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Relationships between Age and White Matter Integrity in Children with Phenylketonuria

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Relationships between Age and White Matter Integrity in Children with Phenylketonuria

by
Erika Mayfield Wesonga

A thesis presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the
degree of Master of Arts

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I would first like to acknowledge Dr. Desiree A. White for her support and encouragement throughout this study. I would also like to acknowledge our collaborators, Anna Hood, Dorothy K. Grange (Department of Pediatrics, Division of Genetics and Genomic Medicine, Washington University School of Medicine, St. Louis Children’s Hospital), Robert D. Steiner (Marshfield Clinic Research Foundation), Shawn E. Christ (Department of Psychological Sciences, University of Missouri), Jo Ann V. Antenor-Dorsey, Tamara Hershey, Jerrel Rutlin (Department of Psychiatry, Washington University School of Medicine, St. Louis), Joshua S. Shimony, and Robert C. McKinstry (Mallinckrodt Institute of Radiology, Washington University School of Medicine). 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). I would like to acknowledge Suzin Blankenship and Christen Bass for their contributions to study management, and I also wish to thank the Chancellor's Graduate Fellowship Program (CGFP) for providing me with academic and financial support.
ABSTRACT OF THE THESIS

Relationships between Age and White Matter Integrity in Children with Phenylketonuria

by

Erika Mayfield Wesonga

Master of Arts in Psychology

Washington University in St. Louis, 2015

Professor Desiree White, Chair

Objective: Phenylketonuria (PKU) is a hereditary metabolic disorder associated with cognitive compromise. Diffusion tensor imaging (DTI) has allowed detection of poorer microstructural white matter integrity in children with PKU, with decreased mean diffusivity (MD) in comparison with healthy children. However, very little research has been conducted to examine the trajectory of white matter development in this population. The present study investigated potential differences in the developmental trajectory of MD between children with early- and continuously-treated PKU and healthy children across a range of brain regions.

Methods: Children with PKU (n = 31, mean age = 12.2 years) were recruited through metabolic clinics, and their MD findings across 10 brain regions of interest (ROIs) were compared with those of healthy control children (n = 51, mean age = 12.0 years). Hierarchical linear regressions, including age, group, and the age by group interaction, were performed on MD for each ROI. For ROIs with significant interactions, Pearson correlations between age and MD were obtained and compared across groups.
Results: The age by group interaction was significant for the splenium and genu of the corpus callosum, the optic radiation, and the hippocampus \((p < 0.05\) in all instances). The relationship between MD and age was significant for all 4 of these ROIs within the PKU group but none within the control group. In all instances, MD decreased as a function of increasing age. The relationship between age and MD was significantly different between the PKU and control groups for the optic radiation, hippocampus, and genu of the corpus callosum \((z < -1.96\) in all instances).

Conclusions: A stronger age-related decrease in MD was identified for children with PKU in comparison with healthy children in 4 ROIs, indicating 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 PKU.
Introduction

Phenylketonuria (PKU) 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 (De Groot, Hoeksma, Blau, Reijngoud, & Van Spronsen, 2010). Dietary restriction of foods with high Phe (i.e., high protein foods) such as beans, dairy, 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 (Mitchell, Trakadis, & Scriver, 2011; Paine, 1957). 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 mood, psychosocial functioning, academic achievement, and psychiatric outcomes compared with the general population (Enns et al., 2010; Moyle, Fox, Arthur, Bynevelt, & Burnett, 2007; Van Spronsen, Huijbregts, Bosch, & Leuzzi, 2011). In addition, individuals with early- and continuously-treated PKU exhibit lower IQ (Ris, Williams, Hunt, Berry, & Leslie, 1994) and subtle cognitive deficits, particularly in executive abilities such as working memory, inhibitory control, and strategic processing (Christ, Huijbregts, de Sonneville, & White, 2010; DeRoche & Welsh, 2008; Moyle, Fox, Arthur, Bynevelt, & Burnett, 2007). 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 (Hood, Grange, Christ, Steiner, & White, 2014).

