problems that are characterized by high affective involvement or demand flexible appraisals of the affective significance of stimuli. Hot EFs were investigated with only one recent study, which concluded that adolescents with ECT-PKU have a degree of impairment on social-cognitive functioning and social skills (Jahja et al., 2016). EFs in everyday life were explored in four studies (only with the parental version of the BRIEF—Behavior Rating Inventory of Executive Function). Three studies displayed an executive impairment in everyday life, especially in the metacognition domain. None of these studies compared the BRIEF parental rating to executive performance-based tests. When executive dysfunction was found, its specificity was not systematically studied by comparing it to intellectual level (45% of the studies on EFs controlled this variable). Executive difficulties persisted in 89% of studies on EFs when FSIQ was controlled. Only four studies (i.e., 9% of the studies) on EFs have examined executive dysfunction specificity by comparing it to nonexecutive cognitive abilities (Antshel & Waisbren, 2003a; Griffiths et al.,

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

2005; Stemerdink et al., 1999; Welsh et al., 1990). In all these studies, executive impairments were still observed when non-executive abilities were controlled.

Executive deficits could potentially explain an overlap of clinical phenotypes between PKU and ADHD (Barkley, 1997; Sonuga-Barke et al., 2008). Antshel and Waisbren (2003a, 2003b) showed that 13% of their sample of children with ECT-PKU met criteria for diagnosis of ADHD (2.5 times higher than controls), with a higher proportion of inattentive symptoms. There was no significant difference for hyperactive/impulsive symptoms. Arnold et al. (2004) showed that medication for attention problems was used by 26% of their sample of children with ECT-PKU (5 times more than controls). No study has examined EFs related to the presence or absence of ADHD in children with ECT-PKU. One study showed that children with ECT-PKU exhibited more impulsivity than children with a diagnosis of ADHD combined type (without PKU) on a Go/No-Go task (Wiersema et al., 2005) but this study did not specify whether some of the ECT-PKU participants met the diagnostic criteria for ADHD.

Processing speed

In some studies (Feldmann et al., 2002; Weglage et al., 1999), executive difficulties were interpreted as a slower information processing speed. In five studies, processing speed was controlled in studying executive performances (Antshel & Waisbren, 2003a; Christ et al., 2006; Huijbregts et al., 2003; Janos et al., 2012; White et al., 2001, i.e., 12% of the studies on EFs). In 60% of these studies, executive difficulties were observed when processing speed was controlled.

Information processing speed was poorly explored with specific tasks. Seven studies (13% of the literature) used simple reaction time tasks or tests involving the processing speed index of Wechsler scales. Six out of seven studies (86%) have shown a slower information processing speed (Anderson et al., 2004, 2007; Antshel & Waisbren, 2003a; Huijbregts et al., 2002c, 2003; Janos et al., 2012).

Cognition, Biochemical Markers, and Treatments

Blood phenylalanine level

Currently, blood phenylalanine level is the most widely used measure to monitor metabolic control and adapt treatment. Average phenylalanine levels (i.e., mean or median) have been shown to predict neuropsychological outcome (Waisbren et al., 2007). Early initiated and continued dietary treatment is crucial for the intellectual development of patients (see Brumm & Grant, 2010). Two meta-analyses (Fonnesbeck et al., 2013; Waisbren et al., 2007) on patients with ECT-PKU showed significant correlations between FSIQ and (1) phenylalanine levels during childhood and adolescence (e.g., critical period) and (2) mean lifetime phenylalanine level. Significant but moderate correlations were found between FSIQ and concurrent phenylalanine levels (i.e., within months prior to evaluation or collected at the same day of evaluation). Moreover, Waisbren et al. (2007) suggested safe upper target of blood phenylalanine concentrations between 320 and 420 μmol/L until the age of 12 years. Fonnesbeck et al. (2013) indicated that a mean concentration of 400 μmol/L was associated with an increased risk of an FSIQ less than 85. It should be noted that many candidate studies were excluded from these meta-analyses due to incomplete reporting of data or results. Moreover, there is a notable lack of consistent methodologies across studies considered. From a clinical perspective, this provides a basis for being cautious in interpreting measures of these results. Recent researches suggested that phenylalanine levels continue to have a negative impact on FSIQ scores during adulthood (Koch et al., 2002; Waisbren et al., 2007), which requires dietary restriction throughout life [for American guidelines, see Camp et al. (2014) and Vockley et al. (2014); for European guidelines, see van Spronsen et al. (2017)]. While a causal relationship between blood phenylalanine levels and brain dysfunction is well-demonstrated, a recent longitudinal study showed that disease-independent individual factors may influence the consequences of the biochemical alteration, contributing to an individual vulnerability to phenylalanine and interindividual variability in FSIQ outcome of ECT-PKU (Manti et al., 2017).

For the other cognitive abilities, correlations between phenylalanine levels and performances in the tests are inconsistent from one task to another [see Christ et al. (2010a) for EFs; Janzen & Nguyen (2010) and Luciana et al. (2001) for nonexecutive cognitive abilities]. However, long-term memory performances were intact when the mean blood phenylalanine concentrations (whether concurrent phenylalanine or lifetime phenylalanine levels) were under 360 μmol/L, in comparison with ECT-PKU children with phenylalanine levels above 360 μmol/L (Leuzzi et al., 2004b; Smith et al., 2000). Similar results have been obtained for EFs (De Sonneville et al., 1990; Diamond et al., 1997; Huijbregts et al., 2002c, 2002d; Smith et al., 2000), in particular in younger children (i.e., under 11 years) (Huijbregts et al., 2002a). In a recent study with younger ECT-PKU children (i.e., under 12 years), only those patients with phenylalanine levels under 240 μmol/L (rather than 360 μmol/L) obtained similar executive performances than controls (Jahja et al., 2014). Longitudinal studies of ECT-PKU showed less executive deficits during adolescence, despite a significant increase of phenylalanine levels, raising the hypothesis of a decrease vulnerability of PKU patients against elevated phenylalanine levels with aging (Nardecchia et al., 2015; Weglage et al., 2009). Only few studies employed within-subject designs where phenylalanine levels are manipulated through dietary changes. Strong effects of phenylalanine manipulation were found on EF performances (Huijbregts et al., 2002b) and reaction time (Leuzzi et al., 2014a), but not on short-term and long-term memory, or fine motor coordination (Griffiths et al., 1998). Sensitivity to increase of phenylalanine was higher in younger (i.e., under 13 years) as compared to older people with PKU (Leuzzi et al., 2014a).

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

Fluctuation in phenylalanine concentrations

Recent studies suggested that variability of blood phenylalanine levels over time appeared to correlate inversely and strongly with FSIQ (Burgard et al., 1996; Hood et al., 2014; Vilaseca et al., 2010) and with executive performances (Arnold et al., 1998; Hood et al., 2014; Jahja et al., 2014). However, in some studies, the correlation between fluctuation in phenylalanine and FSIQ was at the trend level of significance (Anastasoaie et al., 2008) or was not significant (Viau et al., 2011). Different indices of variability in phenylalanine have been used in the literature: *SD* (standard deviation, degree of dispersion in phenylalanine around a regression line), *SEE* (standard error of estimate, residual variation in phenylalanine around a regression line), and Spikes (number of phenylalanine levels that were at least 600 μmol/L greater than either the preceding or succeeding phenylalanine level). Interpretation and comparison of findings were limited by inconsistencies in tasks and indices of variability used across the studies.

