Shared and distinct white matter abnormalities in adolescent-onset schizophrenia and adolescent-onset psychotic bipolar disorder

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Abstract

Background. While adolescent-onset schizophrenia (ADO-SCZ) and adolescent-onset bipolar disorder with psychosis (psychotic ADO-BPD) present a more severe clinical course than their adult forms, their pathophysiology is poorly understood. Here, we study potentially state- and trait-related white matter diffusion-weighted magnetic resonance imaging (dMRI) abnormalities along the adolescent-onset psychosis continuum to address this need. **Methods.** Forty-eight individuals with ADO-SCZ (20 female/28 male), 15 individuals with psychotic ADO-BPD (7 female/8 male), and 35 healthy controls (HCs, 18 female/17 male) underwent dMRI and clinical assessments. Maps of extracellular free-water (FW) and fractional anisotropy of cellular tissue (FA_T) were compared between individuals with psychosis and HCs using tract-based spatial statistics and FSL's Randomise. FA_T and FW values were extracted, averaged across all voxels that demonstrated group differences, and then utilized to test for the influence of age, medication, age of onset, duration of illness, symptom severity, and intelligence. **Results.** Individuals with adolescent-onset psychosis exhibited pronounced FW and FA_T abnormalities compared to HCs. FA_T reductions were spatially more widespread in ADO-SCZ. FW increases, however, were only present in psychotic ADO-BPD. In HCs, but not in individuals with adolescent-onset psychosis, FA_T was positively related to age. **Conclusions.** We observe evidence for cellular (FA_T) and extracellular (FW) white matter abnormalities in adolescent-onset psychosis. Although cellular white matter abnormalities were more prominent in ADO-SCZ, such alterations may reflect a shared trait, i.e. neurodevelopmental pathology, present across the psychosis spectrum. Extracellular abnormalities were evident in psychotic ADO-BPD, potentially indicating a more dynamic, state-dependent brain reaction to psychosis.

Background

Psychosis spectrum disorders have serious, lifelong consequences for affected individuals and their families (Stentebjerg-Olesen, Pagsberg, Fink-Jensen, Correll, & Jeppesen, 2016; Tiffin & Kitchen, 2015). Given that adolescence is a critical period characterized by accelerated brain maturation and heightened neural plasticity, it is not surprising that many individuals with an age of onset during adolescence experience an even less favorable long-term clinical outcome than individuals with a later onset (Androutsos, 2012; Bartlett, 2014; Halfon, Labelle, Cohen, Guile, & Breton, 2013; Mollon & Reichenberg, 2018; Radmanovic, 2012; Reddy & Srinath, 2000; Remschmidt & Theisen, 2012). Thus, while adolescent-onset psychosis is relatively rare (Androutsos, 2012; Radmanovic, 2012; Wolf & Wagner, 2003), with an estimated cumulative incidence and prevalence rate of around 0.5% or less (Gillberg, Wahlstrom, Forsman, Hellgren, & Gillberg, 1986; Pedersen et al., 2014), it is still essential to study these vulnerable populations.

Despite the diagnostic dichotomy of adolescent-onset schizophrenia (ADO-SCZ) and adolescent-onset bipolar disorder with psychosis (psychotic ADO-BPD), these conditions present many clinical similarities and exhibit symptoms that overlap with other disorders (Bartlett, 2014; Citrome & Goldberg, 2005; Jerrell, McIntyre, & Deroche, 2017;

Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009; Singh, Ketter, & Chang, 2014; Skokauskas & Frodl, 2015; Waris, Lindberg, Kettunen, & Tani, 2013). The presence of a substantial genetic contribution (Asarnow & Forsyth, 2013; Faraone, Glatt, & Tsuang, 2003), a high prevalence of neurodevelopmental comorbidities, and lifelong cognitive impairments in adolescent-onset psychoses (Agnew-Blais et al., 2017; Khandaker, Stochl, Zammit, Lewis, & Jones, 2014) all reflect trait-related features that may indicate common neurodevelopmental aberrations occurring in ADO-SCZ and psychotic ADO-BPD. However, while ADO-SCZ and psychotic ADO-BPD may share several trait-related features, state-related differences, such as fluctuating clinical presentation, may occur throughout both illnesses. Therefore, more advanced research approaches that allow for the increased understanding of the biological causes underlying trait- and state-related features and differentiate them along the psychotic spectrum will be necessary.

In vivo magnetic resonance imaging (MRI) provides a promising and non-invasive way to increase our knowledge of the neurobiological bases of ADO-SCZ and psychotic ADO-BPD. Expressly, studies utilizing diffusion-weighted MRI (dMRI), an imaging method sensitive to pathologies affecting white matter microstructure and connectivity, have provided evidence for widespread white matter abnormalities in both ADO-SCZ (Drakesmith et al., 2016; Epstein et al., 2014; Moran et al., 2015; Tang et al., 2010) and psychotic ADO-BPD (Adler et al., 2006; Barnea-Goraly, Chang, Karchemskiy, Howe, & Reiss, 2009; Frazier et al., 2007; Kafantaris et al., 2009; Lagopoulos et al., 2013; Mahapatra, Khandelwal, Sharan, Garg, & Mishra, 2017; Mwangi et al., 2015; Pavuluri et al., 2009; Roberts et al., 2016; Versace et al., 2010). These findings suggest that adolescent-onset psychosis may result from faulty information integration from different brain systems rather than an impairment restricted to a single system (Friston, 1997). While several imaging studies have investigated adult-onset schizophrenia and bipolar disorder (Anderson et al., 2013; Hermens et al., 2019; Lu, Zhou, Keedy, Reilly, & Sweeney, 2011; Skudlarski et al., 2013; Sussmann et al., 2009), only one study has compared healthy controls (HCs) to a combined group of individuals with ADO-SCZ and psychotic ADO-BPD (White, Langen, Schmidt, Hough, & James, 2015). This work demonstrated reduced fractional anisotropy (FA) in ADO-SCZ and psychotic ADO-BPD and interpreted findings as overlapping white matter abnormalities in both populations. However, the authors did not investigate whether the observed anomalies were indicators of shared trait-related neurodevelopmental abnormalities or state-related brain features.

