



## Relationship between age and white matter integrity in children with phenylketonuria



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### ARTICLE INFO

#### Article history:

Received 12 March 2016

Accepted 13 March 2016

Available online 8 April 2016

#### Keywords:

Phenylketonuria

Brain

White matter

Diffusion tensor imaging

Children

### ABSTRACT

Diffusion tensor imaging (DTI) has shown poorer microstructural white matter integrity in children with phenylketonuria (PKU), specifically decreases in mean diffusivity (MD), in comparison with healthy children. However, little research has been conducted to investigate the relationship between age and white matter integrity in this population. The present study examined group differences in the relationship between age and MD across a range of brain regions in 31 children with early- and continuously-treated PKU and 51 healthy control children. Relationships among MD, age, and group were explored using hierarchical linear regression and Pearson correlation. Results indicated a stronger age-related decrease in MD for children with PKU in comparison with healthy children in 4 of the 10 brain regions examined, suggesting that the trajectory of white matter development is abnormal in children with PKU. Further research using longitudinal methodology is needed to fully elucidate our understanding of white matter development in children with PKU.

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### 1. Introduction

Phenylketonuria (PKU<sup>1</sup>) is an autosomal recessive metabolic disorder characterized by a dysfunctional or absent enzyme, phenylalanine hydroxylase (PAH), which is responsible for the metabolism of the amino acid phenylalanine (Phe). With little to no functional PAH, Phe accumulates in the blood and brain of individuals with PKU [1]. Dietary restriction of foods high in Phe (i.e., high protein foods) such as beans, dairy products, and meats is necessary to maintain Phe levels within clinically recommended ranges. To maintain adequate protein requirements, the PKU diet is supplemented with drinkable Phe-free formulas.

If untreated, PKU typically has devastating consequences, including severe intellectual disability [2,3]. Widespread newborn screening programs implemented in the 1960s largely eradicated the incidence of untreated cases in developed nations. However, even when PKU is diagnosed early and treated continuously, affected individuals demonstrate poorer psychosocial functioning, academic achievement, and psychiatric outcomes compared with the general population

[4–6]. In addition, individuals with early- and continuously-treated PKU exhibit slightly lowered IQ [7] and subtle cognitive deficits, particularly in processing speed [8] and executive abilities such as working memory, inhibitory control, and strategic processing [9,10]. Recent work has demonstrated that both elevated Phe levels and greater variability in Phe levels are associated with poorer IQ and executive performance in the early- and continuously-treated PKU population [11].

In terms of brain mechanisms that may underlie PKU-related deficits, a deficiency in the neurotransmitter dopamine has long been hypothesized as a primary factor [1]. In healthy individuals, the action of PAH converts Phe to tyrosine, which is a precursor of dopamine and other catecholaminergic neurotransmitters. When this metabolic pathway is disrupted in individuals with PKU, lower levels of dopamine are observed [12]. Dopaminergic projections to the prefrontal cortex are crucial to a number of frontally-mediated, higher-order abilities, including working memory, inhibitory control, attention, and cognitive flexibility [13,14]. It is likely that the impact of reduced dopamine on this cognitive skill set contributes to the poorer functional outcomes observed in individuals with early- and continuously-treated PKU.

Of particular relevance to the current study, PKU research has increasingly investigated the white matter of the brain, which facilitates the efficient flow of neural signals among interconnected brain regions. Past studies using structural magnetic resonance imaging (MRI) have identified decreased white matter volume and hyperintensities in the white matter that primarily occur in periventricular brain regions

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<sup>1</sup> Abbreviations used: PKU, Phenylketonuria; PAH, phenylalanine hydroxylase; Phe, phenylalanine; MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; MD, mean diffusivity; ROI, region of interest; CC, corpus callosum

[15–19]. This structural imaging approach, however, is not ideal for studying individuals with early- and continuously-treated PKU, because gross white matter abnormalities are observed less frequently than in less rigorously treated individuals. In addition, the majority of structural MRI studies have used a qualitative approach to categorize rather than quantify white matter abnormalities.

