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Review

A narrative literature review of white matter microstructure in individuals at clinical high risk for psychosis

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Abstract

Schizophrenia is a severe psychiatric disorder characterized by widespread white matter (WM) alterations, manifesting as neurodevelopmental deficits and dysconnectivity abnormalities. Over the past two decades, studies have focused on the clinical high-risk (CHR) stage of psychosis and have yielded fruitful information on WM abnormalities that exist prior to the full onset of psychosis, shedding light on biological mechanisms underlying psychosis development. This review presents a summary of current findings on cross-sectional and longitudinal WM alterations in individuals with CHR and their links to clinical symptoms and neurocognitive dysfunction. Next, we review the utilization of WM characterization in predicting clinical outcomes. Taken together, the literature suggests the clinical significance of WM characteristics and their great potential in predicting the conversion to psychosis, despite some methodological and conceptual challenges that remain to be addressed in future studies. Future CHR research would greatly benefit from utilizing WM to guide pharmacological and non-pharmacological targeted treatments, optimize clinical prediction models, and enable more accurate clinical care.

Keywords: diffusion tensor imaging; white matter microstructure; clinical high risk for psychosis; cross-sectional alteration; longitudinal development; prediction of transition risk

Introduction

Schizophrenia (SZ) is a serious psychiatric disorder that affects about 1% of the world population (Tandon *et al.*, 2008). Patients with SZ exhibit a heterogeneous complex of symptoms and cognitive deficits, which may progress over time and cause chronic disabilities in everyday functioning, such as maintaining employment, social relationships, and living independently, while suffering from poor physical health (Harvey *et al.*, 2019; Kahn *et al.*, 2015). It is noted that early intervention is associated with better functional outcomes and maintenance of symptom remission (Kane *et al.*, 2016). Therefore, over the past two decades, emerging studies have focused on the clinical high-risk (CHR) stage of psychosis (Fusar-Poli *et al.*, 2020), in the hope that identifying early signs prior to the onset of psychosis will minimize impairment and prevent the full onset of psychotic disorders (Zhang *et al.*, 2017). Furthermore, capturing the biological changes in the CHR population might provide new insights into the neural mechanisms underlying psychosis and provide clues for facilitating better prognosis and intervention.

The diagnostic criteria for the CHR (also known as "prodromal" or "at-risk mental state") include two sets of criteria: basic symptoms (BS) and ultra-high risk (UHR) criteria. The UHR criteria require the presence of one or more of the following: attenuated psychotic symptoms (APS), brief limited intermittent psychotic episode (BLIP), trait vulnerability plus a marked decline in psychosocial functioning [genetic risk and deterioration syndrome (GRD)], and unspecified prodromal symptoms (UPS) (Fusar-Poli *et al.*, 2013). In this paper, we will only use the abbreviation 'CHR'. Although CHR provides a great time window for early detection and intervention, the average risk of transition to psychosis is 0.15 at 1 year, 0.19 at 2 years, and 0.25 at 3 years (Salazar de Pablo *et al.*, 2021a). The others either remit or suffer from persistent syndromes. Therefore, more refined and robust biomarkers are needed to better elucidate the potential pathophysiology underlying the heterogeneous symptoms and facilitate the prediction of clinical outcomes in the CHR population.

It is posited that SZ is a cognitive and behavioral disorder that shows significant impairments in information processing (Kahn *et al.*, 2015). As white matter (WM) contains many axonal projections to other neurons and functional brain areas, microstructural changes may underlie the disturbed communication between different brain regions (Peters *et al.*, 2010a) and thus account for the core psychotic and cognitive symptoms in schizophrenia (Kochunov *et al.*, 2017). In this context, diffusion tensor imaging (DTI) studies in the CHR population have revealed dynamic alterations in WM microstructure before and after the onset of psychosis. These studies offer valuable information on preexisting WM abnormalities and hold great potential to reveal the underlying mechanisms and predict the prognosis of psychosis.

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In general, the neurodevelopmental hypothesis postulates that SZ is caused by genetic risk factors and/or environmental insults that occur during the perinatal period, early childhood, or adolescence. These factors perturb axonal pruning and myelination, which causes disruption of WM integrity and deviation from the normal developmental trajectory, and consequently, set the stage for SZ (Kochunov *et al.*, 2012; Murray *et al.*, 2017; Rapoport *et al.*, 2012). Firstly, several lines of evidence, including genetic and postmortem studies, have pinpointed the role of demyelination and oligodendrocyte dysfunction in the pathogenesis of SZ (Davis *et al.*, 2003; Tkachev *et al.*, 2003). The myelination of WM occurs in a posterior to anterior, caudal to cranial trajectory (Giorgio *et al.*, 2010). The maturation of lower-order tracts responsible for basic processes (such as sensorimotor and vision processing) begins in the first and second decades of life (Karlsgodt *et al.*, 2012; Lebel *et al.*, 2012). In contrast, long-range association tracts and higher-order cognition typically peak in late adolescence and early adulthood (Peters *et al.*, 2014), which coincides with the timing of peak risk for developing SZ (15–25 years old) (Kochunov and Hong, 2014). Secondly, the development of myelin is paralleled by synaptic pruning and changes in axonal diameters and neurite density, which have long been implicated in the pathogenesis of SZ and might even serve as a treatment target (Patel *et al.*, 2021). Such characteristics could be captured by different imaging metrics. Furthermore, changes in WM microstructure may be confounded by a series of intertwined effects such as cumulative antipsychotic exposure, neuroinflammation, metabolism changes raised by medication, and the illness stage of psychosis (Najjar and Pearlman, 2015; Szeszko *et al.*, 2014). Since medication-associated factors are usually not present in CHR individuals, WM studies in CHR thus offer a unique perspective for identifying early-stage alterations in WM pathology, and provide an opportunity to fully characterize the underlying mechanisms contributing to the transition to psychosis.

The dysmyelination hypothesis suggests that dysfunctional oligodendrocytes, which produce and maintain myelin in the central nervous system, may underlie abnormal or inefficient communication between neural cells (Kubicki and Lyall, 2018). This abnormal communication may occur between spatially disparate cerebral regions and result in a failure of proper functional integration within the brain (Ellison-Wright and Bullmore, 2009; Konrad and Winterer, 2008), leading to psychotic symptoms such as hallucinations, delusions, and thought disorders in SZ (Kochunov *et al.*, 2017; Kubicki and Lyall, 2018). In addition to providing structural connections for gray matter, myelin sheaths also play a major role in modulating the conduction velocity of axons (Caminiti *et al.*, 2013), which significantly impacts the efficiency and speed of information transmission (Hilal *et al.*, 2021) and could be a key reason for the wide range of cognitive deficits in psychosis (H. Zhang *et al.*, 2019). This hypothesis has been strengthened by many structural imaging studies that reported alterations in higher-order GM regions connected by those long-range association WM tracts (van Erp *et al.*, 2018). Moreover, it is worth noting that SZ is a disorder with high heterogeneity in clinical and biological features. An important perspective suggests that the phenotypic differences are also manifested in WM, with WM impairments correlated with cognitive impairments and symptom severity in SZ (K. H. Karlsgodt, 2016). Therefore, exploring biomarkers and treatment methods based on different subtypes and neurobiological profiles could be more effective than treating it as a whole. As individuals with CHR may also experience attenuated or intermittent psychotic symptoms and cognitive dysfunctions (Fusar-Poli, 2017; Pukrop *et al.*, 2006), studying WM in CHR could greatly aid in understanding the biological underpinnings of the heterogeneous symptoms of SZ. This may lead to the identification of potential biomarkers for early recognition and prognostic prediction, as well as the development of new treatment targets for interventions (Karlsgodt, 2016).