Free-water (FW) imaging (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009) provides a way to increase the biological specificity (Pasternak, Kubicki, & Shenton, 2016) of dMRI findings by differentiating the dMRI signal into two compartments. The first compartment models the amount of unrestricted free water within a voxel (FW). The second compartment models restricted or hindered water diffusion, from which fractional anisotropy of the tissue (FA_T) is derived. FW imaging has been used to study various states and disorders. Expressly, it has provided evidence for co-occurring cellular and extracellular pathologies in adult-onset schizophrenia and bipolar disorder populations across the illness trajectories (Bergamino, Kuplicki, Victor, Cha, & Paulus, 2017; Bergamino, Pasternak, Farmer, Shenton, & Hamilton, 2016; Chad, Pasternak, Salat, & Chen, 2018; Guttuso et al., 2018; Hoy et al., 2017; Ji et al., 2017; Kaufmann et al., 2017; Lyall et al.,

2018; Oestreich et al., 2017; Pasternak et al., 2012; Pasternak, Westin, Dahlben, Bouix, & Kubicki, 2015; Tang et al., 2019; Tuozzo et al., 2018; Yang et al., 2019).

FW imaging is an indirect measure of pathologies and has not been directly related to state- and trait-related white matter abnormalities. However, findings from earlier studies employing FW imaging have provided convergent evidence that cellular pathologies (i.e., FA_T) might be more stable and extracellular pathologies (i.e., FW) might be more transient. Indeed, previous research has demonstrated that imaging metrics of cellular white matter phenotypes are highly heritable (Voineskos, 2015). Moreover, the development of cellular white matter across the lifespan is modulated by genetic factors (Gilmore, Knickmeyer, & Gao, 2018). Studies in adult individuals with psychosis have demonstrated that FA_T is altered before the onset of the first episode (Di Biase et al., 2021a; Nägele et al., 2021; Tang et al., 2019) and remains affected throughout the disease course (Lyall et al., 2018; Nägele et al., 2021; Oestreich et al., 2017; Pasternak et al., 2012, 2015; Sun et al., 2009). These findings suggest that neurodevelopmental FA_T abnormalities in individuals with psychosis may reflect cellular white matter changes associated with a greater risk of developing psychosis (Hoptman et al., 2008; Sprooten et al., 2011), constituting an underlying etiologic feature of the disorder (Cetin-Karayumak et al., 2020; Kelly et al., 2018).

On the other hand, extracellular white matter pathologies (as measured by FW) have been proposed to reflect an acute brain response to the emergence of psychosis potentially related to immune activation (Di Biase et al., 2020, 2021b). FW is elevated most prominently during the first-psychotic episode and correlates with symptom severity suggesting an acute and potentially state-related response to the onset of psychosis (Guo et al., 2020; Nägele et al., 2021). In addition, a large-scale multisite study in adult individuals with psychosis showed that average whole-brain white matter FW levels are associated with higher peripheral inflammatory markers like interleukin-6 and tumor necrosis factor-alpha (Di Biase et al., 2021b). Likewise, translational studies using preclinical models link FW elevations to the activation of an interferon-gamma-mediated immune pathway (Di Biase et al., 2020; Febo et al., 2020), which has been shown to be associated with the severity of positive symptoms in individuals with schizophrenia (Febo et al., 2020; Kovacs et al., 2019).

Here, we aim to utilize FW imaging to study trait- *v.* state-related white matter abnormalities in a unique cohort of ADO-SCZ and psychotic ADO-BPD individuals. We combine data from two samples (Douaud et al., 2007; James et al., 2011; Savadjiev et al., 2014) to examine (a) differences between individuals with psychosis and HCs, as well as (b) shared and distinct white matter abnormalities between the two diagnostic groups, which may determine whether structural white matter differences in individuals with psychotic ADO-BPD and ADO-SCZ are part of the same continuum. We hypothesize to find abnormal FA_T and abnormal development of FA_T with age in psychotic ADO-BPD and ADO-SCZ, potentially indicative of a shared trait marker of abnormal white matter neurodevelopment across the psychosis spectrum. Furthermore, we predict that FW elevations will be present in psychotic ADO-BPD and ADO-SCZ and that these elevations will be associated with symptom severity, potentially indicating the current psychotic state.

Methods

The study was completed with the Oxford Psychiatric Research Ethics Committee's approval. Written informed consent was obtained from all participants. If the participant was under 16, their parents also provided written informed consent. Institutional Review Board (IRB) approval was obtained to analyze de-identified data at Brigham and Women's Hospital, Harvard Medical School.

Participants

Participants were recruited as part of two separate studies [for detailed recruitment protocols, see original publications (Douaud et al., 2007; James et al., 2011; Savadjiev et al., 2014)]. It is important to note that the number of participants in the present study is higher than that in the original papers due to further recruitment under the same conditions outlined therein (Douaud et al., 2007; James et al., 2011; Savadjiev et al., 2014). Forty-eight individuals with ADO-SCZ and 16 with psychotic ADO-BPD were enrolled in the present study.

The first study (Douaud et al., 2007; Savadjiev et al., 2016) recruited individuals with ADO-SCZ and age and sex-matched HCs. All individuals with ADO-SCZ were recruited from the Oxford regional adolescent unit and surrounding units. Individuals with ADO-SCZ were diagnosed according to the DSM-IV (Diagnostic And Statistical Manual of Mental Disorders: DSM-IV, 1994), which was confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996). Symptom severity was determined using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). All individuals included in this sample attended mainstream schools. Exclusion criteria for all participants were a full-scale intelligence quotient (FS-IQ) below 60, a history of substance abuse, pervasive developmental disorders, significant head injury, neurological disorders, or a major medical disorder. HCs were recruited from the community through general practitioners. Additional exclusion criteria for HCs were any history of emotional, behavioral, or medical problems.

