An Anterior-to-Posterior Shift in Midline Cortical Activity in Schizophrenia During Self-Reflection

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Background: Deficits in social cognition, including impairments in self-awareness, contribute to the overall functional disability associated with schizophrenia. Studies in healthy subjects have shown that social cognitive functions, including self-reflection, rely on the medial prefrontal cortex (mPFC) and posterior cingulate gyrus, and these regions exhibit highly correlated activity during "resting" states. In this study, we tested the hypothesis that patients with schizophrenia show dysfunction of this network during self-reflection and that this abnormal activity is associated with changes in the strength of resting-state correlations between these regions.

Methods: Activation during self-reflection and control tasks was measured with functional magnetic resonance imaging in 19 patients with schizophrenia and 20 demographically matched control subjects. In addition, the resting-state functional connectivity of midline cortical areas showing abnormal self-reflection-related activation in schizophrenia was measured.

Results: Compared with control subjects, the schizophrenia patients demonstrated lower activation of the right ventral mPFC and greater activation of the mid/posterior cingulate gyri bilaterally during self-reflection, relative to a control task. A similar pattern was seen during overall social reflection. In addition, functional connectivity between the portion of the left mid/posterior cingulate gyrus showing abnormally elevated activity during self-reflection in schizophrenia, and the dorsal anterior cingulate gyrus was lower in the schizophrenia patients compared with control subjects.

Conclusions: Schizophrenia is associated with an anterior-to-posterior shift in introspection-related activation, as well as changes in functional connectivity, of the midline cortex. These findings provide support for the hypothesis that aberrant midline cortical function contributes to social cognitive impairment in schizophrenia.

Key Words: Cingulate gyrus, connectivity, fMRI, medial prefrontal cortex, schizophrenia, self

Specific deficits in social cognition have been found to predict quality of life and other real-world outcomes in schizophrenia (1,2). For example, one recent study found that capacity for self-reflection correlated with work performance in chronic schizophrenia patients (3). Moreover, there is evidence that some types of social cognitive deficits in schizophrenia are linked; for example, impairments in self-referential processing have been associated with deficits in theory-of-mind (4) and affect recognition (5) in schizophrenia. This suggests that these deficits may be associated with a common neural abnormality. Consistent with these findings is functional neuroimaging evidence for interdependence of social cognitive functions (6), such as self and person representations (7–10), in healthy people. Thus, a disruption of circuitry commonly recruited for a range of social cognitive functions could explain the pervasive nature of the impairment in this domain in schizophrenia patients.

Although the neurobiological basis of these deficits in schizophrenia has not been identified, studies conducted in healthy subjects have shown that many introspective mental processes, including self-reflection, rely on coordinated activity of two reciprocally connected, midline cortical regions: the medial prefrontal cortex and the posterior cingulate gyrus (11). Activity in these structures is typically elevated during task-free, "resting" states (12) and during introspectively focused tasks, compared with externally directed cognitive or sensory tasks (13). These regions represent important nodes within a larger network of regions demonstrating elevated activity during resting states—the default network (13). The components of the default network also show a high degree of stable functional coherence at rest, with correlated low frequency (<.1 Hz) fluctuations in spontaneous, stimulus-independent blood oxygen level–dependent (BOLD) activity (14), that reflect in part the strength of the anatomic connections among the network's components (15,16).

In this study, we sought to assess the function of this midline cortical network in patients with schizophrenia during conscious self-reflection, because previous work has demonstrated impairments in self-awareness in schizophrenia (2,5,17). Subjects performed a well-validated self-reflection task, judging the self-relevance of trait adjectives, which reliably engages the medial prefrontal cortex and posterior cingulate gyrus (11,18,19). In previous studies conducted in healthy subjects, performance of this self-reflection task has been associated with no change or a small decrease in activation of these midline regions relative to a low-level baseline, whereas control, nonintrospective tasks have shown greater deactivation of this network compared with self-reflection (20).

We predicted that patients with schizophrenia would show impaired midline cortical activity during self-reflection. In addition, because abnormalities in resting-state functional connectivity of these midline cortical regions have been reported in schizophrenia (21), a second goal of the study was to measure the functional connectivity of loci exhibiting abnormal self-reflection-related activity in the patients, to determine whether regions exhibiting aberrant function during self-reflection also show changes in functional connectivity.

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Methods and Materials

Participants

Nineteen patients with DSM-IV–diagnosed schizophrenia and 20 healthy control subjects were enrolled in the study. Patients with clinically stable schizophrenia, diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (22), were recruited and characterized by the MGH Schizophrenia Clinical and Research Program recruitment team. Healthy control subjects were recruited via advertisement. All subjects were right-handed and native speakers of English. The healthy control subjects did not have any psychiatric or neurologic disorders, as determined during screening using the SCID (22). Subjects with a history of substance abuse or dependence or who had used illicit substances during the 3 months before the study, and potential subjects with contraindications for magnetic resonance imaging (MRI) scanning (e.g., claustrophobia, metal implants) were excluded. Written informed consent was obtained from all subjects before enrollment in accordance with the guidelines of the Partners HealthCare Institutional Review Board. Three control subjects and one patient were excluded from the task-based fMRI analysis because of poor behavioral or imaging data quality, and one control and one patient were excluded from the resting functional connectivity analysis because of poor data quality; thus, 17 control subjects and 18 patients were included in the task-based functional MRI (fMRI) analysis, and 19 control subjects and 18 patients were included in the resting-state functional connectivity analysis. The two groups in each analysis were matched with respect to mean age, gender, parental socioeconomic status, IQ, and ethnicity (see Table 1 for means and additional demographic information about the subjects).

