Effects of Psychotic State and Task Demand on Prefrontal Function in Schizophrenia: An fMRI Study of Overt Verbal Fluency

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Objective: Impaired prefrontal cortical function is regarded as a central feature of schizophrenia. Although many neuroimaging studies have found evidence of abnormal prefrontal activation when patients with schizophrenia perform cognitive tasks, the extent to which this abnormality depends on the presence of active psychotic symptoms and on the demands of the task is unclear. The authors tested the hypothesis that prefrontal functional abnormalities in schizophrenia would be more evident in patients with active psychosis than in patients who were in remission and would become more apparent in the face of increasing task demands.

Method: The authors used functional magnetic resonance imaging (fMRI) to examine prefrontal cortical activity during a paced letter verbal fluency task in three groups of subjects: acutely psychotic patients with schizophrenia, schizophrenia patients in remission, and healthy volunteers. Online subject performance was measured by utilizing a clustered fMRI acquisition sequence that allowed overt verbal responses to be made in the relative absence of scanner noise.

Results: Patients with schizophrenia showed less activation than the healthy comparison subjects in the anterior cingulate and the inferior frontal and right middle frontal cortices, independent of psychotic state and task demand. Acutely psychotic patients showed less activation than the healthy comparison subjects, but these differences were less marked than the differences between the patients in remission and the healthy comparison subjects. Acutely psychotic patients had less activation than the comparison subjects in the anterior cingulate but no significant difference in lateral prefrontal activation. Increasing task demand led to greater anterior cingulate and middle frontal activation in patients with active psychosis than in patients in remission.

Conclusions: Schizophrenia is associated with impaired prefrontal function, but its manifestation depends on the severity of psychotic symptoms and the level of task difficulty.

Ingvar and Franzen (1) coined the term “hypofrontality” to describe a lower ratio of anterior to posterior cerebral activity in patients with schizophrenia, relative to healthy comparison subjects. Hypofrontality has since become the functional neuroimaging finding most associated with schizophrenia (2), notwithstanding dissenting views and contentious evidence (reviewed in references 3 and 4). Early studies examined subjects in the “resting state” (1, 5–10), but resting state hypofrontality has not been consistently replicated (11–17), nor is it specific to schizophrenia (reviewed in reference 4).

Attenuated prefrontal activation may also be evident when patients with schizophrenia perform cognitive tasks that engage the prefrontal cortex (8, 18). However, as patients with schizophrenia often perform such tasks more poorly than comparison subjects, this difference could simply reflect impaired performance (18–20). Researchers have thus sought to match the performance of schizophrenia patients and comparison subjects, usually by reducing the demands of the task so that patients can perform it as well as can the comparison subjects. The results of these studies have also been inconsistent, with reports of “hypofrontality” (21–23), no difference in frontal activation (24, 25), and “hyperfrontality” (26, 27) in the patients with schizophrenia. The potentially confounding effects of impaired performance can also be examined by experimentally manipulating the demands of the task. Recent studies suggest that prefrontal activity in schizophrenia depends not only on the nature of the task, but also on the level of task difficulty (23, 27–32).

Finally, prefrontal activation in schizophrenia may vary with the severity of symptoms at the time of scanning. Lower activity in the prefrontal cortex in patients with active psychosis during a joystick movement task resolves when these patients are subsequently in remission (33). The presence of positive psychotic symptoms such as auditory hallucinations, delusions of passivity, and thought disorder have each been associated with abnormal (usually attenuated) activation in prefrontal and other regions during a variety of cognitive paradigms (32–36).
The aim of the present study was to examine the effects of both task demand and current mental state on prefrontal function in schizophrenia. We utilized a letter verbal fluency task, which is associated with activation in the prefrontal cortex in healthy volunteers (37–39). Verbal fluency in schizophrenia has been reported to be associated with impaired activation in the middle and inferior frontal gyri and in the anterior cingulate gyrus (21, 25, 40, 41). However, some paced studies in which performance in patients was comparable to that in healthy subjects have failed to find differences in prefrontal activation (33, 36, 42–44). The effects of symptoms and task demand on activation during verbal fluency in schizophrenia have not been explicitly examined previously, although Sommer et al. (36) found that the current severity of hallucinations was correlated with greater engagement of the right prefrontal cortex.

