ORIGINAL ARTICLE
http://dx.doi.org/10.4306/pi.2015.12.3.367

Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Microstructural Changes of Anterior Corona Radiata in Bipolar Depression

I. Fatih Karababa[1], Huseyin Bayazıt[1], Nihat Kılıçaslan[2], Mustafa Celik[3], Hasan Cece[2], Ekrem Karakas[2], and Salih Selek[4,5] ✉

[1]Department of Psychiatry, Faculty of Medicine, University of Harran, Sanliurfa, Turkey
[2]Department of Radiology, Faculty of Medicine, University of Harran, Sanliurfa, Turkey
[3]Department of Psychiatry, Diyarbakir Training and Research Hospital, Diyarbakir, Turkey
[4]Department of Psychiatry, Faculty of Medicine, University of Medeniyet, Istanbul, Turkey
[5]Department of Psychiatry and Behavioral Sciences, Harris County Psychiatric Center, The University of Texas Health Science Center at Houston, Houston, TX, USA

Objective In bipolar disorder, dysregulation of mood may result from white matter abnormalities that change fiber tract length and fiber density. There are few studies evaluating the white matter microstructural changes in bipolar I patients (BD) with depressive episodes. The present study aimed to evaluate anterior corona radiata in BD patients with depressive episode using Diffusion Tensor Imaging (DTI).

Methods Twenty-one patients with bipolar depression and 19 healthy controls were investigated and groups were matched for age and gender. Diffusion-weighted echoplanar brain images (DW-EPI) were obtained using a 1.5 T MRI scanner. Regions of interest (ROIs) were manually placed on directional maps based on principal anisotropy. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values of white matter were measured in the anterior corona radiata (ACR) bilaterally by diffusion tensor imaging.

Results There was not a significant difference between groups of age and gender ($p>0.05$). Significantly lower FA was observed in bilateral ACR in bipolar patients with depression compared with healthy individuals. And there is significantly higher ADC values in the left frontal corona radiate in bipolar patients.

Conclusion White matter abnormalities can be detected in patients with BD using DTI. The neuropathology of these abnormalities is unclear, but neuronal and axonal loss, myelin abnormalities and reduced white matter fiber density are likely to be relevant.

Psychiatry Investig 2015;12(3):367-371

Key Words Diffusion tensor imaging, Anterior corona radiate, Bipolar disorder, Depression, White matter.

INTRODUCTION

Bipolar I disorder (BD) is comprised by periods of depressed, elevated or irritable mood. Despite much research into BD, the underlying neural pathophysiology of BD remains unclear and reliable biomarkers are few. Neuroimaging markers such as decreased activation and gray matter content and increased activation in the parahippocampal gyrus extending to the thalamus, and the caudate nucleus and some peripheral biochemical compounds such as BDNF, oxidative stress related compounds, cytokines, etc. are appealing candidates.[1-3] It is found that bipolar disorder patients have effectively shorter WM fiber tracts and comparatively reduced WM fiber density in a major tract connecting limbic system structures to the frontal lobe.[4] A breakdown in the architecture of normal WM tracts which connect brain regions involved in emotion regulation has been reported.[5]

Diffusion Tensor Imaging (DTI) is neuroimaging technique to elucidate the abnormalities of white matter tissue in the brain. DTI presents the opportunity to measure the organization of fibers within specific white matter tracts even when macrostructural changes are absent.[6] Noninvasive mapping of white matter tracts using DTI is potentially useful in enlightening anatomical connectivity in the human brain. There are several parameters indicating microstructural integrity of white matter such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC). FA is scalar measure derived by DTI and it

Received: May 5, 2014 **Revised:** August 22, 2014
Accepted: August 28, 2014 **Available online:** July 6, 2015

