Archival Report

Disruptions in White Matter Maturation and Mediation of Cognitive Development in Youths on the Psychosis Spectrum

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ABSTRACT

BACKGROUND: Psychosis onset typically occurs in adolescence, and subclinical psychotic experiences peak in adolescence. Adolescence is also a time of critical neural and cognitive maturation. Using cross-sectional data from the Philadelphia Neurodevelopmental Cohort, we examined whether regional white matter (WM) development is disrupted in youths with psychosis spectrum (PS) features and whether WM maturation mediates the relationship between age and cognition in typically developing (TD) youths and youths with PS features.

METHODS: We examined WM microstructure, as assessed via diffusion tensor imaging, in 670 individuals (age 10–22 years; 499 TD group, 171 PS group) by using tract-based spatial statistics. Multiple regressions were used to evaluate age × group interactions on regional WM indices. Mediation analyses were conducted on four cognitive domains—executive control, complex cognition, episodic memory, and social cognition—using a bootstrapping approach.

RESULTS: There were age × group interactions on fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF) and retrolenticular internal capsule. Follow-up analyses revealed these effects were significant in both hemispheres. Bilateral SLF FA mediated the relationship between age and complex cognition in the TD group, but not the PS group. Regional FA did not mediate the age-associated increase in any of the other cognitive domains.

CONCLUSIONS: Our results showed aberrant age-related effects in SLF and retrolenticular internal capsule FA in youths with PS features. SLF development supports emergence of specific higher-order cognitive functions in TD youths, but not in youths with PS features. Future mechanistic explanations for these relationships could facilitate development of earlier and refined targets for therapeutic interventions.

Keywords: Cognition, Development, DTI, Mediation, Psychosis spectrum, Psychotic-like experiences, Subclinical psychosis, Superior longitudinal fasciculus

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Schizophrenia (SZ) has a lifetime prevalence of 0.75% (1), but, consistent with our understanding of a psychosis continuum (2,3), psychotic-like experiences (PLEs) are reported more frequently (5%–8% of the population) (4,5). These subclinical symptoms are qualitatively similar to the hallmark psychotic symptoms of SZ but with decreased severity and frequency. Although below the clinical threshold, such symptoms are still distressing and are associated with lower reported happiness (6), increased suicidality (7,8), and significant occupational and social impairments (9). PLEs also share etiological risk factors, cognitive correlates, and symptom profiles with SZ (3) and can precede subsequent full-blown illness. Similar to transition rates for clinical high-risk youths (10), up to 25% of individuals who report PLEs convert to a diagnosed psychotic disorder by adulthood (11,12). In individuals who do not convert to a diagnosed psychotic disorder, approximately 30% to 40% continue to experience PLEs into early adulthood (13,14) and potentially throughout life (15).

The onset period for SZ begins in late adolescence, and similarly, subclinical psychotic symptoms peak during adolescence (3), coinciding with periods of dynamic change in cognition and brain connectivity, including white matter (WM) maturation. The typical linear increase in WM volume from childhood until early adulthood (16,17) is thought to reflect axon growth, organization of axons into bundles, and myelination (18). WM integrity is putatively reflected by the principal diffusion tensor imaging (DTI) measure, fractional anisotropy (FA) (19–22). DTI studies have shown regional age-related changes with the overarching trend of FA increasing into adulthood (23,24). Although both early-onset and chronic SZ have been associated with reduced FA [for review see (25,26)], whether and how developmental trajectories of WM in youths who develop SZ diverge from those in typically developing (TD) youths is unknown. In this study, we used TD and psychosis spectrum (PS) groups from the Philadelphia Neurodevelopmental Cohort (PNC) to explore how psychosis

affects age-associated regional changes in WM. One previous study reported an age × group interaction on regional gray matter volume in this cohort (27); however, no studies have investigated such interactions on DTI-assessed WM indices.

As with SZ, PLEs have been associated with cognitive deficits, both generally and in specific domains (28–32). However, despite the demonstrated link between psychosis and cognition and the known relationship of WM to cognitive development (33–35), it is not yet established whether regional WM mediates the relationship between age and cognitive deficits associated with psychosis. To address these questions, we first evaluated whether the age-related pattern of regional WM development was disrupted in youths with elevated PLEs. We then conducted post hoc analyses on tracts with significant interactions to evaluate whether FA mediated the relationship between age and cognition and whether that relationship differed between TD youths and youths with PS features.

METHODS AND MATERIALS

Participants

The PNC is a publicly available population-based sample of more than 9500 individuals (age range: 8–22 years) [for description see (36)]. All subjects provided medical history, clinical, and cognitive data. A subset of participants underwent neuroimaging, with DTI scans acquired for 1312 individuals. All data presented here were collected at the University of Pennsylvania and analyzed at the University of California, Los Angeles. Psychopathology self-report and parent-report ratings and medical histories were obtained from the GOASSESS structured computerized instrument.

