

White matter abnormalities and illness severity in major depressive disorder

James Cole, Christopher A. Chaddock, Anne E. Farmer, Katherine J. Aitchison, Andrew Simmons, Peter McGuffin and Cynthia H. Y. Fu

Background

White matter abnormalities have been implicated in the aetiology of major depressive disorder; however, the relationship between the severity of symptoms and white matter integrity is currently unclear.

Aims

To investigate white matter integrity in people with major depression and healthy controls, and to assess its relationship with depressive symptom severity.

Method

Diffusion tensor imaging data were acquired from 66 patients with recurrent major depression and a control group of 66 healthy individuals matched for age, gender and IQ score, and analysed with tract-based spatial statistics. The relationship between white matter integrity and severity of depression as measured by the Beck Depression Inventory was examined.

Results

Depressive illness was associated with widespread regions of decreased white matter integrity, including regions in the corpus callosum, superior longitudinal fasciculus and anterior corona radiata, compared with the control group. Increasing symptom severity was negatively correlated with white matter integrity, predominantly in the corpus callosum.

Conclusions

Widespread alterations in white matter integrity are evident in major depressive disorder. These abnormalities are heightened with increasing severity of depressive symptoms.

Declaration of interest

None.

Increasing evidence implicates white matter as a key component of the structural brain changes in major depressive disorder, in which a 'disconnection' between regions is purported to be responsible for impairments in emotion processing.¹ White matter integrity is commonly measured using the magnetic resonance imaging (MRI) technique of diffusion tensor imaging. Studies using this technique have reported abnormalities associated with major depressive disorder in adolescent patients,² middle-aged patients,^{3,4} elderly patients,^{5–7} and in adolescents at high familial risk of major depressive disorder.⁸ The most widely used diffusion tensor imaging measure, fractional anisotropy, provides an index of the 'directionality' of diffusion within a voxel. The axonal structure of white matter tracts is generally highly linear, hence reductions in fractional anisotropy are thought to reflect pathological microstructural changes related to the integrity of the white matter.⁹ Reduced fractional anisotropy in major depressive disorder has been reported in a number of frontal,^{7,10} temporal and midbrain regions,¹¹ along with fibre tracts such as the corpus callosum,¹² internal capsule,^{13,14} and superior longitudinal fasciculus.¹⁵ The findings from individual reports indicate a widespread pattern of alterations, but there has been limited reproducibility between studies, perhaps due to methodological differences.

Moreover, the extent of white matter abnormalities may be associated with clinical features. Increased severity of illness and poorer treatment outcomes have been associated with increased white matter hyperintensities,¹⁶ indicating that patients with greater illness burden are more likely to have microstructural white matter alterations and possibly ischaemic damage. Yet, as a state marker of a depressive episode in major depressive disorder, diffusion tensor imaging studies of fractional anisotropy measures have shown mixed results, with reports of no relationship between depression rating scores and fractional anisotropy,^{3,10–12,17–20} significant differences between patients in remission and in an acute episode,^{5,12,21} as well as negative

correlations between fractional anisotropy and current illness severity.^{13,14,22–24} In this study we investigated white matter tracts using tract-based spatial statistics in a large and well-characterised group of adult patients with recurrent major depression and a matched healthy control group.²⁵ We examined the relationship between depressive symptoms and diffusion-weighted measures of white matter, expecting that reductions in white matter integrity would be found in patients with major depressive disorder and would be greater in those with more severe symptoms.

Method

The study participants included 66 persons with recurrent major depressive disorder and a control group of 66 healthy individuals matched for age, gender, IQ score and years of full-time education. All patients had experienced two or more depressive episodes of at least moderate severity and met DSM-IV diagnostic criteria for recurrent major depressive disorder,²⁶ assessed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).²⁷ Control group participants were interviewed to ensure they had never experienced depressive symptoms. All participants were screened for contraindications to MRI; other exclusion criteria were a diagnosis of neurological disorder, head injury leading to loss of consciousness or conditions known to affect brain structure or function (including alcohol or substance misuse), ascertained during clinical interview. Potential participants were also excluded if they or a first-degree relative had ever fulfilled criteria for mania, hypomania, schizophrenia or mood-incongruent psychosis. Current depressive symptoms were measured using the Beck Depression Inventory (BDI).²⁸ The participants' IQ scores were assessed using the Wechsler Abbreviated Scale of Intelligence.²⁹ Information regarding current use of antidepressant medication was also obtained from the participants with depressive disorder.

All participants had previously participated in genetic association studies,^{30,31} and were of White European ancestry. The study received local ethics committee approval and all participants gave written informed consent.

Image acquisition and pre-processing

Diffusion-weighted acquisition data were collected using a 1.5 T Signa HDx system (General Electric, Milwaukee, Wisconsin, USA).³² Sixty contiguous near-axial slice locations with a 24 cm² field of view and isotropic (2.5 mm³) voxels were imaged with the following parameters: echo time 101.3 ms, effective repetition time varied between participants (12–20 R–R intervals), diffusion gradient duration 17.3 ms, diffusion weighting 1300 mm². At each location, 60 diffusion-weighted directions were acquired plus 7 B0 images per individual.

