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Original Article

Effects of antidepressant therapy on white matter in patients with first-episode major depressive disorder

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Purpose: To explore antidepressant effect on the microstructural integrity of white matter (WM) by diffusion tensor imaging (DTI) in patients with first-episode major depressive disorder (MDD).
Methods: In this prospective study, we recruited 32 first-episode patients who met the criteria of the Fourth Edition of Diagnostic and Statistical Manual of Mental Disorders for MDD and 35 age- and sex-matched healthy controls. Brain DTI was used to determine fractional anisotropy (FA) in preselected WM regions before and after the patients received sertraline for 12 weeks. The severity of depression was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS).
Results: Only 11 patients (34.38%) completed post-treatment MRI exam. Patients with MDD displayed lower baseline FA values, predominantly in bilateral upper frontal WM at 10mm above the anterior commissure-posterior commissure (AC-PC) plane, than healthy controls. The correlation between baseline HDRS scores and FA values was inversely significant in left lower frontal WM at 10mm below the AC-PC plane. After treatment, FA values significantly increased in bilateral upper frontal WM at 10mm above the AC-PC plane.
Conclusion: Antidepressants administered for 12 weeks to first-episode MDD patients increase FA values. WM microstructure subnormalities may develop early in the course of the illness.

Key words: antidepressant, diffusion tensor imaging (DTI), fractional anisotropy (FA), major depressive disorder (MDD), white matter (WM)

Introduction

Emerging evidence has implicated abnormalities in frontal-subcortical circuits in the pathophysiology of major depressive disorder (MDD).[1-4]. Studies on depression have reported microstructural white matter (WM) abnormalities in several brain regions, such as prefrontal cortex, cingulate cortex, hippocampus, amygdala, and parietal lobe.[5-9] These findings further suggest that WM structural abnormalities play a role in the pathophysiology of MDD.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique for assessing WM integrity and neural fiber tracts in vivo via the measurement of the movement of water molecules.

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[10]. Fractional anisotropy (FA), a measure of the directionality of diffusion anisotropy,[11] has been used to study the integrity of WM fibers in psychiatric illnesses. Previous studies using DTI in patients with MDD have shown a variety of abnormalities in WM fibers, such as those of the left superior longitudinal fasciculus,[4,12,13] left inferior front-occipital fasciculus to posterior thalamic radiation,[12,14] unilateral or lateral parahippocampus,[12,15] bilateral internal capsule and external capsule,[12,16] and cingulum to posterior corpus callosum.[14,15] However, several of these studies were performed on geriatric patients treated with antidepressants. Therefore, the findings may have been confounded by age-related pathologies or by antidepressant effects.[4,12]

It has been reported that the abnormalities revealed on DTI correlate with clinical severity in various WM pathologies.[17,18] In addition, there is an inverse relationship between FA values of certain frontal brain regions and symptom severity in patients with late-life depression and MDD.[5,19] However, due to differences in sample age, sex distribution, medication exposure, age of illness onset, illness duration and number of acute episodes, results have been inconsistent.

DTI studies performed on MDD antidepressant-naive patients have demonstrated decreases in the FA values of different brain regions, including dorsolateral prefrontal cortex, fronto-limbic system, and WM regions of thalamus and hippocampus.[12,15,20-23] However, there have been few studies on WM changes following antidepressant treatment in patients with first-episode MDD. Sertraline is an antidepressant and a selective serotonin reuptake inhibitor (SSRI). SSRIs control the brain's level of serotonin, a neurotransmitter thought to affect mood, sleep and cognition. Functional MRI studies have demonstrated that depression is characterized by impaired functional connectivity between cortical and limbic regions, while antidepressant response is accompanied by improved functional connectivity.[32,34] To the best of our knowledge, no such study has been undertaken in Taiwan. The aim of this study was to use DTI to examine the WM integrity in patients with first-episode MDD compared with healthy controls and to investigate WM changes after treatment with sertraline.

