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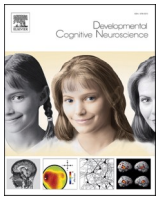

Adolescents at risk for depression show increased white matter microstructure with age across diffuse areas of the brain

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ABSTRACT

Maternal history of depression is a strong predictor of depression in offspring and linked to structural and functional alterations in the developing brain. However, very little work has examined differences in white matter in adolescents at familial risk for depression. In a sample aged 9–14 (n = 117), we used tract-based spatial statistics (TBSS) to examine differences in white matter microstructure between adolescents with (n = 42) and without (n = 75) maternal history of depression. Microstructure was indexed using fractional anisotropy (FA). Threshold-free cluster enhancement was applied and cluster maps were thresholded at whole-brain family-wise error < .05. There was no significant main effect of risk status on FA. However, there was a significant interaction between risk status and age, such that large and diffuse portions of the white matter skeleton showed relatively increased FA with age for youth with a maternal history of depression compared to those without. Most tracts identified by the interaction were robust to controlling for sex, youth internalizing, in-scanner motion, neighborhood SES, and intra-cranial volume, evidence that maternal depression is a unique predictor of white matter alterations in youth. Widespread increases in FA with age may correspond to a global pattern of accelerated brain maturation in youth at risk for depression.

1. Introduction

Depression is one of the most debilitating psychological disorders, yet relatively little is known about the neuro-structural mechanisms that may contribute to disorder onset. Diffusion weighted imaging has permitted examination of how depressive phenotypes are associated with divergent white matter architecture, and broad-ranging alterations in white matter microstructure have been observed in both depressed adults and depressed adolescents. However, comparisons of youth with and without depression does not address whether observed differences in white matter precede depression onset or are correlates of the disorder. To date, relatively little is known about white matter deviations that may predispose youth to depression. A better understanding of the white matter alterations that may underlie depression onset is needed to inform mechanistic models of depression etiology. Early/pre- adolescence is a critical window for examining potential white matter mechanisms underlying depression onset, as this developmental period is prior to the sharp increases in depression symptoms seen in mid-adolescence and the peak onset for depressive disorders seen in late adolescence (Solmi et al., 2022). Thus, we examined differences in white matter microstructure that may be associated with depression onset by investigating youth with and without a high-risk for depression.

White matter microstructure is a broad term referring to the myelination, axon density, fiber coherence, etc. of white matter tracts, and metrics reflecting these microstructural properties can be extracted from diffusion weighted imaging. The most commonly reported diffusion metric is fractional anisotropy (FA), a measure that represents the directionality of water molecule diffusion in tissue, with higher values found in white matter (compared to grey matter and cerebrospinal fluid) where water diffusion is directionally constrained along axons. The FA metric is influenced by a number of factors (Beaulieu, 2002; Curran et al., 2016); however, greater FA is generally interpreted as representing greater structural coherence of white matter tracts (but see Figley et al., 2022 for a more thorough discussion). Across development, FA shows normative increases across childhood and adolescence (Lebel and Beaulieu, 2011; see Lebel et al., 2017 for review), peaking in late adolescence through early adulthood and decreasing through old age (Lebel et al., 2012; Schilling et al., 2022). While FA was our primary

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dependent variable of interest, we also examined mean diffusivity (MD), another common diffusivity metric that represents overall diffusion unconstraint in tissue and is generally inversely related to FA (Lebel et al., 2017; Schilling et al., 2022). Across adolescence, lower diffusivity (higher FA and lower MD) generally corresponds to increasing structural coherence of white matter seen in neural maturation.

Despite a growing number of studies examining the relationship between white matter and depression, relatively little is known about how alterations in white matter microstructure might be related to the etiology of depression. Across different developmental periods, depression has been associated with relatively reduced FA across a range of white matter tracts, including the corpus callosum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps major, and anterior limb of the internal capsule (ALIC), with many of these tracts showing alterations across both human and animal studies of depression (for review, see Abraham et al., 2022). A large-scale study by van Velzen et al. (2020) examining 1305 depressed adults and 1602 healthy controls found depression was associated with global reductions in FA.

In children and adolescents with depression, findings largely mirror the associations between depression and reduced FA found in studies of adults (e.g., LeWinn et al., 2014; Vilgis et al., 2017; Vulser et al., 2018). Using the ABCD dataset, Shen et al. (2021) found associations between depression in youth (aged 9–11) and global reductions in FA, with significant differences between healthy control youth ($n > 6000$) and those with both youth-reported ($n = 180$) and caregiver-reported ($n = 194$) youth depression diagnosis. Further, Shen and colleagues found an association between global reductions in FA and caregiver-reported depressive symptoms in youth. However, another relatively large-scale study conducted by van Velzen et al. (2020), that drew upon a much wider age-range of adolescents (aged 12–21), did not find differences in FA between those with depression ($n = 372$) and healthy controls ($n = 290$); however, given the sample's heterogeneity in age, it is possible this study was underpowered to find a main effect.

While the pattern of reduced FA in depression is relatively consistent across studies, comparisons of those with and without depression does not address whether reduced FA precedes depression or is a correlate of the disorder. To examine white matter deviations associated with the risk for depression, high-risk study designs are needed. In infants and children exposed to maternal depression in-utero, findings are mixed. Some studies report reduced white matter coherence (Dean et al., 2018; El Marroun et al., 2018; Graham et al., 2020; Hay et al., 2020; Posner et al., 2016; Rifkin-Graboi et al., 2013), other studies have found no differences in white matter (Jha et al., 2016; Roos et al., 2022), and yet other studies found increased white matter coherence in young children exposed to maternal depression in-utero (Lebel et al., 2016; Roos et al., 2022). Thus, it remains unclear how exposure to depression in-utero may affect white matter.

