- Original Investigation -

Title: Altered grey matter cortical and subcortical T1-weighted/T2-weighted ratio in premature-born adults

Short title: Altered GM T1w/T2w 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 T1w and T2w MRI signal intensity (T1w/T2w ratio) is a proxy for myelin content. We hypothesized altered grey 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 very premature-born adults (<32 weeks of gestation and/or birthweight <1500g, VP/VLBW) and 109 full-term controls at 26 years of age, controlled for voxel-wise volume alterations. Cognitive performance was assessed by verbal, performance, and full-scale intelligence quotient (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.

Abbreviations

BLS – Bavarian longitudinal study

BW – birth weight

CI – confidence interval

FDR – false discovery rate

FOV – field of view

FT – full-term

FWE – family-wise error

GA – gestational age

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

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

1. Introduction

Premature birth (i.e., <37 weeks of gestation) is associated with an increased risk for aberrant neurocognitive development. For example, very premature-born adults have, on average, more than 10 points lower intelligence quotient (IQ) scores, and lasting macroscopic and microscopic brain alterations, which mediate cognitive impairments (1,2). Macroscopic structural brain alterations affect grey matter (GM) and white matter (WM) through volume reductions, aberrant cortical architecture, and disturbed white matter 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, R1 (1/T1-weighted) signal and the ratio of T1-weighted and T2-weighted signal intensity (T1w/T2w ratio). The T1w/T2w ratio has been suggested to provide a simple and broadly available measure which 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 deep GM, in occipital and temporal lobes as well as in WM T1w/T2w ratio have been reported in very preterm (VP) born children (28,29).

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 after premature birth compared to full-term (FT) controls, 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 very premature-born adults (i.e., <32 weeks of gestation and/or birth weight <1500g) and 109 FT controls at 26 years of age by T1w- and T2w-MRI, and IQ assessment.

2. Methods

2.1 Participants

Our study sample has been previously described (30,32–37): 101 VP (<32 weeks of gestation) and/or born with very low birth weight (VLBW, birth weight <1500g; VP/VLBW) subjects and 111 FT controls underwent MRI at 26 years of age (see S1 for more details). 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 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.

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 (38). Birth weight (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 six 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).

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" (WIE), the German adaptation of the Wechsler Adult Intelligence Scale, Third edition (WAIS-III) (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).

2.4 MRI data acquisition

MRI data acquisition has been previously described (30,42): At both sites, Bonn and Munich, MRI data acquisition was performed on Philips Achieva 3T TX systems or Philips Ingenia 3T system using an 8-channel SENSE head coil. Subject distribution among scanners (Table 1): 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. Distribution of the two groups across scanners was significantly different (p=0.001) since 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 ANOVA with factor 'scanner-ID' [Bonn 1, Bonn 2, Munich 1, Munich 2]; $F(3,182)=1.84$, $p=0.11$). A high-resolution T1w 3D-MPRAGE sequence (TI=1300ms, TR=7.7ms, TE=3.9ms, 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 3D sequence (TR=2500 ms, TE=364 ms, flip angle=90°; field of view=512 mm x 512 mm, echo train length=120, reconstructed isotropic voxel size=0.5 mm^3) were acquired. All images were visually inspected for artefacts.

Two FT subjects had to be excluded due to the lack of T2w images. Hence, the final sample included 101 VP/ VLBW subjects and 109 FT subjects.

2.5 MRI processing and T1w/T2w ratio mapping

Images saved as DICOMs 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 T2-w image was co-registered to the T1-w image through rigid body transformation, the T1-w and T2-w images were subjected to bias correction and intensity calibration, and the ratio was calculated to generate the T1w/T2w image. In order to obtain GM masks, T1w images were preprocessed using the Computational Anatomy Toolbox (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 ratio within GM was extracted. Finally, the GM T1w/T2w ratio maps were smoothed with a Gaussian kernel of 6 mm full-width at half maximum.

2.6 Statistical analysis

2.6.1 Thresholding and correction for multiple testing

All voxel-wise analyses were conducted using SPM12 and corrected for multiple comparisons to control the false discovery rate (FDR). Statistical significance was defined as $p<0.05$, FDR-corrected, 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., Armonk, NY, USA) 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 $p<0.05$, FDR-corrected.

2.6.2 Group comparison of grey matter T1w/T2w ratio

To identify areas in which the T1w/T2w ratio in GM was significantly different in VP/VLBW individuals compared to FT controls, 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 voxel-wise 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 individuals compared to FT controls. General linear models were used to test if sex had a significant effect on T1w/T2w ratio in these regions.

To confirm the voxel-wise 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 individuals compared to FT controls. Second, we repeated the group comparison using regions of interest (ROIs) derived from the Harvard-oxford atlas (see S2) (48–51). Third, we repeated the group comparison using a ROI-based approach after applying ComBat, a technique that removes unwanted sources of scan variability (see S3) (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 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 voxel-wise two-tailed multiple regression (see S4.1).

Age was not included as a covariate in our analyses, as VP/VLBW subjects and FT controls had the same mean age of 26 years (p=0.147).

2.6.3 Grey matter 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 voxel-wise two-tailed multiple regression (see S4.2).

Because T1w/T2w ratio in bilateral 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.

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

Table 1 presents group demographic and clinical background variables. There was no significant difference between the VP/VLBW group and FT group regarding sex ($p=0.850$) and age at scanning ($p=0.147$). By design of the study, VP/VLBW subjects had significantly lower GA ($p<0.001$) and lower BW ($p<0.001$). Furthermore, VP/VLBW subjects had significantly lower GM volume ($p<0.001$), full-scale IQ scores ($p<0.001$), verbal IQ scores ($p=0.001$), and performance IQ scores ($p<0.001$) compared to FT controls.

3.2 Altered grey matter 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 to FT controls, 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 superior temporal gyrus (STG). The left cluster spans 65 voxels, the right cluster spans 91 voxels. There was no significant effect of sex on the T1w/T2w ratio for VP/VLBW>FT ($F(1,203)=0.376$, $p=0.540$), and for VP/VLBW<FT ($F(1,203)=2.788$, $p=0.097$). Furthermore, there was no significant effect of scanner on the T1w/T2w ratio for VP/VLBW>FT (scanner dummy-variable 1: $F(1,203)=0.012$, $p=0.914$; scanner dummy-variable 2: : $F(1,203)=0.050$, $p=0.822$; $F(1,203)=3.474$, scanner dummy-variable 3: $p=0.064$), and for VP/VLBW<FT (scanner dummy-variable 1: $F(1,203)=0.793$, $p=0.374$; scanner dummy-variable 2: $F(1,203)=0.082$, $p=0.775$; scanner dummy-variable 3: $F(1,203)=3.702$, $p=0.056$).

Significantly higher T1w/T2w ratio in VP/VLBW subjects compared to FT controls, 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 ROI-based approach (see S2), and after applying ComBat to control for possible scanner effects (see S3).

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 scatter plots in Figure 2. There was no significant linear relationship between birth variables and T1w/T2w ratio for VP/VLBW>FT (see Figure 2A and S4.1). For VP/VLBW<FT, there was a significant positive linear relationship between GA ($p=0.017$) and BW ($p=0.004$), and T1w/T2w ratio (see 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.

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

3.3 Functional relevance of grey matter 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 and 3B, and S4.2).

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. There was a significant positive relationship between T1w/T2w ratio in left STG and full-scale IQ ($p=0.007$) as well as verbal IQ ($p=0.004$, see Figure 4A and B). There was no significant relationship

between T1w/T2w ratio in left STG and performance IQ, and between T1w/T2w ratio in right STG and full-scale IQ, verbal IQ, or performance IQ.