In terms of brain mechanisms that may underlie PKU-related deficits, a deficiency in the neurotransmitter dopamine has long been hypothesized as the primary factor (De Groot et al., 2010). In healthy individuals, the action of PAH converts Phe into 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 (Scriver, 2007). Dopaminergic projections to the prefrontal cortex are crucial to a number of frontally-mediated, higher-order abilities, including working memory, response inhibition, attention, and cognitive flexibility (Diamond & Baddeley, 1996; Volkow et al., 1998). 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, recent PKU research has increasingly investigated the white matter of the brain, which facilitates the efficient flow of information between 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 (Anderson et al., 2004; Cleary et al., 1995; Leuzzi et al., 1993; Manara et al., 2009; Thompson et al., 1993). This structural imaging approach, however, is not ideal for studying individuals with early- and continuously-treated PKU because gross white matter abnormalities are rarely observed in this group. 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 more refined quantitative MRI approach to investigate white matter pathology in individuals with PKU (Antenor-Dorsey et al., 2013; Peng, Peck, White, & Christ, 2013; White et al., 2010; White et al., 2013). DTI provides information regarding the microstructural integrity of the white matter by measuring the movement, or diffusion, of water molecules (Sener, 2004). Two DTI measures are frequently reported: (1) fractional anisotropy (FA), which reflects the degree of asymmetry of water diffusion and (2) 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 consistently reported (Dezortova, Hajek, Tintěra, Hejcmanova, & Sykova, 2001; Kono et al., 2005; White et al., 2013), suggesting restricted diffusion within axons. Reduced MD in individuals with early- and continuously- treated PKU has been associated with higher blood Phe levels, as well as increased variability in blood Phe levels (Hood et al., 2015). With regard to cognition, reduced MD has also been associated with lower IQ and poorer performance on executive tasks (Antenor-Dorsey et al., 2013; Vermathen et al., 2007; White et al., 2010).

From a developmental perspective, there is limited knowledge regarding the age-related trajectory of 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 (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005). In relation to our population of interest, White et al. (2010) observed an age-related decrease in MD in anterior regions of the corpus callosum in children with early- and continuously-treated PKU, but this is the only DTI study in which white matter integrity has been examined in PKU from a developmental perspective.

The present study was conducted to more thoroughly investigate the developmental trajectory of 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 children. To investigate this hypothesis, we examined MD in relation to age across 10 brain regions in school-aged children with early- and continuously-treated PKU and demographically matched healthy control children.

**Methods**

**Participants**

Participants were children with PKU (n = 31; 16 girls, 15 boys) and healthy control children (n = 51; 26 girls, 25 boys) recruited 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 the Division of Genetics and Genomic Medicine in the Department of Pediatrics at St. Louis Children’s Hospital and Washington University in St. Louis, Missouri (WUSTL) and through the Metabolic Clinic at the Child Development and Rehabilitation Center at Doernbecher Children’s Hospital and Oregon Health & Science University in Portland, Oregon (OHSU). All children with PKU were diagnosed soon after birth.
and received early and continuous treatment through dietary management of Phe intake. Phe levels over the lifetime were provided by the referring metabolic clinics and ranged from 230 - 1574 µmol/L (M = 530.2 SD = 334.9). Healthy control children were recruited from the St. Louis and Portland communities.

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.

Procedure

Approval to conduct the study was obtained from Human Research Protection Offices at WUSTL and OHSU. Informed consent and assent were obtained from all participants and their guardians before administration of any study procedures. A cognitive battery was administered as part of a larger study, but measures from this battery were not analyzed for this report.

Neuroimaging

Structural images were acquired on a Siemens TIM Trio 3.0 T imaging system (Erlangen, Germany) with a standard Siemens 12 channel head coil. These images included a T1-weighted
(T1W) sagittal, magnetization-prepared rapid gradient echo [MPRAGE; repetition time (TR) = 2000 ms, echo time (TE) = 3.03 ms (WU), flip angle = 8°, FOV = 256 × 256 pixels, voxel resolution = 0.88 × 0.88 × 0.9 mm and a T2-weighted (T2W) fast spin echo [TR = 3200, TE = 475, flip angle = 120°, FOV = 256 × 256 pixels, voxel resolution = 0.88 × 0.88 × 0.9 mm]. DTI was acquired using an echo planar imaging (EPI) sequence [TR = 12,437 (WU) and 9900 (UM), TE = 102 (WU and UM), flip angle = 90° (WU and UM), FOV = 864 × 864 (WU) and 768 × 768 (UM), voxel resolution = 2.0 × 2.0 × 2.0 (WU and UM)]. Diffusion weighted images (DWI) with variable b factor up to 1000 s/mm2 maximum were acquired along 25 non-collinear diffusion gradient orientations. DWIs were registered first to the b = 0 unsensitized image, then to the T2W, then to the best T1W (MPRAGE), and finally to a WUSTL in-house atlas.

