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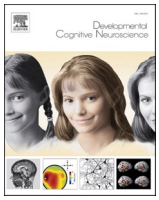

Individual differences in T1w/T2w ratio development during childhood

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ABSTRACT

Myelination is a key developmental process that promotes rapid and efficient information transfer. Myelin also stabilizes existing brain networks and thus may constrain neuroplasticity, defined here as the brain's potential to change in response to experiences rather than the canonical definition as the process of change. Characterizing individual differences in neuroplasticity may shed light on mechanisms by which early experiences shape learning, brain and body development, and response to interventions. The T1-weighted/T2-weighted (T1w/T2w) MRI signal ratio is a proxy measure of cortical microstructure and thus neuroplasticity. Here, in pre-registered analyses, we investigated individual differences in T1w/T2w ratios in children (ages 4–10, n = 157). T1w/T2w ratios were positively associated with age within early-developing sensorimotor and attention regions. We also tested whether socioeconomic status, cognition (crystallized knowledge or fluid reasoning), and biological age (as measured with molar eruption) were related to T1w/T2w signal but found no significant effects. Associations among T1w/T2w ratios, early experiences, and cognition may emerge later in adolescence and may not be strong enough to detect in moderate sample sizes.

1. Introduction

The cerebral cortex becomes increasingly myelinated throughout development (Norbom et al., 2021) in order to promote rapid and efficient information transfer across neural systems (Lebel and Deoni, 2018). Animal model studies show that myelin can also act like "glue" to stabilize existing brain networks and prevent major remodeling (Hensch, 2005; McGee et al., 2005; Werker and Hensch, 2015; Williamson and Lyons, 2018). Myelin can therefore constrain neuroplasticity. Neuroplasticity is canonically defined as the *process* of brain change in response to experiences and environments but can also be defined as the brain's *potential* to change. Cortical myelination is uniquely protracted in humans (Sherin and Bartzokis, 2011), which sets up an intriguing tension: extending windows of neuroplasticity to allow more time for the slow development of complex cognitive functions (Gopnik, 2020; Gopnik et al., 2020), but also for exposure to adverse experiences that increase vulnerability to psychiatric disorders (Fields, 2008; Miller et al., 2012). Investigating variability in myelination across cortex may therefore be critical for understanding individual variability in response to early experiences and neuropsychological and educational interventions.

Current neuroimaging methods can be harnessed to better understand individual differences in human neuroplasticity. Signal intensities from T1-weighted magnetic resonance imaging (MRI) scans can be

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divided by those from T2-weighted scans to create a T1w/T2w ratio image. The T1w/T2w ratio is characterized by an increased contrast between gray and white matter in the brain. Intensities extracted from these T1w/T2w ratio images can therefore serve as proxy measures of microstructural properties of the cortex, including myelin (Ganzetti et al., 2014, 2015; Glasser et al., 2014, 2021; Glasser and Van Essen, 2011; Shafee et al., 2015). Consistent with the notion that myelination restricts the brain's potential to change with experience, greater T1w/T2w signal in frontoparietal regions predicts less learning following one hour of practice on a working memory task (Boroshok et al., 2022). The T1w/T2w ratio also strongly covaries with other potential markers of brain plasticity, including neuronal density (Glasser et al., 2014; Glasser and Van Essen, 2011). However, the full extent of microstructural markers that the T1w/T2w ratio captures has recently been debated, as this signal is weakly correlated with subcortical myelin water fraction measurements and could also reflect other membrane content or axonal diameter and density (Arshad et al., 2017; Genc et al., 2023; Hagiwara et al., 2018; Ritchie et al., 2018; Uddin et al., 2018, 2019).

T1w/T2w ratios have recently been used in studies attempting to characterize patterns of typical variability in cortical myelination across the lifespan. A number of recent studies have demonstrated global, linear increases in T1w/T2w ratios from late childhood to early adulthood (Baum et al., 2022; Grydeland et al., 2013, 2019; Norbom et al., 2020, 2022; Shafee et al., 2015), with the strongest age-related increases found in sensorimotor areas. These results are highly consistent with a body of research in human and non-human animals demonstrating that the temporal sequence of cortical maturation occurs in a spatially ordered fashion, whereby transmodal association cortices develop over a more protracted period than sensorimotor cortices (commonly referred to as the sensorimotor-association [S-A] cortical axis; reviewed by Sydnor et al., 2021). This temporal gradient of cortical refinement, which includes protracted myelination in association cortices, may lead to an extended period of plasticity within these areas. Such extended plasticity could support the development of complex cognitive functions unique to humans while simultaneously leaving such cortical areas vulnerable to various developmental insults.

