

Review Article

Cite this article: Xu EP, Nguyen L, Leibenluft E, Stange JP, Linke JO (2023). A meta-analysis on the uncinate fasciculus in depression. *Psychological Medicine* **53**, 2721–2731. <https://doi.org/10.1017/S0033291723000107>

Received: 22 August 2022

Revised: 29 December 2022

Accepted: 9 January 2023

First published online: 13 April 2023

Keywords:

comorbid anxiety; depression; first-degree relatives; fractional anisotropy; radial diffusivity; uncinate fasciculus; white matter

Corresponding author:

Ellie P. Xu; E-mail: xuellie@gmail.com

A meta-analysis on the uncinate fasciculus in depression

Ellie P. Xu¹ , Lynn Nguyen², Ellen Leibenluft², Jonathan P. Stange^{1,3} and Julia O. Linke^{2,4}

¹Department of Psychology, University of Southern California, Los Angeles, CA, USA; ²National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA; ³Department of Psychiatry and Behavioral Sciences, University of Southern California, Los Angeles, CA, USA and ⁴Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, Houston, TX, USA

Abstract

Aberrant microstructure of the uncinate fasciculus (UNC), a white matter (WM) tract implicated in emotion regulation, has been hypothesized as a neurobiological mechanism of depression. However, studies testing this hypothesis have yielded inconsistent results. The present meta-analysis consolidates evidence from 44 studies comparing fractional anisotropy (FA) and radial diffusivity (RD), two metrics characterizing WM microstructure, of the UNC in individuals with depression ($n = 5016$) to healthy individuals ($n = 18\,425$). We conduct meta-regressions to identify demographic and clinical characteristics that contribute to cross-study heterogeneity in UNC findings. UNC FA was reduced in individuals with depression compared to healthy individuals. UNC RD was comparable between individuals with depression and healthy individuals. Comorbid anxiety explained inter-study heterogeneity in UNC findings. Depression is associated with perturbations in UNC microstructure, specifically with respect to UNC FA and not UNC RD. The association between depression and UNC microstructure appears to be moderated by anxiety. Future work should unravel the cellular mechanisms contributing to aberrant UNC microstructure in depression; clarify the relationship between UNC microstructure, depression, and anxiety; and link UNC microstructure to psychological processes, such as emotion regulation.

Major depressive disorder (MDD), a leading cause of disability worldwide (World Health Organization, 2017), has been linked to the habitual use of dysfunctional emotion regulation strategies (Joormann & Stanton, 2016). Neurobiological models of MDD have proposed that alterations in cortical-limbic pathways contribute to these deficits in emotion regulation (Kupfer, Frank, & Phillips, 2012; Mayberg, 1997). In particular, the altered microstructure of the uncinate fasciculus (UNC), a white matter (WM) tract that connects key regions of the cortico-limbic circuit (i.e. amygdala and ventral prefrontal cortex), has been hypothesized to lead to aberrant emotion regulation in individuals with MDD (Zheng et al., 2018). However, evidence regarding perturbed UNC microstructure in individuals with MDD is mixed. Numerous studies that use a tract-of-interest (TOI) approach report atypical UNC microstructure in MDD (Table 1), but whole-brain meta-analyses yield null findings (Chen et al., 2016; Jiang et al., 2017; Liao et al., 2013; Murphy & Frodl, 2011; Zhou et al., 2022). To answer the question of whether atypical UNC microstructure represents a neurobiological mechanism and potential treatment target for depression, the present meta-analysis extends the existing literature on UNC microstructure in MDD by consolidating evidence from 44 TOI studies.

UNC microstructure is most commonly quantified as fractional anisotropy (FA), a metric derived from diffusion tensor imaging (DTI) that correlates positively with the directionality and coherence of fibers within a WM bundle (Basser, Mattiello, & LeBihan, 1994). Other indices used to characterize WM are axial diffusivity (AD) indicating diffusion along the main direction of the fibers, radial diffusivity (RD) measuring diffusion orthogonal to the main direction of the fibers, and mean diffusivity (MD) describing the rotationally invariant magnitude of diffusion. These three metrics have been associated with different tissue properties. AD is thought to reflect axonal organization and degeneration (Budde, Xie, Cross, & Song, 2009; Harsan et al., 2006), RD has been shown to relate to the degree of myelination in animals (Song et al., 2002), and MD has been proposed to reflect variations within the intra- and extracellular space and a reduction in neuropil (Selemon & Goldman-Rakic, 1999). Aside from FA, RD is the metric that has been most intensely studied and discussed in the context of MDD (Dillon, Gonenc, Belleau, & Pizzagalli, 2018). However, similar to the status of UNC FA, findings regarding UNC RD in depression are largely inconsistent (Table 1). Thus, it is of particular importance to integrate available evidence on these metrics (i.e., FA and RD), but integration of evidence regarding the other two metrics (i.e., AD and MD) might also advance

Table 1. Characteristics of studies comparing fractional anisotropy or radial diffusivity in the uncinate fasciculus between individuals with depression and healthy controls

Study Information			Individuals with Depression							Healthy Control Individuals		
First Author & Year	DTI Processing Pipeline	RD	<i>n</i>	Mean Age (Years)	Female (%)	Illness Duration (Years)	Taking Psychotropic Medications (%)	HDRS-17 Score	Comorbid Lifetime Anxiety (%)	<i>n</i>	Mean Age (Years)	Female (%)
Aghajani et al. (2014)	TBSS	X	25	15.60	84.00	–	0.00	–	72.00	21	14.70	85.71
Benedetti et al. (2011)	Tractography	X	15	50.50	66.67	19.70	100.00	–	0.00	21	46.40	47.62
Bhatia, Henderson, Hsu, & Yim (2018)	Tractography		103	34.50	52.43	14.10	100.00	–	–	74	39.20	48.65
Canu et al. (2015)	Tractography	X	71	45.04	80.28	7.75	100.00	23.25	29.58	71	45.30	80.28
Carballedo et al. (2012)	Tractography		37	40.40	67.57	14.10	64.86	28.20	0.00	42	36.30	59.52
Charlton et al. (2014)	Tractography	X	23	65.65	82.61	–	0.00	–	0.00	23	66.30	69.57
Choi et al. (2016)	Tractography		50	–	–	–	–	–	0.00	30	–	–
Choi et al. (2016)	Tractography		36	–	–	–	–	–	0.00	34	–	–
Cullen et al. (2020)	Tractography		44	15.90	25.00	–	6.80	–	45.45	37	16.30	32.40
Davis et al. (2019)	TBSS		165	35.73	62.78	–	0.00	–	–	103	33.20	63.90
de Kwaasteniet et al. (2013)	Tractography		18	44.60	77.78	–	33.33	19.17	–	24	40.20	66.67
Deng et al. (2018)	Tractography		31	30.10	58.06	3.17	0.00	25.60	–	44	28.30	38.64
Dillon et al. (2018)	Tractography	X	38	33.45	55.26	14.03	0.00	–	42.00	52	33.75	48.08
Doolin et al. (2019)	Tractography		14	44.21	71.43	–	85.71	24.36	–	12	40.75	66.67
Green et al. (2021)	TBSS		227	56.90	74.89	–	–	–	–	537	60.40	51.21
Han et al. (2018)	Tractography		95	43.14	80.00	3.80	53.68	15.00	–	65	40.20	69.23
Harada et al. (2016)	Tractography		45	60.20	57.78	10.60	91.11	–	4.44	61	62.90	72.13
Heij et al. (2019)	TBSS	X	49	48.98	34.69	–	30.61	–	42.86	39	52.10	48.72
Hermens et al. (2018)	Tractography		94	21.50	57.40	5.40	67.02	13.70	62.00	59	23.80	64.40
Ho et al. (2021)	Tractography	X	48	16.32	70.80	4.16	47.90	–	50.00	35	15.75	54.30
Jiang et al. (2015)	Tractography		35	29.54	51.43	1.07	0.00	27.70	0.00	34	31.91	50.00
Kochunov et al. (2021)	Tractography		2248	63.40	64.19	–	–	–	26.82	15 131	64.90	50.23
Koreki et al. (2021)	Tractography		15	34.60	80.00	3.40	0.00	19.70	–	27	34.70	70.37
Korgaonkar, Williams, Song, Usherwood, & Grieve (2014)	TBSS		80	33.80	50.00	11.30	0.00	21.00	3.75	34	31.50	47.06
Koshiyama et al. (2020)	TBSS	X	398	47.70	54.02	–	–	–	–	958	35.40	46.76
Liang et al. (2019)	Tractography		116	26.13	62.07	2.34	26.72	22.45	26.72	118	26.01	60.17
Liu et al. (2021)	Tractography		27	28.92	70.37	–	0.00	19.07	0.00	28	26.78	60.71
Long et al. (2022)	Tractography	X	51	31.45	100.00	–	0.00	–	0.00	49	31.86	100.00
Mak et al. (2021)	Tractography	X	27	23.96	66.67	2.99	0.00	–	96.30	27	22.70	62.96
Mettenburg, Benzinger, Shimony, Snyder, & Sheline (2012)	TBSS	X	51	68.30	68.63	–	100.00	–	–	16	68.10	68.75
Na et al. (2018)	Tractography	X	90	41.67	75.56	3.94	–	14.48	0.00	90	39.68	70.00
Ota et al. (2015)	TBSS		21	42.30	47.62	9.30	–	17.81	–	37	40.00	56.76