✉ **Correspondence:** Salih Selek, MD
Department of Psychiatry, Faculty of Medicine, University of Medeniyet, D-100 Mevkii, 34700 Kadikoy, Istanbul, Turkey
Tel: +90 (216) 566 6600-4331, **Fax:** +90 (216) 3183192, **E-mail:** drselek@yahoo.com

reflects the directional coherence of water diffusion and is sensitive to microstructural WM differences in integrity and organization. FA is defined on a scale ranging from mostly isotropic (FA value nearing 0) indicating poor integrity of the axons to mostly anisotropic (FA value nearing 1) indicating intact WM.[7] Lower diffusion anisotropy is commonly observed concurrent with CNS pathology.[8] Apparent diffusion coefficient (ADC) as a scalar index of the rate of water diffusion among different diffusion directions under a Gaussian distribution.[9] A high value of ADC indicates less restricted diffusion and implies the presence of fewer organized structures in the white matter which supporting the presence of abnormalities in the structural integrity of white matter in bipolar disorder.

Converging evidence from genetic and neuroimaging studies indicates that white matter abnormalities may be involved in BD. A significantly lower fractional anisotropy (FA) was observed in the corona radiata and in the genu of corpus callosum, right inferior and left superior longitudinal fasciculus and significantly higher apparent diffusion coefficient (ADC) in the frontal lobe in bipolar patients showing WM microstructural alterations.[3,10-12] Several researches have shown that there may be microstructural WM alterations even in remitted BP patients.[11,13,14] Few DTI researches have focused on BD patients with depressive episode. Benedetti et al.[15] found lower FA in WM tracts of the genu of corpus callosum, bilateral anterior corona radiata and in right superior and posterior corona radiate in Bipolar depression. Zanetti et al.[16] found decreased FA in ventromedial prefronto-limbic-striatal WM in Bipolar depressive patients compared to bipolar remitted patients.

The anterior corona radiate (ACR) is part of the limbic-thalamo-cortical circuitry and includes thalamic projections from the internal capsule to the cortex including those prefrontal cortex gray matter areas that have been associated with impaired top-down emotion regulation systems.[17-19] Since ACR is the "crossroads" of those pathways it may be involved with bipolar depression. Therefore, the present study aimed to evaluate anterior corona radiata in BD patients with depressive episode by DTI.

METHODS

Twenty-one participants with a DSM-IV diagnosis of Bipolar I Disorder, who were on depressive episode at the time of enrollment, were recruited through Harran University Research Hospital, Psychiatry Clinic. Nineteen healthy volunteer controls were enrolled from the hospital staff. Patient and control groups have similar distribution in age, sex and smoking status. Exclusion criteria for all participants included a history of chronic systemic diseases such as diabetes mellitus, hypertension, neurological illness, metal implants, pregnancy, personality disorders (Axis II disorders), alcohol and substance abuse disorders, and severe head injury. After complete description of the study to the subjects, a written informed consent was obtained from all subjects. Ethics committee of the Harran University Medical School approved the trial.

A semi-structured form was used to detect several sociodemographic and clinical variables such as gender, age, co-morbid conditions. The patients who had co-morbid axis I or II conditions due to DSM-IV criteria were excluded from the study. Additionally pregnancy, severe systemic diseases, epilepsy, diabetes mellitus, hypertension, drug and alcohol dependence, severe head injury, were the exclusion criteria of the study. Mood symptoms were evaluated in all participants on the day of the scan using the Turkish version of Young Mania Rating Scale (YMRS) and the Turkish version of 21-item Hamilton Depression Rating Scale (HDRS) by one psychiatrist.[20,21] Bipolar participants were eligible if they had a YMRS score lower than or equal to 7, a 21-item HDRS score higher than 7, and had been depressive by self-report.[22]

All images were obtained on a 1.5 Tesla MRI scanner (Magnetom, Symphony-Quantum, Siemens, Erlangen, Germany). Initially, 3D T1-weighted MP-RAGE images of the whole brain was acquired (matrix 256×256, FOV 250 mm, number of partitions 172 for a nominal slice thickness of 1 mm, Average=4 slices, 0 mm gap). Finally, axial DTI scans were acquired with a pulsed gradient, double spin echo, EPI sequence (TR/TE=3100/98 ms, 128×128 matrix, FOV 230 mm, b=1000 s/mm^2, Average=4 slices, 5 mm slice thickness, 0 mm gap). The images were transferred to a computer workstation (Leonardo, Siemens Medical Solutions, Forcheim, Germany). Regions of interest (ROIs) were manually placed on directional maps based on principal anisotropy (Figure 1). The FA and ADC values of white matter were measured in the anterior corona radiata bilaterally. The measurements were obtained by two experienced ra-

