Archival Report

Biological Psychiatry: CNNI

Altered Gray Matter Cortical and Subcortical T1-Weighted/T2-Weighted Ratio in Premature-Born Adults

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ABSTRACT

BACKGROUND: Microscopic studies in newborns and animal models indicate impaired myelination after premature birth, particularly for cortical myelination; however, it remains unclear whether such myelination impairments last into adulthood and, if so, are relevant for impaired cognitive performance. It has been suggested that the ratio of T1-weighted (T1w) and T2-weighted (T2w) magnetic resonance imaging signal intensity (T1w/T2w ratio) is a proxy for myelin content. We hypothesized altered gray matter (GM) T1w/T2w ratio in premature-born adults, which is associated with lower cognitive performance after premature birth.

METHODS: We analyzed GM T1w/T2w ratio in 101 adults born very premature (VP) and/or at very low birth weight (VLBW) (<32 weeks of gestation and/or birth weight <1500 g) and 109 full-term control subjects at 26 years of age, controlled for voxelwise volume alterations. Cognitive performance was assessed by verbal, performance, and full scale IQ using the Wechsler Adult Intelligence Scale.

RESULTS: Significantly higher T1w/T2w ratio in VP/VLBW subjects was found bilaterally in widespread cortical areas, particularly in frontal, parietal, and temporal cortices, and in putamen and pallidum. In these areas, T1w/T2w ratio was not related to birth variables, such as gestational age, or IQ scores. In contrast, significantly lower T1w/T2w ratio in VP/VLBW subjects was found in bilateral clusters in superior temporal gyrus, which was associated with birth weight in the VP/VLBW group. Furthermore, lower T1w/T2w ratio in left superior temporal gyrus was associated with lower full scale and verbal IQ.

CONCLUSIONS: Results demonstrate GM T1w/T2w ratio alterations in premature-born adults and suggest altered GM myelination development after premature birth with lasting and functionally relevant effects into early adulthood.

https://doi.org/10.1016/j.bpsc.2022.02.013

Premature birth (i.e., <37 weeks of gestation) is associated with an increased risk for aberrant neurocognitive development. For example, adults born very premature (VP) have, on average, more than 10 points lower IQ scores as well as lasting macroscopic and microscopic brain alterations, which mediate cognitive impairments (1,2). Macroscopic structural brain alterations affect gray matter (GM) and white matter (WM) through volume reductions, aberrant cortical architecture, and disturbed WM integrity (3–11). On a microscopic level, inflammation, hypoxia-ischemia, and/or stress-related events are potential causes of disrupted cellular development including axonal injury, subplate neuron injury, and impaired pre-oligodendrocyte (pre-OL) development, leading to disturbed cortical microstructure and myelination (12–16). More specifically, primary injury or death of pre-OLs is followed by replenishment of the pre-OL pool; however, subsequent maturation to myelin-producing OLs fails (12,13,17–19).

The cortex contains myelinated axons exhibiting distinct myeloarchitectures. Magnetic resonance imaging (MRI) allows for the indirect study of myelin in vivo using measures such as magnetization transfer imaging, T1 relaxation rate, and the ratio of T1-weighted (T2w) and T2-weighted (T2w) signal intensity (T1w/T2w ratio). The T1w/T2w ratio has been suggested to provide a simple and broadly available measure that eliminates the MR-related image intensity bias and enhances the contrast-to-noise ratio for myelin (20). It has, for example, been applied to study intracortical myelin content (21,22). Moreover, T1w/T2w ratio has been used to assess diseases affecting brain structure, such as Alzheimer's disease, Parkinson's disease, and schizophrenia (23–26). Furthermore, intracortical myelin, as measured with the T1w/T2w ratio, is linked with cognitive functioning (27).

With respect to premature birth, alterations in T1w/T2w ratio in deep GM and occipital and temporal lobes as well as in WM T1w/T2w ratio have been reported in VP-born children (28,29).

ISSN: 2451-9022

Although it remains unknown whether T1w/T2w ratio is lastingly altered into adulthood after premature birth, other measures of GM structure, such as volume or cortical architecture, exhibit long-term alterations (4,5,7,30). Therefore, we hypothesized that GM T1w/T2w ratio is altered in premature-born adults, possibly in deep GM and occipital and temporal lobes as suggested by previous studies in children (28,29). However, because myelination is a highly dynamic process, hypothesizing a direction for T1w/T2w ratio alterations is difficult. Furthermore, it is known that IQ is lower in children after premature birth compared with full-term (FT) control subjects and that these deficits persist into adulthood (1,2,31,32). In VP-born children, Vandewouw *et al.* (28) showed a link between T1w/T2w ratio in thalamus, amygdala, and hippocampus as well as in temporal lobes and cognitive performance. Therefore, we hypothesized that altered GM T1w/T2w ratio might be associated with lower IQ after premature birth in adulthood, possibly in these previously implicated regions. To address these two hypotheses, we investigated 101 VP-born adults (i.e., <32 weeks of gestation and/or birth weight [BW] <1500 g) and 109 FT control subjects at 26 years of age by T1w and T2w MRI and IQ assessment.

METHODS AND MATERIALS

Participants

Our study sample has been previously described (30,32–37): 101 VP (<32 weeks of gestation) and/or very low birth weight (VLBW) (BW <1500 g) subjects and 111 FT control subjects underwent MRI at 26 years of age (see Supplement for more details). 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 ethics committee of the Klinikum rechts der Isar, Technische Universität München, and the University Hospital Bonn. All study participants gave written informed consent. They received travel expenses and a small payment for participation.