Stimulus Presentation and Task

During fMRI scanning, 144 trait adjectives (e.g., lazy, honest, proud, stingy) were presented over three functional runs in a block design. Half of the words were positively valenced, and half were negatively valenced (23); half were printed in lowercase letters, and half were printed in uppercase letters. Each word was presented for 3 sec in 18-sec blocks (six words/block), with eight blocks per run. During the functional runs, subjects were asked to perform four tasks (each twice per run): 1) self-reflection (SR; does this word describe you?), 2) affect labeling (AL; is this a desirable or undesirable trait?), 3) other-reflection (OR; does this word describe your mother?), and 4) perceptual (P; is this word printed in uppercase or lowercase letters?). Subjects responded by pressing a button on a button box with the index finger of each hand (i.e., if the word describes you, or is a desirable trait/describes your mother/is in upper case letters), respond with the right hand, if it doesn't describe you (or is an undesirable trait/doesn't describe your mother/is in lower case letters), respond with the left hand). The conditions were matched with respect to mean valence, length, and frequency of the words. An instruction screen appeared for 3 sec before each block, and each block was preceded and followed by a 21-sec fixation period (nine per run). The order of the tasks within each run was pseudo-random, and run order was counterbalanced across subjects. The assignment of the left or right hand for the two responses of a task was counterbalanced across subjects. Reaction times and response types were recorded.

MRI Data Acquisition

Imaging took place in a 3-Tesla Siemens TIM Trio magnetic resonance scanner (Siemens Medical Systems, Iselin, New Jersey) with echoplanar imaging capability. Subjects underwent two conventional high-resolution three-dimensional structural T1 magnetization prepared rapid acquisition gradient-echo (MPRAGE) scans (8 min 7 sec,128 sagittal slices, 1.33-mm thickness, repetition time (TR) = 2530 msec, echo time = 3.39 msec, flip angle = 7°, resolution = 1.3 × 1 × 1.3 mm). Following the collection of the anatomical scans, three 6-min and 9-sec–long functional runs were collected, during which T2*-weighted echoplanar images were acquired (33 × 3 mm thick slices, 3 × 3 mm in-plane resolution), using a gradient echo sequence (TR = 3000 msec; TE = 30 msec; flip angle = 90°). Immediately preceding and immediately following the three task-related functional runs, a 6-min and 20-sec resting BOLD scan (TR =

Table 1. Demographic and Clinical Characteristics of the Participants in Each Analysis

	Task-Based fMRI Analysis				Resting-State Functional Connectivity Analysis			
	Control $n = 17$, 6 Female		Schizophrenia $n = 18$, 6 Female		Control $n = 19$, 7 Female		Schizophrenia $n = 18$, 6 Female	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	40.0	12.5	35.9	13.7	36.6	12.8	35.7	13.4
Mean Parental Education (years)	13.8	3.3	14.8	2.2	14.5	3.2	14.7	2.2
Mean Parental SES[a]	2.5	1.1	2.1	.8	2.3	1.0	2.1	.8
Premorbid Verbal IQ[b]	112.1	7.5	108.3	5.0	112.7	7.6	109.0	5.4
Head Motion (mm)[c]	1.4	.8	1.9	1.2	1.2	.6	1.8	1.0
PANSS Total			47.3	10.0			49.1	12.8
PANSS Positive Subscale			11.7	3.6			12.4	5.1
PANSS Negative Subscale			11.4	3.2			12.3	4.7
PANSS General Subscale			24.2	5.3			24.3	5.4
Duration of Illness (years)			13.2	12.8			12.6	11.9
Chlorpromazine Equivalents			374.1	364.0			329.5	348.5

There were no significant differences between the control and schizophrenia groups for the demographic measures. Two (task-based analysis) or one (resting-state analysis) of the patients and two of the controls were African American, and one control was Asian; the remaining subjects were Caucasian. Two of the 19 patients were taking a first-generation antipsychotic (haloperidol or fluphenazine), and three patients were antipsychotic-free at the time of the scanning; the remaining patients were taking second-generation antipsychotics (e.g., clozapine, $n = 5$; risperidone, $n = 1$; olanzapine, $n = 2$; quetiapine, $n = 3$; and aripirazole, $n = 5$). Each patient's symptoms were evaluated using the PANSS (58) on the day of scanning by the same trained rater (the first author).

fMRI, functional magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale; SES, socioeconomic status.

[a]Measured with the Hollingshead index.

[b]Measured with the Adult North American Reading Test.

[c]Mean total vector translation in mm.

5000 msec; TE = 30 msec; flip angle = 90°; 55 × 2 mm thick slices, 2 × 2 mm in-plane resolution) was acquired (two resting-state scans in total), during which subjects were instructed to fixate on a centrally located cross-hair.

MRI Data Analysis

Preprocessing. The two T1-MPRAGE scans for each participant were averaged together and then subjected to an automated segmentation procedure (http://surfer.nmr.mgh.harvard.edu).

The native functional volumes for each subject were first corrected for motion using the Analysis of Functional NeuroImages algorithm and for temporal drift, then intensity normalized and spherically smoothed using a three-dimensional spatial filter (full width at half maximum = 6 mm) and then global intensity variations were removed. The cortical surface of each individual was morphed/normalized to an average spherical surface representation. Intersubject averaging and between-group comparisons of functional data were conducted in a common spherical surface coordinate system using the General Linear Model with random effects.

fMRI Task-Related Analyses. Activation during the SR and AL conditions was compared, because these two tasks are well-matched in difficulty, and the SR versus AL contrast has been found in previous studies (18,24) to be associated with significant activation of the midline cortical network in healthy subjects. Responses during the AL task served as a general index of neural responses during affective appraisal/nonintrospective evaluation. Because affective appraisals of the words likely also occurred while subjects performed the SR task, the SR minus AL contrast is designed to control for neural activity associated with the affective appraisal of the words (and abnormalities associated with affective appraisal processes in schizophrenia [25,26]), thus isolating SR-related activity.

