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An analysis of MRI derived cortical complexity in premature-born adults: Regional patterns, risk factors, and potential significance

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ABSTRACT

Premature birth bears an increased risk for aberrant brain development concerning its structure and function. Cortical complexity (CC) expresses the fractal dimension of the brain surface and changes during neurodevelopment. We hypothesized that CC is altered after premature birth and associated with long-term cognitive development.

One-hundred-and-one very premature-born adults (gestational age <32 weeks and/or birth weight <1500 g) and 111 term-born adults were assessed by structural MRI and cognitive testing at 26 years of age. CC was measured based on MRI by vertex-wise estimation of fractal dimension. Cognitive performance was measured based on Griffiths-Mental-Development-Scale (at 20 months) and Wechsler-Adult-Intelligence-Scales (at 26 years).

In premature-born adults, CC was decreased bilaterally in large lateral temporal and medial parietal clusters. Decreased CC was associated with lower gestational age and birth weight. Furthermore, decreased CC in the medial parietal cortices was linked with reduced full-scale IQ of premature-born adults and mediated the association between cognitive development at 20 months and IQ in adulthood.

Results demonstrate that CC is reduced in very premature-born adults in temporoparietal cortices, mediating the impact of prematurity on impaired cognitive development. These data indicate functionally relevant long-term alterations in the brain's basic geometry of cortical organization in prematurity.

1. Introduction

Premature birth, i.e. birth before 37 weeks of gestation and/or birth weight below 2500 g, has a worldwide prevalence of around 11% (Howson et al., 2013). It has been shown that prematurity has an impact on brain structure both on a microscopic (Back et al., 2002; Ball et al., 2013; Buser et al., 2012; Dean et al., 2013; Deng, 2010; Kinney et al., 2012; Salmaso et al., 2014) and macroscopic level (Ball et al., 2014, 2012; Grothe et al., 2017; Meng et al., 2016; Nosarti et al., 2008).

One way to conceive brain structure is through describing the complexity of its surface shape. The corresponding metric, cortical complexity (CC) can be measured by using the fractal dimension (FD) of the brain's cortical surface, and it has been shown to indicate a highly conserved principle across mammalian brains, namely self-similarity and scale-invariance (Hofman, 1991; Mota and Herculano-Houzel, 2015; Seely et al., 2014; Yotter et al., 2011). Formally, FD is a unitless measure which characterizes a power-law relationship between increases of a

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Abbreviations

ANOVA	Analysis of variance
BLS	Bavarian Longitudinal Study
BW	Birth weight
CC	Cortical complexity
CI	Confidence interval
DARTEL:	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
FD	Fractal dimension
FS-IQ	Full-scale IQ
FT	Full-term
FWE	Family-wise error
FWHM	Full-width at half maximum
GA	Gestational age
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic resonance imaging
ROI	Region of interest
SE	Standard error
SES	Socioeconomic status
TE	Time to echo
TFCE	Threshold-free cluster enhancement
TI	Time to inversion
TR	Time to repetition
VLBW	Very low birth weight
VP	Very preterm
VP/VLBW	Very preterm/very low birth-weight
WAIS	Wechsler Adults Intelligence Scale

certain geometrical attribute of an object (e.g. length, area, volume) as the measurement scale decreases (Mandelbrot, 1967). This can be transferred to cortical surfaces of mammalian brains and leads to the measure CC which quantifies the spatial frequency of cortical shape details in a single numeric value (Hofman, 1991; Kapellou et al., 2006; Sandu et al., 2014a; Yotter et al., 2011). As the cerebral cortex is a convoluted surface in three-dimensional space, its FD, i.e. its CC is expected to lie between 2 and 3, with higher values representing a higher level of detail or irregularities in cortical shape (Hofman, 1991; Sandu et al., 2014a; Yotter et al., 2011). Thus, CC can be considered a measure of gyrification by combining multifactorial information from sulcal depth, folding frequency, convolution of gyral shape, and cortical thickness into one single value (Im et al., 2006; King et al., 2010).

In humans, CC changes during brain development and aging: it rises during intrauterine and postnatal phases until adolescence and then starts to steadily decrease during the course of adulthood (Blanton et al., 2001; Kalmanti and Maris, 2007; Madan and Kensinger, 2016; Shyu et al., 2010). Moreover, CC has been shown to be altered in disease: reduced CC is associated with long-term cognitive development and cognitive decline in patients with Alzheimer's dementia (King et al., 2010; Mustafa et al., 2012; Sandu et al., 2014b). Recently, we described long-term alterations of gyrification in premature-born adults, suggesting that the development of the brain's basic geometry – i.e., the geometrical relations on the brain's surface - follows a distinct trajectory after premature birth (Hedderich et al., 2019).

Based on the link between CC and both brain development and cognitive functioning over the life-course, we hypothesized that alterations of CC – as a marker of brain surface geometry – could be detected as a long-term effect of early disruptions of neurodevelopment, which premature-born individuals are at increased risk for. Furthermore, we hypothesized that these alterations in CC link with cognitive abilities and their long-term development. We tested these hypotheses by using structural MRI, geometric modeling of cortex surface, and intelligence assessments together with canonical statistical testing and mediation analyses in a large cohort of very premature-born young adults (VP/VLBW) and age-matched controls born at full-term (FT).

