



White matter microstructure and the clinical risk for psychosis: A diffusion tensor imaging study of individuals with basic symptoms and at ultra-high risk

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ABSTRACT

Background: Widespread white matter abnormalities are a frequent finding in chronic schizophrenia patients. More inconsistent results have been provided by the sparser literature on at-risk states for psychosis, i.e., emerging subclinical symptoms. However, considering risk as a homogenous construct, an approach of earlier studies, may impede our understanding of neuro-progression into psychosis.

Methods: An analysis was conducted of 3-Tesla MRI diffusion and symptom data from 112 individuals (mean age, 21.97 ± 4.19) within two at-risk paradigm subtypes, only basic symptoms ($n = 43$) and ultra-high risk ($n = 37$), and controls ($n = 32$). Between-group comparisons (involving three study groups and further split based on the subsequent transition to schizophrenia) of four diffusion-tensor-imaging-derived scalars were performed using voxelwise tract-based spatial statistics, followed by correlational analyses with Structured Interview for Prodromal Syndromes responses.

Results: Relative to controls, fractional anisotropy was lower in the splenium of the corpus callosum of ultra-high-risk individuals, but only before stringent multiple-testing correction, and negatively correlated with General Symptom severity among at-risk individuals. At-risk participants who transitioned to schizophrenia within 3 years, compared to those that did not transition, had more severe WM differences in fractional anisotropy and radial diffusivity (particularly in the corpus callosum, anterior corona radiata, and motor/sensory tracts), which were even more extensive compared to healthy controls.

Conclusions: These findings align with the subclinical symptom presentation and more extensive disruptions in converters, suggestive of severity-related demyelination or axonal pathology. Fine-grained but detectable differences among ultra-high-risk subjects (i.e., with brief limited intermittent and/or attenuated psychotic symptoms) point to the splenium as a discrete site of emerging psychopathology, while basic symptoms alone were not associated with altered fractional anisotropy.

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1. Introduction

Schizophrenia is a highly debilitating psychiatric disorder with a complex symptom presentation and an unclear etiopathogenesis. Disorder-related dysfunctions have been observed across many biological levels, including genetics (Birnbaum and Weinberger, 2017), epigenetics (Smigielski et al., 2020), and neurotransmitter systems (Brisch et al., 2014) as well as brain structure (Van Erp et al., 2018) and functional networks (Dong et al., 2018). In this context, white matter (WM) abnormalities seem to be particularly well positioned to account for cognitive, affective, and perceptual symptoms observed in schizophrenia. Specifically, WM microstructural characteristics largely impact information transmission through the conduction velocity of axons (Caminiti et al., 2013; Tuladhar et al., 2015), corresponding with the pervasive cognitive difficulties reported by patients (Zai et al., 2017; Zanelli et al., 2019). Multiple lines of evidence also indicate schizophrenia is a disorder of disrupted brain connectivity, both functionally and structurally (Pettersson-Yeo et al., 2011; Stämpfli et al., 2019; Zalesky et al., 2011). Axonal bundles are physically associated with grey matter structures (O'Muircheartaigh and Jabdi, 2018), and brain connectivity is largely linked to oligodendroglia and myelination (Davis et al., 2003). WM also has properties that may explain the progression of schizophrenia. Specifically, WM maturational processes for lower-order tracts (e.g., motor tracts) occur before those for higher-order tracts, with the fiber projections not being refined until late adolescence or early adulthood (Bava et al., 2010). This time window coincides with frequent onset of psychotic disorders. Furthermore, many schizophrenia liability genes overlap with known WM genetic variants (Bohken et al., 2016; Chavarría-Siles et al., 2016; Roussos and Haroutunian, 2014; Van Scheltinga et al., 2013; Zhao et al., 2021). Indeed, the existing evidence for the involvement of WM deficits in schizophrenia seems robust (Kubicki et al., 2007; Tamnes and Agartz, 2016; Vitolo et al., 2017), with the largest-to-date ENIGMA consortium meta-analysis (2359 controls, 1963 patients) reporting widespread microstructural abnormalities across all major WM fasciculi (Kelly et al., 2018). Beyond to between-group differences from healthy controls (HC), numerous studies have identified significant associations between WM markers and (predominantly positive) symptoms (Bopp et al., 2017; Cheung et al., 2011; Stämpfli et al., 2019), core cognitive functions (Kochunov et al., 2017), but also theory of mind abilities (Kim et al., 2021) and poor insight into illness (Antonius et al., 2011; Gerretsen et al., 2019). These associations were especially evident for frontal, fronto-temporal, and fronto-limbic tracts, the superior longitudinal fasciculus, and inter-hemispheric connections (Kuswanto et al., 2012; Parnanzone et al., 2017). Notably, a large body of literature also points to the corpus callosum as the epicenter of schizophrenia-related abnormalities (Koshiyama et al., 2018; Madigand et al., 2019; Patel et al., 2011).

The microstructure of WM tracts can be quantified non-invasively *in vivo* using diffusion weighted imaging (DWI) data and diffusion tensor imaging (DTI) models (Podwalski et al., 2020; Shizukuishi et al., 2013). Published DWI/DTI studies support the involvement of progressive (Cetin-Karayumak et al., 2020) and subtype-related aspects of WM microstructure abnormalities in schizophrenia, as exemplified in differences between hallucinating versus non-hallucinating patients (Beresniewicz et al., 2021) or those with persistent negative symptoms versus non-deficit patients (Podwalski et al., 2021). In this context, investigating differential fine-grained symptoms emerging before onset of a full-blown disorder may greatly inform our understanding of the neural processes underlying mental illness. Early detection of low-grade symptoms may also have measurable clinical implications, leading to early interventions, with the goal of decreasing functional disability, improving overall health outcomes, and reducing negative societal impacts (Correll et al., 2018; Lieberman et al., 2019). The clinical risk of psychosis paradigm has evolved for research purposes and as a clinical staging model (Fusar-Poli et al., 2020). The established risk criteria were developed to capture the pre-psychotic stage and include basic

symptoms (BS), ultra-high risk (UHR) criteria, and genetic risk and deterioration syndrome (GRD) (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015). Specifically, the BS category reflects subtle subjective experiences based on cognitive-perceptive basic symptoms (COPER) and/or cognitive disturbances (COGDIS) (Schultze-Lutter and Theodoridou, 2017). UHR has been hypothesized as an imminent risk for psychosis and is identified based on the presence of either brief limited intermittent psychotic symptoms (BLIPS) and/or attenuated psychotic symptoms (APS) and/or genetic risk combined with a functional decline (Schultze-Lutter et al., 2011). BS are thought to feature an earlier at-risk phase, compared to UHR (Fusar-Poli et al., 2013), while GRD is proportionally rare (Fusar-Poli et al., 2016). According to a recent meta-analysis, 25% of those meeting high-risk criteria developed psychosis within 3 years, and the likelihood increased over time (de Pablo et al., 2021). Fig. 1 depicts a schematic model of early psychosis onset (Fusar-Poli et al., 2013).