Shakeel et al. (2021)	Tractography	91	19.42	72.53	-	-	43.96	47	19.85	61.70
Tatham et al. (2016)	Tractography	55	36.40	-	11.20	0.00	21.50	18	33.20	-
Taylor et al. (2007)	Tractography	10	69.60	60.00	48.10	100.00	-	19	72.20	63.20
Thomas et al. (2020)	Tractography	17	27.76	88.24	-	-	14.88	13	24.38	61.54
Victoria et al. (2019)	TBSS	20	70.40	60.00	-	-	0.00	20	72.45	60.00
Viglis, Vance, Cunningham, & Silk (2017)	Tractography	X	12.10	0.00	-	4.00	68.00	25	11.90	0.00
Won et al. (2017)	Tractography	103	43.08	81.55	3.71	53.40	15.08	83	39.62	68.67
Wu et al. (2020)	Tractography	36	15.60	66.67	0.84	0.00	23.19	37	15.60	51.35
Wu et al. (2018)	Tractography	31	28.84	58.06	1.84	0.00	23.02	62	28.69	58.06
Yuen et al. (2014)	Tractography	45	69.99	62.22	14.00	0.00	15.62	43	70.60	62.79
Zhang et al. (2012) & Lamar et al. (2013)	Tractography	X	55.13	60.26	-	0.00	18.76	46	57.74	52.17
Zhang et al. (2022)	Tractography	X	28.97	63.27	2.61	69.39	27.04	59	31.58	67.80
Zheng et al. (2018)	Tractography	20	33.50	70.00	-	0.00	22.70	20	34.00	70.00

Abbreviations: DTI, diffusion tensor imaging; HDRS-17, Hamilton Depression Rating Scale (17-item); RD, radial diffusivity.

Note: Bolded studies provided missing data upon request. One study (Choi et al., 2016) compared UNC FA between individuals with depression and healthy controls using two samples with different genotypes.

our understanding of the neurobiological underpinnings of and potential treatment targets for depression.

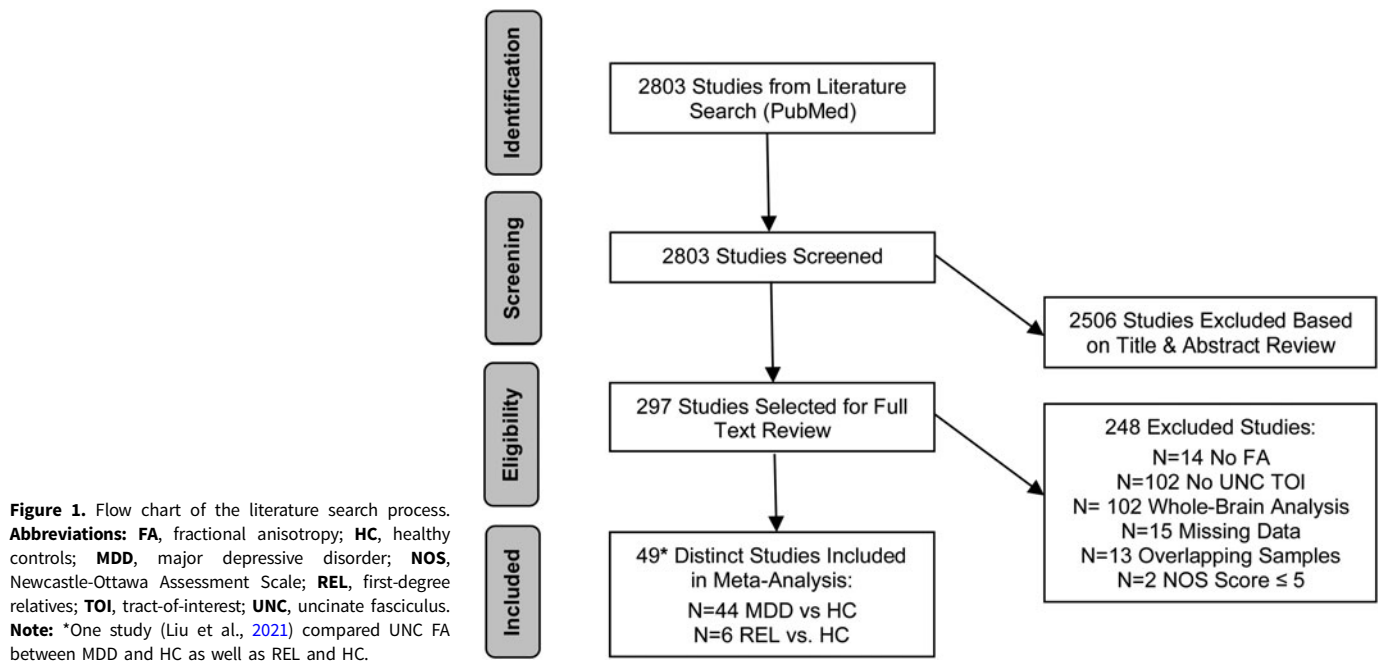
Given the overarching goal of a personalized medicine approach for MDD, it is further necessary to understand which sociodemographic and clinical factors contribute to the heterogeneity in UNC findings across studies. Specifically, age might be an essential factor as the UNC matures until mid-adulthood (Lebel et al., 2012). Further, FA in the UNC has been shown to be lower in women than men (Taylor, MacFall, Gerig, & Krishnan, 2007). There might also be a diagnosis-by-sex interaction, as RD in the UNC appears to be higher in men with MDD than men without MDD (van Velzen et al., 2020).

Clinical features, such as illness duration (Jenkins et al., 2016), severity of depressive symptoms (Charlton et al., 2014; Greenberg et al., 2021), or medication use (Hu, Stavish, Leibenluft, & Linke, 2020), may also contribute to inconsistencies in UNC findings. Further, depression frequently co-occurs with anxiety. In fact, more than 50% of individuals with depression also meet the criteria for anxiety (Kessler et al., 2003). Individuals with a primary diagnosis of anxiety have also shown reduced FA in the UNC (Phan et al., 2009; Tromp et al., 2012, 2019), suggesting that atypical UNC microstructure might be a common mechanistic pathway for both depression and anxiety.

Lastly, differences in processing pipelines could contribute to variance in UNC findings (Kuchling et al., 2018). In DTI research, TOIs are defined in two ways. One strategy is to calculate the intersection between regions of a WM atlas and a sample-specific WM skeleton derived from the tract-based spatial statistics (TBSS) pipeline implemented in FSL (i.e. ENIGMA approach; <http://enigma.ini.usc.edu/ongoing/dti-working-group/>). A second strategy is to track fibers between relevant gray matter regions (here, amygdala and ventral prefrontal cortex; tractography approach). Notably, a recent meta-analysis using the ENIGMA approach (i.e., TBSS) did not find atypical UNC FA in individuals with MDD (van Velzen et al., 2020). However, most original studies reporting aberrant UNC microstructure in MDD use a tractography approach, which is particularly sensitive to WM alterations (Kuchling et al., 2018).

To advance our understanding of the role of atypical UNC microstructure in the risk architecture of MDD, it is further necessary to address whether such abnormalities represent a vulnerability for MDD (i.e., are also observable in individuals with an elevated risk of developing the disorder). First-degree relatives (REL) of individuals with MDD are at an increased risk for MDD themselves (Wilde et al., 2014). Indeed, earlier work suggests reduced FA in the UNC in REL compared to healthy control individuals (HC) (Huang, Fan, Williamson, & Rao, 2011). Although the number of studies in REL is limited, we believe it would be useful to synthesize this data to examine whether initial evidence supports reduced FA in the UNC as a vulnerability marker of MDD.

In summary, the present meta-analysis is the first to integrate available studies using a TOI approach to examine UNC microstructure in depression to extend existing literature in four ways. First, it consolidates evidence to determine whether reduced FA in the left and right UNC is a neurobiological marker of depression. Second, we examine whether higher RD in the left and right UNC is also a neurobiological marker of depression. Third, we test whether sociodemographic and clinical characteristics or the processing pipeline contribute to heterogeneity in UNC findings. Finally, we explore (a) whether other DTI metrics such as AD and MD also differ between individuals with and without



MDD, and (b) whether atypical UNC microstructure is also present in first-degree relatives of individuals with MDD.