4. Discussion

Using the MRI-based T1w/T2w ratio as a proxy for myelination, we investigated whether GM myelination was altered in a group of 101 VP/VLBW individuals compared to 109 FT-born adults. We found that T1w/T2w ratio was higher in VP/VLBW subjects compared to FT controls in widespread cortical areas bilaterally, particularly in frontal, parietal and temporal cortices, and in putamen and pallidum, which was not related to both birth variables and 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 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.

4.1 Widespread higher T1w/T2w ratio after premature birth

We found higher T1w/T2w ratio in VP/VLBW adults compared to FT controls 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 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 introduction, hypomyelination is thought to be a hallmark of premature birth. Consistently, Vandewouw et al. (28) found lower T1w/T2w ratio in WM, thalamus, putamen and amygdala, and in the occipital and temporal lobes in four-year-old children born VP, indicating hypomyelination. However, in seven-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 aged 3–21 years, 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 lifespan 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. Since 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/different methods such as neurite orientation dispersion and density imaging (NODDI) are needed to investigate this issue. Nevertheless, it has been shown that T1w/T2w ratio significantly differed between demyelinated and myelinated cortex, as determined by anti-proteolipid protein antibody staining in patients with multiple sclerosis (Nakamura et al., 2017).

4.2 Lower T1w/T2w ratio in bilateral superior temporal gyrus

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 four-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 which is highly myelinated in the normative population (55), hence, our findings could indicate that STG might show lastingly impaired myelination after premature birth, possibly due 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 (4,60,61). 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 (62,63). Hence, potential explanations for distinct vulnerability of STG in prematurity include subplate neuron injury and pre-OL death. This is in line with particular significant increases in subplate thickness in temporal brain regions based on intra-uterine MRI at 20-26 gestational weeks, suggesting highly dynamic subplate development in this region (64).

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.

4.3 Functional relevance of grey matter T1w/T2w ratio alterations

There was a significant positive relationship between T1w/T2w ratio after premature birth in left STG and full-scale as well as verbal IQ, indicating that impaired myelination is functionally 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 lifespan, 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 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 (65–67). 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 (60).

4.4 Strengths and limitations

The current sample is biased towards VP/VLBW adults with less severe neonatal complications, fewer functional impairments, and higher IQ. Individuals with more birth complications in the initial BLS sample were more likely to be excluded due to exclusion criteria for MRI. Thus, the reported differences in T1w/T2w ratio between VP/VLBW and FT controls 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 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, there are individual, social, and environmental factors that influence the association between brain structural features and cognitive performance.

As mentioned above, T1w/T2w ratio signal is not specific to myelination and potentially confounded by other factors affecting water magnetization such as lipophile drugs, cholesterol levels or tissue perfusion (68). 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 get 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 controls had the same age of 26 years at the time of the MRI scan.

Lastly, generalizability of our findings is enhanced by the large sample size of our study (101 VP/VLBW and 109 FT adults).

5. Conclusion

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.

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Disclosures

No potential conflicts of interest.

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Figure legends

Figure 1: Group comparison of T1w/T2w ratio.

Voxel-wise group comparison controlling for GM volume in a voxel-wise way, and with sex and scanner as additional covariates. Statistical significance was defined as $p<0.05$, FDR-corrected, cluster size ≥10 voxels.

A. Areas in which T1w/T2w ratio was significantly higher in VP/VLBW subjects compared to FT controls. The t-values are color-coded, warm colors indicate higher t-values. Both hemispheres are shown in medial and lateral views, and two axial slices are included to illustrate results.

B. Areas in which T1w/T2w ratio was significantly lower in VP/VLBW subjects compared to FT controls. The t-values are color-coded, warm colors indicate lower t-values. Two sagittal slices and an axial slice are shown to illustrate results.

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

Figure 2: Relationship between T1w/T2w ratio and variables of premature birth.

A. Associations between GA, BW, and INTI and T1w/T2w ratio – in areas in which it was significantly higher in VP/VLBW subjects compared to FT controls – are shown as scatter plots. GA in weeks, BW in grams, and INTI are each plotted on the x-axes, T1w/T2w ratio is plotted on the y-axes. Linear regression lines as well as beta coefficients and p-values were added. Bold letters indicate statistical significance defined as $p<0.05$, FDR-corrected.

B. Associations between GA, BW, and INTI and T1w/T2w ratio – in areas in which it was significantly lower in VP/VLBW subjects compared to FT controls – are shown as scatter plots. GA in weeks, BW in grams, and INTI are each plotted on the x-axes, T1w/T2w ratio is plotted on the y-axes. Linear regression lines as well as beta

coefficients and p-values were added. Bold letters indicate statistical significance defined as $p<0.05$, FDR-corrected.

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

Figure 3: Relationship between T1w/T2w ratio and cognitive performance.

A. Associations between T1w/T2w ratio – in areas in which it was significantly higher in VP/VLBW subjects compared to FT controls – and full-scale IQ, verbal IQ, and performance IQ are shown as scatter plots. T1w/T2w ratio is plotted on the x-axes, full-scale IQ, verbal IQ, and performance IQ are each plotted on the y-axes. Linear regression lines as well as beta coefficients and p-values were added. Bold letters indicate statistical significance defined as $p<0.05$, FDR-corrected.

B. Associations between T1w/T2w ratio – in areas in which it was significantly lower in VP/VLBW subjects compared to FT controls – and full-scale IQ, verbal IQ, and performance IQ are shown as scatter plots. T1w/T2w ratio is plotted on the x-axes, full-scale IQ, verbal IQ, and performance IQ are each plotted on the y-axes. Linear regression lines as well as beta coefficients and p-values were added. Bold letters indicate statistical significance defined as $p<0.05$, FDR-corrected.

Abbreviations: FT, full-term; IQ, intelligence quotient; VP/VLBW, very preterm and/or very low birth weight.

Figure 4: Relationship between T1w/T2w ratio in left and right superior temporal gyrus and cognitive performance.

A. Associations between T1w/T2w ratio in left STG and full-scale IQ, verbal IQ, and performance IQ are shown as scatter plots. T1w/T2w ratio is plotted on the x-axes, full-scale IQ, verbal IQ, and performance IQ are each plotted on the y-axes. Linear

regression lines as well as beta coefficients and p-values were added. Bold letters indicate statistical significance defined as $p<0.05$, FDR-corrected.

B. Associations between T1w/T2w ratio in right STG and full-scale IQ, verbal IQ, and performance IQ are shown as scatter plots. T1w/T2w ratio is plotted on the x-axes, full-scale IQ, verbal IQ, and performance IQ are each plotted on the y-axes. Linear regression lines as well as beta coefficients and p-values were added. Bold letters indicate statistical significance defined as $p<0.05$, FDR-corrected.

Abbreviations: IQ, intelligence quotient.

- Supplement -

Title: Altered grey matter cortical and subcortical T1w/T2w ratio in premature-born adults

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S1: Participants – Bavarian Longitudinal Study

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 (36,37). 682 infants were born VP (<32 weeks of gestation) and/or with very low birth weight (VLBW, birth weight <1500g). Informed written consent from a parent and/or legal guardian was obtained. From the initial 916 FT born infants born at the same obstetric hospitals who 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. 260 of the VP/VLBW group and 229 controls participated in psychological assessments (32). All subjects were screened for MR-related exclusion criteria, including (self-reported): claustrophobia, inability to lie still for >30 minutes, 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. However, the most frequent reason not to perform the MRI exam was that subjects declined to participate.

