2015

Evidence from structural and diffusion tensor imaging for frontotemporal deficits in psychometric schizotypy

P. DeRosse
Northwell Health

G. C. Nitzburg
Northwell Health

T. Ikuta

B. D. Peters
Northwell Health

A. K. Malhotra
Hofstra Northwell School of Medicine

See next page for additional authors

Schizophrenia Bulletin vol. 41 no. 1 pp. 104–114, 2015
doi:10.1093/schbul/sbu150
Advance Access publication November 11, 2014

Evidence From Structural and Diffusion Tensor Imaging for Frontotemporal Deficits in Psychometric Schizotypy

Pamela DeRosse*[,1,2], George C. Nitzburg[1], Toshikazu Ikuta[3], Bart D. Peters[1,2], Anil K. Malhotra[1,2,4], and Philip R. Szeszko[1,2,4]

[1]Center for Translational Psychiatry, The Feinstein Institute for Medical Research, Manhasset, NY; [2]Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore–Long Island Jewish Health System, Glen Oaks, NY; [3]Department of Communication Sciences and Disorders, School of Applied Sciences, University of Mississippi, University, MS; [4]Hofstra North Shore – LIJ School of Medicine, Departments of Psychiatry and Molecular Medicine, Hempstead, NY

*To whom correspondence should be addressed; The Zucker Hillside Hospital, North-Shore-Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004, US; tel: 718-470-8601, fax: 718-343-1659, e-mail: pderosse@lij.edu

Background: **Previous studies of nonclinical samples exhibiting schizotypal traits have provided support for the existence of a continuous distribution of psychotic symptoms in the general population. Few studies, however, have examined the neural correlates of psychometric schizotypy using structural and diffusion tensor imaging (DTI).** ***Methods:*** **Healthy volunteers between the ages of 18 and 68 were recruited from the community and assessed using the Schizotypal Personality Questionnaire and received structural and DTI exams. Participants with high (N = 67) and low (N = 71) psychometric schizotypy were compared on gray and white matter volume, and cortical thickness in frontal and temporal lobe regions and on fractional anisotropy (FA) within 5 association tracts traversing the frontal and temporal lobes.** ***Results:*** **Higher levels of schizotypy were associated with lower overall volumes of gray matter in both the frontal and temporal lobes and lower gray matter thickness in the temporal lobe. Regionally specific effects were evident in both white matter and gray matter volume of the rostral middle frontal cortex and gray matter volume in the pars orbitalis. Moreover, relative to individuals who scored low, those who scored high in schizotypy had lower FA in the inferior fronto-occipital fasciculus as well as greater asymmetry (right > left) in the uncinate fasciculus.** ***Conclusions:*** **These findings are broadly consistent with recent data on the neurobiological correlates of psychometric schizotypy as well as findings in schizotypal personality disorder and schizophrenia and suggest that frontotemporal lobe dysfunction may represent a core component of the psychosis phenotype.**

Key words: schizotypy/MRI/DTI/healthy subjects

Introduction

Large-scale genome-wide association studies[1,2] have provided strong evidence that the etiology of schizophrenia (SZ) is complex and multifactorial. Moreover, such studies have demonstrated that hundreds to thousands of common genetic variants with small effects contribute to the behavioral expression of psychotic-like phenomena across traditional diagnostic boundaries.[3] Such findings provide strong support for a dimensional model in which phenomenological, genetic, and cognitive factors interact to affect the behavioral expression and severity of psychotic symptoms.[4] At the phenotypic level, evidence suggests the existence of a continuous distribution of psychotic symptoms in the general population ranging from mild, or subclinical, to severe and clinically significant, with additional evidence indicating etiological continuity between subclinical and clinically significant psychosis phenotypes.[5] The continuity between subclinical psychosis at the population level and the clinically significant levels of psychosis observed in SZ spectrum disorders may provide a unique opportunity to elucidate the pathophysiology of psychotic disorders free of the potentially confounding effects of treatment-related factors.

Although several approaches have been employed to measure subclinical psychosis in nontreatment seeking populations, the measurement of schizotypal traits is among the most common.[6] Schizotypy was initially conceptualized by Rado[7], and later elaborated by Meehl[8,9], to denote the genetically determined predisposition to SZ and may be measured in nonclinical samples using psychometric self-report questionnaires such as the Schizotypal Personality Questionnaire (SPQ)[10] or the Chapman Scales.[11] Studies have generally demonstrated

schizotypy to have dimensional factor structures analogous to those observed in SZ.[12–14] Moreover, several independent studies[15–18] have shown an increased incidence of schizotypy in relatives of SZ patients that are likely related to shared genetic variation.[19,20] Thus, the examination of psychometric schizotypy within nonpsychiatric populations is ideally suited for studies seeking to better characterize the neurobiology of psychosis.[21]

Several studies have examined the neurobiological basis of schizotypal personality disorder (SPD), a disorder characterized by severe schizotypal traits including asocial tendencies, difficulties with language, paranoia, odd behavior, and magical thinking. Recent reviews[22–24] suggest that at the structural level, SPD is associated with temporal lobe abnormalities comparable to those observed in SZ while frontal lobe regions may be more spared. Moreover, the aforementioned reviews also suggest that low fractional anisotropy (FA), a measure broadly associated with white matter integrity, in the uncinate fasciculus (UF) and temporal lobe is present in SPD; a finding generally consistent with those observed in SZ.[25] To date, however, relatively few studies have examined the neurobiological basis of psychometric schizotypy, or subclinical psychosis, in otherwise healthy adults.

