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RESEARCH REPORT

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White matter alterations associated with lifetime and current depression in adolescents: Evidence for cingulum disruptions

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Abstract

Introduction: Compared to research on adults with depression, relatively little work has examined white matter microstructure differences in depression arising earlier in life. Here we tested hypotheses about disruptions to white matter structure in adolescents with current and past depression, with an a priori focus on the cingulum bundles, uncinate fasciculi, corpus collosum, and superior longitudinal fasciculus.

Methods: One hundred thirty-one children from the Preschool Depression Study were assessed using a Human Connectome Project style diffusion imaging sequence which was processed with HCP pipelines and TRACULA to generate estimates of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD).

Results: We found that reduced FA, reduced AD, and increased RD in the dorsal cingulum bundle were associated with a lifetime diagnosis of major depression and greater cumulative and current depression severity. Reduced FA, reduced AD, and increased RD in the ventral cingulum were associated with greater cumulative depression severity.

Conclusion: These findings support the emergence of white matter differences detected in adolescence associated with earlier life and concurrent depression. They also highlight the importance of connections of the cingulate to other brain regions in association with depression, potentially relevant to understanding emotion dysregulation and functional connectivity differences in depression.

KEYWORDS

adolescence, brain development, cingulum, depression, white matter

1 | INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability (Leigh et al., 2020; Kovess-Masfety et al., 2007; Murray & Lopez, 1996; Wang et al., 2007). Diffusion magnetic resonance imaging (dMRI) has been used to investigate white matter microstructure and alterations associated with depression. A focus on white matter structure may be particularly important for understanding depression, as it may index the integrity of structural connections among brain regions that may contribute to alterations in brain function and connectivity (Lichenstein et al., 2016). Compared to research on adults, relatively little work has examined depression arising early in life when white matter is still undergoing considerable developmental change (Lebel et al., 2019). A key overarching framework of the current work is that disruptions in the communication between brain regions involved in emotion processing and emotion regulation are associated with risk for depression and that such disruption may reflect alterations in the

structural integrity of the pathways that normally allow for effective communication among these circuits (Cardoso de Almeida & Phillips, 2013; Zheng et al., 2018). However, it is still not clear how early these arise in development, and whether they are associated with a greater ongoing experience of depression, either because they are risk factors for recurrent depression, or because they reflect the "scars" of ongoing depression. Here we tested hypotheses about such disruptions to white matter structure among adolescents with and without a lifetime history of MDD, as well as in relationship to current depression severity and cumulative lifetime severity of depression from early childhood to adolescence.

One approach to examining white matter is to use dMRI, a noninvasive technique that produces in vivo MRI images based on water molecular diffusion (Coloigner et al., 2019; Liao et al., 2013; Podwalski et al., 2021; van Velzen et al., 2020). One commonly used approach to dMRI generates indices of four different diffusion properties: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) (Baliyan et al., 2016). FA is sensitive to microstructural changes to white matter, but is not specific to any particular source of changes, and could reflect myelin damage, changes to axonal diameter or density, or changes in membrane permeability (Chang et al., 2017). MD is the average diffusion across the three spatial axes of the diffusion tensor (i.e., weighted average of AD and RD). It has been interpreted as an index of the magnitude of fluid viscosity and cellularity sensitivity (Jütten et al., 2019; Soares et al., 2013) and is sensitive to disruption in either axonal or myelin integrity (Lichenstein et al., 2016). AD is the diffusivity along the principal diffusion axis (Alexander et al., 2007) and has been related to axonal integrity, with AD decreasing as axonal loss increases (Winklewski et al., 2018). RD is a measure of diffusivity perpendicular to the principle axis of diffusion (Curran et al., 2016) and has been shown to increase as myelination decreases (Winklewski et al., 2018).