S2: ROI-based group comparison of grey matter T1w/T2w ratio

In order to confirm the voxel-wise results, we repeated the group comparison using a ROI-based approach. For each subject, the T1w/T2w ratio image was segmented into 47 bilateral cortical ROIs and 15 subcortical ROIs derived from the Harvard-Oxford atlas, using a tissue probability threshold of 50% (48-51). General linear models were used to test for significant group differences of T1w/T2w ratio within these ROIs. T1w/T2w ratio values were entered as dependent variables, group as fixed factor and grey matter volume, sex and scanner as covariates. Analyses were corrected for multiple comparisons, statistical significance was defined as $p < .05$, FDR-corrected. Supporting our voxel-wise approach, ROI-based group comparison showed widespread ROIs in which T1w/T2w ratio was significantly higher in VP/VLBW subjects compared to FT controls (see Table S2.1), particularly in frontal, parietal and temporal cortices, and in putamen, pallidum, hippocampus and amygdala, and one ROI, planum polare, in which T1w/T2w ratio was significantly lower in VP/VLBW subjects compared to FT controls (see Table S2.2).

Table S2.1: Group differences in T1w/T2w ratio for VP/VLBW>FT.

Cortical ROI	**p-value**	**Subcortical ROI**	**p-value**
Frontal Pole	**<0.001**	Left Putamen	**0.003**

Insular Cortex	**0.004**	Left Pallidum	**0.007**
Middle Frontal Gyrus	**0.014**	Left Hippocampus	**0.028**
Inferior Frontal Gyrus, pars triangularis	**0.002**	Left Amygdala	**0.007**
Inferior Frontal Gyrus, pars opercularis	**<0.001**	Left Accumbens	**0.007**
Precentral Gyrus	**0.033**	Right Putamen	**0.003**
Temporal Pole	**<0.001**	Right Pallidum	**0.004**
Superior Temporal Gyrus, anterior division	**<0.001**	Right Hippocampus	**0.012**
Middle Temporal Gyrus, temporooccipital part	**0.027**	Right Amygdala	**0.009**
Inferior Temporal Gyrus, anterior division	**<0.001**	Right Accumbens	**0.018**
Inferior Temporal Gyrus, posterior division	**0.001**	Left Thalamus	0.290
Inferior Temporal Gyrus, temporooccipital part	**<0.001**	Brain Stem	0.070
Postcentral Gyrus	**0.004**	Right Thalamus	0.446
Supramarginal Gyrus, anterior division	**0.001**		
Supramarginal Gyrus, posterior division	**0.005**		
Angular Gyrus	**0.014**		
Lateral Occipital Cortex, superior division	**0.012**		
Lateral Occipital Cortex, inferior division	**0.017**		
Intracalcarine Cortex	**0.006**		
Frontal Medial Cortex	**0.007**		
Subcallosal Cortex	**0.005**		
Paracingulate Gyrus	**0.007**		
Cingulate Gyrus, anterior division	**0.016**		
Cingulate Gyrus, posterior division	**0.013**		
Cuneal Cortex	**0.025**		
Frontal Orbital Cortex	**0.017**		
Parahippocampal Gyrus, posterior division	**0.005**		
Lingual Gyrus	**<0.001**		
Temporal Fusiform Cortex, anterior division	**0.001**		
Temporal Fusiform Cortex, posterior division	**0.011**		
Temporal Occipital Fusiform Cortex	**0.004**		
Occipital Fusiform Gyrus	**0.005**		
Frontal Operculum Cortex	**0.001**		
Central Opercular Cortex	**0.001**		
Parietal Operculum Cortex	**0.008**		
Planum Temporale	**0.006**		
Superior Frontal Gyrus	0.104		
Middle Temporal Gyrus, anterior division	0.852		
Middle Temporal Gyrus, posterior division	0.059		
Superior Parietal Lobule	0.125		
Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex)	0.100		
Precuneous Cortex	0.049		
Parahippocampal Gyrus, anterior division	0.041		
Heschl's Gyrus (includes H1 and H2)	0.113		

Occipital Pole	0.095

ROIs in which T1w/T2w ratio was higher in VP/VLBW subjects compared to FT controls with the respective p-values. Bold letters indicate statistical significance defined as $p<0.05$, FDR- corrected.
Abbreviations: ROI, region of interest.

Table S2.2: Group differences in T1w/T2w ratio for VP/VLBW<FT.

Cortical ROI	**p-value**	**Subcortical ROI**	**p-value**
Planum Polare	**0.002**	Left Caudate	0.286
Supracalcarine Cortex	0.820	Right Caudate	0.074

ROIs in which T1w/T2w ratio was lower in VP/VLBW subjects compared to FT controls with the respective p-value. Bold letters indicate statistical significance defined as $p<0.05$, FDR- corrected.
Abbreviations: ROI, region of interest.

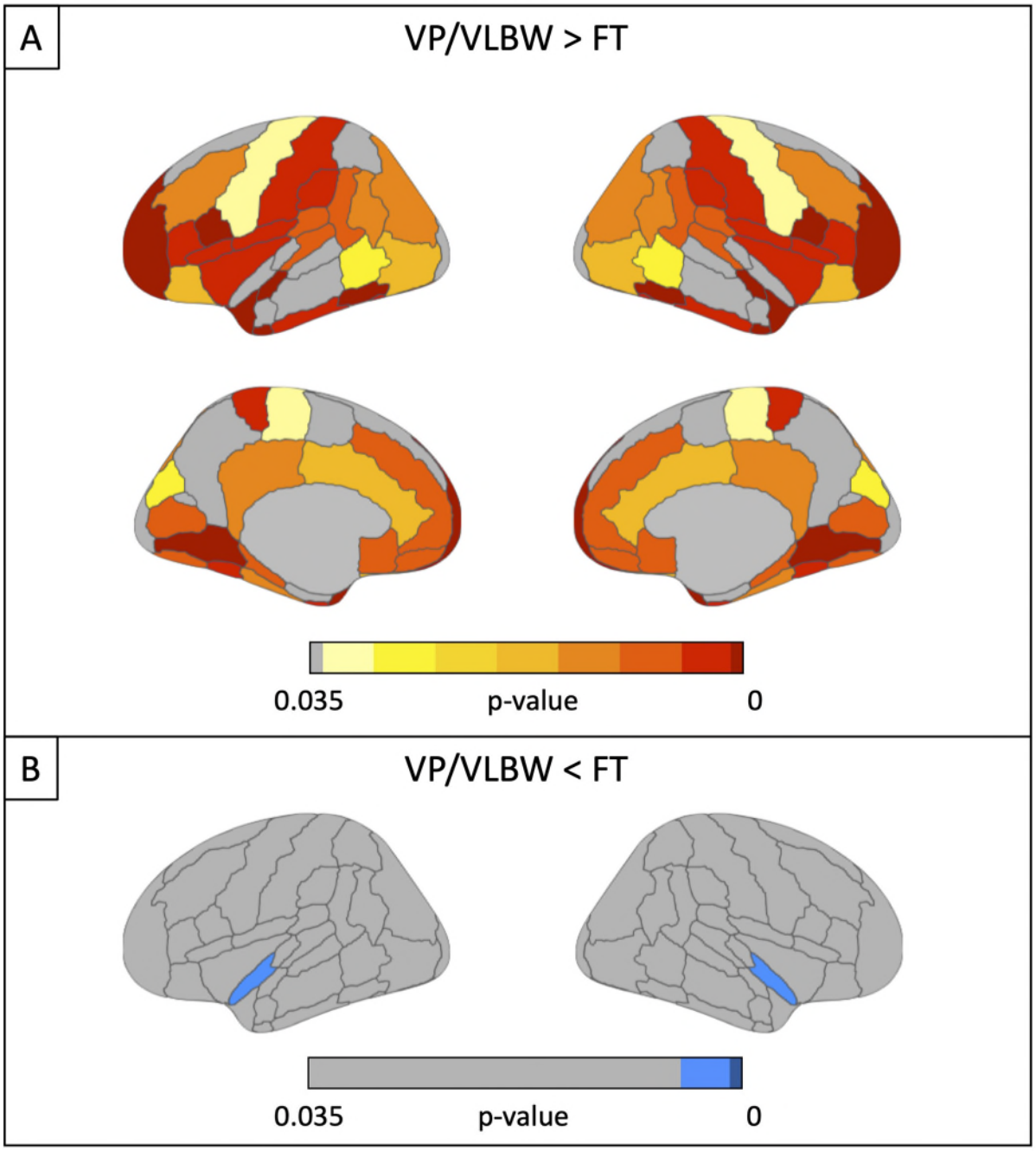


Figure S2.3: ROI-based group comparison of T1w/T2w ratio.