Phenylalanine-to-tyrosine ratios

PAH deficiency causes increase in blood phenylalanine, decrease in tyrosine, and therefore theoretically an increase in phenylalanine-tyrosine ratio. A high phenylalanine-tyrosine ratio indicates that phenylalanine levels are in a range that could interfere with the transport of available tyrosine across the blood–brain barrier, resulting in a decreased availability of tyrosine for dopamine synthesis. Therefore, phenylalanine-tyrosine ratio might be of interest considering the fact that tyrosine levels are more closely related to dopamine levels than phenylalanine levels (Diamond et al., 1997). Clinical relevance of this ratio as an outcome measure is unknown. Recent studies suggested that high lifetime phenylalanine-tyrosine ratios (Diamond et al., 1997; Jahja et al., 2014; Luciana et al., 2001; Sharman et al., 2009a, 2009b, 2015) and high concurrent phenylalanine-tyrosine ratios (Jahja et al., 2014; Luciana et al., 2001) could explain executive impairments in children with ECT-PKU. Currently, it is difficult to determine the threshold above which a high phenylalanine-tyrosine ratio is harmful.

Nutritional status

Even if it is not clear that PKU leads to a specific nutrient deficiency (Camp et al., 2014), dietary treatment of PKU has been associated with deficiencies in several antioxidant vitamins and cofactors, such as selenium and coenzyme Q10 (Artuch et al., 2004; Colomé et al., 2003; Lombeck et al., 1996; Przyrembel & Bremer, 2000; van Bakel et al., 2000). Many nutrients have roles in cognition. For example, selenium status has been linked to attention performances in children with ECT-PKU, but not with FSIQ, verbal learning, fine motor, spatial, and executive tasks (Gassió et al., 2008). Currently, there is a paucity of studies on nutritional status and its role as a determinant of neuropsychological outcome.

Tetrahydrobiopterin or sapropterin therapy

The tetrahydrobiopterin cofactor is essential for PAH activity (Erlandsen & Stevens, 2001). Until recently, the main treatment for PKU was phenylalanine-restricted diet. Since 2008, an additional synthetic analogue to tetrahydrobiopterin has been developed (Burton et al., 2007; Levy et al., 2007). A subgroup of patients has been shown to respond to treatment with tetrahydrobiopterin. The frequency of tetrahydrobiopterin responsiveness varies, depending on genotype, severity of PKU, and residual PAH activity (Heintz et al., 2013; Karacic et al., 2009; Zhang et al., 2005). Significant decrease in blood phenylalanine levels were seen in children with ECT-PKU following oral administration of tetrahydrobiopterin (Fiege & Blau, 2007; Leuret et al., 2012; Longo et al., 2015). Moreover, sapropterin may increase stability in blood phenylalanine levels (Burton et al., 2010) and could play a role in microstructural white matter integrity as an evidence using diffusion tensor imaging (White et al., 2013). Few studies regarding neuropsychological outcomes of children with ECT-PKU with tetrahydrobiopterin treatment have been conducted. In tetrahydrobiopterin-responsive children with PKU and ADHD symptoms, sapropterin treatment resulted in significant improvement of ADHD inattentive symptoms on the ADHD-Rating Scale (but not on ADHD hyperactivity/impulsivity scores) and on metacognition score of parental BRIEF inventory (but not on behavioral regulation score). These improvements were maintained throughout 26 weeks of treatment (Burton et al., 2015). In a mixed sample of 12 tetrahydrobiopterin-responsive children and adults with PKU, tetrahydrobiopterin treatment was associated with improvements in working memory *n*-back task performances after 6 months of treatment. Younger participants with PKU showed greater gains in working memory performance (Christ et al., 2013). The first studies comparing ECT-PKU group of children and adolescents treated by tetrahydrobiopterin- *versus* dietary-treatment did not show significant difference on FSIQ, visual–spatial, fine motor functions, and EFs (Gassió et al., 2010), or social cognition (Jahja et al., 2016).

Large neutral amino acid supplements

LAT1, the large neutral amino acid (LNAA) transporter 1, is the predominant transport system for all LNAAs at the blood–brain barrier (Smith, 2000). LAT1 shows a high affinity to phenylalanine. As a consequence, brain phenylalanine in PKU is increased and other LNAA concentrations decreased (Pietz et al., 1999). Therefore, reduced non-phenylalanine LNAAs may possibly impair cerebral neurotransmitter and/or protein synthesis (Pardridge, 1998; Surtees & Blau, 2000). LNAA supplementation (excluding phenylalanine) has been used on a limited number of patients with PKU. phenylalanine-free LNAA supplements were shown to potentially have some effect on decreasing blood phenylalanine concentrations (Matalon et al., 2006) but this effectiveness was not consistent nor predictable (Matalon et al., 2007). Restoring reduced brain LNAA concentrations in patients with PKU

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

may improve neuropsychological outcome. The clinical significance of reduced non-phenylalanine LNAAs in PKU patients has not been fully elucidated. The use of LNAAs may be beneficial in terms of attention and EFs to adolescents and young adults with elevated blood phenylalanine levels who have stopped or do not follow dietary treatment guidelines (Berry et al., 1990; Schindeler et al., 2007). However, optimal composition and dose of LNAA treatment is currently unknown, limiting its clinical application. LNAA is contraindicated in young children due to a lack of data on safety and efficacy.

SYNTHESIS, LIMITS, AND PROSPECTIVE

The neuropsychological profile of children with ECT-PKU has been studied across many cognitive domains (for a synthesis, see Figure 2). Consistent with previous reviews, the hypothesis of a potentially specific and central executive impairment in children with ECT-PKU was suggested. Although many studies have found neuropsychological deficits, general consensus has yet to be reached with regard to the nature and the severity of these impairments, their pathogenesis, or their impacts on everyday life. This may stem in part from methodological variations across studies. In this context, several issues stand out and new research opportunities can be proposed (for a synthesis, see key recommendations in Table 4).

A Systematic Analysis of Intellectual Functioning

FSIQ score is indicative of global functional outcome, the final common path of an individual's gene, biology, cognition, education, and experience (Dennis et al., 2009). Our review indicates that the intelligence of children with ECT-PKU is usually in the average range, although it can be potentially somewhat lower than the intelligence of demographically and/or age-matched controls (see Figure 2). Research that includes genetically related controls such as unaffected parents and siblings is recommended.

A majority of studies that identify a slight intellectual downward shift in FSIQ used full intelligence scales (compared to abbreviated forms of these scales or *g* factor tests). In children with ECT-PKU, only a few studies addressed the issue of the difference between verbal and perceptual reasoning. A systematic analysis of these verbal/nonverbal discrepancies may lead to a more refined understanding of the slight downward shift in FSIQ. That said, impairments in EFs, processing speed, and nonverbal functions seem to be the main characteristics of the cognitive profile of children with ECT-PKU (see Figure 2).

Because intelligence tests measure multiple and correlated abilities, it is misguided and generally unjustified to attempt to control for FSIQ differences by matching procedures or by using FSIQ scores as covariates in children with neurodevelopmental disorders (Dennis et al., 2009). In 41% of the studies, intellectual level was measured in order to compare specific cognitive measures between individuals with the same intellectual level. Future research will need to address these issues of controls and covariates in studying the neuropsychological profile of children with ECT-PKU.

