Changes in negative symptoms are linked to white matter changes in superior longitudinal fasciculus in individuals at ultra-high risk for psychosis

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A B S T R A C T
Aim: Growing evidence suggests that subtle white matter (WM) alterations are associated with psychopathology in individuals at ultra-high risk for psychosis (UHR). However, the longitudinal relationship between symptom progression and WM changes over time remains under-explored. Here, we examine associations between changes in clinical symptoms and changes in WM over six months in a large UHR-cohort.

Methods: 110 UHR-individuals and 59 healthy controls underwent diffusion weighted imaging at baseline and after six months. Group × time effects on fractional anisotropy (FA) were tested globally and in four predefined regions of interest (ROIs) bilaterally using linear modelling with repeated measures. Correlations between the changes in clinical symptoms and FA changes in the ROIs were examined with Pearson’s correlation. A partial least squares correlation-technique (PLS-C) explored multivariate associations between patterns of changes in psychopathology, regional FA and additional WM indices.

Results: At baseline, UHR-individuals displayed significantly lower FA globally (p = 0.018; F = 12.274), in right superior longitudinal fasciculus (p = 0.02; Adj R² = 0.07) and in left uncinate fasciculus (p = 0.048; Adj R² = 0.058) compared to controls (corrected). We identified a group × time interaction in global FA and right superior longitudinal fasciculus, but the finding did not survive multiple comparisons. However, an increase of negative symptoms in UHR-individuals correlated with FA increase in right superior longitudinal fasciculus (p = 0.048, corrected, r = 0.357), and this finding was supported by the multivariate PLS-C.

Conclusion: We found a positive correlation with a moderate effect between change in negative symptoms and FA change over 6 months in right superior longitudinal fasciculus. This link appeared mainly to reflect a subgroup of UHR-individuals, which already at baseline presented as vulnerable.

1. Introduction
The ultra-high risk state (UHR) designates a putative prodromal phase, which may convert into frank psychosis. The UHR-state is defined by criteria of attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, and/or a genetic risk along with a functional decline (Yung et al., 2005). Research is critical for early intervention, considering the potential detrimental effects of psychosis (Bora et al.,...
Studies have shown cerebral white matter (WM) to be implicated in the pathophysiology of patients with psychotic disorders (Friston and Frith, 1995; Park and Friston, 2013), typically measured as lower fractional anisotropy (FA). Lower FA is often interpreted as impaired WM microstructure (Jones et al., 2013). The understanding of the underlying biological processes reflected in FA changes is aided by applying additional WM indices, such as axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). Combinations of these indices have been linked to loss of axonal coherence, demyelination, or neurodegeneration (Alexander et al., 2011, 2007; Pandyan et al., 2009; Song et al., 2002).

Studies have also demonstrated affected WM in UHR-individuals, although the changes appear more subtle than in patients with a psychotic disorder (Carletti et al., 2012). Frequently affected WM regions are the major association bundles interconnecting the frontal regions with the temporal and limbic regions (Clemm Von Hohenberg et al., 2014; Karlsgodt et al., 2009; Rigucci et al., 2016; Schmidt et al., 2015; Vijayakumar et al., 2016; Wang et al., 2016), as well as the large projection bundles connecting the subcortical structures (Katagiri et al., 2015; Saito et al., 2017).

Growing evidence suggests that WM alterations in UHR-individuals (Canu et al., 2015; Karlsgodt et al., 2012; Peters et al., 2010a; Pettersson-Yeo et al., 2011; Samartzis et al., 2014; Wheeler and Voineskos, 2014) are associated with progression to psychosis (Kristensen et al., 2021; Peters et al., 2010b; Sommer and Kahn, 2015) and to functional outcome (Krakauer et al., 2017). Cross-sectional studies have found regional lower FA to be associated with more severe attenuated psychotic symptoms (Nägeli et al., 2020), and widespread brain regions have been identified (Lagopoulos et al., 2013). In a previous cross-sectional study on an independent UHR-cohort, we identified links between clinical symptoms and functional level, and a pattern of aberrant WM, mainly lower regional FA (Krakauer et al., 2017). Furthermore, in a previous cross-sectional study on the current sample (Kristensen et al., 2019), we identified lower FA predominantly in superior longitudinal fasciculus, and demonstrated that widespread lower FA at baseline was associated with worse cognitive functioning in UHR-individuals.

