Neuroendocrinology Letters Volume 35 No. 8 2014
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

White matter abnormalities in medication-naïve adult patients with major depressive disorder: Tract-based spatial statistical analysis

Yanfang Wang [1], Cheng Xu [2], Aixia Zhang [2], Xi-Nian Zuo [4], Qiang Gao [1], Xia Li [3], Zhifen Liu [2], Xiaohua Cao [2], Kerang Zhang [2]

1 Department of Psychiatry, First Hospital of Shanxi Medical University, People's Republic of China
2 Department of Magnetic Resonance Imaging, People's Hospital of Shanxi Province, People's Republic of China
3 Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, People's Republic of China
4 Department of Psychiatry, Shanxi Corps Hospital of Chinese People's Armed Police Forces, Taiyuan, People's Republic of China

Correspondence to: Prof. Ke-Rang Zhang, MD.
Department of Psychiatry, First Hospital of Shanxi Medical University,
No. 85 Jiefang South Road, Taiyuan 030001, China.
TEL/FAX: +8603514639456; E-MAIL: kerangzhang1696@126.com

Submitted: 2014-12-05 Accepted: 2014-12-20 Published online: 2015-01-18

Key words: **major depressive disorder; diffusion tensor imaging; white matter; nerve fiber regeneration**

Neuroendocrinol Lett 2014; **35**(8):697–702 **PMID:** 25702298 NEL350814A04

Abstract

OBJECTIVE: While increasing evidence suggests that major depressive disorder (MDD) is coincident with the altered white matter microstructure in many brain regions including the prefrontal cortex, parietal lobe, ventral tegmental area and limbic system, it remains controversial in the nature of white matter structural changes and in its relationship with depression syndrome. We believe that the age of patients and the antidepressant treatment to them would contribute to that controversy. Here in this study we explored the microstructural changes of the entire brain white matter of the adult patients with first-episode, antidepressant drug-naïve MDD.

DESIGN: We performed the diffusion tensor imaging (DTI) among a relatively large sample size of patients and age-matched control individuals (forty-one MDD patients and forty-one control subjects) and used recently developed tract-based spatial statistics to analyze the difference of mean fractional anisotropy (FA) between patients and control individuals.

RESULTS: We surprisingly found that MDD patients exhibited a significantly greater mean FA, which is used to elucidate the structural organization of the neural fibers, than control subjects in the whiter matter of the left superior longitufinal fasciculus. However, this change in the white matter of MDD patient did not correlate with depressive clinical features (HMAD, illness duration and initial age) in the present study.

CONCLUSION: Our data suggest that a potential compensatory regeneration of nerve fibers occurs in the early course of MDD development. Advanced understanding of the potential nerve fiber regeneration in the early course of MDD and its associated mechanisms will possibly shade light on a better strategy for MDD prevention and treatment.

ORIGINAL ARTICLE

INTRODUCTION

Major depressive disorder (MDD) (also known as clinical depression) is a mental disorder characterized by a feeling of sadness and helplessness, a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. In recent years, depressive disorders are leading causes of disability worldwide according to the World Health Organization report (http://www.who.int/mental_health/management/depression/definition/en/index1.html). Although the big picture of the depression pathogenesis remains elusive, several hypotheses propose that biological, psychological and social factors can all play a crucial role in causing depression. More importantly, non-invasive neuroimaging studies in clinic settings have significantly advanced our knowledge of the brain structural and functional changes associated with MDD (Drevets 2000). In addition to the structural changes in the prefrontal cortex, cingulate gyrus, basal ganglia, hippocampus and thalamus have been investigated (Drevets *et al.* 2008), cerebral white matter (WM), consisting of axonal bundles that connect brain cortex regions and create proximal and distal neural networks for facilitating complex behaviors and mood, has also attracted much attention given that WM can mediate functional connections between multiple neural systems (Le Bihan 2003).

Diffusion tensor imaging (DTI) is a noninvasive method that measures the microstructural alteration of major neuronal fiber pathways *in vivo* by measuring the diffusion of water in neural tissues. Numerous studies using DTI in depressive patients have found diffusion fractional anisotropy (FA; A common measurement for elucidating the structural organization of the neural fibers in WM) abnormalities in certain brain regions, suggesting that WM structural anomalies exist in depression (Taylor *et al.* 2001; Yang *et al.* 2007). To date, the majority of the DTI studies suggest a loss of coherence in WM bundles among MDD patients. For example, several DTI studies have found frontal and temporal reduced FA in depression (Nobuhara *et al.* 2006; Wu *et al.* 2011). In addition, the relationship between the observed loss of white matter coherence and the mental state of MDD patients has been exploited by a measurement based on the Hamilton Depression Rating Scale (HAMD) (Dalby *et al.* 2010). However, the outcome of these investigations has revealed an absence of correlation between the reduced FA value and the depressive state that was evaluated by the HAMD test (Li *et al.* 2007).

