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Reduced anterior callosal white matter in risk for psychosis associated with processing speed as a fundamental cognitive impairment

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ABSTRACT

Background: Previous research in psychotic disorders discovered associations between reduced integrity of white matter (WM) in the corpus callosum (CC) and impaired cognitive functions, suggesting processing speed as a central construct. However, it is still largely unexplored to what extent disruption in callosal WM is related to cognitive deficits during the risk stage prior to psychosis.
Methods: To address this gap, we measured the WM integrity in CC by fractional anisotropy (FA) and assessed cognition in 60 clinical-high risk for psychosis (CHR) patients during adolescence/young adulthood and 38 healthy control (HC) subjects. We employed tract based spatial statistics to examine group differences and associations between CC-FA and processing speed, executive function, and spatial working memory.
Results: We revealed deficits in processing speed, executive function, and spatial working memory of CHR patients, and reductions in FA of the genu and the body of the CC ($p < 0.05$, corrected for multiple comparisons) compared to HC. A mediation analysis using the combined sample (CHR + HC) showed that processing speed mediates the associations between the impaired CC structure and executive function and spatial working memory, respectively. Exploratory analyses between CC-FA and the cognitive domains located associations of processing speed in the genu and the body of CC with distinct spatial distributions of executive function and spatial working memory.
Conclusion: We suggest processing speed as a subordinate cognitive factor contributing to the associations between callosal WM, executive function and working memory. These results extend findings in psychotic disorders to the prior risk stage.

1. Introduction

Beside positive psychotic symptoms, impairments in cognition contribute to severity of illness in psychotic disorders (Kahn and Keefe, 2013). Prior to psychosis, cognitive impairments characterize the prodrome and contribute to diagnose clinical-high risk (CHR) patients for developing psychotic disorders (Fusar-Poli et al., 2013; Kendler et al., 2016). Over the course of psychotic disorders, cognitive deficits represent stable traits, which predict functional outcome (Sheffield et al., 2018). Neuropsychological studies in psychotic disorders and CHR reported deficits in the core cognitive domains of processing speed (Klauser et al., 2021; Knowles et al., 2010; Randers et al., 2021), working memory (Forbes et al., 2009) and executive function (Reichenberg and Harvey, 2007). Further investigation of aetiological factors suggest that cognitive impairments and positive psychotic symptoms originate based on similar genetic and environmental factors (McCutcheon et al., 2023). Accordingly, cognitive functions play an essential role in early detection and intervention and are of particular interest to understand the pathophysiology in psychosis.

The framework of schizophrenia as a neurodevelopmental disorder proposes that abnormalities in brain development may emerge years before clinical diagnosis and underlie cognitive impairments and psychotic symptoms (Insel, 2010). Neuroimaging studies over the last two decades comparing schizophrenia patients and healthy subjects reported

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functional (Kambeitz et al., 2016) and structural (Chan et al., 2011) abnormalities. Further, structures of gray (Sowell et al., 1999) and white matter (WM) (Lebel and Deoni, 2018) in prefrontal cortical areas (PFC) undergo an intensive brain maturation process during adolescence and early adulthood – life periods which often mark the onset of cognitive impairments, attenuated psychotic symptoms, and the first psychotic episode (Häfner, 2019).

White matter integrity is reduced in full blown psychosis in various parts of the brain such as the superior longitudinal fasciculus, the cingulum bundle, the uncinate fasciculus, the fornix or the corpus callosum (CC) (Ellison-Wright and Bullmore, 2009; Kelly et al., 2018; Stämpfli et al., 2019). The CC seems to have special importance in the development of psychosis possibly due to its role in interhemispheric communication (Friston and Frith, 1995). Thus, numerous studies reported patient-control differences of CC in psychotic disorders (Kelly et al., 2018; Kochunov et al., 2017; Madigand et al., 2019; Patel et al., 2011; Shahab et al., 2018; Stämpfli et al., 2019; Vitolo et al., 2017; Zhuo et al., 2016), that have been traced back to CHR stages (Katagiri et al., 2015; Saito et al., 2017; Smigielski et al., 2022; Su et al., 2022). Strikingly, brain-wide regional comparisons in a large-sample study in schizophrenia of the ENIGMA consortium revealed the greatest effects in the anterior corona radiata and the CC (Kelly et al., 2018). The structure of the CC with large WM fiber-tracts between both hemispheres enables wide-range cortical network activities related to cognitive processing (Bressler, 1995; Friedrich et al., 2020).

Additional studies in psychotic disorders reported associations between deficits of WM in the CC with psychotic symptoms (Whitford et al., 2010; Wigand et al., 2015) and impaired functions such as formal thinking (Cavelti et al., 2018), motor coordination (Viher et al., 2021), social function (Koshiyama et al., 2018), processing speed (Karbasforoushan et al., 2015a; Kochunov et al., 2016, 2017), working memory (Kochunov et al., 2017) and executive function (Ohoshi et al., 2019) – highlighting the CC as a central structure involved in network activities of diverse functions. Kochunov et al. (2017) revealed that processing speed mediates the association between WM and working memory and found the largest mediation effects in the body and the genu of CC. However, despite previous findings in psychotic disorders and in CHR, direct evidence to what extent impaired cognitive core functions could be associated with structural deficits in the CC prior to psychosis in CHR stage is still missing.