In this review, we provide an up-to-date summary of findings on WM characteristics and the links with psychopathology in individuals with CHR. We then offer a synthesis of the current utilization of WM in predicting clinical outcomes, and discuss future trends in light of recent progress in hypotheses and methodologies. Additionally, we discuss the potential for WM to facilitate early interventions, as well as the opportunities and challenges for future studies.

Methods

In this literature review, we searched three scientific databases (PubMed, Scopus, and Web of Science) till Sep. 2023. We used the following query terms: ("white matter") AND ("clinical high risk" OR "prodromal" OR "at-risk mental state" OR "CHR" OR "ultra-high risk" OR "UHR") AND ("diffusion MRI" OR "diffusion tensor imaging" OR "diffusion weighted imaging"). Two authors (Su and Tang) manually screened the titles and abstracts independently. Only original peer-reviewed research articles with full texts available, written in English, and focusing on white matter microstructures in CHR were included. We obtained 136 articles from PubMed, 209 from Scopus, and 16 from Web of Science. There were 255 articles after removing duplicates. After we reviewed the full texts, 47 articles fulfilling the above inclusion criteria were identified (Tables 1–3 and supplementary eTables 1–3). We used the Joanna Briggs Institute Critical Appraisal Tools for the quality assessment of included cross-sectional studies, with the maximum score (signifying high quality) of 8 points (Moola *et al.*, 2020).

Results

When summarizing the findings of this literature review, we focused on the cross-sectional and longitudinal WM alterations in CHR with conventional DTI measures, advanced WM microstructural measures in CHR, clinical and neurocognitive correlates of WM changes in CHR, and WM predictors of the clinical outcomes of CHR (Fig. 1).

Cross-sectional WM alterations in CHR

Fractional Anisotropy

As the most commonly reported index of WM integrity, fractional anisotropy (FA), which represents the normalized variance of the eigenvalues, has been interpreted as a measure reflecting fiber density, axonal diameters, and WM/myelin integrity (Alba-Ferrara and de Erausquin, 2013; González-Reimers *et al.*, 2019). The FA findings in CHR have been mixed. Nearly one-third of the studies reported negative findings in case-control differences at baseline (Bernard *et al.*, 2015, 2017; Bakker *et al.*, 2016; Di Biase *et al.*, 2021; Nägele *et al.*, 2021; Tomyshev *et al.*, 2017; Tomyshev *et al.*, 2019; Vargas *et al.*, 2019; Waszczuk *et al.*, 2022; Whitford *et al.*, 2018). Two studies reported higher FA in the CHR (Langhein *et al.*, 2023; Schmidt *et al.*, 2015). Most of the studies reported a significantly lower FA in CHR individuals compared with HC in fibers such as frontotemporal, fronto-occipital, interhemispheric, and thalamocortical regions. Here, we summarize those well-replicated results based on different WM tracts (Chen *et al.*, 2023; Cho *et al.*, 2016; Fitzsimmons *et al.*, 2020; Katagiri *et al.*, 2015; Krakauer *et al.*, 2017;

Table 1: Cross-sectional studies on white matter (WM) microstructure in clinical or ultra-high risk (CHR or UHR) for psychosis as compared to healthy controls (HC).

Study	Sample	WM Measures				Major findings of WM alterations		Quality
		FA	MD	AD	RD	Between-group differences	Association with symptoms/cognitive functions	
Rigucci *et al.*, 2016	27 UHR (10 UHR-P), 26 HC	✓	✓	✓	✓	Lower FA in the CC, left SLF and ILF, left IFOF, and forceps and higher RD in the CC, forceps, bilateral anterior thalamic radiation, and CB in UHR-P than HC.	/	8/8
Schmidt *et al.*, 2015	28 ARMS, 24 HC	✓	✓	/	/	Higher FA in the right ATR, bilateral IFOF, left SLF, left UF, forceps major, and right ILF and lower MD in the bilateral ILF, left IFOF, and left SLF in ARMS.	A positive correlation between FA in the right SLF and positive symptoms.	8/8
Bakker *et al.*, 2016	23 UHR, 33 HC	✓	✓	✓	✓	Higher mean MD, RD, and AD in the CC, ATR and cortical fasciculi in UHR than HC; no significant FA differences.	No significant correlations between voxel-wise FA, AD and RD, and positive or negative symptoms.	8/8
Cho *et al.*, 2016	37 CHR, 37 HC	✓	/	/	/	Lower FA in thalamo-orbitofrontal cortex in CHR.	A positive correlation between thalamo-orbitofrontal connectivity and the GAF scores in CHR.	8/8
Krakauer *et al.*, 2017	45 UHR, 45 HC	✓	/	✓	✓	Lower FA, AD, and mode of anisotropy (MO) concomitant with higher RD in widespread brain regions in UHR.	Partial least-squares correlation analysis revealed five significant latent variables (LVs) associated with symptoms and level of functioning. The first LV indicated a pattern where severer symptoms and poor functioning correlated to lower FA, AD, MO, and higher RD.	7/8
Tomyshev *et al.*, 2017	27 UHR, 27 HC	✓	✓	✓	✓	Higher RD in the left ATR and higher AD in the right posterior CB in UHR.	FA/AD in the left anterior CB negatively correlated with positive and negative symptoms; RD positively correlated with positive symptoms; FA in the right anterior cingulum negatively correlated with positive and negative symptoms.	7/8
Whitford *et al.*, 2018	51 ESZ, 40 CHR, 59 HC	✓	/	/	✓	CHR vs. HC not significant.	/	8/8
Kristensen *et al.*, 2019	116 UHR, 43 HC	✓	✓	✓	✓	Lower FA in the SLF and cingulate gyrus in UHR.	Higher FA associated with better cognitive functioning in UHR, but not in HC. Patterns of cognitive functions were associated with an interaction effect on regional FA in the fornix, medial lemniscus, UF, and superior cerebellar peduncle.	8/8
Tomyshev *et al.*, 2019	30 UHR, 30 HC	✓	✓	✓	✓	Higher RD in the left ATR in UHR.	No significant correlations between RD in the left ATR and clinical symptoms or medication.	7/8
Vargas *et al.*, 2019	49 CHR, 49 HC	✓	/	/	/	CHR vs. HC not significant.	/	8/8
Fitzsimmons *et al.*, 2020	20 CHR, 23 HC	✓	✓	✓	✓	Lower FA, higher RD, higher trace in the CB in CHR, but no difference in AD.	No significant correlations between DTI measures in the CB and clinical symptoms or cognitive scores.	8/8
Saito *et al.*, 2020	30 ARMS	✓	/	/	/	Laterality index of FA was positive in the CB (leftward) and negative in the UF (rightward).	Laterality index of FA in the CB was positively correlated with the social function score.	/[a]
Straub *et al.*, 2020	18 psychosis risk, 19 HC	✓	/	/	/	CHR group showed decreased FA in WM tracts connecting the limbic striatum with the limbic cortical network.	/	7/8