Method

Literature review

The present meta-analysis has been pre-registered in PROSPERO (ID #CRD42021276200). To identify relevant studies, we used the search engine PubMed with the following search terms: depression and WM. We included all original research articles published before July 9th, 2022, that used a TOI approach to compare FA of the left and right UNC between individuals with a lifetime diagnosis of depression or REL and HC. Depression was broadly defined as a lifetime diagnosis of MDD, persistent depressive disorder, or other specified depressive disorders. REL were defined as first-degree relatives of an individual who either (1) met criteria for MDD, or (2) scored higher than the clinical cut-off on a dimensional depression rating scale. We excluded book chapters, conference abstracts, review articles, and case reports. We identified 49 different studies that met our inclusion criteria (Fig. 1). In addition to including individuals with current depression, one study also included individuals with lifetime depression who were currently in remission (Shakeel et al., 2021). Two studies with overlapping samples (Lamar et al., 2013; Zhang et al., 2012) were combined and included in the present meta-analysis. One study used two samples with different genotypes to compare UNC FA between MDD and HC (Choi et al., 2016); here, we included data from both samples separately.

Data extraction

From all studies, we extracted means and standard deviations of FA and, if available, RD, MD, and AD, of the left and right UNC separately for each study group. We also pulled information about participants' mean age (43 studies, $n_{\text{MDD}} = 4930$), sex ratio (42 studies, $n_{\text{MDD}} = 4875$), mean illness duration (24 studies,

$n_{\text{MDD}} = 1339$), the percentage of participants using psychotropic medication (35 studies, $n_{\text{MDD}} = 1818$), and the percentage of subjects with lifetime comorbid anxiety disorder (30 studies, $n_{\text{MDD}} = 3803$). Further, we extracted Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) mean scores (23 studies, $n_{\text{MDD}} = 1227$), given that it was the most frequently reported measure of depressive symptom severity. In line with prior work, we standardized scores across different versions of the HDRS (Hu et al., 2020). Finally, we also noted whether TBSS or tractography was used to process DTI data.

We contacted corresponding authors when information regarding UNC FA or RD, or the percentage of individuals with comorbid anxiety, was missing. We obtained the requested data from 36 studies (Table 1; online Supplementary Table S1). We evaluated the quality of all studies using the Newcastle-Ottawa assessment scale (NOS; online Supplementary Table S2) and excluded two studies with NOS scores below 5 (Niida, Niida, Kuniyoshi, Motomura, & Uechi, 2013; Pines, Sacchet, Kullar, Ma, & Williams, 2018) (online Supplementary Table S3). EX initially extracted all available data, and LN cross-checked it independently.

Data analyses

All analyses used the metafor package (version 3.4-0) for R software (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>). We calculated the effect sizes for each study as standardized mean difference values (Cohen's d) and used the effect sizes to conduct random-effects inverse-variance weighted meta-analyses. We tested whether lower FA or higher RD in the bilateral UNC differentiated MDD or REL from HC, and considered effects significant at $p < 0.025$, correcting for tests in two hemispheres. As an exploratory analysis, we also tested whether there were differences in MD and AD in the bilateral UNC when comparing MDD and HC. Publication bias was determined using Egger's test for asymmetry, and the robustness of results was assessed using jackknife sensitivity

analyses. Using a meta-analytic fixed-effects model, we compared FA effect sizes in the left and right hemispheres in individuals with MDD. Using this approach, we also indirectly compared FA effect sizes between REL and individuals with MDD to determine whether the effect size was similar in these study groups.

We conducted meta-regression analyses to investigate whether age, sex, illness duration, depressive symptom severity, medication use, comorbid anxiety, and DTI processing pipeline contributed to heterogeneity across studies. Using Bonferroni correction to correct for multiple comparisons, we set a final statistical threshold for significance of $p_{\text{uncorrected}} < 0.007$ (in other words, $p_{\text{corrected}} < 0.05$). Recommendations suggest that meta-regression analyses should include at least 20 studies to produce robust findings. Thus, we examined sources of heterogeneity for studies comparing FA between MDD to HC ($n = 44$), but not for studies comparing RD between MDD and HC ($n = 15$) or studies investigating FA between REL and HC ($n = 6$). We also did not examine sources of heterogeneity for studies comparing MD between MDD and HC ($n = 17$) or for studies comparing AD between MDD and HC ($n = 12$). Data and code supporting this study's findings are publicly available on the Open Science Forum (<https://osf.io/hdp57/>).

Results

Literature review and quality assessment

Our initial literature search encompassed 2803 studies (Fig. 1). After screening the titles and abstracts, we reviewed the full text of 297 studies. We excluded studies if they (1) did not examine FA, (2) did not include the UNC as a TOI, (3) used a whole-brain approach, (4) did not provide FA data, (5) used a sample that overlapped with another study already included in our meta-analysis, or (6) yielded a NOS quality score ≤ 5 (Fig. 1, online Supplementary Table S3). A total of 49 studies were included in our meta-analysis (Fig. 1). Overall demographic and clinical characteristics of studies included in the meta-analysis are reported in Table 2, accompanied by specific details for each study in Table 1 and online Supplementary Table S1. Meta-regression analyses were conducted in subsets of studies that provided the relevant information on age ($n = 43$), sex ($n = 42$), mean illness duration ($n = 24$), mean HDRS scores ($n = 23$), medication use ($n = 35$), and comorbid anxiety ($n = 30$). All studies provided information on the DTI processing pipeline. There were missing data on demographic characteristics (age: 1 study missing data; sex: 2 studies missing data) and clinical characteristics (mean illness duration: 20 studies missing data; mean HDRS scores: 21 studies missing data; medication use: 10 studies missing data; comorbid anxiety: 14 studies missing data).

Fractional anisotropy in the uncinate fasciculus

The Egger's test indicated no publication bias among the studies that reported FA in the left ($z = 0.79$, $p = 0.432$; Figure 2) and right UNC ($z = -0.01$, $p = 0.993$; Figure 2), so we included all studies in the final analysis. We found that individuals with MDD showed reduced FA in the right UNC (WMD = -0.25 , 95% CI [-0.42 to -0.09], $p = 0.003$; Figure 2); however, this effect was only marginally significant in the left UNC (WMD = -0.21 , 95% CI [-0.42 to 0.01], $p = 0.059$; Figure 2). FA effect sizes between the left and right UNC did not differ ($p = 0.735$), suggesting no significant difference between the two hemispheres. In the right UNC,

Table 2. Overall demographic and clinical characteristics of studies included in the meta-analysis

	MDD vs. HC		REL vs. HC
	FA	RD	FA
Number of Studies	44	15	6
Sample Size (Total)	23 441	2619	647
Sample Size (MDD/REL)	5016	1087	116
Mean Age (Years)	38.91	38.60	19.87 ^b
Female (%)	61.47	62.00	51.02 ^a
Illness Duration (Years)	8.89 ^a	7.88 ^a	0.00 ^a
Medicated (%)	32.42	34.76	–
Mean HDRS-17 Score	20.58 ^a	20.88 ^b	3.23 ^b
Comorbid Anxiety (%)	23.31 ^a	34.67	–

Abbreviations: FA, fractional anisotropy; HC, healthy controls; HDRS-17, Hamilton Depression Rating Scale (17-item); MDD, major depressive disorder; RD, radial diffusivity; REL, first-degree relatives at-risk for depression.

^aThese means are based on less than 75% of studies, which reported this information in the published manuscript.

^bThese means are based on less than 50% of studies, which reported this information in the published manuscript.

jackknife sensitivity analysis found that no single study drove these results. For the left UNC, jackknife sensitivity analysis showed that the effect became significant ($p = 0.013$) when leaving out one particular study, which consisted of individuals with MDD who experienced moderate anxiety symptoms (Doolin et al., 2019).

Heterogeneity in fractional anisotropy findings

Comorbid anxiety explained variability in findings in the left ($\beta = 0.01$, $z = 2.00$, $R^2 = 15\%$, $p_{\text{uncorrected}} = 0.046$, $p_{\text{corrected}} = 0.322$) but not right UNC ($\beta = 0.00$, $z = 1.46$, $R^2 = 4\%$, $p_{\text{uncorrected}} = 0.146$, $p_{\text{corrected}} \geq 1$; online Supplementary Table S4). Specifically, comorbid anxiety attenuated the group difference between individuals with MDD and HC in the left UNC. We found no evidence that age, sex, duration of illness, the severity of depressive symptoms, medication use, or the DTI processing pipeline contributed to variance in UNC findings in individuals with MDD (all $p_{\text{uncorrected}} > 0.124$, all $p_{\text{corrected}} > 0.868$).

