Supplementary Materials

Participants

First-episode psychosis

Seventy-three individuals experiencing a first episode psychosis (FEP) were recruited from Orygen Youth Health's Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, Australia between 1995-1999. FEP-specific inclusion criteria were; (1) current DSM–IIIa(1) Axis I diagnosis of a psychotic disorder; and (2) less than 6 months of neuroleptic treatment. The current study also excluded FEP patients with a primary mood diagnosis. The Royal Park Multidiagnostic Instrument for Psychosis (RPMIP)(2) and the Structured Diagnostic Interview for DSM-III (SCID-I/P)(3) were used to determine diagnosis. Further information about the methodology has been described previously(4). Healthy control (HC) participants ($N = 57$) were recruited from the same catchment area as patients. HCs with a history of psychiatric illness were excluded. Exclusion criteria for FEP and HC included: significant head injury and/or loss of consciousness for > 1 minute; preferred language other than English; known history of learning disability; DSM diagnosis of substance abuse or dependence; neurological disease; baseline age >30. Current IQ was measured using four subtests of the Wechsler Adult Intelligence Scale (WAIS) – Revised (5) and premorbid IQ was estimated using the National Adult Reading Test (6). Ethics approval was obtained from the Human Research and Ethics Committees of the North Western Mental Health Program, the Victorian Department of Human Services, the Australian Institute of Health and Welfare, and relevant area mental health services. All participants provided informed consent and had adequate English comprehension. For the purposes of the current study, FEP patients receiving treatment with clozapine (n = 3) were also excluded.

Chronic schizophrenia

Data from 153 individuals with chronic schizophrenia and 168 healthy control subjects were obtained from the Australian Schizophrenia Research Banks (ASRB), a register of research data collected by scientific collaborators across five Australian sites, between 2007-2011. ASRB exclusion criteria for participants included: i) a history of organic brain disorder, ii) electroconvulsive therapy in the previous 6 months, iii) current substance dependence, iv) movement disorders, or v) brain injury

with post-traumatic amnesia. Healthy controls with a personal or family history of psychosis or bipolar I disorder were also excluded. Detailed information regarding the consent procedures have been published previously (7). The Diagnostic Interview for Psychosis (8) was used to obtain clinical symptom ratings and confirm patient diagnoses according to ICD-10 or DSM-IV criteria. Study procedures were approved by the Melbourne Health Human Research Ethics Committee. For the purposes of the current study, chronic patients receiving treatment with clozapine (n = 37) were also excluded.

Treatment-resistant schizophrenia

Forty-seven individuals with TRS were recruited from inpatient and outpatient clinics in Melbourne, Australia between 2012-2017. Treatment resistance was defined as at least two unsuccessful trials of two or more different antipsychotic types and currently taking clozapine (9, 10). Inclusion criteria for the TRS group included a diagnosis of schizophrenia, aged 18-65 years, illness duration >5 years, and currently prescribed and taking clozapine. Fifty-four healthy control participants with similar socioeconomic and educational background were recruited from the general community. The Mini International Neuropsychiatric Interview (MINI)(11) was used to confirm a diagnosis of schizophrenia in individuals with TRS, and to rule out current or past psychopathology in healthy controls. The study was approved by the Melbourne Health Human Research Ethics Committee (MHREC ID 2012.069); and all participants provided written informed consent prior to participation.

Methods

Clinical measures

In FEP patients, current IQ was measured using four subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) and premorbid IQ was estimated using the National Adult Reading Test (6). In CSZ and TRS patients, current IQ was measured using the 2-subtest short form (Vocabulary and Matrix Reasoning) of the WAIS-III (12) and premorbid IQ was estimated using the Wechsler Test of Adult Reading (13). In CSZ and TRS patients, negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS)(14). In CSZ patients, positive symptoms were measured using the hallucinations and delusions items from the Diagnostic Interview for Psychosis (DIP)(8). In FEP and TRS patients, positive and negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (15).

Imaging data acquisition

FEP

Magnetic resonance images were acquired using a General Electric Medical Systems 1.5T Signa scanner. T1-weighted images comprised 124 coronal slices of 1.5mm thickness. Imaging parameters were as follows: echo time = 3.3 milliseconds; repetition time = 14.3 milliseconds; flip angle = 30°; matrix size = 256 × 256; field of view = 240 × 240 mm^2; and voxel dimensions, 0.94 × 0.94 × 1.5 mm^3.

CSZ

T1-weighted (MPRAGE) structural scans were acquired using Siemens Avanto 1.5T scanners located at five different sites in Australia. The same acquisition sequence was used at each site and a Siemens phantom was periodically imaged at each site to

evaluate potential inter-site differences. T1-weighted images comprised 176 sagittal slices of 1 mm thickness without gap; field of view = 250 × 250 mm^2; repetition time = 1980 ms, echo time = 4.3 ms; data matrix size = 256 × 256; voxel dimensions = 1.0 × 1.0 × 1.0 mm^3.

TRS

Magnetic resonance images were acquired using a Siemens Avanto 3T Magnetom TIM Trio scanner. T1-weighted images were acquired using an optimized Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. The sequence parameters were: 176 sagittal slices of 1 mm thickness without gap, field of view = 250 × 250 mm^2, repetition time = 1980 ms, echo time = 4.3 ms, flip angle = 15°, using an acquisition matrix of 256 × 256 resulting in a final reconstructed voxel resolution of 0.98 × 0.98 × 1.0 mm^3.