ROI-based group comparison with GM volume, sex and scanner as covariates. Statistical significance was defined as $p<0.05$, FDR-corrected.

- **A.** ROIs in which T1w/T2w ratio was significantly higher in VP/VLBW subjects compared to FT controls. The p-values are color-coded, red colors indicate lower p-values. Both hemispheres are shown in medial and lateral views.
- **B.** ROIs in which T1w/T2w ratio was significantly lower in VP/VLBW subjects compared to FT controls. The p-values are color-coded, darker blue indicates lower p-values. Both hemispheres are shown in lateral views.

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

S3: ROI-based group comparison of grey matter T1w/T2w ratio after applying ComBat

In order to control for possible scanner effects, we repeated the group comparison using a ROI-based approach after applying ComBat, a technique that removes unwanted sources of scan variability (43). General linear models were used to test for significant group differences of ComBat-harmonized T1w/T2w ratio within the ROIs. ComBat-harmonized T1w/T2w ratio values were entered as dependent variables, group as fixed factor and grey matter volume and sex as covariates. Analyses were corrected for multiple comparisons, statistical significance was defined as $p < .05$, FDR-corrected.

Supporting our previous results, ROI-based group comparison after applying ComBat showed widespread ROIs in which T1w/T2w ratio was significantly higher in VP/VLBW subjects compared to FT controls (see Table S3.1), particularly in frontal, parietal and temporal cortices, and in putamen and pallidum, and one ROI, planum polare, in which T1w/T2w ratio was significantly lower in VP/VLBW subjects compared to FT controls (see Table S3.2).

Table S3.1: Group differences in ComBat-harmonized T1w/T2w ratio for VP/VLBW>FT.

Cortical ROI	**p-value**	**Subcortical ROI**	**p-value**
Frontal Pole	**0.002**	Left Putamen	**0.010**
Insular Cortex	**0.019**	Left Pallidum	**0.010**
Inferior Frontal Gyrus, pars triangularis	**0.011**	Left Amygdala	**0.023**
Inferior Frontal Gyrus, pars opercularis	**0.001**	Left Accumbens	**0.017**
Temporal Pole	**0.001**	Right Caudate	**0.016**
Superior Temporal Gyrus, anterior division	**<0.001**	Right Putamen	**0.007**
Inferior Temporal Gyrus, anterior division	**0.003**	Right Pallidum	**0.007**
Inferior Temporal Gyrus, posterior division	**0.003**	Left Thalamus	0.459
Inferior Temporal Gyrus, temporooccipital part	**0.002**	Brain Stem	0.163
Postcentral Gyrus	**0.012**	Left Hippocampus	0.073
Supramarginal Gyrus, anterior division	**0.003**	Right Thalamus	0.734
Supramarginal Gyrus, posterior division	**0.019**	Right Hippocampus	0.046
Intracalcarine Cortex	**0.013**	Right Amygdala	0.030
Frontal Medial Cortex	**0.018**	Right Accumbens	0.042
Subcallosal Cortex	**0.014**		
Paracingulate Gyrus	**0.025**		
Parahippocampal Gyrus, posterior division	**0.018**		
Lingual Gyrus	**0.001**		
Temporal Fusiform Cortex, anterior division	**0.003**		
Temporal Occipital Fusiform Cortex	**0.017**		
Occipital Fusiform Gyrus	**0.019**		
Frontal Operculum Cortex	**0.005**		
Central Opercular Cortex	**0.006**		
Planum Temporale	**0.017**		
Superior Frontal Gyrus	0.213		
Middle Frontal Gyrus	0.071		

Precentral Gyrus	0.111
Middle Temporal Gyrus, posterior division	0.184
Middle Temporal Gyrus, temporooccipital part	0.079
Superior Parietal Lobule	0.225
Angular Gyrus	0.033
Lateral Occipital Cortex, superior division	0.034
Lateral Occipital Cortex, inferior division	0.039
Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex)	0.165
Cingulate Gyrus, anterior division	0.051
Cingulate Gyrus, posterior division	0.035
Precuneous Cortex	0.099
Cuneal Cortex	0.094
Frontal Orbital Cortex	0.055
Parahippocampal Gyrus, anterior division	0.112
Temporal Fusiform Cortex, posterior division	0.037
Parietal Operculum Cortex	0.044
Heschl's Gyrus (includes H1 and H2)	0.292
Occipital Pole	0.138

ROIs in which ComBat-harmonized T1w/T2w ratio was higher in VP/VLBW subjects compared to FT controls with the respective p-values. Bold letters indicate statistical significance defined as $p<0.05$, FDR- corrected. Abbreviations: ROI, region of interest.

Table S3.2: Group differences in ComBat-harmonized T1w/T2w ratio for VP/VLBW<FT.

Cortical ROI	**p-value**	**Subcortical ROI**	**p-value**
Planum Polare	**<0.001**	Right Caudate	**0.016**
Middle Temporal Gyrus, anterior division	0.644	Left Caudate	0.130
Supracalcarine Cortex	0.479		

ROIs in which ComBat-harmonized T1w/T2w ratio was lower in VP/VLBW subjects compared to FT controls with the respective p-value. Bold letters indicate statistical significance defined as $p<0.05$, FDR- corrected. Abbreviations: ROI, region of interest.