To interrogate processes specific to risk for depression, high-risk study designs with samples of pre- / early- adolescents offer two primary advantages. First, as those with a family history of depression have a three-times higher risk of developing depression (Weissman et al., 2016), studies utilizing samples with a familial history of depression offer the opportunity to examine vulnerability factors in a population at known risk for experiencing depression. Second, studying high-risk offspring before the peak age of risk provides necessary temporal sequencing to identify risk factors before disorder onset. Depression has a low incidence before puberty, but prevalence begins to rise in early adolescence (Maughan et al., 2012), with first symptoms showing a peak onset of 15.5 years and depressive disorder showing a peak onset of 19.5 years (Solmi et al., 2022). Thus, investigating the pre- / early- adolescent developmental period offers an essential window for examining processes specific to risk for depression, before the critical onset period for depression.

To date, there are few studies of youth at high familial risk and white matter microstructure, and those studies have shown mixed results. Hung et al. (2017) compared youth ages 8–14 with ($n = 20$) and without ($n = 20$) parental history of depression and did not find a main effect of parental history of depression on FA, but found an interaction whereby FA was inversely related to age for the high-risk youth in frontal-limbic tracts. In an older sample of 66 adolescents aged 12–16, Jones et al. (2019) found that greater aggregation of family history of psychopathology (including depression, anxiety, substance use, and anti-social personality disorder) was associated with reduced FA at baseline but increasing FA with age across several tracts in dorsal regions, such that by age 18, there was no association between risk status and age in these regions. The same study also found that at-risk youth showed persistently lower FA across the study period in the posterior limb of the internal capsule. Examining adolescents at risk for developing depression ($n = 18$) and control adolescents ($n = 13$) ranging in age from 12 to 20, Huang et al., (2012) found that a parental history of depression was associated with reduced FA across a number of tracts. In a sample ranging in age from 12 to 25, Shakeel et al. (2021) examined healthy controls ($n = 36$), those with diagnosed depression ($n = 70$), those at high-risk due to familial history of serious mental illness ($n = 30$), and other groups with sub-syndrome levels of symptom severity (combined $n = 120$). They found lower FA only in the depressed group, suggesting that reductions in microstructure coherence occurred following depression onset, rather than being present in those at high-risk or pre-morbid states. Across studies of high-risk youth, most have relied on small samples and/or wide age ranges, have produced mixed findings regarding the directionality of associations between risk status and FA, and have also shown associations across discrepant white matter tracts. Thus, further research is needed to define patterns in white matter microstructure in youth that may be associated with a predisposition to depression.

We examined differences in white matter microstructure between adolescents at high- and low- risk for depression. As maternal history of depression is among the strongest predictors of depression in offspring (Goodman et al., 2011; Klein et al., 2005), high-risk status was operationalized by maternal lifetime history of depression. Our sample was comprised of adolescents aged 9–14 years old, a developmental period prior to the peak age of depression onset. Given that previous studies of risk have produced mixed results of in terms of the directionality of effects and specific tracts identified, we choose to use tract-based spatial statistics (TBSS; Smith et al., 2006), a whole-brain, data-driven approach to examine FA differences within the white matter skeleton between the high- and low- risk groups. Because white matter undergoes relatively rapid change during the adolescence (Lebel and Beaulieu, 2011; Lebel et al., 2012), we examined whether associations between FA and age and FA and puberty (Herting et al., 2012; Herting and Sowell, 2017) differed by offspring risk status. Additionally, to isolate effects in white matter microstructure that were associated with risk for depression rather than effects related to depression itself, we examined whether effects of offspring risk status persisted when controlling for youth internalizing symptoms. As the TBSS method offers hypothesis-free, whole-brain analysis, we outlined two primary aims for this study, without a priori hypotheses regarding the direction of effects. First, we examined the main effect of white matter microstructure in youth with a high- versus low- risk for depression. Second, we examined whether the two risk-status groups showed differences in age-related increases in white matter microstructure. Finally, to test the robustness of findings, we conducted sensitivity analyses including child internalizing, socio-economic status, in-scanner motion, and intracranial volume as covariates.

2. Method

2.1. Participants and samples

Participants were drawn from the Temple Adolescent Development Study, a prospective longitudinal study of reward function development. This study was approved by the Institutional Review Board at Temple

University. English-speaking children aged 9–14 years old at baseline who had at least one biological parent living in the home were invited to participate. Exclusion criteria included child or parental history of bipolar disorder or psychotic spectrum disorder and child diagnosis of serious neurological illness, head injury, learning disabilities, or developmental disabilities, including autism spectrum disorders. Youth were also excluded if they had a history of neurological or cardiovascular diseases that affected central nervous system blood flow or if they were taking any psychotropic medications at the time of recruitment or scan. General intellectual function was assessed at baseline, and participants with an IQ falling two standard deviations or more below the mean were excluded from participation (Kaufman Brief Intelligence Test – Second Edition [KBIT-2] Full Scale IQ < 70; Kaufman and Kaufman, 2004). Finally, youth who could not participate in imaging assessments were not eligible for inclusion (e.g., individuals with non-removable metallic implants, braces, or with conditions such as uncorrectable vision or claustrophobia that would make completing MRI assessments unsafe). Parents provided written informed consent for their child to participate in the study, and all youths provided written assent.

One hundred and fifty-seven children completed a diffusion-weighted scan at study baseline, and these data were included in the preprocessing pipeline prior to quality control exclusions. Of the 119 child participants whose diffusion weighted data passed quality control, maternal history of depression data was available for 117 child participants, comprising the full sample (girls = 59.8%; minorities = 57% of the 68% reporting race; mean age = 11.76, std dev of age = 1.5). Of these 117 participants, data on child internalizing symptoms was available for 91 participants, comprising the CBCL subsample (girls = 56.0%; minorities = 59% of the 69% reporting race; mean age = 11.7, std dev of age = 1.5). Child age reflects the youth's age at the time of scanning.

2.2. Clinical and other psychosocial covariates

2.2.1. Structured clinical interview for DSM disorders (SCID)

Mothers completed the Structured Clinical Interview for DSM-V (SCID-V-RV; First et al., 2015), to assess clinical diagnoses of various mental disorders. Maternal history of depression was operationalized as lifetime history of major depression or persistent depression. In primary analyses, maternal history of depression was present in 35.9% (n = 42) of mothers.