Birth Variables

Gestational age (GA) was estimated from maternal reports on the first day of the last menstrual period and serial ultrasound scans 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 (38). BW and intensity of neonatal treatment index (INTI), quantifying duration and intensity of medical treatment after birth, were obtained from obstetric records (34,39). Daily assessments of care level, respiratory support, feeding dependency, and neurological status (mobility, muscle tone, and neurological excitability) were performed. Each of the 6 variables was scored on a 4-point rating scale (0–3) by the method of Casaer and Eggermont (40). 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).

Cognitive Performance in Adulthood

To assess global cognitive performance at age 26, before 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 (41). This test was carried out by trained psychologists who were blinded to group membership and used to derive full scale IQ, verbal IQ, and performance IQ estimates (32,36).

MRI Data Acquisition

MRI data acquisition has been previously described (30,42). At both sites, Bonn and Munich, MRI data acquisition was performed on a Philips Achieva 3T TX system (Philips Healthcare) or Philips Ingenia 3T system (Philips Healthcare) using an 8-channel SENSE head coil. Subject distribution among scanners was as follows (Table 1): Bonn Achieva 3T: 5 VP/VLBW, 12 FT; Bonn Ingenia 3T: 33 VP/VLBW, 17 FT; Munich Achieva 3T: 60 VP/VLBW, 65 FT; Munich Ingenia 3T: 3 VP/VLBW, 17 FT. Distribution of the two groups across scanners was significantly different (p = .001), as most of the prematurity cohort was imaged in Munich on a 3T Achieva system. 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 T1w three-dimensional magnetization-prepared rapid acquisition gradient-echo sequence (inversion time = 1300 ms, repetition time = 7.7 ms, echo time = 3.9 ms, flip angle = 15°, field of view = 256 mm × 256 mm, reconstruction matrix = 256 × 256, reconstructed isotropic voxel size = 1 mm^3) and a high-resolution T2w three-dimensional sequence (repetition time = 2500 ms, echo time = 364 ms, flip angle = 90°, field of view = 512 mm × 512 mm, echo train length = 120, reconstructed isotropic voxel size = 0.5 mm^3) were acquired. All images were visually inspected for artifacts. Two FT subjects were excluded owing to the lack of T2w images. Hence, the final sample included 101 VP/VLBW subjects and 109 FT subjects.

MRI Processing and T1w/T2w Ratio Mapping

Images saved as DICOM files were converted to NIfTI format using dcm2nii (43). MRI data were preprocessed using MRTool, which implements a processing workflow for the generation of the T1w/T2w images within SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) as previously described by Ganzetti *et al.* (23,44). For each subject, the original T2w image was coregistered to the T1w image through rigid body transformation, the T1w and T2w images were subjected to bias correction and intensity calibration, and the ratio was calculated to generate the T1w/T2w image. To obtain GM masks, T1w images were preprocessed using CAT12 (http://www.neuro.uni-jena.de/cat/) within SPM12. Images were normalized to a template space and segmented into GM, WM, and cerebrospinal fluid. Using the GM mask, T1w/T2w

Table 1. Demographical, Clinical, and Cognitive Data

	VP/VLBW (n = 101)	FT (n = 109)	p Value
Sex, Female/Male, n	43/58	45/64	.850
Age, Years	26.7 ± 0.6 (25.7–28.3)	26.9 ± 0.7 (25.5–28.9)	.147
GA, Weeks	30.5 ± 2.1 (25–36)	39.7 ± 1.1 (37–42)	<.001[a]
BW, g	1325 ± 313 (630–2070)	3391 ± 447 (2120–4670)	<.001[a]
INTI, Days	11.6 ± 3.8 (3–18)	NA	NA
GM, mm^3	683.1 ± 62.9 (524.0–839.3)	714.0 ± 56.4 (555.1–861.2)	<.001[a]
Full Scale IQ[b]	94.1 ± 12.7 (64–131)	102.4 ± 11.9 (77–130)	<.001[a]
Verbal IQ[b]	98.8 ± 14.0 (62–137)	105.7 ± 14.2 (77–143)	.001[a]
Performance IQ[b]	89.8 ± 13.5 (56–118)	98.5 ± 10.4 (69–125)	<.001[a]
Scanner, n (%)			.001[a]
Bonn Achieva 3T	5 (5.0%)	11 (10.1%)	
Bonn Ingenia 3T	33 (32.7%)	17 (15.6%)	
Munich Achieva 3T	60 (59.4%)	64 (58.7%)	
Munich Ingenia 3T	3 (3.0%)	17 (15.6%)	

Data are mean ± SD (range) except where noted. Statistical comparisons: sex and scanner with χ^2 statistics; age, GA, BW, GM, full scale IQ, verbal IQ, and performance IQ with two-sample t tests.

BW, birth weight; FT, full-term; GA, gestational age; GM, gray matter; INTI, intensity of neonatal treatment index; NA, not applicable; VP/VLBW, very preterm and/or very low birth weight.

[a]Statistical significance, defined as $p < .05$.

[b]Data are based on 97 VP/VLBW subjects and 106 FT-born control subjects.

ratio within GM was extracted. Finally, GM T1w/T2w ratio maps were smoothed with a Gaussian kernel of 6 mm full width at half maximum.