Some work has examined variation in T1w/T2w ratios in relation to stressful experiences. An early study in adults showed that veterans experiencing post-traumatic stress showed higher T1w/T2w ratios in the hippocampus (Chao et al., 2015). Most of the developmental work on this question has focused on socioeconomic status (SES), a complex, multidimensional construct often captured using parent education and family income (Long and Renbarger, 2023), because low SES is associated with elevated risk for a variety of psychosocial and physical stressors (Evans and Kim, 2013). SES is also associated with experiences other than stress, including cognitive enrichment or deprivation and environmental toxins (Farah, 2017; Lawson et al., 2013; Sheridan et al., 2017). Youth from lower SES families show higher T1w/T2w ratios broadly across the cortex compared to their peers from higher SES families (Norbom et al., 2022), though effects in this study were specific to parental education and occupation and not family income. This work is consistent with a broader literature suggesting that early life stress is associated with accelerated structural cortical development (Tooley et al., 2021), though there are some inconsistencies in results due to heterogeneity in sample demographics, measurements of SES, and imaging procedures across studies (reviewed in Rakesh and Whittle, 2021). In line with the accelerated development hypothesis, animal studies have shown that early life stress can cause myelination and alter other markers of cellular and synaptic plasticity, such as long-term potentiation and density of perineuronal nets (Bath et al., 2016; Brunson et al., 2005; Ivy et al., 2010; McGee et al., 2005; Naninck et al., 2015; Tooley et al., 2021; Yang et al., 2015). If children from low-SES backgrounds do experience accelerated brain development, windows of high neuroplasticity may close more quickly in these children which may reduce the sensitivity of their brains to future experiences, such as learning.

T1w/T2w ratios have also been linked to cognitive development, but the directionality of the observed associations has similarly varied across studies. Lower T1w/T2w ratios are associated with stronger general cognitive ability, inhibition, attention, reading, vocabulary, and working memory within anterior cortical regions in the multi-site Pediatric Imaging, Neurocognition, and Genetics (PING) study (Norbom et al., 2020). Another study of 8–19 year-olds found that intra-individual response time variability on a response inhibition task is more stable in individuals with higher T1w/T2w ratios in right-lateralized cortices, independent of general intellectual abilities (Grydeland et al., 2013). However, another study showed widespread positive associations between T1w/T2w ratios and intelligence, language, and visual-motor abilities across the cortex in four-year-old children born preterm and full term (Vandewouw et al., 2019). Therefore, relationships between proxy markers of cortical myelin and cognition are likely complex and may vary by developmental stage or environment.

Early biological maturation may also be a risk factor for accelerated brain development. Increases in pubertal hormones in late childhood and early adolescence have been linked to changes in cortical and subcortical gray and white matter volume and functional activity development (Laube et al., 2020; Laube and Fuhrmann, 2020; Peper et al., 2011). In adolescent girls, advanced self-reported pubertal stage is associated with thicker cortex in parietal, posterior, and occipital areas; however, associations with pubertal hormones are much weaker (Byrne et al., 2022). Puberty is notoriously difficult to measure, especially in young children during the earliest stages of adrenarche, so it may be important to investigate other biological markers of accelerated maturation early in development. For instance, the timing of permanent molar eruption occurs earlier in children from lower SES backgrounds and is a strong predictor of cognitive ability (McDermott et al., 2021, 2023). However, very little is currently understood about how T1w/T2w ratios vary with markers of somatic maturation.

Here, we investigate the maturation of the T1w/T2w signal across the cortex in children. Middle childhood is a time of rapid cognitive change and reorganization of cortical architecture (Tooley et al., 2022b) and may be a particularly critical period to study T1w/T2w signal variability. An improved understanding of individual differences in cortical myelination in childhood may illuminate key windows of neuroplasticity and help optimize the timing of educational and neuropsychological interventions. In a series of pre-registered analyses, we first aim to replicate previously reported positive associations between T1w/T2w signal and age (Baum et al., 2022; Grydeland et al., 2013, 2019; Norbom et al., 2020), with a focus on children between the ages of 4–10 years. We next examine associations between T1w/T2w signal and SES as well as cognitive development. Finally, we ask for the first time whether the T1w/T2w signal is associated with somatic maturation, as indexed by molar eruption. Broadly, this work seeks to clarify relationships between cortical microstructure development and childhood experiences and developmental outcomes.

2. Methods

This study was approved by the Institutional Review Board of the University of Pennsylvania. All parents provided informed, written consent and children over the age of eight provided informed, written assent. All analyses were pre-registered at https://osf.io/ztxdv and https://osf.io/4wyjr.

2.1. Participants

Children between the ages of 4 and 10 years (*Mean* = 6.31 years, *SD* = 1.42) and their parents were recruited from the greater Philadelphia area as part of two larger neuroimaging studies. Previous studies of this sample have measured functional activation during a naturalistic movie paradigm (Park et al., 2022), resting-state functional connectivity (Park et al., 2021), functional brain network segregation (Tooley et al.,

2022b), and molar eruption (McDermott et al., 2021, 2023). Participants were recruited through advertisements on public transportation, partnerships with local schools, outreach programs, community family events, and social media ads. Participants were screened prior to participation and were excluded from the studies if they had a diagnosed psychiatric, neurological, or learning disorder, were born more than six weeks premature, were adopted, or had any contraindications for MRI scanning. 192 children participated, but 13 did not finish MRI scanning and 22 were excluded for unusable T1-weighted or T2-weighted data. Sample sizes vary across analyses based on whether demographic, maturational, and cognitive measures were available (age: $n = 157$; family income: $n = 147$; parental education: $n = 154$; molar eruption: $n = 106$; two cognitive subtests: $n = 128$ and $n = 127$). Associations among socioeconomic status measures, molar eruption, and cognition, as well as the distributions of these variables are available in Supplemental Fig. 1.

