

# Supporting Information

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## SI Text

**Participants.** Participants were excluded if they had any lifetime diagnosis of substance dependence, neurological disease, history of head injury or medical illness with documented cognitive sequelae, sensory impairments, ever received electroconvulsive shock treatment, MRI exclusions (e.g., pregnancy, metal in the body), or an IQ less than 70. Relatives and controls were free of current psychotropic medications. The study received approval from the human research committees of the Massachusetts Mental Health Center, Massachusetts General Hospital, Brigham and Women's Hospital, Boston Veteran's Administration Healthcare (Jamaica Plain Division), Harvard University, and other recruitment sites. Participants 18 years of age and older gave informed consent. For children younger than 18 years of age, parents gave informed consent and the youngster gave assent. Subjects received an honorarium for participating.

Members of the patient group were recruited for the study during or shortly after their first inpatient hospitalization. Among these patients, 6 were diagnosed with paranoid schizophrenia, 1 was diagnosed with disorganized schizophrenia and 1 with residual schizophrenia, 4 were diagnosed with schizoaffective disorder (2 depressed type and 2 bipolar type) and 1 was diagnosed with schizophreniform disorder. Ten patients were receiving psychotropic medications. Five patients were taking multiple medications (1 was on olanzapine, escitalopram oxalate, quetiapine and risperidone; 1 was on clozapine and divalproex sodium; 1 was on quetiapine and fluoxetine hydrochloride; 1 was on bupropion and duloxetine hydrochloride; and 1 was on loxapine and sertraline), and 5 patients were on 1 medication each (olanzapine, risperidone, clonazepam, escitalopram oxalate, and 1 medication that the participant could not name).

For the relatives group, 11 of the schizophrenia probands (to whom the relatives group were related) were diagnosed with paranoid schizophrenia and 2 were diagnosed with undifferentiated schizophrenia. None of the relatives and patients in the study came from the same families.

To obtain a demographically comparable control group, control families with children in the same age range were recruited from the same geographic area, parental socioeconomic status, and ethnicity as the patient families. Advertisements were placed in the geographic areas of the hospitals from which the patients were ascertained (i.e., metropolitan Boston). This included posted advertisements in hospitals, neighborhood clinics, and local newspapers. Control participants went through the same clinical screening process as the relative group participants, except that control participants could not have a family history of psychotic disorder. Among the control participants, none had parents with a lifetime diagnosis of an Axis I psychiatric disorder.

**Psychiatric Assessment.** Patients were assessed using the Structured Clinical Interview for *DSM-IV* (1) and the SANS/SAPS (2, 3). Relatives and controls were assessed using the Diagnostic Interview for Genetic Studies (4) and the Family Interview for Genetic Studies (5). Relatives of schizophrenia probands were screened for the presence of psychosis and substance use with the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (6). The Psychosis, Mood Disorders, and Substance Abuse modules of the WASH-U-KSADS were administered to establish other inclusion and exclusion criteria. To assess general psychopathology in these nonreferred samples, psychiatric symptoms were assessed using the SCL-90-R (7). All participants were administered a neuro-

developmental questionnaire to establish other inclusion and exclusion criteria. On the day of scanning, participants were assessed using the Profile of Mood States (8) to determine their mood during the week before brain imaging.

**Neuropsychological Testing.** General intellectual ability (IQ) was prorated using 2 subtests (Vocabulary and Block Design) from the Wechsler Intelligence Scale for Children—Third Edition (9) for subjects younger than 17 years of age or the Wechsler Adult Intelligence Scale—Third Edition (10) for subjects aged 17 years and older. The Reading subtest of the Wide Range Achievement Test III (11) was used as an estimate of intellectual potential. Handedness was assessed using the scale developed by Annett (12).

**Neuroimaging.** Imaging was conducted on a Siemens Sonata 1.5-T full-body MRI scanner at the Massachusetts General Hospital Martinos Center. A sagittal localizer scan was performed for placement of slices, followed by a coronal T2-weighted sequence to rule out unexpected neuropathological findings. Two sagittal 3D magnetization prepared rapid gradient echo (MPRAGE) (T1-weighted, nonselective inversion prepared, spoiled gradient echo pulse) sequences were collected (repetition time [TR]/echo time [TE]/TI/flip = 2.73 s/3.39 ms/1.0 s/7deg, bandwidth = 190 Hz/pixel, sampling matrix = 256 × 192 pixels, field of view [FOV] = 256 × 256 mm, effective slice thickness = 1.33 mm on a 170-mm slab of 128 partitions) for anatomical localization of the functional imaging data. Two whole-brain gradient echo planar imaging acquisitions, 21 contiguous axial slices parallel to the anterior commissure–posterior commissure line (5 mm, 1-mm skip, TR/TE/flip = 2s/40ms/90deg; voxel size = 3.1 × 3.1 × 5 mm, FOV = 200 mm), were collected during cognitive tasks