Table S1. Medication information

	FEP (n = 70)	CSZ (n = 153)	TRS (n = 47)
Medications (% using)			
Amitriptyline hydrochloride			4.26
Amulsipride		15.03	4.26
Ariprazole		13.73	8.51
Chlorpromazine	25.71		
Clozapine			100.00
Flupenthixol decanoate		1.31	
Fluphenazine decanoate	1.43	1.96	
Haloperidol	2.86	0.65	
Haloperidol decanoate		1.96	
Olanzapine	11.43	32.68	8.51
Paliperidone			6.38
Paliperidone palmitate			2.13
Quetiapine fumerate	1.43	21.57	2.13
Risperidone	51.43	12.42	4.26
Risperidone consta		9.15	4.26
Thioridazine hydrochloride	1.43	0.65	
Trifluoperazine hydrochloride	2.86	3.27	
Ziprasidone hydrochloride		2.61	
Zuclopenthixol decanoate		3.92	2.13
Zuclopenthixol dihydrochloride		0.65	

Results

Table S2. Regions of significant cortical thinning in first-episode psychosis patients ranked by effect size

		Patients		Controls			
Hemisphere	Region	Mean	SD	Mean	SD	*t*-statistic	Effect size (Cohen's *d*)
Right	Superior temporal sulcus	2.40	0.12	2.50	0.14	4.68	0.42
Right	Middle occipital gyrus (O2, lateral occipital gyrus)	2.52	0.17	2.68	0.20	4.56	0.41
Left	Anterior occipital sulcus	2.13	0.17	2.27	0.24	4.15	0.37
Left	Precentral sulcus (superior part)	2.22	0.14	2.34	0.18	4.09	0.37
Right	Inferior frontal sulcus	2.32	0.16	2.42	0.16	3.60	0.32
Right	Intraparietal sulcus and transverse parietal sulci	2.00	0.12	2.08	0.15	3.44	0.31
Left	Circular sulcus of the insula (inferior segment)	2.70	0.20	2.80	0.19	3.32	0.30
Right	Precentral sulcus (inferior part)	2.32	0.16	2.41	0.15	3.29	0.29
Left	Superior temporal gyrus (planum temporale)	2.45	0.19	2.57	0.20	3.28	0.29
Left	Precuneus	2.47	0.15	2.56	0.16	3.24	0.29
Right	Anterior occipital sulcus and preoccipital notch	2.20	0.22	2.31	0.25	3.17	0.28
Left	Intraparietal sulcus and transverse parietal sulci	2.06	0.11	2.13	0.15	3.17	0.28
Right	Postcentral sulcus	1.99	0.13	2.06	0.13	3.16	0.28
Right	Superior frontal sulcus	2.41	0.18	2.50	0.15	3.13	0.28
Right	Cingulate sulcus (marginal branch)	2.15	0.16	2.23	0.14	3.13	0.28
Right	Precentral sulcus (superior part)	2.20	0.16	2.29	0.18	3.11	0.28
Right	Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus	2.15	0.17	2.25	0.21	3.08	0.28
Left	Superior temporal sulcus	2.38	0.11	2.44	0.12	2.97	0.27
Right	Lateral occipito-temporal sulcus	2.31	0.24	2.43	0.21	2.89	0.26
Left	Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus	2.24	0.16	2.32	0.18	2.87	0.26
Left	Superior parietal lobule	2.23	0.15	2.32	0.18	2.84	0.25
Left	Angular gyrus	2.53	0.22	2.65	0.25	2.80	0.25
Right	Circular sulcus of the insula (inferior segment)	2.66	0.20	2.76	0.21	2.79	0.25
Right	Inferior temporal sulcus	2.37	0.18	2.46	0.19	2.78	0.25
Right	Inferior frontal gyrus (opercular part)	2.70	0.24	2.82	0.20	2.78	0.25
Right	Circular sulcus of the insula (superior segment)	2.68	0.18	2.76	0.17	2.67	0.24
Left	Postcentral sulcus	2.02	0.12	2.09	0.15	2.67	0.24
Left	Inferior frontal sulcus	2.34	0.13	2.40	0.15	2.66	0.24
Left	Lateral occipito-temporal sulcus	2.36	0.21	2.46	0.22	2.66	0.24
Right	Middle frontal sulcus	2.34	0.15	2.42	0.15	2.61	0.23
Right	Cingulate gyrus and sulcus (middle-posterior part)	2.60	0.18	2.68	0.19	2.60	0.23

Left	Middle occipital gyrus (O2, lateral occipital gyrus)	2.52	0.19	2.60	0.19	2.59	0.23
Right	Circular sulcus of the insula (anterior segment)	2.81	0.27	2.94	0.29	2.57	0.23
Right	Subparietal sulcus	2.32	0.23	2.42	0.22	2.57	0.23

Table S3. Regions of significant cortical thinning in chronic schizophrenia patients ranked by effect size

