HHS Public Access

Author manuscript

J Psychiatr Res. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

J Psychiatr Res. 2023 February ; 158: 71–80. doi:10.1016/j.jpsychires.2022.12.033.

Disrupted white matter microstructure correlates with impulsivity in children and adolescents with bipolar disorder

Tianjia Zhu[1,2,#], **Alessio Simonetti**[3,4,#], **Minhui Ouyang**[1,6], **Sherin Kurian**[4,5], **Johanna Saxena**[4,5], **Jair C. Soares**[7], **Kirti Saxena**[4,5,*], **Hao Huang**[1,6,*]

[1]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

[2]Department of Bioengineering, School of Engineering and Applied Science, University of Pennsylvania, Philadelphia, PA, USA.

[3]Department of Neuroscience, Section of Psychiatry, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy.

[4]Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA.

[5]Baylor College of Medicine-Texas Children's Hospital, Houston, TX, USA.

[6]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

[7]Department of Psychiatry, McGovern Medical School at UTHealth, Houston, TX, USA

Abstract

Altered white matter (WM) microstructure likely occurs in children with bipolar disorder (BD) with impulsivity representing one of the core features. However, altered WM microstructures and their age-related trendlines in children with BD and those at high-risk of developing BD, as well as correlations of WM microstructures with impulsivity, have been poorly investigated. In this study, diffusion MRI, cognitive, and impulsivity assessments were obtained from children/adolescents diagnosed with BD, offspring of individuals with BD (high-risk BD) and age-matched healthy controls. A novel atlas-based WM skeleton measurement approach was used to quantify WM microstructural integrity with all diffusion-tensor-imaging (DTI) metrics including fractional

[*]**Corresponding authors:** Hao Huang, Ph.D., 3401 Civic Center Blvd, Department of Radiology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, 19104, huangh6@chop.edu; Kirti Saxena, M.D., 8080 North Stadium Dr., Section of Child/Adolescent Psychiatry at Texas Children's Hospital, Department of Psychiatry, Baylor College of Medicine, Houston, TX, 77054, kxsaxen1@texaschildrens.org.

[#]These two authors shared the first authorship.

Author contribution statement

Hao Huang, Kirti Saxena designed the study; Tianjia Zhu, Alessio Simonetti, Minhui Ouyang, Sherin Kurian, Johanna Saxena, Jair C. Soares, Kirti Saxena, and Hao Huang performed research; Tianjia Zhu analyzed data; Tianjia Zhu, Alessio Simonetti, Minhui Ouyang and Hao Huang wrote the paper.

Conflict of Interest disclosure:

The authors declare no conflict of interest.

anisotropy, axial, mean and radial diffusivity to survey entire WM tracts and ameliorate partial volume effects. Among all DTI-derived metric measures, radial diffusivity quantifying WM myelination was found significantly higher primarily in corpus callosum and in the corona radiata in children with BD compared to controls. Distinguished from age-related progressively decreasing diffusivities and increasing fractional anisotropy in healthy controls, flattened age-related trendlines were found in BD group, and intermediate developmental rates were observed in high-risk group. Larger radial diffusivity in the corpus callosum and corona radiata significantly correlated with shorter response times to affective words that indicate higher impulsivity in the BD group, whereas no such correlation was found in the healthy control group. This work corroborates the progressive nature of pediatric BD and suggests that WM microstructural disruption involved in affective regulation and sensitive to impulsivity may serve as a biomarker of pediatric BD progression.

Keywords

Bipolar disorder; high risk; children; white matter microstructure; diffusion MRI; impulsivity

1. Introduction

Bipolar disorder (BD) is a devastating illness characterized by extreme mood swings, including emotional highs (mania) and lows (depression) (MacQueen et al., 2001; Quraishi and Frangou, 2002; Simonetti et al., 2019). Individuals with BD are usually accompanied by significant cognitive impairments, including psychomotor retardation, impaired executive function, declarative memory, visual memory, and attention (Sanches et al., 2015). Pediatric BD portends greater chronicity, comorbidity, a more progressive worsening course, and greater resistance to medication than adult-onset BD (Janiri et al., 2021). Symptoms of pediatric BD include chronic irritability, anger outbursts, increased energy, frequent mood swings, and impulsivity (Janiri et al., 2021). Impulsivity represents an early marker of bipolarity (e.g. Goldstein et al., 2005; Simonetti et al., 2021; Wessa et al., 2015), and is linked to other behavioral alterations in bipolar youth such as drug abuse, anger outburst, risky and self-harm behaviors (Najt et al., 2007). Impulsivity could be assessed with rating scales (Strasser et al., 2016), or through behavioral tasks such as Go/No-go paradigms (Torres et al. 2013). Other than behavioral manifestations, brain white matter (WM) abnormalities play an important role in the neurobiology of BD based on converging evidence from neuropathology, genetics, and neuroimaging (Mahon et al., 2010). Impulsivity has been well linked to WM microstructure in other brain disorders (e.g. Huber et al., 2021; Huang et al., 2020) and in healthy populations (e.g. Ikuta et al., 2018). However, there are only a few pediatric BD WM studies and little information about quantitative relationships between impulsivity and WM microstructural abnormalities in pediatric BD. Identifying the brain WM abnormalities in pediatric BD and their correlation with impulsivity may offer informative biomarkers for early intervention.

Diffusion tensor imaging (DTI) (Basser et al., 1994), one type of magntic resonance imaging (MRI), can effectively reveal brain WM microstructural changes by probing the diffusion of water molecules within fiber bundles. Despite that DTI-derived fractional anisotropy

(FA) (Beaulieu, 2002; Pierpaoli et al, 1996) has been most widely used to quantify WM microstructural integrity, other DTI-derived metrics including mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD) offer complementary WM microstructural properties. For example, RD changes have been considered to be more specifcally linked to WM myelin change (Ouyang et al., 2019a; Song et al., 2003;). DTI-based microstructural measurements have been indicative of the underlying neurodevelopment such as myelination and axonal growth (Dubois et al., 2008; Dubois et al., 2014; Jeon et al., 2015; Lebel et al., 2012, 2018; Yu et al., 2020) in typical brain development, as well as WM microstructural alteration in a wide range of pediatric brain disorders such as autism (e.g. Ouyang et al., 2016; Travers et al., 2012), schizophrenia (e. g. James et al., 2011; White et al., 2009), and BD (e.g. Cabeen et al., 2018; Pavuluri et al., 2009). In adult BD, DTI studies have also suggested microstructural alterations in several WM tracts such as the limbic tracts (Barysheva et al., 2013), the corona radiata (CR) and corpus callosum (CC) (Bauer et al., 2016; Bauer et al., 2015). Besides group comparisons, since affective symptoms in adult-onset BD have been linked to brain microstructural disruption (de Zwarte et al., 2014), it is reasonable to extend such link to pediatric BD. However, relationship of the disrupted WM microstructure and impulsivity, an early marker of pediatric BD, is not known. WM microstructure in the pediatric high-risk (HR) BD population has also been rarely studied. Limited literature showed reduced FA in superior longitudinal fasciculus (SLF) (Frazier et al., 2007) and altered WM microstructure in CC and temporal associative tracts (Versace et al., 2010). More comprehensive understanding of the WM microstructure alterations and age-related trendlines of pediatric HR BD group in comparisons to BD and healthy control (HC) group is then needed. Detecting the WM abnormalities in pediatric HR BD and BD and their correlation with impulsivity may offer biomarkers for early intervention of the disease.

We have developed a novel atlas-based WM skeleton measurement approach (Huang et al., 2012a,2012b, 2011; Ouyang et al., 2020, 2016). This method enabled data-driven survey of entire WM microstructure at the cluster and tract level while accounting for partial volume effects (Jeon et al., 2012; Smith et al., 2006) by measuring on the core of WM tracts with skeletonization procedure in tract-based spatial statistics (TBSS) and parcellating entire WM into tracts and tract groups (i.e., limbic, commissural, association, projection and brain stem tract groups) (Wakana et al., 2004) by transferring WM tract labels from a digital atlas (Mori et al., 2008) to subject image. With all major 50 WM tract labels from a digital atlas (Mori et al., 2008) transferred to subject data by registering all images to the atlas template, anatomical identification as well as microstructural measurements at the disrupted cluster and tract level are simultaneously available. This approach will be used to accurately measure the WM microstructural alterations, to characterize cross-sectional age-related tract-level changes of BD, HR BD and HC groups, as well as to identify behavioral correlates of the microstructural alterations.

In this study, we aimed to characterize whole brain WM abnormalities as well as age-related WM microstructural changes in pediatric BD and HR BD, and to identify sensitive imaging biomarkers that are significantly correlated with cognitive and behavior measures in individuals with BD. Diffusion MRI (dMRI) was acquired to map the whole brain WM microstructure in 18 pediatric BD, 9 offspring of BD (HR), and 22 controls. All major WM

tracts were surveyed with full tensor characterization including all four DTI-derived metrics FA, MD, AxD, and RD. Atlas-based quantification on whole-brain WM skeleton was conducted to alleviate partial volume effects and to attribute WM abnormalities to specific functional tracts. Correlations between WM microstructural abnormalities and cognitive and behavioral measures were also conducted.

