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Longitudinal diffusion weighted imaging of limbic regions in patients with major depressive disorder after 6 years and partial to full remission

Kelly Doolin[a,*], Sinaoife Andrews[a], Angela Carballedo[a], Hazel McCarthy[a], Erik O'Hanlon[a], Leonardo Tozzi[b], Thomas Frodl[c]

[a] Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland
[b] Department of Psychiatry and Behavioural Sciences, Stanford University, Stanford, CA 94305, USA
[c] Department of Psychiatry and Psychotherapy, Otto von Guericke University, 39120 Magdeburg, Germany

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ABSTRACT

The objective of this study was to determine the effect of major depressive disorder (MDD) on white matter microstructures after a 6-year period compared to healthy controls (HC). This study included a small sample size of 26 participants, including 14 patients with MDD clinically diagnosed at baseline, and 12 HCs. MRI brain scans were conducted at baseline and follow-up, 75.32 (± 2.25) months after the initial scan. Tractography of 7 regions including the fornix, cingulum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus and uncinate fasciculus were conducted using ExploreDTI software. Both groups showed significant reduction in tract integrity between time points. MDD diagnosis was shown to have an effect on longitudinal FA of the left dorsal cingulum and the left parahippocampal cingulum. A significant inverse relationship was found between ΔFA [baseline FA – follow-up FA] of the right uncinate fasciculus and the left rostral cingulum with ΔHAM-D [baseline HAM-D – follow-up HAM-D] within the MDD group. These preliminary findings support the hypothesis that limbic structures including the cingulum are involved in MDD pathophysiology and may be affected even after remission. Moreover, they indicate that recovery from depression symptoms may slow the rate of WM degradation associated with aging in these regions of interest.

ANOVA	analysis of variance
BDI	Beck's Depression Inventory
BDNF	brain-derived neurotrophic factor
CSD	Constrained Spherical Deconvolution
DTI	diffusion tensor imaging
DC	dorsal cingulum
ELA	early life adversity
FA	fractional anisotropy
FOV	field of view
HAM-A	Hamilton rating scale for anxiety
HAM-D	Hamilton rating scale for depression
HARDI	high angular resolution diffusion imaging
HPA	hypothalamic-pituitary-adrenal
iFOF	inferior fronto-occipital fasciculus
LLD	late-life depression
MD	mean diffusivity
MDD	Major Depressive Disorder
MRI	magnetic resonance imaging
PC	parahippocampal cingulum
PSQI	Pittsburgh sleep quality index
RC	rostral cingulum
ROI	region of interest
SEM	standard error of the mean
SLF	superior longitudinal fasciculus
TIV	total intracranial volume
UF	uncinate fasciculus
WM	white matter

1. Introduction

Major Depressive Disorder (MDD) is a debilitating disorder that affects about 300 million people worldwide (World Health Organization, 2017). Structural anomalies have been reported in MDD and are thought to play a role in its pathophysiology. Diffusion tensor imaging (DTI) is a neuroimaging method that allows for the three-dimensional visualisation of white matter (WM) microstructures in the brain (Catani et al., 2002). DTI methods are known to suffer from an inability to accurately model complex WM architecture such as multiple

* Corresponding author.
E-mail address: doolink@tcd.ie (K. Doolin).

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fibre orientations and crossing fibres, therefore this study pursued a higher order model that have been shown to offer a more accurate capability to model complex fibre orientations (Tournier et al., 2011). High Angular Resolution Data Imaging (HARDI), the diffusion weighted imaging (DWI) technique used in this study, requires an increased number of gradient directions during acquisition, typically greater than 50, to permit more advanced tractography models. Constrained spherical resolution has been shown to provide robust representations of crossing fibre orientations and thus provides more accurate tract delineations than DTI in regions of complex fibre orientations (Tournier et al., 2007, 2008). The use of this advanced imaging analysis technique may improve our understanding of the WM alterations that occur in conjunction with MDD.

A common DTI metric for assessing the structural brain connectivity is fractional anisotropy (FA). FA is a measure of WM integrity or tissue organization, and a reduced FA score may suggests loss of axonal integrity and tract disruption (Beaulieu, 2002). In the absence of routine alternative diffusion metrics, particularly regarding data that does not feature the multi-shell acquisition that is necessary for Kurtosis Imaging, the typical DTI metrics can still be applied to HARDI data using the Constrained Spherical Deconvolution (CSD) based model (Dell'Acqua et al., 2013; Raffelt et al., 2012).

1.1. The role of the limbic system in MDD

The limbic system is composed of a number of interconnected grey matter and WM structures which are involved in emotion and memory (Mark et al., 1993). Neuroimaging studies have revealed the importance of the limbic system in the pathophysiology of mood disorders, notably MDD. For example, functional imaging studies have found imbalances in cortico-limbic activity and connectivity in MDD, including increased activity of various limbic regions (Anand et al., 2005; Drevets, 2000; Mayberg et al., 1999).

This study focused on limbic and related WM structures including the fornix, cingulum, uncinate fasciculus (UF), inferior fronto-occipital fasciculus (iFOF) and superior longitudinal fasciculus (SLF). For the purposes of this study, the cingulum was segmented into three divisions: the rostral cingulum (RC), dorsal cingulum (DC) and parahippocampal cingulum (PC) (Jones et al., 2013).

1.2. Aging and WM microstructure

Normal aging is associated with both structural and functional changes in the brain. There is a general trend for decreasing FA with increasing age (Madden et al., 2012). The global percentage WM volume loss per year in healthy subjects has been reported as being from 0.02% at 35 years of age, increasing to 0.47% at the age of 70 years (Schippling et al., 2017). There also appears to be differential aging of WM tracts. The “last-in-first-out” hypothesis suggests that tracts latest to develop are the first to be affected by age-related deterioration (Raz, 2000). Several neurobiological mechanisms exist in which this WM reduction may occur, including both axonal and myelin degeneration (Madden et al., 2012).

Imaging studies have indicated a relationship between WM integrity and age-related decline in cognition. In general, there appears to be a decline in fluid cognitive abilities with age (Madden et al., 2012). A reduction in processing speed and poorer working memory were shown to be associated with WM degradation in anterior regions, while reduced inhibition and greater task switching costs were associated with WM decline in posterior regions. Finally, WM decline in central regions was linked to poorer episodic memory (Kennedy and Raz, 2009).

1.3. Altered tractography in MDD

Changes in brain structure and function in healthy aging are comparable to the changes seen in the brain of a depressed patient. DTI studies of depression report a number of differences compared to HCs. For example, a previous tractography study found lower FA values in the SLF, UF, iFOF and cingulum in adolescents with MDD (Cullen et al., 2010). A meta-analysis of DTI studies of MDD found decreased FA in WM tracts connecting the prefrontal cortex with cortical and subcortical areas in depressed patients (Liao et al., 2013). A family history of MDD increases the risk for developing the illness (Weissman et al., 2005). It has been shown that a family history of MDD is associated with reduced FA values in the cingulum, SLF, UF and iFOF (Huang et al., 2011; Keedwell et al., 2012). In these individuals, WM structure alterations could act as a marker of vulnerability for developing MDD. In addition, a meta-analysis of microscructural brain abnormalities in MDD patients summarized that FA reduction in white matter of the right cerebellum hemispheric lobule, body of the corpus collosum, and bilateral superior longitudinal fasciculus were shown in patients who had undergone medication washout (Jiang et al., 2017).

