Loss of White Matter Integrity in Major Depressive Disorder: Evidence Using Tract-Based Spatial Statistical Analysis of Diffusion Tensor Imaging

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Abstract: White matter (WM) has been shown to be affected in elderly patients with major depressive disorders (MDD). There is only limited evidence of WM structural abnormalities in nongeriatric MDD patients. This study investigates WM microstructural integrity in nongeriatric MDD patients recruited as part of the International Study to Predict Optimized Treatment in Depression clinical trial and establishes the validity of diffusion tensor imaging measures for the investigation of depression. Baseline diffusion tensor imaging data from 29 nongeriatric MDD participants (11 with melancholia) and 39 healthy control participants were used in this analysis. We performed tract-based spatial statistics analyses to evaluate WM microstructural integrity (1) between all healthy controls and all MDD participants, (2) between melancholic and nonmelancholic MDD participants, and (3) between each subgroup (melancholic and nonmelancholic) and controls. Significant WM integrity deficits were seen only for the melancholic MDD participants compared with controls. Compared with controls, melancholic participants showed an average reduction of 7.8% in fractional anisotropy over WM regions associated with the limbic system, dorsolateral prefrontal cortex, thalamic projection fibers, corpus callosum, and other association fibers. These fractional anisotropy deficits were also associated with decreased axial and increased radial diffusivity in these WM regions, suggesting a pattern of decreased myelination or other degeneration change. Our findings of WM structural abnormalities associated with the limbic system, the frontal cortex, and the thalamus support the prevailing theory of limbic-dorsolateral prefrontal cortex-thalamic dysfunction in depression. Our results also suggest that these deficits are most prominent in the melancholic subtype of MDD. *Hum Brain Mapp* 32:2161–2171, 2011. © 2010 Wiley Periodicals, Inc.

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INTRODUCTION

Magnetic resonance imaging (MRI) provides a noninvasive means to measure structural differences between individuals, and it has greatly enhanced the understanding of the structure–function relationship in the human brain. Diffusion tensor imaging (DTI) is an MRI modality, which is sensitive to diffusion processes in solution and can be used to measure microscopic tissue orientation characteristics in vivo [Basser et al., 1994]. In the brain, because this diffusion is affected by the orientation and integrity of the underlying axonal microstructure, DTI can noninvasively study the white matter (WM) architecture and structural connectivity. DTI-based quantitative measures, such as fractional anisotropy (FA), the degree of anisotropy in diffusion; mean diffusivity (MD), the direction-independent average diffusion; axial diffusivity (AD), and radial diffusivity (RD), the diffusion along or perpendicular to the principle direction of diffusion, respectively, have been shown to be useful markers of changes and degradation of WM [Bennett et al., 2010; Yuan et al., 2009]. An increase in RD has been shown to be a sensitive indicator of demyelination or dysmyelination in animal models of axonal disease [Song et al., 2002]. Interpretation of changes in AD is somewhat more complex than for RD; however, it is known to be sensitive to a number of developmental and pathological processes, including changes in fiber coherence and axonal injury [Dubois et al., 2008; Song et al., 2003].

Major depressive disorder (MDD) is a common disorder with a chronic pattern of recurrence and a lifetime prevalence of 16.2% [Kessler et al., 2003]. It is the fourth most disabling medical condition worldwide based on disability-adjusted life years (years of life lost because of premature death and years lived with a disability of specified severity and duration) [Greenberg et al., 1993]. Several preliminary studies have found WM abnormalities in MDD patients. Using mainly region-of-interest (ROI) analysis approaches, patient populations with MDD have been shown to have reduced anisotropy in the frontal lobe [Bae et al., 2006; Li et al., 2007; Shimony et al., 2009; Taylor et al., 2004] and temporal lobe [Nobuhara et al., 2006; Steele et al., 2005; Yang et al., 2007]. Reduced frontal WM FA has also been associated with greater severity of depression [Nobuhara et al., 2006] and poor response to antidepressant medications (ADMs) [Alexopoulos et al., 2002, 2008]. Other DTI studies using voxel-based and tract-based analysis approaches have demonstrated decreased FA in other regions, including the corpus callosum, internal capsule, superior longitudinal fasciculus

(SLF), sagittal stratum, and occipital and parietal cortices [Kieseppa et al., 2010; Ma et al., 2007; Zou et al., 2008].

