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RESEARCH ARTICLE

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Depression is associated with dimensional and categorical effects on white matter pathways

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Background: Diffusion tensor imaging (DTI) studies report reduced fractional anisotropy (FA) in major depressive disorder (MDD). However, whether FA covaries with key depressive symptoms, such as anhedonia, is unclear.

Methods: Magnetic resonance imaging data were acquired from 38 unmedicated adults with MDD and 52 healthy controls. DTI metrics were extracted from regions of interest that have consistently shown reduced FA in MDD. Analyses focused first on identifying group differences, and then determining whether reduced FA in depressed adults was related to individual differences in anhedonia and depressive severity. To establish specificity to depression, these analyses controlled for symptoms of anxiety.

Results: Relative to controls, depressed adults showed reduced FA in the genu of the corpus callosum, the anterior limb of the internal capsule (ALIC), the cingulum bundle near the anterior cingulate cortex, and the uncinate fasciculus (UF). In the depressed group, anhedonia negatively correlated with FA in the genu, cingulum, and UF, but positively correlated with radial diffusivity (RD)—a metric previously linked to demyelination—in the genu and ALIC. Depressive severity positively correlated with RD in the ALIC. These relationships remained significant after accounting for anxiety.

Conclusion: Anhedonia was positively correlated with reduced FA and increased RD in white matter pathways that connect regions critical for value coding, representing stimulus-reward associations, and guiding value-based action selection. Thus, a cardinal symptom of MDD—anhedonia—was lawfully related to abnormalities in reward network connectivity.

KEYWORDS
anhedonia, anxiety, corpus callosum, depression, white matter

1 | INTRODUCTION

Meta-analyses of the diffusion tensor imaging (DTI) literature report reduced fractional anisotropy (FA) in major depressive disorder (MDD) (Chen et al., 2016; Jiang et al., 2016; Liao et al., 2013; Wise et al., 2016). FA reflects the tendency for water to diffuse in one direction, and FA increases in white matter because axons constrain diffusion to occur parallel to fibers (Alexander, Lee, Lazar, & Field, 2007). Consequently, reduced FA suggests white matter abnormalities. In MDD, FA is consistently reduced in the genu of the corpus callosum, the uncinate fasciculus (UF), and the anterior limb of the internal capsule (ALIC) (Bracht, Linden, & Keedwell, 2015; Chen et al., 2016). These tracts connect the frontal lobes to each other, to anterior temporal regions (e.g., amygdala), and to subcortical structures (e.g., striatum). Given the importance of these connections for cognition, emotion regulation, and motivated behavior, their disruption may contribute to MDD (Liao et al., 2013).

It would be useful to know whether FA covaries with anhedonia. Anhedonia is a cardinal symptom of MDD (APA, 2013) that may be related to reduced FA in reward networks. Functional neuroimaging has linked anhedonia to abnormal reward responses in the striatum and ventromedial prefrontal cortex (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005), and DTI studies (see Bracht, Linden et al., 2015) have linked anhedonia to decreased FA in the cingulum and medial forebrain bundle (MFB), a pathway that connects the ventral tegmental area and nucleus accumbens (Coenen, Schlaepfer, Maedler, & Panksepp, 2011; in many DTI studies, data from the ALIC may include overlapping fibers from the MFB; Bracht, Linden et al., 2015). For

instance, Bracht et al. (2014) found a negative correlation between loss of pleasure and MFB FA, while cingulum FA was positively correlated with hedonic tone and reduced in women with a family history of depression (Keedwell et al., 2012).

Thus, anhedonia has been associated with reduced FA in the MFB/ALIC and the cingulum. Whether anhedonia is related to FA in other regions is less clear. Furthermore, whether reduced FA in the MFB/ALIC and cingulum specifically reflects anhedonia or involves a contribution from comorbid symptoms, such as anxiety, has not been established. The Mood and Anxiety Symptoms Questionnaire (MASQ; Watson et al., 1995) is ideal for addressing this issue, as it includes scales particularly relevant for depression (anhedonic depression: MASQ-AD) versus anxiety (anxious arousal: MASQ-AA), with other scales capturing general distress due to depression (MASQ-GDD) and anxiety (MASQ-GDA). Keedwell et al. (2012) reported a correlation between cingulum FA and MASQ-AD scores but did not test whether this relationship held when controlling for anxiety, which is critical for establishing specificity. Finally, because antidepressants may affect DTI variables (Sijens et al., 2008; Taylor et al., 2011), use of unmedicated samples is critical.

Therefore, we examined MASQ and DTI data from unmedicated adults with MDD and healthy controls who completed functional magnetic resonance imaging (MRI) studies (Dillon, Dobbins, & Pizzagalli, 2014; Dillon & Pizzagalli, 2013). Guided by recent meta-analyses, we extracted FA values from *a priori* regions of interest (ROIs), such as the genu of the corpus callosum, the cingulum bundle near the anterior cingulate cortex (ACC) and hippocampus, the UF, ALIC, and MFB. We also extracted FA values from the anterior corona radiata, as reduced FA in this region has been reported in depression (Cole et al., 2012).

