Archival Report

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Intracortical Myelin in Youths at Risk for Depression

Anna Nazarova, Vladislav Drobinin, Carl A. Helmick, Matthias H. Schmidt, Jacob Cookey, and Rudolf Uher

ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is a leading cause of disability. To understand why depression develops, it is important to distinguish between early neural markers of vulnerability that precede the onset of MDD and features that develop during depression. Recent neuroimaging findings suggest that reduced global and regional intracortical myelination (ICM), especially in the lateral prefrontal cortex, may be associated with depression, but it is unknown whether it is a precursor or a consequence of MDD. The study of offspring of affected parents offers the opportunity to distinguish between precursors and consequences by examining individuals who carry high risk at a time when they have not experienced depression.

METHODS: We acquired 129 T1-weighted and T2-weighted scans from 56 (25 female) unaffected offspring of parents with depression and 114 scans from 63 (34 female) unaffected offspring of parents without a history of depression (ages 9 to 16 years). To assess scan quality, we calculated test-retest reliability. We used the scan ratios to calculate myelin maps for 68 cortical regions. We analyzed data using mixed-effects modeling.

RESULTS: ICM did not differ between high and low familial risk youths in global (B = 0.06, SE = 0.03, p = .06) or regional (B = 0.05, SE = 0.03, p = .08) analyses. Our pediatric sample had high ICM reliability (intraclass correlation coefficient = 0.79; 95% CI, 0.55–0.88).

CONCLUSIONS: Based on our results, reduced ICM does not appear to be a precursor of MDD. Future studies should examine ICM in familial high-risk youths across a broad developmental period.

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Major depressive disorder (MDD), or depression, is characterized by persistent sadness, loss of interest, fatigue, and an increased risk of suicide (1,2). The onset of MDD typically occurs during late adolescence or early adulthood (3). Depression is the most prevalent mood disorder, affecting 1 in 5 people worldwide (4). The negative impact of depression on daily functioning and the associated cost of health care demand advancement of treatment and earlier detection to improve prognosis (5).

Early detection of risk can be informed by knowledge of factors involved in the development of depression. MDD is influenced by genetic and environmental factors, both of which affect brain development (6,7). Cortical thinning, abnormalities in subcortical structure volumes, white matter abnormalities, and aberrant functional connectivity networks characterize patients with depression (8). Whether these brain abnormalities develop during the illness or preexist is unknown. It has been suggested that abnormal structure and function of several key brain regions may lead to the development of symptoms seen in depression (9).

Brain abnormalities manifest globally across the entire brain and regionally in specific cortical areas. For example, depression is associated with global cortical thinning across both hemispheres (10). A cortical region of particular interest is the lateral prefrontal cortex (LPFC). The LPFC is involved in executive control functions such as working memory, attention, emotion regulation, and behavioral planning through extensive connections to other cortical and subcortical regions (11), the impairment of which is associated with poorer prognosis among individuals with depression (12). Functional and structural abnormalities of the LPFC have been found in adults with depression, suggesting a neural link between depression and difficulties with executive control and emotional regulation (13–17).

Abnormalities at the cellular level have been found in depression, such as decreased cell number, size, and density of oligodendrocyte lineage cells (18). Oligodendrocytes are responsible for creating myelin sheaths, which are fatty coverings around axons that increase action potential speed and improve the brain's processing capacity. Abnormalities of white matter myelin sheaths and slower processing capacity are associated with depression (19). Adults with depression have reduced fractional anisotropy in the corpus callosum, corona radiata, internal capsule, external capsule, uncinate fasciculi, and the cingulate gyrus (20). Poorer structural integrity of these white matter tracts may contribute to the deficits in mood regulation seen in depression (8,21). However, myelinated axons are also found in the cerebral cortex, where they create the intricate myeloarchitecture of the brain (22).

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Studies that have examined neonatal separation of rat pups from their mothers have linked reduced intracortical myelination (ICM) in the LPFC to increased anxiety and decreased working memory (23). Reduced ICM has been associated with depression in adults (14,24,25). Furthermore, oligodendrogenesis of the PFC is sensitive to environmental stressors and poor physical health (26,27). During human development, ICM follows an inverted U-shaped trajectory, with a rapid increase during the teenage and early adult years, a peak during the mid-30s, and a decline in later adult years (28). However, the later part of the ICM developmental trajectory may be altered in adults with mood disorders, especially within the frontal, parietal, and temporal regions (29). Neuroimaging and histological studies have converged in identifying the LPFC as the brain region where ICM is most consistently affected in adults with mood disorders (14,17,24).

Cellular vulnerability to environmental, psychological, and physiological conditions increases the risk of ICM disruptions, especially during adolescence when myelination is most rapid. The rapid development of ICM during adolescence and early adulthood coincides with the period of greatest risk for mood and psychotic disorders (30). However, it is unknown whether early disruptions of ICM development may increase the risk of depression onset (31). Familial high-risk (FHR) studies have been used to investigate whether neural abnormalities predate the onset of MDD or are a consequence of the disorder. Youths at high familial risk have similar patterns of neural abnormalities compared to adults with MDD, specifically in cortical volume and functional connectivity networks (31–33). Reduction of white matter integrity has also been observed in high-risk offspring in the cingulum, corpus callosum, and uncinate fasciculus, with reduced fractional anisotropy in the cingulum being related to elevated depression scores (34,35). Compared to the general population, high-risk youths have an increased probability of mood disorder onset due to their genetic and environmental relationships with family member(s) who have a severe mental disorder (36–38). Familial risk is known from birth or an early age, making it possible to study development in individuals who are at risk at a time when they have not experienced depression. Furthermore, adolescents at high familial risk are typically naïve to psychiatric medications, removing the possibility of psychopharmacological influences on clinical and neural measures (39).

One key challenge to understanding whether ICM disruptions increase the risk of depression is measuring ICM in living humans. Histological studies provide accurate information about myelin content in postmortem brains (40). Magnetic resonance imaging (MRI) studies provide insight into myelination in the living brain; however, the accuracy of MRI methods, especially in the pediatric age range, has not yet been established (41). To confirm our measure of ICM in youths, we assessed reliability concurrently and provided test-retest data of ICM in our developmental sample.

It is unclear whether reductions of global and regional ICM are precursors or consequences of MDD. In the current study, we addressed this gap by examining whether ICM abnormalities are a neural risk factor that predates depression onset. We implemented a FHR study design to investigate whether global and regional levels of ICM differ between FHR and familial low-risk (FLR) youths. We focused on an age range younger than the typical age of onset of depression to examine brain development in youths who are at high risk before depression develops. First, we hypothesized that there would be a reduction in global ICM in FHR youths. Second, we hypothesized that there would be a reduction of ICM in the LPFC in FHR youths. We anticipated that FHR youths would have a reduction of ICM, similar to adults with MDD, thereby reproducing a similar trend found in family high-risk studies that have investigated other brain modalities (31,33,42).