Statistical Analysis

Thresholding and Correction for Multiple Testing. All voxelwise analyses were conducted using SPM12 and corrected for multiple comparisons to control the false discovery rate (FDR). Statistical significance was defined as FDR-corrected $p < .05$, and cluster size was set to ≥10 voxels to be considered significant (45). Linear regression analyses of extracted T1w/T2w ratio were performed using IBM SPSS Version 26 (IBM Corp.) and corrected for multiple comparisons across all 6 regressions regarding birth variables and across all 12 regressions regarding cognitive performance using the Benjamini-Hochberg procedure (46). Statistical significance was defined as $p_{FDR} < .05$.

Group Comparison of GM T1w/T2w Ratio. To identify areas in which the T1w/T2w ratio in GM was significantly different in VP/VLBW subjects compared with FT control subjects, we performed a two-sample t test using the DPABI toolbox, which is based on SPM12 (47). To control for possible effects of GM atrophy in a voxelwise way, the GM segmented images were entered as covariate images. Sex and scanner were entered as covariates. The analysis was constrained within a standardized group GM mask.

To test for possible sex effects, T1w/T2w ratio was extracted in areas in which it was significantly different in VP/VLBW subjects compared with FT control subjects. General linear models were used to test if sex had a significant effect on T1w/T2w ratio in these regions.

To confirm the voxelwise results and to further control for possible scanner effects, we conducted the following control analyses. First, general linear models were used to test if scanner had a significant effect on T1w/T2w ratio in the regions in which it was significantly different in VP/VLBW subjects compared with FT control subjects. Second, we repeated the group comparison using regions of interest derived from the Harvard-Oxford atlas (see Supplement) (48–51). Third, we repeated the group comparison using a region-of-interest–based approach after applying ComBat, a technique that removes unwanted sources of scan variability (see Supplement) (52).

To investigate whether group differences in GM T1w/T2w ratio were specifically related to prematurity, in the VP/VLBW group, the extracted T1w/T2w ratio values (for VP/VLBW<FT and VP/VLBW>FT, respectively) were entered into a linear regression analysis in SPSS as the dependent variable with GA, BW, and INTI as independent variables. GM volume, sex, and scanner were entered as covariates of no interest. To identify regionally specific correlation for VP/VLBW>FT, we performed voxelwise two-tailed multiple regression (see Supplement). Finally, age was not included as a covariate in our analyses, as VP/VLBW subjects and FT control subjects had the same mean age of 26 years (p = .147).

GM T1w/T2w Ratio and Cognitive Performance. To explore the relationship between altered GM T1w/T2w ratio after premature birth and cognitive performance, as measured by full scale IQ, verbal IQ, and performance IQ, the extracted T1w/T2w ratios for VP/VLBW<FT and VP/VLBW>FT clusters, respectively, were entered into a linear regression analysis in SPSS as independent variables with full scale IQ, verbal IQ, and performance IQ, respectively, as dependent variables in the VP/VLBW group. GM volume, sex, and scanner were entered as covariates of no interest. To identify regionally specific correlation for VP/VLBW>FT, we performed voxelwise two-tailed multiple regression (see Supplement).

Because T1w/T2w ratio in bilateral superior temporal gyrus (STG) was at trend related to verbal IQ and because left STG is

particularly involved in language processing, we performed linear regression analysis with T1w/T2w ratio in left STG and right STG, respectively, as independent variables and full scale IQ, verbal IQ, and performance IQ, respectively, as dependent variables in the VP/VLBW group. GM volume, sex, and scanner were entered as covariates of no interest.

Data Availability Statement

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

RESULTS

Sample Characteristics

Table 1 presents group demographic and clinical background variables. There was no significant difference between the VP/VLBW group and FT group regarding sex ($p = .850$) and age at scanning ($p = .147$). By design of the study, VP/VLBW subjects had significantly lower GA ($p < .001$) and lower BW ($p < .001$). Furthermore, VP/VLBW subjects had significantly lower GM volume ($p < .001$), full scale IQ scores ($p < .001$), verbal IQ scores ($p = .001$), and performance IQ scores ($p < .001$) compared with FT control subjects.

Altered GM T1w/T2w Ratio in Premature-Born Adults

Figure 1 illustrates group differences of GM T1w/T2w ratio. We found widespread cortical areas bilaterally with significantly higher T1w/T2w ratio in VP/VLBW subjects compared with FT control subjects, particularly in frontal, parietal, and temporal cortices, including operculum and temporal pole, as well as in bilateral lateral thalamus, putamen, pallidum, hippocampus, and amygdala. We found significantly lower T1w/T2w ratio in small bilateral clusters in STG. The left cluster spans 65 voxels, and the right cluster spans 91 voxels. There was no significant effect of sex on the T1w/T2w ratio for VP/VLBW>FT ($F_{1,203} = 0.376$, $p = .540$) and for VP/VLBW<FT ($F_{1,203} = 2.788$, $p = .097$). Furthermore, there was no significant effect of scanner on the T1w/T2w ratio for VP/VLBW>FT (scanner dummy-variable 1: $F_{1,203} = 0.012$, $p = .914$; scanner dummy-variable 2: $F_{1,203} = 0.050$, $p = .822$; $F_{1,203} = 3.474$, scanner dummy-variable 3: $p = .064$) and for VP/VLBW<FT (scanner dummy-variable 1: $F_{1,203} = 0.793$, $p = .374$; scanner dummy-variable 2: $F_{1,203} = 0.082$, $p = .775$; scanner dummy-variable 3: $F_{1,203} = 3.702$, $p = .056$). Significantly higher T1w/T2w ratio in VP/VLBW subjects compared with FT control subjects, particularly in frontal, parietal, and temporal cortices as well as in bilateral putamen and pallidum, and significantly lower T1w/T2w ratio in STG were confirmed using a region-of-interest–based approach (see Supplement) and after applying ComBat to control for possible scanner effects (see Supplement).