In addition, to determine whether any between-group differences found with this contrast were attributable to a specific deficit in self-reflection (relative to other-reflection [OR]) or to a general abnormality in introspection, follow-up exploratory analyses were conducted with two additional contrasts: 1) SR versus OR and 2) SR + OR versus AL. Lastly, the P task served as indicator of attentional engagement, because it was the only task of the four with objectively correct answers.

On the basis of the evidence of Vogt and colleagues for cytoarchitechtonically distinct dorsal and ventral divisions of the posterior cingulate gyrus (27–29), we measured average percentage signal change, relative to a baseline of average signal intensity, in three a priori regions of interest (regions-of-interest [ROIs]): 1) the medial prefrontal cortex (mPFC), 2) the middle and dorsal-posterior cingulate cortex (m/pCC), and 3) the ventral-posterior cingulate and retrosplenial cortices (pC/RSC; Figure 1A). The boundaries of these anatomic regions were defined using an automated parcellation method, which delineates boundaries between cortical areas using known sulcal landmarks in each individual subject's anatomic scan (30). The mPFC ROI was constructed by merging the FreeSurfer "medialorbitofrontal" and "rostralanteriorcingulate" labels. The middle cingulate/dorsal-posterior cingulate cortex (m/pCC) ROI was defined using the FreeSurfer "posterior cingulate" label, and the ventral-posterior cingulate/retrosplenial cortex (pC/RSC) ROI was defined using the FreeSurfer "isthmus cingulate" label. Percent signal change (SR or AL vs. a low-level baseline, where low-level baseline = mean BOLD signal intensity across the entire task-based fMRI runs) was compared across conditions and between the two groups using a 2 (task: SR, AL) × 3 (region: mPFC, m/pCC, pC/RSC) × 2 (hemisphere: left, right) × 2 (group: patients, control subjects) analysis of variance. Significant ($p < .05$) main effects or interactions with group were followed by planned Student's *t* tests.

In parallel, a cortical surface based analysis (31) of activation to the SR versus AL contrast was conducted because of its greater sensitivity (compared with the anatomical ROI analysis) to spatially restricted effects. This analysis was also limited to a search territory comprised of the three previously described ROIs. Significant clusters of activated voxels were identified on the basis of a Monte Carlo simulation (corrected $p < .05$). Locations of the activation peaks on the cortical surface were identified using the FreeSurfer cortical parcellation and confirmed using the Talairach atlas (32).

Resting-State Functional Connectivity Analyses

Standard preprocessing techniques (33) were used to selectively capture variance in the BOLD signal corresponding to low-frequency (<.08 Hz) fluctuations in neural activity. Nuisance regressors, including the six parameters computed from the rigid-body motion correction, the averaged signal within a ventricular ROI, a region within the deep white matter, and the signal averaged over the whole brain, were used to remove systematic variance associated with these variables. The first temporal derivative of each regressor was also included to account for temporal shifts in the BOLD signal.

To create whole-brain correlation images, the averaged time series across all voxels comprising a seed ROI was used as the variable of interest in a linear regression with the time series corresponding to each voxel across the brain. All statistical analyses of correlation data were performed on Fisher *z* transforms (34) and were restricted to positive correlations only (33). Loci exhibiting significant between-group differences in the task-based fMRI analysis were used as seeds for the group and between-group voxel-wise functional connectivity analyses (15). Within-group and between-group analyses were conducted using SPM2 (http://www.fil.ion.ucl.ac.uk/spm) and were limited to the mPFC and posterior cingulate gyrus, using the WFU PickAtlas toolbox (35). Loci exhibiting positive correlations with the seed, and between-group differences in the magnitude of these positive correlations, were considered significant if they met a voxel-level height threshold of $p < .005$ and an overall cluster-corrected threshold of $p < .05$. For the between-group comparisons, loci meeting a voxel-level height threshold of $p < .05$ and a cluster-corrected threshold of $p < .05$ are also reported.

Results

Behavior

There were no significant differences between the two groups in response times for the SR ($t = .88$, $df = 33$, $p = .39$) or AL ($t = 1.74$, $df = 33$, $p = .09$) tasks, or in the percentages of trials rated as self-descriptive during the SR blocks ($t = .111$, $df = 33$, $p = .91$), or rated as desirable during the AL blocks ($t = .54$, $df = 33$, $p = .59$). See Table 2 for means and additional behavioral results.

