Original Investigation

Mediation of Developmental Risk Factors for Psychosis by White Matter Microstructure in Young Adults With Psychotic Experiences

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IMPORTANCE White matter (WM) abnormalities have been identified in schizophrenia at the earliest stages of the disorder. Individuals in the general population with psychotic experiences (PEs) may show similar changes, suggesting dysfunction due to aberrant neurodevelopment. Studying such people is a powerful means of understanding the nature of neurodevelopmental problems without the confound of clinical management and allows other potential risk factors associated with the schizophrenia spectrum to be taken into account.

OBJECTIVES To compare WM microstructure and myelination in young adults with and without PEs identified from a population-based cohort using diffusion and relaxometry magnetic resonance imaging and to quantify potential mediating effects of WM on several known risk factors for psychosis.

DESIGN, SETTING, AND PARTICIPANTS In this case-control study, participants were drawn from the UK Avon Longitudinal Study of Parents and Children. Psychotic experiences were assessed using a semistructured interview. Magnetic resonance imaging was carried out at age 20 years in 123 participants who had PEs and 124 individuals serving as controls. Participants with PEs were subdivided into those with operationally defined suspected PEs, definite PEs, and psychotic disorder.

MAIN OUTCOMES AND MEASURES Diffusion tensor magnetic resonance imaging and relaxometry-derived myelin water fractions were used to measure WM microstructure and myelination, respectively. Differences in quantitative WM indices were assessed using tract-based spatial statistics. A binary model and a continuum-like ordinal model of PEs were tested.

RESULTS Among the 123 participants who had PEs (mean [SE] age, 20.01 [0.004] years), 37 were male and 86 were female. Among the 124 controls (mean [SE] age, 20.11 [0.004] years), 49 were male and 76 were female. Fractional anisotropy in left frontomedial WM was significantly reduced in individuals with PEs (Montreal Neurological Institute [MNI] coordinates, −18, 37, −2; $P = .0046$). The ordinal model identified a similar but more widespread effect, with a corresponding increase in radial diffusivity (MNI coordinates, −15, 29, 21; $P = .0042$). Low birth weight ($\rho = -0.155$; $P = .015$) and childhood IQ ($\rho = -0.188$; $P = .003$) were associated with the presence of PEs. Results of mediation analysis were consistent with the association between birth weight (21.1% mediation effect; $P = 6.20 \times 10^{-3}$) and childhood IQ (7.9% mediation effect; $P = .041$) and by PEs being mediated by fractional anisotropy changes in these regions.

CONCLUSIONS AND RELEVANCE The results of the study imply the presence of abnormal WM microstructure in young adults with PEs. The results are consistent with the hypothesis that neurodevelopmental factors cause alterations in the cellular composition of WM circuits critical to higher cognitive function. Such alterations may first manifest in childhood as reduced IQ and later contribute to PEs in early adulthood.

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White matter (WM) abnormalities have been identified in several structures in schizophrenia using diffusion tensor magnetic resonance imaging (DT-MRI).[1] Among the most heavily implicated regions are the cingulum, corpus callosum, uncinate, and arcuate fasciculi.[2-4] However, these findings are variable across studies[5,6] and cover diverse regions. Other studies focusing on specific properties of WM axons, such as myelination,[7,8] from MRI[9-13] have implicated reduced myelination in frontomedial WM[7,14] in patients with schizophrenia.

To delineate structural brain differences related to the development of psychosis, it is important to exclude the confounding effects of medication or chronic illness. Studies of patients with drug-naive or first-episode schizophrenia achieve some control of these confounding effects, as do studies focused on high-risk groups. These groups can include individuals presenting with the At-Risk Mental State, clinical ultra-high risk,[15,16] schizotypal personality traits,[17] or psychotic experiences (PEs).[18-20] Such individuals are widely regarded as lying on a psychosis continuum.[18,19,21] Studies[17,22-24] of WM microstructure in clinically high-risk individuals have found changes in, for example, the genu of the corpus callosum and thalamic radiations, with a general trend for reduced fractional anisotropy (FA) even in the absence of transition to psychosis.[25] The locations of these abnormalities, although dispersed, have tended to be those of late-maturing brain regions that underlie higher-order cognitive functions.[26]

Understanding the role of WM abnormalities in the development of psychosis necessitates consideration of numerous risk factors, many of which have been implicated in altered microstructure[27-74] (**Table 1**). These risk factors include obstetric and developmental factors as well as substance abuse. Reduced IQ in children and adolescents is one such factor and is generally interpreted as evidence of an aberrant neurodevelopmental process.[27,29,30] The biological mechanisms whereby such factors contribute to psychosis and how they relate to the brain abnormalities noted above are not clear, and there are most likely multiple pathways.[75] The accumulation of risk across several of these factors significantly influences WM microstructure,[76] although the mediating effects of WM microstructure on PEs are not known. There is some limited evidence that brain volume may be one such intermediate factor.[77]