We examined the influence of psychotic state on activation by comparing patients with schizophrenia who had active psychosis and patients who were in remission. To investigate the effects of task demand, we used both “easy” and “difficult” letters as cues; the letters differed in the number of words that subjects could generate from them (45). However, to minimize potentially confounding effects of between-group differences in task performance, we used a paced version of the task that allowed the patients to perform at a behavioral level similar to that of the comparison subjects, and we acquired overt verbal responses with a “clustered” functional magnetic resonance image (fMRI) acquisition sequence so that subjects could respond in the absence of scanner acoustic noise and task performance could be measured online.

We tested the hypothesis that, independent of psychopathology or task demand, patients with schizophrenia would show attenuated prefrontal activation, relative to healthy comparison subjects. As psychotic phenomena appear to be at least partly mediated by prefrontal areas, we predicted that this difference would be more marked in acutely psychotic patients than in those in remission. We also predicted that higher levels of task demand would exacerbate abnormalities of prefrontal activation in patients with active psychosis but would have little effect on activation in remitted patients.

### Method

#### Subjects

Twenty subjects with a DSM-IV diagnosis of schizophrenia and no comorbid diagnoses and 11 healthy comparison subjects participated. Diagnoses were made by means of semistructured clinical interview with a research psychiatrist (C.H.Y.F. or P.K.M.), review of patients’ hospital records, and discussions with their clinical psychiatrist. All subjects were male, native English speaking, right-handed (46), and free of neurological illnesses and a history of head injury. All gave written informed consent, and the study was approved by the Institute of Psychiatry and South London and Maudsley National Health Services Trust Ethical Committee.

All subjects had normal premorbid intelligence, on the basis of school and work history, and normal premorbid IQ, estimated with the National Adult Reading Test (47). Severity of symptoms at the time of scanning was rated by a psychiatrist (C.H.Y.F.) with the Scale for the Assessment of Positive Symptoms (SAPS) (48) and the Scale for the Assessment of Negative Symptoms (SANS) (49), and presence of depressive symptoms was rated with the Calgary Depression Scale (50). The study was designed to recruit patients who either had marked positive symptoms or were in clinical remission from an acute psychotic episode; patients with formal thought disorder were excluded. The two subgroups were defined according to their SAPS scores: patients with acute psychosis, who were experiencing hallucinations or delusions weekly or more frequently and who scored a minimum of 3 (of 5) on these SAPS criteria, and patients in remission, who scored no more than 2 on any criterion of the SAPS. Analysis of behavioral responses during scanning revealed that one subject in the acute psychosis group did not perform the task correctly, as he repeated the same word for each letter cue, and his imaging data were excluded. As intended, the acute psychosis group and the group in remission had significantly different SAPS scores (t=5.71, df=17, p<0.001, independent t test) (Table 1) but did not differ in their scores on the SANS (t=1.54, df=17, p=0.14, independent t test) or the Calgary Depression Scale (t=1.03, df=17, p=0.32, independent t test). Patients were not specifically selected to have low levels of negative symptoms, but these symptoms were at a low level in both groups. SAPS and SANS ratings were corroborated with clinical information from patient case notes and the clinical teams.

All the patients had a duration of illness of more than 3 years (defined as time since first admission for psychosis), with no significant difference between the acute psychosis group and the group in remission (t=1.32, df=17, p=0.21, independent t test) (Table 1). All were taking regular doses of antipsychotic medication. In the acute psychosis group, three patients were receiving conventional depot neuroleptics, and six were taking atypical antipsychotics. In the acute psychosis group, three patients were receiving conventional depot neuroleptics, and six were receiving atypical antipsychotics. In the group in remission, one patient

### Table 1. Demographic and Clinical Characteristics of Schizophrenia Patients With Acute Psychosis, Schizophrenia Patients in Remission, and Healthy Comparison Subjects in an fMRI Study of Prefrontal Function During a Verbal Fluency Task