Although several studies have reported structural differences between healthy participants with high levels of subclinical positive symptoms vs low levels, overall findings have been mixed.[26–28] However, several studies have reported cortical thickness abnormalities among healthy individuals with high levels of schizotypy compared with low levels[29,30] that are broadly consistent with findings in SZ patient samples.[31] Additionally, diffusion tensor imaging (DTI) studies have provided complementary evidence for white matter alterations in psychometrically defined schizotypy similar to those observed in SZ, but these findings have also been inconsistent. While some studies have found higher FA in some regions but lower FA in others,[32] others have found consistent reductions in FA in several regions[33,34] and yet others have found increases in FA[35] related to high levels of subclinical psychotic symptoms. Taken together these studies implicate aberrant neurodevelopmental processes in subclinical psychosis that are similar to those believed to underlie the neurobiology of SZ without the associated confound of antipsychotic medications and suggest that the examination of psychometric schizotypy in nonpsychiatric populations may provide insight into the neurobiology of psychosis. Samples examined in prior work, however, have been relatively small and have not comprehensively assessed the brain using multimodal imaging. Moreover, several prior studies examined adolescent and young adult samples that may still be at risk for developing psychosis. In the present study, we thus investigated both gray and white matter structural variation in relation to psychometric schizotypy using structural and DTI in a large sample of healthy adults. Consistent with observations of less gray matter volume in SZ[36] and with models of frontotemporal lobe dysfunction in SZ,[37–39] we hypothesized that individuals characterized by high schizotypy would demonstrate less gray matter volume, lower cortical thickness, and lower FA in frontal and temporal lobe regions, compared with those characterized by low schizotypy.

Methods

Participants

The present sample comprised 138 (72 M/66 F) healthy volunteers ages 18–68 ($Mean_{age}$ = 35.69 ± 13.02). Participants were recruited from the general population via word of mouth, newspaper and internet advertisements, and posted fliers for an National Institute of Mental Health-funded study of subclinical psychosis (MH086756 to P.D.). Participation in the imaging component of the study was optional. A total of 38 additional participants were screened for participation in the present study but were not included because they met one or more exclusion criteria. Exclusion criteria included having a first-degree family member with a psychotic illness, present or past psychotic or affective disorder diagnosis as determined by clinical interview using the nonpatient edition of the Structured Clinical Interview for the DSM-IV, Non-Patient edition (SCIDI-N/P),[40] evidence of an intellectual disability (operationally defined as a Wide Range Achievement Test-Third Edition-Reading Subtest [WRAT-3] reading score of <70), active or recent substance abuse (as assessed by urine toxicology testing), magnetic resonance imaging (MRI) contraindications (eg, pacemaker, internal defibrillator, infusion pump, insulin pump, cochlear implant, hearing aid, iron/steel on or in the body), pregnancy, or significant medical illness as determined by a medical history questionnaire. This study was approved by the North Shore-Long Island Jewish Health System Institutional Review Board and all participants provided written, informed consent.

Clinical Assessments

All assessments were conducted by Master's or PhD level clinicians or psychometricians who have extensive training in the administration of clinical and cognitive assessments.

Diagnostic Assessments. Participants were initially administered the SCIDI-N/P[40] to rule out a past or present affective or psychotic disorder. Information obtained from the SCID was compiled into a narrative case summary and presented to 2 senior members of the Zucker Hillside Hospital clinical faculty. Absence of pathology was determined by consensus after the presentation of the narrative case summary and discussion of any relevant symptomatology.

Psychometric Schizotypy. To assess schizotypal symptom severity we utilized the SPQ,[10] which is a well-validated, 74-item, self-report questionnaire. The SPQ

provides an overall measure of psychometric schizotypy that includes 9 dimensions, each reflecting a criterion for DSM-IV schizotypal personality disorder, including ideas of reference, excessive social anxiety, odd beliefs or magical thinking, unusual perceptual experiences, odd or eccentric behavior, no close friends, odd speech, constricted affect, and suspiciousness.

Estimated IQ. We utilized the WRAT-3 as an estimate of IQ. The WRAT-3 is a test that assesses single word reading skill and is highly correlated with full scale IQ.[41]

Handedness. All individuals were classified as either right or left-handed based on a modified version of the Edinburgh Inventory. The total number of right and left hand items was scored and the laterality quotient was computed according to the following formula: (Total R − Total L)/(Total R + Total L) yielding a range from +1.00 (totally dextral) to −1.00 (totally nondextral).

Magnetic Resonance Imaging

Image Acquisition. MRI exams were conducted at the North Shore University Medical Center on a GE 3T Signa HDx, whole body superconducting imaging system. A radiologist reviewed all scans for gross anatomic pathology that would preclude participation in this study. We minimized movement by stabilizing the head with cushions prior to scanning. We acquired 3D spoiled gradient images using a 1-mm thick slice acquisition with the following image parameters: repetition time (TR) = 7.5 ms, echo time (TE) = 3 ms, matrix = 256 × 256, field of view (FOV) = 240 mm, 216 contiguous images. We also acquired DTI data using a total of 36 DTI volumes from each subject, including 31 volumes with diffusion gradients applied along 31 nonparallel directions with b = 1000 s/mm^2 and, and 5 volumes without diffusion weighting (b = 0 s/mm^2). Each volume consisted of 51 contiguous 2.5-mm axial slices acquired parallel to the anterior-posterior commissural line using a ramp sampled, spin-echo, single-shot echoplanar imaging method (TR = 1400 ms, TE = min, matrix = 128 × 128, FOV = 240 mm).

Structural Imaging Methods. Cortical reconstruction and volumetric segmentation was performed using Freesurfer image analysis software (version 5.0.0), which is documented and freely available online (http://surfer.nmr.mgh.harvard.edu). Technical details of these procedures are described in prior publications.[42–44] Processing includes motion correction, removal of non-brain tissue,[45] automated Talairach transformation, segmentation of the subcortical regions and deep gray matter structures[43] intensity normalization,[46] tessellation of the gray matter-white matter boundary, automated topology correction,[47,48] and surface deformation following intensity gradients.[49] Gray matter volume, white matter volume, and cortical thickness measures were computed and subsequently assigned to either the frontal or temporal lobes. Individual regions comprising the frontal (N = 11) and temporal (N = 9) lobes were determined a priori based on prior work.[50] The frontal lobe included the superior frontal, rostral middle frontal, caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral orbital frontal, medial orbital frontal, precentral, paracentral, and frontal pole regions. The temporal lobe included the superior temporal, middle temporal, inferior temporal, banks of the superior temporal sulcus, fusiform gyrus, transverse temporal, entorhinal, temporal pole, and parahippocampal regions. These regions are illustrated in figure 1.