Most studies in UHR-individuals are based on cross-sectional data and only few longitudinal studies with small sample sizes investigate WM changes over time and associations to changes in symptomatology (Bernard et al., 2017). Knowledge on the interconnected influence of neurobiology and psychopathology changing over the course of disease progression is lacking (Cannon, 2016). A major obstacle is the pronounced diagnostic heterogeneity of UHR-individuals (Stefanis et al., 2002). UHR-individuals range diagnostically from no psychiatric diagnoses, to severe comorbidity comprising affective-, anxiety-, and personality disorders, with a majority not transitioning to psychosis (Beck et al., 2019). Cross-sectional studies are inadequate for the identification of longitudinal WM changes specifically linked to symptom progression, particularly since shared regional WM changes have been demonstrated across diagnoses among patients with schizophrenia, autism spectrum disorders, and bipolar disorder (Dong et al., 2018; Jenkins et al., 2016; Koshiyama et al., 2020).

Longitudinal studies are required to identify the specific dynamic changes in WM and the relation to clinical changes (Merritt et al., 2021). A recent systematic review of longitudinal structural neuroimaging findings in high risk studies reported a group × time interaction on WM, primarily reporting lower regional FA (Merritt et al., 2021). In our previous independent longitudinal study comprising 30 UHR-individuals, we found that increase in FA in the superior longitudinal fasciculus correlated with a worsening of negative symptoms (Krakauer et al., 2018). Contradicting this finding, another study on longitudinal WM changes in the corpus callosum of UHR-individuals over one year reported a FA decrease in the genu of corpus callosum, which significantly correlated with worsening of negative symptoms (Saito et al., 2017). Studies in patients with schizophrenia have mainly indicated a negative correlation between FA and negative symptoms (Wolkin et al., 2003; Yang et al., 2017), frequently localized to WM extending from frontal regions to temporal and limbic regions (Vihriälä et al., 2016; Wible et al., 2001). Hence, the directionality of FA changes may depend on the patient population and the region examined, as demonstrated in a study by Thomason et al. (Thomason and Thompson, 2011). Consequently, replications are warranted.

Findings of disturbed WM underlying the frontal cortex consistently have been demonstrated in psychosis (Deroosse et al., 2015; Edbro et al., 2015; van den Heuvel et al., 2010; Weinberger et al., 2001). Studies have suggested, that WM alterations in frontal fasciculi may be the underlying biological substrate for i.e. negative symptoms (Wang et al., 2020), positive symptoms (Schmidt et al., 2015) and general psychopathology (Yang et al., 2017). Thus, we have predefined four WM regions of interest (ROIs) bilaterally, extending from the anterior part of the brain, and we specifically investigate the regions of the superior longitudinal fasciculus (SLF), the uncinate fasciculus (UF), the anterior corona radiata (ACR), and the anterior limb of internal capsule (ALIC).

1.1. Aims

This study aimed to investigate potential associations between changes in regional WM and changes in psychopathology over six months. We expected UHR-individuals to present with lower FA globally and in the predefined ROIs at baseline and six months follow-up when compared to matched HCs.

Our main analysis pertained to the examination of correlations between FA changes in the predefined ROIs and positive UHR-symptoms, negative symptoms, and functional level within the UHR-group. We aimed to replicate results from the previous longitudinal study from our group (Krakauer et al., 2018) on an independent sample, and we specifically expected that increase in FA in the SLF correlated to a worsening of negative symptoms.

Finally, we explored multivariate correlations between patterns of regional changes in FA, AD, RD, and MD and changes in clinical symptomatology using PLS-C analyses. We aimed to investigate the directionality of changes in WM indices across the preselected ROIs, when associated to clinical changes.

2. Methods

Data was acquired from a randomized clinical trial (RCT) examining the effect of cognitive remediation compared to treatment as usual (TAU) in UHR-individuals (The FOCUS-trial) (Glențoiţă et al., 2015). Participants were allocated to TAU (medication, contact to primary practitioner, supportive counselling, and psychotherapeutic interventions); or TAU plus cognitive remediation (manipulated neurocognitive and social cognitive remediation once a week for 20 weeks). Recruitment were from the psychiatric in- and outpatient facilities in Copenhagen, Denmark from April 2014 to December 2017. The trial protocol was approved by the Committee on Health Research Ethics of the Capital Region Denmark (H-6-2013-015). All participants provided written informed consent prior to inclusion.

The experimental intervention did not result in improvements in global cognition, level of functioning, or clinical symptoms (the primary and secondary outcomes of The FOCUS-trial) (Glențoiţă et al., 2020). As a sub study of the FOCUS-trial, we investigated the effect of cognitive remediation on WM changes in UHR-individuals (Kristensen et al., 2020), but found no global nor regional effect of allocation to treatment. Nevertheless, we included trial allocation as a covariate when testing within-group changes for UHR-individuals in WM and clinical symptoms. In the current study, we have extended the examination of longitudinal WM changes by including not previously analyzed longitudinal MRI-data from healthy controls (HCs), as well as novel analyzes of associations to longitudinal changes of clinical symptoms.
2.1. Participants