Radial diffusivity in the uncinate fasciculus

For the left UNC, Egger's test indicated one outlier that showed greatly elevated RD in individuals with MDD (Koshiyama et al., 2020). After excluding this study, Egger's test showed no publication bias in the left UNC ($z = -0.73$, $p = 0.466$; online Supplementary Fig. S1). In the right UNC, Egger's test suggested no publication bias ($z = -0.72$, $p = 0.475$; online Supplementary Fig. S1). Thus, for the final analysis, we excluded one study (Koshiyama et al., 2020) for the left UNC and included all studies for the right UNC. We found no differences in RD in the left (WMD = -0.01 , 95% CI [-0.19 to 0.17], $p = 0.936$; online Supplementary Fig. S1) or right UNC (WMD = 0.11 , 95% CI [-0.10 to 0.31], $p = 0.307$; online Supplementary Fig. S1) when comparing individuals with MDD to HC. RD effect sizes were comparable between the left and right UNC ($p = 0.416$).

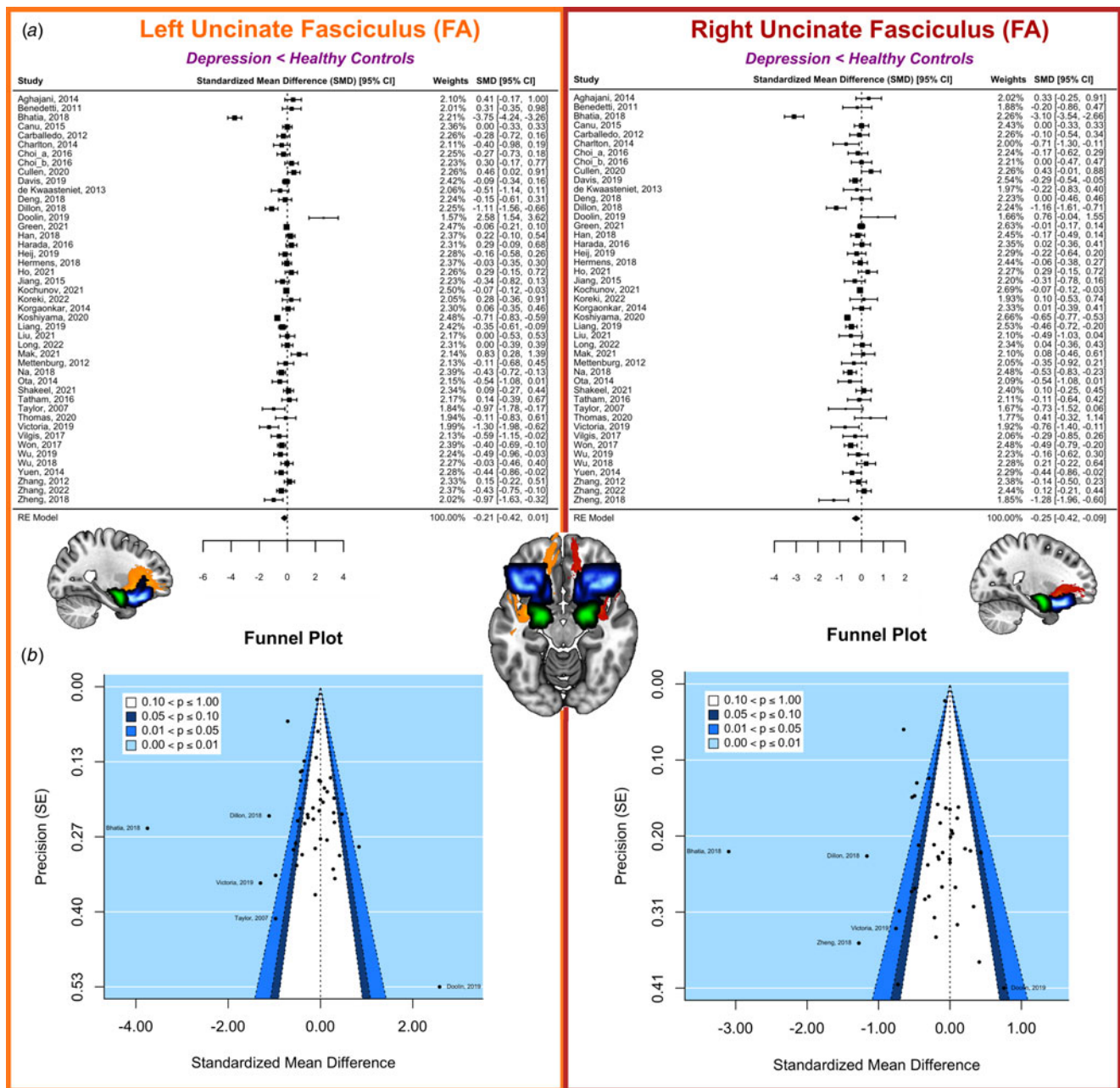


Figure 2. Tract-of-interest meta-analysis comparing fractional anisotropy in the uncinate fasciculus between individuals with depression and healthy controls. Here, the left uncinate fasciculus (in orange) and right uncinate fasciculus (in red) are depicted. These tracts interconnect the amygdala (in green) to the orbito-frontal cortex (in blue). (a) Forest plots, with the black diamond representing the overall effect size of each study. (b) Funnel plots, with the dotted line representing the overall effect size. Symmetric funnel plots indicate an absence of publication bias, with a majority of studies falling in the area of statistical non-significance ($p > 0.1$). The five most extreme points on each funnel plot are labeled with the study author and year. **Abbreviations:** CI, confidence interval; FA, fractional anisotropy; RE model, random-effect model; SE, standard error.

Exploratory analysis

We found no FA differences in the left or right UNC when comparing REL to HC (online Supplementary Fig. S2). Indirect comparisons of UNC FA between hemispheres also yielded no significant results ($p = 0.811$). However, indirect comparisons of UNC FA between REL and individuals with MDD yielded significant results in the right UNC (WMD = 0.33, 95% CI [0.06 to 0.60], $p = 0.019$) and marginally significant results in the left UNC (WMD = 0.33, 95% CI [-0.05 to 0.71], $p = 0.093$). In other words, individuals with MDD showed reduced UNC

FA compared to REL. Separately, we found no differences in MD or AD in the left or right UNC when comparing individuals with MDD to HC (online Supplementary Figs S3 and S4).

Discussion

The present meta-analysis, which integrates data from 5016 individuals with MDD and 18 425 HC, associates MDD with reduced FA in the uncinate fasciculus, suggesting perturbed coherence of this tract. We also provide preliminary evidence for a laterality

effect potentially related to comorbid anxiety. In contrast to our hypothesis, this effect was not related to alterations in RD, which was comparable between individuals with ($N_{MDD} = 1087$) and without MDD ($N_{HC} = 1532$). We also found no support for the hypothesis that aberrant UNC FA represents a vulnerability for MDD. However, the available sample of REL was small ($N_{REL} = 116$, $N_{HC} = 531$), and thus must be cautiously interpreted.

Consistent with neurobiological models of depression (Kupfer et al., 2012; Mayberg, 1997) that state that aberrancies in cortical-limbic pathways are implicated in perturbed emotion regulation, we associate MDD with reduced FA in the UNC, which links the ventral prefrontal cortex and the amygdala. Prior work links reduced FA in the UNC to less effective reappraisal (d'Arbeloff et al., 2018; Eden et al., 2015; Zuurbier, Nikolova, Åhs, & Hariri, 2013) and less amygdala regulation in response to emotional stimuli (Hein et al., 2018). However, these studies focused on non-depressed individuals. Thus, future studies should investigate the relationship between UNC microstructure and emotion regulation deficits in individuals with MDD, possibly by integrating DTI and task-based functional magnetic resonance imaging.

Integrating information from 44 TOI studies, we extend findings from a prior meta-analysis that found reduced UNC FA when examining three whole-brain and TOI studies on individuals with late-life depression (Wen, Steffens, Chen, & Zainal, 2014). Specifically, we provide more conclusive evidence of reduced UNC FA in individuals with depression across the lifespan. However, our meta-analysis contrasts prior whole-brain meta-analyses that found no alterations in UNC FA in individuals with MDD (Chen et al., 2016; Jiang et al., 2017; Liao et al., 2013; Murphy & Frodl, 2011; Zhou et al., 2022). Indeed, a recent report (Winter et al., 2022) shows a large overlap in the distribution of neurobiological markers including whole-brain FA between individuals with depression and HCs. However, unlike TOI approaches, whole-brain approaches are less sensitive to effects in small tracts such as the UNC. In contrast to a recent meta-analysis that also found no differences in UNC FA between individuals with MDD and HC using the ENIGMA approach (van Velzen et al., 2020), 80% of the studies included in our meta-analysis used a tractography (rather than a TBSS) approach, which has been shown to be more sensitive to capturing WM alterations (Kuchling et al., 2018). Thus, methodological heterogeneity might explain diverging findings in meta-analyses of WM in MDD.