DTI Methods and Tractography. Image processing was conducted using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/). Eddy-current induced distortions and head-motion displacements were corrected through affine registration of the 31 diffusion volumes to the first b0 volume using FSL's Linear Registration Tool (FLIRT).[51] The b-vector table (ie, gradient directions) for each participant was then adjusted according to the rotation parameters of this linear correction. Non-brain tissue was removed using FSL's Brain Extraction Tool. FA was then calculated at each voxel of the brain by fitting a diffusion tensor model to the raw diffusion data using weighted least squares in FSL's Diffusion Toolbox.

FA within 5 association tracts traversing the frontal and temporal lobes were assessed, including the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), cingulum bundle, superior longitudinal fasciculus (SLF), and UF. These tracts are illustrated in figure 2. Detailed delineation criteria regarding the individual tracts are provided in our prior study.[52] Within-voxel probability density functions of the principal diffusion direction were estimated using Markov Chain Monte Carlo sampling in FSL's BEDPOSTX tool.[53] A spatial probability density function was then estimated across voxels based on these local probability density functions using FSL's PROBTRACKX tool,[53] in which 5000 samples were taken for each input voxel with a 0.2 curvature threshold, 0.5-mm step length, and 2000 steps per sample. For each tract, seed masks, way-points, termination, and exclusion masks were defined on the MNI152 T1 1-mm template. Masks were normalized to each subjects' diffusion space using FLIRT,[51] applying the affine parameters obtained by coregistering the first b0 volume to the MNI152 1-mm T1 brain. The resulting tracts were thresholded at a normalized probability value.

Statistical Analysis

In all analyses, the distribution of the dependent measures was first inspected to ensure normality. Although

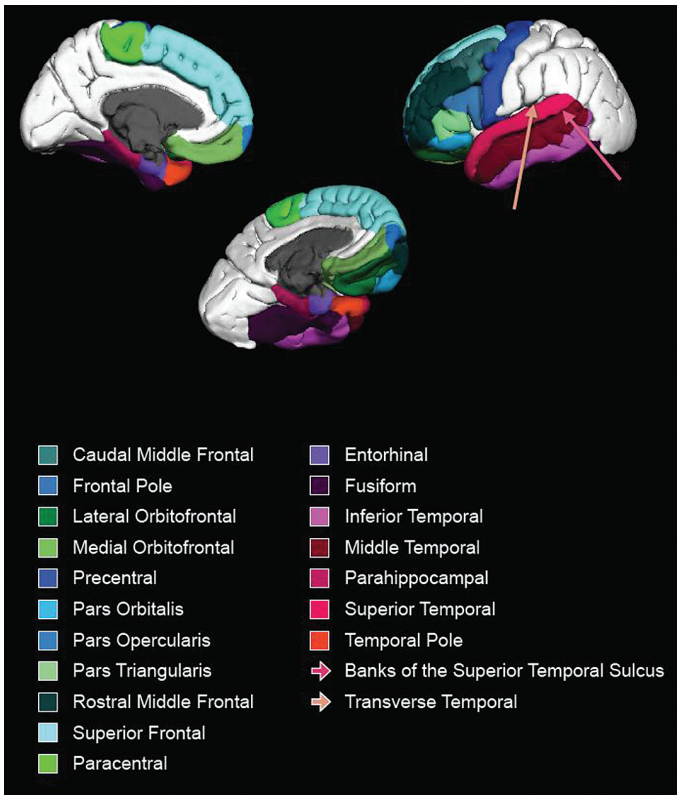

Fig. 1. Freesurfer segmentation of fronto-temporal regions examined in the present study for association to psychometric schizotypy.

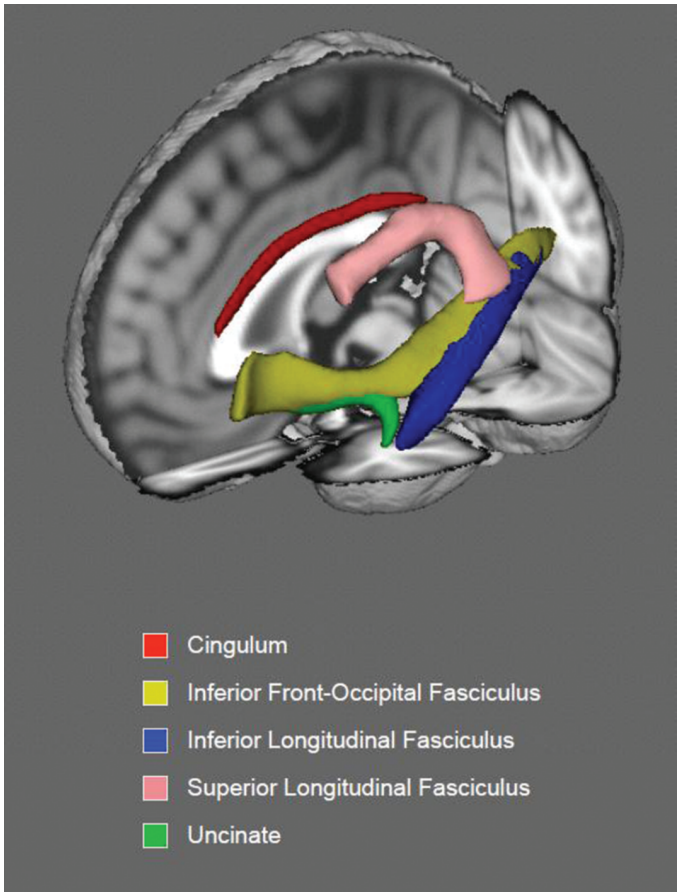

Fig. 2. Five association tracts traversing the frontal and temporal lobes examined in the present study for association to psychometric schizotypy.

we initially considered using the SPQ Total score as a continuous measure in regression models, this approach was not statistically valid because neither the SPQ scores, nor the residuals produced by the regression models, were normally distributed. Therefore, we dichotomized the sample, using a median split, into those who scored higher (high schizotypy: $N = 67$) and those who scored lower (low schizotypy: $N = 71$) on the SPQ.

