Original Investigation

White Matter Differences Among Adolescents Reporting Psychotic Experiences
A Population-Based Diffusion Magnetic Resonance Imaging Study

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IMPORTANCE Abnormal brain connectivity is thought to have a key role in the pathophysiology of schizophrenia and other psychotic disorders. White matter (WM) abnormalities have been reported in patients with schizophrenia and patients with prodromal syndromes. To our knowledge, no studies have yet reported on WM differences among adolescents who report psychotic experiences, a known vulnerability group for later severe psychopathology, including psychotic illness.

OBJECTIVE To study WM differences using diffusion-weighted imaging (whole-brain and tractography analyses) in adolescents who report psychotic experiences.

DESIGN, SETTING, AND PARTICIPANTS A population-based case-control study of 28 adolescents 13 to 16 years old who reported psychotic experiences and a matched sample of 28 adolescents who did not report psychotic experiences drawn from a sample of 212 young people recruited from primary schools in North Dublin and Kildare, Ireland. The study dates were 2008 to 2011.

INTERVENTIONS High-angular resolution diffusion-weighted imaging data were used to conduct whole-brain WM analysis using tract-based spatial statistics. Based on this exploratory analysis, a tractography-based approach with constrained spherical deconvolution was performed.

RESULTS Compared with control group participants, adolescents who reported psychotic experiences showed WM differences bilaterally in striatal regions in proximity to the putamen (increased fractional anisotropy, $P = .01$, false discovery rate corrected), and tractography identified significant WM differences bilaterally in the uncinate fasciculus (increased fractional anisotropy in the right [$P = .001$] and axial diffusivity in the left [$P = .01$] uncinate fasciculus, respectively). Similar patterns of WM differences between groups survived adjustment for other psychopathology, indicating some specificity for psychotic experiences. Exploratory along-tract analyses showed WM differences between groups in the frontal projections of the right inferior fronto-occipital fasciculus (reduced radial diffusivity in approximately 32% of the tract segment [$P \leq .0001$] and increased fractional anisotropy in approximately 16% of the tract segment [$P \leq .0009$]).

CONCLUSIONS AND RELEVANCE In a population-based study of adolescents reporting psychotic experiences, we found a number of WM differences in the region of the putamen located between the inferior fronto-occipital fasciculus and the uncinate fasciculus and in the left parietal regions that include the fiber bundle of the superior longitudinal fasciculus. These findings suggest that subtle structural changes to WM microstructure are not merely a consequence of disorder but may index vulnerability to psychosis even at a very early age.

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Abnormalities in connectivity have been proposed as a key feature of psychosis.[1-4] Techniques such as diffusion-weighted imaging and diffusion-tensor imaging have shown widespread dysconnectivity, as indexed by decreased fractional anisotropy (FA) measures, a putative tensor-based measure of white matter (WM) integrity, in patients with schizophrenia, particularly in the frontotemporal connections.[5-7] Attention has recently focused on the prodromal period, and frontotemporal connectivity abnormalities have also been reported in individuals with at-risk mental states.[8-16] However, individuals with at-risk mental states are far along the psychosis continuum and are already often help seeking. The aim of the present study was to examine dysconnectivity in individuals at an earlier point on the psychosis continuum using a population-based sample of school-going adolescents who reported psychotic experiences.

In contrast to the low prevalence of psychotic disorder (approximately 0.5%-1%), studies[17-22] have shown that psychotic experiences occur at a high prevalence in the community. A meta-analysis[21] of all community-based studies of psychotic experiences demonstrated median prevalences of 17% among children between 9 and 12 years old and 7.5% among adolescents between 13 and 18 years old. Longitudinal studies have shown that psychotic experiences in childhood are associated not only with increased risk (7.4%) for psychotic disorders later in life[20,23-26] but also a wide range of nonpsychotic psychiatric disorders,[14,27,28] in particular severe psychopathology characterized by multimorbidity (ie, the presence of multiple co-occurring disorders) and suicidal behavior.[29-31] Therefore, psychotic experiences in the population (an extended psychosis phenotype) represent an important marker of risk for severe mental disorders beyond simply an increased risk for psychotic disorder.

The objective of the present study was to investigate putative WM anomalies in adolescents who report psychotic experiences. Based on the literature, we hypothesized that WM abnormalities (specifically reduced FA in frontotemporal regions) would be present in nonclinical populations with psychotic experiences but that these differences would be more subtle than in clinical populations.

