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RESEARCH ARTICLE

Decreased cortical thickness mediates the relationship between premature birth and cognitive performance in adulthood

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Abstract

Cortical thickness (CTh) reflects cortical properties such as dendritic complexity and synaptic density, which are not only vulnerable to developmental disturbances caused by premature birth but also highly relevant for cognitive performance. We tested the hypotheses whether CTh in young adults is altered after premature birth and whether these aberrations are relevant for general cognitive abilities. We investigated CTh based on brain structural magnetic resonance imaging and surface-based morphometry in a large and prospectively collected cohort of 101 very premature-born adults (<32 weeks of gestation and/or birth weight [BW] below 1,500 g) and 111 full-term controls at 26 years of age. Cognitive performance was assessed by full-scale intelligence quotient (IQ) using the Wechsler Adult Intelligence Scale. CTh was reduced in frontal, parietal, and temporal associative cortices predominantly in the left hemisphere in premature-born adults compared to controls. We found a significant positive association of CTh with both gestational age and BW, particularly in the left hemisphere, and a significant negative association between CTh and intensity of neonatal treatment within limited regions bilaterally. Full-scale IQ and CTh in the left hemisphere were positively correlated. Furthermore, CTh in the left hemisphere acted as a mediator on the association between premature birth and full-scale IQ. Results provide evidence that premature born adults have widespread reduced

Abbreviations: ANOVA, analysis of variance; BLS, Bavarian longitudinal study; BW, birth weight; CI, confidence interval; CNS, central nerve system; CTh, cortical thickness; FDR, false discovery rate; FOV, field of view; FT, full-term; FWE, family-wise error; GA, gestational age; GABA, gamma aminobutyric acid; GLM, general linear model; INTI, intensity of neonatal treatment index; IQ, intelligence quotient; MPRAGE, magnetization prepared rapid acquisition gradient echo; MRI, magnetic resonance imaging; ROI, region of interest; SE, standard error; TE, echo time; TFCE, threshold-free cluster enhancement; TI, inversion time; TIV, total intracranial volume; TR, repetition time; VLBW, very low birth weight; VP, very preterm; VP/VLBW, very preterm and/or very low birth weight; WAIS, Wechsler adult intelligence scale.

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CTh that is relevant for their general cognitive performance. Data suggest lasting reductions in cortical microstructure subserving CTh after premature birth.

KEYWORDS
brain development, cortical thickness, intelligence quotient, premature birth, structural magnetic resonance imaging

1 | INTRODUCTION

Premature birth (<37 weeks of gestation) has a high and increasing worldwide prevalence of almost 11% (Chawanpaiboon et al., 2019). Its associations with increased mortality and neurological-psychiatric morbidity as well as with reduced social outcomes and academic performance make it a crucial global health issue (D'Onofrio et al., 2013). Individuals born premature show alterations in brain development leading to macroscopic (Meng et al., 2016; Nosarti et al., 2002; Skranes et al., 2007) and microscopic (Back et al., 2002; Salmaso, Jablonska, Scafidi, Vaccarino, & Gallo, 2014; Volpe, 2009) structural brain aberrations. These structural aberrations are not only related to prematurity but also have functional implications up to adulthood, such as reduced general cognitive performance (Hedderich et al., 2019; Nosarti et al., 2008). It has repeatedly been reported and investigated in meta-analyses that the intelligence quotient (IQ) is lower after premature birth compared with controls (Twilhaar et al., 2018). These deficits persist into adulthood (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2015). Wolke, Johnson, and Mendonça (2019) reviewed cognitive outcomes after very preterm (VP) birth and concluded that low IQ is one of the major sequelae of VP birth.

Proposed pathomechanisms underpinning impaired brain development include several processes. First, preoligodendrocyte dysmaturation with activation of microglia and reactivity of astrocytes, second, axonal injury and third, neuronal injury to thalamic, subplate as well as to late migrating GABAergic neurons (Volpe, 2009, 2019). The mature cerebral cortex is organized in six horizontal layers. It consists of radial units in which progenitor cells of cortical neurons—that originate from several clones in the ventricular zone but share the same birthplace—settle after migrating along a common pathway of radial glial fascicles (Rakic, 1988). Cortical thickness (CTh) represents these radial columns of the cortex. It depends on the number of neuronal and glial cells, synaptic contacts, dendritic and axonal processes, including bidirectional fibers between the cortex and other cortical and subcortical structures, mainly the thalamus (Carlo & Stevens, 2013; Huttenlocher & Dabholkar, 1997; Rakic, 1995; Sowell et al., 2004). Cortical gray matter volume and CTh are age dependent. They show large expansion starting from the second and third trimester and continuing on into the neonatal period, marking the beginning of dendritic and axonal development as well as synaptogenesis, which peaks during childhood (Mills et al., 2016; Shaw et al., 2008). Then they decrease through the second decade due to various processes including pruning and increased myelination (Mills et al., 2016; Paus, 2005; Shaw et al., 2008; Sowell et al., 2004; Wilke, Krägeloh-Mann, & Holland, 2007). Recently, it has been shown that high IQ scores and high temporal CTh scores associate with larger, more complex dendrites of human pyramidal neurons (Goriounova et al., 2018). A positive relationship between general intelligence and CTh has been found in healthy adults (Menary et al., 2013; Narr et al., 2007). Hence, it seems that CTh represents cortical properties, which are not only most vulnerable to developmental disturbances caused by premature birth but also highly relevant for cognitive performance, and could serve as a valid biomarker for this investigation.