2. Methods and Materials

2.1 Children with BD, bipolar offspring, and healthy control

This study was approved by the Baylor College of Medicine Institutional Review Board. 18 children and adolescents diagnosed with BD (Mean age: 12.1 ± 3.45 years, 7M/11F, BD type I/BD type II/BD-not otherwise specified: 12/0/6, Depressed/(Hypo) manic/Mixed/Euthymic: 1/4/5/8), 9 age-matched offspring (HR BD) (Mean age: 13.5 ± 2.92 years, 5M/4F), and 22 age-matched HC (Mean age: 12.0 ± 3.33 years, 10M/12F) were recruited from the child and adolescent outpatient psychiatric clinic at the Texas Children's Hospital in Houston. Bipolar offspring (i.e. HR BD, having a biological parent with BD) have not been diagnosed with BD and have no lifetime history of any psychiatric or neurological disorder. The exclusion criteria include schizophrenia, eating disorders, Attention-deficit/hyperactivity disorder without comorbid pediatric BD, anxiety disorders without comorbid pediatric BD, substance use disorder, intellectual disability, autism spectrum disorder, and severe neurological conditions. BD type I and BD type II were diagnosed through Diagnostic and Statistical Manual of Mental Disorders 5th Edition criteria; a diagnosis of BD-not otherwise specified was made per the Course and Outcome of Bipolar Youth research criteria (Axelson et al., 2006). Signed informed consent from a parent/legal guardian was obtained before initiating the study. Demographics of participants are summarized in Table 1.

2.2 Clinical assessments

All participants were assessed using: (i) the 7.0.1 version of the Mini International Neuropsychiatric Interview and the parent MINI-KID (Sheehan et al., 1998) to determine psychiatric diagnoses; (ii) the Wechsler Abbreviated Scale of Intelligence – II (WASI-II) (Wechsler et al., 1999) to determine age- and sex-corrected general intelligence (composite IQ score); (iii) the Children Depression Rating Scale-Revised (CDRS-R) (Mayes et al., 2010) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) to determine severity of depressive and manic symptoms at time of testing. Clinical characteristics of participants are also summarized in Table 1. YMRS and CDRS-R of two HR BD and two HC were not successfully recorded. To reveal potential group-level differences in clinical assessments among BD, HR BD, and HC, analysis of variance (ANOVA) tests was carried out for YMRS, CDRS-R, and WASI-II IQ scores. Post-hoc pair-wise t-tests were also carried out with Bonferroni correction to find pair-wise differences between groups.

2.3 Neuropsychological assessment

All participants went through Cambridge Neuropsychological Test Automated Battery (CANTAB) cognition tests (Robbins et al., 1994) to assess their cognitive functions. Impulsivity was assessed with the Affective Go/No-Go (AGN) test in CANTAB, in which

participants are required to respond to a “go” task, and to withhold a response when a “no-go” stimulus is shown. Outcome measures are response times (RT), i.e., a classically indexed measure of impulse dyscontrol and brain stability/instability (Kropotov, 2016), for positive (AGN-RT-positive) and negative (AGN-RT-negative) words. In the AGN task, RT of the participants in correct trials were recorded. One BD and four HC participants’ RT to both positive and negative stimuli, and one HC participant’s RT to negative stimuli were not successfully recorded. To reveal potential group-level differences in cognitive tests among BD, HR BD, and HC, ANOVA tests were carried out for cognitive tests related to impulsivity, specifically AGN RTs to both positive and negative stimuli. Post-hoc pair-wise t-tests were also carried out to find pair-wise differences between groups.

2.4 DTI data acquisition and image preprocessing

All MRI images were acquired on a 3T Philips Ingenia scanner at the University of Texas Health Science Center in Houston. Whole-brain dMRI were acquired using a spin echo-planar imaging protocol. Image acquisition parameters were as follows: repetition time=12400 ms, echo time=77 ms, slice thickness = 3mm without slice gap, imaging matrix= 128×128, slice number =44, in-plane imaging resolution = 2×2 mm^2. Diffusion weighting was encoded along 30 independent directions with b-value 1000 s/mm^2. The tensor fitting was conducted using DTIStudio (Jiang et al., 2006) to generate DTI-derived metrics. FA, RD, MD and AxD after affine transformation of diffusion weighted images to b0 image using the automatic image registration (AIR) function in DTIStudio (Jiang et al., 2006) to correct distortion caused by eddy current and head motion. DMRI data of 16 BD, 9 HR, and 22 HC were used for further analysis after discarding dMRI of two BD participants due to incomplete acquisition or severe motion artifacts.

2.5 Statistical analyses on WM skeleton

2.5.1 Atlas-based tract and tract group level quantification on WM skeleton—

The atlas-based labeling of WM skeleton is as follows. Briefly, after nonlinear registration to a single-subject template used in digital WM atlas (JHU ICBM-DTI-81) (Mori et al. 2008), all the FA images of three groups were averaged in this template space. The skeleton of the averaged FA map was generated with tract-based spatial statistics (TBSS) (Smith et al. 2006) of FSL software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/) to extract the core of the WM tracts and alleviate partial volume effects, similar to the procedures described in detail in our previous publications (Huang et al. 2011, 2012b; Yu et al., 2020). After each WM tract label from the JHU ICBM-DTI-81 atlas was transferred to the WM skeleton in the template space, each WM skeleton voxel was categorized into one tract and one tract group (Figure 1A–C) (Wakana et al. 2004). More details of the atlas-based WM microstructural quantification can be found in Supplementary material.

2.5 2 Full tensor-based voxel-wise statistical analysis on WM skeleton—

For full tensor characterization, non-FA metrics AxD, RD, and MD of all subjects were mapped to the template space using the same transformation as for FA images. Non-FA metrics were also projected onto the WM skeleton in JHU ICBM-DTI-81 space. Voxel-wise statistics across participants adjusted for gender and age were carried out on each voxel of the FA, AxD, RD, and MD skeleton using permutation-based non-parametric testing (RANDOMISE

– as implemented in FSL) to compare differences among three groups using ANOVA and to compare differences of BD vs HC, BD vs HR BD and HR BD vs HC. Threshold-free cluster enhancement (TFCE) (Smith et al., 2009) correction for multiple comparisons was applied. Contours of parcellated tracts from JHU ICBM-DTI-81 atlas was overlaid on WM skeleton. Significant clusters found with voxel-wise statistical analysis were automatically segmented into significant clusters of different WM tracts (Figure 1A–1C). To avoid false positive results due to noise, we only kept and reported significant clusters containing greater than 10 voxels with p value smaller than 0.05. Boxplots were generated with DTI metric measurements averaged across voxels in the clusters of each subject in each group (Figure 2). T-tests of these measurements were conducted between BD and HC with correction of false discovery rate (FDR).

To quantify WM microstructural developmental rates among BD, HC and HR groups, tract-wise skeletonized WM DTI metric (FA, MD, AxD and RD) measurements in all 50 WM tracts underwent linear regression with respect to age. To reveal age-group interactions among BD, HC, and HR groups, regression models underwent analysis of covariance (ANCOVA) where the DTI metric measurements of each tract were set as the dependent variable, with age, diagnosis group, and age-group interaction as predictors. ANCOVA p value less than 0.05 indicates developmental rates are significantly different among three groups. For those tracts with significantly different development rates among three groups, pair-wise t-tests were also conducted to find pair-wise differences of BD vs HR, BD vs HC, or HR vs HC.

2.6 Correlation between DTI measures and cognitive assessments

To examine relationship between WM microstructure and cognitive test results, skeletonized DTI-derived metric measurements in voxels with significant difference in each tract were linearly correlated to cognitive assessments from CANTAB. An FDR correction was used to correct the *p*-value for multiple comparisons.

3. Results

3.1 Demographics and clinical characteristics

The demographic and clinical characteristics for BD, HR, and HC are shown in Table 1. There was no significant difference in age, gender, race, or ethnicity among the three groups (Chi-squared test, p value greater than 0.1), while significant differences in clinical scores were found among three groups. Specifically, BD showed higher YMRS and CDRS-R scores. Both BD and HR exhibited significantly lower IQ score than HC, but no significant difference was observed between BD and HR. No significant difference in AGN RT were identified among three groups (Table 2).

3.2 Altered white matter microstructural properties of children and adolescents with bipolar disorder in commissural, association and projection tracts

Children and adolescents with BD exhibited significant changes only in RD measures in several WM tracts across the commissural, association, and projection tract groups (Figure 1, Figure 2, Supplemental table 1). Boxplots of RD measurements averaged in clusters

across WM tracts by tract groups were summarized in Figure 2. Clusters with increased RD in the commissural tract group were found in the body, genu, splenium of CC (BCC, GCC, and SCC) and left Tapetum (Tapetum-L) (Figure 1 and 2A). Three clusters with higher RD in the association tract group were located in the left external capsule (EC-L), left SLF, and left superior fronto-occipital fasciculus (SFO-L) (Figure 1 and 2B), and seven clusters in the projection tract groups were located in the bilateral anterior CR (ACR-L and ACR-R), left anterior limb of internal capsule (ALIC-L), left posterior CR (PCR-L), left posterior limb of internal capsule (PLIC-L), left posterior thalamic radiation (PTR-L), and left superior CR (SCR-L) (Figure 1 and 2C). The largest clusters with significant higher RD were found in the SCR-L and GCC tracts. Higher RD were also found in superficial WM (SWM) clusters, located in the superficial left superior parietal, precentral and postcentral WM (Figure 1C). No significant differences between HR and HC or between HR and BD were found in any DTI metric measure.