DWI/DTI studies on high clinical risk have been less frequent and have employed smaller sample sizes than those on schizophrenia or first-episode psychosis (Waszczuk et al., 2021). These studies tend to converge on the type and spatial location of WM abnormalities observed in schizophrenia and indicate their lower severity (Bernard et al., 2015; Clemm von Hohenberg et al., 2014; Krakauer et al., 2017). However, treating risk as a homogenous construct may simultaneously undermine efforts to understand the mechanisms underlying psychotic symptoms (Fusar-Poli et al., 2016). From a clinical perspective, what particularly matters is the prediction of full-blown psychosis. While dedicated screening interviews are generally very sensitive in differentiating at-risk from healthy individuals, accurately predicting the transition to a formal diagnosis within at-risk groups remains much more challenging and has involved the application of rather poorly validated predictive models (Montemagni et al., 2020). Neuroimaging may potentially help in objectively formulating such prognoses, as exemplified by the relatively few studies that have identified specific local WM abnormalities in those individuals that later developed psychosis (León-Ortiz et al., 2020; Rigucci et al., 2016). Finding a reliable biomarker or at least achieving some biomarker-informed improvement in prognostic accuracy could revolutionize early recognition and intervention. There is an ongoing discussion of whether the transition may be marked by dramatic changes in WM microstructure or rather follows a more subtle pattern (Di Biase et al., 2021).

To the best of our knowledge, no previous study has explicitly compared whole-brain WM for different typologies of symptoms within the clinical high-risk paradigms. Accordingly, this work was conducted to investigate possible differences in the WM microstructure using DTI metrics among three thoroughly characterized groups: HC, only BS, and UHR. We postulated fractional anisotropy would be lowest in the UHR group, followed by the only BS group in an intermediate position and, lastly, the HC group. Given the composition of our sample was restricted to the subclinical portion of the psychosis spectrum and our use of a relatively conservative measure of DTI, we hypothesized rather subtle differences would be observed. In terms of spatial effects, we expected to see differences in WM tracts of key importance in schizophrenia, i.e., long-range association tracts (such as the superior longitudinal fasciculus), projection tracts (such as the thalamic radiation), and/or the corpus callosum. Additionally, we explored possible associations with WM indices and early perceptual-cognitive and functional deficits, as assessed by well-established instruments in the field. Finally, we explored the putative WM differences in dependency of the subsequent conversion to a formal diagnosis of schizophrenia (i.e., transition criterion).

2. Methods

2.1. Participants

The study was part of the multimodal Zurich Program for Sustainable

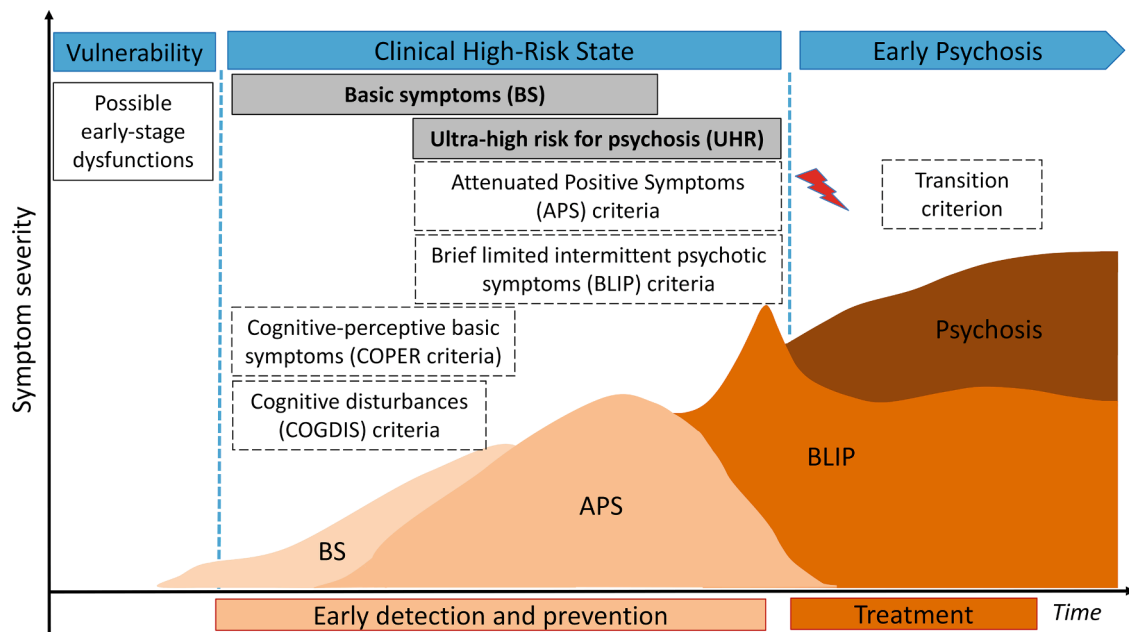


Fig. 1. Model of the severity- and time-specific course of psychosis including basic symptoms and ultra-high-risk states. Adapted from Fusar-Poli et al. (2013) and used with the authors' permission.

Development of Mental Health Services (ZInEP) project (Theodoridou et al., 2014). Subjects (males and females aged 16–33) were recruited by specialized psychiatric early recognition units in the Greater Zurich Area (BS/UHR) and using announcements (HC). The Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) was administered in the HC group to rule out any present or past psychiatric illnesses. Basic symptoms were assessed using the adult (Schultze-Lutter et al., 2007) or child/youth (Schultze-Lutter and Koch, 2010) versions of the Schizophrenia Proneness Instrument. Specifically, individuals were assigned to the BS group when at least one COPER symptom or at least two COGDIS symptoms were present. The UHR criteria were assessed using the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2001) and met when at least one BLIPS or one APS state-trait criterion was fulfilled. Intelligence was estimated using a multiple-choice vocabulary intelligence test (Mehrfachwahl Wortschatz Test, Version B; MWT-B) (Lehr, 1999) and for those aged below 20 years using a fluid nonverbal intelligence test (Leistungsprüfsystem, subtest 3; LPS-3) (Horn, 1983). Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Meeting any of the following criteria resulted in study exclusion: any past or present mental illness, standard contraindications to magnetic resonance imaging (MRI) examination, pregnancy, history of neurological disease or brain trauma, substance or alcohol dependence, or the inability to provide informed consent. All procedures contributing to this work were approved by the Cantonal Ethics Committee Zurich and comply with the ethical standards of the national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all participants and additionally, for those under 18 years of age, from their parents or legal guardians.