Although it is common to observe a reduced FA value in the MDD patient brain by analyzing DTI images with the methods of region-of-interest (ROI) (Yang *et al.* 2007) analysis or voxel-based analysis (VBA) (Zou *et al.* 2008), a few studies (Blood *et al.* 2010) report a significantly greater FA value in the right ventral tegmental area in depressive patients. This discrepancy may result from the analysis sensitivity and the individual's age given that both young (McKinnon *et al.* 2009) and late-life MDD patients were subjected to these investigations. To eliminate the artificial errors and minimize the effects of misalignment, Smith and colleagues (Smith *et al.* 2006) proposed a tract-based spatial statistics (TBSS) approach that conducts statistical analysis along individual white matter skeletons in the entire brain.

In the present study, using a TBSS analyzed-DTI study approach, we investigated the white matter integrity in medication-naïve adult MDD patient brain, especially focused on the regions that connect emotion-related limbic and cortical areas. To our surprise, we found that MDD patients exhibited a significantly greater mean FA value than control subjects in the white matter of the left superior longitudinal fasciculus. In addition, by performing a HAMD test, we examined whether the observed WM changes was correlated with the mental state of the MDD patients. Although the observed white matter change in left superior longitudinal fasciculus failed to be correlated with depressive mental state in the present study, our data suggest a potential compensatory regeneration of nerve fibers may occur in the early course of MDD pathogenesis.

MATERIALS AND METHODS

Participants

The human subjects recruited for this study were approved by the Medical Ethics Committee of the Shanxi Medical University. All MDD patients and the control subjects were made aware of the objectives of the study and signed informed consent documents prior to being enrolled in the research.

Forty-one right-handed, medication-naïve patients with current MDD (male/female [M/F]: 21/20, mean age: 32.35 years, standard deviation [SD]:6.52, mean years of education: 13.29 years, SD: 4.11) were recruited from outpatient and inpatient units in the Department of Psychiatry, First Hospital of Shanxi Medical University. The MDD patients must meet all the following criteria to be recruited: 1) Eighteen to fifty years of age; 2) right-handed; 3) meeting diagnosis of current MDD based on Diagnostic and Statistical Manual-IV criteria; 4) having a total score of Hamilton Depression Rating Scale (HAMD17)>17 and a total score of Hamilton Anxiety Scale (HAMA) <14. Diagnoses of MDD were based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P) and consensus of at least two psychiatrists.

Forty-one right-handed, age and gender-matched control subjects (M/F: 21/20, mean age: 32.58 years, SD: 5.32, mean years of education: 14.55 years, SD: 3.12) were recruited from the nearby community with matching the following criteria: 1) inconformity axis I MDD diagnosis in DSM-IV; 2) having a total score of HAMD <7 and a total score of HAMA<7.

All patients and control subjects have no history of head injury, systemic medical illness, other primary psychiatric diagnosis, substance abuse, pregnancy, claustrophobia, serious physical illness, treatment with antidepressants, previous electroconvulsive therapy, suicidal tendencies and self-injury, family history of mental disorders, and the usual MRI contraindications.

Data acquisition and preprocessing

Magnetic resonance images were acquired at the People's Hospital of Shanxi Province (3-T Siemens, Magnetom Trio, A Tim System). Subjects were placed in a supine position with eyes closed and in an awakened state, wearing headphones to reduce background noise. The subjects were restrained on foam pads to minimize head motion. A standard head coil was used for radio frequency transmission and reception of the magnetic resonance signal. Whole-brain 3D T1-weighted images were acquired using a sagittal 3-dimensional FLASH with the following parameters: repetition time (TR), 2300 milliseconds; echo time (TE), 2.95 milliseconds; resolution, 256×256; 160 continuous slices; acquisition time, 9 minutes 14 seconds. Diffusion tensor data were acquired using a coronal diffusion-weighted single-shot spin-echoplanar imaging sequence, 12 diffusion gradient directions, diffusion sensitive factor b=1000 s/mm^2; TR, 6000 milliseconds; echo time (TE), 90 milliseconds; flip angle, 90°; field of view, 240×240; 45 continuous slices, 3-mm-thick sections; sections gaps, 0; matrix-size, 128×128 voxels; acquisition time, 4 minutes 14 seconds.

