

Prefrontal Brain Network Connectivity Indicates Degree of Both Schizophrenia Risk and Cognitive Dysfunction

Paul G. Unschuld^{*1,2}, Alison S. Buchholz¹, Mark Varvaris¹, Peter C. M. van Zijl^{3,4}, Christopher A. Ross^{1,5,6}, James J. Pekar^{3,4}, Christoph Hock², John A. Sweeney⁷, Carol A. Tamminga⁷, Matcheri S. Keshavan⁸, Godfrey D. Pearlson^{9,10}, Gunvant K. Thaker¹¹, and David J. Schretlen^{1,3}

¹Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD; ²Division of Psychiatry Research and Psychogeriatric Medicine, University of Zürich, Zürich, Switzerland; ³The Russell H. Morgan Department of Radiology and Radiological Science, Division of MR Research, Johns Hopkins University School of Medicine, Baltimore, MD; ⁴F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD; ⁵Department of Neurology and ⁶Department of Neuroscience and Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD; ⁷Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX; ⁸Department of Psychiatry, Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston, MA; ⁹Olin Neuropsychiatry Research Center, Hartford Hospital, Hartford, CT; ¹⁰Department of Psychiatry and Neurobiology, Yale University School of Medicine, New Haven, CT; ¹¹Department of Psychiatry, University of Maryland, School of Medicine, Baltimore, MD

*To whom correspondence should be addressed; Division of Psychiatry Research and Psychogeriatric Medicine, University of Zürich, Minervastrasse 145, CH-8032 Zürich, Switzerland; tel: +41-44-3891-453, fax: +41-44-3891-447, e-mail: paul.unschuld@uzh.ch

Objective: Cognitive dysfunction is a core feature of schizophrenia, and persons at risk for schizophrenia may show subtle deficits in attention and working memory. In this study, we investigated the relationship between integrity of functional brain networks and performance in attention and working memory tasks as well as schizophrenia risk. **Methods:** A total of 235 adults representing 3 levels of risk (102 outpatients with schizophrenia, 70 unaffected first-degree relatives of persons with schizophrenia, and 63 unrelated healthy controls [HCs]) completed resting-state functional magnetic resonance imaging and a battery of attention and working memory tasks (Brief Test of Attention, Hopkins Verbal Learning Test, and Brief Visuospatial Memory Test) on the same day. Functional networks were defined based on coupling with seeds in the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), and primary visual cortex. Networks were then dissected into regional clusters of connectivity that were used to generate individual interaction matrices representing functional connectivity within each network. **Results:** Both patients with schizophrenia and their first-degree relatives showed cognitive dysfunction compared with HCs. First canonicals indicated an inverse relationship between cognitive performance and connectivity within the DLPFC and MPFC networks. Multivariate analysis of variance revealed multivariate main effects of higher schizophrenia risk status on increased connectivity within the DLPFC and MPFC networks. **Conclusions:** These data suggest that excessive

connectivity within brain networks coupled to the DLPFC and MPFC, respectively, accompany cognitive deficits in persons at risk for schizophrenia. This might reflect compensatory reactions in neural systems required for cognitive processing of attention and working memory tasks to brain changes associated with schizophrenia.

Key words: resting state/fMRI/default-mode network/attention/working memory

Introduction

Schizophrenia is a chronic and disabling neuropsychiatric illness associated with genetic and environmental risk factors for abnormal brain development.^{1,2} Although the diagnosis of schizophrenia is predominantly defined by signs of psychosis,³ cognitive impairment is a key characteristic of the disease and might predict long-term functional outcome more strongly than the severity of psychotic symptoms.^{4–6} Moreover, cognitive dysfunction in schizophrenia typically precedes the onset of psychotic symptoms⁷ and is seen in unaffected first-degree relatives of patients with schizophrenia, thus potentially reflecting an early phenotype of brain changes associated with elevated risk for schizophrenia.^{8–13} Although patients with schizophrenia experience deficits in various cognitive skills, attention and working memory are particularly affected.^{14–19} Many tests are available to assess attentional and working memory performance levels. In this study,

we used the Brief Test of Attention (BTA) and the first learning trials of both the Hopkins Verbal Learning Test-Revised (HVLT-R) and Brief Visuospatial Memory Test-Revised (BVM-T-R) as described below.^{20–24}

Functional magnetic resonance imaging (fMRI) using the blood oxygen level-dependent (BOLD) contrast is a standard technique for noninvasively measuring neuronal activity based on changes in magnetization by imaging the hemodynamic variance.^{25,26} Patterns of neuronal interaction can be assessed based on changes in functional connectivity as measured by synchrony of BOLD signal in spatially remote brain regions.^{27–29} Functional connectivity may be assessed by applying independent component analysis^{30–33} or seed-driven approaches^{34–39} to identify altered functional coupling in neuropsychiatric disease. Seed-driven functional connectivity analysis can delineate functional topography and disease-related changes by dissociating functionally and anatomically heterogeneous brain regions of interest.^{40–44} An integrated approach of assessing seed-based functional connectivity and component-based reduction of noise has been published recently.^{45,46}