The second study (James et al., 2011) recruited individuals with psychotic ADO-BPD and age and sex-matched HCs. Individuals with psychotic ADO-BPD were again recruited from the Oxford regional adolescent unit and surrounding units. The diagnosis was obtained using the DSM-IV (Diagnostic And Statistical Manual of Mental Disorders: DSM-IV, 1994) and Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1996). Individuals were administered the PANSS (Kay et al., 1987), the Beck's Depression Inventory (Beck & Beamesderfer, 1974), and the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978). At the time of examination, all individuals with psychotic ADO-BPD were euthymic according to DSM-IV criteria. Given the previously reported difficulty in differentiating psychotic ADO-BPD from ADO-SCZ and other disorders (Bartlett, 2014; Citrome & Goldberg, 2005; Jerrell et al., 2017; Rapoport et al., 2009; Singh et al., 2014; Skokauskas & Frodl, 2015; Waris et al., 2013), the initial diagnosis was reviewed by experienced child and adolescent psychiatrists for at least 6 months. None of the subjects in the present sample changed diagnosis within this follow-up period. All individuals attended mainstream schools. Exclusion criteria for all participants were an FS-IQ below 70, a history of illegal drug

use (any psychoactive substance at any time, apart from possible one-time experimentation), pervasive developmental disorders, significant head injury, neurological disorders, or a major medical disorder. Healthy individuals were recruited from the community through general practitioners, and additional exclusion criteria for HCs were any history of emotional, behavioral, or medical problems.

Cognitive assessment

A trained clinical neuropsychologist conducted a comprehensive neuropsychological assessment and administered the Wechsler-Abbreviated Scale of Intelligence to assess the FS-IQ. Note that five participants did not complete the full assessment and have missing FS-IQ values.

Image acquisition

All individuals were scanned on the same scanner and underwent the same imaging protocols, including dMRI on a 1.5T Sonata MR imager (Siemens, Erlangen, Germany). A diffusion-weighted echo-planar imaging (EPI) sequence was utilized with the following parameters: TE = 89 ms, TR = 8500 ms, 60 axial slices, bandwidth = 1869 Hz/voxel, voxel size $2.5 \times 2.5 \times 2.5$ mm^3 with 60 isotropically distributed orientations for the diffusion-sensitizing gradients at a b value of 1000 s/mm^2 and five $b = 0$ s/mm^2 images. The acquisition of the diffusion-weighted sequence was repeated three times for each participant to increase the signal-to-noise ratio. Critical for the present study, all individuals were scanned with the same protocols, which meant that we could use the same processing pipelines and process everyone as if acquired as part of the same study.

Image analysis

All dMRI data underwent a thorough quality control pipeline, including visually inspecting the images for movement artifacts, EPI distortions, and structural abnormalities in 3D Slicer [v.4.5, www.slicer.org (Fedorov et al., 2012)]. We excluded one individual with psychotic ADO-BPD due to severe signal dropouts, which led to a final sample of 15 psychotic ADO-BPD individuals with complete clinical and imaging data. Images were corrected for head motion and eddy currents [FLIRT, https://fsl.fmrib.ox. ac.uk/fsl/fslwiki/FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002)]. Next, the three diffusion acquisitions were averaged. Quality-checked images were then masked to exclude non-brain areas using the Brain Extraction Tool [BET, https://fsl.fmrib.ox. ac.uk/fsl/fslwiki/BET (Smith, 2002)].

Following the preprocessing of dMRIs, we computed diffusion tensors utilizing a least-squares fit, after which FA maps were calculated from the tensors. Furthermore, by fitting the two-compartmental FW imaging model to the dMRIs using a regularized non-linear fit, we obtained FW maps and FW-corrected FA$_T$ maps (Pasternak et al., 2009).

We created a study-specific template with antsMultivariateTemplateCreation2.sh [www.github.com/ANTsX/ANTs (Avants et al., 2011; Keihaninejad et al., 2012)]. This template was subsequently used as the registration target in the Tract-Based Spatial Statistics (TBSS) pipeline (Smith et al., 2006). A white matter skeleton was created based on the averaged registered FA images and thresholded at FA > 0.25. We then projected FA$_T$ and FW values onto the skeleton to perform statistical analyses.

Statistical analyses

We performed all analyses using FSL's Randomise, SPSS Version 24, and GraphPad Prism 8.2.0.

Group comparisons in FSL's Randomise: the spatial extent of white matter abnormalities

Given the lack of previously published imaging studies in ADO-SCZ and psychotic ADO-BPD, we did not have a tract-specific anatomical *a-priori* hypothesis. Thus, we elected to conduct whole-brain white matter voxel-wise analyses to compare the three groups as our primary analyses. We followed established pipelines (Smith & Nichols, 2009; Winkler, Ridgway, Webster, Smith, & Nichols, 2014) and performed two non-parametric permutation *F* tests, testing for group differences in FA_T and FW separately, utilizing FSL's Randomise (Winkler et al., 2014). We compared data with a null distribution generated with 5000 permutations for each contrast using threshold-free cluster enhancement (Smith & Nichols, 2009) and family-wise error (FWE) correction at a significance level of $p < 0.05$. Group (HCs, ADO-SCZ, psychotic ADO-BPD) was the independent variable. Age and sex were included as covariates in the design matrix. Significant voxel-wise *F* test maps provide clusters of voxels that demonstrate the locations of significant between-group differences across any of the three groups. We then compared the extent of FA_T and FW abnormalities between the individual groups as additional supplementary analyses. We, therefore, performed six post-hoc *t* tests using FSL's Randomise (Winkler et al., 2014) to compare (1) ADO-SCZ and HCs, (2) psychotic ADO-BPD and HCs, and (3) ADO-SCZ and psychotic ADO-BPD, again controlling for age and sex (online Supplementary Fig. S1).

Post-hoc analyses utilizing FA_T and FW averages: testing for the strength of group differences

In the event of a significant group difference in the FSL's Randomise *F* test, we extracted FA_T/FW values averaged over all voxels that displayed significant differences between groups. This approach provided us with an average FA_T and FW value per individual, referring to the same collection of voxels in each person. We utilized the averaged FA_T and FW values for all subsequent analyses.

We compared the average FA_T or FW values between groups (HCs, ADO-SCZ, psychotic ADO-BPD) utilizing analyses of covariance (ANCOVAs), post-hoc *t* tests (Bonferroni-corrected for three tests, threshold $p < 0.017$), and Cohen's *d* effect sizes to determine the strength of group differences. First, we corrected our analysis for age and sex. Next, given that medication and duration of psychosis differed between the psychotic ADO-BPD and ADO-SCZ groups, we additionally corrected for the duration of psychosis and chlorpromazine equivalents (CPZEQ) in a separate ANCOVA model. Lastly, we included FS-IQ and PANSS positive and negative symptom scores into our model.

