Dysfunction of a Cortical Midline Network during Emotional Appraisals in Schizophrenia

Daphne. J. Holt,1,2,3 Balaji Lakshmanan,4 Oliver Freudenreich,1,2 Donald C. Goff,1,2 Scott L. Rauch,5,2 Gina R. Kuperberg6,1,2,3

Abstract - 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 and 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. We found that 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.

Keywords - cingulate cortex, default mode network, delusions, emotion, fMRI, medial prefrontal cortex

INTRODUCTION

Abnormalities in affective processing and social cognition are central features of schizophrenia1-7. 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 processing8,9. Functional neuroimaging studies in healthy individuals have found that the medial prefrontal cortex and posterior cingulate cortex, which have reciprocal connections10, are recruited during the performance of simple, evaluative11-13, as well as during more complex14-16, social cognitive tasks. These two 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 which require attending to the external environment17-19.

Recent work suggests that the function of these cortical midline structures is compromised in schizophrenia. Abnormally elevated activity20, 21 and aberrant functional connectivity22-24 of the posterior cingulate cortex has been reported in schizophrenia, and a popular pharmacological model of the symptoms of schizophrenia, intoxication with the NMDA receptor antagonist ketamine25, has been linked to abnormal modulation of the posterior cingulate cortex that is predictive of the severity of psychotic symptoms26, 27. Also, activity within medial prefrontal23, 24 and posterior cingulate23 cortices have been found to correlate with the severity of psychotic symptoms, and one fMRI study found that schizophrenia patients with psychotic symptoms exhibited larger responses within the medial prefrontal cortex than those without psychotic symptoms and healthy individuals28.

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, non-salient stimuli during emotional processing29-37, which in some studies has been linked to psychotic symptoms33, 38, or specifically to delusions29, 31, 37, 39. This abnormal response to neutral stimuli has been proposed to reflect a tendency to attend preferentially (or misattribute motivational salience) to non-salient information during psychotic states40-42 and has been linked to abnormalities in emotional appraisal31.

1 Psychiatry Department, Massachusetts General Hospital, Boston, MA.
2Harvard Medical School, Boston, MA.
3Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA.
4The Kennedy Krieger Institute, Baltimore, MD.
5McLean Hospital, Belmont, MA.
6Psychology Department, Tufts University, Medford, MA.
In the current study, we hypothesized that dysfunction of the medial frontal and posterior cingulate cortices during emotional appraisals plays an important role in psychosis. We used a novel paradigm, developed and normed by our group\(^4^\), in which participants appraised two-sentence social vignettes which 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)\(^4^3, 4^5\), which can include activation of networks subserving emotional and social cognitive processing\(^4^6-4^9\). For example, previous studies have found that limbic and paralimbic regions, including the medial prefrontal\(^4^7, 4^8\) and posterior cingulate \(^4^7\) cortices, are active while people are reading\(^4^9\) or hearing\(^4^6\) words describing an emotionally-salient situation, or while reading neutral words which were previously encountered in an emotional context47, 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. Critically, we predicted that, compared to 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**

15 patients with DSM-IV-diagnosed schizophrenia and 19 control subjects completed the study. Medicated patients with clinically stable schizophrenia were recruited through the MGH 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\(^3^0\) and were native speakers of English. The healthy control subjects did not have any psychiatric or neurologic disorders, as determined during screening using the SCID\(^3^1\). Subjects who had used illicit substances during the three 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% non-response or random responding). The two groups were matched with respect to age, gender, premorbid verbal IQ and parental SES (see Table 1).

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Each patient’s symptoms were evaluated by a trained rater using the Schedule for the Assessment of Positive Symptoms (SAPS)\(^3^2\) and the Schedule for the Assessment of Negative Symptoms (SANS)\(^3^3\).