To address this gap, we examined the WM of the CC in CHR patients during adolescence and young adulthood in comparison to healthy controls (HC). We focused on CC aiming to extend the previous work of Kochunov et al. (2017) to psychosis risk stages.

Thus, we hypothesized that processing speed as a subordinate cognitive impairment mediates the association between deficient CC structures and the higher-ordered cognitive functions of executive function and working memory. These mediator models require the following assumptions/secondary hypotheses to be tested: 1) CHR patients show impairments in cognitive functions compared to HC; 2) FA measurements of the CC are significantly reduced in CHR patients in contrast to HC; 3) The cognitive functions are associated with the deficient structures of the CC. Additionally, we aim to provide an exploratory topological view about the associations between the substructures of the CC and the cognitive domains. Based on previous findings (Holleran et al., 2020), we assume that FA in general positively correlates with cognition independent of diagnosis, so we test our hypotheses in combined (CHR + HC) and in CHR sample analyses.

2. Materials and methods

2.1. Participants

The patients were recruited via the Bern Early Detection and Intervention Center for Mental Crisis between 2018 and 2021 (FETZ Bern, Switzerland; www.upd.ch/fetz; (Michel et al., 2022)). Data were drawn from the FETZ Bern Cohort Study (approved by the Ethics Committee of the Canton of Bern; ID 2018-00951).

Here, we included patients and assigned them to the clinical high-risk group (CHR) who met at least one criterion of the European Psychiatric Association (EPA; (Schmidt et al., 2015; Schultze-Lutter et al., 2015)), and used the following exclusion criteria: (1) diagnosis of a psychotic disorder according to DSM-IV or ICD-10, currently or in the past; (2) diagnosis of a neurological disease; and (3) drug treatment impairing functions of the central nervous system.

With respect to previous findings showing WM peak maturation in schizophrenia at the age of 27 and in healthy subjects at the age of 33 years (Cetin-Karayumak et al., 2020), we set the upper limit to the age of 30 years (centered between the peaks of both populations). The final CHR group included 60 subjects (age range: 11.5 to 28.7 years).

We recruited healthy controls (HC) via advertisements. The subjects gave their informed consent to participate and were included if they did not meet criteria of CHR nor any other mental disorder (ICD-10/DM-IV). The HC group (n = 38; age range: 13.8 to 29.3 years) underwent the same clinical assessments as CHR.

2.2. Clinical assessments

Raters with prior training over 3 months (supervision of the co-author CM) conducted the clinical interviews to assess the CHR symptoms. We diagnosed CHR by using two sets of symptom criteria: (1) ultra-high risk (UHR) criteria: attenuated (APS) or brief (limited) intermittent psychotic symptoms (B(*L*)IPS) and genetic risk and functional decline (GRFD); and (2) basic symptom (BS) criteria: cognitive disturbances (COGDIS) and cognitive-perceptive basic symptoms (COPER) (Schultze-Lutter et al., 2015). The criteria for ultra-high risk (UHR) (Yung et al., 2006) were assessed by using the Structured Interview for Psychosis-Risk Syndromes (SIPS) (Montesano, 2012) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005) and the basic symptoms (Schultze-Lutter et al., 2016) including COPER and COGDIS by the Schizophrenia Proneness Instruments (SPI-A/SPI-CY) (Schultze-Lutter et al., 2004; Schultze-Lutter and Koch, 2010). We diagnosed axis I disorders according to the DSM-IV for mood, anxiety, eating, somatoform, obsessive-compulsive, substance use and post-traumatic stress disorders by using the Mini-International Neuropsychiatric Interviews (MINI/MINI-Kid; (Sheehan et al., 2010, 1998)). Current social and occupational functioning during the last month of the subjects was estimated by ratings of the Social and Occupational Functioning Assessment Scale (SOFAS) as an independent measurement of the overall severity of the individual's symptoms (Goldman et al., 1992).

2.3. Cognitive assessments

We used the Digit Symbol Substitution Test (DST) (Kaplan et al., 1991) of the WAIS-III (David, 1997), to measure processing speed as previously used in related studies (Karbasforoushan et al., 2015b; Kochunov et al., 2017, 2016). The DST is a paper-pencil test in which the participants sequentially assign numbers to symbols according to a code from 1 to 9. The participants were instructed to draw the correct symbols in boxes under the corresponding numbers as fast and accurate as possible. Processing speed scores were obtained by the number of correct number-symbol assignments within 120 s.

Performance in executive function was assessed by the TMT-B (Strauss et al., 2006). The participants had the task to connect with a pen randomly distributed numbers (from 1 to 13) and letters (from A to L) on a paper sheet, alternately, in ascending order and as quickly as possible. To quantify executive function, the time was taken of correct task completion.

