

Reconciling Variable Findings of White Matter Integrity in Major Depressive Disorder

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Diffusion tensor imaging (DTI) has been used to evaluate white matter (WM) integrity in major depressive disorder (MDD), with several studies reporting differences between depressed patients and controls. However, these findings are variable and taken from relatively small studies often using suboptimal analytic approaches. The presented DTI study examined WM integrity in large samples of medication-free MDD patients ($n = 134$) and healthy controls ($n = 54$) using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) approaches, and rigorous statistical thresholds. Compared with health control subjects, MDD patients show no significant differences in fractional anisotropy, radial diffusivity, mean diffusivity, and axonal diffusivity with either the VBM or the TBSS approach. Our findings suggest that disrupted WM integrity does not have a major role in the neurobiology of MDD in this relatively large study using optimal imaging acquisition and analysis; however, this does not eliminate the possibility that certain patient subgroups show WM disruption associated with depression.

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INTRODUCTION

Major depressive disorder (MDD) is highly prevalent and a leading cause of worldwide disability (McKenna *et al*, 2005). Despite decades of research, the neurobiology of MDD remains poorly understood. MDD is increasingly viewed as a disorder of neural circuitry, in which a network of brain regions involved in mood regulation is dysfunctional (Drevets *et al*, 2008a; Mayberg, 2009). In an effort to better understand the pathophysiology of MDD and develop more effective treatments, much research has focused on delineating the structure and function of this mood regulation network. Although many studies have focused on the function of the network (Drevets *et al*, 2008b; Hafeman *et al*, 2012; Mayberg, 2003a, b; Murray *et al*, 2011; Phillips, 2006), including functional connectivity between

key brain regions (Craddock *et al*, 2009, 2012; Greicius, 2008, 2007; James *et al*, 2009; Seminowicz *et al*, 2004; Sheline *et al*, 2010), others have focused on the structural connectivity of the network, ie, the white matter (WM) pathways between brain regions (Abe *et al*, 2010; Blood *et al*, 2010; Cole *et al*, 2012; Cullen *et al*, 2010; Kieseppa *et al*, 2010; Korgaonkar *et al*, 2011; Ma *et al*, 2007; Tha *et al*, 2013; Wu *et al*, 2011; Zhu *et al*, 2011; Zou *et al*, 2008).

Diffusion tensor imaging (DTI) is a noninvasive, magnetic resonance imaging (MRI) technique used to assess the integrity and fiber orientation of WM. Diffusion measurements reflect the degree of diffusion directionality because diffusion perpendicular to main fiber direction is more hindered by myelin layers and cell membranes than diffusion along the main direction (Le Bihan *et al*, 2001; Pierpaoli and Basser, 1996). The most commonly used diffusion measurement is fractional anisotropy (FA). In addition to FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity are frequently used for diffusion measurements. MD reflects the total magnitude of diffusion and higher MD has been reported with increased tissue water in edema. RD appears to be modulated by myelin in WM, whereas axial diffusivity is more specific to axonal degeneration (Song *et al*, 2002).

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Regions of interest (ROIs) and voxel-based analyses have been commonly used to analyze differences in DTI data between groups or within subjects over time. ROI-based analyses have the advantage of being hypothesis directed and less statistically constrained by control for multiple comparisons. However, ROI analyses can be biased because of manual and non-standardized selection of ROIs, and the analyses limited to ROIs cannot identify any differences outside of the chosen ROIs. Voxel-based methods have the advantage of allowing whole-brain analyses and can be fully automated. This eliminates investigator bias (eg, from manual ROI selection).

Two common voxel-based approaches for DTI analyses include voxel-based morphometry (VBM) and track-based spatial statistics (TBSS). VBM of DTI data is a fully automated method that allows investigation of WM integrity in the whole brain, at each voxel (Ashburner and Friston, 2000; Good *et al*, 2001). TBSS is a newer analytic technique developed to reduce the alignment and smoothing problems that have been reported with VBM (Smith *et al*, 2006, 2007). Both approaches have been used to assess for differences in WM integrity in a variety of psychiatric disorders including MDD (Bae *et al*, 2006; Li *et al*, 2009; Xie *et al*, 2006).