Almost all MRI studies of depression to date have examined cohorts of advanced age [Bae et al., 2006; Nobuhara et al., 2006; Shimony et al., 2009; Taylor et al., 2004; Yang et al., 2007]. The implicit assumption contained within many of these studies is that any anatomical abnormalities seen are secondary or compounded by age-related pathology. Of the small number of DTI studies in nongeriatric patients, the outcomes have either been of reduced significance or of limited consensus in terms of the WM regions affected. However, these studies provide the basis to hypothesize the presence of connectivity abnormalities occurring in MDD in a nongeriatric setting [Kieseppa et al., 2010; Li et al., 2007; Ma et al., 2007; Zou et al., 2008]. It is also not clear from the current evidence how the loss of WM connectivity varies with subtypes of depression. The known substantial heterogeneity of this illness may be a possible reason for lack of consolidation in outcomes from these studies [Rush, 2007; Stewart et al., 2007].

Based on the results of functional imaging studies, it has been postulated that frontal–limbic network dysregulation occurs with depression [Drevets, 2000; Drevets et al., 2008; Johnstone et al., 2007]. Using an integrative neuroscience approach, our group has also recently shown the influence of gene–environment interactions and limbic–prefrontal structural changes on the level of risk and symptoms of depression [Gatt et al., 2009]. These observations lead us to postulate that the same cortical network will also be affected at the underlying subcortical WM level.

This study was conducted as part of the International Study to Predict Optimized Treatment in Depression (iSPOT-D), an ongoing multicentre, international, randomized, prospective, open-label clinical trial (Williams et al., submitted for publication) designed to evaluate a number of potentially useful clinical, cognitive, genetic, and MRI measures that might inform treatment strategy in outpatients with nonpsychotic MDD. This study was aimed to use the baseline data from the imaging subset of the first 15% of the iSPOT-D cohort to establish the validity of DTI for the investigation of depression. We also used tract-based spatial statistics (TBSS) analysis of the DTI data from this subset of nongeriatric MDD patients to test the working hypothesis that patients in an acute phase of MDD will differ from matched healthy controls with regard to corticolimbic WM connectivity, and that these differences may be more profound in the melancholic subtype of MDD because of the more severe phenotypic expression of this subtype.

MATERIALS AND METHODS

Participants

Participants were drawn from the first 15% of patients who provided MRI data at Westmead Hospital (University of Sydney Medical School) as part of the baseline data collection for the iSPOT-D study (i.e., 30 of the total 200 MDD patients, aged 18–65, estimated to be tested at this site) (Williams et al., submitted for publication). Of this first 15%, DTI data were not collected at one patient's baseline visit because of time constraints. Hence, a total of 29 MDD patients provided DTI data for this analysis. At the time of analysis, a total of 39 healthy control participants had been scanned as part of the study, and DTI data from these control participants were included for comparison.

A complete description of the iSPOT-D study protocol, clinical assessments, inclusion/exclusion criteria, and diagnosis procedures is provided in Williams et al. (submitted for publication). In short, the Mini-International Neuropsychiatric Interview [Sheehan et al., 1997, 1998], according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria, and a 17-item Hamilton Rating Scale for Depression [Hamilton, 1960] score ≥ 16 confirmed primary diagnosis of MDD. All MDD patients were either ADM naïve or had undergone a wash out period if previously prescribed an ADM. MDD participants with a score >7 on the Clinical Outcome in Routine Evaluation scale were categorized as having melancholic depression, whereas those with a score ≤ 7 were categorized as having nonmelancholic depression [Parker and Hadzi-Pavlovic, 1996]. Healthy control participants were extensively screened for the absence of Axis I disorders using the Mini-International Neuropsychiatric Interview and for a 17-item Hamilton Rating Scale for Depression score < 7 , and could not meet the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria for single or recurrent nonpsychotic MDD. This study was conducted according to the principles of the Declaration of Helsinki 2008 (World Medical Association Declaration of Helsinki: <http://www.wma.net/en/30publications/10policies/b3/index.html>). After the study procedures were fully explained in accordance with the ethical guidelines of the institutional review board, participants provided written informed consent.

Image Acquisition

Magnetic resonance images were acquired using a 3.0 Tesla GE Signa HDx scanner (GE Healthcare, Milwaukee, WI). Acquisition was performed using an eight-channel head coil. Three-dimensional T1-weighted images were acquired in the sagittal plane using a three-dimensional SPGR sequence (TR, 8.3 ms; TE, 3.2 ms; flip angle, 11°; TI, 500 ms; NEX, 1; ASSET, 1.5; and frequency direction, S/I). A total of 180 contiguous 1-mm slices were acquired using a 256×256 matrix with an in-plane resolution of $1 \text{ mm} \times 1$

mm that results in isotropic voxels. Diffusion tensor images were acquired using a spin-echo DTI-Echo Planar Imaging sequence. Seventy contiguous 2.5-mm slices were acquired in an axial orientation with an in-plane resolution of $1.72 \text{ mm} \times 1.72 \text{ mm}$ and a 128×128 matrix (TR, 17,000 ms; TE, 95 ms; fat saturation, ON; NEX, 1; and frequency direction, R/L). A baseline image ($b = 0$) and 42 different diffusion orientations were acquired with a b -value of 1,250.