By using the Subject Ordered Pointing Task (Petrides and Milner, 1982), we assessed spatial working memory. This task included 12 trials in which four images - with 6, 8, 10 and 12 objects, spatially arranged in

different ways on each image - were shown to subjects three times. In each trial, the subjects were asked to point to an object in the image that they had not pointed out before. To measure the performance, the number of errors was calculated over the 12 trials.

We examined these neuropsychological tests as cognitive domains of interest and part of the cognitive test battery of the FETZ (Michel et al., 2022).

2.4. MRI data acquisition

MRI data was acquired by a 3 T Siemens Prisma scanner (Siemens, Germany) with a customized 64-channel head coil. We recorded diffusion-weighted imaging (DTI) data by using an echo-planar imaging sequence with the following parameters: isotropic voxel resolution of 2.2 mm; repetition time = 3700 ms; echo time = 82 ms; field of view = 211 × 211 mm; 56 slices; plane resolution of 96 × 96; and a multi-band acceleration factor of 2.

The diffusion detection was conducted along 122 directions with 8 different b-values (350, 650, 1000, 1350, 1650, 2000, 2650, 3000) and the DTI scanning time lasted 7:55 min.

For anatomical referencing, a T1-weighted whole brain image was acquired by magnetization-prepared 2 rapid acquisition with a gradient echo (MP2RAGE) sequence and the following parameters: echo time = 2.98 ms; repetition time = 5000 ms; inversion time 1/2 = 700/2500 ms; flip angle 1/2 = 4/5 degrees; number of slices = 176; field of view = 256 × 256 mm; slice thickness = 1 mm; isotropic voxel size = 1 mm.

2.5. White matter analyses

To preprocess DTI, we first corrected the data for motion artifacts using the *mcflirt* script implemented in FSL tools (Analyses Group, FMRIB Software Library, Oxford, UK, v6.0; (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009)). Next, we conducted brain extraction (*bet*, FSL tools) and tensor fitting (*dtifit*, FSL tools) to obtain images of fractional anisotropy (FA).

To prepare the FA images for statistical analyses, we conducted the pipeline of Tract-Based Spatial Statistics (TBSS, (Smith et al., 2006), FSL tools). Images were first cleaned by removing the brighter voxels at the edges of the brain (*tbss_1_preproc*) and registered on the 1 × 1 × 1 mm standard MNI space (FMRIB58_FA_1mm; *tbss_2_reg*). Next, the mean FA map and the mean FA skeleton were calculated (*tbss_3_postreg*) and the individual FA data was projected onto the mean skeleton (*tbss_4_postreg*, threshold = 0.2).

Finally, for our region of interest (ROI) approach targeting CC, we included only voxels within the three CC subareas of the genu, the body, and the splenium according to the JHU ICBM-DTI-81 White-Matter Atlas by integrating a mask in statistical analyses.

2.6. Statistical analyses

For CC-FA group differences and associations with the cognitive domains, we conducted threshold-free cluster enhancement statistics (TFCE, 5000 permutations) with correction for the family wise error rate (FWE) and controlled for subject's age as a covariate. To obtain the effect size of the group difference, we extracted the averaged FA of the significant clusters of the previous TFCE statistics per subject and conducted an independent sample *t*-test based on residuals corrected by age. In addition to control for the potential influence of substance use on FA group differences, we conducted a post-hoc t-test on the same way, but based on the residuals corrected by age and substance use (n = 5 CHR patients) as a dummy-coded variable.

In the CHR sample, we computed exploratory association analyses between CC-FA and cognition by using MATLAB 2018a (MathWorks, Natick, USA). We imported CC-FA by functions of SPM 12 (Wellcome Department of Cognitive Neurology, https://www.fil.ion.ucl.ac.uk/spm/) and conducted voxel-wise partial correlations with age as a covariate. Based on our assumption of positive correlations between FA and cognition, we show and further investigated only significant associations of the assumed direction (see Fig. S4).

To compute spatial association patterns (for Fig. 3d and Fig. S4 d), we obtained the number of significant voxels per CC subarea (genu, body, and splenium) based on coordinates (JHU ICBM-DTI-81 White-Matter Atlas) and divided these numbers by the total number of significant voxels in CC.

To analyze demographic and symptom data, we used independent sample *t*-tests, Chi-squared tests and Pearson correlations.

We analyzed mediation modelling with the PROCESS macro (https://www.processmacro.org; version 4.1) integrated in SPSS (IBM Corp., Version 25). The number of bootstrap samples was set to 5000 and age was included as a covariate. We integrated in the models the extracted mean FA values per subject of the CC substructure which significantly differed between CHR and HC, based on results of 3.2.

For all statistical analyses the *p*-value was set at $p < 0.05$ (two-sided). In addition to SPSS, data analyses were performed by MATLAB 2018a (MathWorks, Natick, USA).