		Patients		Controls			
Hemisphere	Region	Mean	SD	Mean	SD	*t*-statistic	Effect size (Cohen's *d*)
Right	Orbital gyri	2.86	0.18	2.97	0.19	5.26	0.29
Left	Orbital gyri	2.81	0.18	2.92	0.18	5.07	0.28
Right	Temporal pole	3.35	0.24	3.48	0.23	4.79	0.27
Right	Superior temporal gyrus (lateral aspect)	3.11	0.19	3.21	0.19	4.75	0.27
Left	Superior temporal gyrus (lateral aspect)	3.06	0.20	3.17	0.19	4.58	0.26
Right	Circular sulcus of the insula (superior segment)	2.53	0.14	2.59	0.14	4.54	0.25
Left	Superior temporal sulcus (parallel sulcus)	2.44	0.12	2.50	0.12	4.46	0.25
Right	Circular sulcus of the insula (anterior segment)	2.77	0.23	2.88	0.24	4.45	0.25
Left	Temporal pole	3.30	0.23	3.43	0.21	4.43	0.25
Right	Inferior frontal gyrus (opercular part)	2.78	0.18	2.87	0.18	4.32	0.24
Left	Superior temporal gyrus (planum polare)	3.42	0.33	3.56	0.27	4.18	0.23
Left	Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus	2.25	0.16	2.33	0.15	4.17	0.23
Left	Inferior temporal sulcus	2.45	0.18	2.54	0.18	4.14	0.23
Right	Orbital sulci (H-shaped sulci)	2.65	0.20	2.75	0.22	4.13	0.23
Left	Inferior temporal gyrus	3.07	0.18	3.16	0.17	4.05	0.23
Left	Circular sulcus of the insula (anterior segment)	2.77	0.24	2.88	0.23	4.02	0.23
Left	Middle frontal sulcus	2.28	0.14	2.34	0.16	4.01	0.22
Left	Inferior frontal gyrus (triangular part)	2.71	0.20	2.78	0.18	3.95	0.22
Right	Superior temporal sulcus (parallel sulcus)	2.51	0.13	2.56	0.12	3.95	0.22
Left	Parahippocampal gyrus	3.05	0.25	3.16	0.24	3.92	0.22
Right	Inferior frontal sulcus	2.31	0.12	2.36	0.14	3.92	0.22
Left	Medial orbital sulcus (olfactory sulcus)	2.30	0.22	2.38	0.21	3.88	0.22
Left	Precentral sulcus (inferior part)	2.43	0.13	2.49	0.14	3.88	0.22
Right	Precentral sulcus (inferior part)	2.44	0.12	2.49	0.15	3.87	0.22
Left	Middle temporal gyrus	3.13	0.16	3.21	0.19	3.85	0.22
Left	Middle frontal gyrus	2.71	0.15	2.78	0.16	3.83	0.21
Left	Posterior-dorsal part of the cingulate gyrus	2.95	0.20	3.02	0.17	3.80	0.21
Right	Superior temporal gyrus (planum temporale)	2.59	0.20	2.68	0.20	3.79	0.21
Right	Middle temporal gyrus	3.20	0.18	3.27	0.17	3.77	0.21
Left	Inferior occipital gyrus and sulcus	2.41	0.19	2.48	0.19	3.68	0.21
Left	Inferior frontal gyrus (orbital part)	2.81	0.28	2.93	0.24	3.65	0.20
Right	Straight gyrus, Gyrus rectus	2.61	0.20	2.70	0.23	3.59	0.20

Right	Sulcus intermedius primus (of Jensen)	2.31	0.20	2.40	0.20	3.58	0.20
Right	Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus	2.24	0.16	2.29	0.15	3.58	0.20
Left	Circular sulcus of the insula (superior segment)	2.52	0.15	2.57	0.14	3.54	0.20
Right	Inferior frontal gyrus (triangular part)	2.76	0.18	2.83	0.21	3.52	0.20
Right	Inferior temporal gyrus	3.09	0.18	3.16	0.17	3.41	0.19
Right	Superior frontal gyrus	2.91	0.15	2.97	0.18	3.34	0.19
Left	Short insular gyri	3.56	0.26	3.68	0.25	3.28	0.18
Right	Transverse frontopolar gyri and sulci	2.65	0.19	2.73	0.20	3.28	0.18
Left	Transverse temporal sulcus	2.30	0.28	2.42	0.33	3.25	0.18
Right	Posterior ramus of the lateral sulcus	2.43	0.16	2.48	0.16	3.25	0.18
Right	Anterior cingulate gyrus and sulcus	2.69	0.15	2.76	0.17	3.17	0.18
Left	Subcentral gyrus (central operculum) and sulci	2.69	0.19	2.76	0.18	3.03	0.17
Left	Anterior transverse collateral sulcus	2.53	0.30	2.64	0.30	3.01	0.17
Left	Middle-anterior cingulate gyrus and sulcus	2.67	0.17	2.73	0.17	2.99	0.17
Right	Short insular gyri	3.54	0.26	3.64	0.33	2.97	0.17
Right	Circular sulcus of the insula (inferior segment)	2.70	0.21	2.76	0.20	2.96	0.17
Right	Superior temporal gyrus (planum polare)	3.28	0.26	3.35	0.26	2.95	0.17
Right	Inferior occipital gyrus and sulcus	2.63	0.20	2.69	0.20	2.90	0.16
Left	Inferior frontal gyrus (opercular part)	2.77	0.17	2.83	0.19	2.89	0.16
Left	Anterior cingulate gyrus and sulcus	2.72	0.16	2.78	0.20	2.85	0.16
Right	Middle-anterior cingulate gyrus and sulcus (aMCC)	2.74	0.17	2.80	0.17	2.85	0.16
Left	Lateral occipito-temporal gyrus (fusiform gyrus)	2.77	0.16	2.83	0.17	2.84	0.16
Right	Precentral sulcus (superior part)	2.34	0.16	2.39	0.17	2.84	0.16
Left	Inferior frontal sulcus	2.30	0.12	2.34	0.13	2.82	0.16
Right	Inferior frontal gyrus (orbital part)	2.90	0.25	2.99	0.26	2.79	0.16
Left	Orbital sulci (H-shaped sulci)	2.62	0.21	2.70	0.23	2.76	0.15
Right	Anterior transverse collateral sulcus	2.47	0.29	2.56	0.28	2.76	0.15
Right	Lateral occipito-temporal gyrus (fusiform gyrus)	2.77	0.17	2.83	0.17	2.72	0.15
Right	Lateral orbital sulcus	2.29	0.25	2.36	0.26	2.70	0.15
Left	Circular sulcus of the insula (inferior segment)	2.77	0.18	2.81	0.18	2.66	0.15
Right	Inferior temporal sulcus	2.50	0.18	2.56	0.17	2.65	0.15
Right	Transverse temporal sulcus	2.50	0.29	2.57	0.29	2.63	0.15
Right	Subcentral gyrus (central operculum) and sulci	2.71	0.20	2.77	0.21	2.55	0.14
Right	Middle frontal gyrus	2.76	0.16	2.80	0.17	2.50	0.14
Left	Superior frontal gyrus	2.94	0.16	2.99	0.19	2.49	0.14
Left	Posterior ramus of the lateral sulcus	2.4	0.16	2.42	0.16	2.47	0.14
Left	Straight gyrus, Gyrus rectus	2.75	0.18	2.80	0.20	2.46	0.14