2.2.2. Child behavior checklist (CBCL)

Mothers completed the Child Behavior Checklist (CBCL; Achenbach, 2009) to provide dimensional assessments of their child's current behavioral and emotional problems. The CBCL contains 119 items on problem behaviors in childhood scored as 0 = Not True, 1 = Somewhat or Sometimes True, and 2 = Very True or Often True. To quantify the child's own internalizing symptoms, we used the internalizing scale, including 32 items reflecting anxiety and depression symptoms (see Supplemental Method for details regarding computation of the internalizing variable). CBCL data was available for 91 subjects.

2.2.3. Pubertal development scale

Youth pubertal development was assessed using the Pubertal Development Scale (PDS; Petersen et al., 1988). This measure has been extensively used in studies of pubertal development and validated against Tanner stages (Coleman and Coleman, 2002). The PDS assesses pubertal development across adrenal and gonadal hormone systems. In this study, we relied on an overall index of pubertal development across both systems, developed to correspond to the Tanner stages (Shirtcliff et al., 2009; code for computing the overall puberty index available from these authors). Pubertal data was available for 91 subjects. Pubertal stage scores were used in lieu of age in supplemental analyses.

2.2.4. Neighborhood SES

SES data is available at the census tract level through the American Community Survey (ACS; United States Census Bureau, 2013–2017). Census tract-level SES variables were linked to individual participants via geocoding of individual household address. Participant address was collected during an initial phone screen. Using data from the 2013–2017 ACS Five Year Estimates (United States Census Bureau, 2013–2017), we computed a neighborhood SES composite variable of the average z-scores of the percent of individuals within the census tract who (1) had high school degree or greater, (2) had a bachelor's degree or greater, (3) were receiving food stamps (reverse coded), (4) were below the poverty line (reverse coded); the percent of families within the census tract who (5) were below the poverty line (reverse coded); and the (6) median and (7) mean income within the census tract.

2.3. Diffusion weighted imaging

2.3.1. Diffusion image acquisition

Diffusion imaging data were acquired using single-shot pulsed gradient spin-echo echo-planar imaging sequence on a 3 T Philips Ingenia scanner. The following acquisition parameters were used: flip angle = 90°; TR = 6.4 s; TE = 1.2 s; FOV = 240 mm x 240 mm x 121; matrix = 96 × 96; voxel size = 2.5 mm × 2.5 mm× 2.75 mm; 44 interleaved axial slices. Acquired volumes included 19 volumes without diffusion weighting (b = 0 s/mm^2) and 30 volumes with diffusion gradients (b = 800 s/mm^2) applied in 30 directions. A SENSE factor of 2.3 was used to speed data acquisition.

2.3.2. Preprocessing

The imaging data were converted to NIfTI format and preprocessed using the MRtrix3 package (Tournier et al., 2019) and the FMRIB Software Library (FSL v6.0.2; Smith et al., 2004). MRtrix3 was used to extract and average the b0 volumes and non-brain tissue was removed from the averaged b0 image using FSL's automated brain extraction tool (BET; Smith, 2002). Several corrections were applied to the imaging data. First, denoising and degibbing corrections were applied using MRtrix3. Next, the FMRIB Diffusion Toolbox's *eddy* tool was used to correct for eddy current-induced distortions and in-scanner head movements, with registration of the diffusion-weighted images to the first b0 volume and adjustment of the gradient table to account for registration (Andersson and Sotiropoulos, 2016). Within eddy correction, outlier detection and replacement of outlier volumes was performed (Andersson et al., 2016). Following eddy correction, images were screened for intensity artifacts, motion, and other quality-related issues by several trained analysts. Subjects with greater than five problematic volumes and/or truncation of the white matter skeleton from the field of view were excluded from further analyses. Consensus across multiple analysts was sought when there was uncertainty about data-quality. In total, 38 subjects were excluded, leaving 119 subjects for further analyses. Using FSL's *dtifit* program, a diffusion tensor was fit at each voxel to generate the principal eigenvectors and fractional anisotropy (FA) maps and mean diffusivity (MD) maps for each subject in native anatomical space.

2.3.3. Tract-based spatial statistics (TBSS)

Individual subject FA maps were fed into FSL's Tract-Based Spatial Statistics (TBSS) tool (Smith et al., 2006). The TBSS procedure included nonlinear registration of all FA images to the 1×1x1mm standard FMRIB58_FA template (which is in MNI152 1-mm standard space), creation of a mean FA map averaged across all subjects, and creation of a mean white matter skeleton, representing the center of major white matter fibers, common to all subjects. The mean skeleton image was thresholded at .2 to suppress low mean FA values and/or high variability in FA across subjects. Next, each subject's FA data was projected onto the mean FA skeleton, to produce an FA skeleton map for each subject where the mean FA skeleton voxels were replaced with FA values from

the local center of the subject's nearest relevant tract. Mean whole-brain FA was extracted from each subject and compared between the high- and low- risk groups.

2.3.4. Voxelwise GLMs and contrasts across skeletonised FA data

Using FSL's *randomise* tool for nonparametric permutation inference (Winkler et al., 2014), a series of general linear models (GLMs) were estimated to test for voxel-level effects within the 4D skeletonized FA data (see Table 1 for summary of all GLMs and contrasts). In the full sample (n = 117), three GLMs were estimated. Within model one, we examined the main effects of family risk status (MatHxDepr n = 42, NoMatHxDepr =75), age, and sex assigned at birth. Each effect was considered as a positive and negative association, controlling for the other variables. Model 1b was estimated with the same set of predictors but with the puberty index replacing age. Within model 2, we examined the interaction between offspring risk-status and age, with sex included as a covariate. Model 2b was estimated with the same set of predictors but with the puberty index replacing age, such that model 2b examined the interaction of offspring risk-status and puberty. Within model 3, we examined the interaction between family risk status and sex, with age included as a covariate. While FA was our primary dependent variable of interest, models 1, 2, and 3 were also estimated with mean diffusivity (MD) as the dependent variable as a supplementary analysis. In an exploratory analysis within the full sample, maternal history of depression was coded in terms of course specifiers, with mothers who had not experienced depression (n = 75), mothers who had only experienced a single episode of any type of depressive disorder (n = 16), and mothers who met criteria for either chronic or recurrent depression (n = 26).