Results on CTh after premature birth are heterogeneous and decreases as well as increases have been reported (Lax et al., 2013; Martinussen et al., 2005; Rimol et al., 2019). As outlined above, CTh is age dependent, and the different developmental stages of the cortex present during childhood and adolescence may lead to conflicting data from these age groups. It has been suggested that CTh stabilizes in adulthood (Mills et al., 2016; Shaw et al., 2008); however, there are only very few studies investigating CTh in premature-born adults (Pascoe, Melzer, Horwood, Woodward, & Darlow, 2019; Rimol et al., 2019). These studies found reduced frontolateral, parietal and temporal CTh bilaterally as well as increased CTh in in frontomedial regions, occipital lobes and in small temporopolar clusters. While, to our knowledge, there are no investigations of the relationship between CTh and IQ in premature-born adults, some studies in premature-born adolescents reported a positive relationship between CTh and IQ (Bjuland, Løhaugen, Martinussen, & Skranes, 2013; Martinussen et al., 2005; Skranes et al., 2012).

In the current study, we tested three main hypotheses based on brain MRI and surface-based morphometry in a large and prospectively collected cohort of 101 VP and/or very low birth weight (VLBW) adults and 111 matched full-term (FT) controls at 26 years of age, respectively. (a) We hypothesized CTh to be altered after premature birth. We had no specific hypothesis regarding reductions or increases in CTh, since both have been reported in previous studies. (b) We hypothesized alterations in CTh to be specifically related to premature birth. Therefore, we hypothesized that CTh correlates with variables of premature birth. (c) Since premature birth has been associated with lower IQ scores compared to FT controls and positive associations between IQ scores and CTh have been reported in healthy adults, we hypothesized that lower CTh in specific regions after premature birth might be associated with lower IQ. To extend previous findings, we correlated CTh aberrations with full-scale IQ as a measure of general cognitive performance. Finally, we investigated

whether aberrant CTh is a mediator of the effects of premature birth on impaired cognitive performance of VP/VLBW individuals compared to FT controls by means of mediation analyses.

2 | METHODS

2.1 | Participants

All subjects were part of the Bavarian Longitudinal Study (BLS), a geographically defined, whole-population sample of neonatal at-risk children and healthy FT controls who were followed from birth, between January 1985 and March 1986, into adulthood (Riegel, Orth, Wolke, & Österlund, 1995; Wolke & Meyer, 1999; Wolke, Ratschinski, Ohrt, & Riegel, 1994). Then, 682 infants were born VP (<32 weeks of gestation) and/or with VLBW (birth weight [BW] <1,500 g). From the initial 916 FT born infants born at the same obstetric hospitals that were alive at 6 years, 350 were randomly selected as control subjects within the stratification variables of sex and family socioeconomic status in order to be comparable with the VP/VLBW sample. Of these, 411 VP/VLBW individuals and 308 controls were eligible for the 26-year follow-up assessment. Also, 260 from the VP/VLBW group and 229 controls participated in psychological assessments (Breeman et al., 2015). All of these subjects were screened for MR-related exclusion criteria including (self-reported): claustrophobia, inability to lie still for >30 min, unstable medical conditions (e.g., severe asthma), epilepsy, tinnitus, pregnancy, nonremovable, MRI-incompatible metal implants and a history of severe CNS trauma or disease that would impair further analysis of the data. However, the most frequent reason not to perform the MRI exam was a lack of motivation. Finally, 101 VP/VLBW subjects and 111 FT controls underwent MRI at 26 years of age (see Figure S1). The MRI examinations took place at two sites: The Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München, (n = 145) and the Department of Radiology, University Hospital of Bonn (n = 67). The study was carried out in accordance with the Declaration of Helsinki and was approved by the local institutional review boards. All study participants gave written informed consent. They received travel expenses and a small payment for participation. The study sample has previously been described in more detail (Bäuml et al., 2015; Grothe et al., 2017).

2.2 | Birth variables

Gestational age (GA) was estimated from maternal reports on the first day of the last menstrual period and serial ultrasounds during pregnancy. In cases in which the two measures differed by more than 2 weeks, clinical assessment at birth with the Dubowitz method was applied (Dubowitz, Dubowitz, & Goldberg, 1970). BW and intensity of neonatal treatment (INTI), quantifying duration and intensity of medical treatment after birth, were obtained from obstetric records (Gutbrod, Wolke, Soehne, Ohrt, & Riegel, 2000; Riegel et al., 1995). Daily assessments of care level, respiratory support, feeding dependency and neurological status (mobility, muscle tone, and neurological excitability) were performed. Each of the six variables was scored on a 4-point rating scale (0–3) by the method of Casaer and Eggermont (1985) (see Table S2 for a description of the variables). The INTI was computed as the mean score of daily ratings during the first 10 days of life or until a stable clinical state was reached (total daily scores <3 for 3 consecutive days), depending on which occurred first, ranging from 0 (best state) to 18 (worst state).

2.3 | Cognitive performance in adulthood

To assess global cognitive performance at the age of 26, prior to and independent of the MRI examination, study participants were asked to complete a short version of the "Wechsler Intelligenztest für Erwachsene," the German adaptation of the Wechsler Adult Intelligence Scale, Third edition (von Aster, Neubauer, & Horn, 2006). This test was carried out by trained psychologists who were blinded to group membership, and used to derive full-scale IQ estimates. This version included six subtests (vocabulary, similarities, letter- number-sequence, block design, matrix reasoning, and digit symbol coding) (Breeman et al., 2015; Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015).