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Schizophrenia</th>
<th>Patients in Remission</th>
<th>Comparison Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=9)</td>
<td>(N=10)</td>
<td>(N=11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean 34.6 SD 7.5</td>
<td>Mean 36.0 SD 10.2</td>
<td>Mean 30.4 SD 6.2</td>
</tr>
<tr>
<td>IQ</td>
<td>106.2 SD 9.5</td>
<td>110.2 SD 11.9</td>
<td>115.3 SD 8.6</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>9</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Scale for the Assessment of Positive Symptoms score</td>
<td>25.2 SD 5.4</td>
<td>8.7 SD 5.7</td>
<td></td>
</tr>
<tr>
<td>Scale for the Assessment of Negative Symptoms score</td>
<td>5.7 SD 8.9</td>
<td>5.3 SD 3.7</td>
<td></td>
</tr>
<tr>
<td>Calgary Depression Scale score</td>
<td>2.7 SD 1.7</td>
<td>1.9 SD 1.5</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic medication dose (mg/day of chlorpromazine equivalents)</td>
<td>522.2 SD 268.2</td>
<td>415.0 SD 356.7</td>
<td></td>
</tr>
</tbody>
</table>
was receiving a conventional depot neuroleptic, three were taking oral conventional antipsychotics, and six were taking atypical antipsychotics. The average dose of medication in chlorpromazine equivalents was 522.2 mg/day (SD=268.2) for the acute psychosis group and 415.0 mg/day (SD=356.7) for the group in remission (t=0.73, df=17, p=0.47, independent t test). As for adjunctive medication for treatment of persistent psychotic symptoms, three patients in remission and one patient with active psychosis were also taking fluoxetine, two patients in remission were taking valproate, and one patient in remission was taking carbamazepine.

The comparison group included 11 healthy volunteers recruited from the local community. Exclusion of psychiatric and medical illnesses was performed by clinical interview (by C.H.Y.F. or P.K.M.). The three groups were matched for age and IQ, with no significant differences in mean age (F=1.42, df=2, 27, p=0.26, analysis of variance [ANOVA]) or premorbid IQ (F=2.04, df=2, 27, p=0.15, ANOVA) (Table 1).

**Verbal Fluency Task**

In the experimental condition, the subjects were instructed to overtly generate a word in response to a visually presented letter presented at a rate of one letter every 4 seconds. They were also told to not use proper names or a grammatical variation of the previous word and not to repeat previous responses (37, 38). If subjects were unable to think of a response they were asked to say “pass.” In the easy condition, one of two sets of letters consisting of T, L, B, R, S and T, C, B, P, S was presented; in the difficult condition, one of the following two sets was presented: O, A, N, E, G and I, P, N, E, G. This number of stimuli has provided sufficient power to detect regional activation in healthy individuals (45). Subjects were presented with one set of easy and difficult letters in separate blocked runs with the order of presentation randomized between subjects. Each condition was presented in blocks lasting 28 seconds, with seven presentations of a given letter per block and five blocks of each condition. Each subject participated in two runs, for a total of 10 block presentations of each condition (70 trials of each condition). The experimental condition alternated with the control condition, which consisted of repetition of the word “rest” presented at the same rate. Verbal responses were recorded on Cool Edit 2000 (Syntrillium Software Corp., [Adobe Systems Inc., San Jose, Calif.]) by means of a microphone that was compatible with the magnetic resonance imaging (MRI) apparatus. Incorrect responses were defined as pass responses and words that were proper names, repetitions, or grammatical variations of the previous word (37, 38).

**fMRI Image Acquisition**

Seventy-four T₂*-weighted gradient-echo single-shot echo-planar images were acquired on a 1.5-T, neuro-optimized IGE LX System (General Electric, Milwaukee) at the Maudsley Hospital, South London National Health Services Trust, U.K. Twelve non-contiguous axial planes (7-mm thickness, slice skip: 1 mm) parallel to the anterior commissure-posterior commissure line were collected over 1100 msec in a clusterized acquisition (TE=40 msec, flip angle=70°). Immediately after each acquisition a letter was presented (remaining visible for 750 msec, height: 7 cm, subtending a 0.4° field of view), and a single overt verbal response was made during the remaining silent portion (entire duration=2900 msec) of each repetition (TR=4000 msec).

Head movement was minimized by a forehead strap. To ensure that subjects heard their responses clearly, their speech was amplified by a computer sound card and then relayed to the subject through an acoustic MRI sound system (Ward Ray, Hampton Court, U.K.) and noise-insulated, stereo headphones at a mean volume of 91 dB (SD=2).

