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DTI Study of White Matter Fiber Tracts in Pediatric Bipolar Disorder and Attention Deficit Hyperactivity Disorder

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Abstract

Objective—To investigate microstructure of white matter fiber tracts in pediatric bipolar disorder (PBD) and attention deficit hyperactivity disorder (ADHD).

Methods—A diffusion tensor imaging (DTI) study was conducted at 3 Tesla on age and IQ-matched children and adolescents with PBD (n=13), ADHD (n=13), and healthy controls (HC) (n=15). Three DTI parameters, fractional anisotropy (FA), apparent diffusion coefficient (ADC), and regional fiber coherence index (r-FCI), were examined in eight fiber tracts: Anterior corona radiata (ACR); anterior limb of the internal capsule (ALIC); superior region of the internal capsule (SRI); posterior limb of the internal capsule (PLIC); superior longitudinal fasciculus (SLF); inferior longitudinal fasciculus (ILF); cingulum (CG); splenium (SP).

Results—Significantly lower FA was observed in ACR in both PBD and ADHD relative to HC. In addition, FA and r-FCI values were significantly lower in ADHD relative to PBD and HC in both the ALIC and the SRI. Further, ADC was significantly greater in ADHD relative to both the PBD and HC in ACR, ALIC, PLIC, SRI, CG, ILF, and SLF.

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DISCLOSURE

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Conclusions—Decreased FA in ACR implies an impaired fiber density or reduced myelination in both PBD and ADHD in this prefrontal tract. These abnormalities, together with the reduced fiber coherence, extended to cortico-bulbar tracts in ADHD. Increased ADC across multiple white matter tracts in ADHD indicates extensive cellular abnormalities with less diffusion restriction in ADHD relative to PBD.

Keywords

Bipolar disorder; ADHD; diffusion tensor imaging; white-matter fiber tracts; fraction anisotropy; apparent diffusion coefficients

INTRODUCTION

While we are beginning to understand the functional pathophysiology of grey matter (GM) in pediatric bipolar disorder (PBD) (1) and attention deficit hyperactivity disorder (ADHD) (2), little is known about the white matter (WM) fibers that connect the widely distributed components of functional neural systems in these disorders. Further, there is a general dearth of neurobiological information that effectively distinguishes PBD from ADHD. The absence of such knowledge limits development of new therapeutic interventions, and increases the risk for misdiagnosis.

Attentional deficits are common to both PBD and ADHD (3,4). Problems of attention often persists during the euthymic periods in PBD (3–5) and adult BD (6–8), and the presence of attentional symptoms during these inter-episodic periods of PBD does not necessarily indicate ADHD. However, with this and other overlapping symptoms, PBD is often mistaken for ADHD and mistreated with stimulant therapy leading to worsening of manic symptoms (9–13), and ADHD is similarly misdiagnosed as PBD leading to the prescription of mood stabilizers that can worsen attentional disturbances (14). In this context, externally validating biological markers that differentiate these disorders can be valuable.

Few studies have directly compared ADHD or PBD to identify the distinguishing brain circuitry abnormalities that characterize these two disorders. Current evidence from functional magnetic resonance imaging (fMRI) studies suggests that fronto-striatal abnormalities are common to both ADHD and PBD, which is consistent with their shared behavioral problems of attention and response inhibition (2). Studies that used paradigms such as Stroop (15) and response inhibition tasks (16–21) in ADHD have shown decreased activation of ventrolateral prefrontal cortex (VLPFC), anterior cingulate and caudate, compared to healthy controls (HC). Similarly, a recent fMRI study in PBD probing voluntary behavioral inhibition showed decreased activation in right VLPFC and bilateral striatum compared to HC, implicating fronto-striatal dysfunction (22). In contrast, it appears that the fronto-limbic circuitry supporting affect regulation is impaired in PBD (23–25).