2. Material and methods

2.1. Participants

The participants examined in this study are part of the Bavarian Longitudinal Study (BLS), a geographically defined, whole-population sample of neonatal at-risk children and healthy full term controls who were followed from birth into adulthood (Riegel et al., 1995; Wolke and Meyer, 1999). Of the initial 682 infants born very preterm (VP; <32 weeks) and/or with very low birth weight (VLBW; < 1500 g), 411 were eligible for the 26-year follow-up assessment, and 260 (63.3%) participated in psychological assessments (Breeman et al., 2015). Of the initial 916 full-term born infants from 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, 308 were eligible for the 26-year follow-up assessment, and 229 (74.4%) participated in psychological assessments. All of the 260 subjects from the VP/VLBW group underwent an initial screening for MR-related exclusion criteria, which included: (self-reported) claustrophobia, inability to lie still for > 30 min, unstable medical conditions (e.g. severe asthma), epilepsy, tinnitus, pregnancy, non-removable, MRI-incompatible metal implants and a history of severe CNS trauma or disease that would impair further analysis of the data. The most frequent reason not to perform the MRI exam, however, was a lack of motivation. The remaining eligible, 101 VP/VLBW and 111 FT individuals underwent MRI at 26 years of age. All participants underwent screening for neuropsychiatric disorders using the "Munich Composite International Diagnostic Interview" which is a reliable and well-validated tool (Wittchen et al., 1995; Wittchen and Nelson, 1996). The distribution of gestational age and birth weight in the VP/VLBW group is depicted in the appendix (Fig. A1).

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. Written consent was obtained from all participants. All study participants received travel expenses and a small payment for participation. A more detailed description of participants, including incidental brain MRI findings can be found in previous publications (Bauml et al., 2015; Grothe et al., 2017).

2.2. Birth-related 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 where the two measures differed by more than two weeks, clinical assessment at birth with the Dubowitz method was applied (Dubowitz et al., 1970). Maternal age, birth weight (BW) and duration of hospitalization, were obtained from obstetric records. Family socioeconomic status (SES) was assessed through structured parental interviews within 10 days of childbirth. SES was computed as a weighted composite score based on the profession of the self-identified head of each family together with the highest educational qualification held by either parent (Bauer, 1988).