Volumetric Analysis of MRI Data

The T1-weighted MRI data were processed using a previously described optimized protocol that uses Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London; <http://www.fil.ion.ucl.ac.uk/spm/>), running under MATLAB 6.5 software (MathWorks, Natick, MA) [Ashburner and Friston, 2000; Grieve et al., 2005]. WM regional volume measurements were made using custom templates as previously described in Grieve et al. [2007].

Tract-Based Spatial Statistical Analysis of DTI Data

DTI data were preprocessed and analyzed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Diffusion Toolbox [Behrens et al., 2003] and TBSS [Smith et al., 2006] software tools as part of the FMRIB Software Library (FSL) release 4.1.3 (<http://www.fmrib.ox.ac.uk/fsl>) [Smith et al., 2004]. The raw DTI data for each participant were first corrected for head movement and eddy current distortions. A binary brain mask was generated using the baseline nondiffusion weighted ($b = 0$) image. Diffusion tensor models were then fitted independently for each voxel within the brain mask and images of FA, MD, first (λ_1), second (λ_2), and third (λ_3) eigen values were generated for each participant.

FA images from each participant were then aligned to the FMRIB58_FA template and transformed into Montreal Neurological Institute 152 mm^3 standard space using the non-linear registration tool FNIRT [Andersson et al., 2007a,b]. Next, an average FA image was generated and thinned to create a WM skeleton representing the centers of all WM tracts common to all participants. This FA skeleton was then thresholded to $\text{FA} \geq 0.3$ to include the major WM pathways but avoid peripheral tracts that are more vulnerable to interparticipant variability and/or partial volume effects with grey matter. Each participant's aligned FA image was then projected onto the mean FA skeleton by assigning each skeleton voxel by the maximum FA value found in a direction perpendicular to the tract. This accounts for any residual registration misalignments and variability in exact tract location between participants.

Voxel-wise cross-participant statistics were then performed on this skeletonized participant data using the Randomise (v2.1) permutation testing software in FSL. We performed three sets of FA comparisons: (1) between all

TABLE I. Selected demographic features and structural volumetric data

	Controls (<i>n</i> = 39)	All MDD participants (<i>n</i> = 29)	Melancholic (<i>n</i> = 11)	Nonmelancholic (<i>n</i> = 18)
Demographics				
Age (years)	29.6 ± 12.7	40.5 ± 15.8 ^a	43.1 ± 15.3 ^a	38.9 ± 16.3 ^a
Male gender (%)	46.2	41.3	36.4	44.4
Education (years)	14.7 ± 3.4	14.5 ± 3.2	14.7 ± 3.8	14.7 ± 3.4
Alcohol consumers (%)	53.8	39.3	36.4	41.2
Left handers (%)	7.7	13.8	18.2	11.1
DASS Depression	0.82 ± 1.06	9.76 ± 4.18 ^a	9.10 ± 4.38 ^a	10.2 ± 4.14 ^a
DASS Anxiety	0.79 ± 1.09	5.04 ± 3.16 ^a	5.00 ± 3.37 ^a	5.07 ± 3.13 ^a
DASS Stress	2.08 ± 1.63	8.84 ± 4.46 ^a	8.50 ± 5.76 ^a	9.07 ± 3.56 ^a
HRSD ₁₇	1.3 ± 1.5	19.1 ± 3.0 ^a	20.1 ± 3.2 ^a	18.4 ± 2.7 ^a
CORE	0.3 ± 0.8	9.1 ± 4.3 ^a	12.0 ± 3.0 ^a	7.3 ± 4.1 ^{a, b}
Volumetric MRI				
Global GM (mL)	776.9 ± 82.8	726.1 ± 83.8 ^a	717.6 ± 71.4 ^a	731.1 ± 92.0
Global WM (mL)	470.0 ± 42.2	475.5 ± 54.4	480.2 ± 50.0	472.8 ± 58.1
Global CSF (mL)	348.1 ± 187.8	413.9 ± 164.8	422.2 ± 207.6	409.1 ± 140.8
Frontal lobe WM (mL)	151.4 ± 14.3	154.1 ± 20.4	156.5 ± 18.9	152.6 ± 21.8
Parietal lobe WM (mL)	89.0 ± 8.4	89.9 ± 11.2	90.1 ± 10.8	89.8 ± 11.8
Occipital lobe WM (mL)	52.8 ± 5.8	52.7 ± 6.2	53.4 ± 7.0	52.3 ± 5.8
Temporal lobe WM (mL)	64.3 ± 5.5	64.8 ± 7.7	66.0 ± 7.7	64.1 ± 7.8