Data analysis

Diffusion-weighted images were analyzed using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). Briefly, fat saturation was first used to remove scalp signal to avoid disrupting neural signal owing to chemical shift or ghosting artifacts, and the effects of gradient coil eddy currents were adjusted. Then, whole-brain voxel-wise analysis of FA data was performed by aligning each subject's FA image into a higher-resolution FA standard space (Montreal Neurological Institute [MNI] according to a nonlinear registration algorithm implemented in TBSS). Next, FA maps were averaged to generate a mean FA image after image registration. The gained mean FA image was minimized to produce a template skeleton that embodies the center of all tracts. The FA skeleton was set at threshold to FA>0.2 to exclude peripheral tracts. Each subject's aligned FA data were projected onto this template skeleton. The final data were then estimated using voxel-wise between-subject statistics (Randomise [a TBSS statistical tool] *http://www.fmrib.ox.ac.uk/fsl/randomise/index.html*) and were analyzed by cluster size with Threshold-Free Cluster Enhancement (TFCE).

A paired two-tailed *t*-test was used to compare group difference in mean FA between MDD patients and control subjects. The correlation of the FA value with the mental state of depression (HAMD), the illness course, or age of onset of the depression disorder was examined by a two-tailed Spearman's correlation analysis. $p<0.05$ was considered statistically significant.

RESULTS

Participants

The current MDD patient and control groups were matched by age, gender ratio and years of education. Of all the depressive subjects, the average initial age was 32.35±6.52 years. The average illness course was 6.05±3.21 months, and the average HAMD score was 23.78±6.11.

TBSS-base FA difference between MDD patients and control subjects

In the present study, we analyzed our DTI images using the TBSS approach. Across the regions that connect emotion-related limbic and cortical areas we focused on, we found that MDD patients exhibited a significantly greater mean FA value than control subjects in the white matter of the left superior longitudinal fasciculus (MNI x, y, z coordinates, −27, −22, 21; $t=4.88$; $p<0.001$) (Figure 1), which was inconsistent with the previous study (cite TZ Jiang's paper, PLoS ONE 7(5): e37561. doi:10.1371/journal.pone.0037561). Given that we had a larger sample size and set a higher threshold for TBSS analysis compared to the previous research, we believe our data represent the WM changes in this specific brain region, which suggests a potential compensatory regeneration of nerve fibers may occur in the early course of MDD pathogenesis.

Correlations analysis

Using a two-tailed Spearman's correlation analysis, we analyzed the correlation between FA value of the left superior longitudinal fasciculus and HAMD, duration of illness or age of depression onset. No significant correlations were found between the FA value and the MDD patients' HAMD score ($p>0.05$; Figure 2A), illness duration ($p>0.90$; Figure 2B), or age at illness onset ($p>0.05$; Figure 2C). These results were consistent with previous imaging reports (Drevets 2000; Yang *et al.* 2007; Zhu *et al.* 2011), and suggested that the white matter alteration in the left superior longitudinal fasciculus might occur prior to depressive disorder genesis.

DISCUSSION

In our study, we provided evidence that white matter alteration occurred in the left superior longitudinal fasciculus in adult MDD patients, which concurred with previous imaging reports (Dalby *et al.* 2010; Zhu *et al.* 2011; Zuo *et al.* 2012). However, our TBSS-based DTI studies among a relatively large sample size of