METHODS AND MATERIALS

Participants

FHR participants were those who had at least one biological parent with a lifetime diagnosis of MDD according to DSM-5. FLR participants were offspring of parents without any history of mental illnesses. FHR participants were recruited by clinical referral by physicians treating the parent. FLR participants were recruited from schools and communities with similar socioeconomic characteristics to those of the FHR participants.

Inclusion criterion was age between 9 and 16 years. The rationale behind this was that it allows measurement in representative samples of individuals at high and low familial risk who are also at a developmental stage before the typical age of onset of the first major mood episode (43,44). Exclusion criteria were a current or previous diagnosis of a major mood, psychotic, substance use, or autism spectrum disorder according to DSM-5; neurological disorders; a history of head trauma with loss of consciousness; or contraindications to the MRI.

This study was approved by the Nova Scotia Health Authority Research Ethics Board. All participants and their parents or legal guardians signed informed consent forms.

Procedure

The participants and their parents completed semistructured diagnostic interviews and provided their demographic information during assessments. Separate groups of assessors collected information about the parents and the offspring.

Participants were scheduled for an MRI within 2 weeks of their initial assessment. The scans took place at the Biomedical Translational Imaging Centre at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. All participants were safety screened by an MRI technologist before the scan. The MRI session lasted for approximately 35 minutes.

To capture the development of ICM over time, we invited eligible participants to repeat the procedure annually, including parent and participant clinical interviews, MRI scan, and demographic questionnaires. Because there has been rolling recruitment for 5 years, the number of eligible participants became progressively smaller with the number of annual repeats. For this reason, the number of follow-ups varies among participants (see Table S1 for details). In addition, to establish test-retest reliability, we invited a proportion (25%) of the participants to repeat scans within 2 weeks of their annual scan date.

Measures

Semistructured Interviews. To assess FHR status, researchers who assessed the parents completed a Structured Clinical Interview for DSM-5 with each parent (45). If a parent was unable to attend the interview, their health records were reviewed, and informant information was obtained using the Family Interview for Genetic Studies to classify their history of mental illness. Overall, 76% of participants had both parents interviewed, and 24% had 1 parent interviewed, meaning that for 24% of participants, 1 parent's data was reported indirectly.

Researchers assessing the youths completed a Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version for DSM-5 with each youth participant, using a standard protocol of first speaking with the parent about the youth followed by speaking with the youth alone (46).

All interviews were performed by assessors trained to achieve high interrater reliability on the diagnostic interviews. Assessors who completed youth interviews were blind to parental diagnostic status and vice versa. The Structured Clinical Interview for DSM-5 and Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version are validated instruments that establish diagnoses of mood disorders with high interrater reliability (46,47). DSM-5 for the youth and parents were confirmed in separate consensus meetings with licensed adult and child psychiatrists who were blinded to diagnoses of other family members.

Depressive Symptoms. We measured depressive symptoms with the depression subscale of the Youth Experience Tracker Instrument. The Youth Experience Tracker Instrument is a 26-item self-report questionnaire that tracks antecedent symptoms in youths. Its 5-item depression subscale is a validated measure of depressive symptoms that closely corresponds to measures used in clinical care (48,49). Every participant completed the Youth Experience Tracker Instrument before their MRI scan session. We calculated a composite score (potential range 0–15) for the depressive symptom items and used it as a covariate in sensitivity analyses (50–52).

Demographic Information. Information about sex, age, ethnicity, height (cm), and weight (kg) was gathered during the annual assessment. We indexed socioeconomic status (SES) as a composite of maternal and paternal levels of education, family household annual income, ownership of primary residence, and ratio of bedrooms to residents in the household (53). We measured Full Scale IQ with the Wechsler Abbreviated Scale of Intelligence. We computed body mass index (BMI) using participant height and weight. We determined puberty stage using 2 questionnaires. The Pearson's Puberty Development Scale includes questions on body hair, skin changes, growth of facial hair for males, and age of menarche for females (54). The Sexual Maturation Scale comprises 5 drawings depicting progressive stages in pubertal development of secondary sexual characteristics (55,56). Both the Puberty Development Scale and the Sexual Maturation Scale were scored on a scale from 1 to 5 and then averaged to create the puberty stage score (54).

Imaging Methods

Image Acquisition. We acquired MRI images with a 3T General Electric Discovery MR750 scanner equipped with a 32-channel radiofrequency head coil. We collected a T1-weighted (T1-w) brain volume imaging sequence with whole-brain coverage, 1-mm^3 isotropic resolution, matrix = 224 × 224, field of view = 224 mm, 168 sagittal slices at 1-mm thickness, repetition time = 5.9 ms, echo time = 2.2 ms, inversion time = 450 ms, flip angle = 12°, and scan duration = 5 minutes. We also collected a T2-weighted (T2-w) FLAIR sequence using a T2 prep contrast option with identical coverage, resolution, and acquisition orientation to the T1-w sequence, repetition time = 5100 ms, echo time = 98 ms, inversion time = 1427 ms, echo train length = 250 echoes, flip angle = 90°, with prospective-motion correction enabled, and scan duration = 5 minutes.

Image Preprocessing. We processed the T1-w and T2-w scans using the HCP (Human Connectome Project) Minimal Preprocessing Pipeline (57). The HCP pipeline is a well-documented set of scripts that uses open-source MRI processing software including FreeSurfer 6 and the FMRIB Software Library (58). This pipeline was optimized for the current data by replacing the Montreal Neurological Institute template with an age-appropriate pediatric template for registration (59). The modified pipeline is available and freely accessible online at https://github.com/GitDro/YouthReliability. We implemented quality control to minimize artifacts, especially motion artifacts, that may affect the results (60). Quality control was carried out manually, using trained raters, and with Qoala-T, an automated supervised-learning tool (61). We excluded 24 of 267 scans due to large motion artifacts, which left 243 scans for analyses.

T1-w/T2-w Ratio Myelin Maps. Cortical myelin maps were created during processing with our modified HCP pipeline following a method developed through the HCP (62) using a ratio of coregistered T1-w to T2-w images. In the brain, myelin-bound cholesterol dominates the T1 signal, while water dominates the T2 signal (63). Therefore, myelin can be mapped by the ratio of T1/T2 signal, which quantifies regional differences in myelin content in the cortex (62) that correspond to myelin content in postmortem histology (41,64). This method of intracortical myelin registration has high reliability in adult samples (65). A FreeSurfer automated tool segmented the cortex into 68 regions based on the Desikan-Killiany atlas (66), which provided a total of 68 cortical myelin measurements, 34 per hemisphere.