Childhood trauma is a known risk factor for MDD (Chapman et al., 2004; Heim et al., 2008). While there is an abundance of evidence to support the existence of structural grey matter changes in subjects with a history of childhood trauma it is less clear whether white matter changes exist in such subjects (Heim and Binder, 2012; Paquola et al., 2018). A meta-analysis reported that white matter volume decreases in subjects with childhood trauma were more common than increases compared to those without trauma, and that the corpus callosum and cingulum were most frequently found to have volume differences (Daniels, 2015). Studies have found that childhood neglect in MDD patients results in hippocampal white matter changes (Frodl et al., 2010), however the interaction between childhood maltreatment, MDD, and WM alterations in limbic regions remains unclear (Tatham et al., 2016).

1.4. Longitudinal DTI

Longitudinal DTI studies of healthy adults show consistent findings of decreased FA across the WM tracts of the brain (Bender et al., 2016; Sexton et al., 2014). However, there have been very few longitudinal DTI studies of MDD to date. In a recent longitudinal study of late-life depression (LLD), patients during both the depressed and remitted phases showed higher diffusivity values in the left anterior cingulate cortex-posterior superior temporal gyrus tract, implying demyelination of this WM tract (Harada et al., 2018).

Treatment of MDD has also been shown to affect WM microstructure in longitudinal DTI studies. FA values were shown to increase in frontal and limbic structures of depressed patients after treatment with electroconvulsive therapy, indicating recovery of the WM integrity (Lyden et al., 2014). A follow-up study of LLD found that, following a 12-week clinical trial of sertraline, patients who do not remit from depression showed less change in the FA of the anterior cingulate cortex compared to HCs and remitted-depressed patients (Taylor et al., 2011).

1.5. Objectives

The objective of this study was to determine the effect of MDD on WM microstructures over a 6-year period compared to HCs and to determine which structures play a role in MDD longitudinally. Also, to determine the effect of remission from MDD on the rate of tract degradation, and to observe whether or not group differences are sustained over time. Finally, to determine if childhood trauma scores at baseline or improvement of psychiatric symptoms longitudinally were related to loss of tract integrity.

2. Methods

2.1. Participants

During the baseline investigation of this cohort, 46 patients

clinically diagnosed with MDD and 46 HCs were investigated (Ugwu et al., 2015). The follow-up investigation occurred 6 years later and included 14 of the MDD patients and 12 HCs. At the time of initial recruitment and baseline data collection, all MDD patients were undergoing treatment at the mental health services of Tallaght Hospital, Dublin and St. James's Hospital, Dublin. MDD was clinically diagnosed by consultant psychiatrists based on DSM-IV criteria. HCs were recruited from the local community.

Inclusion criteria at baseline for the MDD group included a current diagnosis of unipolar MDD, a HAM-D score of ≥17, and to be aged ≥18 years. Exclusion criteria included any other medical condition, regular use of medication other than psychiatric medications, pregnancy, and any condition that would exclude them from undergoing an MRI scan. For HCs, exclusion criteria included any chronic illness or psychiatric disorder, regular use of any medication, pregnancy, and any other contraindication for an MRI scan.

At the follow-up time point, subjects were re-assessed for medical history and medication use during the time between scans, and excluded if they had developed other chronic medical conditions or contraindications to an MRI scan. At the time of follow-up, 4 subjects had developed conditions that would exclude them from participation in the follow-up including current pregnancy, death, or metal implants that prevented them from being scanned. Thirty-eight were lost to follow-up, defined by the inability to contact them by telephone or mail. Twenty-two chose not to give their consent for the follow-up due to relocation, lack of interest, or other factors. Also, 2 subjects were consented and received structural MRI scans but did not complete the DWI portion of data collection.

Written informed consent was obtained from participants at both baseline and follow-up. The study was designed and performed in accordance with the ethical standards laid out by the Declaration of Helsinki and was approved by the ethics committee of Tallaght and St. James's Hospitals in cooperation with Trinity College Dublin.

2.2. Rating scales

Self-rated and observer-rated scales were completed for all participants at both times points. These included the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), Beck's Depression Inventory (BDI-II) (Beck et al., 1996), the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Depressed patients were considered fully remitted if they had a HAM-D score of <7 points at the follow-up visit, and partially remitted if their HAM-D score was ≥7 and ≤16 points at follow-up. A HAM-D score of ≥17 is considered indicative of current depression. One MDD patients met the "current depression" criteria, and therefore was excluded from DWI analysis.

The Childhood Trauma Questionnaire (CTQ) was administered only at baseline, as it has demonstrated high internal consistency and retest reliability (Scher et al., 2001). It is a standardised 28-item self-report instrument that assesses five categories of childhood maltreatment including emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein et al., 2003). This study used the CTQ global score, which takes the sum of the scores of all five categories. Participants scoring in the moderate to severe range in at least one of the five categories were classified as being positive for early life adversity (ELA).

2.3. Diffusion weighted imaging

Magnetic resonance images were obtained with a Philips Achieva MRI scanner operating at 3T at baseline and follow-up. High angular resolution diffusion imaging (HARDI) with 61 diffusion directions was obtained [field of view (FOV): 200 × 257 × 126 mm, voxel size: 1 × 1 × 1 mm, TR/TE = 12,561/59 ms, flip angle = 90°, half k-space acquisition was used (half scan factor = 0.68), SENSE parallel imaging factor = 2.5, b values = 0, 1200 s/mm^2, with SPIR fat suppression and dynamic stabilization in an image acquisition time of 15 min 42 s].

2.4. DWI data pre-processing

Data were pre-processed using ExploreDTI (www.exploredti.com) (Leemans et al., 2009) in the following order: (1) data conversion from PAR/REC (baseline) or DICOM (follow-up) formats to NIfTI and B-matrix text-file formats; (2) signal drift correction; (3) Gibb's ringing correction; (4) the right-left orientation was checked using the flip/permute plugin; (5) conversion to MAT files; (6) the orientation of the MAT files was checked using the glyph plugin; (7) correction for subject motion and eddy current/EPI distortions using a cubic spline interpolation.

2.5. Tractography

All data were normalized into MNI space using the ExploreDTI software. Seed point resolution was 2 × 2 × 2 mm, with a 1 mm step size and a seed FE-FA threshold of 0.2. Deterministic tractography based on constrained spherical deconvolution (Tournier et al., 2007) was applied using ExploreDTI. Whole-brain tractography was carried out in each participant. The ExploreDTI software allows the isolation of tracts passing though regions of interest (ROIs) using the "AND", "OR" and "NOT" Boolean operators. A number of tracts that have previously shown to be affected by MDD were chosen for examination.

All ROIs were drawn on the FA-weighted coloured maps and the investigator was blind to the diagnosis. Atlas-based tractography was employed to carry out the WM extraction. The template subject was a control and an average of the group in terms of age and sex, and was visually inspected to confirm that the DWI image was "standard" and undistorted.