In addition to the PNC's exclusion for medical problems impacting brain function (36), participants were excluded if they had more than 2.5 mm of total Euclidean distance movement during the DTI scan ($n = 44$), a history or current diagnosis of autism spectrum disorder ($n = 13$), or other neurological or nonpsychotic psychiatric diagnoses ($n = 452$) (see Supplement). Owing to the limited number of younger individuals with PS features, participants younger than 10 years of age ($n = 122$) were also excluded to match groups for age distribution. After excluding participants who met one or more of the aforementioned criteria, 707 individuals remained for analysis.

Subclinical Grouping

Psychosis screening and classification of individuals into groups were performed as described by Calkins *et al.* (37) (see Supplement). Although our primary analysis consisted of PS and TD groups, we included a third group, limited PS (LPS), with symptom severity between TD and PS in secondary analyses to allow for preliminary investigation of subtle dimensional changes. These individuals were included only in secondary analyses owing to the small sample size. In our sample of 707 youths, 499 were in the TD group, 171 were in the PS group, and 37 were in the LPS group.

Cognitive Data

Cognitive testing was administered via the Computerized Neurocognitive Battery developed at the University of Pennsylvania. Scores for complex cognition (language reasoning, nonverbal reasoning, and spatial ability), executive control (mental flexibility, attention, and working memory), episodic memory (verbal memory, face memory, and spatial memory), and social cognition (emotion identification, emotion differentiation, and age differentiation) were calculated as previously described (38). Our analyses focused on efficiency scores—obtained via the PNC data release and based on the entire neurocognitive sample ($N = 9138$)—which reflect the sum of Z scores for accuracy and speed. Analyses of covariance, with age and sex as covariates, were used to evaluate group differences in efficiency scores. A Bonferroni correction for each of the four domains was applied, resulting in a significance threshold of $p < .05/4 = .0125$.

DTI Processing

The PNC protocol divides a 64-direction diffusion-weighted imaging set into two independent 32-direction sequences (b value: 1000 s/mm^2) [see Supplement and (36) for parameter details]. The two sequences were concatenated before applying standard preprocessing using tools from FMRIB Software Library's Diffusion Toolbox. Specifically, Eddy Correct was used to correct for distortions due to eddy currents and head motion. Registered b0 and concatenated files were skull stripped and masked using Brain Extraction Tool. FA images were calculated by fitting a diffusion tensor model at each voxel with DTIFit. We then implemented tract-based spatial statistics (39) in accordance with the ENIGMA-DTI pipeline (http://enigma.ini.usc.edu/protocols/dti-protocols) (40) and extracted regions of interest (ROIs) from the Johns Hopkins University White-Matter Tractography Atlas (41–43). Bilateral ROIs were generated by averaging across both hemispheres. We tested the average FA for 25 total ROIs (Supplemental Figure S1; Supplemental Table S1).

FA was our principal measure of interest. Additional diffusivity measures were examined in follow-up analyses. Axial diffusivity (AD) reflects diffusivity parallel to the axon and is thought to reflect fiber organization (44). Radial diffusivity (RD) is perpendicular to axons and an indirect measure of myelination (44). Mean diffusivity (MD) is an average of diffusivity across all three axes (20). AD, MD, and FA were calculated by DTIFit, whereas RD was computed as the average of the second and third eigenvalue images. Non-FA DTI measures also underwent ENIGMA tract-based spatial statistics processing.

Statistical Analysis

Statistical analyses and graphical representations were performed using Stata 15 software (StataCorp LP, College Station, TX). For each tract, individuals whose FA exceeded 1.5 interquartile ranges (IQRs) either below the first quartile ($Q_1 - [1.5 \times IQR]$) or above the third quartile ($Q_3 + [1.5 \times IQR]$) were deemed outliers and excluded from subsequent analysis of that tract. The number of individuals used in analysis of each tract is reported in Supplemental Table S1. To test for an age × group interaction and main effect of group on regional FA, a

regression model including age, sex, and group (TD and PS) was used. The regression was followed by evaluation of marginal effects, computed at 1-year age intervals, for interaction analyses. A corrected significance threshold for all regression analyses was set at $p < .05/25 = .002$, which corrects for the 25 tracts analyzed.

In tracts where significant age × group interactions for FA were detected, we conducted a series of follow-up analyses. To conduct preliminary exploration of whether the extent of PLEs affected age-associated FA changes, analyses including youths with LPS features as a third group were conducted to determine if an age × group (TD, LPS, and PS) interaction was still present. Post hoc contrasts compared the slope of marginal effects between groups to determine whether LPS represented an intermediate phenotype. We also tested for age × group interactions on hemispheric FA and non-FA measures. A significance threshold of $p < .05/2 = .025$ was applied to account for the two tracts undergoing follow-up analyses.

Post Hoc Mediation Analyses

For tracts with significant age × group interactions, we conducted post hoc mediation analyses to evaluate whether the relationship between age and any of the cognitive domains was mediated by FA and, if so, whether that mediation differed between TD and PS groups. Individuals missing a score for a given cognitive domain were excluded from mediation analyses for that particular domain.