^aSignificant difference with control group at $P < 0.05$.

^bSignificant difference with melancholic group at $P < 0.05$. CSF, cerebrospinal fluid; CORE, Clinical Outcome in Routine Evaluation; DASS, Depression Anxiety Stress Scales; GM, gray matter; HRSD₁₇, 17-Item Hamilton Rating Scale for Depression; MDD, major depressive disorder; WM, white matter.

healthy controls and all participants with MDD, (2) between melancholic and nonmelancholic participants, and (3) between each subgroup (melancholic and nonmelancholic) and controls. Age was found to be significantly different between the groups, and, accordingly, age was included as a covariate of no interest in all analyses, as was gender. Permutation testing was performed using 5,000 permutations with the threshold-free cluster enhancement option. This option enables the finding of clusters without setting an initial cluster threshold [Smith and Nichols, 2009]. Statistical maps corrected for multiple comparisons at the cluster level ($P < 0.05$) were used for assessment. The Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 WM labels atlas [Mori et al., 2008] was used to label clusters with significant FA differences. For clusters not labeled using this atlas, assignments were made using custom templates created with reference to both the high-resolution image and segmented images of the Montreal Neurological Institute single-participant brain, which have previously been described [Grieve et al., 2007]. A binary mask of the cluster in each label was also generated to extract the mean FA in each identified label for each participant.

Following analysis of FA, the diffusional characteristics of the significant clusters were characterized using the diffusion parameters MD, AD, and RD. For comparisons with no-FA significant differences, the other diffusion parameters were not evaluated (see later). The non-FA images (MD, λ_1 , λ_2 , and λ_3) were first projected onto the

skeleton using the same nonlinear warping parameters, and skeleton projection vectors calculated for the FA images. The generated cluster binary mask in each label was then used to calculate the respective average diffusion parameter value for each participant. λ_1 values were used to represent AD, and the average of the λ_2 and λ_3 values were used to represent RD. Significant differences in MD, AD, and RD between the melancholic and control group were evaluated using analysis of variance in SPSS.

RESULTS

Volumetric Analysis of MRI Data

The demographic features and structural volumetric data for the control, all MDD, melancholic, and nonmelancholic groups are presented in Table I. Global grey matter volume was found to be significantly lower for the MDD group (-6.5% ; $P = 0.02$) and the melancholic subgroup (-7.6% ; $P = 0.04$) compared with the control group. There were no significant differences between the control group and any MDD subgroup regarding the other gross brain volumetric measurements or regional WM volumes.

TBSS Analysis of DTI Data

Significant WM FA differences were observed between the melancholic subgroup and the control group. No significant WM FA differences were found between the

Figure 1.

Three-dimensional rendered view of the WM tract skeleton (Montreal Neurological Institute space) with areas of significantly lower fractional anisotropy ($P < 0.05$, family-wise error corrected) for the melancholic participant subgroup compared with healthy controls shown in red (upper row). Bottom two rows

show selected axial slices of the three-dimensional rendering overlaid on the Montreal Neurological Institute standard brain: WM tract skeleton = green; significant WM clusters = red. Images are in radiological convention.

control vs. all MDD, control vs. nonmelancholic, or melancholic vs. nonmelancholic groups. Because no significant FA clusters were found, these comparisons were not further evaluated using the other diffusion measures.