To date, no one has specifically compared WM fiber tracts in ADHD and PBD. This is potentially important, as the alteration in reciprocal pathways from brainstem to neocortex could contribute to neural circuitry dysfunction in these disorders. This might include noradrenergic pathways from the locus ceruleus in brain stem and dopaminergic pathways from midbrain tegmentum and serotonergic projections from the dorsal raphe nucleus (26–30). While we know that regulatory monoamine systems are altered in both PBD and ADHD, it is not clear whether there is a specific disturbance in cortical terminal fields or whether there are structural alterations in WM pathways that project from brainstem nuclei to neocortex.

Diffusion Tensor Imaging (DTI) is a magnetic resonance imaging technique that can be used to infer the architecture of WM fiber tracts by characterizing the orientational dependence of

the diffusion process of water molecules (31). Typically, the information is obtained through two parameters: fractional anisotropy (FA), which describes the directional preference of diffusion processes, and the apparent diffusion coefficient (ADC) or mean diffusivity (MD), which represent the average diffusion rate among different diffusion directions under a Gaussian distribution (32). Preliminary studies in BD have indicated a decrease in FA in adolescents and adults (33,34), asymmetric decrease and increase (35) or an increase (36) in adults, and an increase in ADC in adults (34) in the prefrontal regions, corpus callosum, and thalamic and occipital radiations. One study in ADHD reported decreased FA values in right premotor cortex, in the anterior limb of the internal capsule and left middle cerebellar peduncle, cerebellum and parieto-occipital areas (37). In these preliminary studies, two methods were followed. In the first set of studies, ROIs in WM were chosen that were adjacent to GM ROIs in the orbitofrontal cortex, superior frontal gyrus, middle frontal gyrus, corpus callosum and posterior cortical regions (33,34,36). In contrast, whole-brain analyses using tract-based spatial statistics (TBSS) has been employed by others (35,38). In the current study, in contrast to selecting ROIs based on their proximity to GM regions of interest or the TBSS method that does not take into account the overlapping fiber tracts rendering it difficult to identify abnormalities in specific pathways (39), we examined the integrity of well defined WM fiber tracts. We used orientation-coded FA maps to identify individual fiber tracts of interest (40–42). We previously examined these parameters in PBD (n=13) and HC (n=13) in anterior corona radiata (ACR: prefrontal-bulbar tract) and inferior longitudinal fasciculus (ILF: frontotemporo-occipital tract). We showed decreased FA and increased ADC in both the ACR and ILF in PBD, relative to HC (41,42).

Having established feasibility and methodology, the current study investigated WM integrity in PBD and ADHD using two conventional DTI parameters: FA and ADC, and a new DTI metric, the regional fiber coherence index (r-FCI) that evaluates the degree of coherence in a given fiber tract (43). Our main hypothesis was that the FA and the fiber coherence of the WM fiber tracts extending between frontal cortex and brainstem are involved in ADHD and PBD based on previous findings of fMRI studies (22–25,44) and neurochemical studies of neocortex and brainstem (26–30). As there are variable reports of ADC changes in bipolar disorder with increase (34) or no change (33), and an increase in ADHD studies (37), we also explored whether ADC is affected in either of these illnesses.

METHODS

Subjects

All subjects (n=41) in this study were recruited from the University of Illinois at Chicago child psychiatry outpatient clinic as well as the surrounding community under an approved IRB protocol. Informed consent was obtained from at least one parent, and assent was obtained from all subjects. MRI studies were performed on PBD and ADHD patients and age, gender, and IQ-matched HC (Table 1). Images from conventional MRI scans (T1- and T2-weighted imaging without contrast; see below for details) were examined by a board-certified neuroradiologist to exclude any anatomical abnormalities, which served as an exclusion criterion. Each child in the study and the parent or legal guardian were interviewed using the Washington University Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; 45). Current and lifetime DSM-IV (Diagnostic and Statistical Manual-IV; 46) diagnosis was made based on a consensus decision from information gained from independent clinical interview, other available clinical data, and ratings on the WASH-U-KSADS. The PBD patients had a history of bipolar type I disorder. An additional Axis I diagnosis was an exclusion criterion for both the PBD and the ADHD subjects to avoid confounds. All subjects were right handed. All PBD patients were euthymic for at least 3 months, not having met DSM-IV criteria for major depression, dysthymia, mania, or hypomania. The PBD patients were excluded if