3.3 Atypical microstructural developmental trends in white matter of children and adolescents with bipolar disorder

With ANCOVA analysis, significant microstructural developmental differences among BD, HR and HC group (Figure 3 and Supplemental Table 2) were primarily found in projection tracts: ACR-R (p=0.037) with RD measure, ICP-R (p=0.015) and PLIC-R (p=0.044) with AxD measure, and ACR-L (p=0.041) and ACR-R (p=0.014) with FA measure. As shown in Figure 3, relatively flattened age-dependent trendlines of DTI metrics were observed in BD. Interesting, HR exhibited intermediate developmental rates (plotted in gray in Figure 3) between BD and HR groups. The p values of pair-wise comparisons of microstructures in the tracts with significant ANCOVA differences (before multiple comparison correction; not significant after correction) are also listed in Supplemental Table 2.

3.4 White matter microstructural alterations in children and adolescents with bipolar disorder correlate with impulsivity

We further examined the relationship between altered WM microstructure in children and adolescents with BD or HR and impulsivity. Shorter RT in AGN tasks indicates higher impulsivity. Since BD exhibited significant WM microstructural changes compared to HC in RD only with t tests while HR did not in any DTI-derived metric measurements (see section 3.2), correlations between RD and impulsivity were only conducted in BD. The RD values of BD group decreased significantly with RT in clusters across commissural, projection, and association tracts, whereas no association was found in HC group (Figures 4 and 5), suggesting that more severe myelin disruption in BD corresponds to higher impulsivity. The significant negative correlations held for both RT to AGN-positive and AGN-negative stimuli in BD. Specifically, significant correlations between RD and RT to AGN-positive stimuli were discovered in GCC ($r = -0.55$, FDR-corrected $p = 0.027$), SCC ($r = -0.56$, FDR-corrected $p = 0.024$), and Tapetum-L ($r = -0.55$, FDR-corrected $p = 0.034$) of the commissural tract group (Figure 4A), EC-L ($r = -0.62$, FDR-corrected $p = 0.013$) and SLF-L ($r = -0.53$, FDR-corrected $p = 0.043$) of the association tract group (Figure 4C), and ACR-L ($r = -0.59$, FDR-corrected $p = 0.016$) and PCR-L ($r = -0.52$, FDR-corrected $p = 0.036$) of the projection tract group (Figure 4B). Similarly, for RT to AGN-negative stimuli, the correlations are significant in Tapetum-L (Figure 5A, $r = -0.55$, FDR-corrected

$p = 0.034$), EC-L (Figure 5C, $r = -0.62$, FDR-corrected $p = 0.013$), and PCR-L (Figure 5B, $r = -0.60$, FDR-corrected $p = 0.017$). These findings between RTs in AGN tasks and RD demonstrate significant association between WM microstructural alterations and impulsivity in children and adolescents of BD.

4. Discussion

This study found widely altered WM microstructure in children and adolescents with BD using atlas-based WM skeleton measurement approach and revealed significant correlations between WM alterations and impulsivity. It sheds light on the WM microstructural alterations in the less studied pediatric BD and HR pediatric BD populations. Elevated RD in BD across several commissural, projection and association tracts suggests myelination disruption of WM regions and complements existing literature showing alterations in these WM tracts in BD. Different developmental rates of DTI metrics between BD and HC groups were found primarily in projection tracts, with intermediate developmental rates of HR BD identified in the same tracts. Flattened WM microstructural changes in BD and intermediate developmental rates in HR BD corroborates the neuro-progressive nature of BD. Consistent with functions of the altered WM tracts in impulse control, disrupted WM microstructure in these WM tracts was significantly correlated with impulsivity in BD. These WM alterations in pediatric BD sensitive to impulsivity may serve as biomarkers, potentially predicting impulsive behavior and setting the stage for early behavioral intervention.

4.1 Disrupted myelination in commissural, projection, and association tract groups and superficial white matter in bipolar disorder

Elevated RD was found widespread over the commissural, projection, and association tract groups in BD. Previous DTI studies in pediatric BD have consistently reported decreased FA in WM fibers (Barnea-Goraly et al., 2009; Gao et al.,2013; James et al., 2011; Pavuluri et al., 2009; Saxena et al., 2012). However, FA decreases can be contributed by both axonal injury and altered myelination. By contrast, RD can be directly associated with myelin disruption (Ouyang et al., 2019a; Song et al., 2003). The widespread myelin disruption characterized by elevated RD in our study may be due to decreased levels of oligodendrocytes in BD evidenced by previous optical dissector-based studies (Bellani et al., 2016; Uranova et al., 2004). In Figures 1 and 2, higher RD in the commissural tracts (e.g. BCC, GCC, SCC, Tapetum-L) is consistent with increased RD in CC in previous pediatric BD studies (Lagopoulos et al., 2013; Linke et al., 2020). Raised RD in projection tracts (e.g. ALIC-L, SCR-L, PCR-L, and PTR-L, and bilateral ACR) is either in line with previous pediatric BD studies (e.g. Lu et al., 2012) or observed in adult BD (Benedetti et al., 2011). Elevated RD in association tracts such as SLF also corroborates existing findings (Hu et al., 2020). Besides alterations in deep WM, alterations in SWM were consistent with abnormalities in superficial left superior parietal WM (Zhang et al., 2018) and superficial left precentral and postcentral WM (Ji et al., 2019) in adult BD.

Interestingly children and adolescents with BD showed altered developmental rates in several major projection tracts in Figure 3, while high-risk BD showed intermediate developmental rates in these tracts. Shown in Figure 3, the present study suggests the pattern

of higher initial WM integrity characterized by lower RD, higher AxD, and higher FA in BD reversed after around 10 years of age due to flattened age-related changes. Such gradual deviations of WM microstructure in pediatric BD from typical development trajectory may account for eventual significant differences in FA, AxD, and MD in adult BD (e.g., Barysheva et al., 2013; Bauer et al., 2016., 2015; Bellani et al., 2016). The intermediate developmental rates of HR BD between BD and HC groups suggest WM microstructural change rates may serve as early biomarker of the disease (Schneider et al., 2012) and may be linked to increased genetic susceptibility to BD (de Zwarte et al., 2014), resulting in lower WM integrity in adult BD.

4.2 Disrupted white matter microstructure correlates with impulsivity in bipolar disorder

We found the correlation between RD and impulsivity in the SCC, GCC, and Tapetum-L, in the EC-L and SLF-L, and in the ACR-L and PCR-L, in pediatric BD in Figures 4 and 5. This is consistent with a prior lesion study that found associations between impulsivity with injuries to the ACR-L, GCC, and SLF-L (McDonald et al., 2017). Notably, the ACR-L, GCC, and SLF-L tracts participate in several networks such as thalamo-limbic-cortical circuitry associated with impulse control (Karababa et al., 2015). Frontoparietal systems innervated by fibers of the PCR and the SCC are part of the frontoparietal network and the cingulo-opercular network, which support the flexible control of human goal-directed behavior (Cole et al., 2014). Impairments in fibers belonging to these affective networks may result in the inability to rapidly regulate behavior when emotionally or motivationally charged, potentially leading to impulsive reactions. Consistent with associations revealed by lesion studies (e.g., McDonald et al., 2017), previous DTI studies also revealed associations between WM microstructure and impulsivity in healthy populations as well as adult BD. For instance, BD patients with prior suicide attempts that indicate higher impulsivity showed decreased FA in the left orbital frontal WM compared to patients without any suicide attempts (Mahon et al., 2012). In healthy adolescents, reduced FA in the ACR was associated with higher impulsivity (Seghete et al., 2013). Our study did not replicate the latter finding. The discrepancy might be related to the task used in the study on HC, which did not include an affective cue. Impairment in systems described above is present for either positive or negative stimuli. Negative bias has been proposed as a trait marker of BD (Leppänen, J. M., & Hietanen), whereas positive bias has been recently related to the predisposition to mania (Simonetti et al., 2019), i.e. the core manifestation of BD type I subtype (Kotzalidis et al., 2017). Since most of the study participants have a diagnosis of BD type I, the present findings might reflect the sample's diagnostic heterogeneity. To the best of our knowledge, we found correlations between WM microstructure disruption and impulsivity in children and adolescents with BD for the first time. Taken together, our findings elucidate the relationship between disrupted WM myelination and impulsivity and reveal that elevated RD may serve as a biomarker for impulsivity in pediatric BD.

4.3 Technical considerations and future directions

The novel atlas-based WM skeleton measurement approach applied in this study enhanced accuracy and enabled data-drive survey of entire WM microstructure at the cluster and tract level while accounting for partial volume effects. Characterization of all diffusion tensor-derived metrics including FA, MD, AxD and RD contributed to comprehensively

delineation of the microstructural alterations. Significant alterations and atypical age-related microstructural trendlines measured with RD are likely associated with myelin disruption in pediatric BD and atypical myelination process in BD and HR BD groups, respectively.