Numerous DTI studies have looked for WM integrity differences in patients with MDD (Abe *et al*, 2010; Blood *et al*, 2010; Cole *et al*, 2012; Cullen *et al*, 2010; Kiesepa *et al*, 2010; Korgaonkar *et al*, 2011; Ma *et al*, 2007; Tha *et al*, 2013; Wu *et al*, 2011; Zhu *et al*, 2011; Zou *et al*, 2008). However, the findings have been highly variable with respect to the location and direction of the difference in FA (Table 1). Six studies report a reduction of FA (in various regions) in MDD patients compared with healthy controls (HCs), whereas another five studies show either an increase or no difference in FA between the groups. The source of this heterogeneity is unclear, but may reflect clinical heterogeneity of different patient cohorts, small samples (and publication bias), and/or the use of suboptimal acquisition/analytic methods. Regarding the last possibility, interpretation and analysis of DTI data may be complicated by a small number of diffusion-weighted directions (more directions yield higher integrity data), anisotropic voxel size, and susceptibility distortion.

In an effort to provide a more definitive analysis of potential WM abnormalities in depressed patients, DTI was performed as part of two large, similarly designed studies on depressed patients and in a group of HCs, all scanned using a common protocol (Dunlop *et al*, 2012a, b). Using optimized processing methods, VBM and TBSS were performed on these data to assess for differences in FA between the groups. A strict threshold for statistical significance was applied.

MATERIALS AND METHODS

Participants

Fifty-four HCs and one hundred and thirty-four MDD patients participated in accordance with Institutional Review Board policies at Emory University. All patients were participants in one of two clinical trials designed to identify treatment-specific imaging biomarkers of treatment outcomes. One trial selected for MDD patients who had

never received antidepressant treatment during their lifetime ($N=98$; Dunlop *et al*, 2012a). The other trial enrolled patients who had prior antidepressant treatment but were medication free for at least 2 weeks before the scanning ($N=36$; Dunlop *et al*, 2012b; McGrath *et al*, 2013). All participants, including HC, were evaluated for current or past psychiatric disorders using the Structured Clinical Interview for DSM-IV (First *et al*, 1995) and an interview with a study psychiatrist. HCs were required to have no current or past diagnosis of a mood or psychotic disorder, and no current psychiatric diagnosis other than specific phobia. Current or past medical or neurological disorders were evaluated via medical history, vital signs assessment, physical exam, electrocardiogram, and routine laboratory screening tests, including urine drug screens. Participants with uncontrolled medical conditions (including hypertension or diabetes) or medical or neurological conditions that could interfere with the conduct of the study or interpretation of the study results were excluded, as were those with contraindication to MRI or currently pregnant or breastfeeding women. Eligible depressed patients were adults between 18 and 65 years of age who met criteria for a primary diagnosis of MDD without psychotic features. Patients were excluded if they met lifetime criteria for a lifetime diagnosis of psychotic disorder or bipolar disorder, current obsessive compulsive disorder, substance dependence in the past year, or substance abuse in the past 3 months. Depressed patients were required to have a minimum Hamilton Depression Rating Scale (HDRS) 17-item score of ≥ 18 at the screening visit to be eligible for the study. Table 2 shows the demographic information and clinical characteristics of all participants.

Data Acquisition

Data were acquired on a 3T Tim Trio MRI scanner (Siemens Medical Solutions, Malvern, PA, USA) that permits maximum gradient amplitudes of 40 mT/m. A 12-channel head array coil was used. DTI and T_1 -weighted data were collected within a single session for each subject and foam cushions were used to minimize head motion. A single-shot spin-echo echo-planar imaging sequence was used with generalized auto-calibrating parallel acquisition with two-fold acceleration ($R=2$; Griswold *et al*, 2002). The parameters used for DTI were: FOV = 256×256 ; b value = 1000 s/mm^2 ; voxel resolution = $2 \times 2 \times 2 \text{ mm}$; number of slices = 64; matrix = 128×128 ; TR/TE = 11 300/104 ms; 60 non-collinear directions with four non-diffusion-weighted images ($b=0$) were acquired twice: once with phase encoding in the anterior to posterior (A-P) direction and once in the posterior to anterior (P-A) direction. To compensate susceptibility distortion, both phase up and down images were acquired. In addition to susceptibility distortion correction, we used slightly longer TR and TE than a typical diffusion protocol because of mechanical vibration of the patient table that caused by the low-frequency gradient switching associated with the diffusion weighting. High-resolution T_1 images were collected using a 3D magnetization-prepared rapid gradient-echo sequence with following parameters: TR/TI/TE = 2600/1100/3 ms; voxel resolution = $1 \times 1 \times 1 \text{ mm}$; number of slices = 176; matrix = 224×256 .