they had a history of ADHD prior to the onset of PBD or if the onset of attentional symptoms was prior to 7 years of age. By choice of the patient and the parents and with informed consent, patients were recruited who were free from psychotropic medications for at least seven days prior to the MRI scan, with the exception of stimulants that were allowed until 36 hours prior to the scan. This was done to minimize potential drug effects on neural chemistry or water content that could affect DTI measures. Medication dosages were reduced gradually over a three-week period prior to the scanning. However, three PBD patients showed some worsening in clinical symptoms on withdrawing medication. This resulted in the mean Young Mania Rating Scale (YMRS; 47) score of 13.4 (Table 1), marginally above the cut off score of 12 that is considered clinically significant for hypomania. We put them back on medication for ethical reasons and in accordance with the IRB approved study plans, but were able to scan each of these three PBD patients. All PBD patients were previously on mood stabilizers and/or second generation antipsychotics, with (on history, stimulants were given as a symptomatic treatment for inattention at school) or without stimulants among the PBD group; and stimulants in case of ADHD group. None of the patients were on aripiprazole or fluoxetine that would have required greater than the three week period to washout the metabolites.

The HC were also interviewed using WASH-U-KSADS to ensure the absence of any DSM IV Axis I diagnoses. Exclusion criteria for both patient groups and the HC included history of head trauma with loss of consciousness for more than 10 minutes, neurological symptoms, speech or hearing difficulties, an IQ less than 70, substance use disorder, and any contraindications to MRI scans, such as metal implants, retractors or braces, and claustrophobia.

Image Acquisition

All participants underwent MRI scans performed on a 3.0 Tesla GE Signa HDx scanner (General Electric Health Care, Waukesha, Wisconsin) with a quadrature head coil. The MRI protocol included 3D T1-weighted (T1W) imaging using a fast spoiled gradient echo sequence (TR/TE = 25/3.0ms, flip angle = 40°), 2D axial multi-slice T2-weighted (T2W) imaging using fast spin echo (TR/TE = 4000/80 ms), and 2D axial multi-slice DTI scan using a customized single-shot echo planar imaging (EPI) sequence with additional eddy current correction capabilities (48). The key data acquisition parameters for the DTI scan were TR = 5200ms, TE = 81.3ms, FOV = 22cm, slice thickness = 5mm, slice gap = 1mm, number of slice = 20, k-space matrix = 132×132, imaging matrix = 256×256, number of diffusion gradient directions = 27, b = 0, and 750 s/mm², number of averages = 2, and the total scan time = 5.03min.

Data Processing

The diffusion-weighted images were processed using customized software (Diffusion Imaging Visualization Environment, or DIVE) developed using IDL (ITT Visual Information Solutions, Boulder, Colorado). The axial diffusion-weighted images at a given location were first aligned to remove gross distortion. The three diffusion eigenvalues and the principle diffusion eigenvector were then computed on a pixel-by-pixel basis using a singular value decomposition algorithm (49). The eigenvalues were used to calculate the FA and ADC (i.e., mean diffusivity), while the principle eigenvector was used to obtain the r-FCI in the selected fiber tracts (43).

Color Coding

The direction of the eigenvector associated with the largest eigenvalue is color coded in symmetrical manner with respect to all color axes across all the selected fiber tracts. Rotation and tilt angle of the head was considered when defining the color coordinate system, i.e. the color axes are aligned with the patient anatomy (green = Anterior-Posterior running parallel to the inter-hemispheric gap, red= Left-Right, blue = Head-Foot). Further, image brightness

was modulated with the degree of anisotropy. Such color coded FA maps allowed differentiation between various fiber tracts for quantitative analysis.