Several limitations need to be considered. Due to the limited sample size of the HR BD group (n=9), no significant differences were found with voxel-wise ANOVA analyses across three groups (BD, HR, HC).Future studies will benefit from larger sample sizes which may offer statistical power to reveal microstructural alterations not only in pairwise t-tests, but also in ANOVA analysis. Additionally, the cross-sectional developmental rate finding did not survive the multiple comparison correction due to the limited sample size of the HR group. Based on the cross-sectional finding on age-related WM maturational trendlines of BD, high-risk BD and HC groups, future longitudinal studies are warranted to characterize developmental trajectories of WM microstructure in these groups. Integrating the present study's assessment of impulsivity with data from different tasks, such as delay discounting tasks, and controlling the present result for possible confounding variables such as predominant polarity (Janiri et al 2020) and psychotropic medications (Sani et al., 2013) will be helpful for controlling these variables in WM microstructure analysis.. Future research focusing on examining GM microstructure in BD (Pan et al., 2021) in relation to impulsivity is warranted. More advanced dMRI analysis techniques such as diffusion kurtosis (Jensen et al., 2005; Ouyang et al., 2019b; Zhu et al, 2021), multiple tensors (Mishra et al., 2014) and neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) may reveal additional microstructural changes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The study was supported by grants from National Institutes of Health (R01MH092535, R01MH125333, R01MH129981, R01EB031284, R21MH123930 and P50HD105354) and John S. Dunn Foundation.

Data Availability Statement:

The data will be made available upon reasonable request.

References

Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M. 2006. Phenomenology of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry. 63:1139–48. doi: 10.1001/archpsyc.63.10.1139. [PubMed: 17015816]

Barnea-Goraly N, Chang KD, Karchemskiy A, Howe ME, & Reiss AL 2009. Limbic and corpus callosum aberrations in adolescents with bipolar disorder: a tract-based spatial statistics analysis. Biological psychiatry, 66(3), 238–244. doi: 10.1016/j.pscychresns.2015.02.007 [PubMed: 19389661]

Barysheva M, Jahanshad N, Foland-Ross L, Altshuler LL, & Thompson PM 2013. White matter microstructural abnormalities in bipolar disorder: a whole brain diffusion tensor imaging study. NeuroImage: clinical, 2, 558–568. doi: 10.1016/j.nicl.2013.03.016 [PubMed: 24179807]

Basser PJ, Mattiello J, & LeBihan D 1994. MR diffusion tensor spectroscopy and imaging. Biophysical journal, 66(1), 259–267. doi: 10.1016/S0006-3495(94)80775-1. [PubMed: 8130344]

Bauer IE, Ouyang A, Mwangi B, Sanches M, Zunta-Soares GB, Keefe RS, Huang H, & Soares JC 2015. Reduced white matter integrity and verbal fluency impairment in young adults with bipolar disorder: a diffusion tensor imaging study. Journal of psychiatric research, 62, 115–122. doi: 10.1016/j.jpsychires.2015.01.008 [PubMed: 25684152]

Bauer IE, Wu MJ, Meyer TD, Mwangi B, Ouyang A, Spiker D, Zunta-Soares GB, Huang H, & Soares JC 2016. The role of white matter in personality traits and affective processing in bipolar disorder. Journal of psychiatric research, 80, 64–72. doi: 10.1016/j.jpsychires.2016.06.003 [PubMed: 27302871]

Beaulieu C 2002. The basis of anisotropic water diffusion in the nervous system–a technical review. NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In Vivo, 15(7–8), 435–455. doi: 10.1002/nbm.782

Bellani M, Boschello F, Delvecchio G, Dusi N, Altamura CA, Ruggeri M, Ruggeri M, Brambilla P 2016. DTI and myelin plasticity in bipolar disorder: integrating neuroimaging and neuropathological findings. Frontiers in psychiatry, 7, 21. doi: 10.3389/fpsyt.2016.00021 [PubMed: 26973545]

Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, … & Brambilla P 2011. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. Biological psychiatry, 69(4), 309–317. doi: 10.1016/j.biopsych.2010.07.028. [PubMed: 20926068]

Cabeen RP, Laidlaw DH, Ruggieri A, & Dickstein DP 2018. Preliminary mapping of the structural effects of age in pediatric bipolar disorder with multimodal MR imaging. Psychiatry research. Neuroimaging, 273, 54–62. doi: 10.1016/j.pscychresns.2017.12.006 [PubMed: 29361347]

Cole MW, Repovš G, & Anticevic A 2014. The frontoparietal control system: a central role in mental health. The Neuroscientist, 20(6), 652–664. doi: 10.1177/1073858414525995 [PubMed: 24622818]

de Zwarte SM, Johnston JA, Cox Lippard ET, & Blumberg HP 2014. Frontotemporal White Matter in Adolescents with, and at-Risk for, Bipolar Disorder. Journal of clinical medicine, 3(1), 233–254. doi: 10.3390/jcm3010233 [PubMed: 26237259]

Dubois J, Dehaene-Lambertz G, Perrin M, Mangin JF, Cointepas Y, Duchesnay E, … & Hertz-Pannier L 2008. Asynchrony of the early maturation of white matter bundles in healthy infants: quantitative landmarks revealed noninvasively by diffusion tensor imaging. Human brain mapping, 29(1), 14–27. doi: 10.1002/hbm.20363 [PubMed: 17318834]

Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Hüppi PS, & Hertz-Pannier L 2014. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. Neuroscience, 276, 48–71. doi: 10.1016/j.neuroscience.2013.12.044. [PubMed: 24378955]

Frazier JA, Breeze JL, Papadimitriou G, Kennedy DN, Hodge SM, Moore CM, … & Makris N 2007. White matter abnormalities in children with and at risk for bipolar disorder. Bipolar disorders, 9(8), 799–809. doi: 10.1111/j.1399-5618.2007.00482.x. [PubMed: 18076529]

Gao W, Jiao Q, Qi R, Zhong Y, Lu D, Xiao Q, … & Su L 2013. Combined analyses of gray matter voxel-based morphometry and white matter tract-based spatial statistics in pediatric bipolar mania. Journal of affective disorders, 150(1), 70–76. doi: 10.1016/j.jad.2013.02.021 [PubMed: 23477846]

Goldstein TR, Birmaher B, Axelson D, Ryan ND, Strober MA, Gill MK, Valeri S, Chiappetta L, Leonard H, Hunt J and Bridge JA, 2005. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. Bipolar disorders, 7(6), 525–535. doi: 10.1111/j.1399-5618.2005.00263.x. [PubMed: 16403178]

Hu R, Stavish C, Leibenluft E, & Linke JO 2020. White matter microstructure in individuals with and at risk for bipolar disorder: evidence for an endophenotype from a voxel-based meta-analysis. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 5(12), 1104–1113. doi: 10.1016/j.bpsc.2020.06.007 [PubMed: 32839153]

Huang H, Fan X, Weiner M, Martin-Cook K, Xiao G, Davis J, Devous M, Rosenberg R, & Diaz-Arrastia R 2012a. Distinctive disruption patterns of white matter tracts in Alzheimer's disease with full diffusion tensor characterization. Neurobiology of aging, 33(9), 2029–2045. doi: 10.1016/j.neurobiolaging.2011.06.027 [PubMed: 21872362]

Huang H, Gundapuneedi T, & Rao U 2012b. White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 37(12), 2693–2701. doi: 10.1038/npp.2012.133 [PubMed: 22850736]

Huang H, Fan X, Williamson DE, & Rao U 2011. White matter changes in healthy adolescents at familial risk for unipolar depression: a diffusion tensor imaging study. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 36(3), 684–691. doi: 10.1038/npp.2010.199 [PubMed: 21085111]

Huang S, Yang W, Luo J, Yan C, & Liu J 2020. White matter abnormalities based on TBSS and its correlation with impulsivity behavior of methamphetamine addicts. Frontiers in psychiatry, 11, 452. doi: 10.3389/fpsyt.2020.00452 [PubMed: 32528325]

Huber RS, McGlade EC, Legarreta M, Subramaniam P, Renshaw PF, & Yurgelun-Todd DA 2021. Cingulate white matter volume and associated cognitive and behavioral impulsivity in Veterans with a history of suicide behavior. Journal of affective disorders, 281, 117–124. doi: 10.1016/j.jad.2020.11.126. [PubMed: 33316716]

Ikuta T, Del Arco A, & Karlsgodt KH 2018. White matter integrity in the fronto-striatal accumbofrontal tract predicts impulsivity. Brain imaging and behavior, 12(5), 1524–1528. doi: 10.1007/s11682-017-9820-x [PubMed: 29302916]

James A, Hough M, James S, Winmill L, Burge L, Nijhawan S, … & Zarei M 2011. Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). Schizophrenia research, 128(1–3), 91–97. doi: 10.1016/j.schres.2011.02.014. [PubMed: 21388791]

Janiri D, Conte E, De Luca I, Simone MV, Moccia L, Simonetti A, … & Sani G 2021. Not Only Mania or Depression: Mixed States/Mixed Features in Pediatric Bipolar Disorders. Brain Sciences, 11(4), 434. doi: 10.3390/brainsci11040434 [PubMed: 33805270]

Jeon T, Mishra V, Ouyang M, Chen M, & Huang H 2015. Synchronous changes of cortical thickness and corresponding white matter microstructure during brain development accessed by diffusion MRI tractography from parcellated cortex. Frontiers in neuroanatomy, 9, 158. doi: 10.3389/fnana.2015.00158 [PubMed: 26696839]

Jeon T, Mishra V, Uh J, Weiner M, Hatanpaa KJ, White CL III, … & Huang H 2012. Regional changes of cortical mean diffusivities with aging after correction of partial volume effects. Neuroimage, 62(3), 1705–1716. doi: 10.1016/j.neuroimage.2012.05.082 [PubMed: 22683383]

Jensen JH, Helpern JA, Ramani A, Lu H, & Kaczynski K 2005. Diffusional kurtosis imaging: the quantification of non - gaussian water diffusion by means of magnetic resonance imaging. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 53(6), 1432–1440. doi: 10.1002/mrm.20508.