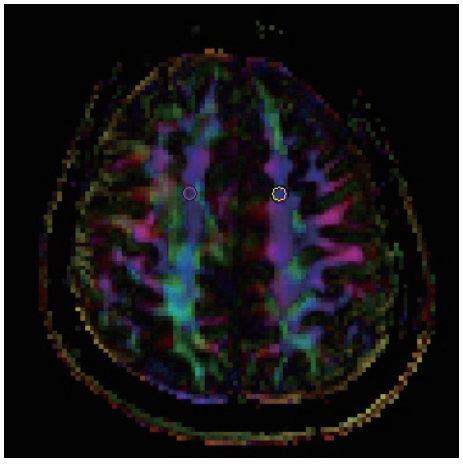

Figure 1. Region of interest placement for diffusion tensor imaging analysis.

Table 1. Sociodemographic and clinical characteristics of the patients and controls

	BD patients	Controls	p value
Age (mean±SD)	34±10.75	34.42±9.43	0.896
Gender (male/female)	6/15	8/11	0.370
Duration of education (years)	4.7±4.7	12±4	<0.01
Duration of illness (years)	11.8±7.3	N/A	
Ham-D total scores	19.2±4.8	N/A	
Number of episodes		N/A	
Mania±SD	2.62±1.9		
Depression±SD	2.86±1.6		

N/A: not applicable, SD: standart deviation, Ham-D: Hamilton depression Rating Scale

Table 2. FA and ADC values of patients and control subjects in the ACR

	BD patients	Controls	p
ACR right FA	463.24±96.9	568.32±94.3	0.001
ACR left FA	423.67±66.6	550.58±92.0	<0.001
ACR right ADC	761.43±27.0	759.00±30.7	0.839
ACR left ADC	783.24±32.1	746.79±49.1	0.003

FA: fractional anisotropy, ADC: apparent diffusion coefficient, ACR: anterior Corona radiata

diologists in consensus.

The analyses were performed using the SPSS for Windows 15.0 (SPSS Inc.). Data were presented as mean±standard deviation for parametric variables. The continuous variables were compared between groups by using t-test for independent samples. Differences were accepted as significant when $p<0.05$.

RESULTS

The bipolar disorder patients and healthy control groups did not differ significantly in age or gender ($p>0.05$). Some of the demographical data of the patients and control subjects are given in Table 1.

We found significantly lower FA values in bilateral anterior corona radiata in bipolar patients compared with healthy individuals (Table 2). And there is significantly higher ADC values in the left frontal corona radiate in bipolar patients.

DISCUSSION

We found decreased FA values in the bilateral ARC in bipolar patients with depressive episode compared with healthy controls. FA is defined on a scale ranging from mostly isotropic (FA value nearing 0) indicating poor integrity of the axons to mostly anisotropic (FA value nearing 1) indicating intact WM 7. Increases or decreases in FA have often been interpreted as markers of changes in tract coherence due to alterations in the myelination, axonal organization, density, alignment, or diameter of WM fibers or exposure to medication.[23] Benedetti et al.[24] found that bipolar depressive patients have lower FA in WM tracts of the genu of corpus callosum, bilateral anterior corona radiate. Differences in FA indicate variations in diffusion anisotropy, thus providing exclusive information on the directionality of axons in the brain and could indicate a loss of axonal and myelin integrity. This suggests that axonal myelination during maturation may be altered in BD. Skudlarski et al.[25] found decreased FA in bipolar disorders at early stage and that wasn't progressive. This is consistent with the growing evidence in bipolar disorder suggesting neuronal abnormalities, with increasing implication of oligodendrocyte involvement.[26]