This study used a large epidemiologic birth cohort to examine the association between WM microstructure and PEs in young adults.[18,20] We tested the hypothesis that abnormalities in WM are associated with PEs and that they center on pathways critical for higher-order cognitive functions. This approach has several advantages. In particular, it allows the examination of PEs without relying on presentation to clinical services, thereby reducing selection biases around help seeking and secondary effects of illness. The cohort has accrued rich longitudinal data on developmental, clinical, and psychosocial variables that can constitute risk factors for psychosis. The availability of these data provides the opportunity to explore how developmental variables of putative etiologic relevance to psychosis, WM metrics, and PEs might be related. Testing whether the hypothesized association between WM and PEs changes after adjusting for confounders is an important step. However, in this study we went one step further and tested a biologically plausible causal model wherein certain developmental risk factors are considered to be primary factors (eg, birth weight) leading to changes in WM that may in turn partially mediate the appearance of PEs.

Key Points

Question: Are there any differences in white matter microstructure in young adults with psychotic experiences, and do such changes mediate the effects of risk factors for psychosis?

Findings: One hundred twenty-three young adults with psychotic experiences and 124 serving as controls were taken from an epidemiologic cohort and scanned with diffusion magnetic resonance imaging. We found altered microstructure in left frontomedial white matter, which partially mediated the effects of birth weight and childhood IQ on psychotic experiences.

Meaning: Early neurodevelopmental factors alter the cellular composition of white matter circuits critical to higher cognitive function, contributing to the development of psychotic experiences in early adulthood.

Table 1. Studies of Relating Environmental and Developmental Factors Indicating an Association With White Matter and Schizophrenia

Risk Factor	Associated With Schizophrenia[a]	Associated With White Matter[a]
Childhood IQ	27-30	31
Depression and anxiety disorders	Reviewed in[32]	33,34
Parental socioeconomic status	35,36	37,38
Birth weight	39-41	42-45
Perinatal trauma (eg, hypoxia)	46-48	49,50
Traumatic childhood events	51-53	54-57
Handedness	58-60	61
Tobacco consumption	Reviewed in[62]	63-67
Cannabis consumption	Reviewed in[68]	Reviewed in[69]
Alcohol consumption	Reviewed in[70]	Reviewed in[71]
Month of birth	72,73	74

[a] Numbers indicate references.

Methods

Participants

Participants were recruited from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) cohort[78,79] (eAppendix 1 in the Supplement provides a full description). A total of 126 participants who were previously assessed using the Psychotic-Like Symptoms Semi-Structured Interview[80,81] underwent MRI scanning. Psychotic episodes were further categorized as suspected, definite, and clinical disorders.[20] An equal number of individuals without PEs serving as controls were also scanned. At the time of scanning all participants were approximately aged 20 years (**Table 2**). Four participants did not complete the full protocol or were excluded because of poor data quality, reducing the final PE and control group sizes to 123 and 124, respectively. Written informed consent was

Table 2. Descriptive and Inferential Statistics for the Selected Developmental Risk Factors