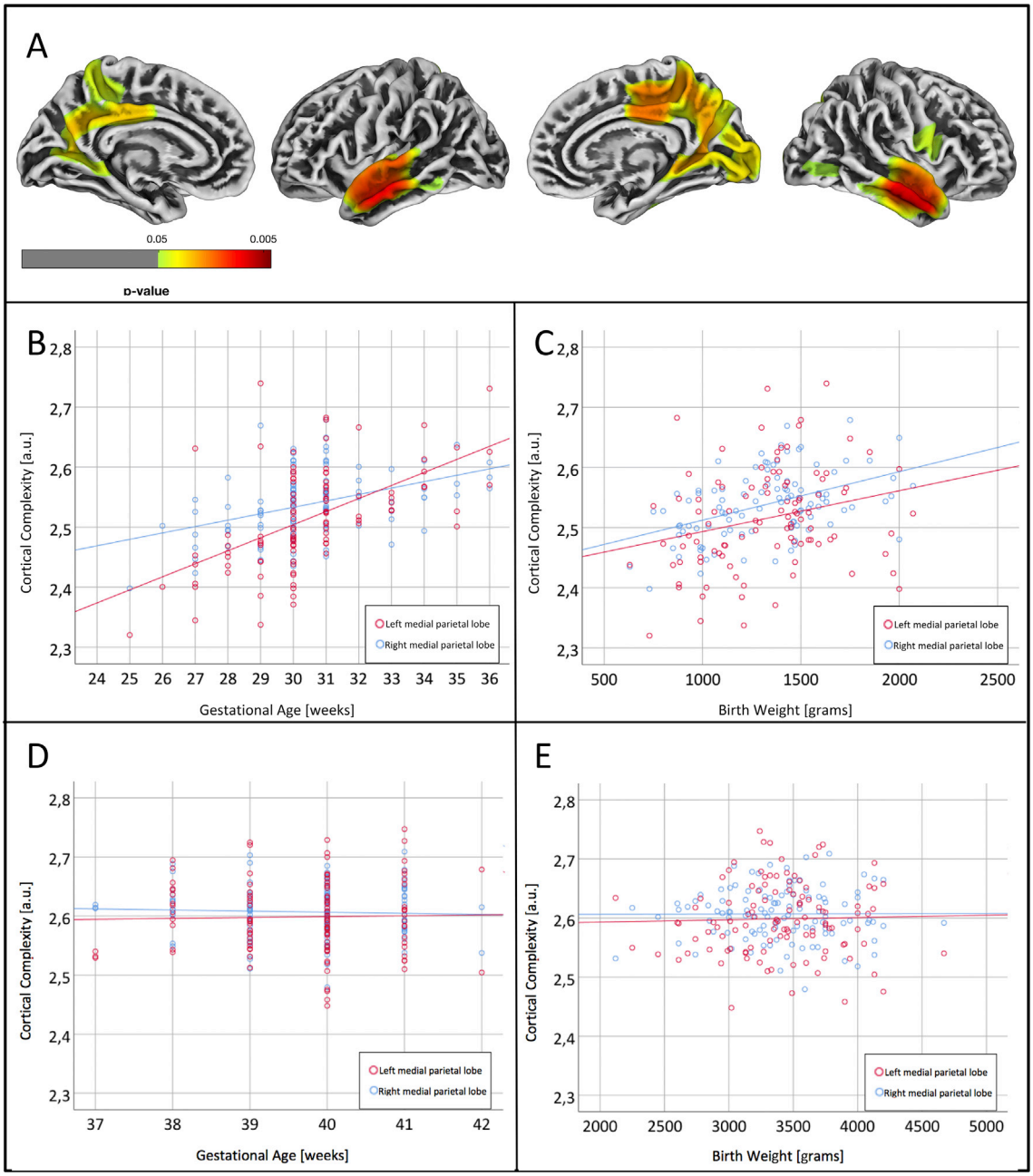

Fig. 1. A) Cortical complexity is decreased in premature-born adults in bilateral temporoparietal clusters. Statistical parametric map of group comparison of CC between VP/VLBW and FT adults. Bihemispheric lateral and medial views are shown. Two-sample *t*-test, $p < 0.05$, FWE-corrected, threshold-free cluster enhancement was used. Color bars indicate p-values for decreased CC in the VP/VLBW group. Warm colors represent lower p-values. **B) Association between cortical complexity and gestational age in premature-born adults.** CC values (y-axis) are plotted against gestational age at birth in weeks (x-axis) for the medial parietal lobe of the right hemisphere (blue dots) and the left hemisphere (red dots) in VP/VLBW individuals. Linear regression lines are added for the medial parietal lobe of the right hemisphere (blue line) and the left hemisphere (red line).**C) Association between cortical complexity and birth weight in premature-born adults.** CC values (y-axis) are plotted against birth weight in grams (x-axis) for the medial parietal lobe of the right hemisphere (blue dots) and the left hemisphere (red dots) in VP/VLBW individuals. Linear regression lines are added for the medial parietal lobe of the right hemisphere (blue line) and the left hemisphere (red line).**D) Association between cortical complexity and gestational age in adults born at full-term.** CC values (y-axis) are plotted against gestational age at birth in weeks (x-axis) for the medial parietal lobe of the right hemisphere (blue dots) and the left hemisphere (red dots) in FT individuals. Linear regression lines are added for the medial parietal lobe of the right hemisphere (blue line) and the left hemisphere (red line).**E) Association between cortical complexity and birth weight in adults born at full-term.** CC values (y-axis) are plotted against birth weight in grams (x-axis) for the medial parietal lobe of the right hemisphere (blue dots) and the left hemisphere (red dots) in FT individuals. Linear regression lines are added for the medial parietal lobe of the right hemisphere (blue line) and the left hemisphere (red line).

Abbreviations: CC: cortical complexity, FT: full-term, VP/VLBW: very preterm and/or very low birth weight.

2.3. Neurocognitive assessment

At 20 months of age, children were administered the Griffith Mental Development Scale Developmental Quotient items (Brandt, 1983). At 26 years of age, study participants were assessed using a short version of the German Wechsler Adults Intelligence Scale, Third edition (WAIS-III) (von Aster et al., 2006): The assessment took place prior to and independent of the MRI scan and was carried out by trained psychologists who were blinded to group membership. Consecutively, full-scale intelligence quotient (FS-IQ) performance was computed. School success between age six to age 13 was rated on an ordinal scale from 1 (little success) to 9 (high success). Detailed levels of the ordinal rating scale can be found in Table S1.

2.4. MRI data acquisition

MRI examinations were performed at both sites on either a Philips Achieva 3T or a Philips Ingenia 3T system using 8-channel SENSE head-coils. Subject distribution among scanner was as follows: Bonn Achieva 3T: 5 VP/VLBW, 12 FT, Bonn Ingenia 3 T: 33 VP/VLBW, 17 FT, Munich Achieva 3T: 60 VP/VLBW, 65 FT, Munich Ingenia 3T: 3 VP/VLBW, 17 FT. To account for possible confounds by the scanner-specific differences, all statistical analyses included categorical dummy regressors for scanner identity as covariates of no interest. Across all scanners, sequence parameters were kept identical. Scanners were checked regularly to provide optimal scanning conditions. 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 (SNR) was not significantly different between scanners (one-way ANOVA with factor "scanner-ID" [Bonn 1, Bonn 2, Munich 1, Munich 2]; $F(3,182) = 1.84$, $p = 0.11$). The image protocol included a high-resolution T1-weighted, 3D-MPRAGE sequence (TI = 1300 ms, TR = 7.7 ms, TE = 3.9 ms, flip angle 15°; field of view: 256 mm × 256 mm) with a reconstructed isotropic voxel size of 1 mm^3. All images were visually inspected for artifacts and passed homogeneity control implemented in the CAT12 toolbox (Gaser and Dahnke, 2016).

2.5. Surface-based morphometry analysis

First, all images saved as DICOMs were transformed to Nifti-format using dcm2nii (Li et al., 2016). The CAT12 toolbox comprises a processing pipeline for surface-based morphometry, which includes an established novel algorithm for extracting the cortical surface (Dahnke et al., 2013), which then allows for the computation of multiple morphometric parameters, including CC based on spherical harmonic reconstructions (Yotter et al., 2011).

In brief, T1-weighted images underwent tissue segmentation into grey matter, white matter and cerebrospinal fluid. Topological correction is performed through an approach based on spherical harmonics (Yotter et al., 2011). An adapted volume-based diffeomorphic DARTEL algorithm was then applied to the surface for spherical registration. Local CC was computed as described previously (Yotter et al., 2011). Central cortical surfaces were created for both hemispheres separately. Finally, all scans were re-sampled and smoothed with a Gaussian kernel of 30 mm (FWHM).