Mediation was tested using methods described by MacKinnon et al. (45). Path coefficients between the independent (X), dependent (Y), and mediator (M) variables were determined using three regression equations (Figure 1). We first determined whether initial criteria for mediation were met. Specifically, whether path coefficients a (effect of age on FA), b (effect of FA on cognition), and c (effect of age on cognition) all were significant (Figure 1). If these criteria were satisfied, we continued to test the significance of the indirect (i.e., mediated) effect, computed as the product of regression coefficients a and b (46). We used a bootstrapping approach, in which data were resampled with replacement 1000 times, to assess for significance of the indirect effect. Bootstrapping allows for confidence intervals to be built from resampled data without assumptions of normality. To reduce the chance of type I errors, we increased our confidence interval to 99%. Confidence

intervals including 0 were deemed as nonsignificant. Finally, we determined the proportion of the total effect that was mediated by dividing the indirect effect (ab) by the total effect ($c = c' + ab$).

For tracts that significantly mediated a cognitive domain, supplementary analyses were conducted to determine if non-FA measures mediated the age-cognition relationship and whether FA mediated cognition accuracy and speed (rather than the combined efficiency score) (see Supplement).

RESULTS

Participants

There were no significant differences between groups in age or sex distribution (Table 1).

DTI Analysis

Multiple regression analyses, including age, sex, and group, for each of the 25 tracts revealed that only the superior longitudinal fasciculus (SLF) and retrolenticular internal capsule (RLIC) showed a significant age × group interaction (TD vs. PS; $p < .002$). The SLF (Figure 2A) was the only tract with a significant main effect of group (Supplemental Table S1). Additional tracts showed age × group interactions meeting the thresholds for trend-level significance ($p < .004$) and uncorrected significance ($p < .05$) (Supplemental Table S2).

Superior Longitudinal Fasciculus. All three variables (age, sex, and group) in the regression model significantly explained SLF FA ($R^2 = .14$, $F_{4,660} = 26.86$, $p = 1.15 \times 10^{-20}$), with a significant interaction between age and group ($\beta = -.002$, $F_{1,660} = 13.20$, $p = 3.0 \times 10^{-4}$) (Figure 2B) and each variable independently significantly contributing to the model (Supplemental Table S3). Evaluation of regression coefficients for each group revealed that whereas FA increased with age in the TD group ($\beta = .003$, $p = 3.68 \times 10^{-19}$), there was no significant relationship in the PS group ($\beta = 4.9 \times 10^{-4}$, $p = .48$). Confirmatory analyses indicated no significant group × sex ($F_{1,660} = 2.04$, $p = .15$) or age × group × sex ($F_{1,657} = 1.18$, $p = .28$) interactions on SLF FA.

Secondary analyses revealed significant age × group interactions in both the right ($\beta = -.0032$, $F_{1,660} = 15.51$, $p = 1.0 \times 10^{-4}$) and the left ($\beta = -.0022$, $F_{1,660} = 8.51$, $p = .0036$) SLF. Of the three non-FA SLF diffusivity measures, both RD

$$Y = i_1 + cX + e_1 \quad (1)$$

$$Y = i_2 + c'X + bM + e_2 \quad (2)$$

$$M = i_3 + aX + e_3 \quad (3)$$
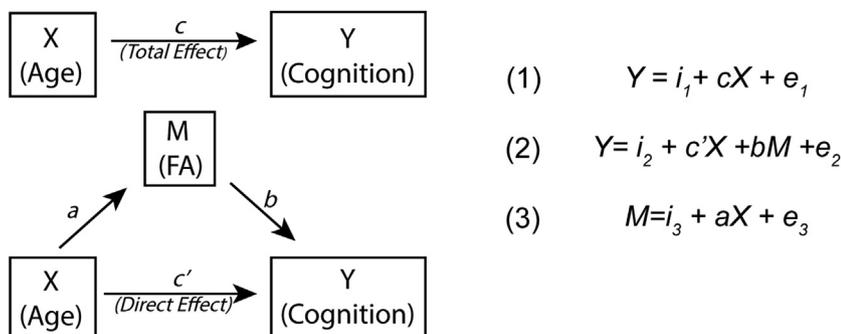
Figure 1. Schematic of a simple mediation model. We examined whether regional fractional anisotropy (FA) significantly mediated the effect of age on cognition. In a mediation model, the relationship between an independent variable (X) and a dependent variable (Y) is influenced by the (nonobservable) mediator variable (M). Intercepts and residuals for each equation are denoted by i and e, respectively. The total effect (c) is the sum of both the direct (c') and mediated (ab) effects. The total effect, c, was determined with equation (1). Coefficients a and b were determined with equation (2) and equation (3), respectively. The direct effect (c') was determined with equation (2). Mediation is determined by assessing the significance of the mediated effect (ab) with a bootstrapping approach.