A Comprehensive Examination of Executive Functioning

"Cool EFs" are identified as areas of weakness for children with ECT-PKU (see Figure 2). Some discrepancies in the literature may be related to variations in psychometric properties of tasks or modalities for measurement. Multiple tests of the same executive process (planning, inhibition, shifting, and working memory), within a developmental and conceptual framework of EFs (e.g., Anderson, 2002; Dennis, 2006; Diamond, 2013), could strengthen findings. There is some recent evidence that executive aspects involved in the emotional, affective, and motivational contexts were impaired (Jahja et al., 2016), but more systematic research on "hot EFs" is needed to support this. From a clinical point of view, the evaluation of the EFs on everyday life constitutes an essential quality of life index in addition to the laboratory tests (for a review, see Chevignard et al., 2012). Behavioral inventories, such as the BRIEF, are often useful tools for EF assessments in individuals with PKU (Huijbregts et al., 2013; van Spronsen et al., 2011). To date, the ratings have been based exclusively on parents' reports. Recommendations for future studies are to include teachers' ratings, as well as a systematic analysis of rating scale index scores (e.g., behavioral regulation *vs.* metacognition). Comparisons with performances on "laboratory tasks" are needed because of their potentially complementary nature (Gioia et al., 2010; McCandless & O' Laughlin, 2007; Toplak et al., 2008).

Another finding from a limited number of studies was that executive impairment tended to persist when intellectual level, nonexecutive abilities, and processing speed were controlled. An important challenge for further investigations will be to devise EF assessment protocols that examine quantitative (e.g., number of errors and latency) and qualitative (e.g., fluctuation of performances) aspects of performance, as well as cognitive-process (e.g., strategies) scores in EF performances (Anderson, 2002).

Stevenson and McNaughton (2013) suggested that a subset of individuals with ECT-PKU and individuals with ADHD (without PKU) have overlapping dysfunction in cognitive inhibition. If symptoms are similar between these two clinical groups, medication utilized for ADHD could be an additional effective treatment to reduce ADHD-related cognitive and behavioral symptoms in PKU patients. To date, no study has provided a systematic analysis of the links between ADHD and PKU. Further research comparing EFs of children with ECT-PKU with and without ADHD phenotype to children with ADHD without PKU is needed to better understand the pathogenesis of the observed impairments.

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

An Integrative Approach of Other Cognitive Impairments

Because of the significant overlap between EFs and memory functions, learning difficulties may appear when there are significant executive strategy demands (Janzen & Nguyen, 2010). No study has systematically examined distinct long-term memory processes (i.e., encoding, storage, and retrieval). Moreover, there may be other cognitive aspects involved in memory test performance such as language and visual–spatial processing. Futures studies are needed to understand the interrelationships between learning, EFs, language, and nonverbal abilities.

Children with ECT-PKU seemed to show more deficits in visual construction than in visual–spatial functions. The ROCF was most often used to examine visual construction in children with ECT-PKU. Although there are various abilities involved in this test including visual–spatial processing and EFs, lower ROCF performance may stem from deficits in action planning rather than to visual–spatial deficits *per se* (Roy et al., 2010). The nature of nonverbal impairments in children with ECT-PKU needs to be closely examined with assessments that distinguish between specific visual–spatial and visual construction demands, as well as EFs and fine motor skills.

A Neuropsychological Approach of Academic Performance

Language and academic achievement have not been well studied in children with ECT-PKU. Limited studies have identified widespread academic difficulties, consistent with previous review (Janzen & Nguyen, 2010). Overall, it appeared that children with ECT-PKU tend to display substantial deficits in mathematics, more than in written language (see Figure 2). Further studies should systematically investigate each component of written language (e.g., phonology, syntax, and semantics) and mathematics (e.g., calculations and word problems) in order to understand which domains are difficult for children with ECT-PKU.

Moreover, the links between academic performance and cognitive domains need to be examined. As with other neurodevelopmental disorders such as ADHD, autism, or Neurofibromatosis type 1 (Roy et al., 2012), the hypothesis of impairment in EFs and prefrontal network functioning can offer new paradigms for understanding academic difficulties. Executive impairments can adversely affect learning abilities in general and mathematics in particular (Bull et al., 2008).

A Systematic Study of Biochemical Markers and Treatments, in Relation to Neuropsychological Outcome

The phenylalanine concentration is the crucial factor to adjust treatments. However, other parameters such as fluctuation of phenylalanine levels, phenylalanine-tyrosine ratio, and nutritional components (such as selenium) seemed to be correlated with cognitive impairments. These other markers could be interesting in addition to blood phenylalanine measurements but the advantages of these markers still have to be determined.

The goal of the therapy should be to lower blood phenylalanine enough to reach optimal neuropsychological and quality of life outcome, without negative consequences. Dietary compliance remains the cornerstone of the therapy to control phenylalanine levels and to reach suboptimal neuropsychological outcomes. However, the phenylalanine-restricted diet is socially demanding and hard to comply with (MacDonald, 2000). Starting in adolescence, 60%–80% of the patients were shown to have partially or totally disrupted the treatment (dos Santos et al., 2006), resulting in a risk of neuropsychological impairment. Other treatments might directly affect cerebral metabolism, increase dietary tolerance, and allow dietary expansion such as sapropterin (for responsive patients) and LNAA (without phenylalanine). Studies with these other treatments are still in their early stages and additional studies are needed to confirm safety and efficacy on patients' neuropsychological outcome.

Our understanding of the optimal therapies for PKU is still incomplete. Although many studies suggest a primary neurobiological explanation for neuropsychological problems in children with ECT-PKU, psychosocial and quality of life cannot be ignored. In particular, the stress associated with this chronic disorder is likely to play a role in the increased neuropsychological symptoms among children and adolescents with PKU (Weglage et al., 2000).

A Developmental Perspective in Etiology-Related Profiles

A number of longitudinal studies suggest that the severity of visual perception, fine motor, and executive disorders may decrease with age, contrasting with stability of FSIQ and slower processing speed with age (Feldmann et al., 2005; Michel et al., 1990; Nardecchia et al., 2015; Weglage et al., 1999). Findings suggest the value of longitudinal study of the age-related course of neuropsychological profiles of children with ECT-PKU, in relation with metabolic control. The hypothesis of an individual resilience or vulnerability to phenylalanine with age has been a scarcely studied topic and deserves further investigations (Manti et al., 2017; Nardecchia et al., 2015). Currently, individual factors that account for the vulnerability to phenylalanine have not been identified.

Another challenge in studying the neuropsychology of ECT-PKU is to examine status in relation to metabolic control. Phenylalanine concentrations have strong effects on cognitive performance. Notwithstanding the positive effects of decreasing blood phenylalanine levels, the paucity of studies makes it difficult to reach an international consensus about the phenylalanine-level upper target for optimal development. European guidelines set a phenylalanine blood concentration of 360 µmol/L as the upper target for the first 12 years of life and 600 µmol/L for older children (van Spronsen et al., 2017). American guidelines advise 360 µmol/L throughout life (Camp et al., 2014; Vockley et al., 2014). Thus, it might be important to study

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press

neuropsychological outcomes of patients with different age and different upper of phenylalanine levels (e.g., ≤240, 240–360, and ≥360 µmol/L). In particular, data about adolescents and adults are scarce. Further data collection within long-term international collaborative studies is needed.