Diffusion-weighted data were corrected for eddy current distortions and head movements, then masked to remove non-brain voxels using Brain Extraction Tool.³³ A single tensor model was fitted to the data to generate measures of fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity and mode of anisotropy (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl/).³⁴ Fractional anisotropy was the main dependent variable, whereas mean, radial and axial diffusivity offered complementary information about the pattern of diffusion to aid in the interpretation of fractional anisotropic changes. Mode of anisotropy is a relative measure of the 'linearity' of the diffusion,³⁵ and is mathematically orthogonal to fractional anisotropy.³⁶ Lower mode of anisotropy indicates more planar diffusion, likely to be found in areas of crossing fibres, whereas higher mode is thought to reflect more linear diffusion, indicative of regions where a single fibre orientation predominates.

Tract-based spatial statistics

Between-group diffusion tensor imaging comparisons were conducted using TBSS version 1.2.²⁵ Fractional anisotropic images from all participants were aligned to the Johns Hopkins University – International Consortium of Brain Mapping DTI-81 white matter atlas (JHU DTI atlas),³⁷ using FMRIB's non-linear image registration tool (FNIRT) in FSL. A mean voxel-wise fractional anisotropic image was generated and subsequently skeletonised and thresholded (optimised to include white matter only at fractional anisotropy ≥ 0.3). This procedure generates a mean fractional anisotropic 'skeleton', representing the centres of tracts common to all participants. The aligned maps were then projected onto this skeleton, allowing voxel-wise statistical analysis to be conducted. The individual mean, radial and axial diffusivity and mode of anisotropy maps were projected on the skeleton for each individual, in order to ensure that analyses were restricted to the centre of the all common tracts.

Randomise in FSL was used to investigate differences between the depressive disorder and control groups in all diffusion measures across the skeletonised brain maps. The analysis used threshold-free cluster enhancement and conducted 5000 permutations per contrast to generate voxel-wise probability values corrected for multiple testing (significant at $P < 0.05$, family-wise error corrected). To examine the influence of clinical characteristics on white matter integrity, current symptom severity (i.e. BDI score), antidepressant use and the presence of melancholic characteristics were analysed within the major depressive disorder group. All Randomise contrasts included age, gender and IQ score as nuisance variables, which were 'de-meant' prior to analysis.

Regions of crossing fibres can result in fractional anisotropy reductions that are unrelated to white matter integrity; hence, mode of anisotropy data were employed to obviate this problem. A voxel-wise mean mode of anisotropy map, generated by averaging across all participants, was then masked by the mean fractional anisotropic skeleton to ensure that the former map was limited to common white matter tracts. This mean mode of anisotropy skeleton was then thresholded (mode of anisotropy ≥ 0.5) and overlaid on the fractional anisotropic P -value map for the group contrast. Significant between-group differences in fractional anisotropy that survive the high mode of anisotropy threshold are likely to be highly linear, giving greater confidence that such differences are due to systematically differing white matter integrity rather than crossing fibres.

Statistical analysis

To localise significant voxel effects *post hoc*, contrast maps were subdivided according to the 48 regions of the JHU DTI atlas (online Table DS1). This allowed quantification of the number of significantly different voxels per region, along with identification of the peak voxel. Independent t -tests were run for the effect of group on each skeletonised region, producing values that were then used to calculate regional effect sizes (Cohen's d). Raw diffusion metrics across the fractional anisotropic skeleton were extracted per participant and analysed in SPSS version 19.0 on Windows XP to test for relationships with demographic and clinical variables: age, gender, IQ score, treatment resistance, history of electroconvulsive therapy (ECT) and number of melancholic symptoms.

Results

There was no significant difference in age, gender, IQ score or years of education between the depressive disorder and control groups, but a significant difference in BDI score ($P < 0.001$) was found as expected (Table 1). Significant widespread reductions in fractional anisotropy were found in the participants with major depressive disorder compared with controls, including brain regions in the splenium, genu and body of the corpus callosum, bilateral superior longitudinal fasciculus, anterior and posterior corona radiata, and anterior and posterior limbs of the internal capsule (online Fig. DS1, Table DS2). Significantly higher radial diffusivity was found in similarly widespread regions (Fig. DS2A), along with increased mean diffusivity in the corpus callosum and several right hemisphere regions in the depressive disorder group compared with controls (Fig. DS2B). There was no significant group difference in axial diffusivity or mode of anisotropy. This pattern of increased radial and mean diffusivity without alteration in axial diffusivity indicates that abnormally high levels of diffusion were occurring in the white matter tracts of the participants with major depressive disorder, and that these changes were perpendicular to the primary diffusion direction.