Initially, group differences in demographic characteristics were assessed using independent group's t tests or chi-square tests. Repeated measures ANCOVA was used to assess group differences in brain structure volume and thickness, and FA within tracts. In brain structure volume and cortical thickness analyses, group served as the between-subjects factor. We summed right and left hemisphere volumes for gray matter and white matter structures, respectively and averaged right and left cortical thickness given the lack of group × hemisphere interactions for these measures. Gray matter volume, white matter volume, and cortical thickness served as the within-subjects factors in separate analyses investigating the frontal and temporal lobes. We used the Greenhouse-Geisser correction in these analyses given that the Mauchly's test of sphericity was significant. There were significant group by hemisphere effects for the FA measures and thus, we did not average these measures for subsequent analyses. Thus, hemisphere served as a within-subjects factor in FA analyses, which were conducted separately by tract given their functional and neuroanatomical heterogeneity.[52] In all analyses, age, sex, and intracranial volume were included as covariates. Alpha was set to .05 and all analyses were 2 tailed.

Results

Comparison of high vs low schizotypy groups on the total SPQ score confirmed that the groups significantly differed ($M_{High} = 8.52 \pm 6.66$ vs $M_{Low} = 0.75 \pm 0.82$; $t = 9.49$; $P < .001$). Moreover, the relatively low mean of the high schizotypy group suggested symptom levels were reflective of subclinical psychometric schizotypy rather than schizotypal personality disorder. Comparison of high and low schizotypy groups on additional demographic characteristics revealed no significant differences (all P's > .05) in age ($M_{High} = 36.17 \pm 13.93$ vs $M_{Low} = 35.23 \pm 12.18$), estimated IQ ($M_{High} = 101.91 \pm 11.09$ vs $M_{Low} = 101.39 \pm 9.80$), or handedness ($M_{High} = 0.77 \pm 0.50$ vs $M_{Low} = 0.80 \pm 0.38$). Examination of sex distributions revealed that the proportion of females in the high schizotypy group (56.72%) was significantly greater than in the low schizotypy group (39.44%) ($\chi^2 = 4.13$, $P = .04$).

Mean (SD) values for the frontal and temporal lobe white matter and gray matter volumes are provided in table 1 with univariate analyses provided for descriptive purposes only. In the primary repeated measures ANCOVA, there were significant main effects of group for both frontal ($F_{(1,133)} = 4.50$, $P = .036$) and temporal ($F_{(1,133)} = 4.40$, $P = .038$) gray matter volumes such that high schizotypy individuals had less volume overall compared with low schizotypy individuals. There were also significant group × region interactions for frontal white ($F_{(1,133)} = 2.40$, $P = .049$) and gray ($F_{(1,133)} = 3.89$, $P = .003$) matter volume. Post-hoc analysis indicated lower volumes of white matter in the rostral middle frontal cortex ($F_{(1,133)} = 3.95$, $P = .049$), gray matter pars orbitalis ($F_{(1,133)} = 4.06$, $P = .046$), and gray matter rostral middle frontal cortex ($F_{(1,133)} = 8.15$, $P = .005$) in high schizotypy participants compared with low schizotypy participants. No main effects of group were observed for frontal or temporal white matter volume. There was a significant main effect of group for temporal gray matter thickness ($F_{(1,133)} = 4.40$, $P = .038$), but not for frontal gray matter thickness. Specifically, high schizotypy participants exhibited lower gray matter thickness compared with low schizotypy participants. The group-by-region interactions were not statistically significant for gray matter thickness in either the frontal or temporal lobes (P's > .05). The frontal and temporal lobe gray matter thickness measures are provided in table 2 with univariate analyses provided for descriptive purposes only.

Analysis of FA using the tract-based measures revealed a significant main effect of group for the IFOF ($F_{(1,133)} = 4.90$, $P = .029$) such that high schizotypy individuals had lower FA compared with low schizotypy individuals. In addition, there was a significant group × hemisphere interaction for the UF ($F_{(1,133)} = 6.29, 133$, $P = .013$). Post-hoc analysis revealed that high schizotypy individuals had significantly greater asymmetry (R > L; $t_{(136)} = -2.78$, $P = .006$) in the UF compared with low schizotypy individuals. There were no significant group differences in FA in either the right or left UF. Neither the main effects of group nor group-by-hemisphere interactions were statistically significant for the SLF, ILF, or cingulum bundle. Mean (SD) FA values for the tracts are provided in table 3 with univariate analyses provided for descriptive purposes only.

To determine whether having both volume and thickness abnormalities was associated with greater psychometric schizotypy, we conducted 3 supplementary logistic regression analyses to predict group membership for regions that differed significantly between groups including gray matter volume (rostral middle frontal and pars orbitalis), white matter volume (rostral middle frontal), and average temporal lobe gray matter thickness. Classes of regions (gray matter, white matter, and thickness) were entered into the logistic regression in blocks to determine whether the overall model improved significantly by adding the last block. Thus, as an example, in one logistic regression gray matter and white matter volumes were entered into the model as the first block followed by temporal gray matter thickness in the second block to determine whether the addition of the latter

Table 1. Average Frontal and Temporal Gray Matter Volumes (mm^3) for Healthy Individuals With High and Low Psychometric Schizotypy

