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RESEARCH ARTICLE

Brain White Matter Development Over the First 13 Years in Very Preterm and Typically Developing Children Based on the T_1-w/T_2-w Ratio

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Abstract

Background and Objectives

To investigate brain regional white matter development in full-term (FT) and very preterm (VP) children at term equivalent and 7 and 13 years of age based on the ratio of T_1- and T_2-weighted MRI (T_1-w/T_2-w), including (1) whether longitudinal changes differ between birth groups or sexes, (2) associations with perinatal risk factors in VP children, and (3) relationships with neurodevelopmental outcomes at 13 years.

Methods

Prospective longitudinal cohort study of VP (born <30 weeks' gestation or <1,250 g) and FT infants born between 2001 and 2004 and followed up at term equivalent and 7 and 13 years of age, including MRI studies and neurodevelopmental assessments. T_1-w/T_2-w images were parcellated into 48 white matter regions of interest.

Results

Of 224 VP participants and 76 FT participants, 197 VP and 55 FT participants had useable T_1-w/T_2-w data from at least one timepoint. T_1-w/T_2-w values increased between term equivalent and 13 years of age, with little evidence that longitudinal changes varied between birth groups or sexes. VP birth, neonatal brain abnormalities, being small for gestational age, and postnatal infection were associated with reduced regional T_1-w/T_2-w values in childhood and adolescence. Increased T_1-w/T_2-w values across the white matter at 13 years were associated with better motor and working memory function for all children. Within the FT group only, larger increases in T_1-w/T_2-w values from term equivalent to 7 years were associated with poorer attention and executive function, and higher T_1-w/T_2-w values at 7 years were associated with poorer mathematics performance.

Discussion

VP birth and multiple known perinatal risk factors are associated with long-term reductions in the T_1-w/T_2-w ratio in white matter regions in childhood and adolescence, which may relate to alterations in microstructure and myelin content. Increased T_1-w/T_2-w ratio at 13 years appeared to be associated with better motor and working memory function and there appeared to be developmental differences between VP and FT children in the associations for attention, executive functioning, and mathematics performance.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

FDR = false discovery rate; **FLIRT** = FMRIB linear image registration tool; **FT** = full term; **JHU** = Johns Hopkins University; **M-CRIB-WM** = Melbourne Children's Regional Infant Brain White Matter; **VP** = very preterm.

Myelin is an important building block in the brain, ensheathing axons for rapid transmission of nerve impulses. The ratio of image intensity on T_1- and T_2-weighted MRI, that is, T_1-w/T_2-w, may provide information on tissue characteristics including microstructure and myelin content.[1,2] A major advantage of the T_1-w/T_2-w technique over other myelin mapping approaches is its simplicity, making it more likely to be adopted for clinical studies because it can be readily computed from T_1-w and T_2-w images that are routinely acquired in short time frames during clinical MRI examinations.

Considering the maturation of oligodendrocytes to form mature myelin is rapid during early childhood,[3] and myelin maturation continues into adolescence,[4] the period from infancy to adolescence is a critical time to study white matter development and to investigate potential deviations from typical white matter development. Compared with infants born full term (FT; ≥37 weeks' gestation), infants born very preterm (VP; <32 weeks' gestation) are known to have a developmental myelination vulnerability.[5]

Sex-related differences in myelin development are poorly documented, with conflicting findings.[3] More evidence is required to demonstrate whether myelin dysmaturation is a mechanism by which perinatal factors such as neonatal brain abnormalities, intrauterine growth restriction, postnatal infection, and bronchopulmonary dysplasia disrupt VP brain development.[6–9]

The neurodevelopmental consequences of differing myelination trajectories from infancy to adolescence remain to be determined. Alterations to myelin development in VP children may help explain their higher rates of neurodevelopmental impairments compared with FT children.[10–13]

The specific aims were as follows:

1. Compare T_1-w/T_2-w values in 48 major white matter regions between VP and FT groups and boys and girls at term equivalent and 7 and 13 years of age and determine whether the longitudinal development of T_1-w/T_2-w values from term equivalent to 13 years of age differs between VP and FT groups or between sexes
2. Determine whether perinatal variables, including moderate to severe brain abnormality, being small for gestational age, infection, and bronchopulmonary dysplasia, are related to cross-sectional or longitudinal T_1-w/T_2-w values in VP children
3. Determine whether cross-sectional or longitudinal changes in T_1-w/T_2-w values are related to intelligence, motor, working memory, attention, language, executive functioning, memory and learning, academics, and behavioral functioning at age 13 years in all children and whether relationships differed between birth groups.

Methods

Participants

Participants were recruited from The Royal Women's Hospital in Melbourne, Australia, as part of the Victorian Infant Brain Study prospective longitudinal cohort. The VP group comprised surviving children born at <30 weeks' gestation or very low birth weight (<1,250 g) who did not have genetic or congenital abnormalities, all recruited at birth. The FT group comprised healthy children born at ≥37 and ≤42 weeks' gestation, recruited at birth and 2 years of age. Participants were followed up at age 7 and 13 years corrected for prematurity. Perinatal and neurodevelopmental data collection is detailed in eAppendix 1, links.lww.com/WNL/B725.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Human Research and Ethics Committees of The Royal Women's and The Royal Children's Hospitals. Parents gave written informed consent for their child to participate.

MRI Acquisition

At each time point, participants underwent a brain MRI scan at The Royal Children's Hospital without sedation. At term-equivalent age, infants were scanned using a 1.5T General Electric MRI scanner and structural T_1-weighted images and T_2-weighted images were acquired. At 7 and 13 years, MRI was an optional part of the follow-up and participants were required to pass a mock MRI to proceed with the scan. At 7 years' corrected age, children were scanned using a 3T Trio Siemens MRI scanner and we acquired T_1-w images and T_2-w images. At 13 years' corrected age, children were scanned on the same 3 Tesla Trio Siemens MRI scanner, again with T_1-w images and T_2-w images being acquired. Full MRI details including MRI acquisition measures are provided in eAppendix 1, links.lww.com/WNL/B725.

Tissue Segmentation

At term-equivalent age, total CSF volumes were obtained from the T_2-w images using the morphologically adaptive neonatal tissue segmentation (MANTiS) technique.[14] At age 7 and 13 years, CSF volumes were obtained from the T_1-w images using Statistical Parametric Mapping version 12 (fil.ion.ucl.ac.uk/spm/www.fil.ion.ucl.ac.uk/spm/).