Variable	Descriptive Statistics[a]					Inferential Statistics[b]		
		PEs						
	No PEs	Suspect	Definite	Clinical	Total With PEs	2-Group Binary Classification	4-Group Ordinal Classification	Proportion Imputed
Standard Covariates (Included in All Analyses)								
Total	125	44	47	32	123	NA	NA	NA
Proportion tested								
Sex								0
Male	49	14	16	7	37	$\chi^2 = 2.28$ $P = .131$	$\chi^2_{CA} = 3.00$ $\rho = 0.09$	
Female	76	30	31	25	86			
Age, y	20.11 (0.004)	20.14 (0.013)	19.88 (0.011)	20.04 (0.015)	20.01 (0.004)	$t = 1.49$ $\rho = 0.14$	$\rho = -0.14$ $P = .020$	0
Variables Included in Mediation Analyses								
1. Childhood IQ	111.44 (0.12)	104.65 (0.31)	106.79 (0.32)	103.13 (0.42)	105.07 (0.12)	$t = 3.46$ $P = .001$	$\rho = -0.19$ $P = .003$	0.137
2. CIS-R Score	6.30 (0.05)	9.16 (0.17)	12.26 (0.18)	16.78 (0.34)	12.33 (0.08)	$t = -5.90$ $P = 1.2 \times 10^{-8}$	$\rho = 0.41$ $P = 2.3 \times 10^{-11}$	0.065
3. Parental social class[c]								
I	10	4	5	0	9	$\chi^2_{CA} = 9.23$ $P = .002$	$\rho = 0.20$ $P = .001$	0.173
II	54	10	16	5	31			
III(N)	52	24	23	20	67			
III(M)	6	0	0	2	2			
IV	3	5	2	3	10			
V	0	1	1	2	4			
4. Highest maternal educational level[d]								
None	11	8	5	5	18	$\chi^2_{CA} = 9.02$ $P = .003$	$\rho = -0.20$ $P = .002$	0.065
Vocational	6	5	3	1	9			
O-level	39	16	21	19	56			
A-level	34	7	7	4	18			
Degree	35	8	11	3	22			
5. Birth weight, g	3466.2 (4.0)	3323.4 (12.6)	3401.7 (9.7)	3165.3 (18.5)	3312.2 (4.3)	$t = 2.33$ $P = .020$	$\rho = -0.16$ $P = .015$	0.060
6. Resuscitated at birth								
No	106	33	38	27	98	$\chi^2 = 1.54$ $P = .463$	$\chi^2_{CA} = 0.14$ $P = .707$	0.387
Yes	19	11	9	5	25			
7. Stressful life events								
No	111	36	40	23	99	$\chi^2 = 3.30$ $P = .069$	$\chi^2_{CA} = 4.45$ $P = .035$	0.173
Yes	14	8	7	9	24			
8. Handedness								
Right	92	36	34	22	92	$\chi^2_{CA} = 0.001$ $P = .971$	$\rho = 0.02$ $P = .737$	0.411
No dominance	25	6	9	7	22			
Left	8	2	4	3	9			
9. Tobacco consumption (cigarettes per day)[e]	0.59 (0.02)	1.27 (0.08)	0.44 (0.04)	2.23 (0.14)	1.20 (0.03)	$t = -1.72$ $P = .087$	$\rho = 0.02$ $P = .737$	0.472
10. Cannabis consumption[f]								
Never	87	28	32	19	79	$\chi^2_{CA} = 1.59$ $P = .208$	$\rho = 0.08$ $P = .226$	0.411
Once or twice	11	6	4	1	11			
Less than monthly	25	6	8	10	24			
Monthly or more	2	4	3	2	9			

(continued)

Table 2. Descriptive and Inferential Statistics for the Selected Developmental Risk Factors (continued)

Variable	Descriptive Statistics[a]					Inferential Statistics[b]		
		PEs				2-Group Binary Classification	4-Group Ordinal Classification	Proportion Imputed
	No PEs	Suspect	Definite	Clinical	Total With PEs			
11. Alcohol consumption[g]								
Never	16	6	2	0	8			
Once or twice	23	5	9	6	20			
Less than monthly	12	5	9	6	20	χ^2_{CA} = 1.05 P = .307	ρ = 0.05 P = .408	0.020
Monthly	52	21	19	14	54			
Weekly or more	22	7	8	6	21			
12. Month of birth[h]	2.30 (7.52)	1.72 (7.33)	1.31 (7.50)	2.18 (7.51)	1.71 (7.44)	F = 1.57 P = .212	ρ = 0.09 P = .384	0

Abbreviations: CA, Cochrane-Armitage; CIS-R, revised Clinical Interview Schedule; M, manual labor; N, nonmanual labor; NA, not applicable; PEs, psychotic experiences.

[a] Descriptive statistics for continuous variables are reported as mean (SE) for each group. Descriptive statistics for ordinal and categorical variables are reported as frequencies.

[b] Inferential statistics for the 2-group classification uses the *t* test for continuous variables, the χ^2 test for categorical variables, and the Cochrane-Armitage χ^2 test (denoted χ^2_{CA}) for ordinal variables. Inferential statistics for the 4-group ordinal classification uses the Spearman ρ correlation for continuous and ordinal variables and the χ^2_{CA} test for categorical variables.

[c] Based on the Office of Population Censuses and Surveys. Classes are I, professional; II, managerial and technical; III(N), nonmanual skilled; III(M), manual skilled; IV, partly skilled; and V, unskilled.

[d] Typical attainments for secondary education and postcompulsory further education in the United Kingdom.

[e] The mean number of cigarettes that the participant smoked every day in the past 30 d.

[f] From a multiple-choice question asking how many times the participant used cannabis in the past 12 mo (all substance use data gathered at ages 17-18 years).

[g] Six or more units of alcohol in the past year.

