

Dysfunction of a Cortical Midline Network During Emotional Appraisals in Schizophrenia

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A cardinal feature of schizophrenia is the poor comprehension, or misinterpretation, of the emotional meaning of social interactions and events, which can sometimes take the form of a persecutory delusion. It has been shown that the comprehension of the emotional meaning of the social world involves a midline paralimbic cortical network. However, the function of this network during emotional appraisals in patients with schizophrenia is not well understood. In this study, hemodynamic responses were measured in 14 patients with schizophrenia and 18 healthy subjects during the evaluation of descriptions of social situations with negative, positive, and neutral affective valence. The healthy and schizophrenia groups displayed opposite patterns of responses to emotional and neutral social situations within the medial prefrontal and posterior cingulate cortices—healthy participants showed greater activity to the emotional compared to the neutral situations, while patients exhibited greater responses to the neutral compared to the emotional situations. Moreover, the magnitude of the response within bilateral cingulate gyri to the neutral social stimuli predicted delusion severity in the patients with schizophrenia. These findings suggest that impaired functioning of cortical midline structures in schizophrenia may underlie faulty interpretations of social events, contributing to delusion formation.

Key words: cingulate cortex/default mode network/
delusions/emotion/fMRI/medial prefrontal cortex

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Introduction

Abnormalities in affective processing and social cognition are central features of schizophrenia.^{1–7} Because the psychotic symptoms of schizophrenia, hallucinations and delusions, often appear to represent distortions or errors in comprehending the social world, it has been proposed that these symptoms arise from dysfunction of brain networks supporting social information processing.^{8,9} Functional neuroimaging studies in healthy individuals have found that the medial prefrontal cortex and posterior cingulate cortex, which have reciprocal connections,¹⁰ are recruited during the performance of simple, evaluative,^{11–13} as well as during more complex,^{14–16} social cognitive tasks. These 2 cortical midline structures are also part of a larger neural system (the default network) that is more active during processes that are reliant on internally focused attention, including self-reflection, “mentalizing,” and retrieval of autobiographical memories, than during sensory or motor processes that require attending to the external environment.^{17–19}

Recent work suggests that the function of these cortical midline structures is compromised in schizophrenia. Abnormally elevated activity^{20,21} and aberrant functional connectivity^{22–24} of the posterior cingulate cortex have been reported in schizophrenia, and a popular pharmacological model of the symptoms of schizophrenia, intoxication with the *N*-methyl-D-aspartic acid receptor antagonist ketamine,²⁵ has been linked to abnormal modulation of the posterior cingulate cortex that is predictive of the severity of psychotic symptoms.^{26,27} Also, activity within medial prefrontal^{23,24} and posterior cingulate²³ cortices has been found to correlate with the severity of psychotic symptoms, and one functional magnetic resonance imaging (fMRI) study found that schizophrenia patients with psychotic symptoms exhibited larger responses within the medial prefrontal cortex than those without psychotic symptoms and healthy individuals.²⁸

Given the evidence for abnormalities within this network in schizophrenia and the increasing evidence for the central importance of this network in social cognition, the goal of the current study was to test the hypothesis that these cortical midline regions are modulated abnormally in schizophrenia during the appraisal of social information.

A number of previous studies of emotional processing in schizophrenia have found evidence for a behavioral bias or an elevated neural response to affectively neutral, nonsalient stimuli during emotional processing,^{29–37} which in some studies has been linked to psychotic symptoms^{33,38} or specifically to delusions.^{29,31,37,39} This abnormal response to neutral stimuli has been proposed to reflect a tendency to attend preferentially, or misattribute motivational salience, to nonsalient information during psychotic states^{40–42} and has been linked to abnormalities in emotional appraisal.³¹

In the current study, we hypothesized that dysfunction of the medial prefrontal and posterior cingulate cortices during emotional appraisals plays an important role in psychosis. We used a novel paradigm, developed and normed by our group,⁴³ in which participants appraised 2-sentence social vignettes that are either explicitly emotional (positive or negative) or neutral in valence. Recent behavioral and neuroimaging studies indicate that comprehension of language triggers a neural “simulation” of the experience depicted (including sensory, motor, and temporal details),^{44,45} which can include activation of networks subserving emotional and social cognitive processing.^{46–49} For example, previous studies have found that limbic and paralimbic regions, including the medial prefrontal^{47,48} and posterior cingulate⁴⁷ cortices, are active while people are reading⁴⁹ or hearing⁴⁸ words describing an emotionally salient situation or while reading neutral words that were previously encountered in an emotional context,⁴⁷ suggesting that comprehending the emotional meaning of words requires a reactivation of circuitry initially involved in encoding the emotional experience.

Therefore, in the current study, we predicted that both patient and control groups would show activity in medial prefrontal and posterior cingulate cortices while evaluating descriptions of social situations and events. In addition, we predicted that, compared with healthy controls, patients with schizophrenia would demonstrate elevated responses within this network as they evaluated descriptions of neutral social situations and that these increases would be greatest in patients with delusions.

Methods

Participants

A total of 15 patients with *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)–diagnosed schizophrenia and 19 control subjects completed the study. Medicated patients with clinically stable schizophrenia were recruited through the Massachusetts General Hospital Schizophrenia Clinical and Research Program. Healthy control subjects were recruited via advertisement. All subjects were right-handed, as assessed using the modified Edinburgh Handedness Inventory,⁵⁰ and were native speakers of English. The healthy control subjects did not have any psychiatric

or neurologic disorders, as determined using screening using the Structured Clinical Interview for DSM-IV Axis I Disorders.⁵¹ Subjects who had used illicit substances during the 3 months prior to the study and potential subjects with contraindications for MRI scanning (claustrophobia, metal implants, etc) were excluded. Written informed consent was obtained from all subjects prior to enrollment in accordance with the guidelines of the Partners Healthcare Institutional Review Board. The data of one schizophrenia patient and one healthy control were excluded following scanning because of poor performance on the task (greater than 10% nonresponse or random responding). The 2 groups were matched with respect to age, gender, premorbid verbal IQ, and parental socioeconomic status (see table 1).