Ji E, Guevara P, Guevara M, Grigis A, Labra N, Sarrazin S, … & Houenou J 2019. Increased and decreased superficial white matter structural connectivity in schizophrenia and bipolar disorder. Schizophrenia bulletin, 45(6), 1367–1378. doi: 10.1093/schbul/sbz015 [PubMed: 30953566]

Jiang H, Van Zijl PC, Kim J, Pearlson GD, & Mori S 2006. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. Computer methods and programs in biomedicine, 81(2), 106–116. doi: 10.1016/j.cmpb.2005.08.004. [PubMed: 16413083]

Karababa IF, Bayazıt H, Kılıçaslan N, Celik M, Cece H, Karakas E, & Selek S 2015. Microstructural changes of anterior corona radiata in bipolar depression. Psychiatry investigation, 12(3), 367. doi: 10.4306/pi.2015.12.3.367 [PubMed: 26207131]

Kotzalidis GD, Rapinesi C, Savoja V, Cuomo I, Simonetti A, Ambrosi E, Panaccione I, Gubbini S, De Rossi P, De Chiara L, Janiri D, Sani G, Koukopoulos AE, Manfredi G, Napoletano F, Caloro M, Pancheri L, Puzella A, Callovini G, Angeletti G, … Del Casale A 2017. Neurobiological Evidence for the Primacy of Mania Hypothesis. Current neuropharmacology, 15(3), 339–352. doi: 10.2174/1570159X14666160708231216. [PubMed: 28503105]

Kropotov JD, 2016. Functional Neuromarkers for Psychiatry: Applications for Diagnosis and Treatment. 1st ed. London, England: Academic Press.

Lagopoulos J, Hermens DF, Hatton SN, Tobias-Webb J, Griffiths K, Naismith SL, … & Hickie IB 2013. Microstructural white matter changes in the corpus callosum of young people with bipolar disorder: a diffusion tensor imaging study. PloS one, 8(3), e59108. doi: 10.1371/journal.pone.0059108 [PubMed: 23527101]

Lebel C, Gee M, Camicioli R, Wieler M, Martin W, & Beaulieu C 2012. Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage, 60(1), 340–352. doi: 10.1016/j.neuroimage.2011.11.094 n. [PubMed: 22178809]

Lebel C, & Deoni S 2018. The development of brain white matter microstructure. Neuroimage, 182, 207–218. doi: 10.1016/j.neuroimage.2017.12.097 [PubMed: 29305910]

Leppänen JM, & Hietanen JK 2004. Positive facial expressions are recognized faster than negative facial expressions, but why?. Psychological research, 69(1–2), 22–29. doi: 10.1007/s00426-003-0157-2 [PubMed: 14648224]

Linke JO, Stavish C, Adleman NE, Sarlls J, Towbin KE, Leibenluft E, & Brotman MA 2020. White matter microstructure in youth with and at risk for bipolar disorder. Bipolar disorders, 22(2), 163–173. doi: 10.1111/bdi.12885. Epub 2020 [PubMed: 31883419]

Lu LH, Zhou XJ, Fitzgerald J, Keedy SK, Reilly JL, Passarotti AM, … & Pavuluri M 2012. Microstructural abnormalities of white matter differentiate pediatric and adult-onset bipolar disorder. Bipolar disorders, 14(6), 597–606. doi: 10.1111/j.1399-5618.2012.01045.x [PubMed: 22882719]

MacQueen GM, Young LT, & Joffe RT 2001. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatrica Scandinavica, 103(3), 163–170. doi: 10.1034/j.1600-0447.2001.00059.x [PubMed: 11240572]

Mahon K, Burdick KE, & Szeszko PR 2010. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neuroscience & Biobehavioral Reviews, 34(4), doi: 533–554. 10.1016/j.neubiorev.2009.10.012 [PubMed: 19896972]

Mahon K, Burdick KE, Wu J, Ardekani BA, & Szeszko PR 2012. Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study. Bipolar disorders, 14(1), 80–89. doi: 10.1111/j.1399-5618.2012.00984.x. [PubMed: 22329475]

Mayes TL, Bernstein IH, Haley CL, Kennard BD, & Emslie GJ 2010. Psychometric properties of the Children's Depression Rating Scale-Revised in adolescents. Journal of child and adolescent psychopharmacology, 20(6), 513–516. doi: 10.1089/cap.2010.0063 [PubMed: 21186970]

McDonald V, Hauner KK, Chau A, Krueger F, & Grafman J 2017. Networks underlying trait impulsivity: evidence from voxel-based lesion-symptom mapping. Human brain mapping, 38(2), 656–665. doi: 10.1002/hbm.23406 [PubMed: 27667777]

Mishra V, Guo X, Delgado MR, & Huang H 2015. Toward tract-specific fractional anisotropy (TSFA) at crossing-fiber regions with clinical diffusion MRI. Magnetic resonance in medicine, 74(6), 1768–1779. doi: 10.1002/mrm.25548 [PubMed: 25447208]

Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl P, & Mazziotta J 2008. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. NeuroImage, 40(2), 570–582. doi: 10.1016/j.neuroimage.2007.12.035 [PubMed: 18255316]

Najt P, Perez J, Sanches M, Peluso MAM, Glahn D, & Soares JC 2007. Impulsivity and bipolar disorder. European neuropsychopharmacology, 17(5), 313–320. doi: 10.1016/j.euroneuro.2006.10.002. [PubMed: 17140772]

Ouyang M, Cheng H, Mishra V, Gong G, Mosconi MW, Sweeney J, Peng Y, & Huang H 2016. Atypical age-dependent effects of autism on white matter microstructure in children of 2–7 years. Human brain mapping, 37(2), 819–832. doi: 10.1002/hbm.23073 [PubMed: 26663516]

Ouyang M, Dubois J, Yu Q, Mukherjee P, & Huang H 2019a. Delineation of early brain development from fetuses to infants with diffusion MRI and beyond. Neuroimage, 185, 836–850.doi: 10.1016/j.neuroimage.2018.04.017 [PubMed: 29655938]

Ouyang M, Jeon T, Sotiras A, Peng Q, Mishra V, Halovanic C, … & Huang H 2019b. Differential cortical microstructural maturation in the preterm human brain with diffusion kurtosis and tensor imaging. Proceedings of the National Academy of Sciences, 116(10), 4681–4688. doi: 10.1073/pnas.1812156116.

Ouyang M, Peng Q, Jeon T, Heyne R, Chalak L, & Huang H 2020. Diffusion-MRI-based regional cortical microstructure at birth for predicting neurodevelopmental outcomes of 2-year-olds. Elife, 9, e58116. doi: 10.7554/eLife.58116 [PubMed: 33350380]

Pan N, Wang S, Zhao Y, Lai H, Qin K, Li J, … & Gong Q 2021. Brain gray matter structures associated with trait impulsivity: A systematic review and voxel-based meta-analysis. Human Brain Mapping, 42(7), 2214–2235. [PubMed: 33599347]

Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, … & Zhou XJ 2009. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Biological psychiatry, 65(7), 586–593. doi: 10.1016/j.biopsych.2008.10.015 [PubMed: 19027102]

Pierpaoli C, & Basser PJ 1996. Toward a quantitative assessment of diffusion anisotropy. Magnetic resonance in Medicine, 36(6), 893–906. doi: 10.1002/mrm.1910360612 [PubMed: 8946355]

Quraishi S, & Frangou S 2002. Neuropsychology of bipolar disorder: a review. Journal of affective disorders, 72(3), 209–226 doi: 10.1016/s0165-0327(02)00091-5 [PubMed: 12450638]

Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, & Rabbitt P 1994. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia and geriatric cognitive disorders, 5(5), 266–281. doi: 10.1159/000106735

Sanches M, Bauer IE, Galvez JF, Zunta-Soares GB, & Soares JC 2015. The management of cognitive impairment in bipolar disorder: current status and perspectives. American journal of therapeutics, 22(6), 477. doi: 10.1097/MJT.0000000000000120. [PubMed: 25383489]