WM Tract Selection and ROI Analyses

The fibers of interest were first identified in an atlas of fiber tracts (40). The identified fibers were then mapped onto the FA images for each subject by a neuroradiologist who had no knowledge of information about subjects' psychiatric history. To minimize the impact of partial volume effects, we concentrated on relatively large fiber tracts (>4mm) that were clearly identifiable on at least three slices. The following fibers were selected: anterior corona radiata/ACR, anterior limb of the internal capsule (ALIC), superior region of the internal capsule (SRI), posterior limb of the internal capsule (PLIC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus/ILF, cingulum (CG), and splenium (SP). Within each selected fiber tract, a minimum of six ROIs (Figure 1) were identified bilaterally with the consensus of a radiologist. To avoid regions of crossing or branching fibers, all ROIs were selected based on the color-coded FA maps (Figure 1), instead of the grey-scale FA images. For each fiber, the ROIs were chosen at a known distance from an easily identifiable anatomic landmark by the radiologist. For example, the ROIs of ACR were determined at 6, 14, and 22mm from the point where the red color (i.e., the genu) turned to green in the color-coded FA map. The ROIs in the SRI were equally spaced along the tract with a distance of ~1cm on each side. The ROIs in the SP were also equally spaced with ~4mm gap and centered about the midline bilaterally. The analyses were first carried out by a neuroradiologist who was blind to the group identity (SY). ROIs were independently retraced by another neuroanatomist to estimate the test-retest reliability, which overall was 0.98. The size of each ROI typically consisted of 8 to 16 pixels.

Statistical Analyses

DTI data were analyzed using repeated measures ANOVAs for each measure (FA, ADC, and r-FCI) and Region). Group (PBD, ADHD, and HC) was the between-subjects factor, and each region (ACR, ALIC, SRI, SL, PLIC, SLF, IFO/ILF, and CG) was the within-subjects factor. When a significant group effect was found within region in step down analyses, we conducted post-hoc pair-wise group comparisons to clarify the effect.

RESULTS

Demographic and Clinical Data

Demographic and clinical data are summarized in Table 1. The groups did not differ based on mean age or IQ. Group differences were significant on the YMRS and the Child Depression Rating Scale-Revised (CDRS-R; 50) scores, with the PBD group having higher scores on the affective symptom scales than ADHD and HC subjects. Although PBD patients were euthymic for at least 3 months at the time of consent, three subjects showed worsening in clinical symptoms after withdrawing medication. This resulted in the mean YMRS score of 13.4 (Table 1), marginally above the cut off score of 12 for hypomania/mania. These three patients had their treatment resumed, but were still able to be scanned. Mean IQ was 103 ± 15.4 with no significant group differences ($p > .05$). We attempted to also match the groups based on gender as well, but they had uneven gender representation in our final samples. The percent of males was higher in the ADHD (92%; $n=12$) and the PBD groups (77%; $n=10$) compared to HC (40%; $n=6$) ($p < .01$). Therefore, we controlled for gender difference throughout the analyses. With regards to race, BD group had 77% Caucasian, 15% African American, and 8% Hispanic patients; ADHD group had 54% African American, 38% Caucasian, and 8% Hispanic patients; and HC had 53% Caucasian, 40% Hispanic and 7% Asian youths.

DTI Data

FA Measurements—FA was reduced in ACR in both the PBD group and the ADHD group compared to the HC group ($F=7.04$, $df=2,38$, $p<.001$). FA was also significantly low in ALIC ($F=4.14$, $df=2,38$, $p<.01$) and SRI ($F=4.10$, $df=2,38$, $p<.05$) in ADHD group compared to the PBD group and the HC group, with no significant group differences between PBD and HC. There were no significant differences in the FA values across the three groups in PLIC ($F=.14$, $df=2,38$, $p=.15$), SLF ($F=.42$, $df=2,38$, $p=.43$), ILF ($F=2.14$, $df=2,38$, $p=.13$), CG ($F=.49$, $df=2,38$, $p=.61$) and SP ($F=2.49$, $df=2,38$, $p<.09$) (see Table 2).