To test whether the group differences described above are specifically related to premature birth, we performed linear regression analyses within the VP/VLBW group. Results are listed in Table 2, and the relationships between birth variables and T1w/T2w ratio are shown as scatterplots in Figure 2. There was no significant linear relationship between birth variables and T1w/T2w ratio for VP/VLBW>FT (Figure 2A and Supplement). For VP/VLBW<FT, there was a significant positive linear relationship between GA ($p = .017$) and BW ($p = .004$) and T1w/T2w ratio (Figure 2B). However, only the relationship between BW and T1w/T2w ratio survived FDR correction. There was no significant relationship between INTI and T1w/T2w ratio.

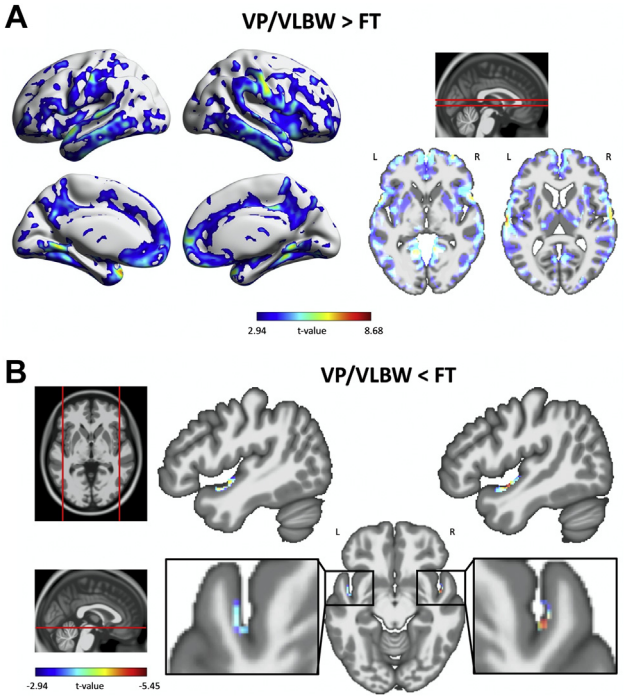

Figure 1. Group comparison of T1-weighted/T2-weighted ratio. Voxelwise group comparison controlling for gray matter volume in a voxelwise way and with sex and scanner as additional covariates. Statistical significance was defined as false discovery rate–corrected $p < .05$, cluster size ≥10 voxels. **(A)** Areas in which T1-weighted/T2-weighted ratio was significantly higher in very preterm and/or very low birth weight (VP/VLBW) subjects compared full-term (FT) control subjects. The *t* values are color coded; warm colors indicate higher *t* values. Both hemispheres are shown in medial and lateral views, with 2 axial slices included to illustrate results. **(B)** Areas in which T1-weighted/T2-weighted ratio was significantly lower in VP/VLBW subjects compared with FT control subjects. The *t* values are color coded; warm colors indicate lower *t* values. Two sagittal slices and an axial slice are shown to illustrate results. L, left; R, right.

In summary, T1w/T2w ratio was higher in VP/VLBW subjects compared with FT control subjects in widespread cortical areas bilaterally, particularly in frontal, parietal, and temporal cortices and in putamen and pallidum, which was not related to birth variables. T1w/T2w ratio was lower in bilateral clusters in STG, which was associated with BW in the VP/VLBW group.

Functional Relevance of GM T1w/T2w Ratio Alterations

To explore the functional relevance of altered GM T1w/T2w ratio after premature birth, we performed linear regression analyses within the VP/VLBW group. There was no significant relationship between T1w/T2w ratio and full scale IQ, verbal IQ, or performance IQ (Table 3; Figure 3A, B; Supplement).

Table 2. Relationship Between T1w/T2w Ratio and Variables of Premature Birth

Risk Factor	T1w/T2w Ratio	β Coefficient	*p* Value
GA	VP/VLBW>FT	−0.065	.530
	VP/VLBW<FT	0.246	.017
BW	VP/VLBW>FT	0.082	.460
	VP/VLBW<FT	0.314	.004[a]
INTI	VP/VLBW>FT	−0.028	.781
	VP/VLBW<FT	−0.114	.273

β coefficients and *p* values from linear regression analysis in the VP/VLBW group between the T1w/T2w ratio in areas in which it was significantly smaller in VP/VLBW subjects compared with FT control subjects and areas in which it was significantly greater in VP/VLBW subjects compared with FT control subjects, respectively, as dependent variables and variables of premature birth as independent variables. GM, sex, and scanner were entered as covariates.

BW, birth weight; FT, full-term; GA, gestational age; INTI, intensity of neonatal treatment index; T1w, T2w, T1-weighted/T2-weighted; VP/VLBW, very preterm and/or very low birth weight.

[a]Statistical significance, after false discovery rate correction using the Benjamini-Hochberg procedure.

However, T1w/T2w ratio in bilateral STG showed a positive relationship with verbal IQ, which was at trend to significance. Therefore, and because left STG is particularly involved in language processing, we repeated linear regression analysis per hemisphere (Table 4). There was a significant positive relationship between T1w/T2w ratio in left STG and full scale IQ ($p = .007$) and left STG and verbal IQ ($p = .004$) (Figure 4A, B). There was no significant relationship between T1w/T2w ratio in left STG and performance IQ or between T1w/T2w ratio in right STG and full scale IQ, verbal IQ, or performance IQ.