Strength of association of FA_T and FW with age and symptom severity

We conducted exploratory post-hoc correlation analyses to test how the between-group differences in FA_T and FW are related to age and the clinical presentation of psychosis. Given that previous studies have reported an increase of FA with age during adolescence, we wanted to test whether white matter microstructure develops differently with age in HCs compared to individuals with adolescent-onset psychosis. Therefore, we performed Spearman correlations of average FA_T and FW with age in (1) HCs, (2) the

combined individuals with adolescent-onset psychosis cohort, and (3) individuals with ADO-SCZ and psychotic ADO-BPD, separately. Additional Spearman correlations were computed between FW imaging metrics (FA_T/FW) and positive and negative clinical symptoms for (1) the combined individuals with adolescent-onset psychosis cohort and (2) individuals with ADO-SCZ and psychotic ADO-BPD separately. Lastly, in supplementary analyses, we also conducted Spearman correlations between FW imaging metrics (FA_T/FW) and FS-IQ, age of onset, duration of illness, and CPZEQ.

Given the relatively small sample sizes, we opted to utilize non-parametric Spearman correlations for all analyses. Also note that we did not correct correlation analyses for multiple comparisons given the post-hoc, exploratory nature of the correlation analyses. Therefore, all *p* values will be reported as uncorrected.

Results

Demographics

There was no significant difference in age and sex between ADO-SCZ, psychotic ADO-BPD, and HCs (Table 1). However, FS-IQ differed significantly between the three groups, with HCs displaying the highest FS-IQ, psychotic ADO-BPD intermediate, and ADO-SCZ the lowest ($F_{(2,90)} = 12.95$, $p < 0.0001$, partial eta$^2 = 0.22$). Individuals with ADO-SCZ did not significantly differ from individuals with psychotic ADO-BPD in the age of onset. Note that while the average age of onset was 14 years, eight individuals with ADO-SCZ and four individuals with psychotic ADO-BPD disorder presented with an age of onset between 11 and 13 years. Psychosis duration was significantly longer in individuals with ADO-SCZ ($T = 2.37$, df = 61, $p = 0.021$, Cohen's $d = 0.70$). Similarly, the positive and negative symptom burden was higher in ADO-SCZ than that in psychotic ADO-BPD (Table 1). Finally, individuals with ADO-SCZ displayed higher medication dosages than individuals with psychotic ADO-BPD. However, group comparisons for medication dosage were not significant ($T = 1.99$, df = 61, $p = 0.051$, Cohen's $d = 0.59$).

See Table 1 for more information regarding the distribution of the demographic and clinical variables.

Group comparisons in FSL's Randomise: the spatial extent of white matter abnormalities

The two *F* tests with the independent variable group (HCs, ADO-SCZ, psychotic ADO-BPD), the dependent variable diffusion parameter (FA_T or FW), and covariates age and sex revealed significant group differences in FA_T and FW. Fourteen percent of the skeleton displayed significant FA_T differences (Fig. 1a). Group differences in FW were less pronounced, affecting 6% of the skeleton, but were still spatially widespread (Fig. 1b). Post-hoc voxel-wise *t* tests comparing the single groups revealed spatially more widespread FA_T abnormalities in ADO-SCZ than in psychotic ADO-BPD. However, FW abnormalities were only present in psychotic ADO-BPD (online Supplementary Fig. S1).

Post-hoc analyses utilizing FA_T and FW averages: testing for the strength of group differences

We extracted one FA_T and one FW value for each individual averaged across all voxels that demonstrated group differences in the *F* test to examine the effect size of group differences. Note that we opted to utilize averaged values derived from the *F* test because

Table 1. Demographics

	HCs ($n = 35$)	Individuals with ADO-SCZ ($n = 48$)	Individuals with psychotic ADO-BPD ($n = 15$)	Test statistic
Age (mean ± s.d., range)	15.65 ± 1.44, 13.55–18.88	16.28 ± 1.26, 13.18–18.38	15.52 ± 1.83, 12.03–18.18	$F_{(2,95)} = 2.75$, $p = 0.069$[a]
Sex (male/female)	17/18	28/20	8/7	$\chi^2 = 0.77$, df = 2, $p = 0.68$[a,b]
FS-IQ (n, mean ± s.d., range)	35, 106.89 ± 15.71, 64–127	43, 88.56 ± 15.92, 62–123	15, 95.27 ± 16.01, 70–123	$F_{(2,90)} = 12.95$, $p < 0.0001$[a]
Age at onset (n, years, mean ± s.d., range)		48, 14.46 ± 1.63, 11.00–16.80	15, 14.25 ± 1.98, 11.00–16.10	$t = 0.41$, df = 61, $p = 0.68$[c]
Duration of psychosis (n, years, mean ± s.d., range)		48, 1.84 ± 1.38, 0.59–5.88	15, 0.97 ± 0.61, 0.32–2.08	$t = 3.43$, df = 53.44, $p < 0.001$[c,d]
PANSS positive symptoms (n, mean ± s.d., range)		48, 22.52 ± 2.85, 17–29	15, 18.80 ± 4.49, 10–25	$U = 181.50$, $z = -2.90$, $p = 0.0040$[c,e]
PANSS negative symptoms (n, mean ± s.d., range)		48, 16.17 ± 3.23, 9–23	15, 10.20 ± 2.65, 7–15	$U = 58.50$, $z = -4.88$, $p < 0.001$[c,e]
CPZEQ (n, mg, mean ± s.d., range)		48, 356.50 ± 230.69, 50–1000	15, 230.67 ± 139.46, 0–400	$t = 1.99$, df = 61, $p = 0.051$[c]
Beck's Depression Inventory[f] (n, mean ± s.d.)			15, 6.60 ± 1.40	
Young Mania Rating Scale[f] (n, mean ± s.d.)			15, 1.40 ± 0.80	

