

ORIGINAL ARTICLE

Cortical thickness and its relationship to cognitive performance and metabolic control in adults with phenylketonuria

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Abstract

Despite good control of phenylalanine (Phe) levels during childhood and adolescence, adults with phenylketonuria (PKU) often show abnormalities in the white matter of the brain, which have been associated with poorer cognitive performance. However, whether such a relationship exists with cortical gray matter is still unknown. Therefore, we investigated cortical thickness and surface area in adults with early-treated PKU and their relationship to cognitive functions and metabolic control. We included 30 adult patients with early-treated and metabolically well-controlled PKU (median age: 35.5 years) and 54 healthy controls (median age: 29.3 years). Surface-based morphometry was derived from T1-weighted magnetic resonance images using FreeSurfer, and general intelligence, executive functions, and attention were assessed. Concurrent plasma Phe, tyrosine, and tryptophan levels were measured in patients. In addition, Phe levels were collected retrospectively to calculate the index of dietary control. Patients showed a thinner cortex than controls in regions of the bilateral

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temporal, parietal, and occipital lobes (effect size $r = -0.34$ to -0.42 , $p < 0.05$). No group differences in surface area were found. In patients, accuracy in the working memory task was positively correlated with thickness in the left insula ($r = 0.45$, $p = 0.013$), left fusiform gyrus ($r = 0.39$, $p = 0.032$), and right superior temporal gyrus ($r = 0.41$, $p = 0.024$), but did not survive false discovery rate correction. Neither concurrent nor historical metabolic parameters were related to cortical thickness. Taken together, adults with PKU showed widespread reductions in cortical thickness despite good metabolic control in childhood and adolescence. However, alterations in cortical thickness were unrelated to metabolic parameters and cognitive performance.

KEYWORDS

brain structure, cognition, cortical thickness, gray matter, phenylketonuria, working memory

1 | INTRODUCTION

Phenylketonuria (PKU; OMIM: 261600) results from a genetic defect of phenylalanine (Phe) hydroxylase (612349), leading to the accumulation of Phe in the blood, brain, and other tissues. This affects the structure and function of the brain. Past research indicates that adult patients with early-treated PKU generally show poorer cognitive performance than comparable healthy controls, particularly in the domains of intelligence, executive functions, and attention.^{1,2} However, interindividual variance is large with one study reporting test scores within the norm in more than half of the adults with early-treated PKU.³ It is still unclear whether the difference in cognitive outcomes can be attributed to patients' concurrent and historical metabolic control or other amino acid imbalances.

Prior studies suggest that white matter alterations in patients with PKU could be in part associated with altered cognitive performance (for a review, see Anderson & Leuzzi⁴). However, to what extent PKU may be related to gray matter (GM) alterations is even less understood. The small number of studies investigating GM in heterogeneous samples of patients with PKU greatly vary. On the one hand, Bodner et al.⁵ and Pfaendner et al.⁶ found smaller whole-brain volume in patients with PKU, whereas Aldridge et al.⁷ and Hawks et al.⁸ could not find any differences. On a more regional level, smaller volumes in brain areas of the bilateral parietal and occipital lobes⁹ and the motor and premotor cortex¹⁰ were reported in patients with PKU in comparison to healthy controls.

Most studies investigated volume measures to evaluate cortical GM architecture in PKU. However, cortical volume is essentially the product of cortical thickness

and cortical surface area, and these two distinct measures respond differently to intrinsic and extrinsic factors.¹¹

Previous morphometric studies on patients with PKU have focused on linking structural abnormalities to general intelligence (see e.g. Christ et al.⁹ and Pérez-Dueñas et al.¹⁰) without examining other particularly affected cognitive domains such as executive functions and attention. Linking structural characteristics of the GM to cognitive functions known to be vulnerable to PKU is of major importance in unraveling factors associated with cognitive performance in this patient group.

In summary, it remains unclear how structural brain characteristics relate to cognitive performance and metabolic control in individuals with PKU. In this study, we examined whether there are (a) differences in cortical thickness and surface area between patients and healthy controls and (b) whether these alterations relate to metabolic parameters and (c) cognitive performance.

2 | METHODS

2.1 | Participants

Data for this cross-sectional study were derived from the PICO study (Phenylalanine and its Impact on COgnition¹²), an ongoing clinical trial, which was approved by the Cantonal Ethics Committee Bern, Switzerland (2018-01609), registered on clinicaltrials.gov (NCT03788343), and conducted in accordance with the Declaration of Helsinki in the current (2013) version. All participants provided written informed consent before study participation.