**Stimuli**

Two-sentence descriptions of social situations (see Supplementary Table 1 and Holt et al, in press\(^3^4\) for examples and additional details about the stimuli), for each of three experimental conditions (neutral, positive and negative), were used. For each pair of sentences, the first sentence was neutral and ambiguous in content, providing a non-constraining 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, i.e., “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 three 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 two-sentence social scenarios were seen in all three conditions. Each of the three 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 1000ms, depending on whether the critical word was the sixth or fifth word of the sentence, respectively; this allowed the critical word to appear 7s after trial onset in every trial. The first sentence was presented as a whole for 3.5s (100ms interstimulus interval (ISI)). The second sentence was presented one word at a time (500ms per word, 100ms ISI). Following the presentation of the sentence pair, a question mark appeared for a variable duration (1880-3600ms), depending on the total number of words in the second sentence, to allow the total trial length to equal 12s for all trials. The ISI between trials (a fixation cross) was jittered (0-19000ms). 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 which were consistent with the \textit{a priori} classifications of the three conditions were compared across conditions and between the two groups using ANOVAs, and significant main effects and condition by group interactions were followed up by planned, paired Student’s \textit{t}-tests.
TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS.

<table>
<thead>
<tr>
<th></th>
<th>Control n=18: 4 female</th>
<th>Schizophrenia n=14: 3 female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.7 ± 8.3</td>
<td>42.9 ± 11.9</td>
</tr>
<tr>
<td>Length of education (years)</td>
<td>14.2 ± 1.9</td>
<td>13.9 ± 2.0</td>
</tr>
<tr>
<td>Mean parental education (years)</td>
<td>13.6 ± 3.0</td>
<td>13.9 ± 2.3</td>
</tr>
<tr>
<td>Mean parental SES</td>
<td>2.8 ± 1.3</td>
<td>2.9 ± 1.3</td>
</tr>
<tr>
<td>Premorbid verbal I.Q.</td>
<td>116.0 ± 6.6</td>
<td>110.8 ± 7.4</td>
</tr>
<tr>
<td>Head motion (mm)</td>
<td>3.3 ± 0.8</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>SAPS total</td>
<td>23.4 ± 17.2</td>
<td></td>
</tr>
<tr>
<td>SAPS global delusion item</td>
<td>2.4 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>SAPS global hallucination item</td>
<td>3.1 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>SAPS global thought disorder item</td>
<td>1.4 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>SANS total</td>
<td>38.8 ± 13.7</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>19.6 ± 12.7</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalents</td>
<td>448.4 ± 453.2</td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences between the two groups in mean age, years of education, parental education, parental SES, premorbid verbal I.Q., and head motion during the scanning. 8 of the 14 patients had active delusions (SAPS global delusion score > 2) which 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, ziprasidone, risperidone, clozapil) (n=8); fluphenazine decanoate (n=2); fluphenazine decanoate plusquetiapine (n=1); unmedicated (n=3). a=measured with the Hollingshead index; b=measured with the Adult North American Reading Test (ANART); c=mean total vector translation in mm. No subject showed greater than 5 mm mean vector translation.

MRI data acquisition

Imaging took place on a 3 Tesla MR scanner (Siemens Trio) with echoplanar (EP) imaging capability. Subjects underwent a conventional high-resolution 3D structural scan, constituting a spoiled GRASS (SPGR) sequence (128 sagittal slices, 1.33 mm thickness, TR = 2530 ms, TE = 3.77 ms, flip angle = 7 degrees, bandwidth = 200 Hz, in-plane resolution = 1 mm x 1.33 mm) and then viewed the three types of sentence-pairs and fixation trials over six functional runs. Each functional run lasted 380 seconds during which T2*-weighted echoplanar (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 (GR) sequence (TR = 2 sec; TE = 25 msec; flip angle = 100 grad). A second high-resolution 3D structural scan was acquired following the functional imaging.

MRI data analysis

In order to increase the signal-to-noise ratio, the two 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 2D 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 3D spatial filter (full-width-half-max: 8.7 mm) and global intensity variations were removed. The functional images were analyzed using a General Linear Model (GLM) using a finite impulse response (FIR) 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 smoothed onto the surface using an iterative nearest-neighbor averaging procedure equivalent to applying a two-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 3D spatial filter with a full-width-half-maximum of 8 mm, were also conducted in order to measure responses of the amygdala and hippocampus.