In adults with depression, there is growing evidence of structural changes and disruptions in white matter fibers associated with MDD, particular in tracts that connect regions involved in responding to and processing emotionally evocative experiences and those involved in regulating such experiences. including significant FA reduction in the cingulum (Bhatia et al., 2018; Bracht et al., 2015; Coloigner et al., 2019; Kliamovich et al., 2021; Marečková et al., 2019; van Velzen et al., 2020; Vulser et al., 2018; Wu et al., 2018) and uncinate fasciculi (UF) (Bhatia et al., 2018; Hanson et al., 2015; Jenkins et al., 2016; Zhang et al., 2012). The cingulum bundle is a critical white matter tract that runs from the subgenual cingulate to the occipital lobe adjacent to the corpus callosum (Bubb et al., 2018). The long fibers in the cingulum bundle extend from the subgenual cingulate to amygdala and hippocampus caudally (Wakana et al., 2004). Previous studies have suggested that disruptions in the cingulum bundle are involved in depression pathophysiology, potentially due to their disruption of communication from subcortical to cortical limbic regions (Bracht et al., 2015; LeWinn et al., 2014). There is also evidence that subdivisions of the cingulum may have differential associations with psychiatric illness, with the dorsal cingulum bundle (connecting the frontal lobe to the cingulate) versus the ventral cingulate bundle (connecting more posterior cingulate regions to the medial temporal lobe) being particularly associated with depression (Coloigner et al., 2019; Cullen et al., 2010; De diego-Adeliño et al., 2014; van Velzen et al., 2020; Vulser et al., 2018).

The UF is bidirectional long white matter tracts, where the medial stems extend from the subgenual cingulate (Wakana et al., 2004). Reduced white matter integrity in UF has been found related to depression (Bhatia et al., 2018; Bracht et al., 2015; Jenkins et al., 2016; LeWinn et al., 2014; Zhang et al., 2012). There is also evidence for reduced microstructural integrity in the corpus callosum (L. Chen et al., 2016; G. Chen et al., 2017; Coloigner et al., 2019; Han et al., 2014; Korgaonkar et al., 2011; Liao et al., 2013; Ota et al., 2015) and superior longitudinal fasciculi (Ota et al., 2015) in adults with depression, as well as individuals with high polygenic risk scores for depression (Shen et al., 2017). Shen et al. (2017) found that polygenic risk for depression was significantly associated white matter microstructure, including variation in both cingulum and UF, consistent with the larger literature on depression. However, they also found associations with the superior longitudinal fasciculi and forceps major and minor of the callosum, tracts less consistently investigated in the context of depression, though the superior longitudinal fasciculi are critical for connecting components of frontal parietal brain regions involved in emotion regulation, making this integrity of this tract highly relevant to theories of depression development and maintenance.

The presence of white matter disruptions in depressed children and adolescents is less clear, a period of particular interest given the ongoing development of white matter tracts (Lebel et al., 2019). Some studies of white matter development in children and adolescents provide evidence of reduced FA in uncinate and/or cingulum in adolescents with depression (Cullen et al., 2010; Ho et al., 2021; Kliamovich et al., 2021; Shen et al., 2021; Uchida et al., 2021), but other studies have not (Cullen et al., 2020; Ho et al., 2021; Roelofs et al., 2021). There is also some intriguing evidence that reduced FA in the dorsal cingulum and uncinate may be related to risk for depression (Huang et al., 2011; Hung et al., 2016; Keedwell et al., 2012). However, most studies have typically only examined cross-sectional relationships to current diagnosis or current depression severity. Thus, the primary goal of the current study was to examine whether, in adolescents, a lifetime history of major depression, prospectively assessed cumulative depression severity or current depression severity were associated with white matter disruptions. Given the existing literature in adults, the analyses here focus on the cingulum (both dorsal and ventral), the UF, the corpus collosum, and the superior longitudinal fasciculi. We predicted that both current and lifetime depression would be associated with reductions in FA in the cingulum bundle (particularly the dorsal component) as well as in the UF. We did not have strong a priori hypotheses as to whether MD would also be reduced and/or whether AD or RD would be altered. We also hypothesized that FA in the corpus collosum and superior longitudinal fasciculi would be reduced in association with depression, though there is somewhat less consistent evidence of alterations in these regions in prior studies of depression.