Patients were recruited between August 2019 and February 2022 for the baseline measurements through

TABLE 1 Demographics of patients and controls

		Patients (n = 30)	Controls (n = 54)	U/χ^2	p	r_{rb}/ϕ
Age	Median (IQR)	35.5 years (12.3)	29.3 years (9.4)	943.0	0.216	0.16
	Range	19–48 years	18–53 years			
Sex	Female	13	26	0.0	0.845	0.30
	Male	17	27			
Education	Median (IQR)	6.0 (2.8)	5.0 (3.8)	4.6	0.707	0.23

Note: All values were gathered at the time of the MRI. Education was categorized into 1—Secondary Education; 2—Apprenticeship; 3—Vocational Education; 4—High School; 5—College of Higher Education; 6—Bachelor or equivalent; 7—Master or equivalent; 8—Doctorate. See Table S1 for the different education levels per group.

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging; U , Mann–Whitney U -statistic; χ^2 , Chi-squared statistic; effect sizes are reported as rank-biserial correlations (r_{rb}) for Mann–Whitney U -tests and as phi (ϕ) for chi-squared tests.

their metabolic specialists at the University Hospitals of Bern, Zurich, Lausanne, Basel, and the Cantonal Hospital St. Gallen (all in Switzerland), the Hospitals in Ulm (Germany), Hamburg (Germany), and Innsbruck (Austria). Healthy controls were recruited in and around Bern and Zurich through advertisements and word-of-mouth between July 2019 and April 2022. A total of 30 individuals with early-treated classical PKU and 55 healthy controls of comparable age, sex, and education were included in the study. One control participant had to be excluded from the analysis due to an incidental magnetic resonance imaging (MRI) finding affecting the results of the morphometric analysis. Demographics of the final sample of 30 individuals with PKU and 54 controls are described in Table 1. For details on education level see Table S1.

Adult patients (≥ 18 years) were eligible for participation with a PKU-positive newborn screening resulting in the implementation of a Phe-restricted diet within 1 month after birth, and if Phe concentrations 6 months before study participation did not exceed 1600 $\mu\text{mol/L}$. Additionally, patients with an untreated vitamin B₁₂ deficiency and pregnant or breastfeeding patients were excluded from participation. Finally, patients and controls were excluded if they had a condition interfering with cognitive testing or MRI acquisition (see Trepp et al.¹² for further details).

2.2 | Metabolic parameters

2.2.1 | Concurrent metabolic parameters

Before the MRI assessment, blood was drawn from each patient with PKU after an overnight fasting period. Plasma Phe, Tyrosine (Tyr), and Tryptophan (Trp) levels were measured by high-performance ion-exchange liquid chromatography with postcolumn photometric detection

of ninhydrin-derivatized amino acids. Further details about laboratory analysis methods can be found elsewhere.¹³ Additionally, concurrent Phe and Tyr levels were used to calculate the Phe:Tyr ratio (see Table 2 for concurrent metabolic parameters in patients). In 26.7% (8 out of 30) of patients, concurrent Phe levels were within the target range recommended by the current European guidelines.¹⁴

2.2.2 | Historical blood Phe levels

Phe levels previously measured throughout patients' lifetime by either plasma or dry blood spot measurements were collected from medical files. We did not apply a correction factor due to the great variability in analysis methods.¹⁵ The index of dietary control (IDC) indicates metabolic control, which accounts for missing data in different age periods. It was calculated by averaging the yearly medians until the day of the baseline measurement. The medians of Phe levels were then grouped into five different age categories according to developmental spurts during childhood and adolescence: Childhood 0–5 years, Childhood 6–12 years, Adolescence 13–17 years, Adulthood ≥ 18 years, and Lifetime (Table 2). Per patient, a minimum of 10 values had to be available for each age band (procedure adapted from Weglage et al.¹⁶). Otherwise, the respective category was not included in the analysis.