ADC Measurements—In ADHD group, ADC was significantly higher than PBD and HC across seven WM tracts: ACR ($F=8.7$, $df=2,38$, $p<.001$), ALIC ($F=11.2$, $df=2,38$, $p<.001$), SRI ($F=10.7$, $df=2,38$, $p<.001$), PLIC ($F=9.5$, $df=2,38$, $p<.001$), SLF ($F=9.5$, $df=2,38$, $p<.001$), ILF ($F=7.9$, $df=2,38$, $p<.001$), and CG ($F=6.5$, $df=2,38$, $p<.01$). There were no significant group differences in ADC between the PBD and HC in these seven tracts. The ADC was significantly greater in SP in PBD and ADHD when compared to HC ($F=7.4$, $df=2,38$, $p<.01$) (see Table 2).

r-FCI Measurements—The r-FCI was reduced in SP ($F=3.7$, $df=2,38$, $p<.05$) in both the PBD group and the ADHD group compared to the HC group. The r-FCI was also significantly lower in ALIC ($F=5.5$, $df=2,38$, $p<.01$) and SRI ($F=7.2$, $df=2,38$, $p<.01$) in ADHD group compared to the PBD group and the HC group, with no significant group differences between PBD and HC. There were no significant differences in the r-FCI values across the three groups in ACR, ($F=2.8$, $df=2,38$, $p=.07$), PLIC ($F=3.01$, $df=2,38$, $p=.06$), SLF ($F=.04$, $df=2,38$, $p=.96$), ILF ($F=.41$, $df=2,38$, $p=.66$), and CG ($F=1.3$, $df=2,38$, $p=.29$) (see Table 2).

DISCUSSION

To our knowledge, this is the first study to employ DTI to compare individual color-coded WM tracts in PBD, ADHD and HC, and to utilize the new DTI parameter -r-FCI to study these groups. Our central results indicate that FA is significantly lower in the ACR, the cortical part of the cortico-tectal WM fibers that project broadly to prefrontal regions that include both VLPFC and DLPFC, both in PBD group and ADHD group relative to HC. Further, the ADHD group, relative to the PBD group and HC, showed significantly lower FA and r-FCI in WM fibers of the internal capsule that project between neocortex and brainstem i.e., the SRI and the ALIC. Also in ADHD, relative to HC and PBD, ADC was significantly higher in all eight WM tracts. In PBD patients, ADC was increased only in the splenium. Therefore, microstructural changes in WM are wide spread in ADHD suggesting extensive developmental dysmaturation in ADHD, while they are limited to prefrontal ACR and the posterior part of the cingulum or SP in PBD.

WM Tract Abnormalities in ADHD vs PBD

WM tract abnormalities must be interpreted with two main caveats. First, precise terminal fields in grey matter of the ascending ‘neuromodulatory’ chemical neurotransmitter systems, notably the catecholamine (dopamine and noradrenaline) and the indoleamine serotonin systems can not be ascertained in human clinical neuroimaging. Second, it is possible that there are important WM alterations outside the eight well-defined WM tracts that we measured. Therefore, while our contributions are a significant step forward in this area, investigations of the integrity of other complex WM pathways are needed.

One can postulate that ACR involvement with decreased FA, similar to that seen in other DTI studies in adult BD (33–36) and ADHD (37), may contribute to prefrontal GM dysfunction associated with inattention common to both these disorders (2–5,16–22), and affect modulation

disturbances central to PBD (23–25). The ACR is, indeed, a fiber pathway that contains both descending and ascending axons that carries important projections between frontal cortex and the brainstem. It is associated with the cortico-pontine, cortico-bulbar and spinal tracts, and targets basal ganglia along these pathways (51,52). The alteration of connectivity provided by ACR fibers between brainstem and neocortex may contribute to the fronto-striatal GM dysfunctions observed in both PBD and ADHD.