2 | MATERIALS AND METHODS

2.1 | Participants

The Preschool Depression Study is a 17-year longitudinal study where a total of 306 children participants, oversampled for depression, aged 3 to 5 years were recruited from daycare centers, preschools, and their primary caregivers at the Washington University School of Medicine (WUSM) using the Preschool Feelings Checklist (PFC) (Luby et al., 2004). These children were then followed and assessed approximately yearly. At school age (~7–12 years), healthy children and those with a history of depression and/or anxiety were invited to participate in brain imaging; an additional 42 healthy children were also recruited (N = 210 completed the first wave of imaging). We completed five waves of imaging over childhood and adolescence. See Supporting Information for exclusions.

The diffusion data of focus in the current report were collected at imaging Waves 4 (ages 13–19) and 5 (ages 15–21). Of the children involved in the imaging component of the study, 157 and 173 participated in the fourth and fifth waves of imaging, respectively. However, diffusion scans were an add on and only run if sufficient time was available, and thus were acquired in a subset of youth (72 and 103 respectively for Waves 4 and 5). As described below, we used the first available wave with complete diffusion scans for each youth, resulting in data from 131 youth. Written/verbal informed consent and assent were obtained from all participants. All procedures were approved by WUSM Institutional Review Board.

2.2 | Measures

2.2.1 | Psychopathology diagnoses

Trained staff from the Early Emotional Development Program conducted up to 10 in-person assessment sessions with participants and their primary caregivers over the course of the study. The children were between the ages of 3–5 years at the time of their first clinical interview (T1) and between the ages of 15–21 at the most recent assessment wave (T10/MRI5). The Preschool-Age Psychiatric Assessment (PAPA) (Egger, 2009; Egger et al., 2006) was the diagnostic assessment when children were age 3–7 years. The PAPA is designed for diagnostic use with the caregivers of children ages 2 (Egger et al., 2006). It consists of questions about developmentally appropriate symptom manifestations of DSM-IV criteria for all Axis I disorders, including MDD, attention deficit hyperactivity disorder (ADHD), and anxiety disorders. The Childhood and Adolescent Psychiatric Assessment (CAPA) was then used for caregivers and children beginning at age 8, with the Kiddie Schedule for Affective Disorders used for child and parent report (Kobak & Kaufman, 2015). The criteria used for determining whether a symptom was present or absent were based on the criteria outlined in these structured interviews and used the standard in the field to count either parent or child endorsement of a symptom as positive. Inter-rater reliability among clinicians was high for a diagnosis of depression (κ = 1.0; ICC = 0.98). The median number of assessments for youth was 9, with a mean of 8.1 (SD = 1.85), a minimum of 3, and a maximum of 10. Eighty-five percent of youth had five or more interviews. Youth were grouped into three groups based on the clinical interview: (1) healthy controls with no lifetime history of any psychiatric disorder (HC; N = 23); (2) lifetime history of major depression (MDD; N = 69), with or without a history of additional diagnoses; and (3) youth with a lifetime history of a disorder other than major depression, primarily anxiety and (OTHDX; N = 39).

2.2.2 | Cumulative depression severity

We created a cumulative depression score by averaging the number of depression items endorsed at each assessment wave. Of note, the results were similar if we used a sum weighted by the number of interviews or an area under the curve approach.

2.2.3 | Current depression severity

Current depression severity was assessed by summing the number of depression items endorsed at the diffusion wave.

2.2.4 | Early life income to needs ratio

Early life income-to-needs ratio also predicts white matter integrity in many of the same brain regions associated with depression (Dufford et al., 2020). Thus, we controlled for income-to-needs in all our analyses, calculated by dividing the total family income by the federal poverty level.

2.3 | Diffusion imaging methods

2.3.1 | MRI data acquisition

Youth completed up to five imaging waves, with any missing waves due to scheduling challenges. The last two imaging waves used a 3.0T Siemens Prisma whole-body scanner with a 32-channel head coil. Data acquisition included: (a) one 3D T1-weighted scan; (b) one 3D T2-weighted scan; and (c) two diffusion-weighted scans [TR 2500 ms, TE 79.4 ms, 80 1.75 mm slices acquired in an axial-oblique orientation approximately aligned with the plane of the anterior/posterior commissure], 120 × 120 matrix with a 210 mm field of view, yielding 1.75 mm in-plane spatial resolution; 6/8 phase partial Fourier; multiband (MB) acceleration factor of 4, acquired using the MB sequences of the Center for Magnetic Resonance Research at the University of Minnesota [https://www.cmrr.umn.edu/multiband]). See Supporting Information for imaging sequence details.