3. Results

3.1. Demographic and symptom data

Comparisons of demographic and symptom characteristics between CHR and HC are shown in Table 1. Between group-comparisons revealed no significant differences regarding age, gender, and handedness. As hypothesized, we observed lower performance measurements in processing speed, executive function, and spatial working memory in CHR

Table 1
Demographic and symptom characteristics of the study sample.

	HC (n = 38)	CHR (n = 60)	t/χ^2	*p* (Cohen's d)
Age (years)	19.33 ± 0.60	18.00 ± 0.43	1.86	0.07
Male	47 %	53 %	0.33	0.57
Handedness r/l	32/6	54/6	0.73	0.39
Processing speed (# correct)	84.42 ± 2.54	69.50 ± 2.32	4.21	**<0.001 (0.87)**
Executive function (sec)	49.17 ± 2.73	63.08 ± 3.28	−2.94	**0.004 (−0.62)**
Spatial working memory (# errors)	3.26 ± 0.36	5.87 ± 0.50	−3.78	**<0.001 (−0.78)**
SOFAS score	87.26 ± 0.69	58.12 ± 1.51	14.74	**<0.001 (3.06)**
SIPS p1	0.97 ± 0.06	3.45 ± 0.17	−11.38	**<0.001 (−2.36)**
SIPS p2	0.13 ± 0.07	2.38 ± 0.21	−8.20	**<0.001 (−1.70)**
SIPS p3	0.05 ± 0.04	0.6 ± 0.12	−3.58	**<0.001 (−0.74)**
SIPS p4	0.45 ± 0.15	3.50 ± 0.16	−12.73	**<0.001 (−2.64)**
SIPS p5	0.24 ± 0.10	0.73 ± 0.12	−2.88	**0.005 (−0.60)**
SIPS Positive	1.84 ± 0.24	10.67 ± 0.49	−13.67	**<0.001 (−2.84)**
AP-medication	–	16.67 %	–	–

Age in years; Number of male subjects in percent; Handedness right/left; Processing speed, number correct; Executive function, time in seconds; Spatial working memory, number errors; AP-medication, CHR patients with antipsychotic medication (number of patients in percent); SOFAS social and occupational functioning; SIPS standard; Interview for psychosis risk syndromes, positive symptoms scores (p1, unusual thought content/delusional ideas; p2, suspiciousness/persecutory ideas; p3, grandiose ideas; p4, perceptual abnormalities/hallucinations; p5, disorganized communication) and positive sum score. Data are means ± SEM. P-values of statistical comparisons between groups by using Chi-square or unpaired t-tests. Significant group differences are marked by *p*-values and effect sizes in bold.

compared to HC.

Association analyses between symptom characteristics and cognition within the CHR sample revealed correlations between the SIPS p4 score (perceptual abnormalities/hallucinations) with processing speed ($r = -0.38$, $p = 0.003$), and executive function ($r = 0.29$, $p = 0.026$), and no other associations between SIPS and SOFAS scores (see Table S1 for an overview of variables and scale descriptions) and the three cognitive domains (p-values >0.05). Regarding potential influences of medication on cognition, our analyses revealed no significant differences in cognitive functions between CHR patients with and without antipsychotic medication (see Table S2).

3.2. Tract-based spatial statistics of CC-FA in CHR versus HC

The TBSS analyses revealed significant reduced FA in the body and the genu of the CC in CHR in contrast to HC (three clusters with a total number of 1300 voxels and an averaged effect of Cohen's d = 0.78; Fig. 1). An additional post-hoc comparison to control for the potential influence of substance use (n = 5 diagnosed cases of the CHR group) including age and substance use as covariates still revealed the significance of this cluster (uncorrected $p < 0.001$) and a similar effect size (Cohen's d = 0.85).

3.3. Processing speed mediates the associations between the reduced anterior CC-FA and cognitive functions

To test our third hypothesis, we investigated in the combined sample (CHR + HC) to what extent processing speed mediates the associations between the impaired CC-FA structure based on results of Fig. 1 and executive function and spatial working memory. Thus, we extracted the averaged FA per subject of the significant cluster of the previous between group comparison, located within the anterior (a)CC, and named this variable aCC-FA.

The mediation model including executive function as the dependent variable revealed at first the following significant associations (aCC-FA & executive function: $c = -0.27$, $p = 0.008$; aCC-FA & processing speed: $a = 0.22$, $p = 0.014$; and processing speed & executive function: $b = -0.56$, $p < 0.001$) fulfilling the pre-assumptions of mediation modelling (Fig. 2a). By including processing speed as a mediator into the model, the direct effect between aCC-FA and executive function became reduced and nonsignificant ($c' = -0.14$, $p = 0.107$) and an additional bootstrap analysis confirmed the significance of the mediation effect (see Table S3). Dividing the indirect effect ($c - c' = -0.13$) by the total effect ($c = -0.27$) revealed that processing mediates around 48 % of the influence of aCC-FA on executive function.