Right	Horizontal ramus of the anterior segment of the lateral sulcus	2.29	0.23	2.36	0.23	2.42	0.14
Left	Anterior occipital sulcus and preoccipital notch	2.29	0.18	2.34	0.16	2.42	0.14
Right	Parahippocampal gyrus	3.12	0.23	3.20	0.24	2.41	0.14
Left	Long insular gyrus and central sulcus of the insula	3.19	0.28	3.28	0.29	2.38	0.13
Right	Supramarginal gyrus	2.84	0.18	2.89	0.17	2.36	0.13
Left	Suborbital sulcus	2.54	0.29	2.63	0.32	2.33	0.13
Left	Lateral orbital sulcus	2.28	0.29	2.39	0.31	2.29	0.13
Right	Medial orbital sulcus (olfactory sulcus)	2.21	0.19	2.25	0.21	2.27	0.13
Right	Angular gyrus	2.88	0.19	2.93	0.17	2.27	0.13
Right	Anterior transverse temporal gyrus (of Heschl)	2.49	0.21	2.55	0.22	2.24	0.13

Table S4. Regions of significant cortical thinning in treatment-resistant schizophrenia patients ranked by effect size

		Patients		Controls			
Hemisphere	Region	Mean	SD	Mean	SD	*t*-statistic	Effect size (Cohen's *d*)
Left	Circular sulcus of the insula (superior segment)	2.47	0.15	2.64	0.14	7.34	0.74
Left	Inferior occipital gyrus and sulcus	2.29	0.16	2.46	0.15	6.03	0.61
Left	Superior temporal sulcus	2.39	0.11	2.49	0.10	6.02	0.60
Left	Middle-anterior cingulate gyrus and sulcus	2.54	0.19	2.73	0.20	5.94	0.60
Right	Circular sulcus of the insula (superior segment)	2.48	0.16	2.64	0.14	5.92	0.59
Right	Circular sulcus of the insula (inferior segment)	2.60	0.17	2.80	0.23	5.87	0.59
Left	Superior frontal gyrus	2.72	0.17	2.88	0.15	5.70	0.57
Left	Temporal pole	3.18	0.26	3.43	0.20	5.51	0.55
Left	Inferior temporal gyrus	2.80	0.16	2.97	0.18	5.39	0.54
Right	Superior frontal gyrus	2.66	0.16	2.81	0.14	5.31	0.53
Left	Middle temporal gyrus	2.97	0.18	3.12	0.14	5.29	0.53
Right	Middle-anterior cingulate gyrus and sulcus	2.49	0.17	2.66	0.17	5.27	0.53
Right	Middle temporal gyrus	2.97	0.15	3.10	0.15	5.24	0.53
Left	Inferior part of the precentral sulcus	2.34	0.17	2.47	0.12	5.10	0.51
Right	Orbital sulci (H-shaped sulci)	2.23	0.19	2.44	0.22	5.06	0.51
Left	Inferior temporal sulcus	2.40	0.18	2.56	0.15	5.06	0.51
Right	Middle-posterior cingulate gyrus and sulcus	2.47	0.13	2.59	0.15	5.04	0.51
Left	Inferior frontal gyrus (opercular part)	2.65	0.17	2.80	0.14	5.02	0.50
Right	Superior temporal sulcus	2.44	0.13	2.54	0.10	4.89	0.49
Right	Long insular gyrus and central sulcus of the insula	3.22	0.29	3.48	0.26	4.78	0.48
Right	Inferior temporal sulcus	2.47	0.17	2.62	0.16	4.76	0.48
Left	Circular sulcus of the insula (anterior segment)	2.65	0.21	2.82	0.19	4.68	0.47
Right	Inferior occipital gyrus and sulcus	2.56	0.23	2.75	0.21	4.67	0.47
Right	Posterior ramus of the lateral sulcus	2.45	0.17	2.57	0.15	4.58	0.46
Right	Temporal pole	3.23	0.25	3.44	0.21	4.56	0.46
Left	Middle-posterior cingulate gyrus and sulcus	2.48	0.16	2.59	0.17	4.56	0.46
Left	Medial orbital sulcus (olfactory sulcus)	2.22	0.17	2.37	0.17	4.52	0.45
Left	Lateral occipito-temporal gyrus (fusiform gyrus)	2.77	0.17	2.91	0.16	4.49	0.45
Left	Intraparietal sulcus and transverse parietal sulci	2.03	0.11	2.13	0.11	4.49	0.45
Right	Posterior-dorsal cingulate gyrus	2.79	0.19	2.93	0.18	4.46	0.45
Left	Parieto-occipital sulcus	2.11	0.16	2.23	0.14	4.45	0.45
Left	Circular sulcus of the insula	2.74	0.20	2.89	0.21	4.43	0.45