Basal neural activity of brain systems associated with cognitive processing is reflected by the presence of several low-frequency networks at rest.^{30,34,38,47–49} Resting-state functional networks that are implicated in processing of attentional and working memory tasks include the cingulo-opercular (CON), default-mode (DMN), frontoparietal (FPN), and visual processing (VIN) networks. Brain regions that comprise these functional networks can be identified based on BOLD signal coupling to seeds located in the dorsal anterior cingulate cortex (dACC), medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), and primary visual cortex (BA17), respectively.^{50–57}

Although several studies reported alterations of functional brain network connectivity in patients with schizophrenia and their siblings,^{58–64} schizophrenia-related attention and working memory deficits also have been correlated with distinct alterations of functional coupling, particularly hyperactivity of the DMN.^{39,65,66} One recent study reported increased activity of the DMN during a working memory task and also at rest in both patients with schizophrenia and unaffected siblings compared with healthy controls (HCs), suggesting an impact of network connectivity on schizophrenia-related thought disturbances and also on risk for the illness.³⁹ However, to our knowledge, no studies have been published addressing the relationship between basal neural activity within networks associated with cognitive brain systems implicated in processing of attention and working memory tasks, and respective test performance in a schizophrenia population.

Given that dysfunction of systems involved in attention and working memory is a core feature of schizophrenia,^{14,18,19,50} we hypothesized that individual risk for

schizophrenia may be associated with distinct functional network properties related to performance in these domains and thereby reflect the integrity of implicated brain systems. To answer this question, 235 individuals with differing levels of schizophrenia risk status were administered a battery of attention and working memory tasks and BOLD-fMRI at rest the same day. Low-frequency brain networks were identified based on coupling with the dACC, MPFC, DLPFC, and BA17 as a reflection of the cognitive systems relevant to decreased cognitive performance in schizophrenia. Connectivity matrices were generated for each network, and multivariate statistics were used to test the relationship of within-network connectivity to schizophrenia risk status and cognitive performance by applying multivariate analysis of covariance (MANCOVA) and canonical variate analyses, respectively.

Methods

Study Sample

Study participants were recruited from the Maryland site sample of the Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP).⁶² In brief, we included 102 patients with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia (“patients with schizophrenia”) and 133 unaffected adults recruited from clinics and other research studies conducted at the Maryland Psychiatric Research Center and the Johns Hopkins University Hospital in Baltimore, Maryland. The unaffected sample included 70 adults who had a first-degree relative with schizophrenia (“schizophrenia-relatives”) and 63 HCs with no known family history of schizophrenia or any other psychotic disorder. This resulted in 3 groups with a stepwise increase in risk for schizophrenia: HCs, schizophrenia-relatives, and patients with schizophrenia. The structured clinical interview for DSM-IV axis I disorders^{3,67} was conducted by trained clinical raters to establish diagnoses. This study was approved by the Johns Hopkins School of Medicine and University of Maryland Institutional Review Boards. Written informed consent was obtained from every participant in accordance with the Declaration of Helsinki.⁶⁸ None of the participants had a history of severe neurologic illness or known substance abuse fulfilling criteria for DSM-IV. Level of education was assessed as highest grade in school completed (maximum = 20). As age, education, and sex differed across groups, all 3 were used as covariates in analysis of covariance (ANCOVA) and MANCOVA analyses (table 1). Seven schizophrenia-relatives and 5 HCs reported specific serotonin reuptake inhibitor (SSRI) medication use within the last 4 weeks. Patients with schizophrenia were clinically stable with constant medication doses for at least 4 weeks. Medications of patients with schizophrenia within the last 4 weeks included: mood stabilizers (20), typical antipsychotics (19), atypical antipsychotics

Table 1. Demographics of the Included Study Population

	Healthy Controls (<i>n</i> = 63)	Schizophrenia-Relatives (<i>n</i> = 70)	Patients With Schizophrenia (<i>n</i> = 102)	<i>F</i> _{2,232}	<i>P</i>
Age (y)	44 (11.3)	45.3 (13.7)	37 (12.7)	11	<.01
Sex (% females)	57%	71%	33%	15.1	<.01
Race (Caucasian/African/other)	57/39/4	45/50/5	44/53/3	1.8	.17
Education (y)	14.6 (2.4)	14.1 (2.8)	12.8 (2.2)	12.1	<.01

(89), benzodiazepines (14), tricyclic antidepressants (1), SSRIs (42), and psychostimulants (2); antipsychotic medication was converted to chlorpromazine (CPZ) equivalent doses.⁶⁹ Mean (SD) antipsychotic medication in the schizophrenia sample was equivalent to a daily CPZ dose of 21.9 (15.7) mg. Among patients, psychotic psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS).⁷⁰ Mean (SD) positive, negative, and general psychopathology scores were 15.0 (6.2), 15.4 (5.6), and 26.2 (6.6), respectively. The mean disease duration for patients with schizophrenia was 15.3 (11.7) years.