We used several innovative techniques. First, high-angular resolution diffusion-weighted imaging[32,33] with constrained spherical deconvolution–based fiber tractography was used to provide a more accurate approach than diffusion-tensor imaging–based tractography for investigating subtle WM structure and connectivity differences.[34-39] Second, tract segmentation approaches allowed us to investigate subtle differences along tracts, which were deemed necessary in a nonclinical population. Third, a range of diffusion metrics, including axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD), as well as FA, was used to provide a greater degree of information on the diffusion properties related to axonal packing and myelination.[40,41]

Methods

Participants

The study dates were 2008 to 2011. A sample of 212 young people between 11 and 13 years old was recruited from primary schools in North Dublin and Kildare, Ireland, as part of the Adolescent Brain Development Study.[42] All 212 participants attended a diagnostic clinical interview with trained raters (I.K., S.R., M.H. and M.C.). For further details on the recruitment and interviewing, refer to Kelleher et al.[42,43] Psychotic symptoms were assessed using the psychosis section of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS).[44] This schedule is a well-validated, semistructured research diagnostic interview for the assessment of current and lifetime *DSM-IV* Axis I psychiatric disorders in children and adolescents. The psychosis section contains questions designed to assess hallucinations and delusions. If any psychotic experience was reported, a full written account detailing the reported experience was taken. A consensus committee comprising an adult psychiatrist (M.C.), a child and adolescent psychiatrist (M.H.), and a psychologist (I.K.) met after the interviews to discuss the transcripts and determine whether any experiences elicited could be considered definite psychotic experiences or not. Factors associated with the experience, such as timing, content, frequency, attribution, severity, and distress, were taken into account in classifying experiences as definite or possible. The most common symptom reported was auditory verbal hallucinations and was present in more than 90% of those reporting symptoms.[43]

A subsample of 100 participants with no contraindications to magnetic resonance imaging agreed to take part in a subsequent neuroimaging study that took place 1 to 3 years after the original interview. Of the 100 individuals imaged, 28 adolescents 13 to 16 years old met criteria for the presence of a definite psychotic experience. These individuals were classified as the psychotic experiences group (PE group). From the remaining 72 participants, a group of 28 adolescents who had not reported psychotic experiences at the initial interview were chosen to match the PE group for age (at the time of imaging), sex, and handedness; these individuals formed the control group. All control subjects were screened before imaging to exclude newly emerging psychotic symptoms. We did not include individuals with possible psychotic experiences in this analysis.

Ethical approval was obtained for the experimental protocol for this study from the Medical Research Ethics Committee, Beaumont Hospital, Dublin, and the School of Psychology, Trinity College, Dublin. Written parental consent and participant assent were obtained before the study.