We also extracted estimates of radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD) from each ROI. In rodents, demyelination is correlated with increased RD, which corresponds to diffusivity perpendicular to white matter, but is less strongly related to AD, corresponding to diffusivity parallel to white matter, or MD, corresponding to overall diffusivity (Budde et al., 2007; Song et al., 2005). Research in humans with multiple sclerosis has also linked demyelination to increased RD (Klawiter et al., 2011). Thus, if MDD is associated with decreased FA and increased RD, this would suggest an association between MDD and demyelination. Interpretation of RD can be difficult, especially where crossing fibers are present (Wheeler-Kingshott & Cercignani, 2009). Nevertheless, we predicted that depressed adults would show reduced FA, and that anhedonia and depressive severity would be negatively related to FA but positively related to RD, even after controlling for anxiety.

2 | MATERIALS AND METHODS

2.1 | Participants

DTI data were collected from 38 unmedicated adults who met DSM-IV criteria for current MDD and 52 healthy controls (Dillon et al., 2014; Dillon & Pizzagalli, 2013). Psychiatric history was assessed with the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002). Depressed participants had to meet criteria for current MDD with no history of psychosis and had to be unmedicated, although past use of psychotropic compounds was allowed (no use in the preceding 2 weeks for benzodiazepines, 6 weeks for selective serotonin reuptake inhibitors, 6 months for dopaminergic drugs). Comorbid anxiety was allowed if secondary to depression. Controls reported no current or past Axis I diagnosis, and no participant presented with neurological conditions or significant medical history, or met criteria for lifetime substance dependence or substance abuse in the past year. The studies were approved by the Harvard University Committee on the Use of Human Subjects in Research and the Partners HealthCare Human Research Committee. Participants were right handed and 18–64 years old; they provided informed consent and were paid $25/hr.

2.2 | Data acquisition

2.2.1 | Diffusion tensor imaging

DTI data were collected on a Siemens 3T Tim Trio scanner using a protocol (Holmes et al., 2015) that began with a localizer scan, an autoalign scout (van der Kouwe et al., 2005), and collection of T1-weighted (van der Kouwe et al., 2008) and T2-weighted anatomical data. DTI was conducted next (TE = 85 ms, FOV = 220 × 220 mm, voxels = 1.4 × 1.4 × 3.0 mm, *b* value = 1,000 s/mm^2, six directions). During data collection, the TR used during DTI acquisition changed from 5,960 to 6,110 ms; there was no group difference on this variable (5,960 ms: 15 MDD, 29 controls; 6,110 ms: 23 MDD, 23 controls; $\chi^2(1) = 1.73$, $P = 0.19$).

2.2.2 | Questionnaires

Participants completed the Beck Depression Inventory-II (Beck et al., 1996) and the MASQ. MASQ data were not collected for one control and one depressed participant. For correlations with DTI metrics, only MASQ scores were considered because they allowed us to test whether relationships with anhedonia and depression severity remained when accounting for anxiety.

2.3 | Data analysis

2.3.1 | Diffusion tensor imaging

Preprocessing was conducted using the fMRIB Software Library (FSL; Smith et al., 2004) and included skull stripping, motion correction, and eddy correction with reorientation of the *b* matrix. The method used to correct echoplanar imaging (EPI)/susceptibility distortions has been described (Irfanoglu, Walker, Sarlls, Marenco, & Pierpaoli, 2012). To avoid inclusion of gray matter and cerebrospinal fluid, DTI values were extracted from voxels with FA values > 0.2. After correction of the diffusion-weighted images, FA values were obtained with nonlinear least squares tensor fitting as it provides accurate noise modeling. Participant maps were registered to a study-specific template constructed using a subset of 20 participants and the DTI toolkit (Wang et al., 2011; Zhang et al., 2006), an optimized tensor-based registration tool that yields better results than scalar-based registration (Adluru et al., 2012). All diffusion tensor maps were normalized to this