Task-Related BOLD Responses

Anatomic ROI analysis (SR or AL vs. a low-level baseline). In this analysis, a significant Region by Task by Group interaction ($F = 3.31$; $df = 2$; $p = .04$), with no Region by Task by Group by Hemisphere interaction ($F = .326$; $df = 2$, $p = .72$; Figure 1B–1D), was found. Follow-up, planned comparisons revealed larger responses in the m/pCC in the patients, compared with the control subjects, during SR ($F = 2.11$; $df = 1,33$, $p = .04$) but not AL ($F = .80$, $df = 1,33$, $p = .43$). In contrast, there were no significant between-group differences in activation found in the mPFC or pC/RSC during SR or

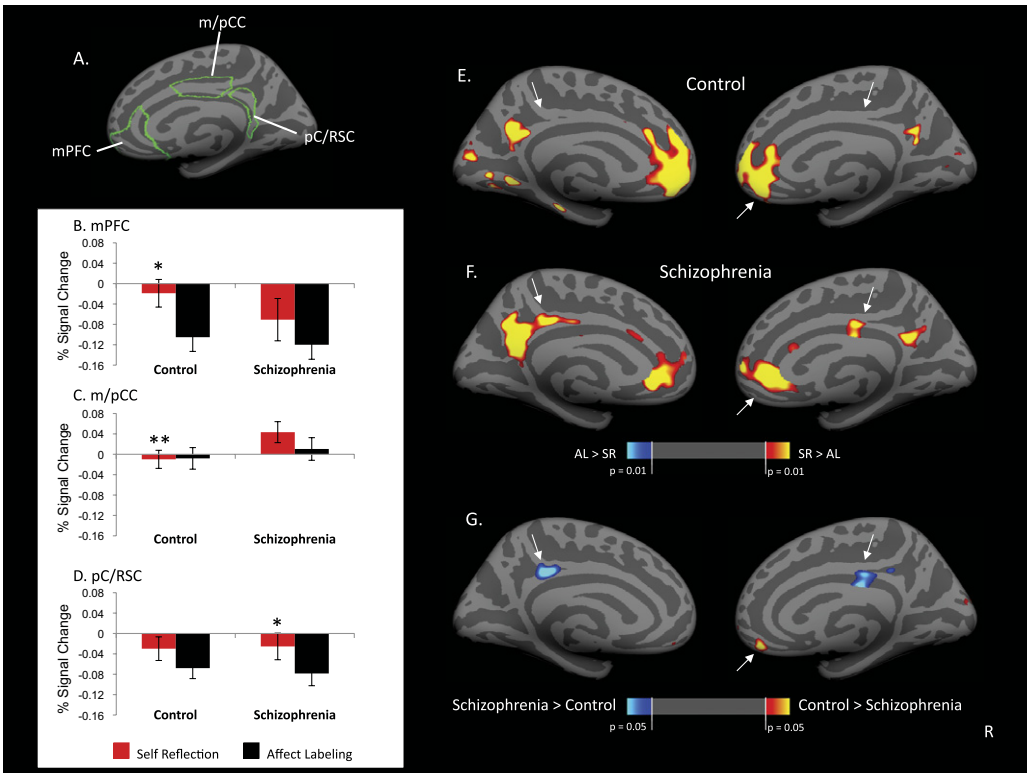


Figure 1. The results of the anatomical region of interest (ROI) and cortical surface–based funtional magnetic resonance imaging analyses. **(A)** The borders of the three anatomically-defined ROI (the medial prefrontal cortex [mPFC], the middle and dorsal-posterior cingulate cortex [m/pCC], the ventral-posterior cingulate and retrosplenial cortices [pC/RSC]) are shown on this left, medial view of a representative cortical surface. These ROIs were defined in each individual subject's anatomical magnetic resonance imaging scan, using an automated parcellation system (FreeSurfer; see Methods and Materials). **(B–D)** Average percentage signal change during the self-reflection (SR) and affect labeling (AL) tasks, relative to a mean blood oxygen level–dependent signal intensity baseline, was extracted from the three anatomic ROIs, the mPFC **(B),** m/pCC **(C),** and pC/RSC **(D).** An analysis of variance revealed a significant Region by Task by Group interaction (see Results); differential responses to SR, relative to AL, were found in the mPFC in the control group ($n = 17$) and in the pC/RSC in the patient group ($n = 18$; * within-group difference, $p < .05$) **(A, C),** and significantly greater SR-related activation in the schizophrenia patients, compared with the control subjects, was found in the m/pCC region (** between-group difference, $p < .05$) **(B).** There were no activation differences between the two groups during the AL condition in any region. Error bars represent standard errors of the mean. **(E–G)** Cortical surface activation maps showing the activation patterns within the control ($n = 17$) **(E)** and patient ($n = 18$) **(F)** groups, and the results of the between-group comparison **(G),** for the SR versus AL contrast. In panels E and F, warm colors indicate vertices with significantly greater activation during SR compared with AL. There were no clusters with greater activation during AL compared with SR that met significance. In panel G, warm colors indicate vertices with significantly greater SR compared with AL activation in the control group, in comparison to the patient group, whereas cool colors indicate vertices with greater SR compared with AL activation in the patient group, in comparison to the control group. White arrows indicate the locations of between-group differences. In these analyses, the portion of the brain ventral to the corpus callosum is excluded and thus is masked in these images. R, right.

AL. Within-group comparisons revealed that the control subjects showed a greater response (less deactivation) during SR compared with AL in the mPFC ($t = 3.86$; $df = 16$, $p = .001$) but not in the m/pCC or pC/RSC, whereas the patients showed a greater response during SR compared with AL in the pC/RSC ($t = 2.51$, $df = 17$, $p = .02$) but not in the mPFC and m/pCC. See Table S1 in Supplement 1 for effect sizes (Cohen's *d*) of these differences.

Cortical surface— based analysis (SR vs. AL). Within both the control and schizophrenia groups, clusters with greater responses during SR, compared with AL, were seen in bilateral mPFC, posterior cingulate gyrus, and retrosplenial cortex (Figure 1E and 1F, Table 3). A direct, between-group comparison of the SR versus AL activation maps revealed that the patients showed significantly lower recruitment of the right ventral mPFC (Brodmann area [BA] 10, 11) and significantly greater recruitment of the right (BA 23) and left (BA 23, 31) m/pCC, in comparison with the control subjects (Figure 1G).