2.2. Demographic questionnaires

Parents reported their child's date of birth, sex, race, and ethnicity. Parents were asked to report their child's gender and were provided four response options: "Female," "Male," "Other," and "Prefer Not to Answer." We acknowledge that the wording of this question does not fully reflect the array of gender identities and conflates sex and gender. We chose to use the terms "female" and "male" henceforth in this paper. However, the wording of our questionnaire makes it impossible for us to investigate the relation between brain measures and the child's gender identity, whether within or outside the binary. Any observed effects could be driven by biological sex or socially constructed gender differences. Fifty-four percent of the children were reported to be male, and 46% were reported to be female; none were reported to be other, suggesting that there may not be any intersex children in our sample. This distribution is not unexpected given the sample size and the prevalence of intersex children in the United States. The racial and ethnic makeup of the sample was as follows: 46% Black, 31% White, 13% multiracial or other, 11% Hispanic/Latino, 4% Asian, and 3% American Indian. Percentages sum to greater than 100% because parents could endorse multiple responses.

2.3. Socioeconomic status

Parents reported their total annual family income in one of 11 income bins (less than $5,000; $5000- $11,999; $12,000-$15,999; $16,000-$24,999; $25,000-$34,999; $35,000-$49,999; $50,000-$74,999; $75000-$99,999; $100,000-$149,999; $150,000-$199,999; and $200,000 or greater). Annual family income was estimated as the median value of each income bracket. Family income ranged from $2,500 to $200,000 (*Median* = $62500, *SD* = $66,950, $n = 147$). For context, the median income of Philadelphia County during the years of this study was $49,127 (U.S. Census Bureau QuickFacts: Philadelphia County, Pennsylvania, 2022). Parents also reported their highest education level (possible responses ranged from "less than high school" to "professional degree (J.D., M.D., Ph.D.)"), as well as the highest education level of their partner, if applicable. Values were recoded to indicate total years of education, ranging from 10 to 20 years total. Average parental education ranged from 10 to 20 years (*Mean* = 15.13 years, *SD* = 2.82 years; 52% with bachelor's degree or higher education, $n = 154$).

2.4. Molar eruption

Molar eruption data was available for 106 children aged seven years or younger. Each participant's T2w MRI scan was rated by a dental student at the University of Pennsylvania's School of Dental Medicine, under the supervision of a faculty with expertise in oral and maxillofacial radiology (McDermott et al., 2021). The rating scale and procedure was generated based on previous experience in dental imaging and is similar to other scales relying on dental radiographs, including the Demirjian method (Demirjian et al., 1973). Molar eruption status was rated on a scale from 1 (unerupted) to 4 (fully erupted). In stage 1, molars and the follicular space are fully embedded in the alveolar bone. In stage 2, molars are partially erupted, though still partially submerged within soft tissues; the follicular space is also reduced. In stage 3, molars have partially erupted into the oral cavity but the maxillary and mandibular molars are not yet in contact (in occlusion). In stage 4, molars have fully erupted and are in full occlusion; there is also no remaining follicular space. Each participant's four permanent molars were rated for eruption status. These ratings were then averaged to create a continuous molar eruption value for each participant.

2.5. Cognitive assessment

Children between the ages of 4 years and 7-years 7-months completed two subtests from the Wechsler Preschool & Primary Scale of Intelligence (WPPSI-IV; Wechsler, 2012): Matrix Reasoning ($n = 128$) and Information ($n = 127$). Matrix Reasoning is a measure of fluid reasoning that requires children to select missing pieces to complete a visual pattern. Information consists of general, crystallized knowledge questions. Scaled scores were used in all analyses. Missing subtest scores are due to differences in study protocols, administration errors, or lack of child understanding or compliance. The small number of older children in our sample completed similar measures of cognition on the Wechsler Intelligence Scale for Children (WISC-V), though we did not originally pre-register separate analyses for this small subsample. Results did not differ when scaled WPPSI-IV and WISC-V scores were combined into a single, non-pre-registered analysis; thus, we report only pre-registered analyses of WPPSI-IV data for ease of interpretation.

2.6. MRI data acquisition

Imaging was performed at the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) at the University of Pennsylvania. Scans were conducted using a Siemens MAGNETOM Prisma 3-Tesla MRI scanner with a 32-channel head coil. A whole-brain, high-resolution, T1-weighted 3D-encoded multi-echo structural scan (MEMPRAGE) was collected (acquisition parameters: TR = 2530 ms, TI = 1330 ms, TEs = 1.69 ms/3.55 ms/5.41 ms/7.27 ms, BW = 650 Hz/px, 3x GRAPPA, flip angle = 7°, voxel size = 1 mm isotropic, matrix size = 256 × 256 ×176, FOV = 256 mm, total scan time = 4:38). This sequence used interleaved volumetric navigators to prospectively track and correct for subject head motion (Tisdall et al., 2012). A whole-brain T2-weighted 3D-encoded variable flip angle turbo spin echo structural image (T2 SPACE) was also acquired (acquisition parameters: TR = 3200 ms, TE = 4.06 ms, variable flip angle, voxel size = 1 mm isotropic, matrix size = 256 ×256, 176 sagittal slices, FOV = 256 mm).