DISCUSSION

Using MRI-based T1w/T2w ratio as a proxy for myelination, we investigated whether GM myelination was altered in a group of 101 VP/VLBW adult subjects compared with 109 FT-born adult control subjects. We found that T1w/T2w ratio was higher in VP/VLBW subjects compared with FT control subjects in widespread cortical areas bilaterally, particularly in frontal, parietal, and temporal cortices and in putamen and pallidum, which was not related to either birth variables or IQ scores. T1w/T2w ratio was significantly lower in bilateral clusters in STG, which was associated with BW in the VP/VLBW group. Furthermore, T1w/T2w ratio in left STG was associated with full scale IQ and verbal IQ. Our results demonstrate, to the best of our knowledge for the first time, that GM myelination is altered in premature-born adults. Data suggest altered GM myelination development after premature birth with lasting and functionally relevant effects into adulthood.

Widespread Higher T1w/T2w Ratio After Premature Birth

We found higher T1w/T2w ratio in VP/VLBW subjects compared with FT control subjects in widespread cortical areas bilaterally, particularly in frontal, parietal, and temporal cortices and in putamen and pallidum, which was not associated with birth variables. Hence, these alterations seem to be generally observable in premature-born subjects. Results could indicate that higher GM T1w/T2w ratio after premature birth is a consistent effect of later development rather than birth circumstances.

As mentioned in the beginning of this article, hypomyelination is thought to be a hallmark of premature birth. Consistently, Vandewouw *et al.* (28) found lower T1w/T2w

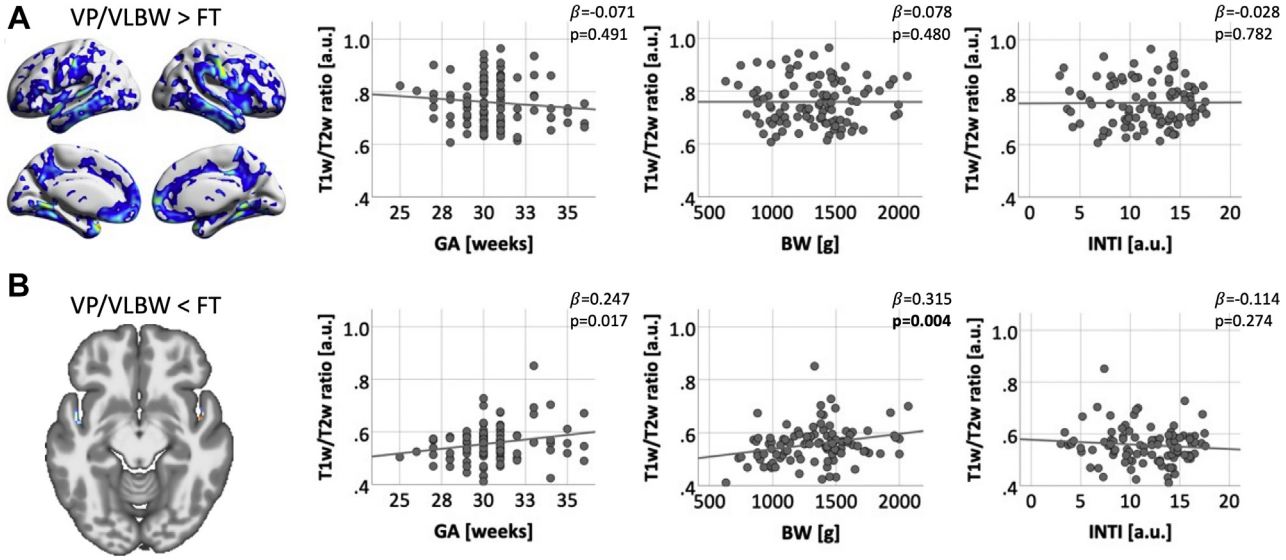

Figure 2. Relationship between T1-weighted/T2-weighted (T1w/T2w) ratio and variables of premature birth. **(A)** Scatterplots showing associations between gestational age (GA), birth weight (BW), and intensity of neonatal treatment index (INTI) and T1w/T2w ratio in areas in which it was significantly higher in very preterm and/or very low birth weight (VP/VLBW) subjects compared with full-term (FT) control subjects. **(B)** Scatterplots showing associations between GA, BW, and INTI and T1w/T2w ratio in areas in which it was significantly lower in VP/VLBW subjects compared with FT control subjects. GA (in weeks), BW (in grams), and INTI are each plotted on the x-axes, and T1w/T2w ratio is plotted on the y-axes. Linear regression lines as well as β coefficients and *p* values were added. Bold value indicates statistical significance, defined as false discovery rate–corrected $p < .05$.

Table 3. Relationship Between T1w/T2w Ratio and Cognitive Performance

T1w/T2w Ratio	Cognitive Performance	β Coefficient	*p* Value
VP/VLBW>FT	Full scale IQ	0.037	.715
VP/VLBW<FT	Full scale IQ	0.111	.258
VP/VLBW>FT	Verbal IQ	0.093	.360
VP/VLBW<FT	Verbal IQ	0.189	.057
VP/VLBW>FT	Performance IQ	−0.048	.633
VP/VLBW<FT	Performance IQ	−0.020	.838

β coefficients and *p* values from linear regression analysis in the VP/VLBW group between the T1w/T2w ratio in areas in which it was significantly smaller in VP/VLBW subjects compared with FT control subjects and areas in which it was significantly greater in VP/VLBW subjects compared with FT control subjects, respectively, as independent variables and full scale IQ as dependent variable. Gray matter, sex, and scanner were entered as covariates.