Additional models were estimated within the CBCL subsample (n = 91). First, specific contrasts that produced significant effects in the full sample were re-estimated in the CBCL subsample to determine whether effects survived. Model 4 examined main effects of child internalizing, controlling for age, sex, and family risk status. Finally, models 5 and 6 examined the sensitivity of the risk-status by age interaction results. Specifically, model 5 examined the interaction between offspring risk-status and age, with sex and child internalizing included as a covariates; and model 6 further added neighborhood SES, mean relative in-scanner motion, and intra-cranial volume to the covariates included in model 5 (see below for a description of how neuroimaging covariates were calculated).

In all models, threshold-free cluster enhancement (TFCE; Smith and Nichols, 2009) was applied to detect significant clusters, accounting for both the height and spatial extent of signal. Voxel-wise p-values were calculated and corrected for whole-brain family-wise error (FWE) with permutation testing (5000 permutations). The resulting TFCE-corrected cluster maps were thresholded at a FWE < .05, and a binarized mask was created for each set of supra-thresholded results.

2.3.5. Identifying tracts and presentation of results

FSL's *atlasquerry* command was used with the John Hopkins University ICBM-DTI-81 Atlas (Mori et al., 2008) to identify tracts within each supra-thresholded results mask. For follow-up analyses, subject-level FA values were extracted from masks using FSL's *fslstats* command and plotted using ggplot2 in R (Wickham, 2016). For improved visualization, FSL's *tbss_fill* command was applied for improved visualization of overlaid results (Fig. 1 in orange).

2.3.6. Complementary tract-based analyses

While our primary analysis approach was whole-brain, as a complementary set of analyses, FA was also extracted from ROIs generated from the 50 tracts and regions available in the JHU ICBM-DTI-81 atlas (Mori et al., 2008). See the Supplemental for additional details of the method used and a summary of the results.

Table 1
Specific general linear models and contrasts estimated to test for voxel-level effects within the 4D skeletonized FA data. All GLMs tested for both positive (greater FA) and negative (reduced FA) effects. As the extracted clusters were not very informative (see Supplemental Table 2), voxel-wise p-values were calculated across the full set of tracts and regions resulting from each analysis and were corrected for whole-brain family-wise error (FWE) with permutation testing (5000 permutations).

Specific Contrasts in Full Sample (n = 117)	Interpretation	p-value
GLM 1: Main Effects of Offspring Risk Status, Age, Sex, Controlling Other Variables		
FA (pos) ~ offspring risk status	more FA MatHxDepress > NoMatHxDepress	.561
FA (neg) ~ offspring risk status	more FA NoMatHxDepress > MatHxDepress	.259
*FA (pos) ~ age	increasing FA with age	< .001
FA (neg) ~ age	decreasing FA with age	.803
FA (pos) ~ sex	more FA girls > boys	.100
FA (neg) ~ sex	more FA boys > girls	.865
GLM 2: Interaction of Offspring Risk Status and Age, Controlling Sex		
*FA (pos) ~ offspring risk status x age	increased FA (greater slope) with age for MatHxDepress > NoMatHxDepress	.003
FA (neg) ~ offspring risk status x age	increased FA (greater slope) with age for NoMatHxDepress > MatHxDepress	.986
GLM 3: Interaction of Offspring Risk Status and Sex, Controlling Age		
FA (pos) ~ offspring risk status x sex	increased FA (greater slope) for girls > boys for MatHxDepress > NoMatHxDepress	.805
FA (neg) ~ offspring risk status x sex	increased FA (greater slope) for girls > boys for NoMatHxDepress > MatHxDepress	.126
in CBCL Subsample (n = 91)		
Survival of Significant Results from Full Sample		
*FA (pos) ~ age	increasing FA with age	< .001
*FA (pos) ~ offspring risk status x age	increased FA (greater slope) with age for MatHxDepress > NoMatHxDepress	.009
GLM 4: Main Effects Child Internalizing, Controlling Offspring Risk Status, Age, Sex		
FA (pos) ~ youth internalizing	increasing FA with greater internalizing	.105
FA (neg) ~ youth internalizing	decreasing FA with greater internalizing	.888
Sensitivity Analyses: Replication of Interaction Effect (GLM 2), Adding Covariates		
*FA (pos) ~ offspring risk status x age, controlling sex + youth internalizing	effect of increased FA with age for MatHxDepress > NoMatHxDepress is independent of covariates	.012
*FA (pos) ~ offspring risk status x age, controlling sex + youth internalizing + SES + motion + ICV		.007