Application of a mode of anisotropy threshold (≥ 0.5) to the fractional anisotropy analysis revealed greater specificity in the fractional anisotropy reductions in the depressive disorder group (Fig. DS3, Table DS3). In particular, all three subregions of the corpus callosum, the left internal capsule and the posterior thalamic radiation showed persistent significant fractional anisotropic reductions consistent with deficits in white matter integrity rather than potential contamination due to the effects of crossing fibres. Conversely, the bilateral superior longitudinal fasciculi, right external capsule and all corona radiata regions contained substantially fewer significant voxels when using the mode of anisotropy mask, potentially indicating that these

Table 1 Demographic and clinical characteristics of participants

	MDD group ^a (n = 66)	Control group (n = 66)
Age, years: mean (s.d.)	48.6 (8.2)	50.4 (7.9)
Male/female, n/n	23/43	30/36
Full-scale IQ, mean (s.d.)	119.4 (10.1)	120.5 (8.7)
Education, years: mean (s.d.)	14.6 (3.2)	15.2 (2.7)
BDI score, mean (s.d.)	15.9 (11.6)	1.8 (2.1)
Antidepressants (unmedicated/medicated), n/n	19/47	
Years since illness onset, mean (s.d.)	21.3 (10.4)	
History of ECT (yes/no), n/n	3/63	
Melancholic/non-melancholic, n/n	19/46	
Number of melancholic symptoms, mean (s.d.)	3.3 (1.4)	

BDI, Beck Depression Inventory; ECT, electroconvulsive therapy; MDD, major depressive disorder.
a. There was no significant group difference in age ($t = 1.36$, $P = 0.18$), gender ($\chi^2 = 1.55$, $P = 0.21$), full-scale IQ ($t = 0.67$, $P = 0.50$) or years of education ($t = 1.17$, $P = 0.24$), but there was an expected significant difference in BDI score ($t = 9.78$, $P < 0.001$).

fractional anisotropy alterations might be due to increased numbers of crossing fibres rather than pathological mechanisms affecting white matter structure.

Effect of depression severity on white matter integrity

Voxel-wise regression analysis indicated that there was a significant negative linear relationship between BDI score and fractional anisotropy in several regions (Fig. 1), including the corpus callosum and right posterior tracts, whereby fractional anisotropy decreased as BDI score increased (Fig. DS4A, Table DS2). Furthermore, a positive linear relationship between BDI score and radial diffusivity was found in an overlapping set of white matter regions, although not for mean or axial diffusivity, indicating that greater symptom severity is associated with white matter disruptions in these regions (Fig. DS4B, Table DS3). Extracting mean fractional anisotropy within JHU DTI atlas regions showed further negative correlations with BDI score of a relatively widespread nature (Table DS4). Scores on the BDI ranged from 0 to 51 with a median of 14, indicating that half of the patients were experiencing at least a mild depressive episode at the time of the MRI scan. Demographic analysis indicated that BDI score was negatively correlated with IQ score in the major depressive disorder group ($r = -0.33$, $P = 0.007$) but not in controls ($r = -0.11$, $P = 0.38$), justifying the removal of variance explained by IQ score in the within-patients regression model. The BDI score was not significantly related to age or gender within the major depressive disorder group.

Clinical characteristics and white matter measures

At the time of the study, 47 of the 66 patients with major depressive disorder were taking antidepressants, whereas 19 had not taken an antidepressant for at least 4 weeks prior to scanning (Table DS5). There was a significant effect of medication status on fractional anisotropy, whereby patients currently taking antidepressants showed fractional anisotropy reductions in the corpus callosum and left posterior white matter (see Table DS3, Fig. DS5A) and widespread increases in radial diffusivity across several regions, including the corpus callosum, bilateral corona radiata and cingulum (Table DS3, Fig. DS5B). There was a trend towards increased BDI scores in patients with major depressive disorder taking antidepressant medications compared with unmedicated patients ($t = 1.84$, $P = 0.072$), but no other significant difference between groups in terms of age, gender or IQ score.

The depressive disorder group consisted of 19 persons with melancholic disorder and 46 with no melancholic symptoms (1 patient unspecified owing to insufficient data).³⁸ There was no significant voxel-wise fractional anisotropic difference between these two subgroups, nor did melancholic symptoms correlate with mean skeleton-wise fractional anisotropy or radial, mean or axial diffusivity. There was a significant correlation of the sum of melancholic symptoms with BDI score ($r = 0.328$, $P = 0.008$).

Age was negatively correlated with fractional anisotropy ($r = -0.26$, $P = 0.003$) and mode of anisotropy ($r = -0.27$, $P = 0.002$), and positively correlated with radial ($r = 0.28$, $P = 0.001$) and mean diffusivity ($r = 0.25$, $P = 0.004$); IQ score was positively correlated with fractional anisotropy ($r = 0.18$, $P = 0.03$). Men and women in the sample did not differ significantly on any diffusion measure. The BDI score for all individuals was negatively correlated with skeleton-wise fractional anisotropy ($r = -0.34$, $P < 0.001$) and was positively correlated with radial ($r = 0.30$, $P = 0.001$) and mean diffusivity ($r = 0.24$, $P = 0.007$), indicating that higher current symptom severity is associated with decreases in the integrity of major white matter fibre bundles.