FA was found to be significantly lower for melancholic patients compared with controls in 13 WM regions identified using the JHU atlas. Figure 1 shows selected slices

displaying the WM skeleton with the significant clusters superimposed in color. The identified WM regions and average FA values for these clusters (corrected for age and gender) are summarized in Table II. The average decreased FA seen over the 13 regions was 7.8%, with a maximum difference of 13.5% seen in the right fornix/stria terminalis and a minimum difference of 3.5% seen in the

TABLE II. Diffusional characteristics of significant white matter clusters

White matter cluster	FA			MD (10^{-4} mm ²)			AD (10^{-4} mm ²)			RD (10^{-4} mm ²)		
	Controls	Melancholic	Difference	Controls	Melancholic	Difference	Controls	Melancholic	Difference	Controls	Melancholic	Difference
Limbic												
L fornix/stria terminalis	0.57 ± 0.01	0.52 ± 0.01	-8.8%	8.30 ± 0.07	8.27 ± 0.13	-0.4%	14.30 ± 0.12	13.50 ± 0.24	-5.5%	5.31 ± 0.07	5.66 ± 0.15	6.7%
R fornix/stria terminalis	0.52 ± 0.01	0.45 ± 0.03	-13.5%	8.12 ± 0.13	8.07 ± 0.26	-0.6%	13.34 ± 0.25	12.44 ± 0.49	-6.7%	5.52 ± 0.14	5.88 ± 0.27	6.5%
Association fibers of DLPFC												
L superior longitudinal fasciculus	0.60 ± 0.01	0.55 ± 0.01	-8.3%	7.58 ± 0.06	7.74 ± 0.12	2.1%	13.53 ± 0.10	13.19 ± 0.20	-2.5%	4.60 ± 0.06	5.02 ± 0.13	9.1%
Projection fibers												
L retrolenticular part of internal capsule	0.57 ± 0.01	0.55 ± 0.01	-3.5%	8.21 ± 0.07	8.42 ± 0.14	2.6%	14.22 ± 0.11	14.19 ± 0.22	-0.2%	5.20 ± 0.07	5.53 ± 0.14	6.3%
R retrolenticular part of internal capsule	0.60 ± 0.01	0.57 ± 0.01	-5.0%	8.11 ± 0.05	8.28 ± 0.11	2.1%	14.51 ± 0.10	14.33 ± 0.20	-1.2%	4.91 ± 0.07	5.25 ± 0.15	7.0%
Other association fibers												
L posterior corona radiata	0.55 ± 0.01	0.51 ± 0.02	-7.3%	8.19 ± 0.06	8.47 ± 0.12	3.4%	13.98 ± 0.11	13.87 ± 0.21	-0.8%	5.29 ± 0.09	5.77 ± 0.18	9.0%
L posterior thalamic radiation	0.67 ± 0.01	0.64 ± 0.01	-4.5%	8.15 ± 0.05	8.23 ± 0.11	1.0%	15.71 ± 0.08	15.37 ± 0.17	-2.1%	4.37 ± 0.07	4.66 ± 0.14	6.6%
R posterior thalamic radiation	0.65 ± 0.01	0.62 ± 0.02	-4.6%	8.18 ± 0.10	8.27 ± 0.20	1.1%	15.39 ± 0.16	15.01 ± 0.32	-2.5%	4.57 ± 0.11	4.90 ± 0.21	7.2%
Other association fibers												
L sagittal stratum	0.59 ± 0.01	0.54 ± 0.01	-8.5%	8.11 ± 0.06	8.52 ± 0.13	5.1%	14.30 ± 0.09	14.26 ± 0.18	-0.3%	5.01 ± 0.08	5.66 ± 0.16	12.8%
R sagittal stratum	0.60 ± 0.01	0.55 ± 0.01	-8.3%	8.06 ± 0.05	8.24 ± 0.10	2.2%	14.32 ± 0.10	13.84 ± 0.19	-3.3%	4.93 ± 0.07	5.44 ± 0.13	10.5%
L external capsule	0.52 ± 0.01	0.48 ± 0.01	-7.7%	7.96 ± 0.07	8.17 ± 0.13	2.6%	13.09 ± 0.09	12.78 ± 0.17	-2.4%	5.40 ± 0.07	5.87 ± 0.14	8.7%
R external capsule	0.54 ± 0.01	0.48 ± 0.02	-11.1%	8.14 ± 0.06	8.31 ± 0.11	2.1%	13.65 ± 0.12	13.07 ± 0.24	-4.2%	5.39 ± 0.08	5.94 ± 0.16	10.2%
Corpus callosum												
Splenium	0.76 ± 0.00	0.73 ± 0.01	-3.9%	7.31 ± 0.05	7.48 ± 0.10	2.3%	15.60 ± 0.11	15.37 ± 0.22	-1.5%	3.16 ± 0.06	3.53 ± 0.11	11.7%
Other clusters												
L frontal WM	0.52 ± 0.01	0.49 ± 0.01	-5.8%	7.99 ± 0.05	8.01 ± 0.10	0.3%	13.09 ± 0.08	12.67 ± 0.16	-3.3%	5.44 ± 0.06	5.69 ± 0.12	4.6%
R frontal WM	0.54 ± 0.01	0.49 ± 0.02	-9.3%	7.87 ± 0.07	8.05 ± 0.14	2.3%	13.03 ± 0.14	12.53 ± 0.28	-3.8%	5.29 ± 0.09	5.81 ± 0.17	10.0%
L temporal WM	0.56 ± 0.00	0.51 ± 0.01	-8.9%	7.86 ± 0.05	8.10 ± 0.09	3.1%	13.40 ± 0.07	13.14 ± 0.14	-1.9%	5.10 ± 0.05	5.58 ± 0.10	9.5%
R temporal WM	0.54 ± 0.01	0.49 ± 0.01	-9.3%	7.85 ± 0.05	8.04 ± 0.09	2.4%	13.20 ± 0.08	12.83 ± 0.15	-2.8%	5.18 ± 0.06	5.65 ± 0.12	9.1%
L parietal WM	0.49 ± 0.00	0.45 ± 0.01	-8.2%	7.34 ± 0.05	7.52 ± 0.10	2.5%	11.63 ± 0.07	11.46 ± 0.14	-1.5%	5.20 ± 0.05	5.55 ± 0.10	6.8%
R parietal WM	0.51 ± 0.01	0.45 ± 0.02	-11.8%	7.71 ± 0.08	7.92 ± 0.16	2.7%	12.15 ± 0.14	11.73 ± 0.29	-3.5%	5.49 ± 0.10	6.02 ± 0.20	9.6%
L occipital WM	0.58 ± 0.00	0.53 ± 0.01	-8.6%	7.51 ± 0.05	7.79 ± 0.10	3.7%	13.13 ± 0.06	12.99 ± 0.13	-1.1%	4.70 ± 0.06	5.19 ± 0.11	10.3%