2.4 | MRI data acquisition

At both sites, Bonn and Munich, MRI data acquisition was performed on Philips Achieva 3 T TX systems or Philips Ingenia 3 T system using an 8-channel SENSE head coil. Subject distribution among scanners: Bonn Achieva 3 T: 5 VP/VLBW, 12 FT, Bonn Ingenia 3 T: 33 VP/VLBW, 17 FT, Munich Achieva 3 T: 60 VP/VLBW, 65 FT, Munich Ingenia 3 T: 3 VP/VLBW, 17 FT. To account for possible confounds by scanner differences, functional and structural data analyses included scanner dummy-variables as covariates of no interest. Across all scanners, sequence parameters were kept identical. Scanners were checked regularly to provide optimal scanning conditions and MRI physicists at the University Hospital Bonn and Klinikum rechts der Isar regularly scanned imaging phantoms, to ensure within-scanner signal stability over time. Signal-to-noise ratio was not significantly different between scanners (one-way analysis of variance with factor "scanner-ID" [Bonn 1, Bonn 2, Munich 1, Munich 2]; $F(3,182) = 1.84$, $p = .11$). A high-resolution T1-weighted 3D-MPRAGE sequence (TI = 1,300 ms, TR = 7.7 ms, TE = 3.9 ms, flip angle = 15°; 180 sagittal slices, FOV = 256 × 256 × 180 mm, reconstruction matrix = 256 × 256; reconstructed isotropic voxel size = 1 mm^3) was acquired. All images were visually inspected for artifacts and passed homogeneity control implemented in the CAT12 toolbox (Gaser & Dahnke, 2016).

2.5 | MRI processing and surface-based morphometry

Images saved as DICOMs were converted to Nifti-format using dcm2nii (Li, Morgan, Ashburner, Smith, & Rorden, 2016). MRI data

were processed using the CAT12 toolbox pipeline for surface-based morphometry, which includes an algorithm for extracting CTh (Dahnke, Yotter, & Gaser, 2013). Data were normalized, segmented, and then smoothed using 15 mm kernels. The surface was then subdivided into 70 gyral-based regions of interest (ROIs), 35 per hemisphere, using the Desikan–Killiany Atlas (Desikan et al., 2006). See Table S3 for a list of the 70 ROIs. Note that the corpus callosum is an ROI of the Desikan–Killiany Atlas, which restricts the boundaries of other regions and which is not measured. Mean CTh within the remaining 34 ROIs per hemisphere was extracted.

After analyzing in which ROIs CTh significantly differed in VP/VLBW individuals compared to FT controls, a weighted mean of CTh per hemisphere was calculated. The CAT 12 toolbox divides cortical ROIs into triangles, which indicate the surface area of the given ROI. To calculate CTh per hemisphere, the number of triangles in each significant ROI was extracted. Using the number of triangles per significant ROI, a weighted mean CTh per hemisphere was calculated for each subject. We will refer to this weighted mean CTh per hemisphere as global CTh.

2.6 | Statistical analysis

2.6.1 | Group comparison for CTh

General linear model (GLM) analysis was performed using the CAT12 toolbox of SPM12 to find ROIs in which CTh was significantly smaller in VP/VLBW individuals compared to FT controls and ROIs in which CTh was significantly greater in VP/VLBW individuals compared to FT controls. Sex and scanner were entered as covariates. Analyses were corrected for multiple comparisons to control the false discovery rate (FDR) as all ROIs were entered into the analyses. Statistical significance was defined as p <.05, FDR-corrected.

As different strategies of analysis can result in different outputs, we wanted to validate our ROI-based results. Hence, the group difference was also tested using a vertex-wise GLM approach to identify areas in which CTh was significantly smaller in VP/VLBW individuals compared to FT controls and areas in which CTh was significantly greater in VP/VLBW individuals compared to FT controls. This was also done using the CAT12 toolbox of SPM12. Sex and scanner were entered as covariates. Threshold-free cluster enhancement was conducted using the TFCE toolbox of CAT12 (Smith & Nichols, 2009). Statistical significance was defined as p < .05, family-wise error (FWE)-corrected.

We did not use total intracranial volume (TIV) as a covariate in our analyses. This is necessary when analyzing structures that scale with head size, such as volume and surface area; however, CTh of a given area does not correlate with TIV (Barnes et al., 2010; Pakkenberg & Gundersen, 1997). Furthermore, head circumference and growth, measures closely related to TIV, have been identified to predict intelligence development and thus can be considered a marker of general developmental impairment after premature birth (Jaekel, Sorg, Baeuml, Bartmann, & Wolke, 2019). Since the purpose of our study is to determine whether developmental impairment after premature birth leads to alterations in CTh, adding TIV would eliminate important variance. Furthermore, age was not included as a covariate in our analyses, as VP/VLBW subjects and FT controls had the same age of 26 years.

2.6.2 | Linking CTh and variables

To investigate whether the group differences are specifically related to premature birth, we wanted to correlate the mean CTh within the ROIs identified with the GLM analysis with GA, BW, and INTI. However, since GA, BW, and INTI are highly correlated we performed a factor analysis, more specifically principal axis factoring, using SPSS. Bartlett's test of sphericity confirmed (p < .001) that the variables GA, BW, and INTI are related. One factor was extracted and a new variable was created for this factor using the regression method. We will refer to this factor score variable as the *prematurity score*. Because we found CTh to be reduced after premature birth in the group comparison, we expected CTh and the prematurity score to be positively correlated. One-tailed partial correlation analyses were conducted in the VP/VLBW group entering mean CTh in the significant ROIs and the prematurity score as variables of interest and sex and scanner as covariates.

For further evaluation of the relationships between CTh and premature birth in the VP/VLBW group, we wanted to test these correlations based on global CTh in the ROIs per hemisphere. One-tailed partial correlation analyses between global CTh values and the prematurity score were performed with sex and scanner as covariates.

To explore functional relevance of aberrations in CTh in the VP/VLBW group, cognitive performance, as measured by full-scale IQ, and CTh within the significant ROIs were entered into partial correlation analyses. Because we found CTh to be reduced after premature birth in the group comparison and because our VP/VLBW sample had lower full-scale IQ scores compared with the FT group, we expected CTh and full-scale IQ to be positively correlated. One-tailed partial correlation analyses were conducted in the VP/VLBW group entering mean CTh in the significant ROIs and full-scale IQ as variables of interest and sex and scanner as covariates.

