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Spontaneous Low-Frequency Fluctuations in the BOLD Signal in Schizophrenic Patients: Anomalies in the Default Network

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Spontaneous low-frequency fluctuations in the blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (MRI) signal have been shown to reflect neural synchrony between brain regions. A "default network" of spontaneous low-frequency fluctuations has been described in healthy volunteers during stimulus-independent thought. Negatively correlated with this network are regions activated during attention-demanding tasks. Both these networks involve brain regions and functions that have been linked with schizophrenia in previous research. The present study examined spontaneous slow fluctuations in the BOLD signal at rest, as measured by correlation with low-frequency oscillations in the posterior cingulate, in 17 schizophrenic patients, and 17 comparable healthy volunteers. Healthy volunteers demonstrated correlation between spontaneous low-frequency fluctuations of the BOLD signal in the posterior cingulate and fluctuations in the lateral parietal, medial prefrontal, and cerebellar regions, similar to previous reports. Schizophrenic patients had significantly less correlation between spontaneous slow activity in the posterior cingulate and that in the lateral parietal, medial prefrontal, and cerebellar regions. Connectivity of the posterior cingulate was found to vary with both positive and negative symptoms in schizophrenic patients. Because these data suggest significant abnormalities in resting-state neural networks in schizophrenia, further investigations of spontaneous slow fluctuations of the BOLD signal seem warranted in this population.

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Spontaneous low-frequency (<0.1 Hz) fluctuations in the blood oxygen level–dependent (BOLD) functional MRI signal have been suggested to reflect coherent networks in the somatosensory, visual, and language processing regions.[1–4] It has been speculated that these slow fluctuations may also be associated with electrophysiological fluctuations in the gamma band.[5,6] A network of spontaneous slow fluctuations in the BOLD signal at rest has recently been defined by 2 groups working independently.[7,8] The network includes the medial prefrontal cortex, anterior and posterior cingulate, inferior temporal, lateral parietal, and cerebellar regions, referred to collectively as the "default network." These regions are generally less active during attention-demanding tasks[9,10] and may be associated with stimulus-independent (endogenously generated) thought, intended speech, and emotions.[11,12] The default network has been found to be negatively correlated with an attention-demanding, "task-related network" that includes the dorsolateral prefrontal cortex, supplemental motor area, inferior parietal lobule, and middle temporal region.[7,8]

Regions involved in the default network such as the anterior and posterior cingulate and cerebellum have been implicated by several models of schizophrenia.[13–15] Activity in the anterior cingulate and medial prefrontal cortex is modulated by dopaminergic activity and projections from temporal lobe and brain stem structures implicated in schizophrenia, while the posterior cingulate is the first to show phencyclidine-induced neurodegeneration in animal models.[14,16,17] The medial prefrontal cortex has also been suggested to be important in monitoring the source of thoughts as endogenously or exogenously generated; this ability may be deficient in schizophrenia.[18] Consequently, it was hypothesized in the present investigation that schizophrenic patients may show some anomalies in spontaneous slow fluctuations in the BOLD signal in default network associated with the resting state. Specifically, it was hypothesized that correlations between the posterior cingulate and other regions in the default network would be stronger in healthy controls than in schizophrenic patients.

Methods

Subjects

Schizophrenic patients (14 males, 3 females) and healthy participants (14 males, 3 females) volunteered for the study after the protocol was fully explained, and written informed consent was obtained according to the guidelines of the Review Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario. Participants were recruited by advertisement within the community and health network of London, Canada. All participants were assessed by a psychiatrist using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[19] Fifteen participants were classified as having paranoid schizophrenia and 2 as having undifferentiated schizophrenia.

The duration of illness, defined as the elapsed time from the first appearance of positive symptoms, for participants with schizophrenia was 117.37 months (*SD* = 159.06). Patients' mean score on the Scale for the Assessment of Negative Symptoms (SANS)[20] was 20.35 (*SD* = 12.5) and mean score on the Scale for the Assessment of Positive Symptoms (SAPS)[21] was 9.06 (*SD* = 10.5) based on symptoms the week before the scan. The mean ages of the patients and controls were 33.54 (*SD* = 13.77) and 30.94 (*SD* = 12.60), respectively. Patients and controls did not differ on the parental education level of the most educated parent, rated on a 4-point scale, or on handedness.[22]

Fifteen participants with schizophrenia were on antipsychotic medications at the time of the scan (1 conventional, 14 atypical, chlorpromazine equivalent doses = 231.88, *SD* = 227.52). None of the participants had a history of head injury, drug, or alcohol abuse in the year before the scan or serious medical illnesses.