The baseline sample consisted of 110 help-seeking individuals, meeting at least one of the three UHR-criteria according to the Comprehensive Assessment of At-Risk Mental States (Yung et al., 2005): attenuated psychotic symptoms, and/or brief limited intermittent psychotic symptoms, and/or trait and vulnerability state along with a significant drop or sustained low functioning for the past year. Exclusion criteria were: a history of a psychotic episode of \( \geq \text{one-week's duration} \); psychiatric symptoms explained by a physical illness with psychotropic effect (e.g. delirium) or acute intoxication (e.g. cannabis use); a diagnosis of a serious developmental disorder (e.g., Asperger's syndrome or IQ < 70); or current treatment with methylphenidate. Fifty-seven HCs were concurrently included and matched to the UHR-individuals based on age, gender, ethnicity, and parental socioeconomic status. HCs had no current or previous psychiatric diagnoses, substance abuse or dependency, and no first-degree relative with a psychotic disorder. For details, see Flowchart at Supplementary Fig. S1.

2.2. Assessments

2.2.1. Image acquisition and processing

The image acquisition and processing details have been described in our previous cross-sectional study on associations between WM and cognition (Kristensen et al., 2019). Briefly, we acquired the MRI scans on a 3 Tesla scanner (Philips Healthcare, Best, the Netherlands). Two diffusion-weighted images using single shot spin-echo echoplanar imaging sequence with 30 noncollinear diffusion-weighted (\( b = 1.000 \text{s/mm}^2 \)) directions and one non-diffusion weighted (\( b = 0 \text{s/mm}^2 \)) in opposite phase encoding directions were acquired, which enabled correction for susceptibility distortions (Andersson et al., 2003). We used tools from the FSL software library v5.0.10 (Jenkinson et al., 2012) and MRtrix3 (www.mrtrix.org) for image processing. DWI data were denoised (Dhollander et al., 2016; Veraart et al., 2016a, 2016b) and the images were corrected for B1 field inhomogeneity (Smith et al., 2004; Zhang et al., 2001). Eddy current and susceptibility artifact correction (Andersson and Sotiropoulos, 2016) was performed, and absolute and relative head motion parameters were extracted. Tract-based spatial statistics (TBSS) (Smith et al., 2006, 2004) was used to align FA data into the FMRIN58 template using the nonlinear image registration tool (FNIRT) (Andersson et al., 2007a; Andersson et al., 2007b). The mean FA image (threshold of 0.2) was thinned to create mean study-specific FA skeleton maps (Smith et al., 2006). Using the JHU WM tractography atlas labels (Hua et al., 2008; Mori and Zijl, 2007), we calculated mean global and regional FA, AD, RD, and MD for each UHR-individual, as the average of the weighted ROIs from skeletonized data (Fig. 1). MRI quality metrics were assessed by visual inspection, and MRI quality metrics from each subject was calculated using a quality assessment method described by Roalf et al. (2016) (Range between “Good” and “Excellent” quality. Supplementary Table S2). Details on image

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Fig. 1. Fractional anisotropy skeleton maps and the predefined white matter regions of interest. Illustrates a) In green the overlaid voxel-based mean fractional anisotropy (FA)-skeleton, aligned from participants FA-data on a standard FA brain template. Tract-based spatial statistics was used to create the skeleton maps. The FA-skeleton is thinned, representing only the centers of FA-tracts. b) Using the FSL-JHU-DTI white-matter atlas labels, we extracted the mean FA, AD, RD and MD values in 4 WM label ROIs bilaterally from the skeletonized data. Each WM-region from the atlas is displayed with a different color code: the anterior limb of internal capsule (ALIC, cobber), the anterior corona radiata (ACR, yellow), the superior longitudinal fasciculus (SLF, blue), and the uncinate fasciculus (UF, red). Abbreviations: A: anterior; AD: axial diffusivity; DTI: diffusion tensor imaging; FA: fractional anisotropy; FSL: FMRIB Software Library; I: inferior; JHU: John Hopkins University; L: left; MD: mean diffusivity; P: posterior; R: right; RD: radial diffusivity; ROI: region of interest; S: superior; WM: white matter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
acquisition and processing are provided in Supplementary Text S3.

2.2. Clinical assessments

Axis I and selected Axis II diagnoses were assessed (schizotypal-, paranoid-, and borderline personality disorder) using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). Level of UHR-symptoms was assessed using the CAARMS composite score, using the positive symptoms subscale of CAARMS (Morrison et al., 2011) (intensity and frequency of attenuated psychotic symptoms and brief limited intermittent psychotic symptoms). Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS, total score) (Andreasen, 1984), and level of functioning using the Social and Occupational Function Assessment Scale (SOFAS) (Morosini et al., n.d.). The clinical assessments were conducted by experienced psychologists and medical doctors with comprehensive training in the assessment instruments. We assessed inter-rater reliability using intraclass correlations for clinical outcomes, revealing excellent inter-rater reliability (Glenthoj et al., 2020).