<table>
<thead>
<tr>
<th>Group</th>
<th>Easy Condition²</th>
<th>Difficult Condition²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with schizophrenia (N=9)</td>
<td>12.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Patients in remission (N=10)</td>
<td>13.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Healthy comparison subjects (N=11)</td>
<td>10.1</td>
<td>10.7</td>
</tr>
</tbody>
</table>

² Subjects were instructed to overtly generate a word in response to a letter presented visually at a rate of one letter every 4 seconds. Easy and difficult conditions differed in the number of words that subjects could generate from the letters that were presented.

**fMRI Data Analysis**

The initial volume images of each time series, acquired while the MR signal was reaching steady state (four images) and responsible for triggering the software program (fifth image), were discarded. Subject movement was corrected by rigid-body realignment of the volumes to the series mean and residual magnetic history effects estimated by an autoregressive model followed by spatial smoothing with a Gaussian kernel (SD=3 mm). The amplitude of response to each event was then estimated by least-squares regression of a linear model, a convolution of the experimental design with two Poisson kernels (lambda=2 seconds and 4 seconds, respectively). A map of responses derived under the null hypothesis of no experimental effect was generated by regression of the model after repeated permutation of the data following orthogonal transformation into the wavelet domain (51).

Median observed and permuted responses, F, were calculated after affine mapping of individual maps into standard stereotactic space (52). Group brain activation maps were created by inference against the permutation distribution. Probabilistic thresholds were set such that the estimated number of type I error voxels across the entire volume was 10, equivalent to p<0.0001 (2, 53).

Differences between task or group were inferred by regression of the general linear model: F=α₀+α₁H+α₂X+e, where F is the response at a particular standard space voxel location, H is a dummy code for the condition or group, X is an optional covariate, and e is the residual error. Maps of the standardized coefficient of task difficulty (αᵩ), which is a measure of task demand, were tested for significance against a two-tailed distribution, generated by repeated randomization of H, sampling the null hypothesis of no difference between groups. To improve sensitivity, spatial information was introduced by thresholding the maps of αᵩ such that only voxels exceeding the critical value (Cᵥ₀.05, corresponding to a voxel-wise test at p<0.05) were retained, and contiguous suprathreshold voxels were aggregated into three-dimensional clusters. For each cluster, the sum of the values of (αᵩ–Cᵥ₀.05), the spatial extent statistic, was then tested for significance against the identically derived randomization distribution at a probabilistic threshold such that the estimated number of false positive clusters across the entire volume was <1 (51).

Group brain activation maps of the overall response (verbal fluency task versus control task, irrespective of difficulty level) were generated for each group. As the data were acquired in a blocked design for each condition, the easy and difficult conditions were contrasted within each group by using a categorical comparison and coding the covariate (X) as the number of erroneous responses produced.

To test our hypotheses, the following contrasts were performed:

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**TABLE 2. Performance During Easy and Difficult Conditions of a Verbal Fluency Task of Schizophrenia Patients With Acute Psychosis, Schizophrenia Patients in Remission, and Healthy Comparison Subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage of Erroneous Responses</th>
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</thead>
<tbody>
<tr>
<td>Easy Condition²</td>
<td>Difficult Condition²</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Patients with schizophrenia (N=9)</td>
<td>12.7</td>
</tr>
<tr>
<td>Patients in remission (N=10)</td>
<td>13.1</td>
</tr>
<tr>
<td>Healthy comparison subjects (N=11)</td>
<td>10.1</td>
</tr>
</tbody>
</table>

² Subjects were instructed to overtly generate a word in response to a letter presented visually at a rate of one letter every 4 seconds. Easy and difficult conditions differed in the number of words that subjects could generate from the letters that were presented.
Prefrontal activation during verbal fluency (easy and difficult conditions combined) in the patients with schizophrenia (the acute psychosis group and the group in remission combined) was compared with prefrontal activation during verbal fluency in the healthy volunteers.

2. The effects of psychotic state on prefrontal activation were examined by comparing the results for the acute psychosis group with those for the group in remission and by comparing the results for both patient groups with those for the healthy volunteers.

3. The interaction between the effects of psychotic state (acute psychosis group versus remission group) and task demand (easy versus difficult conditions) on prefrontal activation was examined. To clarify the basis of this interaction, we also examined the effects of task demand in each group (remission, acute psychosis, and comparison groups).