MD region of interest (ROI) analyses were conducted across a sampling of 10 brain regions, including: prefrontal cortex, centrum semiovale, posterior parietal-occipital cortex, optic radiation, putamen, corpus callosum (CC; genu, body, splenium), thalamus, and hippocampus. 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. The mean and standard deviation (SD) of MD for each ROI are listed in Table 1.
Statistical Analyses

As a starting point, t-tests were used to determine whether MD across the 10 ROIs differed between the PKU and control groups. Results were considered significant if $p < .05$. Hierarchical linear regressions were then performed to determine the proportion of variance in MD for each ROI that was accounted for by age, group, or 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., $z < -1.96$)

Results

The mean and standard deviation (SD) of MD for each ROI are listed in Table 1, along with statistical findings from t-tests examining between-group differences in MD. Significant between-group differences in MD were found for the genu of the CC, centrum semiovale, and posterior parietal occipital cortex. In all instances, MD for the PKU group was lower than for the control group.
With respect to the relationships between age and MD, statistical findings from hierarchical linear regressions are reported in Table 2. Age accounted for a significant proportion of the variance in MD for 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 greater 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.

Correlation analyses were used to further explore these significant interactions. As shown in Table 3, the relationship 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, with significant correlations for the PKU group but not the control group; although no significant between-group difference in correlations was found for the splenium, the pattern of correlations trended in the same direction. In fact, across the genu and splenium of the CC, the optic radiation, and the hippocampus, all correlations between age and MD were significant for the PKU group but not the control group, such that MD decreased as a function of increasing age for the PKU group.

**Discussion**

Subtle cognitive compromise in children with early-and continuously treated PKU has been associated with both gross structural (Anderson et al., 2004) and microstructural (Antenor-Dorsey et al., 2013) 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 (Kono et al., 2005; White et al 2010), 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 (in whom age-related decreases in MD generally plateau by middle childhood).

Results from hierarchical linear regressions provided evidence that the relationship between age and MD differed between these groups. More 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.

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 (Yamada et al., 2000). Thus, in comparison, children with early- and continuously-treated PKU demonstrated substantially protracted developmental changes in this tract.

In contrast with the optic radiation, the white matter of the hippocampus and CC continues to mature into the second decade of life in healthy individuals (Benes et al 1994; Eluvathingal et al., 2007; Giorgio et al. 2008; Lebel et al. 2008; Lebel et al, 2010; Miller et al,
2003; Tamnes et al. 2010). Diffusion measures of the CC generally have greater noise due to their close proximity with cerebrospinal fluid (Mukherjee et al., 2001), 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 in this region slow with increasing age for healthy individuals (Tamnes et al. 2010), but again MD decreased to a greater extent in children with PKU.

Collectively, these observations indicate that microstructural white matter development is disrupted in children with early- and continuously-treated PKU across a variety 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 outcomes) in children with PKU will be crucial. In addition, longitudinal research will be important to investigate potential differences in growth curves of MD between healthy children and children with PKU.
References


## Tables

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

<table>
<thead>
<tr>
<th>ROI</th>
<th>Control</th>
<th>PKU</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenium of the CC</td>
<td>0.79(0.04)</td>
<td>0.79(0.07)</td>
<td>0.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Genu of the CC</td>
<td>0.86(0.06)</td>
<td>0.82(0.08)</td>
<td>2.56</td>
<td>0.01*</td>
</tr>
<tr>
<td>Body of the CC</td>
<td>0.96(0.08)</td>
<td>0.93(0.13)</td>
<td>1.13</td>
<td>0.26</td>
</tr>
<tr>
<td>Optic Radiation</td>
<td>0.85(0.04)</td>
<td>0.85(0.06)</td>
<td>0.33</td>
<td>0.74</td>
</tr>
<tr>
<td>Centrum Semiovale</td>
<td>0.77(0.03)</td>
<td>0.75(0.04)</td>
<td>2.33</td>
<td>0.02*</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>0.77(0.03)</td>
<td>0.78(0.04)</td>
<td>-0.53</td>
<td>0.60</td>
</tr>
<tr>
<td>Post Parietal Occipital</td>
<td>0.81(0.04)</td>
<td>0.77(0.05)</td>
<td>3.08</td>
<td>0.00*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.91(0.03)</td>
<td>0.93(0.05)</td>
<td>-1.80</td>
<td>0.08</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.81(0.03)</td>
<td>0.82(0.04)</td>
<td>-1.91</td>
<td>0.06</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.76(0.02)</td>
<td>0.76(0.03)</td>
<td>0.11</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Note: * p < .05 and medium or large effect size; df = 80 for all analyses. Given a priori hypotheses, all t tests were 1-tailed.
Table 2. Statistical findings from hierarchical linear regressions examining the variance in MD attributable to age, group, and the age x group interaction.