In recent years, diffusion tensor imaging (DTI) has been used as a quantitative MRI approach to investigate white matter pathology in individuals with PKU [20–23]. DTI provides information regarding the microstructural integrity and organization of the white matter by measuring the movement, or diffusion, of water molecules [24,25]. Two DTI measures are frequently reported: fractional anisotropy (FA) which reflects the degree of asymmetry of water diffusion and mean diffusivity (MD) which reflects the overall spatial average rate of water diffusion.

In studies of individuals with PKU, normal FA but reduced MD has been reported consistently [20–22,25–29], suggesting restricted diffusion within axons. Reduced MD in individuals with early- and continuously-treated PKU has been associated with both higher blood Phe levels and increased variability in blood Phe levels [28]. With regard to cognition, reduced MD has also been associated with lower IQ and poorer performance on executive tasks [20].

From a developmental perspective, there is limited information regarding the relationship between age and MD in individuals with PKU. In healthy children, a sharp increase in MD is typically observed in the months after birth, followed by a decrease in MD until middle childhood, at which time a plateau is generally reached and maintained until the elderly stages of life [30–32]. With regard to PKU, one study showed an age-related decrease in MD in anterior regions of the corpus callosum in children with early- and continuously-treated PKU [22], but this is the only DTI study to date in which white matter integrity has been examined from a developmental perspective.

The present study was conducted to more thoroughly investigate the relationship between age and MD in children with early- and continuously-treated PKU across a range of brain regions. We hypothesized that increasing age would be more strongly associated with decreasing MD in children with PKU compared with healthy control children. To investigate this hypothesis, we examined MD in relation to age across 10 brain regions of interest (ROI) in school-aged children with early- and continuously-treated PKU and demographically matched healthy control children.

## 2. Materials and methods

### 2.1. Participants

Participants were children with PKU ( $n = 31$ ; 16 girls, 15 boys) and healthy control children ( $n = 51$ ; 26 girls, 25 boys) recruited from the St. Louis and Portland communities in conjunction with a longitudinal study funded by the National Institute of Child Health and Human Development (R01 HD0449901). Children with PKU were recruited through metabolic clinics at Washington University (WU) and Oregon Health & Science University (OHSU). All children with PKU were diagnosed soon after birth and received early and continuous treatment through dietary restriction of Phe intake. Average Phe levels over the year prior to evaluation were provided by referring metabolic clinics and ranged from 230 to 1574  $\mu\text{mol/L}$  ( $M = 530.2$ ,  $SD = 334.9$ ). Phe levels obtained closest to time of evaluation (i.e., within approximately one month) ranged from 121 to 1574  $\mu\text{mol/L}$  ( $M = 553.8$ ,  $SD = 348.5$ ). There was a significant positive correlation between Phe levels closest to time of evaluation and age, such that Phe levels increased as a function of increasing age ( $r = 0.60$ ,  $p < 0.01$ ).

The age of children in both groups ranged from 7 to 18 years (PKU:  $M = 12.2$ ,  $SD = 3.9$ ; Control:  $M = 12.0$ ,  $SD = 3.3$ ). Education ranged from 1 to 13 years for the PKU group ( $M = 6.4$ ,  $SD = 3.6$ ) and 1 to 14 years for the control group ( $M = 6.2$ ,  $SD = 3.4$ ). IQ ranged from 86

to 139 for the PKU group ( $M = 106.8$ ,  $SD = 11.3$ ) and 84 to 143 for the control group ( $M = 115.2$ ,  $SD = 14.8$ ). Chi square and *t*-test analyses revealed no significant between-group differences in gender, age, or education ( $p > 0.05$  in all instances), but IQ was significantly lower for the PKU than control group ( $p < 0.01$ ). No child had a history of intellectual disability, learning disorder, or major medical disorder unrelated to PKU.