Our findings link MDD most strongly to reduced FA in the right UNC. Effects were less consistent in the left hemisphere. Our findings suggest that comorbid anxiety might contribute to this heterogeneity. Specifically, a higher proportion of patients with comorbid anxiety was associated with higher FA in the left UNC. This finding is consistent with prior work demonstrating a positive relationship between trait anxiety and FA in the left UNC (Modi et al., 2013; Montag, Reuter, Weber, Markett, & Schoene-Bake, 2012). This finding is also consistent with a prior study, which found that individuals with MDD and comorbid anxiety do not show altered UNC microstructure (Canu et al., 2015), though individuals with solely MDD (Table 1) or anxiety (Tromp et al., 2012) do show alterations in the UNC. More work is needed to delineate specific and shared mechanisms of depression and anxiety. Such work might leverage latent variable approaches such as bifactor models (Scopel Hoffmann et al., 2022), which can be used to parse specific and shared factors of symptoms of depression and anxiety, which can then be related to WM microstructure.

Perturbations in UNC microstructure are not specific to MDD. For example, atypical UNC microstructure has been linked to bipolar disorder (Xu et al., 2022), anxiety disorders (Jenkins et al., 2016), and attention-deficit/hyperactivity disorder (van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). A mega-analysis also found atypical UNC microstructure in individuals with schizophrenia (Koshiyama et al., 2020). As the UNC is implicated in the pathophysiology of different disorders, it is pivotal that future work examines more closely its relevance to specific transdiagnostic processes (e.g. emotion regulation).

FA is a sensitive but non-specific indicator of WM microstructure. At a cellular level, FA findings might relate to atypical myelination. Indeed, it has been proposed that myelination, better assessed through RD, is a mechanism of depression (Boda, 2021; Gao et al., 2017; Hemanth Kumar et al., 2014; Hou et al., 2021). Our results do not support this hypothesis. Thus, future work must investigate alternative drivers of aberrant FA, such as vascular and glial changes and axonal branching or pruning (Sampaio-Baptista & Johansen-Berg, 2017). Identifying cellular mechanisms underlying perturbed UNC microstructure in MDD might aid in developing novel therapeutics for this debilitating condition.

Finally, it is essential to place atypical UNC microstructure within the risk architecture of MDD. To this end, we integrated studies examining UNC microstructure in REL of MDD. Differences in UNC microstructure were observed between REL and individuals with MDD, but not between REL and HC. Though preliminary, this suggests that altered UNC microstructure may not represent a vulnerability but develops during MDD, and thus may be a consequence, or a 'scar', of MDD (Rohde, Lewinsohn, & Seeley, 1990; Wichers, Geschwind, van Os, & Peeters, 2010).

Numerous studies have shown that repetition of behaviors and sleep patterns independently modify WM throughout the lifespan (Sampaio-Baptista & Johansen-Berg, 2017). It is conceivable that, during MDD, the well-documented bias towards negative emotional content (Gotlib & Joormann, 2010) and the excessive use of maladaptive emotion regulation strategies such as rumination (Joormann & Stanton, 2016) shape the UNC. Further, perturbed sleep is a frequently reported symptom of depression (Nutt, Wilson, & Paterson, 2008), that often persists during remission. Sleep deprivation has been hypothesized to lead to reduced structural integrity of the UNC (Jamieson, Broadhouse, Lagopoulos, & Hermens, 2020), which is supported by recent findings that associated poor sleep quality with reduced FA and higher RD in the UNC in healthy adolescents (Jamieson et al., 2021). Future work should investigate the relationship between UNC FA and sleep in individuals with MDD, as understanding this association could have implications for the treatment of MDD.

Finally, we like to point out that depression as a diagnostic category might encompass multiple subtypes (Fried, 2017). Thus, it may not be possible to link such a broad phenotype to a specific neurobiological signature (Winter et al., 2022). Instead, future work might consider, alternate phenotyping strategies such as latent profile analysis, when examining the role of WM microstructure in depression, as perturbations in the UNC might only be found in subgroups of patients. This could be an important step towards a personalized treatment approach for depression.

Limitations

While we were well-powered to examine our main question, findings on RD, MD, AD and REL must be considered preliminary,

given the substantially smaller number of studies used in these analyses. Unfortunately, we could not determine whether findings generalize to diverse racial and ethnic backgrounds as the majority of studies ($n = 40$) did not report these variables. It will be important that future studies report participants' racial and ethnic background, as these demographic features may relate to traumatic experiences (Kirkinis, Pieterse, Martin, Agiliga, & Brownell, 2021) and could contribute to inter-study variance in UNC findings.

Conclusion

The present meta-analysis found reduced FA in the UNC in individuals with, but not those at risk for, MDD. However, comorbid anxiety may weaken associations between depression and UNC microstructure. Future work needs to investigate when and how perturbations in UNC microstructure develop and should aim to link it to psychological processes previously implicated in depression, such as impaired emotion regulation.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291723000107>.

Financial support. This work was supported by the National Science Foundation Graduate Research Fellowship Program (DGE: 1842487) and the National Institute of Mental Health Intramural Research Program (ZIA: MH002778-21). The funding source supported the decision to submit the article for publication. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest. We have no conflicts of interest to disclose.