Procedure

Subjects were requested to close their eyes, relax, let their mind wander, and refrain from focusing on any particular thought during the course of a 5.5-min functional scanning run. Both control subjects and subjects with schizophrenia reported being able to fulfill these requirements.

All scanning was conducted at the Robarts Research Institute in London, Ontario. Imaging was conducted using a 4.0 Tesla Varian UNITY INOVA whole-body imaging system equipped with Siemens Sonata actively shielded gradient coils. A 16-element quadrature birdcage radio frequency head coil was used to transmit and receive the MR signal.[23] Subjects' heads were immobilized with foam padding and a Plexiglas head cradle. Imaging parameters were adapted from Fox et al.[8] Functional images were continuously collected using a segmented (2-shot) gradient echo (T_{2*}-weighted) sequence with spiralled gradient waveforms (64 × 64 matrix size, FOV = 25.6 cm, TE = 15 ms, volume acquisition time = 3 seconds, tip-angle = 60°). Slice thickness was 4 mm, resulting in 4 × 4 × 4–mm isotropic voxels.

Statistical Analysis

All image preprocessing steps and statistical analyses were conducted using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK; http://wwwfilionuclacuk/spm.) and were based on the methods reported by Fransson.[7] For each subject, all functional images were realigned to the first image in the series and resliced, and a mean functional image was created. Images were coregistered to the mean functional image and normalized to the EPI template provided in SPM2. Finally, images were smoothed using a 12-mm full-width half-maximum isotropic Gaussian filter.

In the first, single-subject, stage of analysis, low-frequency oscillations in BOLD signal were modeled using a discrete cosine basis set consisting of 60 regressors spanning the frequency range of 0–0.1 Hz.[7] Statistical parametric maps were constructed by computing F-contrasts comparing the effect of signal fluctuation in the frequency range of 0.012–0.1 Hz to the entire frequency range modeled, in order to account for and eliminate the effects of low-frequency oscillations due to nonphysiological sources such as scanner drift. In order to identify a seed region for the connectivity analysis, a preliminary analysis was conducted following the masking method used by Fransson,[7] in which voxels showing activation in all subjects were identified by creating a mask that included only voxels that showed activation above a threshold of $F > 2.53$ (equivalent to $P > .001$). A seed region centered at 0, −56, 20 was chosen from the resulting binary image, which was the closest suprathreshold voxel to the one used by Fransson[7] (which was 0, −56, 30).

Again following Fransson's[7] protocol, the mean signal intensity time course from the voxels inside a spherical region of interest (ROI) (radius 10 mm) was extracted from the resting-state scan for each subject. This time course was then inserted as a regressor into correlation analyses for which the original "resting" scan data were filtered using a phase-insensitive filter (passband 0.012–0.1 Hz). For each subject's ROI, the mean time course was entered into a functional connectivity analysis and contrasts representing regions of positive and of negative correlation with the ROI were constructed. (SPM separates these contrasts for visual clarity.)

At the second level of analysis, a mixed-effects analysis (which treats individual subjects as random variables[24]) was conducted in which the contrast images obtained during the first-level analysis were entered into one model