The fibers of the internal capsule that (36) tread along the basal ganglia and share the same blood supply via lenticulostriate branches of the middle cerebral artery include the SRI, ALIC and PLIC. These fibers and the arteries that provide their blood supply are prone to minor injuries in infancy with ischemic changes (53). Whether ADHD is caused by acquired ischemic changes or genetic factors, striatal regions are known to be involved. Fronto-striatal systems including VLPFC and caudate have been shown to be functionally impaired on probing motor inhibition and attention in ADHD with fMRI (15–21). As mentioned above, WM fibers are impaired with low FA, r-FCI, and high ADC in ACR, SRI and ALIC fibers impaired in PBD. These WM fibers of the internal capsule that funnel into ALIC contains the anterior thalamic peduncle with distinct connections between PFC, cingulate gyrus and thalamic nuclei (54, 55), and extensive pathways between striatum and thalamic nuclei (56). Indeed, lesion studies of striatum in humans have demonstrated cognitive syndrome (57) with impaired WM connectivity between cortico-subcortical regions (54,58). We did not find any FA or r-FCI abnormalities in the WM tracts of the internal capsule in PBD relative to ADHD or HC as we had predicted. This absence of WM abnormalities in PBD may be due to several factors. First, it is possible that functional pathology in cortical target fields may be relatively limited to GM. Second, this alteration may progress with illness progression and WM tract abnormalities may not yet be evident in PBD as have been reported in adult BD (35,36). Third, our sample size may be underpowered for detecting modest differences. Finally, the relatively low spatial resolution employed in this study may impose a further limitation in detecting subtle diffusion parameter changes in WM fiber tracts.

Pattern of Pervasive Impairment in ADC in WM Tracts in ADHD vs PBD

The interpretation of ADC changes is currently debated in relation to an influx of new knowledge on the mechanics of water diffusion through complex media such as the brain tissue. Alteration in the diffusion of water molecules is thought to depend on changes in cellular volume, extracellular space, cell membrane, intra axonal space, extra axonal space, osmotic balance between intra and extra-cellular spaces, transporters such as specific aquaporin channels, and viscosity in the intracellular space (59). Irrespective of the exact mechanism, the increased ADC in ACR, SRI, ALIC, PLIC, SLF, ILF and CG in the ADHD group as compared to that in the PBD and HC groups indicates that there are microstructural changes at the cellular level that result in reduced diffusion restriction in ADHD in several WM tracts. For several of these tracts such as SLF (that spans across frontotemporal and parietal cortex; (60), ILF (that runs between occipital and anterior temporal lobes; (61), and CG (that has long fibers with connectivity to frontal, mesial temporal and striatal structures and shorter fibers to the adjacent portions of the cingulate cortex; (62–64), DTI-MRI allows precise definition of only the stem portion of each fiber pathway. The origin and termination of these WM tracts are inferred from non-human primate tract tracing studies. However, the current findings suggest two possibilities. The widespread findings in ADHD may indicate extensive and widespread involvement of WM tracts serving attention and motor inhibition. This might parallel the common occurrence of attentional problems in acquired or congenital brain disorders (65, 66). Differences in the age of the patients and age of onset of the disorder may also be relevant considerations for the differences between ADHD and PBD. The greater involvement of WM pathway dysmaturation might be associated with the earlier onset of ADHD before age 7. Alternatively, as the duration of illness was twice as long in ADHD patients compared to PBD

patients, it is possible that illness progression effects are more pronounced in ADHD, resulting in the group differences. Future longitudinal studies are needed to shed light on potential maturational and illness progression effects on WM tracts in these disorders.

In the case of SP, both r-FCI and ADC were abnormal in PBD and ADHD. This posterior portion of the corpus callosum that provides interhemispheric interconnection of the temporal, parietal and occipital cortices (67) may be involved in integrative aspects of attentional and perceptual processes. Macrostructural abnormality i.e., significant decrease in circularity of splenium, was previously documented in bipolar adolescents relative to HC (68), adjacent to which the fronto-temporo-parietal abnormalities of grey regions were found (69). The WM abnormality in SP observed in the present study may contribute to dysfunction in the posterior face processing circuit in PBD that has been reported in fMRI studies (41).