2.3.2 | Image processing

The structural data (T1w, T2w scans) were processed using HCP pipelines and FreeSurfer as described previously (Barch et al., 2022) to create the prerequisite anatomical information expected by FreeSurfer's TRACULA tool (Yendiki et al., 2011; Yendiki, Koldewyn, et al., 2014; Yendiki, Reuber, et al., 2014) for automatic construction of white-matter pathways from dMRI data. The diffusion data were preprocessed using the "DiffusionPreprocessing" stream of HCP Pipelines (v4.0.1) (Glasser et al., 2013, 2016) followed by processing using TRACULA (from FreeSurfer v6.0) which included application of FSL's "bedpostx" (Behrens et al., 2007; Hernandez-Fernandez et al., 2019) to estimate the diffusion distribution at each voxel. Average values for FA, MD, RD, and AD within the 20% posterior distribution for each path (tract) of interest were computed as the final step of TRACULA. The mean relative motion estimate from eddy_quad was used as covariate in all analyses. See Supporting Information for processing details.

We focused on the following tracts: (a) cingulum-cingulate gyrus (CCG—dorsal cingulum); (b) cingulum-angular bundle (CAB—ventral cingulum); (c) UF; (d) corpus collosum forceps major (FMAJ); (e) corpus collosum forceps minor (FMIN); and (f) superior longitudinal fasciculi parietal bundle (SLFP). We averaged the left and right tracts together for bilateral tracts. We used the diffusion data from the first available wave completed by a youth (72 from Wave 4 and 59 from Wave 5), for a total of 131 participants. The same results were found if we averaged the diffusion metrics across two waves for any youth with more than one wave.

2.4 | Statistical analyses

Analysis of covariance (ANCOVA) in SPSS version 27 was used to evaluate whether the values of the diffusion metrics differed as a function of diagnostic group. We first examined FA and MD. If either FA or MD showed a significant group difference that passed false discovery rate (FDR) correction (across the six examined tracts), we then examined AD and RD. Multiple linear regression in SPSS version 27 was used to evaluate the relationships of the diffusion metrics to cumulative MDD severity and current depression severity (separate analyses). Sex, age, income-to-needs, and "eddy" QC relative motion estimates were included as covariates in all analyses. FDR correction ($q = 0.05$) was used to correct for multiple comparisons across tracts within each measure (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001).

3 | RESULTS

3.1 | Participant characteristics

There were no significant group differences in age, sex, race, relative motion estimates, or income-to-needs ratio (Table 1). There were significant diagnostic group differences for both current and cumulative depression severity, with post hoc tests indicating that MDD had higher scores for both compared to OTHDX and HC, who did not different significantly from each other. MDD were more likely

TABLE 1 Demographic and clinical data of participants

	MDD ($N = 69$)	Other diagnosis ($N = 39$)	Healthy control ($N = 23$)	F/X^2	p-value
Age, years, mean (SD)	17.54 (1.27)	17.39 (1.42)	17.03 (1.22)	1.34	0.266
Sex, *n* (%)				0.62	0.732
Female	33 (48%)	19 (49%)	9 (39%)	-	-
Male	36 (52%)	20 (51%)	14 (61%)	-	-
Race, *n* (%)				2.25	0.325
White	34 (49%)	26 (67%)	14 (61%)	-	-
Black or African American	23 (33%)	10 (25%)	8 (35%)	-	-
More than one race	12 (18%)	3 (8%)	1 (4%)	-	-
Income-to-needs ratio, mean (SD)	3.57 (2.51)	3.73 (2.27)	3.89 (2.43)	0.17	0.845
QC relative motion, mm, mean (SD)	0.69 (0.34)	0.60 (0.31)	0.57 (0.45)	1.44	0.240
Lifetime history of psychotropic medication, *n* (%)	34 (49%)	7 (18%)	2 (9%)	18.46	<0.001
Taking psychotropic mediation at scan, *n* (%)	10 (15%)	4 (10%)	0 (0%)	3.8	0.150
Current depression severity, mean (SD)[a]	2.59 (2.88)	0.46 (1.02)	0.26 (0.69)	16.06	<0.001
Cumulative depression severity, mean (SD)[b]	2.77 (1.03)	1.12 (0.58)	0.80 (0.48)	73.92	<0.001

Abbreviation: MDD, major depressive disorder.