2.2. MRI data acquisition

Neuroimaging data were collected using a 3 T whole-body MRI scanner (Achieva, Philips Healthcare, Best, the Netherlands) and an 8-channel head coil. A diffusion-weighted single-shot spin-echo echoplanar imaging sequence with an isotropic resolution of 2 mm was acquired using the following parameters: repetition time (TR), 13009 ms; echo time (TE), 55 ms; field of view (FOV), 224 × 224 mm²; 75 contiguous transversal slices; slice thickness, 2 mm; acquisition

matrix, 112 × 112; SENSE factor, 2; partial Fourier encoding, 68%. Diffusion acquisition was conducted along 32 directions ($b = 1000$ s/mm²) in addition to one $b = 0$ s/mm² volume. The total scan time was 8 min 42 s. Moreover, T1-weighted 1-mm isotropic images were collected for anatomical referencing with a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence using the following parameters: TR, 8.3 ms; TE, 3.8 ms; FOV, 240 × 240 mm²; flip angle, 8°; 160 sagittal slices; slice thickness, 1 mm, in-plane-resolution, 1 × 1 mm². One individual from the HC group, one from the BC group, and three from the UHR group (altogether 5 out of 117) were excluded from the final analyses owing to signal artifacts identified in the quality assessment. The four calculated DTI scalars were fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) and were investigated, because they may provide refined information on the underlying WM architecture (Aung et al., 2013) and, in some studies, they revealed a distinct pattern in patients with the same conditions, such as schizophrenia (Clark et al., 2011; Klauser et al., 2017).

2.3. Pre-processing and quality assessment

Pre-processing of diffusion data and quality assessment were performed prior to statistical analysis. The pipeline details are described as follows. A multiple-step assessment was implemented to maximize the signal quality evaluation and detect image artifacts. First, denoising of the diffusion data was performed in MRtrix3 (Brain Research Institute, Melbourne, Australia, v0.3.12) (Tournier et al., 2012) to quantify the noise level based on the truncated spherical harmonics fit. Second, tensor residuals were calculated after fitting a tensor model to the diffusion data, and nine slices across all slices and diffusion directions containing the highest residuals were generated for visual inspection. Third, mean signal intensity for each acquired diffusion direction was plotted and inspected along the three orthogonal directions (slice, read, and phase), and T1 contour overlays onto the non-diffusion-weighted $b = 0$ image were computed in sagittal, axial, and coronal planes to check for remaining distortions. The datasets were pre-processed to correct for subject motion and distortions by using eddy in FSL (Analysis Group, FMRIB Software Library, Oxford, UK, v6.0) tools (Andersson and Sotiropoulos, 2016; Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). The brain extraction was performed using bet (Smith,

2002) to remove non-brain tissue and to conduct skull stripping. Additionally, residual susceptibility-induced distortions caused by EPI sequences were corrected by the *bdp* algorithm in BrainSuite (Bhushan et al., 2015) incorporating the T1-weighted MPRAGE image as reference. Finally, the tensor fitting and computation of four tensor metrics were performed. FA (most broadly used), computed as the variance among the three orthogonal eigenvectors of diffusion tensors (Hagmann et al., 2006; Mandl et al., 2008), is considered a proxy of WM integrity and most probably reflects its geometrical properties that may be influenced by the geometrical fiber configuration, density, and axon diameter, as well as myelination (Friedrich et al., 2020). MD is an overall and rotationally invariant diffusion marker (Landman et al., 2007), AD reflects axonal integrity associated with damage or fragmentation (Budde et al., 2009), and RD has been primarily linked to myelin properties and fiber coherence (Sun et al., 2006).

2.4. Data analysis

Voxelwise analysis steps were performed using the Tract-Based Spatial Statistics (TBSS) pipeline (Smith et al., 2006) implemented in FSL. FA maps were aligned to a $1 \times 1 \times 1$ mm standard space, by using nonlinear registration to the MNI152 (Montreal Neurological Institute) template. A mean FA map was generated from the subject-wise FA images and subsequently skeletonized to include the shared WM tracts. The mean FA skeleton was thresholded at a value of 0.2, and individual FA maps were projected onto the derived skeleton image. All non-FA tensor measures were derived using the *tbss_non_FA* script in FSL, which employs the same operations for non-linear registration, warping, and skeleton projection as for the FA maps. Group-level statistics were performed with Permutation Analysis of Linear Models (PALM) (Winkler et al., 2014) using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) with 10,000 random permutations and a family-wise error (FWE) rate of $p < 0.05$. In contrast to other methods, TFCE does not necessitate defining arbitrary thresholds for cluster size. Six pairwise contrasts were examined, including sex and (demeaned) age as nuisance regressors. Following the computational evidence that ANOVA with pairwise comparisons does not always properly control the error rate in brain imaging studies, the permutation-based approach was applied to correct for multiple hypothesis testing and to adjust the p -values accordingly, as proposed and described in detail by Alberton and colleagues (Alberton et al., 2020). While multiple testing correction standards differ among researchers and specific study objectives, results withstanding the TFCE method with 10,000 permutations in the TBSS analysis may be considered as sufficiently corrected. To enable readers to more thoroughly evaluate the findings, both corrections ($fwep = FWE$ p -value and $cfwep = FWE$ p -value corrected across contrasts in PALM terminology) are clearly reported in the Results section. Additionally, we also explored the TBSS differences between the at-risk subjects who transitioned to a diagnosis of schizophrenia (code F20 according to the 10th Revision of the International Classification of Diseases (World Health Organization, 1992)) (RISK-T) versus those who did not transition (RISK-NT) within a 3-year follow-up period and versus HC individuals. For these analyses, a two-sample t -test using the same nuisance regressors and two contrasts was conducted in PALM. The structures corresponding to significant clusters were identified using the automated atlas query function *autoaq* in FSL based on the ICBM-DTI-81 White Matter Labels, the JHU White Matter Tractography Atlas, and the Juelich Histological Atlas combined with visual inspection. To complement the above analysis with potential neural correlates of symptoms, we calculated partial correlations (controlling for age) between FA, RD, MD, and AD values in 11 regions of interest (ROIs) and individual SIPS subscale scores (Positive, Negative, General, Disorganization) across the at-risk groups. The ROIs (the body, genu, splenium [of the corpus callosum], left and right anterior corona radiata, left and right anterior thalamic radiation, left and right superior longitudinal fasciculus, left and right superior fronto-occipital fasciculus) were

chosen based on their hypothesized associations with symptoms and previously published results in schizophrenia. The anterior thalamic radiation and superior longitudinal fasciculus ROIs were derived from the JHU White Matter Tractography Atlas and thresholded at 20%; all the other ROIs were derived from the JHU White Matter Tractography Atlas. An FDR correction ($p < 0.05$) was applied over 44 tests (11 ROIs, each with four symptom scores) per modality.