What is evident from the pattern of the results from this study is that the WM abnormalities appear more pervasive in ADHD. While disturbances were evident in PBD, there was no single WM abnormality that was present only in PBD. These results need to be interpreted with caution as the findings need to be replicated in larger samples and maturational and disease progression effects need to be explored in longitudinal studies. Although there were gender differences between groups in this study, analyses were controlled for gender differences. This sample of unmedicated and IQ-matched ADHD and PBD patients and HC provides a rare and unique set of findings, albeit preliminary, and may be of considerable pathophysiological significance.

CONCLUSION

The decreased FA in the ACR and the r-FCI in the SP suggest impaired density, myelination or fiber coherence of WM pathways that connect frontal cortex with brainstem and also fibers providing interhemispheric connections for posterior cortical regions in PBD and ADHD. Further, ADC increases across multiple cortico-cortical and cortico-bulbar WM tracts in ADHD indicates extensive microstructural abnormalities in this disorder, relative to both PBD and HC. This may represent maturational delay and at least relative to PBD, it appears to be an abnormality that is specific to ADHD.

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Figure 1.

DTI images illustrating the eight White Matter (WM) tracts measured in this study. Anterior corona radiata (ACR) - WM tract extending from dorsolateral and ventrolateral prefrontal cortex primarily to prepectum. WM fibers of the internal capsule including: Anterior limb of the internal capsule (ALIC), Superior region of the internal capsule (SRI) and Posterior limb of the internal capsule (PLIC); Superior longitudinal fasciculus II (SLF II) which connects the PFC and the caudal inferior parietal lobule; Inferior longitudinal fasciculus (ILF) comprised of U-shaped fibers connecting extrastriate visual association areas and temporal regions involved in transferring visual signals to anterior temporal regions and also including projections from amygdala to early visual areas; Cingulum bundle (CG) that includes WM fibers that connect to prefrontal cortex, anterior cingulate cortex, thalamus and somatosensory regions; Splenium (SP) including posterior bulb of the corpus callosum that joins the posterior cortical regions across the cerebral hemispheres. For all regions, with the exception of SP, the ADHD group exhibited significantly greater values than the other two groups, which did not differ from each other. For SP only, the ADHD and PBD groups did not differ from each other, and exhibited greater values than HC. * $p < 0.001$; ** $p < 0.001$.

Table 1

Demographic and Clinical Characteristics for PBD, ADHD and HC

	PBD (n=13)	ADHD (n=13)	HC (n=15)	F (2,38), <i>p</i>
	Mean(SD)	Mean(SD)	Mean(SD)	
Variable				
Age in Years	14.8 (2.5)	13.4 (3.0)	13.7 (2.7)	.90,.41
Estimated IQ [§]	101.2 (12.3)	94.0 (13.7)	113.7 (13.5)	1.0,.17
YMRS	13.4 (9.9)	5.9 (4.6)	0.5 (1.4)	15.09, <.001 PBD>ADHD=HC
CDRS-R	32.1 (14.9)	19.7 (3.4)	18.6 (2.3)	9.92, <.001 PBD>ADHD=HC
Mean Duration of Illness in Years	7 (2.2)	13 (1.3)	-	18.04, <.001 ADHD>PBD

[§]Estimated with Wechsler Abbreviated Scale of Intelligence (WASI; Matrix Reasoning and Vocabulary Subtests); YMRS = Young Mania Rating Scale; CDRS-R=Child Depression Rating Scale-Revised; PBD=Pediatric Bipolar Disorder; HC = Healthy Control; ADHD=Attention Deficit Hyperactivity Disorder. Note: Age of onset of ADHD is difficult to characterize as parents often reported difficulties based on recall very early in life.