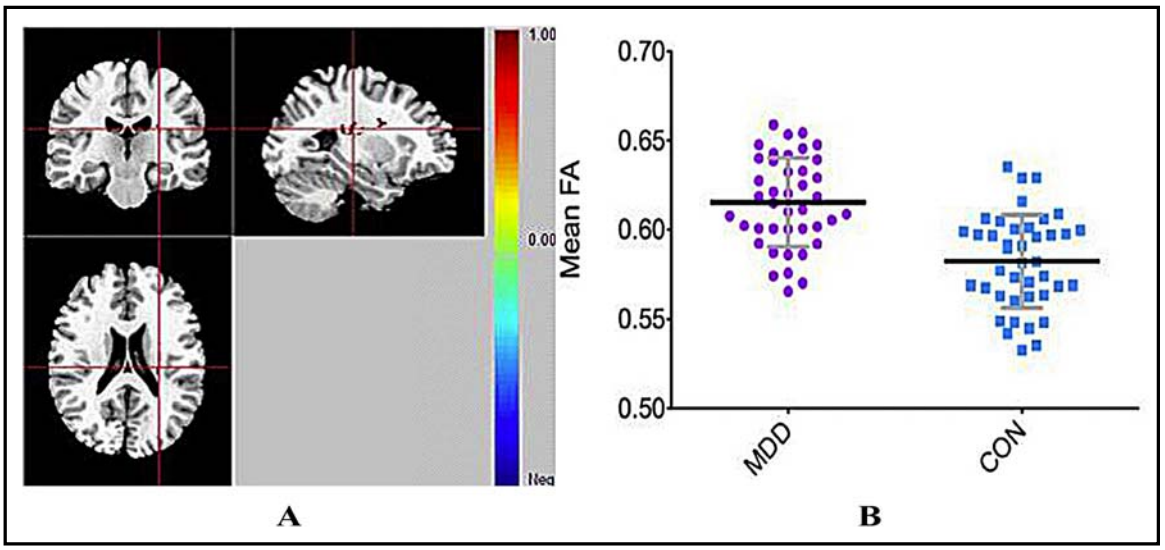

Fig. 1. The anatomical locations of the ROI derived by the TBSS method and the quantification of FA in the targeted ROI.
(A) The average FA skeleton maps from 41 pairs of MDD patients and controls were masked, and the red voxels show the region in which FA is greater in MDD patients compared to that of in controls ($p<0.001$ corrected for multiple comparisons at cluster level). The location with the detected greater FA value is the left superior longitudinal fasciculus. Coordinates of the origo are x=–27, y=–22, and z=21 mm. The standard MNI152 brain was used as the background image.
(B) Quantification of the mean FA value demonstrated that MDD patients showed higher FA values in the left superior longitudinal fasciculus compared to healthy controls ($p<0.001$).

patient pool revealed an increased mean FA value in the left superior longitudinal fasciculus of medication-naïve adult patients with MDD. Given that FA value is believed to be an indicator for the structural organization of the neural fibers in white matter, the increased FA value in MDD patients suggested a potential compensatory regeneration of nerve fibers that might occur in the early course of MDD development. Advanced understanding of the potential nerve fiber regeneration in the early course of MDD and its associated mechanisms will possibly shade light on a better strategy for MDD prevention and treatment.

The superior longitudinal fasciculus trajectory starts mainly from the forehead dorsolateral cerebrum hemisphere to the parietal lobe of the ipsilateral cerebral hemisphere, which constitutes the forehead dorsolateral cortex-parietal neural circuit (Schmahmann *et al.* 2007). It has been reported that the forehead dorsolateral cortex and its related neural circuits was thought to play a role in emotional dysregulation in affective disorders (Tekin & Cummings 2002). We did observe a change in the left superior longitudinal fasciculus white matter (WM) area, which suggested that this observed WM alteration might be involved in the depressive disorders. In our current study, we found a greater FA value in the left superior longitudinal fasciculus among patients with MDD compared to that was found in control subjects. This is inconsistent with