CONCLUSION

Similar to other reviews on the neuropsychological profile of individuals with ECT-PKU, this review suggested a potentially specific and central executive impairment in children with ECT-PKU. However, data are limited or inconsistent with regard to the nature and the severity of the impairments, their persistence over time, their impact on everyday life, and their pathogenesis. Neuropsychological status and outcome remain critically important in determining the threshold phenylalanine level and in medical decision-making for PKU patients. In this context, this review highlights a number of future clinical and research directions. It would be important to use an integrative developmental approach to neuropsychological research with this population. Considering EFs, we recommend a conceptual and longitudinal approach, in particular to incorporate processing speed into the study of EF status and developmental trajectories. Secondly, future investigations of ECT-PKU could focus the complex interrelationships between neuropsychological domains, academic skills, and ADHD symptoms. Finally, as phenylalanine concentrations have strong effects on neuropsychological performances, systematic and additional studies are needed to determine how new treatments that address metabolic control affect neuropsychological outcome and the quality of life of children with ECT-PKU.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617719000146

ACKNOWLEDGEMENTS

The authors have no financial interest or conflict of interest to declare.

REFERENCES

Acosta, P.B. & Matalon, K.M. (2010). *Nutrition Management of Patients with Inherited Metabolic Disorders*. Boston, MA: Jones and Bartlett Publishers (pp. 119–174).

Anastasoaie, V., Kurzius, L., Forbes, P., & Waisbren, S. (2008). Stability of blood phenylalanine levels and IQ in children with phenylketonuria. *Molecular Genetics and Metabolism*, *95*(1), 17–20.

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology*, *8*(2), 71–82.

Anderson, P. & Leuzzi, V. (2010). White matter pathology in phenylketonuria. *Molecular Genetics and Metabolism*, *99*, 3–9.

Anderson, P., Wood, S.J., Francis, D.E., Coleman, L., Anderson, V., & Boneh, A. (2007). Are neuropsychological impairments in children with early-treated phenylketonuria (PKU) related to white matter abnormalities or elevated phenylalanine levels? *Developmental Neuropsychology*, *32*(2), 645–668.

Anderson, P., Wood, S.J., Francis, D.E., Coleman, L., Warwick, L., Casanelia, S., Anderson, V., & Boneh, A. (2004). Neuropsychological functioning in children with early-treated phenylketonuria: impact of white matter abnormalities. *Developmental Medicine and Child Neurology*, *46*(4), 230–238.

Anderson, V., Anderson, P., Northam, E., Jacobs, R., & Mikiewicz, O. (2002). Relationships between cognitive and behavioral measures of executive function in children with brain disease. *Child Neuropsychology*, *8*(4), 231–240.

Antshel, K.M. & Waisbren, S.E. (2003a). Timing is everything: executive functions in children exposed to elevated levels of phenylalanine. *Neuropsychology*, *17*(3), 458–468.

Antshel, K.M. & Waisbren, S.E. (2003b). Developmental timing of exposure to elevated levels of phenylalanine is associated with ADHD symptom expression. *Journal of Abnormal Child Psychology*, *31*(6), 565–574.

Araujo, G.C., Christ, S.E., Grange, D.K., Steiner, R.D., Coleman, C., Timmerman, E., & White, D.A. (2013). Executive response monitoring and inhibitory control in children with phenylketonuria: effects of expectancy. *Developmental Neuropsychology*, *38*(3), 139–152.

Araujo, G.C., Christ, S.E., Steiner, R.D., Grange, D.K., Nardos, B., McKinstry, R.C., & White, D.A. (2009). Response monitoring in children with phenylketonuria. *Neuropsychology*, *23*(1), 130–134.

Arnold, G.L., Kramer, B.M., Kirby, R.S., Plumeau, P.B., Blakely, E.M., Cregan, L.S., & Davidson, P.W. (1998). Factors affecting cognitive, motor, behavioral and executive functioning in children with phenylketonuria. *Acta Paediatrica*, *87*(5), 565–570.

Arnold, G.L., Vladutiu, C.J., Orlowski, C.C., Blakely, E.M., & DeLuca, J. (2004). Prevalence of stimulant use for attentional dysfunction in children with phenylketonuria. *Journal of Inherited Metabolic Disease*, *27*(2), 137–143.

Artuch, R., Colomé, C., Sierra, C., Brandi, N., Lambruschini, N., Campistol, J., Ugarte, D., & Vilaseca, M.A. (2004). A longitudinal study of antioxidant status in phenylketonuric patients. *Clinical Biochemistry*, *37*(3), 198–203.

Banerjee, P., Grange, D.K., Steiner, R.D., & White, D.A. (2011). Executive strategic processing during verbal fluency performance in children with phenylketonuria. *Child Neuropsychology*, *17*(2), 105–117.

Barkley, R.A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*(1), 65–94.

Berry, H.K., Brunner, R.L., Hunt, M.M., & White, P.P. (1990). Valine, isoleucine, and leucine: a new treatment for phenylketonuria. *American Journal of Diseases of Children*, *144*(5), 539–543.

Blau, N., van Spronsen, F.J., & Levy, H.L. (2010). Phenylketonuria. *The Lancet*, *376*(9750), 1417–1427.

Brumm, V.L. & Grant, M.L. (2010). The role of intelligence in phenylketonuria: a review of research and management. *Molecular Genetics and Metabolism*, *99*, 18–21.

Bull, R., Espy, K.A., & Wiebe, S.A. (2008). Short-term memory, working memory, and executive functioning in preschoolers: longitudinal predictors of mathematical achievement at age 7 years. *Developmental Neuropsychology*, *33*(3), 205–228.

Burgard, P., Rey, F., Rupp, A., Abadie, V., & Rey, J. (1997). Neuropsychologic functions of early treated patients with phenylketonuria, on and off diet: results of a cross-national and cross-sectional study. *Pediatric Research*, *41*(3), 368–374.

Burgard, P., Schmidt, E., Rupp, A., Schneider, W., & Bremer, H.J. (1996). Intellectual development of the patients of the German Collaborative Study of children treated for phenylketonuria. *European Journal of Pediatrics*, *155*(1), 33–38.

Burton, B.K., Bausell, H., Katz, R., LaDuca, H., & Sullivan, C. (2010). Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU). *Molecular Genetics and Metabolism*, *101*(2), 110–114.

Burton, B.K., Grange, D.K., Milanowski, A., Vockley, G., Feillet, F., Crombez, E.A., Abadie, V., Cederbaum, S., Dobbelaere, D., Smith, A., & Dorenbaum, A. (2007). The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study. *Journal of Inherited Metabolic Disease*, *30*(5), 700–707.

Burton, B., Grant, M., Feigenbaum, A., Singh, R., Hendren, R., Siriwardena, K., Phillips, J., Sanchez-Valle, A., Waisbren, S., Gillis, J., Prasad, S., Merilainen, M., Lang, W., Zhang, W., Yu, S., & Stahl, S. (2015). A randomized placebo-controlled, double-blind study of sapropterin to treat ADHD symptoms and executive function impairment in children and adults with sapropterin-responsive phenylketonuria. *Molecular Genetics and Metabolism*, *114*(3), 415–424.

Camp, K.M., Parisi, M.A., Acosta, P.B., Berry, G.T., Bilder, D.A., Blau, N., Bodamer, O.A., Brosco, J.P., Brown, C.S., Burlina, A.B., Burton, B.K., Chang, C.S., Coates, P.M., Cunningham, A.C., Dobrowolski, S.F., Ferguson, J.H., Franklin, T.D., Frazier, M., Grange, D.K., Greene, C.L., Groft, S.C., Harding, C.O., Howell, R.R., Huntington, K.L., Hyatt-Knorr, H.D., Jevaji, I.P., Levy, H.L., Lichter-Konecki, U., Lindegren, L.M., Lloyd-Puryear, M.A., Matalon, K., MacDonald, A., McPheeters, M.L., Mitchell, J.J., Mofidi, C., Moseley, K.D., Mueller, C.M., Mulberg, A.E., Nerurkar, L.S., Ogata, B.M., Pariser, A.R., Prasad, S., Pridjiann, G., Rasmussen, S.A., Reddy, U.M., Rohr, F.J., Singh, R.H., Sirrs, S.M., Stremer, S.E., Tagle, D.A., Thompson, S.M., Urv, T.K., Utz, J.R., van Spronsen, F., Vockley, J., Waisbren, S.E., Weglicki, L.S., White, D.A., Whitley, C.B., Wilfond, B.S., Yannicelli, S., & Young, J.M. (2014). Phenylketonuria Scientific Review Conference: state of the science and future research needs. *Molecular Genetics and Metabolism*, *112*(2), 87–122.