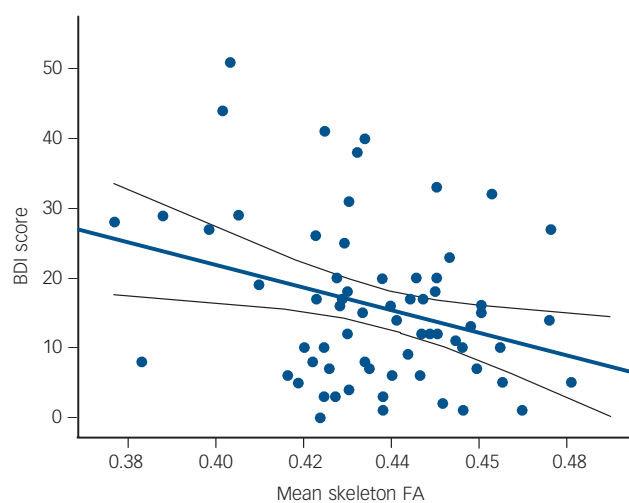


Fig. 1 Individual Beck Depression Inventory (BDI) scores plotted against mean skeleton-wise fractional anisotropy (FA) for each participant.

The blue line derived from the regression analysis illustrates the linear relationship between increasing symptom severity and decreasing fractional anisotropy (R^2 linear 0.093).

Discussion

Widespread alterations in white matter integrity were evident in participants with major depressive disorder in comparison with a healthy control group. Impairments were observed in 75% of white matter regions (36 of 48 atlas regions), probably reflecting reduced axonal density, axonal diameter and dysmyelination.³⁹ Moreover, increasing severity of depression was associated with greater disruptions in white matter integrity. The findings from the large and well-characterised groups in our study, importantly using improved acquisition and analysis procedures, demonstrate the extent of white matter abnormalities in major depressive disorder and lend weight to models of major depressive disorder as a disorder of neurocircuitry.^{1,40}

White matter abnormalities in depression

The most pronounced white matter reductions were observed in the main body and genu of the corpus callosum, consistent with some,^{4,41} but not all,^{3,12,23,42} diffusion tensor imaging reports in depression. Corpus callosum abnormalities may be reflected in the aberrant interhemispheric synchrony reported in male major depressive disorder,⁴³ whereas reduced corpus callosum volume has been associated with impaired working memory capacity and speed in older adults,⁴⁴ resembling the cognitive characteristics of major depressive disorder.⁴⁵ Reduced volume and deformations in the corpus callosum have been observed in major depressive disorder,⁴⁶ suicidal behaviour,⁴⁷ bipolar depression,⁴⁸ dysthymia,⁴⁹ and in adolescents with a parental history of depression,⁸ as well as in schizophrenia and Alzheimer's disease.^{50,51} Together, these findings suggest that impairments in corpus callosum tracts may be involved in the aetiology of depressive symptoms, not only in major depressive disorder itself but also in other psychiatric disorders that contain a depressive component in their symptomatology.

We also found significant white matter integrity reductions in the left superior longitudinal fasciculus, consistent with other reports in major depressive disorder.^{14,15,24} This is the major association pathway connecting frontal regions with all other cerebral lobes, in particular from the dorsolateral prefrontal cortex, itself an important region in an emotion-regulating circuit.⁵² Ischaemic changes in the dorsolateral prefrontal cortex predispose elderly individuals to major depressive disorder, and imaging findings indicate that more subtle microstructural and functional alterations in this region's connectivity may also be a contributory factor to depression in earlier adulthood.^{53,54} Interestingly, Versace *et al* found fractional anisotropy decreases in the superior longitudinal fasciculus of patients with bipolar disorder but not major depressive disorder.⁴² Although not a direct comparison of major depressive disorder and bipolar disorder, our results indicate that abnormalities of the superior longitudinal fasciculus are not specific to bipolar disorder, perhaps underlying depressive symptoms in both disorders. Furthermore, we observed widespread disruptions in white matter integrity between cortical and limbic regions, including association fibres such as the sagittal stratum and external capsule, and projection fibres including the internal capsule, corona radiata and thalamic radiation, supporting the notion of aberrant neurocircuitry in major depressive disorder.⁴⁰

White matter deficits and symptom severity

In participants with major depressive disorder there was a significant negative correlation between fractional anisotropy and the severity of depression, indicating greater deficits in white

matter integrity with greater severity of symptoms. A positive correlation between BDI score and radial diffusivity was also found, implicating increases in diffusivity parallel to the tracts in line with increased severity. This indicates that demyelination, as opposed to abnormalities in axonal diameter or density, might occur more frequently in patients with more severe current symptom severity. The relationship between symptom severity and white matter integrity was strongest in the corpus callosum but also included the corona radiata and posterior thalamic radiation. Lamar *et al* found a correlation between decreased integrity and increased severity in a large region of interest that included the corpus callosum;²² however, our tract-based analysis gives considerably greater precision in characterising the regions involved. Interestingly, Lamar *et al* studied a sample consisting solely of euthymic patients with major depressive disorder, indicating that the relationship persists into remission. Other similar findings of increased severity with decreased integrity have been reported for inferior frontal regions,²³ the anterior limb of the internal capsule,^{13,14} left superior longitudinal fasciculus and right uncinate,²⁴ as well as for decreased grey matter volume in prefrontal and cingulate regions.⁵⁵ The varied pattern of brain regions implicated by the literature indicates that further research is necessary to improve our understanding of the specificity of the relationship between depressive symptom severity and brain changes and how this relates to functional impairments in people with major depressive disorder.