Table 1. Participants' Demographic Information

	Group			Statistic	Significance (p)
	TD	PS	LPS		
Age, Years, Mean ± SD	15.75 ± 3.36	15.83 ± 2.89	15.32 ± 3.13	$F_{2,706} = 0.371$	.690
TD vs. PS				$t_{1,668} = -0.28$	.784
TD vs. LPS				$t_{1,534} = 0.75$	.454
PS vs. LPS				$t_{1,206} = 0.95$	.342
Number (% Female)	499 (49.1%)	171 (53.2%)	37 (37.8%)	$\chi^2_{2,707} = 2.99$	.224
TD vs. PS				$\chi^2_{1,670} = 0.864$	.353
TD vs. LPS				$\chi^2_{1,536} = 1.75$	.186
PS vs. LPS				$\chi^2_{1,208} = 2.88$	.09
GAF, Mean ± SD	79.81 ± 21.07	69.22 ± 19.7	73.22 ± 15.86	$F_{2,654} = 16.14$	1.44×10^{-7}
TD vs. PS				$t_{1,623} = 5.53$	4.8×10^{-8}
TD vs. LPS				$t_{1,499} = 1.74$	.083
PS vs. LPS				$t_{1,186} = -1.079$	.282
Education, Years, Mean ± SD	8.61 ± 3.27	8.13 ± 2.64	8.08 ± 3.06	$F_{2,704} = 1.797$	.167
TD vs. PS				$t_{1,668} = 1.73$	.084
TD vs. LPS				$t_{1,534} = 0.949$	.343
PS vs. LPS				$t_{1,206} = 0.952$	.342

GAF, Global Assessment of Functioning Score; LPS, limited psychosis spectrum; PS, psychosis spectrum; TD, typically developing.

($\beta = 3.30 \times 10^{-6}$, $F_{1,660} = 17.21$, $p = 3.8 \times 10^{-5}$) (Figure 2C) and MD ($\beta = 2.54 \times 10^{-6}$, $F_{1,660} = 13.46$, $p = 2.6 \times 10^{-4}$) (Figure 2D) showed a significant age × group interaction. Youths in the TD group showed significant decreases in RD ($\beta = -4.47 \times 10^{-6}$, $p = 3.8 \times 10^{-32}$) and MD with age ($\beta = -3.82 \times 10^{-6}$, $p = 6.8 \times 10^{-32}$). Youths in the PS group also showed lower RD ($\beta = -1.36 \times 10^{-6}$) and MD ($\beta = -0.13 \times 10^{-6}$) with increasing age, but this association was not significant ($p > .025$). There was no significant interaction between age and group for AD (Figure 2E).

Analyses including youths with LPS features as a third group in the regression also resulted in a significant age × group interaction ($F_{2,695} = 6.68$, $p = .0013$) (Figure 2F). Post hoc contrasts revealed that the slope of the relationship between age and FA for the LPS group did not significantly differ from the TD ($t_{1,695} = 0.43$, $p = .664$) or the PS ($t_{1,695} = -0.144$, $p = .149$) group.

Retrolenticular Internal Capsule. In the RLIC (Figure 3A), all three variables in the multiple regression analysis collectively explained FA ($R^2 = .037$, $F_{4,657} = 6.24$, $p = .0001$), with a significant interaction between age and group on RLIC FA ($\beta = -.002$, $F_{1,657} = 10.44$, $p = .0013$) (Figure 3B) but no significant main effect of group ($p > .002$) (Supplemental Table S4). Evaluation of regression coefficients for each group indicated that TD and PS groups exhibited opposite patterns, with a gradual linear increase in RLIC FA across development for the TD group ($\beta = .001$, $p = .001$) and a nonsignificant decrease in the PS group ($\beta = -.001$, $p = .062$) with increasing age. Confirmatory analyses indicated no significant group × sex ($F_{1,657} = 0.21$, $p = .644$) or age × group × sex ($F_{1,654} = 0.17$, $p = .681$) interactions.

Secondary analyses of RLIC FA indicated there were significant age × group interactions in both the left ($\beta = -.0021$, $F_{1,654} = 7.72$, $p = .0056$) and the right ($\beta = -.0024$, $F_{1,647} = 9.40$, $p_{ROI} = .0023$) hemispheres. Of the three non-FA diffusivity

measures, both RD ($\beta = 2.92 \times 10^{-6}$, $F_{1,657} = 14.21$, $p = 2.00 \times 10^{-4}$) (Figure 3C) and MD ($\beta = 7.58 \times 10^{-7}$, $F_{1,656} = 7.90$, $p = .0051$) (Figure 3D) showed a significant age × group interaction. TD youths showed a significant decrease in RLIC RD ($\beta = -2.5 \times 10^{-6}$, $p = 9.1 \times 10^{-13}$) and MD ($\beta = -2.9 \times 10^{-6}$, $p = 3.4 \times 10^{-16}$) with increasing age. In youths with PS features, there were no significant relationships between age and RLIC RD ($\beta = 4.97 \times 10^{-7}$, $p = .50$) or MD ($\beta = -6.8 \times 10^{-7}$, $p = .39$). Neither group showed a significant age × group interaction on AD (Figure 3E).

Inclusion of youths with LPS features as a third group in the regression model also resulted in a significant age × group interaction ($F_{2,692} = 5.36$, $p = .0049$) (Figure 3F). Post hoc contrasts revealed that the slope of the relationship between age and FA for the LPS group did not significantly differ from the TD ($t_{1,692} = -0.02$, $p = .982$) or the PS ($t_{1,695} = -0.166$, $p = .097$) group.