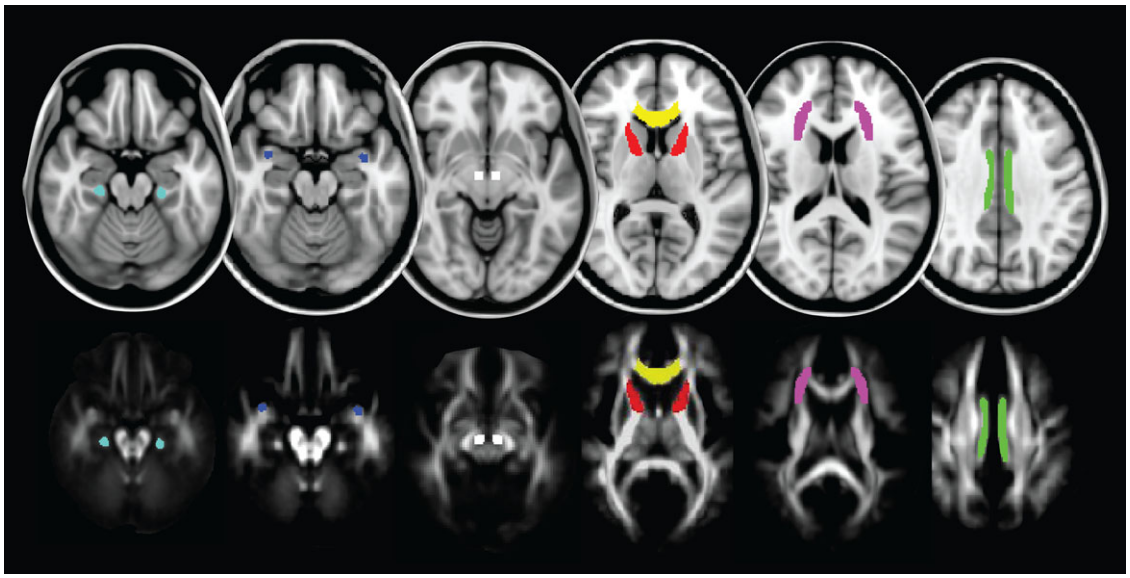

FIGURE 1 FA, RD, AD, and MD were extracted from ROIs in (from left to right) the cingulum of the hippocampus (cyan), uncinate fasciculus (blue), median forebrain bundle (white), corpus callosum (yellow), anterior limb of the internal capsule (ALIC; red), anterior corona radiata (purple), and cingulum of the anterior cingulate cortex (ACC; green). The ROI for the median forebrain bundle appears rectangular in this plane but was actually a 3-mm sphere

template with rigid, affine, and diffeomorphic alignments and interpolated to 1.4 mm^3 voxels. Finally, the Johns Hopkins International Consortium for Brain Mapping FA template was warped to the study-specific template space using Advanced Normalization Tools (Avants et al., 2011). Images were visually inspected to ensure adequate registrations.

2.3.2 | Regions of interest

We extracted FA, RD, AD, and MD data from six ROIs in the Johns Hopkins University ICBM-DTI-81 atlas (Hua et al., 2008): the genu of the corpus callosum (CC), ALIC, cingulum of the ACC, cingulum of the hippocampus, anterior corona radiata, and UF (Fig. 1). To assess the MFB, we used 3-mm radius spheres around published MNI coordinates (±6, −14, −8; Schlaepfer, Bewernick, Kayser, Mädler, & Coenen, 2013); the spheres did not overlap with any other ROI. ROIs were bilateral (2 hemispheres × 7 ROIs = 14 values). DTI data were available from the CC for all participants, but in the other ROIs we excluded poor quality data from two healthy and three depressed participants.

2.3.3 | Statistics

First, we computed a *Group* × *Gender* × *ROI* × *Hemisphere* ANCOVA on mean FA values, with SNR and age as covariates. The Greenhouse–Geisser correction was applied in case of violations of sphericity. A separate *Group* × *Gender* × *Hemisphere* ANCOVA was run for the genu as more data were available for this structure than for the other ROIs. Second, for ROIs showing reduced FA in MDD, we computed *Group* × *Gender* × *ROI* × *Hemisphere* ANCOVAs for AD, RD, and MD. Third, in ROIs that revealed group differences in DTI metrics, we computed partial correlations with MASQ-GDD or MASQ-AD scores in the depressed participants, again regressing out SNR and age. To test specificity, we performed hierarchical multiple regressions in which MASQ-GDA and MASQ-AA scores were entered first and MASQ-GDD or MASQ-AD scores were entered second. For these exploratory analyses, we did not correct for multiple comparisons. Alpha was set to 0.05, and all tests were two tailed.

TABLE 1 Mean (SD) Demographic and Self-Report Data

Variable	Controls $n = 52$	Depressed $n = 38$	*P* Value	Effect Size
Gender	25 F, 27 M	21 F, 17 M	0.65	0.07
Age	33.75 (13.46)	33.45 (10.44)	0.12	0.03
Education (years)	16.00 (1.83)	15.97 (2.27)	0.95	0.01
BDI-II	1.51 (2.10)	23.97 (9.10)	0.001	3.68
MASQ-GDA	13.47 (3.30)	25.03 (6.00)	0.001	2.50
MASQ-AA	18.37 (1.85)	25.00 (8.36)	0.001	1.18
MASQ-GDD	13.76 (2.57)	38.41 (10.23)	0.001	3.56
MASQ-AD	46.41 (11.36)	82.89 (8.77)	0.001	3.53

P values reflect two-sample *t*-tests except for *gender* (chi-square test). Effect size is given as the absolute value of Hedges' *g* (Cramer's *V* for *gender*). The mean Beck Depression Inventory-II (BDI-II) score in the MDD group indicates moderate depression.
F, female; M, male.

3 | RESULTS

3.1 | Demographics and clinical data

There were no group differences in gender, age, or education (Table 1). The MASQ showed that, relative to controls, depressed adults were experiencing more distress, AA, and anhedonia.