Available historical Phe levels show that patients were usually well-adjusted during childhood and adolescence. Between 0 and 5 years, the IDC of 1 patient (out of 17 patients, 5.9%) was above the recommended level of 360 $\mu\text{mol/L}$ (401 $\mu\text{mol/L}$). Between 6 and 12 years, the IDC of five patients (out of 19 patients, 26.3%) was above 360 $\mu\text{mol/L}$ (from 370 to 431 $\mu\text{mol/L}$). During adolescence, 6 patients (out of 21 patients, 28.6%) were above the recommended level of

TABLE 2 Concurrent and historical metabolic parameters in patients with PKU

Time of measurement	Parameter	n	Median	IQR	Min	Max
Concurrent	Phe ($\mu\text{mol/L}$)	30	741	358	380	1208
	Tyr ($\mu\text{mol/L}$)	30	38	12	28	71
	Trp ($\mu\text{mol/L}$)	30	38	10	21	54
	Phe:Tyr ratio	30	19	11	10	38
Historical	IDC childhood 0–5 ($\mu\text{mol/L}$)	17	276	97	129	401
	IDC childhood 6–12 ($\mu\text{mol/L}$)	19	255	126	153	431
	IDC adolescence 13–17 ($\mu\text{mol/L}$)	21	459	261	135	783
	IDC adult ≥ 18 ($\mu\text{mol/L}$)	18	640	478	408	1494
	IDC lifetime ($\mu\text{mol/L}$)	14	390	208	237	876

Abbreviations: IDC, index of dietary control; IQR, interquartile range; Max, maximum value; Min, minimum value; Phe, phenylalanine; PKU, phenylketonuria; Trp, Tryptophan; Tyr, Tyrosine.

600 $\mu\text{mol/L}$ (from 601 to 783 $\mu\text{mol/L}$). During adulthood, 11 out of 18 patients (61.1%) were above 600 $\mu\text{mol/L}$ (from 602 to 1494 $\mu\text{mol/L}$).

2.3 | Cognitive assessment

From the cognitive test battery of the PICO study,¹² the domains of intelligence, executive functions, and attention were selected for this study as performance in these domains is often found to be worse in patients with PKU when compared with healthy controls.^{1,2} First, general intelligence was assessed using the subtests Matrix Reasoning, Vocabulary, Arithmetic, and Symbol Search from the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV).^{17,18} Executive functions were evaluated according to the model of Miyake et al.¹⁹ which suggests the following components to be core executive functions: working memory (assessed with the n-back task; Test of Attentional Performance [TAP]),²⁰ inhibition, and cognitive flexibility (assessed with the Color-Word Interference Test conditions 3 and 4, respectively; Delis–Kaplan Executive Function System [D-KEFS]).²¹ Finally, attention was assessed with tasks on alertness, divided attention, and sustained attention (TAP).²⁰ Age-standardized test scores (i.e., T-scores and Scale Scores) are reported to facilitate clinical interpretation of the cognitive data (except for working memory accuracy for which no standardized score exists).

2.4 | Neuroimaging

2.4.1 | MRI acquisition

Brain MRI was performed on all participants on a 3.0 T Siemens Prisma MRI scanner with a 64-channel head coil.

As part of the study protocol,¹² structural high-resolution T1-weighted images (Magnetization Prepared-Rapid Gradient Echo, MPRAGE) were collected (repetition time TR = 1950 ms, echo time TE = 2.26 ms, inversion time TI = 900 ms, flip angle = 9, in-plane resolution = 1×1 mm, slice thickness = 1 mm, number of slices = 176, field of view FoV = 256×256 mm, matrix = 256×256) and evaluated for the present contribution.

2.4.2 | T1-weighted image postprocessing

Volumetric segmentation and cortical reconstruction of all T1-weighted images were performed with the automatic FreeSurfer recon-all pipeline (version 6.0). Computation was performed on the UBELIX High-Performance-Computing cluster of the University of Bern. The procedure involves several processing steps extensively described in prior publications.²² Automatic parcellation of the cortex results in cortical regions of interest (ROIs) based on the Desikan–Killiany atlas.²³ In total, 60 ROIs (30 for each hemisphere) were extracted, excluding the cingulate cortex, as this region often shows lower reliability.^{24,25} For each ROI, cortical thickness and cortical surface area were estimated and included in the analyses. For better comparability with the findings of other studies, cortical volume was included in all analyses, and results are described in Table S2.

2.4.3 | Lobe mapping

For calculating the cortical surface area for the frontal, temporal, parietal, and occipital lobes of each hemisphere, corresponding ROIs according to the Desikan–Killiany atlas were merged. To account for different sizes of the ROIs, we calculated the average cortical thickness

per hemisphere and lobe, weighted by the corresponding surface area. For thickness calculations of each lobe, the thickness measure of each ROI was multiplied by the corresponding surface area of the ROI. The results were added and then divided by the sum of the surface area of all included ROIs within a lobe. Due to its location, the insula was excluded from lobar calculations but included as a separate ROI.