Neuropsychological Assessment

All participants completed a battery of 3 tests for assessment of attention and working memory performance. One test was the BTA.^{23,24} In this computer-assisted test of auditory attention, lists of letters and numbers (eg, F-3-7-R-4-7-2-Q) are presented, and the examinee must ignore the numbers and count how many letters were presented (or vice versa). The total number of correctly monitored lists was recorded. The other 2 tests included the revised HVLt-R^{20,21} and the revised BVMT-R.^{22,71} These 2 tests assess learning and memory for words and designs, respectively. The total numbers of words (HVLt-R) and designs (BVMT-R) recalled after the first presentation trial of each test were taken as measures of working memory performance. The scores for all 3 measures were converted to *z* scores based on the entire sample (*n* = 235), and each person's mean *z* score was computed as a composite measure of attention and working memory. Internal consistency of the test battery used for generation of the composite attention and working memory performance score was tested using average measures intraclass correlation for estimation of Cronbach's coefficient α .^{72,73} One-way ANCOVA was used to assess main effects of schizophrenia risk status on test performance, with age, sex, and years of education as covariates (SPSS for MAC OS, version 19.0; Statistical Package for the Social Sciences, IBM, 1968).

Acquisition and Preparation of fMRI Data

The fMRI data were acquired using a Siemens Magnetom Trio 3 Tesla machine at the Johns Hopkins Hospital.

A standard gradient-echo echo-planar imaging pulse sequence (repetition time [TR]: 2210 ms; echo time [TE]: 30 ms; flip angle: 70°; voxel size: 3.4 × 3.4 × 3.0 mm; slice thickness: 3 mm effective slice thickness; 30 slices; 140 time points; scan time: 5 minutes, 10 seconds) was used. Participants were asked to remain awake with their head still and eyes open during the fMRI sequence. To limit potential head movement and subsequent motion artifact, a head coil cushion and additional lateral cushioning were used.

The fMRI data were preprocessed using Matlab 7.12 (64 bit; MathWorks, Inc), Statistical Parametric Mapping (SPM8) software⁷⁴ (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>), Matlab signal processing toolbox (V 6.15), and functional connectivity toolbox (V 13g, <http://www.nitrc.org/projects/conn/>).⁴⁶ Individual fMRI data were preprocessed by an initial correction for timing differences between slices, realignment, spatial normalization to Montreal Neurological Institute (MNI) standardized space (<http://www.mni.mcgill.ca/>), high-pass frequency filter (128 second), correction for temporal autocorrelation and spatial smoothing with a 6 mm³ full-width half-maximum Gaussian kernel. The art tool (www.nitrc.org/projects/artifacts/artifact_detect/) was used to explore fMRI data for artifacts and to generate a matrix of outlier time points, which were used as first-level covariates for estimation of functional networks.⁴⁶ To increase specificity for gray matter signals and to reduce impact of physiological noise such as white matter and cerebrospinal fluid signals, a bandpass filter (0.01–0.1 Hz) and the anatomical component-based noise correction method (CompCor)⁴⁵ were applied using the Conn toolbox.⁴⁶

Statistical Analysis and Assessment of Functional Network Integrity

Spherical seeds of 6 mm in diameter were located in regions representing central nodes of the functional brain networks of interest. These brain regions included (1) left DLPFC (Brodmann area [BA] 46, MNI -46/36/16), (2) MPFC (BA 32, MNI -4/54/-8), (3) dACC (BA 24/32, MNI -9/28/20), and (4) striate visual cortex (BA 17, MNI -13/-89/2). Locations of seeds are based on standard coordinates included in the Conn toolbox that are consistent with earlier reports on seed-based functional

connectivity^{36,37,39,46,75} and were thus independent from our data. The Region of Interest Extraction Tool (<http://web.mit.edu/swg/rex/rex.m>) was used to generate sets of peak-based coherent clusters for each local maximum area of BOLD synchrony within each of the 4 networks, applying default clustering parameters: Regions of interest representing the networks to be analyzed were defined at a height threshold of $P < .01$ (voxel level) and extent threshold of familywise error corrected $P < .005$ (cluster level). Clusters were defined for the whole group of 235 participants by extracting 1 data set separately for each local-maximum area within each region of interest file, representing mean connectivity values (minimum distance between peaks of 20 mm, maximum peaks per cluster = 32).

Matlab Statistics Toolbox (version 7.5) and Symbolic Math Toolbox (version 5.7) were used to generate correlation matrices of BOLD synchrony between all clusters in each of the 4 networks for each of the 235 study participants as a multivariate representation of within-network functional connectivity. Correlation matrices were converted to normally distributed z scores to facilitate parametric statistical analysis. For each cluster, eigenvalues reflecting within-network interaction were estimated. In a next step, for each network, canonical variates representing linear estimates of multivariate cluster coupling with largest separation of groups were generated.^{76,77} MANCOVA^{22,71} was used to test main effects of schizophrenia risk status (HCs, schizophrenia-relatives, and patients with schizophrenia) including age, sex, and education as covariates. Adjustment of significance levels for multiple comparisons (correction for testing 4 network specific

hypotheses, $\alpha = 0.0125$ for $P < 5\%$) was performed by applying the Bonferroni–Holm method.⁷⁸ In addition, partial correlation analysis was performed to test for relationships between canonical variates and cognitive performance after controlling for potential effects of age, sex, and education.