	(inferior segment)						
Left	Medial occipito-temporal and lingual sulcus	2.39	0.19	2.52	0.15	4.32	0.43
Left	Middle frontal gyrus	2.53	0.15	2.65	0.15	4.24	0.43
Left	Precentral sulcus (superior part)	2.33	0.14	2.44	0.14	4.15	0.42
Right	Precentral sulcus (inferior part)	2.28	0.16	2.39	0.14	4.13	0.41
Left	Posterior-dorsal cingulate gyrus	2.82	0.21	2.96	0.19	4.12	0.41
Right	Superior occipital sulcus and transverse occipital sulcus	2.02	0.17	2.13	0.14	4.03	0.41
Right	Anterior transverse collateral sulcus	2.57	0.20	2.73	0.20	3.94	0.40
Left	Angular gyrus	2.54	0.15	2.65	0.17	3.90	0.39
Left	Anterior cingulate gyrus and sulcus	2.55	0.16	2.67	0.18	3.86	0.39
Left	Superior occipital gyrus	2.06	0.19	2.19	0.18	3.81	0.38
Right	Inferior temporal gyrus	2.89	0.20	3.01	0.16	3.74	0.38
Left	Middle occipital gyrus	2.47	0.18	2.59	0.14	3.73	0.37
Left	Lateral occipito-temporal sulcus	2.39	0.23	2.53	0.15	3.72	0.37
Left	Subparietal sulcus	2.29	0.16	2.39	0.13	3.69	0.37
Left	Posterior ramus of the lateral sulcus	2.36	0.17	2.47	0.19	3.63	0.36
Left	Supramarginal gyrus	2.64	0.16	2.74	0.16	3.62	0.36
Left	Superior temporal gyrus (planum temporale)	2.52	0.20	2.64	0.14	3.61	0.36
Right	Superior frontal sulcus	2.21	0.14	2.31	0.15	3.57	0.36
Right	Lateral occipito-temporal sulcus	2.53	0.18	2.65	0.17	3.54	0.36
Left	Long insular gyrus and central sulcus of the insula	3.14	0.24	3.27	0.18	3.51	0.35
Left	Superior occipital sulcus and transverse occipital sulcus	1.98	0.17	2.08	0.16	3.50	0.35
Left	Sulcus intermedius primus (of Jensen)	2.20	0.33	2.42	0.36	3.50	0.35
Right	Parieto-occipital sulcus	2.18	0.18	2.28	0.14	3.47	0.35
Left	Paracentral lobule and sulcus	2.26	0.15	2.37	0.19	3.44	0.35
Left	Posterior transverse collateral sulcus	1.97	0.27	2.15	0.23	3.43	0.34
Right	Precentral sulcus (superior part)	2.29	0.17	2.40	0.15	3.42	0.34
Left	Postcentral sulcus	2.05	0.13	2.15	0.14	3.36	0.34
Left	Middle occipital sulcus and lunatus sulcus	1.92	0.18	2.04	0.18	3.31	0.33
Left	Precuneus	2.42	0.17	2.52	0.15	3.31	0.33
Right	Lateral occipito-temporal gyrus (fusiform gyrus)	2.85	0.19	2.96	0.16	3.29	0.33
Left	Anterior transverse collateral sulcus	2.63	0.29	2.81	0.27	3.27	0.33
Left	Orbital sulci (H-shaped sulci)	2.49	0.18	2.62	0.21	3.26	0.33
Left	Precentral gyrus	2.79	0.19	2.89	0.13	3.26	0.33
Right	Superior temporal gyrus (planum temporale)	2.51	0.18	2.61	0.17	3.26	0.33
Left	Anterior occipital sulcus and preoccipital notch	2.15	0.17	2.27	0.17	3.26	0.33
Right	Intraparietal sulcus and transverse parietal sulci	2.05	0.14	2.13	0.12	3.23	0.32
Right	Middle frontal gyrus	2.45	0.13	2.53	0.13	3.21	0.32

Right	Supramarginal gyrus	2.66	0.15	2.75	0.16	3.18	0.32
Left	Superior frontal sulcus	2.33	0.17	2.41	0.11	3.12	0.31
Left	Short insular gyri	3.50	0.20	3.61	0.19	3.09	0.31
Right	Parahippocampal gyrus	3.07	0.27	3.25	0.31	3.07	0.31
Right	Middle occipital gyrus	2.57	0.17	2.65	0.14	3.05	0.31
Right	Precentral gyrus	2.70	0.21	2.81	0.16	3.03	0.30
Left	Occipital pole	1.96	0.16	2.04	0.14	3.02	0.30
Left	Superior temporal gyrus (planum polare)	3.31	0.23	3.44	0.26	3.02	0.30
Right	Orbital gyri	2.59	0.17	2.69	0.14	2.97	0.30
Left	Orbital gyri	2.61	0.17	2.69	0.12	2.90	0.29
Right	Inferior frontal gyrus (opercular part)	2.66	0.15	2.74	0.16	2.89	0.29
Right	Precuneus	2.42	0.15	2.49	0.14	2.88	0.29
Right	Short insular gyri	3.45	0.23	3.57	0.20	2.88	0.29
Right	Subparietal sulcus	2.33	0.16	2.41	0.14	2.87	0.29
Left	Parahippocampal gyrus	3.02	0.30	3.17	0.27	2.86	0.29
Right	Middle occipital sulcus and lunatus sulcus	2.06	0.19	2.15	0.17	2.83	0.28
Right	Inferior frontal sulcus	2.04	0.13	2.10	0.13	2.79	0.28
Right	Anterior occipital sulcus and preoccipital notch	2.34	0.18	2.42	0.15	2.73	0.27
Right	Superior temporal gyrus (lateral aspect)	3.02	0.20	3.11	0.17	2.71	0.27
Left	Inferior frontal gyrus (orbital part)	2.67	0.21	2.78	0.25	2.67	0.27
Right	Angular gyrus	2.63	0.16	2.70	0.15	2.66	0.27
Right	Medial occipito-temporal sulcus and lingual sulcus	2.45	0.17	2.53	0.16	2.66	0.27
Right	Calcarine sulcus	1.87	0.14	1.94	0.15	2.65	0.27
Right	Inferior frontal gyrus (triangular part)	2.49	0.16	2.57	0.17	2.64	0.27
Left	Inferior frontal gyrus (triangular part)	2.57	0.19	2.66	0.18	2.62	0.26
Left	Horizontal ramus of the anterior segment of the lateral sulcus	2.16	0.27	2.30	0.28	2.60	0.26
Right	Posterior-ventral cingulate gyrus (isthmus of the cingulate gyrus)	2.72	0.29	2.86	0.28	2.57	0.26
Left	Subcentral gyrus and sulci	2.66	0.21	2.75	0.19	2.49	0.25
Right	Posterior transverse collateral sulcus	2.13	0.25	2.23	0.18	2.48	0.25
Left	Lingual gyrus	1.95	0.14	2.01	0.13	2.44	0.24
Left	Superior parietal lobule	2.29	0.17	2.35	0.12	2.38	0.24
Right	Superior temporal gyrus (planum polare)	3.20	0.24	3.31	0.28	2.38	0.24
Right	Anterior cingulate gyrus and sulcus	2.32	0.17	2.40	0.19	2.32	0.23
Left	Anterior transverse temporal gyrus (of Heschl)	2.42	0.24	2.51	0.22	2.21	0.22
Left	Inferior frontal sulcus	2.17	0.15	2.23	0.15	2.20	0.22
Right	Inferior frontal gyrus (orbital part)	2.61	0.21	2.71	0.22	2.18	0.22
Left	Superior temporal gyrus (lateral aspect)	3.07	0.20	3.15	0.19	2.17	0.22