[h] As a scale from 0 (January 1) to 12 (December 31). A Watson-Williams, 2-sample *F* test and circular-linear ρ correlation were performed using the circular statistics toolbox.[82]

obtained prior to scanning, and participants received financial compensation. Approval was granted by the Cardiff University and the ALSPAC Ethics Committees.

Risk Factors

Variables hypothesized to contribute to psychosis risk were identified from the ALSPAC database (http://www.bristol.ac.uk /alspac/researchers/access/). These variables included demographic, environmental, and other risk factors: (1) IQ at age 8 years estimated from the Wechsler Intelligence Scale for Children,[83] (2) current general psychopathology at age 17 to 18 years measured using the computerized revised Clinical Interview Schedule (CIS-R),[84] (3) parental social class using occupational categories based on the Office of Population Censuses and Surveys (I, professional; II, managerial and technical; III(N), nonmanual skilled; III(M), manual skilled; IV, partly skilled; V, unskilled; 1991 Census; https://census.ukdataservice.ac.uk/media/51162/1991_defs.pdf), (4) maternal educational level, (5) birth weight, (6) resuscitation at birth, (7) stressful life events at age 15 to 16 years measured on the Development and Well-being Assessment,[85] (8) handedness, (9) tobacco use, (10) cannabis consumption, (11) alcohol consumption, and (12) month of birth. Missing data points for each participant were estimated using regression imputation[86] across the entire cohort. Prior to imputation, nonordinal categorical variables were recoded as sets of binary variables. Consistency of imputation and generalizability of the MRI sample to the full cohort were tested (eAppendix 2 and eAppendix 3 in the Supplement). Descriptive and inferential statistics of all selected variables are detailed in Table 2.

Diffusion MRI

The MRI data were acquired on a 3-T MRI system (HDx; GE Medical Systems). High angular resolution, diffusion-weighted images[87] with 60 gradient orientations (b = 1200 seconds/mm^2) were acquired and corrected for motion and field distortions[88,89] (eAppendix 4 and eAppendix 5 in the Supplement). Diffusion tensors were estimated, and FA, axial diffusivity, radial diffusivity (RD), and mean diffusivity were computed.

MRI Relaxometry

Myelination was estimated using multicomponent-driven, equilibrium single-pulse observation of T1 and T2 (mcDESPOT).[90] Data were corrected for head motion and field distortions (eAppendix 4 in the Supplement). Maps of myelin water fraction and longitudinal relaxation rate (R1 = 1/T1) were computed.

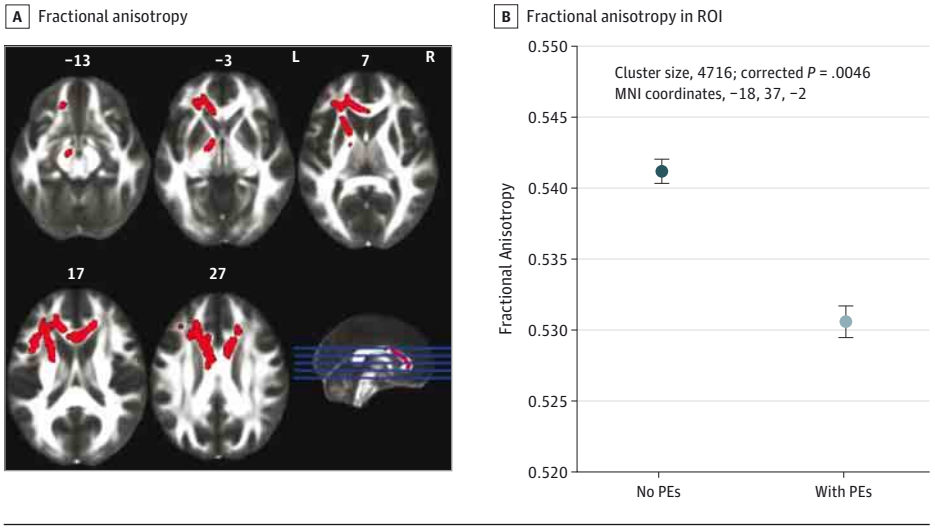
Tract-Based Spatial Statistics

Differences in WM metrics were analyzed using tract-based spatial statistics in the FMRIB Software Library.[91] All participants' FA maps were normalized, and a mean FA image was computed and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each participant's aligned DT/mcDESPOT data were then projected onto this skeleton.