Neurocognitive Efficiency Results

Youths in the PS groups had significantly ($p < .0125$) lower efficiency scores in all four cognitive domains (Figure 4; Supplemental Table S5).

Post Hoc Mediation Analyses

Superior Longitudinal Fasciculus. The PS group did not satisfy initial requirements for mediation of the effect of age on any cognitive domain, as both *a* (coefficient for effect of age on SLF) and *b* (coefficient for effect of SLF on cognition) were nonsignificant ($p > .05$) for all domains. However, in the TD group, path coefficients *a* and *b* were significant for complex cognition and episodic memory; scores increased with both age and SLF FA (Table 2). Evaluating mediation in TD with a bootstrapping approach indicated that only the relationship between age and complex cognition was significantly mediated by SLF FA, with SLF FA accounting for 27.6% of the total
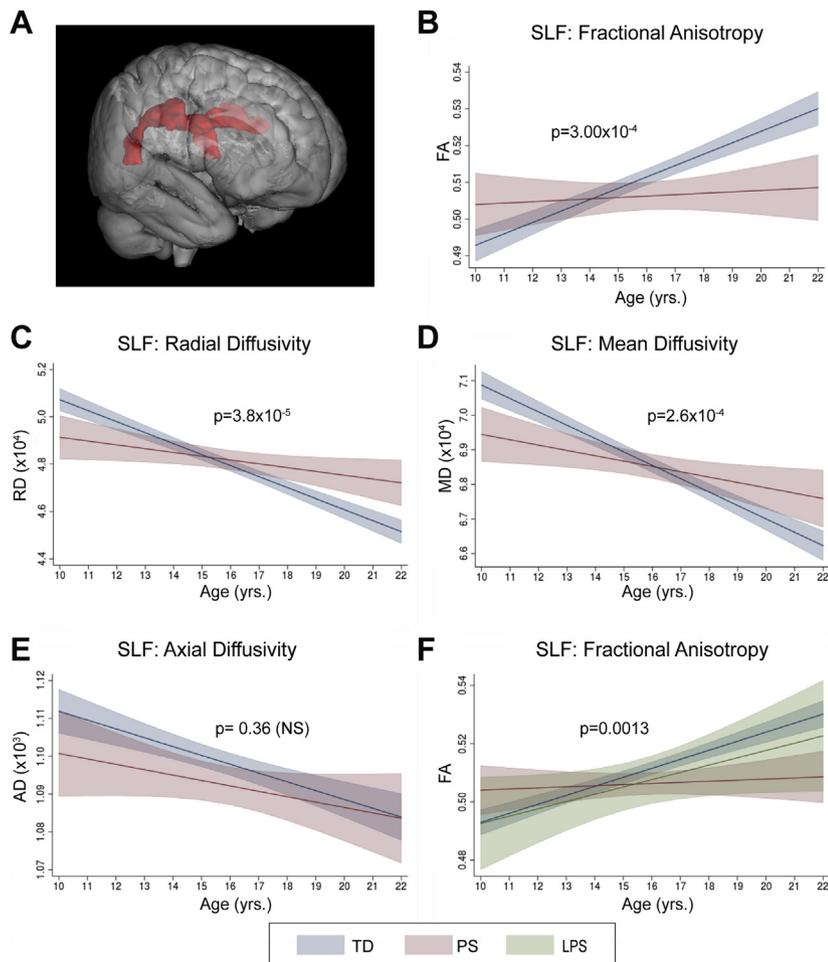
Figure 2. Age-associated changes in the superior longitudinal fasciculus (SLF). **(A)** Three-dimensional representation of SLF tract. In analyses of typically developing (TD) and psychosis spectrum (PS) groups, there was a significant ($p < .002$) interaction between age and group on SLF fractional anisotropy (FA) **(B)**. Follow-up analyses revealed additional significant ($p < .025$) age $\times$ group interactions on radial diffusivity (RD) **(C)** and mean diffusivity (MD) **(D)**, but not on axial diffusivity (AD) **(E)**. **(F)** Follow-up analyses including a third group, limited psychosis spectrum (LPS), also revealed a significant age $\times$ group interaction on SLF FA. Graphs show predicted margins with 95% confidence intervals. Significance values represent corrected p values for age $\times$ group interactions. $p < .025$. NS, not significant.

effect between age and complex cognition. (See Supplement for path coefficients of mediation analyses for executive control and social cognition [Supplemental Table S6], complex cognition by non-FA SLF measures [Supplemental Table S7], and complex cognition accuracy and speed by SLF FA [Supplemental Table S8]).

Retrolenticular Internal Capsule. In contrast to the SLF, the effect of age on RLIC FA (a) was significant for both TD ($\beta = -3.75 \times 10^{-6}$, $F_{1,491} = 46.18$, $p = 3.13 \times 10^{-11}$) and PS ($\beta = -3.03 \times 10^{-6}$, $F_{1,164} = 4.99$, $p = .027$) groups. However, RLIC FA did not significantly explain any cognitive score in either the TD group or the PS group ($p > .05$). Thus, criteria for the mediation of the relationship between age and each cognitive domain were not met, and no further analyses were conducted.