Follow-up cortical surface–based analyses (SR vs. OR; SR + OR vs. AL). For the SR vs. OR contrast, both groups exhibited weak midline cortical activations but no significant between-group differences (Figure S1A, Table S2 in Supplement 1). For the SR + OR vs. AL contrast, activation within the mPFC and posterior cingulate gyri was found in both groups, similar to the pattern seen with the SR versus AL contrast. A direct comparison of the responses of the two groups for the SR + OR versus AL contrast revealed significantly lower mPFC and greater m/pCC activation bilaterally in the schizophrenia patients in comparison with the healthy control subjects (Figure S1B, Table S3 in Supplement 1).

Resting-State BOLD Activity Correlations

Maps of resting-state BOLD correlations for the three loci exhibiting abnormal SR versus AL activation in schizophrenia (the right ventral mPFC, the right and left m/pCC) revealed significant correlations with cortical midline regions in both groups (Figure 2, Table 4).

Comparisons of the magnitude of the correlations of these loci between the two groups revealed that the healthy control subjects exhibited higher connectivity than the schizophrenia patients between the left m/pCC and the dorsal anterior cingulate gyrus (BA 32; Talairach coordinates of peak voxel of cluster [x, y, z]: −1, 30, 28; $z = 3.53$; $k = 77$; Figure 3). At a lowered threshold (voxel-level $p < .05$, cluster-corrected $p < .05$), patients with schizophrenia showed

Table 2. Behavioral Results

	Reaction Times (Milliseconds)											
	Self-Reflection			Other-Reflection			Affect Labeling			Perceptual		
	Mean	SD	*p* Value	Mean	SD	*p* Value	Mean	SD	*p* Value	Mean	SD	*p* Value
Controls	1472	239	0.39	1522	251	0.97	1411	217	0.09	916	151	0.05
Patients	1538	206		1525	204		1532	197		1066	261	
	Response Types (%)											
	Self-Reflection (% Like Self)			Other-Reflection (% Like Other)			Affect Labeling (% Positive)			Perceptual (% Correct)		
	Mean	SD	*p* Value	Mean	SD	*p* Value	Mean	SD	*p* Value	Mean	SD	*p* Value
Controls	49.0	6	0.91	48.9	5	0.66	49.3	5	0.59	98.0	4	0.13
Patients	49.3	8		47.8	8		48.1	7		94.0	10	

Mean reaction times, mean percentage response types, and *p* values for the independent Student's *t* tests comparing the means of the two groups, for the four experimental tasks. The total percentage of trials in which subjects made responses (across all four tasks) was high in each group (Mean ± SD): 98% ± 3% in the controls and 97% ± 2% in the schizophrenia patients. Also, during the self-reflection task, both groups showed a comparably large bias to rate the positively valenced adjectives as "self" and the negatively valenced adjectives as "not self" (percentage of words rated as "self" that were positively valenced: controls: mean ± SD = 86.9 ± 9 %; patients: mean ± SD = 85.1 ± 9%; $t = .57$, $df = 34$, $p = .57$).

higher connectivity than the control subjects between the left m/pCC and the ventral mPFC (BA 25: 4, 10, −16; $z = 3.04$; $k = 312$) and between the right m/pCC and the ventral mPFC (BA 11/32: −1, 22, −17; $z = 2.63$, $k = 282$).

Effects of Potential Confounds and Symptoms

There were no significant correlations between the changes found in task-related activation or resting-state functional connectivity in the schizophrenia patients and potential confounds (antipsychotic dose or duration of illness) or symptom levels.

Discussion

In this study, patients with schizophrenia showed abnormally elevated activation of the right and left m/pCC during self-reflection, compared to a low-level baseline and to responses during a nonintrospective task. Also, in a cortical surface-based analysis, the schizophrenia patients showed abnormally reduced responses during self-reflection, compared with a nonintrospective task, within the right ventral mPFC. Lastly, this abnormal pattern of task-dependent activation in schizophrenia was accompanied by decreased functional connectivity between the left m/pCC and the dorsal anterior cingulate gyrus and, at a more liberal threshold, increased connectivity between the right and left m/pCC and the ventral mPFC, in schizophrenia patients compared with control subjects.

It is noteworthy that the elevation in activity of the m/pCC in the schizophrenia patients was detected in both of the task-based fMRI analyses (the anatomic ROI and the cortical surface–based), whereas the reduced mPFC response in the patients was found only in the cortical surface–based analysis. Because the between-group

Table 3. Within-Group Activations and Between-Group Differences in Activation for the Self-Reflection (SR) Versus Affect-Labeling (AL) Contrast in the Cortical Surface–Based Analysis