Each patient’s symptoms were evaluated by a trained rater using the Schedule for the Assessment of Positive Symptoms (SAPS)⁵² and the Schedule for the Assessment of Negative Symptoms (SANS).⁵³

Stimuli

Two-sentence descriptions of social situations (see Supplementary Table 1 and Holt et al⁴³ for examples and additional details about the stimuli), for each of 3 experimental conditions (neutral, positive, and negative), were used. For each pair of sentences, the first sentence was neutral and ambiguous in content, providing a nonconstraining context for the second sentence. The emotional meaning of the sentence pair was conferred by a positively valenced, negatively valenced, or neutral word (the critical word) that was the fifth or sixth word of the second sentence, ie, “Sandra’s old boyfriend stopped by her apartment today. This time he brought a rose/gun/letter (positive, negative, neutral word, respectively) with him.”

The final stimuli set was divided into 3 lists, using a Latin square design. The stimuli were counterbalanced between participants such that no participant encountered the same sentence pair more than once and such that, across subjects, all 2-sentence social scenarios were seen in all 3 conditions. Each of the 3 lists included 135 sentence pairs, with 45 sentence pairs for each condition. Thus, during fMRI scanning, each participant viewed 135 different sentence pairs.

Stimulus Presentation and Task

During fMRI scanning, each trial began with the presentation of a fixation cross for 500 or 1000 milliseconds, depending on whether the critical word was the sixth or fifth word of the sentence, respectively; this allowed the critical word to appear 7 seconds after trial onset in every trial. The first sentence was presented as a whole for 3.5 seconds (100-ms interstimulus interval [ISI]). The second sentence was presented one word at a time (500 ms per word, 100-ms ISI). Following the presentation of the sentence pair, a question mark appeared for a variable duration (1880–3600 ms), depending on the total number

Table 1. Demographic and Clinical Characteristics of the Participants

	Control (<i>n</i> = 18: 4 female)		Schizophrenia (<i>n</i> = 14: 3 female)	
	Mean	SD	Mean	SD
Age (y)	43.7	8.3	42.9	11.9
Length of education (y)	14.2	1.9	13.9	2.0
Mean parental education (y)	13.6	3.0	13.9	2.3
Mean parental socioeconomic status ^a	2.8	1.3	2.9	1.3
Premorbid verbal IQ ^b	116.0	6.6	110.8	7.4
Head motion (mm) ^c	3.3	0.8	3.0	0.8
SAPS total			23.4	17.2
SAPS global delusion item			2.4	1.7
SAPS global hallucination item			3.1	2.0
SAPS global thought disorder item			1.4	1.5
SANS total			38.8	13.7
Duration of illness (y)			19.6	12.7
Chlorpromazine equivalents			448.4	453.2

Note: There were no significant differences between the 2 groups in mean age, years of education, parental education, parental socioeconomic status, premorbid verbal IQ, and head motion during the scanning. Eight of the 14 patients had active delusions (SAPS global delusion score ≥ 2) that were persecutory/referential (6/8) or grandiose/religious (3/8) in content. Antipsychotic medications of the 14 patients were as follows: 1–2 atypical agents (aripiprazole, ziprasadone, risperidone, clozaril) (*n* = 8), fluphenazine decanoate (*n* = 2), fluphenazine decanoate plus quetiapine (*n* = 1), unmedicated (*n* = 3). SAPS, Schedule for the Assessment of Positive Symptoms; SANS, Schedule for the Assessment of Negative Symptoms.

^aMeasured with the Hollingshead index.

^bMeasured with the Adult North American Reading Test.

^cMean total vector translation in millimeters. No subject showed greater than 5 mm mean vector translation.

of words in the second sentence, to allow the total trial length to equal 12 seconds for all trials. The ISI between trials (a fixation cross) was jittered (0–19900 ms). Participants were instructed to judge whether the sentence pairs depicted a pleasant, unpleasant, or neutral situation; person; or event. They responded by pressing a button box that was placed in their dominant hand.

Behavioral Data Analysis

Reaction times (RTs) and the percentage of participants' responses that were consistent with the a priori classifications of the 3 conditions were compared across conditions and between the 2 groups using analyses of variance, and significant main effects and condition-by-group interactions were followed up by planned, paired Student *t* tests.

MRI Data Acquisition

Imaging took place on a 3T Siemens Trio scanner (Siemens Medical Systems, Iselin, NJ) with echoplanar (EP) imaging capability. Subjects underwent a conventional high-resolution 3-dimensional structural scan, constituting a spoiled GRASS sequence (128 sagittal slices, 1.33 mm thickness, repetition time [TR] = 2530 ms, echo time [TE] = 3.77 ms, flip angle = 7°, bandwidth = 200 Hz, in-plane resolution = 1 × 1.33 mm), and then viewed the 3 types of sentence pairs and fixation trials over 6 functional runs. Each functional run lasted 380 seconds during which T₂*-weighted EP images were acquired (30 slices

covering the whole brain, 3 mm thickness, in-plane resolution of 3.125 mm, slices oriented approximately 30/grad axially, 1 mm skip between slices), using a gradient echo sequence (TR = 2 s, TE = 25 ms, flip angle = 100/grad). A second high-resolution 3-dimensional structural scan was acquired following the functional imaging.

MRI Data Analysis

In order to increase the signal-to-noise ratio, the 2 structural scans for each participant were averaged together, after motion correction, to create a single volume. This resulting high signal:noise volume was then subjected to an automated segmentation procedure by which the surface representing the gray/white border was reconstructed and inflated to yield a 2-dimensional representation of the cortical surface using the FreeSurfer software.^{54,55}

The native functional volumes for each subject were first corrected for motion using the AFNI algorithm. Images were corrected for temporal drift, normalized, and spherically smoothed using a 3-dimensional spatial filter (full-width-half-maximum: 8.7 mm), and global intensity variations were removed. The functional images were analyzed using a general linear model using a finite impulse response model (estimated using 18 TRs), with the FreeSurfer Functional Analysis Stream.

The cortical surface of each individual was morphed/registered onto an average spherical surface representation. Each participant's functional data was then

Table 2. Behavioral Results

	Control (<i>n</i> = 18)	Schizophrenia (<i>n</i> = 14)	All Subjects (<i>n</i> = 32)
Positive RT (ms)	869 (171)	1184 (311)	1007 (286)
Negative RT (ms)	825 (197)	1193 (223)	986 (276)
Neutral RT (ms)	1117 (332)	1375 (223)	1230 (313)
Overall RT (ms)	937 (212)	1230 (227)	1074 (267)
% correspondence: positive	85 (11)	76 (18)	81 (15)
% correspondence: negative	92 (6)	81 (13)	87 (11)
% correspondence: neutral	73 (16)	64 (23)	69 (19)
Overall % correspondence	83 (5)	74 (13)	79 (11)

Note: Means are provided with SDs in parentheses. RT = reaction time. % correspondence refers to the percentage of responses of the subjects who took part in the functional magnetic resonance imaging study that corresponded to the a priori classifications (based on preratings).

smoothed onto the surface using an iterative nearest-neighbor averaging procedure equivalent to applying a 2-dimensional Gaussian smoothing kernel with an FWHM of approximately 8.5 mm. Intersubject averaging and between-group comparisons were performed in a common spherical coordinate system using random effects analyses.