2.5 | Statistical analysis

In line with Im et al.²⁶ and Pintzka et al.²⁷ preanalyses showed that age was significantly related to thickness and surface area measures, whereas sex was not. Additionally, the estimated total intracranial volume as calculated by FreeSurfer greatly influenced surface area measures, also aligning with the literature.^{26,28} Therefore, these variables were included as covariates in the morphometric analyses.

To facilitate statistical analysis, we extracted the raw residuals of all morphometric and cognitive variables after regressing out the corresponding confounding variables (e.g., age). Residuals indicate the difference between the data points (observed values) from the regression line (predicted values). In other words, residuals are the error terms, which are not explained by the regression line. In more detail, linear regression models were built with each morphometric index as the dependent variable and age and intracranial volume (the latter only for the surface area) as independent variables. Residuals for thickness and surface area of each bilateral lobe and all bilateral ROIs were calculated for the patient and control group using the linear model of the control group. The same was done for all raw scores of the cognitive variables (except for intelligence quotient, IQ), which were controlled for age. The extracted residuals were used for group comparisons and correlation analyses.

Data were examined hierarchically to reduce the number of comparisons between morphometric and cognitive/metabolic variables. Only significant hemispheres were further analyzed on a lobar level. Likewise, only ROIs within lobes with significant group differences were examined. Additionally, only ROIs and cognitive variables with significant group differences were included in further analyses.

Sex differences between patients and controls were analyzed using a Chi-squared test with ϕ as the corresponding effect size. Due to the non-normal distribution of most continuous variables, medians and interquartile ranges (IQRs) were reported. Group differences were analyzed using Mann-Whitney U -tests, and corresponding effect sizes were reported as rank-biserial correlations

(r_{rb}). The r_{rb} value can be interpreted in the same manner as any other correlation coefficient (i.e., as a value between -1 and 1). The relationship between morphometric and cognitive residuals and metabolic variables was evaluated using Spearman correlations (r_s). Confidence intervals for Spearman correlations were computed by bootstrapping ($n = 1000$).

The p -values < 0.05 are considered significant and are reported as uncorrected p -values (p), for which we further specify if they survive correction for multiple comparisons using the false discovery rate (FDR).²⁹ In the FDR correction procedure, p -values for each hypothesis were calculated, ranked from smallest to largest p -value, and the corrected p -values were calculated as follows: $p\text{-value} * [(\text{total number of comparisons}) / (\text{rank of the } p\text{-value})]$. If the corrected p -value was smaller than 0.05 , the comparison survived FDR correction. Effect sizes were interpreted as suggested by Funder and Ozer³⁰: $r \geq 0.05$, $r \geq 0.10$, $r \geq 0.20$, $r \geq 0.30$, and $r \geq 0.40$ represent very small, small, medium, large, and very large effects, respectively. All analyses were conducted on R version 4.1.2.³¹

3 | RESULTS

3.1 | Cognitive performance and metabolic parameters

Group medians of patients were within the normal range throughout all cognitive domains (see T-scores and Scale Scores in table 3). Nevertheless, patients had a lower IQ than controls. After correcting for age, patients performed significantly worse in working memory, cognitive flexibility, and sustained attention. All significant group differences survive FDR correction.

In patients, there was no significant correlation between the measures of cognitive performance and concurrent or historical metabolic parameters.

3.2 | Morphometric parameters in patients and controls

On a whole-brain level, patients showed a smaller total thickness (Median (IQR) patients = 2.53 mm (0.07), controls = 2.59 mm (0.11); $p = 0.018$, $r_{rb} = -0.31$, 95% CI $[-0.53, -0.07]$) and a smaller thickness of the left (patients = 2.55 mm (0.07), controls = 2.60 mm (0.11); $p = 0.013$, $r_{rb} = -0.33$, 95% CI $[-0.54, -0.08]$) and right hemisphere (patients = 2.53 mm (0.08), controls = 2.58 mm (0.10); $p = 0.036$, $r_{rb} = -0.28$, 95% CI $[-0.50, -0.03]$). However, surface area on a whole-brain level