Data Analysis

To test our first hypothesis, we computed global ICM by averaging the ICM values across all 68 cortical regions. We followed this global analysis by testing the right and left hemisphere separately. To test our second hypothesis, we first computed the total ICM of the bilateral LPFC, by averaging 12 cortical regions (6 from each hemisphere) that anatomically comprise the LPFC, including the caudal middle frontal, rostral middle frontal, pars opercularis, pars triangularis, pars orbitalis, and orbital frontal regions (66,67). We followed this regional analysis by testing the right and left LPFC separately.

We indexed test-retest reliability as the intraclass correlation coefficient (ICC) between the short repeat scans for each of the 68 cortical regions and mean reliability for our global (total, left and right hemispheres) and regional (total, right, and left LPFC) analysis. We used the following criteria to classify reliability: poor (<0.40), fair (0.41–0.59), good (0.60–0.74), and excellent (>0.74) (68).

We tested the global and regional hypotheses in mixed-effects linear regression models. Familial risk status was treated as a fixed effect while global ICM, left hemisphere ICM, right hemisphere ICM, global LPFC, left LPFC, and right LPFC were used as dependent variables. We accounted for the nonindependence of multiple scans (i.e., short- and long-term repeats) from the same participant and related participants through nested random effects of individual and family. We included sex, age, and intracortical volume as covariates in all models to account for sex differences, brain size, and developmental changes in brain structure (69–71). We used the Bonferroni correction to adjust for multiple testing across the global (adjusted p value across 6 tests = .008) and regional (adjusted p value across 6 tests = .008) hypotheses. In the sensitivity analyses, we included SES, IQ, BMI, subthreshold depressive symptoms, and puberty stage as additional fixed covariates to control for other factors that may affect brain measures (72–78). We completed all statistical tests in RStudio (R Version 4.0.3; RStudio version 1.2.5033).

RESULTS

Participants

After quality control, we retained 243 scans (119 baseline, 86 long-term follow-ups, 38 short-term follow-ups) from 119 youths (56 FHR, 63 FLR) for analysis (Table 1). Participants ranged between 9 and 16 years of age (mean = 11.89, SD = 1.95). They were predominantly Caucasian (87%). The groups had an equal distribution of males and females and similar subthreshold depressive scores, IQ, BMI, SES, puberty stage, and intracortical volume.

Test-Retest Reliability

We found excellent ICM test-retest reliability across the entire brain (ICC = 0.79; 95% CI, 0.55–0.88) and across the left (ICC = 0.78, 95% CI, 0.55–0.88) and right (ICC = 0.79; 95% CI, 0.56–0.89) hemispheres separately (Figure 1). We also found good to excellent test-retest reliability in the total (ICC = 0.72; 95% CI, 0.43–0.84), left (ICC = 0.74; 95% CI, 0.47–0.85), and right (ICC = 0.75; 95% CI, 0.48–0.86) LPFC.

Global ICM

We confirmed the expected developmental trend for the total ICM to increase with age (B = 0.03, SE = 0.007, $p < .001$) regardless of familial risk status (Figure 2). We tested our first hypothesis by examining the effect of familial risk group on ICM across the entire brain, as well as separately across the left and right hemispheres. We found a slight trend for higher total and right and left hemisphere ICM in the FHR group (Table 1, Figure 3). The linear mixed-effects regression model showed that global ICM did not differ significantly between FHR and FLR youths (B = 0.06, SE = 0.03, $p = .06$) (Table 2). Although there was no significant group difference in ICM of the right (B = 0.06, SE = 0.03, $p = .06$) hemisphere, ICM in the left hemisphere showed a slight increase in FHR youths (B = 0.06, SE = 0.03, $p = .048$) (Table 2). The results were similar for

Table 1. Descriptive Statistics for Participants

Variable	Group		Test Statistic
	High Risk, n = 56	Low Risk, n = 63	
Age, Years	11.62 (1.91)	12.13 (1.96)	$t_{117} = 1.43$, $p = .15$
Sex, Female	25 (44.6%)	34 (53.9%)	$\chi^2_{119} = 1.03$, $p = .31$
YETI Score	1.65 (1.75)	1.4 (1.74)	$t_{101} = 0.72$, $p = .47$
Intracranial Volume × 10^6 mm^3	1.40 (1.45)	1.50 (1.37)	$t_{117} = 0.38$, $p = .69$
IQ	104.31 (12.72)	108.44 (12.65)	$t_{115} = 1.75$, $p = .08$
Puberty Stage	2.7 (1.3)	3.02 (1.42)	$t_{87} = 1.11$, $p = .27$
SES	3.05 (1.38)	3.70 (1.06)	$t_{117} = 1.23$, $p = .22$
BMI	20.36 (4.06)	19.59 (3.95)	$t_{98} = 0.96$, $p = .33$
Scan Times	High Risk, n = 129	Low Risk, n = 114	–
Baseline	56 (43.4%)	63 (55.2%)	–
Long-term follow-up	49 (37.9%)	37 (32.5%)	–
Short-term reliability	24 (18.6%)	14 (12.2%)	–
Global ICM	1.29 (0.21)	1.24 (0.22)	$t_{234} = -2.03$, $p = .04$[a]
Right hemisphere	1.29 (0.21)	1.23 (0.22)	$t_{234} = -1.94$, $p = .05$
Left hemisphere	1.30 (0.21)	1.25 (0.21)	$t_{234} = -2.1$, $p = .04$[a]
LPFC ICM	1.19 (0.2)	1.14 (0.21)	$t_{234} = -1.83$, $p = .07$
Right hemisphere	1.16 (0.21)	1.11 (0.21)	$t_{234} = -1.87$, $p = .06$
Left hemisphere	1.22 (0.21)	1.17 (0.22)	$t_{234} = -1.76$, $p = .08$

Values are presented as mean (SD) or n (%). Due to 16 missing YETI scores, the mean was averaged across 51 high-risk and 52 low-risk participants. Due to 2 missing IQ values, the mean was averaged across 55 high-risk and 62 low-risk participants. Due to 30 missing puberty scores, the mean was averaged across 43 high-risk and 46 low-risk participants. Due to 19 missing BMI values, the mean was averaged across 49 high-risk and 51 low-risk participants.