Cappelletti, S., Cotugno, G., Goffredo, B.M., Nicolò, R., Bernabei, S.M., Caviglia, S., & Di Ciommo, V. (2013). Cognitive findings and behavior in children and adolescents with phenylketonuria. *Journal of Developmental & Behavioral Pediatrics*, *34*(6), 392–398.

Chang, P.N., Gray, R.M., & O'Brien, L.L. (2000). Patterns of academic achievement among patients treated early with phenylketonuria. *European Journal of Pediatrics*, *159*(14), 96–99.

Chevignard, M.P., Soo, C., Galvin, J., Catroppa, C., & Eren, S. (2012). Ecological assessment of cognitive functions in children with acquired brain injury: a systematic review. *Brain Injury*, *26*(9), 1033–1057.

Christ, S.E., Huijbregts, S.C., De Sonneville, L.M., & White, D.A. (2010a). Executive function in early-treated phenylketonuria: profile and underlying mechanisms. *Molecular Genetics and Metabolism*, *99*, 22–32.

Christ, S.E., Moffitt, A.J., & Peck, D. (2010b). Disruption of prefrontal function and connectivity in individuals with phenylketonuria. *Molecular Genetics and Metabolism*, *99*, 33–40.

Christ, S.E., Moffitt, A.J., Peck, D., & White, D.A. (2013). The effects of tetrahydrobiopterin (BH4) treatment on brain function in individuals with phenylketonuria. *NeuroImage: Clinical*, *3*, 539–547.

Christ, S.E., Steiner, R.D., Grange, D.K., Abrams, R.A., & White, D.A. (2006). Inhibitory control in children with phenylketonuria. *Developmental Neuropsychology*, *30*(3), 845–864.

Colomé, C., Artuch, R., Vilaseca, M.A., Sierra, C., Brandi, N., Lambruschini, N., Cambra, F.J., & Campistol, J. (2003). Lipophilic antioxidants in patients with phenylketonuria. *The American Journal of Clinical Nutrition*, *77*(1), 185–188.

Da Silva, G.K. & Lamônica, D.A. (2010). Performance of children with phenylketonuria in the Developmental Screening Test-Denver II. *Prò-fono*, *22*(3), 345–351.

de Groot, M.J., Hoeksma, M., Reijngoud, D.J., de Valk, H.W., Paans, A.M., Sauer, P.J., & van Spronsen, F.J. (2013). Phenylketonuria: reduced tyrosine brain influx relates to reduced cerebral protein synthesis. *Orphanet Journal of Rare Diseases*, *8*(1), 133–141.

Dennis, M. (2006). Prefrontal cortex: typical and atypical development, In J. Risberg &J. Grafman (Eds.), *The frontal lobes: development, function and pathology* (pp. 128–162). New York: Cambridge University Press.

Dennis, M., Francis, D.J., Cirino, P.T., Schachar, R., Barnes, M.A., & Fletcher, J.M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychological Society*, *15*(3), 331–343.

DeRoche, K. & Welsh, M. (2008). Twenty-five years of research on neurocognitive outcomes in early-treated phenylketonuria: intelligence and executive function. *Developmental Neuropsychology*, *33*(4), 474–504.

De Sonneville, L.M., Schmidt, E., Michel, U., & Batzler, U. (1990). Preliminary neuropsychological test results. *European Journal of Pediatrics*, *149*(1), 39–44.

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135–168.

Diamond, A. & Herzberg, C. (1996). Impaired sensitivity to visual contrast in children treated early and continuously for phenylketonuria. *Brain*, *119*(2), 523–538.

Diamond, A., Prevor, M.B., Callender, G., & Druin, D.P. (1997). Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. *Monographs of the Society for Research in Child Development*, *62*(4), 1–206.

dos Santos, L.L., de Castro Magalhães, M., Januário, J.N., de Aguiar, M.J.B., & Carvalho, M.R.S. (2006). The time has come: a new scene for PKU treatment. *Genetics and Molecular Research*, *5*(1), 33–44.

Dyer, C.A. (1999). Pathophysiology of phenylketonuria. *Developmental Disabilities Research Reviews*, *5*(2), 104–112.

Erlandsen, H. & Stevens, R.C. (2001). A structural hypothesis for BH4 responsiveness in patients with mild forms of hyperphenylalaninaemia and phenylketonuria. *Journal of Inherited Metabolic Disease*, *24*(2), 213–230.

Feldmann, R., Denecke, J., Grenzebach, M., & Weglage, J. (2005). Frontal lobe-dependent functions in treated phenylketonuria: blood phenylalanine concentrations and long-term deficits in adolescents young adults. *Journal of Inherited Metabolic Disease*, *28*(4), 445–455.

Feldmann, R., Denecke, J., Pietsch, M., Grenzebach, M., & Weglage, J. (2002). Phenylketonuria: no specific frontal

lobe-dependent neuropsychological deficits of early-treated patients in comparison with diabetics. *Pediatric Research*, *51*(6), 761–765.

Fiege, B. & Blau, N. (2007). Assessment of tetrahydrobiopterin (BH4) responsiveness in phenylketonuria. *The Journal of Pediatrics*, *150*(6), 627–630.

Fonnesbeck, C.J., McPheeters, M.L., Krishnaswami, S., Lindegren, M.L., & Reimschisel, T. (2013). Estimating the probability of IQ impairment from blood phenylalanine for phenylketonuria patients: a hierarchical meta-analysis. *Journal of Inherited Metabolic Disease*, *36*(5), 757–766.

Gassió, R., Artuch, R., Vilaseca, M.A., Fusté, E., Boix, C., Sans, A., & Campistol, J. (2005). Cognitive functions in classic phenylketonuria and mild hyperphenyl-alaninaemia: experience in a paediatric population. *Developmental Medicine and Child Neurology*, *47*(7), 443–448.

Gassió, R., Artuch, R., Vilaseca, M.A., Fusté, E., Colome, R., & Campistol, J. (2008). Cognitive functions and the antioxidant system in phenylketonuric patients. *Neuropsychology*, *22*(4), 426–431.

Gassió, R., Vilaseca, M.A., Lambruschini, N., Boix, C., Fusté, M.E., & Campistol, J. (2010). Cognitive functions in patients with phenylketonuria in long-term treatment with tetrahydrobiopterin. *Molecular Genetics and Metabolism*, *99*, 75–78.

Gioia, G.A., Kenworthy, L., & Isquith, P.K. (2010). Executive function in the real world: BRIEF lessons from Mark Ylvisaker. *The Journal of Head Trauma Rehabilitation*, *25*(6), 433–439.

Griffiths, P., Campbell, R., & Robinson, P. (1998). Executive function in treated phenylketonuria as measured by the one-back and two-back versions of the continuous performance test. *Journal of Inherited Metabolic Disease*, *21*(2), 125–135.