Table 1: Continued

Study	Sample	WM Measures				Major findings of WM alterations		Quality
		FA	MD	AD	RD	Between-group differences	Association with symptoms/cognitive functions	
Sato *et al.*, 2021	56 CHR, 49 FEP, 33 HC	✓	✓	✓	✓	Lower FA in the bilateral external capsule, ALIC, PLIC, cerebral peduncle, and right PCR; higher MD in the right ILF and IFOF; higher RD in the right SLF, ILF, IFOF, PCR, UF, bilateral external capsule, ALIC, PLIC, and cerebral peduncle in CHR.	Higher MD in the left hemisphere (SLF, ILF, IFOF, CST) correlated with hallucination severity in CHR and FEP.	7/8
Steinmann *et al.*, 2021	29 CHR, 21 HC	✓	/	/	/	Greater rightward asymmetry (right > left) of the SLF-III in female CHR.	Laterality index of SLF-III for CHR females associated with poorer working memory functioning.	8/8
Kristensen, *et al.*, 2021a	110UHR (10 UHR-P)	✓	/	/	/	Higher global FA in UHR who remitted and sustained UHR than UHR-P.	Global FA predicted level of symptoms and functional level at 6-months but not at 12-months follow-up.	7/8
Langhein *et al.*, 2023	26 CHR (7 CHR-P), 13 HC	✓	/	/	/	Higher structural connectivity in the right AF than HC; no significant differences in structural connectivity between CHR-P and CHR-NP.	No significant correlation between structural connectivity and clinical symptoms.	7/8
León-Ortiz *et al.*, 2022	33 CHR (7 CHR-P), 38 HC	✓	/	/	/	Lower FA values in posterior thalamic radiation in CHR-P than CHR-NP and HC.	In CHR-P, negative symptoms were correlated with FA in the ACC and SFOF without survived from the correction for multiple comparison.	6/8
Smigielski *et al.*, 2022	Two at-risk subtypes (37 UHR and 43 individuals with basic symptoms), 32 HC	✓	✓	✓	✓	Lower FA in the splenium of CC but only before multiple-testing correction in UHR; at-risk individuals who converted to psychosis had lower FA and higher RD (in the CC, ACR, and motor/sensory tracts).	In at-risk individuals, FA in the splenium of CC, ACR, ATR, and left SFOF negatively correlated with general symptom; FA in the left SFOF negatively correlated with negative symptoms.	8/8
Su *et al.*, 2022	66 CHR, 70 HC	✓	✓	/	✓	Widespread lower FA and higher MD and RD in CHR.	MD negatively associated with GAF current scores, but positively associated with GAF score drops and negative symptoms; RD negatively associated with GAF current scores and positively associated with GAF drops.	8/8
Waszczuk *et al.*, 2022	12 UHR, 33 HC	✓	✓	/	/	No significant between-group differences.	Negative correlations between MD in the left ILF and negative and general symptoms.	7/8
Chen *et al.*, 2023	42 APSS, 51 HC	✓	✓	✓	✓	Lower FA and AD in APSS, but higher MD and RD in APSS in regions including the callosum forceps minor, left and right cingulum cingulate, IFOF, right CST, left SLF, and AF.	Positive associations between AD in the bilateral CGC and GAF current scores and between AD in the right CST and negative symptoms and reasoning and problem-solving scores.	8/8

AD, axial diffusivity; AF, arcuate fasciculus; APSS, attenuated positive symptom syndrome; ARMS, at-risk mental state; ATR, anterior thalamic radiation; CB, cingulum bundle; CC, corpus callosum; CHR, clinical high-risk for psychosis; CHR-P (or UHR-P), CHR (or UHR) who later converted to psychosis; CR, corona radiata; CST, corticospinal tract; EOS, early-onset schizophrenia; FA, Fractional Anisotropy; FEP, individuals with first-episode psychosis; GAF, Global Assessment of Functioning Scale; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; MTL, medial temporal lobe; RD, radial diffusivity; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; UHR, ultra-high risk for psychosis; UHR-NP, UHR who later did not converted to psychosis; WM, white matter.
[a]This study only included ARMS patients but no healthy controls.

Krakauer *et al.*, 2018; Kristensen *et al.*, 2019; Kristensen *et al.*, 2021b; Leon-Ortiz *et al.*, 2022; Rigucci *et al.*, 2016; Roalf *et al.*, 2020; Saito *et al.*, 2017; Sato *et al.*, 2021; Smigielski *et al.*, 2022; Straub *et al.*, 2020; Su *et al.*, 2022a; Tang *et al.*, 2019; Wang *et al.*, 2016).

One of the most consistent findings is the interhemispheric callosal fibers, with lower FA in genu (GCC), body (BCC), and splenium of CC (SCC) found in CHR (Chen *et al.*, 2023; Katagiri *et al.*, 2015; Rigucci *et al.*, 2016; Roalf *et al.*, 2020; Saito *et al.*, 2017; Smigielski *et al.*, 2022; Su *et al.*, 2022b; Tang *et al.*, 2019). As the largest WM bundle in the brain, CC connects homologous regions of two cerebral hemispheres and plays crucial roles in the interhemispheric communication and integration of high-level cogni-

Table 2: Longitudinal trajectory of white matter (WM) microstructure in patients at clinical or ultra-high risk (CHR or UHR) for psychosis.

Study	Sample	WM Measures				Major findings of WM alterations		
		FA	MD	AD	RD	Between-group differences at baseline	Between-group differences at follow-up	Association with symptoms/cognitive functions
Bernard *et al.*, 2015	26 UHR, 21 HC	✓	/	/	/	No significant between-group differences	Hippocampal-thalamic FA decreased in UHR but increased in HC over 12-month follow-up.	Higher baseline hippocampal-thalamic FA was predictive of severer positive symptoms at follow-up.
Katagiri *et al.*, 2015	41 ARMS, 16 HC	✓	/	/	/	Reduced FA in part of genu and body of the corpus callosum in ARMS than HC.	No significant interaction of group and time for comparison of FA between ARMS-NN and ARMS-NA.	ARMS-N group showed a significant improvement in sub-threshold positive symptoms at follow-up, which was correlated with an increase in FA in a part of genu and body of CC.
Bernard *et al.*, 2017	26 UHR (3 UHR-P), 24 HC	✓	/	/	/	No significant between-group differences	Increased FA in the Lobule V-thalamic tract segment and the thalamo-prefrontal tract segment in HC but decreased FA in UHR.	/
Saito *et al.*, 2017	46 ARMS (7 ARMS-P), 16 HC	✓	/	/	/	Smaller FA in the entire CC and the genu, trunk, and splenium of the CC in ARMS; Smaller FA in the genu and truck of the CC in ARMS-NP than ARMS-P.	Smaller FA in the trunk of CC in ARMS-NP than ARMS-P at 52-week follow-up.	FA reduction in the genu of CC correlated with a deterioration of negative symptoms in ARMS.
Krakauer *et al.*, 2018	30 UHR, 23 HC	✓	/	/	/	Lower FA in the left CST, right ATR, and left SLF in UHR.	Increased FA in the left SLF in UHR, and increased FA in the left UF in HC, but no between-group differences in FA changes.	FA changes in the left IFOF, ATR and SLF positively correlated to change in negative symptoms.
Roalf *et al.*, 2020	46 patients at subthreshold persistent psychosis risk, 98 HC	✓	✓	✓	✓	Lower whole-brain FA (forceps major, IFO, CGH, CST, ILF, SLF and ATR) and higher RD (IFO and forceps major), but no AD or MD alterations in patients at persistent psychosis risk.	Lower whole-brain FA (CGH, CST) and higher RD, but not AD or MD alterations in patients at persistent psychosis risk at longitudinal follow-up.	Higher mean AD and MD positively correlated with positive symptoms; higher MD and AD associated with lower neurocognitive factor scores.
Kristensen *et al.*, 2021a	110 UHR, 59 HC	✓	✓	✓	✓	Lower global and regional (right SLF and left UF) FA in UHR	Between-group global FA differences remained at 6-month follow-up, but regional FA differences did not.	Increase of negative symptoms correlated with FA increase in the right SLF in UHR.