3. Results

3.1. Demographic and symptom data

Table 1 provides detailed participant characteristics. The three groups did not significantly differ in age, sex, handedness, or estimated IQ. There were significant differences among the at-risk groups for the General ($p < 0.001$), Positive ($p < 0.001$), and Negative ($p < 0.047$) symptoms of the SIPS, with higher scores present in the UHR group, but not for the Disorganization SIPS symptoms. Both at-risk groups also differed in the Global Assessment of Functioning, notably, with significantly higher scores present in the BS group ($p = 0.042$). Most of the participants in the UHR group (29 out of 37) also met the BS criteria. Nine individuals from each of the two at-risk groups were receiving antipsychotic medication. Eleven participants (four BS subjects and seven UHR subjects) transitioned to schizophrenia within a 3-year period (mean time to transition, 11.27 months; range, 2–33 months).

Table 1
Demographic and symptom characteristics of the study sample.

	HC (<i>n</i> = 32)	BS (<i>n</i> = 43)	UHR (<i>n</i> = 37)	Test statistic (χ^2 , <i>F</i> , <i>U</i>)	<i>p</i> - value
Age (years)	21.72 (3.84)	23.09 (4.12)	20.89 (4.34)	<i>F</i> = 2.931	0.058
Sex, male/female (% male)	14/18 (43.75)	22/21 (51.11)	23/14 (62.16)	χ^2 = 2.398	0.302
Handedness, r/l/a ^a	25/4/3	40/1/2	34/2/0	χ^2 = 6.652	0.156
Estimated IQ ^b	112.30 (14.08)	104.89 (10.64)	108.38 (14.22)	<i>F</i> = 2.989	0.055
GAF	NA	57.90 (16.16)	52.28 (12.16)	<i>U</i> = 937.5	0.042
SIPS Positive	NA	4.84 (3.07)	10.3 (3.48)	<i>U</i> = 186.5	<0.001
SIPS Negative	NA	10.93 (5.51)	13.47 (5.40)	<i>U</i> = 590	0.047
SIPS General	NA	2.81 (1.84)	5.35 (2.54)	<i>U</i> = 315.5	<0.001
SIPS Disorganization	NA	7.28 (3.22)	8.22 (3.37)	<i>U</i> = 640.5	0.137
CPZ equivalent n medicated	NA	39.56 (115.71) <i>n</i> = 9	21.72 (55.27) <i>n</i> = 9	<i>U</i> = 781	0.853
Transition to F20 (by 3-year follow-up), % group, mean time in months	NA	4 (RISK- T), 9.3%, 9.50	7 (RISK- T), 18.9%, 12.29		

Abbreviations: BS, basic symptoms group; CPZ, chlorpromazine; GAF, Global Assessment of Functioning; HC, healthy controls group; r/l/a, right/left/ambidextrous; SIPS, Structured Interview for Prodromal Syndromes; UHR, ultra-high risk for psychosis group. ^ameasured by the Edinburgh Handedness Inventory; ^bmeasured by the multiple-choice vocabulary intelligence test (MWT-B) for those aged <20 years and by the fluid nonverbal intelligence test (LPS-3) for those aged >20 years. Values are means and standard deviations, unless otherwise stated. Statistics: χ^2 , Chi-square test statistic; *F*, ANOVA *F*-statistic; *U*, Mann-Whitney *U* test statistic. Significance was assessed at $p < 0.05$.

3.2. Tract-based spatial statistics: at-risk groups and controls

In the whole-brain TBSS analyses, UHR and HC groups differed in FA in the splenium of the corpus callosum. Specifically, FA in this region was found to be reduced in UHR individuals, compared to controls (cluster size, 420 voxels; max at $X = -10, Y = -32, Z = 25$; $f_{wep} < 0.05$; Cohen's $d = 0.12$; Fig. 2). However, the significance of this finding did not remain after additional correction over contrasts performed within the modality and therefore should be considered as indicative of subtle differences. The f_{wep} threshold of 0.05 corresponded to the cf_{wep} threshold of approximately 0.23 in this analysis with six pairwise contrasts. No further significant results at either level of thresholding were found for any of the examined contrasts (i.e., UHR vs. HC, UHR vs. BS, BS vs. HC) or modalities (i.e., FA, RD, MD, AD).

3.3. Associations with subclinical symptoms

Significant negative partial correlations after the FDR correction between DTI values and symptomatic presentation were found for the SIPS General symptoms and FA in the following ROIs: the splenium ($-0.313, p_{uncor} = 0.005$), the left and right anterior corona radiata ($-0.302, p_{uncor} = 0.007$; $-0.296, p_{uncor} = 0.008$), the left and right anterior thalamic radiation ($-0.349, p_{uncor} = 0.002$; $-0.310, p_{uncor} = 0.005$), and the left superior fronto-occipital fasciculus ($-0.315, p_{uncor} = 0.005$). There was also an effect for the left superior fronto-occipital fasciculus and the SIPS Negative symptoms ($-0.306, p_{uncor} = 0.006$). There were no other significant findings in this analysis. Fig. 3 depicts the relevant scatterplots.

3.4. Tract-based spatial statistics: transition to schizophrenia

Further explorations of the whole brain WM between the RISK-NT ($n = 67$) and RISK-T ($n = 11$) groups, as well as between the HC ($n = 32$) and RISK-T ($n = 11$) groups were conducted at the thresholds corrected ($cf_{wep} < 0.05$) and uncorrected ($f_{wep} < 0.05$) for contrasts. The cf_{wep} threshold of 0.05 corresponded to the f_{wep} threshold of approximately 0.03 in this analysis. To increase the methodological homogeneity, the RISK-T group was comprised of converters to schizophrenia only, and two individuals diagnosed with a brief psychotic disorder (F23) were excluded from this analysis. The RISK-NT versus RISK-T groups did not differ in age ($p = 0.392$), sex ($p = 0.602$), or estimated IQ ($p = 0.147$). Similarly, no differences in these variables were found in the HC versus RISK-T groups ($p = 0.668, p = 0.255, p = 0.052$, respectively). In the RISK-T individuals (compared to the RISK-NT individuals), a cluster of

lower FA was found at a stringent significance threshold and further clusters of lower FA and higher RD were found at a more lenient significance threshold. Large clusters of lower FA and of higher RD in the RISK-T individuals, relative to HC individuals, were identified at both significance thresholds. The findings include the whole corpus callosum, forceps minor, forceps major, anterior and superior corona radiata, anterior thalamic radiation, fornix, and corticospinal tract (Table 2, Fig. 4).

4. Discussion

This study compared WM microstructure in three groups, from subjects with a symptom burden in the lower portion of the spectrum of the psychosis continuum prior to any formal diagnosis (UHR and BS only) and from reference control individuals (HC). The main finding was specific to the splenium and limited to the UHR versus HC contrast for FA at a non-conservative correction threshold. FA in this area was negatively associated with the general domain of prodromal symptoms. In those who transitioned into schizophrenia within 3 years (relative to those who did not transition and healthy controls), lower FA and higher RD, particularly in the corpus callosum, corona radiata, and motor/sensory tracts, were found, conforming to a more severe WM disruption pattern. No differences were found for MD and AD in any of these analyses.