T_1-w/T_2-w Image Analysis

T_1-w and T_2-w images were bias field corrected.[15] The T_1-w and T_2-w images were coregistered using the FMRIB linear image registration tool (FLIRT) from the Functional MRI of the Brain Software Library (FSL).[16] The ratio of the T_1-w to T_2-w image (i.e., the whole brain T_1-w/T_2-w map) was calculated. The term equivalent T_2-w images[17] and the T_1-w images for the 7- and 13-year time points[18] were brain extracted, then registered to the respective T_2-w images from the Melbourne Children's Regional Infant Brain White Matter (M-CRIB-WM) atlas[19] and the T_1-w images from the matching Johns Hopkins University (JHU) adult white matter template[20] using FLIRT and nonlinear registration with advanced normalization tools.[21] The combined linear and nonlinear transformation matrices were then applied to the whole brain T_1-w/T_2-w maps to bring them into the M-CRIB-WM or JHU template space. The T_1-w/T_2-w map from each participant was then normalized by the mean of T_1-w/T_2-w values in the CSF for each different sequence profile acquired within the term equivalent time point, as well as the mean T_1-w/T_2-w values in the CSF for all participants at the 7- and 13-year time points, to account for intensity differences across sequences and scanners over time. The normalized whole brain T_1-w/T_2-w maps in template space were parcellated into white matter regions of interest using the M-CRIB-WM[19] or JHU adult white matter labels atlas[20] as appropriate. Average T_1-w/T_2-w values for 48 regions for each participant were calculated at the 3 time points. T_1-w/T_2-w values across all regions were averaged to create an additional mean white matter T_1-w/T_2-w value.

Statistical Analyses

Analyses were conducted using Stata 15.0. For aim 1, linear mixed effects modeling was used. Models were applied to all the available T_1-w/T_2-w data for VP and FT children from term equivalent to 13 years of age, separately for each white matter region of interest. Group (VP or FT) and sex (male or female) were included as fixed effects, with a random intercept to allow for correlations between the repeated observations within participants at the different assessment time points. Age was included as a 3-level variable (term equivalent, 7, or 13 years of age). Although age is continuous, it was decided to treat age as discrete due to the narrow range of observation times compared with the intervals between the time points. Interactions were included to investigate whether longitudinal changes in T_1-w/T_2-w values differed between VP and FT children (group by time) and between sexes (sex by time), or if there were sex differences in T_1-w/T_2-w values based on birth group (group by sex). "Linear combinations" and "margins" commands were used to report results for birth group or sex differences in T_1-w/T_2-w values at each time point and in between time points.[22] p Values were corrected for multiple comparisons across regions using the false discovery rate (FDR) based on Benjamini and Yekutieli (first method), as previously described.[23]

For aim 2, linear mixed effects modeling was used in a similar fashion. The perinatal factors (moderate to severe brain abnormality, small for gestational age, postnatal infection, and bronchopulmonary dysplasia) were included as fixed effects, with a random intercept to allow for correlations between the repeated observations within participants at the different assessment time points. Again, age was included as a 3-level variable (term equivalent, 7, or 13 years of age). Interactions were included to investigate whether longitudinal changes in T_1-w/T_2-w values differed between the categories of the perinatal factors. Sex was included in the model as a covariate. p Values were FDR-corrected across regions.

For aim 3, linear regression models were applied to all available T_1-w/T_2-w data for VP and FT children, separately for each region of interest at each time point, as well as the change from term equivalent to 7 years of age, and the change from 7 to 13 years of age. Change over time for each region was calculated as follows: (T_1-w/T_2-w value at time 2 − T_1-w/T_2-w value at time 1)/(age at MRI in years at time 2 − age at MRI in years at time 1). Sex, age at neurodevelopmental assessment, and social risk at 13 years were included as covariates. Interactions were included to examine whether relationships between cross-sectional T_1-w/T_2-w values or changes in T_1-w/T_2-w values over time and neurodevelopmental outcomes differed between groups (VP or FT). p Values were FDR-corrected across regions.

Throughout this article, FDR-adjusted p values are interpreted on a continuous scale representing the strength of evidence against the null hypothesis of no association, with smaller FDR-adjusted p values representing stronger evidence.

Data Availability

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request. The MRI data are not publicly available due to ethical restrictions.

Results

Participants

A total of 224 VP participants were recruited at birth and 76 FT participants were recruited (44 at birth and 32 at age 2 years). At approximately term equivalent age, 224 VP and 44 FT eligible infants were scanned without sedation, of whom 207 VP and 42 FT infants were scanned within the desired window of 38–42 weeks' gestation. At 7 years' corrected age, 198 VP and 70 FT children were followed up, of whom 159 VP and 36 FT children were scanned. At 13 years' corrected age, 179 VP and 61 FT children were followed up, of whom 140 VP and 48 FT children were scanned. The main reasons for loss to follow-up included families declining or withdrawing from the study, living in other countries, or not being contactable.

A total of 139 VP and 19 FT infants had good-quality T_1-w and T_2-w scans to use for T_1-w/T_2-w maps at term-equivalent age, 141 VP and 34 FT children had useable T_1-w/T_2-w data at 7 years, and 76 VP and 29 FT children had useable T_1-w/T_2-w data at 13

years; 197 VP and 55 FT children had useable T_1-w/T_2-w data for at least one time point, and all these children were included in the analyses. Exclusion of scans was due to motion or other artifact in the MRI.

Characteristics of participants with useable data are summarized in Table 1. Rates of perinatal characteristics listed in Table 1 were similar between participants included in the study and those initially recruited but not included in the study (data not shown).

T_1-w/T_2-w Trajectories, Group and Sex Differences

In all children, there was evidence that T_1-w/T_2-w values in most white matter regions (except the left superior cerebellar peduncle and the right uncinate fasciculus) increased between term equivalent and 7 years of age (eTable 1A, links.lww.com/WNL/B725). There was evidence that T_1-w/T_2-w values in all white matter regions increased between 7 and 13 years of age (eTable 1B). There was little evidence that changes in T_1-w/T_2-w values over time differed between VP and FT groups (eTable 1, A and B) or between sexes (eTable 2, A and B).

There was little evidence that T_1-w/T_2-w values differed between VP and FT groups at term-equivalent age (eTable 3A, links.lww.com/WNL/B725). At 7 years of age, there was evidence that T_1-w/T_2-w values in the right and left cingulum (cingular part) were lower in the VP compared with the FT group (eTable 3B). At 13 years of age, there was evidence that T_1-w/T_2-w values in the right and left cingulum (cingular part), right cingulum (hippocampal part), and left tapetum were lower in the VP compared with the FT group (eTable 3C). Post hoc analyses indicated these group differences remained present after additionally adjusting for multiple births and social risk. T_1-w/T_2-w values from key regions are displayed in Figure 1.

There was little evidence that T_1-w/T_2-w values differed between boys and girls at term-equivalent age (eTable 4A, links.lww.com/WNL/B725). At 7 years, there was evidence that T_1-w/T_2-w values were higher in girls than boys, mainly for the whole white matter, splenium of the corpus callosum, left anterior and superior corona radiatae, left superior fronto-occipital fasciculus, bilateral posterior thalamic radiations, and the right tapetum (Figure 2; eTable 4B). At 13 years of age, there was little evidence that T_1-w/T_2-w values differed between boys and girls (eTable 4C). There was little evidence of birth group by sex interactions for T_1-w/T_2-w values in any region ($p > 0.74$; data not shown).

Neonatal Brain Abnormality

There was little evidence that moderate to severe brain abnormality was associated with T_1-w/T_2-w values at term-equivalent age in VP children, except for the right fornix (crus)/stria terminalis (Figure 3A; eTable 5A, links.lww.com/WNL/B725). However, there was evidence that moderate to severe brain abnormality was associated with lower T_1-w/T_2-w values in the corpus callosum, cingulum (cingular parts), and left tapetum at age 7 years (Figure 3B; eTable 5A), and in the corpus callosum, fornix (column and body), cingulum (cingular parts), and tapeta at age 13 years (Figure 3C; eTable 5A). There was little evidence that moderate to severe brain abnormality was associated with changes in T_1-w/T_2-w values over time (eTable 5B).