Three contrasts of interest were examined at the predicted peak of the hemodynamic response (3-7s 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 mm$^3$ on the cortical surface (100 mm$^3$ in the volume) and threshold for rejection of the null hypothesis at *p*=0.05. Smaller cortical activations (100-300 mm$^3$) are also reported if they were found within the two *a priori* regions of interest: 1) the medial prefrontal cortex, defined as the medial frontal and orbital gyri (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). Activations within the precuneus (BA 7) are reported alongside of those within the posterior cingulate gyrus, since these two regions are adjacent to one another and reciprocally connected. The anatomical location of the peak voxel of each cluster was determined using an automated parcellation of the common cortical surface, which delineates boundaries between cortical areas using known gyral and sulcal landmarks. These locations were confirmed using the Talairach atlas.

**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’s Rho with alpha set to .05. For correlations between cingulate gyrus responses to all three conditions and other clinical measures (SAPS total, SAPS global hallucination score, SANS total score, 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 scans; it included the anterior, middle and posterior portions of the cingulate gyrus. Follow-up, exploratory correlations were also conducted, using the responses at loci within the cingulate gyrus that showed significant between-group differences.

**Results**

**Behavioral**

**RTs**

A main effect of Affect (df=2; *F*=25.8; *p*=3.22 x 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 x 10^-6) and negative (df=31; *t*=5.94; *p*=1.43 x 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 to 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 x 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*=.03; *p*=.92).

**Functional MRI**

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 gyrus (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 two subject groups showed opposite patterns of task-induced deactivation to the two conditions in the posterior cingulate gyrus: in the right and left posterior cingulate gyrus, 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.
### TABLE 2. BEHAVIORAL RESULTS.

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

**Table 2. Behavioral results.** Means are provided, with standard deviations in parentheses. RT = reaction time; ms = milliseconds. % correspondence refers to the percentage of responses of the subjects who took part in the fMRI study that corresponded to the a priori classifications (based on pre-ratings).
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TABLE 3. SIGNIFICANT BETWEEN-GROUP DIFFERENCES IN ACTIVATION.

A. NEGATIVE > NEUTRAL, CONTROL > SCHIZOPHRENIA

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Area (mm^2)</th>
<th>Tal (x, y, z)</th>
<th>P-value</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L posterior cingulate gyrus</td>
<td>23</td>
<td>188</td>
<td>-7, -25, 41</td>
<td>0.0008</td>
<td>3.36</td>
</tr>
<tr>
<td>R posterior cingulate gyrus</td>
<td>23</td>
<td>520</td>
<td>6, -20, 35</td>
<td>0.002</td>
<td>3.12</td>
</tr>
<tr>
<td>R posterior cingulate gyrus/precuneus</td>
<td>31/7</td>
<td>369</td>
<td>10, -42, 56</td>
<td>6 x 10^{-5}</td>
<td>4.01</td>
</tr>
<tr>
<td>R parieto-occipital sulcus</td>
<td>19</td>
<td>414</td>
<td>19, -76, 27</td>
<td>0.008</td>
<td>2.67</td>
</tr>
</tbody>
</table>