Indications of abnormalities of the corpus callosum with a particular role of the splenium in schizophrenia date from early histological research (Innocenti et al., 2003) and subsequent MRI studies (Kelly et al., 2018; Patel et al., 2011). The splenium is a bulbous structure overlapping with the tela choroidea of the third ventricle and the mid-brain (Knyazeva, 2013). Splenial FA was found to be lowest in schizophrenia patients with impaired illness awareness, as compared to patients with intact illness awareness and healthy controls (Gerretsen et al., 2019). A handful of studies examined DTI indices in at-risk individuals, revealing distinct effects in the corpus callosum. For example, FA in the splenium in UHR individuals was positioned intermediate compared to individuals with first-episode psychosis and controls (Carletti et al., 2012). Significant FA reductions relative to controls were also identified in at-risk mental state individuals, specifically in the whole corpus callosum (genu, trunk, splenium) (Saito et al., 2017), in a subsection of it (Katagiri et al., 2015), and in its left portion, among other regions (Wang et al., 2016). In contrast, some studies detected no difference in FA between UHR individuals and controls (Bakker et al., 2016; Clemm von Hohenberg et al., 2014; Peters et al., 2010), while another investigation identified a significant difference in the corpus

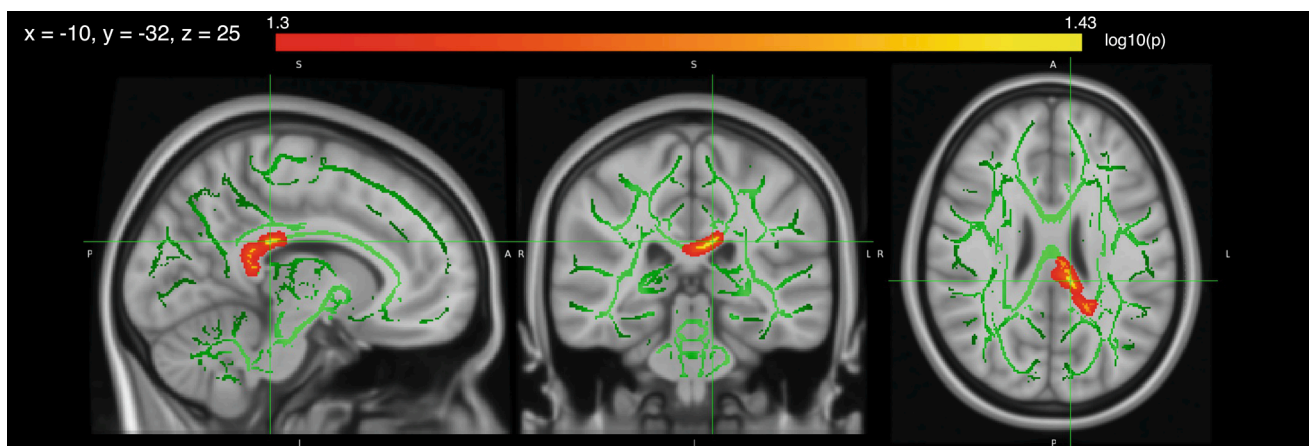


Fig. 2. Output from the main tract-based spatial statistics. The findings are visualized in red on the green TBSS skeleton and using the MNI152 brain template. The results were computed using Threshold-Free Cluster Enhancement with 10,000 permutations and a family-wise error rate of $p < 0.05$, but with no further correction over the contrasts performed. Red areas depict reduced fractional anisotropy in the splenium of UHR individuals, compared to controls (420 voxels). Results were visually emphasized for presentation using the *tbss_fill* function in FSL.

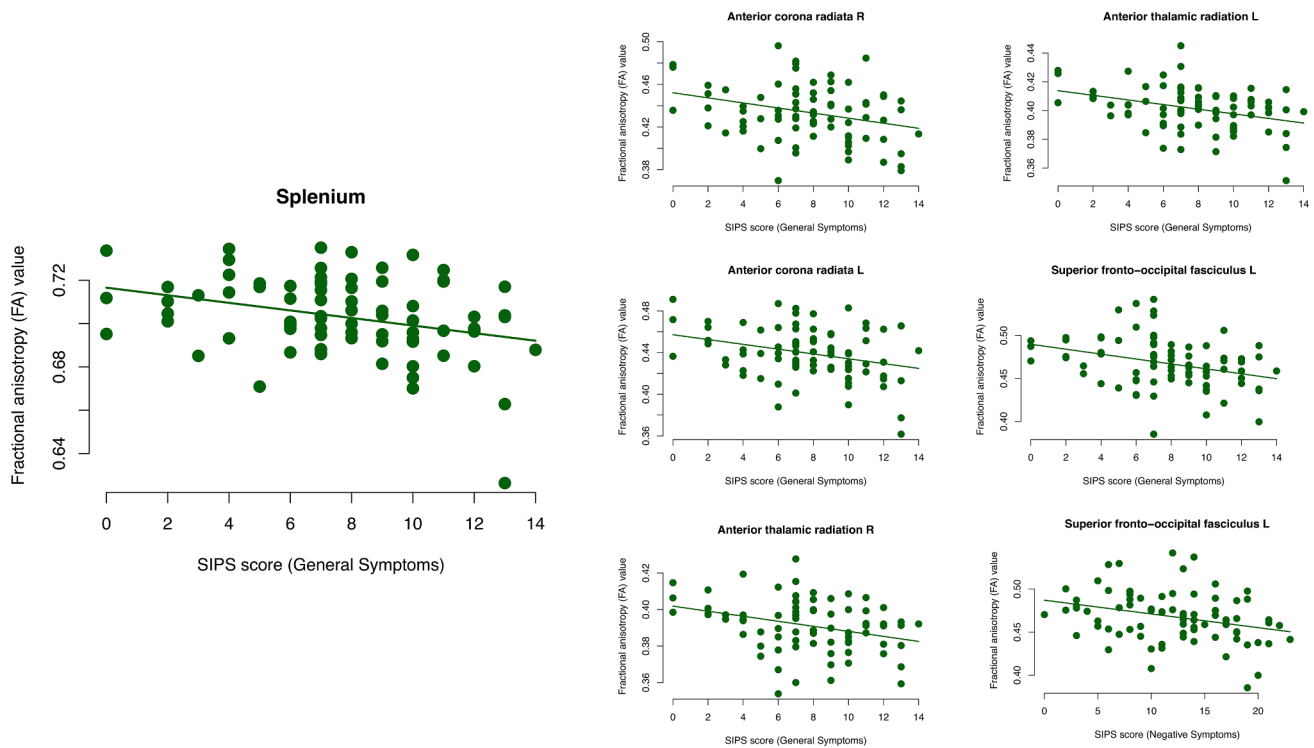


Fig. 3. Scatterplots of significant associations between fractional anisotropy and symptoms. Partial correlations controlling for age were calculated among the pooled at-risk individuals (UHR + BS only groups; $n = 80$; $p < 0.05$, FDR-corrected). SIPS, Structured Interview for Prodromal Syndromes.