DISCUSSION

Our results provide compelling evidence that subclinical PLEs are associated with disrupted age-related changes of WM in the SLF and RLIC. We have also demonstrated that WM development in the SLF partially mediates the relationship between age and complex cognition in TD youths but not in

youths with PS features. These findings suggest that alterations in WM neurodevelopment may potentially contribute to cognitive deficits in psychosis.

Psychosis has been increasingly conceptualized as having a neurodevelopmental component (47), with an age-related progression from high-risk and prodromal stages to first-episode and, eventually, chronic illness [for review see (48)]. Longitudinal imaging studies relate this evolution of illness in part to disruptions in traditional WM trajectories, particularly when the disease onset occurs in childhood or adolescence [for review see (49)]. Understanding the link between the trajectories of psychosis and WM at all stages of the disease is necessary for developing age-appropriate targeted interventions. We contribute to elucidating this relationship by identifying aberrant age-related effects in specific WM tracts.

Of the 25 tracts evaluated, only the SLF and RLIC reached the corrected threshold for a significant age $\times$ group interaction. The SLF is an associative tract with ipsilateral fronto-parietal connections (50) that shows pronounced development across adolescence (24,51,52) and has a well-established role in fundamental cognitive processes, such as working memory, language, and attention (53–55). The RLIC is a projection tract containing motor and sensory fibers that carry projections
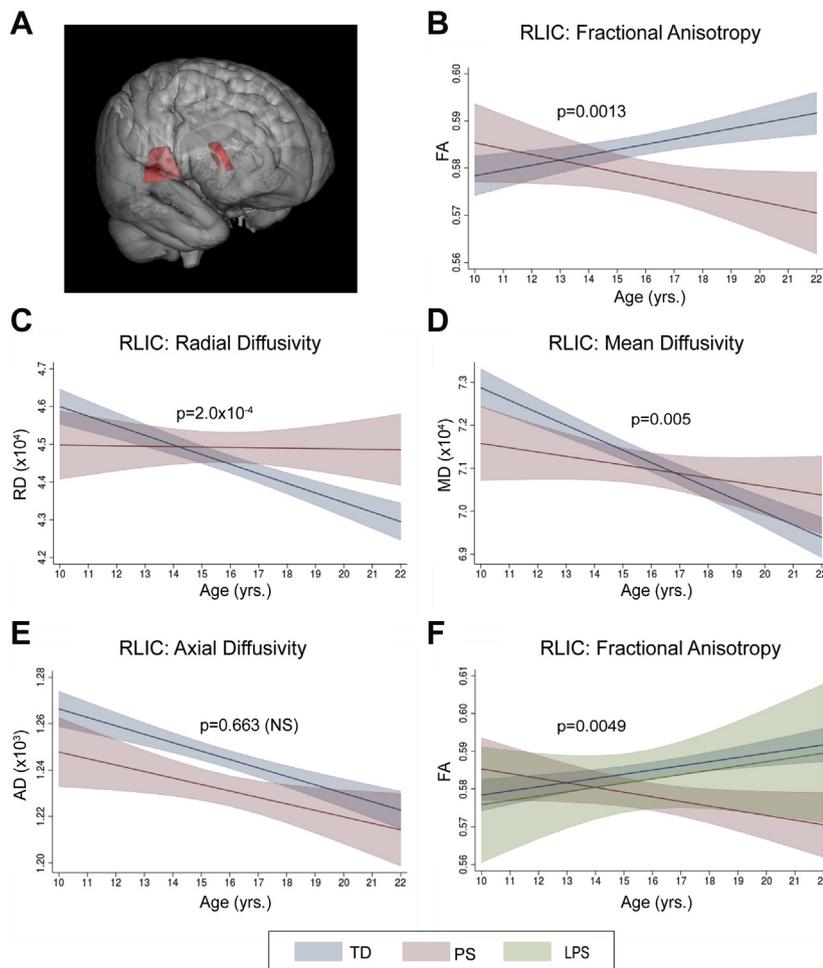
Figure 3. Age-associated changes in the retro-lenticular internal capsule (RLIC). **(A)** Three-dimensional representation of RLIC tract. In analyses of typically developing (TD) and psychosis spectrum (PS) groups, there was a significant interaction ($p < .002$) between age and group on RLIC fractional anisotropy (FA) **(B)**. Follow-up analyses revealed significant age × group interactions ($p < .025$) on radial diffusivity (RD) **(C)** and mean diffusivity (MD) **(D)**, but not on axial diffusivity (AD) **(E)**. **(F)** Follow-up analyses including a third group, limited psychosis spectrum (LPS), also revealed a significant ($p < .025$) age × group interaction on RLIC FA. Graphs show predicted margins with 95% confidence intervals. Significance values represent corrected p values for age × group interactions. NS, not significant.

from the thalamic pulvinar and lateral geniculate nuclei to association and visual cortices (56). Consistent with existing studies of WM maturation during typical development (24), we found a linear increase in FA in both the SLF and the RLIC in the TD group. The PS group, however, did not show any significant age-related changes in either SLF FA or RLIC FA, suggesting disrupted maturation. Together with our findings of age × group interactions for RD, these results collectively suggest that the altered relationships in youths with PS features may be driven by decreased regional myelination, rather than axonal degeneration or differences in tract organization (57–59).