B. POSITIVE > NEUTRAL, CONTROL > SCHIZOPHRENIA

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Area (mm^2)</th>
<th>Tal (x, y, z)</th>
<th>P-value</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L anterior cingulate cortex/orbital cortex</td>
<td>32/10/11</td>
<td>396</td>
<td>-6, 35, -8</td>
<td>0.016</td>
<td>2.39</td>
</tr>
<tr>
<td>R anterior cingulate cortex/orbital cortex</td>
<td>32/24/10/1</td>
<td>744</td>
<td>4, 31, 11</td>
<td>0.009</td>
<td>2.60</td>
</tr>
<tr>
<td>R anterior cingulate gyrus</td>
<td>24</td>
<td>217</td>
<td>6, 7, 26</td>
<td>0.0005</td>
<td>3.46</td>
</tr>
<tr>
<td>L posterior cingulate gyrus</td>
<td>23/31</td>
<td>252</td>
<td>-3, -25, 37</td>
<td>0.002</td>
<td>3.18</td>
</tr>
<tr>
<td>R posterior cingulate gyrus/precuneus</td>
<td>31/7</td>
<td>202</td>
<td>10, -43, 54</td>
<td>3 x 10^{-7}</td>
<td>5.14</td>
</tr>
<tr>
<td>R posterior cingulate gyrus</td>
<td>23/31</td>
<td>158</td>
<td>14, -37, 35</td>
<td>0.034</td>
<td>2.12</td>
</tr>
<tr>
<td>L precentral cortex</td>
<td>4</td>
<td>665</td>
<td>-43, -1, 34</td>
<td>0.004</td>
<td>2.86</td>
</tr>
<tr>
<td>R precentral cortex/inferior frontal gyrus</td>
<td>44</td>
<td>562</td>
<td>49, 10, 27</td>
<td>0.002</td>
<td>3.05</td>
</tr>
<tr>
<td>L middle frontal sulcus/superior frontal sulcus</td>
<td>8</td>
<td>311</td>
<td>-18, 43, 19</td>
<td>0.0003</td>
<td>3.62</td>
</tr>
<tr>
<td>R middle frontal gyrus/inferior frontal sulcus</td>
<td>46</td>
<td>354</td>
<td>44, 41, 16</td>
<td>0.005</td>
<td>2.81</td>
</tr>
<tr>
<td>L occipital pole/middle occipital gyrus</td>
<td>18</td>
<td>678</td>
<td>-23, -100, 1</td>
<td>0.0003</td>
<td>3.65</td>
</tr>
</tbody>
</table>

C. NEGATIVE > POSITIVE, SCHIZOPHRENIA > CONTROL

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Area (mm^2)</th>
<th>Tal (x, y, z)</th>
<th>P-value</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L anterior cingulate cortex/orbital cortex</td>
<td>32/24/11</td>
<td>256</td>
<td>-6, 30, -10</td>
<td>0.006</td>
<td>2.75</td>
</tr>
<tr>
<td>R anterior cingulate cortex/orbital cortex</td>
<td>32/25/11</td>
<td>486</td>
<td>13, 30, -21</td>
<td>0.008</td>
<td>2.67</td>
</tr>
</tbody>
</table>

TABLE 3. SIGNIFICANT BETWEEN-GROUP DIFFERENCES IN ACTIVATION.

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 with 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.
Figure 1. Negative vs. Neutral

Controls > Patients: Negative > Neutral

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.
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Figure 2. **Positive vs. Neutral 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 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 to the patient group. (In C, there were no clusters showing greater activation in the patients compared to 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.
FIGURE 3. NEGATIVE VS. POSITIVE CONTRAST, MEDIAL CORtical SURFACE.

MEN activation maps, displayed on the medial cortical surface, showing significant clusters of activation ($p < 0.05$) 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 indicate clusters showing greater activation for the negative > positive contrast in the patient group compared to 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.
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Figure 4.

A.  

B.  

Figure 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.

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 cortices (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 relative 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 two 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=0.04) and left (Rho=0.59, p=0.02) cingulate gyri (Figure 4), indicating that the smaller the deactivation of the cingulate gyrus 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 (ps >.66), except for an inverse relationship with global thought disorder within the left cingulate gyrus (Rho = -.62; p=.02). There were no correlations between responses of the cingulate gyri to the negative and positive conditions and any clinical measure (ps >.29). Also, there were no correlations between response magnitudes in the cingulate gyri and antipsychotic dose (ps >.1) or duration of illness (ps >.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 which approached significance were found for foci within the right anterior cingulate (Rho=.53, p=.05) and the left posterior cingulate (Rho=.51, p=.065) gyr.