The second mediation analyses with spatial working memory as the dependent variable revealed the following significant associations between the variables (aCC-FA & spatial working memory: $c = -0.22$, $p = 0.031$; aCC-FA & processing speed: $a = 0.22$, $p = 0.014$; and processing speed & spatial working memory: $b = -0.25$, $p = 0.038$; Fig. 2b). After including processing speed as a mediator, the association between aCC-FA and spatial working memory became nonsignificant ($c' = -0.17$, $p = 0.105$). Here, processing speed as a significant mediator (see Table S3) mediates 23 % (indirect effect $c - c' = -0.05$ divided by the total effect $c = -0.22$) of the influence of aCC-FA on spatial working memory.

To conduct additional analyses in the CHR sample, we failed to find significant associations between aCC-FA and cognitive functions to fulfill the pre-assumptions of mediation modelling (see Table S4).

3.4. Tract-based spatial statistics of associations between CC-FA and cognitive functions

We conducted tract-based spatial statistics to investigate associations between the cognitive functions and CC-FA. Combined sample analyses (TFCE statistics; FWE corrected, $p < 0.05$; controlled by age) revealed significant associations in all three cognitive functions (Fig. 3). As assumed, values of high FA correspond to measurements of high cognitive performances.

For processing speed (Fig. 3a), we found significant associations in the left GCC and the anterior BCC (Fig. 3a). The analyses of executive function (Fig. 3b) revealed more distributed clusters with associations in GCC, BCC and anterior SCC (Fig. 3b), whereas associations with spatial working memory were mainly located in GCC (Fig. 3c). Overall, the number of voxels with significant associations per CC subarea illustrates distinct topographical patterns of the cognitive functions (Fig. 3d).

TBSS analyses limited to the CHR sample revealed no significant associations between CC-FA and cognitive functions after the FWE correction.

Additional uncorrected voxel-wise correlation analyses (see methods) showed similar topographical patterns in CHR compared to the combined sample results, except for additional associations between spatial working memory and SCC structures in CHR (see Fig. S5).

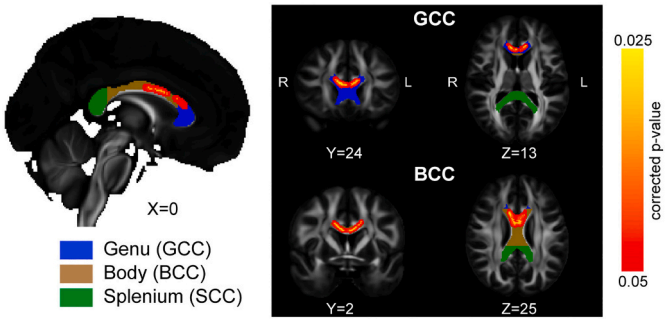

Fig. 1. Tract-based spatial statistics of CC-FA in CHR versus HC. Results of Threshold-Free Cluster enhancement statistics (TFCE statistics; family wise error corrected, $p < 0.05$). Red and yellow areas mark significant reduced FA in the genu and the body as subareas of CC in CHR in contrast to HC (using tbss_fill function implemented in FSL). See the left panel for sagittal view and the right panels for coronal and horizontal plans of the genu (GCC, upper panel) and the body (BCC, lower panel). The genu, the body and the splenium as CC subareas are marked in blue, brown, and green, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Here, we examined to what extend impaired cognitive functions are linked to structural deficits within the CC in CHR patients. In addition to prominent cognitive deficits in processing speed, executive function and working memory, we found significantly reduced FA in WM of the anterior CC in CHR compared to HC. Further, processing speed mediated the associations between the impaired CC structures and the higher-ordered domains of executive function and working memory. Our results indicate processing speed as a fundamental cognitive deficit functionally related to impaired WM of the anterior CC. Thus, we provide novel evidence to characterize the interplay of cognitive deficits and brain structure in risk stages.

We confirmed our first hypothesis on cognitive impairments in processing speed, executive functions and working memory in CHR patients, in line with previous studies (Mensi et al., 2023; Randers et al., 2021; Yong et al., 2014). Additionally, our results with relatively large effect sizes (Cohen's d > 0.6) highlight the role of neurocognitive measurements to discriminate between CHR and HC.

Testing our second hypothesis, we found impaired WM in CC. Accordingly, previous studies showed impaired WM in the CC during the CHR stage (Katagiri et al., 2015; Saito et al., 2017; Smigielski et al., 2022; Su et al., 2022), and in schizophrenia over the life span (Cetin-Karayumak et al., 2020). Correspondingly to our finding of impaired structures in the anterior CC, Kelly and colleagues reported (based on a large sample) greater effects of schizophrenia-control differences in the