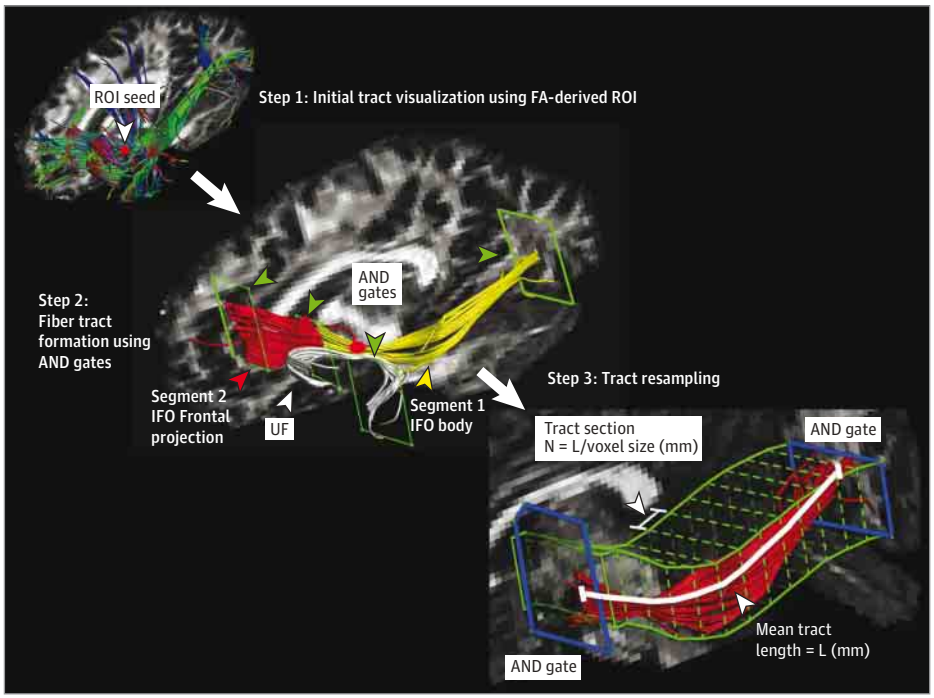
Diffusion-Weighted Imaging Acquisition

Whole-brain high-angular resolution diffusion-weighted imaging data with 61 gradient directions were acquired for each participant on a 3.0-T magnetic resonance system (Intera Achieva; Philips) equipped with an 8-channel head coil. All imaging was performed on the same magnetic resonance system in Trinity College Institute of Neuroscience, Dublin.

Diffusion Data Analyses

A concise description of the imaging methods used is given below, and in-depth detailed descriptions of the methods are provided in the supplementary online material (eMethods in the Supplement). Preprocessing and tractography analyses were performed using a diffusion magnetic resonance imaging toolbox (ExploreDTI; http://www.Exploredti.com[45]).

Figure 1. Tractography Analysis Strategy



Step 1, Initial tract identification mechanism using the fractional anisotropy (FA)–derived region of interest (ROI) (shown as a red sphere) and subsequent fiber bundles determined using constrained spherical deconvolution–based tractography. Step 2, Tract formation using AND gates (shown as green boxes). Each pair of gates acts as inclusion criteria where the fibers must pass through both gates to be selected, permitting specific tract selection (frontal inferior fronto-occipital [IFO], IFO body, uncinate fasciculus [UF], and superior longitudinal fasciculus [SLF]). Step 3, Tract resampling demonstrated on the IFO body. The length of tract between the inclusion gates is denoted as L and is subdivided into an equal number of sections (N), shown as green rectangular slabs partitioning the tract over its length. The number of slabs required is determined by L divided by voxel size (in millimeters).

Global WM Analysis

Tract-based spatial statistics[46,47] (part of the FSL toolbox; http://www.fmrib.ox.ac.uk/fsl[48]) was used to conduct whole-brain voxelwise analysis for the FA, MD, AD, and RD images independently. Voxelwise between-group analyses were performed using nonparametric rank order Brunner-Munzel tests[49] within a software package (MRIcron; http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html[50]), with false discovery rate[51] correction applied at $P = .01$.

Tractography

WM Tract Visualization and Selection

Significant FA differences were used as initial seed masks for deterministic tractography modeled using constrained spherical deconvolution to identify the WM tracts in proximity to these regions of interest.[52] Initial visualization of all tracts through each region of interest (eMethods in the Supplement) was used and subsequently followed by a tract isolation strategy using inclusion AND with exclusion NOT gates, resulting in the identification and delineation of the inferior fronto-occipital (IFO) tract (including the frontal projections) bilaterally, the left superior longitudinal fasciculus (SLF), and the uncinate fasciculus (UF) bilaterally (**Figure 1**).

A population atlas-based tractography approach[41,53] using robust inclusion AND and exclusion NOT gates was used to accurately select the WM tract segments for investigation. The IFO was divided into 2 segments. Segment 1 comprised the main fibers traversing from the anterior extension (commencing at the approximate position where the frontal arc of the UF merges with the IFO bundle) to the posterior extension of the IFO. Segment 2 comprised the frontal IFO projections (see step 2 of Figure 1). To our knowledge, this is the first time that the IFO has been analyzed in this fashion, but similar methods have been used previously to subdivide other tracts such as the cingulum, corpus callosum, and corticospinal tract.[34,54,55]

Tract-Averaged Segment Analysis

For each tract segment, FA, MD, AD, and RD values were obtained, which were calculated for the entire segment of the tract.

Along-Tract Analysis

Tract resampling was performed to assess WM variations over the length of fiber tract bundle.[56-59] Each tract of interest was subsampled into equal sections (N) (ie, the mean fiber bundle length divided by the voxel size) (Figure 1, step 3). Parameter values were extracted at each of these evenly spaced sections, allowing pointwise correspondence across individuals (eMethods in the Supplement).