AD, axial diffusivity; ARMS, patients with at-risk mental state; ARMS-N, ARMS who did not transition; ALIC, anterior limb of the left internal capsule; ATR, anterior thalamic radiation; CC, corpus callosum; CGH, Cingulum bundle of the hippocampus; CHR, patients at clinical high-risk for psychosis; CHR-P (or UHR-P), CHR (or UHR) who later converted to psychosis; CST, corticospinal tract; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; RD, radial diffusivity; SCR, superior corona radiata; SFOF, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; UHR, patients at ultra-high risk for psychosis; UHR-NP, UHR who later did not convert to psychosis; WM, white matter.

tive functions. Unsurprisingly, individuals with CHR exhibited significantly decreased FA in long-range association and language-related connections, such as the superior longitudinal fasciculus (SLF) (Krakauer *et al.*, 2017; Krakauer *et al.*, 2018; Kristensen *et al.*, 2019; Kristensen *et al.*, 2021b; Rigucci *et al.*, 2016; Roalf *et al.*, 2020; Su *et al.*, 2022b; Tang *et al.*, 2019) and the inferior fronto-occipital fasciculus (IFOF) (Chen *et al.*, 2023; Krakauer *et al.*, 2017; Rigucci *et al.*, 2016; Roalf *et al.*, 2020). These two fibers were also characterized by an abnormal maturation and decline trajectory in SZ (Cetin-Karayumak *et al.*, 2020).

The fronto-limbic area fibers, including cingulum (including hippocampus and cingulate parts, CGH, CGC), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), and fornix (FX) have been linked with lower FA in the CHR (Chen *et al.*, 2023; Fitzsimmons *et al.*, 2020; Krakauer *et al.*, 2017; Kristensen *et al.*, 2019; Kristensen *et al.*, 2021b; Roalf *et al.*, 2020; Straub *et al.*, 2020;

Table 3: Advanced measures of white matter (WM) microstructure in patients at clinical or ultra-high risk (CHR or UHR) for psychosis.

Study	Sample	Advanced WM measures	Major findings of WM alterations		
			Between-group differences at baseline	Between-group differences at follow-up	Association with symptoms/cognitive functions
Wang *et al.*, 2016	87 ARMS (10 ARMS-P), 37 HC	Free-water corrected FA, AD, MD, and RD	Lower FA and AD in frontal-striatal-thalamic WM tracts and the cingulum in ARMS; lower FA and AD in forceps minor in ARMS-P than ARMS-NP.	/	Neurocognitive level correlated with FA decreases in the left IFOF, UF, and ATR.
Tang *et al.*, 2019	50 CHR (11 CHR-P), 50 HC	Free-water corrected FA_T, AD_T, and RD_T; FW	Lower FA, FA_T and AD_T, but no RD_T or FW changes in CHR.	/	Positive correlation of age and FA_T in HC but not in CHR.
Di Biase *et al.*, 2021	230 CHR (25 CHR-P) 56 HC	Free-water corrected FA_T, FW	No significant between-group differences among CHR-P, CHR-U, and HC.	Higher FA_T in CHR-P and CHR-U adolescence; older CHR-P displayed 4% higher FW in the forceps major.	FA and FA_T but not FW associated with neurobehavioral score; upturns in symptoms severity and functioning accompanied decreased FA and FA_T in the cingulum and forceps minor and increased FW in the forceps major.
Nägele *et al.*, 2021	30 CHR (8 CHR-P), 24 HC	Free-water corrected FA_T, FW	Widespread lower FA, lower FA_T (in the CC, CR, PTR), and higher FW in CHR-P than CHR-NP.	/	FA and FA_T inversely correlated with positive symptoms; FW positively correlated with positive symptoms.
Zhang *et al.*, 2021	115 CHR, 93 HC	FA_{DTI}, FA_{DKI}, FA_{MKC}, MK_{DKI}, MK_{MKC}	Lower FA-based (FA_{DTI}, FA_{DKI} and FA_{MKC}) and MK-based (MK_{DKI} and MK_{MKC}) measures in CHR.	/	Lower MK and FA correlated with a decline in functioning and more severe symptoms.
Hua *et al.*, 2023	41 CHR (9 CHR-P), 74 HC	Rich-club connections, local connections, density, modularity, transitivity, and global efficiency	Fewer connections among rich-club regions and greater modularity in CHR-P than CHR-NP.	/	No association of symptom severity and antipsychotic dosage with any connectome metrics.

AD, axial diffusivity; ARMS, patients with at-risk mental state; ARMS-NP, ARMS who later did not transition; ARMS-P, ARMS who later converted to psychosis; ATR, anterior thalamic radiation; CC, corpus callosum; CHR, patients at clinical high-risk for psychosis; CHR-P, CHR who later converted to psychosis; CHR-NP, CHR who later did not convert to psychosis; CHR-U, CHR with unknown transition outcome; CR, corona radiata; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; FW, free water; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; MK, mean kurtosis; MKC, MK-Curve; PTR, posterior thalamic radiation; RD, radial diffusivity; SCR, superior corona radiata; SFOF, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus.

Su *et al.*, 2022b). Coinciding with these findings, a large-sample study in SZ also demonstrated the fibers connecting the limbic area as an abnormal early development cluster, in which FA decrease emerges in the early lifespan and before the onset of SZ and remains evident across the entire course of psychosis (Cetin-Karayumak *et al.*, 2020). Moreover, the sensorimotor domain has been found to effectively identify CHR and predict the onset of psychosis (Damme *et al.*, 2021). This point was further supported by studies that reported a significantly decreased FA in the thalamic-orbitofrontal cortex (Cho *et al.*, 2016), frontal-striatal-thalamic circuits (Wang *et al.*, 2016), anterior (ACR) (Krakauer *et al.*, 2017; Krakauer *et al.*, 2018; Roalf *et al.*, 2020) and posterior thalamic radiations (PCR) (Krakauer *et al.*, 2017; Leon-Ortiz *et al.*, 2022; Su *et al.*, 2022b), and corticospinal tract (CST) (Chen *et al.*, 2023; Krakauer *et al.*, 2017; Krakauer *et al.*, 2018; Roalf *et al.*, 2020) in CHR participants.

Radial Diffusivity, Mean Diffusivity, and Axial Diffusivity

Radial diffusivity (RD) refers to the average of the two minor eigenvectors perpendicular to axonal fibers and appears to be more strongly correlated with myelin abnormalities (Song *et al.*, 2002). In contrast, axial diffusivity (AD) refers to the magnitude of the largest eigenvector, which is in parallel to fiber tracts and characterizes axonal degeneration (Song *et al.*, 2002). Mean diffusivity (MD) describes the overall diffusion and is calculated by averaging the three eigenvalues of the diffusion tensor, which represents a non-specific but sensitive measure that can be affected by many variations within the intra- and extracellular space and/or index