Table 1 Summary of Diffusion Tensor Imaging Studies in Patients with Major Depressive Disorder using Corrected Whole-Brain Analysis

Study	Participants							Imaging parameters					Findings after rigorous threshold	
	Healthy control			MDD				DTI resolution (mm)	Number of diffusion direction	Number of average	Data processing	Analysis method	Reduction	Increase
	n	Age (mean (SD))	Gender (M/F)	n	Age (mean (SD))	Gender (M/F)	Magnet strength							
Tha et al (2013)	19	36.5 (12.5)	13/6	19	38.6 (14.5)	12/7	1.5T	1.875 * 1.875 * 5	12	2	No distortion correction Study-specific template SPM	VBM	Bilateral frontal WM Anterior limbs of internal capsule Let putamen Right thalamus Bilateral cerebellar hemispheres	
Cole et al (2012)	66	50.4 (7.9)	23/43	66	48.6 (8.2)	30/36	1.5T	2.5 * 2.5 * 2.5	60	1	No distortion correction JHU DTI template FSL	TBSS ROI regions	Splenium Genu and body of corpus callosum Bilateral superior longitudinal fassiculus anterior and posterior corona radiata Anterior and posterior limbs of internal capsule	
Zhu et al (2011)	25	20.33 (1.68)	10/15	25	20.55 (1.86)	10/15	1.5T	2 * 2 * 4	12	1	No distortion correction MNI template FSL	TBSS	Left anterior limb of internal capsule Right parahippocampa gyrus Left posterior cingulate cortex	
Wu et al (2011)	21	30.4 (8.2)	9/12	23	31.4 (8.8)	10/13	1.5T	0.94 * 0.94 * 4	12	5	No distortion correction MNI template DTIStudio and SPM	VBM	Right superior longitudinal fassiculus Right middle frontal Left inferior parietal	
Korgaonkar et al (2011)	39	29.6 (46.2)	18/21	29	40.5 (15.8)	12/17	3.0T	1.72 * 1.72 * 2.5	42	1	No distortion correction MNI template FSL	TBSS	No difference between MDD vs controls Reduction between meloncholic and controls in corpus callosum, dosalateral prefontal, thalamic projection fiber	

Table 1 (Continued)

Study	Participants							Imaging parameters					Findings after rigorous threshold		
	Healthy control			MDD				DTI resolution (mm)	Number of diffusion direction	Number of average	Data processing	Analysis method	Reduction	Increase	
	n	Age (mean (SD))	Gender (M/F)	n	Age (mean (SD))	Gender (M/F)	Magnet strength								
Abe <i>et al</i> (2010)	42	48 (13.2)	22/20	21	48.1 (13.5)	11/10	1.5T	1.875 * 1.875 * 5	6	4	Image-based distortion correction Study-specific template FSL	VBM	No difference		
Kieseppa <i>et al</i> (2010)	20	42 (11.6)	10/10	16	48.4 (10.3)	2/14	1.5T	1.75 * 1.75 * 5	12	1	No distortion correction MNI template FSL	TBSS	No difference		
Cullen <i>et al</i> (2010)	14	16.81 (1.5)	6/8	14	16.79 (1.29)	4/10	3.0T	2 * 2 * 2	30	1	Field map distortion correction Study-specific template FSL	TBSS	No difference		
Blood <i>et al</i> (2010)	22	35.3 (11.6)	10/12	22	36.3 (12.1)	10/12	3.0T	2 * 2 * 2	6	6	No distortion correction MNI template FSL and Freesurfer	ROI regions	Dorsolateral prefrontal cortex Left precentral gyrus	Ventral tegmental area Substantia nigra Right calcarine cortex	
Zou <i>et al</i> (2008)	45	31 (10.3)	15/30	45	33.2 (8.9)	15/30	3.0T	1.875 * 1.875 * 3	14	2	No distortion correction MNI template DTIStudio and SPM	VBM	Left anterior limb of internal capsule Left superior longitudinal fasciculus		
Ma <i>et al</i> (2007)	14	27.1 (6.7)	2/12	14	28.9 (8)	2/12	1.5T	1.875 * 1.875 * 4	12	5	No distortion correction MNI template SPM	VBM	Right middle frontal gyrus Left lateral occipitotemporal gyrus Subgyral WM of the right parietal lobe Right angular gyrus		