Results

Cognitive Performance of Patients With Schizophrenia and Unaffected Relatives Is Significantly Worse Than That of HCs

A one-way ANCOVA with age, sex, and education as covariates revealed significant differences in cognitive performance between controls, schizophrenia-relatives, and patients with schizophrenia for all 3 neuropsychological tests and the attention and working memory composite (BTA: $F_{2,229} = 25.219$); HVL: $F_{2,229} = 10.428$; BVMT: $F_{2,229} = 9.005$; attention and working memory composite: $F_{2,229} = 25.326$). No significant effect on cognitive performance was found for any of the covariates (table 2). Internal consistency for the set of attention and working memory tests applied is indicated by significant intraclass correlation (Cronbach’s coefficient $\alpha = 0.71$, $F_{234,468} = 3.45$). Moreover, no significant relationship could be observed between psychopathology (PANSS total score) and cognitive performance ($r = -.072$, $P = .45$) or psychopathology and CPZ equivalents ($r = .14$, $P = .89$). Also, when testing relationships with positive symptoms (PANSS-positive symptom score), no significant correlation could be observed with cognitive performance ($r = -.10$, $P = .92$) or CPZ equivalents ($r = .004$, $P = .96$).

Table 2. Cognitive Performance by Study Group and Effects of Schizophrenia Risk (SZ Risk), Age, Sex, and Education on the Respective Test Performance Scores

		Hopkins Verbal Learning Test, First Trial	Brief Visuospatial Memory Test, First Trial	Brief Test of Attention	Composite Score, Test Performance
Means (SD)	Healthy controls ($n = 63$)	1.4 (0.9)	1.4 (0.9)	1.6 (0.7)	1.5 (0.6)
	Schizophrenia relatives ($n = 70$)	1.2 (1)	1.1 (1)	1.2 (0.8)	1.2 (0.7)
	Patients with schizophrenia ($n = 102$)	0.6 (0.9)	0.7 (1)	0.5 (1.1)	0.6 (0.8)
SZ risk	$F_{2,229}$	10.428	9.005	25.219	25.326
	Significance (P)	.00005	.0002	.00001	.00001
	Partial η^2	0.084	0.073	0.181	0.182
Age	$F_{1,229}$	1.688	5.34	0.665	4.039
	Significance (P)	.99	.352	.99	.736
	Partial η^2	0.007	0.023	0.003	0.017
Sex	$F_{1,229}$	0.041	1.097	0.511	0.079
	Significance (P)	.99	.99	.99	.99
	Partial η^2	0	0.005	0.002	0.003
Education	$F_{1,229}$	5.31	6.604	1.468	7.59
	Significance (P)	.352	.176	.99	.096
	Partial η^2	0.023	0.028	0.006	0.032