Statistical Analysis

Voxelwise statistics were performed on the skeletonized images using the general linear model. Multiple comparisons were corrected for using permutation testing[92] with threshold-free cluster enhancement (5000 permutations).[93] Regions of

Figure 1. Tract-Based Spatial Statistics Results for Binary Classification of Psychotic Experiences (PEs)



A, Significant effects of PEs on fractional anisotropy (FA) using the binary classification of PEs. Regions of significant effect are shown in red; blue lines indicate position of axial sections shown in the sagittal plane. B, Mean (SE) of FA values in significant region of interest (ROI), with binary classification of PEs. L indicates left; MNI, Montreal Neurological Institute; and R, right.

significant effect were labeled using The Johns Hopkins University WM atlas[94] (eAppendix 6 in the Supplement).

Two designs were tested. The first design treats PE status as a binary classification (PEs vs without PEs). The second model uses a 4-point ordinal scale (no PEs > suspected PEs > definite PEs > clinical disorder). In both cases, age and sex were treated as covariates. Maps of permutation-corrected *P* values were computed for each microstructural metric (eg, FA and myelin water fraction) and each design. Effects are treated as significant at corrected $P < .05$.

To further examine the effects of putative risk factors on the association between WM and PEs, the ordinal analysis was repeated but with each factor specified as a covariate. Within the region of interest of significant effects, the change in effect size between the results with and without the additional covariate was estimated from the corrected *P* values using the inverse Gaussian cumulative density function.

To test the hypothesis that possible risk factors for PEs are mediated by WM abnormalities, mediation analysis was applied to the variables listed in Table 2 (except age and sex) and the tract-based spatial statistics data[91,92] (eAppendix 7 in the Supplement). First, regions of significant mediation were identified,[95] where corrected *P* value maps showed (1) a significant association between the risk factor and PEs, (2) a significant association between the risk factor and WM, (3) a significant association between WM and PEs after covarying for the risk factor, and (4) a reduced association between the risk factor and PEs when the effects of WM were controlled for. Second, in regions satisfying these criteria, the 95% CIs of the mediation effect and corresponding *P* values following permutation-based correction were estimated.[96]

Results

MRI Findings and Psychotic Experiences

Binary Classification

There was a significant decrease in FA in a region of left anterior, medial-frontal WM (**Figure 1**) in association with the presence of PEs. The region incorporates the genu and anterior portion of the corpus callosum and the left anterior corona radiata (peak effect: Montreal Neurological Institute [MNI] coordinates, −18, 37, −2l; $P = .0046$ corrected). There were no significant effects in other DT-MRI indices or in R1 or myelin water fraction.

Ordinal Model

There was a significant negative effect in FA in widespread regions of WM with some left lateralization (**Figure 2**A-C) in association with the presence of PEs. Participants with the highest PE scores had the lowest FA compared with the controls. Effects were seen mostly in the genu, anterior part of the corpus callosum (peak effect: MNI coordinates, −18, 37, −2; $P = .0012$ corrected), and to a lesser extent, the anterior thalamic radiation, anterior parts of left cingulum, left superior longitudinal fasciculus, and fornix. There was a similar spatial pattern of positive effects noted in RD (peak effect: MNI coordinates, −15, 29, 21; $P = .0042$), which extended into cerebellar WM. Mean diffusivity was also implicated in a small region of right frontomedial WM. No effects were seen in other DT-MRI or myelination metrics.