2.6. Statistical analysis

To determine differences in CC between groups, a two-sample *t*-test was performed in SPM12, adjusting for sex and scanner as covariates of no interest. Contrasts were processed using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) with 5000 permutations and statistical significance was defined as $p < 0.05$, family-wise error (FWE) corrected. CC raw values of the group difference clusters (VP/VLBW < FT) were extracted and analyzed with SPSS version 25 (IBM Corp., Armonk, NY, USA). Effects of sex on CC group difference clusters were assessed using a general linear model. Effects of socioeconomic status on CC group difference clusters were assessed in the whole cohort using a general linear model. Correlations between school success and CC in group difference clusters were analyzed using Spearman's rho. Based on the hypothesis that school success would be positively correlated with CC, Spearman analyses were one-sided. All other analyses were two-sided at $p < 0.05$. To determine associations between CC, aspects of premature birth and cognitive performance, partial correlation analyses and mediation analyses were performed corrected for sex and scanner for the VP/VLBW and FT group separately. In order to test whether CC mediates the association between cognitive development at 20 months of age and full-scale IQ in adulthood, a mediation analysis was performed using the PROCESS toolbox (version 3.0) (Hayes, 2017). In the mediation model, Griffiths Mental Development Scale at 20 months (DQ-20) was entered as causal variable, adult FS-IQ as the outcome variable, individual raw CC values from group difference clusters as the mediator variable, and MRI scanner and sex as covariates of no interest. Path coefficients for total effect, direct effect and indirect effect were estimated using (unstandardized) regression coefficients from multiple regression analyses, and statistical significance of the indirect effect was tested using a nonparametric bootstrap approach (with 20.000 repetitions) to obtain 95% confidence intervals. We calculated p-values for indirect effects based on 95% confidence intervals, standard error and estimated effect as described by Altman and Bland (2011). In order to test

Table 1
Demographical, clinical, and cognitive data.

	VP/VLBW (n = 101)			FT (n = 111)			p value
	M	SD	Range	M	SD	Range	
Sex (male/female)	58/43			66/45			0.167
Age (years)	26.71	±0.61	25.7–28.3	26.84	±0.74	25.5–28.9	0.765
GA (weeks)	30.5	±2.1	25–36	39.7	±1.1	37–42	<0.001
BW (g)	1325	±313	630–2070	3398	±444	2120–4670	<0.001
Hospitalization (days)	72.2	±26.4	24–170	6.9	±3.0	2–26	<0.001
SES[a] (a.u.)	29/44/28		1–3	35/50/26		1–3	0.760
Maternal age (years)	29.5	±4.8	16–41	29.4	±5.2	18–42	0.889
Full-scale IQ[b] (a.u.)	94.1	±12.7	64–131	102.5	±11.9	77–130	<0.001
DQ at 20 months	103.3	±14.8	65–143	110.1	±14.9	77–143	0.001
School success[c]	5	4–9	1–9	8	5–9	1–9	<0.001

Statistical comparisons: sex, SES with χ^2 statistics; age, GA, BW, Hospitalization, maternal age, IQ, DQ with two sample t-tests.
Abbreviations: BW, birth weight; DQ, developmental quotient; FT, full-term; GA, gestational age; IQ intelligence quotient; M, Mean; maternal age, maternal age at birth; SD, standard deviation; SES, socioeconomic status at birth; VP/VLBW, very preterm and/or very low birthweight.
[a] 1 = upper class, 2 = middle class, 3 = lower class.
[b] Data are based on 97 VP/VLBW and 108 FT-born individuals.
[c] Median and interquartile range are given instead of mean and standard deviation.

the specificity of CC as mediator, additional mediation analyses were performed exchanging CC values with GA and BW as mediators.

2.7. Data availability statement

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

3. Results

3.1. Sample characteristics

Group demographic and clinical background variables are shown in Table 1. The distribution of GA and BW in the VP/VLBW group is depicted in Appendix Fig. A1. There were no significant differences between the VP/VLBW and FT group regarding age at scanning ($p = 0.765$), sex ($p = 0.167$), SES at birth ($p = 0.492$), and maternal age ($p = 0.889$). By design, VP/VLBW subjects had significantly lower GA ($p < 0.001$) and lower BW ($p < 0.001$), they were hospitalized for a longer time after birth ($p < 0.001$). VP/VLBW subjects had significantly lower developmental quotient (DQ) scores at 20 months ($p < 0.001$) and adult FS-IQ scores ($p < 0.001$). School success was significantly lower for VP/VLBW individuals (median scores and interquartile range 5 [4–9] and 8 [5–9] for VP/VLBW and FT individuals, respectively; $p < 0.001$) as measured on an ordinal scale ranging from 1 (low success) to 9 (high success) (for more information about measured school success, please see Table S1). No statistical differences between groups were detected regarding neuropsychiatric disorders based the "Munich Composite International Diagnostic Interview". In the following absolute incidences and percentages are given: Mood disorder (VP/VLBW: 22 (22.9%) vs. FT: 19 (17.8%); $p = 0.361$), anxiety disorder (VP/VLBW: 28 (29.2%) vs. FT: 31 (29.0%); $p = 0.976$), substance abuse disorder (VP/VLBW: 0 (0.0%) vs. FT: 0 (0.0%); $p =$ n.a.), and eating disorder (VP/VLBW: 1 (1.0%) vs. FT: 5 (4.7%); $p = 0.127$).

3.2. Widespread decreases in cortical complexity in premature-born adults

Group comparison of FT vs. VP/VLBW subjects revealed significantly decreased CC in the premature-born adults cohort. CC decrease was more pronounced for the right hemisphere. Overall, six clusters were identified: Major clusters could be found bilaterally in the lateral temporal cortex and the medial parietal cortex including the posterior cingulate gyrus and spreading to the medial occipital cortex. The group difference of CC in the medial parietal cortex was pronounced in the right hemisphere, whereas CC decreases in VP/VLBW subjects were distributed rather symmetrically in the lateral temporal cortex. Additionally, two smaller clusters were identified in the right hemisphere: One cluster was located in the frontal operculum and another one in the occipitotemporal junction. CC decrease clusters in VP/VLBW subjects are depicted in Fig. 1A. As sex potentially influences cortical brain structure, we tested for effects of sex on CC in the group difference clusters. We observed a significant association between sex and CC in the bilateral medial parietal clusters ($p = 0.018$ and $p = 0.004$ for the right and left side, respectively). There were no interaction effects between sex and history of premature birth. Detailed results regarding the effect on sex on CC can be found in the supplemental material (see Tables S2 and S3). No group differences of CC were seen in the opposite direction (VP/VLBW > FT).