Griffiths, P., Demellweek, C., Fay, N., Robinson, P., & Davidson, D.C. (2000). Wechsler subscale IQ and subtest profile in early treated phenylketonuria. *Archives of Disease in Childhood*, *82*(3), 209–215.

Griffiths, P., Robinson, P., Davies, R., Hayward, K., Lewis, K., Livingstone, K., & Plews, S. (2005). Speed of decision-making and set-switching: subtle executive deficits in children with treated phenylketonuria. *Educational and Child Psychology*, *22*(2), 81–89.

Griffiths, P., Tarrini, M., & Robinson, P. (1997). Executive function and psychosocial adjustment in children with early treated phenylketonuria: correlation with historical and concurrent phenylalanine levels. *Journal of Intellectual Disability Research*, *41*(4), 317–323.

Griffiths, P., Ward, N., Harvie, A., & Cockburn, F. (1998). Neuropsychological outcome of experimental manipulation of phenylalanine intake in treated phenylketonuria. *Journal of Inherited Metabolic Disease*, *21*(1), 29–38.

Heintz, C., Cotton, R.G., & Blau, N. (2013). Tetrahydrobiopterin, its mode of action on phenylalanine hydroxylase, and importance of genotypes for pharmacological therapy of phenylketonuria. *Human Mutation*, *34*(7), 927–936.

Holtzman, N.A., Kronmal, R.A., Doorninck, W.V., Azen, C., Koch, R., & Writing Committee for the Collaborative Study of Children Treated for Phenylketonuria. (1986). Effect of age at loss of dietary control on intellectual performance and behavior of children with phenylketonuria. *New England Journal of Medicine*, *314*(10), 593–598.

Hood, A., Grange, D.K., Christ, S.E., Steiner, R., & White, D.A. (2014). Variability in phenylalanine control predicts IQ and executive abilities in children with phenylketonuria. *Molecular Genetics and Metabolism*, *111*(4), 445–451.

Huijbregts, S.C., De Sonneville, L.M., Licht, R., Sergeant, J., & van Spronsen, F.J. (2002a). Inhibition of prepotent responding and attentional flexibility in treated phenylketonuria. *Developmental Neuropsychology*, *22*(2), 481–499.

Huijbregts, S.C., De Sonneville, L.M., Licht, R., van Spronsen, F.J., & Sergeant, J.A. (2002b). Short-term dietary interventions in children and adolescents with treated phenylketonuria: effects on neuropsychological outcome of a well-controlled population. *Journal of Inherited Metabolic Disease*, *25*(6), 419–430.

Huijbregts, S.C., De Sonneville, L.M., Licht, R., van Spronsen, F.J., Verkerk, P.H., & Sergeant, J.A. (2002c). Sustained attention and inhibition of cognitive interference in treated phenylketonuria: associations with concurrent and lifetime phenylalanine concentrations. *Neuropsychologia*, *40*(1), 7–15.

Huijbregts, S.C., De Sonneville, L.M., van Spronsen, F.J., Berends, I.E., Licht, R., Verkerk, P.H., & Sergeant, J.A. (2003). Motor function under lower and higher controlled processing demands in early and continuously treated phenylketonuria. *Neuropsychology*, *17*(3), 369–379.

Huijbregts, S.C., De Sonneville, L.M., van Spronsen, F.J., Licht, R., & Sergeant, J.A. (2002d). The neuropsychological profile of early and continuously treated phenylketonuria: orienting, vigilance, and maintenance versus manipulation-functions of working memory. *Neuroscience & Biobehavioral Reviews*, *26*(6), 697–712.

Huijbregts, S.C., Gassió, R., & Campistol, J. (2013). Executive functioning in context: relevance for treatment and monitoring of phenylketonuria. *Molecular Genetics and Metabolism*, *110*, 25–30.

Jahja, R., Huijbregts, S.C., De Sonneville, L.M., van Der Meere, J.J., & van Spronsen, F.J. (2014). Neurocognitive evidence for revision of treatment targets and guidelines for phenylketonuria. *The Journal of Pediatrics*, *164*(4), 895–899.

Jahja, R., van Spronsen, F.J., De Sonneville, L.M., van der Meere, J.J., Bosch, A.M., Hollak, C.E., Rubio-Gozalbo, M.E., Brouwers, M.C., Hofstede, F.C., de Vries, M.C., Janssen, M.C., van der Ploeg, A.T., Langendonk, J.G., & Huijbregts, S.C. (2016). Social-cognitive functioning and social skills in patients with early treated phenylketonuria: a PKU-COBESO study. *Journal of Inherited Metabolic Disease*, *39*(3), 355–362.

Janos, A.L., Grange, D.K., Steiner, R.D., & White, D.A. (2012). Processing speed and executive abilities in children with phenylketonuria. *Neuropsychology*, *26*(6), 735–743.

Janzen, D. & Nguyen, M. (2010). Beyond executive function: non-executive cognitive abilities in individuals with PKU. *Molecular Genetics and Metabolism*, *99*, 47–51.

Jurado, M.B. & Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychology Review*, *17*(3), 213–233.

Karačić, I., Meili, D., Sarnavka, V., Heintz, C., Thöny, B., Ramadža, D.P., Fumić, K., Mardeşić, D., Barić, I., & Blau, N. (2009). Genotype-predicted tetrahydrobiopterin (BH4)-responsiveness and molecular genetics in Croatian patients with phenylalanine hydroxylase (PAH) deficiency. *Molecular Genetics and Metabolism*, *97*(3), 165–171.

Koch, R., Azen, C., Friedman, E.G., & Williamson, M.L. (1984). Paired comparisons between early treated PKU children and their matched sibling controls on intelligence and school achievement test results at eight years of age. *Journal of Inherited Metabolic Disease*, *7*(2), 86–90.

Koch, R., Burton, B., Hoganson, G., Peterson, R., Rhead, W., Rouse, B., Scott, R., Wolff, J., Stern, A.M., Guttler, F.,

Nelson, M., de la Cruz, F., Coldwell, J., Erbe, R., Geraghty, M.T., Shear, C., Thomas, J., & Azen, C (2002). Phenylketonuria in adulthood: a collaborative study. *Journal of Inherited Metabolic Disease*, *25*(5), 333–346.

Lehto, J.E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: evidence from children. *British Journal of Developmental Psychology*, *21*(1), 59–80.

Leuret, O., Barth, M., Kuster, A., Eyer, D., De Parscau, L., Odent, S., Gilbert-Dussardier, B., Feillet, F., & Labarthe, F. (2012). Efficacy and safety of BH4 before the age of 4 years in patients with mild phenylketonuria. *Journal of Inherited Metabolic Disease*, *35*(6), 975–981.

Leuzzi, V., Mannarelli, D., Manti, F., Pauletti, C., Locuratolo, N., Carducci, C., Carducci, C., Vanacore, N., & Fattapposta, F. (2014a). Age-related psychophysiological vulnerability to phenylalanine in phenylketonuria. *Frontiers in pediatrics*, *57*(2), 1–11.

Leuzzi, V., Pansini, M., Sechi, E., Chiarotti, F., Carducci, C., Levi, G., & Antonozzi, I. (2004b). Executive function impairment in early-treated PKU subjects with normal mental development. *Journal of Inherited Metabolic Disease*, *27*(2), 115–125.

Levin, H.S., Culhane, K.A., Hartmann, J., Evankovich, K., Mattson, A.J., Harward, H., Ringholz, G., Ewing-Cobbs, L., & Fletcher, J.M. (1991). Developmental changes in performance on tests of purported frontal lobe functioning. *Developmental Neuropsychology*, *7*(3), 377–395.