As shown in Table 2, 29% of depressed participants were in their first episode, with the rest in recurrence. Depressed participants were unmedicated; 61% reported no prior psychotropic medication. Of 38

TABLE 2 Clinical Information for Depressed Participants

Clinical Variable	Value
N (%) in first MDE	11 (29%)
N (%) in recurrent MDE	27 (71%)
Mean (SD) past MDEs in recurrent group	4.67 (2.86)
Mean (SD) years since onset of first MDE	14.03 (10.02)
N (%) reporting past psychotropic use	15 (39%)
N (%) reporting no past psychotropic use	23 (61%)
N (%) with comorbid anxiety disorder	16 (42%)
N (%) with no comorbid anxiety disorder	22 (58%)

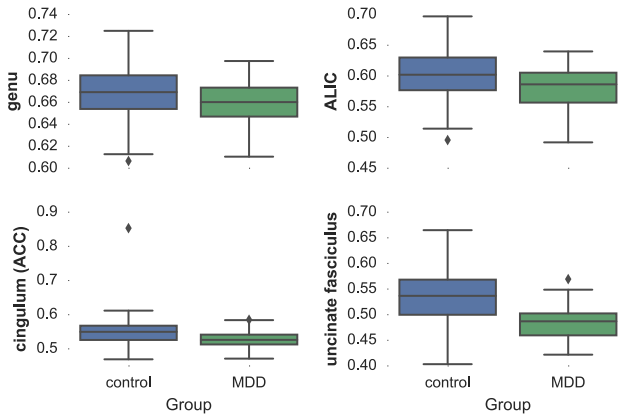

FIGURE 2 FA was reduced in the MDD group relative to the control group in four of seven ROIs: the genu of the corpus callosum, the anterior limb of the internal capsule (ALIC), the cingulum bundle near the ACC, and the uncinate fasciculus. The group difference in the cingulum remained significant after removal of the extreme outlier in the control group. Boxes show quartiles (center line indicates the median), with whiskers extending to 1.5 times the interquartile range

depressed participants, 42% met full criteria for a comorbid anxiety disorder, including social phobia (n = 10), panic disorder (n = 2), specific phobia (n = 1), social phobia and panic disorder (n = 1), or social phobia, specific phobia, and panic disorder (n = 2). Current binge eating disorder was diagnosed in two depressed participants.

3.2 | Fractional anisotropy

Mean (±SD) SNR was similar in the MDD (7.45 ± 0.87) and control (7.25 ± 0.66) groups, $t(88) = -1.26$, $P = 0.21$, Hedges' $g = -0.27$. The ANCOVA on genu FA revealed an effect of *Group*, $F(1, 83) = 4.26$, $P = 0.04$, $\eta_p^2 = 0.05$. As shown in Figure 2, this reflected reduced FA in MDD. The ANCOVA on the remaining ROIs also yielded an effect of *Group*, $F(1, 79) = 20.61$, $P < 0.001$, $\eta_p^2 = 0.21$, which was qualified by a *Group* × *Gender* interaction, $F(1, 79) = 3.97$, $P < 0.05$, $\eta_p^2 = 0.05$. Post hoc Tukey tests revealed lower FA values in depressed versus healthy males (mean ± SE: controls = 0.55 ± 0.07, MDD = 0.52 ± 0.07, $P < 0.001$); the effect was not significant in females (controls = 0.53 ± 0.07, MDD = 0.52 ± 0.07, $P = 0.28$). Importantly, there was also a *Group* × *ROI* interaction, $F(4, 277) = 11.62$, $P < 0.001$, $\eta_p^2 = 0.13$. Follow-up ANCOVAs yielded no effect of *Group* in the MFB, cingulum near the hippocampus, or corona radiata, Fs < 1. However, there were *Group* effects in the ALIC, $F(1, 79) = 9.78$, $P = 0.002$, $\eta_p^2 = 0.11$, cingulum near the ACC, $F(1, 79) = 8.91$, $P = 0.004$, $\eta_p^2 = 0.10$, and UF, $F(1, 79) = 29.50$, $P < 0.001$, $\eta_p^2 = 0.27$, all reflecting reduced FA in MDD (Fig. 2). The difference in the cingulum remained after removing an outlier from the controls, $F(1, 80) = 8.66$, $P = 0.004$, $\eta_p^2 = 0.10$.

3.3 | Mean diffusivity, axial diffusivity, and radial diffusivity

In the ROIs that showed group differences in FA, we conducted *Group* × *Gender* × *ROI* × *Hemisphere* ANCOVAs on MD, AD, and RD. For all three measures, the *Group* x *Hemisphere* interaction was significant, Fs > 4.30, Ps < 0.05. In controls, follow-up Tukey tests revealed lower values in the left versus right hemisphere for MD (mean ± SE: left = 0.70 ± 0.01, right = 0.73 ± 0.01, $P < 0.001$), AD (left = 1.03 ± 0.01, right = 1.05 ± 0.01, $P < 0.03$), and RD (left = 0.54 ± 0.01, right = 0.57 ± 0.01, $P < 0.001$). None of these measures differed by hemisphere in the MDD group (MD: left = 0.73 ± 0.01, right = 0.74 ± 0.01, $P = 0.61$; AD: left = 1.05 ± 0.01, right = 1.04 ± 0.01, $P = 0.99$; RD: left = 0.57 ± 0.01, right = 0.58 ± 0.01, $P = 0.17$). Left hemisphere RD values were lower in healthy versus depressed participants, $t(109) = -2.76$, $P = 0.03$. No other effects involving *Group* were significant.