TABLE 3 Cognitive performance in patients and controls

			Patients (<i>n</i> = 30)		Controls (<i>n</i> = 54)			
			Median (IQR)	Median (IQR)	<i>U</i>	<i>p</i>	<i>r</i> _{rb}	[95% CI] for <i>r</i> _{rb}
IQ	Intelligence	Index scores ^a	97.0 (16.0)	109.0 (20.0)	498	0.004*	−0.39	[−0.58, −0.15]
Executive functions	Working memory	Raw scores	94.5 (7.0)	98.0 (3.0)	478	0.002*	−0.41	[−0.60, −0.17]
		Residuals ^a	−2.4 (7.0)	0.8 (3.2)	490	0.003*	−0.40	[−0.59, −0.16]
	Inhibition	Scale scores (time) ^a	10.0 (2.5)	11.0 (3.8)	654	0.143	−0.19	[−0.43, 0.06]
		Residuals ^b	0.1 (13.7)	−0.7 (11.5)	931	0.261	0.15	[−0.11, 0.39]
	Cognitive flexibility	Scale scores (time) ^a	10.0 (2.0)	12.0 (3.0)	457	0.001*	−0.44	[−0.62, −0.21]
		Residuals ^b	6.4 (10.3)	−2.31 (11.8)	1175	0.001*	0.45	[0.22, 0.63]
Attention	Alertness	T-scores (median reaction time) ^a	45.5 (9.8)	47.0 (12.0)	672	0.199	−0.17	[−0.41, 0.09]
		Residuals ^b	3.2 (37.4)	−0.8 (32.7)	899	0.409	0.11	[−0.15, 0.35]
	Divided attention	T-scores (total omissions) ^a	48.0 (13.0)	53.0 (13.0)	698	0.418	−0.11	[−0.35, 0.15]
		Residuals ^b	−0.05 (1.9)	−0.6 (2.1)	978	0.063	0.25	[−0.01, 0.47]
	Sustained attention	T-scores (SD in reaction time) ^a	46.0 (9.0)	52.0 (9.0)	453	0.002*	−0.41	[−0.60, −0.17]
		Residuals ^b	28.5 (48.8)	−9.4 (50.4)	1100	0.003*	0.40	[0.17, 0.60]

Note: *Survives FDR correction; residuals are the error terms after regressing out the confounding variable age.

Abbreviations: CI, confidence interval; IQR, interquartile range; *p*, *p*-value; effect sizes are reported as rank-biserial correlations (*r*_{rb}) for Mann–Whitney *U*-tests; *U*, Mann–Whitney *U*-statistic.

^aThe higher/the more positive the score, the better performance.

^bThe lower/the more negative the score, the better performance.

did not differ between patients and controls. Lobar analyses were therefore only conducted on thickness indices. On a lobar level, patients showed a significantly thinner cortex in the left and right temporal, parietal, and occipital lobes (see Figure 1 and Table S3).

In the next step, ROI-based analysis was conducted within the lobes that showed group differences in cortical thickness (i.e., ROIs of all lobes except for the ROIs of the frontal lobe). In patients, the thickness was decreased in 17 of the 38 included ROIs with medium to large effect sizes (see Figure 2 and Table S4). Of these, 11 survived FDR correction (see Table S4). The largest effect sizes were found for the left inferior parietal cortex, the left insula, and the left superior temporal gyrus (see Table S4).

3.3 | Cortical thickness, metabolic parameters, and cognitive performance

Within the patient group, there was no correlation between the thickness of ROIs showing significant group differences and any of the metabolic parameters, neither concurrent nor historical.

In patients, correlation analysis on a ROI level revealed a positive association between performance in the working memory task and thickness of the left fusiform gyrus ($r_s = 0.39$, $p = 0.032$, 95% CI [0.04, 0.69]), the left insula ($r_s = 0.45$, $p = 0.013$, 95% CI [0.05, 0.76]), and the right superior temporal gyrus ($r_s = 0.41$, $p = 0.024$, 95% CI [0.04, 0.71]). These correlations did not survive FDR correction.

In controls, none of the cognitive variables were significantly correlated with the thickness of the 17 ROIs (the ROIs with significant group differences in the first analysis step).

4 | DISCUSSION

Cortical thickness in adult patients with early-treated and developmentally well-controlled PKU was significantly lower in all but the frontal lobes compared with healthy controls. In addition, ROI analysis within these lobes showed significantly decreased cortical thickness in 17 out of 38 analyzed ROIs, of which 11 survived FDR correction. In contrast, no group differences in surface area were found. Within the patient group, accuracy in