3.3. Decreased cortical complexity correlates with premature birth variables

Partial correlation analyses between individual CC values and variables of premature birth in the VP/VLBW group were most consistently shown for the bihemispheric clusters identified in the medial parietal lobe (Fig. 1B&C). Medial parietal CC showed significant correlations with gestational age for both sides (right hemisphere: $r = 0.295$; $p = 0.014$, left hemisphere: $r = 0.395$; $p < 0.001$) and with birth weight for the right hemisphere ($r = 0.447$; $p < 0.001$). Lateral temporal CC was significantly correlated with birth weight in the right hemispheric cluster ($r = 0.377$; $p = 0.002$). No correlations with variables of premature birth or neonatal treatment were observed for the smaller cluster in the right frontal opercular cortex and the right occipitotemporal junction.

3.4. Decreased cortical complexity correlates with measures of mental development and cognitive performance

Full-scale IQ measured by the Wechsler Adults Intelligence Scale correlated positively with CC in both medial parietal cortex clusters (right hemisphere: $r = 0.338$; $p = 0.002$, left hemisphere: $r = 0.255$; $p = 0.020$) and the left hemispheric lateral temporal cortex cluster ($r = 0.227$; $p = 0.039$) in VP/VLBW subjects. Mental development at age 20 months as measured by DQ-20 was significantly correlated only with medial parietal CC in the right hemisphere ($r = 0.364$, $p = 0.001$). Please see Fig. 2.

3.5. Potential socioenvironmental influences on cortical complexity

Recapitulating our results from the group comparison, we found bilateral clusters of decreased cortical complexity in the medial parietal and lateral temporal lobes in premature-born adults. We interpreted this finding as mainly driven by both altered brain aging and delayed cortical development after premature birth. However, further factors such as socioeconomic or cognitive developmental factors might also contribute to altered CC. Therefore, to test for additional factors influencing cortical structure, we analyzed the association between CC of group difference clusters with socioeconomic status at birth and school success. Based on a general linear model, there was no significant association between SES and CC (for detailed results, please see Table S4). We found significant associations between CC and school success in the left lateral temporal lobe (Spearman's rho = 0.260; $p = 0.005$) and in the right medial parietal lobe (Spearman's rho = 0.184; $p = 0.037$).

3.6. Mediation analyses on long-term cognitive development

We tested whether decreased CC mediates the association between mental development at 20 months and adult full-scale IQ. Conceptually, DQ-20 measures cognitive performance at an earlier stage than adult FS-IQ, which is why we chose DQ-20 as causal variable and FS-IQ as outcome variable. CC can be considered a surrogate for the result of long-term brain development and thus served as mediator. The mediation analysis path diagram is shown in Fig. 2B. Mediation analyses were performed for VP/VLBW and FT individuals separately. In a first mediation analysis using subject-wise CC values from the right hemispheric medial parietal cluster as mediator, the total effect of DQ-20 on FS-IQ in the regression model was $c = 0.481 \pm 0.121$; 95%-CI: 0.241–0.721; $p = 0.001$. The direct effect of DQ at 20 months on adult FS-IQ remained significant ($c' = 0.390 \pm 0.128$; 95%-CI: 0.135–0.645; $p = 0.0031$). The indirect effect mediated by right medial parietal CC was statistically significant as determined by the 95%-CI ($ab = 0.091 \pm 0.054$; 95%-CI: 0.003–0.213; $p = 0.046$). However the size of the indirect effect on the association between mental development at 20 months of age and adult full-scale IQ was very low. As determined by 95%-CI, no statistically significant indirect effect of GA or BW was shown in the same mediation scheme (GA: 0.039 ± 0.041; 95%-CI: -0.052-0.112; $p = 0.017$; BW: 0.075 ± 0.054; 95%-CI: -0.008-0.200; $p = 0.083$). We conclude that there is no mediation effect for GA or BW on the association between mental development at 20 months of age and adult full-scale IQ. For FT individuals, no statistically significant mediation effect could be observed: Total effect of DQ-20 on FS-IQ in the regression model: $c = 0.328 \pm 0.178$; 95%-CI: -0.026-0.682; $p = 0.069$, direct effect of DQ at 20 months on adult FS-IQ ($c' = 0.324 \pm 0.180$; 95%-CI: -0.033-0.680; $p = 0.075$), indirect effect mediated by right medial parietal CC ($ab = 0.004 \pm 0.026$;