The protocol for extracting the WM tracts were as follows:

a) *Rostral cingulum (RC).* An AND ROI was drawn around the RC on the most inferior axial slice in which the body of the corpus callosum was seen clearly in full profile. A second AND ROI was placed around the RC on an axial slice taken through the middle of the genu. Finally, the third AND ROI was placed around the RC on the lowest axial slice in which the genu was joined across the midline. A single NOT ROI was placed in the mid-sagittal plane to exclude fibres projecting medially (Ugwu et al., 2015).
b) *Dorsal cingulum (DC).* The first AND ROI was placed around the DC on the most posterior coronal slice where the genu was seen in full profile. An AND ROI was also drawn around the DC on the most anterior coronal slice where the splenium was seen in full profile. A coronal slice was taken midway between the two previous ROIs and a third AND ROI was drawn around the DC. NOT ROIs were placed mid-sagittally and axially to exclude fibres branching out to the cortex (Ugwu et al., 2015).
c) *Parahippocampal cingulum (PC).* The most ventral axial slice of the splenium was located and an AND ROI was placed around the PC. An axial slice was taken 4 slices above this and the second AND ROI was drawn around the PC. A coronal NOT ROI was placed 5 slices caudal to the midpoint of the corpus callosum to exclude fibres from the dorsal cingulum. A mid-sagittal NOT ROI was also used (Jones et al., 2013).
d) *Uncinate fasciculus (UF).* The most posterior coronal slice in which the temporal lobe is separated from the frontal lobe (as seen in the T1 image) was located. One AND ROI was placed around the entire temporal lobe while another was drawn around the UF to include the entire projections toward the frontal lobe. NOT regions were placed mid-sagittally, coronally and axially to exclude fibres from the iFOF and the cingulum (Ugwu et al., 2015).
e) *Fornix.* The coronal slice was located where the fornix descends inferiorly, posterior to the anterior commissure. An OR ROI was

drawn around the columns of the fornix in this slice. An axial slice was taken just inferior to the anterior commissure and an AND ROI was drawn to include the crus of the fornix. NOT regions were placed both anterior and posterior to the fornix in the coronal view, as well as superior and inferior to the fornix in the axial view to exclude projecting fibres (Metzler-Baddeley et al., 2013).

f) *Superior longitudinal fasciculus (SLF)*. The most inferior axial slice where the fornix was visible as a single intense structure was located and a coronal slice was taken midway through the posterior limb of the internal capsule. An AND ROI was placed around the SLF in this slice. A second AND ROI was drawn around the SLF on the coronal slice taken midway through the splenium. A mid-sagittal NOT ROI was used as well as NOT regions to exclude fibres from the iFOF and corticospinal tract (Luck et al., 2011).

g) *Inferior fronto-occipital fasciculus (iFOF)*. The first AND ROI was placed around the iFOF on the coronal slice at the level where the anterior commissure crossed the midline. A coronal slice was taken midway through the pontine crossing fibres as seen in the mid-sagittal plane and the second AND ROI was drawn arund the iFOF. NOT regions were drawn in the mid-sagittal plane and coronally to exclude fibres from the UF (Kvickstrom et al., 2011).

Examples of tractography images produced for each of each of these structures can be found in the appendix [Appendix A].

2.6. Statistics

Statistical analysis was carried out using SPSS software. Baseline demographic and clinical data were analysed by *t*-test for continuous variables and Chi-squared test for categorical variables. The effect of time on longitudinal psychiatric rating scale scores was assessed by a repeated measures ANOVA. Baseline data were analysed using a general linear model using age, sex, and total intracranial volume (TIV) as covariates to assess initial differences between MDD and HC subjects. Longitudinal DWI data including FA measures were analysed by repeated measures ANOVA, using age at baseline, months between scans, and sex as covariates. Between-groups analysis and group*time were assessed. False Discovery Rate (FDR) correction of 0.05 was used to address multiple comparisons for DWI data. Delta (Δ) values of tractography measures and psychiatric rating scale scores were calculated by subtracting follow-up values from baseline values [baseline – follow-up]. As such, a larger ΔHAM-D value would indicate greater recovery from depressive symptoms. A larger ΔFA value is indicative of greater loss of tract integrity. Correlational analyses between delta ΔFA values with baseline CTQ and ΔHAM-D was conducted using partial correlations controlling for age at baseline, months between scans, and sex.

3. Results

3.1. Demographic results

In this study, 12 HCs aged 40.75 years (± 16.4), and 14 MDD patients aged 44.21 years (± 8.03) were scanned and assessed at baseline and follow-up time points. There was no difference in baseline age or sex distribution [Table 1]. The average time between the baseline and follow-up scans was 75.32 (± 2.25) months, and there was no difference in the months between scans between groups ($t = 0.095$, $p = 0.924$).

At baseline, MDD patients had average HAM-D scores of 24.36 (± 4.39), a score indicative of severe MDD. HCs exhibited depression rating scale scores indicative of psychiatric well-being at both baseline and follow-up [Table 1]. There were significant differences between the psychiatric rating scale scores of the HC group and the MDD group at baseline, including HAM-D ($t = 16.424$, $p = 0.010$), BDI ($t = 9.592$, $p < 0.001$), and HAM-A ($t = 7.394$, $p = 0.004$). There was no significant difference in PSQI scores between groups ($t = 5.953$, $p = 0.177$) at baseline.

At the follow-up scan, of the 14 participants from the MDD group, only 1 had a HAM-D score that indicated current depression (HAM-D score ≥ 17), 6 were considered partially remitted (HAM-D score ≥ 7 and ≤ 16), and 7 were fully remitted (HAM-D score < 7) at the follow-up time point.

The mean score of HAM-D for patients in the MDD group at the follow-up scan was 8.00 (± 4.39). In the MDD group, there was a significant reduction of HAM-D and BDI scores ($p < 0.001$) over time, however the HAM-A and PSQI scores did not reduce significantly. For the HC group, there was no effect of time on HAM-D or PSQI scores, but BDI ($F = 6.765$, $p = 0.025$) and HAM-A scores ($F = 6.000$, $p = 0.032$) were significantly reduced. Detailed psychiatric rating scale data can be observed in Table 1.

3.2. Tractography

Tractography was conducted in all participants at baseline and follow-up in the seven regions previously described. The resultant means of FA measures for each region for MDDs and HCs are displayed in Table 2.

3.3. Effect of time on FA

In the HC group, time had a significant effect on reduction of FA in five brain regions. These included the fornix ($F = 6.913$, $p = 0.023$), left RC ($F = 11.225$, $p = 0.006$), left SLF ($F = 84.293$, $p < 0.001$), left iFOF ($F = 11.753$, $p = 0.006$) and right UF ($F = 9.837$, $p = 0.009$) [Table 2]. Four of these comparisons survived FDR correction for 13 regions. These were the left RC ($p = 0.026$), left SLF ($p < 0.001$), left iFOF ($p = 0.026$), and the right UF ($p = 0.029$).

Within the MDD group, FA was significantly reduced over time in four regions including fornix ($F = 10.013$, $p = 0.008$), left RC ($F = 18.893$, $p = 0.001$), left DC ($F = 12.372$, $p = 0.004$) and left iFOF ($F = 20.579$, $p = 0.001$) [Table 2]. Three regions survived FDR comparison, including the fornix ($p = 0.026$), left RC ($p = 0.007$), and left iFOF ($p = 0.007$).

3.4. Effect of group (MDD versus healthy control) on FA

A significant effect of group was found on the FA of the left DC ($F = 5.698$, $p = 0.026$), indicating greater reduction of FA in the left DC in the MDD group between baseline and follow up compared to HCs [Figs. 1a and 2]. The FA of the left PC was also shown to be significantly affected by diagnosis ($F = 7.069$, $p = 0.014$) [Figs. 1b and 3] indicating greater reduction of FA in the left DC in the HC than the MDD group between baseline and follow up. The significant effects of group on longitudinal FA were not sustained following an FDR correction for the 13 regions analysed.

3.5. Group*time effect on tractography measures

No significant interactions were identified between MDD diagnosis and time for FA measures. However, some trends were observed. There was a non-significant trend indicated for group*time effect for the FA of the left DC ($F = 3.246$, $p = 0.085$) [Fig. 1a] and for the FA of the left SLF ($F = 3.196$, $p = 0.087$).

3.6. Correlations between psychiatric rating scale scores in MDD patients and tractography measures

Correlational analysis revealed a significant inverse relationship between the MDD group's CTQ global scores at baseline and ΔFA of the right SLF ($r = -0.831$, $p = 0.003$, df = 8). Scores indicative of greater childhood trauma were related to less loss of tract integrity of the right SLF as indicated by ΔFA.