2.7. T1w/T2w ratio images

Following Boroshok et al. (2022), we created subject-specific, myelin-enhanced T1w/T2w ratio images using the publicly available MRTool toolbox (version 1.4.3; https://www.nitrc.org/projects/mrtool/) for SPM12 (Boroshok et al., 2022; Ganzetti et al., 2014, 2015; Glasser et al., 2014, 2021; Glasser and Van Essen, 2011). Using a rigid-body transformation, each participant's T2w image was coregistered to their respective T1w image. Next, bias correction was applied to both images to ensure spatial equalization of the coil sensitivity profiles. The intensity inhomogeneity correction tool in SPM12 was separately used on both images to correct for transmission-field inhomogeneities in image intensity and contrast. The intensity values of both bias-corrected images were separately standardized using a non-linear external calibration approach (MRTool image calibration option #1: Non-linear histogram matching-external calibration), in order to accurately

capture inter-individual differences in myelin contrast (Ganzetti et al., 2014, 2015). Subject-specific masks corresponding to CSF, skull, and soft tissues (i.e., dura mater) were extracted using SPM's Segmentation tool in both anatomical (T1w) and template (MNI) space. Then, intensity histograms for all three masks were generated in both spaces and a non-linear mapping function (cubic spline interpolation) between them was computed. The corresponding cubic polynomial was used to calibrate the intensities of the bias-corrected T1w and T2w images. The ratio between each participant's bias-corrected and calibrated T1w and T2w images was calculated and used to create a corresponding T1w/T2w ratio map in native subject space. Using segmentations defined in FreeSurfer's LookUp Table (Desikan et al., 2006; Destrieux et al., 2010; Fischl, 2012), we masked out white matter and cerebrospinal fluid from each T1w/T2w ratio map to ensure that parameter estimates reflected only signal within gray matter. Individual T1w/T2w ratio map volumes in subject space were then projected to surface space using surfaces previously reconstructed using FreeSurfer version 6.3 (Fischl, 2012). Surfaces were individually inspected for issues in gray-white matter boundary definitions and were edited as needed; six children were excluded for low image quality that resulted in inaccurate surfaces. Finally, each participant's T1w/T2w ratio image in surface space was then resampled to a standard brain (*fsaverage*) and smoothed with a 5-mm full-width half-maximum kernel. T1w/T2w ratio maps were manually examined between processing steps for image quality issues and all intensity histograms were visually inspected for outlying values.

2.8. Whole-brain group-level T1w/T2w ratio analyses

General linear models were constructed using FreeSurfer's *mri_glmfit* tool (Hagler et al., 2006) to test for associations between T1w/T2w ratios and variables of interest. Following pre-registration #1 (https://osf.io/ztxdv), we first tested for associations with age (see deviations from pre-registrations below). Following pre-registration #2 (https://osf.io/4wyjr), we then tested for associations with family income, average parent education, molar eruption, and cognition (as summarized in Information and Matrix Reasoning scaled scores). All analyses controlled for age. Molar eruption analyses controlled for sex because molar eruption timing differs by sex (McDermott et al., 2021; Pahel et al., 2017). Analyses of molar eruption were run with and without controlling for body mass index (BMI), as BMI is positively associated with eruption of first and second permanent molars (Pahel et al., 2017). BMI was computed based on height and weight measurements taken directly before the scan. Results did not differ with or without controlling for BMI. T1w image quality rating was not related to age, sex, SES, cognition, or molar eruption. Missing data was handled through pairwise deletion. Whole-brain analyses were cluster-corrected for multiple comparisons using permutation testing (cluster-wise $p < .05$, adjusted for both hemispheres; Hagler et al., 2006). A cluster-forming threshold was set to $p < .005$, $z = 2.3$. For full transparency of the pattern of results across the cortex, we present both corrected and uncorrected results.

2.9. System-of-interest analyses

In a series of exploratory analyses, we extracted parameter estimates from the publicly released seven-system partition from Yeo et al. (2011) using the *freesurferformats* package in *R* to test whether effects were specific to early-developing cortical systems (Schäfer, 2022; Yeo et al., 2011). Exploratory analyses within these functional systems enable comparisons with the large number of studies that have explored the structural and functional development of these systems (for instance, our previous work in Tooley et al., 2022a). Further, restricting analyses to seven systems instead of a large number of gyri and sulci in other cortical parcellations, reduced the number of statistical tests performed and maximized biological and cognitive interpretability. For each participant, the median intensity within each system was extracted and used in all linear models and correlation plots. We used median rather than mean to avoid influences of outlying intensities. We tested associations between T1w/T2w values and age, molar eruption, family income, average parent education, and cognition using linear models in R. Age was included as a covariate in all system-of-interest models. We used the Benjamini-Hochberg false discovery rate (FDR; (Benjamini and Hochberg, 1995) to account for tests across the seven systems.

2.10. Deviations from pre-registrations

Pre-registration #1 also included plans to analyze relationships between T1w/T2w values and salivary levels of pubertal hormones. However, due to insufficient sample sizes, we chose not to complete the hormone analyses. Data collection was interrupted by the COVID-19 pandemic, and not all families consented to this portion of the study; thus, only 66 saliva samples were analyzed. Due to high mucus content, 22 of these samples could not be assayed in duplicate for all three hormones of interest (dehydroepiandrosterone [DHEA], DHEA-S, and testosterone), leaving only 44 children who had usable data for at least one hormone. After excluding samples provided by children who did not complete MRI scanning ($n = 4$) or did not have usable T1w ($n = 1$) *and* T2w ($n = 1$) scans, the remaining sample sizes (DHEA: $n = 41$; DHEA-S: $n = 38$; testosterone [children reported male only]: $n = 15$) were underpowered for planned individual differences analyses. Further, we concluded that running pre-registered brain analyses for males and females separately would be underpowered and difficult to interpret.