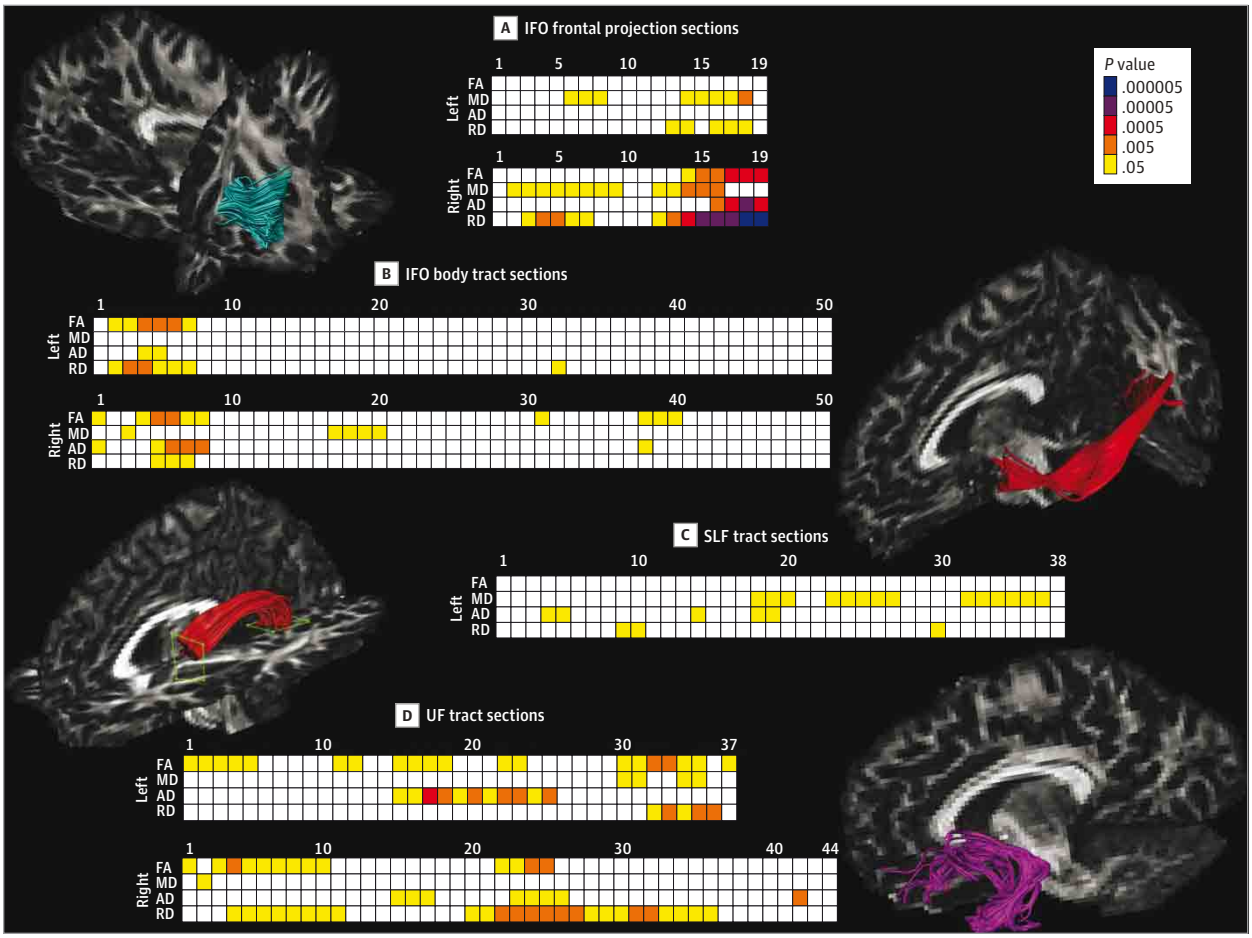
Statistical Analysis

All extracted diffusion metrics were systematically inspected to remove outliers before the statistical analyses using a software program (SPSS, version 21; IBM). Analysis of covariance (with age and sex as covariates) was used to compare between-group differences per metric. Bonferroni correction was applied at .05, divided by the number of sections times 3 diffusivity parameters (eigen values λ_1, λ_2, and λ_3). Uncorrected significance levels per section are shown graphically in **Figure 2**.