Table 1
Demographic and clinical characteristics in HCs and MDD patients.

Measure	HC (n = 12)	MDD (n = 14)	Between-group statistics
Age at baseline (years)	40.75 (16.14)	44.21 (8.03)	t = −0.675, p = 0.509
Months between scans	76.00 (10.34)	75.57 (12.40)	t = 0.095, p = 0.925
Sex (F/M)	8/4	10/4	X^2 = 0.069, p = 0.793
BMI at baseline	25.57 (6.18)	26.17 (5.32)	t = −0.264, p = 0.794
Smoking (Y/N)	2/10	6/8	X^2 = 2.081, p = 0.149
Antidepressant use (Y/N)	0/12	12/2	X^2 = 19.102, p < 0.001***
CTQ Global Score	30.75 (5.45)	49.71 (24.66)	t = −2.799, p = 0.014*
ELA (Y/N)	3/9	7/7	X^2 = 1.706, p = 0.191

	Baseline	Follow-up	Within-Subjects (F, p)	Baseline	Follow-up	Within-Subjects (F, p)	Between-Group (F, p)
HAM-D	2.67 (2.10)	1.25 (2.09)	4.496, 0.058	24.36 (4.48)	8.00 (4.39)	97.544, <0.001***	240.783, <0.001***
BDI	2.00 (2.17)	0.42 (0.67)	6.765, 0.025*	29.93 (10.64)	15.93 (12.14)	18.755, <0.001***	158.401, <0.001***
HAM-A	2.50 (2.88)	0.50 (1.00)	6.000, 0.032*	17.33 (6.83)	11.22 (8.89)	3.610, 0.094	79.073, <0.001***
PSQI	4.08 (2.91)	2.67 (2.99)	1.268, 0.284	12.00 (3.86)	9.70 (3.86)	1.330, 0.279	5.267, <0.001***

Data are depicted as mean and standard deviation in parenthesis. Baseline statistics were calculated using a Student's t-test for continuous variables, and a Chi-squared test for categorical variables. Repeated measured ANOVA used to calculate within-subjects and between-subjects statistics for longitudinal psychiatric rating scale scores. BDI = Beck's Depression Inventory; BMI = Body mass index; CTQ = Childhood Trauma Questionnaire; ELA = Early life adversity; F/M = Female/Male; HAM-A = Hamilton anxiety rating scale; HAM-D = Hamilton depression rating scale; HC=Healthy controls; MDD = Major Depressive Disorder; PSQI = Pittsburgh Sleep Quality Index; Y/N = Yes/No. *p < 0.05; **p < 0.01; ***p < 0.001.

Table 2
FA measures of tractography in regions of interest.

Region	HC (n = 12)			MDD (n = 13)			Statistics (F, p)	
	Baseline	Follow-up	Within group	Baseline	Follow-up	Within group	Group	Group*time
Medial								
Fornix	0.320 (0.005)	0.300 (0.006)	F = 6.913, p = 0.023*	0.320 (0.005)	0.310 (0.006)	F = 10.013, **p = 0.008***	0.299, 0.637	0.031, 0.863
Left hemisphere								
RC	0.350 (0.009)	0.292 (0.016)	F = 11.225, **p = 0.006****	0.354 (0.012)	0.305 (0.008)	F = 18.893, **p = 0.001****	0.369, 0.537	0.169, 0.685
DC	0.410 (0.007)	0.390 (0.010)	F = 2.343, p = 0.154	0.400 (0.009)	0.350 (0.010)	F = 12.372, p = 0.004**	5.698, 0.026*	3.246, 0.085
PC	0.312 (0.008)	0.302 (0.007)	F = 2.370, p = 0.152	0.287 (0.011)	0.280 (0.010)	F = 0.278, p = 0.608	7.069, 0.014*	0.310, 0.583
SLF	0.397 (0.007)	0.370 (0.006)	F = 84.293, **p<0.001*****	0.376 (0.007)	0.363 (0.006)	F = 3.081, p = 0.105	3.143, 0.090	3.196, 0.087
iFOF	0.413 (0.005)	0.393 (0.005)	F = 11.753, **p = 0.006****	0.405 (0.005)	0.383 (0.006)	F = 20.579, **p = 0.001****	2.125, 0.158	0.042, 0.840
UF	0.286 (0.009)	0.294 (0.007)	F = 1.485, p = 0.249	0.310 (0.009)	0.305 (0.007)	F = 0.437, p = 0.521	3.125, 0.086	1.602, 0.218
Right hemisphere								
RC	0.330 (0.014)	0.311 (0.015)	F = 2.210, p = 0.165	0.331 (0.017)	0.312 (0.012)	F = 0.889, p = 0.364	0.001, 0.977	0.018, 0.895
DC	0.380 (0.009)	0.39 (0.010)	F = 0.825, p = 0.383	0.370 (0.006)	0.370 (0.010)	F = 0.586, p = 0.459	2.027, 0.168	1.373, 0.253
PC	0.299 (0.008)	0.297 (0.009)	F = 0.056, p = 0.818	0.290 (0.008)	0.289 (0.008)	F = 0.003, p = 0.955	0.680, 0.418	0.014, 0.906
SLF	0.379 (0.008)	0.39 (0.007)	F = 1.997, p = 0.185	0.371 (0.007)	0.377 (0.007)	F = 1.284, p = 0.279	1.347, 0.258	0.239, 0.629
iFOF	0.398 (0.006)	0.403 (0.006)	F = 0.365, p = 0.558	0.394 (0.005)	0.387 (0.009)	F = 0.851, p = 0.374	1.609, 0.217	1.176, 0.289
UF	0.288 (0.010)	0.265 (0.007)	F = 9.837, **p = 0.009****	0.295 (0.008)	0.278 (0.008)	F = 2.968, p = 0.111	1.013, 0.325	0.325, 0.574

Data represent mean and SEM in parenthesis. Measures of FA were calculated with ExploreDTI and statistics calculated with SPSS. DC = Dorsal cingulum; HC=Healthy control; iFOF = Inferior fronto-occipital fasciculus; MDD = Major Depressive Disorder; PC = Parahippocampal cingulum; RC = Rostral cingulum; SLF = Superior longitudinal fasciculus; UF = Uncinate fasciculus.
Bolded p-values indicate those that survived FDR correction.
* p < 0.05.
** p < 0.01.
*** p < 0.001.

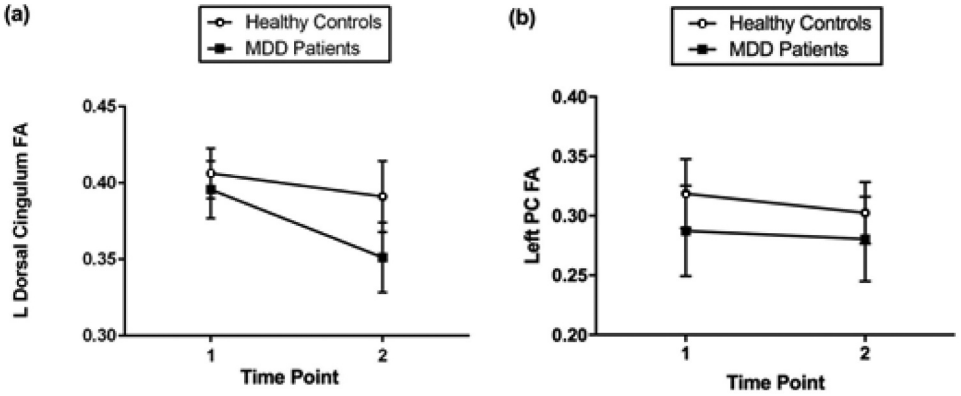

Fig. 1. Left dorsal cingulum and parahippocampal cingulum FA measures. Mean and SEM of FA of the (a) left dorsal cingulum and left parahippocampal cingulum (PC) in MDD patients and HCs at baseline and follow-up time points (1 = Baseline, 2 = Follow-Up).