<table>
<thead>
<tr>
<th>ROI</th>
<th>$R^2$</th>
<th>$F$</th>
<th>$p$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F$</th>
<th>$p$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenium of the CC</td>
<td>0.12</td>
<td>10.61</td>
<td>0.01*</td>
<td>0.00</td>
<td>0.00</td>
<td>0.97</td>
<td>0.05</td>
<td>4.22</td>
<td>0.04*</td>
</tr>
<tr>
<td>Genu of the CC</td>
<td>0.04</td>
<td>2.90</td>
<td>0.09</td>
<td>0.07</td>
<td>6.47</td>
<td>0.01*</td>
<td>0.09</td>
<td>8.44</td>
<td>0.01*</td>
</tr>
<tr>
<td>Body of the CC</td>
<td>0.20</td>
<td>19.38</td>
<td>0.01*</td>
<td>0.02</td>
<td>1.65</td>
<td>0.20</td>
<td>0.00</td>
<td>0.09</td>
<td>0.77</td>
</tr>
<tr>
<td>Optic Radiation</td>
<td>0.11</td>
<td>10.25</td>
<td>0.01*</td>
<td>0.00</td>
<td>0.09</td>
<td>0.77</td>
<td>0.07</td>
<td>6.60</td>
<td>0.01*</td>
</tr>
<tr>
<td>Centrum Semiovale</td>
<td>0.44</td>
<td>63.74</td>
<td>0.01*</td>
<td>0.07</td>
<td>10.62</td>
<td>0.01*</td>
<td>0.02</td>
<td>2.68</td>
<td>0.11</td>
</tr>
<tr>
<td>Prefrontal White Matter</td>
<td>0.18</td>
<td>17.04</td>
<td>0.01*</td>
<td>0.01</td>
<td>0.57</td>
<td>0.45</td>
<td>0.01</td>
<td>0.97</td>
<td>0.33</td>
</tr>
<tr>
<td>Post Parietal Occipital</td>
<td>0.36</td>
<td>45.68</td>
<td>0.01*</td>
<td>0.11</td>
<td>16.91</td>
<td>0.01*</td>
<td>0.02</td>
<td>3.63</td>
<td>0.06</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.20</td>
<td>19.37</td>
<td>0.01*</td>
<td>0.05</td>
<td>5.70</td>
<td>0.02*</td>
<td>0.06</td>
<td>6.56</td>
<td>0.01*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.21</td>
<td>20.74</td>
<td>0.01*</td>
<td>0.05</td>
<td>5.16</td>
<td>0.03*</td>
<td>0.01</td>
<td>0.82</td>
<td>0.37</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.27</td>
<td>30.14</td>
<td>0.01*</td>
<td>0.00</td>
<td>0.00</td>
<td>0.99</td>
<td>0.00</td>
<td>0.03</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Note: * $p < 0.05$.

Table 3. Correlations and between-group differences in correlations between age and MD for the PKU and control groups.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Correlation between age and MD</th>
<th>Group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PKU</td>
</tr>
<tr>
<td>Splenium of the CC</td>
<td>-0.17</td>
<td>-0.51*</td>
</tr>
<tr>
<td>Genu of the CC</td>
<td>0.10</td>
<td>-0.49*</td>
</tr>
<tr>
<td>Optic Radiation</td>
<td>-0.11</td>
<td>-0.55*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.21</td>
<td>-0.62*</td>
</tr>
</tbody>
</table>

Note: * $p < 0.05$. 