Table 2 Demographic and Clinical Characteristics of Participants

	Healthy control (n = 54)	MDD (All n = 134 matched n = 54)	Statistics		
			F or χ^2	df	p
<i>All participants</i>					
Age (years)	34.42 (10.06)	38.49 (11.09)	0.6	186	0.4
Gender (males/females)	28/26	64/70	0.25	1	0.6
HDRS score		19.28 (3.47)			
Duration of illness (years)		9.34 (10.38)			
<i>Age and gender matched</i>					
Age (years)	34.42 (10.06)	34.41 (8.9)	2.19	106	0.7
Gender (males/females)	28/26	28/26	0	1	1
HDRS score		18.74 (3.33)			
Duration of illness (years)		7.77 (8.41)			

Data Preprocessing

MRI data were preprocessed using FSL software (<http://www.fmrib.ox.ac.uk/fsl>; Analysis Group, FMRIB, Oxford, UK; Smith *et al*, 2004). Non-brain regions of T₁ and diffusion-weighted data (both A-P and P-A) were removed using the BET toolbox. To estimate and correct susceptibility-induced distortion of the diffusion-weighted images, a phase reversal distortion correction method (also called Topup correction tool in FSL) was applied on obtained A-P and P-A diffusion data (Andersson *et al*, 2003). This phase reversal distortion correction method assumes that different phase-encoding diffusion images are caused by an identical magnitude of susceptibility distortion in the phase-encoding direction, and can be resolved by estimating the underlying magnetic field map. By combining the images acquired in opposite phase-encoding directions, the distortion can then be corrected. To help confirm correction, deterministic and probabilistic tractography results of well-known brain WM bundles are inspected for evidence of distortion.

FA, RD, MD, and axonal diffusivity maps were generated from phase-reversal distortion-corrected diffusion-weighted data. To improve the signal-to-noise ratio of diffusion tensor fitting, four non-diffusion-weighted images (b_0) are averaged after three of them are aligned to one reference image by affine transformation. Diffusion-weighted image data were aligned to averaged non-diffusion-weighted image by rigid body affine transformation to remove motion and eddy current-induced artifact (Jenkinson *et al*, 2002). Diffusion tensor, eigenvector, and eigenvalue were then calculated by a tensor fitting model for quantification of directional diffusion and FA (Fdt function within FSL toolbox, Oxford, UK; Behrens *et al*, 2003).

Study-Specific FA Template

A study-specific FA template was created using all 188 subjects (MDD and control groups combined). First, each subject's FA image was transformed to a standard FA template (FMRIB58_FA, http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html) using rigid body affine transformation

(degree of freedom: 6, FLIRT, FSL) followed by Gaussian smoothing with 3 mm full-width half-maximum (FWHM) and then averaged across subjects to create the initial study-specific FA template. A second FA template was created by performing a similar process, but using linear co-registration (degree of freedom: 12) to the first FA template map, followed by blurring with a 3-mm FWHM Gaussian kernel. The final template was created by averaging across subjects. This process was iterated six times using nonlinear image registration (FNIRT, FSL). Results were visually inspected after each iteration for quality control (Supplementary Figure S1). For analyses, each subject's FA map was co-registered to the study-specific template map by performing a linear (FLIRT, dof 12) transformation followed by a nonlinear (FNIRT) transformation. Individual subject FA transformation information to study-specific FA template was saved and used for the other measurement (RD, MD, axonal diffusivity) normalization.