Table 2
Results of the analysis comparing converters and non-converters to schizophrenia.

Contrast	Modality	Threshold	Voxels	Max X	Max Y	Max Z	Corresponding structure
RISK-T < RISK-NT	FA	cfwep, $p < 0.05$	301	-17	14	35	BCC, SCR l, ACR l, CCG l
RISK-T < RISK-NT	FA	fwep, $p < 0.05$	1907	10	-42	15	SCC, FMa, FST l/r, ATR l
			1244	-17	14	35	BCC, GCC, SCR l, ACR l, FMI, PCR l, CT l, CCG l
			1029	17	-7	35	BCC, GCC, SCR r, ACR r, FMI, PCR r
			218	4	-21	-2	ATR r
			50	19	-15	-7	CT r, PLIC r
			28	-15	-21	-15	CT r
RISK-T > RISK-NT	RD	fwep, $p < 0.05$	1528	-17	15	36	BCC, GCC, SCR l, ACR l/r, FMI, PCR l, CT l, CCG l
			852	11	-42	15	SCC, PTR l, FMa
RISK-T < HC	FA	cfwep, $p < 0.05$	9403	-17	14	35	BCC, SCC, GCC, ACR l/r, SCR l/r, PTR r, IFOF r, ILF r, CT r
			117	26	-52	16	SCC, FMa, PCR r, PTR r
RISK-T < HC	FA	fwep, $p < 0.05$	13,894	-14	-45	12	BCC, SCC, GCC, ACR l/r, SCR l/r, PTR r, F, FMa, FMI, CT l
			781	4	-20	-2	ATR r
			129	14	-20	-16	CT r
			60	0	-10	17	F
			55	18	-90	17	FMa, ILF r, IFOF r
RISK-T > HC	RD	cfwep, $p < 0.05$	7803	-12	-45	18	BCC, SCC, GCC, ACR l/r, SCR l/r, F, FMa, FMI
			327	13	-28	13	ATR r, F
			26	15	-34	56	CT r
			18	3	-10	-1	ATR r
RISK-T > HC	RD	fwep, $p < 0.05$	22,735	-10	-42	17	BCC, SCC, GCC, ACR l/r, SCR l/r, ATR l/r, F, FMa, FMI, SLF l/r, CT l/r

Abbreviations: cfwep, family-wise error (FEW) p -value corrected across contrasts; FA, fractional anisotropy; fwep, family-wise error (FEW) p -value; HC, healthy controls; l, left hemisphere; r, right hemisphere; RD, radial diffusivity; RISK-NT, non-converters (those who did not transition) to schizophrenia; RISK-T, converters (those who transitioned) to schizophrenia. Tracts: ACR, anterior corona radiata; ATR, anterior thalamic radiation; BCC, body of corpus callosum; CCG, cingulum (cingulate gyrus); CT, corticospinal tract; GCC, genu of corpus callosum; F, fornix; FMa, forceps major; FMI, forceps minor; FST, fornix stria terminalis; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; PCR, posterior corona radiata; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; SCC, splenium of corpus callosum; SCR, superior corona radiata; SLF, superior longitudinal fasciculus.

callosus body and splenium only in UHR subjects who developed psychosis over a 36-month follow-up period (Rigucci et al., 2016). Thus, the results hitherto should be considered inconsistent. While our key finding was not significant after correction across all contrasts, we interpret this outcome as correspondent with the subclinical portion of the psychosis continuum examined, with stronger results expected under increased symptom severity and persistence (DeRosse and Karlsgodt, 2015; Van Os

et al., 2009). Accordingly, the disruption of WM integrity in the splenium may be an early subclinical vulnerability marker of psychosis. This effect possibly reflects a focal disruption in neurons or axons, related to abnormally organized or less densely packed fibers, as occurs with compromised intra-axonal microtubular density, altered cell membrane permeability, or lower degrees of myelination. The fibers in this region include functionally important projections from the temporal, parietal,