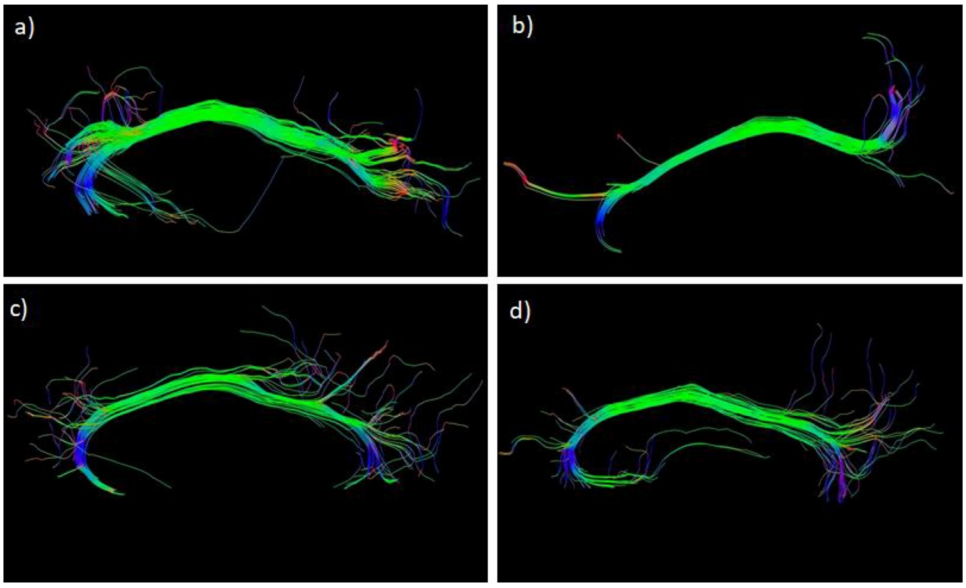

Fig. 2. Left dorsal cingulum tractography. Left dorsal cingulum (DC) tractography in a HC subject at (a) baseline and (b) follow-up, and in a MDD patient at (c) baseline and (d) follow-up.

There were also significant relationships between MDD patients' ΔHAM-D scores and ΔFA of several microstructures. The ΔFA of the left RC was inversely related to ΔHAM-D score ($r = -0.701$, $p = 0.024$, df = 8) [Fig. 4a]. The ΔFA of the right UF was significantly inversely correlated ($r = -0.784$, $p = 0.007$, df = 8) [Fig. 4b]. Analysis also revealed an inverse relationship on the cusp of significance between ΔHAM-D score and ΔFA of the left DC ($r = -0.626$, $p = 0.053$, df = 8).

These correlation findings did not survive FDR correction due to the small sample size of 13 patients.

4. Discussion

This longitudinal study examined the integrity of four association tracts (cingulum, SLF, iFOF and UF) and one commissural tract (fornix) in patients with MDD and HCs. To our knowledge, this is one of the first long-term longitudinal studies of DWI in MDD. There was a significant reduction in FA over the 6 years in the left DC in the depressed group, in the left SLF and right UF in the control group and in the fornix, left RC and left iFOF in both groups. Improvement of HAM-D scores of MDD patients were related to maintenance of tract FA for two regions, the left RC and right UF, indicating that recovery from depression symptoms may slow the rate of WM degradation associated with aging in these regions of interest. Baseline CTQ scores were inversely correlated with FA reduction of the right SLF within the MDD group, indicating that MDD patients with more childhood trauma may have greater preservation of the left SLF tract integrity over time.

In this longitudinal study, both the depressed and control groups showed a decrease in tract integrity in varying regions over the 6 years.

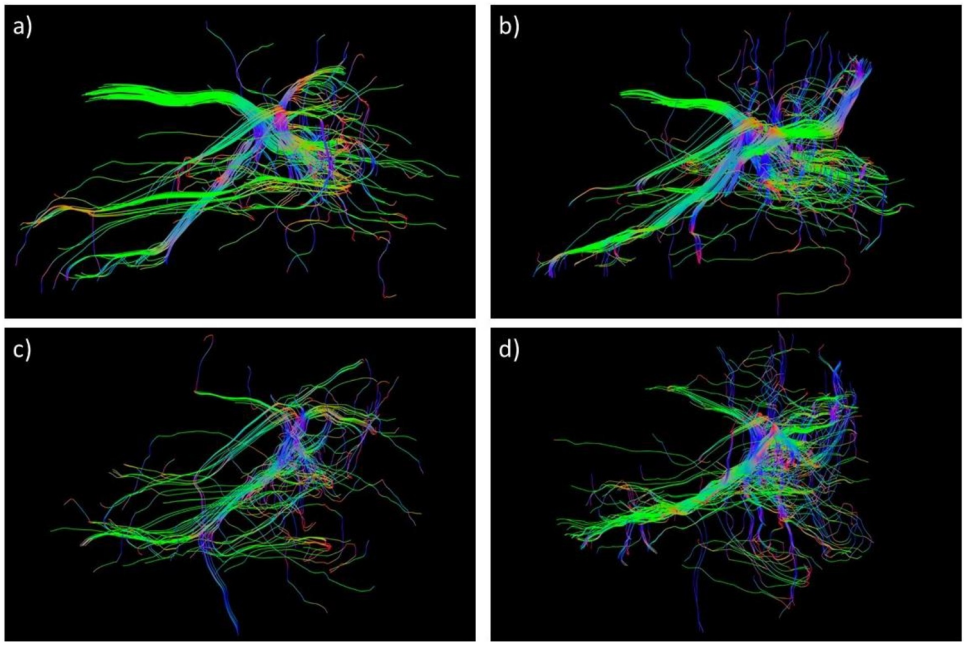

Fig. 3. Left parahippocampal cingulum tractography. Left parahippocampal cingulum (PC) tractography in a HC subject at (a) baseline and (b) follow-up, and in a MDD patient at (c) baseline and (d) follow-up.

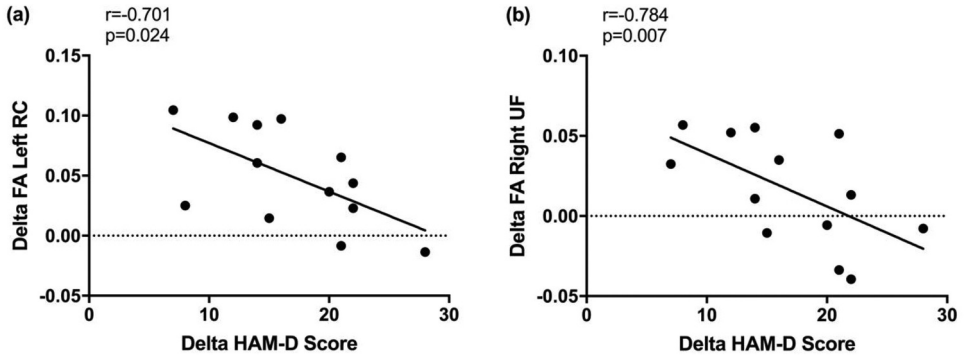

Fig. 4. Correlational analysis between ΔHAM-D and ΔFA in MDD group. Relationship between ΔHAM-D and ΔFA of the (a) left rostral cingulum (RC) and (b) right uncinate fasciculus (UF) in the MDD group assessed by partial correlation controlling for age at baseline, months between scans, and sex.