Analyses in a common Talairach space, following smoothing using a 3-dimensional spatial filter with a full-width-half-maximum of 8 mm, were also conducted in order to measure responses of the amygdala and hippocampus.⁵⁶

Three contrasts of interest were examined at the predicted peak of the hemodynamic response (3–7 s following the appearance of the critical word): negative vs neutral, positive vs neutral, and negative vs positive, comparing trials across each of the original conditions. All trials were included and were binned in the analyses using the a priori ratings in order to maximize power and to maintain a fully counterbalanced, matched set of conditions in both subject groups.

A *t* statistic was generated at each voxel. To correct for multiple comparisons, significant clusters of activated voxels were identified on the basis of a Monte Carlo simulation, using a cluster size threshold of 300 mm² on the cortical surface (100 mm³ in the volume) and threshold for rejection of the null hypothesis at $P < .05$. Smaller cortical activations (100–300 mm²) are also reported if they were found within the 2 a priori regions of interest: the medial prefrontal cortex, defined as the medial frontal and orbital gyri (Brodmann area [BA] 10, 9, 11) and the anterior cingulate gyrus (BA 24, 25, and 32, *y* coordinate > 0), and 2) the posterior cingulate gyrus (BA 23 and 31).^{14,57,58} Activations within the precuneus (BA 7) are reported alongside of those within the posterior cingulate gyrus because these 2 regions are adjacent to one another and reciprocally connected.^{15,59} The anatomical location of the peak voxel of each cluster was determined using an automated parcellation of the common cortical surface, which delin-

eates boundaries between cortical areas using known gyral and sulcal landmarks.⁶⁰ These locations were confirmed using the Talairach atlas.⁵⁶

Correlations

To test our a priori hypothesis, correlations between the response to the neutral condition (relative to an implicit baseline: mean signal intensity) at the response peak within the cingulate gyrus and the SAPS global delusion score were performed using Spearman ρ with α set to .05. For correlations between cingulate gyrus responses to all 3 conditions and other clinical measures (SAPS total, SAPS global hallucination score, SAPS global thought disorder score, SANS total score, duration of illness, chlorpromazine equivalents), the significance level was determined using a Bonferroni correction. The anatomical cingulate gyrus region of interest was constructed with an automated parcellation system (see above) using each individual subject's high-resolution anatomical scan; it included the anterior, middle, and posterior portions of the cingulate gyrus.⁶⁰ Follow-up, exploratory correlations were also conducted, using the responses at foci within the cingulate gyri that showed significant between-group differences.

Results

Behavioral RTs

A main effect of affect ($df = 2$, $F = 25.8$, $P = 3.22 \times 10^{-7}$) was due to longer RTs for classifying the neutral situations relative to both the positive ($df = 31$, $t = 5.36$, $P = 7.63 \times 10^{-6}$) and negative ($df = 31$, $t = 5.94$, $P = 1.43 \times 10^{-6}$) sentence pairs (see table 2). Mean RTs for the positive and negative sentence pairs did not differ ($df = 31$, $t = 0.86$, $P = .39$). A main effect of group ($df = 1$, $F = 16.2$, $P < .0005$) was due to significantly longer overall RTs of the patients compared with the controls. There was no group-by-affect interaction ($df = 2$, $F = 1.11$, $P = .32$).

Percentage of Consistent Classifications

A main effect of affect ($df = 2$, $F = 13.73$, $P < .0002$) was due to the fact that subjects' classifications of the neutral sentence pairs were less likely to correspond to the a priori classifications than the classifications of the positive ($df = 31$, $t = 2.79$, $P = .009$) or negative ($df = 31$, $t = 5.01$, $P = 2.06 \times 10^{-5}$) sentence pairs. Also, the correspondence between the a priori classifications and subjects' classifications was lower for the positive relative to the negative sentence pairs ($df = 31$, $t = 3.14$, $P < .004$). A main effect of group ($df = 1$, $F = 8.2$, $P < .009$) was due to the fact that the classification responses of the patients were less likely to correspond to the prior classifications than the control subjects. There was no group-by-affect interaction ($df = 2$, $F = 0.03$, $P = .92$).

Functional Magnetic Resonance Imaging

Foci of significant between-group differences and the contributing within-group activations within the medial prefrontal and posterior cingulate cortices are reported below; additional findings outside of the a priori regions are shown in figures 1–4, and all significant within-group activations are listed in Supplementary Table 2.

Negative Vs Neutral

The healthy subjects demonstrated a greater hemodynamic response to the negative relative to the neutral sentence pairs in the right posterior cingulate gyrus and right precuneus and in the left posterior cingulate gyrus. In contrast, the schizophrenia patients demonstrated the opposite pattern of activation, with greater responses to the neutral relative to the negative sentence pairs in the right and left posterior cingulate gyri (figure 1A–C, Supplementary Table 2, and table 3A). An examination of the responses to each condition within the foci that displayed between-group differences (figure 1D) revealed that the 2 subject groups showed opposite patterns of task-induced deactivation to the 2 conditions in the posterior cingulate gyri; in the right and left posterior cingulate gyri, the healthy subjects demonstrated greater deactivation to the neutral than to the negative sentence pairs, while in the right posterior cingulate gyrus the patients showed greater deactivation to the negative than to the neutral sentence pairs.

Positive Vs Neutral

The healthy subjects demonstrated greater responses to the positive relative to the neutral sentence pairs in the left and right posterior cingulate gyri and right precuneus, as well as in the right medial frontal and anterior cingulate gyri. However, the patients exhibited greater activation to the neutral relative to the positive sentence pairs within the right posterior cingulate gyrus and also within the left and right anterior cingulate and orbital cor-

tices (figure 2A–C, Supplementary Table 2, and table 3B). An examination of the responses to each condition within the foci that displayed between-group differences (figure 2D) revealed that both groups showed task-induced deactivation in the posterior cingulate gyri and anterior cingulate and orbital cortices in response to both the positive and neutral sentence pairs, which for the patients was relatively attenuated for the neutral compared to the positive condition.