Table 2
Differences in DTI parameters between PBD, ADHD and HC

DTI Measure and Region	PBD(n=13)	HC(n=15)	ADHD(n=13)	Analysis
	Mean (SD)	Mean (SD)	Mean (SD)	F (2,38), p
FA				
ACR	0.48 (.46)	0.54 (.05)	0.50 (.02)	7.04, <.001 ADHD=PBD<HC
ALIC	0.578 (.03)	0.58 (.03)	0.54 (.07)	4.14, <.01 ADHD<PBD=HC
SRI	0.506 (.05)	0.49 (.03)	0.45 (.05)	4.10, <.05 ADHD<PBD=HC
SP	0.782 (.07)	0.82 (.03)	0.78 (.04)	2.49, .09 ADHD=PBD=HC
PLIC	0.685 (.02)	0.69 (.04)	0.66 (.03)	0.14, .15 ADHD=PBD=HC
SLF	0.518 (.08)	0.59 (.06)	0.50 (.06)	0.42, .43 ADHD=PBD=HC
ILF	0.554 (.05)	0.59 (.06)	0.54 (.07)	2.14, .13 ADHD=PBD=HC
CG	0.483 (.07)	0.50 (.06)	0.50 (.04)	0.49, .61 ADHD=PBD=HC
ADC (10⁻³mm²/s)				
ACR	0.750 (.07)	0.73 (.06)	0.83 (.07)	8.74, <.001 ADHD>PBD=HC
ALIC	0.697 (.05)	0.68 (.04)	0.76 (.07)	11.23, <.001 ADHD>PBD=HC
SRI	0.685 (.04)	0.67 (.03)	0.75 (.07)	10.66, <.001 ADHD>PBD=HC
SP	0.767 (.09)	0.70 (.02)	0.80 (.08)	7.38, <.01 ADHD=PBD>HC
PLIC	0.674 (.05)	0.67 (.02)	0.75 (.08)	9.52, <.001 ADHD>PBD=HC
SLF	0.708 (.05)	0.67 (.02)	0.76 (.08)	9.46, <.001 ADHD>PBD=HC
ILF	0.782 (.06)	0.74 (.05)	0.83 (.07)	7.94, <.001 ADHD>PBD=HC
CG	0.712 (.08)	0.69 (.04)	0.78 (.08)	6.51, <.01 ADHD>PBD=HC
r-FCI				
ACR	0.991 (.01)	0.99 (.00)	0.99 (.00)	2.82, .07 ADHD=PBD<HC
ALIC	0.998 (.00)	0.10 (.00)	0.10 (.00)	5.45, <.01 ADHD<PBD=HC
SRI	0.997 (.00)	0.10 (.00)	0.10 (.00)	7.2, <.01 ADHD<PBD=HC

DTI Measure and Region	PBD(n=13)	HC(n=15)	ADHD(n=13)	Analysis
	Mean (SD)	Mean (SD)	Mean (SD)	F (2,38), <i>p</i>
SP	0.999 (.00)	0.10 (.00)	0.10 (.00)	3.68, <.05 ADHD=PBD<HC
PLIC	0.997 (.00)	0.10 (.00)	0.10 (.00)	3.01, .06 ADHD=PBD=HC
SLF	0.994 (.00)	0.99 (.004)	0.10 (.00)	0.04, .96 ADHD=PBD=HC
ILF	0.995 (.00)	0.10 (.003)	0.10 (.01)	0.41, .66 ADHD=PBD=HC
CG	0.994 (.01)	0.10 (.003)	0.10 (0.002)	1.28, .29 ADHD=PBD=HC

DTI=Diffusion Tensor Imaging; PBD=Pediatric Bipolar Disorder; ADHD=Attention Deficit Hyperactivity Disorder; HC=Healthy Controls; FA=Fractional Anisotropy; ADC=Apparent Diffusion Co-efficient; r-FCI= Regional Fiber Coherence Index; ACR=Anterior Corona Radiata; ALIC: Anterior Limb of the Internal Capsule; SRI=Superior Region of the Internal Capsule; PLIC=Posterior Limb of the Internal Capsule; SLF=Superior Longitudinal Fasciculus; ILF=Inferior Longitudinal Fasciculus; CG=Cingulate Gyrus; SP=Splenium.