WM tracts have been found to show differential age-related decline. For example, one study found that association fibres show the most prominent decline with age which conforms to the "last-in-first-out" hypothesis of brain aging (Bender et al., 2016). This hypothesis proposes that WM tracts which are last to develop in the adult brain are the first to be affected by aging (Raz, 2000). This literature supports the age-related decline of the association tracts seen in this present study.

There have been multiple findings of reduced brain matter volumes in MDD. For example, studies have reported reduced volume in the hippocampus, amygdala, cingulate gyrus and prefrontal cortex in patients with depression compared to HCs (Campbell et al., 2004; Drevets et al., 1997; Frodl et al., 2008; Sheline et al., 1999). In addition, WM integrity reductions represented by a decreased FA score have been observed in areas such as the anterior limb of the internal capsule, cingulum and SLF in MDD (Cullen et al., 2010; Zou et al., 2008).

In this study, the left DC longitudinal FA was shown to be affected by MDD diagnosis. The cingulum bundle as a whole is thought to be involved in the motivational and emotional aspects of behaviour as well as spatial working memory (Schmahmann et al., 2007). Specifically, the DC is believed to be a component of the default-mode network which is active during resting state and associated with self-directed thought (Catani et al., 2013). The activity of this functional network decreases during goal-directed tasks (Raichle et al., 2001). The default-mode network has been shown to have altered activity in neuropsychiatric disorders including MDD (Broyd et al., 2009), and is thought to be responsible for the self-referential and introspective thoughts of depression (Sheline et al., 2009). Many of the functions of the DC are disrupted in depression, therefore the findings of this study indicate a potential role of this structure in MDD, supporting the existing literature.

Further supporting the involvement of the left DC in MDD pathophysiology, this study found that the FA reduction of the left DC was nearly significantly inversely correlated with depressive symptom improvement as indicated by the ΔHAM-D score ($p = 0.053$). This might imply that a greater recovery from depression results in greater maintenance of left DC WM integrity.

This study also showed an effect of MDD diagnosis on left PC FA, indicative of reduced FA in patients compared to controls in both baseline and follow-up. The PC, along with the fornix, are involved in the hippocampal-diencephalic-retrosplenial functional network which is involved in memory and spatial orientation (Catani et al., 2013). Alterations to these areas are associated with memory deficits. Altered memory function is characteristic of MDD (Dillon and Pizzagalli, 2018), therefore this finding may be relevant to understanding the importance of this structure in MDD pathophysiology.

In this study, the change in FA in the left RC was also negatively correlated with change in depression symptom scores. The RC, also known as the subgenual cingulum, has been used as a target for deep brain stimulation in treatment-resistant depression (Mayberg et al., 2005; Sakas and Panourias, 2006). The chronic stimulation of this region has been shown to result in a significant reduction of depressive symptoms (Mayberg et al., 2005). Our finding that tract FA of this region was more preserved in patients with greater depression symptom recovery is in line with the literature that suggests an important role of the left RC in MDD.

This study found that right UF tract integrity reduction was inversely correlated with HAM-D score improvement. The UF acts as a connecting structure between limbic regions and is a major component of the temporo-amygdala-orbitofrontal functional network which has a role in integrating visceral and emotional states with cognition and behaviour (Catani et al., 2013). It has been found that disruption of the UF and this network are associated with mood disorders including MDD (Carballedo et al., 2012; Zhang et al., 2012). Both these studies found depressed patients to have reduced FA in the UF compared to HCs. Since it is believed that the UF is involved in regulating emotional states, the present study's finding of its relationship to longitudinal MDD symptom recovery is reassuring.

It is unknown how remission might affect the biological changes associated with MDD. Remission from MDD following antidepressant treatment has been shown to associated with an increase in brain-derived neurotrophic factor (BDNF) which is consistently found to be lower in MDD (Sen et al., 2008). In terms of neuroimaging studies of remission of MDD, few have been conducted. Some studies have shown that response to antidepressants can be predicted by WM. For example, depressed patients undergoing antidepressant treatment who failed to remit had higher FA values in the cingulum and frontal regions (Korgaonkar et al., 2014; Taylor et al., 2008). One study of late-life depression found that remitted-depressed patients showed similar microstructure reduction to controls after one year (Taylor et al., 2011). Specifically, the non-remitted depressed patients showed less aging in the anterior cingulate cortex compared to both the remitted-depressed patients and the controls. The present study occurred over a longer follow-up period than any known study of remission from MDD. Research is lacking in this area therefore our findings are novel and informative as to how WM reduction occurs in remission.

Another key finding of this study was that greater childhood trauma scores at baseline were associated with less reduction of FA in the right SLF between time points. This indicates that, for depressed patients, stressful childhood events may be related to greater maintenance of WM integrity in this tract. The SLF makes bidirectional connections between the frontal cortex and the parietal, temporal and occipital lobes. It has been shown to have many functions including initiation of motor activity, spatial attention and most interestingly, working memory (Schmahmann et al., 2007). Impaired memory has been associated with experiences of childhood trauma (Anda et al., 2006), therefore this finding is surprising and calls for further investigation.

Childhood trauma is a strong risk factor for developing MDD later in life (Gilbert et al., 2009; Klein et al., 2009). Neuroimaging studies have

revealed differences between those who have suffered childhood trauma and HCs. For instance, altered FA values in the cingulum, UF, iFOF and fornix, as well as the arcuate fasciculus which is a component of the SLF, were found in subjects with a history of childhood adversity in previous DTI studies (Choi et al., 2009; Ugwu et al., 2015). A longitudinal DTI study of adolescents exposed to childhood maltreatment found that these individuals had lower FA in the SLF, cingulum, and iFOF at baseline in comparison to HCs (Huang et al., 2012). Furthermore, the adolescents who developed MDD at follow-up had reduced FA in the SLF and cingulum in comparison to those who did not develop MDD. On the other hand, white matter density increases have also been reported in depressed populations with childhood trauma (Sheu et al., 2010). This suggests that individuals exposed to childhood trauma undergo WM disruptions which may increase the risk of developing MDD, and that there are long-term effects of childhood maltreatment in the form of limbic scarring (Dannlowski et al., 2012). The findings of the present study further support the hypothesis of a lasting effect of childhood trauma on WM structures during aging, however the directionality of FA changes seems to differ between regions, and further investigation into larger cohorts is required.

This study indicates that limbic structures, in particular the cingulum, have a role in MDD longitudinally. The hippocampus is a major component of the brain's limbic system, and many studies have suggested atrophy occurs in the hippocampus in patients with MDD. For example, several studies have found hippocampal volume reduction in depressed patients compared to HCs (Campbell et al., 2004; Roddy et al., 2019; Sapolsky, 2000; Sheline et al., 1996). Reduced functional activity of the hippocampus and limbic structures has also been observed in MDD (Drevets et al., 2008; Zhang et al., 2011). Moreover, animal models of depression have shown that hippocampal neurogenesis is necessary for the behavioural effects of antidepressants (Santarelli et al., 2003), strengthening the hypothesis that this structure is highly involved in MDD pathophysiology.