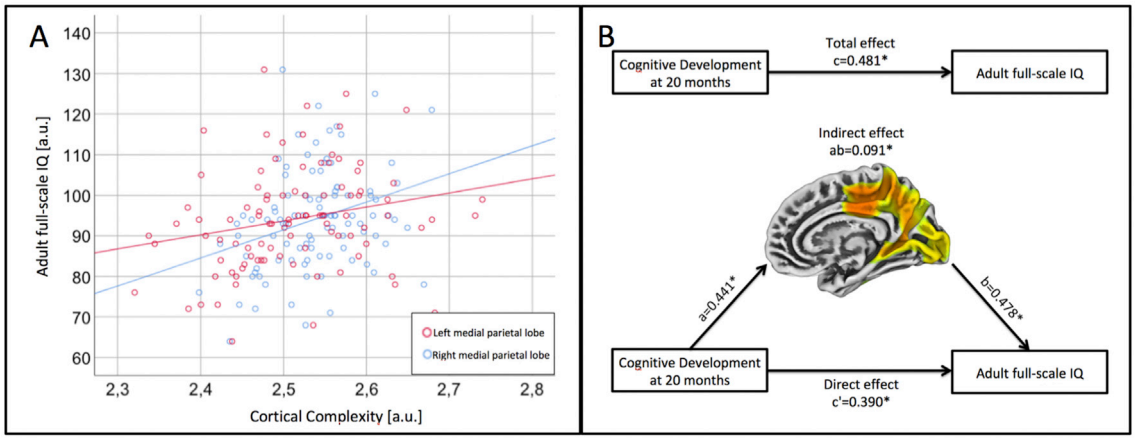

Fig. 2. A) Association between cortical complexity and adult full-scale IQ. CC values (x-axis) are plotted against adult FS-IQ (y-axis) for the medial parietal lobe of the right hemisphere (blue dots) and the left hemisphere (red dots) in VP/VLBW individuals. Linear regression lines are added for the medial parietal lobe of the right hemisphere (blue line) and the left hemisphere (red line).**B) Cognitive development at 20 months predicts adult full-scale IQ mediated by right medial parietal CC.** A two-way path diagram is shown in order to illustrate the result of the mediation analysis. DQ-20 scores significantly predict adult full-scale IQ in the regression model correcting for sex and scanner (total effect). Right medial parietal cortical complexity exhibits mediating effects of the association between DQ-20 and adult FS-IQ. All regression analyses are corrected for scanner and sex. The figure includes the following standardized regression coefficients: a, the effects of DQ-20 on right medial parietal CC; b, the effects of right medial parietal CC on adult FS-IQ when adjusting for DQ-20; c, the total effect of DQ-20 on FS-IQ; c', the direct effect of DQ-20 on FS-IQ when adjusting for right medial parietal CC; and ab, the indirect effect of DQ-20 on FS-IQ mediated by right medial parietal CC. Significant regression coefficients ($p < 0.05$) are marked with an asterisk.
Abbreviations: DQ-20: Griffith Mental Developmental Scale, Developmental Quotient at 20 months; FS-IQ: full-scale intelligence quotient; VP/VLBW: very preterm and/or very low birth weight.

95%-CI: -0.036-0.076; $p = 0.438$).

4. Discussion

Using structural MRI and longitudinal intelligence assessments, we demonstrated for the first time in premature-born adults that cortical complexity is decreased after premature birth, namely in medial parietal and lateral temporal cortices. The spatially distinct decrease in cortical complexity was strong with lower birth weight and shorter gestational period, indicating its premature birth-related origins. Cortical complexity of temporoparietal clusters was associated with reduced cognitive performance in premature-born adults. Furthermore, right hemispheric medial parietal CC significantly mediated the association between mental development at 20 months and adult full-scale IQ, thus being a potential cortical marker of long-term cognitive development.

4.1. Cortical complexity as a marker of brain surface geometry is reduced after premature birth

Cortical complexity is decreased in the adult brain after premature birth, namely in medial parietal and lateral temporal cortices (Fig. 1A). CC decrease is linked with GA and BW, indicating its relation with prematurity (Fig. 1B and C). Interestingly, there is no correlation between GA and BW and CC in the FT control group (Fig. 1D and E) and CC values from the VP/VLBW cohort reach levels comparable to the mean values in the FT cohort with increasing GA and seemingly normalize at around 36 weeks GA. As outlined in the introduction, CC can be considered a measure of gyrification by combining multifactorial information from sulcal depth, folding frequency, convolution of gyral shape, and cortical thickness into one single value (Im et al., 2006; King et al., 2010). Based on this interpretation of CC, we conclude that the combination of many microscopic factors of prematurity, ranging from subplate neuron impairment to damaged pre-oligodendrocytes and aberrant cortical expansion result in aberrant processes of developing surface geometry (Dean et al., 2013; McQuillen et al., 2003; Sun and Hevner, 2014).

While the exact contributions of the above-mentioned cerebral cortex properties to CC are not yet fully clear, several more general biological aspects with possible associations have been identified. Most notably, CC has been shown to reflect changes of brain surface geometry over the life span (Blanton et al., 2001; Mustafa et al., 2012). During intrauterine life, childhood and adolescence an increase in cortical folding leads to higher CC values (Blanton et al., 2001; Shyu et al., 2011; Wu et al., 2009). Thus, an increase in CC is expected during brain development and relatively decreased CC reflects developmental delay as reported in a study in premature-born toddlers with or without intrauterine growth restriction (IUGR) and term-born controls (Esteban et al., 2010). After a continuous rise in CC until adolescence, a bihemispheric decrease of CC in frontal and parietal has been identified starting in post-adolescence (Sandu et al., 2014a). Post-adolescence or young adulthood can be seen as tipping point followed by a steady decrease in CC with aging as gyri become thinner and sulci become wider (Kalmanti and Maris, 2007; Madan and Kensinger, 2016; Sandu et al., 2014b). The link between CC and neurodevelopment is emphasized by reports from neurodevelopmental disorders: Aberrations in cortical complexity were demonstrated for schizophrenia patients compared to healthy controls (Sandu et al., 2008; Yotter et al., 2011). Moreover, changes in CC were distinct for different clinical phenotypes of schizophrenia patients (Nenadic et al., 2014). Additionally, aberrations in cortical thickness and complexity were demonstrated in William's syndrome, a genetic disease associated with aberrant development of the human brain cortex (Thompson et al., 2005). However, the published data is scarce and does not include major neurodevelopmental pathologies such as autism spectrum disorder.