FT, full-term; T1w, T2w, T1-weighted/T2-weighted; VP/VLBW, very preterm and/or very low birth weight.

ratio in WM, thalamus, putamen, and amygdala and in the occipital and temporal lobes in 4-year-old children born VP, indicating hypomyelination. However, in 7-year-old children, T1w/T2w ratio was increased in WM and deep GM, indicating stronger myelination, which is in line with our results in adulthood (29). Considering impaired pre-OL maturation after premature birth, one would expect hypomyelination, and therefore cellular correlates of increased myelination remain unknown. In general, GM myelination is an ongoing process with prolonged development well beyond childhood (22,27,53–55). For example, Norbom *et al.* (22) investigated a sample of typically developing individuals 3–21 years of age and found an age-related increase in T1w/T2w ratio across the cortical surface throughout childhood, adolescence, and young adulthood, supporting protracted myelination of the cortex. Furthermore, Grydeland *et al.* (27) studied intracortical T1w/T2w ratio across the life span and reported an inverted U–shaped trajectory for the majority of regions with a steep increase until the end of the 30s, followed by a relatively stable period, and a decrease from the end of the 50s. Because T1w/T2w ratio in early adulthood is still increasing, reaching onset of stability at 34 years for the whole brain trajectory (55), one could interpret our findings of increased T1w/T2w ratio after premature birth at 26 years of age as accelerated maturation, as the transition between development and aging might be shifted. However, cross-sectional studies cannot answer questions regarding developmental trajectories. Therefore, longitudinal data across different age groups are needed to further explore myelin development after premature birth.

Interpreting our results, one has to bear in mind that the exact histological substrate of what we are measuring with the T1w/T2w ratio remains unclear, and it has been suggested that the T1w/T2w ratio may be influenced by other factors besides myelin content (56–59). For example, the analysis of T1w/T2w ratio values of postmortem imaging and histopathological measurements showed a strong correlation with dendrite density in late-stage multiple sclerosis brain donors (56). Therefore, an alternative interpretation of increased T1w/T2w ratio could be altered GM microarchitecture determined by factors such as dendrite density. Further studies using alternative or different methods, such as neurite orientation dispersion and density imaging, are needed to investigate this issue. Nevertheless, it has been shown that T1w/T2w ratio significantly differed between demyelinated and myelinated

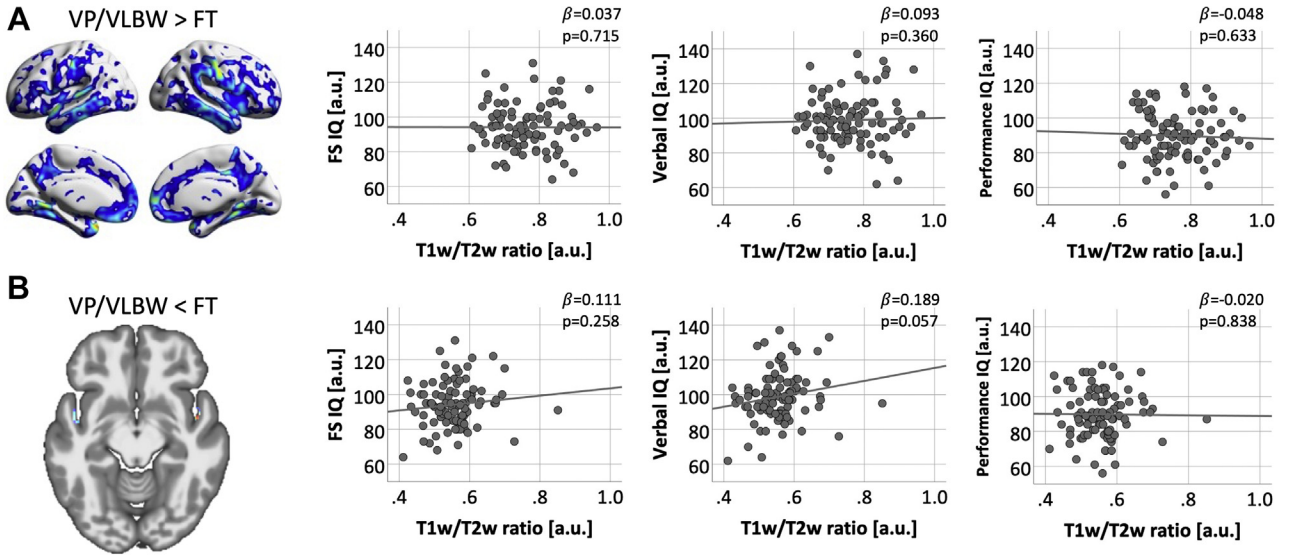

Figure 3. Relationship between T1-weighted/T2-weighted (T1w/T2w ratio) and cognitive performance. **(A)** Scatterplots showing associations between T1w/T2w ratio and full scale IQ (FSIQ), verbal IQ, and performance IQ in areas in which it was significantly higher in very preterm and/or very low birth weight (VP/VLBW) subjects compared with full-term (FT) control. **(B)** Scatterplots showing associations between T1w/T2w ratio and FSIQ, verbal IQ, and performance IQ in areas in which it was significantly lower in VP/VLBW subjects compared with FT control subjects. T1w/T2w ratio is plotted on the x-axes, and FSIQ, verbal IQ, and performance IQ are each plotted on the y-axes. Linear regression lines as well as β coefficients and *p* values were added. Statistical significance was defined as false discovery rate–corrected $p < .05$.