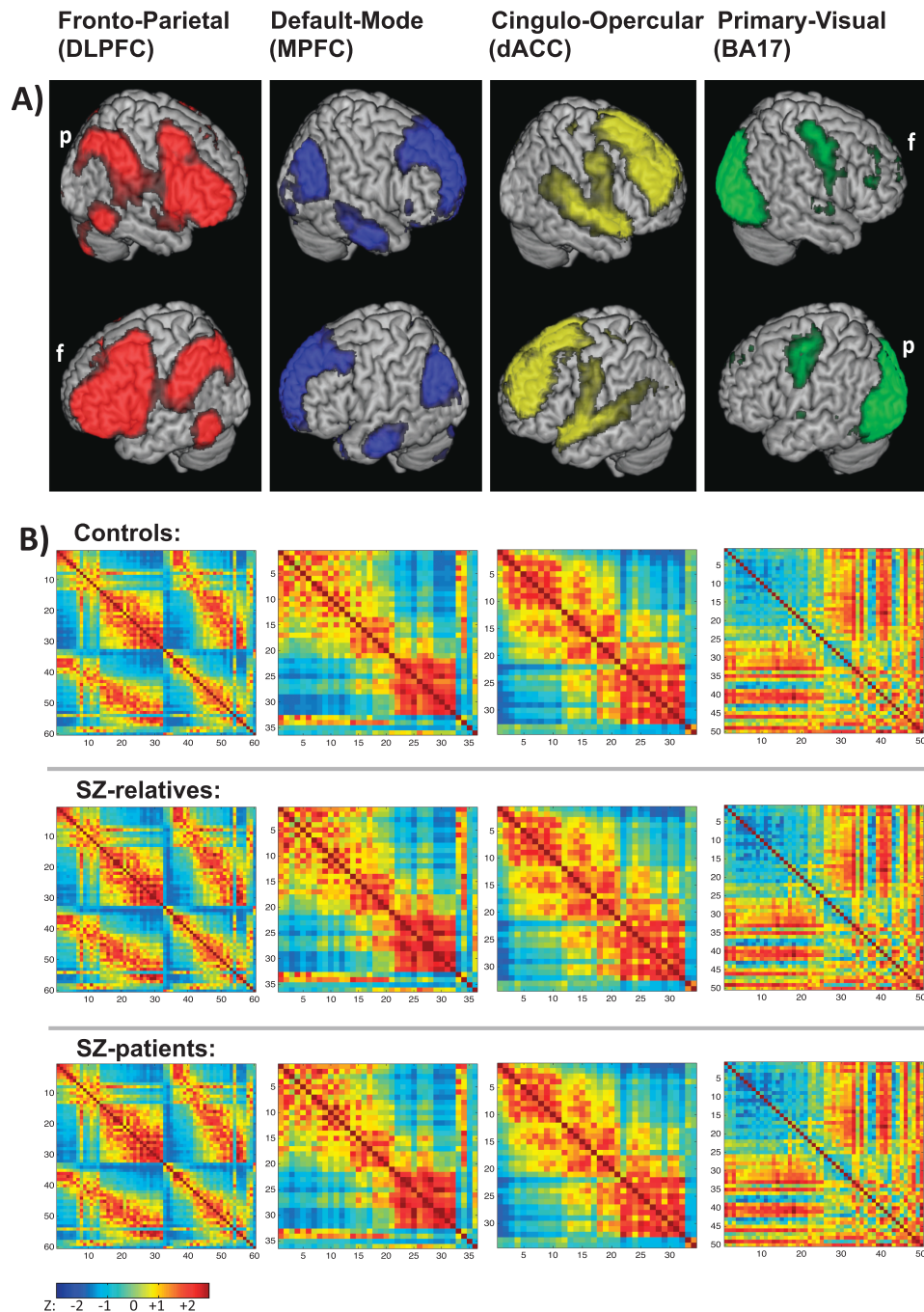


Fig. 1. (A) Definition of 4 functional networks using maps of blood oxygen level-dependent synchrony with seeds in the left hemisphere (dorsolateral prefrontal cortex [DLPFC], dorsal anterior cingulate cortex [dACC], medial prefrontal cortex [MPFC], and primary visual cortex [BA17]). (B) Functional coupling of clusters within each network and schizophrenia (SZ) risk group, displayed are z scores representing mean within-network connectivity.

Identification of Low-Frequency Brain Networks at Rest and Clustering of Functional Subunits of Regional BOLD Synchrony

Seeds located in the MPFC, DLPFC, dACC, and BA17 were used to generate functional connectivity maps consistent with earlier reported low-frequency brain networks, present at rest (DMN, FPN, CON, and primary visual [V1N]) involving selected brain regions^{48,49,51,53}

(figure 1A; table 3). Mean (SD) sizes of networks (voxel) for the 3 groups were (a) FPN: Controls 60 619 (5272), relatives 61 066 (5988), patients 60 182 (5946); (b) DMN: Controls 55 622 (6203), relatives 57 257 (6532), patients 55 862 (6411), (c) CON: Controls 77 215 (9446), relatives 76 944 (9276), patients 78 881 (9996); (d) V1N: Controls 42 666 (2924), relatives 42 077 (2908), patients 42 479 (2800). Using ANCOVA with age, sex, and education as

Table 3. Brain Regions Included Within the Respective Networks and Size in Voxels

Network	Brain Region	Brodmann Area	Cluster Size (Voxel)	Cluster Size (%)
FPN	Total	—	60 562	100
	Inferior parietal lobule	40	9301	15.36
	Premotor cortex	6	8432	13.92
	Anterior prefrontal cortex	10	6922	11.43
	Area frontalis granularis	9	4590	7.58
	Area parietalis superior	7	4007	6.62
	Insular cortex	13	3796	6.27
	Occipitotemporal area	37	3525	5.82
	Cerebellum	—	3215	5.31
	Orbital area	47	3036	5.01
	Superior frontal cortex	8	2568	4.24
DMN	Total	—	56 213	100
	Superior frontal cortex	8	8931	15.89
	Posterior cingulate cortex	31	5642	10.04
	Lateral temporal cortex	21	4605	8.19
	Anterior prefrontal cortex	10	4420	7.86
	Medial orbital gyrus	11	4154	7.39
	Parietal cortex	39	4058	7.22
	Subgenual cingulate	25	3169	5.64
	Entorhinal area	28	3116	5.54
	Perirhinal cortex	35	2893	5.15
	Area frontalis granularis	9	2745	4.88
CON	Total	—	77 858	100
	Area parietalis superior	7	15 629	20.07
	Premotor cortex	6	14 477	18.59
	Superior frontal cortex	8	10 324	13.26
	Anterior prefrontal cortex	10	8874	11.4
	Dorsal anterior cingulate	32	5029	6.46
	Insular cortex	13	4468	5.74
	Area supramarginalis	40	4076	5.24
	Temporopolar area	38	3146	4.04
	Superior temporal area	22	2834	3.64
	Subgenual cingulate	25	2546	3.27
V1N	Total	—	42 409	100
	Visual association area, parastriate area	18	10 239	24.14
	Visual association area, peristriate area	19	8958	21.12
	Area parietalis superior	7	6078	14.33
	Premotor cortex	6	4474	10.55
	Occipitotemporal area	37	4257	10.04
	Area retrosplenialis agranularis	30	2504	5.9
	Anterior prefrontal cortex	10	1937	4.57
	Ectorhinal area	36	852	2.01
	Primary auditory cortex	41	704	1.66
	Parahippocampal gyrus	27	654	1.54
	Medial orbital gyrus	11	573	1.35

Note: FPN, fronto parietal network; DMN, default-mode network; CON, cingulo-opercular network; V1N, visual processing network.

covariates, no significant group effect could be identified in either of the networks: (a) CON: $F_{2,229} = 1.03$, $P = .36$; (b) FPN: $F_{2,229} = .49$, $P = .61$; (c) DMN: $F_{2,229} = 1.36$, $P = .26$; (d) V1N: $F_{2,229} = .75$, $P = .47$. Also, no significant relationship could be observed between network size and the cognitive performance composite score: (a) CON: $r = .01$, $P = .91$; (b) FPN: $r = -.07$, $P = .26$; (c) DMN: $r = .02$, $P = .81$; (d) V1N: $r = -.06$, $P = .31$. For each network, voxels were clustered into functional subunits based on regional strength of coupling. This resulted in 36 subunits

for the DMN, 60 for the FPN, 34 for the CON, and 50 for the V1N, with a mean size of 1373 (SD = 1165) voxels.