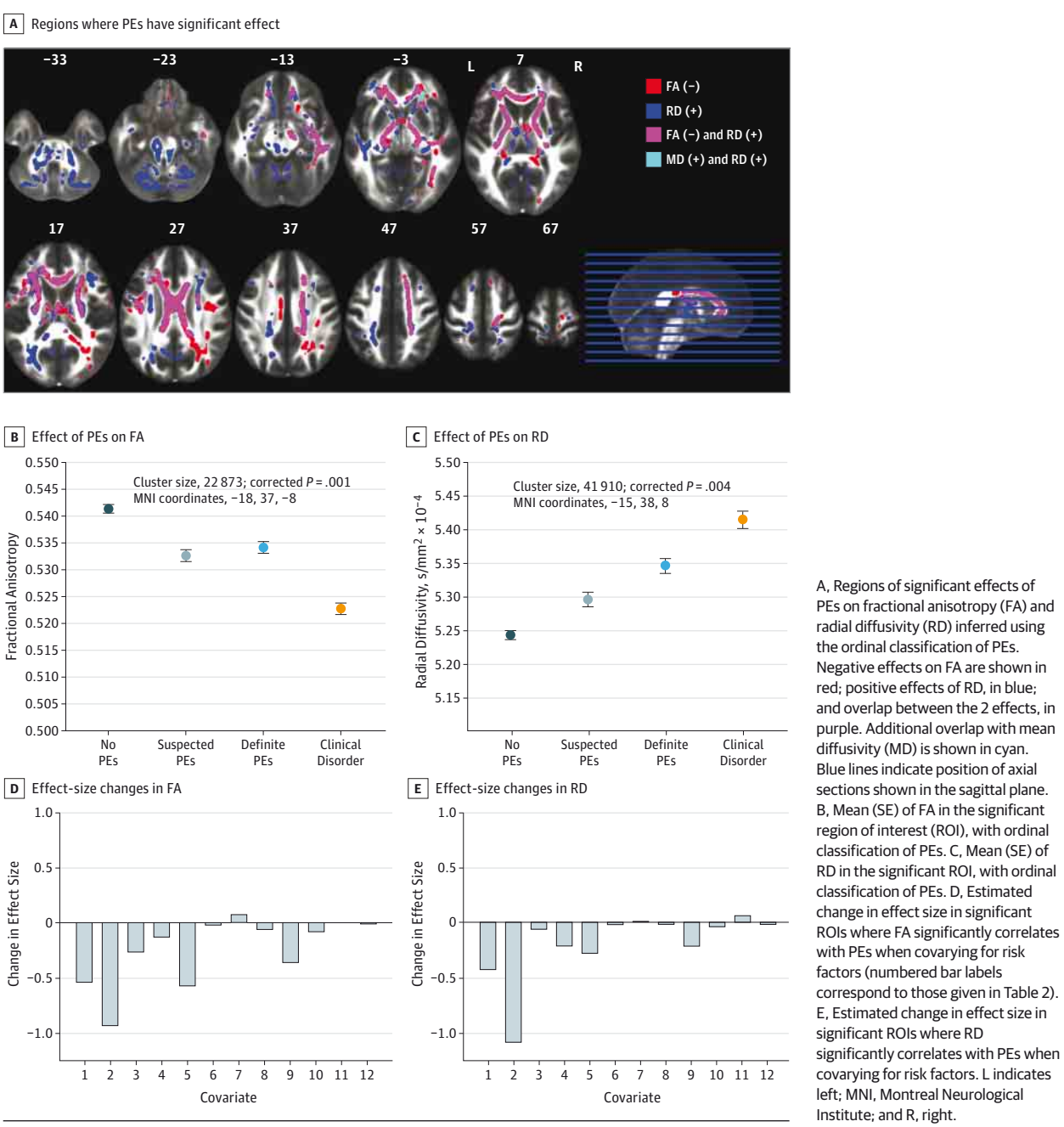
Social and Developmental Risk Factors

The association between PEs and each hypothesized risk factor are summarized in Table 2. Childhood IQ, CIS-R scores, parental social class, and maternal educational level all showed strong evidence of association with both binary and ordinal classifications of PEs (all $P < .01$). Evidence of an association was also observed for birth weight ($P < .05$) and for stressful life events ($P < .05$ only in the ordinal model) but not for the other factors examined.

Confounding Effect of Risk Factors

Changes in effect size owing to covariation for each risk factor in the 2 regions identified in the ordinal analysis are presented in Figure 2D-E. All risk factors showed small changes in effect size (<0.5 SDs) when controlled for except for CIS-R, which showed a large reduction (approximately 1 SD) in both FA and RD.

Figure 2. Tract-Based Spatial Statistics Results for Ordinal Classification of Psychotic Experiences (PEs) and Changes in Effect Size When Covarying for Risk Factors



A, Regions of significant effects of PEs on fractional anisotropy (FA) and radial diffusivity (RD) inferred using the ordinal classification of PEs. Negative effects on FA are shown in red; positive effects of RD, in blue; and overlap between the 2 effects, in purple. Additional overlap with mean diffusivity (MD) is shown in cyan. Blue lines indicate position of axial sections shown in the sagittal plane. B, Mean (SE) of FA in the significant region of interest (ROI), with ordinal classification of PEs. C, Mean (SE) of RD in the significant ROI, with ordinal classification of PEs. D, Estimated change in effect size in significant ROIs where FA significantly correlates with PEs when covarying for risk factors (numbered bar labels correspond to those given in Table 2). E, Estimated change in effect size in significant ROIs where RD significantly correlates with PEs when covarying for risk factors. L indicates left; MNI, Montreal Neurological Institute; and R, right.