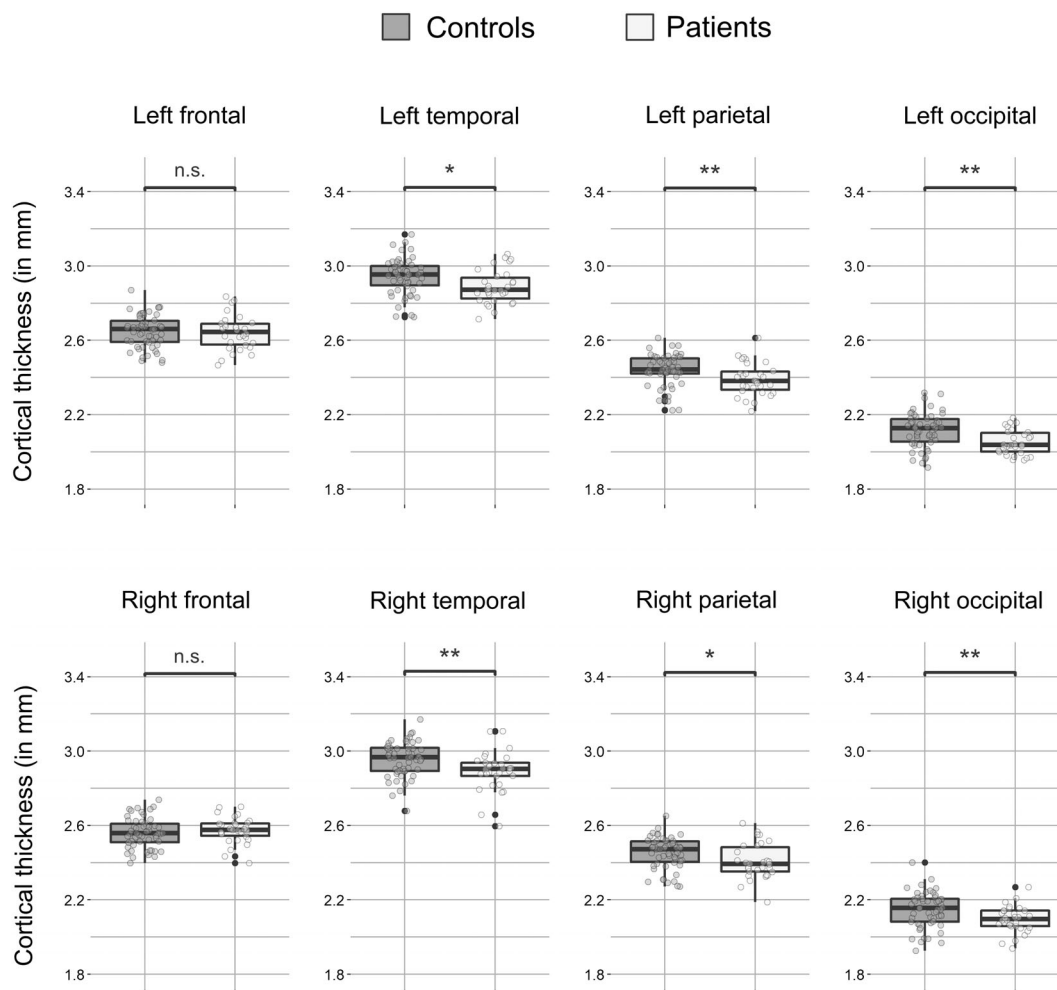


FIGURE 1 Group differences in cortical thickness of lobes of the left hemisphere (upper row) and right hemisphere (bottom row) between patients (white) and controls (light gray). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. n.s., not significant. All significant comparisons survive FDR correction

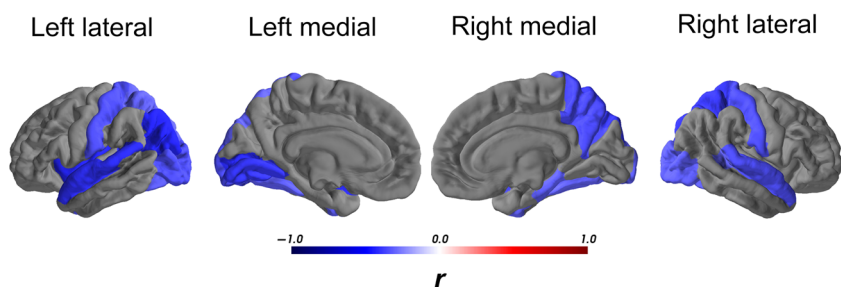


FIGURE 2 Significant differences in cortical thickness between patients and controls in the left hemisphere (first two columns) and the right hemisphere (last two columns). Color scale shows the magnitude of the effect (r = rank-biserial correlation coefficient for Mann-Whitney U -test) with negative r -values (blue) indicating a thinner cortex in patients

the working memory task was positively related to thickness in the left fusiform gyrus, right superior temporal gyrus, and left insula, although not surviving FDR correction. Neither concurrent nor historical metabolic parameters were related to cortical thickness.