References

- Aghajani, M., Veer, I. M., Van Lang, N. D. J., Meens, P. H. F., Van Den Bulk, B. G., Rombouts, S. A. R. B., ... Van Der Wee, N. J. (2014). Altered white-matter architecture in treatment-naïve adolescents with clinical depression. *Psychological Medicine*, 44(11), 2287–2298.
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1), 259–267. [https://doi.org/10.1016/S0006-3495\(94\)80775-1](https://doi.org/10.1016/S0006-3495(94)80775-1).
- Benedetti, F., Absinta, M., Rocca, M. A., Radaelli, D., Poletti, S., Bernasconi, A., ... Filippi, M. (2011). Tract-specific white matter structural disruption in patients with bipolar disorder. *Bipolar Disorders*, 13(4), 414–424.
- Bhatia, K. D., Henderson, L. A., Hsu, E., & Yim, M. (2018). Reduced integrity of the uncinate fasciculus and cingulum in depression: A stem-by-stem analysis. *Journal of Affective Disorders*, 235, 220–228.
- Boda, E. (2021). Myelin and oligodendrocyte lineage cell dysfunctions: New players in the etiology and treatment of depression and stress-related disorders. *European Journal of Neuroscience*, 53(1), 281–297. <https://doi.org/10.1111/ejn.14621>.
- Budde, M. D., Xie, M., Cross, A. H., & Song, S. K. (2009). Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: A quantitative pixelwise analysis. *Journal of Neuroscience*, 29(9), 2805–2813. <https://doi.org/10.1523/JNEUROSCI.4605-08.2009>.
- Canu, E., Kostić, M., Agosta, F., Munjiza, A., Ferraro, P. M., Pesic, D., ... Filippi, M. (2015). Brain structural abnormalities in patients with major depression with or without generalized anxiety disorder comorbidity. *Journal of Neurology*, 262(5), 1255–1265. <https://doi.org/10.1007/s00415-015-7701-z>.
- Carballedo, A., Amico, F., Ugwu, I., Fagan, A. J., Fahey, C., Morris, D., ... Frodl, T. (2012). Reduced fractional anisotropy in the uncinate fasciculus in patients with major depression carrying the met-allele of the Val66Met brain-derived neurotrophic factor genotype. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 159(5), 537–548.
- Charlton, R. A., Lamar, M., Zhang, A., Yang, S., Ajilore, O., & Kumar, A. (2014). White-matter tract integrity in late-life depression: Associations with severity and cognition. *Psychological Medicine*, 44(7), 1427–1437. <https://doi.org/10.1017/S0033291713001980>.
- 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(1), 21825. <https://doi.org/10.1038/srep21825>.
- Choi, S., Han, K.-M., Kang, J., Won, E., Chang, H. S., Tae, W. S., ... Ham, B.-J. (2016). Effects of a polymorphism of the neuronal amino acid transporter SLC6A15 gene on structural integrity of white matter tracts in major depressive disorder. *PLoS One*, 11(10), e0164301. <https://doi.org/10.1371/journal.pone.0164301>.
- Cullen, K. R., Brown, R., Schreiner, M. W., Eberly, L. E., Klimes-Dougan, B., Reigstad, K., ... Mueller, B. A. (2020). White matter microstructure relates to lassitude but not diagnosis in adolescents with depression. *Brain Imaging and Behavior*, 14(5), 1507–1520.
- d'Arbeloff, T. C., Kim, M. J., Knodt, A. R., Radtke, S. R., Brigidi, B. D., & Hariri, A. R. (2018). Microstructural integrity of a pathway connecting the prefrontal cortex and amygdala moderates the association between cognitive reappraisal and negative emotions. – PscNET. *Emotion (Washington, D.C.)*, 18(6), 912–915. <https://doi.org/10.1037/emo0000447>.
- Davis, A. D., Hassel, S., Arnott, S. R., Harris, J., Lam, R. W., Milev, R., ... Hall, G. B. (2019). White matter indices of medication response in major depression: A diffusion tensor imaging study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 4(10), 913–924.
- de Kwaasteniet, B., Ruhe, E., Caan, M., Rive, M., Olabarriaga, S., Groefsema, M., ... Denys, D. (2013). Relation between structural and functional connectivity in major depressive disorder. *Biological Psychiatry*, 74(1), 40–47.
- Deng, F., Wang, Y., Huang, H., Niu, M., Zhong, S., Zhao, L., ... Huang, R. (2018). Abnormal segments of right uncinate fasciculus and left anterior thalamic radiation in major and bipolar depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 81, 340–349.
- Dillon, D. G., Gonenc, A., Belleau, E., & Pizzagalli, D. A. (2018). Depression is associated with dimensional and categorical effects on white matter pathways. *Depression and Anxiety*, 35(5), 440–447.
- Doolin, K., Andrews, S., Carballedo, A., McCarthy, H., O'Hanlon, E., Tozzi, L., & Frodl, T. (2019). Longitudinal diffusion weighted imaging of limbic regions in patients with major depressive disorder after 6 years and partial to full remission. *Psychiatry Research: Neuroimaging*, 287, 75–86. <https://doi.org/10.1016/j.psychres.2019.04.004>.
- Eden, A. S., Schreiber, J., Anwender, A., Keuper, K., Laeger, I., Zwanzger, P., ... Dobel, C. (2015). Emotion regulation and trait anxiety are predicted by the microstructure of fibers between amygdala and prefrontal cortex. *Journal of Neuroscience*, 35(15), 6020–6027. <https://doi.org/10.1523/JNEUROSCI.3659-14.2015>.
- Fried, E. (2017). Moving forward: How depression heterogeneity hinders progress in treatment and research. *Expert Review of Neurotherapeutics*, 17(5), 423–425. <https://doi.org/10.1080/14737175.2017.1307737>.
- Gao, Y., Ma, J., Tang, J., Liang, X., Huang, C.-X., Wang, S., ... Tang, Y. (2017). White matter atrophy and myelinated fiber disruption in a rat model of depression. *Journal of Comparative Neurology*, 525(8), 1922–1933. <https://doi.org/10.1002/cne.24178>.
- Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology*, 6, 285–312. <https://doi.org/10.1146/annurev.clinpsy.121208.131305>.
- Green, C., Shen, X., Stevenson, A. J., Conole, E. L., Harris, M. A., Barbu, M. C., ... Whalley, H. C. (2021). Structural brain correlates of serum and epigenetic markers of inflammation in major depressive disorder. *Brain, Behavior, and Immunity*, 92, 39–48.
- Greenberg, T., Bertocci, M. A., Versace, A., Lima Santos, J. P., Chase, H. W., Siffler, R., ... Phillips, M. L. (2021). Depression and anxiety mediate the relationship between frontotemporal white matter integrity and quality of life in distressed young adults. *Journal of Psychiatric Research*, 132, 55–59. <https://doi.org/10.1016/j.jpsychires.2020.10.001>.

- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23, 56–62. <https://doi.org/10.1136/jnnp.23.1.56>.
- Han, K. M., Choi, S., Kim, A., Kang, J., Won, E., Tae, W. S., ... Ham, B. J. (2018). The effects of 5-HTTLPR and BDNF Val66Met polymorphisms on neurostructural changes in major depressive disorder. *Psychiatry Research: Neuroimaging*, 273, 25–34.
- Harada, K., Matsuo, K., Nakashima, M., Hobara, T., Higuchi, N., Higuchi, F., ... Watanabe, Y. (2016). Disrupted orbitomedial prefrontal limbic network in individuals with later-life depression. *Journal of Affective Disorders*, 204, 112–119.
- Harsan, L. A., Poulet, P., Guignard, B., Steibel, J., Parizel, N., Loureiro de Sousa, P., ... Ghandour, M. S. (2006). Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. *Journal of Neuroscience Research*, 83(3), 392–402. <https://doi.org/10.1002/jnr.20742>.
- Heij, G. J., Penninx, B. W., van Velzen, L. S., van Tol, M. J., van der Wee, N. J., Veltman, D. J., & Aghajani, M. (2019). White matter architecture in major depression with anxious distress symptoms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 94, 109664.
- Hein, T. C., Mattson, W. I., Dotterer, H. L., Mitchell, C., Lopez-Duran, N., Thomason, M. E., ... Monk, C. S. (2018). Amygdala habituation and uncinate fasciculus connectivity in adolescence: A multi-modal approach. *NeuroImage*, 183, 617–626. <https://doi.org/10.1016/j.neuroimage.2018.08.058>.
- Hemanth Kumar, B. S., Mishra, S. K., Trivedi, R., Singh, S., Rana, P., & Khushu, S. (2014). Demyelinating evidences in CMS rat model of depression: A DTI study at 7T. *Neuroscience*, 275, 12–21. <https://doi.org/10.1016/j.neuroscience.2014.05.037>.
- Hermens, D. F., Hatton, S. N., Lee, R. S., Naismith, S. L., Duffy, S. L., Paul Amminger, G., ... Hickie, I. B. (2018). In vivo imaging of oxidative stress and fronto-limbic white matter integrity in young adults with mood disorders. *European Archives of Psychiatry and Clinical Neuroscience*, 268(2), 145–156.
- Ho, T. C., Sisk, L. M., Kulla, A., Teresi, G. I., Hansen, M. M., Wu, H., & Gotlib, I. H. (2021). Sex differences in myelin content of white matter tracts in adolescents with depression. *Neuropsychopharmacology*, 46(13), 2295–2303.
- Hou, G., Lai, W., Jiang, W., Liu, X., Qian, L., Zhang, Y., & Zhou, Z. (2021). Myelin deficits in patients with recurrent major depressive disorder: An inhomogeneous magnetization transfer study. *Neuroscience Letters*, 750, 135768. <https://doi.org/10.1016/j.neulet.2021.135768>.
- Hu, R., Stavish, C., Leibenluft, E., & Linke, J. O. (2020). White matter microstructure in individuals with and at risk for bipolar disorder: Evidence for an endophenotype from a voxel-based meta-analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5(12), 1104–1113. <https://doi.org/10.1016/j.bpsc.2020.06.007>.
- Huang, H., Fan, X., Williamson, D. E., & Rao, U. (2011). White matter changes in healthy adolescents at familial risk for unipolar depression: A diffusion tensor imaging study. *Neuropsychopharmacology*, 36(3), 684–691. <https://doi.org/10.1038/npp.2010.199>.
- Jamieson, D., Broadhouse, K. M., Lagopoulos, J., & Hermens, D. F. (2020). Investigating the links between adolescent sleep deprivation, fronto-limbic connectivity and the Onset of Mental Disorders: A review of the literature. *Sleep Medicine*, 66, 61–67. <https://doi.org/10.1016/j.sleep.2019.08.013>.
- Jamieson, D., Schwenn, P., Beaudequin, D. A., Shan, Z., McLoughlin, L. T., Lagopoulos, J., & Hermens, D. F. (2021). Short strides to important findings: A short interval longitudinal study of sleep quality, psychological distress and microstructure changes to the uncinate fasciculus in early adolescents. *International Journal of Developmental Neuroscience*, 81(1), 82–90. <https://doi.org/10.1002/jdn.10077>.
- Jenkins, L. M., Barba, A., Campbell, M., Lamar, M., Shankman, S. A., Leow, A. D., ... Langenecker, S. A. (2016). Shared white matter alterations across emotional disorders: A voxel-based meta-analysis of fractional anisotropy. *NeuroImage: Clinical*, 12, 1022–1034. <https://doi.org/10.1016/j.nicl.2016.09.001>.
- Jiang, J., Zhao, Y.-J., Hu, X.-Y., Du, M.-Y., Chen, Z.-Q., Wu, M., ... Gong, Q.-Y. (2017). 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: JPN*, 42(3), 150–163. <https://doi.org/10.1503/jpn.150341>.
- Jiang, W., Gong, G., Wu, F., Kong, L., Chen, K., Cui, W., ... Wang, F. (2015). The papez circuit in first-episode, treatment-naïve adults with major depressive disorder: Combined atlas-based tract-specific quantification analysis and voxel-based analysis. *PLoS One*, 10(5), e0126673.
- Joormann, J., & Stanton, C. H. (2016). Examining emotion regulation in depression: A review and future directions. *Behaviour Research and Therapy*, 86, 35–49. <https://doi.org/10.1016/j.brat.2016.07.007>.
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., ... Wang, P. S. (2003). The epidemiology of major depressive disorder results from the national comorbidity survey replication (NCS-R). *JAMA*, 289(23), 3095–3105. <https://doi.org/10.1001/jama.289.23.3095>.
- Kirkinis, K., Pieterse, A. L., Martin, C., Agiliga, A., & Brownell, A. (2021). Racism, racial discrimination, and trauma: A systematic review of the social science literature. *Ethnicity & Health*, 26(3), 392–412. <https://doi.org/10.1080/13557858.2018.1514453>.
- Kochunov, P., Ryan, M. C., Yang, Q., Hatch, K. S., Zhu, A., Thomopoulos, S. I., ... Hong, L. E. (2021). Comparison of regional brain deficit patterns in common psychiatric and neurological disorders as revealed by big data. *NeuroImage: Clinical*, 29, 102574.
- Koreki, A., Niida, R., Niida, A., Yamagata, B., Anamizu, S., & Mimura, M. (2021). Comparison of white matter structure of drug-naïve patients with bipolar disorder and major depressive disorder using diffusion tensor tractography. *Frontiers in Psychiatry*, 12, 2528.
- Korgaonkar, M. S., Williams, L. M., Song, Y. J., Usherwood, T., & Grieve, S. M. (2014). Diffusion tensor imaging predictors of treatment outcomes in major depressive disorder. *The British Journal of Psychiatry*, 205(4), 321–328.
- Koshiyama, D., Fukunaga, M., Okada, N., Morita, K., Nemoto, K., Usui, K., ... Hashimoto, R. (2020). White matter microstructural alterations across four major psychiatric disorders: Mega-analysis study in 2937 individuals. *Molecular Psychiatry*, 25(4), 883–895. <https://doi.org/10.1038/s41380-019-0553-7>.
- Kuchling, J., Backner, Y., Oertel, F. C., Raz, N., Bellmann-Strobl, J., Ruprecht, K., ... Scheel, M. (2018). Comparison of probabilistic tractography and tract-based spatial statistics for assessing optic radiation damage in patients with autoimmune inflammatory disorders of the central nervous system. *NeuroImage: Clinical*, 19, 538–550. <https://doi.org/10.1016/j.nicl.2018.05.004>.
- Kupfer, D. J., Frank, E., & Phillips, M. L. (2012). Major depressive disorder: New clinical, neurobiological, and treatment perspectives. *The Lancet*, 379 (9820), 1045–1055. [https://doi.org/10.1016/S0140-6736\(11\)60602-8](https://doi.org/10.1016/S0140-6736(11)60602-8).
- Lamar, M., Charlton, R. A., Ajilore, O., Zhang, A., Yang, S., Barrick, T. R., ... Kumar, A. (2013). Prefrontal vulnerabilities and whole brain connectivity in aging and depression. *Neuropsychologia*, 51(8), 1463–1470. <https://doi.org/10.1016/j.neuropsychologia.2013.05.004>.
- Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., & Beaulieu, C. (2012). Diffusion tensor imaging of white matter tract evolution over the lifespan. *NeuroImage*, 60(1), 340–352. <https://doi.org/10.1016/j.neuroimage.2011.11.094>.
- Liang, S., Wang, Q., Kong, X., Deng, W., Yang, X., Li, X., ... Li, T. (2019). White matter abnormalities in major depression biotypes identified by diffusion tensor imaging. *Neuroscience Bulletin*, 35(5), 867–876.
- 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: JPN*, 38(1), 49–56. <https://doi.org/10.1503/jpn.110180>.
- Liu, Z., Kang, L., Zhang, A., Yang, C., Liu, M., Wang, J., ... Sun, N. (2021). Injuries in left corticospinal tracts, forceps major, and left superior longitudinal fasciculus (temporal) as the quality indicators for major depressive disorder. *Neural Plasticity*, 2021, e2348072. <https://doi.org/10.1155/2021/2348072>.
- Long, X., Zhou, Y., Zhang, F., Li, F., Wang, X., Meng, Y., ... Jia, Z. (2022). Altered MRI diffusion properties of the white matter tracts connecting frontal and thalamic brain regions in first-episode, drug-naïve patients with postpartum depression. *Journal of Magnetic Resonance Imaging*, 57(3), 899–906.
- Mak, A. D. P., Leung, O. N. W., Chou, I. W. Y., Wong, S. L. Y., Chu, W. C. W., Yeung, D., ... Lee, S. (2021). White matter integrity in young medication-naïve bipolar II depressed adults. *Scientific Reports*, 11(1), 1–10.

- Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 9 (3), 471–481. <https://doi.org/10.1176/jnp.9.3.471>.
- Mettenburg, J. M., Benzinger, T. L., Shimony, J. S., Snyder, A. Z., & Sheline, Y. I. (2012). Diminished performance on neuropsychological testing in late life depression is correlated with microstructural white matter abnormalities. *NeuroImage*, 60(4), 2182–2190.
- Modi, S., Trivedi, R., Singh, K., Kumar, P., Rathore, R. K. S., Tripathi, R. P., & Khushu, S. (2013). Individual differences in trait anxiety are associated with white matter tract integrity in fornix and uncinate fasciculus: Preliminary evidence from a DTI based tractography study. *Behavioural Brain Research*, 238, 188–192. <https://doi.org/10.1016/j.bbr.2012.10.007>.
- Montag, C., Reuter, M., Weber, B., Markett, S., & Schoene-Bake, J.-C. (2012). Individual differences in trait anxiety are associated with white matter tract integrity in the left temporal lobe in healthy males but not females. *Neuroscience*, 217, 77–83. <https://doi.org/10.1016/j.neuroscience.2012.05.017>.
- Murphy, M. L., & Frodl, T. (2011). Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. *Biology of Mood & Anxiety Disorders*, 1(1), 3. <https://doi.org/10.1186/2045-5380-1-3>.
- Na, K. S., Won, E., Kang, J., Kim, A., Choi, S., Tae, W. S., ... Ham, B. J. (2018). Differential effect of COMT gene methylation on the prefrontal connectivity in subjects with depression versus healthy subjects. *Neuropharmacology*, 137, 59–70.
- Niida, A., Niida, R., Kuniyoshi, K., Motomura, M., & Uechi, A. (2013). Usefulness of visual evaluation of the anterior thalamic radiation by diffusion tensor tractography for differentiating between Alzheimer's disease and elderly major depressive disorder patients. *International Journal of General Medicine*, 6, 189–200. <https://doi.org/10.2147/IJGM.S42953>.
- Nutt, D., Wilson, S., & Paterson, L. (2008). Sleep disorders as core symptoms of depression. *Dialogues in Clinical Neuroscience*, 10(3), 329–336. <https://doi.org/10.31887/DCNS.2008.10.3/dnutt>.
- Ota, M., Noda, T., Sato, N., Hattori, K., Hori, H., Sasayama, D., ... Kunugi, H. (2015). White matter abnormalities in major depressive disorder with melancholic and atypical features: A diffusion tensor imaging study. *Psychiatry and Clinical Neurosciences*, 69(6), 360–368.
- Phan, K. L., Orlichenko, A., Boyd, E., Angstadt, M., Coccaro, E. F., Liberzon, I., & Arfanakis, K. (2009). Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. *Biological Psychiatry*, 66(7), 691–694. <https://doi.org/10.1016/j.biopsych.2009.02.028>.
- Pines, A. R., Sacchet, M. D., Kullar, M., Ma, J., & Williams, L. M. (2018). Multi-unit relations among neural, self-report, and behavioral correlates of emotion regulation in comorbid depression and obesity. *Scientific Reports*, 8(1), 14032. <https://doi.org/10.1038/s41598-018-32394-2>.
- Rohde, P., Lewinsohn, P. M., & Seeley, J. R. (1990). Are people changed by the experience of having an episode of depression? A further test of the scar hypothesis. *Journal of Abnormal Psychology*, 99(3), 264–271. <https://doi.org/10.1037/0021-843X.99.3.264>.
- Sampaio-Baptista, C., & Johansen-Berg, H. (2017). White matter plasticity in the adult brain. *Neuron*, 96(6), 1239–1251. <https://doi.org/10.1016/j.neuron.2017.11.026>.
- Scopel Hoffmann, M., Moore, T. M., Kvitko Axelrud, L., Tottenham, N., Zuo, X.-N., Rohde, L. A., ... Salum, G. A. (2022). Reliability and validity of bifactor models of dimensional psychopathology in youth. *Journal of Psychopathology and Clinical Science*, 131(4), 407–421. <https://doi.org/10.1037/abn0000749>.
- Selemon, L. D., & Goldman-Rakic, P. S. (1999). The reduced neuropil hypothesis: A circuit based model of schizophrenia. *Biological Psychiatry*, 45(1), 17–25. [https://doi.org/10.1016/S0006-3223\(98\)00281-9](https://doi.org/10.1016/S0006-3223(98)00281-9).
- Shakeel, M. K., Hassel, S., Davis, A. D., Metzack, P. D., MacQueen, G. M., Arnott, S. R., ... Lebel, C. (2021). White matter microstructure in youth at risk for serious mental illness: A comparative analysis. *Psychiatry Research: Neuroimaging*, 312, 111289.
- 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(3), 1429–1436. <https://doi.org/10.1006/nimg.2002.1267>.
- Tatham, E. L., Ramasubbu, R., Gaxiola-Valdez, I., Cortese, F., Clark, D., Goodyear, B., ... Hall, G. B. (2016). White matter integrity in major depressive disorder: Implications of childhood trauma, 5-HTTLPR and BDNF polymorphisms. *Psychiatry Research: Neuroimaging*, 253, 15–25.
- Taylor, W. D., MacFall, J. R., Gerig, G., & Krishnan, R. R. (2007). Structural integrity of the uncinate fasciculus in geriatric depression: Relationship with age of onset. *Neuropsychiatric Disease and Treatment*, 3(5), 669–674.
- Thomas, P. J., Panchamukhi, S., Nathan, J., Francis, J., Langenecker, S., Gorka, S., ... Ajilore, O. A. (2020). Graph theoretical measures of the uncinate fasciculus subnetwork as predictors and correlates of treatment response in a transdiagnostic psychiatric cohort. *Psychiatry Research: Neuroimaging*, 299, 111064.
- Tromp, D. P. M., Grupe, D. W., Oathes, D. J., McFarlin, D. R., Hernandez, P. J., Kral, T. R. A., ... Nitschke, J. B. (2012). Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder. *Archives of General Psychiatry*, 69(9), 925. <https://doi.org/10.1001/archgenpsychiatry.2011.2178>.
- Tromp, D. P. M., Williams, L. E., Fox, A. S., Oler, J. A., Roseboom, P. H., Rogers, G. M., ... Kalin, N. H. (2019). Altered uncinate fasciculus microstructure in childhood anxiety disorders in boys but not girls. *American Journal of Psychiatry*, 176(3), 208–216. <https://doi.org/10.1176/appi.ajp.2018.18040425>.
- van Ewijk, H., Heslenfeld, D. J., Zwiers, M. P., Buitelaar, J. K., & Oosterlaan, J. (2012). Diffusion tensor imaging in attention deficit/hyperactivity disorder: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, 36(4), 1093–1106. <https://doi.org/10.1016/j.neubiorev.2012.01.003>.
- van Velzen, L. S., Kelly, S., Isaev, D., Aleman, A., Aftanas, L. I., Bauer, J., ... Schmaal, L. (2020). White matter disturbances in major depressive disorder: A coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. *Molecular Psychiatry*, 25(7), 1511–1525. <https://doi.org/10.1038/s41380-019-0477-2>.
- Victoria, L. W., Alexopoulos, G. S., Ilieva, I., Stein, A. T., Hoptman, M. J., Chowdhury, N., ... Gunning, F. M. (2019). White matter abnormalities predict residual negative self-referential thinking following treatment of late-life depression with escitalopram: A preliminary study. *Journal of Affective Disorders*, 243, 62–69.
- Virgis, V., Vance, A., Cunningham, R., & Silk, T. J. (2017). White matter microstructure in boys with persistent depressive disorder. *Journal of Affective Disorders*, 221, 11–16.
- Wen, M.-C., Steffens, D. C., Chen, M.-K., & Zainal, N. H. (2014). Diffusion tensor imaging studies in late-life depression: Systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, 29(12), 1173–1184. <https://doi.org/10.1002/gps.4129>.
- Wichers, M., Geschwind, N., van Os, J., & Peeters, F. (2010). Scars in depression: Is a conceptual shift necessary to solve the puzzle? *Psychological Medicine*, 40(3), 359–365. <https://doi.org/10.1017/S0033291709990420>.
- Wilde, A., Chan, H.-N., Rahman, B., Meiser, B., Mitchell, P. B., Schofield, P. R., & Green, M. J. (2014). A meta-analysis of the risk of major affective disorder in relatives of individuals affected by major depressive disorder or bipolar disorder. *Journal of Affective Disorders*, 158, 37–47. <https://doi.org/10.1016/j.jad.2014.01.014>.
- Winter, N. R., Leenings, R., Ernsting, J., Sarink, K., Fisch, L., Emden, D., ... Hahn, T. (2022). Quantifying deviations of brain structure and function in major depressive disorder across neuroimaging modalities. *JAMA Psychiatry*, 79(9), 879–888. <https://doi.org/10.1001/jamapsychiatry.2022.1780>.
- Won, E., Han, K. M., Kang, J., Kim, A., Yoon, H. K., Chang, H. S., ... Ham, B. J. (2017). Vesicular monoamine transporter 1 gene polymorphism and white matter integrity in major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 77, 138–145.
- World Health Organization (2017). *Depression and other common mental disorders: Global health estimates*. Geneva, Switzerland: World Health Organization.
- Wu, F., Tu, Z., Sun, J., Geng, H., Zhou, Y., Jiang, X., ... Kong, L. (2020). Abnormal functional and structural connectivity of amygdala-prefrontal circuit in first-episode adolescent depression: A combined fMRI and DTI study. *Frontiers in Psychiatry*, 10, 983.

- Wu, Y., Zhang, F., Makris, N., Ning, Y., Norton, I., She, S., ... O'Donnell, L. J. (2018). Investigation into local white matter abnormality in emotional processing and sensorimotor areas using an automatically annotated fiber clustering in major depressive disorder. *NeuroImage*, 181, 16–29.
- Xu, E., Nguyen, L., Hu, R., Stavish, C. M., Leibenluft, E., & Linke, J. O. (2022). The uncinate fasciculus in individuals with and at risk for bipolar disorder: A meta-analysis. *Journal of Affective Disorders*, 297, 208–216. <https://doi.org/10.1016/j.jad.2021.10.045>.
- Yuen, G. S., Gunning, F. M., Woods, E., Klimstra, S. A., Hoptman, M. J., & Alexopoulos, G. S. (2014). Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *Journal of Affective Disorders*, 166, 179–186.
- Zhang, A., Leow, A., Ajilore, O., Lamar, M., Yang, S., Joseph, J., ... Kumar, A. (2012). Quantitative tract-specific measures of uncinate and cingulum in major depression using diffusion tensor imaging. *Neuropsychopharmacology*, 37(4), 959–967. <https://doi.org/10.1038/npp.2011.279>.
- Zhang, H., Li, H., Yin, L., Chen, Z., Wu, B., Huang, X., ... Gong, Q. (2022). Aberrant white matter microstructure in depressed patients with suicidality. *Journal of Magnetic Resonance Imaging*, 55(4), 1141–1150.
- Zheng, K.-Z., Wang, H.-N., Liu, J., Xi, Y.-B., Li, L., Zhang, X., ... Li, B.-J. (2018). Incapacity to control emotion in major depression may arise from disrupted white matter integrity and OFC-amygdala inhibition. *CNS Neuroscience & Therapeutics*, 24(11), 1053–1062. <https://doi.org/10.1111/cns.12800>.
- Zhou, L., Wang, L., Wang, M., Dai, G., Xiao, Y., Feng, Z., ... Chen, G. (2022). Alterations in white matter microarchitecture in adolescents and young adults with major depressive disorder: A voxel-based meta-analysis of diffusion tensor imaging. *Psychiatry Research: Neuroimaging*, 323, 111482. <https://doi.org/10.1016/j.psychresns.2022.111482>.
- Zuurbier, L. A., Nikolova, Y. S., Åhs, F., & Hariri, A. R. (2013). Uncinate fasciculus fractional anisotropy correlates with typical use of reappraisal in women but not men. *Emotion (Washington, D.C.)*, 13(3), 385–390. <https://doi.org/10.1037/a0031163>.