HCs, healthy controls; ADO-SCZ, adolescent-onset schizophrenia; psychotic ADO-BPD, adolescent-onset bipolar disorder with psychosis; FS-IQ, full-scale intelligence quotient; PANSS, Positive and Negative Syndrome Scale; CPZEQ, chlorpromazine equivalents; s.d., standard deviation.
[a]Age, sex, and FS-IQ were compared between all three groups.
[b]Kruskal–Wallis test.
[c]Age of onset, duration of illness, PANSS positive and negative symptoms, and CPZEQ were compared between ADO-SCZ and ADO-BPD.
[d]Welsh t test because variances are not homogenous.
[e]Non-parametric group comparisons.
[f]Beck's Depression Inventory and Young Mania Rating Scale were only administered for individuals with psychotic ADO-BPD. In addition, we only had access to the mean and standard deviation for the present study, but not the individual values.
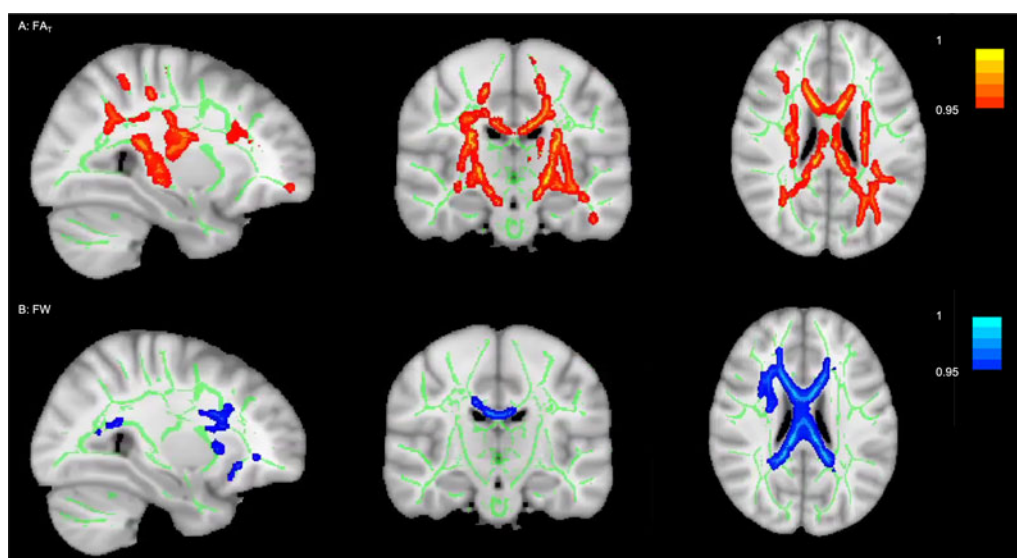

Fig. 1. Group differences between HCs, individuals with ADO-SCZ and psychotic ADO-BPD ($p < 0.05$, FWE-corrected). The figure displays the results from TBSS and Randomise (Smith & Nichols, 2009; Winkler et al., 2014). The white matter skeleton is displayed in green on top of an average of the registered FA images. Voxels that demonstrated significant group differences are thickened to increase visibility and are displayed in red for FW-corrected FA (i.e., FA_T) and in blue for FW. Images are presented in radiological convention and as '1 – family-wise error corrected p'; consequently, 1 is most significant. Panel A: 14% of the white matter skeleton showed group differences for FA_T. Voxels that demonstrated significant group differences were in the areas of the corona radiata, corpus callosum, fornix, superior longitudinal fasciculus, internal and external capsule, thalamic radiation, cerebral peduncle, inferior fronto-occipital fasciculus, uncinate fasciculus, corticospinal tract, cingulum, inferior longitudinal fasciculus. Panel B: 6% of the white matter skeleton showed group differences for FW. Voxels that demonstrated significant group differences were in the areas of the corona radiata, corpus callosum, superior longitudinal fasciculus, superior fronto-occipital fasciculus, internal and external capsule, uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, corticospinal tract, cingulum.
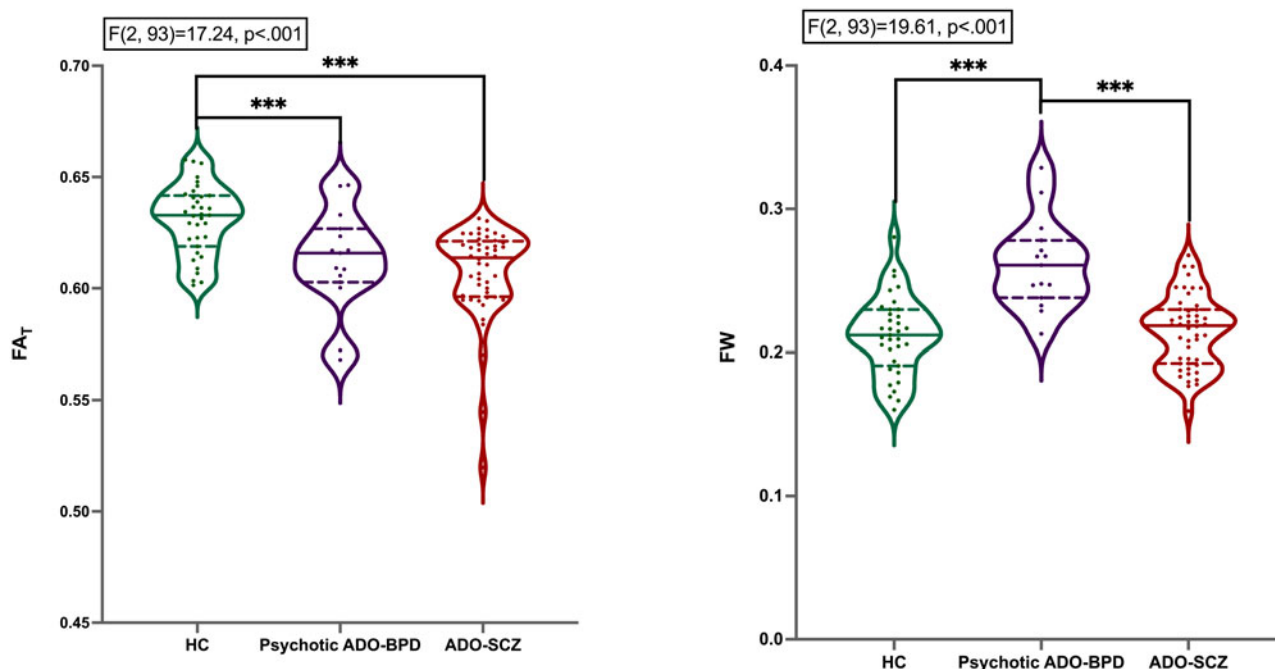
Fig. 2. Violin plots for FA$_T$ and FW values averaged across significant *F* test clusters for HCs, individuals with ADO-SCZ, and individuals with psychotic ADO-BPD. As displayed on the left, individuals with ADO-SCZ and psychotic ADO-BPD demonstrate significantly lower FA$_T$ values when compared to HCs. As shown on the right, individuals with psychotic ADO-BPD present significantly higher FW values when compared to HCs and individuals with ADO-SCZ. The violin plots present the median (line in the middle), quartiles (dotted line), and distribution of individual points for all groups.