In order to test for the functional relevance of global CTh aberrations in the VP/VLBW group, one-tailed partial correlation analyses were performed between the CTh values per hemisphere and full-scale IQ, with sex and scanner as covariates.

All partial correlation analyses were conducted using IBM SPSS Version 25 (IBM Corp., Armonk, NY) and FDR-corrected for multiple comparisons using the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995). Statistical significance was defined as p < .05.

2.6.3 | Mediation analysis

Finally, to test our hypothesis that CTh might mediate the effect of very premature birth/VLBW on cognitive outcomes, a mediation

analysis was carried out using the PROCESS toolbox (Version 3.4). The simple mediation model includes a causal variable, X, an outcome variable, Y, and an intervening variable, M. X is proposed to influence Y through M. One can estimate a direct, an indirect, and a total effect of X. The direct effect, c', describes the change in Y when X is altered by one unit and M remains equal, that means independent of the effect of M on Y. The indirect effect, *ab*, consists of two components, the effect of X on M, described by *a*, and the effect of M on Y, described by *b*. The indirect effect measures the change in Y as a result of the effect of X on M, which then affects Y, when X is altered by one unit. The total effect, *c*, measures the effect of X on Y. The PROCESS toolbox uses ordinary least squares regression to estimate each regression equation of the model separately with bootstrap confidence intervals used for inference (Hayes, 2017).

Group membership was entered as the causal variable, X, full-scale IQ as the outcome variable, Y, CTh in the left and right hemispheres as mediators, M, and sex and scanner as covariate controls.

3 | RESULTS

3.1 | Sample characteristics

See Table 1 for group demographic and clinical background variables. There was no significant difference between the VP/VLBW group and FT group regarding sex (p = .765) and age at scanning (p = .182). By design of the study, VP/VLBW subjects had significantly lower GA (p < .001) and lower BW (p < .001). For more detailed information on GA and BW in the VP/VLBW group, please see Table S4. For additional information on variables related to premature birth classifying early health (ventilation, duration of hospitalization and intraventricular hemorrhage), please see the supplement (S5). Furthermore, VP/VLBW subjects had significantly lower full-scale IQ scores (p < .001). For more detailed information on VP/VLBW and FT subjects, which had full-scale IQ scores below 80 or above 120, please see Table S6.

3.2 | Reduced CTh in premature-born adults

To test the hypothesis that CTh is altered after premature birth, we performed ROI-based GLM analysis. The group comparison of CTh in VP/VLBW individuals and controls showed significantly (p < .05, FDR-corrected) lower CTh in VP/VLBW subjects in frontolateral areas such as middle and inferior frontal gyrus bilaterally, in left supramarginal gyrus as well as in both temporal lobes. Differences were more pronounced in the left hemisphere. The ROIs are listed in Table 2 and visualized in the upper row of Figure 1a. There were no ROIs in which CTh was significantly greater in VP/VLBW subjects compared to FT controls.

In order to verify the results from the ROI-based analysis independently from the statistical method used, we performed a vertex-wise assessment of group differences. This analysis yielded significant (p < .05, FWE-corrected) decreases of CTh in frontal, parietal and temporal lobes with a predominance of the left hemisphere, supporting our findings from the ROI-based approach. Significant differences in CTh are visualized in the second row of Figure 1a. Again, the vertex-wise GLM analysis did not show any areas in which CTh was significantly greater in VP/VLBW subjects compared to FT controls.

Our findings support the hypothesis that CTh is altered in VP/VLBW subjects compared to FT controls, and show certain regions in the frontal, parietal and temporal lobes, predominantly in the left hemisphere, in which CTh is reduced.

To further investigate differences in CTh between VP/VLBW individuals and FT controls on a global level per hemisphere, we calculated weighted means of CTh. See the supplement (Table S7) for percentages of each significant ROI with regard to the whole hemisphere.

To test whether the group differences described above are specifically related to premature birth, we correlated ROI-based CTh from clusters showing group differences with perinatal variables defining premature birth represented by the prematurity score. The prematurity score was most highly and positively correlated with GA (r = .743), less and negatively correlated with INTI (r = −.650) and least and positively correlated with BW (r = .415).

TABLE 1 Demographical, clinical, and cognitive data

	VP/VLBW (n = 101)			FT (n = 111)			
	Mean	***SD***	**Range**	**Mean**	***SD***	**Range**	***p*-Value**
Sex (male/female)	58/43			66/45			.765
Age (years)	26.7	±0.61	25.7–28.3	26.8	±0.74	25.5–28.9	.182
GA (weeks)	30.5	±2.1	25–36	39.7	±1.1	37–42	**<.001**
BW (g)	1,325	±313	630–2,070	3,398	±444	2,120–4,670	**<.001**
INTI	11.6	±3.8	3–18	n.a.	n.a.	n.a.	n.a.
Full-scale IQ[a] (a.u.)	94.1	±12.7	64–131	102.5	±11.9	77–130	**<.001**

Note: Statistical comparisons: sex with χ^2 statistics; age, GA, BW, and FS-IQ with two-sample t tests. Bold letters indicate statistical significance defined as p < .05.

Abbreviations: BW, birth weight; FT, full-term; GA, gestational age; INTI, intensity of neonatal treatment index; IQ, intelligence quotient; *SD*, standard deviation; VP/VLBW, very preterm and/or very low birth weight.

[a]Data are based on 97 VP/VLBW and 108 FT-born individuals.