Multivariate Analysis Reveals Relationships Between Functional Connectivity Within the FPN and DMN With Cognitive Performance and Schizophrenia Risk

For each of the 235 participants, 4 correlation matrices were generated, reflecting functional connectivity assessed by BOLD synchrony between brain regions

defined by functional clusters in the CON, FPN, DMN, and primary visual networks (figure 1B).

A one-way MANCOVA was used to test for differences between functional coupling within each network and individual schizophrenia risk status (control, unaffected

relatives, and patients with schizophrenia). Significant multivariate main effects resulted for the FPN (Wilks' $\lambda = 0.199$, $F_{120,340} = 1.33$, $P = .003$, partial $\eta^2 = 0.332$, observed power = 0.99) and DMN (Wilks' $\lambda = 0.415$, $F_{72,388} = 1.31$, $P = .016$, partial $\eta^2 = 0.197$, observed

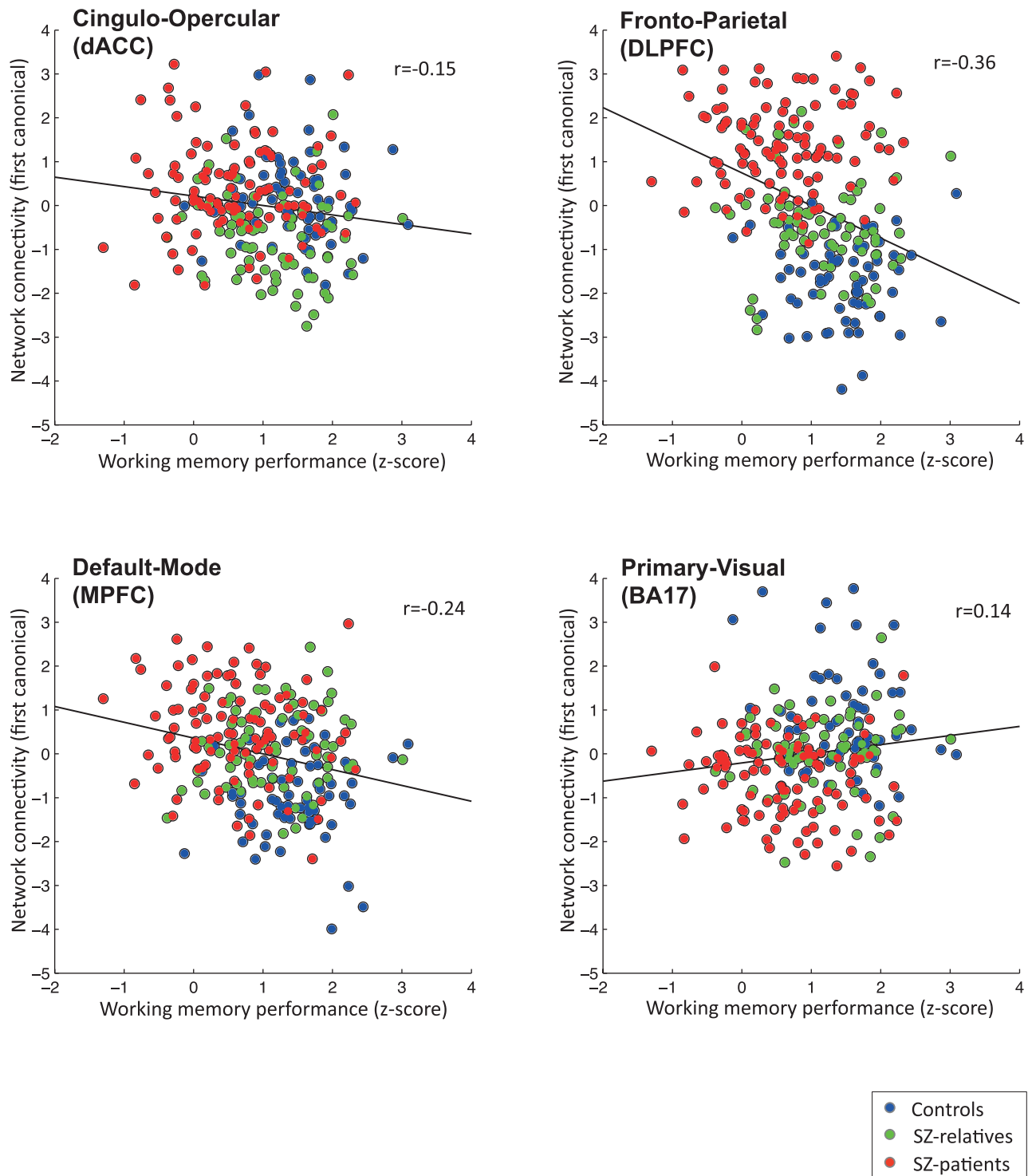


Fig. 2. Relationship between within-network coupling and cognitive performance for each of the functional networks assessed. Network connectivity is indicated based on standardized canonical variates, with strongest separation between groups as estimated by multivariate analysis of covariance.

