A Diffusion Tensor Imaging Study on Pediatric Bipolar Disorder

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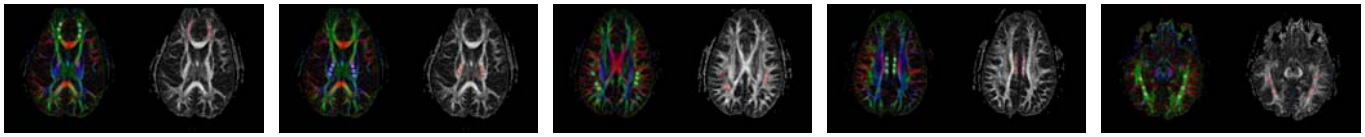
Introduction Pediatric bipolar disorder is a serious disorder with severe affect dysregulation, high levels of suicidal behavior, and persistent cognitive dysfunction [1~3]. Functional imaging studies have shown fronto-temporal/limbic, fronto-parietal and fronto-striatal dysfunction underlying the affective and cognitive psychopathology in pediatric and adult bipolar patients [3~5]. Therefore, our goal was to study the microstructural abnormalities directly using diffusion tensor imaging (DTI) in specific white matter fiber tracts that connect the structures underlying these functional abnormalities.

Recent studies using DTI have indicated a decrease in fractional anisotropy (FA) in adolescents and adults [6, 7] and an increase in apparent diffusion coefficient (ADC) in adults [8]. The regions of interest (ROI) in these studies were variable, including the orbitofrontal cortex, superior frontal gyrus, middle frontal gyrus [8] and additional posterior cortical regions [7]. Building on these previous studies and based on our data on functional imaging, we hypothesize that FA, ADC, as well as fiber coherence index (FCI) [9], will be affected in specific white matter fiber tracts that support the connectivity of functional gray matter in pediatric bipolar disorder.

Methods Thirteen pediatric bipolar patients (mean age: 15 year old; age range: 11-18 year old; female: 3) and equal number of age, race, gender and IQ matched healthy controls (mean age: 14 year old; age range: 10-18 year old; female: 7) were recruited for this study under an IRB approved protocol. DTI scans were performed on a GE 3T Signa HD MRI scanner (General Electric Healthcare, Milwaukee, WI) with an eight-channel head coil. A set of diffusion-weighted images was acquired using a single-shot echo planar imaging sequence with additional eddy current correction capabilities [10]. The key data acquisition parameters were TR = 5200ms, TE = 81.3ms, FOV = 22cm, slice thickness = 5mm, slice gap = 0, number of slice = 20, k-space matrix = 132×132, imaging matrix = 256×256, number of diffusion gradient directions = 27, b = 0, and 750 s/mm^2, number of averages = 2, and the total data acquisition time = 5min. The set of diffusion-weighted images was transferred to a PC and processed using customized software (Diffusion Imaging Visualization Environment, or DIVE) developed using IDL (ITT Visual Information Solutions, Boulder, Colorado). For each subject, FA, ADC, and FCI maps were computed, and ROI analyses were performed on the following five white-matter fiber tracts bilaterally: anterior region of corona radiata (ACR), posterior limb of internal capsule (PLIC), cingulum (CG), superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF). At least three ROIs were selected, by a radiologist, on each fiber tract unilaterally (Fig. 1). Fiber selection was guided by the color-coded FA maps to avoid regions with crossing or branching fibers. At each ROI, the mean and standard deviation were recorded for each of the three DTI metrics. Measurements from individual subjects were combined within each group for statistical analyses. A t-test was used to determine the group difference at a confidence level of no less than 95%.



(a) **(b)** **(c)** **(d)** **(e)**

Fig. 1. Representative DTI images showing the ROIs selected on the five fiber tracts**:** (a) ACR, (b) PLIC, (c) SLF, (d) CG, and (e) ILF.