Small for Gestational Age

There was little evidence that being small for gestational age was associated with T_1-w/T_2-w values at term equivalent or 13 years of age in VP children (eTable 6A, links.lww.com/WNL/B725). However, there was evidence that being small for gestational age was associated with lower T_1-w/T_2-w values at age 7 years in many regions (Figure 4A; eTable 6A). There was evidence that being born small for gestational age was associated with less increase in T_1-w/T_2-w between term equivalent and 7 years compared with those born appropriate for gestational age, largely in the same regions that differed at 7 years (Figure 4B; eTable 6B), but little evidence for such a relationship with changes in T_1-w/T_2-w values from 7 to 13 years of age (eTable 6B).

Postnatal Infection

There was little evidence that postnatal infection was associated with T_1-w/T_2-w values at term equivalent or 7 years of age in VP children (eTable 7A, links.lww.com/WNL/B725). However, there was evidence that infection was associated with lower T_1-w/T_2-w values, with the greatest evidence for the pontine crossing tract, corticospinal tracts, and medial lemnisci at 13 years of age (Figure 4C; eTable 7A). There was little evidence that infection was associated with changes in T_1-w/T_2-w values over time (eTable 7B).

Bronchopulmonary Dysplasia

There was little evidence that bronchopulmonary dysplasia was associated with T_1-w/T_2-w values at any age in VP children (eTable 8A, links.lww.com/WNL/B725) or with changes in T_1-w/T_2-w values over time (eTable 8B).

Intelligence

There was little evidence that T_1-w/T_2-w values at any age (eTable 9, A–C, links.lww.com/WNL/B725), or the change over time between term equivalent and 7 years of age (eTable 9D), were associated with IQ at 13 years. However, there was weak evidence that faster increases in T_1-w/T_2-w values between 7 and 13 years of age were associated with higher IQ, across all children, mainly for the left uncinate fasciculus (Figure 5A; eTable 9E).

Motor

There was little evidence of associations between T_1-w/T_2-w values at term equivalent (eTable 10A, links.lww.com/WNL/B725) or 7 years of age (eTable 10B) and motor outcomes. There was evidence that higher T_1-w/T_2-w values in most brain regions at 13 years of age were associated with better motor functioning across all children (Figure 5B; eTable 10C). There was little evidence of associations

Table 1 Characteristics of the Participants With Useable T_1-Weighted/T_2-Weighted Data for at Least 1 Time Point

	Very preterm (n = 197)	Full term (n = 55)	*p* Value
Gestational age at birth, wk	27.5 (1.9), 22–32	39.1 (1.3), 37–42	<0.001
Birth weight, g	961 (223), 414–1,425	3,330 (518), 2,220–4,290	<0.001
Birth weight SD score[a]	−0.58 (0.94)	0.09 (0.92)[b]	<0.001
Small for gestational age[a]	18 (9.1)	1 (2.5)[b]	0.16
Multiple birth	87 (44.2)	3 (5.5)	<0.001
Male sex	100 (50.8)	29 (52.7)	0.80
Administered antenatal corticosteroids	175 (89.3)[c]	0 (0)[b]	<0.001
Administered postnatal corticosteroids	18 (9.2)[c]	0 (0)[b]	0.05
Bronchopulmonary dysplasia[d]	67 (34.0)	0 (0)[b]	<0.001
Postnatal infection[e]	70 (35.5)	0 (0)[b]	<0.001
Moderate to severe neonatal brain abnormality[f]	51 (26.0)[c]	0 (0)[b]	<0.001
Cerebral white matter	35 (17.9)[c]	0 (0)[b]	0.004
Cortical gray matter	34 (17.4)[c]	0 (0)[b]	0.004
Deep gray matter	44 (22.5)[c]	3 (7.5)[b]	0.03
Cerebellar	49 (25.0)[c]	0 (0)[b]	<0.001
Cystic periventricular leukomalacia[g]	7 (3.6)	0 (0)[b]	0.22
Intraventricular hemorrhage grade 3 or 4[g]	6 (3.1)	0 (0)[b]	0.26
Higher social risk at age 13 years	89 (56.3)[h]	13 (28.3)[i]	0.001
Postmenstrual age at term-equivalent MRI, wk	40.5 (1.1), 38.1–42.9[j]	40.9 (1.0), 38.7–42.3[k]	0.10
Age at term-equivalent MRI, y	0.01 (0.03), −0.18-0.05[j]	0.02 (0.02), −0.02–0.04[k]	0.14
Age at 7-year MRI, y	7.5 (0.3), 6.6–8.1[l]	7.6 (0.2), 7.2–8.0[m]	0.11
Age at 13-year MRI, y	13.3 (0.3), 11.8–13.9[n]	13.2 (0.5), 12.3–14.2[o]	0.35

All ages for the very preterm group have been corrected for prematurity; *p* values are derived from *t* tests for continuous variables and χ^2 tests for dichotomous variables. Values are mean (SD), minimum–maximum; mean (SD); or n (%).
[a] Birth weight SD score was calculated relative to the British Growth Reference dataset. Small for gestational age was defined as birth weight *z* score < −2 SD.[2]
[b] n = 40.
[c] n = 196.
[d] Bronchopulmonary dysplasia was defined as requirement for supplemental oxygen at 36 weeks.
[e] Postnatal infection was defined as proven sepsis or necrotizing enterocolitis.
[f] Scored on term-equivalent age MRI using the Kidokoro et al.[43] qualitative reporting system.
[g] Cystic periventricular leukomalacia and intraventricular hemorrhage were recorded from cranial ultrasound; intraventricular hemorrhage was graded according to Papile et al.[44]
[h] n = 158.
[i] n = 46.
[j] n = 139.
[k] n = 19.
[l] n = 141.
[m] n = 34.
[n] n = 76.
[o] n = 29.

between changes in T_1-w/T_2-w values over time and motor outcome (eTable 10, D and E).