Adjustment for Psychopathology

Comorbid *DSM-IV* mental disorders were more prevalent among the PE group than among controls. To assess whether PEs predicted neuroarchitectural differences beyond those predicted simply by the presence of a mental disorder, we con-

Figure 2. Along-Tract Analysis



Results of the along-tract analysis for inferior fronto-occipital (IFO) frontal projections (A), IFO body (B), left superior longitudinal fasciculus (SLF) (C), and uncinate fasciculus (UF) (D). All 4 diffusion metrics are detailed for each resampled tract section. Uncorrected significance levels per section are shown pictorially, with the typical color scale of significance provided for values at $P \leq .05$. Values at $P > .05$ are shown in white. Bonferroni correction was then applied at .05, divided by the number of sections times 3 diffusivity parameters. AD indicates axial diffusivity; MD, mean diffusivity; and RD, radial diffusivity.

Table 1. Tract-Based Spatial Statistics White Matter (WM) Fractional Anisotropy (FA) Differences

Region of Interest	Size, mm^3	MNI x, y, z Coordinates, mm	Location of Structure or Fiber Tract	Effect Direction[a]	z Score[b]
1	10	26, 15, −9	Right WM putamen, including IFO and UF	PE ↑ FA	5.86
2	40	−30, −7,−10	Left WM putamen, including IFO and UF	PE ↑ FA	5.26
3	5	−42,−20, 33	Left cerebral WM, including SLF, extending to the temporal part	PE ↑ FA	4.19
4	9	−38, 20, 18	Left cerebral WM, including SLF, UF, and IFO	PE ↓ FA	4.93

Abbreviations: IFO, inferior fronto-occipital fasciculus; MNI, Montreal Neurological Institute; PE, psychotic experiences; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus.

[a] Arrows indicate effect direction relative to controls.

[b] Indicates false discovery rate corrected at $P = .01$.

ducted a subanalysis that included only the participants with mental disorders.

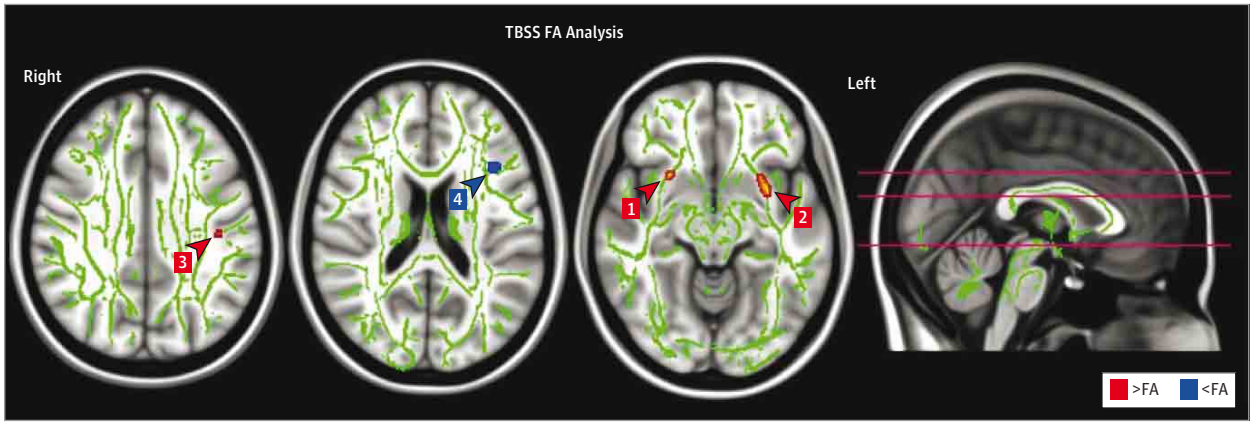
Results

Demographics

There were no significant differences between those imaged and not imaged. The groups were similar in age ($\chi^2_{3,211} = 0.51$, $P = .91$), sex ($\chi^2_{1,210} = 1.25$, $P = .26$), handedness ($\chi^2_{1,157} = 0.18$, $P = .66$), presence of psychotic experiences ($\chi^2_{1,211} = 0.83$, $P = .36$), socioeconomic status ($\chi^2_{1,165} = 1.76$, $P = .18$), personal psychiatric history ($\chi^2_{1,208} = .003$, $P = .95$), and family psychiatric history ($\chi^2_{1,206} = 1.55$, $P = .21$).