While the cortical surface area was unaffected in our patient sample, cortical thickness was significantly decreased in all but the frontal lobes compared with healthy controls. Notably, the difference in cortical

thickness between patients and controls was 0.06 mm (2.3%), which is larger than the measurement errors of FreeSurfer demonstrated by a previous study on a group level of $\sim 0.5\%$.²⁵ Our results align with Christ et al.⁹ indicating that structural changes in PKU primarily occur in the posterior cortices. Phylogenetically older brain regions that develop earlier, such as the visual cortex,³² might be more vulnerable to the effects of PKU than late-maturing regions such as the prefrontal cortex. In

contrast, the absence of group differences in GM indices between controls and children and adolescents has also been described.⁸ This might indicate that the effects of treated PKU slowly accumulate during childhood and adolescence, with GM differences becoming apparent only in adulthood. Taken together, past studies and our current findings suggest a neurodevelopmental basis for the effects of PKU.

The pattern of cortical thickness alterations includes brain regions crucially involved in the default mode network (namely, the precuneus and inferior parietal lobe).³³ This network is active during rest and has previously been linked to reduced functional connectivity in patients with PKU.³⁴ Alterations in cortical thickness in default mode network hubs might be linked to disruptions in functional connectivity within this network. In patients with multiple sclerosis, altered connectivity within the default mode network has been related to fatigue and depression³⁵ (symptoms also reported by some patients with PKU^{36,37}).

Prior research on structural alterations in patients with PKU greatly vary, with some reporting GM volume reductions across the brain,^{5,6,10} whereas others showed no group differences.³⁸ The lack of consensus on cortical GM alterations in PKU could be attributed to different issues. On the one hand, the inclusion of heterogeneous patient samples (early-treated and late-treated PKU) and broad age ranges (from children to adults in one sample) makes it difficult to compare results between studies. On the other hand, the existing literature focused on cortical volume as a proxy for structural brain alterations without paying attention to the fact that volume reductions could be driven by changes in thickness, surface area, or both.¹¹ Cortical thickness and surface area are genetically uncorrelated,¹¹ influenced by different neurodevelopmental processes,^{39,40} and can be differentially affected by environmental factors⁴¹ or genetic deficits.⁴² While the cortical surface area is thought to be driven by the number of columns in the cortical mantle, cortical thickness reflects the number and size of cells within a column, the packing density, and dendritic arborization, among others.^{43,44} Histopathological studies on untreated patients with PKU primarily suggest changes in cortical thickness (i.e., reductions in dendritic arborization and nerve cell size⁴⁵ and a reduced number of stained neurons⁴⁶). Additionally, animal models of PKU showed globally reduced synaptic density⁴⁷ and reduced dendritic arborization.⁴⁸ These microanatomical findings imply a disruption in cortical thickness on a macroanatomical level. Therefore, cortical thickness could be a particularly vulnerable measure of change in cortical GM architecture in PKU. In the context of our results, we, therefore, speculate that findings on cortical volume in PKU are

essentially driven by alterations in cortical thickness rather than surface area.

Interestingly, these cortical thickness alterations in patients were unrelated to their Phe levels during different developmental stages. This aligns with Pfaendner et al.⁶ also reporting no correlation between GM and Phe levels during 0–5 and 0–12 years of age. Conversely, Bodner et al.⁵ and Christ et al.⁹ found a relationship between Phe and GM integrity. Nevertheless, they used Phe levels of the last month and last year before study participation, making it difficult to compare outcomes across studies. Besides, transport of Phe across the blood–brain barrier varies among individuals, indicating interindividual differences in vulnerability to high Phe concentrations,^{49,50} which further explains the lack of agreement on the association between historical Phe levels and the brain structure. As regards concurrent Phe levels, they might be much stronger related to functional brain activation than GM structure. A recent study by our group found a relationship between neural activation during a working memory task and concurrent but not historical Phe levels within a subsample of the present cohort.¹³ Christ et al.³⁴ found a similar relationship between recent Phe levels and decreased functional connectivity. Since plasma Phe levels correlate with brain Phe levels,⁵¹ it seems reasonable to assume that plasma Phe levels on the day of testing or shortly before can directly influence functional neural correlates.

Patients with PKU performed significantly worse than controls in IQ, working memory, cognitive flexibility, and sustained attention. This is in line with previous literature (for review, see Hofman et al.² and Palermo et al.⁵²) and suggests that patients with PKU have difficulties particularly in tasks with high cognitive demands, such as working memory performance which is often worse in patients.⁵² Our patients showed significantly lower accuracy rates in verbal working memory, but group medians generally were within the normative range. Similarly, our group has previously shown lower accuracy in visuospatial working memory.¹³ Accordingly, these results point toward subtle cognitive alterations in adult patients with PKU.