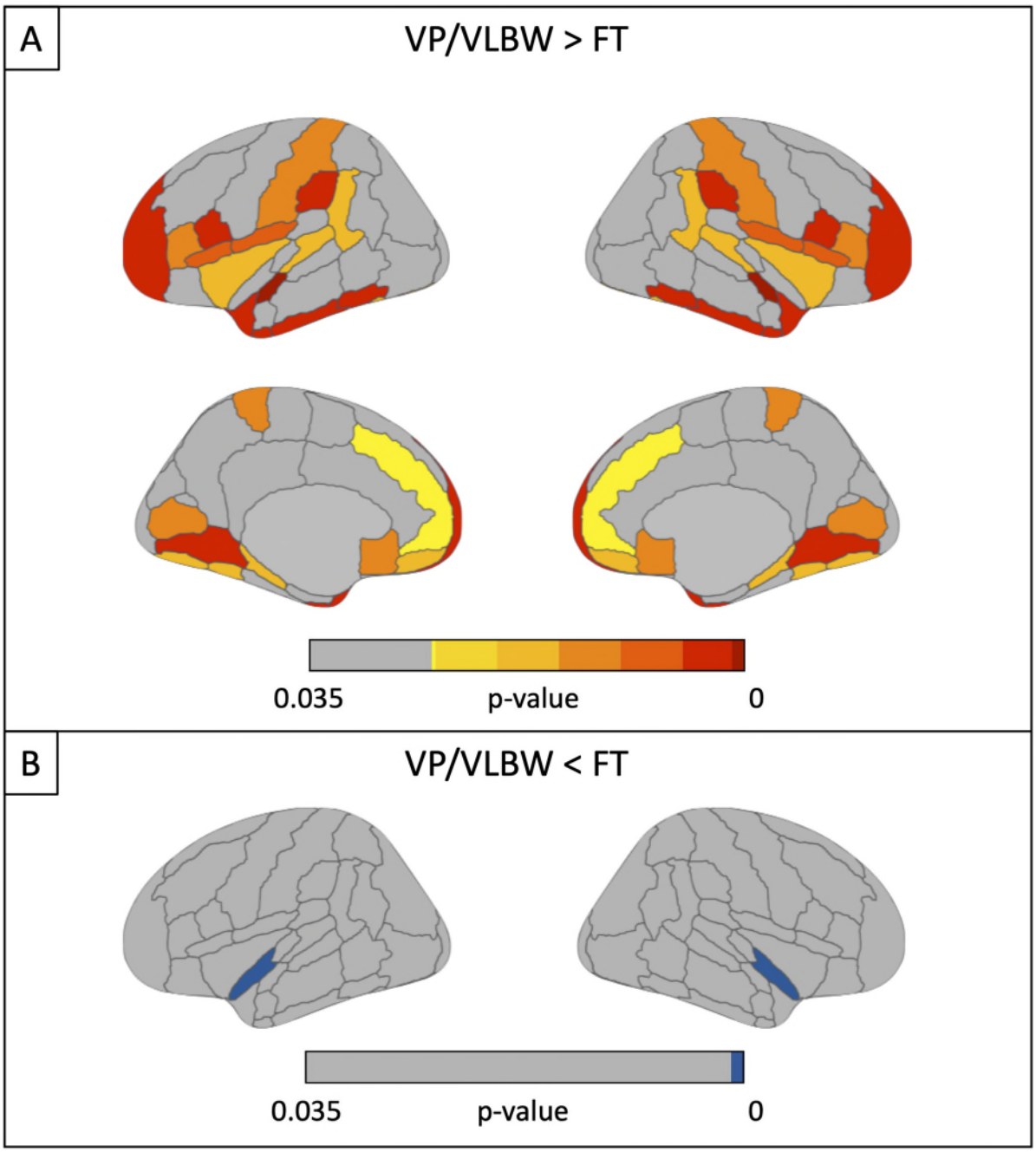


Figure S3.3: ROI-based group comparison of T1w/T2w ratio after applying ComBat.

ROI-based group comparison with GM volume, sex and scanner as covariates. Statistical significance was defined as $p<0.05$, FDR-corrected.

- **A.** ROIs in which ComBat-harmonized T1w/T2w ratio was significantly higher in VP/VLBW subjects compared to FT controls. The p-values are color-coded, red colors indicate lower p-values. Both hemispheres are shown in medial and lateral views.
- **B.** ROIs in which ComBat-harmonized T1w/T2w ratio was significantly lower in VP/VLBW subjects compared to FT controls. The p-values are color-coded, darker blue indicates lower p-values. Both hemispheres are shown in lateral views.

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

S4: Voxel-wise multiple regression analyses

S4.1 Relationship between T1w/T2w ratio and variables of premature birth

To identify regionally specific correlation of T1w/T2w ratio and variables of premature birth in areas in which T1w/T2w ratio was significantly greater in VP/VLBW individuals compared to FT controls, we performed voxel-wise two-tailed multiple regression using SPM12 in the VP/VLBW group. T1w/T2w ratio was entered as dependent variable, and GA, BW or INTI as independent variables, respectively. The analyses were restrained within a mask of areas in which T1w/T2w ratio was significantly greater in VP/VLBW individuals compared to FT controls, FDR-corrected. GM volume, sex and scanner were entered as covariates.

There were no areas in which there was a significant ($p<0.05$, FDR-corrected, cluster size ≥10 voxels) positive or negative relationship between GA, BW or INTI, and T1w/T2w ratio.

S4.2 Relationship between T1w/T2w ratio and cognitive performance

To identify regionally specific correlation of T1w/T2w ratio with cognitive performance in areas in which T1w/T2w ratio was significantly greater in VP/VLBW individuals compared to FT controls, we performed two-tailed multiple regression analyses in the VP/VLBW group in a voxel-wise approach using SPM12. T1w/T2w ratio was entered as independent variable, and full-scale IQ, verbal IQ, or performance IQ as dependent variables, respectively. The analyses were restrained within a mask of areas in which T1w/T2w ratio was significantly greater in VP/VLBW individuals compared to FT controls, FDR-corrected. GM volume, sex and scanner were entered as covariates.

There were no areas in which there was a significant ($p<0.05$, FDR-corrected, cluster size ≥10 voxels) positive or negative relationship between T1w/T2w ratio and full-scale IQ, verbal IQ, or performance IQ.

Table S5: Comparison between VP/VLBW subjects with MRI data and without MRI data

	VP/VLBW with MRI (n=101)		**VP/VLBW without MRI (n=159)**		
	Mean	**SD**	**Mean**	**SD**	**p value**
GA (weeks)	30.5	± 2.1	30.6	± 2.3	0.656
BW (g)	1324	± 313	1323	± 320	0.980
INTI	11.6	± 3.8	12.1	± 4.1	0.281
Full-scale IQ[a] (a.u.)	94.1	± 12.7	79.5	± 22.9	**<0.001**

Statistical comparisons: GA, BW and FS-IQ with two sample t-tests. Bold letters indicate statistical significance defined as $p<0.05$.

Abbreviations: BW, birth weight; GA, gestational age; INTI, intensity of neonatal treatment index; IQ, intelligence quotient; SD, standard deviation; MRI, magnetic resonance imaging; VP/VLBW, very preterm and/or very low birth weight.

[a] Data are based on 97 VP/VLBW subjects with MRI data and 120 VP/VLBW subjects without MRI data

Tables

Table 1: Demographical, clinical and cognitive data

	VP/VLBW (n=101)			FT (n=109)			
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**p-value**
Sex (male/female)	58/43			64/45			0.850
Age (years)	26.7	± 0.6	25.7 – 28.3	26.9	± 0.7	25.5 – 28.9	0.147
GA (weeks)	30.5	± 2.1	25 – 36	39.7	± 1.1	37 – 42	**<0.001**
BW (g)	1325	± 313	630 – 2070	3391	± 447	2120 – 4670	**<0.001**
INTI (days)	11.6	± 3.8	3 – 18	n.a.	n.a.	n.a.	n.a.
GM (mm^3)	683.1	± 62.9	524.0 – 839.3	714.0	± 56.4	555.1 – 861.2	**<0.001**
Full-scale IQ[a]	94.1	± 12.7	64 – 131	102.4	± 11.9	77 – 130	**<0.001**
Verbal IQ[a]	98.8	± 14.0	62 – 137	105.7	± 14.2	77 – 143	**0.001**
Performance IQ[a]	89.8	± 13.5	56 – 118	98.5	± 10.4	69 – 125	**<0.001**
Scanner	**n**	**%**		**n**	**%**		**0.001**
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		

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. Bold letters indicate statistical significance defined as $p<0.05$.
Abbreviations: BW, birth weight; FT, full-term; GA, gestational age; GM, grey matter; INTI, intensity of neonatal treatment index; IQ, intelligence quotient; SD, standard deviation; VP/VLBW, very preterm and/or very low birthweight.
[a] Data are based on 97 VP/VLBW and 106 FT-born individuals.

Table 2: Relationship between T1w/T2w ratio and variables of premature birth

Risk factor	T1w/T2w ratio	Beta coefficient	p-value
GA	VP/VLBW>FT	-0.065	0.530
	VP/VLBW<FT	0.246	0.017
BW	VP/VLBW>FT	0.082	0.460
	VP/VLBW<FT	0.314	**0.004**
INTI	VP/VLBW>FT	-0.028	0.781
	VP/VLBW<FT	-0.114	0.273

Beta 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 individuals compared to FT controls, and areas in which it was significantly greater in VP/VLBW individuals compared to FT controls, respectively, as dependent variables, and variables of premature birth as independent variables. GM, sex and scanner were entered as

covariates. Bold letters indicate statistical significance after FDR correction using the Benjamini-Hochberg procedure.
Abbreviations: BW, birth weight; FT, full-term; GA, gestational age; INTI, intensity of neonatal treatment index; VP/VLBW, very preterm and/or very low birthweight.