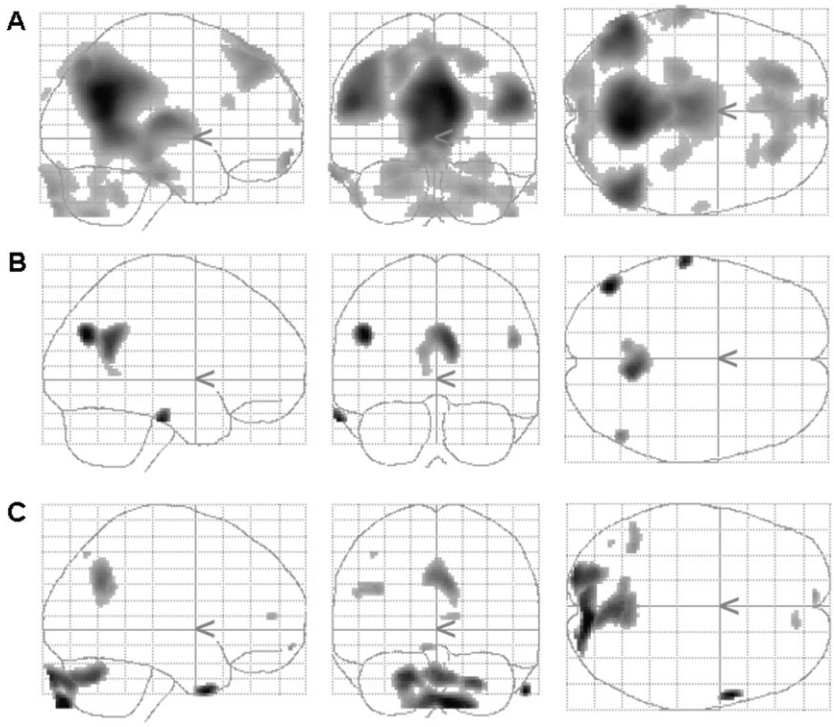

Fig. 1. Areas of positive correlation with posterior cingulate (0, −56, 20) in (A) healthy control subjects ($N = 17$) and (B) subjects with schizophrenia ($N = 17$), thresholded at $P < .001$ for visual clarity. (C) Areas in which control subjects showed significantly greater positive correlation with the right posterior cingulate than subjects with schizophrenia, thresholded at $P < .005$.

comparing positive correlation with the posterior cingulate seed region between groups and a second model comparing negative correlation with the seed region. The resulting SPM[T] maps of activated voxels were thresholded at $P < .005$, uncorrected. This threshold is consistent with other studies, as described in Britton et al.[25] Moreover, because this is the first study to investigate resting-state connectivity in the default network in schizophrenia, whole-brain analyses were conducted that had the potential to identify any brain region showing positive or negative connectivity with the posterior cingulate seed region, instead of restricting analyses to regions in the default network implicated in a priori hypotheses. The $P < .005$ threshold was thought to reflect a reasonable balance between false-positive and false-negative results (see Boksman et al[26] for further discussion).

In order to investigate the possibility that posterior cingulate connectivity in the schizophrenic subjects was correlated with symptom severity, 2 further random effects models were constructed. The first used patients' positive symptoms, as measured using the SAPS, as a regressor in a correlation analysis and the second used patients' negative symptoms, as measured using the SANS, in a similar analysis. These analyses showed areas of the brain where connectivity with the posterior cingulate seed region varied with symptom severity.

Results

Significant between-group differences were observed in both positive and negative connectivity between the posterior cingulate seed region (centered at 0, −56, 20) and the rest of the brain. Moreover, connectivity with the seed region was modulated in the schizophrenic group by severity of both positive and negative symptoms.

In healthy control subjects, the resting fluctuations in activity in the posterior cingulate were found to correlate with activity in a number of cortical areas, including surrounding regions of the posterior cingulate and precuneus, the anterior cingulate and medial prefrontal cortex, and the cerebellum, thalamus, and bilateral lateral parietal regions (figure 1A, which is thresholded at $P < .001$ for clarity of presentation,[26] and table 1). In schizophrenic patients, areas of significant positive correlation with the seed region were found in the posterior cingulate and precuneus, left middle and inferior temporal gyrus, and right middle temporal gyrus (figure 1B, which is thresholded at $P < .001$ for clarity of presentation, and table 1). Direct statistical comparison of posterior cingulate connectivity between the 2 groups showed that control subjects had significantly greater positive correlation than schizophrenics (thresholded at $P < .005$) between the posterior cingulate seed region and other areas in the posterior cingulate and precuneus, the medial frontal gyrus/anterior cingulate, the left

Table 1. Areas Showing Positive Correlation With the Posterior Cingulate Seed Region