Table 4. Relationship Between T1w/T2w Ratio in Left and Right STG and Cognitive Performance

T1w/T2w Ratio	Cognitive Performance	β Coefficient	*p* Value
Left STG	Full scale IQ	0.190	.007[a]
Right STG	Full scale IQ	0.109	.111
Left STG	Verbal IQ	0.205	.004[a]
Right STG	Verbal IQ	0.120	.082
Left STG	Performance IQ	0.116	.103
Right STG	Performance IQ	0.065	.344

β coefficients and *p* values from linear regression analysis in the VP/VLBW group between the T1w/T2w ratio in areas in which it was significantly smaller in VP/VLBW subjects compared with FT control subjects and areas in which it was significantly greater in VP/VLBW subjects compared with FT control subjects, respectively, as independent variables and full scale IQ as dependent variable. Gray matter, sex, and scanner were entered as covariates.

FT, full-term; STG, superior temporal gyrus; T1w, T2w, T1-weighted/T2-weighted; VP/VLBW, very preterm and/or very low birth weight.

[a]Statistical significance, after false discovery rate correction using the Benjamini-Hochberg procedure.

cortex, as determined by anti-proteolipid protein antibody staining in patients with multiple sclerosis (60).

Lower T1w/T2w Ratio in Bilateral STG

We found lower T1w/T2w ratio in small bilateral clusters in STG, which was associated with BW in the VP/VLBW group. First, these results are partly in line with results from Vandewouw *et al.* (28), who also reported lower T1w/T2w ratio in the temporal lobes in 4-year-old VP children. As described above, maturation of pre-OLs to mature, myelin-producing OLs is impaired after premature birth, causing hypomyelination (12,13,17–19). STG is a cortical area that is highly myelinated in the normative population (55); hence, our findings could indicate that STG might show lastingly impaired myelination after premature birth, possibly owing to pre-OL dysmaturation.

Second, findings of lower T1w/T2w ratio were strongly restricted within clusters in STG. These results are consistent with findings of other alterations in STG after premature birth, e.g., aberrant gyrification, altered diffusion tensor imaging–based microstructure, and decreased blood oxygenation level–dependent fluctuations in resting-state functional MRI (4,61,62). Furthermore, we recently found decreased connection probability between bilateral temporal cortices and bilateral anterior thalami using diffusion-weighted imaging (45). Correct development of thalamocortical connections depends on subplate neurons (63,64). Hence, potential explanations for distinct vulnerability of STG in prematurity include subplate neuron injury and pre-OL death. This is in line with particularly significant increases in subplate thickness in temporal brain regions based on intrauterine MRI at 20 to 26 gestational weeks, suggesting highly dynamic subplate development in this region (65). Considering that T1w/T2w ratio may be influenced by other factors besides myelin content, such as dendrite density, an alternative interpretation of lower T1w/T2w ratio could be altered GM microarchitecture determined by these factors.

Functional Relevance of GM T1w/T2w Ratio Alterations

There was a significant positive relationship between T1w/T2w ratio after premature birth in left STG and full scale IQ as well as verbal IQ, indicating that impaired myelination is functionally