Table 3: Relationship between T1w/T2w ratio and cognitive performance

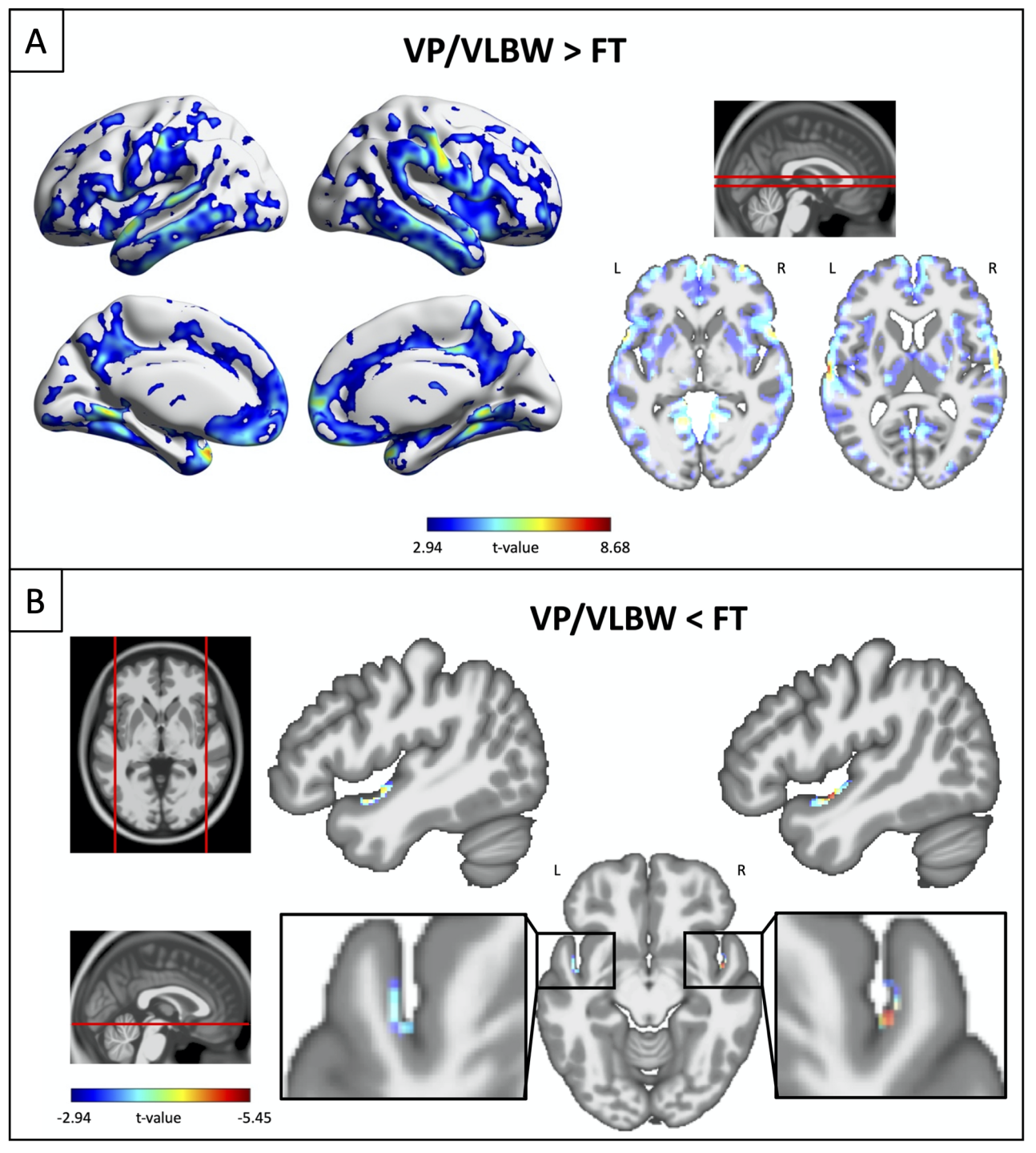
T1w/T2w ratio	Cognitive performance	Beta coefficient	p-value
VP/VLBW>FT	Full-scale IQ	0.037	0.715
VP/VLBW<FT	Full-scale IQ	0.111	0.258
VP/VLBW>FT	Verbal IQ	0.093	0.360
VP/VLBW<FT	Verbal IQ	0.189	0.057
VP/VLBW>FT	Performance IQ	-0.048	0.633
VP/VLBW<FT	Performance IQ	-0.020	0.838

Beta 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 individuals compared to FT controls, and areas in which it was significantly greater in VP/VLBW individuals compared to FT controls, respectively, as independent variables, and full-scale IQ as dependent variable. GM, sex and scanner were entered as covariates. Bold letters indicate statistical significance after FDR correction using the Benjamini-Hochberg procedure.
Abbreviations: FT, full-term; IQ, intelligence quotient; VP/VLBW, very preterm and/or very low birthweight.

Table 4: Relationship between T1w/T2w ratio in left and right superior temporal gyrus and cognitive performance

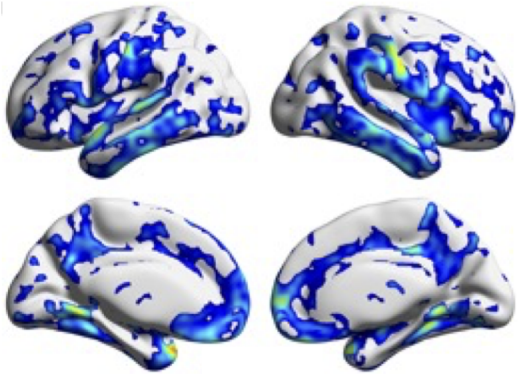
T1w/T2w ratio	Cognitive performance	Beta coefficient	p-value
Left STG	Full-scale IQ	0.190	**0.007**
Right STG	Full-scale IQ	0.109	0.111
Left STG	Verbal IQ	0.205	**0.004**
Right STG	Verbal IQ	0.120	0.082
Left STG	Performance IQ	0.116	0.103
Right STG	Performance IQ	0.065	0.344

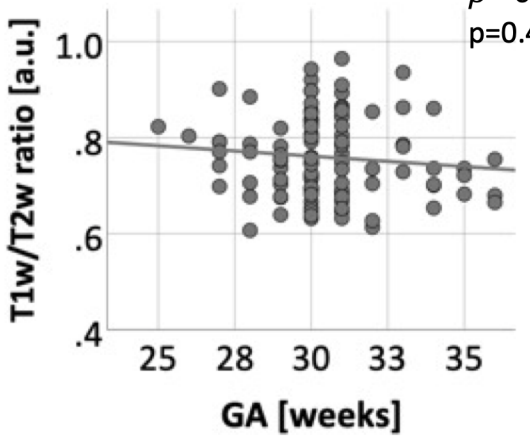
Beta coefficients and p-values from linear regression analysis in the VP/VLBW group between the T1w/T2w ratio in areas in which it was significantly smaller in VP/VLBW individuals compared to FT controls, and areas in which it was significantly greater in VP/VLBW individuals compared to FT controls, respectively, as independent variables, and full-scale IQ as dependent variable. GM, sex and scanner were entered as covariates. Bold letters indicate statistical significance after FDR correction using the Benjamini-Hochberg procedure.
Abbreviations: FT, full-term; IQ, intelligence quotient; VP/VLBW, very preterm and/or very low birthweight.