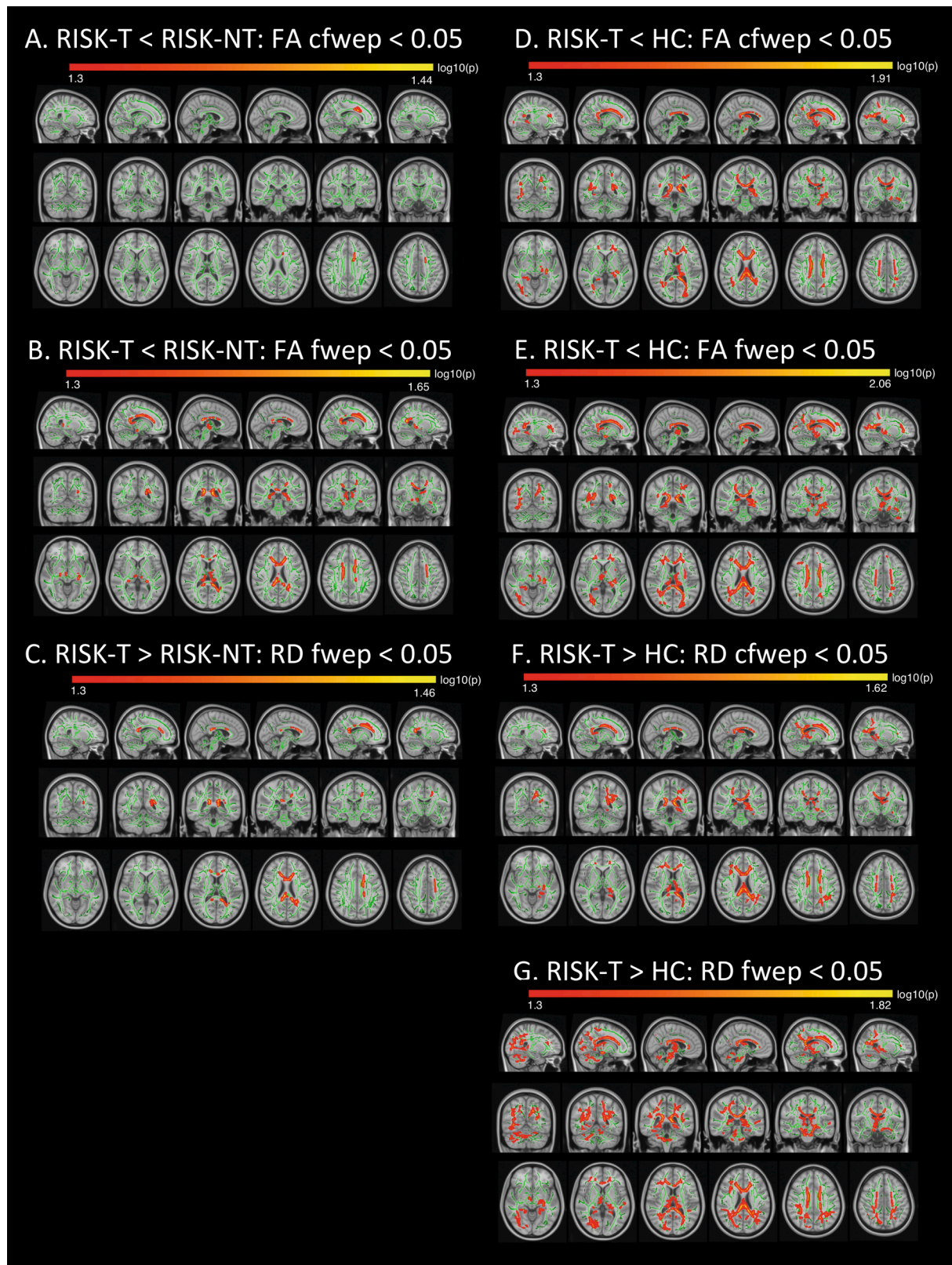


Fig. 4. Output from the tract-based spatial statistics analysis for converters versus non-converters to schizophrenia (left panel A–C) and converters versus healthy controls (right panel D–G). The findings are visualized in red on the green TBSS skeleton and using the MNI152 brain template. The results were computed using Threshold-Free Cluster Enhancement with 10,000 permutations and a family-wise error rate of $p < 0.05$ (fwep). Additional correction for contrasts is marked as cfwep. Results were visually emphasized for presentation using the *tbss_fill* function in FSL. FA, fractional anisotropy; HC, healthy controls; RD, radial diffusivity; RISK-NT, risk individuals who did not transition to schizophrenia; RISK-T, risk individuals who transitioned to schizophrenia.

and occipital cortices (Raybaud, 2010). The observed subtle abnormality in this major interhemispheric WM tract also supports the theory of structural dysconnectivity (Pettersson-Yeo et al., 2011). The corpus callosum myelinates from birth to adolescence, with the genu and splenium each following distinct trajectories (Giedd et al., 1999; Tanaka-Arakawa et al., 2015), i.e., higher FA and a lower isotropic diffusion coefficient for the splenium (Schneider et al., 2004), indicative of earlier myelination. Thus, an early structural deficiency or maldevelopment of the splenium could affect the speed and quality of interhemispheric communication. This may further lead to cognitive-perceptual deficits in dependency of other factors, such as environmental exposures (Davis et al., 2016), and spread along a severity continuum. Supporting this view, a recent study identified stage-specific effects in schizophrenia, with callosal microstructural alterations at an early disorder stage and volumetric callosal macrostructural alterations at a late stage (Madigand et al., 2019). Our discussion would be incomplete without mentioning possible developmental WM processes, as exemplified by a recent finding on dynamic age-related and fiber-specific changes across the time-course of schizophrenia (Cetin-Karayumak et al., 2020). In a large sample, FA was shown to be up to 7% lower across the whole lifespan in schizophrenia patients, compared to controls, as well as characterized by an earlier peak maturation (at 27 years versus 33 years). In addition, early developmental abnormalities were found in limbic fibers, both abnormal maturation and accelerated aging were found in long-range association fibers, and, of particularly relevance to the present work, severe abnormalities and accelerated aging were found in callosal fibers (Cetin-Karayumak et al., 2020). Our results indicate that the spatial sequence of WM development for individuals within the at-risk window may indeed differ from a normal healthy course.

A lack of significant effects for the only BS group suggests that this subclinical syndrome is not yet matched by measurable changes in WM microstructure. Notably, the rare findings in BS described in the literature have pointed to functional differences, such as a loss of typical anticorrelation between task positive and task negative brain networks (Wotruba et al., 2014) and abnormal anterior insula-driven network co-activation patterns (Bolton et al., 2020), suggesting a disjunction between internally and externally directed states. Reported structural dissimilarities include lower grey matter volumes in temporo-limbic regions compared to controls, with additional cortical reductions in frontal areas compared to UHR individuals (Koutsouleris et al., 2009), and increasing structural-functional pathology of the hippocampus spanning HC, BS, and UHR groups (Hurlmann et al., 2008), enabling distinction between the two at-risk groups. A common finding from these few functional and morphometric brain studies on early and late risk for psychosis is deterioration as a function of increasing risk. This aligns with general observations of cognitive functions indicating that BS individuals overall perform intermediate to controls and UHR individuals (Schultze-Lutter et al., 2016). In support of this view, a recent study showed that individuals meeting both BS and UHR criteria demonstrated more advanced grey matter volume reductions, compared to those from BS or UHR groups only (Hubl et al., 2020). Some investigations have reported higher odds of a transition to psychosis for the subpopulation satisfying both criteria (Ruhrmann et al., 2010; Schultze-Lutter et al., 2014), but this finding has not been replicated (Hengartner et al., 2017; Youn et al., 2020). While our work did not provide evidence that persons manifesting only BS differ from HC and UHR individuals in WM microstructure, DTI may be insufficiently sensitive to detect the earliest signs of psychotic deterioration below the diagnostic cutoff. Another explanation may be that in their formulation, BS criteria are a heterogeneous set of immediate self-experienced disturbances across domains and functions. Thus, a more differentiated clustering of BS may help to elucidate the underlying brain mechanisms of this early symptomatic expression (Schultze-Lutter et al., 2016).

We observed a negative correlation between the FA values, which range between 0 (reflecting perfectly isotropic diffusion) and 1

(reflecting extremely anisotropic diffusion) (Pierpaoli et al., 1996) and primarily the general symptom domain of the SIPS. Notably, the effect was found for the splenium among other regions. These findings add to the current literature on WM neural correlates of symptoms across the psychosis spectrum (Parnanzone et al., 2017; Waszczuk et al., 2021). The association of FA with general symptoms, which include sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance of stress, may be interpreted as deteriorations contributing to the overall unspecific symptomatic presentation. This may be an early marker of transdiagnostic relevance, as suggested by a review indicating that WM pathology, especially that affecting the corpus callosum, is shared across several neuropsychiatric disorders (Sagarwala and Nasrallah, 2020); this conclusion was also supported by a recent mega-analysis (Koshiyama et al., 2020), making the corpus callosum a promising structural candidate underlying a high-order psychopathology “p” factor (Caspi and Moffitt, 2018). Another study using a latent factor approach further demonstrated that the properties of the corpus callosum are related to general psychopathology, while second-order factors are reflected in abnormalities of more specific WM tracts (Hinton et al., 2019). Compromised WM integrity in the splenium may represent not only a biomarker, but also a therapeutic target. Notably, excitatory repetitive transcranial magnetic stimulation was found to induce increases in WM FA in various conditions, such as depression (Hassan et al., 2021) and stroke (Allendorfer et al., 2012). It has been suggested that the observed amelioration of illness awareness in schizophrenia after neuro-stimulation is caused by restored hemispheric balance (Chang et al., 2018). As seen in a small sample of at-risk patients, symptomatic improvement was associated with FA increases in the corpus callosum longitudinally (Katagiri et al., 2015). The other observed correlations involved the bilateral anterior corona radiata (a prominent part of the limbic-thalamo-cortical circuitry and the key element of the emotional and cognitive control network), the bilateral thalamic radiation (a major projection from the thalamus penetrating the anterior limb of the internal capsule), and the left superior fronto-occipital fasciculus (a subcallosal association bundle connecting the frontal and occipital lobes).