### 2.2. Procedures

Approval to conduct the study was obtained from Human Research Protection Offices at WU and OHSU. Informed consent and assent were obtained from all guardians and participants before administration of any study procedures. A cognitive battery was administered as part of a larger study, but findings from only measures of relevance to the current study are reported here. Cognitive testing and neuroimaging procedures were administered during a single session lasting approximately 4 h. Findings from neuroimaging procedures have been previously reported [22], but not in relation to age across multiple ROIs.

### 2.3. Neuroimaging

Neuroimaging procedures are reported in greater detail elsewhere [22]. Briefly, structural images were acquired using a Siemens Sonata 1.5T system at WU and a Siemens TIM Trio 3.0T system at OHSU. Of the 31 children with PKU, 15 were imaged at WU and 16 at OHSU. Of the 51 control subjects, 48 were imaged at WU and 3 at OHSU. Although different proportions of children in the PKU and control groups were imaged at WU versus OHSU, the pattern of results did not change when imaging site was controlled in analyses. Similarly, the pattern of results did not change when gender was controlled in analyses. As such, the reported analyses include neither imaging site nor gender.

Scans included a T1-weighted (T1W) sagittal, magnetization-prepared rapid gradient echo (MPRAGE) and a T2-weighted (T2W) fast spin echo. DTI was acquired using an echo planar imaging sequence [2.5 mm (OHSU) and 3.0 mm (WU) isotropic voxels, diffusion sensitization of  $b$ -values = 0 and 1000  $\text{s/mm}^2$ ] along 25 non-collinear diffusion gradient orientations. Diffusion weighted images were registered first to the  $b = 0$  unsensitized image, then to the T2W, then to the best T1W (MPRAGE), and finally to a WU in-house atlas. T2W images were visually inspected to ensure that measurements were acquired from normal-appearing white matter without hyperintensities.

MD analyses were conducted across 10 ROIs, including: prefrontal cortex, centrum semiovale, posterior parietal-occipital cortex, optic radiation, putamen, thalamus, hippocampus, and the genu, body, and splenium of the corpus callosum (CC). These regions were selected based on a well-established DTI atlas [33] to provide a sampling of white matter tracts across the brain and were verified by a neuroradiologist. We chose to perform ROI analyses rather than undertake a voxel-wise approach to minimize type 1 error due to multiple comparisons and to avoid imperfect smoothing effects [34]. Furthermore, previous research has indicated no observable difference between the use of ROI versus voxel-based analyses when examining mean diffusivity in children [35].

The diffusion tensor and its three eigenvalues were calculated using log-linear regression in each voxel for each ROI. Using standard methods, MD was computed as the average of the three eigenvalues, and a parametric map was then generated for MD. ROIs were then applied to each participant's MD parametric map and sampled using Analyze version 8.0 (Mayo Clinic, Rochester). Values from left and right homologous regions were averaged.

### 2.4. Statistical analyses

Hierarchical linear regression analyses were performed to determine the proportion of variance in MD for each ROI that was

**Table 1**  
Mean (SD) for MD of ROIs.

ROI	MD	
	Control	PKU
Splenium of the CC	0.79 (0.04)	0.79 (0.07)
Genu of the CC	0.86 (0.06)	0.82 (0.08)
Body of the CC	0.96 (0.08)	0.93 (0.13)
Optic radiation	0.85 (0.04)	0.85 (0.06)
Centrum semiovale	0.77 (0.03)	0.75 (0.04)
Prefrontal	0.77 (0.03)	0.78 (0.04)
Post parietal–occipital	0.81 (0.04)	0.77 (0.05)
Hippocampus	0.91 (0.03)	0.93 (0.05)
Thalamus	0.81 (0.03)	0.82 (0.04)
Putamen	0.76 (0.02)	0.76 (0.03)