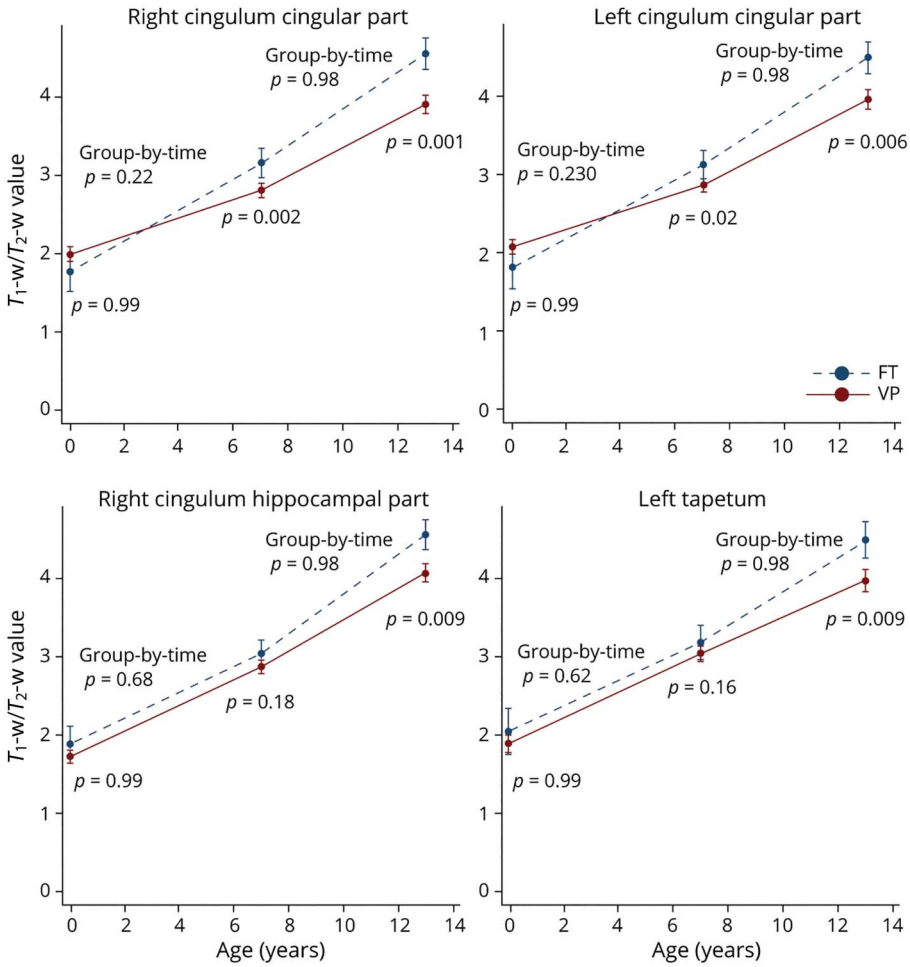
Working Memory

There was little evidence of associations between T_1-w/T_2-w values at term equivalent (eTable 11A, links.lww.com/WNL/B725) or 7 years of age (eTable 11B) and working memory outcomes across all children. There was evidence that higher T_1-w/T_2-w values in most brain regions at 13 years of age were associated with concurrent higher working memory scores across VP and FT children (Figure 5C; eTable 11C). There was little evidence of associations between changes in T_1-w/T_2-w values over time and working memory performance (eTable 11, D and E).

Attention

There was little evidence that T_1-w/T_2-w values at any age were associated with attention outcomes across all children

Figure 1 T_1-w/T_2-w Trajectory in Key Regions for Very Preterm Compared With Full-Term Birth



False discovery rate–corrected *p* values for cross-sectional and trajectory group differences are provided.

(eTable 12, A–C, links.lww.com/WNL/B725). There was evidence of group interactions for the association between T_1-w/T_2-w values between term equivalent and 7 years of age and attention in all regions except pontine crossing tract and left superior cerebellar peduncle, where higher T_1-w/T_2-w values in FT children only were associated with poorer attention scores (Figure 6A; eTable 12D). There was little evidence that T_1-w/T_2-w values between 7 and 13 years of age were associated with attention outcomes (eTable 12E).

Executive Function

There was little evidence that T_1-w/T_2-w values at any age were associated with executive functioning outcomes across all children (eTable 13, A–C, links.lww.com/WNL/B725). There was evidence of group interactions for the association between T_1-w/T_2-w values between term equivalent and 7 years of age and executive function, where higher T_1-w/T_2-w values in almost all regions (with trends for genu and splenium of corpus callosum and fornix column and body) in FT children only were associated with poorer executive functioning scores (Figure 6B; eTable 13D). There was little evidence that T_1-w/T_2-w values between 7 and 13 years of age were associated with executive functioning (eTable 13E).

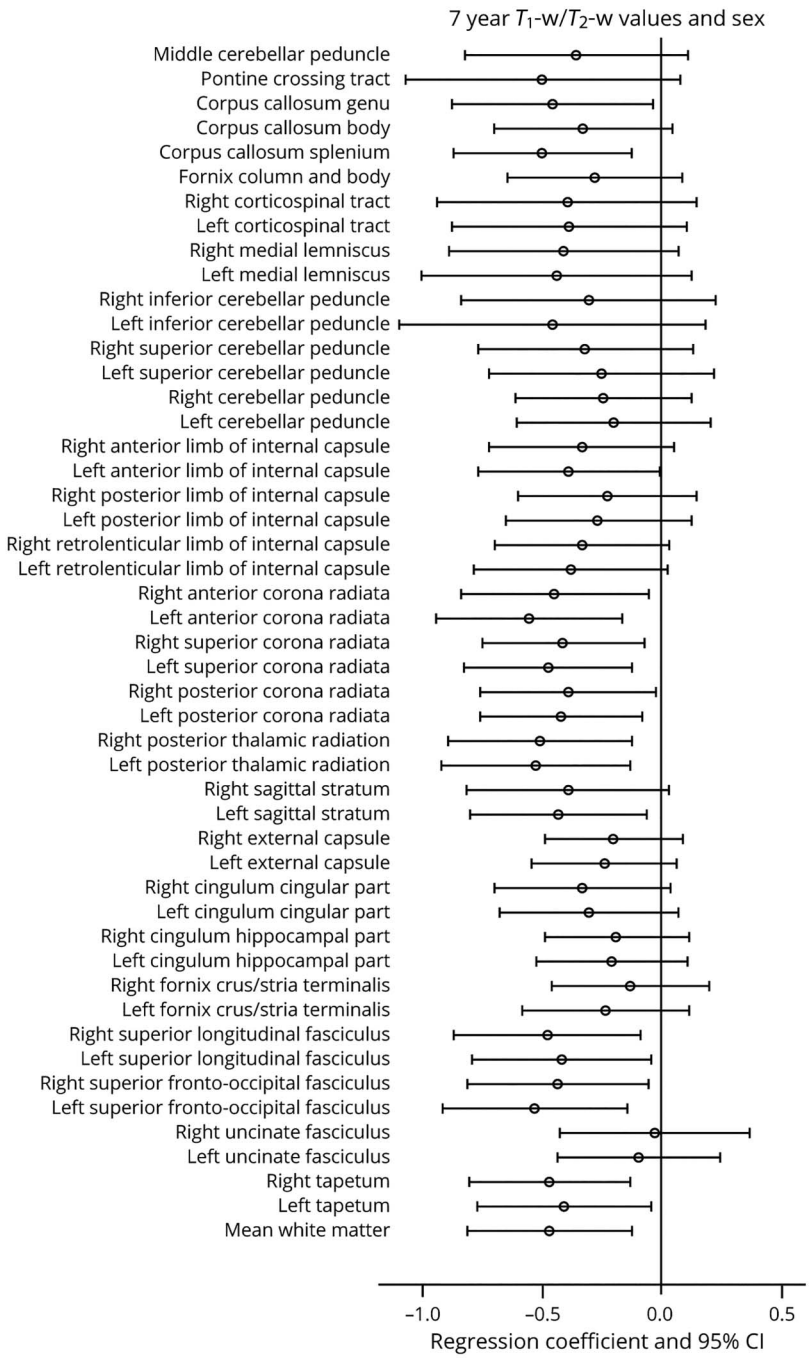
Mathematics

There was little evidence of associations between T_1-w/T_2-w values at term equivalent and mathematics performance across all children (eTable 14A, links.lww.com/WNL/B725). There was evidence for group interactions for the associations between T_1-w/T_2-w values at 7 years of age and mathematics, where higher T_1-w/T_2-w values in many regions in FT children only were associated with poorer mathematics performance (Figure 6C; eTable 14B). There was little evidence that T_1-w/T_2-w values at 13 years (eTable 14C), or the change in T_1-w/T_2-w values over time, were associated with mathematics performance across all children (eTables 4D and 14E).