Negative Vs Positive

The healthy subjects demonstrated greater hemodynamic responses to the negative relative to the positive sentence pairs in the left posterior cingulate gyrus and precuneus and to the positive relative to the negative sentence pairs in the right anterior cingulate and medial frontal gyri. In contrast, the patients with schizophrenia showed increased activation to the negative relative to the positive sentence pairs in the right and left posterior cingulate gyri, the left precuneus and the right and left anterior cingulate, and orbital cortices (figure 3A–C, Supplementary Table 2, and table 3C). An examination of the responses to each condition within the foci that displayed between-group differences (figure 3D) revealed that again the 2 groups showed opposite patterns of task-induced deactivation in the anterior cingulate and orbital cortices; in the healthy subjects, diminished or absent deactivation to the positive sentence pairs relative to prominent deactivation to the negative sentence pairs was seen, while in the patients, there was prominent deactivation to the positive sentence pairs and diminished or absent deactivation to the negative sentence pairs.

Correlations

Because the pattern of between-group differences was relatively consistent across the entire cingulate gyri (see figures 1–3), we measured the degree of association between responses within the cingulate gyrus as a whole (anatomically defined within each subject, see “Methods”) and symptom levels in the patient group. Severity of delusional thinking was significantly correlated with responses to the neutral sentence pairs in both the right ($\rho = 0.55$, $P = .04$) and left ($\rho = 0.59$, $P = .02$) cingulate gyri (figure 4), indicating that the smaller the deactivation of the cingulate gyri to the neutral sentence pairs the greater the severity of delusions in these patients. There was no evidence for correlations between responses of the cingulate gyri to the neutral sentence pairs and other clinical measures (P 's $> .66$), except for an inverse relationship with global thought disorder within the left cingulate gyrus ($\rho = -0.62$, $P = .02$). There were no correlations between responses of the cingulate gyri to the negative and positive conditions and any clinical measure (P 's $> .29$). Also, there were no correlations between response magnitudes in the

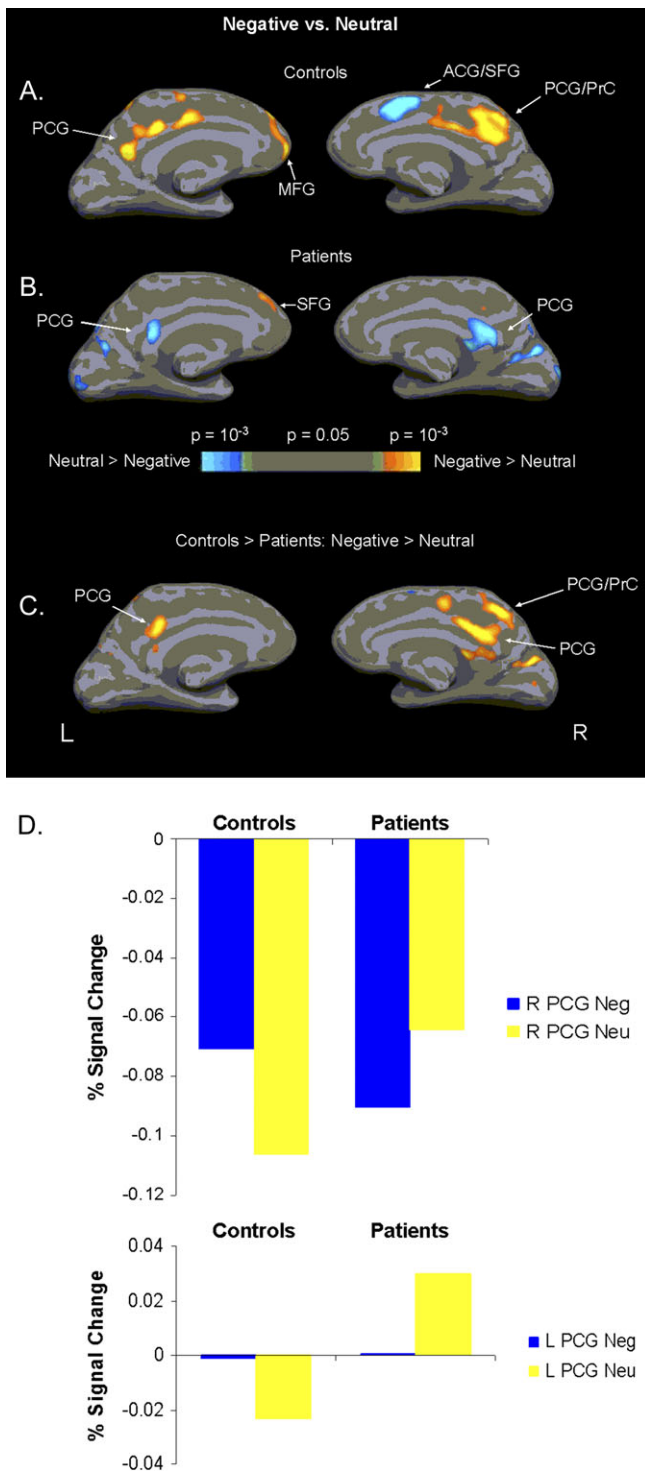


Fig. 1. Negative Vs Neutral Contrast, medial cortical surface. Mean activation maps showing significant clusters of activation ($P < .05$) for the healthy control ($n = 18$) (A) and schizophrenia ($n = 14$) (B) group and the map of the between-group differences (C) for the negative vs. neutral contrast. For the within-group maps (A and B), warm colors indicate clusters showing greater responses to the negative relative to the neutral sentence pairs, while cold colors indicate clusters with greater activation to the neutral relative to the negative sentence pairs. For the map of the between-group differences (C), warm colors indicate clusters showing greater

cingulate gyri and antipsychotic dose (P 's $> .1$) or duration of illness (P 's $> .09$).

To further explore the association between delusion severity and the responses of the cingulate gyri to the neutral sentence pairs, we tested for associations between delusion severity and responses to the neutral sentence pairs for specific clusters that had shown between-group differences (see figures 1C and 2C). Correlations between delusion severity and responses to the neutral condition that approached significance were found for foci within the right anterior cingulate ($\rho = 0.53$, $P = .05$) and the left posterior cingulate ($\rho = 0.51$, $P = .065$) gyri.