2.3. Statistical analyses

2.3.1. Univariate analyses

All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25.0, (Armonk, NY: IBM). Descriptive variables were reported as percent, means and standard deviations. Chi-square tests and general linear modelling (GLM) were used to compare UHR-individuals to HCs on descriptive variables. Within- and between-group effect of time, as well as time × group effects on global and regional FA were tested using GLM with repeated measures. Significance was corrected for multiple comparisons using Bonferroni correction (Jean Dunn, 1961) (uncorrected p × [9 regions (Global, and ALIC, ACR, SLF, UF bilaterally) × 2 groups (UHR-individuals and HCs)]).

Pearson's correlation analyses were performed to test associations between percentual FA changes in the predefined ROIs and percentual changes on the clinical measures. Percentual change-scores were calculated as: \[\text{(numerical follow-up score–numerical baseline score)/numerical baseline score} \times 100\]. Numerical change-scores were tested post hoc (Supplementary Table S4). The significant results was consistent, and we report the percentual change-score in the manuscript, as the interpretation are more comprehensible than the extreme small numerical values of dMRI measures; as well as according the intention to normalize with respect to the baseline differences for distribution of numerical and percentual change, see Fig. S5). Significance was corrected for multiple comparisons using Bonferroni correction (Jean Dunn, 1961) (uncorrected p × [8 regions × 3 clinical measures]).

Post hoc, we explored the effect of selected predictors of FA change. First, univariate Chi-square tests and linear regression analyses were performed entering baseline variables on age, gender, level of functioning, estimated intelligence, CAARMS score, number of neurocognitive training sessions, total number of received treatment sessions, antipsychotic- and antidepressant medication, recreational substance use, duration of illness, and baseline FA as predictors. Next, significant predictors were entered in a multivariate regression model using forward selection. Exploratory we tested within-group change of global and regional FA for UHR-individuals and HCs using GLM repeated measures. Finally, we compared UHR-individuals with increase- versus decrease of FA in right SLF on similar sociodemographic and clinical variables using Chi-square tests and univariate GLM.

2.3.2. Multivariate analyses

Cross-sectional within-group differences on FA in the four ROIs bilaterally were tested using MANOVA, including age, gender, absolute and relative motion in MRI scanner, and additionally for UHR individuals trial allocation and antipsychotic medication at baseline, as covariates. Significance was corrected for multiple comparisons using Bonferroni (Jean Dunn, 1961) (uncorrected p × [2 multivariate tests × 2 groups]).

The PLS-C analyses (Abdi and Williams, 2013; McIntosh and Lobaugh, 2004) were performed using MATLAB software (version 2017b). We included measures of percentual change on the three clinical scales, and FA, AD, RD, and MD values of the four predefined WM regions. We used the within-group PLS-C analysis (Jessen et al., 2018) to analyze the covariation between changes in WM and changes in clinical measures. In short, here we use the PLS-C for analyzing the relative impact (salience) of the largest shared information between two domains (i.e. neuroimaging and psychopathology). From the data, PLS-C identifies the latent variables (LVs), which express the maximum covariance when including both domains, and designates the whole pattern of correlations between all variables that may be interrelated. For a more detailed description of PLS-C, see Supplementary text S6. Both the significance level of the omnibus test (Reisfeld and Mayeno, 2013) and of the individual LVs were assessed using permutation testing (100,000 permutations) to obtain a p-value based on non-rotated sampling distribution of singular values (Kovacevic et al., 2013). For the omnibus test, the Inertia index (calculated as the sum of all singular values of all the LVs identified by PLS-C), was used for permutations testing (Abdi and Williams, 2013). LVs with a p < 0.05 were considered significant. Only LVs with a cross-block covariance larger than 5% are reported (Grigg and Grady, 2010). The reliability of saliences was assessed using bootstrapping (100,000 bootstraps with procrastuter rotation) to obtain 95% confidence intervals. Confidence intervals of the saliences that did not cross zero were considered reliable (Krishnan et al., 2011).

3. Results

Demographic characteristics of participants at baseline and follow-up are reported in Table 1. Of the total baseline sample of 110 UHR-individuals, 88 (80%) attended the 6-months follow-up assessments, and 22 (20%) dropped out. There were no sociodemographic or clinical baseline differences on measures of positive UHR-symptoms, negative symptoms or functional level between UHR-individuals completing follow-up assessments versus dropouts. However, UHR-individuals who dropped out had lower global FA at baseline (p = 0.008, F = 7.23) (Supplementary Table S7).