Reading, Spelling, Language, Memory and Learning, Behavior

There was little evidence for associations between T_1-w/T_2-w values and reading (eTable 15, A–E, links.lww.com/WNL/B725), spelling (eTable 16, A–E), language (eTable 17, A–E),

Figure 2 Associations Between T_1-w/T_2-w Values and Sex at 7 Years of Age



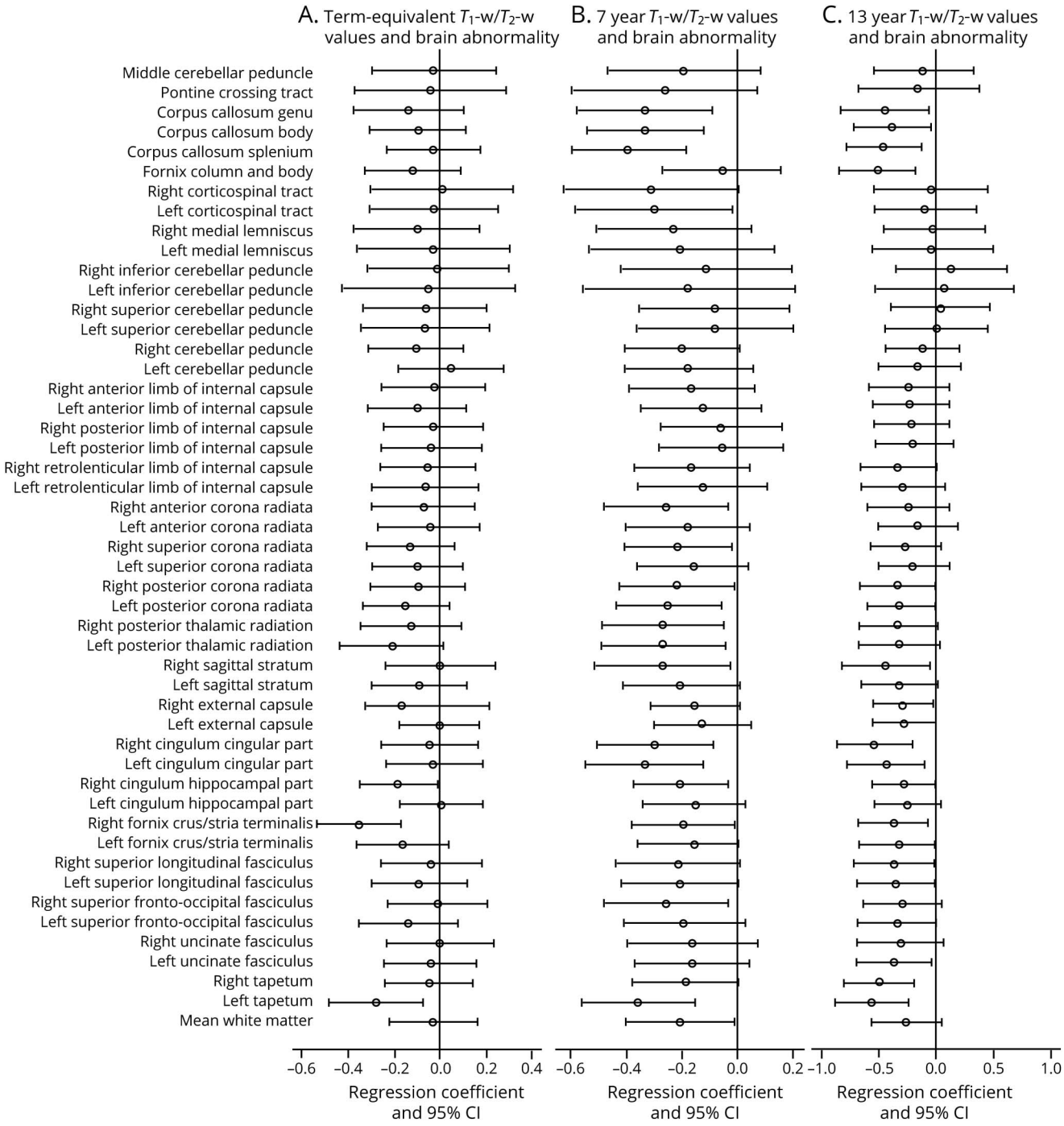
Regression coefficients derived from linear mixed effects models incorporating time, group, and sex with interaction terms. Positive coefficients indicate higher T_1-w/T_2-w values in boys compared with girls; negative coefficients indicate lower T_1-w/T_2-w values in boys compared with girls. CI = confidence interval.

memory and learning (eTable 18, A–E), or behavioral scores (eTable 19, A–E).

Discussion

We found that T_1-w/T_2-w values in many white matter regions increased from term equivalent to 13 years of age in all children, which may reflect ongoing development, such as white matter microstructural organisation and myelination throughout childhood.[3,4] We did not find evidence that changes in T_1-w/T_2-w values at term-equivalent age or over time differed between VP and FT children, despite there being some group differences evident at both 7 and 13 years. This lack of evidence for a relationship may reflect normal development in the population rather than a VP group difference, lack of statistical power, limitations with the T_1-w/T_2-w technique, or scan heterogeneities across time points. We previously investigated brain development from infancy to adolescence in the same cohort, based on volumetric