* Indicates a significant contrast, corrected for whole-brain family-wise error

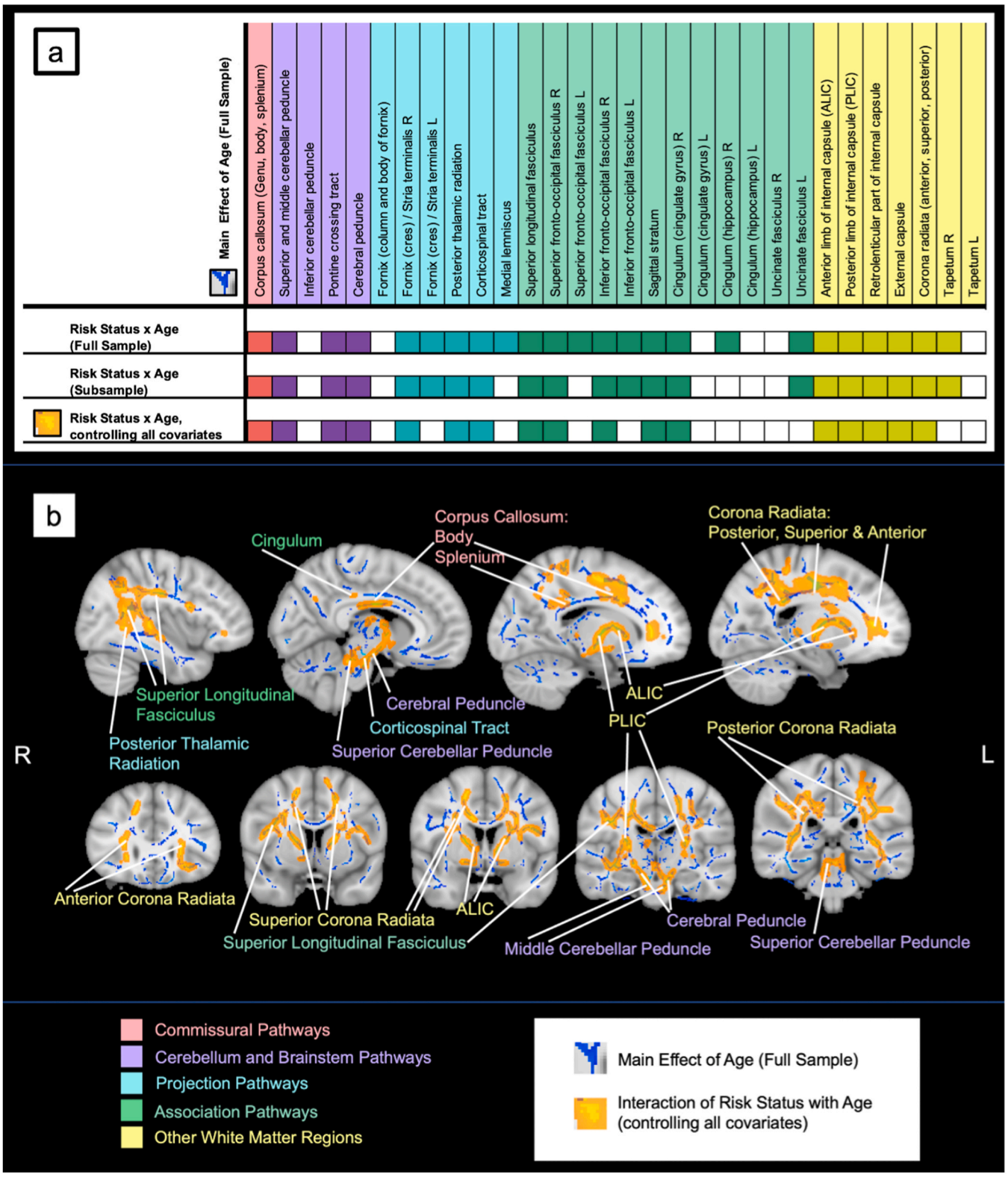

Fig. 1. Tracts and regions showing increased FA in main effect and interaction analyses. The main effect of age identified diffuse tracts and regions in which FA was increased with age, as listed at the top of the chart (1a); white matter results are grouped according to pathway type (commissural, cerebellum and brainstem, projection, and association) or other white matter region, and are visualized in the brain image (1b) in blue. Many of these same tracts and regions were also identified by different interaction analyses (full sample, subsample, and controlling all covariates) and are indexed at the bottom of the chart (1a). Tracts and regions identified by the interaction of risk-status and age when controlling all covariates are visualized in the brain image (1b) in orange; these tracts and regions showed greater increases with age for high-risk youth compared to low-risk youth. While both main effect and interaction analyses were conducted within the narrow white matter skeleton, only the interaction results (in orange) have been inflated and are overlaid for better visualization. In the chart above, results for tracts and regions are bilateral unless otherwise noted.

2.4. Additional neuroimaging covariates

2.4.1. Mean relative in-scanner motion

Output from FSL's eddy correction included motion parameters for the root-mean square of voxel displacement, relative to those of the previous volume. These volume-level parameters were averaged within subject to create a *Mean Relative Motion* covariate.

2.4.2. Intra-cranial volume (ICV)

Gross brain volume varies with height and biological sex so it is important to control for ICV in structural brain measurements. High-resolution T1-weighted structural images were acquired in the axial plane using an MPRAGE 3D sequence with the following acquisition parameters: flip angle = 9°; TR = 7.1 s; TE = 3.2 s; FOV = 250 mm x 250 mm x 135 mm; matrix = 512 × 512; voxel size = .49 mm x .49 mm x 1 mm; 135 axial slices. Data were processed with FreeSurfer 6.0. The processing pipeline involved motion correction (Reuter et al., 2010), skull stripping (Ségonne et al., 2004), Talairach transformation, segmentation of subcortical grey and white matter (Fischl et al., 2002), surface tessellation, and determination of the grey matter/white matter and grey matter/cerebral-spinal fluid boundaries based on image intensity gradients (Dale et al., 1999). ICV was computed using the procedure described by Buckner et al. (2004) and this variable was used as a covariate.

3. Results

3.1. Demographic and covariate summary statistics

Summary statistics for participant demographics and other covariates are presented in Table 2. High-risk and low-risk youth did not significantly differ on age, pubertal stage scores, percentages of racial minorities, neighborhood SES, mean in-scanner motion, intra-cranial volume, or whole-brain FA (see Table 2). There was a significantly greater proportion of girls in the high-risk than low-risk group within both the full sample and CBCL subsample. Finally, the high-risk youth had significantly higher levels of internalizing problems than the low-risk youth.

3.2. Voxelwise GLMs and contrasts across skeletonised FA data

Table 1 provides a summary of the specific GLMs and contrasts estimated and interpretation of effects, and Supplemental Table 2 provides the maximum t-stat and peak coordinates for individual clusters identified for each significant contrast. Named tracts and regions identified by primary analyses of interest are indexed in Fig. 1a.

From model 1, the only significant effect was the positive association between FA and age (p_{FWE} <.001 in full sample), and this effect survived in the subsample (p_{FWE} <.001). As anticipated, FA increased with age (see Fig. 1a, top of chart; Fig. 1b, results in blue). There were no significant associations between FA and sex assigned at birth. There were no main effects of offspring risk status in either the positive or negative direction (all p_{FWE} >=.25). Model 1b, where pubertal stage replaced age as a predictor, did not find a main effect of pubertal stage, but did find a significant main effect of sex, such that girls had higher FA than boys when pubertal stage was accounted for (p_{FWE} =.029; see Supplemental Table 3).