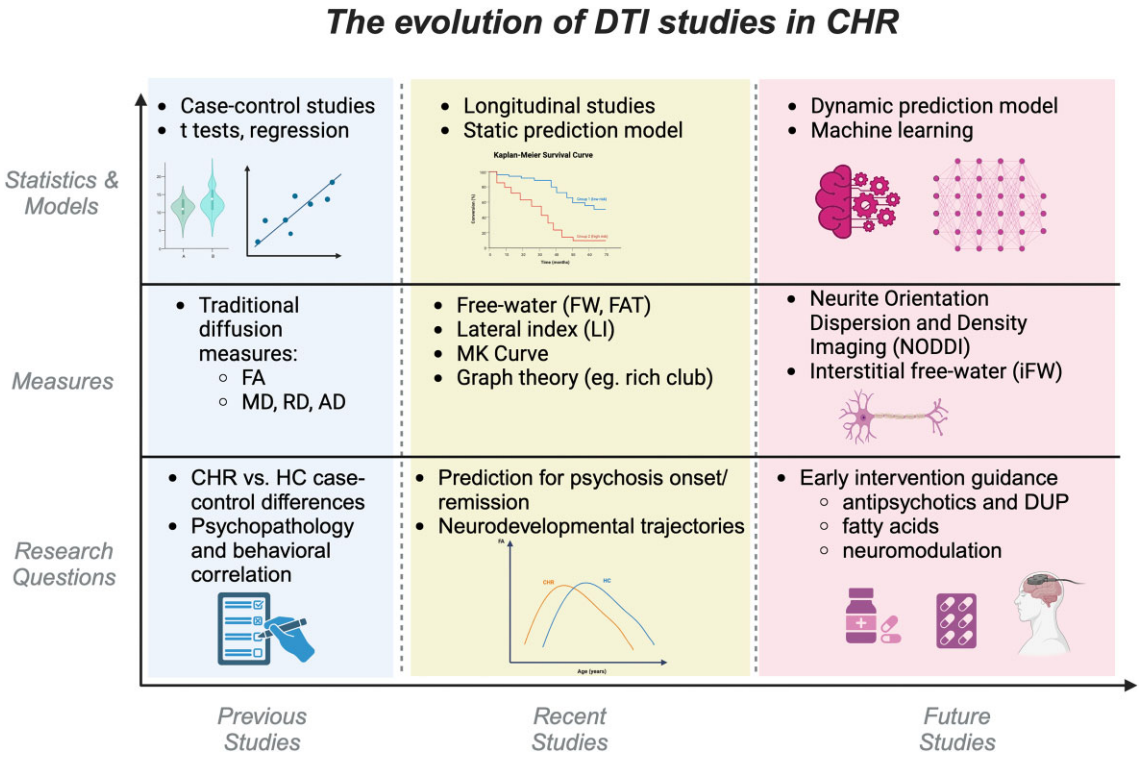

Figure 1: The evolution of diffusion tensor imaging (DTI) studies in patients at clinical high risk for psychosis (CHR). Biorender generated the figure: https://www.biorender.com/.

global alterations in cerebrospinal fluid (CSF) (Beaulieu, 2002). In addition to the FA, these indexes measure different aspects of WM pathology.

Most of the studies reported higher MD and/or RD in CHR subjects (Bakker *et al.*, 2016; Chen *et al.*, 2023; Fitzsimmons *et al.*, 2020; Krakauer *et al.*, 2017; Rigucci *et al.*, 2016; Roalf *et al.*, 2020; Sato *et al.*, 2021; Smigielski *et al.*, 2022; Su *et al.*, 2022a; Tomyshev *et al.*, 2017; Tomyshev *et al.*, 2019; von Hohenberg *et al.*, 2014), some reported an unchanged MD and/or RD (Carletti *et al.*, 2012; Cooper *et al.*, 2018; Smigielski *et al.*, 2022; Wang *et al.*, 2016; Waszczuk *et al.*, 2022; Whitford *et al.*, 2018), and one study reported lower MD in several brain regions (Schmidt *et al.*, 2015). Evidence of higher MD has been found in several regions, including inter-hemispheric fibers (Chen *et al.*, 2023; Su *et al.*, 2022a; von Hohenberg *et al.*, 2014), primary motor fibers (CST, cerebral peduncle) (Chen *et al.*, 2023; Su *et al.*, 2022a), and language-related fibers (SLF, IFOF) (Chen *et al.*, 2023; Sato *et al.*, 2021) which have been lined with the core symptoms of psychosis such as hallucination (Sato *et al.*, 2021). Regarding the RD measure, although the findings appear to be widespread throughout the brain, most of the findings align with the regions with lower FA and are usually interpreted as a myelin degradation of CHR, including CC (Chen *et al.*, 2023; Rigucci *et al.*, 2016; Roalf *et al.*, 2020; Smigielski *et al.*, 2022; Su *et al.*, 2022a), CR (Sato *et al.*, 2021; Smigielski *et al.*, 2022; Su *et al.*, 2022a), anterior thalamic radiation (ATR) (Krakauer *et al.*, 2017; Rigucci *et al.*, 2016; Tomyshev *et al.*, 2017; Tomyshev *et al.*, 2019), IFOF (Chen *et al.*, 2023; Krakauer *et al.*, 2017; Roalf *et al.*, 2020; Sato *et al.*, 2021), SLF (Chen *et al.*, 2023; Krakauer *et al.*, 2017; Sato *et al.*, 2021; Smigielski *et al.*, 2022), ILF (Krakauer *et al.*, 2017; Sato *et al.*, 2021), and cingulum bundle (CB) (Chen *et al.*, 2023; Fitzsimmons *et al.*, 2020; Krakauer *et al.*, 2017; Rigucci *et al.*, 2016; Su *et al.*, 2022a). However, it is important to note that RD should not be considered as a "supplement" to FA. In CHR, there were also findings of higher RD but unchanged FA (Bakker *et al.*, 2016; Tomyshev *et al.*, 2017), which was likely due to the 'compensatory effect' of higher AD, since FA is the nonlinear mapping of RD and AD. Although histopathology studies have suggested that higher RD might be a more specific marker of myelin pathology, changes in axonal diameters or density may also influence RD (Solowij *et al.*, 2017). Therefore, more advanced methodology and markers are required to differentiate the contributions of different biological underpinnings and unravel the complexity of microstructural pathology in the onset of psychosis.

Evidence of AD alteration in CHR is relatively sparse, with mostly negative findings so far (Cooper *et al.*, 2018; Fitzsimmons *et al.*, 2020; Rigucci *et al.*, 2016; Roalf *et al.*, 2020; Sato *et al.*, 2021; Smigielski *et al.*, 2022; Tomyshev *et al.*, 2019; von Hohenberg *et al.*, 2014). Of all the studies with minimal findings, the results of three studies converged to lower AD in limbic areas such as the cingulum (Chen *et al.*, 2023; Tomyshev *et al.*, 2017; Wang *et al.*, 2016), while one study reported lower AD in widespread regions (Krakauer *et al.*, 2017) and another reported higher AD in CC and ATR and cortical fasciculi (Bakker *et al.*, 2016). Although most recent studies usually include RD, AD, and MD along with FA for a more detailed WM characterization, it is worth noting that over a decade ago, nearly half of the studies only used FA as the primary outcome measure. Thus, the results above should be interpreted with caution.

Longitudinal WM Alterations in CHR

Currently, evidence of longitudinal WM changes in the CHR population is still quite sparse. Four studies have performed longitudinal dMRI scans within 12 months. Interestingly, three of them reported a group × time effect in thalamic tracts, with the CHR group showing increased FA over time but HC showing decreased FA over time in cerebellar-thalamic tracts (Mittal *et al.*, 2014), hippocampal-thalamic (Bernard *et al.*, 2015), Lobule V-thalamic

tract segment, and the thalamo-prefrontal tract segment (Bernard *et al.*, 2017). Another study did not find a group × time interaction but showed different longitudinal changes between CHR and HC. The CHR group showed increased FA in the left SLF and HC showed increased FA in the left UF, suggesting delayed frontal WM maturation in CHR individuals (Krakauer *et al.*, 2018). Furthermore, two other studies also reported less 'abnormal' FA at the follow-up scan compared to the baseline. One of them reported the disappearance of regional FA abnormalities but only global differences at the 6-month follow-up (Kristensen *et al.*, 2021b), while the other showed fewer regions of FA alterations at 20.4 months compared to the widespread baseline findings (Roalf *et al.*, 2020). These results suggest that the microstructure may be dynamic during the CHR stage, either progressing or showing resilience, due to various factors, including psychosis onset and normal development.