White matter impairments in bilateral frontal regions have been associated with a poorer clinical outcome.^{5,56} The degree and extent of white matter disruptions may implicate a more treatment-resistant form of depression, complementary to structural and functional abnormalities that are predictive of clinical response.^{57–60} Dynamic changes to white matter tracts have been reported in response to training, with working memory training correlating with increases in the intraparietal sulcus and corpus callosum,⁶¹ and fractional anisotropy increases in the corona radiata evident after meditation training.⁶² If white matter integrity is measurably plastic and related to both symptom severity and cognitive performance, this has implications for the potential use of diffusion tensor imaging in a clinical setting. Longitudinal effects of treatment on white matter integrity in adult major depressive disorder have not been examined to date, but it may be postulated that successful treatment would be accompanied by a normalisation of white matter integrity, as reported in some structural and functional MRI studies.^{63–66} This normalisation might be region-specific, as our findings indicate that although widespread changes distinguish between patients and controls, fewer regions correlate with severity. For example, the corpus callosum might be more responsive to depressive states than other areas, with heightened impairments in tandem with increasing severity and improvements during periods of remission, with the more substantive widespread abnormalities perhaps reflecting a trait feature of depression.

Clinical features and white matter integrity

We found greater disruptions of white matter integrity in participants who were currently taking antidepressants. This could be interpreted to show that decreased fractional anisotropy is a marker of antidepressant use, and it has previously been reported that increased white matter lesions have been associated with long-term antidepressant use in elderly people with major depressive disorder.⁶⁷ Nevertheless, fractional anisotropy reductions have also been reported in young adults with major depressive disorder who have never taken antidepressant medication.^{13,15,19} Additionally, in our sample there was a trend

towards increased symptom severity in medicated patients which may explain this apparent antidepressant effect. We did not detect any difference between patients with melancholic and non-melancholic disorder or a relationship between number of melancholic symptoms and white matter integrity. In contrast to the findings of Korgaonkar *et al.*⁴ group differences were not limited to melancholic major depressive disorder, as we found widespread abnormalities in all patients with recurrent major depressive disorder. Furthermore, it appears that a relationship with melancholic depression may be more likely to be a function of the trend towards increased severity in this group, rather than the melancholic symptoms *per se*.

Limitations

The study is limited in its cross-sectional design, preventing inferences of causality in the relationship between current illness severity and decreased white matter integrity. It is possible that the relationship between severity and brain structure is bi-directional, or may result from changes in correlated latent variables. The sample included patients with somewhat heterogeneous medication histories; nonetheless, we were able to examine differences between patients taking antidepressants and those who were not. Three participants also had a history of ECT, which may affect white matter structure. Much of the extant research into white matter in major depressive disorder has been conducted in people over 65 years old,^{7,11,12,56,68,69} which may offer greater sensitivity to detect abnormalities in white matter, particularly for associations with age-related neurovascular changes.

Our use of tract-based spatial statistics focused solely on white matter regions from a 'skeleton' template, causing the exclusion of potentially interesting areas of peripheral white matter. However, this approach benefits considerably by being less susceptible to partial volume effects and does not require arbitrary spatial smoothing,²⁵ in contrast to voxel-based diffusion tensor imaging analysis.^{7,14,19,21} Additional tractographic analysis could be used to follow up our findings to characterise fibre tract architecture and assess integrity of individual tracts. The interpretation of diffusion tensor images can also be limited by the presence of crossing white matter fibres which may result in reductions in fractional anisotropy that are not pathological in origin. Nevertheless, our novel implementation of a 'mode of anisotropy' mask of the fractional anisotropy results indicates that in the corpus callosum in particular, the microstructural configuration is highly linear, thus any anisotropy reductions are unlikely to be the result of crossing fibre orientations. Furthermore, we employed a protocol with 60 diffusion gradient directions. Increasing the number of gradient directions has been shown to increase contrast-to-signal variance ratio and improve visualisation of white matter structures, and our figure far surpasses the minimum 20 directions recommended for accurate diffusion tensor calculation by Giannelli *et al.*⁷⁰ In fact, only a few diffusion tensor imaging studies of major depressive disorder have exceeded Giannelli *et al.*'s quality threshold,^{2,4,7,8,11,24,71,72} and in these studies sample sizes have been small, the largest being that of Yang *et al.* ($n = 31$).¹¹ Sparse acquisition of gradient directions or small samples may have considerably hampered the statistical power to detect widespread white matter changes, particularly in studies that used a whole brain approach. Region of interest studies have included larger samples, although some *a priori* excluded the corpus callosum,^{6,12,41} the area where we report the strongest effects. Our use of 'high-directional' data acquisition combined with a relatively large sample size and tract-based spatial statistical analysis is likely to have improved statistical

power and thus the sensitivity to microstructural effects, adding credence to the findings.