Model 2 that examined the interactions between offspring risk status and sex did not produce any significant results. From model 3, which examined the interaction between offspring risk status and age, only the positive association between risk status and age was significant, such that the diffuse increases in FA seen with age were greater for those in the high-risk group, compared to low-risk group. This interaction effect was significant in both the full sample (p_{FWE} =.003) and the subsample (p_{FWE} =.009). Moreover, this interaction remained significant for many of the identified tracts and regions when controlling for all covariates including child internalizing, neighborhood SES, mean relative in-scanner motion, and intra-cranial volume (all p_{FWE} <=.01). Model 2b, where pubertal stage replaced age as a predictor, did not find a significant interaction of between offspring risk status and pubertal stage (see Supplemental Table 3). See Fig. 1a (bottom rows of chart) for the named tracks and regions identified by the interaction when estimated in different samples and with different covariates included. The tracts and regions identified by the interaction when all covariates were included

Table 2
Participant demographic and covariate summary statistics.

	Full Sample					CBCL Subsample				
	MatHxDepr (n = 42) Mean (SD) or Frequency	NoMatHxDepr (n = 75)	X^2	t-stat	p-value	MatHxDepr (n = 31) Mean (SD) or Frequency	NoMatHxDepr (n = 60)	X^2	t-stat	p-value
Age	11.31 (1.49)	11.84 (1.48)		-1.83	.070	11.40 (1.61)	11.86 (1.48)		-1.35	.181
Pubertal Stage	2.85 (.59) (of 79% reporting)	3.00 (.62) (of 77% reporting)		-1.11	.269	2.84 (.57) (of 94% reporting)	2.97 (.62) (of 85% reporting)		-0.95	.343
Sex Assigned at Birth (Female)	76%	51%	6.27 *		.012	74%	47%	5.22 *		.022
Racial Minority	62% (of 69% reporting)	54% (of 67% reporting)	.21		.644	60% (of 65% reporting)	58% (of 72% reporting)	0.00		1
CBCL Internalizing	*only available in subsample*					38.72 (6.72)	35.19 (3.97)		3.15**	.002
Neighborhood SES Composite	.00 (.85)	.00 (.95)		.02	.983	.08 (.87)	-.03 (.95)		.55	.587
Mean Relative In-Scanner Motion	.38 (.27)	.38 (.30)		.03	.977	.39 (.27)	.39 (.33)		-.05	.958
Intra-Cranial Volume in mm^3	1494,434 (104,813)	1504,221 (114,128)		-.46	.648	1517,243 (100,639)	1511,849 (103,235)		.24	.812
Whole-Brain FA	.42 (.02)	42 (.01)		-.50		.42 (.02)	.42 (.02)		-.38	.705

* Indicates p < .05
** Indicates p < .01

in the model are shown in Fig. 1b (results in orange). See Fig. 2 for a visualization of the interaction effect.

There were no main effects (positive or negative effects) of either sex assigned at birth or child internalizing symptoms, and no analyses produced a significant effect whereby any variable was associated with reduced FA (all p_{FWE} >=.1). When models 1, 2, and 3 were estimated with mean diffusivity as the dependent variable, results were in line with (inverse to) the FA-based models, given that mean diffusivity is generally negatively correlated with FA (see Supplemental Table 4). The omnibus test examining the effect of the course specifiers of maternal history of depression (comparing those with no maternal depression, single-episode maternal depression, and chronic or recurrent maternal depression) was not significant (p_{FWE} =.539), possibly due to the small size of the single-episode (n = 16) versus chronic/recurrent (n = 26) groups.

3.3. Complementary tract-based analyses

Results of the tract-based analyses are presented in Supplementary Table 5 and Supplementary Figure 1. As show in Supplementary Figure 1, differences between the high- and low- risk groups were generally less apparent when FA was extracted from tract-based ROIs and averaged across the aggregate of the tract-based ROI.

4. Discussion

Our overarching aim was to characterize patterns in white matter microstructure that may be associated with a predisposition for depression, before the critical period for depression onset, by comparing FA in youth with a high- versus low-risk for depression as indexed by a maternal history of depression. Consistent with known patterns of brain maturation during adolescence, FA was positively associated with age across diffuse areas of the brain (Lebel and Beaulieu, 2011; Lebel et al., 2012). Importantly, we found a significant interaction whereby those in the high-risk, compared to low-risk, group showed a steep increase in FA with age across many of the same brain regions identified by the main effect of age (see Fig. 1b for a comparison of the main effect of age (in blue) versus regions with increased FA seen in the high-risk group in orange). When primary models were estimated with mean diffusivity as the dependent variable, results were inverse to the FA-based models. Given that mean diffusivity is negatively correlated with FA (Lebel and Deoni, 2018; Schilling et al., 2022), this provides evidence for the consistency of results across different indexes of diffusivity. Most tracts and regions identified by the interaction were robust to the inclusion of covariates including sex assigned at birth, youth internalizing symptoms, in-scanner motion, neighborhood SES, and intra-cranial volume. Controlling for all covariates, adolescents with a maternal history of depression showed steep increase in FA with age in a broad range of tracts and regions including commissural, projection, and association pathways, along with cerebellar and brainstem pathways and a number of other white matter regions. These widespread increases in FA with age may correspond to a global pattern of accelerated brain maturation in youth at risk for depression.

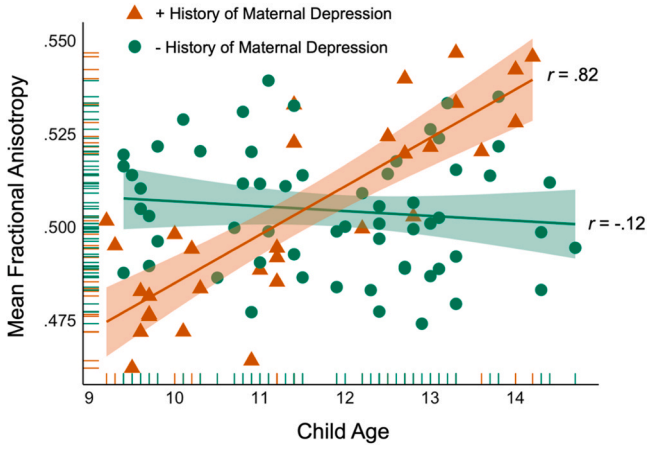

Fig. 2. Adolescents with a maternal history of depression showed an increase in FA across age compared to adolescents without a maternal history of depression. Individual mean FA values were extracted from a mask comprised of all tracts and regions identified by the interaction, controlling for all covariates. Mean FA values (Y-axis) are plotted against cross-sectional age (X-axis) and fit lines represent zero-order correlations between FA and age for each group.