Advanced WM measures in CHR

Measures from Free-Water Imaging and Neurite Orientation Dispersion and Density Imaging

Model-based approaches, such as free-water imaging and neurite orientation dispersion and density imaging (NODDI), were proposed to disentangle the complex nature of WM pathology and improve the specificity of traditional FA. The free-water imaging method separates diffusion properties into two parts (Pasternak *et al.*, 2009): (i) the fractional volume of the free-water compartment (FW), which quantifies the contribution of extracellular free-water signal and thus serves as a proxy of ventricle size change, atrophy, and neuroinflammation; (ii) the fractional anisotropy of the cellular tissue (FA_T), which is more specific to alternations within neuronal tissue than the conventional FA after the elimination of the extracellular free-water. Similarly, the NODDI method separates diffusion properties into three compartments (the intracellular, extracellular, and free-water fractions) (Zhang *et al.*, 2012). It enables the estimations of neurite density index (NDI), orientation dispersion index (ODI), and the free-water fraction (FWF).

Recently, A meta-analysis reported higher FW of SZ in widespread WM regions, including CR, IC, SLF, ILF, CB, and CC (Carreira Figueiredo *et al.*, 2022), supporting the hypothesis that neuroinflammation might damage oligodendrocytes and myelin, playing an important role in the etiology of psychosis (Chew *et al.*, 2013). Another meta-analysis of NODDI studies reported increased NDI in projection fibers, decreased NDI in commissural and association fibers, and widespread increase in ODI in medication-naïve FEP, while widespread decreases in NDI but no ODI changes in medicated FEP (Kraguljac *et al.*, 2023). The NODDI findings in patients with chronic psychosis spectrum disorder are mixed. However, minimal findings were reported in CHR. So far, only three studies have investigated the cellular and extracellular changes in the CHR. Tang *et al.* (2019) first reported unchanged FW but lower FA_T in the CHR group in CC, right ACR and PCR, and bilateral SLF. The other two studies found no between-group differences in FA_T or FW (Di Biase *et al.*, 2021; Nägele *et al.*, 2021). It is also posited that extracellular changes might emerge in the early onset of SZ but decrease in the chronic stage. In contrast, the tissue abnormalities show the opposite dynamics (Pasternak *et al.*, 2018), indicating that the pathophysiological changes might vary at different stages of psychosis. Overall, despite the mostly negative findings in CHR, these studies did highlight the significance of cellular and extracellular WM alterations in the conversion of psychosis and neurodevelopment, which will be detailed further in the following context.

Other Measures: Lateral Index, Mean-Kurtosis Curve, and Rich-Club Connectivity

Recently, new methodologies have emerged in studies focusing on other characteristics of WM microstructure in individuals with CHR. For example, two studies investigated the lateral asymmetry of WM. One of these studies reported a leftward lateral index (LI) in the CB and a rightward LI in the UF of the CHR (Saito *et al.*, 2020). Another study found greater right > left asymmetry of the SLF in female CHR rather than in males (Steinmann *et al.*, 2021). These findings supported the pathogenesis hypothesis that SZ is caused by anomalous development of cerebral asymmetry (Crow *et al.*, 1989). Recent studies also suggest the changes in the rich-club connectivity (Hua *et al.*, 2023) and altered mean-kurtosis (MK) curve (Zhang *et al.*, 2021) in CHR. Furthermore, correcting for MK curve significantly improves the sensitivity of diffusion parameters to reveal group differences and clinical relevance (Zhang *et al.*, 2021), highlighting the crucial role of advanced diffusion measures in uncovering the complexity of WM pathology in early psychosis.

Clinical and Neurocognitive Correlates of WM Changes in CHR

Since the dysconnectivity hypothesis posited that disrupted myelin sheaths could be responsible for abnormal or inefficient communication leading to psychotic symptoms such as hallucinations (Kochunov *et al.*, 2017; Kubicki and Lyall, 2018), many studies have investigated the association between WM microstructure and positive symptoms in CHR. Positive symptoms have been associated with lower FA in the left anterior cingulum bundle (Tomyshev *et al.*, 2017), lower FA_T and higher FW in the whole-brain regions (Nägele *et al.*, 2021), and higher MD in the left SLF and IFOF (Sato *et al.*, 2021). However, there are also studies indicating an opposite direction, with more severe positive symptoms correlated with higher FA in the right SLF (Schmidt *et al.*, 2015) and stronger trace in the left uncinate (Peters *et al.*, 2008). One possible interpretation for this counter-intuitive direction has been proposed by SZ research (Whitford *et al.*, 2010), suggesting that psychotic symptoms may arise when the brain attempts to integrate mildly dysmetric activity. On the contrary, more severe discoordination might not be able to be integrated and result in psychotic symptoms.

More severe negative symptoms have been associated with lower FA in the left SFOF (Smigielski *et al.*, 2022) and bilateral anterior cingulum bundle (Tomyshev *et al.*, 2017), lower MD in the left ILF (Waszczuk *et al.*, 2022), and higher AD in the right CST (Chen *et al.*, 2023). For general and total symptoms, evidence has also been found in both directions (Di Biase *et al.*, 2021; Smigielski *et al.*, 2022; Straub *et al.*, 2020; Tomyshev *et al.*, 2017; Wang *et al.*, 2016; Waszczuk *et al.*, 2022). However, a certain number of results reported no association between WM measures and symptom severity (Bakker *et al.*, 2016; Fitzsimmons *et al.*, 2020; Hua *et al.*, 2023; Langhein *et al.*, 2023; Leon-Ortiz *et al.*, 2022; Saito *et al.*, 2017; Tang *et al.*, 2019; Tomyshev *et al.*, 2019). Overall, previous studies have not reached a consensus on the clinical correlates of WM changes.

Global and neurocognitive dysfunction are key signatures as potential detection and prognostic biomarkers for CHR (Catalan *et al.*, 2021). A higher global function has been associated with a stronger thalamic-orbitofrontal connectivity (Cho *et al.*, 2016), higher AD in the CGC (Chen *et al.*, 2023), and lower global MD and RD in the CHR (Su *et al.*, 2022a). Furthermore, our previous study found that in the CHR group, functional decline within 12

months was correlated with FA_T, FA, and the RD and AD calculated from the tissue compartment's tensor (AD_T and RD_T), but uncorrelated with FW (Tang *et al.*, 2019). These results are consistent with the findings of the North American Prodrome Longitudinal Study (NAPLS-3), in which both FA and FA_T, but not FW measures, were significantly associated with the composite neurobehavioral performances (Di Biase *et al.*, 2021). These results suggested that in the CHR stage, functional decline might be biologically more related to cellular deterioration instead of extracellular changes. Disrupted WM in CHR individuals is also associated with deficits in some neurocognitive domains, such as reasoning and problem-solving, verbal fluency, processing speed, and working memory (Di Biase *et al.*, 2021; Kristensen *et al.*, 2019). In addition, there is evidence linking the laterality index with social function (Saito *et al.*, 2020) and working memory (Steinmann *et al.*, 2021), suggesting the role of WM asymmetry in neurocognitive profiles.