## Analyses

**Artifact Detection.** Outliers in the blood oxygenation level-dependent (BOLD) intensity time series (>3 SD from the mean) were identified to determine the degree of noise/artifacts in the data. There were 168 time points per session, 2 sessions, and 13 subjects per group, which resulted in 4,368 time points per group. On average, 1% of the trials were identified as outliers for each subject, and there was no significant difference among groups ( $P > 0.26$ ) in the number of identified outliers. Motion parameters were included as confounds in the single-subject General Linear Model to reduce residual motion-related variance after realignment. Because it has been shown that group differences in levels of stimulus-correlated motion can create artifactual between-group differences in activation (13), aggregate stimulus-correlated motion was calculated for each subject and for each group. There were no significant differences among groups in stimulus-correlated motion ( $P > 0.22$ ), permitting valid between-group comparisons.

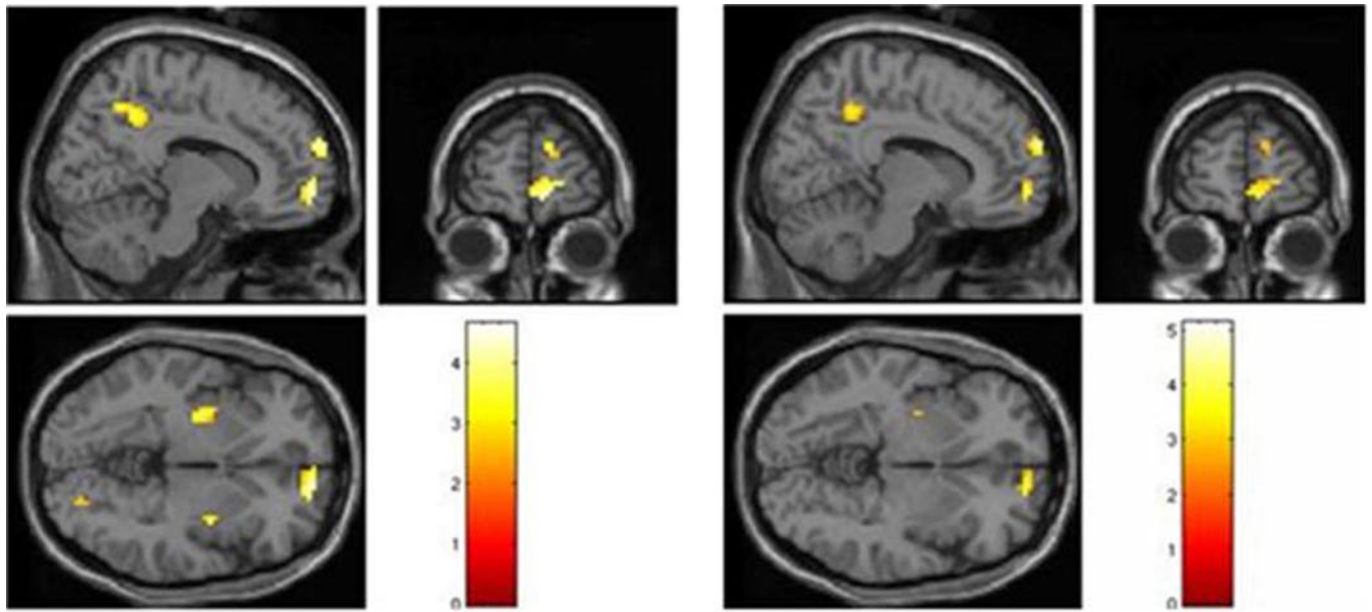
**Functional Connectivity.** Four seeds (MPFC, PCC, left lateral parietal, and right lateral parietal) were selected from the literature (14), and were thus independent of our data. For each group (controls, relatives, and patients), 4 sets of whole-brain connectivity maps ( $r$ -maps) were generated from each ROI seed for rest and for task. Correlations during rest and task were calculated in 1 of 2 ways. In the first approach, correlation maps were generated following the method described in the literature (14, 15). Several sources of spurious variance were removed from the data through linear regression: estimated motion param-

ters, global average BOLD signal, and average BOLD signals in ventricular and white matter ROIs. Cardiac-induced variations have been shown to be greater in areas with large vessels (16), whereas respiratory-induced variations tend to be localized in cerebrospinal fluid and surrounding tissue (17). Removing signals correlated with the global signal as well as with ventricles and white matter is a method of reducing nonneuronal contributions to BOLD correlations (14, 15, 18). This method, however, might be susceptible to confounding between-group effects attributable to possible group differences in these signals in patients versus controls. The second method was a direct calculation of Pearson's correlation coefficient between the band pass-filtered time series of each ROI and every voxel in the brain for the time points that corresponded to the relevant task/condition. For both methods, the resulting  $r$ -maps for each individual seed were then converted to  $z$ -scores using the Fisher transform and averaged across seeds to produce a single measure characterizing average correlations with default network areas.