3.4 | Relationships with anhedonia and depressive severity

3.4.1 | Fractional anisotropy

There was a negative relationship between depressive severity (MASQ-GDD) and FA in the genu ($r = -0.44$, $P < 0.01$). Anhedonia (MASQ-AD) was negatively related with FA in the genu ($r = -0.42$, $P = 0.01$), the cingulum near the ACC ($r = -0.43$, $P = 0.01$), and the UF ($r = -0.42$, $P = 0.02$). Hierarchical regressions indicated that the association between depressive severity and genu FA was not significant after accounting for anxiety (MASQ-GDA and MASQ-AA), $\beta = -.31$, $P = 0.10$. By contrast, higher anhedonia remained related to lower FA in the genu, cingulum near the ACC, and UF after accounting for anxiety, βs < −0.36, Ps < 0.03. Moreover, adding MASQ-AD scores improved the models in each ROI, Fs > 5.69, Ps < 0.03, ΔR^2s > 0.13. These relationships are shown in Figure 3.

3.4.2 | Radial diffusivity

RD was positively associated with depressive severity and anhedonia in the genu (severity: $r = 0.36$, $P = 0.04$; anhedonia: $r = 0.44$, $P = 0.01$) and ALIC (severity: $r = 0.37$, $P = 0.04$; anhedonia: $r = 0.36$, $P = 0.04$). The relationship between severity and RD in the genu did not remain significant after accounting for anxiety, $\beta = 0.20$, $P = 0.29$. However, the link between anhedonia and genu RD did, $\beta = 0.41$, $P < 0.01$, as did both relationships with RD in the ALIC (anhedonia: $\beta = 0.39$, $P = 0.02$; severity: $\beta = 0.54$, $P = 0.005$), all Fs > 5.7, all $\Delta R^2 > 0.14$. These associations are shown in Figure 4.

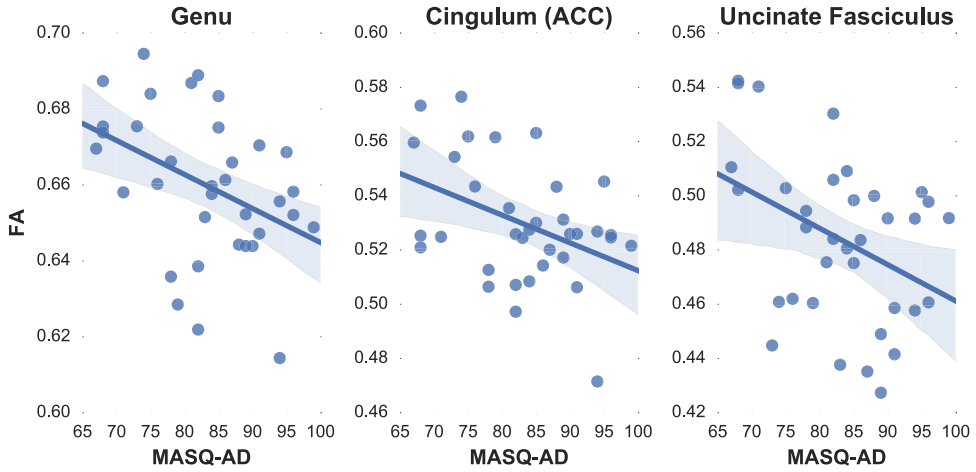

FIGURE 3 Individual differences in anhedonia are related to variation in FA in the genu of the corpus callosum, the cingulum bundle near the ACC, and the uncinate fasciculus

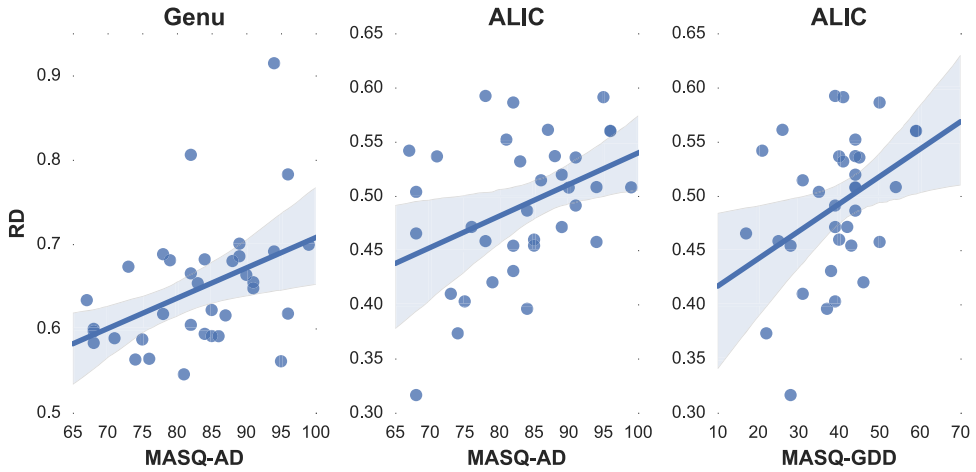

FIGURE 4 Individual differences in anhedonia are related to variation in RD in the genu of the corpus callosum (left) and the anterior limb of the internal capsule (ALIC) (middle); individual differences in depressive severity are also related to variation in RD in the ALIC (right)