Region	BA	Area (mm^2)	Tal (x, y, z)	*p* Value
Control Group ($n = 17$)				
L Medial Frontal and Anterior Cingulate Gyri	32/10	2443	−11, 44, 2	.00003
L Medial and Middle Frontal Gyri	10/9	585	−24, 50, 12	.0007
L Middle Frontal Gyrus	9	224	−21, 36, 28	.0002
R Medial Frontal Gyrus	10	1949	10, 52, 3	.00008
L Posterior Cingulate Gyrus	23/31	831	−9, −56, 28	.0001
R Posterior Cingulate Gyrus	23	428	8, −56, 20	.001
Schizophrenia Group ($n = 18$)				
L Anterior Cingulate Gyrus	32	1792	−6, 32, −6	.00009
R Anterior Cingulate Gyrus	24/32	1815	7, 31, −3	.00005
R middle cingulate gyrus	23/24	458	5, −16, 31	.001
L Posterior Cingulate Gyrus/RSC	23/30	2266	−8, −51, 20	.0001
R Posterior Cingulate Gyrus/RSC	23/30	575	8, −50, 22	.0007
Control > Schizophrenia				
R Medial Orbitofrontal Gyrus	10/11	116	8, 42, −15	.005
Schizophrenia > Control				
L Mid/Posterior Cingulate Gyrus	23/31	236	−6,−30, 34	.002
R Mid/Posterior Cingulate Gyrus	23	321	5, −21, 31/0, −16, 24	.002

Location and size of clusters of vertices that showed significant SR > AL activation for the controls ($n = 17$) and the patients with schizophrenia ($n = 18$), with the Talairach coordinates and *p* value for the local p minimum for each cluster. There were no loci that showed significantly greater activation for the AL condition, relative to SR. Loci which showed significantly more activation in the controls compared with the patients and those that showed more activation in the patients compared to the controls are also listed.

AL, affect labeling; BA, Brodmann area; L, left; R, right; RSC, retrosplenial cortex; SR, self-reflection; Tal, Talairach coordinates.

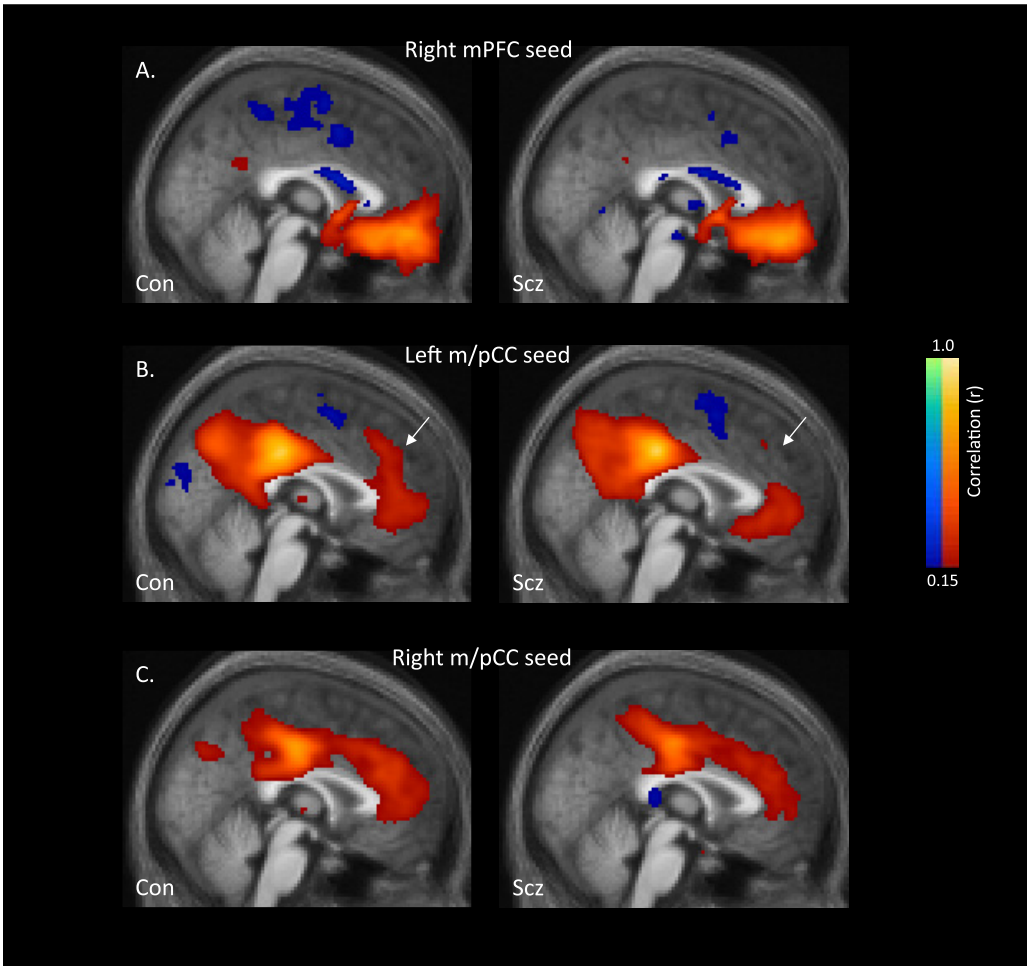


Figure 2. Group-average maps of resting-state correlations for the healthy control subjects and schizophrenia patients. Average correlation maps (Pearson's *r* for the control subjects [$n = 19$] and the patients with schizophrenia [$n = 18$] for the right mPFC (Talairach coordinates of seed center: 8, 42, –15) **(A),** left m/pCC (Talairach coordinates of seed center: –5, –30, 34) **(B)** and right m/pCC (Talairach coordinates of seed center: 6, –22, 32 **(C),** at the midline ($x = 0$), are displayed. Voxels that are positively correlated with the seed are labeled orange-yellow, and voxels that are negatively correlated with the seed are labeled blue. In panel A, the high degree of local positive connectivity for the right mPFC seed is evident; additional positive connectivity with the posterior cingulate gyrus (Table 3) is not visible in this slice. In panel B, the classic default mode connectivity pattern is found in both groups for the left m/pCC seed, although in the control group, connectivity of this seed extends into the dorsal mPFC, whereas for the patients, connectivity of this seed is more prominent in ventral mPFC. The location of the between-group difference in functional connectivity in the dorsal mPFC (i.e., the dorsal anterior cingulate cortex, also see Figure 3) is indicated with white arrows. In panel C, a connectivity pattern that is characteristic of the middle and dorsal-posterior cingulate cortex is seen in both groups (28). Con, control group; Scz, schizophrenia group; mPFC, medial prefrontal cortex; m/pCC, middle and dorsal-posterior cingulate cortex.