Regardless of method, between-group differences revealed by the random effects analyses on the  $z$ -maps revealed that the patients were more correlated within the default network regions than the controls during rest.

**Anticorrelations.** We performed a one-sided  $t$  test looking for negative correlations with the MPFC seed region on the  $z$ -transformed  $r$ -maps for all subjects and defined a mask from the false discovery rate-corrected ( $P < 0.05$ ) anticorrelation results (for all participants,  $n = 39$ ). We then used this mask, which, on average, defines the regions that show anticorrelations with the MPFC, to restrict the between-group analyses of the  $z$ -transformed connectivity maps. This masking facilitates the interpretation, because results are now limited to regions showing anticorrelations only. For example, between-group connectivity comparisons testing a one-sided patient [SZ] > control [CON] contrast will identify regions with larger anticorrelations for CON than SZ (*cf.* without masking, it would also identify regions with larger positive correlations for SZ than CON).

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**Fig. S1.** Whole-brain between-group differences in task-related suppression as estimated with one-way ANOVA (*Left*) and one-way ANCOVA (*Right*) controlling for between-group differences in working memory performance (accuracy). Results were thresholded at  $P < 0.001$  uncorrected. Group differences remain similar after controlling for performance accuracy.

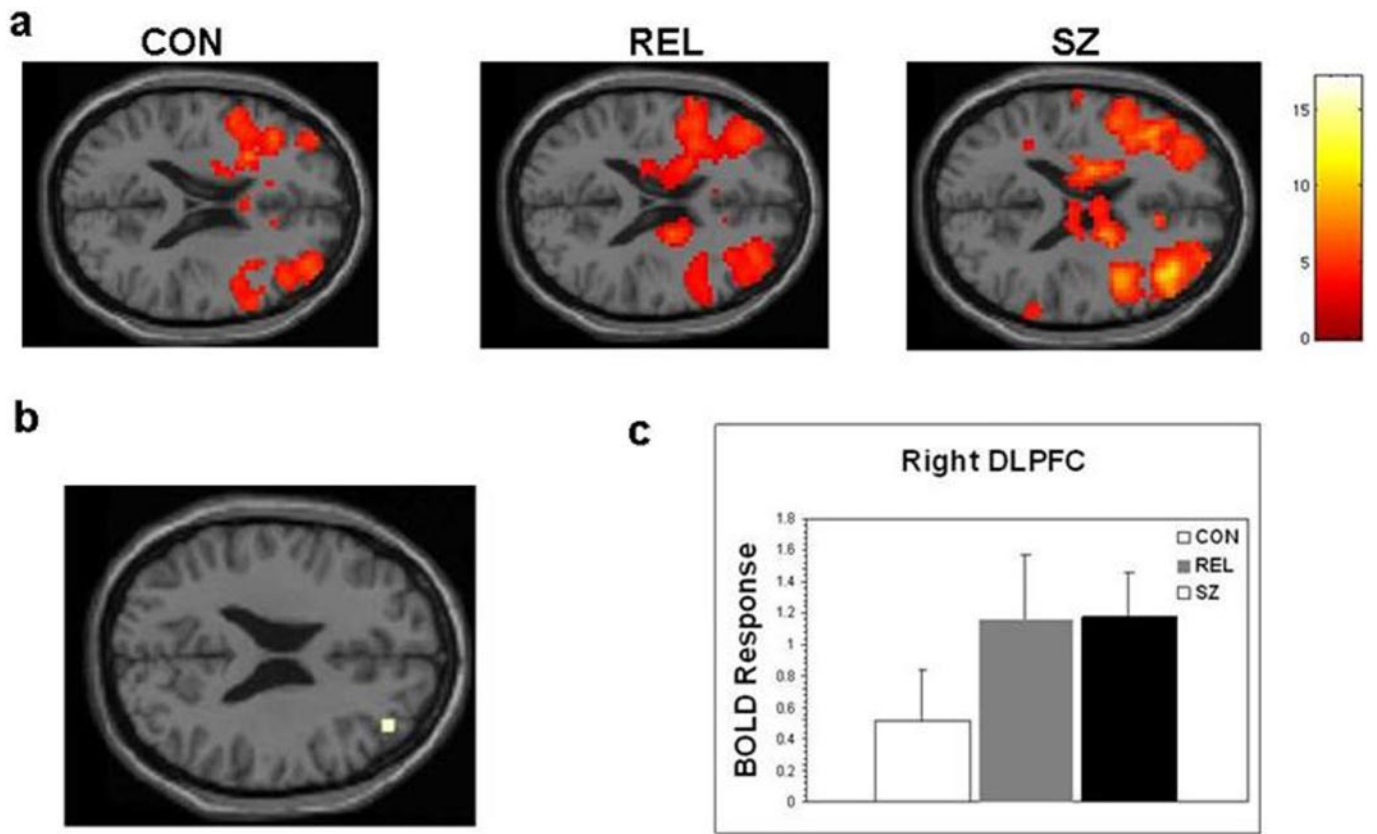


Fig. S2. Task-related activation. (a) Greater activation during task (2-back WM) than rest in right DLPFC for controls (CON), relatives (REL), and patients (SZ). (b) Region of significant differences among groups (BA46, peak: [43, 47, 25]). (c) Task-related activation (with 95% confidence intervals) in DLPFC cluster. There was significantly more task activation for patients and relatives than for controls.