The hippocampus is also of great interest in MDD research due to its role in hypothalamic-pituitary-adrenal (HPA) axis regulation. The HPA axis is the body's stress response system, and dysregulation of this axis has been reported consistently in MDD research (Doolin et al., 2017; Pariante and Lightman, 2008). In depression, sustained elevation of cortisol levels is believed to reduce efficacy of glucocorticoid receptor function, ultimately resulting in an un-suppressed inflammatory response (Cohen et al., 2012; Farrell and O'Keane, 2016; Pariante and Miller, 2001; Raison and Miller, 2003). Elevated presence of inflammatory cytokines in the central nervous system may lead to mechanisms of WM deterioration. Studies have shown that immune system activation could cause damage to neurons via dendrite shrinkage, axonal degradation or even neuronal death, suggesting that the elevated inflammatory response in MDD could contribute to reduced brain volumes (Block and Hong, 2005; Calabrese et al., 2015).

It is worth noting that HAM-A and PSQI scores did not reduce over time in MDD patients. When considering the findings of this study, it is important to note that while the MDD group showed varying degrees of remission from depression, this group showed no significant change in anxiety and sleep disturbances rating scale scores, symptoms which often co-occur with depression.

4.1. Strengths and limitations

This study would benefit from further research as there were several limitations. It is a limitation that this study had a small sample size. Many of the original participants had changed their contact details, moved out of the country, developed conditions that excluded them from the study, or had other reasons that would exempt them from having an MRI scan.

Another limitation was that there was no chronically-depressed patient group to compare to the remitted-depressed and control groups. Out of the 14 MDD patients that returned for follow-up analysis, only one patient was still currently depressed. One of the reasons for this could be that chronically depressed patients may have less motivation to participate in research and return for follow-up analysis.

Additionally, the majority of the MDD patients were taking antidepressants at the time of the baseline scan. It is important to note that the use of medication could have potentially affected the degree of tract disruption. MDD patients' number of distinct depressive episodes and remissions between the two study time-points was unable to be determined based on patient interviews, and is therefore another limitation.

However, there are several strengths to this study, including that it is one of the first reported long-term longitudinal tractography studies of patients with MDD. This study also benefited from the superior imaging methodology of CSD HARDI as opposed to DTI, which suffers from difficulties in measuring crossing fibres (Tournier et al., 2007, 2008). In the HARDI method, the FA metric can routinely be extracted for the delineated tracts with the added benefit of more accurately modelled complex WM orientation which have been shown to have a much greater abundance in the brain with some estimates (Jeurissen et al., 2013; Vos et al., 2012). Finally, this study also benefited from the collection of clinical data such as CTQ scores for indication of childhood trauma, in addition to documenting MDD symptoms at both time points.

4.2. Conclusions

In this study, it was shown that MDD diagnosis has an effect on WM tract integrity reduction associated with aging in substructures of the cingulum. Other structures including the fornix, a region hypothesised to play a role in MDD, showed no difference between groups. The lack of group effect on the fornix and other WM microstructures may be explained by mechanisms resulting from remission of MDD symptoms. The results also showed a relationship between depression symptom recovery and maintenance of WM tracts over time, strengthening the hypothesis that depression and its remission may be related to different rates of brain aging. The findings of this study highlight the involvement of specific limbic structures in the aging of MDD patients.

CRediT authorship contribution statement

Kelly Doolin: Writing - original draft, Supervision, Data curation. **Sinaoife Andrews:** Writing - original draft, Formal analysis. **Angela Carballedo:** Methodology. **Hazel McCarthy:** Data curation. **Erik O'Hanlon:** Methodology. **Leonardo Tozzi:** Formal analysis. **Thomas Frodl:** Supervision, Methodology.

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Contributors

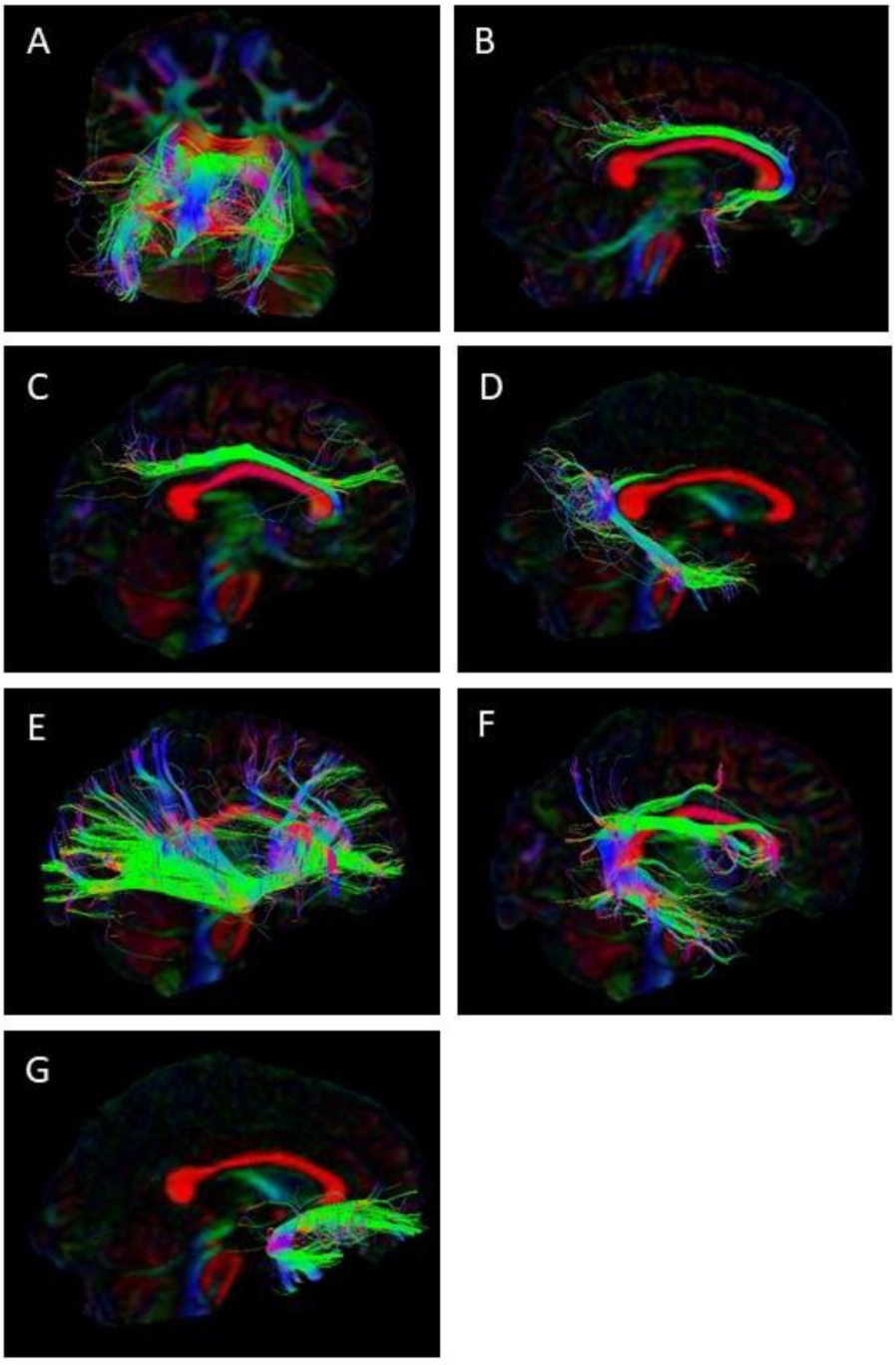
TF and AC designed this study. KD and HM coordinated and conducted recruitment of participants, scan collection, and psychiatric data collection. SA, LT, and EO were responsible for data analysis. KD and SF were responsible for manuscript write-up.