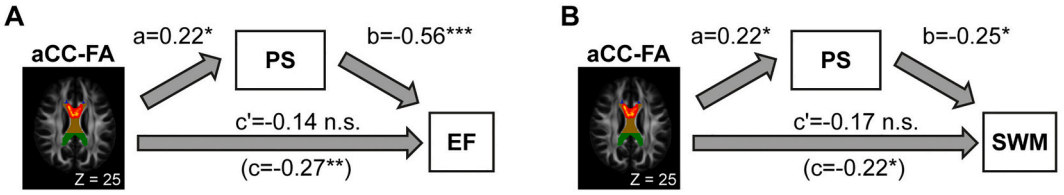

Fig. 2. Processing speed mediates the associations between the reduced anterior (a)CC-FA and cognition. Schematic models illustrate total and mediated effects and their standardized coefficients (a, b, c and c') between the reduced fractional anisotropy located within the anterior part of CC (aCC-FA; based on analyses of Fig. 1) and cognitive functions with processing speed (PS) as a mediator, in (A) executive function (EF) and (B) spatial working memory (SWM), respectively. Note, significant total effects (c) are shown in brackets, while the direct effects (c') are unsignificant in both mediation models, indicating complete mediation by processing speed. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, n.s. (not significant) $p > 0.05$.

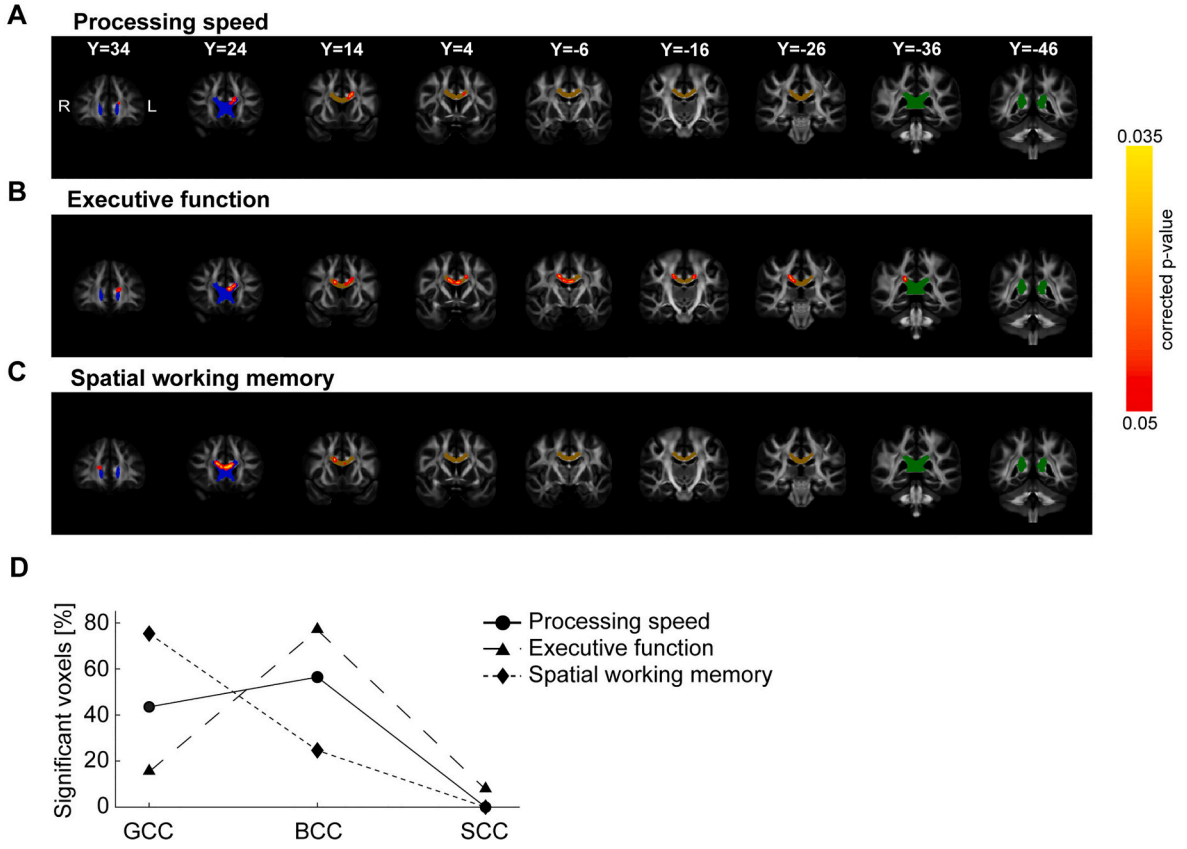

Fig. 3. Combined sample tract-based spatial statistics of associations between CC-FA and cognitive functions. Results of Threshold-Free Cluster enhancement statistics (TFCE statistics; family wise error corrected, $p < 0.05$). Red and yellow areas mark significant clusters of CC-FA associated to cognitive functions: A) processing speed, B) executive function and C) spatial working memory, respectively (using tbss_fill function implemented in FSL). The splenium, the body and the genu as CC subareas are marked in green, brown, and blue, respectively. D) Line plots illustrate distinct distributions in percent of significant voxels over CC subareas of the different cognitive functions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

body (Cohen's d = 0.39) and the genu (Cohen's d = 0.37) in comparison to the splenium (Cohen's d = 0.22) of CC (Kelly et al., 2018), which suggest a prefrontal dominance in structural alteration. In contrast, other studies in CHR failed to find group differences in WM of the CC (Bakker et al., 2016; Peters et al., 2010; Tomyshev et al., 2017). However, these non-findings might underlie study-specific differences such as small sample sizes (n < 30 in all three studies), whole brain instead of region-specific analyses and heterogeneity within CHR populations (Fusar-Poli et al., 2016). Taken our data and previous research together, we suggest early deficits in WM of the anterior CC as a neural substrate of early risk, which might prolong in later stages of psychotic disorders.