We have found widespread bilateral clusters of decreased CC in premature-born adults, expressing persistent changes in cortical shape. Based on the presumed biological substrate of decreased CC the implication is altered cortical shape in terms of less convoluted gyri, more shallow sulci, and decreased folding frequency (Im et al., 2006) in premature-born adults, which fits quite well with previous studies on adult or adolescent cortical surface shape after premature birth (Eikenes et al., 2011; Skranes et al., 2013). Moreover, the difference in CC links neurodevelopmental psychiatric disorders with structural brain abnormalities in premature-born individuals, who have been showed to be at increased risk for psychiatric illness (Nosarti et al., 2012; Saigal and Doyle, 2008).

In our study, we observed a correlation between school success and cortical complexity in the right medial parietal lobe and the left lateral temporal lobe, which highlights the potential influence of socio-environmental factors on adult brain structure. These factors should also be taken into account and larger studies with more biographical information about the participants are needed in order to explore these influences. In the context of CC changing over the life span as discussed above, two other non-exclusive interpretations of our findings arise: On the one hand, the observed decrease in CC reflects delayed cortical development shifted towards a different developmental trajectory, on the other hand, it is the manifestation of accelerated localized brain aging. Owing to the cross-sectional study design, we cannot make certain inferences from our data, however the spatial distribution might help with the interpretation as discussed more below.

4.2. Spatially distinct clusters of decreased cortical complexity after premature birth

We have observed decreased CC in two large, bilateral temporal and parietal clusters and in two smaller clusters in the right frontoopercular and occipitotemporal region. While the lateral temporal CC clusters are rather symmetrical, the medial parietal cluster is more sizeable on the right side than its counterpart in the left hemisphere. Regarding the cerebral cortex, the most distinct aberrations in premature-born individuals have been shown for the lateral temporal and insular region with reduced volumes in adolescence and an association with gestational age (Nosarti et al., 2014, 2008; Shang et al., 2019, 2018). Other volumetric studies on premature-born individuals also reported grey matter reductions mostly in the temporolateral cortices (Kesler et al., 2008; Lemola et al., 2017; Scheinost et al., 2017; Zhou et al., 2018). Cortical thickness was reported to be reduced in left temporoparietal cortices in premature-born adolescents and widespread areas of surface reduction spanned large portions of frontotemporoparietal cortices (Bjuland et al., 2013; Sølsnes et al., 2015). In addition to reduced regional brain volume, a difference in brain function was shown as measured by decreased amplitudes of low-frequency fluctuations on resting state functional MRI in lateral temporal cortices (Shang et al., 2018). In conclusion, the lateral temporal cortex can be considered a region that is notoriously affected by premature birth and shows lasting aberrations.

In contrast, the medial parietal clusters affect regions that have so far not been identified regularly as abnormal after prematurity. The medial parietal cortex comprises the precuneus and the posterior cingulate cortex, thus two cytoarchitectonically distinct, albeit highly interrelated cortices (Cavanna and Trimble, 2006; Zilles and Palomero-Gallagher, 2001) belonging to the associative and limbic cortices, respectively. The precuneus plays an important role at implementing higher-order cognitive functions, such as visuo-spatial information processing (Cavanna and Trimble, 2006; Culham et al., 1998; Simon et al., 2002), episodic memory retrieval (Frackowiak et al., 1997; Tulving, 1983), and self-processing, i.e. subserving the representation of the self in relationship with the outside world (Vogeley and Fink, 2003). It cannot be expected that general cognitive performance can be pinned down to one specific brain area. However, as the integration of several brain regions is essential to the medial parietal lobe, it might also be an important area for high-level cognitive functioning, e.g. as measured by FS-IQ. The medial parietal cortex gained special importance in identification of resting state functional brain networks and is an integral part of the default-mode network (DMN) (Fransson and Marrelec, 2008). In fact, our group has observed functional aberrations of the right medial parietal cortex in a subset of the cohort reported here (Daamen et al., 2015). In particular, right medial parietal cortex recruitment was increased in VP/VLBW subjects compared to FT controls as a function of working memory load. These enhanced activity changes were interpreted as a compensatory mechanism in response to increased working memory load, contrasting with frequent observations of impaired task-related DMN inhibition in pathological brain states, e.g. Alzheimer's disease (Anticevic et al., 2012; Greicius et al., 2004).

4.3. Decreased cortical complexity mediates the impact of prematurity on cognitive development

We found that reduced temporo-parietal CC was associated with reduced cognitive performance in premature-born adults. Furthermore, we used a mediation model to investigate the long-term cognitive development and CC. In this model, early cognitive development, as measured by DQ-20, served as causal variable and late cognitive development, as measured by adult FS-IQ served as outcome variable. We introduced CC into this relationship as a mediator, reflecting the result of long-term cortical development. We observed a significant indirect effect of right medial parietal CC in our mediation analyses. This means that for any fixed value of DQ-20 an increase in medial parietal CC leads to higher FS-IQ in adulthood which is in line with our hypothesis that higher CC reflects higher FS-IQ in VP/VLBW individuals (Hayes and Rockwood, 2017). However, it has to be stated, that the indirect effect size was very small, which means that the effect of CC on long-term cognitive development is comparably low. We hypothesize that other major factors exist that may influence the complex process of cognitive development in premature-born individuals. The relationship between cognitive performance and brain surface geometry has been studied most prominently through estimation of the gyrification index (Gregory et al., 2016; Schaer et al., 2008). Gregory et al. identified frontotemporoparietal cortical clusters, predicting more than 11% of the variance of general cognitive ability through their local gyrification index (Gregory et al., 2016). Using a different metric of brain surface geometry – cortical curvature – Luders et al. showed a correlation between cortical folding and intelligence quotient, most significantly in the outermost portions of the posterior cingulate gyrus (Luders et al., 2008). A small study corroborates the importance of cortical geometry by showing an association between the complexity of the cortical shape and years of education and intelligence quotient (Im et al., 2006). One has to keep in mind that the studies cited above linking brain surface geometry with cognitive performance provide rather correlational but not causal evidence in either direction between the two. However, in the light of this correlational evidence and the results of our mediation analysis, we conclude that medial parietal CC constitutes a potential cortical marker of long-term cognitive development.