In summary, we examined diffusion tensor imaging-derived measures of white matter integrity in patients with recurrent major depressive disorder. We demonstrated widespread disruptions to several white matter pathways, most notably the corpus callosum and superior longitudinal fasciculi. The majority of the group differences occurred in regions unlikely to contain a high density of crossing fibres, hence are more likely to reflect neuropathological changes. Moreover, we found a correlation between increased depressive symptom severity and decreased white matter integrity, indicating that white matter disruptions are heightened in those with a greater current illness burden, reflecting both trait predispositions and state alterations in the neurocircuitry of depression.

James Cole, PhD, King's College London, Medical Research Council (MRC) Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry; **Christopher A. Chaddock**, PhD, King's College London, Department of Psychosis Studies, Institute of Psychiatry; **Anne E. Farmer**, FRCPsych, **Katherine J. Aitchison**, MRCPsych, King's College London, MRC Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry; **Andrew Simmons**, PhD, King's College London, Department of Neuroimaging, Institute of Psychiatry and National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health and South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London; **Peter McGuffin**, FRCPsych, King's College London, MRC Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry and NIHR Biomedical Research Centre for Mental Health and South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London; **Cynthia H. Y. Fu**, MD, King's College London, MRC Social, Genetic and Developmental Psychiatry Research Centre, and Department of Psychological Medicine, Institute of Psychiatry, London, UK

Correspondence: James Cole, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK. Email: james.h.cole@kcl.ac.uk

First received 8 Oct 2011, final revision 24 Nov 2011, accepted 17 Jan 2012

Funding

J.C. was funded by a Medical Research Council studentship and a Wellcome Trust Value in People award for the duration of this work. The study was funded in part by GlaxoSmithKline UK and by the National Institute of Health Research Biomedical Research Centre for Mental Health at South London and Maudsley National Health Service Foundation Trust and King's College London, Institute of Psychiatry, UK.

References

- Sexton CE, Mackay CE, Ebmeier KP. A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry* 2009; **66**: 814–23.
- Cullen KR, Klimes-Dougan B, Muetzel R, Mueller BA, Camchong J, Hourii A, et al. Altered white matter microstructure in adolescents with major depression: a preliminary study. *J Am Acad Child Adolesc Psychiatry* 2010; **49**: 173–83.
- Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, Inoue H, et al. Voxel-based analyses of gray/white matter volume and diffusion tensor data in major depression. *Psychiatry Res* 2010; **181**: 64–70.
- Korgaonkar MS, Grieve SM, Koslow SH, Gabrieli JD, Gordon E, Williams LM. Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. *Hum Brain Mapp* 2011; **32**: 2161–71.
- Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. *Am J Psychiatry* 2002; **159**: 1929–32.
- Taylor WD, Kuchibhatla M, Payne ME, Macfall JR, Sheline YI, Krishnan KR, et al. Frontal white matter anisotropy and antidepressant remission in late-life depression. *PLoS One* 2008; **3**: e3267.
- Yuan YG, Zhang ZJ, Bai F, Yu H, Shi YM, Qian Y, et al. White matter integrity of the whole brain is disrupted in first-episode remitted geriatric depression. *Neuroreport* 2007; **18**: 1845–9.
- Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med* 1996; **36**: 893–906.
- Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR Biomed* 1995; **8**: 333–44.