BMI, body mass index; ICM, intracortical myelination; LPFC, lateral prefrontal cortex; SES, socioeconomic status; YETI, Youth Experience Tracker Instrument.

[a]$p < .05$.

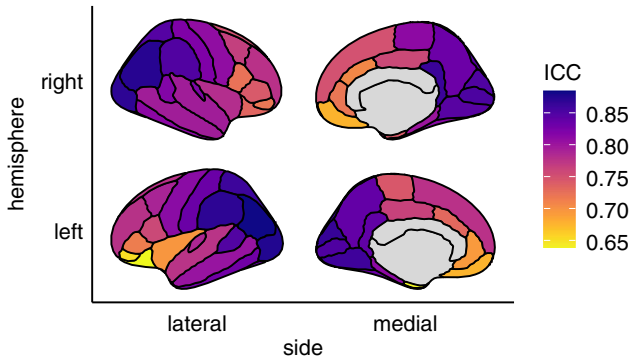

Figure 1. Intracortical myelination test-retest reliability. ICC, intraclass correlation coefficient.

the total brain and right and left hemispheres across a range of sensitivity analyses in which we controlled for SES, IQ, and BMI, with all estimates within 1 SE of the primary analysis estimates (Table S2).

ICM of the LPFC

We tested our second hypothesis by examining the effect of familial risk group on ICM in our region of interest, the LPFC. A trend toward higher LPFC ICM in the FHR group was apparent (Table 1, Figure 3). There was no significant group difference in ICM of the total (B = 0.05, SE = 0.03, p = .08), right (B = 0.06, SE = 0.03, p = .06), or left (B = 0.05, SE = 0.03, p = .17) LPFC (Table 3). The results were similar for the regional sensitivity analyses that controlled for SES, IQ, and BMI (Table S3).

Stratified Analysis

To help understand the unexpected trend toward increased ICM in FHR youths, we conducted a stratified analysis to detect any differences in ICM that might be restricted to males or females. We found no significant differences between males and females in our global or regional analysis after Bonferroni correction. Detailed results of the stratified analyses can be found in Tables S4–S11.

DISCUSSION

The current study is the first to examine ICM in youths at familial risk for depression. We found no association between familial risk and global total or right hemisphere ICM. Although we found higher ICM in FHR youths in the left hemisphere, the difference was small and not statistically significant after correction for multiple testing. There was no association between familial risk status and ICM in the LPFC.

A reduction of white matter and intracortical myelination has been linked to MDD in adults (14,20,24,79). Furthermore, findings from postmortem studies suggest that abnormal ICM may play a role in depression due to a reduced number of oligodendrocytes in MDD (80,81). We used a family risk design to detect whether a reduction of ICM existed prior to illness onset. While we did not discover a significant effect of familial risk group on ICM, we were surprised by the directionality of the result. Contrary to our expectations, we detected a trend toward higher ICM in FHR offspring, which is the opposite of findings in adults with depression. There are several possible explanations for why we did not detect a significant reduction of ICM in high-risk youths.

First, it is possible that a reduction of ICM is a consequence rather than a precursor of MDD. Cortical myelination continues development into middle age. Research suggests that ICM development throughout life allows for fine-tuning of synchronization between cognitive and behavioral networks of the brain (82). Evidence that myelination and white matter structure changes may be a mechanism for brain plasticity can explain how personal and environmental experiences shape the brain (83). However, this also makes ICM vulnerable to disturbances, which may contribute to psychopathology development (28). The rate of myelination differs, with prefrontal cortex ICM continuing development until adulthood (84). Cortical areas are at increased vulnerability at different times, with later-developing areas at greater risk of exposure to

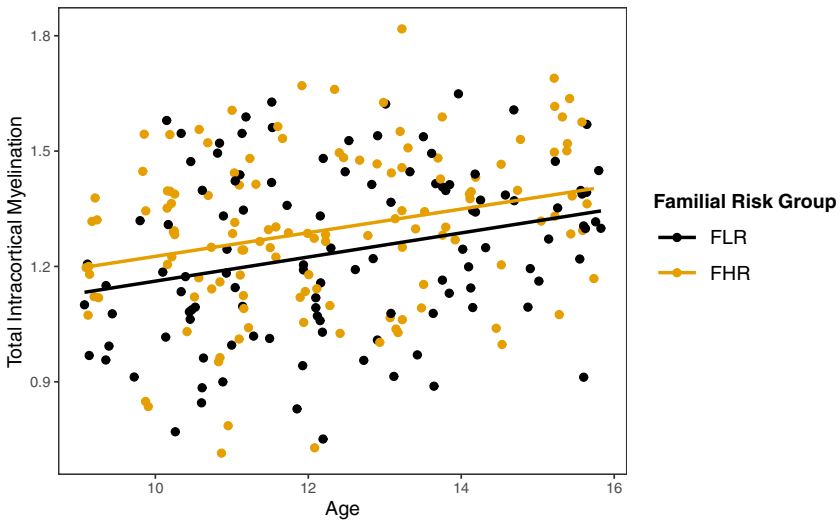

Figure 2. Total intracortical myelin across age with 95% CIs. FHR, familial high risk; FLR, familial low risk.

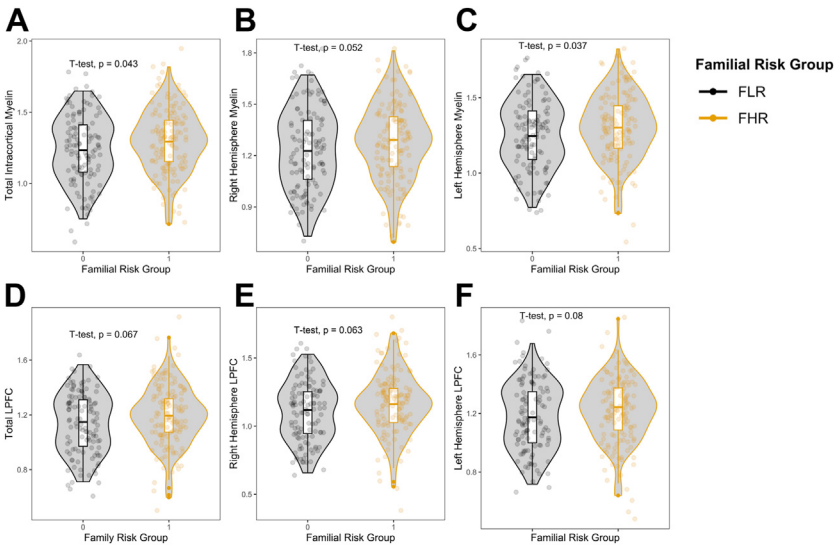

Figure 3. Intracortical myelin in familial high-risk (FHR) and familial low-risk (FLR) youths across the entire cortex **(A)**, right **(B)**, and left **(C)** hemispheres and across the total **(D)**, right **(E)**, and left **(F)** lateral prefrontal cortex (LPFC).

adverse events that may negatively affect ICM development. Thus, it is possible that ICM reduction arises after the onset of the disorder and during psychopathology. This could explain why depression is associated with reduced regional and global ICM in patients, whereas high-risk youths in our study have not been affected (14,24).