	White Matter					Gray Matter				
	Low SPQ (N = 71)	High SPQ (N = 67)				Low SPQ (N = 71)	High SPQ (N = 67)			
	Mean (SD)	Mean (SD)	95% CI[a], Low to High	F	P	Mean (SD)	Mean (SD)	95% CI[a], Low to High	F	P
Frontal										
Caudal middle frontal	13 230 (2217)	12 543 (1954)	−220 to 860	1.38	.24	14 185 (2427)	13 476 (2333)	−345 to 878	0.74	.39
Frontal pole	546 (114)	533 (113)	−34 to 42	0.04	.83	1963 (288)	1972 (312)	−125 to 76	0.24	.63
Lateral orbitofrontal	13 903 (1576)	13 259 (1939)	−170 to 598	1.21	.27	16 685 (1732)	15 972 (1966)	−146 to 644	1.55	.23
Medial orbitofrontal	7588 (1245)	7126 (1393)	−153 to 463	0.99	.32	11 329 (1487)	10 822 (1459)	−234 to 493	0.50	.48
Precentral	27 362 (3503)	26 637 (3710)	−933 to 763	0.04	.84	28 722 (3285)	27 526 (3246)	−387 to 1252	1.09	.30
Pars orbitalis	2164 (280)	2074 (379)	−70 to 86	0.04	.84	5550 (718)	5191 (771)	4 to 438	4.06	<.05
Pars opercularis	7196 (1239)	7107 (1457)	−559 to 99	1.91	.17	9610 (1461)	9572 (1729)	−707 to 66	2.64	.11
Pars triangularis	6713 (878)	6494 (1122)	−230 to 229	0.07	.79	8828 (1313)	8658 (1388)	−476 to 281	0.26	.61
Rostral middle frontal	27 440 (3546)	25 530(4132)	4 to 1888	3.95	<.05	36 893 (4552)	34 147 (5074)	512 to 2823	8.15	.01
Superior frontal	37 816 (4209)	35 842 (5431)	−157 to 1891	2.80	.10	48 954 (4727)	46 567 (6011)	−23 to 2248	3.754	.06
Paracentral	8590 (1125)	8318 (1365)	−287 to 393	0.10	.758	7840 (946)	7548 (1091)	−133 to 416	1.04	.31
Temporal										
Temporal pole	1384 (204)	1327 (217)	−45 to 78	0.28	.60	5210 (608)	5161 (563)	−224 to 159	0.11	.74
Superior temporal	14 562 (1872)	14 032 (2268)	−431 to 456	0.01	.95	25 175 (2778)	24 202 (2995)	−395 to 920	0.62	.43
Middle temporal	11 847 (1450)	11 487 (1833)	−400 to 321	0.05	.83	25 354 (3104)	24 092 (3274)	−301 to 1185	1.39	.24
Inferior temporal	12 156 (1637)	11 772 (2019)	−508 to 345	0.14	.71	23 280 (3191)	22 772 (3221)	−1080 to 543	0.43	.51
Entorhinal	1587 (351)	1540 (402)	−123 to 91	0.09	.77	4203 (720)	3955 (591)	−74 to 320	1.52	.22
Parahippocampal	3521 (453)	3307 (491)	−3 to 253	3.73	.06	4730 (516)	4489 (607)	2 to 342	4.00	<.05
Fusiform	13 605 (1801)	13 179 (2053)	−488 to 440	0.01	.92	21 668 (2584)	20 523 (2580)	−165 to 1207	2.26	.14
Banks of superior temporal sulcus	5779 (891)	5711 (1045)	−381 to 162	0.64	.43	5325 (738)	5196 (835)	−251 to 148	0.26	.61
Transverse	1431 (203)	1424 (227)	−89 to 39	0.60	.44	2172 (391)	2088 (346)	−90 to 127	0.12	.74

Note: df = 138. SPQ, Schizotypal Personality Questionnaire.
[a]Adjusted for age, sex, and intracranial volume. Analyses are presented for descriptive purposes only.

Table 2. Average Frontal and Temporal Cortical Thickness for Individuals With High and Low Psychometric Schizotypy

	Low SPQ (N = 71)		High SPQ (N = 67)				
	Mean	(SD)	Mean	(SD)	95% CI[a], Low to High	F	P
Frontal cortical thickness							
Caudal middle frontal	2.62	0.14	2.30	0.13	−0.02 to 0.06	0.87	.35
Frontal pole	2.89	0.22	2.85	0.22	−0.04 to 0.11	0.99	.32
Lateral orbitofrontal	2.62	0.12	2.61	0.15	−0.02 to 0.06	0.68	.41
Medial orbitofrontal	2.36	0.13	2.37	0.12	−0.06 to 0.03	0.49	.49
Precentral	2.60	0.10	2.56	0.11	−0.003 to 0.06	3.26	.07
Pars orbitalis	2.83	0.17	2.78	0.17	−0.01 to 0.10	2.78	.10
Pars opercularis	2.63	0.13	2.61	0.11	−0.03 to 0.04	0.05	.83
Pars triangularis	2.54	0.13	2.54	0.14	−0.05 to 0.04	0.01	.93
Rostral middle frontal	2.42	0.12	2.40	0.12	−0.02 to 0.05	0.69	.41
Superior frontal	2.75	0.13	2.74	0.12	−0.02 to 0.05	0.55	.46
Paracentral	2.44	0.10	2.41	0.11	−0.01 to 0.06	2.36	.13
Temporal cortical thickness							
Temporal pole	3.81	0.26	3.82	0.26	−0.108 to 0.073	0.14	.71
Superior temporal	2.83	0.13	2.78	0.12	0.003 to 0.083	4.54	.04
Middle temporal	2.96	0.13	2.93	0.13	−0.007 to 0.073	2.73	.10
Inferior temporal	2.88	0.12	2.86	0.13	−0.015 to 0.064	1.52	.22
Entorhinal	3.68	0.27	3.55	0.28	0.034 to 0.225	7.16	.01
Parahippocampal	2.76	0.25	2.73	0.27	−0.036 to 0.132	1.29	.26
Fusiform	2.77	0.12	2.73	0.12	0.004 to 0.077	4.77	.03
Banks of the superior temporal sulcus	2.54	0.13	2.52	0.12	−0.023 to 0.054	0.63	.43
Transverse	2.45	0.15	2.42	0.17	−0.029 to 0.075	0.76	.38

Note: df = 138. SPQ, Schizotypal Personality Questionnaire.
[a]Adjusted for age, sex, and intracranial volume. Analyses are presented for descriptive purposes only.