Figure 3 Associations Between T_1-w/T_2-w Values and Brain Abnormality

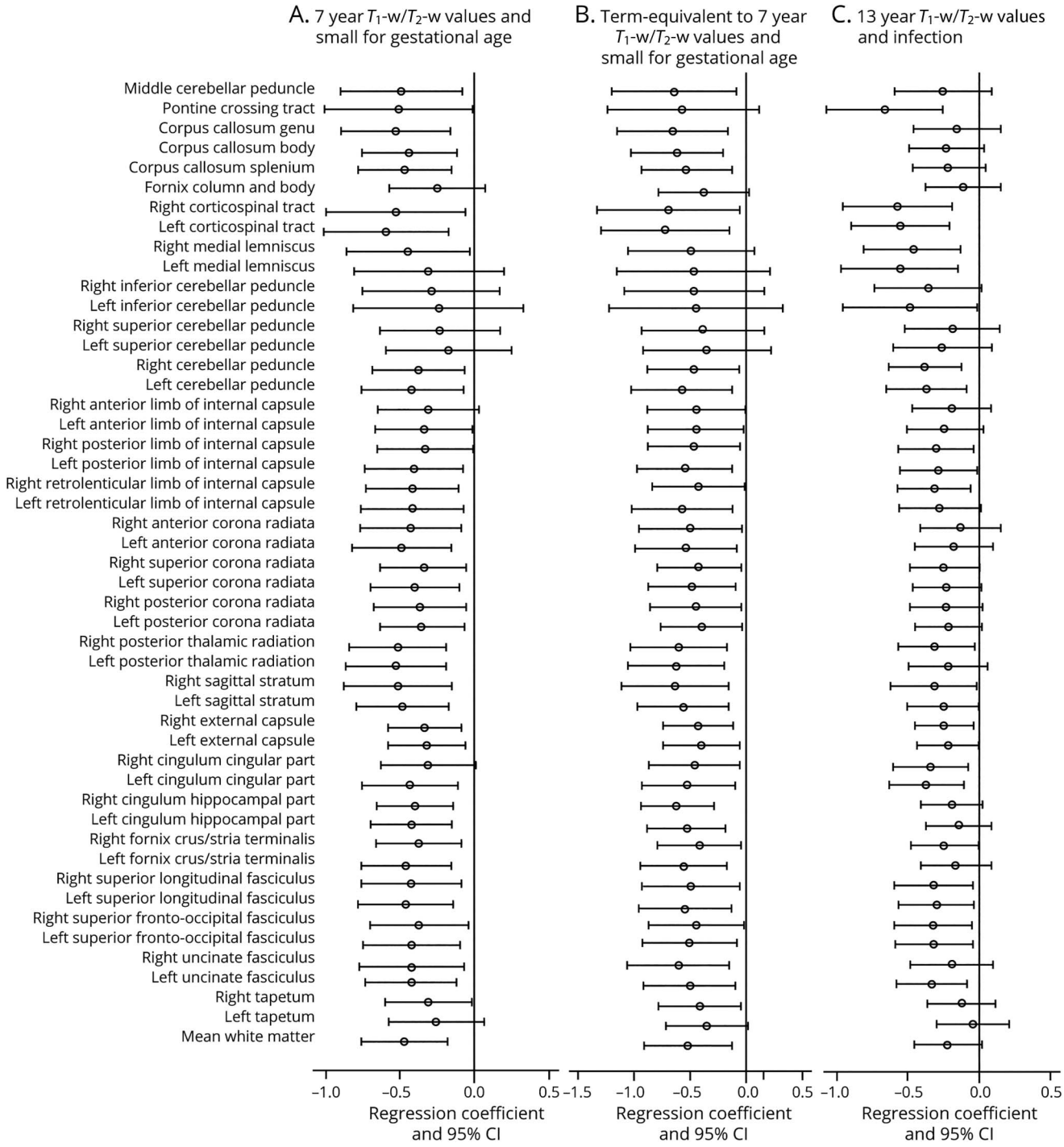


(A–C) Regression coefficients derived from linear mixed effects models incorporating time, perinatal exposure, and sex with a time interaction for the very preterm group only. For individual time points, positive coefficients indicate higher T_1-w/T_2-w values in those with perinatal exposure compared with those without; negative coefficients indicate lower T_1-w/T_2-w values in those with perinatal exposure compared with those without. For trajectories, positive coefficients indicate T_1-w/T_2-w values increased more over time in those who had the perinatal exposure compared with those who did not; negative coefficients indicate T_1-w/T_2-w values increased less over time in those who had the perinatal exposure compared with those who did not.CI = confidence interval.

measures including global white matter and corpus callosum volume.[24] The current study makes an important advance in knowledge by investigating the development of 48 white matter regions based on the T_1-w/T_2-w measure that is thought to provide greater sensitivity to tissue characteristics such as microstructure or myelin content.

At 7 years of age, VP children had lower T_1-w/T_2-w values in the cingulum (cingular part) than FT children. At 13 years of age, VP children had lower T_1-w/T_2-w values than FT children in the cingulum (cingular and hippocampal part) and tapetum. This may suggest an adverse effect of VP birth on white matter properties such as microstructural organization

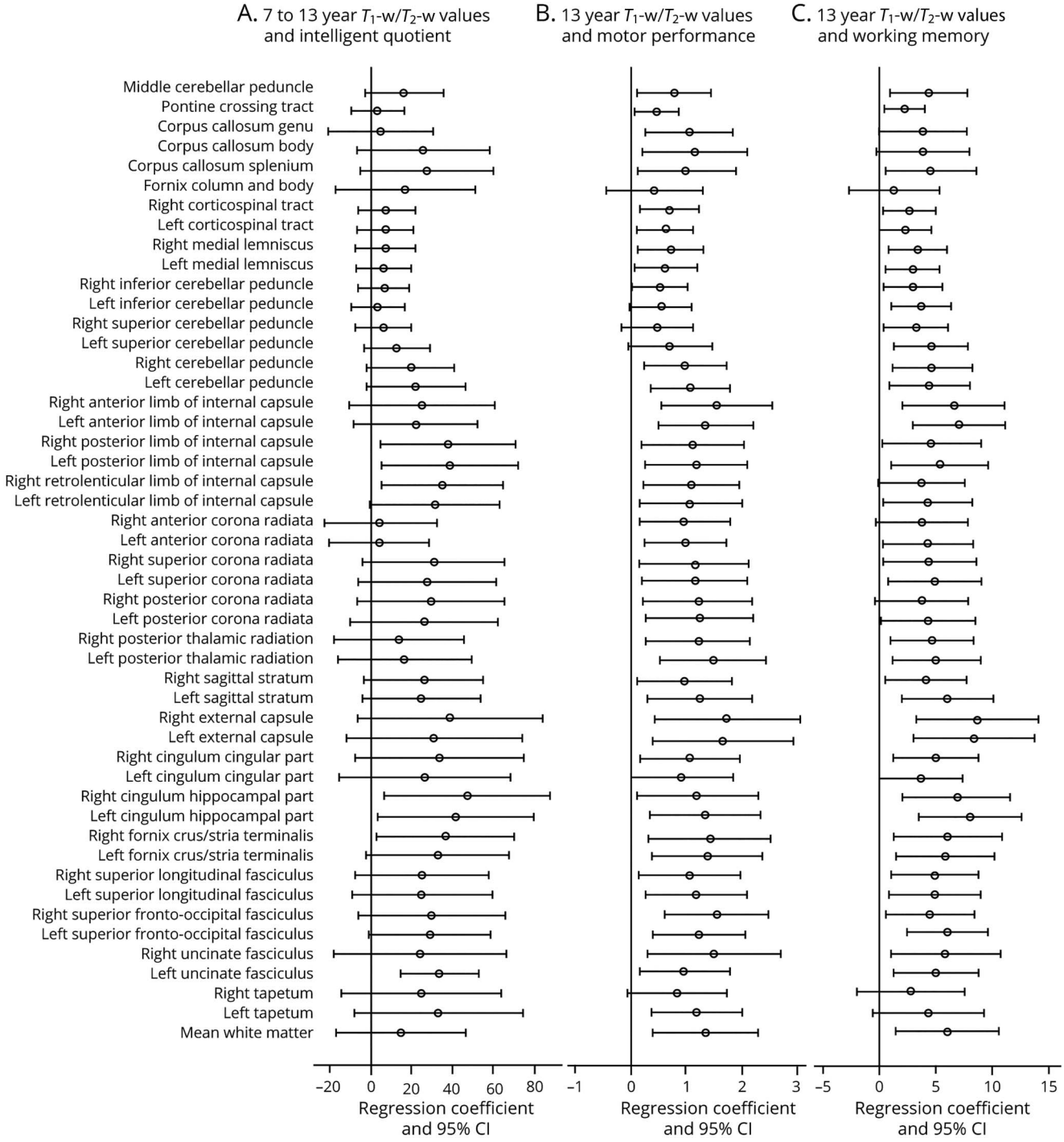
Figure 4 Associations Between T_1-w/T_2-w Values and Small for Gestational Age and Infection