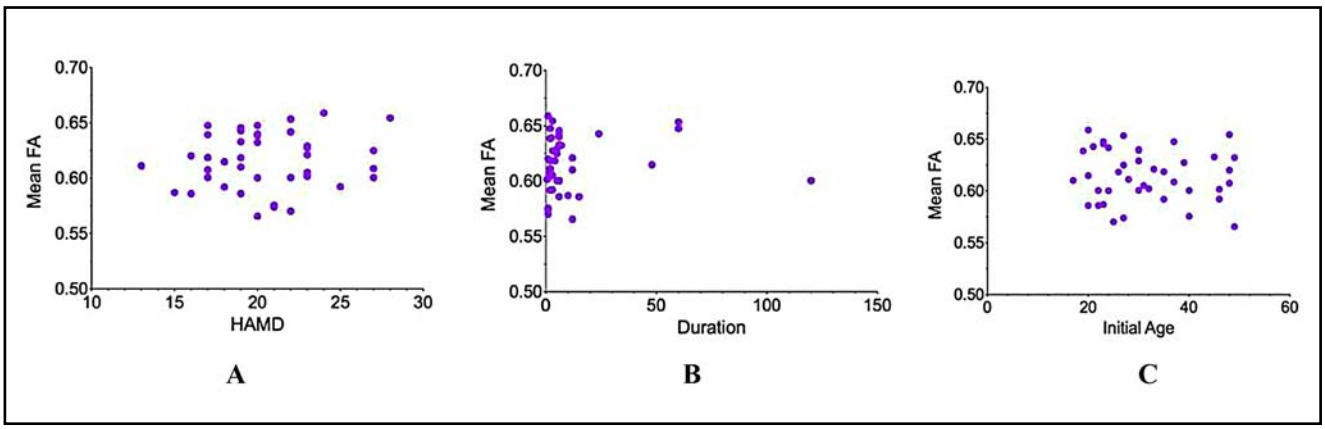

Fig. 2. Correlation between the FA values in the left superior longitudinal fasciculus with HAMD score, duration of illness or the age of illness onset. (A–C) Scatter plot of mean FA values with HAMD scores (A), duration of illness (B) and the initial age of illness onset (C). No significant correlations ($p>0.05$) were detected in MDD patients.

previous studies (Alexopoulos *et al.* 2002; Nobuhara *et al.* 2006; Murphy *et al.* 2007) in which a reduced FA value was reported not only in the left superior longitudinal fasciculus region (Zuo *et al.* 2012) but also in other cortical regions among subjects with later-onset depression. This discrepancy may be due to the differences in the age of subjects, age at onset of depression (Bhagat & Beaulieu 2004), illness duration, depression severity, drug administration (Nugent *et al.* 2006), subjects with hypertension (Pantoni 2002), subjects with early life stress (Mervaala *et al.* 2000), methods of imaging, data processing, and data analysis.

In the adult brain, stress, depression, and other insults may cause axonal damage, but simultaneously, the neurotrophic factors or other molecular players may facilitate neuronal repair, regeneration and reconstruction of the synapses as well to endorse a functional compensation. A previous study (Houenou *et al.* 2007) observed more reconstructed fibers in the left uncinate fasciculus of subjects with bipolar disorder compared to that was found in controls. It is also (Blood *et al.* 2010) found that the FA value was increased in the right ventral tegmental white matter in MDD subjects, which was coincident with a decrease of glial density and an increase of the ratio of axons to cell bodies. In our study, we observed a greater FA in subjects with MDD compared to that of in controls. While the underlined mechanisms remains unclear, it is possible that a compensatory reconstruction of nerve fibers exists in the early course of depression.

In addition, we found no significant correlation between the increased FA values in the left superior longitudinal fasciculus and recorded clinical features of depression, such as severity (as expressed in HAMD scores), duration of illness, and age of illness onset. These results were consistent with previous imaging reports (Ma *et al.* 2007; Yang *et al.* 2007; Zou *et al.* 2008), and suggested that the white matter alteration in the left superior longitudinal fasciculus might occur prior to depressive disorder genesis.

We have to note that there are some limitations in the present study. Since TBSS is a method used to analyze the entire brain, it may yield more false positive findings compared to ROI analysis. Another limitation is the lack of follow-up of the subjects with MDD, which obstructed us to exclude subjects with bipolar disorder without following-up. Finally, the subjects using tobacco and/or alcohol were not eliminated in our analyses.

CONCLUSION

In summary, the observed greater FA value in the left superior longitudinal fasciculus in MDD patients may reflect the WM abnormality in the forehead dorsolateral cortex neural circuit, which is associated with mood regulation among depression patients. To maintain a relatively normal brain function, nerve fiber reconstruction may occur early for the functional compensation within the course of depressive disorder. Understanding of the potential nerve fiber regeneration in the early course of MDD and its associated mechanisms will possibly shade light on a better strategy for MDD prevention and treatment.

ACKNOWLEDGEMENTS

This study was supported by the Natural Science Foundation of China, Grant (Grant Nos. 30971054 and 81171290). All of the authors have read the manuscript and approved for publication. Kerang Zhang had full access to all of the data in the study and took his responsibility for the integrity of the data and Xi-Nian Zuo took his responsibility for the accuracy of data analysis.