To test for a delusion-associated attentional bias toward the neutral stimuli,^{31,37} correlations between RTs to the 3 conditions and delusion severity were measured. A trend toward a correlation between delusion severity and RTs to the neutral sentence pairs was found ($\rho = 0.50$, $P = .066$). There was no evidence for associations between delusion severity and RTs to the negative or positive sentence pairs (P 's $> .26$). Results of additional correlational analyses are included in Supplementary Materials.

Discussion

In this study, we sought to determine whether activity of cortical midline regions during the appraisal of the emotional meaning of social information is abnormal in schizophrenia. We found that healthy subjects and patients with schizophrenia demonstrated opposite patterns of activity within this network. First, in the posterior cingulate gyrus, healthy subjects showed greater responses (reduced deactivation) to the negative, relative to neutral, sentence pairs, while the schizophrenia patients exhibited larger responses to the neutral, relative to the negative, sentence pairs. Second, a similar pattern was found in the relative responses of the 2 groups to the positive and neutral sentence pairs within both the medial prefrontal and posterior cingulate cortices. Third, the magnitude of responses to the neutral sentence pairs within the cingulate gyrus predicted the severity of delusional thinking in the schizophrenia patients. Finally, the patients showed a pattern of valence responsivity (positive vs negative) in the medial prefrontal cortex that was opposite to that of the healthy group; while the healthy subjects exhibited larger responses to the positively valenced sentence pairs, compared with the negative ones, in the right medial prefrontal cortex, the

activation for the negative $>$ neutral contrast in the control group compared with the patient group. (In C, there were no clusters showing greater activation in the patients compared with the controls for the negative $>$ neutral contrast.) In D, percent signal change relative to baseline for the foci exhibiting significant between-group differences in C are displayed; the baseline is mean signal intensity. PCG = posterior cingulate gyrus, MFG = medial frontal gyrus, ACG = anterior cingulate gyrus, SFG = superior frontal gyrus, PrC = precuneus.

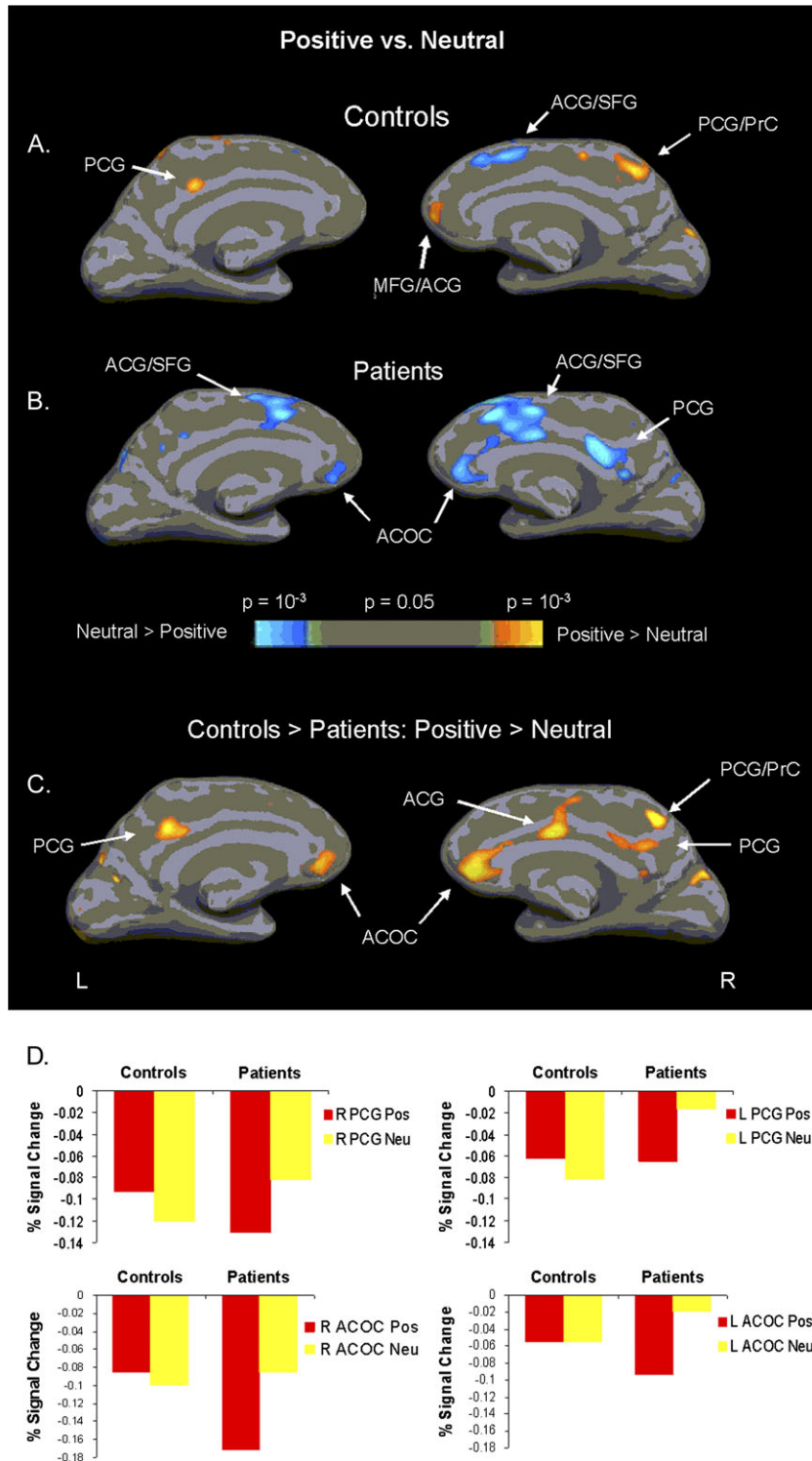


Fig. 2. Positive Vs Neutral Contrast, medial cortical surface. Mean activation maps showing significant clusters of activation ($P < .05$) for the healthy control ($n = 18$) (A) and schizophrenia ($n = 14$) (B) group and the map of the between-group differences (C) for the positive vs neutral contrast. For the within-group maps (A and B), warm colors indicate clusters showing greater responses to the positive relative to the neutral sentence pairs, while cold colors indicate clusters with greater activation to the neutral relative to the positive sentence pairs. For the map of the between-group differences (C), warm colors indicate clusters showing greater activation for the positive > neutral contrast in the control group compared with the patient group. (In C, there were no clusters showing greater activation in the patients compared with the controls for the positive > neutral contrast.) In D, percent signal change relative to baseline for the foci exhibiting significant between-group differences in C are displayed; the baseline is mean signal intensity. PCG = posterior cingulate gyrus, MFG = medial frontal gyrus, ACG = anterior cingulate gyrus, SFG = superior frontal gyrus, PrC = precuneus, ACOC = anterior cingulate and orbital cortices.