Methods

2.1 Study subjects

Thirty-five right-handed patients (13 males, 22 females, mean age 39.14 ± 10.23 years) diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association 1994) were included in the study. Diagnosis was confirmed via medical chart and each patient was interviewed by a board certified psychiatrist using Mini-International Neuropsychiatric Interview (M.I.N.I.).[24] Patients ranged in age from 20 to 55 years and were required to take sertraline for 12 weeks. Sertraline was initiated at 25mg/day and adjusted to maximal 150mg/day according to the clinical condition of each patient (average drug dose 66.07 ± 23.22 mg/day). Three cases in the MDD group withdrew consent before the start of the study. Therefore, only 32 of the patients completed baseline brain MRI exam. Depression was evaluated using Hamilton Depression Rating Scale (HDRS).[25] The severity of depression was classified according to the baseline HDRS scores as mild MDD (HDRS: 15-18, n=1), moderate MDD (HDRS: 19-22, n=10), or severe MDD (HDRS: 23 and over, n=21). Response to sertraline was defined as a ≧50% decrease in HDRS score compared with the baseline value, and remission was defined as HDRS score ≦7 after treatment. Patients were recruited from the psychiatric outpatient clinic at Chung Shan Medical University Hospital in Taiwan from January 2009 to December 2009.

Thirty-five age- and sex-matched right-handed comparison subjects (11 males, 24 females, mean age 39.37±8.5 years) were recruited from the health screening clinic at the same hospital. They were all non-smokers without history of chronic medical illness. They did not present with indication of acute infection and none were pregnant at the time of the study. Comparison subjects were interviewed based on M.I.N.I. and did not have a history of major psychiatric disorder. They were also not taking any psychotropics. This study was approved

by the Institutional Review Board of Chung Shan Medical University Hospital and was conducted in accordance with the Declaration of Helsinki.

To be included in this study, patients were required to have first-episode MDD, to be antidepressant-naive for at least 4 weeks, and to have baseline HDRS score of at least 18. Patients with an Axis I disorder other than MDD or with an Axis II disorder were excluded. Exclusion criteria for both groups were organic brain disease, previous brain injury, substance use, and conventional contradictions to MRI scan. After explaining the purpose of this study and obtaining written informed consent, the following data were collected: age, gender, employment status, education, marital status, and age of onset of MDD.

2.2 Image processing

Comparison subjects and patients (before and after treatment) underwent MRI examination. DTI was performed at Chung Shan Medical University Hospital on a 3-T Siemens vision MR with echo-planar double-spin echo sequence TR=4800 msec, TE=97 msec, 4-mm-thick slices, skip 0, alignment with the anterior commissure–posterior commissure (AC-PC) plane, 128×128 matrix reconstructed to a 256×256 b matrix for which b=2000 sec/mm2. The tensor was computed from 65 images: the b=0 sec/mm2 image and 64 images with b=2000 sec/mm2 with gradients applied in 64 noncollinear directions. Sixty four maps of the apparent diffusion coefficient were computed. Then, 64 independent elements of the diffusion tensor were determined. The eigenvalues and eigenvectors were computed, and scalar measure, FA, was assessed. FA yields values between 0 (i.e., isotropic or unrestricted diffusion, as in CSF) and 1 (i.e., anisotropic or constrained diffusion due to barriers, as in organized WM fibers). All regions of interest (ROIs) were circular and 31.6 mm2 in size. They were positioned bilaterally in the frontal WM of three consecutive images, 8 mm above the AC-PC plane, at the AC-PC plane, and at 8 mm below the AC-PC plane. In addition, circular ROIs were placed in genu and splenium of corpus callosum, as well as bilaterally in occipital and temporal WM (Figure).

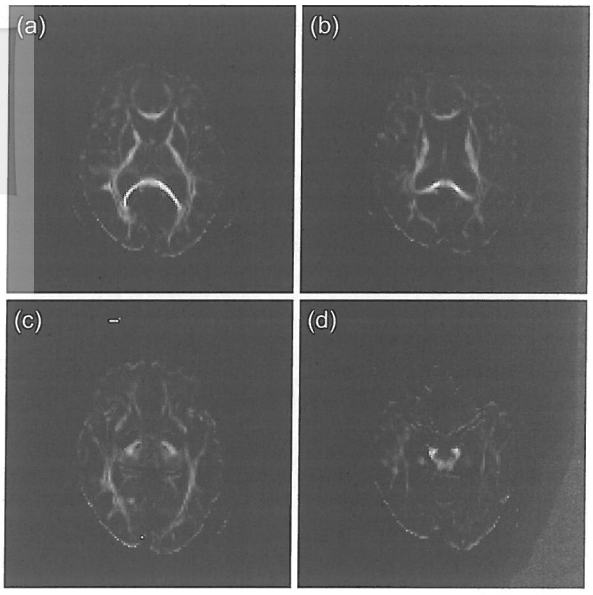

Figure. Maps of representative regions of interest (ROIs) at twelve locations in the brain: (a) right AC-PC, left AC-PC, genu, splenium; (b) 10mm above Right AC-PC, 10mm above left AC-PC, right occipital white matter, left occipital white matter; (c) 10mm below right AC-PC, 10mm below left AC-PC; (d) right temporal white matter, left temporal white matter..