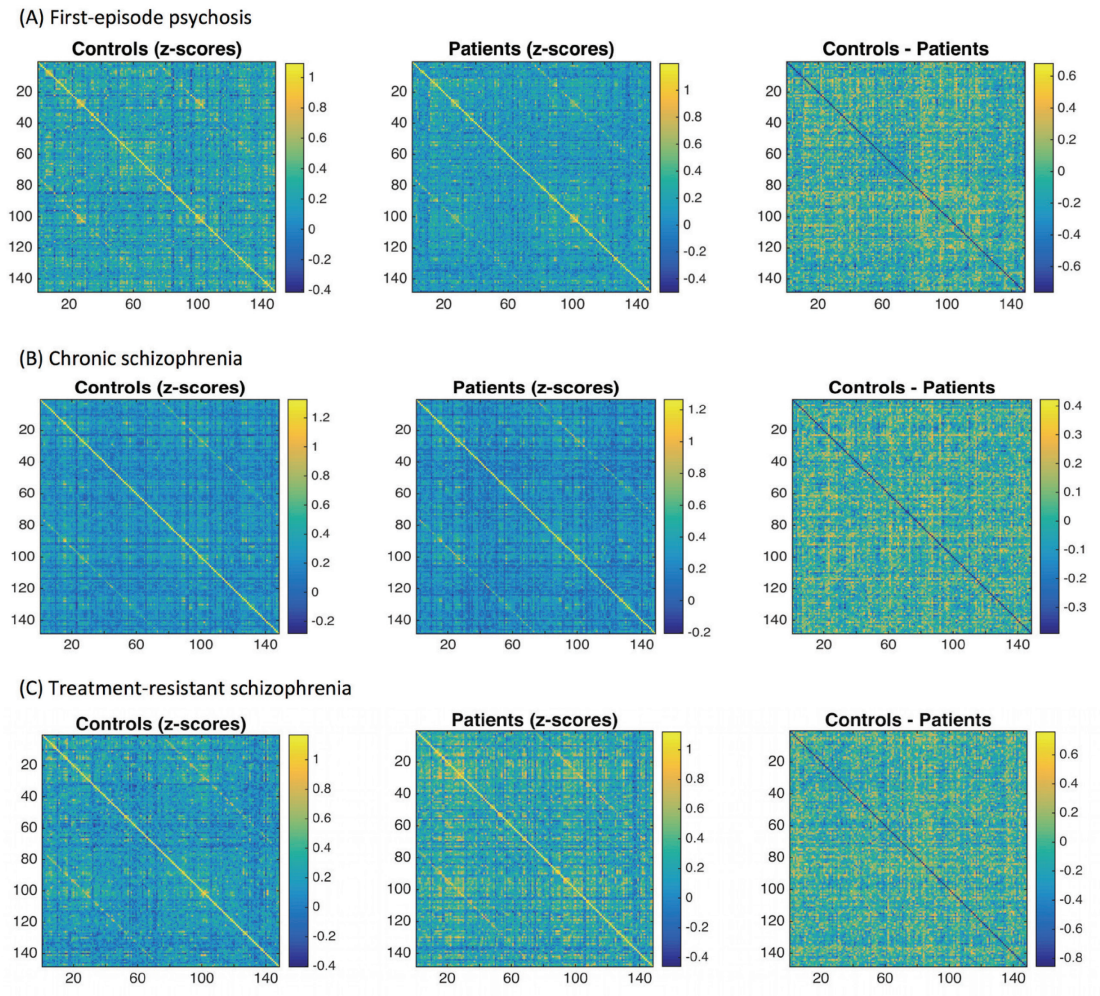

Figure S1. Cortical thickness connectivity matrices for patients and respective healthy controls groups in three cohorts: (A) first-episode psychosis, (B) chronic schizophrenia, and (C) treatment-resistant schizophrenia.