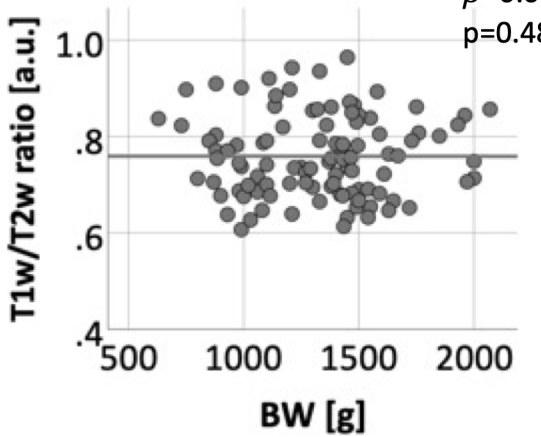

A
VP/VLBW > FT
L
R
L
R
2.94
t-value
8.68
B
VP/VLBW < FT
L
R
-2.94
t-value
-5.45

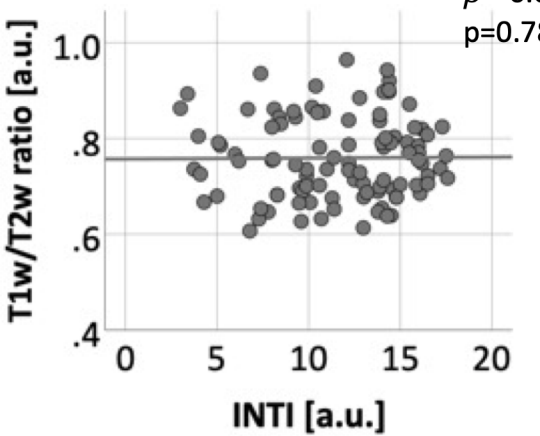
A

VP/VLBW > FT



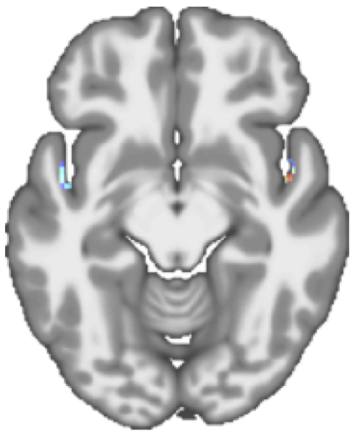


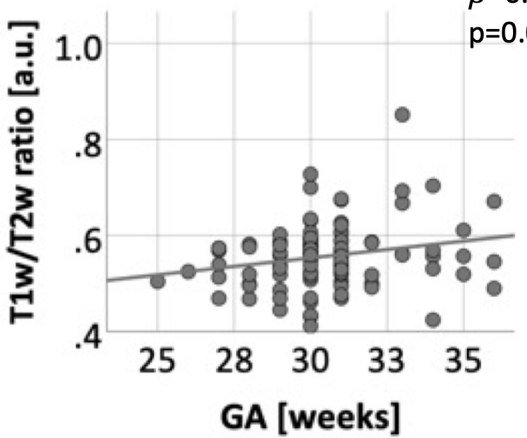


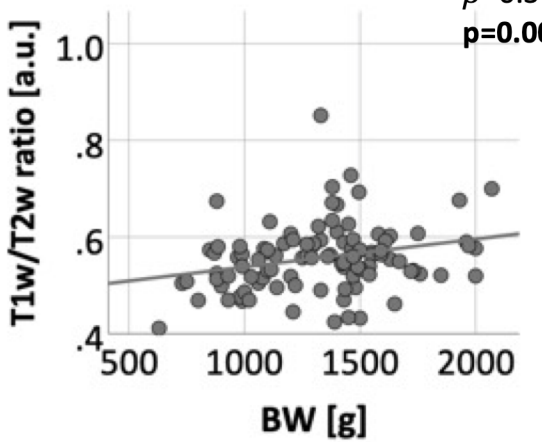


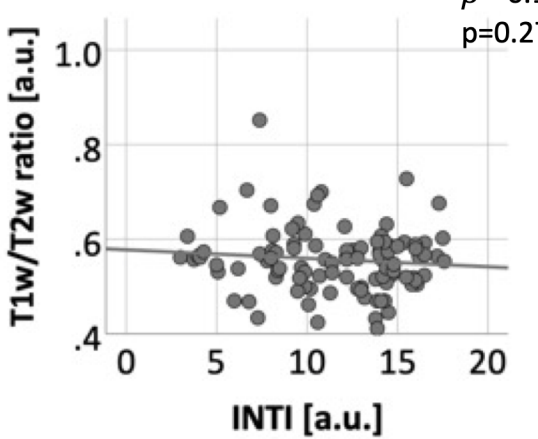
B

VP/VLBW < FT



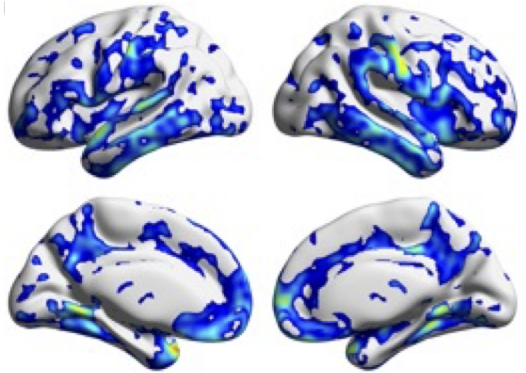


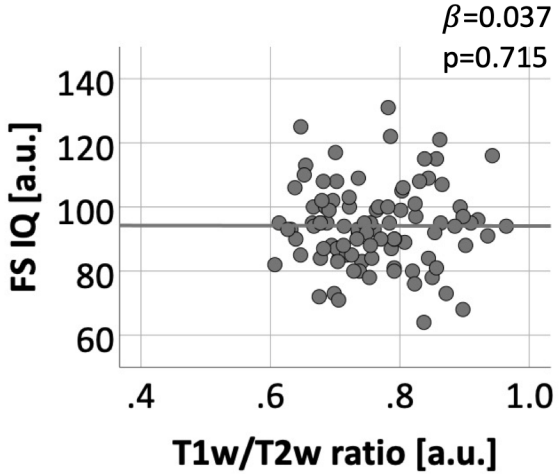


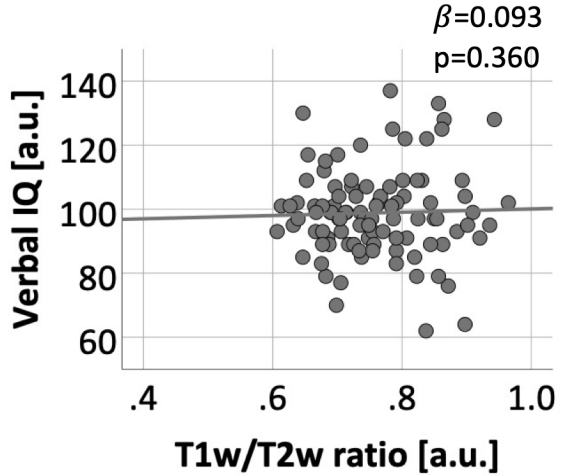


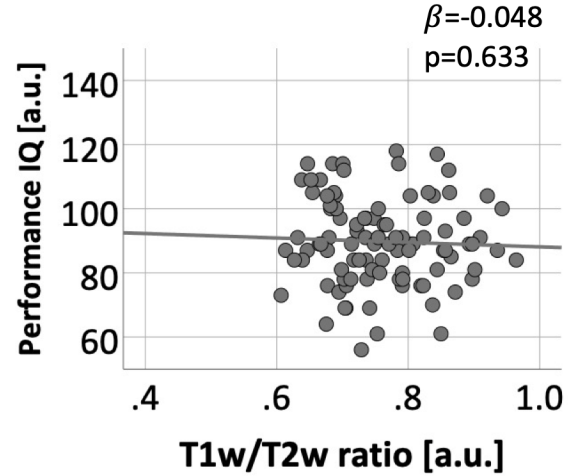
A

VP/VLBW > FT



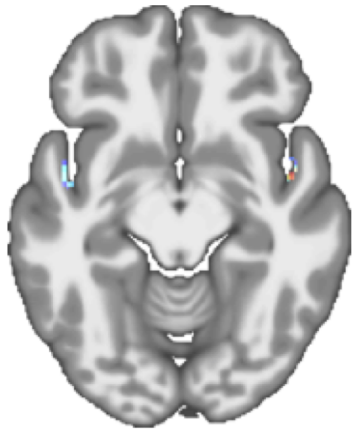