difference in the m/pCC was detected even when activation was averaged over a large, anatomically defined ROI, it is likely that the bilateral m/pCC exhibits a generalized, widespread elevation in activity during self-reflection in schizophrenia patients. Because the cortical surface–based analysis is more sensitive to spatially restricted effects, the finding of a between-group difference in the right mPFC here but not in the ROI analysis suggests that only a portion of the large mPFC ROI showed abnormal responses in schizophrenia during self-reflection, and that this abnormality is likely smaller in magnitude or less consistent in spatial location across subjects than the change in m/pCC function in schizophrenia.

Previous studies of the function of this midline network in schizophrenia during social cognitive tasks have also reported abnormally reduced activation of the mPFC, most frequently within the right hemisphere, in schizophrenia. This abnormality has been observed during performance of theory-of-mind tasks (36,37), empathy and forgivability judgments (38), facial affect discrimination (25), and retrieval of self-generated information (39). In contrast, during attention-demanding, executive control tasks, both hypoactivation (arising from greater task-induced deactivation [TID] in the patients) (40,41) and hyperactivation (arising from weaker TID in the patients) (42–44) of the mPFC in schizophrenia has been reported. The inconsistencies among these previous results are likely due to variation across studies in the difficulty of the executive tasks performed and the related variation in performance differences between the healthy and schizophrenia subjects. In the current study, the control subjects showed the expected pattern of response in the mPFC (less TID during self-reflection relative to affect labeling), whereas the patients with schizophrenia showed pronounced deactivation of the right mPFC during both tasks. The greater TID of the right mPFC during self-reflection in the schizophrenia patients, compared with the control subjects, could reflect greater effort or attentional engagement during self-reflection; however, this possibility is unlikely given that the mean response times during self-reflection (and mean IQ) of the two groups did not

Table 4. Results of the Within-Group Functional Connectivity Analysis: Significant Clusters of Functional Correlations with the Three Seeds Within the Control ($n = 19$) and Schizophrenia ($n = 18$) Groups

Seed	Control Region	BA	*k*	Tal (x,y,z)	*Z* Score	Schizophrenia Region	BA	*k*	Tal (x,y,z)	*Z* Score
L m/pCC	L anterior cingulate gyrus	32	2581	−6, 41, 2	5.35	R anterior cingulate gyrus	32	2565	10, 32, −6	5.13
	L mid/posterior cingulate gyrus	23	678	−1, −34, 24	Inf	L mid/posterior cingulate gyrus	23	682	−4, −34, 24	7.54
R m/pCC	L anterior cingulate gyrus	24/32	2065	−4, 26, 24	5.95	L anterior cingulate gyrus	32	2101	−6, 34, 0	5.63
	R posterior cingulate gyrus/RSC	23/29	453	3, −42, 20	5.35	L posterior cingulate gyrus	23	47	−8, −36, 24	3.67
R mPFC	R anterior cingulate and medial orbitofrontal gyri	32/11	3150	10, 28, −15	7.44	L medial orbitofrontal gyrus	11/10	2818	−6, 39, −18	6.77
	L posterior cingulate gyrus/RSC	23/30	274	−10, −52, 23	3.90	L posterior cingulate gyrus/RSC	23/30	264	−1, −50, 18	3.84

Location (BA and name of region) and size (*k*) of clusters within the midline cortical search area that showed significant connectivity with each of the three seeds for the control subjects ($n = 18$) and the patients with schizophrenia ($n = 18$). Talairach (Tal) coordinates and *Z* scores of the peak voxel within each cluster are also included. The three seed regions-of-interest were each constructed by creating an 8 mm sphere around the voxel showing the peak between-group difference in the cortical surface, task-based functional magnetic resonance imaging analysis (see Methods and Materials). Talairach coordinates (x,y,z) of the center of each seed: 8, 42, −15 (right mPFC); −5, −30, 34 (left m/pCC); 6, −22, 32 (right m/pCC).

BA, Brodmann's area; L, left; mPFC, right medial prefrontal cortex; m/pCC, middle and dorsal-posterior cingulate cortex; R, right; RSC, retrosplenial cortex.

differ. Given that introspective activity typically lessens deactivation of the mPFC (12), this finding could reflect diminished introspective activity in schizophrenia (45).

Although the two groups in this study did not differ on mean reaction times and response types, the *accuracy* of the self-ratings was not measured here; such an index of self-awareness might be more closely linked to the magnitude of neural responses during self-reflection than reaction times or response types during the task. Although admittedly difficult to measure, this type of accuracy has been estimated previously by measuring the concordance between ratings given by participants of the self-descriptiveness of traits and ratings given by relatives or caregivers of the participants (46). Follow-up studies could include such a measure to determine whether impaired self-awareness in schizophrenia predicts dysfunction of the mPFC and/or m/pCC.