3. Results

3.1. Group average T1w/T2w ratios

We first examined variation in the T1w/T2w ratio across cortex in children. T1w/T2w was highest in the inferior edge of posterior cingulate, and lowest in the insula and medial prefrontal cortex (Fig. 1 A). For visual comparisons, we included group average T1w/T2w ratios from a sample of healthy, neurotypical adults (Fig. 1B) ages 18–25 years from a separate T1w/T2w ratio map study with the same acquisition and preprocessing parameters (see Boroshok et al., 2022). In adults, sensorimotor areas and posterior cingulate have the highest T1w/T2w values, and medial prefrontal and insula values remain low. The distribution of T1w/T2w ratios in children is shifted towards lower values compared to the adult sample, as expected.

3.2. Age analyses

T1w/T2w ratios were positively associated with age across the cortex (Fig. 1 C). Following cluster correction for multiple comparisons, significant positive age effects were found in primary sensorimotor and primary visual cortices (Fig. 1D). Exploratory analyses revealed that T1w/T2w ratios were also positively correlated with age within the visual ($t = 2.61$, $p = 0.009$, $p_{FDR} = 0.034$, $\eta^2_p = 0.007$), somatosensory ($t = 2.78$, $p = 0.006$, $p_{FDR} = 0.034$, $\eta^2_p = 0.048$), and ventral attention ($t = 2.47$, $p = 0.014$, $p_{FDR} = 0.034$, $\eta^2_p = 0.038$) systems (Fig. 1E). Effects observed within the frontoparietal ($t = 2.00$, $p = 0.047$, $p_{FDR} = 0.072$, $\eta^2_p = 0.026$), and default mode ($t = 2.02$, $p = 0.045$, $p_{FDR} = 0.066$, $\eta^2_p = 0.025$) systems did not survive FDR correction. There were no significant effects in the dorsal attention or limbic systems.

3.3. Socioeconomic status analyses

T1w/T2w ratios were not significantly associated with parental education or family income at the whole-brain level (Fig. 2A-B). There were no cortical systems within which T1w/T2w ratios were related to either measure of SES (Table 1).