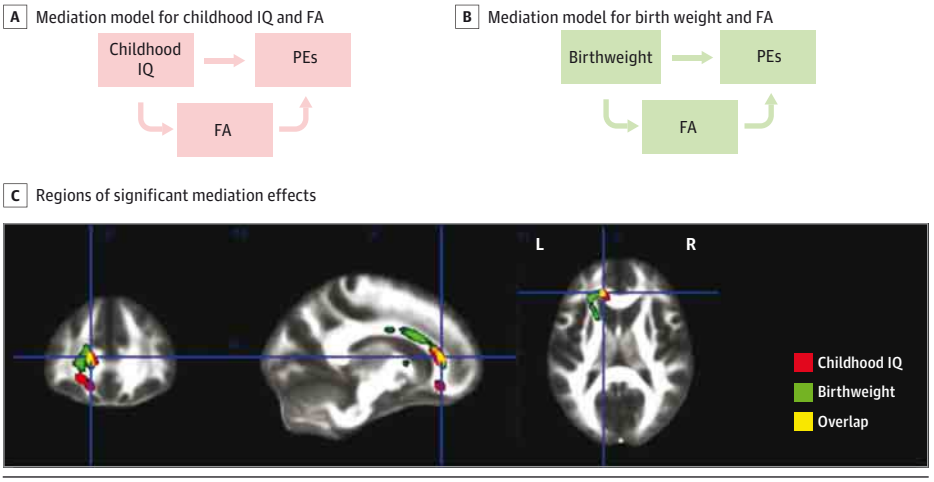
Mediation Effects

Results from the mediation analysis were consistent with FA partially mediating the effects of childhood IQ and birth weight on PEs. Mediation of childhood IQ peaked in the left anterior thalamic projections, the genu, and anterior portions of the corpus callosum and the left internal capsule (**Figure 3**). The mediation by FA in these regions constituted 7.9% of the total effect size ($\mu = 0.051$; $\beta_{11} = -0.710$; $P = .041$ corrected). The mediation of birth weight extended further into the corpus callosum and constituted 21.1% of the total effect size ($\mu = 0.004$; $\beta_{11} = -0.019$; $P = 6.20 \times 10^{-3}$). No other significant mediation effects were identified.

Discussion

We used DT-MRI and multicomponent relaxometry to identify changes in WM microstructure associated with PEs in a large nonclinical sample of young adults included in the ALSPAC cohort. Furthermore, we applied a novel voxelwise

Figure 3. Results of Voxelwise Mediation Analysis



A-B, Mediation effects for which there is evidence in regions of the tract-based spatial statistics skeleton. C, Regions on the white matter skeleton where fractional anisotropy (FA) significantly mediates the association between childhood IQ and psychotic experiences (PEs). L indicates left; R, right.

mediation analysis to test whether WM microstructure abnormalities mediate the effect of some putative risk factors for psychosis. This type of analysis provides insights into the developmental and pathologic mechanisms by which PEs and psychosis can arise.

A simple binary model of psychosis was compared with a continuum-based ordinal model. Both models showed an apparent reduction in FA compared with healthy controls in predominantly frontomedial pathways. The ordinal model revealed a more widespread pattern of affected regions both in FA and RD. One interpretation of this finding is that, although WM microstructure is affected in individuals with PEs, this effect is expressed in varying degrees related to the severity of PEs (Figure 2B and C). Alternatively, the continuum model may afford greater statistical power to detect the association. In any event, the continuum model could be seen as a better approach to detecting pathologic substrates along the spectrum of PEs and provide biological evidence for a continuum of psychosis.[21]

The location of WM changes in predominantly medial-frontal structures is consistent with previous studies[3,17,22-24] in early-stage schizophrenia and associated at-risk groups. Our results for FA, although in the expected direction (ie, reduced FA in patients with PEs), implicate pathways different from those recently reported[97] in a population-based cohort with PEs. This difference could be due to the modest sample size of that study and their younger age (13-16 years).

The application of mediation analysis to DT-MRI data within regions of interest has been reported.[98-103] However, to our knowledge, this is the first time the approach has been applied in a voxelwise analysis of microstructural imaging data, which enables a more spatially agnostic exploration of mediation effects. Mediation analysis applied in this manner identified regions of WM whose microstructure may mediate the contribution of risk factors to psychosis. Although several mostly environmental risk factors showed significant associations with PEs (Table 2), only the effects of childhood IQ and birth weight on the severity of PEs were consistent with mediation by WM microstructure.