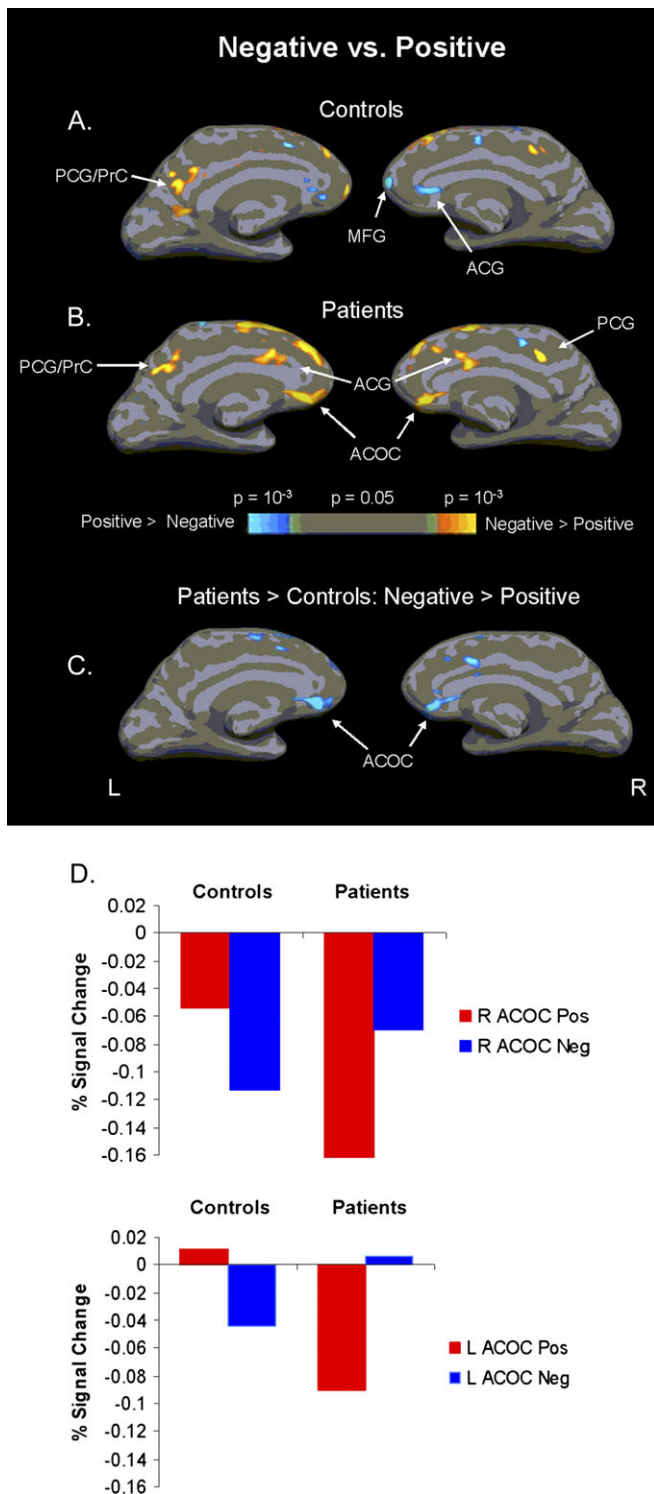


Fig. 3. Negative Vs Positive Contrast, Medial Cortical Surface. Mean activation maps, displayed on the medial cortical surface, showing significant clusters of activation ($P < .05$) for the healthy control ($n = 18$) (A) and schizophrenia ($n = 14$) (B) group and the map of the between-group differences (C) for the negative vs positive contrast. For the within-group maps (A and B), warm colors indicate clusters showing greater responses to the negative relative to the positive sentence pairs, while cold colors indicate clusters with greater activation to the positive relative to the negative sentence pairs. For the map of the between-group differences (C), cold colors

patients showed the reverse pattern, with greater responses to the negative compared with the positive sentence pairs in the medial prefrontal cortex bilaterally.

These results suggest that the processing of emotional information influences activity in cortical midline structures in healthy individuals and patients with schizophrenia in distinct ways. Although the precise function of the medial prefrontal and posterior cingulate cortices, and the larger default network that includes these 2 regions, is not fully understood,⁶¹ many previous functional neuroimaging studies have shown that this network is active during introspective mental activities, including self-reflection, theory-of-mind tasks, and autobiographical memory retrieval.⁶² Also, a number of studies have found that the performance of various cognitive tasks “turns off” or deactivates this network and that the amount of deactivation can be linked to the difficulty of the task⁶³ or performance success.^{64,65} In contrast, emotional processing appears to influence activity within this network in a manner opposite to that of effortful cognitive processing, with less deactivation of the medial prefrontal cortex as emotional “load” increases (accompanied by parallel reductions in activation of lateral prefrontal areas that mediate executive and attentional processes).^{66,67} Similar to emotional processing, self-referential thinking, autobiographical memory retrieval, and other types of internally directed mental activities also lead to attenuated deactivation of default network regions.⁶² This reciprocal modulation of the default network (and of the “task-positive” executive system) is thought to reflect dynamic changes in allocation of neural resources that serve competing demands for introspective versus externally oriented, goal-related processing.⁶⁸

In the current study, the control subjects showed more activation (less deactivation) of medial prefrontal and posterior cingulate cortices in response to the emotionally laden (vs the neutral) descriptions of social situations. We also found, in a recent event-related potential (ERP) study in healthy individuals conducted using the same paradigm of the current study, a larger neurophysiological response between 500 and 700 milliseconds (the late positivity) following the emotional words, compared to the neutral ones.⁴³ Taken together, these results indicate that, in healthy subjects, emotional processing augments both the late positivity and hemodynamic activity

indicate clusters showing greater activation for the negative > positive contrast in the patient group compared with the healthy control group. (In C, there were no clusters showing greater activation for the controls relative to the patients for the negative > positive contrast.) In D, percent signal change relative to baseline for the foci exhibiting significant between-group differences in C are displayed; the baseline is mean signal intensity. PCG = posterior cingulate gyrus, PrC = precuneus, MFG = medial frontal gyrus, ACG = anterior cingulate gyrus, ACOC = anterior cingulate and orbital cortices.