Second, depression-related ICM abnormalities may present differently across the developmental trajectory of ICM. Age-related increases in oligodendrocytes are disrupted in people with psychotic and mood disorders, including depression (85). As a result, people with mood disorders may lack the normal ICM inverse U-shaped trajectory (29). Young adults with bipolar disorder have increased myelin compared with control participants at the start of illness. However, the development of ICM slows down with age, creating an overall flatter trajectory. The trend of our results suggests that youths who are at a greater risk for developing depression may have greater ICM than low-risk control participants. Future studies should examine how ICM changes longitudinally from adolescence into adulthood, starting at youth. This could establish whether the developmental trajectory of ICM itself may be a neural marker for depression.

Third, our results may partially reflect the characteristics of a relatively resilient subgroup of the FHR population. We selected the 9 to 16 years age range to encompass youths who had not yet reached the typical age of depression onset (86). However, some studies have shown that high-risk youths may experience earlier onset of psychopathology than control

Table 2. Linear Mixed-Model Results for Family History Group Predicting Global ICM

	Total ICM			Right Hemisphere ICM			Left Hemisphere ICM		
Predictors	Estimates	95% CI	*p*	Estimates	95% CI	*p*	Estimates	95% CI	*p*
Intercept	0.54	0.17 to 0.9	–	0.55	0.18 to 0.93	–	0.52	0.16 to 0.88	–
Group	0.06	−0.01 to 0.12	.052	0.06	−0.00 to 0.12	.057	0.06	0.00 to 0.12	.048[a]
Age	0.03	0.01 to 0.04	<.001[a]	0.03	0.01 to 0.04	<.001[a]	0.03	0.01 to 0.04	<.001[a]
Sex	0.01	−0.03 to 0.1	.279	0.03	−0.04 to 0.10	.345	0.04	−0.02 to 0.11	.224
Int_Vol	0.23	−0.00 to 0.46	.052	0.20	−0.04 to 0.43	.101	0.26	0.03 to 0.48	.025[a]
Random Effects									
σ^2	0.03			0.04			0.03		
τ_{00fid}	0.01			0.01			0.00		
$\tau_{00pscan\_id}$	0.00			0.00			0.01		
N_{pscan_id}	119			119			119		
N_{fid}	81[b]			81[b]			81		

Results controlled for fixed effects of age, sex, and intracranial volume (Int_Vol) and nested random effects of family (fid) and individual (pscan_id). A total of 243 observations each for total, right hemisphere, and left hemisphere intracortical myelin (ICM) analyses. Marginal R^2 is 0.126 for total ICM. Marginal R^2 is 0.122 for the right hemisphere. Marginal R^2 is 0.129 for the left hemisphere.

[a]$p < .05$.

[b]$p < .001$.

Table 3. Linear Mixed-Model Results for Family History Group Predicting LPFC ICM

	Total LPFC ICM			Right LPFC ICM			Left LPFC ICM		
Predictors	Estimates	95% CI	*p*	Estimates	95% CI	*p*	Estimates	95% CI	*p*
Intercept	0.62	0.26 to 0.98		0.68	0.31 to 1.04		0.57	0.21 to 0.94	
Group	0.05	−0.01 to 0.11	.082	0.06	−0.00 to 0.12	.062	0.05	−0.01 to 0.11	.117
Age	0.02	0.01 to 0.04	.001[a]	0.03	0.01 to 0.04	<.001[a]	0.02	0.01 to 0.04	.003[a]
Sex	0.02	−0.04 to 0.09	.463	0.02	−0.05 to 0.09	.551	0.03	−0.04 to 0.09	.393
Int_Vol	0.14	−0.09 to 0.36	.236	0.06	−0.17 to 0.29	.598	0.21	−0.02 to 0.44	.071
Random Effects									
σ^2	0.04			0.04			0.04		
$\tau_{00\ fid}$	0.00			0.01			0.01		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	119			119			119		
N_{fid}	81[b]			81[b]			81[b]		

Results controlled for fixed effects of age, sex, and intracranial volume (Int_Vol) and nested random effects of family (fid) and individual (pscan_id). A total of 243 observations each for total lateral prefrontal cortex (LPFC), right LPFC, and left LPFC analyses. Marginal R^2 is 0.085 for total LPFC. Marginal R^2 is 0.085 for the right LPFC. Marginal R^2 is 0.085 for the left LPFC.

[a] $p < .05$.

[b] $p < .001$.

offspring (36,38). By selecting asymptomatic youths, we might have missed some of the high-risk sample that had already developed depression. As a result, our sample may be indicative of youths who may have protective factors that reduce their likelihood of developing depression. Studies have found differences in the brain between high-risk youths who go on to develop depression and those who do not (87). For example, asymptomatic high-risk youths have shown greater activation to reward stimuli in the middle frontal gyrus, a trend that has not been observed in high-risk youths with depression and control participants (88). This may point to a compensatory mechanism that allows adaptive cognitive reappraisal of stimuli and is a marker of resilience (89,90). Therefore, it is possible that we did not detect reduced ICM because it was not present in youths who, despite being at risk, may be affected by other neurobiological mechanisms that make them resilient. Future studies need to compare ICM alterations found in asymptomatic and symptomatic FHR youths.

One challenge in the pediatric investigation of ICM is that how accurately ICM can be measured across the developmental age range is unknown. The T1/T2 method is reliable and comparable to other measures of myelin content in the adult brain (65). To examine the quality of myelin measurement in our pediatric sample, we investigated the reliability of the T1-w/T2-w method. Reliability classifies the ability of a measurement to provide the same results under similar circumstances (91). Notably, image artifacts such as head motion can increase measurement error, especially in a pediatric sample that may be more sensitive to scanner noise and therefore produce more movement (92). Overall, we found good reliability across our global and local hypothesis, which increases our confidence in the quality of this imaging data.