3.5 | Clinical heterogeneity

We repeated the ANCOVAs on FA after excluding both participants with binge eating disorder. This reduced the group difference in the genu to a trend, $F(1, 81) = 3.08$, $P = 0.08$, $\eta_p^2 = 0.04$, but all other findings were unchanged. Next, we omitted data from controls and re-ran the ANCOVA on FA values three times, dichotomizing the MDD group to capture important clinical phenomena. First, we grouped depressed participants based on the presence ($n = 16$) versus absence ($n = 22$) of comorbid *Anxiety*. This yielded an *Anxiety* × *ROI* × *Hemisphere* interaction, $F(4, 109) = 4.12$, $P = 0.005$, $\eta_p^2 = 0.12$, but follow-up ANCOVAs in each ROI revealed no main effects of *Anxiety* and only a trend-level ($P = 0.06$) *Anxiety* × *Hemisphere* interaction in the cingulum near the ACC. Next, we grouped the depressed adults based on whether they did ($n = 15$) versus did not ($n = 23$) report a history of *Prior Psychotropics*; no effects involving this factor were significant ($Fs < 1.42$, $Ps > 0.23$). Finally, we grouped depressed adults according to whether they were ($n = 11$) versus were not ($n = 27$) in their first episode. This yielded an *Episode* × *Gender* interaction, $F(1, 29) = 4.59$, $P = 0.04$, $\eta_p^2 = 0.14$; follow-up *t*-tests revealed a gender difference for individuals in their first episode (females = 0.43 ± 0.01, males = 0.45 ± 0.01, $t(9) = -2.60$, $P = 0.03$, $g = 1.76$), but not for those in recurrence (females = 0.43 ± 0.01, males = 0.43 ± 0.01, $t(22) < 1$, $P = 0.83$, $g = 0.09$).

4 | DISCUSSION

This analysis yielded two main results. First, relative to controls, depressed adults showed reduced FA in the genu of the corpus callosum, the ALIC, the cingulum near the ACC, and the UF. This pattern is consistent with prior studies (Bracht, Jones, Müller, Wiest, & Walther, 2015; Chen et al., 2016). Second, partial correlations revealed negative relationships between anhedonia and FA in the genu, the cingulum near the ACC, and the UF, as well as positive relationships between anhedonia and RD in the genu and ALIC, and depressive severity and RD in the ALIC. Critically, these relationships remained significant after accounting for anxiety. This second set of findings is noteworthy because few studies have examined the relationship between FA and anhedonia, and none have demonstrated that such relationships

persist after controlling for anxiety. These results strengthen the case for a negative effect of anhedonia (and depressive severity) on the structural integrity of white matter pathways in depressed adults, with effects again emerging in the genu, cingulum, UF, and ALIC (Bracht, Linden et al., 2015).

The cause of reduced FA in the depressed sample is unclear, but the associations with increased RD are striking as they suggest an underlying mechanism (for additional evidence of reduced FA and increased RD in depression, see Henderson et al., 2013). Specifically, several rodent studies have linked increased RD to reduced myelination. For example, Song et al. (2002) reported that, compared to wild-type mice, shiverer mice—that lack myelin due to a genetic mutation (Readhead & Hood, 1990)—showed normal AD and MD values but significantly elevated RD in several brain regions. Similarly, experimentally manipulating the myelination status of the corpus callosum in wild-type mice caused corresponding changes in RD, not in AD (Song et al., 2005). By contrast, inducing ischemia to damage axons caused rapid reductions in AD and MD but not in RD, indicating that RD is not particularly sensitive to nerve damage (Song et al., 2003). Therefore, increased RD appears to reflect demyelination, not nerve damage. Consistent with this hypothesis, RD was a sensitive marker of demyelination in spinal cord samples taken from humans with multiple sclerosis (Klawiter et al., 2011). Therefore, demyelination may contribute to lowered FA in the MDD group. This account is speculative, and because of technical complexities (Wheeler-Kingshott & Cercignani, 2009), a definitive account of reduced FA in MDD awaits future studies. However, supporting our interpretation, a postmortem study found reduced myelination of deep white matter tracts in adults with unipolar or bipolar depression versus healthy controls (Regenold et al., 2007).

The cause of an association between depression and disrupted myelination is unknown, but Sacchet and Gotlib (2017) highlighted two candidate mechanisms. In a quantitative MRI study, they used the longitudinal relaxation rate R1 (1/T1) as a proxy for myelination status and found that myelination was reduced in depressed versus healthy adults at the whole-brain level and particularly in the nucleus accumbens. Because myelination is dynamic and changes with experience (Fields, 2008), one possibility is that brain activity is reduced overall in depressed adults, which leads to broad reductions in myelination. A second possibility is that psychosocial stress—a potent risk factor for initial depressive episodes (Monroe & Harkness, 2005)—induces inflammation, which produces cytokines that degrade myelin. It is unclear whether either of these accounts is correct, but they offer testable accounts of reduced myelination in depression.