attributable to age, group, and the interaction between age and group. Age was entered in the first step, followed by group (PKU, control), followed by the age by group interaction. The interaction between age and group was of particular interest in terms evaluating whether the relationship between age and MD differed for PKU and control groups. Pearson correlations between age and MD for each group were then obtained to further explore significant age by group interactions revealed by linear regression. Because the sampling distribution of correlations was not normally distributed ( $\rho \neq 0$ ), Fisher  $R \rightarrow Z$  transformations were conducted for each correlation. A  $z$ -test of significance was used with the resulting statistics to determine whether the correlation between age and MD significantly differed between the PKU and control groups. Between-group differences were considered significant if  $p < 0.05$  (i.e.,  $z < -1.96$ ).

### 3. Results

The mean and standard deviation of MD for each ROI are listed in Table 1. Statistical findings from hierarchical linear regression analyses examining the relationships between MD in the 10 ROIs and age, group, and the interaction between age and group are reported in Table 2. Age accounted for a significant proportion of the variance in MD across all ROIs except the genu of the CC. After considering the variance attributable to age, group accounted for a significant proportion of the variance in MD for the genu of the CC, centrum semiovale, posterior parietal–occipital cortex, hippocampus, and thalamus. Of particular interest, the interaction between age and group accounted for a significant proportion of the variance in MD for the splenium and genu of the CC, the optic radiation, and the hippocampus, indicating a differential effect of age on MD for the PKU and control groups.

Correlation analyses were used to further explore the significant interactions between age and group. As shown in Table 3, for the control group there were no significant correlations between age and MD in any of the 4 ROIs examined, although for the PKU group all correlations between age and MD were significant with medium or large effect sizes.

**Table 2**  
Statistical findings from hierarchical linear regression analyses examining the variance in MD attributable to age, group, and the age  $\times$  group interaction.

ROI	Age			Group			Age $\times$ Group		
	$R^2$	$F$	$p$	$\Delta R^2$	$\Delta F$	$p$	$\Delta R^2$	$\Delta F$	$p$
Splenium of the CC	0.12	10.61	0.01*	0.00	0.00	0.97	0.05	4.22	0.04*
Genu of the CC	0.04	2.90	0.09	0.07	6.47	0.01*	0.09	8.44	0.01*
Body of the CC	0.20	19.38	0.01*	0.02	1.65	0.20	0.00	0.09	0.77
Optic radiation	0.11	10.25	0.01*	0.00	0.09	0.77	0.07	6.60	0.01*
Centrum semiovale	0.44	63.74	0.01*	0.07	10.62	0.01*	0.02	2.68	0.11
Prefrontal	0.18	17.04	0.01*	0.01	0.57	0.45	0.01	0.97	0.33
Post parietal–occipital	0.36	45.68	0.01*	0.11	16.91	0.01*	0.02	3.63	0.06
Hippocampus	0.20	19.37	0.01*	0.05	5.70	0.02*	0.06	6.56	0.01*
Thalamus	0.21	20.74	0.01*	0.05	5.16	0.03*	0.01	0.82	0.37
Putamen	0.27	30.14	0.01*	0.00	0.00	0.99	0.00	0.03	0.86

\*  $p < 0.05$ .**Table 3**  
Correlations and between-group differences in correlations between age and MD for the PKU and control groups.

ROI	Correlation between age and MD		Group differences
	Control	PKU	$z$ -score
Splenium of the CC	–0.17	–0.51*	–1.64
Genu of the CC	0.10	–0.49*	–2.68*
Optic radiation	–0.11	–0.55*	–2.13*
Hippocampus	–0.21	–0.62*	–2.17*

\*  $p < 0.05$ .

In terms of between-group differences, the correlation between age and MD was significantly different ( $z < -1.96$ ) between the PKU and control groups for the genu of the CC, optic radiation, and hippocampus; although no significant between-group difference in the correlation was found for the splenium, the correlation trended in the same direction as for the other ROIs. Overall, these results indicate that MD decreased as a function of increasing age for the PKU group but not the control group.