TABLE 2 Group difference in CTh

ROI	*p*-Value
Left hemisphere	
Inferior frontal gyrus, pars orbitalis	.000
Middle temporal gyrus	.016
Rostral middle frontal gyrus	.028
Caudal middle frontal gyrus	.040
Transverse temporal gyrus	.040
Supramarginal gyrus	.040
Inferior frontal gyrus, pars triangularis	.040
Right hemisphere	
Rostral middle frontal gyrus	.007
Inferior frontal gyrus, pars orbitalis	.028
Inferior frontal gyrus, pars triangularis	.029
Transverse temporal gyrus	.040

Note: ROIs in which the CTh of VP/VLBW individuals was significantly lower than the CTh of FT individuals with the respective *p*-values, FDR-corrected.
Abbreviations: CTh, cortical thickness; FDR, false discovery rate; FT, full-term; IQ, intelligence quotient; ROI, region of interest; VP/VLBW, very preterm and/or very low birth weight.

All results of the partial correlation analyses are listed in the supplement (Table S8); all significant results are listed in Table 3. The prematurity score correlated positively with CTh in all ROIs of the left hemispheres and in rostral middle frontal gyrus and pars triangularis of the inferior frontal gyrus in the right hemisphere.

In concordance with the results above, the partial correlation analyses of global CTh with the prematurity score showed significant positive correlation with CTh in both hemispheres. The associations between CTh in the left and right hemisphere and the prematurity score are visualized as scatterplots in Figure 1b. As the *r* values described above indicate, CTh is correlated positively with GA and BW and negatively with INTI. GA contributed most to the relationship between CTh and the prematurity score.

Our results suggest that the reduced CTh, found in certain regions in VP/VLBW subjects compared to FT controls, is specifically related to premature birth.

3.3 | Relationship between CTh and cognitive performance

To test whether CTh aberrations are functionally relevant, we correlated our findings with full-scale IQ as a measure of general cognitive performance. All results are listed in the supplement (Table S9); all significant results are listed in Table 4. The partial correlation analyses of regional CTh with full-scale IQ showed significant positive correlation in left pars orbitalis and pars triangularis of the inferior frontal gyrus and left middle temporal gyrus.

In concordance with the ROI-based approach, the partial correlation analyses of global CTh per hemisphere with full-scale IQ showed significant positive correlation in the left hemisphere. CTh in the right hemisphere did not show a significant correlation. The associations between CTh in the left and right hemisphere and full-scale IQ are visualized as scatterplots in Figure 2a.

Our findings indicate that CTh aberrations in the left hemisphere in VP/VLBW subjects are functionally relevant and correlate with impaired cognitive performance of VP/VLBW subjects compared to FT controls.

3.4 | Effect of CTh on the relationship between prematurity and cognitive performance

Finally, we tested whether aberrant CTh mediates the effects of premature birth on impaired cognitive performance of VP/VLBW subjects compared to FT controls. We conducted a mediation analysis entering premature birth as the causal variable, full-scale IQ as the outcome variable and mean CTh per hemisphere as the mediator. The mediation analysis showed a total effect of premature birth on full-scale IQ of $c = 8.288$, $SE = 1.692$ with 95% CI = 4.953–11.624 and $p < .001$, and a direct effect of $c' = 7.586$, $SE = 1.750$ with 95% CI = 4.136–11.036 and $p < .001$. The model showed a significant mediation effect of mean CTh in the left hemisphere on the relationship between premature birth and full-scale IQ, $ab = 1.361$, $SE = 0.772$, 95% CI = 0.098–3.086, $p = .039$, see Figure 2b. Weighted mean CTh of the right hemisphere, as expected, did not show a significant mediation effect (95% CI = −2.340 to 0.931). See the supplement (S10) for additional information on the results of the mediation analysis.

These results suggest that reduced CTh in the left hemisphere mediates the effects of premature birth on cognitive performance.

4 | DISCUSSION

Based on structural MRI and surface-based morphometry, we demonstrated that CTh is decreased in VP/VLBW subjects compared to FT controls at 26 years of age in frontal, parietal, and temporal associative cortices predominantly in the left hemisphere. As CTh in these regions correlated positively with the prematurity score, these aberrations seem to be specifically related to premature birth. Our results on the one hand replicate very recent findings about altered CTh in adulthood after premature birth; on the other hand, we extend them by demonstrating the specific relevance of CTh reductions for lower general cognitive abilities in associative cortices. This observation suggests associative cortices CTh as a functionally relevant target for monitoring and treating adverse effects of prematurity.

4.1 | Reduced CTh after premature birth

We found lower CTh in VP/VLBW subjects compared to FT controls in frontolateral areas such as middle and inferior frontal gyrus bilaterally, in left supramarginal gyrus as well as in both temporal lobes. CTh