The results of the current study should be interpreted in the context of several limitations. Although we attempted to track progressive changes in ICM across development, not all our participants had multiple long-term repeats. Therefore, we were limited to a cross-sectional analysis. Second, although our sensitivity analysis controlled for IQ, SES, and BMI, some youths might have been exposed to medications or recreational substances or had other characteristics that were not reported and controlled for in our linear mixed models. Third, our sample may have inadvertently been resilient, and therefore our null results are reflective of possible resilience. Furthermore, it is important to note that depression, even given a familial context, may reflect other adversities such as early-life trauma. Fourth, despite the high reliability shown in our study and in adult populations, the T1-w/T2-w may have lower criterion validity than other imaging techniques (93). However, another study that assessed T1-w/T2-w quality found low interparticipant variability and higher sensitivity to myelin content than other methods, pointing toward it being a valid noninvasive tool for myelin mapping in the living brain (65).

Conclusions

In summary, we did not find a reduction of ICM in youths at high familial risk for depression. However, the trend toward higher myelination that we observed in our main and secondary analyses suggests that the developmental trajectory of ICM in youths at high familial risk for depression should be more closely examined across a broader developmental period.

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ARTICLE INFORMATION

From the Department of Psychiatry, Dalhousie University, Abbie J. Lane Memorial Building Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada (AN, VD, CAH, JC, RU); Nova Scotia Health Authority,

Halifax, Nova Scotia, Canada (AN, JC, RU); and Department of Diagnostic Radiology, Dalhousie University, Halifax, Nova Scotia, Canada (MHS).

Address correspondence to Rudolf Uher, M.D., Ph.D., at uher@dal.ca.

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REFERENCES

1. Haroz EE, Ritchey M, Bass JK, Kohrt BA, Augustinavicius J, Michalopoulos L, *et al.* (2017): How is depression experienced around the world? A systematic review of qualitative literature. Soc Sci Med 183:151–162.
2. Lebel C, Walton M, Letourneau N, Giesbrecht GF, Kaplan BJ, Dewey D (2016): Prepartum and postpartum maternal depressive symptoms are related to children's brain structure in preschool. Biol Psychiatry 80:859–868.
3. Malhi GS, Mann JJ (2018): Depression. Lancet 392:2299–2312.
4. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC (2018): Prevalence of depression in the community from 30 countries between 1994 and 2014. Sci Rep 8:2861.
5. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, *et al.* (2022): Time for united action on depression: A Lancet–World Psychiatric Association Commission. Lancet 399:957–1022.
6. Tozzi L, Garczarek L, Janowitz D, Stein DJ, Wittfeld K, Dobrowolny H, *et al.* (2020): Interactive impact of childhood maltreatment, depression, and age on cortical brain structure: Mega-analytic findings from a large multi-site cohort. Psychol Med 50:1020–1031.
7. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 50:668–681.
8. Schmaal L, Pozzi E, Ho TC, van Velzen LS, Veer IM, Opel N, *et al.* (2020): Enigma MDD: Seven years of global neuroimaging studies of major depression through worldwide data sharing. Transl Psychiatry 10:172.
9. Dai L, Zhou H, Xu X, Zuo Z (2019): Brain structural and functional changes in patients with major depressive disorder: A literature review. PeerJ 7:e8170.
10. Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, *et al.* (2017): Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the Enigma Major Depressive Disorder Working Group. Mol Psychiatry 22:900–909.
11. Tanji J, Hoshi E (2008): Role of the lateral prefrontal cortex in executive behavioral control. Physiol Rev 88:37–57.
12. Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, *et al.* (2019): Cognitive function following a major depressive episode: A systematic review and meta-analysis. Lancet Psychiatry 6:851–861.
13. Friedman NP, Robbins TW (2022): The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology 47:72–89.
14. Lake EMR, Steffler EA, Rowley CD, Sehmbi M, Minuzzi L, Frey BN, Bock NA (2017): Altered intracortical myelin staining in the dorsolateral prefrontal cortex in severe mental illness. Eur Arch Psychiatry Clin Neurosci 267:369–376.
15. Lapate RC, Samaha J, Rokers B, Hamzah H, Postle BR, Davidson RJ (2017): Inhibition of lateral prefrontal cortex produces emotionally biased first impressions: A transcranial magnetic stimulation and electroencephalography study. Psychol Sci 28:942–953.
16. Martin DM, McClintock SM, Forster JJ, Lo TY, Loo CK (2017): Cognitive enhancing effects of RTMS administered to the prefrontal cortex in patients with depression: A systematic review and meta-analysis of individual task effects. Depress Anxiety 34:1029–1039.
17. Sampath D, Sathyanesan M, Newton SS (2017): Cognitive dysfunction in major depression and Alzheimer's disease is associated with hippocampal-prefrontal cortex dysconnectivity. Neuropsychiatr Dis Treat 13:1509–1519.
18. Boda E (2021): Myelin and oligodendrocyte lineage cell dysfunctions: New players in the etiology and treatment of depression and stress-related disorders. Eur J Neurosci 53:281–297.
19. Zhou B, Zhu Z, Ransom BR, Tong X (2021): Oligodendrocyte lineage cells and depression. Mol Psychiatry 26:103–117.
20. van Velzen LS, Kelly S, Isaev D, Aleman A, Aftanas LI, Bauer J, *et al.* (2020): White matter disturbances in major depressive disorder: A coordinated analysis across 20 international cohorts in the Enigma MDD Working Group. Mol Psychiatry 25:1511–1525.
21. Sanjuan PM, Thoma R, Claus ED, Mays N, Caprihan A (2013): Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: A diffusion tensor imaging Study. Psychiatry Res 214:260–268.
22. Rowley CD, Bazin PL, Tardif CL, Sehmbi M, Hashim E, Zaharieva N, *et al.* (2015): Assessing intracortical myelin in the living human brain using myelinated cortical thickness. Front Neurosci 9:396.
23. Yang Y, Cheng Z, Tang H, Jiao H, Sun X, Cui Q, *et al.* (2017): Neonatal maternal separation impairs prefrontal cortical myelination and cognitive functions in rats through activation of Wnt Signaling. Cereb Cortex 27:2871–2884.
24. Regenold WT, Phatak P, Marano CM, Gearhart L, Viens CH, Hisley KC (2007): Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. Psychiatry Res 151:179–188.
25. Toschi N, Passamonti L (2019): Intra-cortical myelin mediates personality differences. J Pers 87:889–902.
26. Liu J, Dietz K, DeLoyht JM, Pedre X, Kelkar D, Kaur J, *et al.* (2012): Impaired adult myelination in the prefrontal cortex of socially isolated mice. Nat Neurosci 15:1621–1623.
27. Makinodan M, Rosen KM, Ito S, Corfas G (2012): A critical period for social experience–dependent oligodendrocyte maturation and myelination. Science 337:1357–1360.
28. Haroutunian V, Katsel P, Roussos P, Davis KL, Altshuler LL, Bartzokis G (2014): Myelination, oligodendrocytes, and serious mental illness. Glia 62:1856–1877.
29. Sehmbi M, Rowley CD, Minuzzi L, Kapczinski F, Kwiecien JM, Bock NA, Frey BN (2019): Age-related deficits in intracortical myelination in young adults with bipolar disorder type I. J Psychiatry Neurosci 44:79–88.
30. van Haren NEM, Setiaman N, Koevoets MGJC, Baalbergen H, Kahn RS, Hillegers MHJ (2020): Brain structure, IQ, and psychopathology in young offspring of patients with schizophrenia or bipolar disorder. Eur Psychiatry 63:e5.
31. Toenders YJ, van Velzen LS, Heideman IZ, Harrison BJ, Davey CG, Schmaal L (2019): Neuroimaging predictors of onset and course of depression in childhood and adolescence: A systematic review of longitudinal studies. Dev Cogn Neurosci 39:100700.
32. Nickson T, Chan SW, Papmeyer M, Romaniuk L, Macdonald A, Stewart T, *et al.* (2016): Prospective longitudinal voxel-based morphometry study of major depressive disorder in young individuals at high familial risk. Psychol Med 46:2351–2361.
33. Nazarova A, Schmidt M, Cookey J, Uher R (2022): Neural markers of familial risk for depression – A systematic review. Dev Cogn Neurosci 58:101161.
34. Huang H, Fan X, Williamson DE, Rao U (2011): White matter changes in healthy adolescents at familial risk for unipolar depression: A diffusion tensor imaging study. Neuropsychopharmacology 36:684–691.
35. Hung Y, Saygin ZM, Biederman J, Hirshfeld-Becker D, Uchida M, Doehrmann O, *et al.* (2017): Impaired frontal-limbic white matter maturation in children at risk for major depression. Cereb Cortex 27:4478–4491.
36. Rasic D, Hajek T, Alda M, Uher R (2014): Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. Schizophr Bull 40:28–38.
37. Rudaz D, Vandeleur CL, Gholam M, Castelao E, Strippoli MF, Marquet P, *et al.* (2021): Psychopathological precursors of the onset of mood disorders in offspring of parents with and without mood disorders: Results of a 13-year prospective cohort high-risk study. J Child Psychol Psychiatry 62:404–413.