### 4. Discussion

Subtle cognitive compromise in children with early- and continuously-treated PKU has been associated with both gross structural [15–19] and microstructural [20–23] white matter abnormalities in the brain. Of particular relevance to the current research, a number of studies have shown that MD across a range of brain regions is lower in children with early- and continuously-treated PKU in comparison with healthy controls [20–22,25–29], but little is known about the developmental trajectory of MD in this population. As such, the current study was conducted to assess whether the relationship between age and MD was different between children with PKU and healthy control children.

Results from hierarchical linear regression analyses provided evidence that the relationship between age and MD differed between these groups. Specifically, after considering the variance attributable to age and group, the interaction between age and group accounted for a significant proportion of the variance in MD for the splenium and genu of the CC, optic radiation, and hippocampus. Further correlation analyses showed that, in these four ROIs, MD decreased as a function of increasing age for the PKU group but not the control group. In turn, these findings appear to be associated with the age-related increase in Phe levels in children with PKU, because the age-related DTI findings were no longer significant after Phe levels were controlled in analyses. Overall, these findings suggest that worsening metabolic control with age may underlie worsening microstructural white matter integrity as children with PKU age.

It is interesting to consider the specific brain regions in which age-related decreases in MD were observed for the PKU group. Turning first to the optic radiation, although few human studies have been conducted on the development of this white matter tract, the available

evidence suggests that it reaches maturity within the first few years of life in healthy children [36]. Thus, in comparison, children with early- and continuously-treated PKU demonstrated substantially protracted developmental changes in this tract.

In contrast, the white matter of the hippocampus and CC continues to mature into the second decade of life in healthy individuals [37–41]. Diffusion measures of the CC generally have greater noise due to their close proximity with cerebrospinal fluid [42], which could mask subtle maturational changes. Nonetheless, we observed a decrease in MD in the splenium and genu of the CC as a function of increasing age for the PKU group but not the control group, suggesting that this differential decrease is robust. With regard to the hippocampus, decreases in MD have been shown to slow with increasing age for healthy individuals [43], but in our sample of children with PKU MD decreased to a greater extent than in healthy children.

It is also of interest to consider the possible neural mechanisms underlying the well-established finding of poorer white matter integrity in individuals with PKU compared with healthy controls. Unfortunately, the possible mechanisms that have been suggested to date (e.g., accumulation of intracellular debris [44]) remain speculative. Further research with individuals with PKU and animal models of PKU is clearly needed to elucidate the neural underpinnings of PKU-related disruptions in white matter integrity.

## 5. Conclusions

Collectively, results from our study indicate that microstructural white matter development is disrupted in children with early- and continuously-treated PKU across a range of brain regions. Specifically, there is an abnormal restriction of water diffusion in the white matter that increases as children with PKU age. Although beyond the scope of the current investigation, future research elucidating the impact of disruptions in white matter development on functional outcomes (e.g., neurocognitive, social, psychiatric) in children with PKU will be crucial. In addition, longitudinal research will be important to investigate potential differences in growth curves of MD between children with PKU and healthy children.

## Acknowledgements

This research was supported by a National Institute of Child Health and Human Development grant (R01HD044901) and the Intellectual and Developmental Disabilities Research Center at Washington University with funding from the National Institute of Child Health and Human Development (P30HD062171 and U54HD087011). Drs. White and Grange have served as consultants to and/or received research funding from BioMarin Pharmaceutical Inc. The content of this article has not been influenced by these relationships. We would like to thank the physicians, faculty, and staff of WU and OHSU for their contributions to the study, as well as Suzin Blankenship and Laurie Sprietsma who assisted in study coordination and data collection. Finally, we wish to thank the participants and their families who contributed to this research.

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