Reduced SLF integrity has previously been reported in youths with risk factors for psychosis (60), subclinical symptoms (61,62), recent-onset SZ (47,63), and first-episode SZ (64,65) and adults with established SZ (66). Furthermore, a longitudinal study indicated that high-risk individuals who converted to psychotic disorders had reduced SLF FA at baseline relative to individuals who did not convert (67). Our results extend on these previous findings, collectively suggesting that age-associated alterations of SLF development as early as late childhood may be associated with subclinical psychosis and serve as a putative early biomarker for SZ,

although this possibility awaits confirmation in longitudinal studies. Furthermore, these collective results suggest that abnormalities in SLF FA associated with SZ may be independent of illness confounds, such as medication.

FA of association tracts, such as the SLF, have previously been related to general cognitive function (68–72) as well as development of higher-level cognition during adolescence (33–35,73,74). However, the relationship between the SLF and cognition has been less frequently investigated in youths with psychosis. Furthermore, previous studies have typically evaluated the relationship between cognition and WM separately from that of cognition and age (75) and thus could not rule out that gains in neurocognition may only relate to FA because of a shared association with age.

Our analysis took the novel approach of testing the degree to which WM integrity mediates cognitive development from childhood through young adulthood and how this relationship differs in PS. We found a significant positive relationship of age with complex cognition and SLF FA in TD youths, but not in youths with PS features. Additionally, the association between age and complex cognition in TD youths was significantly mediated by SLF FA, highlighting the importance of the tract in healthy cognitive development. Complex cognition is a
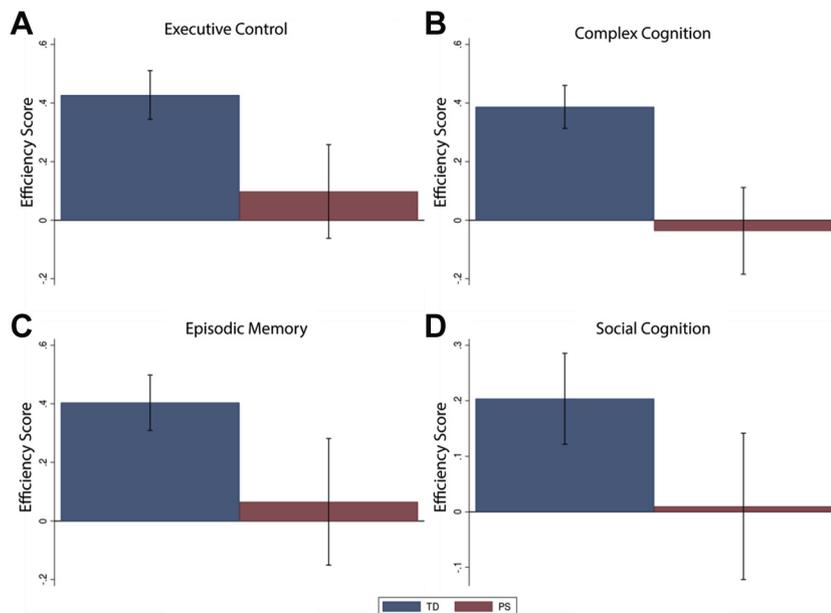
Figure 4. Group differences in cognitive domains. Youths in the psychosis spectrum (PS) group consistently showed significantly ($p < .0125$) lower efficiency scores in all four cognitive domains: **(A)** executive control, **(B)** complex cognition, **(C)** episodic memory, and **(D)** social cognition. Efficiency scores reflect the average Z score (sum of Z score for accuracy and -1 multiplied by Z score for speed) per group, such that higher scores indicate better performance. Error bars represent $\pm$ SE of the group average. TD, typically developing.

reflection of nonverbal reasoning, language reasoning, and spatial attention (38), making our finding consistent with existing studies in which frontoparietal structural connectivity, including the SLF, has been related to attention (76,77), language (77,78), spatial working memory (79,80), and reasoning ability (81) in TD youths. Absence of any significant age-associated changes in complex cognition and SLF FA, and thus any corresponding mediation, in youths with PS features suggests that the presence of subclinical PLEs disrupts maturation of the SLF, which, in turn, affects development of higher-level cognitive functions, as demonstrated by the overall significantly lower complex cognition observed in youths with PS features relative to TD youths. Critically, mediation studies evaluating changes across adulthood into elderly populations found that age-related reductions in SLF FA did not mediate corresponding cognitive decline (82,83), suggesting that its role as a mediator in TD youths may be specific to emergence rather than decline of higher-level cognitive function. The SLF has been divided into as many as five subcomponents (84) with functionally distinct roles. We used a predefined ROI that predominantly includes the

frontoparietal portion [traditionally, SLF I, II, and III (85)] without extensive temporoparietal connections. Future tractography studies could extend our analyses to investigate these subcomponents individually.