Sani G, Kotzalidis GD, Vöhringer P, Pucci D, Simonetti A, Manfredi G, et al. , 2013. Effectiveness of short-term olanzapine in patients with bipolar I disorder, with or without comorbidity with substance use disorder. Journal of clinical psychopharmacology 33 (2), 231–235. doi:10.1097/JCP.0b013e318287019c. [PubMed: 23422396]

Saxena K, Tamm L, Walley A, Simmons A, Rollins N, Chia J, Soares JC, Emslie GJ, Fan X, & Huang H 2012. A preliminary investigation of corpus callosum and anterior commissure aberrations in aggressive youth with bipolar disorders. Journal of child and adolescent psychopharmacology, 22(2), 112–119. doi: 10.1089/cap.2011.0063 [PubMed: 22375854]

Schneider MR, DelBello MP, McNamara RK, Strakowski SM, & Adler CM 2012. Neuroprogression in bipolar disorder. Bipolar disorders, 14(4), 356–374. doi: 10.1111/j.1399-5618.2012.01024.x [PubMed: 22631620]

Seghete KLM, Herting MM, & Nagel BJ 2013. White matter microstructure correlates of inhibition and task-switching in adolescents. Brain research, 1527, 15–28. doi: 10.1016/j.brainres.2013.06.003. Epub 2013 Jun 28. [PubMed: 23811486]

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, … & Dunbar GC 1998. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of clinical psychiatry, 59(20), 22–33 doi: 10.1159/000106735.

Simonetti A, Lijffijt M, Kahlon RS, Gandy K, Arvind RP, Amin P, … & Saxena K 2019. Early and late cortical reactivity to passively viewed emotional faces in pediatric bipolar disorder. Journal of Affective Disorders, 253, 240–247. doi: 10.1016/j.jad.2019.04.076 [PubMed: 31060010]

Simonetti A, Kurian S, Saxena J, Verrico CD, Soares JC, Sani G and Saxena K, 2021. Cognitive correlates of impulsive aggression in youth with pediatric bipolar disorder and bipolar offspring. Journal of affective disorders, 287, pp. 387–396. doi: 10.1016/j.jad.2021.03.044. [PubMed: 33838473]

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, … & Behrens TE 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage, 31(4), 1487–1505. doi: 10.1016/j.neuroimage.2006.02.024. [PubMed: 16624579]

Smith SM, & Nichols TE 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage, 44(1), 83–98.doi: 10.1016/j.neuroimage.2008.03.061 [PubMed: 18501637]

Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, & Neufeld AH 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage, 20(3), 1714–1722. doi: 10.1016/j.neuroimage.2003.07.005 [PubMed: 14642481]

Strasser ES, Haffner P, Fiebig J, Quinlivan E, Adli M, & Stamm TJ 2016. Behavioral measures and self-report of impulsivity in bipolar disorder: no association between Stroop test and

Barratt Impulsiveness Scale. International journal of bipolar disorders, 4(1), 16. doi: 10.1186/s40345-016-0057-1 [PubMed: 27530736]

Torres A, Catena A, Megías A, Maldonado A, Cándido A, Verdejo-García A, & Perales JC 2013. Emotional and non-emotional pathways to impulsive behavior and addiction. Frontiers in human neuroscience, 7, 43. doi: 10.3389/fnhum.2013.00043 [PubMed: 23441001]

Travers BG, Adluru N, Ennis C, Tromp DP, Destiche D, Doran S, … & Alexander AL 2012. Diffusion tensor imaging in autism spectrum disorder: a review. Autism Research, 5(5), 289–313. doi: 10.1002/aur.1243. [PubMed: 22786754]

Uranova NA, Vostrikov VM, Orlovskaya DD, & Rachmanova VI 2004. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophrenia research, 67(2–3), 269–275. doi: 10.1016/S0920-9964(03)00181-6 [PubMed: 14984887]

Versace A, Ladouceur CD, Romero S, Birmaher B, Axelson DA, Kupfer DJ, & Phillips ML 2010. Altered development of white matter in youth at high familial risk for bipolar disorder: a diffusion tensor imaging study. Journal of the American Academy of Child & Adolescent Psychiatry, 49(12), 1249–1259. doi: 10.1016/j.jaac.2010.09.007. [PubMed: 21093774]

Wakana S, Jiang H, Nagae-Poetscher LM, Van Zijl PC, & Mori S 2004. Fiber tract–based atlas of human white matter anatomy. Radiology, 230(1), 77–87. doi: 10.1148/radiol.2301021640. [PubMed: 14645885]

Wechsler D 1999 Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation.

Wessa M, Kollmann B, Linke J, Schönfelder S, & Kanske P 2015. Increased impulsivity as a vulnerability marker for bipolar disorder: evidence from self-report and experimental measures in two high-risk populations. Journal of affective disorders, 178, 18–24. doi: 10.1016/j.jad.2015.02.018 [PubMed: 25770479]

White T, Schmidt M, & Karatekin C 2009. White matter ‘potholes’ in early-onset schizophrenia: a new approach to evaluate white matter microstructure using diffusion tensor imaging. Psychiatry Research: Neuroimaging, 174(2), 110–115. doi: 10.1016/j.pscychresns.2009.04.014.

Young RC, Biggs JT, Ziegler VE, & Meyer DA 1978. A rating scale for mania: reliability, validity and sensitivity. The British journal of psychiatry: the journal of mental science, 133, 429–435. doi:10.1192/bjp.133.5.429 [PubMed: 728692]

Yu Q, Peng Y, Kang H, Peng Q, Ouyang M, Slinger M, Hu D, Shou H, Fang F, & Huang H 2020. Differential White Matter Maturation from Birth to 8 Years of Age. Cerebral cortex (New York, N.Y.: 1991), 30(4), 2673–2689. doi: 10.1093/cercor/bhz268 [PubMed: 31819951]

Zhang H, Schneider T, Wheeler-Kingshott CA, & Alexander DC 2012. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage, 61(4), 1000–1016. doi: 10.1016/j.neuroimage.2012.03.072 [PubMed: 22484410]

Zhang S, Wang Y, Deng F, Zhong S, Chen L, Luo X, … & Huang R 2018. Disruption of superficial white matter in the emotion regulation network in bipolar disorder. NeuroImage: Clinical, 20, 875–882. doi: 10.1016/j.nicl.2018.09.024 [PubMed: 30286386]

Zhu T, Peng Q, Ouyang A, & Huang H 2021. Neuroanatomical underpinning of diffusion kurtosis measurements in the cerebral cortex of healthy macaque brains. Magnetic resonance in medicine, 85(4), 1895–1908. doi: 10.1002/mrm.28548 [PubMed: 33058286]

Highlights:

- Atlas-based tract- and tract-group-quantification on white matter skeleton was used;
- Altered white matter microstructure in pediatric bipolar disorder(BD) was delineated;
- Correlations of white matter microstructure to impulsivity in pediatric BD were found;
- Flattened microstructural age-related trendlines in children with BD were revealed;
- Intermediate developmental rates were observed in high-risk BD group

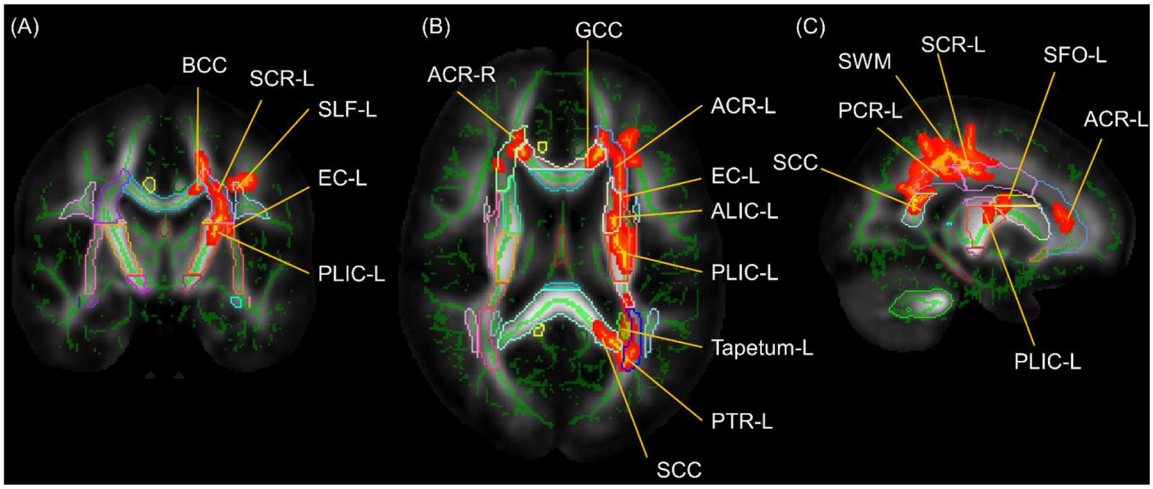

Figure 1.