Results

Behavioral Data

Patients were routinely debriefed about their experiences during scanning, and none reported hallucinations. Across all groups there was a main effect of task demand, with more erroneous responses produced for the difficult condition than for the easy condition (repeated measures F=37.5, df=1, 2,7, p<0.001) (Table 2). No difference in the number of errors generated was evident between the groups (repeated measures F=0.78, df=2, 2,7, p=0.50), and there was no significant interaction of group and task demand (F=0.79, df=2, 2,7, p=0.50).

fMRI Data

Activation during verbal fluency. In the healthy volunteers there was bilateral activation in the inferior and middle frontal gyri, the anterior and posterior cingulate gyri, and the insula. Further activation was evident in the middle and superior temporal gyri, inferior parietal lobule, precuneus, thalamus, caudate, and cerebellum (45). A qualitatively similar distribution of regional activation was observed in the acute psychosis group. In the group in remission, activation was less extensive and mainly restricted to the left hemisphere, with engagement of the left inferior frontal gyrus and insula, the left anterior and posterior cingulate gyr, and the left superior temporal gyrus. Further activation was evident in the left occipital cortex and precuneus and in the inferior parietal lobule bilaterally (coordinates are available upon request). The significance of these differences in activation between the subgroups was formally tested in the between-group comparisons that are reported later, in the section on the effect of psychotic state on activation.

Differences between patients with schizophrenia and healthy volunteers. When all patients with schizophrenia (remission and acute psychosis groups combined) were compared with the healthy comparison group across all verbal fluency trials (difficult and easy conditions combined), the patients showed less activation in the inferior frontal and anterior cingulate cortices bilaterally and in the right (but not the left) middle frontal gyrus. Patients also showed relatively attenuated activation bilaterally in the superior and middle temporal gyri, the medial temporal, inferior occipital, and posterior parietal cortices, and the caudate, thalamus, and cerebellum (Figure 1). There were no areas that were more activated in the patients than in the comparison subjects.

Effect of psychotic state on activation. Comparison of the acute psychosis subgroup and the healthy comparison subjects indicated that there were no significant differences in activation in the lateral prefrontal cortex. However, the acute psychosis group showed less activation bilaterally in the anterior and posterior cingulate cortices, parahippocampal region, basal ganglia, thalamus, lingual gyr, brainstem, and cerebellum. The group in remission showed less activation than the comparison subjects in the right middle frontal gyrus, left anterior and posterior cingulate gyri, inferior parietal and superior temporal lobules, and brainstem and bilaterally in the inferior frontal gyr, insula, parahippocampal region, caudate, thalamus, lingual gyr, and cerebellum.
Direct comparison of the acute psychosis group and the group in remission revealed greater activation in the acute psychosis group in the left middle frontal, superior temporal, and inferior parietal cortices and bilaterally in the anterior cingulate, inferior frontal cortices, and insula. There were no regions that were more activated in the group in remission. All contrasts were covaried for subject performance (Figure 2 and Table 3).

**Activation with increasing task demand.** The effect of task demand was first examined by comparing results for the easy and difficult conditions in each group while covarying for the number of erroneous responses. In the healthy comparison subjects, increasing task demand (difficult condition versus easy condition) was associated with greater activation in the left anterior cingulate (Brodmann’s area 32; Talairach and Tournoux coordinates: x=-8, y=22, z=39; cluster size=128 voxels) (45). In the acute psychosis group, increasing task demand was associated with greater activation in the left anterior insula (x=-30, y=8, z=1; cluster size=52 voxels), the left posterior insula (x=-30, y=-9, z=-1; cluster size=92 voxels), and the left putamen (x=-29, y=-22, z=6; cluster size=16 voxels). These differences reflected an activation that was evident only during the difficult condition. Conversely, the easy condition was associated with greater activation of the right medial temporal cortex (cluster size=348 voxels), extending from the parahippocampal gyrus (x=23, y=-10, z=-16) to the hippocampus (x=37, y=-55, z=-1); lingual gyrus (x=-2, y=-78, z=-3, cluster size=320 voxels); left caudate (extending from z=19, y=17, z=1 to x=12, y=7, z=16, cluster size=128 voxels); right medial prefrontal cortex (extending from Brodmann’s area 10, x=12, y=53, z=24 to Brodmann’s area 8, x=8, y=44, z=40, cluster size=80 voxels); and right postcentral gyrus (x=55, y=-10, z=48, cluster size=16 voxels). These differences reflected activations that were evident only during the easy condition.