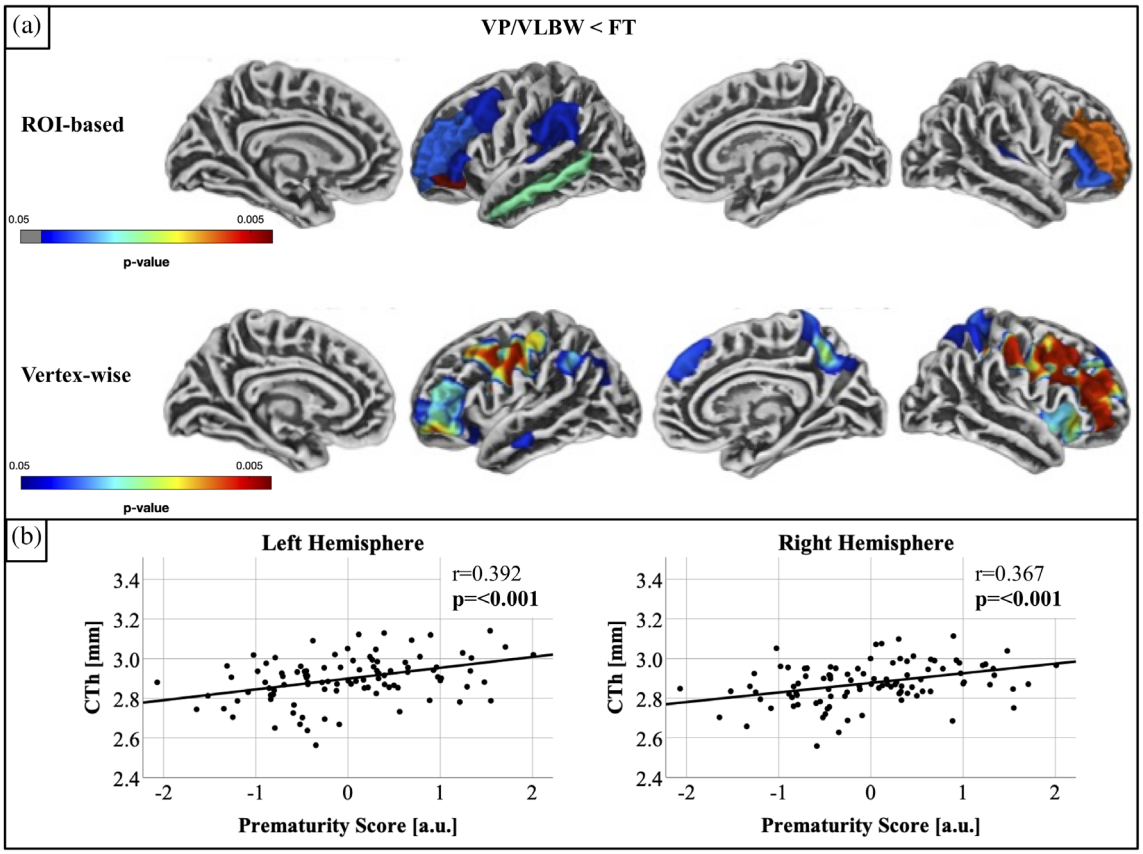

FIGURE 1 (a) Group difference in cortical thickness. The upper row shows all regions of interest (ROIs) in which cortical thickness (CTh) of very preterm and/or very low birth weight (VP/VLBW) individuals was significantly lower than CTh of full-term (FT) individuals. Statistical significance was defined as $p < .05$, FDR-corrected. The second row visualizes the vertex-wise approach and shows the areas in which CTh of VP/VLBW individuals was significantly lower than CTh of FT individuals. Statistical significance was defined as $p < .05$, family-wise error (FWE)-corrected. The p-values are color-coded—warmer colors indicate lower p-values. Both hemispheres are shown in medial and lateral views. (b) Relationship between cortical thickness and the prematurity score. The associations between CTh in each hemisphere and the prematurity score are shown as scatterplots. CTh in millimeters is plotted on the y-axes; the prematurity score is plotted on the x-axes. Linear regression lines as well as correlation coefficients and *p*-values were added. Bold letters indicate statistical significance defined as $p < .05$. Regression line left hemisphere: $Y = 2.90 + 0.05 \times X$. Regression line right hemisphere: $Y = 2.88 + 0.05 \times X$. CTh, cortical thickness; FT, full-term; ROI, region of interest; VP/VLBW, very preterm and/or very low birth weight

in these regions correlated positively with the prematurity score, suggesting that these aberrations are specifically related to premature birth. We confirmed these group differences using both an ROI-based and a vertex-wise approach to ensure that our results are independent of analytic approach. Furthermore, we eliminated the effects of confounding variables by controlling for sex and scanner.

Our finding is partly in line with very recent results found in a sample of premature-born adults aged 27–29, in which bilaterally reduced temporoparietal CTh was reported, and with results from another sample with a mean age of 26 years, in which reduced frontolateral, parietal, and temporal CTh was shown bilaterally (Pascoe et al., 2019; Rimol et al., 2019). However, our findings also differ from these reports: Increased CTh was reported in frontomedial regions, occipital lobes and in small temporopolar clusters, whereas our analyses did not yield any significant increases in CTh of VP/VLBW individuals compared to FT controls (Pascoe et al., 2019; Rimol et al., 2019).

Similar to our findings in premature-born adults, in adolescents aged about 15–20 years CTh was reduced in temporal and parietal lobes and also in frontolateral regions at the age of 20 years (Bjuland et al., 2013; Martinussen et al., 2005; Nagy, Lagercrantz, & Hutton, 2011; Nam et al., 2015). Furthermore, adolescents aged about 15–20 years showed areas of increased CTh especially in frontomedial regions but also in temporal and occipital lobes. Longitudinal analyses showed that in both VP and FT individuals, CTh decreased significantly from age 15 to 20 years; however, in VP adolescents, a more pronounced decrease occurred in similar, but much more widespread regions (Nam et al., 2015).

In concurrence with our findings in adults, prematurely born children showed reduced CTh in temporoparietal regions and, albeit to a lesser extent, in frontolateral regions, as compared with FT children (Hasler, Brown, & Akshoomoff, 2019; Lax et al., 2013; Sølsnes et al., 2015; Sripada et al., 2018; Zubiaurre-Elorza et al., 2012). Furthermore, children also showed areas of increased CTh especially in

TABLE 3 Relationship between CTh and the prematurity score

ROI	Correlation coefficient	*p*-Value
Left hemisphere	0.392	<.001
Inferior frontal gyrus, pars orbitalis	0.272	.004
Middle temporal gyrus	0.313	.001
Rostral middle frontal gyrus	0.358	<.001
Caudal middle frontal gyrus	0.285	.002
Transverse temporal gyrus	0.281	.003
Supramarginal gyrus	0.295	.002
Inferior frontal gyrus, pars triangularis	0.421	<.001
Right hemisphere	0.367	<.001
Rostral middle frontal gyrus	0.319	.001
Inferior frontal gyrus, pars triangularis	0.450	<.001

Note: Significant results of partial correlation analyses between CTh and the prematurity score after FDR correction using the Benjamini–Hochberg procedure.
Abbreviations: CTh, cortical thickness; FDR, false discovery rate; ROI, region of interest.