power = 0.99). Linear representation of within-network connectivity by canonical variates indicates higher degree of coupling to be associated with higher schizophrenia risk (mean, SD): FPN: Controls: -1.70 (0.93), relatives: -0.46 (1.09), patients: 1.37 (0.98); DMN: Controls: -0.97 (0.97), relatives: 0.13 (0.92), patients: 0.51 (1.07) (figure 2). No significant main effects were found for the CON (Wilks' $\lambda = 0.455$, $F_{68,392} = 1.19$, $P = .09$, observed power = 0.99) and V1N (Wilks' $\lambda = 0.330$, $F_{100,360} = 1.02$, $P = .32$, observed power = 0.99). No significant main effects on within-network coupling were found for age, sex, or education.

To test for relationships between functional coupling within each network and cognitive performance, canonical variates were correlated with individual and cognitive composite scores. Significant relationships between high overall within-network functional connectivity and low cognitive performance scores were found for the FPN ($r = -.36$, $P = .001$) and DMN ($r = -.24$, $P = .003$), but not for the CON ($r = -.15$, $P = .12$) or V1N ($r = .14$, $P = .24$) networks (figure 2). No significant relationships were found for either of the networks, when correlations were tested within each group separately: Controls: CON: $r = -.14$, $P = .26$; FPN: $r = -.02$, $P = .91$; DMN: $r = .01$, $P = .95$; V1N: $r = -.16$, $P = .23$; Relatives: CON: $r = -.15$, $P = .22$; FPN: $r = -.07$, $P = .59$; DMN: $r = .13$, $P = .28$; V1N: $r = .06$, $P = .64$; Patients: CON: $r = .01$, $P = .9$; FPN: $r = .05$, $P = .63$; DMN: $r = -.14$, $P = .15$; V1N: $r = -.12$, $P = .22$.

Discussion

In this study, we found a significant relationship between coupling within the FPN and DMN and both cognitive test performance and schizophrenia risk. Although these findings are consistent with earlier data on altered network properties and cognitive deficits in schizophrenia,^{39,63,64} our results point toward the particular relevance of brain systems implicated in attention and working memory performance as reflected by connectivity within the FPN and DMN, for schizophrenia risk-associated pathological brain changes.

To probe integrity of brain networks potentially implicated in attention and working memory performance as well as elevated risk for schizophrenia, functional connectivity maps of brain areas coupled with regions of interest were generated and dissected into clusters of regional BOLD synchrony for a study population consisting of 102 patients with schizophrenia, 70 unaffected schizophrenia-relatives, and 63 HCs. For each study participant, cluster-based correlation matrices of BOLD activity reflecting connectivity within networks coupled to the DLPFC, the MPFC, the dACC, and the striate visual cortex, respectively, were generated and tested for significant main effects of test performance and schizophrenia risk status.

A particular strength of the current data set is the large size of the included study population, resulting in increased power to identify subtle effects of cognitive performance and schizophrenia risk on basal neural activity. As all MR scans were performed on the same scanner using the identical scanning parameters, potential bias through intersite variability could be avoided. By adhering to the standardized inclusion criteria established by the BSNIP consortium, comparability of this presented data with other sites is warranted and prospective cross-site meta-analyses are possible.

The neuropsychological tests used in this study to generate a composite score of attention and working memory performance have been validated earlier in various neuropsychiatric disease populations including schizophrenia, for assessment of attention as well as verbal and visuospatial working memory domains.^{20–24,79} Internal consistency of the composite test performance score was indicated by significant intraclass correlation coefficients and Cronbach's α , suggesting that the chosen tests were measuring a coherent cognitive process associated with attention and working memory performance.^{72,73} Individual cognitive performance levels have been shown to relate to within-network functional connectivity, reflecting the temporal interaction of neuronal populations and brain systems required to process such cognitive tasks.^{29,80} We assessed within-network connectivity by first dissecting the identified networks using a clustering approach and then estimating for each participant individual correlation matrices based on the BOLD time courses of clusters within each network as suggested earlier for multivariate analysis of activity within-cortical networks.⁸¹

Particular advantages of the multivariate approach chosen in this study include the possibility of drawing statistical inferences based on temporal BOLD correlations between network clusters without making assumptions about distinct regional effects or the integration of interactive temporal effects by producing generalized eigenimages. This makes it possible to transform multivariate main effects into linear canonicals that may serve as dimensional markers of effect size.^{65,82–84}