Similarly to the results with cortical thickness, we also found no relationship between concurrent and historical metabolic parameters and cognitive performance, although this link has previously been reported.^{3,53} Metabolic levels of our patients were well controlled during development, which could be why we did not find a relationship between historical Phe levels and cognitive performance. Furthermore, as Romani et al.⁵⁴ pointed out, nonsignificant results between metabolic control and cognition are common. Of the reviewed studies, only 21% of correlations between concurrent Phe and cognitive

performance were significant, whereas around 30% of correlations between cognitive performance and Phe levels during childhood and adolescence were significant. This might be related to the variety of cognitive tests used in these studies. In accordance with Romani et al.⁵⁴ we conclude that with the current findings, it remains unclear whether a strict dietary control during development is particularly beneficial for cognitive performance in adulthood.

In patients, accuracy in the verbal working memory task was positively related to cortical thickness in the left fusiform gyrus, the left insula, and the right superior temporal gyrus. Note that these correlations did, however, not survive FDR correction. Accordingly, we interpret these findings with caution. In an fMRI study, the same brain regions showed altered activation during a similar verbal working memory task in six patients with PKU.⁵⁵ Working memory performance relies on an intricate brain network involving many areas of the frontal and parietal lobes of the brain.^{56,57} The fact that the reported regions are outside the typical working memory network might indicate a general disruption in the structure–function relationship in patients with PKU. It could also imply a compensatory mechanism whereby other brain areas take over to counterbalance dysfunctions of areas with cortical thinning. A different setup is needed to investigate this relation between working memory and cortical thickness, including an independent functional localizer.

The results of this study should be interpreted considering certain limitations. This study was conducted within the framework of the PICO study, a randomized placebo-controlled trial. Therefore, this study might be subject to selection bias since only highly motivated patients with good metabolic control or minimal complaints in everyday life might have participated in the PICO study. Furthermore, although the results on working memory and cortical thickness reached significance and showed large effect sizes, they did not survive FDR correction, CIs were wide, and the lower bound of the CIs showed very small effect sizes. Additionally, the large effect sizes in cortical thickness could be partially explained by the homogeneity of the groups. Hence, numerically small group differences could result in larger effect sizes. Results must therefore be viewed with caution. Finally, due to nonsignificant group differences in surface area on a whole-brain level, we did not further investigate surface area on a regional level. It should be considered that surface area could also be affected by the disease—albeit possibly to a lesser extent.

These findings build on existing evidence that early-treated PKU not only affects cerebral white matter but also cortical GM across the temporal, parietal, and

occipital cortices. We could further illustrate that cortical thickness is a particularly sensitive marker for GM alterations, even in adults with well-controlled PKU during development. However, alterations in cortical thickness were unrelated to metabolic parameters and cognitive performance.

AUTHOR CONTRIBUTIONS

Conception and design: Regula Everts, Roman Trepp, and Raphaela Muri. *Funding acquisition:* Regula Everts, Roman Trepp, Raphaela Muri, and Stephanie Maissen-Abgottspon. *Data collection:* Raphaela Muri and Stephanie Maissen-Abgottspon. *Data analysis:* Raphaela Muri, Michael Rebsamen, and Christian Rummel. *Drafting of the article:* Raphaela Muri. *Reviewing and editing the article:* Stephanie Maissen-Abgottspon, Christian Rummel, Michael Rebsamen, Roland Wiest, Michel Hochuli, Bernadette M. Jansma, Roman Trepp, and Regula Everts. *Supervision:* Regula Everts and Roman Trepp.

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CONFLICT OF INTEREST

Raphaela Muri, Stephanie Maissen-Abgottspon, Christian Rummel, Michael Rebsamen, Roland Wiest, Michel Hochuli, Bernadette M. Jansma, Roman Trepp, and Regula Everts declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The neuroimaging data used in this study is confidential. Raw data allow for an individual reconstruction of the skull and the face and therefore underlie special data protection. However, neuroimaging data, cognitive data, metabolic data, and some demographical variables (age, sex) are available upon reasonable request after signing a confidentiality statement and a data sharing agreement.

ETHICS STATEMENT

All authors were compliant and followed the ethical guidelines, according to the requirements of the JIMD.


PATIENT CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients prior to study participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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