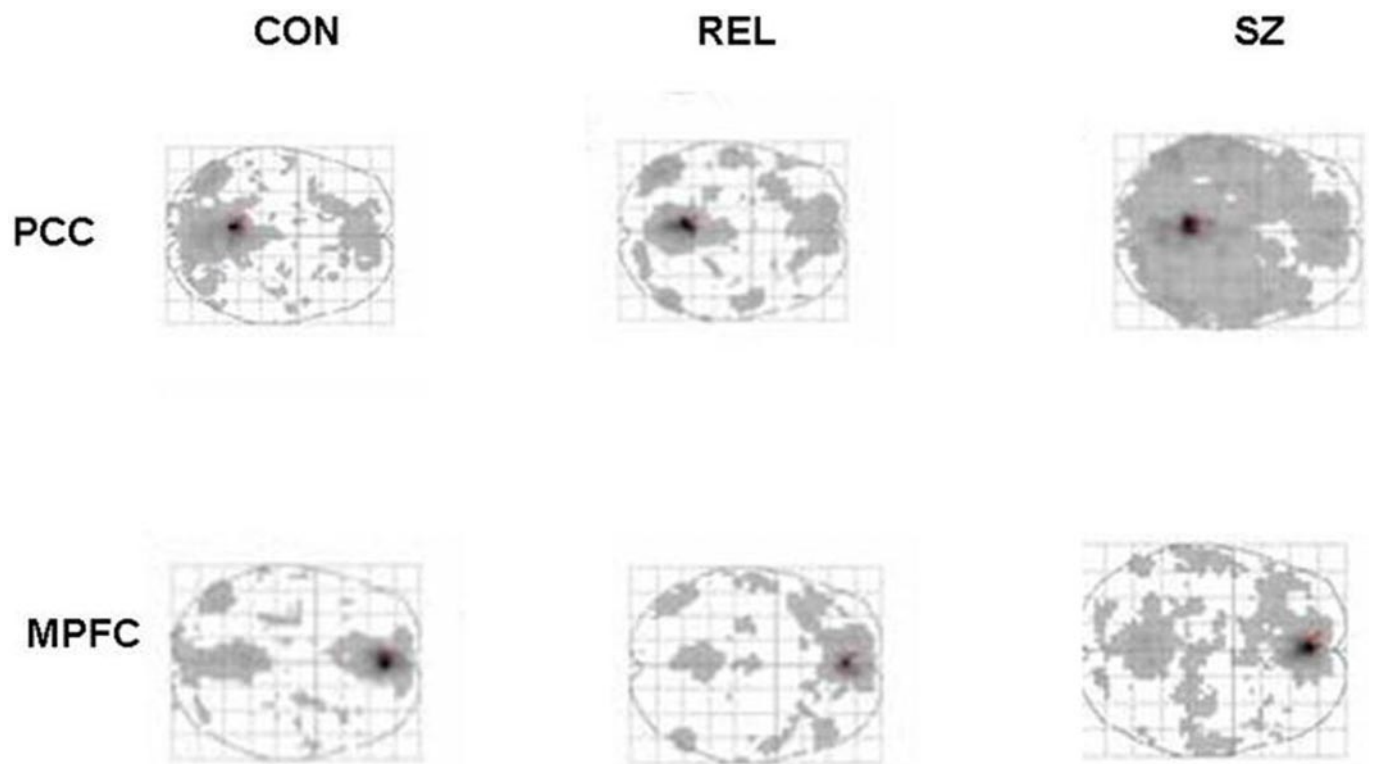
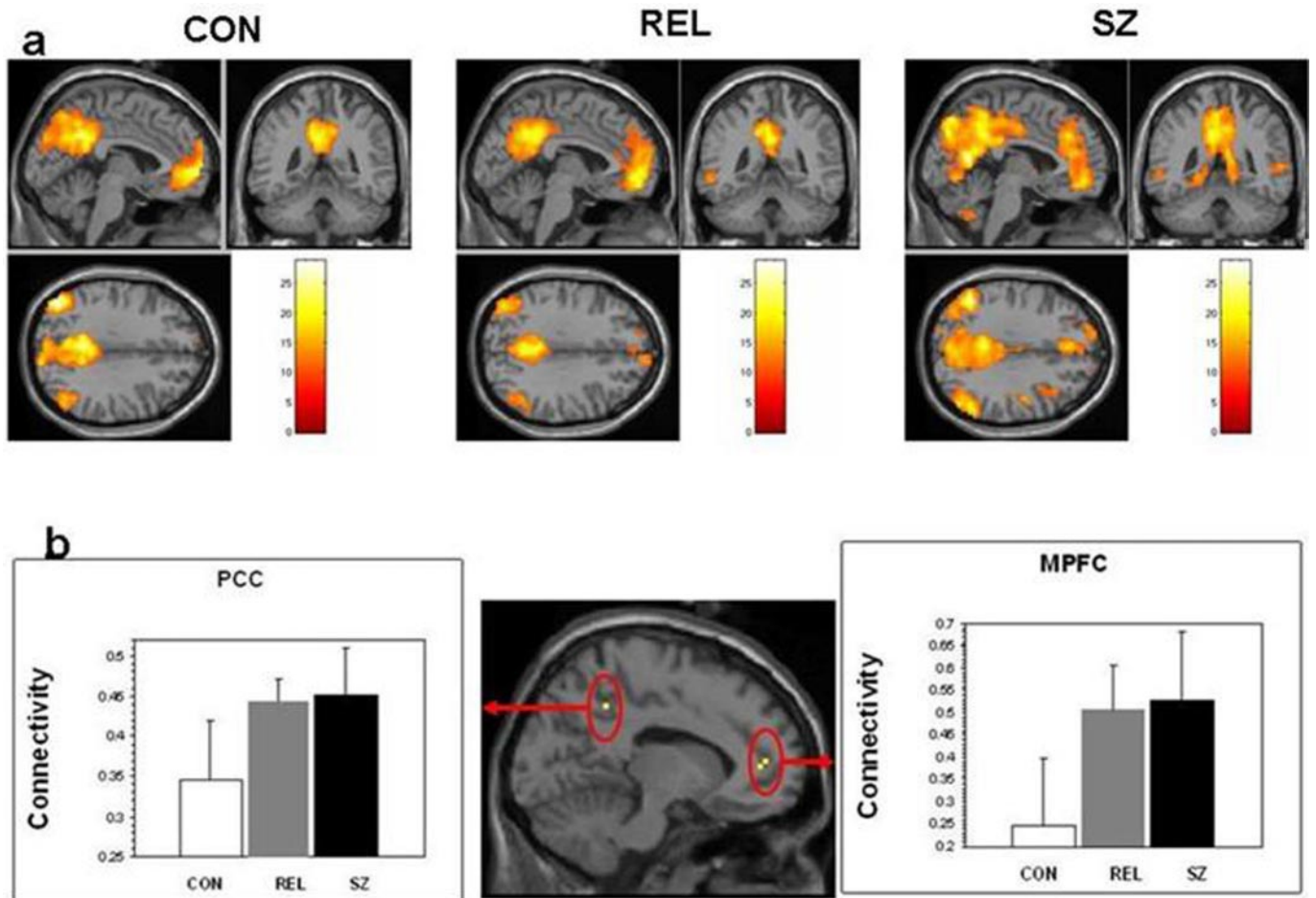