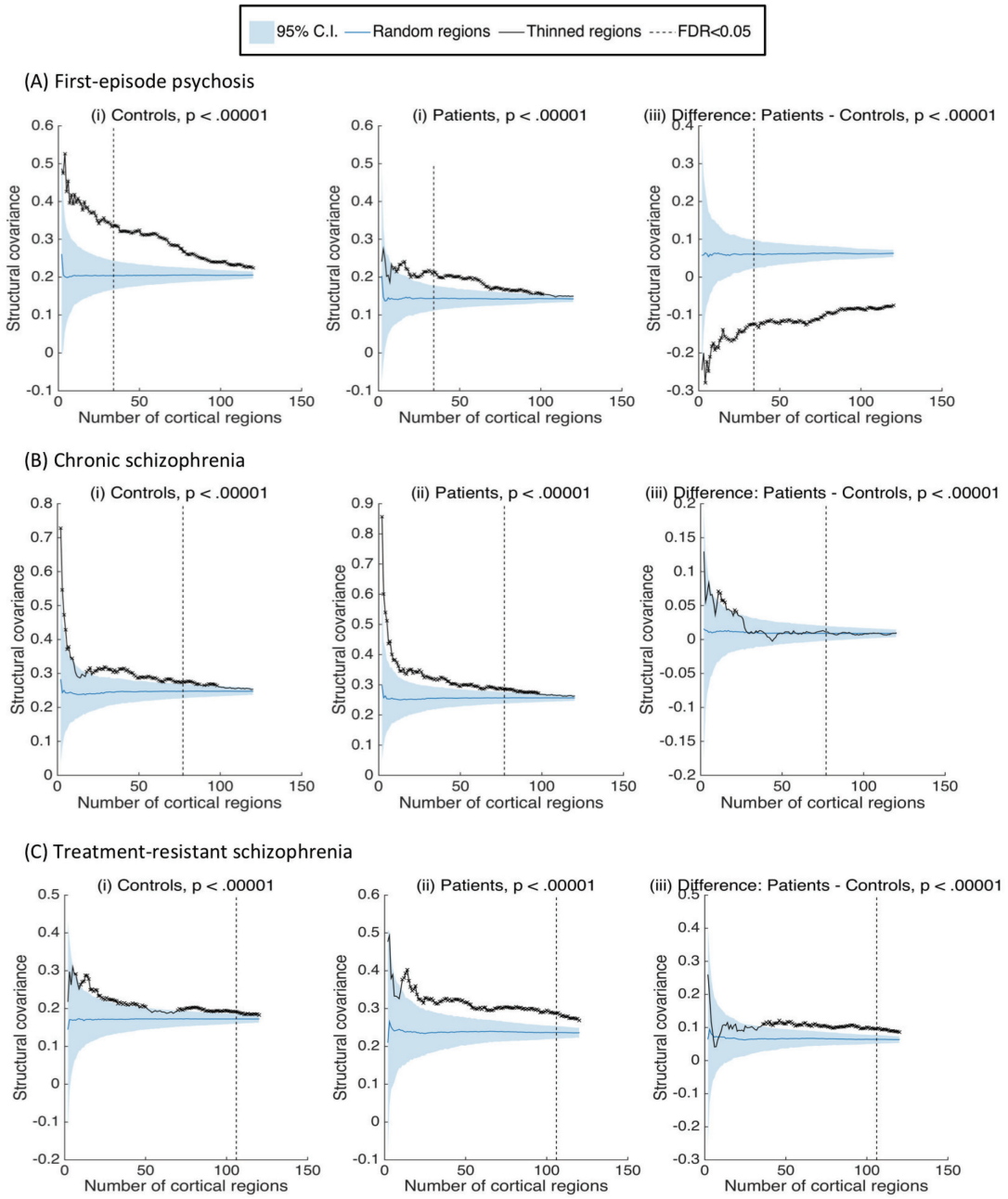

Figure S2. Comparison of the average structural covariance between the top-*n* cortical regions with cortical thickness reductions (CTRs) in (A) first-episode psychosis, (B) chronic schizophrenia, and (C) treatment-resistant schizophrenia patients with the average structural covariance in 5,000 randomly chosen sets of *n* regions, which were matched to the number of nodes within each cerebral hemisphere and the total Euclidean distance between pairs of nodes. Comparisons are shown separately for (i) healthy controls, (ii) patients and (iii) between-group difference. The vertical axis shows structural covariance, which is a r-to-z-transformed Pearson correlation coefficient. Dashed vertical lines represent the boundary between regions with and without CTRs based on a false discovery rate threshold of 5%. Values of *n* marked with a cross indicate that structural covariance was significantly increased between the top-*n* regions with the most extensive CTRs ($p<0.05$). Solid black line is the mean structural covariance in the actual (non-permuted) data. Blue line is the mean structural covariance in the randomized data, averaged across 5000 randomizations. The shaded area denotes 95% confidence intervals across the 5000 randomizations.