The functional relevance of fractal dimension in brain imaging has been emphasized by its association with cognitive decline over the lifespan (Mustafa et al., 2012; Sandu et al., 2014b). In a study on over 200 individuals at age 68 years with available cognitive test scores from age eleven, white matter fractal dimension was determined based on MRI. A positive association between fractal dimension and fluid intelligence at age 68 was observed. Moreover, greater FD predicted less cognitive decline over the life span from early adolescence to late adulthood (Mustafa et al., 2012). This finding of retention of cognitive ability in late life was corroborated in a second study on white matter complexity (Sandu et al., 2014b). Studying the relationship between cognitive decline and brain surface geometry, complexity of the cortical ribbon was shown to be positively correlated with cognitive function in patients with Alzheimer's disease and normal controls (King et al., 2010). In addition, the authors showed that the association between cortex markers and advanced cognitive decline was higher for cortical ribbon fractal dimension compared to cortical thickness and gyrification index (King et al., 2010).

Drawing on evidence from studies suggesting a link between cortical complexity and cognitive development or decay, we connected these observations to sequelae of prematurity. The variance in right medial parietal CC significantly mediated the effect of cognitive development in early infancy on later cognitive performance in adulthood. This indicates that both brain surface geometry and cognitive development follow altered and interrelated trajectories after premature-birth.

4.4. Strengths and limitations

Some points should be carefully considered when interpreting our results. The current sample is biased to VP/VLBW adults with less severe neonatal complications, fewer functional impairments, and higher IQ. Individuals with stronger birth complications and/or severe lasting impairments in the initial BLS sample were more likely both to be excluded in initial screening for MRI due to exclusion criteria for MRI (for example infantile cerebral palsy). Thus, differences in CC between VP/VLBW and term control adults reported here are conservative estimates of true differences. Generally, studies linking certain aspects of brain structure with cognitive functioning are always compromised by focusing on special features and by potential non-linear 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. To further assess how premature birth impacts on CC within the continuum of brain development and aging, longitudinal studies would be necessary. While we consider it a strength of our study that groups were matched according to their SES at birth, we acknowledge the fact that SES may change over the life course and thus have a longitudinally changing effect on cognitive capacities. Since we are investigating long term aberrations of brain structure after premature birth, the data is inherently noisy. This motivates the need to study, investigate and reproduce our findings in larger longitudinal cohorts of premature-born neonates, infants and adolescents.

Our current study population has the strength of a large size (101 VP/VLBW and 111 FT adults), enhancing the generalizability of our findings. Another strength of our study is that a relevant impact of patient age on cortical complexity at the time of the MRI scan is excluded due to the inclusion of preterm and term subjects who had approximately the same age of 26 years.

5. Conclusions

We have shown widespread decreases in cortical complexity between premature-born adults and full-term controls as a reflection of regionally disturbed neurodevelopmental processes after premature birth. This finding is functionally relevant since it correlates with the development of cognitive performance of premature-born individuals from early infancy to adulthood. We propose that measuring cortical complexity can serve as an additional metric for determining effects of prematurity and potentially yields prognostic information. However, more research and translation of our findings into younger cohorts of premature-born individuals is needed in order to better understand cortical development after premature birth. If successful, we propose that CC might become a potential outcome variable in intervention studies that aim at improving neurocognitive outcomes after premature birth.

Author contributions

Dennis M. Hedderich: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing Original Draft, Writing Review & Editing, Visualization.

Josef G. Bäuml: Methodology, Formal Analysis, Investigation, Data curation, Writing Review & Editing, Project administration.

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Claus Zimmer: Resources, Writing Review & Editing, Supervision, Funding acquisition.

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Christian Sorg: Conceptualization, Validation, Investigation, Writing Original Draft, Writing Review & Editing, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116438.

Appendix

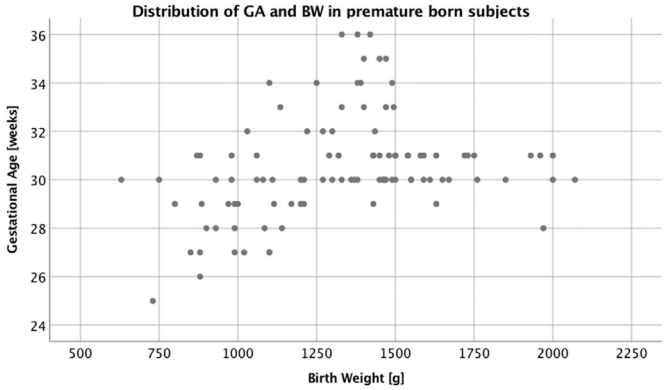

Fig. A1. Scatter-plot showing the distribution of gestational age and birth weight in the premature-born adults cohort. Abbreviations: GA: gestational age; BW: birth weight; g: grams.

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