[a]Post hoc comparisons among groups indicated that the MDD group showed higher current depression severity than both the healthy control ($p < 0.001$) and other diagnosis groups ($p < 0.001$), who did not differ significantly from each other ($p = 0.830$).

[b]Post hoc comparisons among groups indicated that the MDD group showed higher cumulative depression severity than both the healthy control ($p < 0.001$) and other diagnosis groups ($p < 0.001$), who did not differ significantly from each other ($p = 0.173$).

TABLE 2 ANCOVAs examining diagnostic group differences in FA and MD

Tract	*F* value	*p*-value	FDR-adjusted *p*-value (*q*-values)	Effect size (partial ETA squared)
FA				
CCG[a]	5.643	0.005	**0.030**	**0.083**
CAB	2.207	0.114	0.342	0.034
UF	0.341	0.712	0.925	0.005
FMAJ	1.498	0.228	0.456	0.024
FMIN	0.990	0.906	0.925	0.002
SLFP	0.077	0.925	0.925	0.001
MD				
CCG	2.107	0.126	0.378	0.033
CAB	0.0001	1.000	1.000	0.0001
UF	0.489	0.614	0.737	0.008
FMAJ	2.117	0.125	0.378	0.033
FMIN	0.521	0.595	0.737	0.008
SLFP	1.329	0.269	0.538	0.021

Note: Bold values are statistically significant.

Abbreviations: ANCOVA, analysis of covariance; CAB, cingulum-angular bundle; CCG, cingulum-cingulate gyrus; FA, fractional anisotropy; FDR, false discovery rate; FMAJ, corpus collosum forceps major; FMIN, corpus collosum forceps minor; MD, mean diffusivity; MDD, major depressive disorder; SLFP, superior longitudinal fasciculi parietal bundle; UF, uncinate fasciculi.

[a]Post hoc comparisons among groups indicated that the MDD group showed lower CCG FA than both the healthy control ($p = 0.009$) and other diagnosis groups ($p = 0.006$), who did not differ significantly from each other ($p = 0.754$).

to have taken lifetime psychotropic medications than either of the other groups, who did not differ. The groups did not differ significantly on the percentage of youth taking psychotropic medication at the time of scan. All of the results reported below remained significant if lifetime medication use was added as a covariate. There were no significant demographic or clinical differences between participants with or without diffusion data (Supporting Information: Table S1).

3.2 | Diagnostic group differences

As can be seen in Table 2 and Figure 1, only the CCG showed a significant group difference. Post hoc comparisons indicated that MDD showed lower FA than both HC and OTHDX, who did not differ from each other. There were no significant group differences for MD (Table 2). For CCG, there was a significant difference for both AD ($F = 5.611$, $p = 0.005$, $\eta^2_{partial} = 0.083 \eta^2_{partial} = 0.83$) and RD ($F = 5.041$, $p = 0.008$, $\eta^2_{partial} = 0.075$), with MDD showing lower

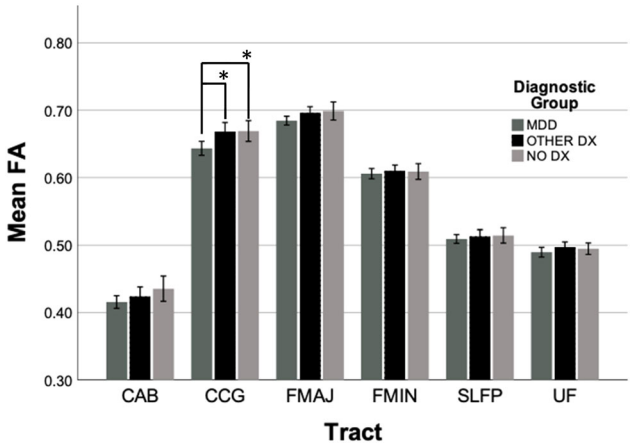

FIGURE 1 Estimated marginal means of FA for MDD, other diagnosis, and healthy control groups. The error bars are standard errors. CAB, cingulum-angular bundle; CCG, cingulum-cingulate gyrus; FMAJ, corpus collosum forceps major; FMIN, corpus collosum forceps major; SLFP, superior longitudinal fasciculi parietal bundle; UF, uncinate fasciculi.