Our results add to existing findings from studies of white matter microstructure in individuals at high-risk for depression. First, the current study illustrates the importance of looking at interactions between risk-related variables of interest and age, particularly when probing the adolescent period. Given that adolescence is a time when neural white matter shows rapid changes (Lebel and Beaulieu, 2011; Lebel et al., 2012) and given that we found a robust and spatially-extensive effect of age on microstructure in our sample, it is perhaps not surprising that our sample did not show a main effect of risk-status. This finding is consistent with several other studies that found interactions between age and risk-related variables but did not find robust or wide-spread main effects of risk-related variables in adolescent samples (Hung et al., 2017; Jones et al., 2019; Shakeel et al., 2021; van Velzen et al., 2020). This study also adds to previous studies demonstrating that parental history (Hung et al., 2017; Huang et al., 2012) and familial history (Shakeel et al., 2021) of psychopathology predicts microstructural alterations in unaffected youth, and demonstrates that maternal history of depression, specifically, is a unique predictor of alterations in white matter, beyond the effects of covariates previously shown to have associations with white matter such as age (Lebel and Beaulieu, 2011; Lebel et al., 2012), intra-cranial volume (Eikenes et al., 2023) and biological sex (Simmonds et al., 2014). Further, our results demonstrate that maternal history of depression uniquely predicts alterations in white matter microstructure in early and pre-adolescents, beyond effects of the youth's own depressive symptoms, which have been typically associated with reduced microstructure coherence (LeWinn et al., 2014; Vilgis et al., 2017; Vulser et al., 2018; Shen et al., 2021).

Differences in white matter microstructure between the high- and low- risk groups was generally less apparent in our tract-based compared to our voxelwise results. This is consistent with the findings from other developmental studies that have highlighted the importance of whole-brain, voxelwise analysis for detecting patterns in white matter development that may not be apparent at the tract-level (e.g., Palmer et al., 2022). There is evidence that white matter maturation occurs in a spatially graded manner (e.g., posterior to anterior) that may not correspond well to borders of specific white matter tracts (that may project across large spatial areas of the brain), and thus maturational patterns detected at the voxel-level may not correspond well to patterns that can be observed when scalars are extracted from and averaged across the aggregate of a whole white matter tract. A review of white matter development by Lebel et al. (2019) found evidence for spatial gradients of maturation across several studies. For example, two studies found evidence for a posterior-to-anterior maturational gradient (Colby et al., 2011; Krogsrud et al., 2016). Lebel and colleagues concluded that "gradients of change are difficult to establish in tractography or region-of-interest studies, as parameters are typically averaged over the tract, collapsing information across different brain areas". Similarly, a large-scale study by Palmer et al. (2022) using the ABCD dataset found that "voxelwise age associations were highly variable within subcortical regions and WM fiber tracts" and concluded that "the heterogeneity of effects along tracts…highlights the importance of voxelwise analyses to provide a more fine-grained understanding of how the brain is changing with age". The current study adds to work demonstrating the critical role of whole-brain, voxelwise analysis for detecting developmental patterns

in white matter microstructure.

Among previous high-risk study designs in youth, the two studies conducted in age ranges similar to the current study found interactions between risk-status and age, but in opposite directions. Hung et al. (2017) found that parental history of depression was associated with reductions in FA across age in 8–14 year olds, whereas Jones et al. (2019) found that the density of family history of psychopathology was associated with increases in FA across age in 12–16 year olds. Our findings align with those of Jones and colleagues, where familial risk was associated with stronger increases in FA across adolescence. Contrasting results across studies should each be interpreted against the known patterns in normative development of white matter as well as known patterns of white matter alteration seen in relation to psychopathology.

Across normative development, white matter shows protracted maturation into adulthood, with relatively rapid changes during the first three years of life (Dubois et al., 2014; Qiu et al., 2015) and during adolescence (Lebel and Beaulieu, 2011; Lebel et al., 2012; Lebel et al., 2017), as reflected in more steep increases in FA (and decreases in MD) during these developmental periods. While increases in FA during infancy appear to be driven largely by increases in myelination and axonal packing (axonal density and axonal bundling), increased FA during the adolescent period may be primarily due to increased axonal packing (Lebel and Deoni, 2018), with increases in FA across both of these developmental periods generally reflecting maturation of white matter.

Given that FA normatively increases across adolescence, our results showing steep increases in FA with age for the high- compared to low-risk group is consistent with accelerated brain maturation in those with a maternal history of depression. This interpretation is in line with life history theory (Belsky et al., 1991; Ellis et al., 2009; Ellis and Garber, 2000), that posits that early experiences program an individual's developmental course to allow them to effectively respond to their environment. In harsh and unpredictable environments, developmental trajectories are shifted towards earlier maturation, and research supports maternal depression as a substantial source of adversity in children's lives that may promote accelerated maturation. For example, a maternal history of depression predicted earlier pubertal timing in daughters, with this relationship fully mediated by stress in the mother's romantic relationship (Ellis and Garber, 2000). Similarly, maternal depression during infancy predicted earlier age of adrenarche in daughters (Belsky et al., 2015). Maternal depression has also been linked specifically to altered neural maturation. Mareckova et al. (2020) found that young adults exposed to higher maternal depression symptoms in-utero showed an elevated 'brain age gap', or patterns of cortical thickness that were similar to those of older individuals, suggesting that maternal depression is linked to accelerated brain maturation.