To test for a delusion-associated attentional bias towards the neutral stimuli, correlations between RTs to the three conditions and delusion severity were measured. A trend towards a correlation between delusion severity and RTs to the neutral sentence-pairs was found (Rho=.50; p=.066). There was no evidence for associations between delusion severity and RTs to the negative or positive sentence-pairs (ps >.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 sentence-pairs. Second, a similar pattern was found in the relative responses of the two 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 versus 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 to the negative ones, in the right medial prefrontal cortex, the patients showed the reverse pattern, with greater responses to the negative compared to 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 two regions, is not fully understood, 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. 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 task or performance success. 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). 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. 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.

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 (versus 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 500ms and 700ms (the Late Positivity) following the emotional words, compared to the neutral ones. Taken together, these results indicate that, in healthy subjects, emotional processing augments both the Late Positivity and hemodynamic activity (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 default network in response to the neutral sentence-pairs. However, this possibility is inconsistent with our behavioral findings which indicate that, like controls, patients showed longer reaction times to the neutral sentence-pairs compared to the emotional ones. Thus we attribute the
reversal of response modulation in the patients to a more specific neurocognitive abnormality in processing emotional material.

A reversal of neural activity to emotional versus neutral material in patients is in line with the results of several previous studies, which have reported larger neural responses to neutral, non-salient stimuli, and reduced responses to aversive or reinforced stimuli, in schizophrenia patients and in people at risk for schizophrenia, compared to healthy control subjects. This reversed hemodynamic activity was observed in the right parahippocampal gyrus during the viewing of neutral and increasingly fearful emotional facial expressions, in the right midbrain in a reward prediction error paradigm, and in at-risk subjects, in the hippocampus, inferior and superior frontal gyri, cuneus and thalamus during the viewing of emotional and neutral facial expressions. 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 two possibilities, because the baseline level of activity within these regions may have differed between the two groups. 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 to controls. Also, a number of functional neuroimaging studies have reported diminished amygdala activity in schizophrenia during appraisals of emotional facial expressions or scenes (see Aleman and Holt and Phillips 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, non-salient stimuli in patients with schizophrenia. 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 patients; 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 much 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, 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, we found little behavioral evidence for elevated processing of affectively neutral information in schizophrenia or delusions. The fact that we did detect a trend towards a correlation between reaction times to the neutral sentence-pairs and delusions (similar to our previous finding), suggests that limited power, due to the smaller number of schizophrenia subjects and lower percentage of neutral stimuli used here, compared to the number of schizophrenia patients, and percentage of neutral stimuli included in our behavioral study, could account for this discrepancy. Consistent with the findings of previous functional MRI studies in schizophrenia, including two which showed elevated activity, but no behavioral bias, to non-salient, neutral stimuli in patients with schizophrenia, 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 to 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, two regions that lie outside of the default network (see Figures 1 and 2 and Supplementary Table 2). These increased response times and the increased activity within these two 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. Future studies that explicitly manipulate response conflict and emotional content will further explore the effects of emotional and semantic ambiguity on activity within prefrontal, executive control centers in healthy subjects and patients with schizophrenia.

An important, related question is whether the abnormalities reported here in midline cortical structures are specific to affective processing, or whether they are related to a sensory or cognitive deficit(s) in schizophrenia? Although basic visual processing deficits have been linked to emotional perception impairments in schizophrenia, visual system
dysfunction in schizophrenia cannot easily account for our findings, since 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 (as opposed to during a cognitive task), and when peripheral measures, rather than behavioral responses, were used as outcome variables.

In addition to assessing the potential role of non-affective 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 versus 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. 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 and fear extinction recall.

Also, several studies have reported abnormal activity levels in schizophrenia in the ventromedial and dorsomedial prefrontal cortices, and in the posterior cingulate cortex, during tasks which 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 which 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.

**CORRESPONDENCE**

Address correspondence to:
Daphne J. Holt, MD, PhD
Massachusetts General Hospital East
Psychiatric Neuroimaging Research Program, Room 2662
149 13th St. Charlestown, MA 02129
e-mail: dholt@partners.org
tel: (617) 726-7618
fax: (617) 726-4078

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