AD ($p = 0.002$) and higher RD ($p = 0.025$) than HC, as well as higher RD than OTHDX ($p = 0.006$). OTHDX and HC did not differ significantly on either AD ($p = 0.12$) or RD ($p = 0.973$).

3.3 | Relationships to cumulative depression severity

As can be seen in Table 3 and Figure 2, both the CCG and the CAB showed a significant relationship to cumulative depression severity which survived FDR correction, with the children with greater cumulative depression severity showing lower FA. There were no significant relationships of cumulative depression severity for MD (Table 3). We examined associations to AD and RD for both CCG and CAB. Cumulative depression severity was significantly associated with reduced AD ($t = -2.436$, *STD* $\beta = -0.207$, $p = 0.016$) and increased RD ($t = 2.398$, *STD* $\beta = 0.208$, $p = 0.018$) for CCG. Similarly, for CAB, cumulative depression severity was significantly associated with both reduced AD ($t = -2.448$, *STD* $\beta = -0.217$, $p = 0.016$) and increased RD ($t = 2.008$, *STD* $\beta = 0.180$, $p = 0.047$). However, all of these analyses were conducted with all three groups combined. When examined only in the MDD group, the direction of the relationships were similar, but none were significant: (i) reduced CCG FA ($t = -0.52$, *STD* $\beta = -0.07$, $p = 0.61$); (ii) reduced CAB FA ($t = -1.3$, *STD* $\beta = -0.17$, $p = 0.21$); (iii) reduced CCG AD ($t = -0.45$, *STD* $\beta = -0.06$, $p = 0.65$); (iv) reduced CAB AD ($t = -1.42$, *STD* $\beta = -0.19$, $p = 0.16$); (v) increased CCG RD ($t = 0.38$, *STD* $\beta = 0.05$, $p = 0.71$); and (vi) increased CAB RD ($t = 1.03$, *STD* $\beta = 0.14$, $p = 0.31$). Thus, these cumulative depression findings seem to reflect group differences more strongly than variability within the MDD group.

TABLE 3 Linear regressions examining the relationship of cumulative depression severity to FA and MD

	Unstandardized *B*	Std. error	Standardized beta	*t*	*p*-value	FDR-adjusted *p*-value (*q*-values)
FA						
CCG	−0.008	0.003	−0.224	−2.603	**0.010**	**0.045**
CAB	−0.008	0.003	−0.223	−2.478	**0.015**	**0.045**
UF	0.001	0.002	0.044	0.512	0.610	0.907
FMAJ	−0.004	0.002	−0.153	−1.760	0.081	0.162
FMIN	0.0001	0.002	−0.020	−0.215	0.907	0.907
SLFP	0.002	0.002	0.003	0.972	0.815	0.907
MD						
CCG	0.00006	0.001	0.079	0.907	0.366	0.828
CAB	0.00007	0.001	0.036	0.409	0.684	0.828
UF	0.00007	0.001	−0.042	−0.470	0.639	0.828
FMAJ	0.0007	0.001	0.036	0.399	0.690	0.828
FMIN	0.00008	0.001	0.002	0.020	0.984	0.984
SLFP	0.00006	0.001	0.119	1.353	0.179	0.828

Note: Bold values are statistically significant.

Abbreviations: CAB, cingulum-angular bundle; CCG, cingulum-cingulate gyrus; FA, fractional anisotropy; FDR, false discovery rate; FMAJ, corpus collosum forceps major; FMIN, corpus collosum forceps minor; MD, mean diffusivity; MDD, major depressive disorder; SLFP, superior longitudinal fasciculi parietal bundle; UF, uncinate fasciculi.