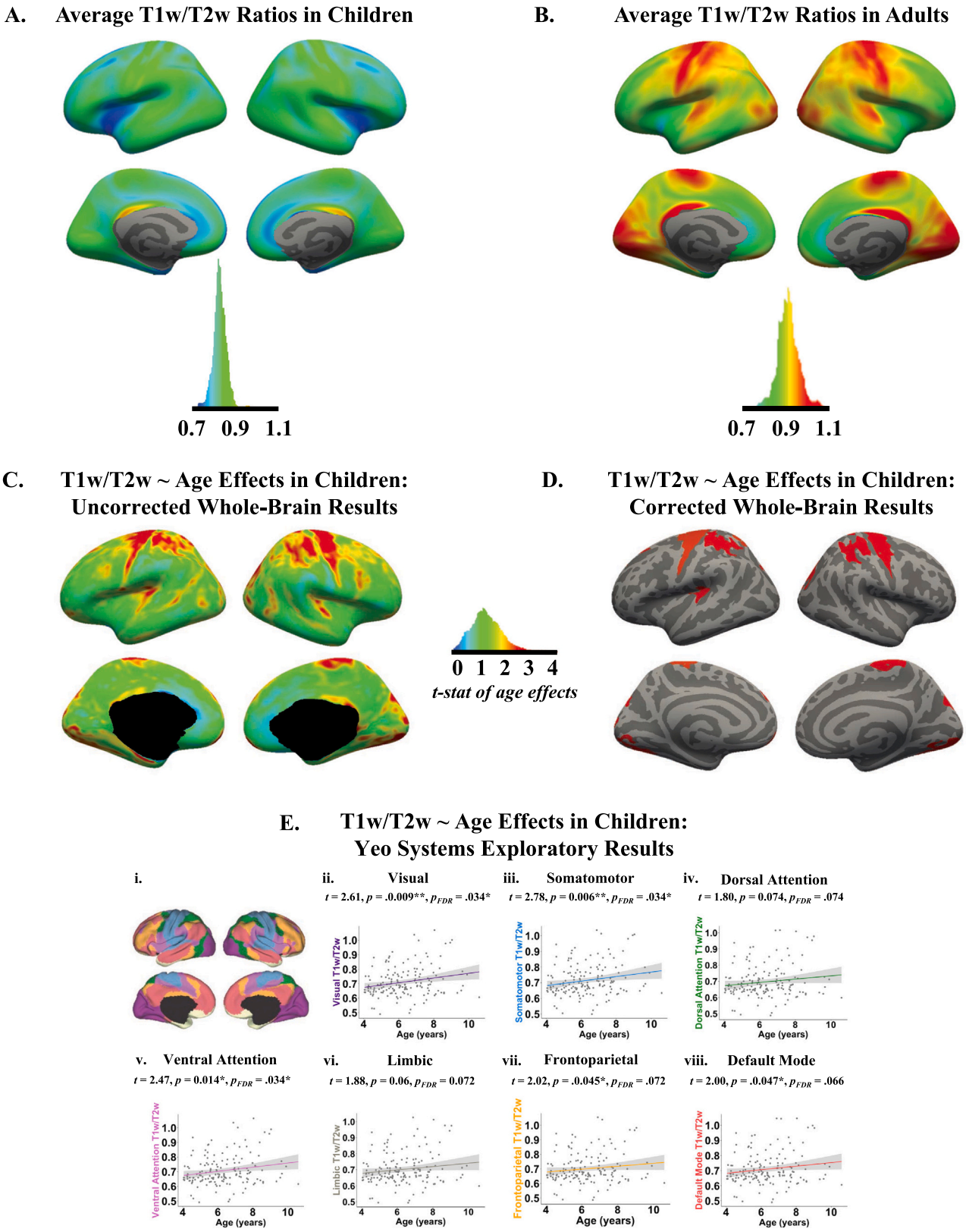

Fig. 1. T1w/T2w ratio group averages and age effects. (A) Group average T1w/T2w ratio maps from the current sample of healthy, neurotypical children ages 4–10 years. (B) Group average T1w/T2w ratio maps from a separate sample of healthy, neurotypical adults ages 18–25 years using the same scan sequence and preprocessing parameters (see Boroshok et al., 2022). (C) Whole-brain, uncorrected T1w/T2w ratio images showing positive associations with age across the cortex. (D) Clusters showing positive associations between T1w/T2w ratio map values and age surviving permutation-based clusterwise correction for multiple comparisons at z = 2.3. (E) i. Cortical system assignments derived by Yeo et al. (2011); ii-vii. Scatter plots showing significant positive associations between age and T1w/T2w ratios extracted from the Yeo et al. (2011) cortical systems.

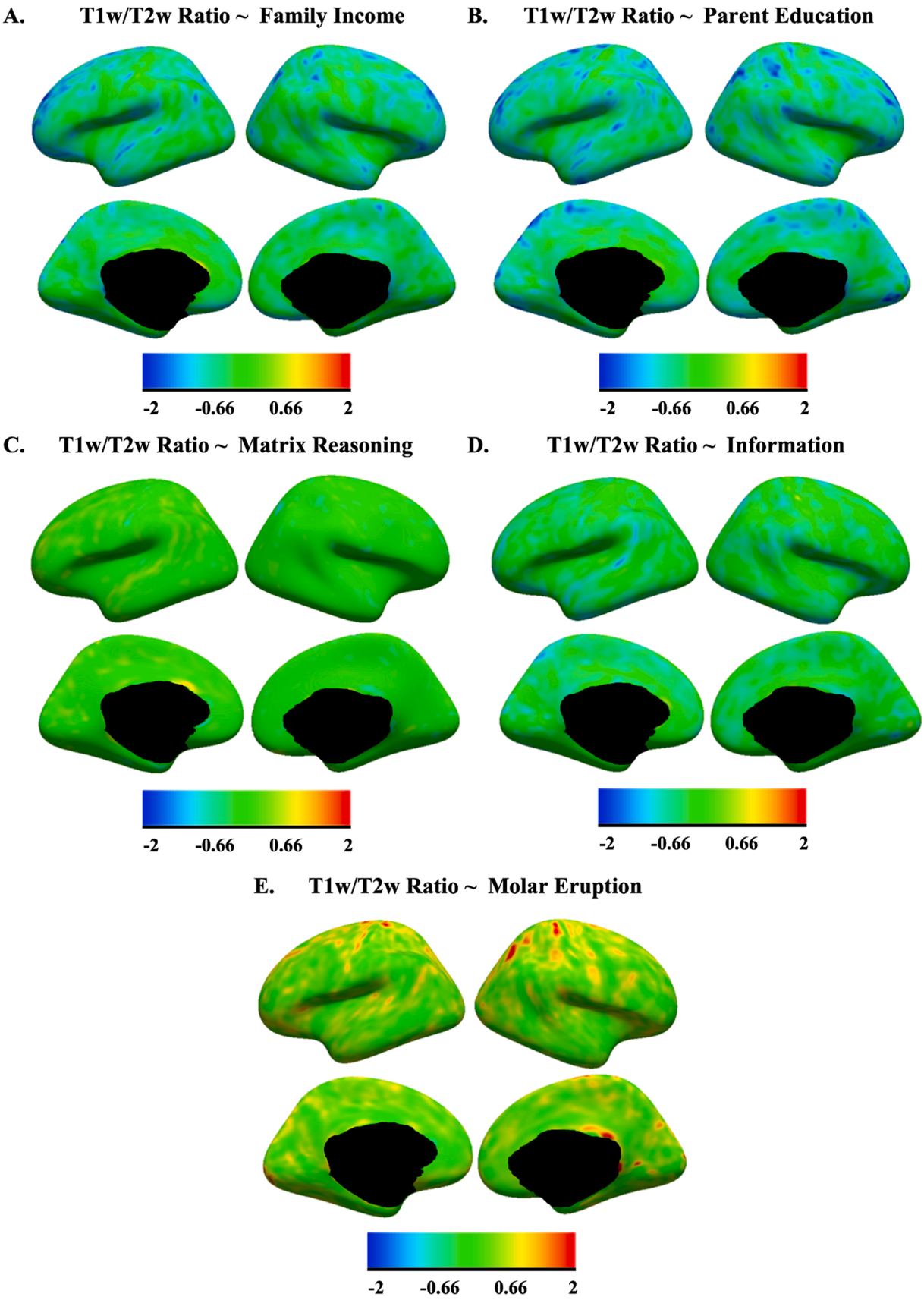

Fig. 2. Whole-brain, uncorrected T1w/T2w ratio images showing associations between T1w/T2w ratios and variables of interest. (A-B) Associations between T1w/T2w ratios and socioeconomic status measures. (C-D) Associations between T1w/T2w ratios and cognition measures. (E) Associations between T1w/T2w ratios and eruption of permanent molars. Color bars represent the values of the intensity histograms generated by FreeSurfer for each overlay.