Conflicts of interest

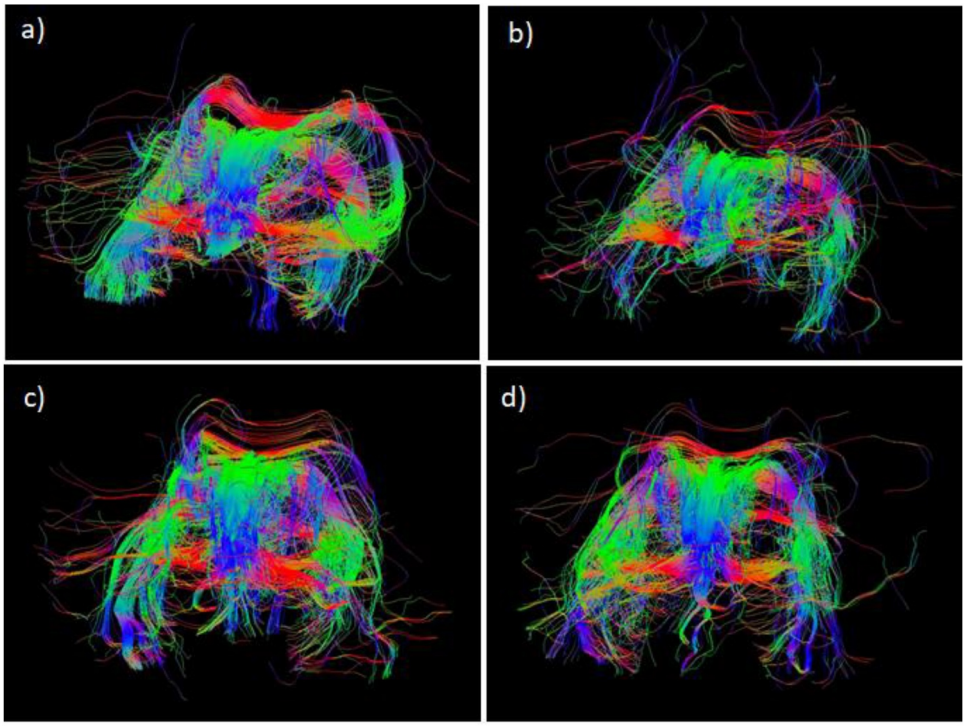
All authors declare no conflict of interest.

Appendix

Appendix A Appendix B–D.



Appendix A. Example images produced using ExploreDTI of the (a) fornix, (b) rostral cingulum, (c) dorsal cingulum, (d) parahippocampal cingulum, (e) inferior fronto-occipital fasciculus, (f) superior longitudinal fasciculus, and (g) uncinate fasciculus. Image (a) is in the coronal view while (b)–(g) are in the sagittal view. Fibres connecting the right and left hemispheres are shown in red. Fibres running superiorly-inferiorly are shown in blue. Fibres running along the rostral-caudal axis are shown in green.



Appendix B. Fornix tractography. Fornix tractography in a healthy control subject at (a) baseline and (b) follow-up, and in an MDD patient at (c) baseline and (d) follow-up.

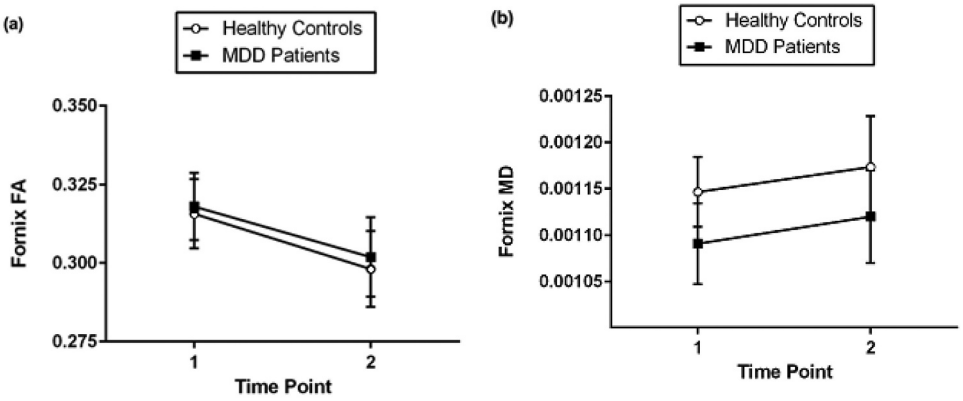
Appendix C

Mean diffusivity (MD) in 13 regions in HC and MDD groups.

Region	HC (n = 12)		MDD (n = 13)		Statistics (F, p)	
	Baseline	Follow-up	Baseline	Follow-up	Group	Group*time
Fornix	0.0010 (1.7E−5)	0.0010 (2.5E−5)	0.0010 (2.0E−5)	0.0010 (2.3E−5)	3.994, 0.058	0.005, 0.943
Left RC	0.0008 (1.3E−5)	0.0008 (1.0E−5)	0.0008 (9.6E−6)	0.0008 (1.3E−5)	0.066, 0.800	0.586, 0.452
Right RC	0.0008 (7.9E−6)	0.0008 (8.9E−6)	0.0008 (1.0E−5)	0.0008 (1.3E−5)	0.090, 0.767	0.328, 0.573
Left DC	0.0008 (9.7E−6)	0.0008 (5.4E−6)	0.0008 (5.8E−6)	0.0008 (1.3E−5)	0.845, 0.368	1.509, 0.232
Right DC	0.0008 (2.6E−6)	0.0008 (5.0E−6)	0.0008 (8.8E−6)	0.0008 (7.8E−6)	3.239, 0.085	0.061, 0.808
Left PC	0.0009 (1.1E−5)	0.0008 (9.7E−6)	0.0009 (8.9E−6)	0.0008 (1.1E−5)	0.098, 0.758	2.394, 0.135
Right PC	0.0008 (9.0E−6)	0.0009 (1.5E−5)	0.0008 (1.1E−5)	0.0009 (9.9E−6)	0.318, 0.578	0.152, 0.700
Left SLF	0.0008 (4.3E−6)	0.0007 (4.6E−6)	0.0008 (8.1E−6)	0.0008 (9.9E−6)	1.426, 0.245	0.170, 0.684
Right SLF	0.0007 (4.4E−6)	0.0007 (6.2E−6)	0.0007 (7.8E−6)	0.0008 (8.9E−6)	1.358, 0.256	0.071, 0.0.792
Left iFOF	0.0008 (4.9E−6)	0.0008 (3.8E−6)	0.0008 (6.8E−6)	0.0008 (7.6E−6)	0.420, 0.523	0.440, 0.514
Right iFOF	0.0008 (3.7E−6)	0.0009 (1.0E−4)	0.0008 (6.7E−6)	0.0008 (5.9E−6)	0.811, 0.377	1.064, 0.313
Left UF	0.0009 (1.0E−5)	0.0015 (7.2E−4)	0.0009 (9.2E−6)	0.0008 (1.2E−5)	1.135, 0.298	1.068, 0.312
Right UF	0.0008 (1.1E−5)	0.0009 (1.0E−5)	0.0008 (9.5E−6)	0.0009 (1.0E−5)	0.063, 0.804	0.084, 0.775

Data represent mean and SEM in parenthesis. MD was calculated with ExploreDTI and statistics calculated with SPSS. DC = Dorsal cingulum; HC=Healthy control; iFOF = Inferior fronto-occipital fasciculus; MDD = Major Depressive Disorder; PC = Parahippocampal cingulum; RC = Rostral cingulum; SLF = Superior longitudinal fasciculus; UF = Uncinate fasciculus.

* $p < 0.05$.



Appendix D. Fornix DTI parameters. Mean and SEM of the (a) FA and (b) MD of the fornix in MDD patients and HCs at baseline and follow-up (1 = Baseline, 2 = Follow-up).

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