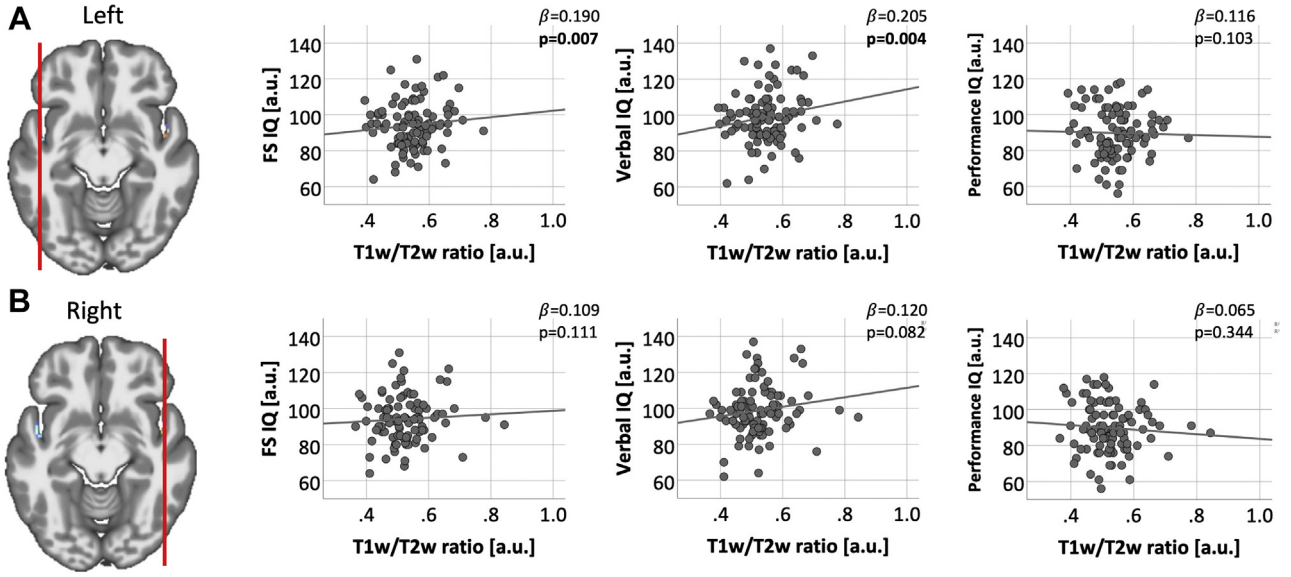

Figure 4. Relationship between T1-weighted/T2-weighted (T1w/T2w) ratio in left and right superior temporal gyrus and cognitive performance. **(A)** Scatterplots showing associations between T1w/T2w ratio in left superior temporal gyrus and full scale IQ (FSIQ), verbal IQ, and performance IQ. **(B)** Scatterplots showing associations between T1w/T2w ratio in right superior temporal gyrus and FSIQ, verbal IQ, and performance IQ. T1w/T2w ratio is plotted on the x-axes, and FSIQ, verbal IQ, and performance IQ are each plotted on the y-axes. Linear regression lines as well as β coefficients and *p* values were added. Bold values indicate statistical significance, defined as false discovery rate–corrected $p < .05$.

relevant. Intracortical myelin may be associated with cognitive functioning; however, results on the relationship between T1w/T2w ratio and cognitive performance are heterogeneous (22,27). For example, Grydeland *et al.* (27) found that a higher degree of intracortical myelin was associated with greater performance stability over the life span; however, the opposite relationship was found in a young subsample of 8- to 19-year-old subjects in posterior regions. In contrast, Norbom *et al.* (22) reported a negative association between T1w/T2w ratio and general cognitive ability across childhood and adolescence, mainly in anterior regions. With respect to prematurity, Vandewouw *et al.* (28) showed a link between T1w/T2w ratio in thalamus, amygdala, and hippocampus as well as in temporal lobes and cognitive performance, which is partly in line with our results and our hypothesis. Particularly, Vandewouw *et al.* (28) reported a significant positive correlation between T1w/T2w ratio in temporal lobes and full scale IQ as well as verbal abilities. STG, particularly in the left hemisphere, is involved in language processing; hence, it is possible that lastingly altered myelination in this area could result in deficits in verbal IQ performance (66–68). This interpretation is supported by findings from diffusion tensor imaging that highlight the key role of left STG for the development of language abilities in preterm children (61).

Strengths and Limitations

The current sample is biased toward VP/VLBW adults with less severe neonatal complications, fewer functional impairments, and higher IQ. Individuals with more birth complications in the initial Bavarian Longitudinal Study sample were more likely to be excluded owing to exclusion criteria for MRI. Thus, the reported differences in T1w/T2w ratio between VP/VLBW subjects and FT control subjects 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 with subjects without MRI data (Table S5). In general, analyses trying to link brain structure with cognitive functioning have to be interpreted with care, as only one specific aspect is investigated, while there are multiple other structural features that have been associated with cognitive performance, such as gyrification, cortical thickness, and WM integrity (4,9,11). Furthermore, individual, social, and environmental factors influence the association between brain structural features and cognitive performance. As mentioned above, T1w/T2w ratio signal is not specific to myelination and is potentially confounded by other factors affecting water magnetization, such as lipophile drugs, cholesterol levels, or tissue perfusion (69). Hence, our interpretation of T1w/T2w ratio signal as myelination index is arguable. In future research, further methods to measure myelination, such as myelin water imaging, might be additionally applied to obtain more nuanced and convergent findings.

One of the strengths of our study is that a relevant impact of age is excluded, as VP/VLBW subjects and FT control subjects were the same age, 26 years, at the time of the MRI scan. Lastly, the generalizability of our findings is enhanced by the large sample size of our study (101 VP/VLBW subjects and 109 FT control subjects).

Conclusions

T1w/T2w ratio in GM is lastingly altered after premature birth, indicating aberrant GM myelination. T1w/T2w ratio in left STG is significantly associated with full scale IQ and verbal IQ, suggesting that altered myelination in premature-born adults is functionally relevant for cognitive performance. Future studies should investigate cellular correlates of T1w/T2w ratio. Furthermore, longitudinal data across different age groups could elucidate myelin development after premature birth.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Deutsche Forschungsgemeinschaft (Grant No. SO 1336/1-1 [to CS]), German Federal Ministry of Education and Science (Grant No. BMBF 01ER0801 [to PB and DW] and Grant No. BMBF 01ER0803 [to CS]), RECAP preterm [Research on European Children and Adults born Preterm] project, an EU Horizon 2020 study (Grant No. 733280 [to DW and PB]), and Kommission für Klinische Forschung, Technische Universität München (Grant No. KKF 8765162 [to CS], Grant No. KKF8700000474 [to DMH], and Grant No. KKF 8700000620 [to BS-K]).

We thank all current and former members of the Bavarian Longitudinal Study Group who contributed to general study organization, recruitment, data collection, and management as well as subsequent analyses, including (in alphabetical order) Barbara Busch, Stephan Czeschka, Claudia Grünzinger, Christian Koch, Diana Kurze, Sonja Perk, Andrea Schreier, Antje Strasser, Julia Trummer, and Eva van Rossum. We thank the staff of the Department of Neuroradiology in Munich and the Department of Radiology in Bonn for their help in data collection. Most importantly, we thank all study participants and their families for their efforts to take part in this study.

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Oct 5, 2021; revised Feb 16, 2022; accepted Feb 28, 2022.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2022.02.013.

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