There were no significant differences between the PE group vs the control group in age (mean [SD] age, 13.7 [1.4] vs 13.6 [1.3] years; $P = .8$), sex (36% vs 39% were male, $P = .8$), or handedness (26 vs 27 were right handed, $P = .6$). There were significant differences between the groups in the presence of comorbid *DSM-IV* disorders (17 vs 7, $P < .05$)

Figure 3. Whole-Brain Tract-Based Spatial Statistics Fractional Anisotropy (TBSS FA) Analysis



Significant between-group FA differences are shown and effect direction relative to controls, with red/yellow clusters indicating increased FA and blue clusters indicating decreased FA. Clusters have been enhanced for visualization purposes and presented on a standard T1-weighted image, including the mean skeletonized FA image shown in green.

Table 2. Tract-Based Spatial Statistics White Matter (WM) Diffusivity Differences

Diffusion Metric	Size, mm^3	MNI x, y, z Coordinates, mm	Location of Structure or Fiber Tract	Effect Direction[a]	z Score[b]
MD	6	−27,−52, 48	Left cerebral WM, including SLF	PE ↓ MD	4.96
AD	8	26, 15,−10	Right WM putamen, including IFO and UF	PE ↑ AD	5.18
	6	−29, 9,−10	Left WM putamen, including IFO and UF	PE ↑ AD	4.37
	17	−31,−66, 2	Left posterior thalamic radiation, including IFO and ILF	PE ↓ AD	5.07
RD	27	−30, 7,−10	Left WM external capsule, including IFO and UF	PE ↓ RD	4.54

Abbreviations: AD, axial diffusivity; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; MNI, Montreal Neurological Institute; PE, psychotic experiences; RD, radial diffusivity; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus.

[a] Arrows indicate effect direction relative to controls.

[b] Indicates false discovery rate corrected at $P = .01$.

Global Voxelwise WM Analyses (Whole-Brain Tract-Based Spatial Statistics)

Fractional Anisotropy

The PE group had increased FA ($P = .01$, false discovery rate corrected) in the following 3 regions: (1) right putamen WM, (2) left putamen WM (including the IFO and UF), and (3) left SLF extending to the temporal area. The PE group had reduced FA in the left SLF, UF, and IFO. These 4 regions of interest were used as seed regions for the initial tract identification (**Table 1** and **Figure 3**), as described in the WM Tract Visualization and Selection subsection of the Tractography section in the Methods.

Diffusivity Measurements

Mean Diffusivity | The PE group showed significantly greater MD ($P = .01$, false discovery rate corrected) in the WM of the left hemisphere, including the SLF. These results are summarized in **Table 2**.

Axial Diffusivity | The PE group showed significantly increased AD bilaterally in the putamen WM, including the IFO and UF tracts. Significant reductions in AD were found in the left posterior thalamic radiation, including the IFO and the inferior longitudinal fasciculus, as well as in the left cerebral peduncle, including the corticospinal tract and thalamic radiation (Table 2).

Radial Diffusivity | The PE group showed RD reductions bilaterally in the putamen WM, including the IFO and UF (Table 2). There was a convergence of effects for FA, AD, and RD localized bilaterally in the putamen WM, including the IFO and UF.

Tractography Analyses

Tract-Averaged Segment Analysis

Table 3 summarizes the results for the tract-averaged analyses. The PE group showed significant increases in FA in the right UF ($P = .001$) and in AD in the left UF ($P = .012$). Strong trends (just above Bonferroni correction) were identified for increased FA in the left UF ($P = .022$) and reduced RD bilaterally in the UF ($P = .040$ left and $P = .031$ right) and the frontal section of the IFO ($P = .031$ left and $P = .023$ right) in the PE group.

Along-Tract Analyses

Results for the along-tract analysis for the frontal IFO, IFO body, left SLF, and UF are shown in Figure 2. Plots for each diffusion metric over the length of each tract segment are detailed in the eResults and eFigure 1 in the Supplement. There were significant differences in the PE group in the frontal IFO segment (detailed below and in Figure 2A). The UF and all other tract segments did not show any significant along-tract variations (Figure 2B-D).