Levy, H.L., Milanowski, A., Chakrapani, A., Cleary, M., Lee, P., Trefz, F.K., Whitley, C.B., Feillet, F., Feigenbaum, A.S., Bebchuk, J.D., Christ-Schmidt, H., & Dorenbaum, A. (2007). Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. *The Lancet*, *370*(9586), 504–510.

Lombeck, I., Jochum, F., & Terwolbeck, K. (1996). Selenium status in infants and children with phenylketonuria and in maternal phenylketonuria. *European Journal of Pediatrics*, *155*, 140–144.

Longo, N., Siriwardena, K., Feigenbaum, A., Dimmock, D., Burton, B.K., Stockler, S., Waisbren, S., Lang, W., Jurecki E., Zhang, C., & Prasad, S. (2015). Long-term developmental progression in infants and young children taking sapropterin for phenylketonuria: a two-year analysis of safety and efficacy. *Genetics in Medicine*, *17*(5), 365–373.

Luciana, M., Sullivan, J., & Nelson, C.A. (2001). Associations between phenylalanine-to-tyrosine ratios and performance on tests of neuropsychological function in adolescents treated early and continuously for phenylketonuria. *Child Development*, *72*(6), 1637–1652.

MacDonald, A. (2000). Diet and compliance in phenylketonuria. *European Journal of Pediatrics*, *159*(14), 136–141.

Manti, F., Nardecchia, F., Paci, S., Chiarotti, F., Carducci, C., Carducci, C., Dalmazzone, S., Cefalo, G., Salvatici, E., Banderali, G., & Leuzzi, V. (2017). Predictability and inconsistencies in the cognitive outcome of early treated PKU patients. *Journal of inherited metabolic disease*, *40*(6), 793–799.

Matalon, R., Michals-Matalon, K., Bhatia, G., Burlina, A.B., Burlina, A.P., Braga, C., Fiori, L., Giovannini, M., Grechanina, E., Novikov, P., Grady, J., Tyring, S.K., & Guttler, F. (2007). Double blind placebo control trial of large neutral amino acids in treatment of PKU: effect on blood phenylalanine. *Journal of Inherited Metabolic Disease*, *30*(2), 153–158.

Matalon, R., Michals-Matalon, K., Bhatia, G., Grechanina, E., Novikov, P., McDonald, J.D., Grady, J., Tyring, S.K., & Guttler, F. (2006). Large neutral amino acids in the treatment of phenylketonuria (PKU). *Journal of Inherited Metabolic Disease*, *29*(6), 732–738.

Mazzocco, M.M., Nord, A.M., van Doorninck, W., Greene, C.L., Kovar, C.G., & Pennington, B.F. (1994). Cognitive development among children with early-treated phenylketonuria. *Developmental Neuropsychology*, *10*(2), 133–151.

McCandless, S. & O'Laughlin, L. (2007). The clinical utility of the Behavior Rating Inventory of Executive Function (BRIEF) in the diagnosis of ADHD. *Journal of Attention Disorders*, *10*(4), 381–389.

Michel, U., Schmidt, E., & Batzler, U. (1990). Results of psychological testing of patients aged 3–6 years. *European Journal of Pediatrics*, *149*, 34–38.

Mitchell, J.J., Trakadis, Y.J., & Scriver, C.R. (2011). Phenylalanine hydroxylase deficiency. *Genetics in Medicine*, *13*(8), 697–707.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., & PRISMA-P Group. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*(1), 1. doi: 10.1186/2046-4053-4-1

Moyle, J.J., Fox, A.M., Arthur, M., Bynevelt, M., & Burnett, J.R. (2007). Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. *Neuropsychology Review*, *17*(2), 91–101.

Nardecchia, F., Manti, F., Chiarotti, F., Carducci, C., Carducci, C., & Leuzzi, V. (2015). Neurocognitive and neuroimaging outcome of early treated young adult PKU patients: a longitudinal study. *Molecular Genetics and Metabolism*, *115*(2), 84–90.

Ozanne, A.E., Krimmer, H., & Murdoch, B.E. (1990). Speech and language skills in children with early treated phenylketonuria. *American Journal on Mental Retardation*, *94*(6), 625–632.

Pardridge, W.M. (1998). Blood-brain barrier carrier-mediated transport and brain metabolism of amino acids. *Neurochemical Research*, *23*(5), 635–644.

Pietz, J., Kreis, R., Rupp, A., Mayatepek, E., Rating, D., Boesch, C., & Bremer, H.J. (1999). Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. *Journal of Clinical Investigation*, *103*(8), 1169–1178.

Przyrembel, H. & Bremer, H.J. (2000). Nutrition, physical growth, and bone density in treated phenylketonuria. *European Journal of Pediatrics*, *159*(14), 129–135.

Roy, A., Le Gall, D., Roulin, J.L., & Fournet, N. (2012). Les fonctions exécutives chez l'enfant: approche épistémologique et sémiologie clinique. *Revue de Neuropsychologie*, *4*(4), 287–297.

Roy, A., Roulin, J.L., Charbonnier, V., Allain, P., Fasotti, L., Barbarot, S., Stadler, J.F., Terrien, A., & Le Gall, D. (2010). Executive dysfunction in children with neurofibromatosis type 1: a study of action planning. *Journal of the International Neuropsychological Society*, *16*(6), 1056–1063.

Schindeler, S., Ghosh-Jerath, S., Thompson, S., Rocca, A., Joy, P., Kemp, A., Rae, C., Green, K., Wilcken, B., & Christodoulou, J. (2007). The effects of large neutral amino acid supplements in PKU: an MRS and neuropsychological study. *Molecular Genetics and Metabolism*, *91*(1), 48–54.

Scriver, C.R. & Kaufman, S. (2001). Hyperphenylalaninemia: phenylalanine hydroxylase deficiency, In C.R. Scriver, A.L. Baudet, W.S. Sly, &D. Valle (Eds.), *The metabolic and molecular bases of inherited disease* (pp. 1667–1724). New York: McGraw Hill.

Sharman, R., Sullivan, K., Young, R., & McGill, J. (2009a). Biochemical markers associated with executive function in adolescents with early and continuously treated phenylketonuria. *Clinical Genetics*, *75*(2), 169–174.

Sharman, R., Sullivan, K., Young, R., & McGill, J. (2009b). A preliminary investigation of the role of the phenylalynine: tyrosine ratio in children with early and continuously treated phenylketonuria: toward identification of "safe" levels. *Developmental Neuropsychology*, *35*(1), 57–65.

Sharman, R., Sullivan, K., Young, R., & McGill, J. (2015). Executive function in adolescents with PKU and their siblings: associations with biochemistry. *Molecular Genetics and Metabolism Reports*, *4*, 87–88.

Smith, M.L., Saltzman, J., Klim, P., Hanley, W.B., Feigenbaum, A., & Clarke, J.T. (2000). Neuropsychological function in mild hyperphenylalaninemia. *American Journal on Mental Retardation*, *105*(2), 69–80.

Smith, Q.R. (2000). Transport of glutamate and other amino acids at the blood-brain barrier. *The Journal of Nutrition*, *130*(4), 1016–1022.

Soleymani, Z., Keramati, N., Rohani, F., & Jalaei, S. (2015). Factors influencing verbal intelligence and spoken language in children with phenylketonuria. *Indian Pediatrics*, *52*(5), 397–401.

Sonuga-Barke, E.J., Sergeant, J.A., Nigg, J., & Willcutt, E. (2008). Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: nosologic and diagnostic implications. *Child and Adolescent Psychiatric Clinics of North America*, *17*(2), 367–384.