Identified clusters (shown in red-yellow) with significantly higher radial diffusivity (RD) in bipolar disorder children and adolescents compared to age-matched healthy controls in coronal (A), axial (B), and sagittal (C) view. The white matter tract parcellation outlined with different colors was enabled by applied atlas-based white matter (WM) skeleton measurement approach. Green skeleton representing core of WM tracts is overlaid on the JHU ICBM atlas (Mori et al., 2008) fractional anisotropy (FA) template. See Table 3 for WM tract abbreviations. L and R represents left and right, respectively.

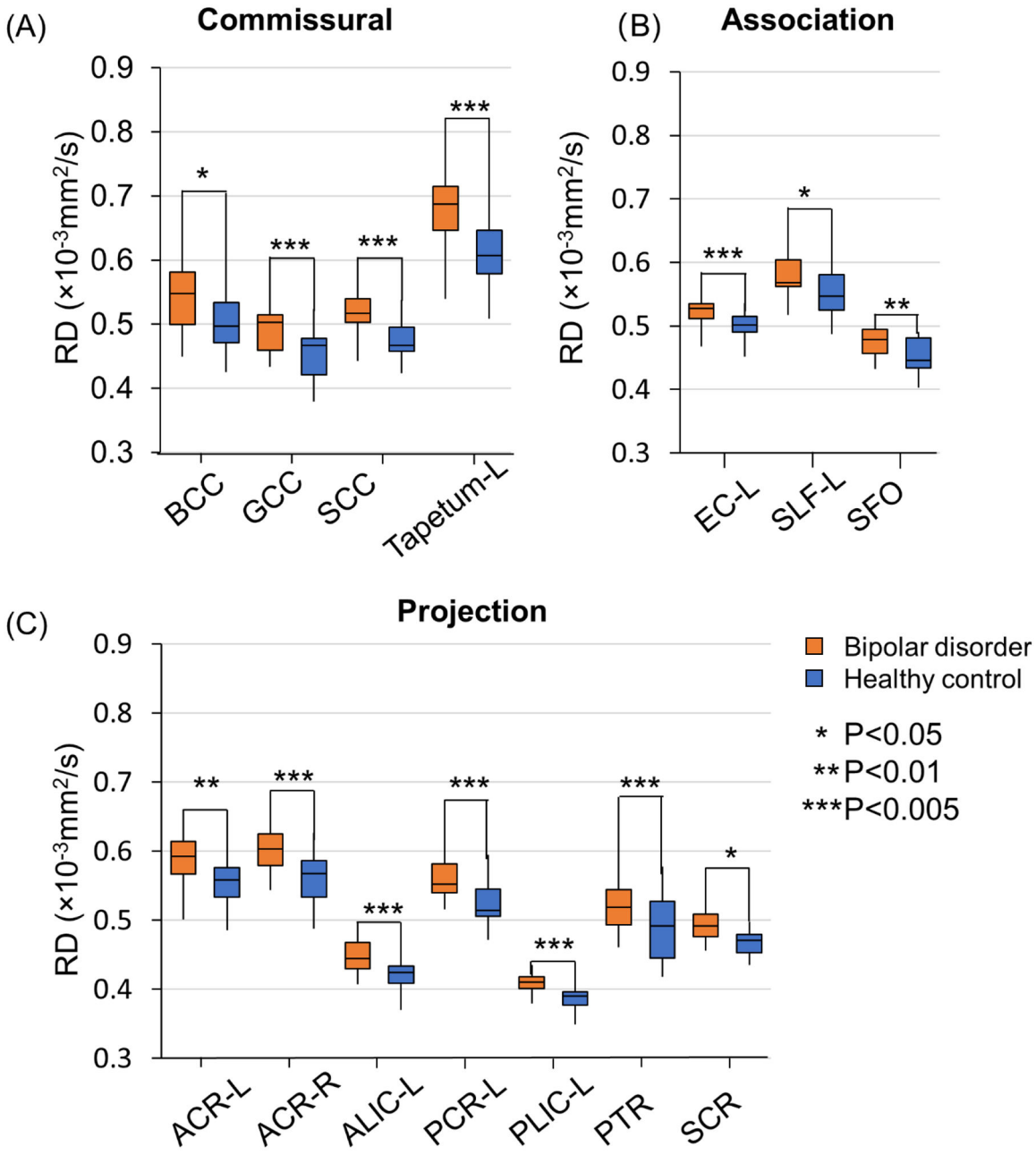

Figure 2.

Boxplots of radial diffusivity (RD) measurements averaged in clusters with significantly higher RD values in bipolar disorder (BD) than in healthy control (HC) across white matter (WM) tracts by tract groups, i.e. commissural (A), association (B) and projection (C) tract groups. * FDR corrected $p < 0.05$; ** FDR corrected $p < 0.01$. *** FDR corrected $p < 0.005$. See Table 3 for WM tract abbreviations.

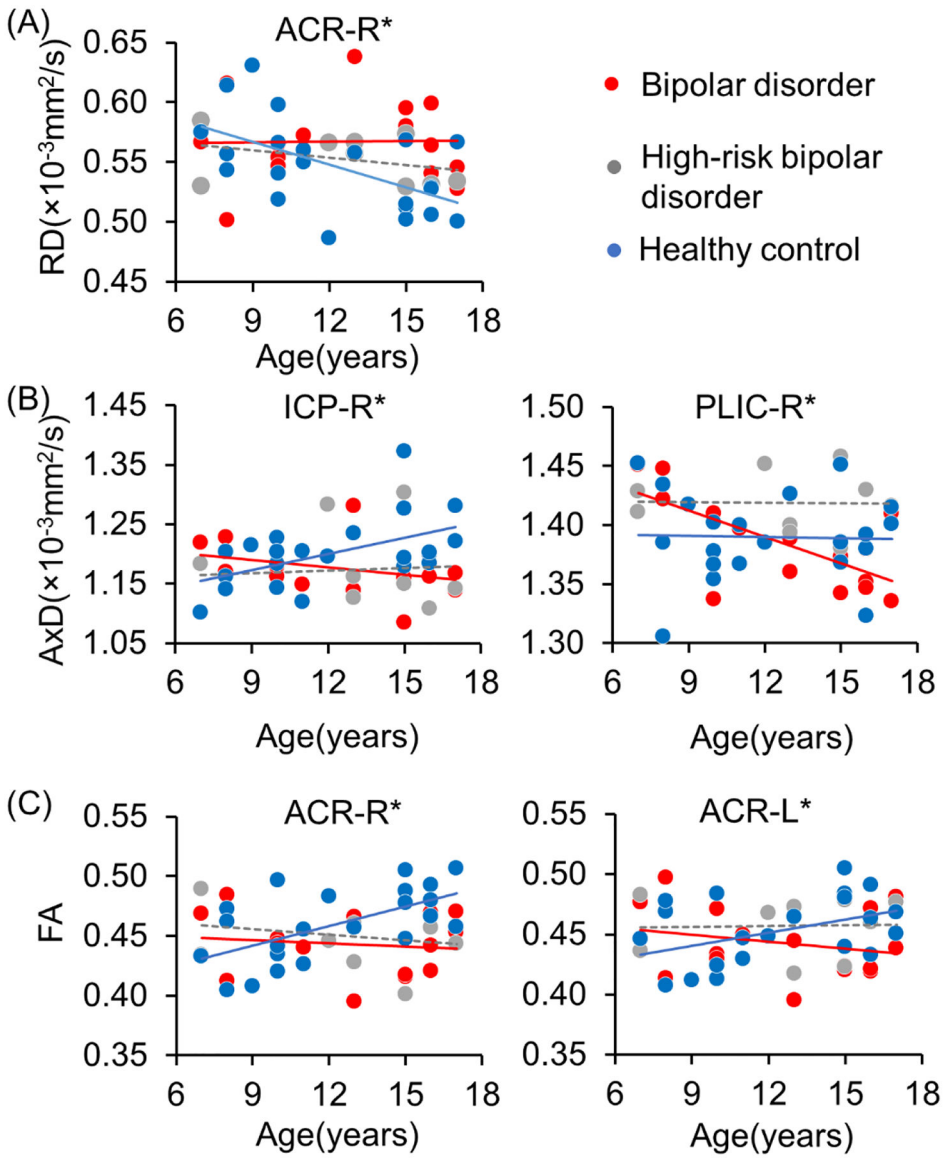

Figure 3.

Bipolar disorder (BD) (red), healthy control (HC) (blue), and high-risk BD (gray) groups show significantly different age-related rates of radial diffusivity (RD) (A), axial diffusivity (AxD), and fractional anisotropy (FA) (C) measurements in certain white matter (WM) tracts. Comparisons were conducted on all white matter tracts, but only results with significant (before multiple comparison correction) differences are shown. *p-value < 0.05 for age-group interaction in BD, HC and high-risk BD groups. See Table 3 for WM tract abbreviations.