There were no differences between UHR-individuals and HCs on the sociodemographic variables of age, gender, parental socioeconomic status, BMI-index, or handedness (Table 1). As expected, we found a significant difference between UHR-individuals and HCs on social- and occupational functioning, activity-level, and estimated intelligence. Moreover, UHR-individuals smoked more tobacco, but had lower alcohol intake, and a recreational use of cannabis similar to HCs.

UHR-individuals improved clinically during the 6-months period, displaying a reduction in positive UHR-symptoms, and an improvement in social- and occupational functioning. There were no group-level significant changes in negative symptoms. The prevalence of antipsychotic medication was increased (Table 2).

3.1. Longitudinal white matter changes

At baseline, UHR-individuals had significantly lower FA globally (AdjR²: 0.110, p = 0.019), in the right SLF (AdjR²: 0.070, p = 0.02, corrected) and in left UF (AdjR²: 0.058, p = 0.048, corrected) when compared to HCs (Supplementary Table S8). This difference remained at 6 months follow-up globally, but not in the right SLF and left UF. We identified a group × time interaction effect, which did not survive multiple comparisons, globally and in right SLF (Fig. 2). No other ROIs demonstrated a group × time effect (Table 3).
3.2. Correlations between changes in regional fractional anisotropy and changes in clinical symptoms

A significant positive correlation \((p = 0.048, \text{corrected})\) with a moderate effect size (Pearson’s \(r = 0.357\)) between percentual change in negative symptoms and FA in right SLF survived multiple comparisons (Table 4, Supplementary Fig. S9), i.e. an increase of FA in right SLF correlated with an increase in negative symptoms over 6 months. Significant correlations between change in negative symptoms and FA change in left UF, as well as change in functional level and FA change in ACR bilaterally did not survive multiple comparisons.

3.3. Multivariate analyses of correlations between changes in white matter indices and changes in clinical symptoms

The within-group PLS-C analysis revealed a significant correlation between a multivariate pattern of change in the clinical measures of positive UHR-symptoms, negative symptoms, functional level, and change in regional FA, AD, RD, and MD (omnibus test \(p = 0.002\)). One significant latent variable (LV1) was identified, explaining 74\% \((p = 0.010)\) of the covariance. Results are illustrated in Fig. 3. LV1 comprised a pattern of improvement in social- and occupational functioning (SOFAS) and negative symptoms (SANS), which contributed reliably to a pattern of regional WM changes. Changes of regional WM which contributed reliably were: in ALIC bilaterally (FA \(\uparrow\)), right SLF \(\downarrow\), right ACR \(\uparrow\), AD \(\downarrow\), RD \(\downarrow\), and MD \(\downarrow\)).

3.4. Post hoc tests

We explored the effect of baseline sociodemographic and clinical variables, as well as baseline global FA as predictors of global FA change. In the multivariate test, baseline global FA \((p = 0.004, F = 9.070)\) was the only significant predictor of change in global FA (Supplementary Table S10), i.e. lower FA at baseline predicted more FA change. In the multivariate test, baseline global FA \(\text{CAARMS Composite score} = 0.77, F = 0.09\)

Table 1

| Variable | UHR (N = 110) | Healthy controls (N = 57) | Significance |
|---------|---------------|---------------------------|--------------|
| Age (SD) | 23.8 (4.2)    | 24.1 (3.0)               | \(p = 0.66\) |
| Gender  |               |                          | \(p = 0.51\) |
| Male    | 46.8%         | 52.6%                    |              |
| Female  | 53.2%         | 47.4%                    |              |
| Estimated IQ | 103.5 (12.5) | 113.4 (13.2)             | \(p < 0.01\) |
| Parental SES |            |                           | \(p = 0.29\) |
| Low     | 10.9%         | 4.3%                     |              |
| Medium  | 37.3%         | 31.9%                    |              |
| High    | 51.8%         | 63.8%                    |              |
| BMI     | 23.4 (4.6)    | 23.2 (3.1)               | \(p = 0.84\) |
| Handedness |             |                           | \(p = 0.35\) |
| Right   | 87.3%         | 87.7%                    |              |
| Left    | 12.7%         | 12.3%                    |              |
| Function (SOFAS) | 54.7 (10.8) | 88.2 (5.9)               | \(p < 0.01\) |
| Activity-level | 14.2 (16.8) | 40.1 (10.2)              | \(p < 0.01\) |
| Alcohol consumption |        |                           | \(p < 0.01\) |
| Daily   | 2.8%          | 3.5%                     | \(p = 0.20\) |
| Weekly  | 32.1%         | 42.1%                    | \(p = 0.30\) |
| Monthly | 35.8%         | 47.4%                    | \(p = 0.29\) |
| Once/twice | 14.7%      | 3.5%                     | \(p = 0.29\) |
| Never   | 14.7%         | 3.5%                     | \(p = 0.29\) |
| Tobacco smoking (last year) | |                           | \(p = 0.02\) |
| Daily   | 41.3%         | 3.5%                     | \(p = 0.11\) |
| Weekly  | 5.5%          | 5.3%                     | \(p = 0.11\) |
| Monthly | 3.7%          | 5.3%                     | \(p = 0.11\) |
| Once/twice | 5.5%      | 3.5%                     | \(p = 0.11\) |
| Never   | 44.0%         | 80.7%                    | \(p = 0.11\) |
| Cannabis smoking (last year) | |                           | \(p = 0.45\) |
| Daily   | 2.8%          | 0.0%                     |              |
| Weekly  | 4.6%          | 7.0%                     |              |
| Monthly | 6.4%          | 3.5%                     |              |
| Once/twice | 15.6%      | 22.8%                    | \(p = 0.67\) |
| Never   | 70.0%         | 66.7%                    | \(p = 0.67\) |