Significant differences ($P < 0.05$) between the healthy controls and melancholic MDD participants are denoted in bold.

AD, axial diffusivity; DLPFC, dorsolateral prefrontal cortex; FA, fractional anisotropy; L, Left; MD, mean diffusivity; R, Right; RD, radial diffusivity; WM, white matter.

retrolenticular part of the left internal capsule. No WM regions with significantly higher FA for melancholic participants than for controls were identified. Numerous significant differences ($P < 0.05$) between the melancholic and control groups were found for the other diffusion measures (Table II). Of the 13 clusters examined, three showed significant AD differences, whereas nine regions showed significant differences in RD. For these significant regions, there was a general pattern of lower AD and higher RD in melancholic participants compared with controls. Regarding MD, only one region showed a small difference between groups (left sagittal stratum, melancholic > controls).

Regarding the significant differences seen in the melancholic group compared with controls, the crus of the fornix and stria terminalis, both associated with the limbic region, showed decreased FA bilaterally (13.5% on the right and 8.8% on the left). The left fornix/stria terminalis showed significantly increased RD (6.7%) and decreased AD (5.5%). No difference in RD or AD was seen on the right in this structure.

Significant diffusional differences were seen in the association fibers related to the external capsule and the sagittal stratum. An FA decrease of approximately 8%, together with RD increases of 12.8%, and 10.5%, was observed for melancholic participants in the left and right sagittal stratum ROIs, respectively. A similar bilateral FA/RD change was also seen in the external capsule (7.7% FA decrease and 8.7% RD increase on the left; 11.1% FA decrease and 10.2% RD increase on the right). An AD decrease of 3.3% and 4.2% was observed in the right-side sagittal stratum and external capsule, respectively, with no significant difference observed in the left side.

Significant decreases in FA for melancholic participants were also observed in other clusters of the projection fiber bundles. These decreases were mainly in the left posterior corona radiata (7.3%) and bilateral regions of the posterior thalamic radiations (4.5% on the left and 4.6% on the right) and retrolenticular part of the internal capsule (3.5% on the left and 5.0% on the right). Significant increases in RD were also seen in the posterior corona radiata (9.0%) and right retrolenticular part of the internal capsule (7.0%) clusters.

Other regions of significant FA/RD changes in melancholic participants were the splenium region of the corpus callosum (3.9% FA decrease and 11.7% RD increase) and the left SLF (8.3% FA decrease and 9.1% RD increase).

A number of WM regions that are not represented in the JHU atlas were detected in our study. These clusters were mainly extensions of the association and projection fiber bundles described above and have been grouped by main brain lobes for interpretation. These regions also showed a similar pattern of FA/AD decrease and MD/RD increase for melancholic participants as was seen for the other WM clusters.