(A–C) Regression coefficients derived from linear mixed effects models incorporating time, perinatal exposure, and sex with a time interaction for the very preterm group only. For individual time points, positive coefficients indicate higher T_1-w/T_2-w values in those with the perinatal exposure compared with those without; negative coefficients indicate lower T_1-w/T_2-w values in those with the perinatal exposure compared with those without. For trajectories, positive coefficients indicate T_1-w/T_2-w values increased more over time in those who had the perinatal exposure compared with those who did not; negative coefficients indicate T_1-w/T_2-w values increased less over time in those who had the perinatal exposure compared with those who did not. CI = confidence interval.

and myelin content, which may become more widespread with age. The only other study to compare T_1-w/T_2-w values between VP and FT children found lower values across much of the white matter in VP compared with FT 4-year-old children, including in the cingulum (cingular and hippocampal parts), consistent with the current study.[25] The vulnerability of the cingulum could be explained by its ongoing maturation, which continues into adulthood.[26] Another study found changes that may be consistent with lower myelin content in 8-year-old children born preterm in the

Figure 5 Associations Between T_1-w/T_2-w Values and 13-Year Neurodevelopmental Outcomes (IQ, Motor, and Working Memory Outcomes)

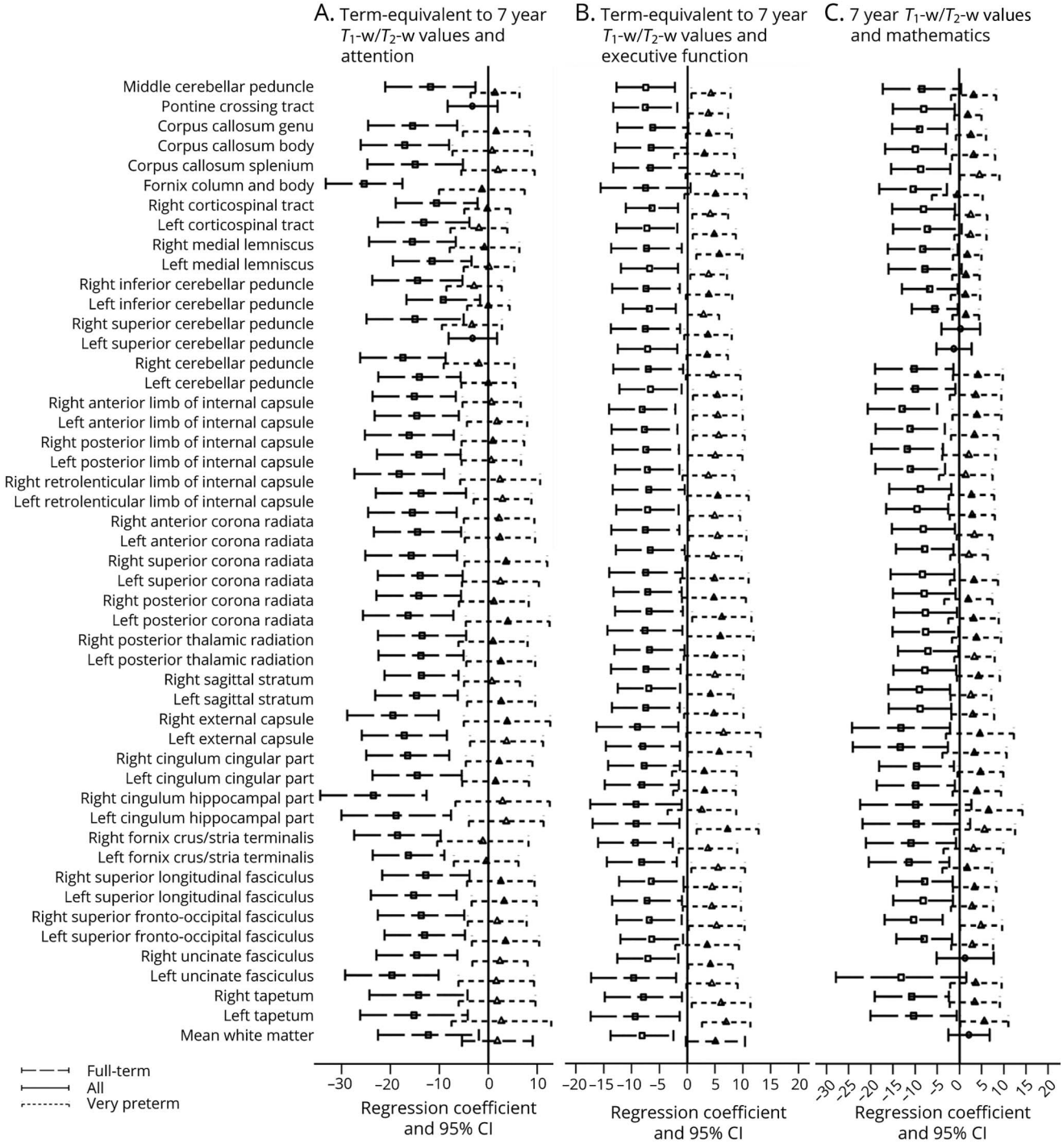


(A–C) Regression coefficients derived from linear regression models adjusted for sex, age at assessment, and social risk at 13 years. For individual time points, positive coefficients indicate higher T_1-w/T_2-w values were associated with better scores; negative coefficients indicate lower T_1-w/T_2-w values were associated with better scores. For trajectories, positive coefficients indicate T_1-w/T_2-w values increased more over time in those with better scores; negative coefficients indicate T_1-w/T_2-w values increased less over time over time in those with better scores. CI = confidence interval.

temporal and motor segments of the corpus callosum compared with FT children based on quantitative T1 relaxometry,[27] similar to our current finding in the tapetum, part of the callosal bundle providing interhemispheric temporal connections.