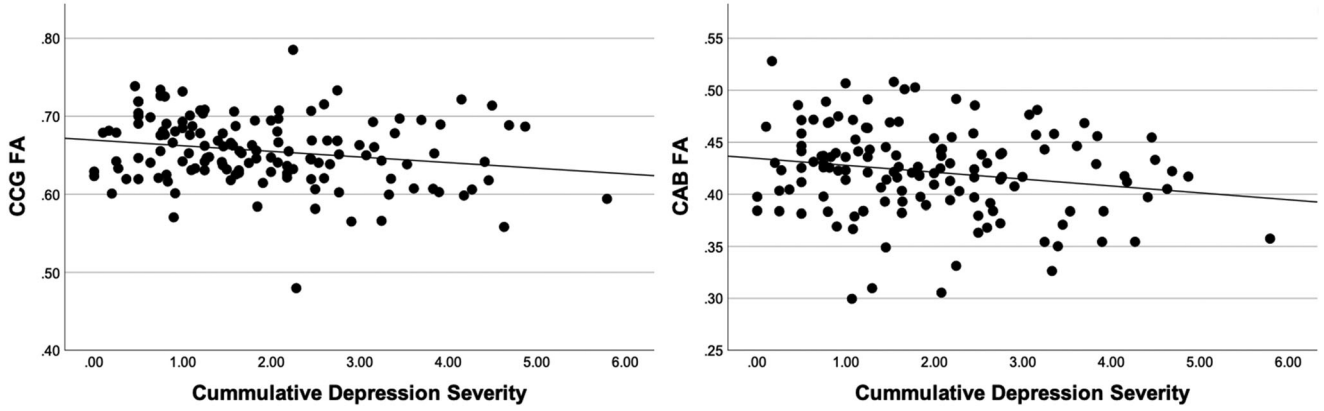

FIGURE 2 Graphs illustrating the relationship between FA in the CCG and CAB and cumulative depression severity based on the raw FA values and depression severity (i.e., not adjusted for covariates). CAB, cingulum-angular bundle; CCG, cingulum-cingulate gyrus; FA, fractional anisotropy.

3.4 | Relationships to current depression severity

We also observed a similar pattern of a relationship of increased RD ($t = 2.121$, *STD* $\beta = 0.183$, $p = 0.036$) to current depression severity in the CCG as seen for cumulative depression severity, but again this was not significant within the MDD group alone ($t = 1.33$, *STD* $\beta = 0.166$, $p = 0.19$). There were no other significant associations with FA (all *STD* $|\beta|s < 0.125$, all $ps > 0.15$). There were no significant associations of current depression severity to MD in any tract (all *STD* $|\beta|s < 0.139$, all $ps > 0.11$).

4 | DISCUSSION

We saw consistent evidence in support of our hypothesis that there would be a relationship between reduced FA in the dorsal cingulum, with reductions related to a lifetime history of major depression diagnosis, cumulative lifetime depression severity, and current depression severity, though the relations to lifetime and current depression seemed to primarily reflect diagnostic group differences. Follow-up analyses for the dorsal cingulum indicated that the reduced FA was accompanied by reduced AD and increased RD. We did not see

evidence in support of our hypothesis of an association between UF FA and depression. There were no associations of MD with any metric of depression.

The greater evidence for an association with the dorsal versus ventral cingulum is consistent with prior studies that have found evidence for a relationship of depression to dorsal but not ventral cingulum (Coloigner et al., 2019; Cullen et al., 2010; De diego-Adeliño et al., 2014; van Velzen et al., 2020; Vulser et al., 2018). The reduction in dorsal cingulum FA was also accompanied by a reduction in AD and an increase in RD, but no significant difference in MD associated with depression. While it is difficult to make specific inferences about the neurobiological sources of differences in diffusion metrics, this pattern was similar to that seen in prior work by (Kliamovich et al., 2021) on depression risk. In a whole brain analysis, these researchers observed a pattern of reduced FA coupled with decreased AD and increased RD in a region that included the dorsal cingulum (but not the ventral cingulum) and which predicted the emergence of depression in adolescence. They hypothesized that this pattern may indicate altered or delayed maturation of fiber tracts given that reduced AD may reflect disrupted axonal properties and increased RD may reflect altered myelination (Kliamovich et al., 2021).