Region	MNI Coordinates	BA	Peak *z* Score
Control subjects			
L superior frontal	−22, 44, 50	8	4.13
R superior frontal	24, 39, 44	8	4.59
L medial prefrontal	−2, 62, −14	11	4.01
L medial prefrontal	−4, 68, 14	10	3.56
R medial prefrontal	4, −68, 14	10	3.42
R precentral	62, −12, −34	4	3.32
L superior temporal/angular gyrus	−52, −60, 24	39	6.74
R superior temporal/angular gyrus	54, −62, 24	39	6.51
Posterior cingulate	8, −57, 29	31	5.89
L inferior temporal	−66, −20, −24	20	4.75
R parahippocampal	30, −28, −18	36	3.56
L parahippocampal	−26, −24, −22	35	4.40
Thalamus	−4, −17, 12	—	5.78
R cerebellum	26, −92, −34	—	3.97
L cerebellum	−22, −94, −30	—	3.79
Schizophrenic subjects			
L angular gyrus	−46, −72, 28	39	3.73
R middle temporal/angular gyrus	50, −64, 26	39	3.33
Posterior cingulate	8, −56, 26	31	3.54
L fusiform gyrus	−64, −22, −26	20	3.65
Controls greater than Schizophrenics			
L medial frontal	−8, 62, −12	11	2.70
R medial frontal	12, 50, 8	10	2.66
L superior parietal	−40, −72, 50	7	2.63
L supramarginal	−40, −56, 28	40	2.73
R precuneus	6, −62, 32	7	2.87
R middle temporal	58, 8, −40	38	2.63
R cerebellum	10, −86, −50	—	3.15
L cerebellum	−18, −94, −30	—	3.03

Note: MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; and R, right.

middle temporal gyrus, and the cerebellum (figure 1C and table 1). These areas differing between groups in positive connectivity with the seed region have been previously associated with the default network.

With regard to negative correlations with the seed region, healthy control subjects exhibited negative correlation between the posterior cingulate seed region and an area of the right parietal cortex, as well as with bilateral temporal regions that included, in the right hemisphere, the middle and superior temporal gyrus, and in the left hemisphere, the middle, superior, and inferior temporal gyrus and the insula (figure 2A and table 2). Schizophrenic patients also showed negative correlation between the posterior cingulate and bilateral temporal regions, as well as the left and right inferior parietal lobules (figure 2B and table 2). There were no areas in which controls showed significantly greater negative correlation with the posterior cingulate than did schizophrenic subjects at a significance threshold of $P < .005$.

In schizophrenic patients, both positive and negative symptoms appear to modulate connectivity with the posterior cingulate. Positive symptoms, as measured by the SAPS, correlate positively with connectivity between the posterior cingulate seed region and other areas of the posterior cingulate, bilateral premotor areas, and bilateral regions of the temporal gyrus that include language areas in the left hemisphere (figure 3A and table 3). Positive symptoms were negatively correlated with connectivity between the posterior cingulate seed region and an area in the right temporal lobe that included the fusiform gyrus (figure 3B and table 3). Negative symptoms, as measured by the SANS, were positively correlated with connectivity between the posterior cingulate and the right fusiform gyrus (figure 4A and table 4). Negative symptoms were negatively correlated with connectivity between the posterior cingulate seed region and right premotor areas, right middle and left superior temporal gyri, left inferior frontal gyrus, right dorsal anterior cingulate gyrus, and the brain stem (including midbrain and pons (figure 4B and table 4).

Discussion

In keeping with earlier studies,[7,8] healthy volunteers were found to have a correlation between spontaneous low-frequency fluctuations in the BOLD signal in the