TABLE 4 Relationship between CTh and cognitive performance

ROI	Correlation coefficient	*p*-Value
Left hemisphere	0.233	.012
Inferior frontal gyrus, pars orbitalis	0.283	.003
Middle temporal gyrus	0.282	.003
Inferior frontal gyrus, pars triangularis	0.245	.009

Note: Significant results of partial correlation analyses between CTh and cognitive performance after FDR correction using the Benjamini–Hochberg procedure.
Abbreviations: CTh, cortical thickness; FDR, false discovery rate; ROI, region of interest; FS IQ, full-scale intelligence quotient.

occipital and frontomedial regions (Hasler et al., 2019; Sølsnes et al., 2015; Sripada et al., 2018; Vandewouw et al., 2019). Longitudinal analyses in children aged 4–12 years showed significant widespread decreases of CTh with age in occipital, frontal and temporal lobes bilaterally in both VP and FT children. CTh within limited occipital regions decreased significantly more with age in VP compared to FT children (Vandewouw et al., 2019).

In conclusion, CTh seems to be reduced in some areas in premature-born adults compared to FT controls. Although cross-sectional studies cannot answer questions regarding developmental trajectories of CTh, in light of the existing data and of our current findings, the following interpretation appears possible. In some regions, such as temporoparietal associative cortices, the cortex does not seem to reach maximum thickness compared to FT controls, as these areas also show reduced CTh in younger premature-born children (Hasler et al., 2019; Sølsnes et al., 2015) while CTh should still be increasing (Shaw et al., 2008). However, other cortical areas, for example, in the frontal and occipital lobes, seem to be thicker in younger ages after premature birth compared to FT controls (Hasler et al., 2019; Sølsnes et al., 2015; Vandewouw et al., 2019) with a more rapid decrease in CTh through adolescence as a possible result of delayed developmental processes (Nam et al., 2015). Ultimately, more longitudinal studies are necessary in order to shed more light on cortical growth trajectories in premature-born individuals through life.

The question remains as to which cellular mechanisms underlie and induce the reductions in CTh in premature-born adults could be induced. CTh depends not only on the number of neuronal and glial cells but also on dendritic and axonal processes as well as synaptic density (Carlo & Stevens, 2013; Huttenlocher & Dabholkar, 1997; Sowell et al., 2004). After premature birth, brain development is thought to be impaired due to cellular processes described in the introduction including neuronal and glial injury and dysmaturation of axons (Volpe, 2009, 2019). Results of an experimental study using a preterm large-animal model indicate cortical growth impairments to be associated with diffuse disturbances in the dendritic arbor and synapse formation of cortical neurons (Dean et al., 2013). Furthermore, in VP infants with slower postnatal growth, a delay in microstructural development of cortical gray matter without changes in white matter has been described, suggesting delayed expansion of neuronal process formations, synaptogenesis, and/or apoptosis in the cerebral cortices as possible mechanisms (Vinall et al., 2013). In conclusion, CTh seems to be reduced in some cortical regions in premature-born adults compared to FT controls due to various mechanisms including dysmaturation of axons and disturbances in dendritic branching and synaptogenesis. These microscopic properties such as dendritic complexity have been linked to intelligence (Goriounova et al., 2018) suggesting that aberrations in CTh may affect cognitive performance.

4.2 | Reduced CTh mediates the effects of premature birth on cognitive performance

Our results showed a positive correlation between CTh in the left hemisphere and full-scale IQ in VP/VLBW individuals, indicating functional relevance of altered CTh after premature birth. Furthermore, we found a mediating effect of CTh in the left hemisphere on the relationship between premature birth and full-scale IQ. We eliminated the effects of confounding variables by controlling for sex and scanner.

Cognitive performance is tightly linked to cortical development and a particularly plastic cortex has been reported to be associated with higher intelligence (Shaw et al., 2006). In healthy adults, a positive relationship between general intelligence and CTh has been found (Menary et al., 2013; Narr et al., 2007). More specifically, correlation of CTh with full-scale IQ showed predominance of the left hemisphere (Choi et al., 2008). Lesion studies supported a lateralization in favor of the left hemisphere (Barbey et al., 2012; Gläscher et al., 2009; Gläscher et al., 2010). More recently, cortical thickening