they refer to the same voxels in all individuals. ANCOVAs confirmed the results obtained with FSL's Randomise. We revealed significant group differences for FA$_T$ ($F_{(2,93)} = 17.24$, $p < 0.001$, partial eta$^2 = 0.27$) and FW ($F_{(2,93)} = 19.61$, $p < 0.001$, partial eta$^2 = 0.30$). Post-hoc comparisons between the three groups showed significantly lower FA$_T$ for both psychotic ADO-BPD ($p = 0.011$, Cohen's $d = 0.93$) and ADO-SCZ ($p < 0.001$, Cohen's $d = 1.28$) individuals compared with HCs, but no significant differences between ADO-SCZ and psychotic ADO-BPD ($p = 0.97$, Cohen's $d = 0.27$). Additionally, psychotic ADO-BPD individuals exhibited higher FW compared to both HCs ($p < 0.001$, Cohen's $d = 1.71$) and ADO-SCZ ($p < 0.001$, Cohen's $d = 1.66$) individuals. ADO-SCZ individuals did not differ from HCs in FW ($p = 1.00$, Cohen's $d = 0.11$) (online Supplementary Table S1 and Fig. 2).

The results remained stable when including the duration of psychosis and CPZEQ as additional covariates. ADO-SCZ individuals were still significantly different from psychotic ADO-BPD for FW ($F_{(1,57)} = 40.10$, $p < 0.001$, partial eta$^2 = 0.41$), but not FA$_T$ ($F_{(1,57)} = 0.45$, $p = 0.50$, partial eta$^2 = 0.008$). The results also remained stable when adding FS-IQ and PANSS positive and negative symptom scores as additional covariates. ADO-SCZ individuals were still significantly different from psychotic ADO-BPD for FW ($F_{(1,49)} = 25.12$, $p < 0.001$, partial eta$^2 = 0.34$), but not FA$_T$ ($F_{(1,49)} = 0.065$, $p = 0.80$, partial eta$^2 = 0.001$).

Strength of association of FA$_T$ and FW with age and symptom severity

FA$_T$ positively correlated with age in HCs, but this was neither observed in the combined cohort of individuals with adolescent-onset psychosis nor in ADO-SCZ or psychotic ADO-BPD, separately (online Supplementary Fig. S2). Significant correlations were not found between FA$_T$ and symptom severity for individuals with psychosis (Table 2).

We did not observe a significant correlation between FW and age in any group. Negative symptoms were negatively associated with FW in all individuals with adolescent-onset psychosis. However, correlations were no longer significant when assessing ADO-SCZ and psychotic ADO-BPD separately (Table 2, online Supplementary Fig. S3).

Additional correlation analyses are presented in online Supplementary Table S2. While results must be interpreted with caution because correlations were conducted post-hoc and not corrected for multiple comparisons, we saw a significant correlation indicating that earlier age of onset and longer duration of illness was related to more FW in ADO-SCZ.

Discussion

When comparing HCs with ADO-SCZ and psychotic ADO-BPD, we find that altered cellular microstructure (FA$_T$) is prominent in individuals with ADO-SCZ and psychotic ADO-BPD but spatially more widespread in ADO-SCZ individuals. However, extracellular abnormalities (FW) are only observed in psychotic ADO-BPD individuals. In line with our hypothesis that cellular abnormalities might indicate shared trait abnormalities, we observed an altered correlation between FA$_T$ and age in the combined group of individuals with adolescent-onset psychosis. Extracellular abnormalities exhibited a trend-level significant correlation with symptom severity in the combined group of individuals with adolescent-onset psychosis.

FA$_T$ abnormalities

The FA$_T$ abnormalities in individuals with adolescent-onset psychosis were very widespread. While TBSS provides a voxel-wise rather than tract-specific output, the voxels that

Table 2. Correlations of FA$_T$ and FW with clinical variables

Clinical variables			Test statistics
FA$_T$	Age (years)	*HCs*	**rho = 0.45, *p* = 0.0060**[a]
		Individuals with psychosis	rho = −0.047, *p* = 0.71
		ADO-SCZ	rho = 0.11, *p* = 0.46
		Psychotic ADO-BPD	rho = −0.36, *p* = 0.19
	Negative symptoms PANSS	*Individuals with psychosis*	rho = −0.23, *p* = 0.067
		ADO-SCZ	**rho = −0.33, *p* = 0.023**[a]
		Psychotic ADO-BPD	rho = −0.007, *p* = 0.98
	Positive symptoms PANSS	*Individuals with psychosis*	rho = −0.24, *p* = 0.060
		ADO-SCZ	rho = −0.25, *p* = 0.081
		Psychotic ADO-BPD	rho = −0.048, *p* = 0.86
FW	Age (years)	*HCs*	rho = −0.022, *p* = 0.90
		Individuals with psychosis	rho = −0.24, *p* = 0.057
		ADO-SCZ	rho = −0.17, *p* = 0.24
		Psychotic ADO-BPD	rho = −0.22, *p* = 0.44
	Negative symptoms PANSS	*Individuals with psychosis*	**rho = −0.25, *p* = 0.047**[a]
		ADO-SCZ	rho = 0.15, *p* = 0.30
		Psychotic ADO-BPD	rho = 0.13, *p* = 0.65
	Positive symptoms PANSS	*Individuals with psychosis*	rho = −0.21, *p* = 0.098
		ADO-SCZ	rho = 0.020, *p* = 0.89
		Psychotic ADO-BPD	rho = 0.014, *p* = 0.96