In addition, some studies have explored associations between longitudinal WM changes and clinical progression or remission. The corpus callosum, for example, has been repeatedly reported in a few studies (Di Biase *et al.*, 2021; Katagiri *et al.*, 2015; Saito *et al.*, 2017), while increased FA in parts of GCC and BCC was found to be associated with the improvement of sub-threshold positive symptoms (Katagiri *et al.*, 2015). Upturns in symptom severity were associated with composite longitudinal WM changes, including decreases in FA and FA_T in the cingulum and forceps minor and increases in FW in the forceps major (Di Biase *et al.*, 2021). Another convergent finding is the thalamic fibers (Bernard *et al.*, 2015, 2017). Baseline FA of the thalamic-hippocampal tracts predicted positive symptoms at the 12-month follow-up (Bernard *et al.*, 2015). Longitudinally, within 12 months, associations were also found between FA changes in thalamic-motor tracts and changes in positive symptoms (Bernard *et al.*, 2017). There is evidence linking changes in negative symptoms over 12 months with FA alterations in the left IFOF, ATR, and SLF (Krakauer *et al.*, 2018), while changes in negative symptoms over 6 months were correlated with FA changes in the right SLF (Kristensen *et al.*, 2021b). These results further highlight the role of both tracts in charge of higher-level cognitive function sensorimotor integration processes in disease progression and prediction.

WM Predictors of the Clinical Outcome of CHR

Recent meta-analysis studies have shown that the average rates of transition to psychosis in CHR were 19–25% (Salazar de Pablo *et al.*, 2021a), and the rates of clinical remission were 41.4–42.4% (Salazar de Pablo *et al.*, 2021b) within 2–3 years. Thus far, various biomarkers have been employed to assess psychosis risk and combinations of biomarkers in the form of individualized 'risk calculators' (Worthington and Cannon, 2021). Some attempts have been made to identify WM measures for predicting the transition and remission of CHR. Baseline WM measures are compared between CHR subgroups based on their clinical outcomes.

Although a few studies reported no difference at baseline (Carletti *et al.*, 2012; Di Biase *et al.*, 2021; Langhein *et al.*, 2023; Peters *et al.*, 2010b; Tang *et al.*, 2019), most studies found that the CHR individuals who later converted to psychosis (CHR-P) showed more 'aberrant' WM at baseline than those who did not convert (CHR-NP) or HC (Hua *et al.*, 2023; Kristensen *et al.*, 2021a; Leon-Ortiz *et al.*, 2022; Nägele *et al.*, 2021; Smigielski *et al.*, 2022; Wang *et al.*, 2016). Significantly lower FA/FA_T was found in the CC (Nägele *et al.*, 2021; Smigielski *et al.*, 2022; Wang *et al.*, 2016), CR (Nägele *et al.*, 2021; Smigielski *et al.*, 2022), motor/sensory tracts including thalamic radiation (Leon-Ortiz *et al.*, 2022; Nägele *et al.*, 2021; Smigielski *et al.*, 2022), fornix, and corticospinal tracts (Smigielski *et al.*, 2022); and tracts related to higher executive function such as SLF, IFO, and ILF (Bloemen *et al.*, 2010). Specifically, one study reported an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.87 when using baseline global FA to predict conversion at 12 months (Kristensen *et al.*, 2021a). Moreover, compared with CHR-NP, a higher FW (Nägele *et al.*, 2021), fewer connections among rich-club regions, and greater modularity (Hua *et al.*, 2023) in CHR-P were also observed, indicating the role of extracellular and network anomalies in the onset of psychosis. It should be noted that in some studies, the evidence was in the opposite direction. Reduced FA in the CHR-NP group has been reported, mainly affecting the genu and trunk of the CC (Katagiri *et al.*, 2015; Saito *et al.*, 2017) and part of the left medial temporal lobe (Bloemen *et al.*, 2010). These results were interpreted while accounting for confounding effects such as duration of untreated illness (DUI), suggesting that longitudinal WM changes could be more informative for predicting psychosis (Saito *et al.*, 2017). Indeed, there was evidence that CHR-P and CHR-NP did not differ at baseline but showed a significant group-by-time effect, that the regional FA increased over time in CHR-NP while the FA decreased over time in CHR-P (Carletti *et al.*, 2012). This suggests that it could be more meaningful to consider the conversion to psychosis as a gradually evolving neurodevelopment process of WM rather than a drastic change.

Discussion

A large-scale meta-analysis showed widespread WM microstructural differences in patients with SZ, presented by globally lower FA across the whole-brain WM skeletons (Kelly *et al.*, 2018). Turning towards the CHR stage before the onset of psychosis provides an opportunity for identifying the trajectory of WM alterations during the illness progression. There has been much progress made in understanding the WM alterations during the early at-risk stage of psychosis. First, the most well-replicated WM changes in CHR are reductions of FA in parts of CC, SLF, and IFOF, as well as increases in MD and/or RD in some WM regions. Second, with the emergence of new methodologies (such as free-water imaging) that can disentangle the nature of WM pathology, fewer intracellular FA_T or extracellular FW changes were found in CHR compared with SZ. Third, longitudinal follow-ups of the clinical outcomes in CHR suggested different WM deficits between CHR-P and CHR-NP, while longitudinal follow-ups of the WM showed different WM trajectories between CHR and HC. There are some challenges remaining in these existing studies.

Although decreases in FA were observed in CHR, the distribution of FA reduction and findings of MD, RD, and AD are mixed. The heterogeneity across the studies and the relatively small sample sizes must be considered. Some studies performed the analysis based on different clinical outcomes of CHR (e.g. CHR-convertors vs. HC) instead of treating converters and non-converters as a single group. This may magnify the observed between-group effects since, theoretically, converters usually have more abnormalities. Many studies used tract-based spatial statistics (TBSS), which constrain the analysis to major fiber tracts and may abandon directionality during the skeletonization process (Smith *et al.*, 2006). This review focused on the WM changes in CHR and correlates of psychotic symptoms. It remains unclear whether these findings are common or distinctive across various psychiatric disorders. These issues limit the value and validity of FA as a specific biomarker and treatment target in translational medicine,

which requires further exploration and improvement through large-scale, cross-disorder studies and meta-analyses.

The effect of medication on WM in CHR individuals is another critical issue. Most studies in CHR did not particularly investigate this topic but only included antipsychotics as a covariate in the analysis. The neuroprotective and neurotoxic effects of antipsychotics have been investigated in many longitudinal DTI studies in SZ (Sagarwala and Nasrallah, 2021; Seitz-Holland *et al.*, 2021; Szeszko *et al.*, 2014; Zeng *et al.*, 2016). Despite that, many guidelines do not recommend the use of antipsychotics as the first-line treatment to prevent psychosis (Galletly *et al.*, 2016; Taylor and Perera, 2015), and the prescribed individuals had a greater risk for conversion (Zeng *et al.*, 2022), statistics based on our SHARP cohort showed that nearly 68% of CHR individuals were prescribed antipsychotics at baseline (Zeng *et al.*, 2022; Zhang *et al.*, 2020). Therefore, it is of high priority to identify the antipsychotic effect on the microstructural level in CHR.