2.3 Statistical analysis

The Shapiro-Wilk test was used to test the normality of the data. Continuous variables in the two groups were compared using independent t-test. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Pre- and post-treatment values of the MDD group were compared using paired t-test. Pearson or Spearman test was performed to determine the correlation between HDRS scores and DTI regional measures. GPower 3.1 was used to calculate the effect size of treatment. All statistical tests were 2-tailed. The significance level was set at 0.05. Correction for multiple comparisons was not performed due to risk of type II error. Data were analyzed using SPSS17 (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics and FA values of both groups are shown in Table 1. There were no significant differences in age, gender or marital

Table 1. ***Demographic findings and fractional anisotropy values of major depressive disorder (MDD) and control groups***

	Control group (n=35) Mean ± SD or n (%)	*MDD group (n=32) Mean ± SD or n (%)*	*P valu*
Age (year)	39.37 ± 8.50	39.38 ± 10.53	0.99
Sex			
Male	11 (31.4%)	11 (34.4%)	0.79
Female	24 (68.6%)	21 (65.6%)	
Education (year)	14.94 ± 3.39	11.97 ± 3.98	0.002
Employment			
Unemployed	3 (8.6 %)	13 (40.6%)	0.004
Employed	32 (91.4%)	19 (59.4%)	
Marital status			
Single	11 (31.4%)	11 (34.4%)	0.75
Married	23 (65.7%)	19 (59.4%)	
Widowed	1 (2.9%)	2 (6.3%)	
Duration of current episode (years)		1.03 ± 0.04	
HDRS score		26.41 ± 4.86	
FA values			
Right AC-PC	0.441 ± 0.083	0.434 ± 0.089	0.734
Left AC-PC	0.427 ± 0.120	0.394 ± 0.080	0.192
Genu	0.768 ± 0.065	0.755 ± 0.073	0.439
Splenium	0.807 ± 0.040	0.792 ± 0.046	0.152
Right AC-PC+10	0.405 ± 0.065	0.369 ± 0.074	0.037*
Left AC-PC+10	0.377 ± 0.058	0.336 ± 0.058	0.006**
Right AC-PC-10	0.480 ± 0.076	0.463 ± 0.098	0.428
Left AC-PC-10	0.477 ± 0.078	0.453 ± 0.087	0.251
Right occipital WM	0.531 ± 0.053	0.515 ± 0.067	0.290
Left occipital WM	0.537 ± 0.065	0.515 ± 0.055	0.130
Right temporal WM	0.524 ± 0.063	0.521 ± 0.074	0.836
Left temporal WM	0.533 ± 0.080	0.526 ± 0.053	0.668

HDRS: Hamilton depression rating scale
**p < 0.05; **p < 0.01*
FA: fractional anisotropy
AC-PC: anterior commissure-posterior commissure
WM: white matter

Table 2. ***Regional white matter fractional anisotropy values in patients with MDD before and after treatment***

	Before treatment (n = 11) Mean ± SD	*After treatment (n = 11) Mean ± SD*	*Effect size*	*P valu*
HDRS scores	26.27 ± 5.12	4.36 ± 2.38	4.68	0.000**
Region of interest				
Right AC-PC	0.436 ± 0.109	0.454 ± 0.096	0.50	0.247
Left AC-PC	0.395 ± 0.070	0.424 ± 0.088	0.38	0.231
Genu	0.734 ± 0.076	0.773 ± 0.066	0.61	0.085
Splenium	0.800 ± 0.057	0.837 ± 0.035	0.74	0.072
Right AC-PC+10	0.339 ± 0.046	0.389 ± 0.054	1.37	0.001**
Left AC-PC+10	0.327 ± 0.046	0.368 ± 0.070	0.88	0.016*
Right AC-PC-10	0.451 ± 0.099	0.467 ± 0.076	0.41	0.248
Left AC-PC-10	0.447 ± 0.078	0.465 ± 0.088	0.45	0.267
Right occipital WM	0.504 ± 0.046	0.539 ± 0.073	0.53	0.074
Left occipital WM	0.501 ± 0.050	0.522 ± 0.071	0.30	0.316
Right temporal WM	0.512 ± 0.070	0.529 ± 0.067	0.19	0.551
Left temporal WM	0.513 ± 0.037	0.522 ± 0.034	0.22	0.519