FA$_T$, free-water corrected fractional anisotropy; FW, free-water; HCs, healthy controls; ADO-SCZ, adolescent-onset schizophrenia; psychotic ADO-BPD, adolescent-onset bipolar disorder with psychosis; PANSS, Positive and Negative Syndrome Scale; CPZEQ, chlorpromazine equivalent.
Note that the relatively small sample size and the fact that positive symptoms were not normally distributed, we utilized non-parametric Spearman correlations for all analyses.
[a]Indicates statistical significance. Results should be considered cautiously given that (a) correlations were not corrected for multiple comparisons, and (b) we do not observe significant correlations for individuals with psychosis subgroups.

demonstrated significant group differences were in the areas of many principal white matter tracts such as the cingulum, corpus callosum, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus. Previous studies utilizing a single-compartment diffusion tensor imaging model also reported reductions in the traditional FA metric in similar areas for psychotic ADO-BPD (Barnea-Goraly et al., 2009; Frazier et al., 2007; Lagopoulos et al., 2013; Mahapatra et al., 2017; Roberts et al., 2016; Versace et al., 2010), and ADO-SCZ (Clark et al., 2012; Douaud et al., 2007; Drakesmith et al., 2016; Moran et al., 2015). Of note, these tracts (in particular, the corpus callosum) have also demonstrated the most consistent differences between healthy individuals and adult individuals with psychosis (Kelly et al., 2018), and our finding of widespread differences between the psychotic groups and HCs is in line with the previously published adult psychosis literature (Cetin-Karayumak et al., 2020; Kelly et al., 2018; Seitz et al., 2016; Seitz-Holland et al., 2021).

Interestingly, we observe that the tissue-related pathologies are more widespread in ADO-SCZ than in psychotic ADO-BPD. Analogous findings have been described in adult-onset populations, suggesting overlapping but more extensive white matter abnormalities in schizophrenia than in bipolar disorder (Arat, Chouinard, Cohen, Lewandowski, & Ongur, 2015; Dong et al., 2017; Skudlarski et al., 2013). Gray matter morphometric studies also report cortical thinning and volume loss in schizophrenia and bipolar disorder, which are more pronounced in

schizophrenia (Brown et al., 2011; Ellison-Wright & Bullmore, 2010; Ivleva et al., 2013; Nazeri et al., 2017; Rimol et al., 2010). Additional evidence from clinical, cognitive, and genetic studies supports the notion, providing convergent evidence of a psychosis spectrum (Argyelan et al., 2014; Knochel et al., 2016; Madre et al., 2016; Skudlarski et al., 2013; Stefanik et al., 2018).

Our finding of a positive correlation between age and FA$_T$ in HCs, but no such correlation between age and FA$_T$ in individuals with adolescent-onset psychosis, paired with the observed group differences in FA$_T$, supports our hypothesis that FA$_T$ might be an indicator for trait-related pathologies related to brain development or maturational processes. Previous developmental studies have reported increases in FA with increasing age throughout childhood and adolescence (Lebel et al., 2012; Lebel, Treit, & Beaulieu, 2019). The lack of a correlation with age in individuals with adolescent-onset psychosis provides additional evidence of a potentially altered (i.e. flattened) maturational trajectory of brain white matter structure in adolescents with psychosis (Cabeen, Laidlaw, Ruggieri, & Dickstein, 2018; Toteja et al., 2015). Moreover, our findings align with previous studies reporting a similar pattern of aberrant white matter development in young adults and adolescents at clinical high-risk for psychosis (Di Biase et al., 2021a; Mittal et al., 2014; Tang et al., 2019), further supporting the notion of a shared neurodevelopmental etiology of both disorders (Arango, Fraguas, & Parellada, 2014).

FW abnormalities

In addition to cellular white matter abnormalities, we observed an elevation in extracellular FW in individuals with adolescent-onset psychosis compared with HCs. Post-hoc tests revealed that significant FW elevations were driven predominantly by the psychotic ADO-BPD group.

At present, there have been two FW imaging studies conducted on adult-onset bipolar disorder (Guo et al., 2020; Tuozzo et al., 2018). In concordance with our findings, these studies reported higher FW in individuals with bipolar disorder than in healthy individuals. This FW increase was interpreted as an indicator of acute brain response, potentially reflecting immune activation (Di Biase et al., 2020, 2021b; Tuozzo et al., 2018). Indeed, postmortem studies report elevated neuroinflammatory markers in the brain tissue of individuals with bipolar disorder, along with increased plasma levels of peripheral inflammatory markers (Mitchell & Goldstein, 2014; Tuozzo et al., 2018). Although the FW imaging metric is not specific to neuroinflammation, as it might be affected by other extracellular components, our study encourages further exploration of the immune hypothesis of bipolar disorder (Benedetti, Aggio, Pratesi, Greco, & Furlan, 2020).

Interestingly, we did not observe a significant increase in FW in ADO-SCZ. Earlier work utilizing FW imaging reported FW elevations in first-episode populations with schizophrenia, while no or a limited increase has been observed in clinical high-risk for psychosis or chronic schizophrenia populations (Di Biase et al., 2021a; Lyall et al., 2018; Nägele et al., 2021; Pasternak et al., 2012, 2015; Tang et al., 2019). Given the duration of illness of fewer than 2 years, it could be argued that the ADO-SCZ individuals in the present study are still in the early stages of the illness course. This divergence from previous reports indicates that the underlying pathology of ADO-SCZ may differ in certain respects from adult-onset SCZ, which has been suggested previously by others (Kyriakopoulos et al., 2009; Zhang et al., 2017). Indeed, ADO-SCZ is far less common than adult-onset schizophrenia (Androutsos, 2012; Radmanovic, 2012). Individuals with ADO-SCZ present with different symptoms (Birmaher & Axelson, 2006; David et al., 2011; Rocha, Zeni, Caetano, & Kieling, 2013) and experience more severe cognitive deficits and neuropsychiatric comorbidities than individuals with adult-onset schizophrenia (Agnew-Blais et al., 2015, 2017; Arican et al., 2019; Biswas, Malhotra, Malhotra, & Gupta, 2007; Dalsgaard et al., 2014; Dalteg, Zandelin, Tuninger, & Levander, 2014; Dreier, Pedersen, Cotsapas, & Christensen, 2019; Fors, Abel, Wicks, Magnusson, & Dalman, 2013). It is also worth noting that (a) the duration of illness in ADO-SCZ in the present study was longer than the duration of illness in psychotic ADO-BPD and that (b) given the complexity of diagnoses within adolescent-onset psychosis populations, the actual duration of illness might have been longer than what is reported. Future longitudinal studies are needed to investigate whether FW elevations are present throughout the illness course of ADO-SCZ and whether they could serve as indicators of acute psychotic states, as observed in previous adult-onset samples.