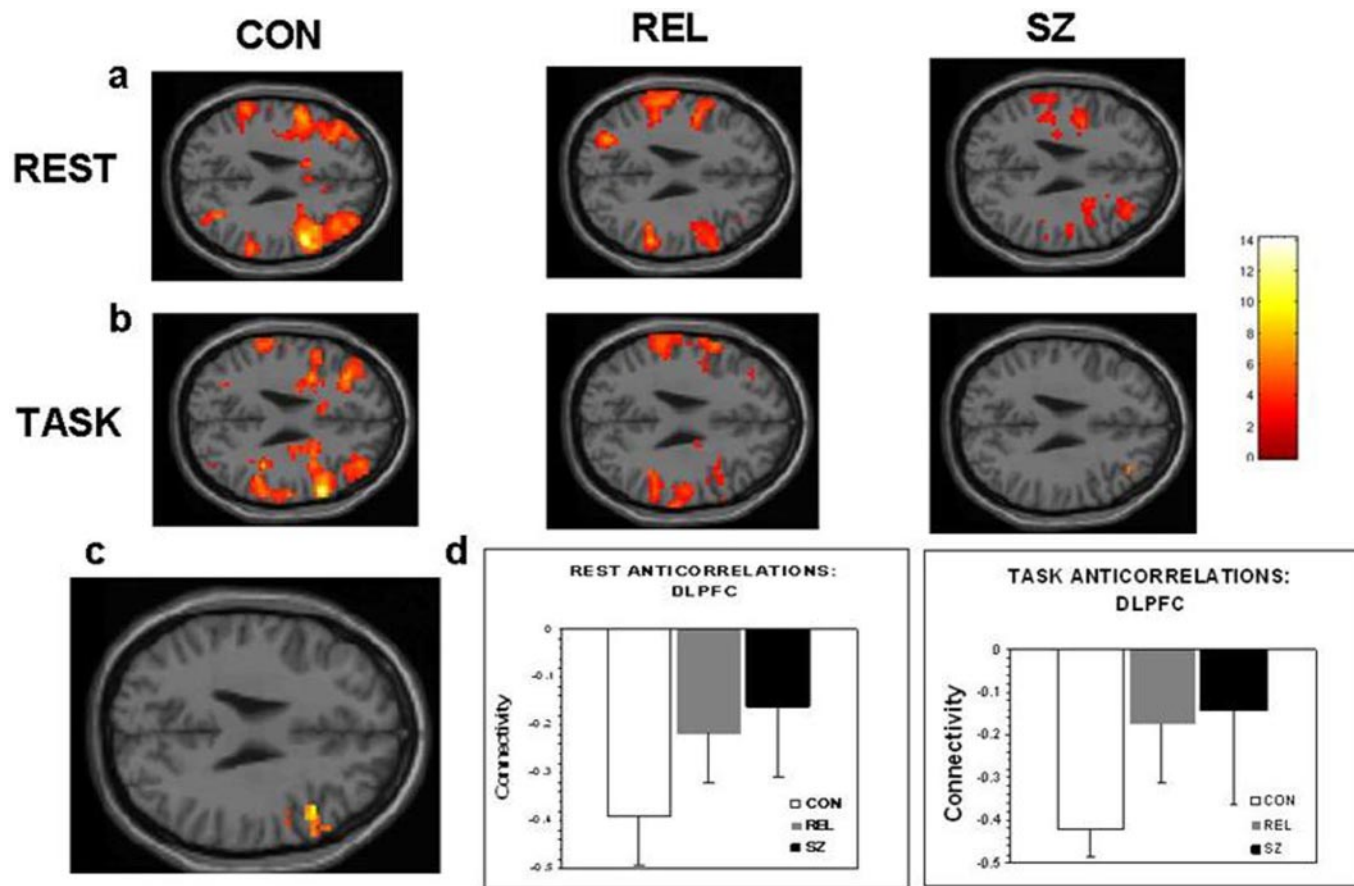