Although several studies using independent component analysis have demonstrated functional changes in schizophrenia vs unaffected individuals,^{61,62,85–87} region-based approaches suggest that hyperconnectivity within frontal brain networks might prove to be a hallmark of schizophrenia-associated brain changes that relate to both psychopathology and cognitive performance, potentially reflecting damage to distinct cognitive brain systems.^{39,58,64–66} In this study, we focused on 4 previously reported low-frequency brain networks with central nodes located in brain regions that are associated with cognitive processing. These include the FPN, DMN, CON, and primary visual networks. Each network was defined by functional coupling at rest to the DLPFC, MPFC, dACC, and striate visual cortex, respectively^{37,38,50–53} using

the Conn toolbox.^{45,46} Single, left-hemispherical seeds of identical shape were used for definition of all networks, making possible a uniform analytic strategy for effects on coupling within the respective connectivity maps and also facilitate comparability with earlier studies on network integrity in schizophrenia,^{39,58} which used similar approaches. Furthermore, single-seed approaches have been shown to be consistent with other techniques for assessment of network connectivity such as independent component analysis.⁸⁰

Consistent with earlier reports, we found significantly worse cognitive performance by patients with schizophrenia and their unaffected relatives, supporting earlier evidence of a close relationship between schizophrenia liability and cognitive deficits as a potential reflection of prefrontal brain dysfunction.^{8–13,19} The fact, however, that there was no significant correlation observable between psychopathology as measured with the PANSS and cognitive performance may be explained by effects of individual medication on psychopathology and cognition, respectively.

Moreover, our finding of relationships between cognitive impairment and heightened connectivity within the FPN and DMN corresponding to increased risk of schizophrenia is consistent with reports of prefrontal hyperconnectivity at rest in schizophrenia.^{39,58,61,63,87} Our finding that the strongest effects involve the FPN, may support earlier associations of DLPFC dysfunction with schizophrenia-associated brain changes and cognitive deficits.⁶⁵ The fact that these relationships were observable for the entire sample only, but not for the individual groups, corroborate the relevance of attention and working memory performance as a cognitive measure closely related to brain alterations that are associated with the diagnosis and risk for schizophrenia and in addition may be consistent with earlier reports on close relationships between schizophrenia risk and cognitive deficits.^{8–13,19}

Recent studies on cognitive performance-related brain activity suggest a complex pattern of changes characterizing the spectrum of individuals ranging from unaffected healthy to clinical populations with schizophrenia,^{88–90} with 1 recent study reporting decreased effective connectivity during working memory tasks in patients.⁹¹ Although altered connectivity has been suggested to be primary pathophysiology in schizophrenia,⁹² our findings of increased resting-state connectivity in the DMN and FPN might reflect deficits in physiologic system dynamics due to damage to the hierarchical organization of prefrontal cortex in schizophrenia.^{93,94} Moreover, our findings of increased connectivity in the DMN are consistent with recent publications including 1 BSNIP study, on reduced anticorrelations characterized by default-mode hyperactivity,^{62,85} and thus may support earlier considerations on prefrontal hyperconnectivity as a compensatory mechanism for schizophrenia-related dysregulation of inhibitory brain circuits.⁹⁵ In addition, our findings may be consistent

with recent findings in other neuropsychiatric disorders, suggesting that increased functional network connectivity might indicate cognitive impairment above traditional diagnostic boundaries.⁹⁶ The Bonferroni–Holm method was used to reduce multiplicity bias caused by testing hypotheses on effects of 4 functional networks; however, as the follow-up correlation analyses were not subject to correction for multiple testing, they may need to be interpreted with caution.⁷⁸

The fact that we do not find associations with networks originating from the dACC (CON) and striate visual cortex (primary visual network) is also consistent with notes on the particular relevance of prefrontal dysfunction in schizophrenia pathology.^{50,97–99}

No significant relationships of network size with schizophrenia risk status and cognitive performance, respectively, were observable in our data set. This might indicate higher power of analytical approaches focusing on changes of functional interaction patterns vs voxel-wise comparisons of network sizes for identifying functional correlates of psychopathology.

Limitations of this study include the fact that groups differed in age, sex, and education status. By including these variables as covariates, we were able to exclude significant contributions to the identified main effects on functional connectivity in FPN and DMN.

Although this study is focused on relative effects of BOLD coupling within each network, additional assessment of between network connectivity may provide further information regarding network interaction, as it has been suggested to be relevant for schizophrenia recently.^{62,63,85} However, a comprehensive assessment of between network connectivity would require additional methods of BOLD fMRI data analysis such as independent component analysis and would exceed the format of a single publication.

Another limitation of this study is the fact that in the group of patients with schizophrenia, representing the subgroup with the highest degree of liability for schizophrenia-associated pathological brain change, most individuals received antipsychotic medications. This could have biased the analysis, as a relationship between antipsychotic medications and BOLD contrast has been suggested and may also affect cognitive performance levels itself.¹⁰⁰ However, as it may be difficult to find a representative unmedicated population of patients with schizophrenia, we also included unaffected first-degree relatives of patients with schizophrenia, as a population with increased risk but without antipsychotic medication. This may have increased power to detect linear main effects consistent with our hypothesis of a relationship between network connectivity and cognitive performance.

Taken together, our data support earlier reports on impaired prefrontal network coupling in schizophrenia and also individuals at risk for schizophrenia. In addition, our study expands this earlier knowledge on schizophrenia

risk-associated brain change by demonstrating hyperactivity within the FPN and DMN, reflecting alterations in cognitive systems necessary for processing of attention and working memory tasks. Additional longitudinal studies will be needed to characterize the time course of damage to the identified brain systems, and their potential use as biomarkers for prospective cognitive enhancement therapies for persons with schizophrenia.

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