Frontal IFO Segment

Analyses of the right IFO frontal projections revealed increased FA and AD, as well as reduced MD and RD, for the PE

Table 3. Constrained Spherical Deconvolution, Derived Tract-Averaged Segment Measures

Fiber Tract or Segment	Diffusion Measure[a]				
	Hemisphere	FA	MD	AD (λ_1)	RD ($\lambda_\perp$)
Frontal IFO	Left	NS	.074 ↓	NS	.031↓[b]
	Right	.084 ↑	NS	NS	.023↓[b]
IFO body	Left	NS	NS	NS	NS
	Right	NS	NS	NS	NS
SLF	Left	NS[c,d]	.067↓[d]	NS	NS
Uncinate fasciculus	Left	.022↑[b]	NS	.012↑[e]	.040↓[b]
	Right	.001↑[e]	NS	NS	.031↓[b]

Abbreviations: AD, axial diffusivity; FA, fractional anisotropy; IFO, inferior fronto-occipital fasciculus; MD, mean diffusivity; NS, not significant; RD, radial diffusivity; SLF, superior longitudinal fasciculus.

[a] *P* values are by analysis of covariance with age and sex covariates. Arrows indicate effect direction relative to controls.

[b] Trend toward significance but above the *P* = .017 threshold.

[c] Significant age effect.

[d] Significant sex effect.

[e] Significant group difference (Bonferroni corrected at .05 / 3 = .017).

group, with more pronounced effects in the most posterior sections. Specifically, 5 of 19 sections revealed significant FA increases ($P \leq .005$) in the PE group, 3 of which (amounting to approximately 16%) survived robust Bonferroni correction for multiple comparisons at $P \leq .0009$ (0.05 of 19 sections times 3 diffusivity parameters). In the PE group, RD was also reduced in 13 sections ($P \leq .05$), 6 of which (approximately 32% of the segment) survived Bonferroni correction with $P \leq .0001$ to $P < .000002$. Increased AD was identified in 4 sections, 3 of which survived Bonferroni correction at $P \leq .0005$. The MD variations along the tract segment were weaker ($P = .023$ to $P = .001$) and more evenly dispersed throughout the tract (Figure 2A).

Adjusting for Psychopathology

Seventeen of the PE group and 7 of the control group had a *DSM-IV* lifetime mental disorder based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children interview. All analyses were repeated, and the whole-brain tract-based spatial statistics findings of increased FA bilaterally within the putamen and left SLF remained significant (eTable 1 in the Supplement). The along-tract analyses also revealed persistent patterns of difference along the tracts but to a lesser extent, probably due to reduced power (eTable 2 and eFigure 2 in the Supplement).

Discussion

In this population-based sample of adolescents reporting psychotic experiences, we found 3 WM microstructural differences. First was increased FA bilaterally in the putamen region located between the IFO and the UF, as well as in the left parietal regions, including the trajectory of the SLF. Differences in AD and RD were also identified within these areas. Second was bilateral significant differences in the UF for tract-averaged measures and strong trends in RD, approaching significance in the right frontal projections of the IFO. Third was significant FA increases in the right frontal projections of the IFO identified by tract resampling.

The merits of using both tract-averaged and tract-resampled measures were evident because the former revealed widespread alterations along tracts (as identified in the UF), while the latter captured more subtle localized along-tract variations[56,57] in the IFO frontal projections. These findings were largely unchanged even when confined only to individuals with mental disorders (with vs without psychotic experiences), demonstrating that these differences are likely to relate to the experience of psychotic symptoms as opposed to simply indexing psychopathology.

Previous Diffusion-Weighted Imaging Findings in Schizophrenia and Psychosis

Contrary to our hypothesis, we found increased FA and AD and reduced MD and RD in adolescents with psychotic symptoms, which is in contrast to the typical FA reductions and MD increases reported by many investigators in both first-episode and chronic schizophrenia.[5,9,11,13,60-62] However, our findings are not without precedent. Although FA is globally decreased in schizophrenia, specific tracts showing increased FA have been reported that appear to be related to auditory hallucinations. For instance, increased FA in the SLF has been reported in patients who report hallucinations compared with those who do not.[63,64] Mulert and Scarr[65] reported increased FA in a subgroup of patients with conversing voices in fiber tracts connecting homotropic auditory pathways via the corpus callosum. There are also several reports (including a meta-analysis) showing increased FA in the arcuate fasciculus in patients with auditory hallucinations compared with controls.[66-69] The findings of increased FA in genetic high-risk, sibling, and ultra-high-risk samples[58,70-72] suggest that increased FA may reflect a vulnerability to developing psychosis. Our findings add to the literature in this area by demonstrating that increased FA in fronto-temporal and frontoparietal projections is related to the propensity to experience auditory hallucinations in young people who do not have a psychotic disorder. Although patients with chronic schizophrenia have a combination of increased and decreased FA (connectivity) in specific brain networks, our findings suggest that increased FA may be more relevant in terms of a vulnerability marker. However, careful in-

terpretation of FA is needed because there is not a simple linear relationship between WM fiber integrity and FA values.[66]