Finally, the fact that Sacchet and Gotlib (2017) detected reduced nucleus accumbens myelination in MDD suggests that white matter changes may contribute to anhedonia in depression. The current findings strengthen this argument. As reviewed by Haber and Behrens (2014), the cingulum bundle and the UF are major dorsal and ventral "limbic" white matter tracts that connect the frontal, temporal, and parietal lobes, while the internal capsule—including the ALIC—connects the PFC with subcortical structures. These pathways join regions that contribute directly to reinforcement learning by coding reward value (ventromedial PFC), maintaining stimulus-reward associations (orbitofrontal cortex), and guiding action selection (dorsal ACC). Therefore, the observation of reliable correlations between anhedonia and both FA and RD in these tracts supports the hypothesis that structural abnormalities in reward network connections contribute to the pathophysiology of AD. In this context, it is noteworthy that the cingulum bundle, UF, and ALIC are all targeted by deep brain stimulation or psychosurgery for depression and anxiety (Haber & Behrens, 2014).

This study is strengthened by the well-characterized and unmedicated depressed sample. However, there are several limitations. First, with only six diffusion-encoding gradient directions, we cannot perform probabilistic tractography or tract-based spatial statistics. Additional research using improved DTI methodologies is clearly warranted. Second, partial volume effects may have occurred during resampling, although we limited this by extracting DTI from voxels with FA values > 0.2. Third, the partial correlations were exploratory and would not survive Bonferroni correction. Finally, there was clinical heterogeneity in our MDD sample, although our analysis of comorbid anxiety, past psychotropic use, and first episode versus recurrence suggested limited effects of these factors.

5 | CONCLUSIONS

This study contributes to the literature on structural connectivity in depression. In addition to replicating previously observed group differences in FA, we related reduced FA and increased RD to variation in anhedonia and depressive severity, controlling for anxiety. It would be valuable to investigate the physiological basis for these effects (Wheeler-Kingshott & Cercignani, 2009). Given the heterogeneity of MDD and evidence that FA may be sensitive to MDD chronicity (Chen et al., 2016), it would also be useful to compare depressive subtypes (melancholic vs. atypical) in larger samples (Bracht et al., 2014).

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REFERENCES

Adluru, N., Zhang, H., Fox, A. S., Shelton, S. E., Ennis, C. M., Bartosic, A. M., … Alexander, A. L. (2012). A diffusion tensor brain template for rhesus macaques. *Neuroimage*, *59*, 306–318.

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, *4*, 316–329.

American Psychiatric Associations. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage*, *54*, 2033–2044.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck depression inventory-II*. San Antonio, TX: Psychological Corporation.

Bracht, T., Horn, H., Werner, S., Federspiel, A., Schnell, S., Hofle, O., … Walther, S. (2014). White matter microstructure alterations of the medial forebrain bundle in melancholic depression. *Journal of Affective Disorders*, *155*, 186–193.

Bracht, T., Jones, D. K., Müller, T. J., Wiest, R., & Walther, S. (2015). Limbic white matter microstructure plasticity reflects recovery from depression. *Journal of Affective Disorders*, *170*, 143–149.

Bracht, T., Linden, D., & Keedwell, P. (2015). A review of white matter microstructure alterations of pathways of the reward circuit in depression. *Journal of Affective Disorders*, *187*, 45–53.

Budde, M. D., Kim, J. H., Liang, H. F., Schmidt, R. E., Russell, J. H., Cross, A. H., & Song, S. K. (2007). Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. *Magnetic Resonance in Medicine*, *57*, 688–695.

Chen, G., Hu, X., Li, L., Huang, X., Lui, S., Kuang, W., … Gong, Q. (2016). Disorganization of white matter architecture in major depressive disorder: A meta-analysis of diffusion tensor imaging with tract-based spatial statistics. *Scientific Reports*, *6*, 21825. DOI: 10.1038/srep21825

Coenen, V. A., Schlaepfer, T. E., Maedler, B., & Panksepp, J. (2011). Cross-species affective functions of the medial forebrain bundle—Implications for the treatment of affective pain and depression in humans. *Neuroscience and Biobehavioral Reviews*, *35*, 1971–1981.

Cole, J., Chaddock, C. A., Farmer, A. E., Aitchison, K. J., Simmons, A., McGuffin, P., & Fu, C. H. (2012). White matter abnormalities and illness severity in major depressive disorder. *British Journal of Psychiatry*, *201*, 33–39.

Dillon, D. G., Dobbins, I. G., & Pizzagalli, D. A. (2014). Weak reward source memory in depression reflects blunted activation of VTA/SN and parahippocampus. *Social Cognitive and Affective Neuroscience*, *9*, 1576–1583.

Dillon, D. G., & Pizzagalli, D. A. (2013). Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. *Psychiatry Research–Neuroimaging*, *212*, 99–107.

Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*, *31*, 361–370.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR Axis I disorders, research version, patient edition (SCID-I/P)*. New York, NY: Biometrics Research, New York State Psychiatric Institute.

Haber, S. N., & Behrens, T. E. J. (2014). The neural network underlying incentive-based learning: Implications for interpreting circuit disruptions in psychiatric disorders. *Neuron*, *83*, 1019–1039.