Results Statistical analysis results for the five fiber tracts are summarized in Table 1. The bipolar patient group showed significantly decreased FA in ACR (p= 0.00002) and ILF (p=0.0001) as compared with the control group. The difference in FA values between the two groups is demonstrated in the histograms (Fig. 2). ACR (p= 0.023), ILF (p=0.031), and SLF (p=0.013) also exhibited significantly higher ADC values in bipolar patients than the healthy controls. A moderate difference in FCI (p=0.046) was also observed in ACR. No significant difference was seen in the FA values of PLIC, CG, and SLF, the ADC values of PLIC, and CG, and the FCI values of PLIC, CG, SLF, and ILF.

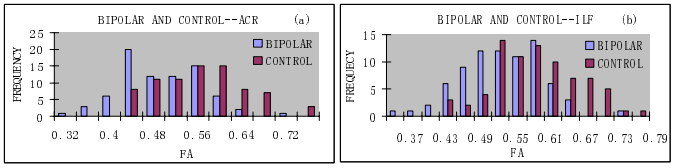


Fig. 2. Histograms of FA values for ACR (a) and ILF (b).

Discussion and Conclusions Several DTI studies have reported changes of white-matter in bipolar disorder [6~8]. A common area of focus is the pre-frontal regions where a decrease in FA [6, 7] or an increase in ADC [8] has been found in adult and adolescent bipolar patients. However, these changes have not been associated with specific fiber tracts. In this study, the measurements were performed on individual fibers suspected to be involved in the disease process. In two key white-matter fiber tracts (ACR and ILF), we observed changes in both FA and ADC. The results of ACR confirm the prefrontal functional changes [3] as well as white matter changes reported by others. The changes in ILF suggest that the temporal regions play a critical role in the disease process with the connections between fronto-temporal and tempero-occipital regions. In addition to the changes in ACR and ILF, we have also seen an increase in ADC of SLF, which has not been reported previously. Changes in SLF may contribute to the cognitive circuitry dysfunction involving DLPFC with tempero-parietal connectivity in this patient population. The relatively small change in FCI of ACR indicates that FCI is not as sensitive as FA and ADC for studying white matter changes associated with bipolar disorder. Alternatively, it could indicate that FCI was not affected in the very early state of the disease process. Therefore, it is still possible that FCI can serve as biomarker of treatment or severity of bipolar diathesis in the early onset illness. Given its potential value, FCI may require additional attention at higher spatial resolution because of its high sensitivity to the partial volume effects. These results have suggested that DTI metrics, such as FA and ADC, can serve as potential biomarkers to reveal changes in fronto-temporal connectivity in pediatric bipolar disorder.

Table 1. Statistical Results

DTI Measure	Bipolar Adolescents (N=13)		Healthy Controls (N=13)		Analysis	
and Region	Mean	Variance	Mean	Variance	t	p
FA						
ACR	0.4726	0.0027	0.5443	0.0038	1.6759	0.00002
ILF	0.5384	0.0019	0.5965	0.0036	1.6759	0.0001
ADC						
ACR	0.7471	0.0038	0.713	0.0034	1.6759	0.0226
ILF	0.7647	0.0019	0.7366	0.0037	1.6759	0.0307
SLF	0.6971	0.002	0.6725	0.0009	1.6802	0.0125
FCI						
ACR	0.9917	0.00005	0.9943	0.00001	1.6924	0.0458

References [1] Dickstein DP, et al. Biol Psychiatry 2004; 55: 32-9. [2] Pavuluri MN, et al. J Am Acad Child Adolesc Psychiatry 2005; 44: 846-71. [3] Pavuluri MN, et al. Am J Psychiatry 2006; 163: 286-93. [4] Blumberg HP, et al. Am J Psychiatry 2003; 160: 1345-7. [5] Chang K, et al. Arch Gen Psychiatry 2002; 61: 781-92. [6] Alder CM, et al. Bipolar disorders 2004; 6: 197-203. [7] Alder CM, et al. Am J Psychiatry 2006; 163: 322-4. [8] John LB, et al. Neuropsychopharmacology 2005; 30: 2225-9. [9] Zhou, XJ. and Leeds, NE, ISMRM Abstracts, Miami, FL, 2005: p. 365. [10] Zhou, XJ, et al. US Patent, 5,864,233, 1999.