**p < 0.05; **p < 0.01*
HDRS: Hamilton depression rating scale
AC-PC: anterior commissure–posterior commissure
WM: white matter

status between patients and controls. Baseline HDRS score of MDD patients (n=32) was 26.41. The duration of current illness was 1.03 ± 0.04 years. A larger number of control subjects were employed (χ^2=9.45, df=1, p=0.004). Moreover, educational level was higher in control group (14.94 years, p=0.002). Nineteen patients completed 12-week antidepressant treatment and all reached remission. Only 11 patients (34.38%) completed post-treatment brain MRI exam.

Compared with healthy controls, patients with MDD demonstrated lower FA values in all ROIs (Table 1). There were significant differences in two regions, left and right upper frontal WM at 10mm above the AC-PC plane (Table 1). There was significant and negative correlation between baseline HDRS scores and FA values in left lower frontal WM at 10mm below the AC-PC plane (r= -0.359, p=0.043).

The patients demonstrated higher FA values in all ROIs after 12-week treatment, predominantly in left and right upper frontal WM at 10mm above the AC-PC plane (Table 2). HDRS scores were decreased significantly (p<0.001) after treatment (Table 2). Due to the high dropout rate (65.62%), we performed an additional analysis to include all patients regardless of subsequent withdrawal from treatment or deviation from the protocol. For those dropouts, baseline FA values were carried forward. The differences in FA values in left and right upper frontal WM at 10mm above the AC-PC plane after treatment remained significant (effect sizes 0.45 and 0.54 respectively) even after intention-to-treat analysis (Table 3).

Discussion

The main finding of this study is that patients

Table 3. ***Intention-to-treat analysis of the regional white matter fractional anisotropy values in patients with MDD before and after treatment***

	Before treatment (n = 32) Mean ± SD	*After treatment (n = 32) Mean ± SD*	*Effect size*	*P valu*
Region of interest				
Right AC-PC	0.434 ± 0.089	0.440 ± 0.085	0.21	0.234
Left AC-PC	0.394 ± 0.080	0.404 ± 0.086	0.22	0.220
Genu	0.755 ± 0.073	0.768 ± 0.068	0.31	0.086
Splenium	0.792 ± 0.046	0.805 ± 0.045	0.33	0.074
Right AC-PC+10	0.369 ± 0.074	0.386 ± 0.073	0.54	0.004**
Left AC-PC+10	0.336 ± 0.058	0.351 ± 0.066	0.45	0.023*
Right AC-PC-10	0.463 ± 0.097	0.468 ± 0.090	0.19	0.233
Left AC-PC-10	0.453 ± 0.087	0.460 ± 0.090	0.23	0.254
Right occipital WM	0.515 ± 0.067	0.527 ± 0.074	0.32	0.077
Left occipital WM	0.515 ± 0.055	0.522 ± 0.062	0.19	0.296
Right temporal WM	0.521 ± 0.074	0.526 ± 0.073	0.10	0.535
Left temporal WM	0.526 ± 0.053	0.529 ± 0.052	0.12	0.487

*$p < 0.05$; **$p < 0.01$
AC-PC: anterior commissure–posterior commissure
WM: white matter

with MDD have significantly lower FA values in bilateral frontal WM 10 mm above the AC-PC plane, when compared with controls. No such relationship was identified in other frontal, occipital or temporal WM, or in the corpus callosum. The FA values of twelve brain microstructures in MDD patients were lower than in controls. After antidepressant treatment, the FA values significantly increased in bilateral frontal WM 10 mm above the AC-PC plane.