Henderson, S. E., Johnson, A. R., Vallejo, A. I., Katz, L., Wong, E., & Gabbay, V. (2013). A preliminary study of white matter in adolescent depression: Relationships with illness severity, anhedonia, and irritability. *Frontiers in Psychiatry*, *4*, 152. https://doi.org/10.3389/fpsyt.2013.00152

Holmes, A. J., Hollinshead, M. O., O'Keefe, T. M., Petrov, V. I., Fariello, G. R., Wald, L. L., … Buckner, R. L. (2015). Brain Genomics Superstruct Project initial data release with structural, functional, and behavioral measures. *Scientific Data*, *2*, 150031. https://doi.org/10.1038/sdata.2015.31

Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., … Mori, S. (2008). Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. *Neuroimage*, *39*, 336–347.

Irfanoglu, M. O., Walker, L., Sarlls, J., Marenco, S., & Pierpaoli, C. (2012). Effects of image distortions originating from susceptibility variations and concomitant fields on diffusion MRI tractography results. *Neuroimage*, *61*, 275–288.

Jiang, J., Zhao, Y. J., Hu, X. Y., Du, M. Y., Chen, Z. Q., Wu, M., … Gong, Q. Y. (2016). Microstructural brain abnormalities in medication-free patients with major depressive disorder: A systematic review and meta-analysis of diffusion tensor imaging. *Journal of Psychiatry & Neuroscience*, *42*, 150–163.

Keedwell, P. A., Andrew, C., Williams, S. C. R., Brammer, M. J., & Phillips, M. L. (2005). The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*, *58*, 843–853.

Keedwell, P. A., Chapman, R., Christiansen, K., Richardson, H., Evans, J., & Jones, D. K. (2012). Cingulum white matter in young women at risk of depression: The effect of family history and anhedonia. *Biological Psychiatry*, *72*, 296–302.

Klawiter, E. C., Schmidt, R. E., Trinkaus, K., Liang, H. F., Budde, M. D., Naismith, R. T., … Benzinger, T. L. (2011). Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords. *Neuroimage*, *55*, 1454–1460.

Liao, Y., Huang, X., Wu, Q., Yang, C., Kuang, W., Du, M., … Gong, Q. (2013). Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *Journal of Psychiatry & Neuroscience*, *38*, 49–56.

Monroe, S. M., & Harkness, K. L. (2005). Life stress, the" kindling" hypothesis, and the recurrence of depression: Considerations from a life stress perspective. *Psychological Review*, *112*, 417–445.

Readhead, C., & Hood, L. (1990). The dysmyelinating mouse mutations shiverer (shi) and myelin deficient (shimld). *Behavior Genetics*, *20*, 213–234.

Regenold, W. T., Phatak, P., Marano, C. M., Gearhart, L., Viens, C. H., & Hisley, K. C. (2007). Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry Research*, *151*, 179–188.

Sacchet, M. D., & Gotlib, I. H. (2017). Myelination of the brain in major depressive disorder: An in vivo quantitative magnetic resonance imaging study. *Scientific Reports*, *7*, 2200. https://doi.org/10.1038/s41598-017-02062-y

Schlaepfer, T. E., Bewernick, B. H., Kayser, S., Mädler, B., & Coenen, V. A. (2013). Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biological Psychiatry*, *73*, 1204–1212.

Sijens, P. E., Mostert, J. P., Irwan, R., Potze, J. H., Oudkerk, M., & De Keyser, J. (2008). Impact of fluoxetine on the human brain in multiple sclerosis as quantified by proton magnetic resonance spectroscopy and diffusion tensor imaging. *Psychiatry Research: Neuroimaging*, *164*, 274–282.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, 208–219.

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage*, *20*, 1714–1722.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*, *17*, 1429–1436.

Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage*, *26*, 132–140.

Taylor, W. D., MacFall, J. R., Boyd, B., Payne, M. E., Sheline, Y. I., Krishnan, R. R., & Doraiswamy, P. M. (2011). One-year change in anterior cingulate cortex white matter microstructure: Relationship with late-life depression outcomes. *American Journal of Geriatric Psychiatry*, *19*, 43–52.

van der Kouwe, A. J. W., Benner, T., Fischl, B., Schmitt, F., Salat, D. H., Harder, M., … Dale, A. M. (2005). On-line automatic slice positioning for brain MR imaging. *Neuroimage*, *27*, 222–230.

van der Kouwe, A. J. W., Benner, T., Salat, D. H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *Neuroimage*, *40*, 559–569.

Wang, Y., Gupta, A., Liu, Z., Zhang, H., Escolar, M. L., Gilmore, J. H., … Styner, M. (2011). DTI registration in atlas based fiber analysis of infantile Krabbe disease. *Neuroimage*, *55*, 1577–1586.

Watson, D., Weber, K., Assenheimer, J. S., Clark, L. A., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology*, *104*, 3–14.

Wheeler-Kingshott, C. A. M., & Cercignani, M. (2009). About "*axial*, " and "radial" diffusivities. *Magnetic Resonance in Medicine*, *61*, 1255–1260.

Wise, T., Radua, J., Nortje, G., Cleare, A. J., Young, A. H., & Arnone, D. (2016). Voxel-based meta-analytical evidence of structural disconnectivity in major depression and bipolar disorder. *Biological Psychiatry*, *79*, 293–302.

Zhang, H., Yushkevich, P. A., Alexander, D. C., & Gee, J. C. (2006). Deformable registration of diffusion tensor MR images with explicit orientation optimization. *Medical Image Analysis*, *10*, 764–785.

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