Confirming our third hypothesis, we found that processing speed mediates the associations of impaired CC WM and the cognitive functions of spatial working memory and executive function. We replicated in a combined sample of CHR patients and HC the results of a large sample study in schizophrenia (Kochunov et al., 2017). Here, the authors reported brain-wide the highest mediation effects via processing speed between FA and working memory in the body and the genu of CC (Kochunov et al., 2017). Consequently, we suggest, that impaired WM fibers in the anterior CC affect processing speed as a subordinate factor influencing other cognitive domains of working memory and executive function. In line with this suggestion, previous behavior analyses revealed shared variance between processing speed, working memory and executive function in healthy and clinical samples (Andersen et al., 2013; Fry and Hale, 2000; Verhaeghen, 2011) and proposed slowed processing speed as a key deficit in CHR affecting other cognitive domains (Randers et al., 2021).

At the neural level, we found consistently in the combined and the CHR sample, associations between processing speed and FA of anterior CC. Accordingly, Kochunov et al. (2017) revealed in schizophrenia the

strongest correlations between processing speed and FA in the body and the genu of CC in comparison to other regions. Anatomical investigations based on diffusion tractography, showed that the anterior part of CC project mainly to prefrontal areas of the cortex (PFC) (Chao et al., 2009; Hofer and Frahm, 2006; Park et al., 2008). To support the assumption, that WM structures in anterior CC with PFC projections underlie processing speed, task-fMRI studies linked processing speed to activities of prefrontal areas (Forn et al., 2013; Motes et al., 2011; Rypma et al., 2006; Sweet et al., 2005; Woodward et al., 2013). Consequently, we suggest that impaired WM in the body and genu of CC in CHR patients distort the information transfer to PFC regions and thus reduce processing speed.

Additionally, we found distinct spatial association patterns between CC-FA and the different cognitive domains over the topology of CC. In comparison to processing speed with significant voxels in the body and the genu, in executive function we localized the largest associated structure in the body and equally smaller amounts of significant voxels in the genu and the splenium in the combined sample and CHR separately. These CC subareas contain projections to distributed cortical regions of the frontal, parietal, temporal and the occipital lobe (Hofer and Frahm, 2006).

In spatial working memory, we found significant voxels mainly in the genu in the combined sample, whereas the CHR sample analyses revealed an additional structure of associations in the anterior splenium of CC with assumed projections to the parietal cortex (Hofer and Frahm, 2006).

Based on these results, we suggest that fibers of the anterior CC are important for processing speed whereas associations in additional structures might represent projections with more distributed cortical networks involved in working memory and executive function.

Regarding schizophrenia as a neurodevelopmental disorder, our findings in CHR suggest that impaired WM in the anterior CC occur in early stages of the disorder and may underlie early functional impairments and the vulnerability to psychosis. Accordingly, simulation modelling of neural development indicates that WM abnormalities predate the onset of schizophrenia and represent a risk factor of psychotic disorders (Kochunov and Hong, 2014). Considering mental health as a non-linear, dynamic system (Nelson et al., 2017), it could be hypothesized that structural abnormalities in WM may contribute to the system shift of the transition from the CHR stage to psychosis. In line with this hypothesis, Saito et al. (2017) reported based on longitudinal data that progressive disruption of WM in the genu of the CC correlates with negative symptoms. Other researchers found greater FA reductions in the CC of CHR patients who converted to psychosis compared to non-converters (Carletti et al., 2012; de Wit et al., 2016; Koutsouleris et al., 2010; Merritt et al., 2021). These results let suggest FA in the CC as a potential neuromarker to predict functional outcome and psychosis.

Recent advances in early detection demonstrated superior predictive accuracy when combining psychopathological measures with brain structure (and function) as compared to each single entity in psychosis research (Coutts et al., 2023; Koutsouleris et al., 2021), which can be considered as a case of personalized medicine.

For example, Koutsouleris et al. (2021) reported that an optimal individual prognostic outcome with regard to transition to psychosis in high-risk samples was reached (balanced accuracy 85.9 % sensitivity, 84.6 %; specificity, 87.3 %) when sequentially integrating clinical-neurocognitive, expert-based, polygenic risk score-based, and gray matter structural MRI-based risk estimates. Our data implicate, that processing speed takes a subordinate role partly explaining deficits in higher other cognitive domains and being related to some of structural deficits found in psychosis. Our results indicate that white matter integrity in the CC could act as a potential neuromarker to predict functional outcome and psychosis. Combining the landmark study of Koutsouleris et al. with our results, we suggest processing speed as a key parameter to indicate cognition and emphasize the additional inclusion of FA measurements in further improving the accuracy of individual prognosis and finding appropriate interventions.