Table 2

| Variable | Baseline (N = 110) | Follow-up (N = 88) | Significance |
|---------|-------------------|--------------------|--------------|
| CAARMS subgroups |                |                    | \(p < 0.01\) |
| APS     | 99.1% (107)       | 82.8% (72)         | \(p = 17.37\) |
| BLIPS   | 2.8% (3)          | 3.4% (3)           | \(p = 0.77\) |
| TS vulnerability | 23.9% (26) |                    |              |
| Diagnoses |                  |                    |              |
| Affective disorder | 57.3% (N) |                    |              |
| Anxiety disorder | 48.2% (N) |                    |              |
| Personality disorder | 33.6% (N) |                    |              |
| Other diagnoses | 19.1% (N) |                    |              |
| Diagnose of current\(^a\) abuse or dependency | 0.9% (1) |                    |              |
| ≥3 diagnoses | 40.9% (N) |                    |              |
| Medication |                |                    | \(p < 0.01\) |
| Antipsychotic-naïve\(^b\) | 57.3% (63) | 30.3% (33)         | \(p = 15.51\) |
| Current\(^a\) antipsychotics | 31.8% (35) | 59.6% (65)         | \(p = 16.50\) |
| Current\(^b\) antidepressants | 26.4% (29) | 23.1% (25)         | \(p = 0.43\) |
| Current\(^b\) mood-stabilizers | 5.5% (6) | 10.1% (11)         | \(p = 0.21\) |
| Current\(^b\) benzodiazepines | 7.3% (8) | 11.9% (13)         | \(p = 0.25\) |
| Clinical symptoms |            |                    | \(p < 0.01\) |
| CAARMS Composite score | 50.79 | 35.63             | \(p = 48.04\) |
| SANS total | 1.53 (0.78) | 1.27 (1.32) | \(p = 0.19\) |
| Functional level (SOFAS) | 54.72 | 60.66             | \(p = 0.01\) |

This table displays the data on baseline and follow-up on clinical and cognitive measures. Time-effect on continuous data was tested using GLM repeated measures, including the covariates of age, gender, antipsychotic medication at baseline, and allocation to experimental intervention. Abbreviations: APS: attenuated psychotic symptoms; BLIPS: brief, limited intermittent psychotic symptoms; CAARMS: comprehensive assessment of at-risk mental state; No.: number; SANS: Scale for the Assessment of Negative Symptoms; SD: standard deviation; SOFAS: social and occupational function assessment scale; TS: trait and state; UHR: ultra-high risk.

\(^a\) Current = the last month.

\(^b\) Atypical antipsychotics in low dose: aripiprazole, amisulpride, olanzapine, paliperidone, quetiapine, risperidone. Significant within-group effect of time is marked in bold.
Fractional anisotropy in individuals at ultra-high risk for psychosis and healthy controls.

|                  | Baseline Mean FA (SD) | Follow up Mean FA (SD) | Interaction \(\Delta\) | Group x time [Corrected \(p\)] |
|------------------|-----------------------|------------------------|-------------------------|---------------------------------|
| **UHR** N = 110  | 0.599 (0.015)         | 0.599 (0.012)          | 0.001                  | 0.069                            |
| **HC** N = 57    | 0.608 (0.015)         | 0.606 (0.013)          |                         |                                 |
| **Significance** | \(p = 0.001\)         | \(p = 0.001\)          |                         |                                 |
|                  | \(0.018\)             | \(0.234\)              |                         |                                 |
|                  | \(12.274\)            | \(6.377\)              |                         |                                 |
| **Anterior limb of internal capsule** |                       |                        |                         |                                 |
| **Right**        | 0.595 (0.025)         | 0.590 (0.026)          | \(p = 0.808\)          | 0.122                            |
| **Left**         | 0.5081 (0.023)        | 0.583 (0.022)          | \(p = 0.523\)          | 0.411                            |
| **Anterior corona radiata** |                   |                        |                         |                                 |
| **Right**        | 0.487 (0.024)         | 0.489 (0.026)          | \(p = 0.613\)          | 0.258                            |
| **Left**         | 0.490 (0.023)         | 0.491 (0.022)          | \(p = 0.501\)          | 0.455                            |
| **Superior longitudinal fasciculus** |                   |                        |                         |                                 |
| **Right**        | 0.536 (0.027)         | 0.539 (0.025)          | \(p = 0.024\)          | 0.478                            |
| **Left**         | 0.532 (0.026)         | 0.533 (0.022)          | \(p = 0.107\)          | 2.630                            |
| **Uncinate fasciculus** |                 |                        |                         |                                 |
| **Right**        | 0.519 (0.037)         | 0.519 (0.038)          | \(p = 0.307\)          | 0.846                            |
| **Left**         | 0.504 (0.040)         | 0.502 (0.039)          | \(p = 0.846\)          | 0.084                            |