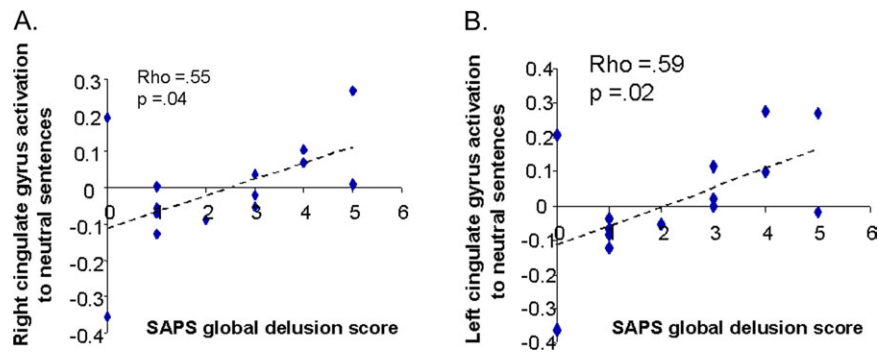


Fig. 4. Correlation Between Delusion Severity and Cingulate Gyrus Response to the Neutral Stimuli in the Schizophrenia Patients. Graphs of the correlations between right (A) and left (B) cingulate gyrus responses (% signal change) to the neutral sentence pairs and delusion severity, measured using the SAPS global delusion item, in the 14 schizophrenia patients.

(attenuating deactivation) within the medial prefrontal and posterior cingulate cortices.

In patients with schizophrenia, the opposite pattern of hemodynamic findings was observed in midline cortical structures: More activation (less deactivation) was seen

to the neutral than to the emotional sentence pairs. One trivial explanation for this response reversal is that, unlike controls, patients found it easier to make emotional judgments about the neutral than the emotional stimuli and therefore failed to deactivate the

Table 3. Significant Between-Group Differences in Activation

Region	BA	Area (mm ²)	Tal (x, y, z)	P Value	Z Score
A. Negative > neutral, control > schizophrenia					
L posterior cingulate gyrus ^a	23	188	-7, -25, 41	.0008	3.36
R posterior cingulate gyrus	23	520	6, -20, 35	.002	3.12
R posterior cingulate gyrus/precuneus	31/7	369	10, -42, 56	6×10^{-5}	4.01
R parieto-occipital sulcus	19	414	19, -76, 27	.008	2.67
B. Positive > neutral, control > schizophrenia					
L anterior cingulate cortex/orbital cortex	32/10/11	396	-6, 35, -8	.016	2.39
R anterior cingulate cortex/orbital cortex	32/24/10/11	744	4, 31, 11	.009	2.60
R anterior cingulate gyrus ^a	24	217	6, 7, 26	.0005	3.46
L posterior cingulate gyrus ^a	23/31	252	-3, -25, 37	.002	3.18
R posterior cingulate gyrus/precuneus ^a	31/7	202	10, -43, 54	3×10^{-7}	5.14
R posterior cingulate gyrus ^a	23/31	158	14, -37, 35	.034	2.12
L precentral cortex	4	665	-43, -1, 34	.004	2.86
R precentral cortex/inferior frontal gyrus	44	562	49, 10, 27	.002	3.05
L middle frontal sulcus/superior frontal sulcus	8	311	-18, 43, 19	.0003	3.62
R middle frontal gyrus/inferior frontal sulcus	46	354	44, 41, 16	.005	2.81
L occipital pole/middle occipital gyrus	18	678	-23, -100, 1	.0003	3.65
C. Negative > positive, schizophrenia > control					
L anterior cingulate cortex/orbital cortex ^a	32/24/11	256	-6, 30, -10	.006	2.75
R anterior cingulate cortex/orbital cortex	32/25/11	486	13, 30, -21	.008	2.67

Note: Location and size of clusters which showed significant activation in the between-group comparisons for the negative vs neutral (A), positive vs neutral (B), and negative vs positive (C) contrasts with Talairach (Tal) coordinates, *P* and *Z* score for the local *P* minimum for each cluster. All clusters reported above met a significance threshold of $P < .05$ corrected, except those labeled with an 'a,' which are smaller activations found within the a priori regions of interest (see "Methods"). BA = Brodmann area; L = left; R = right. Cortex = gyrus + sulcus. Anterior cingulate cortex = anterior cingulate gyrus, pericallosal sulcus, or subcallosal gyrus; orbital cortex = orbital gyrus, orbital sulcus, suborbital sulcus, or rectus gyrus.

default network in response to the neutral sentence pairs. However, this possibility is inconsistent with our behavioral findings that indicate that, like controls, patients showed longer RTs to the neutral sentence pairs compared with the emotional ones. Thus, we attribute the reversal of response modulation in the patients to a more specific abnormality in processing emotional material.

A reversal of neural activity to emotional vs neutral material in patients is in line with the results of several previous studies, which have reported larger neural responses to neutral, nonsalient stimuli and reduced responses to aversive or reinforced stimuli in schizophrenia patients^{33,34} and in people at risk for schizophrenia,⁶⁹ compared with healthy control subjects. This reversed hemodynamic activity was observed in the right parahippocampal gyrus during the viewing of neutral and increasingly fearful emotional facial expressions³³ in the right midbrain in a reward prediction error paradigm³⁴ and in at-risk subjects in the hippocampus, inferior and superior frontal gyri, cuneus, and thalamus during the viewing of emotional and neutral facial expressions⁶⁹. The present study extends these findings to demonstrate that this reversed modulation in schizophrenia occurs within components of the default network during appraisals of emotional and neutral socially relevant information.

In theory, this reversal of modulation to emotional vs neutral material within midline cortical structures in schizophrenia could arise from either (*a*) reduced activity (increased deactivation) during the evaluation of the emotional sentence pairs, and/or (*b*) increased activity (reduced deactivation) during the evaluation of the neutral sentence pairs in these regions. The current pattern of findings does not, alone, allow us to distinguish between these 2 possibilities because the baseline level of activity within these regions may have differed between the 2 groups.^{20,21,23} Nonetheless, on the basis of previous studies, we suggest that both (*a*) and (*b*) contributed to the reversed pattern of activity observed in patients.