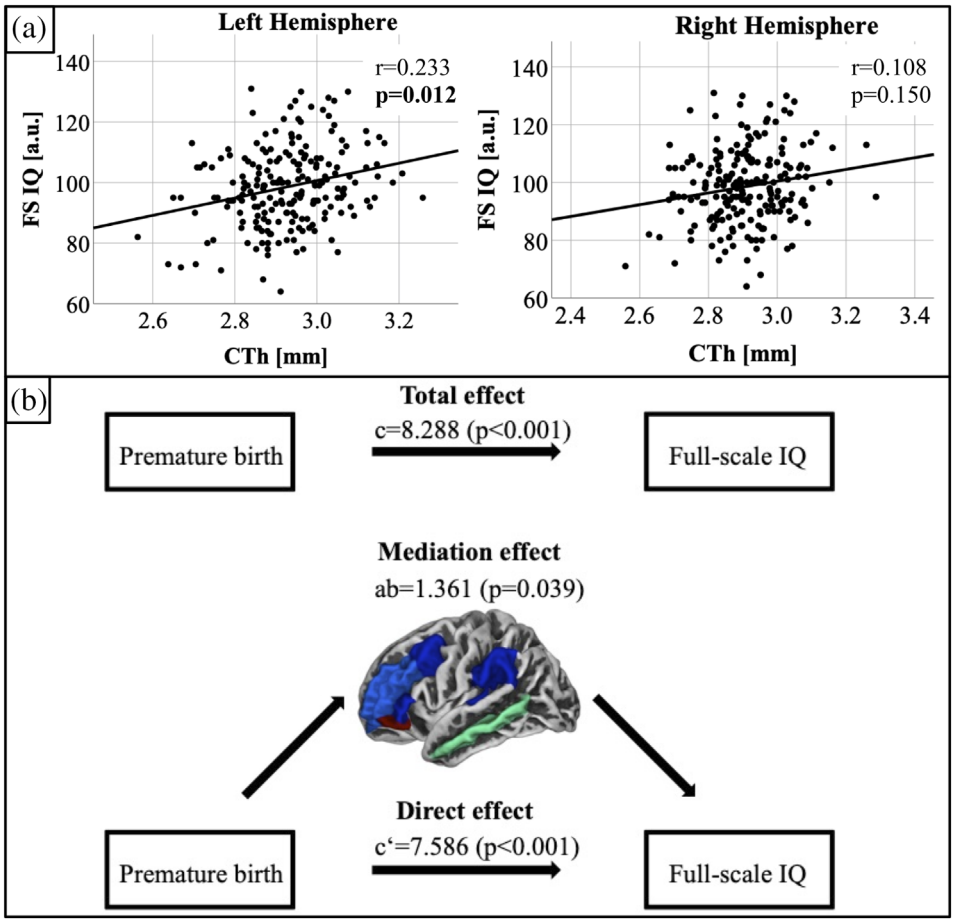

FIGURE 2 (a) Relationship between CTh and cognitive performance. The associations between CTh in the left and right hemisphere and full-scale IQ are shown as scatterplots. Full-scale IQ is plotted on the y-axis and CTh in millimeters is plotted on the x-axis. Linear regression lines as well as correlation coefficients and *p*-values were added. Bold letters indicate statistical significance defined as $p < .05$. Regression line left hemisphere: $Y = 14.49 + 28.72 \times X$. Regression line right hemisphere: $Y = 39.39 + 20.35*X$. (b) Effect of CTh on the relationship between prematurity and cognitive performance. The mediation analysis showed a significant total effect of premature birth on full-scale IQ, *c*. When adjusting for CTh in the left hemisphere there was a significant direct effect, *c′* of prematurity on full-scale IQ. Finally, CTh in the left hemisphere significantly mediates the relationship between premature birth and cognitive performance, *ab*. CTh, cortical thickness; IQ, intelligence quotient

in the left hemisphere has been associated with higher IQ in adulthood (Schnack et al., 2015). These findings in FT adults without a history of brain development impairment are in line with our results in VP/VLBW adults with impaired brain development. Furthermore, our results are consistent with the parieto-frontal integration theory of intelligence, which associates frontal and parietal brain structures with intelligence (Jung & Haier, 2007). In premature-born adolescents, some studies described a positive relationship between CTh and IQ, which is in line with our findings in adults (Bjuland et al., 2013; Martinussen et al., 2005; Skranes et al., 2012). On a cellular level, intelligence is linked with neuronal complexity as high IQ scores and large temporal CTh are associated with larger, more complex dendrites of human pyramidal neurons (Goriounova et al., 2018).

In conclusion, premature birth seems to lead to disturbed cortical development with reduced CTh in adulthood contributing to impaired cognitive performance of VP/VLBW subjects compared to FT controls. However, there are numerous other structural neural correlates of intelligence, such as total and regional brain volumes, surface area, and gyrification, which leads to difficulties in terms of drawing conclusions from one of them alone (Luders, Narr, Thompson, & Toga, 2009; Tottenham, 2020). Hence, our findings will only represent a small part of the relationship between neuroanatomical measures and cognitive performance.

4.3 | Strengths and limitations

Some limitations of the present study must be highlighted. The current sample is biased to VP/VLBW adults with less severe neonatal complications, less functional impairments, and higher IQ (see Table S11). Individuals with more birth complications and/or severe lasting impairments in the initial Bavarian Longitudinal Study sample were more likely to be excluded in initial screening for MRI due to exclusion criteria for MRI (e.g., infantile cerebral palsy). Thus, differences in CTh between VP/VLBW and term control adults reported here are conservative estimates of true differences. However, in terms of GA, BW and INTI, our final sample was still representative of the full cohort as these values were not significantly different in VP/VLBW subjects with MRI data compared to subjects without MRI data (see Table S11).

Generally, studies linking certain aspects of brain structure with cognitive functioning are always compromised by focusing on special features and by potential nonlinear trends between brain structure and cognitive functioning. Moreover, there are other individual, social, and environmental factors that influence the association between brain structural features and cognitive performance such as age, years of education, or socioeconomic status. However, strength of our study is that a relevant impact of patient age on CTh at the time of

the MRI scan is excluded as VP/VLBW subjects and FT controls had the same age of 26 years.

Interpretations of cortical dysmaturation and cognitive development are limited as this study is cross-sectional and only represents a single time-point. Longitudinal studies are needed to better address these questions.

Finally, the current sample has the strength of large size (101 VP/VLBW and 111 FT adults), enhancing the generalizability of our findings. This is supported by narrow 95% confidence intervals of CTh in the significant ROIs and in both hemispheres (see Table S12).

5 | CONCLUSIONS

Our results indicate that premature birth reduces CTh in associative cortices predominantly in the left hemisphere in adulthood. The findings suggest that reduced CTh after premature birth contributes to impaired general cognitive functioning compared to FT controls, as CTh mediates the relationship between premature birth and cognitive performance. Hence, CTh in associative cortices may provide a functionally relevant target for monitoring and treating adverse effects of prematurity.

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DATA AVAILABILITY STATEMENT

Patient data used in this study are not publicly available but stored by the principal investigators of the Bavarian Longitudinal Study.

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SUPPORTING INFORMATION

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