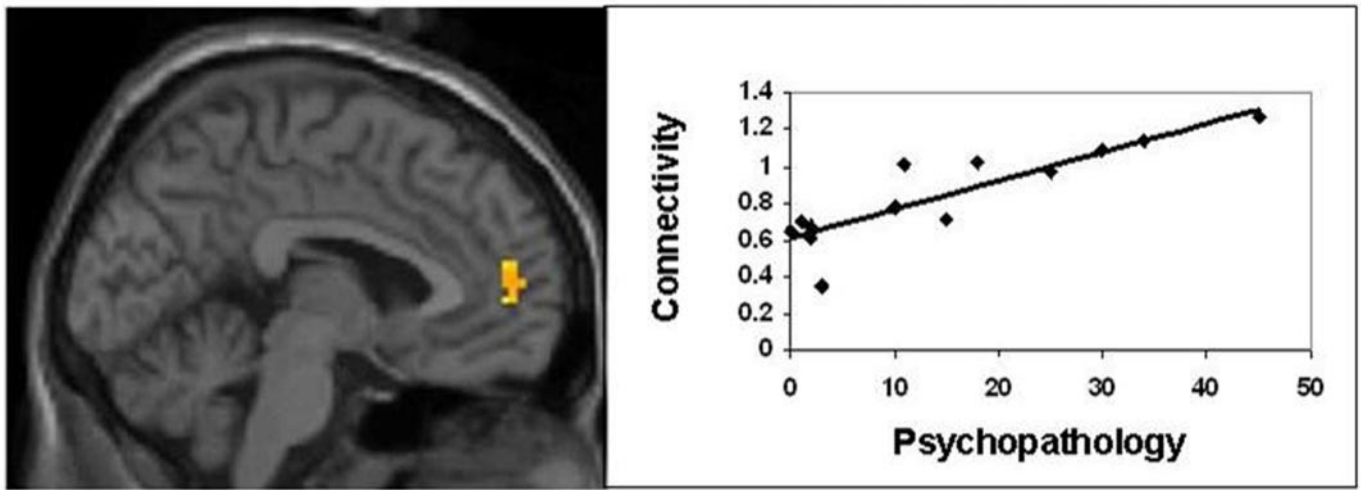
Fig. 53. Functional connectivity during rest for PCC seed region (*Top*) and MPFC seed region (*Bottom*) in controls (CON), relatives (REL), and patients (SZ). Glass brains depict maximum intensity projections.