Support for (*a*)—a reduction in neural activity to the emotionally salient sentence pairs—comes from our recent ERP study in patients and controls; using this paradigm, we found a diminished late positivity response to negative and positive words in patients, compared with controls.⁷⁰ Also, a number of functional neuroimaging studies have reported diminished amygdala activity in schizophrenia during appraisals of emotional facial expressions or scenes (see Aleman¹ and Holt and Phillips⁷ for reviews).

Support for (*b*)—an increase in activity to the neutral condition—comes from several previous fMRI studies that have detected inappropriately elevated neural responses to neutral, nonsalient stimuli in patients with schizophrenia.^{32–34,36} Given that, in the present study, this increased activity to neutral stimuli in patients

occurred within midline cortical structures that have been found to mediate introspective mental activity, one interpretation is that in appraising the meaning of the neutral, relatively ambiguous condition, patients relied on introspective processes to a greater extent than controls.

Of note, our ERP study did not show such an increased response to neutral stimuli in patients⁷⁰; we attribute this discrepancy to the different temporal sensitivities of fMRI and ERP: neural responses to emotionally salient stimuli have been shown to occur very rapidly (detectable by ERPs and fMRI), while responses to neutral, ambiguous information may have a more extended time course that is less closely time locked to a given event (detectable by fMRI only).

The possibility that schizophrenia patients may engage in more introspective activity while appraising the meaning of neutral, ambiguous stimuli is in line with the more general hypothesis that motivational salience is misassigned to unimportant, neutral or affectively ambiguous information in schizophrenia,^{31,40–42,71,72} particularly in patients with active delusions. In the present study, the magnitude of the responses of the cingulate gyrus to the neutral condition correlated with delusion severity within the schizophrenia group, further supporting this hypothesis.

Nonetheless, unlike in a previous study,³¹ we found little behavioral evidence for elevated processing of affectively neutral information in schizophrenia or delusions. The fact that we did detect a trend toward a correlation between RTs to the neutral sentence pairs and delusions (similar to our previous finding³¹) suggests that limited power, due to the smaller number of schizophrenia subjects (14) and lower percentage of neutral stimuli (33%) used here, compared with the number of schizophrenia patients (32) and percentage of neutral stimuli (50%) included in our behavioral study, could account for this discrepancy. Consistent with the findings of previous fMRI studies in schizophrenia,^{34,39,73,74} including 2 which showed elevated activity, but no behavioral bias, to nonsalient, neutral stimuli in patients with schizophrenia,^{34,39} the presence of an abnormal neural response in the absence of a parallel behavioral abnormality suggests that hemodynamic activity can, in some cases, represent a more sensitive index of neurocognitive dysfunction in schizophrenia than behavior.

In the current study, both the controls and the patients showed longer response times to the neutral compared with the emotional conditions. This was accompanied by increased activation to the neutral relative to the emotional sentence pairs, in both groups, of the dorsal anterior cingulate and lateral prefrontal cortices, 2 regions that lie outside of the default network⁶⁸ (see figures 1 and 2 and Supplementary Table 2). These increased response times and the increased activity within these 2 regions may reflect increased response competition and

selection demands associated with evaluating the emotionality of the neutral sentence pairs (inherently ambiguous in this respect), in comparison to the emotional sentence pairs.^{75,76} Future studies that explicitly manipulate response conflict and emotional content can explore the effects of emotional and semantic ambiguity on activity within prefrontal, executive control centers in healthy subjects and patients with schizophrenia.

A related question is whether the abnormalities reported here in midline cortical structures are specific to affective processing, or are they related to a sensory or cognitive deficit(s) in schizophrenia? Although basic visual processing deficits have been linked to emotional perception impairments in schizophrenia,^{77,78} visual system dysfunction in schizophrenia cannot easily account for our findings because the comprehension of language occurs downstream of the visual decoding of sentences, which in our study were well matched with respect to visual features (word and sentence length and >90% of word content) across conditions.

These abnormalities also cannot be easily accounted for by general cognitive impairment. First, the pattern of response times across the patients and controls did not correspond with the pattern of modulation of midline cortical structures to emotional vs neutral sentence pairs. Second, in previous studies, abnormally elevated responses to emotionally neutral material have been observed during passive viewing conditions^{32,35,79} (as opposed to during a cognitive task) and when peripheral measures, rather than behavioral responses, were used as outcome variables.^{35,79}

In addition to assessing the potential role of nonaffective processes in these abnormalities, future studies should measure neural responses during emotional appraisals of unmedicated patients experiencing acute exacerbations, in addition to those of patients with chronic symptoms, in order to determine whether these findings can be extended to acute as well as chronic psychosis and are independent of effects of medication.

An unexpected result of the current study was the abnormal response to valence (negative vs positive) within the medial prefrontal cortex in schizophrenia. In the controls, portions of the right medial prefrontal cortex showed an increased response (less deactivation) to positive vs negative sentence pairs. This finding is in line with studies conducted in rodents and nonhuman primates, as well as functional imaging studies in humans, which have shown that the orbitofrontal cortex is critical for the assessment of the valence of a stimulus; many of these studies have found that the medial orbitofrontal cortex exhibits larger responses to positive than to negative stimuli.⁸⁰ However, here the patients showed a pattern of response that was opposite to that found in the controls, with larger responses to the negative relative to the positive sentence pairs. This finding is broadly consistent with evidence for abnormalities in schizophrenia in processes known to be mediated by

the orbitofrontal/ventromedial cortex, such as reward-driven decision making^{81,82} and fear extinction recall.⁷⁹

Also, several studies have reported abnormal activity levels in schizophrenia in the ventromedial⁸³ and dorsomedial⁸⁴ prefrontal cortices, and in the posterior cingulate cortex,⁸³ during tasks that rely on self-referential processing, suggesting that dysfunction of this midline cortical network may disrupt social cognitive processes in schizophrenia. Given that delusions often appear to arise from errors in social attributions, in particular, misassignments of self-relevance, these data suggest that such errors could be related to impaired functioning of these midline cortical regions during delusion formation.

In conclusion, we have shown that key components of a cortical midline network, the posterior cingulate and medial prefrontal cortices, are abnormally modulated during appraisals of the emotional meaning of social information in schizophrenia. Future studies that compare individuals with psychotic symptoms who are at different stages of the illness can determine whether dysfunction of this network represents a consequence of, or a marker of vulnerability to, psychosis.

Supplementary Material

Supplementary tables 1 and 2 are available at <http://schizophreniabulletin.oxfordjournals.org>.

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