However, the design of the study does not allow explicit differentiation of mediation effects from confounder effects, and causality cannot be conclusively determined. Such interpretations rely on assumptions regarding the likely direction of causality of effects, which may be multidirectional and interactive. A related limitation is that, although repeated measures of many variables and PEs are available in ALSPAC, MRI has been performed only once. Nevertheless, such analyses may help in understanding the data and generating hypotheses that may be tested in studies with longitudinal designs.[104] Such studies will shed light on how developmental and resilience factors can lead to both positive and negative changes in microstructural indices[105-107] and how these changes can manifest in the development of psychosis.[108]

For birth weight, it seems reasonable to infer that FA measured at age 20 years lies on the causal pathway between obstetric variables and PEs.[39-41] A recent study[76] has shown that cumulative risk based on a range of psychosis risk factors can contribute to microstructural changes in WM. The theoretical mediation effect on IQ, although measured in childhood years before the imaging, is less easy to interpret. It is possible that IQ at age 8 was affected by preexisting PEs or WM abnormalities at that age. One construal of the mediation analysis is that common neurodevelopmental factors may be associated with alterations in WM circuitry that manifest in childhood as reduced intellectual capacity and later contribute to PEs in early adulthood. Furthermore, the spatial overlap with mediation of birth weight indicates that such pathology may be related to obstetric difficulties. Indeed, the association between low birth weight, schizophrenia, and cognitive impairment is well established,[40] with hypoxia at birth being perhaps the critical factor.[47]

The regions implicated in this study are consistent with cognitive deficits seen in psychosis and brain changes observed in those with obstetric difficulties. For example, the genu of the corpus callosum is important for prefrontal executive function and social cognition,[109] anterior thalamic projections for motivation and alertness,[110] and the genu for executive dysfunction.[111] The same cohort has previously

shown altered connectome topology[112] similar to that seen in schizophrenia. The present study provides a neuropathologic basis for the alterations in connectome topology in that abnormal axon morphology is most likely impaired, contributing to dysconnectivity at the whole-brain level.

Birth weight and childhood IQ in our sample were within the reference ranges and thus not inherently pathologic. However, the combination of highly sensitive WM imaging techniques and the continuum approach to psychopathology may have uncovered associations that might have otherwise escaped detection.

Another interesting finding is the apparent absence of mediation of the CIS-R score, a measure of common psychopathology, despite correlating with PEs[113] and DT-MRI indices across many brain regions (eAppendix 8 in the Supplement). There is a marked reduction in effect size when the measure is controlled for (Figure 2E), indicating that CIS-R is a confounder (ie, depression contributes to both PEs and changes in WM) or a collider factor (both PEs and WM contribute to depression).

Other risk factors did not yield any significant associations with either PEs or WM. In the case of substance use (eg, cannabis), this lack of association may reflect its biochemically mediated effects[114] that do not, over the timescales considered and levels of consumption[115] in our participants aged 20 years, cause structural changes in WM.[116] Frequency of consumption may be insufficient to characterize risk exposure; age of first use and total lifetime consumption may be more predictive. In addition, our drug consumption variables had a high proportion of missing values that were imputed, which may contribute to false-negatives. Finally, it has been proposed[117] that psychosis associated with cannabis clusters separately from typical neurodevelopmental risk factors, such as low IQ.

No effects were apparent in myelination indices (myelin water fraction or R1), but the indices did correlate with childhood IQ (eAppendix 8 in the Supplement). Taken at face value, the absence of myelination effects on PEs could mean that changes in DT-MRI are driven by other factors, such as axon density, diameter, or orientational dispersion, as reported[118] in older ultra-high-risk and first-episode patients. The changes in FA and RD are found in regions overlapping with those that have previously shown reduced myelination in individuals with schizophrenia and those at ultra-high risk.[7,14] Hence, the observed changes in DT-MRI metrics could reflect a pathologic process that precedes the loss of myelination,[119,120] and that manifest only at more advanced disease states. Another explanation is that there may be different sensitivities of mcDESPOT to myelination compared with magnetization transfer ratio[121] and DT imaging.[122]

This study has several advantages over previous work. To our knowledge, it is the first to identify and localize (using statistical mapping) mediation effects in WM of specific risk factors for psychosis. This study goes beyond reporting associations between risk factors and changes in WM.[76] In addition, we used a large, well-characterized homogeneous cohort, which afforded us considerable statistical power. The nature of the cohort may, however, be a limitation in terms of the generalizability of the findings. Attrition and missing data are also a problem in such cohorts, which can be only partially mitigated using multiple imputation.

Finally, as noted, although our analysis points strongly to the role of WM as a mediator between risk factors and PEs, the direction of causation cannot be conclusively determined from the available data.

Conclusions

We have shown that WM alterations, similar to those seen in schizophrenia, are present in a large epidemiologic cohort of young adults with PEs[20] who were not identified from a selected help-seeking clinical population.

The regions implicated comprise pathways critical to higher order cognitive function. We propose that atypical developmental trajectories contribute to behavioral and cognitive abnormalities, such as those seen in psychosis, via abnormalities in this WM circuitry. We recommend that future studies focus on mediation to further unravel the associations between PEs, risk factors for psychosis, and brain structure.

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