Stemerdink, B.A., Kalverboer, A.F., van der Meere, J.J., van der Molen, M.W., Huisman, J., de Jong, L.W.A., Slijper, F.M.E., Verkerk, P.H., & van Spronsen, F.J. (2000). Behaviour and school achievement in patients with early and continuously treated phenylketonuria. *Journal of Inherited Metabolic Disease*, *23*(6), 548–562.

Stemerdink, B.A., van der Meere, J.J., van der Molen, M.W., Kalverboer, A.F., Hendrikx, M.M.T., Huisman, J., van der Schot, L.W.A., Slijper, F.M.E., van Spronsen, F.J., & Verkerk, P.H. (1995). Information processing in patients with early and continuously-treated phenylketonuria. *European Journal of Pediatrics*, *154*(9), 739–746.

Stemerdink, B.A., van der Molen, M.W., Kalverboer, A.F., van der Meere, J.J., Huisman, J., de Jong, L.W., Slijper, F.M.E., Verkerk, P.H., & van Spronsen, F.J. (1999). Prefrontal dysfunction in early and continuously treated phenylketonuria. *Developmental Neuropsychology*, *16*(1), 29–57.

Stevenson, M. & McNaughton, N. (2013). A comparison of phenylketonuria with attention deficit hyperactivity disorder: Do markedly different aetiologies deliver common phenotypes?. *Brain Research Bulletin*, *99*, 63–83.

Surtees, R. & Blau, N. (2000). The neurochemistry of phenylketonuria. *European Journal of Pediatrics*, *159*(14), 109–113.

Toplak, M.E., Bucciarelli, S.M., Jain, U., & Tannock, R. (2008). Executive functions: performance-based measures and the behavior rating inventory of executive function (BRIEF) in adolescents with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology*, *15*(1), 53–72.

van Bakel, M.M., Printzen, G., Wermuth, B., & Wiesmann, U.N. (2000). Antioxidant and thyroid hormone status in selenium-deficient phenylketonuric and hyperphenylalaninemic patients. *The American Journal of Clinical Nutrition*, *72*(4), 976–981.

van Spronsen, F.J., Huijbregts, S.C., Bosch, A.M., & Leuzzi, V. (2011). Cognitive, neurophysiological, neurological and psychosocial outcomes in early-treated PKU-patients: a start toward standardized outcome measurement across development. *Molecular Genetics and Metabolism*, *104*, 45–51.

van Spronsen, F.J., van Wegberg, A.M., Ahring, K., Bélanger-Quintana, A., Blau, N., Bosch, A.M., Burlina, A., Campistol, J., Feillet, F., Giżewska, M., Huijbregts, S.C., Kearney, S., Leuzzi, V., Maillot, F., Muntau, A.C., Trefz, F.K., van Rijn, M., Walter, J.H., & MacDonald, A. (2017). Key European guidelines for the diagnosis and management of patients with phenylketonuria. *The Lancet Diabetes & Endocrinology*, *5*(9), 743–756.

VanZutphen, K.H., Packman, W., Sporri, L., Needham, M.C., Morgan, C., Weisiger, K., & Packman, S. (2007). Executive functioning in children and adolescents with phenylketonuria. *Clinical Genetics*, *72*(1), 13–18.

Viau, K.S., Wengreen, H.J., Ernst, S.L., Cantor, N.L., Furtado, L.V., & Longo, N. (2011). Correlation of age-specific phenylalanine levels with intellectual outcome in patients with phenylketonuria. *Journal of Inherited Metabolic Disease*, *34*(4), 963–971.

Vilaseca, M.A., Lambruschini, N., Gómez-López, L., Gutiérrez, A., Fusté, E., Gassió, R., Artuch, R., & Campistol, J. (2010). Quality of dietary control in phenylketonuric patients and its relationship with general intelligence. *Nutricion Hospitalaria*, *25*(1), 60–66.

Vockley, J., Andersson, H.C., Antshel, K.M., Braverman, N.E., Burton, B.K., Frazier, D.M., Mitchell, J., Smith, W.E., Thompson, B.H., & Berry, S.A. (2014). Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, *16*(2), 188–200.

Waisbren, S.E., Noel, K., Fahrbach, K., Cella, C., Frame, D., Dorenbaum, A., & Levy, H. (2007). Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Molecular Genetics and Metabolism*, *92*(1), 63–70.

Weglage, J., Grenzebach, M., Pietsch, M., Feldmann, R., Linnenbank, R., Denecke, J., & Koch, H.G. (2000). Behavioural and emotional problems in early-treated adolescents with phenylketonuria in comparison with diabetic patients and healthy controls. *Journal of Inherited Metabolic Disease*, *23*(5), 487–496.

Weglage, J., Pietsch, M., Denecke, J., Sprinz, A., Feldman, R., Grenzebach, M., & Ullrich, K. (1999). Regression of neuropsychological deficits in early-treated phenylketonurics during adolescence. *Journal of Inherited Metabolic Disease*, *22*(6), 693–705.

Weglage, J., Pietsch, M., Fünders, B., Koch, H.G., & Ullrich, K. (1996). Deficits in selective and sustained attention processes in early treated children with phenylketonuria—result of impaired frontal lobe functions?. *European Journal of Pediatrics*, *155*(3), 200–204.

Welsh, M.C., Pennington, B.F., Ozonoff, S., Rouse, B., & McCabe, E.R. (1990). Neuropsychology of early-treated phenylketonuria: specific executive function deficits. *Child Development*, *61*(6), 1697–1713.

White, D.A., Antenor-Dorsey, J.A.V., Grange, D.K., Hershey, T., Rutlin, J., Shimony, J.S., McKinstry, R.C., & Christ, S.E. (2013). White matter integrity and executive abilities following treatment with tetrahydrobiopterin (BH4) in individuals with phenylketonuria. *Molecular Genetics and Metabolism*, *110*(3), 213–217.

White, D.A., Nortz, M.J., Mandernach, T., Huntington, K., & Steiner, R.D. (2001). Deficits in memory strategy use related to prefrontal dysfunction during early development: evidence from children with phenylketonuria. *Neuropsychology*, *15*(2), 221–229.

White, D.A., Nortz, M.J., Mandernach, T., Huntington, K., & Steiner, R.D. (2002). Age-related working memory impairments in children with prefrontal dysfunction associated with phenylketonuria. *Journal of the International Neuropsychological Society*, *8*(1), 1–11.

Wiersema, J.R., van Der Meere, J.J., & Roeyers, H. (2005). State regulation and response inhibition in children with ADHD and children with early-and continuously treated phenylketonuria: an event-related potential comparison. *Journal of Inherited Metabolic Disease*, *28*(6), 831–843.

Williamson, M.L., Koch, R., Azen, C., & Chang, C. (1981). Correlates of intelligence test results in treated phenylketonuric children. *Pediatrics*, *68*(2), 161–167.

Zelazo, P.D. & Müller, U. (2002). Executive function in typical and atypical development, In U. Gaswami (Ed.), *Handbook of childhood cognitive development* (pp. 445–469). Oxford: Blackwell.

Zhang, Z.X., Ye, J., Qiu, W.J., Han, L.S., & Gu, X.F. (2005). Screening and diagnosis of tetrahydrobiopterin responsive phenylalanine hydroxylase deficiency with tetrahydrobiopterin loading test. *Zhonghua er ke za zhi*, *43*(5), 335–339.

https://doi.org/10.1017/S1355617719000146 Published online by Cambridge University Press