Our findings also revealed an age $\times$ group interaction on RLIC FA. Reduced FA in the internal capsule of patients with chronic SZ has been consistently reported, with mixed findings in first-episode and medication-naïve patients [for review see (26,86)]. To our knowledge, there are no studies that focus specifically on the RLIC in relation to psychosis, though there is previous evidence for an association of reduced RLIC FA with psychosis. Nonhuman adolescent primates receiving daily exposure to ketamine (an N-methyl-D-aspartate antagonist used to mimic psychotic symptoms) showed reduced FA in multiple tracts, including the RLIC and SLF (87). Furthermore, a longitudinal study found that patients (20–40 years of age) with SZ showed an attenuated increase in RLIC FA across a 3-year follow-up relative to control subjects (88). Finally, a meta-analysis reported significantly reduced FA in the left RLIC (89), whereas another meta-analysis, using the same 25 ROIs, showed that adults with SZ had lower RLIC FA than healthy

Table 2. Mediation Analysis Results for TD Youths

Dependent Variable	Path Coefficients (SE)					Total Effect Mediated (%)	Bootstrap 99% CI
	Age → SLF *a*	SLF → Cognition *b*	Direct Effect *c'*	Total Effect *c = ab + c'*	Mediated Effect *ab*		
Complex Cognition[c]	0.0030[b] (0.0003)	6.377[b] (1.415)	0.0492[b] (0.0113)	0.0683[b] (0.0107)	0.0189[d] (0.0047)	27.6	0.0066, 0.0311
Episodic Memory[e]	0.0031[b] (0.0003)	3.763[a] (1.85)	0.0860[b] (0.0149)	0.0975[b] (0.014)	0.0115 (0.0058)	11.8	−0.0055, 0.0285

CI, confidence interval; SLF, superior longitudinal fasciculus; TD, typically developing.

[a]$p < .05$.

[b]$p < .001$.

[c]$n = 491$.

[d]Mediation effect significant at 99% CI.

[e]$n = 495$.

control subjects, though the effect size ($d = -.13$) did not meet criteria for corrected significance (90). Considered with our findings, these studies may suggest that abnormalities in RLIC FA are most pronounced during adolescent development, with a compensatory increase occurring later in adulthood, or that some other confound in adult patients, such as long-term medication, affects this measure. Further study of this tract in developmental and adult populations is needed to confirm these results.

Projection tracts such as the internal capsule (and here RLIC) are important for corticospinal and sensory communication and have been less frequently investigated in relation to psychiatric disease than associative tracts. Previous studies have postulated that reduced WM in the internal capsule may lead to functional dysconnectivity between the cortex and subcortical structures (91), with corresponding clinically relevant correlates such as increased positive symptoms (92) and impairments in emotional stability, motivation, and executive function (86,92–94). Although dysfunctional information processing has been increasingly implicated in SZ as a putative contributor to impairments in higher-level cognitive function (95), we did not find a relationship between RLIC FA and the cognitive measures used here. However, there is evidence that motor-related and sensory-related symptoms of psychosis emerge before deficits in higher-order cognition (96). The RLIC contains both motor and sensory fibers (97), and thus it is possible that RLIC FA mediates age-related changes in these systems rather than cognition.

Finally, our exploratory analysis in the LPS group supports the hypothesis that the extent of deviation from typical age-related patterns in RLIC and SLF FA relates to the severity of PLEs. The LPS group showed an intermediate pattern, with FA values falling between those of the TD and PS groups. This is further evidence that abnormalities in age-associated structural changes are emerging even at the lowest end of the psychosis spectrum. However, owing to the small LPS sample size, these findings are preliminary and require additional studies with larger samples.

Strengths of this study include the population-based cohort that allows us to eliminate confounds such as medication and illness chronicity. Our results also expand on our evidence of regionally specific FA disruptions by evaluating non-FA measures. Finally, there is a paucity of studies examining how regional WM measures may mediate the relationship between age and cognitive endophenotypes of SZ. This is likely attributable to the rarity of access to both neuroimaging and cognitive data for a sample size of this magnitude that spans such a broad age range. Future studies incorporating more precise measures of maturation, such as pubertal stage, could help to refine our understanding of these relationships. Additionally, future mediation analyses with tasks designed to investigate more focal areas of cognition implicated in psychosis, such as processing speed, could further elucidate the role of WM in cognitive development. Similarly, additional clinical measures, such as individual symptom scales, would be informative when exploring age-related patterns within subgroups. Finally, the PNC consists of cross-sectional data, which limits our ability to evaluate developmental trajectories. Prospective longitudinal data are essential to determine neural biomarkers that predict subsequent outcome.

Conclusions

In this population-based sample, youths with PLE showed disrupted development of regional WM connectivity and, in contrast to TD youths, did not show mediation of the relationship between age and cognition by SLF FA. These findings suggest that disturbances of age-related changes in SLF and RLIC WM may be an early biomarker for psychosis and that the SLF may contribute to cognitive deficits. Future studies should pursue longitudinal investigations to determine their predictive validity and preclinical experimental studies to provide mechanistic explanations and potentially identify critical temporal and anatomical targets for neurotherapeutic interventions.

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