38. Uher R, Pavlova B, Radua J, Provenzani U, Najafi S, Fortea L, *et al.* (2023): Transdiagnostic risk of mental disorders in offspring of affected parents: A meta-analysis of Family high-risk and registry studies. World Psychiatry 22:433–448.
39. Boccia M, Piccardi L, Guariglia P (2016): How treatment affects the brain: Meta-analysis evidence of neural substrates underpinning drug therapy and psychotherapy in major depression. Brain Imaging Behav 10:619–627.
40. Eickhoff S, Walters NB, Schleicher A, Kril J, Egan GF, Zilles K, *et al.* (2005): High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Hum Brain Mapp 24:206–215.
41. Patel Y, Shin J, Drakesmith M, Evans J, Pausova Z, Paus T (2020): Virtual histology of multi-modal magnetic resonance imaging of Cerebral Cortex in young men. NeuroImage 218:116968.
42. Heinze K, Shen X, Hawkins E, Harris MA, de Nooij L, McIntosh AM, *et al.* (2020): Aberrant structural covariance networks in youth at high familial risk for mood disorder. Bipolar Disord 22:155–162.
43. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen HU (2002): Parental major depression and the risk of depression and other mental disorders in offspring: A prospective-longitudinal community study. Arch Gen Psychiatry 59:365–374.
44. Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G, Poulton R (2010): How common are common mental disorders? evidence that lifetime prevalence rates are doubled by prospective *versus* retrospective ascertainment. Psychol Med 40:899–909.
45. First MB (2015): Structured clinical interview for the DSM(SCID). In: Cautin RL, Lilienfeld SO, editors. The Encyclopedia of Clinical Psychology. Hoboken, NJ: John Wiley & Sons, 1–6.
46. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, *et al.* (1997): Schedule for affective disorders and schizophrenia for school-age children-present and Lifetime version (K-SADS-PL): Initial reliability and Validity data. J Am Acad Child Adolesc Psychiatry 36: 980–988.
47. Osório FL, Loureiro SR, Hallak JEC, Machado-de-Sousa JP, Ushirohira JM, Baes CVW, *et al.* (2019): Clinical validity and intrarater and test–retest reliability of the Structured Clinical Interview for DSM-5 – Clinician Version (SCID-5-CV). Psychiatry Clin Neurosci 73:754–760.
48. Patterson VC, Pencer A, Pavlova B, Awadia A, MacKenzie LE, Zwicker A, *et al.* (2021): Youth Experience Tracker Instrument: A Self-report measure of developmental antecedents to severe mental illness. Early Interv Psychiatry 15:676–685.
49. Angold A, Costello EJ (2001): The epidemiology of depression in children and adolescents. In: Goodyer IM, editor. The Depressed Child and Adolescent. Cambridge: Cambridge University Press, 143–178.
50. Durdurak BB, Altaweel N, Upthegrove R, Marwaha S (2022): Understanding the development of bipolar disorder and borderline personality disorder in young people: A Meta-review of Systematic Reviews. Psychol Med 52:1–14.
51. Pine DS, Cohen E, Cohen P, Brook J (1999): Adolescent depressive symptoms as predictors of adult depression: Moodiness or mood disorder? Am J Psychiatry 156:133–135.
52. van Lang NDJ, Ferdinand RF, Verhulst FC (2007): Predictors of future depression in early and late adolescence. J Affect Disord 97:137–144.
53. Zwicker A, MacKenzie LE, Drobinin V, Bagher AM, Howes Vallis E, Propper L, *et al.* (2020): Neurodevelopmental and genetic determinants of exposure to adversity among youth at risk for mental illness. J Child Psychol Psychiatry 61:536–544.
54. Carskadon MA, Acebo C (1993): A self-administered rating scale for pubertal development. J Adolesc Health 14:190–195.
55. Marshall WA, Tanner JM (1969): Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303.
56. Marshall WA, Tanner JM (1970): Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13–23.
57. Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, *et al.* (2013): The minimal preprocessing pipelines for the Human Connectome Project. NeuroImage 80:105–124.
58. Fischl B (2012). FreeSurfer. Neuroimage 62:774–781.
59. Fonov V, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL, Brain Development Cooperative Group (2011): Unbiased average age-appropriate atlases for pediatric studies. Neuroimage 54:313–327.
60. Marcus DS, Harms MP, Snyder AZ, Jenkinson M, Wilson JA, Glasser MF, *et al.* (2013): Human Connectome Project Informatics: Quality control, database services, and data visualization. Neuroimage 80:202–219.
61. Klapwijk ET, van de Kamp F, van der Meulen M, Peters S, Wierenga LM (2019): Qoala-T: A supervised-learning tool for quality control of FreeSurfer segmented MRI data. Neuroimage 189:116–129.
62. Glasser MF, Van Essen DC (2011): Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J Neurosci 31:11597–11616.
63. Barkovich AJ (2000): Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 21:1099–1109.
64. Grydeland H, Walhovd KB, Tamnes CK, Westlye LT, Fjell AM (2013): Intracortical myelin links with performance variability across the human lifespan: Results from T1- and T2-weighted MRI myelin mapping and diffusion tensor imaging. J Neurosci 33:18618–18630.
65. Ganzetti M, Wenderoth N, Mantini D (2014): Whole brain myelin mapping using T1- and T2-weighted MR imaging data. Front Hum Neurosci 8:671.
66. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.
67. Petrides M (2005): Lateral prefrontal cortex: Architectonic and functional organization. Philos Trans R Soc Lond B Biol Sci 360:781–795.
68. Cicchetti DV (1994): Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 6:284–290.
69. Damoiseaux JS (2017): Effects of aging on functional and structural brain connectivity. Neuroimage 160:32–40.
70. Kaczkurkin AN, Raznahan A, Satterthwaite TD (2019): Sex differences in the developing brain: Insights from multimodal neuroimaging. Neuropsychopharmacology 44:71–85.
71. Wierenga LM, Bos MGN, van Rossenberg F, Crone EA (2019): Sex effects on development of brain structure and executive functions: Greater variance than mean effects. J Cogn Neurosci 31:730–753.
72. Bathelt J, Scerif G, Nobre AC, Astle DE (2019): Whole-brain white matter organization, intelligence, and educational attainment. Trends Neurosci Educ 15:38–47.
73. Colom R, Karama S, Jung RE, Haier RJ (2010): Human intelligence and brain networks. Dialogues in Clin Neurosci 12:489–501.
74. Dekkers IA, Jansen PR, Lamb HJ (2019): Obesity, brain volume, and white matter microstructure at MRI: A cross-sectional UK Biobank study. Radiology 291:763–771.
75. Hackman DA, Farah MJ (2009): Socioeconomic status and the developing brain. Trends Cogn Sci 13:65–73.
76. McDermott CL, Seidlitz J, Nadig A, Liu S, Clasen LS, Blumenthal JD, *et al.* (2019): Longitudinally mapping childhood socioeconomic status associations with cortical and subcortical morphology. J Neurosci 39:1365–1373.
77. Shen X, MacSweeney N, Chan SWY, Barbu MC, Adams MJ, Lawrie SM, *et al.* (2021): Brain structural associations with depression in a large early adolescent sample (the ABCD Study®). EClinicalmedicine 42:101204.
78. Kaczkurkin AN, Sotiras A, Baller EB, Barzilay R, Calkins ME, Chand GB, *et al.* (2020): Neurostructural heterogeneity in youths with internalizing symptoms. Biol Psychiatry 87:473–482.
79. Sacchet MD, Gotlib IH (2017): Myelination of the brain in major depressive disorder: An in vivo quantitative magnetic resonance imaging study. Sci Rep 7:2200.
80. Hayashi Y, Nihonmatsu-Kikuchi N, Yu X, Ishimoto K, Hisanaga SI, Tatebayashi Y (2011): A novel, Rapid, quantitative cell-counting method reveals oligodendroglial reduction in the frontopolar cortex in major depressive disorder. Mol Psychiatry 16:1155–1158.

81. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI (2004): Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: A study from the Stanley Neuropathology Consortium. Schizophr Res 67:269–275.
82. Chorghay Z, Káradóttir RT, Ruthazer ES (2018): White matter plasticity keeps the brain in tune: Axons conduct while Glia Wrap. Front Cell Neurosci 12:428.
83. Kaller MS, Lazari A, Blanco-Duque C, Sampaio-Baptista C, Johansen-Berg H (2017): Myelin plasticity and behaviour-Connecting the dots. Curr Opin Neurobiol 47:86–92.
84. Nickel M, Gu C (2018): Regulation of central nervous system myelination in higher brain functions. Neural Plast 2018:6436453.
85. Vostrikov V, Uranova N (2011): Age-related increase in the number of oligodendrocytes is dysregulated in schizophrenia and mood disorders. Schizophr Res Treatment 2011:174689.
86. McGrath JJ, Al-Hamzawi A, Alonso J, Altwaijri Y, Andrade LH, Bromet EJ, *et al.* (2023): Age of onset and cumulative risk of mental disorders: A cross-national analysis of population surveys from 29 countries. Lancet Psychiatry 10:668–681.
87. Nimarko AF, Garrett AS, Carlson GA, Singh MK (2019): Neural correlates of emotion processing predict resilience in youth at familial risk for mood disorders. Dev Psychopathol 31:1037–1052.
88. Fischer AS, Camacho MC, Ho TC, Whitfield-Gabrieli S, Gotlib IH (2018): Neural markers of resilience in adolescent females at familial risk for major depressive disorder. JAMA Psychiatry 75: 493–502.
89. Bermpohl F, Walter M, Sajonz B, Lücke C, Hägele C, Sterzer P, *et al.* (2009): Attentional modulation of emotional stimulus processing in patients with major depression—Alterations in prefrontal cortical regions. Neurosci Lett 463:108–113.
90. Erk S, Mikschl A, Stier S, Ciaramidaro A, Gapp V, Weber B, Walter H (2010): Acute and sustained effects of cognitive emotion regulation in major depression. J Neurosci 30:15726–15734.
91. Drobinin V, Van Gestel H, Helmick CA, Schmidt MH, Bowen CV, Uher R (2020): Reliability of multimodal MRI brain measures in youth at risk for mental illness. Brain Behav 10:e01609.
92. Ducharme S, Albaugh MD, Nguyen TV, Hudziak JJ, Mateos-Pérez JM, Labbe A, *et al.* (2016): Trajectories of cortical thickness maturation in normal brain development — The importance of quality control procedures. Neuroimage 125:267–279.
93. Arshad M, Stanley JA, Raz N (2017): Test–retest reliability and concurrent validity of in vivo myelin content indices: Myelin water fraction and calibrated T1 w/T2 w image ratio. Hum Brain Mapp 38:1780–1790.