While effective treatments to restore brain structure and thus to prevent transition are still missing (Worthington and Cannon, 2021), oxidative stress has been shown to negatively impact WM structures (Maas et al., 2017) and could be in principle decreased via psychopharmacological and psycho-social treatments (Dwir et al., 2021). These interventions could potentially restore cognition in people with CHR and stop disease progression. Other recent studies (Cella et al., 2020; Glenthøj et al., 2017) have indicated beneficial effects of cognitive remediation in CHR. Finally, our results imply that cognitive remediation in CHR with the intention to improve psychosocial functioning should focus on processing speed as a subordinate function, controlling and/or facilitating other cognitive domains.

Whereas we present here to our knowledge the first study in CHR to examine the associations between callosal WM and cognitive core impairments, our study has limitations due to a reasonable but still limited sample size and cross-sectional data. The region of interest approach limiting to CC can be considered a limitation of our study. This approach excluded the examination of other key structural connections, such as the longitudinal fasciculus and uncinate fasciculus, which link cortical areas and limbic structures, including the hippocampus. Further, our findings rely solely on the TBSS method which represents a standard approach but still has limitations e.g. its sensitivity to alignment errors (Bach et al., 2014). To overcome this limitation, we suggest the replication of our findings in future studies by using alternative methods of tractography and graph analytics as integrated in other research (Alves et al., 2019). Our results of mediation and FA-cognition association analyses are based on combined sample (CHR + HC) analyses. Conducting the same analyses in the CHR sample, we failed to fulfill the pre-assumptions of mediation modelling and to find significant associations between FA and cognition after FWE correction. Based on additional exploratory uncorrected analyses (see Fig. S5), we found similarities in the distributions of significant associations over CC subareas between the FWE corrected combined sample and the uncorrected CHR sample results - providing only limited evidence of generalization. To approve generalization more careful, future research should replicate and extend our findings using whole-brain analyses in a larger sample of CHR patients, in line with previous multi-site studies in schizophrenia (Kelly et al., 2018; Kochunov et al., 2017; Seitz-Holland et al., 2022).

Moreover, in our research and clinical work, we use a clinical staging model to describe the psychosis spectrum that is close to a dimensional construct (McGorry et al., 2018). While CHR takes a position between health and mental disorder such as psychosis, people with CHR are characterized as having significant distress caused by psychiatric symptoms that may lead to help-seeking, differentiating CHR patients from HC. On the other hand, CHR patients have intact reality monitoring and are able to distinguish between their thoughts, perceptions, and beliefs and the external reality, thereby differentiating CHR from first episode psychosis patients. Because of the dimensional character of cognition and FA, and the closeness of the CHR stage to mental health, a combination of both study groups seems acceptable to address research questions about shared features in both groups (versus group specific effects). Moreover, previous studies in the field (Bosma et al., 2023; Holleran et al., 2020; Kochunov et al., 2017, 2016) successfully integrated the approach of combined sample analyses and Holleran et al. (2020) provided robust evidence based on large sample for a general association pattern between cognition and FA independent of diagnosis (schizophrenia and HC).

Further, taking in account that approximately only one third of CHR patients within three years convert to psychosis, while an additional third has persistent symptoms without conversion (Fusar-Poli et al., 2012; McGorry et al., 2018; Salazar De Pablo et al., 2021) – future research should investigate the role of disrupted anterior callosal WM development related to impaired cognition as a transdiagnostic risk marker.

5. Conclusions

Here, we provide novel evidence of the CHR stage by showing established associations in schizophrenia between impaired WM structures of CC with cognitive deficits. Our findings highlight processing speed as a fundamental cognitive impairment of the early risk stage and suggest WM fiber tracts of the anterior CC with assumed projections to PFC as an underlying neural pathway. In addition, our exploratory topological view of FA-cognition relationships, linked executive function and spatial working memory to structures of the anterior and posterior CC with projections to distinct and overlapping cortical areas compared to processing speed. Future studies should consider impaired processing speed related to deficits of anterior callosal WM as markers to advance multi-factorial modelling of risk to improve prospectively prediction and intervention in schizophrenia.

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CRediT authorship contribution statement

Arndt-Lukas Klaassen: Formal analysis, Methodology, Visualization, Writing – original draft. **Chantal Michel:** Data curation, Writing – review & editing, Funding acquisition, Supervision. **Miriam Stüble:** Data curation, Writing – review & editing. **Michael Kaess:** Resources, Supervision, Writing – review & editing, Funding acquisition. **Yosuke Morishima:** Formal analysis, Supervision, Writing – review & editing, Funding acquisition. **Jochen Kindler:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare no conflict of 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.2023.12.026.

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