Our results are consistent with the findings of two previous studies that detected elevated responsivity of the posterior cingulate gyrus in schizophrenia during social perception tasks (25,26). Interestingly, the overall anterior-to-posterior shift in neural activity in schizophrenia observed here mirrors the effects of *N*-methyl-D-aspartate glutamate receptor blockade, a popular pharmacologic model of schizophrenia, on the BOLD signal (47), as well as positron emission tomography findings of abnormally reduced mPFC activity and increased posterior cingulate cortex activity in schizophrenia (48,49). The current study indicates that this shift in midline cortical activity in schizophrenia occurs during social reflection.

It is important to note that much of the posterior cingulate gyrus found to show abnormally elevated responsivity in the schizophrenia group here (Figure 1E-G) is dorsal and anterior to the region that typically exhibits activity during self-reflection in healthy subjects (19,24). This dorsal area most likely corresponds to the posterior midcingulate and dorsal posterior cingulate gyrus, according to Vogt's eight-compartment model of the cingulate gyrus (29). The pattern of functional connectivity of the right m/pCC site showing greater activation in the patients compared to controls (prominent intracingulate functional connectivity; Figure 2C) is also consistent with this designation (27–29). Although the precise function of this region is not fully understood, previous fMRI studies indicate that the medial parietal lobe, including this dorsal portion of the posterior cingulate gyrus, is involved in functions that rely on spatial memory and visuospatial orientation, such as the navigation of the body in space (27,50,51) and first-person (vs. third-person) perspective taking (52). The medial parietal lobe is also recruited during episodic and autobiographical memory retrieval tasks, particularly

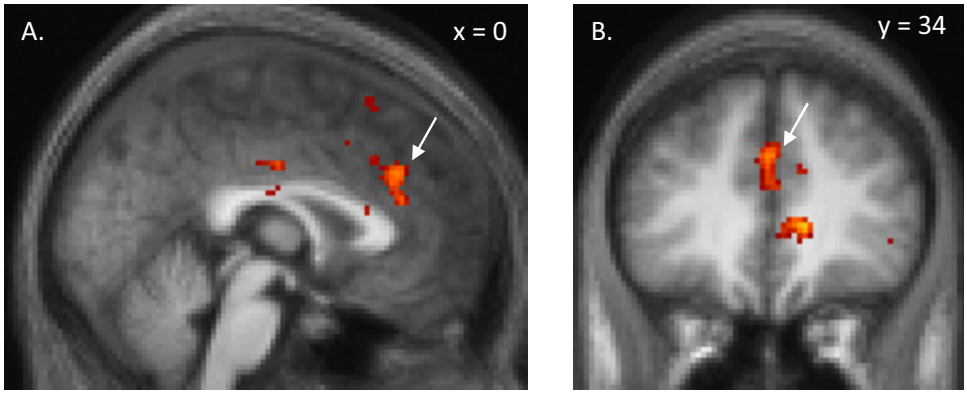


Figure 3. Sagittal **(A)** and coronal **(B)** views of the T map of control ($n = 19$) > schizophrenia ($n = 18$) functional connectivity of the left m/pCC seed, displayed at a threshold of $p < .01$. The Talairach × coordinate of the displayed slice is shown in the right side of each image. White arrows point to the site within the dorsal anterior cingulate cortex showing significantly greater functional connectivity with the left m/pCC seed in the control subjects, in comparison to the patients.

when subjects are asked to recall specific details of past events (53). In light of this literature, one possible interpretation of our results is that patients with schizophrenia rely to a greater extent than healthy subjects on visuospatial simulation and retrieval of specific episodic memories to make judgments about whether trait adjectives describe themselves, whereas during the same task, healthy subjects need only retrieve overlearned, abstracted information about themselves (46). Supporting this possibility is recent work suggesting that the mPFC is associated with the retrieval and storage of semantic aspects of self-knowledge (such as information about one's traits), whereas the pCC mediates retrieval of concrete, imageable details about the self (such as one's physical characteristics) (54).

Analyses of additional contrasts in the current study revealed that overall social introspection (responses during self-reflection combined with responses during other-reflection) produced a pattern of results that was similar to the findings of the primary analysis, but there were no between-group differences found when self-reflection was directly contrasted with other-reflection. These results support the possibility that the abnormality in midline cortical function in schizophrenia during self-reflection is due to a general deficit in introspection or social cognition. However, these secondary analyses must be interpreted with caution because our study used a block design (to maximize power to detect differences between the groups); previous work suggests that differences detected between the neural correlates of self- and other-reflection may be greater in studies which used event-related designs (18,54–56). Follow-up event-related studies can determine whether the anterior-to-posterior shift in midline cortical function in schizophrenia seen here is most prominent during self-referential thinking or associated with a range of social cognitive processes.

The reduction in functional connectivity found in the schizophrenia group between the m/pCC and dorsal anterior cingulate gyrus is consistent with a large body of prior evidence for diminished connectivity and neural synchrony in schizophrenia (57). However, at a lower statistical threshold, we also found elevations in intrinsic functional connectivity between the m/pCC bilaterally and the ventral mPFC. Similarly, a previous study reported abnormally elevated functional connectivity of the mPFC in schizophrenia patients, as well as in first-degree relatives of patients with schizophrenia, within the default network (44). Additional studies that measure connectivity using complementary methods, while controlling for data acquisition-related confounds, will be needed to clarify the precise nature of the changes in default network connectivity in schizophrenia.

In summary, in this study, abnormally elevated activity within the m/pCC and reduced activity of the right ventral mPFC was found in patients with schizophrenia during social reflection. In the same patients, abnormalities in resting-state functional connectivity within this network were also observed. Future studies can test whether some or all of these abnormalities could serve as quantitative neural markers of the social cognitive deficits associated with schizophrenia.

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Supplementary material cited in this article is available online.

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