- 10 Li L, Ma N, Li Z, Tan L, Liu J, Gong G, et al. Prefrontal white matter abnormalities in young adult with major depressive disorder: a diffusion tensor imaging study. *Brain Res* 2007; **1168**: 124–8.
- 11 Yang Q, Huang XB, Hong N, Yu X. White matter microstructural abnormalities in late-life depression. *Int Psychogeriatr* 2007; **19**: 757–66.
- 12 Bae JN, MacFall JR, Krishnan KR, Payne ME, Steffens DC, Taylor WD. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. *Biol Psychiatry* 2006; **60**: 1356–63.
- 13 Zhu X, Wang X, Xiao J, Zhong M, Liao J, Yao S. Altered white matter integrity in first-episode, treatment-naive young adults with major depressive disorder: a tract-based spatial statistics study. *Brain Res* 2011; **1369**: 223–9.
- 14 Zou K, Huang X, Li T, Gong Q, Li Z, Ou-yang L, et al. Alterations of white matter integrity in adults with major depressive disorder: a magnetic resonance imaging study. *J Psychiatry Neurosci* 2008; **33**: 525–30.
- 15 Wu F, Tang Y, Xu K, Kong L, Sun W, Wang F, et al. White matter abnormalities in medication-naive subjects with a single short-duration episode of major depressive disorder. *Psychiatr Res Neuroim* 2011; **191**: 80–3.
- 16 Heiden A, Kettenbach J, Fischer P, Schein B, Ba-Ssalamah A, Frey R, et al. White matter hyperintensities and chronicity of depression. *J Psychiatr Res* 2005; **39**: 285–93.
- 17 Jia Z, Huang X, Wu Q, Zhang T, Lui S, Zhang J, et al. High-field magnetic resonance imaging of suicidality in patients with major depressive disorder. *Am J Psychiatry* 2010; **167**: 1381–90.
- 18 Kieseppa T, Eerola M, Mantyla R, Neuvonen T, Poutanen VP, Luoma K, et al. Major depressive disorder and white matter abnormalities: a diffusion tensor imaging study with tract-based spatial statistics. *J Affect Disord* 2010; **120**: 240–4.
- 19 Ma N, Li L, Shu N, Liu J, Gong G, He Z, et al. White matter abnormalities in first-episode, treatment-naive young adults with major depressive disorder. *Am J Psychiatry* 2007; **164**: 823–6.
- 20 Nobuhara K, Okugawa G, Minami T, Takase K, Yoshida T, Yagyu T, et al. Effects of electroconvulsive therapy on frontal white matter in late-life depression: a diffusion tensor imaging study. *Neuropsychobiology* 2004; **50**: 48–53.
- 21 Zhou Y, Qin LD, Chen J, Qian LJ, Tao J, Fang YR, et al. Brain microstructural abnormalities revealed by diffusion tensor images in patients with treatment-resistant depression compared with major depressive disorder before treatment. *Eur J Radiol* 2011; **80**: 450–4.
- 22 Lamar M, Charlton RA, Morris RG, Markus HS. The impact of subcortical white matter disease on mood in euthymic older adults: a diffusion tensor imaging study. *Am J Geriatr Psychiatry* 2010; **18**: 634–42.
- 23 Nobuhara K, Okugawa G, Sugimoto T, Minami T, Tamagaki C, Takase K, et al. Frontal white matter anisotropy and symptom severity of late-life depression: a magnetic resonance diffusion tensor imaging study. *J Neurol Neurosurg Psychiatry* 2006; **77**: 120–2.
- 24 Dalby RB, Frandsen J, Chakravarty MM, Ahdidan J, Sorensen L, Rosenberg R, et al. Depression severity is correlated to the integrity of white matter fiber tracts in late-onset major depression. *Psychiatr Res Neuroim* 2010; **184**: 38–48.
- 25 Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006; **31**: 1487–505.
- 26 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV)*. APA, 1994.
- 27 Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry* 1990; **47**: 589–93.
- 28 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; **4**: 561–71.
- 29 Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. Psychological Corporation, 1999.
- 30 Cohen-Woods S, Gaysina D, Craddock N, Farmer A, Gray J, Gunasinghe C, et al. Depression Case Control (DeCC) Study fails to support involvement of the muscarinic acetylcholine receptor M2 (CHRM2) gene in recurrent major depressive disorder. *Hum Mol Genet* 2009; **18**: 1504–9.
- 31 Uher R, Perroud N, Ng MY, Hauser J, Henigsberg N, Maier W, et al. Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. *Am J Psychiatry* 2010; **167**: 555–64.
- 32 Jones DK, Williams SC, Gasston D, Horsfield MA, Simmons A, Howard R. Isotropic resolution diffusion tensor imaging with whole brain acquisition in a clinically acceptable time. *Hum Brain Mapp* 2002; **15**: 216–30.
- 33 Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; **17**: 143–55.
- 34 Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; **23**: S208–19.
- 35 Ennis DB, Kindlmann G. Orthogonal tensor invariants and the analysis of diffusion tensor magnetic resonance images. *Magnet Reson Med* 2006; **55**: 136–46.
- 36 Douaud G, Jbabdi S, Behrens TE, Menke RA, Gass A, Monsch AU, et al. DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. *Neuroimage* 2011; **55**: 880–90.
- 37 Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 2008; **40**: 570–82.
- 38 Uher R, Dernovsek MZ, Mors O, Hauser J, Souery D, Zobel A, et al. Melancholic, atypical and anxious depression subtypes and outcome of treatment with escitalopram and nortriptyline. *J Affect Disord* 2011; **132**: 112–20.
- 39 Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 2002; **17**: 1429–36.
- 40 Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology* 2010; **35**: 192–216.
- 41 Shimony JS, Sheline YI, D'Angelo G, Epstein AA, Benzinger TL, Mintun MA, et al. Diffuse microstructural abnormalities of normal-appearing white matter in late life depression: a diffusion tensor imaging study. *Biol Psychiatry* 2009; **66**: 245–52.
- 42 Versace A, Almeida JR, Quevedo K, Thompson WK, Terwilliger RA, Hassel S, et al. Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. *Biol Psychiatry* 2010; **68**: 560–7.
- 43 Knott V, Mahoney C, Kennedy S, Evans K. EEG power, frequency, asymmetry and coherence in male depression. *Psychiatr Res Neuroim* 2001; **106**: 123–40.
- 44 Fling BW, Chapekis M, Reuter-Lorenz PA, Anguera J, Bo J, Langan J, et al. Age differences in callosal contributions to cognitive processes. *Neuropsychologia* 2011; **49**: 2564–9.
- 45 Walsh ND, Williams SC, Brammer MJ, Bullmore ET, Kim J, Suckling J, et al. A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. *Biol Psychiatry* 2007; **62**: 1236–43.
- 46 Walterfang M, Yucel M, Barton S, Reutens DC, Wood AG, Chen J, et al. Corpus callosum size and shape in individuals with current and past depression. *J Affect Disord* 2009; **115**: 411–20.
- 47 Cyprien F, Courtet P, Malafosse A, Maller J, Meslin C, Bonafe A, et al. Suicidal behavior is associated with reduced corpus callosum area. *Biol Psychiatry* 2011; **70**: 320–6.
- 48 Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, et al. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. *Biol Psychiatry* 2011; **69**: 309–17.
- 49 Lyoo IK, Kwon JS, Lee SJ, Han MH, Chang CG, Seo CS, et al. Decrease in genu of the corpus callosum in medication-naive, early-onset dysthymia and depressive personality disorder. *Biol Psychiatry* 2002; **52**: 1134–43.
- 50 Sun J, Maller JJ, Daskalakis ZJ, Furtado CC, Fitzgerald PB. Morphology of the corpus callosum in treatment-resistant schizophrenia and major depression. *Acta Psychiatr Scand* 2009; **120**: 265–73.
- 51 Lyoo IK, Satlin A, Lee CK, Renshaw PF. Regional atrophy of the corpus callosum in subjects with Alzheimer's disease and multi-infarct dementia. *Psychiatry Res* 1997; **74**: 63–72.
- 52 Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 2008; **213**: 93–118.
- 53 Blood AJ, Iosifescu DV, Makris N, Perlis RH, Kennedy DN, Dougherty DD, et al. Microstructural abnormalities in subcortical reward circuitry of subjects with major depressive disorder. *PLoS One* 2010; **5**: e13945.
- 54 Vasic N, Walter H, Sambataro F, Wolf RC. Aberrant functional connectivity of dorsolateral prefrontal and cingulate networks in patients with major depression during working memory processing. *Psychol Med* 2009; **39**: 977–87.
- 55 Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, et al. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry* 2007; **62**: 407–14.
- 56 Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry* 2008; **165**: 238–44.