We also found increased ADC in the left ACR in Bipolar depression but there were no differences in the right ACR. A high value of ADC indicates less restricted diffusion and implies the presence of fewer organized structures in the white matter which supporting the presence of abnormalities in the structural integrity of white matter in bipolar disorder. Increased ADC in the left ACR means that there are microstructural changes at the cellular level that result in reduced diffusion restriction in WM tracts. The ACR is part of the limbic-thalamo-cortical circuitry and includes thalamic projections from the internal capsule to the prefrontal cortex that include both ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC).[17,18] These prefrontal cortex gray matter areas have been associated with impaired top-down emotion regulation systems.[27] WM abnormalities in the ACR could result in many of the cognitive and emotion regulation disturbances via the internal capsule and the thalamus. It's found that lower FA in the ACR in the BD and attention-deficit/hyperactivity disorder (ADHD) and ADC is higher in the ACR in ADHD than BD.[28] Niogi et al.[29] found that integrity of the left ACR is associated with attention control. ACR involvement with increased ADC and decreased FA may contribute to prefrontal cortex dysfunction associated with inattention and emotion.

Yin et al.[30] found correlation between WM leftward asymmetry in ACR and the independent executive control function of attention. Cognitive test performance and neuroimaging studies, reporting more unilateral neural activity in poor cognitive test performance.[31] Asymmetry between the hemispheres may play important role in BD. In this study we found increased ADC in the left ARC on the other side there was no differences in the right side. A DTI study found a significant increase of reconstructed fibers in the subgenual cingulate and amygdalo-hippocampal complex in the left hemisphere of patients with remitted bipolar disorder compared to controls.[32] And abnormalities were found in the structural integrity of the anterior Corpus Callosum in BD and this may contribute to altered inter-hemi-

spheric connectivity in this disorder.[33,34] One sided lesions or asymmetry between hemispheres also may be contributing to etiology of BD. There are many studies that indicate one sided microstructure alterations. Bipolar depression patients showed decreased FA in the left superior longitudinal fasciculus relative.[35] Haznedar et al.[36] found that decreased left and increased right thalamic volume in bipolar disorder II. Adler et al.[37] found that increased gray matter density and volume in the left thalamus in BD I first episode (mania/mixed) subjects. Strakowski et al.[38] found that increased thalamic volumes in both manic and mixed state of BD.

In conclusion, our study indicates that there may be a microstructural changes in ACR showing a network defect in bipolar depression and there have been impaired top-down emotion regulation systems. And asymmetry between the hemispheres may play important role in BD.