Decrease in FA value in the absence of gross pathological findings is reflective of impaired directional coherence of brain microstructures and may represent microstructural abnormalities, diminishing the integrity of the WM tracts.[11] In our study, bilateral frontal WM 10 mm above the AC-PC plane contained fibers of the anterior cingulate and the dorsolateral prefrontal pathways.[7] The reciprocal regulation of dorsal neocortical-ventral limbic structures in these regions might be compromised, leading to a "disconnection syndrome".[1,7] The dorsolateral prefrontal circuit (DLPFC) is involved mainly in executive function and anterior cingulate circuit lesions often present with apathy.[1] These neuroanatomical circuits play an important role in the regulation and modulation of mood and executive function, and contribute to the pathogenesis of major depression.

The FA values of all 12 ROIs were lower in MDD patients even close to disease onset. This implies development of WM microstructural subnormalities early in the disease. Previous DTI studies of non-geriatric patients with MDD who were antidepressant-naive have demonstrated decreases in FA in the WM of the superior longitudinal fasiculus, cingulate, sagittal stratum, posterior thalamic radiation, anterior limb and retrolenticular part of the internal capsule, external capsule, splenium of the corpus callosum, stria terminalis, and other subcortical and deep WM

of the frontal, parietal and temporal lobes.[12,21-23] Additional DTI studies in elderly depressed patients have demonstrated WM abnormalities in widespread frontal brain regions.[5,7,26] Taylor et al. reported that microstructural changes in WM of the right superior frontal gyrus are associated with late-life depression.[26] Alexopoulos et al. showed that microstructural WM abnormalities lateral to the anterior cingulate may be associated with a low rate of remission.[7] Nobuhara et al. also reported abnormal WM anisotropy in widespread regions of the frontal and temporal lobes in patients with late-life depression.[5] On the contrary, no significant difference was observed in the integrity of WM tracts between patients with depression and healthy controls.[27,28] These findings are suggestive of heterogeneity in the areas of the brain that are involved in MDD. It is possible that such heterogeneity is due to methodological differences. The reduction in WM anisotropy observed in our study is suggestive of loss of integrity within frontal and subcortical WM fiber tracts, and supports the hypothesis that neuroanatomical circuit abnormalities are a key factor in the pathophysiology of major depression.

In our study, we found that baseline HDRS score is inversely correlated with FA value of left lower frontal WM at 10mm below the AC-PC plane. This inferior frontal brain region includes the orbital prefrontal cortex and the neural pathways to caudate and other limbic regions.[29] Smaller orbital frontal cortex volumes are associated with functional disability in late-life depression.[30] The results of our study imply that orbitofrontal circuit is involved in symptom severity of major depression.

Antidepressants have been reported to increase corticolimbic connectivity and restore the cortical regulation of abnormal limbic activation.[2,33] Therefore, antidepressants may increase the regulatory influence of cortical mood-regulating regions of limbic regions. After 12-week sertraline treatment, FA values increased in all ROIs, but predominantly in bilateral frontal WM 10 mm above the AC-PC line. This trend remained unaltered even after intention-to-treat analysis. This suggests that antidepressants enhance WM integrity, particularly in frontal brain regions. The functions of frontal–limbic circuits, specifically the amygdala–hippocampal complex and the anterior cingulated region, are central to the conceptual model of MDD and the action of antidepressants. The antidepressant action of electroconvulsive therapy (ECT) significantly increases frontal WM FA in patients with late-life depression.[31] It is possible that antidepressant effect of ECT ameliorates frontostriatal dysfunction.

There are several limitations in this study. First, all of the patients who completed the 12-week sertraline treatment achieved remission. This might be because those patients never had MDD. Sixteen subjects (45.71%) discontinued treatment or refused blood draw. Highly-motivated patients who continued treatment often reported a better outcome. Second, the sample size was small. Nonetheless, we were able to test the hypothesis that antidepressants affect the microstructures in WM. Third, multiple comparisons were not performed. To avoid reducing the validity of this study, we allowed the type II error to increase. Future studies with larger samples and of patients with treatment-refractory MDD using DTI are needed to clarify whether the disruption in cortical-subcortical networks is remodeled after antidepressant treatment.

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Disclosure statement

The authors declare no conflicts of interest.

Author contributions

Conception and design of the study: CTL, TJL, CCC; acquisition and analysis of data: CTL, MHH;

drafting of the manuscript and figures: CCC, CTL, MCW.

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