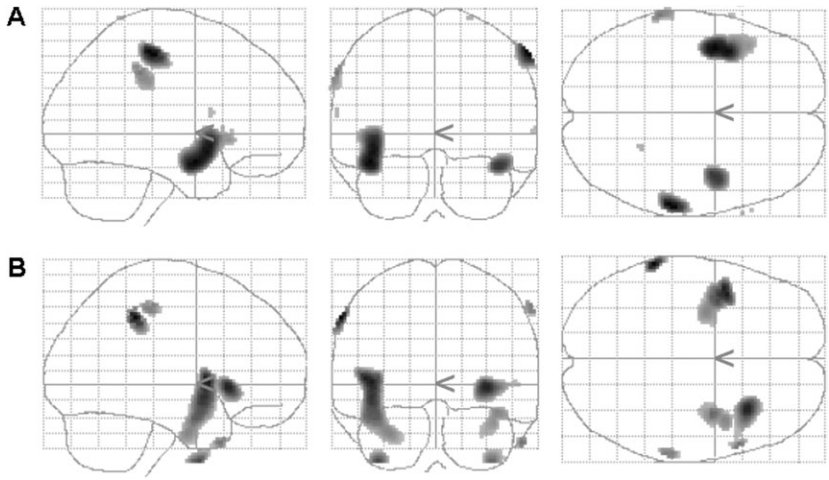

Fig. 2. Areas of negative correlation with right posterior cingulate (0, −56, 20) in (A) healthy control subjects ($N = 17$) and (B) subjects with schizophrenia ($N = 17$), thresholded at $P < .005$. No regions were found to be significantly more correlated with the posterior cingulate in control subjects than in schizophrenic subjects.

posterior cingulate and in medial prefrontal cortices, lateral parietal, and cerebellar regions. Regions of negative correlation in healthy controls occurred in bilateral areas in the medial temporal lobe, extending into the temporal pole, and bilateral inferior parietal regions. These findings also replicated those of previous studies,[7,8] though these other studies also found negative correlation between the posterior cingulate and the orbital gyrus, supplementary motor areas, and dorsolateral prefrontal cortex. One reason for this may be slight differences between the particular regions of the posterior cingulate used as a seed region in these studies—the present study used a seed region that did not appear to extend as far into the precuneus as did the seed regions used in the other 2 studies. This suggests that further studies may show regional differences in posterior cingulate connectivity, which may in turn help to characterize functional networks, including the default network associated with stimulus-independent thought.

Table 2. Areas Showing Negative Correlation With the Posterior Cingulate Seed Region (0, −56, 20)

Region	MNI Coordinates	BA	Peak *z* Score
Controls			
R postcentral gyrus/inferior parietal	62, −28, 52	2/40	4.25
L inferior parietal	−64, −36, 40	40	3.83
L temporal/insula	−40, 8, −12	13	4.16
R fusiform gyrus	42, 0, −20	20	3.83
Schizophrenics			
R inferior frontal	34, 20, −2	47	3.46
R inferior parietal	62, −30, 50	40	2.92
L inferior parietal	−62, −40, 44	40	3.60
L insula	−42, 8, 2	13	3.49
L superior temporal	−42, 6, −8	38	3.37
R superior temporal	40, 6, −18	22/28	2.91
L temporal	−38, 2, −50	38	3.22
R temporal	36, −2, −50	38	3.06
R superior temporal	54, 14, 0	22	2.60

Note: Abbreviations are explained in the footnote to table 1.

Schizophrenic patients in this study had less correlation between spontaneous slow fluctuations in the BOLD signal in the posterior cingulate and in medial prefrontal, lateral parietal, and cerebellar regions. To our knowledge, this is the first report of anomalies in spontaneous slow fluctuations of the BOLD signal associated with the resting-state default network in schizophrenic patients. These results suggest that connectivity between areas of the default network is reduced in schizophrenic patients.

If the default network reflects self-monitoring and stimulus-independent thought, it should not be surprising that there are anomalies in this network in schizophrenic patients. Frith[27] has argued that a failure to recognize internally generated thought as arising endogenously is fundamental to the disorder. (For formal cognitive science analyses of this type of failure of covert cognition in schizophrenia, see Batchhelder and Reifer[28] and R. W. J. Neufeld)[29] The finding of deficient connectivity between the posterior cingulate and the medial prefrontal cortex fluctuations is also consistent with models of schizophrenia based on limbic basal ganglia-thalamocortical neuronal circuits.[16,17]

The positive symptom–dependent correlation between posterior cingulate spontaneous low-frequency fluctuations and auditory cortex was not entirely expected. Functional imaging studies of hallucinating patients have found activity in the auditory cortex. The posterior cingulate was not generally associated with hallucinations.[30–35] It is possible that previous brain imaging