REFERENCES

1. Berk M, Malhi GS, Hallam K, Gama CS, Dodd S, Andreazza AC, et al. Early intervention in bipolar disorders: clinical, biochemical and neuroimaging imperatives. J Affect Disord 2009;114:1-13.
2. Houenou J, Frommberger J, Carde S, Glasbrenner M, Diener C, Leboyer M, et al. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. J Affect Disord 2011;132:344-355.
3. Chaddock CA, Barker GJ, Marshall N, Schulze K, Hall MH, Fern A, et al. White matter microstructural impairments and genetic liability to familial bipolar I disorder. Br J Psychiatry 2009;194:527-534.
4. Torgerson CM, Irimia A, Leow AD, Bartzokis G, Moody TD, Jennings RG, et al. DTI tractography and white matter fiber tract characteristics in euthymic bipolar I patients and healthy control subjects. Brain Imaging Behav 2013;7:129-139.
5. Benedetti F, Absinta M, Rocca MA, Radaelli D, Poletti S, Bernasconi A, et al. Tract-specific white matter structural disruption in patients with bipolar disorder. Bipolar Disord 2011;13:414-424.
6. Bruno S, Cercignani M, Ron MA. White matter abnormalities in bipolar disorder: a voxel-based diffusion tensor imaging study. Bipolar Disord 2008;10:460-468.
7. 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;31:1487-1505.
8. Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G. Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 2001;56:304-311.
9. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 1986;161:401-407.
10. Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A, et al. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. Am J Psychiatry 2006;163:322-324.
11. Beyer JL, Taylor WD, MacFall JR, Kuchibhatla M, Payne ME, Provenzale JM, et al. Cortical white matter microstructural abnormalities in bipolar disorder. Neuropsychopharmacology 2005;12:2225-2229.
12. Regenold WT, D'Agostino CA, Ramesh N, Hasnain M, Roys S, Gullapalli RP. Diffusion-weighted magnetic resonance imaging of white matter in bipolar disorder: a pilot study. Bipolar Disord 2006;8:188-195.
13. Davis KA, Kwon A, Cardenas VA, Deicken RF. Decreased cortical gray and cerebral white matter in male patients with familial bipolar I disorder. J Affect Disord 2004;82:475-485.
14. Brambilla P, Bellani M, Yeh PH, Soares JC. Myelination in bipolar patients and the effects of mood stabilizers on brain anatomy. Curr Pharm Des 2009;15:2632-2636.
15. 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;69:309-317.
16. Zanetti MV, Jackowski MP, Versace A, Almeida JR, Hassel S, Duran FL, et al. State-dependent microstructural white matter changes in bipolar I depression. Eur Arch Psychiatry Clin Neurosci 2009;259:316-328.
17. Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage 2002;17:77-94.
18. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology 2004;230:77-87.
19. Sanjuan PM, Thoma R, Claus ED, Mays N, Caprihan A. Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: a diffusion tensor imaging study. Psychiatry Res 2013;214:260-268.
20. Karadag F, Oral E, Yalçın F. Validity and reliability of young mania rating scale in Turkey. Turk Psychiatry J 2002;13:107-114.
21. Akdemir A,Orsel S, Dag I, Turkcapar H, Iscan N, Ozbay H. Validity, reliability and clinical use of Hamilton Depression Rating Scale. 3P J 1996;4:251-259.
22. McIntyre RS, Fallu A, Konarski JZ. Measurable outcomes in psychiatric disorders: remission as a marker of wellness. Clin Ther 2006;28:1882-1891.
23. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 2003;4:469-480.
24. 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;69:309-317.
25. Skudlarski P, Schretlen DJ, Thaker GK, Stevens MC, Keshavan MS, Sweeney JA, et al. Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. Am J Psychiatry 2013;170:886-898.
26. Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003;362:798-805.
27. Sanjuan PM, Thoma R, Claus ED, Mays N, Caprihan A. Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: a diffusion tensor imaging study. Psychiatry Res 2013;214:260-268.
28. Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, et al. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Biol Psychiatry 2009;7:586-593.
29. Niogi SN, Mukherjee P, Ghajar J, Johnson CE, Kolster R, Lee H, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. Brain 2008;131:3209-3221.
30. Yin X, Han Y, Ge H, Xu W, Huang R, Zhang D, et al. Inferior frontal white matter asymmetry correlates with executive control of attention. Hum Brain Mapp 2013;34:796-813.
31. Kier EL, Staib LH, Davis LM, Bronen RA. MR imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. AJNR Am J Neuroradiol 2004;5:677-691.
32. Houenou J, Wessa M, Douaud G, Leboyer M, Chanraud S, Perrin M, et al. Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. Mol Psychiatry 2007;11:1001-1010.
33. Yurgelun-Todd DA, Silveri MM, Gruber SA, Rohan ML, Pimentel PJ. White matter abnormalities observed in bipolar disorder: a diffusion tensor imaging study. Bipolar Disord 2007;9:504-512.
34. Wang F, Kalmar JH, Edmiston E, Chepenik LG, Bhagwagar Z, Spencer

L, et al. Abnormal corpus callosum integrity in bipolar disorder: a diffusion tensor imaging study. Biol Psychiatry 2008;64:730-733.
35. 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;68:560-567.
36. Haznedar MM, Roversi F, Pallanti S, Baldini-Rossi N, Schnur DB, Licalzi EM, et al. Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. Biol Psychiatry 2005;57:733-742.
37. Adler CM, DelBello MP, Jarvis K, Levine A, Adams J, Strakowski SM. Voxel-based study of structural changes in first-episode patients with bipolar disorder. Biol Psychiatry 2007;61:776-781.
38. Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 1999;56:254-260.