REFERENCES

1 Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO (2002). Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. The American journal of psychiatry **159**: 1929–1932.
2 Bhagat YA, Beaulieu C (2004). Diffusion anisotropy in subcortical white matter and cortical gray matter: changes with aging and the role of CSF-suppression. Journal of magnetic resonance imaging : JMRI **20**: 216–227.
3 Blood AJ, Iosifescu DV, Makris N, Perlis RH, Kennedy DN, Dougherty DD, Kim BW, Lee MJ, *et al.* (2010). Microstructural abnormalities in subcortical reward circuitry of subjects with major depressive disorder. PloS one **5**: e13945.
4 Dalby RB, Frandsen J, Chakravarty MM, Ahdidan J, Sorensen L, Rosenberg R, Videbech P, Ostergaard L (2010). Depression severity is correlated to the integrity of white matter fiber tracts in late-onset major depression. Psychiatry research **184**: 38–48.
5 Drevets WC (2000). Neuroimaging studies of mood disorders. Biological psychiatry **48**: 813–829.
6 Drevets WC, Price JL, Furey ML (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain structure & function **213**: 93–118.
7 Houenou J, Wessa M, Douaud G, Leboyer M, Chanraud S, Perrin M, Poupon C, Martinot JL, *et al.* (2007). Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. Molecular psychiatry **12**: 1001–1010.
8 Le Bihan D (2003). Looking into the functional architecture of the brain with diffusion MRI. Nature reviews Neuroscience **4**: 469–480.
9 Li L, Ma N, Li Z, Tan L, Liu J, Gong G, Shu N, He Z, *et al.* (2007). Prefrontal white matter abnormalities in young adult with major depressive disorder: a diffusion tensor imaging study. Brain research **1168**: 124–128.
10 Ma N, Li L, Shu N, Liu J, Gong G, He Z, Li Z, Tan L, *et al.* (2007). White matter abnormalities in first-episode, treatment-naive young adults with major depressive disorder. The American journal of psychiatry **164**: 823–826.
11 Mckinnon MC, Yucel K, Nazarov A, Macqueen GM (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. Journal of psychiatry & neuroscience: JPN **34**: 41–54.
12 Mervaala E, Fohr J, Kononen M, Valkonen-Korhonen M, Vainio P, Partanen K, Partanen J, Tiihonen J, *et al.* (2000). Quantitative MRI of the hippocampus and amygdala in severe depression. Psychological medicine **30**: 117–125.

13 Murphy CF, Gunning-Dixon FM, Hoptman MJ, Lim KO, Ardekani B, Shields JK, Hrabe J, Kanellopoulos D, *et al.* (2007). White-matter integrity predicts stroop performance in patients with geriatric depression. Biological psychiatry **61**: 1007–1010.
14 Nobuhara K, Okugawa G, Sugimoto T, Minami T, Tamagaki C, Takase K, Saito Y, Sawada S, *et al.* (2006). Frontal white matter anisotropy and symptom severity of late-life depression: a magnetic resonance diffusion tensor imaging study. Journal of neurology, neurosurgery, and psychiatry **77**: 120–122.
15 Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, Zarate CA, Pine DS, *et al.* (2006). Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. NeuroImage **30**: 485–497.
16 Pantoni L (2002). Pathophysiology of age-related cerebral white matter changes. Cerebrovascular diseases **13 Suppl 2**: 7–10.
17 Schmahmann JD, Pandya DN, Wang R, Dai G, D'arceuil HE, De Crespigny AJ, Wedeen VJ (2007). Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain : a journal of neurology **130**: 630–653.
18 Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, *et al.* (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage **31**: 1487–1505.
19 Taylor WD, Payne ME, Krishnan KR, Wagner HR, Provenzale JM, Steffens DC, Macfall JR (2001). Evidence of white matter tract disruption in MRI hyperintensities. Biological psychiatry **50**: 179–183.
20 Tekin S, Cummings JL (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. Journal of psychosomatic research **53**: 647–654.
21 Wu F, Tang Y, Xu K, Kong L, Sun W, Wang F, Kong D, Li Y, *et al.* (2011). Whiter matter abnormalities in medication-naive subjects with a single short-duration episode of major depressive disorder. Psychiatry research **191**: 80–83.
22 Yang Q, Huang X, Hong N, Yu X (2007). White matter microstructural abnormalities in late-life depression. International psychogeriatrics / IPA **19**: 757–766.
23 Zhu X, Wang X, Xiao J, Zhong M, Liao J, Yao S (2011). Altered white matter integrity in first-episode, treatment-naive young adults with major depressive disorder: a tract-based spatial statistics study. Brain research **1369**: 223–229.
24 Zou K, Huang X, Li T, Gong Q, Li Z, Ou-Yang L, Deng W, Chen Q, *et al.* (2008). Alterations of white matter integrity in adults with major depressive disorder: a magnetic resonance imaging study. Journal of psychiatry & neuroscience : JPN **33**: 525–530.
25 Zuo N, Fang J, Lv X, Zhou Y, Hong Y, Li T, Tong H, Wang X, *et al.* (2012). White matter abnormalities in major depression: a tract-based spatial statistics and rumination study. PloS one **7**: e37561.