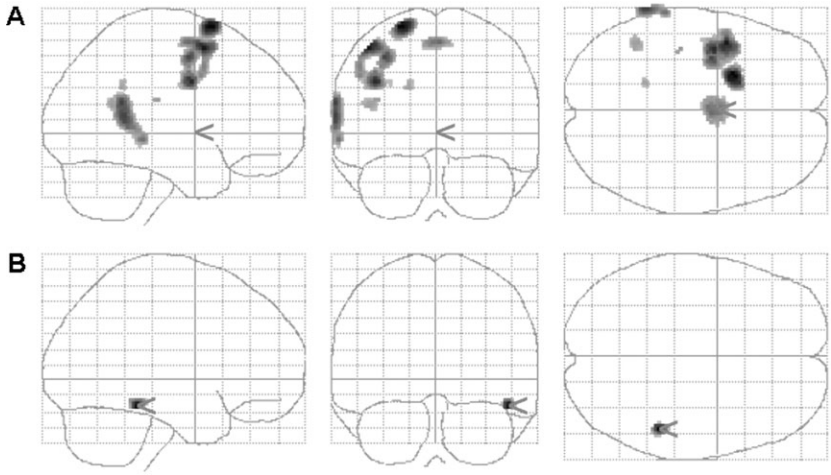

Fig. 3. (A) Areas in which correlation with posterior cingulate (0, −56, 20) in 17 subjects with schizophrenia was positively correlated with degree of positive symptoms, as measured by the SAPS. (B) Areas in which correlation with posterior cingulate (0, −56, 20) in subjects with schizophrenia was negatively correlated with degree of positive symptoms, as measured by the SAPS. Thresholded at $P < .005$.

techniques were not able to detect changes in the posterior cingulate by virtue of high levels of activity associated with both hallucinating and nonhallucinating states. If this is the case, spontaneous slow fluctuations may be a better indicator of functional links between the self-monitoring system and activity in the auditory and attentional regions associated with auditory hallucinations. If self-monitoring in the posterior cingulate is not linked with self-monitoring in the anterior cingulate, internally generated verbal thought may be perceived to be produced elsewhere.

The negative symptom–dependent correlation between the spontaneous low-frequency fluctuation in the posterior cingulate and the brain stem is interesting. Dopaminergic projections from the brain stem modulate basal ganglia-thalamocortical neuronal circuits which have been implicated in the pathophysiology of negative symptoms.[16,17] It is possible that decreased connectivity between the posterior cingulate and medial prefrontal cortex may lead to compensatory changes in the activity of structures which regulate the medial prefrontal cortex, leading to the association with negative symptoms.

The cerebellum has been previously identified as a node in the default network,[7,8] and this study found that it was the area that showed the greatest difference in posterior cingulate connectivity between patients and controls. This finding is inconsistent with earlier work[36] which found increased functional connectivity between the cerebellum and a number of other brain regions. This earlier paper, however, did not isolate the posterior cingulate gyrus but rather identified the parietal lobe as a whole as an area showing increased functional connectivity in schizophrenic patients as compared with earlier controls. This discrepancy between the previous work and the current study, together with differences in the results reported in the present work and in other papers investigating connectivity in the default network in healthy adults, suggest that further work is required that can parse out differences in connectivity occurring in different subregions of the nodes of the default network.

It must also be acknowledged that other factors may account for anomalies in the spontaneous slow fluctuations of the BOLD signal in regions associated with the default network in schizophrenic patients. Such a deficiency could be explained by anxiety, which could make it difficult to reach a self-reflective state. This possibility is not likely because an earlier positron emission study found that healthy, anxious subjects had the same activity levels in the medial prefrontal cortex as subjects with their eyes closed at rest.[37] However, anxious subjects did not show as much reduction in activity in this region when asked to perform an attention-demanding tasks as nonanxious subjects.[37]

Table 3. Areas Showing Significant Correlation Between Posterior Cingulate Connectivity and Positive Symptoms

Region	MNI Coordinates	BA	Peak *z* Score
Positive correlation			
L middle frontal	−22, 12, 70	6	3.61
L middle frontal	−44, 6, 56	6	3.53
L medial frontal	−6, 6, 58	6	2.82
R medial frontal	2, −4, 60	6	3.08
L superior temporal	−66, −46, 12	22	3.30
L superior temporal	−44, −54, 18	39	2.78
Negative correlation			
R fusiform	48, −38, −13	37	3.54

Note: Abbreviations are explained in the footnote to table 1.