At 7 years of age only, T_1-w/T_2-w values were higher in girls than boys for several white matter regions. Some previous diffusion tensor imaging studies found no sex differences in white matter microstructural development during childhood.[3,28] However, others, in line with the current

Figure 6 Associations Between T_1-w/T_2-w Values and 13-Year Neurodevelopmental Outcomes (Attention, Executive Function, and Mathematics Outcomes)



(A–C) Regression coefficients derived from linear regression models adjusted for sex, age at assessment, and social risk at 13 years. For individual time points, positive coefficients indicate higher T_1-w/T_2-w values were associated with better scores; negative coefficients indicate lower T_1-w/T_2-w values were associated with better scores. For trajectories, positive coefficients indicate T_1-w/T_2-w values increased more over time in those with better scores; negative coefficients indicate T_1-w/T_2-w values increased less over time over time in those with better scores. CI= confidence interval.

study, have found higher fractional anisotropy in the splenium of the corpus callosum of female children.[29] Sex differences in the brain during development may be hormonally influenced.[30]

Moderate to severe neonatal brain abnormality was a key perinatal risk factor associated with lower T_1-w/T_2-w values in VP children. It is well documented that neonatal brain abnormalities are associated with poorer brain growth and

development in VP populations, including similar regions to the current study: corpus callosum, fornix, cingulum, and tapetum.[7,31,32] Our findings are also in line with previous studies showing associations between intrauterine growth restriction and impaired brain growth and development.[33,34] Postnatal infection was related to lower T_1-w/T_2-w values in the pontine crossing tract, corticospinal tracts, and medial lemnisci in VP 13-year-old children. These white matter regions are involved in sensorimotor functions, suggesting a possible neurobiological underpinning for the link between postnatal infection and neurosensory and motor impairments.[35] Others have also found that infection leads to white matter injury in VP populations.[6] Our findings based on the T_1-w/T_2-w technique provide increased support for an adverse effect of these perinatal risk factors on development of white matter properties such as myelin or microstructure in VP children.

A faster rate of increase in T_1-w/T_2-w values in the left uncinate fasciculus between age 7 and 13 years was related to higher IQ scores. However, given that our effect size for the left uncinate fasciculus was similar to effect sizes for the associations between T_1-w/T_2-w values in other regions and IQ, we acknowledge that this specific association may have occurred by chance. In contrast, we found strong evidence that T_1-w/T_2-w values throughout the white matter at age 13 years were related to motor scores in all children. This is in line with our previously reported associations between white matter microstructure in widespread regions and motor outcomes.[7,36] Also at 13 years of age, higher T_1-w/T_2-w values in most white matter regions were associated with concurrent higher working memory scores across VP and FT children. Associations included tracts connecting frontoparietal regions, as well as other white matter tracts previously shown to be involved in working memory: the splenium of the corpus callosum and uncinate fasciculus.[37] Although working memory is known to be vulnerable in VP children,[12] associations between T_1-w/T_2-w values and working memory were similar to those of FT children.

Somewhat unexpectedly, larger increases in T_1-w/T_2-w values from term equivalent to 7 years of age in almost all white matter regions in FT children only were associated with poorer attention and executive functioning scores. Also unintuitive was the finding that higher T_1-w/T_2-w values at 7 years of age in many regions, in FT children only, were associated with poorer mathematics performance. It could be that the period up to 7 years represents a transitional developmental phase whereby lower T_1-w/T_2-w values appear to be developmentally advantageous to later functioning. Indeed, from around 2 years of age to puberty, rapid synaptic pruning is occurring.[38] Alternatively, T_1-w/T_2-w values, at least in early childhood, may not be sensitive measures to predict later neurodevelopmental functioning. Although the interpretation of these findings is unclear, it appears that the relationships were only present for the FT group, which may indicate a developmental disadvantage for the VP group.

We acknowledge that the T_1-w/T_2-w ratio technique is sensitive but not specific to tissue characteristics including white matter microstructure and myelin content. T_1-w/T_2-w values may be influenced by the mobility of water between the intracellular and extracellular spaces and the accumulation of water in the extracellular space.[39,40] Also, T_1-w and T_2-w image intensities are sensitive to different pathologic states, such as infection, inflammation, edema, and brain hemorrhage, which may affect the interpretation of the T_1-w/T_2-w values. Comparison with other MRI metrics may aid in interpreting the T_1-w/T_2-w findings. For example, we observed some overlap between the regions with lower T_1-w/T_2-w values in the VP compared with FT group (cingulum and tapetum) and the regions that had lower axonal fiber density in the VP group in a recent fixel-based analysis of diffusion MRI data based on the same cohort.[41] This suggests that these 2 techniques provide complimentary but unique information about the underlying white matter properties. To potentially gain greater insight on the biological properties underlying T_1-w/T_2-w measurements, future studies could examine the correlation between T_1-w/T_2-w measures and other MRI measures sampled from identical white matter regions.[42] In addition, validation of the T_1-w/T_2-w measures with histologic data is needed to provide more direct information on the mechanisms underlying our findings. The current study is one of very few studies with longitudinal MRI data for VP and FT children, but the longitudinal study design presented challenges, such as loss to follow-up over time and change in scanner and sequence acquisition measures between the time points. However, technology is continually evolving, so changes in MRI scanners and techniques are likely to be a limitation of any study that extends over such a long period as our study. The mixed models naturally handle the missing data by enabling individuals with a measurement from at least one time point to be included in the analysis, which helps to mitigate potential bias due to drop out. Although we attempted to account for intensity differences between scanners and sequences by scaling the T_1-w/T_2-w values by CSF intensities, this normalization method assumes that CSF will have stable behavior under T_1-w and T_2-w sequences and that the linear relationships between image intensity and T_1-w and T_2-w relaxation times are constant throughout the image, which are approximately accurate but may not always be the case. Given these limitations, we acknowledge that our results must be interpreted with caution and validated by future studies, preferably using quantitative myelin imaging techniques and, if possible, with identical scanners and sequences over time.

Our findings suggest that the T_1-w/T_2-w measure increases in the white matter from infancy to adolescence. Those born VP may have reduced T_1-w/T_2-w values in the cingulum and tapetum in childhood and adolescence compared with those born FT. There were some sex differences at age 7, with girls displaying higher T_1-w/T_2-w values. Reduced T_1-w/T_2-w values over childhood were associated with multiple known perinatal risk factors in VP children, including brain abnormality, being

born small for gestational age, or infection. Higher T_1-w/T_2-w values at 13 years were associated with better motor and working memory functioning in all children. Earlier T_1-w/T_2-w measures were negatively related to 13-year attention, executive functioning, and mathematics measures within the FT group only. These findings increase knowledge around the typical and atypical development of white matter regions based on the T_1-w/T_2-w ratio technique from infancy to early adolescence and associated neurodevelopmental outcomes.

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Disclosure

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Bonnie Alexander	The Royal Children's Hospital, Parkville, Melbourne, Australia	Acquisition, analysis, or interpretation of the data
Courtney Gilchrist	School of Health and Biomedical Sciences, RMIT University, Bundoora, Melbourne, Australia	Drafting or substantively revising the work
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Katherine J. Lee	Murdoch Children's Research Institute, Parkville, Melbourne, Australia	Acquisition, analysis, or interpretation of the data, drafting or substantively revising the work
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Megan Spencer-Smith	Turner Institute for Brain and Mental Health, Monash University, Clayton, Melbourne, Australia	Drafting or substantively revising the work
Jeffrey J. Neil	Washington University School of Medicine, St. Louis, MO	Drafting or substantively revising the work, analysis or interpretation of the data
Marc L. Seal	Murdoch Children's Research Institute, Parkville, Melbourne, Australia	Drafting or substantively revising the work
Terrie E. Inder	Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Conception or design of the work, drafting or substantively revising the work
Lex W. Doyle	The Royal Women's Hospital, Parkville, Melbourne, Australia	Conception or design of the work, drafting or substantively revising the work
Peter J. Anderson	Turner Institute for Brain and Mental Health, Monash University, Clayton, Melbourne, Australia	Conception or design of the work, acquisition, analysis, or interpretation of the data, drafting or substantively revising the work

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