DTI Data Analysis

For statistical analysis, a permutation-based statistical inference test with threshold-free cluster enhancement (TFCE), using neighborhood voxel information to improve statistical sensitivity. For multiple comparisons, a family-wise error (FWE) correction (corrected $p < 0.05$, 10 000 permutations) was used with estimation of cluster size (TFCE-FWE correction and randomize functions within FSL; Bullmore *et al*, 1999).

VBM

The normalized FA, RD, MD, and axonal diffusivity map for each subject was smoothed using a 5-mm FWHM Gaussian isotropic kernel to remove possible error caused by anatomical mismatching of like-brain regions.

TBSS

TBSS was performed using the same FA maps as used for the VBM analyses. For TBSS, the aligned FA maps were

averaged to create a mean FA map. This mean FA map was then thinned to create a mean FA skeleton representing centers of tracts common to all subjects. FA values less than 0.2 were judged as noise and eliminated to reduce potential confounds introduced by inter-subject variability and partial volume effects (Smith *et al*, 2006; Smith *et al*, 2007). The aligned and threshold FA map of each subject was projected onto the mean FA skeleton for the voxel-wise statistical analysis. The same processing steps were applied to RD, MD, and axonal diffusivity.

Voxel-Wise FA Analysis with MDDs and HCs

Voxel-wise cross-participant statistics were performed on both VBM and TBSS (skeletonized) analysis using TFCE-FWE. Age was used as a covariate and statistical results were adjusted using general linear models. We performed three sets of FA (MD, RD, axonal diffusivity) comparisons: (1) between all 54 HCs and 134 MDD patients; (2) between 98 MDD patients who had never received antidepressant treatment and 36 MDD patients who had previously received antidepressant treatment; and (3) between an age- and gender-matched subset (54 subjects per group) to account for any potential effects because of minor mean age and gender differences among the HCs and MDD patient group (Table 2). In a *post-hoc* analysis, 20 subjects from each group were randomly selected and compared with both VBM and TBSS analysis; this was iterated 100 times using different subsamples—this *post-hoc* analysis was performed to assess for the ‘false positive’ rate in our sample using samples sizes similar to previous analyses.

RESULTS

Voxel-wise statistics adjusted for age revealed no significant differences in FA, MD, RD, and axonal diffusivity between MDD and HC group for either the VBM or the TBSS analysis. With a gradual decrease in statistical threshold, significant FA differences began appearing in genu of corpus callosum with a *p*-value of 0.15 (TFCE-FWE corrected). In addition to full-group comparisons, the voxel-wise statistical analysis of both the never- and previously treated subsets, and the age- and gender-matched control subset, also found no FA differences for either analysis. Finally, there was no correlation between WM integrity measures and depression severity nor illness duration across the depressed sample.

With the 100 interactive FA analyses using 20 subjects/group selected randomly for each comparison, statistically significant FA differences were identified for 10 of the TBSS comparisons and 8 of the VBM comparisons ($p < 0.05$ TFCE-FWE corrected). The brain regions seen in these ‘false positive’ results included a spatially diverse set of WM regions. Of note, the genu of the corpus callosum was seen in 8 of the 10 ‘false positive’ TBSS results and 7 of 8 ‘false’ positive VBM results (Supplementary Figure S2).

DISCUSSION

Despite previous reports of FA abnormalities in depression, this large DTI study found no significant differences in FA (RD, MD, axial diffusivity) between MDD patients and

controls using either VBM or TBSS. This included analyses of a subset of age- and gender-matched subjects. In an exploratory analysis, differences in FA between the groups were only seen when the threshold was decreased to a relatively low level—and, even then, the findings appeared ‘noisy’. Taken together, these results suggest that disrupted WM integrity does not have a major role in the neurobiology of MDD.