Table 1
Associations between T1w/T2w ratios (median of intensities within each cortical system) and variables of interest. Relationships are shown for socioeconomic status, cognitive performance on select subtests of the WPPSI-IV, and eruption of permanent molars. Standardized effect sizes and raw *p*-values are reported in the first row. Partial eta-squared effect sizes are reported in the second row.

Yeo System	Family Income	Parent Education	Matrix Reasoning	Information	Molar Eruption
Visual	-0.01	-0.003	< 0.001	-0.002	0.01
	(0.29)	(0.41)	(0.85)	(0.54)	(0.32)
	η_p^2 = 0.008	η_p^2 = 0.005	η_p^2 = < 0.001	η_p^2 = 0.003	η_p^2 = 0.009
Somatomotor	-0.001	-0.003	< 0.001	-0.002	0.01
	(0.24)	(0.37)	(0.87)	(0.48)	(0.25)
	η_p^2 = 0.009	η_p^2 = 0.005	η_p^2 = < 0.001	η_p^2 = 0.004	η_p^2 = 0.012
Dorsal Attention	-0.01	-0.003	< 0.001	-0.002	0.01
	(0.29)	(0.40)	(0.83)	(0.45)	(0.38)
	η_p^2 = 0.008	η_p^2 = 0.005	η_p^2 = < 0.001	η_p^2 = 0.004	η_p^2 = 0.001
Ventral Attention	-0.01	-0.003	< 0.001	-0.002	0.02
	(0.19)	(0.31)	(0.79)	(0.44)	(0.27)
	η_p^2 = 0.012	η_p^2 = 0.007	η_p^2 = 0.001	η_p^2 = 0.005	η_p^2 = 0.011
Limbic	-0.01	-0.002	< 0.001	-0.001	0.01
	(0.28)	(0.44)	(0.98)	(0.56)	(0.45)
	η_p^2 = 0.008	η_p^2 = 0.004	η_p^2 = 0.014	η_p^2 = 0.003	η_p^2 = 0.006
Frontoparietal	-0.01	-0.003	< 0.001	-0.002	0.01
	(0.22)	(0.34)	(0.76)	(0.44)	(0.39)
	η_p^2 = 0.011	η_p^2 = 0.006	η_p^2 = 0.001	η_p^2 = 0.005	η_p^2 = 0.007
Default Mode	-0.01	-0.003	< 0.001	-0.002	0.01
	(0.27)	(0.41)	(0.84)	(0.46)	(0.38)
	η_p^2 = 0.008	η_p^2 = 0.004	η_p^2 = < 0.001	η_p^2 = 0.004	η_p^2 = 0.007

3.4. Cognitive development analyses

In the whole brain analyses, T1w/T2w ratios were not associated with performance on the Matrix Reasoning or Information subtests of the WPPSI-IV (Fig. 2C-D). There were also no cortical systems within which T1w/T2w ratios were associated with cognitive performance (Table 1).

3.5. Somatic maturation (molar eruption) analyses

At the whole-brain level, there were no clusters where T1w/T2w ratios were associated with eruption status of permanent molars (Fig. 2E). Results did not change when including BMI as a covariate. Molar eruption status was not associated with T1w/T2w ratios within any of the cortical systems (Table 1).

4. Discussion

We investigated age-related individual differences in T1w/T2w ratios, a proxy for cortical microstructure, during childhood. At the whole-brain level, chronological age was strongly and positively associated with T1w/T2w ratios across the cortex, converging with prior work that tested age effects on this measure in children and adolescents (Baum et al., 2022; Grydeland et al., 2013; Norbom et al., 2020; Sydnor et al., 2021, 2023). We did not, however, observe significant associations between T1w/T2w ratios and socioeconomic status, cognition, or markers of biological maturation.

Effects with chronological age were concentrated within sensorimotor cortices, which is consistent with work demonstrating that these areas develop earlier than association cortices (Baum et al., 2020; Burt et al., 2018; Hilgetag and Goulas, 2020; Sydnor et al., 2021). We also found age effects in the superior parietal cortex, consistent with our previous findings showing substantial functional network development in this region in this age range (Tooley et al., 2022a), and functional maturity of the superior parietal cortex by age 10 (Tooley et al., 2022b). Interestingly, T1w/T2w ratios in the medial prefrontal cortex showed no association with age. Slow myelination in this area during childhood may allow for more sophisticated functional remodeling (Tooley et al., 2022b), a possibility that is consistent with findings that the medial prefrontal cortex is already highly functionally segregated in adolescence (Baum et al., 2020).