This table displays the whole-brain and regional mean values of fractional anisotropy (FA) at baseline and follow-up for individuals at ultra-high risk for psychosis (UHR) and healthy controls (HC), and the result from the group x time interaction test. Uncorrected significant results are marked in bold. \(^{*}\) Significance after Bonferroni correction (corrected \(p\)-value displayed in \{\}, see Methods section).

we found that the UHR-individuals with FA increase in right SLF after 6 months had significantly lower baseline FA globally \((p = 0.001, F = 11.931)\) and in right SLF \((p < 0.001, F = 18.297)\) (Supplementary Table S12). No other baseline sociodemographic or clinical differences were significant. At a trend level, UHR-individuals with a FA increase presented at baseline with longer illness duration, received less antipsychotic medication, and with more males.

4. Discussion

As expected, UHR-individuals presented with lower FA at baseline compared to HCs at a global as well as at a regional level in right SLF and left UF. Lower FA globally presented the strongest signal, whereas FA at the regional level explained less variance (7 and 6%, respectively). However, the localization of the regional WM alterations to the SLF and left UF have previously been reported in UHR-studies (Carletti et al., 2012; Clemm Von Hohenberg et al., 2014; Karlsgodt et al., 2009; Wang et al., 2016) and in studies on first-episode psychosis (Walterfang et al., 2012; Walterfang et al., 2016).
Illustrates the significant latent variable (LV1) from the PLS-C analysis on UHR-individuals. On the left side, the patterns of change in clinical measures on 3 symptom scales are displayed in turquoise on the x-axis. Bars turning upwards indicate improvement (measures where higher scores indicated worsening were reversed). The line in the bars indicates the 95% confidence interval (CI). When CI cross zero, the measure does not contribute reliably to the pattern and the bar is colored grey (NC). On the right side, the associated pattern of changes in the 4 WM indices of FA, AD, RD, and MD in four regions of interest (ALIC, ACR, SLF, UF bilaterally) are displayed in blue on the x-axis, and the salience on the y-axis. Bars turning upwards indicate increase, bars turning downwards indicate decrease.

Abbreviations: ACR: anterior corona radiata; AD: axial diffusivity; ALIC: anterior limb of internal capsule; CAARMS: the Comprehensive Assessment of At-Risk Mental State; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity; PLS-C: partial least square correlation; SANS: Scale for the Assessment of Negative Symptoms; SLF: superior longitudinal fasciculus; SOFAS: social and occupational function assessment scale; UF: uncinate fasciculus; UHR: individuals at ultra-high risk; WM: white matter.

We identified a significant time × group interaction globally and in right SLF, which did not survive correction for multiple comparisons. Our previous longitudinal study on an independent cohort of 30 UHR-individuals reported a significant within group increase in FA over one year for both UHR-individuals and HCs (Krakauer et al., 2018), although in different regions. UHR-individuals presented a significant FA increase predominantly in left SLF, whereas HCs presented a FA increase in predominantly left UF. The directionality of the regional FA change corresponds to our results (Fig. 2).

We found no absolute change in negative symptoms at a group level. Nonetheless, our main hypothesis on a positive correlation between a regional increase in FA and negative symptoms were confirmed. Despite different sample sizes, methodology, and follow-up time, this result replicates previous finding in an independent sample (Krakauer et al., 2018). Although our current study confirms a link between the changes in negative symptoms and SLF, the association is moderate, and the directionality of the correlation is opposite of what is commonly reported in patients with schizophrenia (Wolkin et al., 2003; Yang et al., 2017). Hence, the complexity of interpreting the directionality of FA changes is emphasized, depending on the patient sample or region of interest (Thomason and Thompson, 2011). Noticeably, the correlation mainly appears to reflect a development of the subgroup of UHR-individuals characterized by lower baseline FA and FA increase both globally and in right SLF, which additionally presented with a significant increase of negative symptoms from baseline to 6 months.