- 57 Costafreda SG, Chu C, Ashburner J, Fu CH. Prognostic and diagnostic potential of the structural neuroanatomy of depression. *PLoS ONE* 2009; **4**: e6353.
- 58 Nouretdinov I, Costafreda SG, Gammerman A, Chervonenkis A, Vovk V, Vapnik V, et al. Machine learning classification with confidence: application of transductive conformal predictors to MRI-based diagnostic and prognostic markers in depression. *Neuroimage* 2011; **56**: 809–13.
- 59 Fu CH, Mourao-Miranda J, Costafreda SG, Khanna A, Marquand AF, Williams SC, et al. Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. *Biol Psychiatry* 2008; **63**: 656–62.
- 60 Costafreda SG, Khanna A, Mourao-Miranda J, Fu CH. Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. *Neuroreport* 2009; **20**: 637–41.
- 61 Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, et al. Training of working memory impacts structural connectivity. *J Neurosci* 2010; **30**: 3297–303.
- 62 Tang YY, Lu Q, Geng X, Stein EA, Yang Y, Posner MI. Short-term meditation induces white matter changes in the anterior cingulate. *Proc Natl Acad Sci USA* 2010; **107**: 15649–52.
- 63 Soriano-Mas C, Hernandez-Ribas R, Pujol J, Urretavizcaya M, Deus J, Harrison BJ, et al. Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. *Biol Psychiatry* 2011; **69**: 318–25.
- 64 Frodl T, Jager M, Smajstrlova I, Born C, Bottlender R, Palladino T, et al. Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci* 2008; **33**: 423–30.
- 65 Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biol Psychiatry* 2008; **64**: 505–12.
- 66 Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry* 2004; **61**: 877–89.
- 67 Steffens DC, Chung H, Krishnan KR, Longstreth WT, Carlson M, Burke GL. Antidepressant treatment and worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2008; **39**: 857–62.
- 68 Taylor WD, Macfall JR, Boyd B, Payne ME, Sheline YI, Krishnan RR, et al. One-year change in anterior cingulate cortex white matter microstructure: relationship with late-life depression outcomes. *Am J Geriatr Psychiatry* 2011; **19**: 43–52.
- 69 Taylor WD, Macfall JR, Gerig G, Krishnan RR. Structural integrity of the uncinate fasciculus in geriatric depression: Relationship with age of onset. *Neuropsychiatr Dis Treat* 2007; **3**: 669–74.
- 70 Giannelli M, Cosottini M, Michelassi MC, Lazzarotti G, Belmonte G, Bartolozzi C, et al. Dependence of brain DTI maps of fractional anisotropy and mean diffusivity on the number of diffusion weighting directions. *J Appl Clin Med Phys* 2010; **11**: 2927.
- 71 Li W, Liu J, Skidmore F, Liu Y, Tian J, Li K. White matter microstructure changes in the thalamus in Parkinson disease with depression: a diffusion tensor MR imaging study. *AJNR Am J Neuroradiol* 2010; **31**: 1861–6.
- 72 Matthews SC, Strigo IA, Simmons AN, O'Connell RM, Reinhardt LE, Moseley SA. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. *Neuroimage* 2011; **54** (suppl 1): S69–75.

EXTRA
CONTENT
ONLINEOPEN
ACCESS