DISCUSSION

In this study, we present evidence of WM structural involvement in a nongeriatric MDD patient group. Using

DTI data analysis of all major connectivity tracts, we found that these structural differences were found significant for only the melancholic subtype of MDD participants. The nonmelancholic MDD participant group did not show any evidence of significant WM structural differences compared with either the melancholic or control groups. A large number of WM clusters showed significantly reduced FA in melancholic participants compared with controls. When we examined the diffusional characteristics of these significant clusters, the predominant pattern was of normal or slightly decreased AD and increased RD. This pattern may represent decreased myelination; however, it could also result from a decrease in the number of normally myelinated fibers or an altered WM microstructure in the affected WM tracts (e.g., axonal degeneration [Bennett et al., 2010]).

Classification of Significant Clusters

The significant clusters in our study can be classified into five main groups: (1) limbic, (2) association fibers relating to the dorsolateral prefrontal cortex (DLPFC), (3) projection fibers, (4) other association fibers, and (5) corpus callosum. These WM clusters relate to regions with WM, structural, or functional abnormalities previously reported in MDD patients. For example, the Fornix and Stria terminalis are both associated with the amygdala and hippocampus limbic regions [Mori et al., 2008]. Both morphometry and WM abnormalities with depression have been previously reported for both these limbic regions [Frodl et al., 2008; Kronmüller et al., 2009; MacQueen et al., 2003; Yang et al., 2007].

Similarly, the SLF is a primary association tract connecting the frontal cortex with the temporal, occipital, and parietal lobes, with a particular bias toward fibers originating or terminating in the DLPFC. Frontal lobe dysfunction and its association with depression symptomatology has been well established [Koenigs and Grafman, 2009]. There is evidence of severity of depression symptoms to be linked with frontal WM changes in late-life depression [Nobuhara et al., 2006]. It has been previously shown that ischemic changes in the DLPFC predispose elderly patients to depression [Hickie et al., 1997]. FA alterations in the SLF have also been previously reported for both elderly and young depressed individuals [Bae et al., 2006; Zou et al., 2008]. Our study provides strong data to confirm this finding, with both FA and RD differences seen in melancholic participants.

Our study also confirms previous findings of decreased FA in the projection fibers of the internal capsule [Zou et al., 2008] and association fibers within the sagittal stratum [Kieseppa et al., 2010] in MDD patients. Additional identified clusters were mainly present bilaterally in the posterior thalamic radiations and the left posterior corona radiata region. Both these regions carry the thalamocortical projection fibers, which may support the role of thalamic-

cortical connection theories in the etiology of MDD [Lafer et al., 1997].

Limbic-DLPFC-Thalamic Dysfunction in Depression

A number of functional imaging studies have identified the interplay between the limbic and the dorsolateral frontal cortex as a key concept in understanding the mechanism behind MDD [Dannlowski et al., 2009; Hooley et al., 2009; Kito et al., 2008]. Functional studies also implicate both of these regions, with positive treatment response using cognitive behavioral therapy associated with increased metabolic rates in the hippocampus and dorsal cingulate and decreases in the DLPFC [Goldapple et al., 2004]. Similarly, other functional data after pharmacological intervention show modulation of both regions, albeit in the opposite direction of the treatment affect [Kennedy et al., 2001]. These functional findings and the structural evidence support the idea that impaired function both within and between the limbic structures and the associated frontal cortical regions can explain most of the symptomatology and performance changes associated with depression [Drevets et al., 2008].

The other brain regions considered to be an integral part of this depression-related limbic-cortical network are the basal ganglia and the thalamus [Drevets et al., 2008; Lafer et al., 1997]. Functional and structural imaging studies have indicated that abnormalities in the basal ganglia structures are related to depression [Pizzagalli et al., 2009]. Both the basal ganglia and the thalamus are connected topographically to different functional regions of the frontal cortex, with the thalamus playing the important mediator role between these connections [Haber and Calzavara, 2009]. In addition, specific connections exist between different regions of the thalamus and the limbic structures [Taber et al., 2004], suggesting that the thalamus may also have an important role to play in the frontal-limbic dysregulation that is seen in depression. Our data confirm the central involvement of the limbic system with depression, which, combined with our demonstration of decreased WM tract integrity involving the frontal cortex and the thalamus, provides strong support for the prevailing theory of limbic-DLPFC-thalamic dysfunction in melancholic depression.