**Fig. 54.** Functional connectivity with default network during 2-back WM task. (a) Areas showing positive connectivity with default network areas (averaged across 4 ROI seeds) in controls (CON), relatives (REL), and patients (SZ). (b) (Middle) Regions within default network showing significant connectivity differences between groups. Connectivity with default network (with 95% confidence intervals) in MPFC (*Right*, peak [−11, 50, 9]) and PCC/precuneus (*Left*, peak [−9, −45, 42]). There was significantly more connectivity with MPFC for relatives and patients than for controls and significantly more connectivity with PCC/precuneus for patients than for controls.

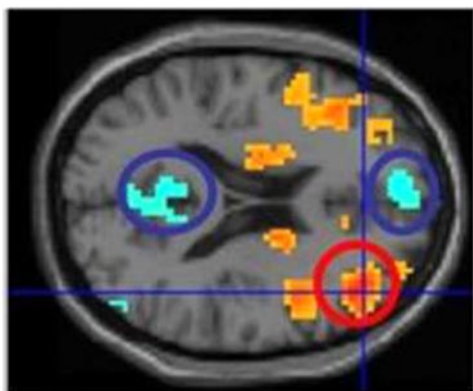
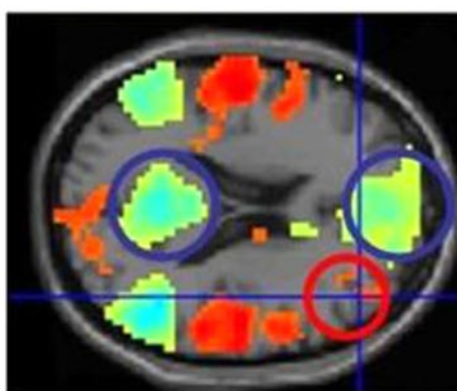
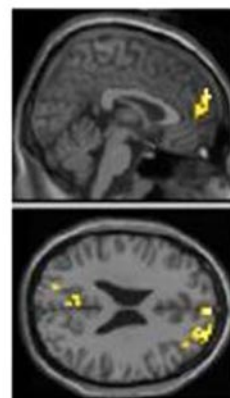
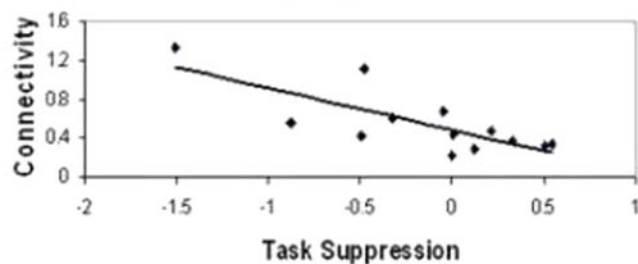
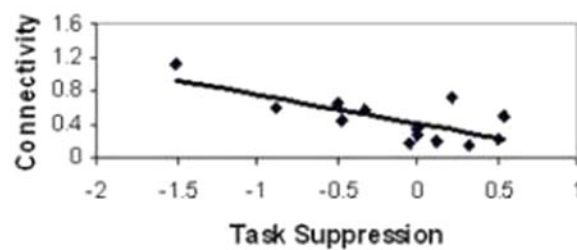


**Fig. S5.** Anticorrelations (negative connectivity) with MPFC during rest and task conditions. Areas with negative connectivity with MPFC during rest (a) and task (b) in controls (CON), relatives (REL), and patients (SZ). (c) DLPFC region (BA46 peak: [48, 18, 27]) showing significant differences between groups during rest. (d) Average MPFC connectivity (and within-group 95% confidence intervals) during rest (Left) and task (Right) conditions with DLPFC cluster. There was significantly more DLPFC anticorrelation with MPFC in controls than in patients and relatives.



**Fig. S6.** Functional connectivity during task correlated with psychopathological findings in patients. Whole-brain correlation between severity of psychopathological findings (composite SAPS score of positive symptomology) and strength of connectivity. Cluster peak in MPFC  $[-12, 51, 12]$ ,  $P < 0.001$ ,  $r = 0.89$ .