Moreover, our findings were directionally consistent with previous work linking SES to T1w/T2w ratios in a larger sample with a wider age range: higher SES was associated with lower T1w/T2w (Norbom et al., 2022). However, we did not find significant effects across the whole brain or within cortical systems. Similarly, a recent preprint also found no associations between SES and T1w/T2w ratios in the Human Connectome Project in Development sample (Weissman et al., 2023). There are a few possible reasons for the null effects of SES in this sample. The most likely explanation is that SES effects are small (smaller than age effects) and our sample was underpowered to discover these effects. It is also possible that we do not see effects because the age range of our sample is younger than that of samples used in previous studies, and differences may widen later in adolescence or young adulthood. However, it is the case that SES-dependent differences in cortical thickness are visible in this age range (Hanson et al., 2013; Lawson et al., 2013; Noble et al., 2012), but are more restricted to early-developing visual regions as compared to SES-dependent differences at later ages. Another explanation may be that the specific measures of SES used in this study—namely, parent education and family income—may reflect a myriad of factors that might dilute SES effects that may be small to begin with. Relatedly, effects of SES on T1w/T2w ratios may be more broadly sensitive to unique experiences across dimensions of threat or deprivation (Sheridan et al., 2017), though we are unable to test this possibility in the current data. We also did not replicate significant associations between T1w/T2w ratios and cognition as found by Norbom et al. (2022), either across the whole brain or within cortical systems. It is similarly possible that cognition effects are small and/or do not emerge until later in adolescence.

For the first time, we tested whether the eruption of permanent molars, a marker of somatic maturation, is correlated with cortical myelination. Though effects were directionally consistent with our hypothesis that greater T1w/T2w ratios would be related to earlier biological maturation, there were no clusters where T1w/T2w ratios were significantly associated with eruption of permanent molars at the whole-brain or cortical system levels. Our analysis plans originally included tests with other biomarkers, specifically with salivary hormones. However, salivary hormones are difficult to measure reliably, and sample sizes were insufficient due to data collection being cut short by the COVID-19 pandemic. Future studies may examine associations between T1w/T2w ratios and molar eruption, pubertal hormones, or alternative biomarkers with larger samples. These studies could also test whether effects vary during adrenarche and gonadarche, the first and second phases of puberty, respectively.

The principal limitation of this study is that the sample size is smaller than previous studies of cortical microstructure (Baum et al., 2022; Grydeland et al., 2013, 2019; Norbom et al., 2019, 2020, 2022) and thus our analyses were likely under-powered to detect significant effects at the whole-brain level (Marek et al., 2022). We share the results of the whole-brain analyses because they were pre-registered, and because it is the most transparent way to represent the full pattern of relationships. Further, these maps could be useful for future meta-analyses. We can consider the size of the effect that we could have detected in system-of-interest analyses. With a Bonferroni correction across the 7 cortical systems (which would be more conservative than an FDR correction), the adjusted alpha level would be 0.007, we would need 195 participants to detect a correlation of 0.25. For comparison, the strongest correlation coefficient in our age analysis was 0.22, and associations

with SES, cognition, and molars were weaker. Further, our analyses were only cross-sectional. Longitudinal work in larger samples is needed to make inferences about the directionality of the observed associations and intra-individual changes in cortical myelin. Longitudinal data are also needed to examine whether changes in T1w/T2w ratios mediate age-related changes in various developmental outcomes, such as learning and mental health.

Interpretations of our study are also constrained by limitations of the T1w/T2w ratio. The T1w/T2w ratio is only a proxy measure for cortical microstructure and is likely sensitive to other cortical features such as iron (Miot-Noirault et al., 1997; Stüber et al., 2014), water concentration (Miot-Noirault et al., 1997), and axonal diameter and dendrite density (Arshad et al., 2017; Genc et al., 2023; Hagiwara et al., 2018; Righart et al., 2017; Ritchie et al., 2018; Uddin et al., 2018, 2019). Despite a number of histological and quantitative relaxometry studies supporting the validity of this measure, the biology of the T1w/T2w ratio is frequently debated. T1w/T2w ratios have been inconsistently associated with other MRI-based proxies of cortical myelin (magnetization transfer in gray matter, myelin water fraction in gray and white matter). It is possible that the observed age effects could reflect a combination of changes in myelin and other membrane properties (Baum et al., 2022). Thus, the T1w/T2w signal is not a direct measure of cortical myelin content and should continue to be interpreted cautiously. Relatedly, there are multiple physical pathways by which the myelin contrast could arise (e.g., T1w/T2w contrast in MPRAGE and SPACE sequences, T2 * contrasts, secondary effects of magnetization transfer). Less is understood about which parameter settings affect this contrast, and most studies do not use consistent T1w or T2w protocols. Therefore, between-study differences in myelin contrast may be explained by variations in sensitivity to one of several physical pathways for the myelin contrast. Finally, the T1w/T2w signal is highly correlated across the cortex, for either biological or acquisition-related reasons that remain unknown. The present findings should be replicated in future longitudinal studies using MRI sequences with improved sensitivity to myelin over time.

In sum, we replicated age effects on T1w/T2w ratios during a period of childhood that has been understudied in previous research but did not replicate previously reported correlations with SES or cognition. Further, we did not observe correlations between T1w/T2w ratios and markers of biological maturation. Future investigations of variability in neuroplasticity may inform how early life experiences shape plasticity and learning, brain and body development, and response to cognitive and psychological interventions.

Data statement

All data and R code used to produce figures and results will be made freely available upon request. Interested parties should contact the corresponding author (Austin Boroshok: boroshok@sas.upenn.edu).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101270.

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