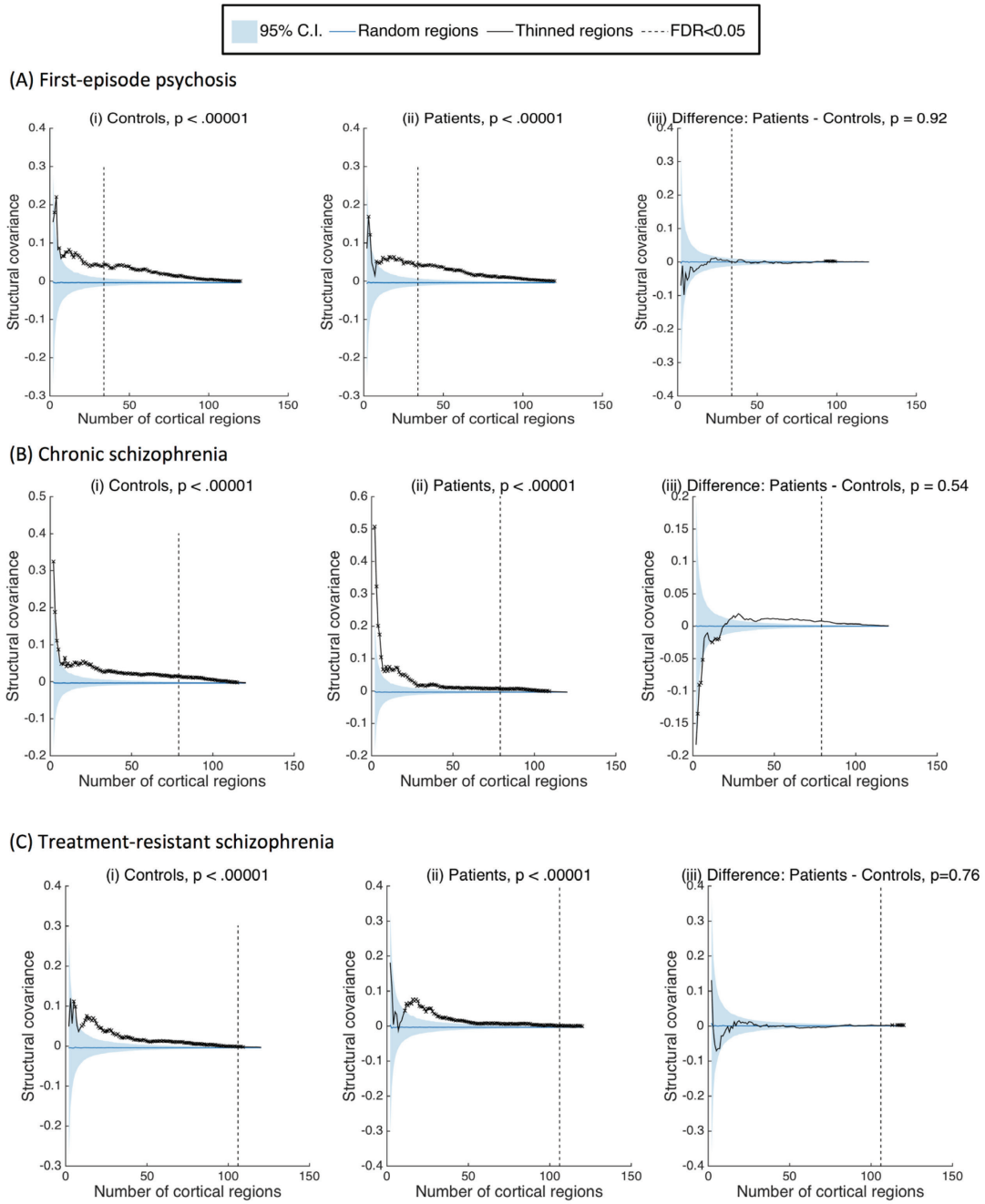

Figure S3. Comparison of the average structural covariance between the top-*n* cortical regions with cortical thickness reductions (CTRs) in (A) first-episode psychosis, (B) chronic schizophrenia, and (C) treatment-resistant schizophrenia patients with the average structural covariance in 5,000 randomly chosen sets of *n* regions, when mean cortical thickness is included as a covariate. Comparisons are shown separately for (i) healthy controls, (ii) patients and (iii) between-group difference. The vertical axis shows structural covariance, which is a r-to-z-transformed Pearson correlation coefficient. Dashed vertical lines represent the boundary between regions with and without CTRs based on a false discovery rate threshold of 5%. Values of *n* marked with a cross indicate that structural covariance was significantly increased between the top-*n* regions with the most extensive CTRs ($p<0.05$). Solid black line is the mean structural covariance in the actual (non-permuted) data. Blue line is the mean structural covariance in the randomized data, averaged across 5000 randomizations. The shaded area denotes 95% confidence intervals across the 5000 randomizations.

Table S5. Structural covariance between regions with significant thinning in at least two of three schizophrenia cohorts. A total of 81 regions (55%) showed significant cortical thickness reductions in at least two of the three cohorts. The probability of this degree of overlap occurring as a matter of chance was remote (p=0.006). Structural covariance was significantly increased among these 81 regions compared to randomly selected sets of 81 regions in both patients and controls for all three cohorts (p<0.05).

	First-episode psychosis			*Chronic schizophrenia*			*Treatment-resistant schizophrenia*		
	SC	***SC Null***	***p-value***	***SC***	***SC Null***	***p-value***	***SC***	***SC Null***	***p-value***
Controls	*0.27*	*0.20±0.02*	*<0.001*	*0.30*	*0.25±0.02*	*<0.001*	*0.18*	*0.15±0.02*	*0.02*
Patients	*0.19*	*0.14±0.02*	*<0.001*	*0.31*	*0.18±0.02*	*<0.001*	*0.30*	*0.23±0.02*	*<0.001*
Difference	*-0.08*	*-0.06±0.02*	*0.02*	*0.01*	*0.01±0.01*	*0.7*	*0.13*	*0.08±0.01*	*<0.001*

SC: structural covariance between 81 cortical regions with significant thinning in at least two of the three cohorts; **SC null**: structural covariance among randomly chosen sets of 81 regions; **Difference**: between-group difference of patients minus controls.

Table S6: Structural covariance between regions with CTRs in randomly selected subsamples of the chronic schizophrenia cohort. Full sample of patients (N=153) and healthy controls (N=168) was reduced to five randomly selected subsamples with the same number of patients (N=47) and controls (N=54) as the smallest cohort (TRS) by sample size. Effects are consistent across the full sample and the five subsamples, except for Subsample 4, where structural covariance was no longer significantly increased in the control group among CTR regions. In all cases, structural covariance was computed among the 81 regions with significant cortical thickness reductions in at least two of the three cohorts.

	SC Controls	*SC Patients*	*Difference*
Full sample	*0.30, p<0.001*	*0.31, p<0.001*	*0.01, p=0.7*
Subsample 1	*0.30, p<0.001*	*0.35, p<0.001*	*0.05, p=0.4*
Subsample 2	*0.28, p<0.001*	*0.32, p<0.001*	*0.04, p=0.1*
Subsample 3	*0.34, p<0.001*	*0.36, p<0.001*	*0.02, p=0.9*
Subsample 4	*0.20, p=0.1*	*0.34, p<0.001*	*0.14, p=0.02*
Subsample 5	*0.30, p<0.001*	*0.35, p<0.007*	*0.05, p=0.2*

SC: structural covariance, **p**: p-value assessing whether structural covariance was increased among the 81 regions with CTRs, compared to the structural covariance between randomly chosen sets of 81 regions.

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