Interpretation of the Findings

The IFO is thought to have a role in the transmission of auditory and visual information between fronto-occipital regions.[73] One could speculate that structural alterations along these pathways may partly explain the neurocognitive processing speed deficits that have been demonstrated in individuals reporting psychotic experiences.[74,75]

Dopamine regulation disruption in the putamen has been reported in schizophrenia.[76-80] Increased dopamine synthesis has been demonstrated in healthy siblings of patients with schizophrenia in this region.[70,81] Our findings of increased FA bilaterally in the putamen might suggest that early WM microstructural insults in this structure could have a role in increasing vulnerability to psychosis.

What Is the Meaning of Increased FA?

The use of high-angular resolution diffusion-weighted imaging-based constrained spherical deconvolution tractography[82-85] with the associated improved representation of crossing fibers[86-88] could potentially sensitize the analysis to capture FA increases.[88,89] Our findings support previous research showing that increased FA and AD, as well as a corresponding decrease in RD, are indicative of reduced WM distribution complexity in the brain.[88,90]

The directionality of diffusion metrics, such as FA, must be considered carefully in the context of developmental periods and diffusion-weighted imaging techniques. Normative developmental maturation processes in the brain are associated with WM increases in FA and AD, as well as with corresponding decreases in MD and RD.[41,91-93] We found that these differences were of much greater magnitude in the young people who have experienced psychotic symptoms, perhaps reflecting an atypical process of brain maturation accompanied by disruption in WM myelination. Indeed, the results provide further evidence that WM alterations reported in schizophrenia are not merely a consequence of the disease but precede illness onset and may therefore be used as potential markers for early detection. One could speculate that increased FA may indicate loss of crossing fibers, which may be more prominent in one direction initially (giving rise to increased FA) before affecting WM more globally with the onset of psychosis.

Strengths and Limitations

The strengths of our study are several. First is the use of a well-controlled, population-based sample. Second is the inclusion of detailed clinical assessments and the verification of interview-derived symptoms by consensus discussion. Third is the utilization of advanced imaging techniques that provide a more accurate representation of multiple fiber orientation and are in closer agreement with known neuroanatomy than its diffusion-tensor imaging-equivalent representation. Fourth is our use of highly sensitive tract-resampling techniques to detect subtle significant WM differences.

There are also some limitations. First, although increased FA could indicate crossing fibers, these crossing fibers were not directly measured in this study because the methods for such analyses are not yet fully validated.[94,95] In the absence of any standardized alternative diffusion measures, we used diffusion-tensor imaging-derived indexes (FA, MD, AD, and RD) applied to our constrained spherical deconvolution-defined tracts.[39] Second, the sample sizes in the present study are not large (although on par with ultra-high-risk samples),[11] but we believe that the unique nature of the cohort and the careful clinical evaluation and control selection compensate for the modest sample sizes. Our findings withstood correction for multiple testing but will need replication in other at-risk groups using similar methods. Third, our findings relate to a specific snapshot of a developmental period of mid-adolescence. Careful consideration is needed when formulating direct comparisons to the findings from studies of older adolescents and young adults in ultra-high-risk and schizophrenia studies. Fourth, the tract selection strategy used does not investigate all well-known tracts; therefore, effects may extend beyond those identified in this study. Fifth, specific correlational analyses were not carried out between WM changes and measures of severity of symptoms in view of the modest sample size and the fact that this analysis only included young people who were considered to have met criteria for definite psychotic symptoms as rated by a panel of clinicians, and those with possible symptoms (ie, less severe) were excluded, thereby reducing the variance between individuals in the PE group on measures of symptom severity.

Conclusions

In conclusion, we stress the need for longitudinal clinical imaging studies to track young people with psychotic symptoms from adolescence through the developmental period to early adulthood to observe the changes in WM as vulnerability progresses (or not) to disorder. Such studies would clarify the mechanisms of the WM differences observed in this study.

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