Table 3. Average Fractional Anisotropy Values for Healthy Individuals With High and Low Psychometric Schizotypy

	Low SPQ (N = 71)		High SPQ (N = 67)				
	Mean	(SD)	Mean	(SD)	95% CI[a]	F	P
Fractional anisotropy (FA)							
Cingulum							
Left	0.563	0.051	0.557	0.044	−0.015 to 0.015	0.001	.98
Right	0.533	0.046	0.535	0.050	−0.02 to 0.013	0.16	.69
Inferior fronto-occipital fasciculus							
Left	0.546	0.026	0.536	0.024	0.0003 to 0.015	4.21	.04
Right	0.542	0.026	0.532	0.024	0.001 to 0.017	4.66	.03
Inferior longitudinal fasciculus							
Left	0.565	0.035	0.557	0.034	−0.006 to 0.017	0.87	.35
Right	0.552	0.039	0.545	0.031	−0.008 to 0.016	0.46	.50
Superior longitudinal fasciculus							
Left	0.518	0.036	0.513	0.037	−0.01 to 0.015	0.14	.71
Right	0.521	0.03.	0.520	0.032	−0.012 to 0.01	0.03	.86
Uncinate fasciculus							
Left	0.510	0.0329	0.504	0.032	−0.007 to 0.016	0.58	.45
Right	0.527	0.0345	0.534	0.032	−0.019 to 0.004	1.75	.19

Note: df = 138. SPQ, Schizotypal Personality Questionnaire.
[a]Adjusted for age, sex, and intracranial volume. Analyses are presented for descriptive purposes only.

variable significantly improved the overall model. None of the regression models were significant ($P > .05$) suggesting that no particular abnormality predicted group membership above and beyond the others.

Supplementary ANCOVA were conducted using 3 groups (low, medium, and high psychometric schizotypy) in contrast to the median split approach to further examine the relationship between subclinical symptoms

and our imaging measures; these analyses yielded results consistent with our original findings. Moreover, the most robust effects were identified between individuals with the highest SPQ total scores compared with the other groups. Specifically, patients with the highest SPQ total scores had significantly ($P < .05$) lower FA within the IFOF, less total gray and white matter in the rostral middle frontal gyrus, lower average temporal thickness, and less total gray matter in the pars orbitalis compared with the other 2 groups. Trend level effects ($P = .08$) for a group-×-hemisphere interaction (likely reflecting the lower statistical power) were evident for asymmetry within the UF such that individuals with the highest total SPQ total scores demonstrated greater asymmetry compared with the other groups.

Although we used sex as a covariate in our analyses, we conducted ancillary analyses by removing the 10 youngest males with low total schizotypy scores from the analysis to better match the groups for sex, which served to equate the sex distribution across groups ($P = .22$) while maintaining the age match, and reran all of our primary analyses. The group main effects for FA in the IFOF, UF FA asymmetry, rostral middle frontal white and gray matter volume, and pars orbitalis gray matter volume all remained statistically significant (Ps > .05).

Discussion

The results of this investigation indicated an association between psychometric schizotypy and measures of gray and white matter using both structural and DTI. Specifically, our study indicated that otherwise healthy adults who exhibit higher levels of psychometric schizotypy demonstrated less frontal and temporal lobe gray matter and lower temporal lobe gray matter thickness compared with participants characterized as lower in schizotypy. Regionally specific effects were also evident such that individuals characterized as higher in psychometric schizotypy had less gray and white matter volume specifically within the rostral middle frontal region compared with individuals characterized as lower in schizotypy. Investigation of cortical thickness measures indicated that individuals higher in schizotypy demonstrated lower temporal (but not frontal) cortical thickness compared with individuals lower in schizotypy. Moreover, the use of probabilistic tractography indicated that compared with individuals characterized as lower in psychometric schizotypy, those who were characterized as higher in schizotypy had lower FA in the IFOF as well as differences in UF asymmetry. Strengths of the current study include the large sample, comprised of healthy adults with no history of an Axis I disorder, and no history of psychotropic medication exposure and the use of multimodal imaging measures.

It is difficult to compare our findings to prior work given that few studies have investigated psychometric schizotypy, especially across a broad range of imaging measures. Our findings are generally consistent, however, with recent data suggesting that high levels of positive schizotypy in otherwise healthy adults is associated with significantly less gray matter volume in medial prefrontal, orbitofrontal, and temporal cortical regions.[28] Our findings also converge with prior work in patients with SZ[54] and SPD,[24] which identified less gray matter in frontal and temporal lobe regions. Moreover, our study identified less gray and white matter that was localized to the rostral middle frontal cortex among individuals higher in psychometric schizotypy compared with those lower in schizotypy. Consistent with our findings, several prior neuroimaging studies in SZ reported less gray[55] and white[56] matter in the rostral middle frontal region and thus, dysfunction involving this region may be particularly relevant for the overlap in phenotypic expression between SZ and schizotypy. It is also noteworthy that dysfunction within the rostral middle frontal region may contribute to abnormal executive functioning,[57] a cognitive domain that is impaired in both SZ[58] and SPD.[59]

Prior work reported that compared with patients with SZ, patients with SPD may demonstrate preservation of some frontal lobe white matter regions[60,61] that could, at least in part, reflect a compensatory mechanism. In contrast, temporal gray matter abnormalities may be a feature shared by both patients with SZ and SPD. This hypothesis is consistent with volumetric findings from the current study wherein a main effect of group was not apparent for frontal lobe white matter volume in contrast to the gray matter where a main effect of group was observed. This suggests white matter volume at the gross anatomic level in the frontal (perhaps except for the rostral middle frontal region) could conceivably be protective for higher levels of psychometric schizotypy and is consistent with the hypothesis that different subregions within the frontal cortex may differentiate SZ from SPD. In addition, neither global nor regionally specific effects were evident between groups in frontal cortical thickness further implicating an additional possible protective mechanism from frank psychosis. It should be noted that while gray matter volume and cortical thickness share similar properties, they are fundamentally different measures.[62,63] For example, although both thickness and area can influence volume, volume may be more closely associated with surface area than cortical thickness,[64] which appears to be specifically influenced by cell type and/or neuronal density.[65]