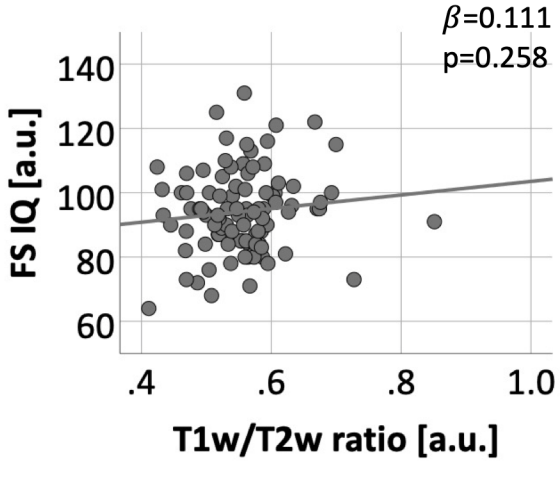


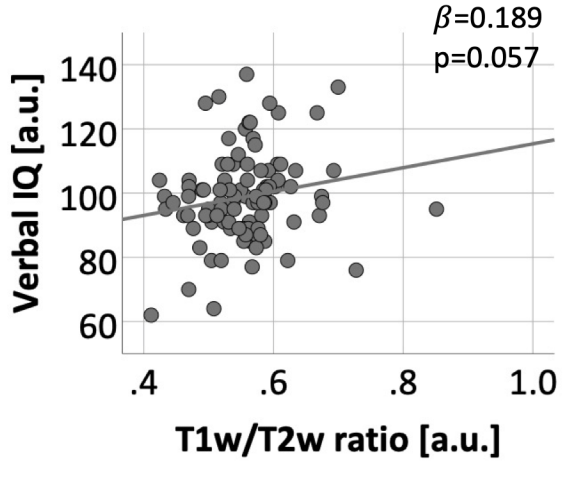


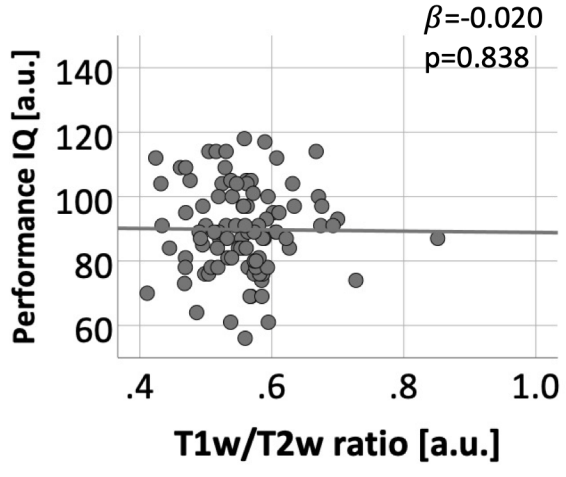
B

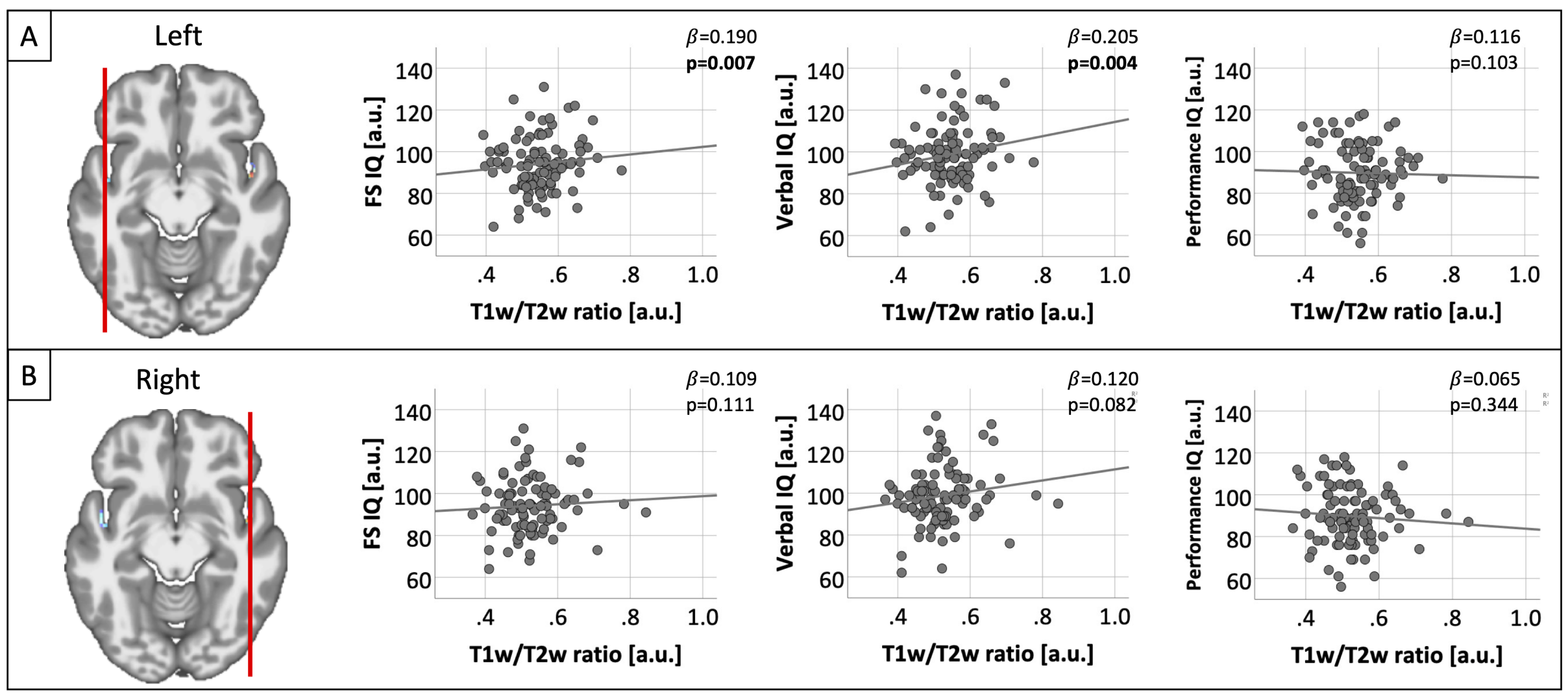
VP/VLBW < FT










A
Left
β=0.190
p=0.007
FS IQ [a.u.]
T1w/T2w ratio [a.u.]
β=0.205
p=0.004
Verbal IQ [a.u.]
T1w/T2w ratio [a.u.]
β=0.116
p=0.103
Performance IQ [a.u.]
T1w/T2w ratio [a.u.]
B
Right
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p=0.111
FS IQ [a.u.]
T1w/T2w ratio [a.u.]
β=0.120
p=0.082
Verbal IQ [a.u.]
T1w/T2w ratio [a.u.]
β=0.065
p=0.344
Performance IQ [a.u.]
T1w/T2w ratio [a.u.]