These findings are not entirely inconsistent with prior DTI studies in MDD. When reviewed *in toto* (Table 1), it is notable that previous studies differ significantly in which brain regions show FA abnormalities. In our *post-hoc* analysis, where a series of smaller, randomly selected subgroups of patients and controls were compared, about 10% of comparisons showed ‘positive’ FA differences despite no differences in the full sample. Similar to the studies in Table 1, the subsample analyses showing FA differences varied considerably in which regions were identified. Interestingly, a region consistently identified as showing FA differences between MDD patients and controls in our *post-hoc* analysis was the genu of the corpus callosum—a region identified in the previously published reports (Cole *et al*, 2012; Korgaonkar *et al*, 2011). Given with the well-known prefrontal distortion in DTI images, it is possible that this region is especially vulnerable to false positive findings in DTI analyses (Wu *et al*, 2008).

There are several strengths of this study that increase confidence in these findings. First, this is the largest published DTI study to date comparing MDD patients and controls; therefore, these findings likely represent a better estimate, compared with smaller studies, of reliable differences in WM integrity between MDD patients and controls. Second, a study-specific DTI template was created using the full sample ($n = 188$) with an iterative normalization method, so that errors due to co-registration were reduced. Third, a phase reversal distortion correction was applied to the diffusion-weighted images to reduce errors related to well-known frontal distortion in DTI images because of the sinuses (Huang *et al*, 2008; Wu *et al*, 2008). Very few of the past published studies have used such a correction that is now relatively standard. Fourth, we utilized the most up-to-date analytic methods to reduce possible errors because of diffusion imaging acquisition and statistical comparison. For instance, four non-diffusion (b_0) images were acquired during each scan session, then manually averaged to improve signal to noise ratio. Sixty non-collinear diffusion directions and isotropic voxels were used to improve angular resolution and data integrity (anisotropic voxels in diffusion acquisition can affect tensor modeling and artificially alter FA values (Oouchi *et al*, 2007)). Finally, well-established diffusion analysis methods were used to calculate FA value, and a rigorous statistical threshold was applied.

Other possibilities exist for why previous reports have identified FA differences in MDD patients *vs* controls while this study did not. Samples selection differences may be a significant contributing factor, although subjects in this study were carefully evaluated to insure they met diagnostic eligibility criteria using structured diagnostic instruments and rating scales; it is therefore unlikely that they differed significantly from other MDD subjects enrolled in earlier studies. It is possible that subgroups of MDD patients (treatment-resistant, late-onset, early trauma exposure, familial, etc.) may be more likely to have WM abnormalities, although this awaits verification; there were not

enough patients with these various subtypes of depression in this sample to assess this. Notable in our analysis is that those contrasts showing positive differences could not be attributed to a randomization bias of the study source of either the MDD patients or the control subjects. In general, prior studies used acquisition and analytic methods that were not optimal compared with current standards. This could introduce bias into the analyses increasing the likelihood of a type I error. Finally, we did not have full data on smoking status and history of hypertension for all subjects—therefore, we were not able to assess the effect of these variables on WM integrity between the groups. However, this would only affect our results in a notable way if controls had much higher rates of smoking and/or hypertension, which seems unlikely.

Although this study found no regional differences in FA between MDD patients and controls, this does not argue against the continued use of diffusion imaging to assess WM in the study of MDD. Despite these negative findings in MDD, diffusion imaging remains a powerful tool in the study of neuropsychiatric disorders, particularly in light of oligodendroglia abnormalities in postmortem studies (Harrison, 2002; Ongur and Heckers, 2004; Rajkowska, 2003). As the field progresses, improved acquisition and analytic techniques may allow for the identification of WM abnormalities between groups that are too subtle for current approaches to distinguish. Further, it may be that certain subgroups of depressed patients are more likely to show WM abnormalities, such as patients with extreme treatment resistance or late-onset depression. In addition, it may be that the pathophysiology of depression does not involve the integrity of WM *per se*, but rather abnormalities in the WM connections between brain regions involved in mood regulation. To this end, structural connectivity analyses, eg, those using various tractography approaches based on diffusion-weighted data, may be more likely to identify such abnormalities (Hagmann et al, 2008; Sporns et al, 2005).

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (<http://www.nature.com/npp>)