The multivariate PLS-C analysis on covariance between patterns of change in clinical symptoms and WM change offers further explanations. Here, a strong association between a pattern of improvements in negative symptoms and functional level was associated with the pattern of regional WM changes explained 74% of the covariance. Interestingly, SLF appeared to differ from the other ROIs, displaying opposite directionality of the changes in WM indices. ALIC, ACR and UF involve more inferior frontal and cortico-subcortical projections, whereas SLF as a superior located association tract spans lengthy from frontal to posterior regions. We speculate if this pattern supports a developmental hypothesis as argued in our previous study (Krakauer et al., 2018). Since the region-wise maturational peaks of WM occur in a posterior to frontal direction (Lebel et al., 2012; Peters et al., 2014), the FA decrease is consequently expected to occur earlier in SLF compared to ALIC, ACR, and UF. Thus, the different directionality of FA changes in the ROIs linked to clinical improvement may reflect the relative maturation process across different WM regions. However, our data cannot confirm this developmental approach, as the interaction between time × age on global and regional FA in UHR-individuals did not survive correction for multiple comparisons.

Another perspective occurred from the exploratory post hoc test comparing UHR-individuals with FA decrease versus increase in right SLF. UHR-individuals with FA increase in the right SLF presented with lower FA at baseline, and at a trend level with more males, a longer illness duration and less antipsychotic treatment at baseline, compared to UHR-individuals with FA decrease. We did find a significant interaction between time × antipsychotic medication at baseline in right SLF when examining FA change within UHR-individuals. This result may reflect the potential neuroprotective effect of antipsychotic medication on WM changes, as demonstrated in patients with first-episode psychosis (Edbrup et al., 2015). Additionally, it would be consistent with UHR-studies reporting gender differences, where males present with more negative symptoms and longer duration of illness when compared to females (Barajas et al., 2015); and with later WM maturation linked to psychopathology in the right hemisphere (Saugstad, 1998). Hence, the positive correlation between increase of negative symptoms and increase in FA in right SLF appear mainly to reflect a subgroup of UHR-individuals presenting with a biological vulnerability (low FA) at baseline, which is mirrored in differentiated neurobiological and psycho-pathological developments.

Finally, the decrease of FA in SLF appears in the multivariate PLS-C strongly linked to an increase of RD, whereas the contribution of AD is...
weaker. RD has been considered an indirect estimate of axonal myelination level (Kochunov et al., 2012), in particular in the case of FA reduction, RD increase and unchanged AD (Haroutunian et al., 2014; Song et al., 2003).

However, although this indication of dysmyelination having a strong impact on the WM changes in right SLF linked to negative symptoms in UHR-individuals, great caution in the interpretation of WM indices must be exhibited, as there is no direct correspondence between the MRI-derived measures and the biological underpinnings (Weinberger and Radulescu, 2020).

4.1. Methodological considerations

Strengths of this study comprise the longitudinal multimodal assessments of WM and clinical symptoms, which is rarely studied in UHR. Furthermore, we present data from a large cohort of UHR-individuals. A general limitation to the study is the fact that the analyses were secondary to an RCT, and the study was not designed to answer the current research question. However, given its longitudinal design and our inclusion of the allocation to experimental treatment in the RCT as covariate in within-group analyses testing effects of time, we trust the consistent association to represent a valuable contribution to the evidence for specific associations between regional WM and psychopathology.

Using percentual change when testing correlations may be statistically suboptimal. However, when post hoc testing the nominal changes, the results showed similar significant associations between changes in WM FA in right SLF and negative symptoms. Hence, we have chosen the pragmatic solution to report percentual change in the main text, and the numerical post hoc test in supplementary.

The study is limited by a follow-up period of 6 months with only two timepoints, which confines the analysis on i.e. variation of positive UHR-symptoms and the power regarding potential transition to psychosis over time. These associations may need a longer follow-up time, ideally three years as suggested by Fusar-Poli et al. (2012). Further studies with longer follow-up at several timepoints, enabling the investigation of clinical correlates to WM changes are encouraged.

Finally, the advantages of using multivariate PLS-C may be counterbalanced by the adequate great caution in interpreting these complex results from modelled data. Nonetheless, the results appear overall aligned across methods, and the findings from PLS-C convey supplementary information.

5. Conclusion

At baseline, UHR-individuals displayed significantly lower FA globally and in the right SLF when compared to HCs. As expected, we found a positive correlation with a moderate effect between change in negative symptoms and FA change in right SLF, which replicates results from previous studies in UHR-individuals. The result appears mainly to reflect a vulnerable subgroup within the UHR-individuals with lower FA at baseline.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.09.014.

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