Our finding of lower FA within the IFOF among individuals higher in psychometric schizotypy is consistent with prior work implicating dysfunction of this tract in the neurobiology of SZ. For example, Yao et al[66] reported white matter deficits in first-episode SZ in the left IFOF using an activation likelihood estimation meta-analysis involving 8 studies that included 271 first-episode patients and 297 healthy controls. Moreover, the observation of

lower FA within the left IFOF among first-episode neuroleptic-naive patients compared with healthy volunteers suggests these effects are not an artifact of antipsychotic medication exposure.[67]

There are several limitations to the current study. Our use of a self-report instrument to assess schizotypy may allow for over or underreporting of positive and negative subclinical psychotic symptoms. In our larger sample comprising 658 participants, however, we found high concordance (rho > 0.80) between several measures of subclinical psychosis, including the SPQ, and symptoms assessed using a clinician administered diagnostic interview (SCID-NP) (P. DeRosse, unpublished data). While this does not rule out the possibility of over- or underreporting, it lends support to the convergent validity of the self-report measure. An additional limitation is that because SPQ scores were not normally distributed, we utilized a median split to identify high and low schizotypy groups. This approach, although maximizing our power, may have limited our ability to detect more subtle relationships between the level of subclinical psychotic symptoms and imaging measures. However, supplementary analyses comparing 3 groups (high, medium, and low SPQ) revealed results nearly identical to those obtained using 2 groups. Another potential weakness of the current study is the observed sex difference between the high and low schizotypy groups. Although we included sex as a covariate in our analyses, to ensure that the sex difference was not driving the result we conducted ancillary analyses demonstrating that this did not contribute to the observed findings. Finally, it should also be noted that tractography measures do not map directly onto the brain regions examined using FreeSurfer and thus, we are limited in our interpretation across imaging modalities.

In sum, the present study provided evidence for a link between psychometric schizotypy and a range of structural and DTI-derived measures encompassing frontotemporal regions in otherwise healthy adults without the confound of antipsychotic medications. These findings contribute to a growing literature suggesting that psychosis can be examined along a continuum of severity and suggest that this continuum may relate to subtle variation in brain structure and function. Moreover, results suggest that some frontal regions, at least at the gross anatomic level, may serve as a compensatory mechanism that may be relevant to the distinction between subclinical and clinically significant psychotic symptoms.

Funding

National Institute of Mental Health (R01 MH076995 to Dr P.R.S., R00 MH086756 to Dr P.D.); the NSLIJ Research Institute General Clinical Research Center (M01 RR018535); an Advanced Center for Intervention and Services Research (P30 MH090590); and a Center for Intervention Development and Applied Research (P50 MH080173).

Acknowledgments

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Ripke S, Sanders AR, Kendler KS, et al. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet*. 2011;43:969–976.
2. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–752.
3. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*. 2013;381:1371–1379.
4. Siever LJ, Davis KL. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. *Am J Psychiatry*. 2004;161:398–413.
5. Linscott RJ, van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychol Med*. 2013;43:1133–1149.
6. Nelson MT, Seal ML, Pantelis C, Phillips LJ. Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. *Neurosci Biobehav Rev*. 2013;37:317–327.
7. Rado S. Dynamics and classification of disordered behavior. *Am J Psychiatry*. 1953;110:406–416.
8. Meehl PE. Schizotaxia, schizotypy, schizophrenia. *Am Psychol*. 1962;17:827.
9. Meehl PE. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *J Pers Disord*. 1990;4:1–99.
10. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull*. 1991;17:555.
11. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. *J Abnorm Psychol*. 1976;85:374–382.
12. Vollema MG, Hoijtink H. The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional Rasch models. *Schizophr Bull*. 2000;26:565–575.
13. Stefanis NC, Hanssen M, Smirnis NK, et al. Evidence that three dimensions of psychosis have a distribution in the general population. *Psychol Med*. 2002;32:347–358.
14. Wuthrich VM, Bates TC. Confirmatory factor analysis of the three-factor structure of the schizotypal personality questionnaire and Chapman schizotypy scales. *J Pers Assess*. 2006;87:292–304.
15. Schulsinger H. A ten-year follow-up of children of schizophrenic mothers. Clinical assessment. *Acta Psychiatr Scand*. 1976;53:371–386.
16. Kety SS, Rosenthal D, Wender PH, Schulsinger F, Jacobsen B. Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. *Behav Genet*. 1976;6:219–225.

17. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon Family Study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch Gen Psychiatry*. 1993;50:527–540.
18. Tienari P, Wynne LC, Läksy K, et al. Genetic boundaries of the schizophrenia spectrum: evidence from the Finnish Adoptive Family Study of Schizophrenia. *Am J Psychiatry*. 2003;160:1587–1594.
19. Fanous A, Gardner C, Walsh D, Kendler KS. Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. *Arch Gen Psychiatry*. 2001;58:669–673.
20. Fanous AH, Neale MC, Gardner CO, et al. Significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy. *Mol Psychiatry*. 2007;12:958–965.
21. Kelleher I, Cannon M. Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychol Med*. 2011;41:1–6.
22. Ettinger U, Meyhöfer I, Steffens M, Wagner M, Koutsouleris N. Genetics, cognition, and neurobiology of schizotypal personality: a review of the overlap with schizophrenia. *Front Psychiatry*. 2014;5:18.
23. Fervaha G, Remington G. Neuroimaging findings in schizotypal personality disorder: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;43:96–107.
24. Hazlett EA, Goldstein KE, Kolaitis JC. A review of structural MRI and diffusion tensor imaging in schizotypal personality disorder. *Curr Psychiatry Rep*. 2012;14:70–78.
25. Kubicki M, McCarley R, Westin CF, et al. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res*. 2007;41:15–30.
26. Modinos G, Mechelli A, Ormel J, Groenewold NA, Aleman A, McGuire PK. Schizotypy and brain structure: a voxel-based morphometry study. *Psychol Med*. 2010;40:1423–1431.
27. Jacobson S, Kelleher I, Harley M, et al. Structural and functional brain correlates of subclinical psychotic symptoms in 11-13 year old schoolchildren. *Neuroimage*. 2010;49:1875–1885.
28. Ettinger U, Williams SC, Meisenzahl EM, Möller HJ, Kumari V, Koutsouleris N. Association between brain structure and psychometric schizotypy in healthy individuals. *World J Biol Psychiatry*. 2012;13:544–549.
29. Kühn S, Schubert F, Gallinat J. Higher prefrontal cortical thickness in high schizotypal personality trait. *J Psychiatr Res*. 2012;46:960–965.
30. Oertel-Knöchel V, Knöchel C, Rotarska-Jagiela A, et al. Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum. *Cereb Cortex*. 2013;23:61–70.
31. Goldman AL, Pezawas L, Mattay VS, et al. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. *Arch Gen Psychiatry*. 2009;66:467–477.
32. Volpe U, Federspiel A, Mucci A, et al. Cerebral connectivity and psychotic personality traits. A diffusion tensor imaging study. *Eur Arch Psychiatry Clin Neurosci*. 2008;258:292–299.
33. Nelson MT, Seal ML, Phillips LJ, Merritt AH, Wilson R, Pantelis C. An investigation of the relationship between cortical connectivity and schizotypy in the general population. *J Nerv Ment Dis*. 2011;199:348–353.
34. Knöchel C, O'Dwyer L, Alves G, et al. Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives. *Schizophr Res*. 2012;140:129–135.
35. Smallman RP, Barkus E, Azadbakht H, et al. MRI diffusion tractography study in individuals with schizotypal features: a pilot study. *Psychiatry Res*. 2014;221:49–57.
36. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry*. 2012;17:1228–1238.
37. Hanlon FM, Houck JM, Klimaj SD, et al. Frontotemporal anatomical connectivity and working-relational memory performance predict everyday functioning in schizophrenia. *Psychophysiology*. 2012;49:1340–1352.
38. Szeszko PR, Goldberg E, Gunduz-Bruce H, et al. Smaller anterior hippocampal formation volume in antipsychotic-naive patients with first-episode schizophrenia. *Am J Psychiatry*. 2003;160:2190–2197.
39. Szeszko PR, Ardekani BA, Ashtari M, et al. White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. *Am J Psychiatry*. 2005;162:602–605.
40. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV - Non-Patient Edition*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
41. Kremen WS, Jacobson KC, Xian H, et al. Heritability of word recognition in middle-aged men varies as a function of parental education. *Behav Genet*. 2005;35:417–433.
42. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage*. 2012;61:1402–1418.
43. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004;14:11–22.
44. Fischl B, Salat DH, van der Kouwe AJ, et al. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004;23(suppl 1):S69–S84.
45. Ségonne F, Dale AM, Busa E, et al. A hybrid approach to the skull stripping problem in MRI. *Neuroimage*. 2004;22:1060–1075.
46. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17:87–97.
47. Fischl B, Liu A, Dale AM. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging*. 2001;20:70–80.
48. Ségonne F, Pacheco J, Fischl B. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging*. 2007;26:518–529.
49. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA*. 2000;97:11050–11055.
50. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31:968–980.
51. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5:143–156.
52. Peters BD, Ikuta T, DeRosse P, et al. Age-related differences in white matter tract microstructure are associated with

cognitive performance from childhood to adulthood. *Biol Psychiatry*. 2014;75:248–256.

53. Behrens TE, Woolrich MW, Jenkinson M, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med*. 2003;50:1077–1088.
54. Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. *Neurosci Biobehav Rev*. 2012;36:1342–1356.
55. Kikinis Z, Fallon JH, Niznikiewicz M, et al. Gray matter volume reduction in rostral middle frontal gyrus in patients with chronic schizophrenia. *Schizophr Res*. 2010;123:153–159.
56. Quan M, Lee SH, Kubicki M, et al. White matter tract abnormalities between rostral middle frontal gyrus, inferior frontal gyrus and striatum in first-episode schizophrenia. *Schizophr Res*. 2013;145:1–10.
57. Grambaite R, Selnes P, Reinvang I, et al. Executive dysfunction in mild cognitive impairment is associated with changes in frontal and cingulate white matter tracts. *J Alzheimers Dis*. 2011;27:453–462.
58. Bilder RM, Goldman RS, Robinson D, et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry*. 2000;157:549–559.
59. Siever LJ, Koenigsberg HW, Harvey P, et al. Cognitive and brain function in schizotypal personality disorder. *Schizophr Res*. 2002;54:157–167.
60. Hazlett EA, Buchsbaum MS, Haznedar MM, et al. Cortical gray and white matter volume in unmedicated schizotypal and schizophrenia patients. *Schizophr Res*. 2008;101:111–123.
61. Suzuki M, Zhou SY, Hagino H, et al. Morphological brain changes associated with Schneider's first-rank symptoms in schizophrenia: a MRI study. *Psychol Med*. 2005;35:549–560.
62. Winkler AM, Kochunov P, Blangero J, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage*. 2010;53:1135–1146.
63. Feczko E, Augustinack JC, Fischl B, Dickerson BC. An MRI-based method for measuring volume, thickness and surface area of entorhinal, perirhinal, and posterior parahippocampal cortex. *Neurobiol Aging*. 2009;30:420–431.
64. Chouinard-Decorte F, McKay DR, Reid A, et al. Heritable changes in regional cortical thickness with age. *Brain Imaging Behav*. 2014;8:208–216.
65. Kanai R, Rees G. The structural basis of inter-individual differences in human behaviour and cognition. *Nat Rev Neurosci*. 2011;12:231–242.
66. Yao L, Lui S, Liao Y, et al. White matter deficits in first episode schizophrenia: an activation likelihood estimation meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;45:100–106.
67. Cheung V, Chiu CP, Law CW, et al. Positive symptoms and white matter microstructure in never-medicated first episode schizophrenia. *Psychol Med*. 2011;41:1709–1719.