Only limited data were available on DTI MRI of non-geriatric patients with depression. Ma et al. [2007] showed FA reductions in the WM of the right middle frontal, left lateral occipitotemporal gyrus, and right parietal lobe in a subgroup ($n = 14$) of patients with MDD. Similar FA reductions in the prefrontal WM of 19 MDD patients were reported by Li et al. [2007]. Zou et al. [2008] also reported findings of decreased FA in the left anterior limb of the internal capsule and the parietal portion of the SLF in a larger group of 45 MDD patients. Although the outcomes from these studies have assumed a homogeneous MDD

population group for the sake of analysis, this study was unable to replicate any of these previous findings in an analysis of the nonstratified MDD patient population.

In contrast, the strongest effects seen in our study were observed in our comparisons of the melancholic subgroup, a finding that suggests that the WM deficits may be specific to the melancholic subcategory of MDD patients. Melancholia is considered to be the most severe and chronic form of depression, with a low remission rate and known biological effects [McGrath et al., 2008; Rush, 2007]. We suggest that the nonmelancholic subtype of depression may not share the same structural basis as the melancholic subtype. Including these patients in our analysis (18 non-melancholics of a total of 29 MDD participants) may have diluted the effect observed by previous studies, which do not document the patient melancholic type characteristics and, hence, may have systematically included more melancholic patients. A possible alternative reason for this study not demonstrating WM effects in the main MDD group is that all the patients recruited into the previous studies were treatment-naïve, whereas a subgroup of participants in our study had been on an ADM before entering a wash-out period before participating in our study. The only other study that did not show any significant FA differences in nongeriatric MDD patients had a subset of patients on prior or existing ADM [Kieseppa et al., 2010]. Nevertheless, our findings confirm the biological effect related to this subtype and suggest that the WM abnormalities seen in MDD patients are more pronounced in melancholia.

Strengths and Limitations

TBSS represents a marked improvement over ROI-based approaches because it permits the detection of brain regions that are involved in disease processes without any need for preconceived “leading” hypotheses regarding the boundaries and locations of regions likely to be involved. This is of considerable importance in a disease process that involves alterations to brain functional dynamics, such as in depression. The current analysis is, however, limited by the inability to ascertain the precise architecture of the involved tracts after their identification. An example of this is the bilateral SLF clusters seen in this study. The axonal fibers in the SLF comprise four groups (SLF I, SLF II, SLF III, and arcuate fascicle) [Makris et al., 2005]. SLF I fibers terminate in the DLPFC and may be implicated in the psychometric defects seen in depression. A second limitation of this study is that detection of static structural abnormalities can only be of limited value in elucidating dysfunction in a dynamic organ such as the brain. Performance data are required to place these data in context. In subsequent studies on the iSPOT-D cohort, we plan to use tensor tractography, functional MRI, and psychometric data to provide a more integrated and functional context for the structural changes demonstrated in this study. The wide age difference between the healthy participant and

melancholic MDD subgroup adds caution to the interpretation of findings of our study. Although we have attempted to statistically correct for this difference in our analysis, these outcomes are required to be validated with closer age-matched cohorts. The target control and MDD patient cohort to be collected as part of the iSPOT-D study will provide us an opportunity to revalidate these outcomes using a larger and closely age-gender-matched samples.

Although our findings seem to correspond to existing models of depression, it is not possible to postulate a causal structural involvement from this cross-sectional study because all of the melancholic participants involved presented with an established diagnosis of melancholic depression. A further exploration of any postulated structural basis for melancholic depression would require a longitudinal study that involves data gathered on participants before onset.

CONCLUSIONS

This study investigated WM structural differences between healthy controls and patients with MDD. Using TBSS on DTI data, we were able to show that these WM structural differences were most prominent in the melancholic subgroup of MDD participants. Compared with controls, melancholic participants showed an average reduction of 7.8% in FA over WM regions associated with the limbic system, DLFC, thalamic projection fibers, corpus callosum and other association fiber bundles. This reduction in FA was also found to be associated with mainly unchanged MD, a 3.3–5.5% decrease in AD, and a 6.7–12.8% increase in RD in these areas, which suggests a pattern of decreased myelination with depression. Specific WM abnormalities associated with the limbic system, the frontal cortex, and the thalamus observed in our study are consistent with the prevailing theory of limbic-DLPFC-thalamic dysfunction in depression. As part of the iSPOT-D clinical trial, our future goals will be to validate these initial preliminary findings using a larger patient population sample and to integrate DTI tractography, functional MRI, and psychometric data to better understand this limbic-DLPFC-thalamic coupling implication in depression.

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