Our exploratory analysis focused on the transition identified more severe WM differences (i.e., decreased FA and increased RD) in the RISK-T group relative to the RISK-NT group, which were even more extensive relative to the HC group. There was high regional overlap between FA and RD findings in this analysis. First, we observed substantial differences in the whole corpus callosum. This corroborates with a recent systematic review of structural brain changes in highrisk individuals, with three out of four included longitudinal studies reporting reduced FA in the corpus callosum in those who transitioned to psychosis (Merritt et al., 2021). We also found effects in the anterior and superior corona radiata. Notably, both corpus callosum (especially the genu and body) and anterior corona radiata were the very top findings in the study by the ENIGMA Schizophrenia DTI Working Group (Kelly et al., 2018). The corona radiata is the crossroads of association, projection, and callosal fibers, connecting the thalamus, brainstem and cortex, especially the prefrontal cortex and anterior cingulate (Wakana et al., 2004). Reductions of FA in the anterior corona radiata have been associated with a formal thought disorder (Chen et al., 2022), hallucinatory experiences (Ćurčić-Blake et al., 2015), and social function (Koshiyama et al., 2018). Moreover, our analysis showed differences in the thalamic radiations and motor fibers, such as the corticospinal tract. The motor domain has been repeatedly indicated as a vulnerable area in schizophrenia (Abboud et al., 2017). Previous work has demonstrated associations of altered WM with motor abnormalities, as exemplified by studies on neurological soft signs (Viher et al., 2022), catatonia (Viher et al., 2020), and motor slowing (Dean et al., 2018), collectively pointing to a close relationship between various symptomatic trajectories in psychosis and tract-specific changes. Notably, coexisting FA decreases and RD increases without simultaneous effects for other indices, such as AD or MD, characterize some preceding DTI studies in

schizophrenia (Hummer et al., 2018; Rigucci et al., 2016; Tønnesen et al., 2018). FA is a proxy of microstructural integrity, being relatively unspecific in terms of underlying pathological processes. RD reflects diffusion perpendicular to the axonal fibers and is presumably better positioned as a proxy of myelination (Alexander et al., 2007). It has been suggested that FA and RD, unlike other indices, are early-stage-specific biomarkers (Acosta-Cabronero et al., 2012), which aligns with our results, i.e., no observed effects for MD or AD. Notably, in a recent study in UHR individuals, global WM FA predicted symptoms at 6 months and a transition to psychosis at 12 months (Kristensen et al., 2021). The pattern of our results for both UHR and RISK-T subgroups aligns with grey matter findings from a largely identical group of participants, as reported in our previous publication (Buechler et al., 2020). Specifically, relative to HC and BS subjects, UHR individuals presented with larger cortical volumes in frontal and parietal regions, which were driven by larger cortical surface areas, while a cortical thinning was identified for RISK-T compared to RISK-NT subjects. These effects might have originated from aberrant pruning linked to a neurodevelopmental delay and stress-induced functional aggravation (Buechler et al., 2020). As repeatedly demonstrated, subcortical, cortical, and WM changes underlying psychotic disorders are anatomically and causally linked (Douaud et al., 2007; Hoistad et al., 2009; Stauffer et al., 2021).

As noted above, an emerging issue involves putative mechanisms leading to observed abnormalities in the splenium and other WM tracts, as well as their implications for the brain system. Neurodegenerative (Kochunov and Hong, 2014) and neuroinflammatory processes (Najjar and Pearlman, 2015) both provide putative explanatory foundations for the origin of brain tissue deterioration. The aggregated evidence links schizophrenia with changes in proinflammatory cytokines (based on protein level, mRNA expression, and gene polymorphism data) (Rodrigues-Amorim et al., 2018), with microglial activation and proliferation in WM, as well as with reduced astroglial density, especially in the cingulum and corpus callosum (Najjar and Pearlman, 2015). Notably, both structures were included in our key findings. A longer neuroinflammatory response in WM may affect oligodendrocytes and myelin sheaths around axons (Chew et al., 2013). These observations of excessive inflammatory states in schizophrenia may further lead to novel prevention or treatment approaches (Cho et al., 2019); however, many factors linking molecular regulatory mechanisms, WM, and manifested psychopathology await deciphering in the future (Murphy et al., 2021).

This study has some limitations. One of them is the non-conservative correction threshold, and the study conclusions should therefore be interpreted proportionally and in light of this. The effects of medication, which was, however, equally distributed in the at-risk groups, is a potential confounding factor that cannot be completely ruled out. Besides, while the BS criteria were exclusively fulfilled by those who qualified for the BS group, most of the participants in the UHR group also met the BS criteria. Although an isolated presentation of BS and UHR criteria is less common, future investigations should further explore the WM microstructure by differentiating between the UHR symptoms with and without concomitant BS symptomatology. In addition, our results are cross-sectional and correlational, which precludes inferences of causality. Future longitudinal studies are necessary to confirm our findings reflect the key neural mechanisms producing the symptoms of psychotic deterioration. Furthermore, while TBSS is considered the leading and state-of-the-art method for voxelwise analysis of diffusion signals, it may generate possible biases in the skeleton projection step for some fiber geometries (Bach et al., 2014). Last but not least, the interpretation of DTI scalars is not unequivocal (Winkowski et al., 2018), and disentangling the exact mechanisms behind the signal differences, such as myelination or fiber architecture, may be improved by using the magnetization transfer ratio or free water imaging contrasts (Mandl et al., 2015).

5. Conclusions

This is the first study, to our knowledge, to investigate the brain WM within two at-risk paradigm subtypes. Based on this work and past studies, the WM microstructure appears to be a meaningful and severity-related brain phenotype associated with the psychosis spectrum. It may be monitored over the course of symptom development from early signs to diagnostically ascertained stages, with the intention of elucidating its role as a putative biomarker or therapeutic target.

CRediT authorship contribution statement

Lukasz Smigielski: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Philipp Stämpfli:** Methodology, Formal analysis, Writing – review & editing. **Diana Wotruba:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing. **Roman Buechler:** Investigation, Data curation, Writing – review & editing. **Stefan Sommer:** Methodology, Formal analysis, Writing – review & editing. **Miriam Gerstenberg:** Investigation, Writing – review & editing. **Anastasia Theodoridou:** Conceptualization, Writing – review & editing, Supervision. **Susanne Walitza:** Resources, Writing – review & editing, Supervision. **Wulf Rössler:** Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition. **Karsten Heekeren:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

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