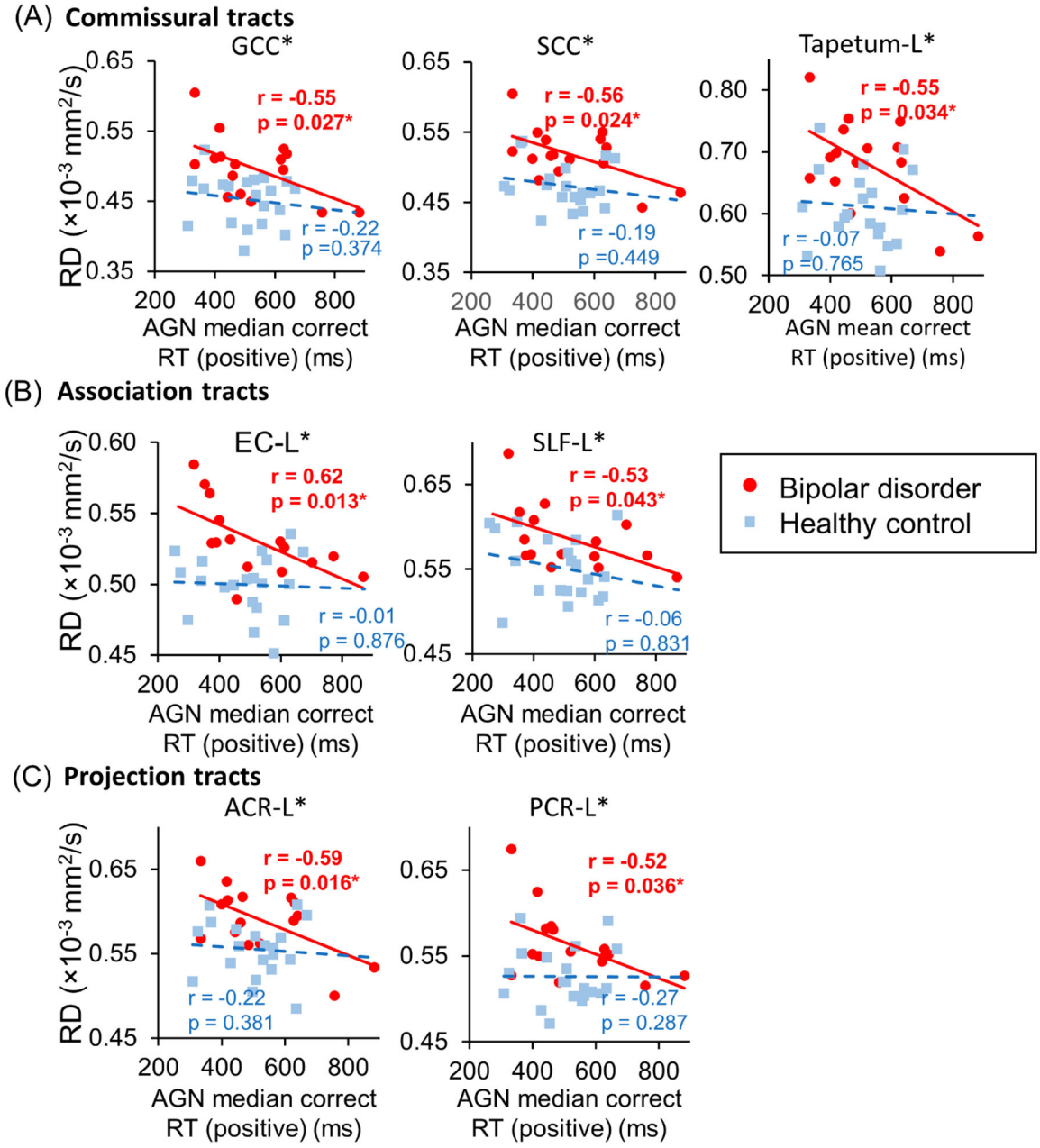

Figure 4.

Significant (p<0.05, after FDR correction) correlation of radial diffusivity (RD) and affective Go/No-Go (AGN) task mean correct response time (RT) to *positive* stimuli were found in bipolar disorder (BD) group (red) but not in age-matched healthy control (HC) group (blue) in commissural tracts including GCC, SCC and Tapetum-L (A), association tracts including EC-L and SLF-L (B), and projection tracts including ACR-L and PCR-L (C). RD values were measured at clusters with significant difference between BD and HC (shown in Figure 1). * FDR corrected $p < 0.05$. See Table 3 for WM tract abbreviations.

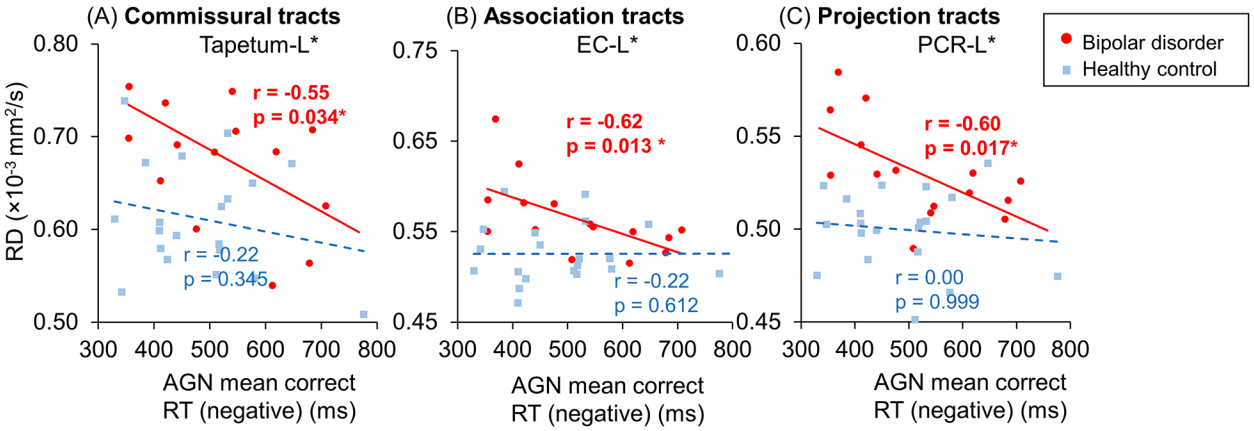

Figure 5.

Significant (p<0.05, after FDR correction) correlation of radial diffusivity (RD) and affective Go/No-Go (AGN) task mean correct response time (RT) to *negative* stimuli were found in bipolar disorder (BD) group (red) but not (p>0.05) in age-matched healthy control (HC) group (blue) in commissural tract Tapetum-L (A), projection tract PCR-L (B), and association tract EC-L (C). RD values were measured at clusters with significant difference between BD and HC (shown in Figure 1). * FDR corrected $p < 0.05$. See Table 3 for WM tract abbreviations.

Table 1.

Demographics and clinical characteristics of participants.

	BD (n = 18)	High-risk BD (n = 9)	HC (n = 22)	ANOVA	Chi-squared	BD vs. high-risk	*p-value* BD vs. HC	High-risk vs. HC
Age (years)	12.1 ± 3.45	13.5 ± 2.92	12.0 ± 3.33	ns	-	-	-	-
Gender (Male/Female)	7/11	5/4	10/12	-	ns	-	-	-
Race (Caucasian/African American/Asian/Mix)	16/2/0/0	7/2/0/0	14/5/2/1	-	ns	-	-	-
Ethnicity (Hispanic/Non-Hispanic)	3/15	4/5	3/19	-	ns	-	-	-
YMRS	13.8±3.64	3.43±2.70	2.25±3.64	2.61×10^{-5}	-	2.18×10^{-2}	5.92×10^{-4}	ns
CDRS-R	34.7±13.7	25.3±7.02	18.5±2.68	3.29×10^{-5}	-	ns	5.17×10^{-4}	ns
WASI-II	97.3±19.4	97.4±10.9	110±8.13	9.81×10^{-3}	-	ns	2.46×10^{-2}	4.20×10^{-3}

Abbreviations: BD: bipolar disorder; high-risk BD: bipolar offspring; HC: healthy control; ANOVA: analysis of variance; YMRS: Young Mania Rating Scale; CDRS-R: Children Depression Rating Scale-Revised; WASI-II: Wechsler Abbreviated Scale of Intelligence-II; ns: not significant.

Table 2.

Affective Go/No-go (AGN) response time (RT) to positive and negative stimuli of participants.

	BD (n=17)	High-risk BD (n=9)	HC (n=18 for positive, 17 for negative)	*p-value*			
				ANOVA	BD vs. high-risk	BD vs. HC	High-risk vs. HC
AGN RT Positive Stimuli (ms)	504±106	468±103	521±155	ns	ns	ns	ns
AGN RT Negative Stimuli (ms)	484±113	468±108	519±122	ns	ns	ns	ns

Analysis of variance (ANOVA) analysis *p*-value among bipolar disorder (BD), offspring (high-risk BD), and healthy control (HC) groups and pair-wise comparisons of two groups are reported. ns: not significant.

Table 3.

List of white matter tract abbreviations by tract group.

Abbreviation	Tract name
Commissural tracts	
BCC	body of corpus callosum
GCC	genu of corpus callosum
SCC	splenium of corpus callosum
Projection tracts	
ACR	anterior corona radiata
ALIC	anterior limb of internal capsule
PCR	posterior corona radiata
PLIC	posterior limb of internal capsule
PTR	posterior thalamic radiation
SCR	superior corona radiata
Association tracts	
EC	external capsule
SLF	superior longitudinal fasciculus
SFO	superior fronto-occipital fasciculus
Brainstem tracts	
ICP	inferior cerebellar peduncle