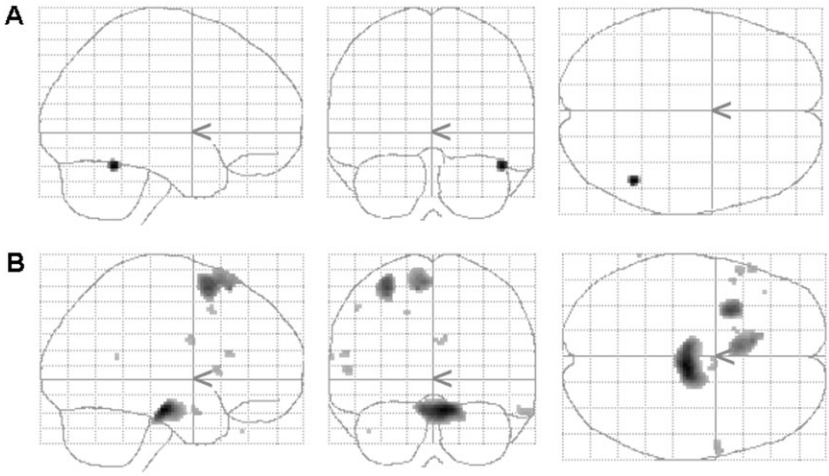

Fig. 4. (A) Areas in which correlation with posterior cingulate (0, −56, 20) in 17 subjects with schizophrenia was positively correlated with degree of negative symptoms, as measured by the SANS. (B) Areas in which correlation with posterior cingulate (0, −56, 20) in subjects with schizophrenia was negatively correlated with degree of negative symptoms, as measured by the SANS. Thresholded at $P < .005$.

Another possibility is that the deficit may be explained by antipsychotic medication. Dopamine has been shown to have an inhibitory effect on neural activity in the medial prefrontal cortex.[38,39] Consequently, medications which block dopamine are not likely to explain the deficits, but a disease-related anomaly in dopamine might.

There are some limitations in this study. First, the schizophrenic participants in this study showed a wide range of positive and of negative symptoms at the time of scanning and were also at different stages of the disorder. Our patient group spanned younger patients who had been diagnosed fairly recently and older patients with chronic schizophrenia. The possibility that the results of this study are influenced by this heterogeneity of the patient group should be taken into account, and future work should attempt to classify schizophrenic participants into subgroups that may potentially show differences in default network activity. Second, between-group differences in functional anatomy, such as increased ventricle size in patients due to brain atrophy, are always a possible confound in studies that normalize all participants' brains to a single template. Like other neuroimaging studies, the present study did not take account of the possible influence of anatomical differences. This study also examined correlations only with the posterior cingulate; it is likely that there are connectivity deficits involving other regions in these patients.[36] Finally, it should be noted that the correlational methods used in this study are able to identify only instantaneous correlation between brain regions and cannot discount the possibility of "time-lagged" correlation between the seed region and other brain areas, in which activity in the posterior cingulate seed region has a delayed effect on activity in other areas of the brain.

Table 4. Areas Showing Significant Correlation Between Posterior Cingulate Connectivity and Negative Symptoms

Region	MNI Coordinates	BA	Peak *z* Score
Positive correlation			
R fusiform	46, −50, −22	37	2.99
Negative correlation			
L middle frontal	−30, 12, 55	6	3.28
L superior frontal	−6, −16, 64	6	3.10
L inferior frontal	−56, 14, 6	45	2.72
R middle frontal	−50, 12, 46	6/8	2.67
R cingulate gyrus	8, −2, 28	24	2.71
L superior temporal	−56, 14, 6	22	2.72
R superior temporal	60, 2, −22	21	2.72
Midbrain	8, −18, −20	—	3.60

Note: Abbreviations are explained in the footnote to table 1.

Conclusions

Schizophrenic patients show anomalous patterns of connectivity between the posterior cingulate and other brain regions associated with the default network. Spontaneous low-frequency oscillations in the BOLD signal during a state of rest can be used to investigate both differences between schizophrenic patients and healthy controls and variability among patients with differing symptom profiles. (Note: After submission of this article, a relevant article[40] became available that examined the differences between patients with schizophrenia and healthy control subjects in default network activity during an auditory oddball task, using independent component analysis. Despite differences in paradigm and in method of data analysis, anomalies in the activity of the default network in schizophrenia were observed by this group, providing additional support for the current results).

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