However, with regards to white matter specifically, the evidence for accelerated versus delayed maturity is mixed, with studies showing reduced (Dean et al., 2018; El Marroun et al., 2018; Graham et al., 2020; Hay et al., 2020; Posner et al., 2016; Rifkin-Graboi et al., 2013), increased (Lebel et al., 2016; Roos et al., 2022) and no differences (Jha et al., 2016; Roos et al., 2022) in white matter coherence in infants or children exposed to maternal depression in-utero, and studies showing reduced (Hung et al., 2017; Huang et al., 2012; Jones et al., 2019), increased (Jones et al., 2019), and no differences (Shakeel et al., 2021) in white matter coherence in youth and young adults with a familial history of psychopathology. Importantly, as demonstrated by Lebel et al., 2017 see Figure 4), when interrogating normative development of white matter, regions of white matter that typically show a curvilinear pattern of FA development across age, may yield a *negative* association between FA and age—depending on the specific age range sampled—even when the overall pattern across the more extensive age-range is positive. This apparent negative association between FA and age when the overall pattern is positive may manifest specifically during adolescence. This finding by Lebel and colleagues may explain why some studies have observed decreased FA with age among at-risk adolescents. As future work seeks to determine whether maternal history of depression is indeed associated with speeded versus delayed microstructural maturity, larger samples with broader ages ranges will be critical in answering this question.

Contrasting findings across high-risk design studies may also reflect early changes in white matter associated with depression itself, rather than risk for depression. While this study, Hung et al. (2017), and Huang et al. (2011) all controlled for offspring internalizing symptoms, it is nevertheless possible that differences in depression symptoms across samples may have influenced differences in observed microstructural patterns. Depression is robustly associated with reduced FA in adults and in adolescents (Abraham et al., 2022; Chen et al., 2016; LeWinn et al., 2014; Shen et al., 2021; van Velzen et al., 2020; Vulser et al., 2018), and in adolescents, depression and anxiety symptoms have been associated with relatively reduced longitudinal increases in FA with age (Albaugh et al., 2017). While some authors have attributed lower microstructural coherence seen in adolescent depression to delayed maturation, the similar patterns of reduced FA seen in depressed adults suggests lower FA may alternatively be due to degenerative processes that co-occur with depression and undermine white matter microstructure. Thus, where research has found reduced white matter coherence in high-risk samples, it may be due to symptom onset rather than risk itself. Several studies support this notion. In a sample of adolescents and young adults (aged 12–25) including healthy controls, those with diagnosed depression, those at familial-risk, and those with sub-syndrome levels of symptom severity, lower FA was found only in the depressed group, suggesting that microstructural differences were related to disorder onset rather than risk for depression (Shakeel et al., 2021). Further, a large-scale study found that reductions in white matter microstructure between adults with and without depression was primarily driven by those with recurrent episodes of depression (van Velzen et al., 2020), again consistent with a degenerative process that co-occurs with depression, with effects accumulating across multiple episodes. While there may be multiple mechanisms through which depression and reduced FA co-occur, one likely mechanism is via neuroinflammatory insults to white matter. Higher concentrations of pro-inflammatory proteins linked to depression have been associated with reduced white matter microstructural coherence in both adults and adolescents (Ho et al., 2022; O'Donovan et al., 2021; Sugimoto et al., 2018; Thomas et al., 2021; Zheng et al., 2022). Systemic inflammation in the periphery promotes neuroinflammation (Murta et al., 2015; Silverman et al., 2014; Sun et al., 2022), and neuroinflammation has been shown to degrade white matter (Di Penta et al., 2013; Ji et al., 2017; Pang et al., 2003).

This study had several notable strengths including a larger sample of youth with a familial history of depression than used in previous high-risk designs examining white matter alterations, a constrained focus on the pre- / early- adolescent period before peak depression onset, as well as controlling for youth internalizing symptoms to isolate white matter patterns related to risk rather than the influence of depression itself, semi-structured diagnostic interviews for mothers to robustly capture maternal history of depression, and over half of the sample comprised of racial minorities, a largely understudied demographic. This study also had several limitations. First, although we controlled for a number of covariates, the influence of risk factors versus symptom onset versus covariates would be better addressed in a very large longitudinal sample where between- versus within- individual effects could be parsed. Given contrasting results across studies of high-risk youth, it is critical to replicate the current findings in a large dataset while also examining the role of other important factors. Second, while the current results fit within known patterns of white matter development and findings of adversity-linked accelerated maturation in youth, it remains unclear whether our observed increases in FA indeed represent speeded maturation, particularly given the cross-sectional nature of the study and limited sample size. Future work could better assess this by examining, within the same sample, the influence of risk status on trajectories of white matter microstructure, along with risk status effects on other

known neural and/or physiological indicators of maturation. Another limitation is that the current data did not include information about the timing of maternal depression. Future work should consider more directly testing effects of maternal depressive episodes on youth white matter at different developmental stages. Finally, the current cross-sectional study cannot address whether increases in FA represent a pre-morbid state that contributes to depression onset or represents a compensatory state that may contribute to resilience to psychopathology. Mixed findings support both hypotheses. Studies by Belsky et al. (2015) and Mareckova et al. (2020) found that exposure to maternal depression was associated with hormonal and neural markers, respectively, of earlier maturation and that earlier maturation was associated with increased symptoms of psychopathology, suggesting that earlier maturation is a risk factor. On the other hand, studies in adults support the hypothesis that increased FA in those at-risk for depression may serve as a protective factor. Studies by Frodl et al. (2012) and Winter et al. (2022) both found that resilient adults with a family history of depression, compared to adults without a family history of depression, showed increased FA across a number of tracts. Further Winter and colleagues found that familial risk was not associated with differences in white matter among those with depression, and Frodl and colleagues found that FA was higher in resilient individuals with greater childhood adversity than resilient individuals with less childhood adversity. Together, these findings suggest that increased FA may be a protective factor among those with higher levels of risk. Future longitudinal work should explore this important open question to disentangle whether alterations in white matter of at-risk youth contribute to risk for or resilience against psychopathology.

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 statement

The neuroimaging and behavioral data are available upon request after publication of the current manuscript.

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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.2023.101307.

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