While the association between FW and symptom severity in the combined individuals with adolescent-onset psychosis group preliminarily supports our assumption that FW changes reflect acute pathologies, a closer look at these correlations is warranted. We acknowledge that the negative direction of the association between FW changes and symptom severity seems counter-intuitive as it suggests that an elevation of the proposed state marker FW is associated with fewer symptoms. Nevertheless, this finding is in line with a previous study by Lyall et al. (2018), which showed that FW increases, attributed to an immune response at the onset of psychosis, were accompanied by better neurocognitive outcomes after 12 weeks of antipsychotic treatment. On the other hand, a recent study in first-episode psychosis suggests that higher FW is associated with a more significant burden of negative symptoms (Guo et al., 2020). Furthermore, it is essential to note that FW correlations fail to remain significant after correction for multiple comparisons or when separating individuals into ADO-SCZ and psychotic ADO-BPD subgroups, indicating a potential lack of power or that group differences may drive the correlations.

Notably, the present study is a cross-sectional study, limiting our ability to conclude the merit of FW as a marker of state-related features of illness. We observed an increase in FW in our psychotic ADO-BPD subgroup, despite all individuals being euthymic on the day of scanning. This finding suggests that the FW increase may not be directly linked to the manifestation of depressive or manic symptoms in individuals with ADO-BPD. Furthermore, while psychotic symptoms are classically considered indicators of clinical state, it could be that the more symptomatic individuals at the time of assessment are more symptomatic in a persistent manner. Therefore, longitudinal studies are needed to disentangle the relationship between symptoms, state, and trait and test the association between the dynamics of FW alterations and psychotic symptoms across the course of bipolar cycles. In addition, while we clinically followed the psychotic ADO-BPD cohort for 6 months, it has previously been suggested that individuals with psychotic ADO-BPD might later convert to schizophrenia. Future investigations should perform longitudinal MRI scans to simultaneously capture the dynamic trajectories of brain alterations and symptomatology in order to understand better the role that FW may play as a potential marker of state-related features of psychosis.

Limitations and future directions

The small sample size, specifically of the psychotic ADO-BPD disorder sample, and cross-sectional study design are the main limitations of the present study. More extensive, longitudinal studies are needed to understand the complex interplay between clinical presentation and brain structure. Specifically, it would be intriguing to map how the trajectories of brain development depend on the age of onset, duration of illness, and developmental state (Frazier et al., 1997; Walker & Bollini, 2002) in children and adolescents. However, given the relatively low prevalence of adolescent-onset psychosis and the difficulties of recruiting adolescent-onset psychosis samples, the current work still represents one of the most extensive dMRI datasets of this population. Additionally, it is essential to note that we utilized stringent statistical approaches, which provide an avenue to observe statistically robust widespread group differences despite the small sample size.

Next, we acknowledge that the imaging markers we use represent proxies for describing brain pathologies. Multi-modal studies (e.g., imaging genetics, including peripheral markers for inflammation) are needed to examine our hypothesis of state- *v.* trait-associated abnormalities in adolescence-onset psychosis. Furthermore, to understand the association between brain structure and symptoms, it is essential to use dimensional symptom

scales (Keshavan et al., 2011), which might better capture the variability in the phenomenology and illness course of psychosis.

Similarly, while we control our analyses for the effect of medication on the day of the scan, and while our finding of no influence of medication on diffusion measures is in line with previous studies (Dietsche, Kircher, & Falkenberg, 2017; Kanaan et al., 2009; Serpa et al., 2017; Zeng et al., 2016), we cannot exclude the potential impact of lifetime medication exposure or differential effect of various antipsychotics (Tishler et al., 2018). Future studies that control for dose-years (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010) and explore the complex interplay between brain structure, medication, and other indicators of the severity of disease (such as number of episodes, number of co-occurring treatments, time spent in hospital) in adolescence are desperately needed (Stampfli et al., 2019).

Given the retrospective nature of our analyses, image acquisition protocols used here do not represent the state-of-the-art, which might influence results (Mandl et al., 2015; Oestreich et al., 2017). Improved protocols on stronger magnets would allow a higher spatial resolution and the acquisition of multiple b-shells, which may have more sensitivity to detecting changes (Bergmann, Henriques, Westin, & Pasternak, 2020; Pasternak et al., 2012).

Lastly, we would like to highlight that the present study is the first to apply the FW model to an adolescent-onset psychosis population. Thus, replicating the current results utilizing similar and different (e.g. tractography v. voxel-wise analysis) processing methods is necessary to increase our understanding of the potential state- and trait-related pathologies in ADO-SCZ and psychotic ADO-BPD.

Conclusion

We report the results of an analysis of two cohorts of ADO-SCZ and psychotic ADO-BPD utilizing FW imaging. In line with earlier studies in adult-onset psychosis, we observe evidence for cellular white matter abnormalities and an acute extracellular pathology. Cellular, potentially trait-related white matter alterations, i.e., FA_T reductions, are existent in psychotic ADO-BPD and ADO-SCZ but are more prominent in individuals with ADO-SCZ. However, extracellular FW increases, suggestive of state-related acute brain response to illness, are only observed for psychotic ADO-BPD. Our study highlights the importance of studying ADO-SCZ and psychotic ADO-BPD together to characterize shared and distinct pathologies in adolescent-onset psychosis to ultimately improve diagnosis and treatment options for this vulnerable population.

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