The dorsal cingulum contains fibers that connect the subgenual and dorsal regions of the anterior cingulate to prefrontal regions, other cingulate regions, motor, temporal and parietal regions, and even subcortical structures highly relevant to depression, including the amygdala, hippocampus, and striatum (Lichenstein et al., 2016). As such, it has been argued that disruptions to the dorsal cingulum may be particularly relevant to emotion processing and emotion regulation, given the central roles that the anterior and subgenual cingulate play in emotion responsivity and regulation (Lichenstein et al., 2016). Further, different regions of the anterior and subgenual cingulate cortices are part of multiple brain networks that are thought to be important for various aspects of emotion processing and regulation, such as the salience network, the frontal-parietal network, and the default mode network (DMN), and which are disrupted in individuals with depression (Brakowski et al., 2017; Hua et al., 2021; Picó-Pérez et al., 2018; Scharnowski et al., 2020). Thus, it is intriguing to speculate that alterations in the structural connectivity of the dorsal cingulum might relate to disrupted functional connectivity of networks that include regions of the subgenual or anterior cingulate. The ventral cingulum provides connections between the posterior cingulate, parahippocampal gyrus, and occipital cortex, regions which may be less relevant for the processes disrupted in depression.

We did not see evidence for an alteration in either FA or MD in the UF, the corpus collosum, or the superior longitudinal fasciculi associated with depression. In adults with depression, a number of studies have found reduced FA in the UF, and there is at least some prior evidence for reduced UF FA among adolescents with depression (Cullen et al., 2010; Shen et al., 2021), though at least two other studies in adolescents that did find reduced cingulum FA did not see reduced UF FA (Kliamovich et al., 2021; Uchida et al., 2021). As such, it is not entirely clear why we did not see evidence for reduced FA in these tracts in the current study, whether associated with current depression, cumulative depression severity, or lifetime depression diagnosis. One hypothesis is that the cingulum might be more likely to show effects of depression across childhood and adolescence because it has a different pattern of developmental change compared to the other tracts. However, a recent review suggests that the developmental timing and pattern of white matter development in the dorsal cingulum is very similar to at least the UF (Lebel et al., 2019).

While this study had strengths in terms of longitudinal prospective assessments of depression and the use of HCP-style diffusion imaging, there were also several limitations. First, we did not have assessments of white matter integrity starting in childhood, so we cannot assess whether the cingulum FA reduction preceded the onset of depression, as in the work of (Kliamovich et al., 2021). Second, we do not know the underlying neurobiological sources of the alterations in the FA, AD, and RD in the cingulum associated with depression, and further work will be needed to isolate the specific white matter alterations that give rise to such a pattern. Third, only a small number of youth participating in the imaging waves of the current study had diffusion imaging at both waves, precluding us from examining change in white matter integrity as a function of change in depression an important direction for future research. Fourth, since all of the youth were scanned in late adolescence, we could not address important questions about the impact of age or puberty on the relationship between depression and white matter integrity.

5 | CONCLUSION

Overall, the current study contributes to the literature by providing robust evidence of a relationship between alteration in the microstructure of white matter in the cingulum bundles in association with several measures of depression in adolescence. This association was present for a lifetime history of depression, cumulative severity of depression from preschool to adolescence, and current depression severity, though the latter two seemed to primarily reflect group differences. Given the importance of the cingulum bundles for connecting regions in the frontal and cingulate cortices that are part of networks important for a range of cognitive and emotional functions that may be disrupted in depression, these data provide clues as to the potential targets for treatments designed to treat or even prevent depression. We also provide evidence that these disruptions are present as early as adolescence in youth with current or past depression.

AUTHOR CONTRIBUTIONS

Deanna Barch: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Roles/Writing-original draft. **Xiao Hua:** Conceptualization; Formal analysis; Writing-original draft. **Sridhar Kandala:** Data curation; Formal analysis; Resources; Software; Writing-review & editing. **Michael Harms:** Investigation; Methodology; Writing-review & editing. **Ashley Sanders:** Conceptualization; Writing-review & editing. **Rebecca Brady:** Conceptualization; Writing-review &

editing. **Rebecca Tillman:** Data curation; Validation; Visualization; Writing-review & editing. **Joan Luby:** Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The author has provided the required Data Availability Statement, and if applicable, included functional and accurate links to said data therein.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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