The duration of untreated psychosis (DUP) has been widely studied in the context of psychosis. In a recent meta-analysis, highly suggestive evidence has been found that longer DUP is associated with more severe negative symptoms, more severe positive symptoms, and a lower chance of remission at follow-up in SZ (Howes *et al.*, 2021). Longer DUP has been well-known to be associated with more severe WM abnormalities (Seitz-Holland *et al.*, 2021), exhibiting a more "accumulative" effect on clinical outcomes. In the CHR population, the length of the period between the onset of attenuated psychotic symptoms and receiving appropriate treatment, which is usually defined as the 'duration of untreated prodromal symptoms' (DUPrS), has been far less studied. Our recent studies found that DUPrS of less than 2 months or more than 6 months could significantly lower the risk for conversion to psychosis (Zhang *et al.*, 2018a). However, no studies have specifically investigated the DUPrS effect on the WM trajectories in CHR so far, which may follow a nonlinear trajectory, similar to our clinical findings (Zhang *et al.*, 2018b). It would also be interesting to investigate whether there are distinct WM microstructural mechanisms underlying symptomatic remission and functional remission.

In recent years, there has been a trend in WM studies to place greater emphasis on the age effects. It is posited that the WM abnormalities observed in CHR may be a reflection of the deviation from the expected age-related developmental trajectories in the WM (Patel *et al.*, 2021). Cross-sectional studies have shown an age-related increase in FA (Karlsgodt *et al.*, 2009) and FA_T (Tang *et al.*, 2019) in HC instead of CHR. A positive correlation between longitudinal FA change in SLF and age was also observed in CHR and not HC, indicating an altered WM maturation in CHR (Krakauer *et al.*, 2018). However, how does the WM developmental trajectory matter in the onset of psychosis? An important study (Di Biase *et al.*, 2021) recently answered this question by mapping the age-related WM trajectories from data collected at multiple time points. The CHR-P group showed an opposite direction of age-related FAT trajectory compared to those with unknown transition outcome (CHR-U) and HC, which resulted in a 'tipping point'. Throughout adolescence and early adulthood, both CHR-P and CHR-U groups displayed higher FAT compared to HC. However, by the age of 30, 4% lower FA_T was found compared to HC. Moreover, higher FW was only found in CHR-P compared with HC at around 20 years of age. These results suggested a shifted maturation peak and premature decline in the WM trajectory of CHR, especially in those who converted to psychosis. Additional analysis revealed that the impact of psychosis onset was not significant across regional FA, FA_T, or FW, suggesting that the transition to psychosis is not marked by any dramatic changes in WM microstructure. This further highlighted the point that instead of predicting the outcome by the WM index collected at a fixed time point, it could be more meaningful to treat the conversion of psychosis from a developmental perspective.

While antipsychotic medications are generally not recommended for CHR patients, the findings of WM alterations may provide some clues for developing new early intervention strategies. One perspective is the intake of fatty acid supplementation, the rationale for which in CHR derives from the physiological underpinnings of myelin sheaths. These sheaths are created from the lipid membranes of oligodendrocytes in the central nervous system. The structural components of membrane phospholipids consist of polyunsaturated fatty acids (PUFAs) (Peters *et al.*, 2013). Essential PUFAs (EPUFAs), which cannot be synthesized and must be obtained through the diet, can influence the rate of phospholipid synthesis, energy supply, and in turn, the quantity and quality of membrane phospholipids (Arvindakshan *et al.*, 2003). Thus, insufficient EPUFA intake might cause myelination/demyelination and disrupted development of WM (Kobayashi *et al.*, 1997), setting the susceptibility to psychosis (Karlsgodt *et al.*, 2012). One study in recent-onset SZ reported a significant positive correlation between erythrocyte membranes PUFA and FA in bilateral UF (Peters *et al.*, 2009), while another reported a positive association of FA in a quite large region, including the CC, bilateral parietal, occipital, temporal, and frontal WM (Peters *et al.*, 2013). Moreover, a recent study identified trend-level associations between plasma fatty acid and global and a few regional FA, MD, and RD in healthy participants but not CHR individuals (Su *et al.*, 2022a). Overall, these studies provided a minimal link between WM microstructure and fatty acids in relatively small samples, which requires to be validated by future studies with larger samples. Another perspective is to enhance the WM plasticity in CHR using modulation techniques such as transcranial magnetic stimulation (TMS). TMS-induced microstructural changes have been identified and linked with the core symptoms remediation in chronic schizophrenia (Xu *et al.*, 2023), major depressive disorder (Ning *et al.*, 2022). Notably, our recent TMS study in 65 CHR individuals found that the stimulation at the parietal-hippocampal network could specifically improve the visuospatial learning performance and showed a lower conversion rate compared with the sham group, indicating it might be a promising intervention target for CHR individuals (Tang *et al.*, 2023). These studies provide excellent examples of using WM to guide precisely personalized neuromodulation and characterize the neurobiological basis of TMS, which has great potential, particularly in CHR, since this population remains a less explored area.

The findings from these prior studies have also provided potential opportunities for future work. (i) Since WM abnormalities could underlie functional communication, future studies can go beyond WM abnormality per se and investigate the functional impact and dynamics of fiber disruptions at the circuit level, which may be particularly informative in CHR studies to reveal the underlying pathophysiology better. Recent studies started to focus on structure-function coupling by combining functional and diffusion MRI (Jiang *et al.*, 2021; Wang *et al.*, 2023; Zhao *et al.*, 2023). (2) Regarding predictive models, innovations in the methodology and enrichment of the outcome measures are needed in CHR studies. Prediction methods such as dynamic modeling and machine learning, widely used in other modalities in CHR research (Koutsouleris *et al.* 2021), could also facilitate the investigation of the prognostic value of WM deficits. Moreover, the importance of enriching outcome measures beyond the binary conversion/non-

conversion should be highlighted again. (3) Another important focus in psychiatric neuroimaging studies is identifying biotypes to uncover the heterogeneity of neurobiological underpinnings by stratification and facilitate a more precise treatment (Voineskos *et al.*, 2020). For example, one recent large-sample study identified two subtypes and two atrophy patterns within those subtypes. These correspondingly relate to different treatment methods (antipsychotics-only and adjunct TMS) in SZ (Jiang *et al.*, 2023). Additional evidence was found in WM based on the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) biotypes (Kelly *et al.*, 2021). This study observed greater discriminations from the HC group for lower FA_T in Biotype 1 and elevated FW in Biotype 2. These findings suggested that biotype findings might be particularly advantageous for unmasking the heterogeneous symptoms and facilitating the development of personalized treatment targets.

Conclusion

Decades of CHR research have yielded fruitful observations about the preexisting WM abnormalities and have great potential in uncovering underlying mechanisms for psychosis. There are findings linking WM with clinical symptoms and neurocognitive deficits and predicting future conversion/remission by cross-sectional WM measures. However, there are still many challenges and great development potential in terms of methodologies and research concepts, such as centering around the developmental trajectory of WM and improving prognostic accuracy by utilizing dynamic models. WM studies also offer numerous possibilities for early intervention and treatment of CHR, including enhancing the understanding of DUPrS and antipsychotic treatment, guiding neuromodulation techniques such as TMS, and exploring adjuvant interventions like fatty acid supplementation and neuro-nutritional approaches. Future CHR research would greatly benefit from utilizing WM to guide pharmacological and non-pharmacological targeted treatments, optimize clinical prediction models, and work towards a precision medicine clinical care model.

Supplementary data

Supplementary data is available at *Psychoradiology* online.

Author contributions

Wenjun Su (Conceptualization, Investigation, Visualization, Writing—original draft), Jijun Wang (Supervision, Writing—review & editing), and Yingying Tang (Supervision, Conceptualization, Visualization, Writing—review & editing).

Conflict of interests

There are no conflicts to declare.

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