**a ACTIVATION****b CONNECTIVITY****c CORRELATION****d****MPFC****PCC**

**Fig. S7.** Correlation of task suppression and connectivity in patients. (a) Regions showing task suppression ( $\text{Rest} > 2b \text{ WM}$  in blue) and task activation ( $2b \text{ WM} > \text{rest}$  in red) in patients. Relative to controls, patients had decreased task suppression in MPFC and PCC and increased task activation in right DLPFC (Fig. 1 and Fig. S1). (b) Regions showing positive correlations with the default network during rest (blue) and regions showing negative correlations with the default network (red) in patients. Patients had increased default correlations with MPFC and PCC and reduced default anticorrelations with DLPFC (Fig. 2 and Fig. S2). (c) Whole-brain correlation of task suppression in MPFC (defined from ANOVA cluster in Fig. 1) and average default network connectivity. (d) There was a significant negative correlation between task suppression in MPFC and average default network connectivity in the above MPFC (BA10 [-6, 60, 30],  $r = -0.76$ ,  $P = 0.003$ ) and PCC/precuneus (BA7 [-12 -45 54],  $r = -0.74$ ,  $P = 0.004$ ) clusters.

**Table S1. Demographic, neurocognitive, and clinical variables in controls (CON), first-degree relatives of persons with schizophrenia (REL), and persons with early-stage schizophrenia (SZ)**

Variable	CON ( <i>n</i> = 13)	REL ( <i>n</i> = 13)	SZ ( <i>n</i> = 13)	CON vs. REL	CON vs. SZ	REL vs. SZ
	Mean (SD)	Mean (SD)	Mean (SD)	<i>t</i> ( <i>P</i> )	<i>t</i> ( <i>P</i> )	<i>t</i> ( <i>P</i> )
Age at MRI (years)	20.5 (3.3)	22.0 (2.9)	22.1 (2.1)	1.18 (0.25)	1.40 (0.18)	0.08 (0.94)
Socioeconomic status*	1.9 (1.0)	3.1 (1.5)	2.7 (1.3)	2.20 ( <i>P</i> < 0.05)	1.57 (0.15)	0.62 (0.54)
Years of education	12.5 (2.7)	12.0 (2.2)	12.5 (1.9)	0.55 (0.51)	0.00 (1.0)	0.66 (0.51)
IQ estimate <sup>†</sup>	110.1 (16.5)	104.2 (15.9)	106.0 (13.7)	0.93 (0.36)	0.65 (0.52)	0.30 (0.76)
Vocabulary <sup>†</sup>	13.2 (3.7)	10.8 (3.4)	11.4 (3.7)	1.73 (0.10)	1.20 (0.25)	0.41 (0.69)
Block Design <sup>†</sup>	11.5 (3.8)	12.2 (3.0)	10.7 (2.6)	0.51 (0.62)	0.67 (0.51)	1.39 (0.18)
WRAT-3 <sup>‡</sup> Reading	108.9 (10.1)	103.8 (12.3)	104.2 (9.4)	1.15 (0.26)	1.21 (0.24)	0.11 (0.92)
0-back % correct	97.4 (4.0)	98.2 (1.2)	91.0 (15.2)	0.76 (0.46)	1.46 (0.17)	1.71 (0.11)
0-back reaction time <sup>§</sup>	0.54 (0.12)	0.57 (0.05)	0.61 (0.11)	0.73 (0.48)	1.66 (0.11)	1.45 (0.17)
2-back task % correct	91.0 (7.9)	81.6 (20.6)	76.4 (21.0)	1.53 (0.15)	2.33 ( <i>P</i> < 0.03)	0.63 (0.54)
2-back reaction time <sup>§</sup>	0.74 (0.16)	0.86 (0.14)	0.83 (0.13)	2.03 ( <i>P</i> < 0.05)	1.57 (0.13)	0.53 (0.60)
	%	%	%	$\chi^2$ ( <i>P</i> )	$\chi^2$ ( <i>P</i> )	$\chi^2$ ( <i>P</i> )
Gender (% male)	62%	77%	69%	0.72 (0.4)	0.17 (0.68)	0.20(0.66)
Ethnicity (% white)	77%	62%	62%	0.72 (0.4)	0.72 (0.4)	0.00 (1.0)
Handedness (% right)	62%	85%	69%	2.64 (0.26)	2.20 (0.33)	0.87 (0.35)
	Mean (SD)	Mean (SD)	Mean (SD)	<i>t</i> ( <i>P</i> )	Controls with <i>t</i> -score >63 <sup>¶</sup>	Relatives with <i>t</i> -score > 63 <sup>¶</sup>
SCL-90-R <sup>¶</sup> Global Severity Index	42.9 (11.7)	50.9 (13.3)	NA	1.65 (0.11)	0 (0.0%)	2 (15.4%)

\*Parental Hollingshead Index (19).

<sup>†</sup>Wechsler Intelligence Scale for Children, Third Edition (9) or Wechsler Adult Intelligence Scale, Third Edition (10) prorated from Block Design and Vocabulary subtests.

<sup>‡</sup>Wide Range Achievement Test, Third Edition (11).

<sup>§</sup>Seconds: *P* < 0.05.

<sup>¶</sup>Symptom Checklist-90-Revised (SCL-90-R) (7) (*t*-score >63 is considered clinically meaningful).