In the group in remission, there were no significant differences in activation between the easy and difficult conditions, although the finding of greater activation of the anterior cingulate cortex with the difficult condition approached significance.

**Interaction between the effects of psychotic state and task demand.** There were only a limited number of significant findings when the differences in activation between the difficult and easy conditions in each patient group were compared with those in the healthy group. The group in remission had a smaller difference in activation in the occipital cortex between the difficult and easy condi-
tions, compared with the healthy volunteers. No significant differences were found between the acute psychosis group and the healthy volunteers. However, when the two patient groups were compared, the acute psychosis group showed greater differences in activation in the right middle frontal gyrus and the left anterior cingulate gyrus, as well as in the left inferior parietal lobule, a region that extended from the left postcentral gyrus to the supramarginal gyrus, and in the precuneus (Figure 3). In all of these regions, the differences reflected an increase in activation with increased task demand in the acute psychosis group and an absence of difference between the difficult and easy conditions in the group in remission. The group in remission showed a greater difference than the acute psychosis group in only one region, which spanned the right medial temporal and inferior temporal cortices (Figure 3). Overall these findings reflected greater activation in the group in remission with increased demand but significantly reduced activation with increased demand in the acute psychosis group.

**Discussion**

Verbal fluency is a classic neuropsychological test of language production in which subjects generate and articulate a word in response to a cue (37, 38). Studies of verbal fluency with fMRI have revealed a consistent set of activated regions (21, 25, 54–58), with the most frequently reported sites of frontal activation being the left inferior frontal gyrus (25, 54–58), left middle frontal gyrus (dorsolateral prefrontal cortex) (21, 25, 54, 56, 57), and anterior cingulate gyrus (54, 58). The healthy comparison group in our study recruited all of these regions.

To assess task performance online we used a paradigm that involved overt speech. Image acquisition during fMRI

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**TABLE 3. Significant Differences in Prefrontal Cortical Activation During a Verbal Fluency Task in Schizophrenia Patients With Acute Psychosis, Schizophrenia Patients in Remission, and Healthy Comparison Subjects**

<table>
<thead>
<tr>
<th>Comparison Groups, Anatomical Region, and Brodmann’s Area</th>
<th>Hemisphere</th>
<th>Talairach Coordinates</th>
<th>Cluster Size (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy comparison subjects versus schizophrenia patients with acute psychosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>Right</td>
<td>16 22 15</td>
<td>105</td>
</tr>
<tr>
<td>Brodmann’s area 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brodmann’s area 23/31</td>
<td>Left</td>
<td>–8 38 30</td>
<td>8</td>
</tr>
<tr>
<td>Brodmann’s area 23</td>
<td>Left</td>
<td>–20 45 23</td>
<td>56</td>
</tr>
<tr>
<td>Brodmann’s area 31</td>
<td>Left</td>
<td>16 24 3</td>
<td>112</td>
</tr>
<tr>
<td>Parahippocampal gyrus: Brodmann’s area 27/30</td>
<td>Left</td>
<td>–13 29 4</td>
<td>80</td>
</tr>
<tr>
<td>Putamen</td>
<td>Right</td>
<td>16 8 4</td>
<td>44</td>
</tr>
<tr>
<td>Head of caudate nucleus</td>
<td>Right</td>
<td>12 20 12</td>
<td>8</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>6 11 12</td>
<td>48</td>
</tr>
<tr>
<td>Left</td>
<td>11 4 16</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>12 1 16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus (extending into cerebellum)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy comparison subjects versus schizophrenia patients in remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>Left &gt; Right</td>
<td>–12 9 42</td>
<td>276</td>
</tr>
<tr>
<td>Brodmann’s area 32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brodmann’s area 29</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Middle frontal gyrus</td>
<td>Right</td>
<td>49 22 24</td>
<td>20</td>
</tr>
<tr>
<td>Brodmann’s area 46</td>
<td>Right</td>
<td>52 20 28</td>
<td>8</td>
</tr>
<tr>
<td>Brodmann’s area 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus: Brodmann’s area 45</td>
<td>Right</td>
<td>48 20 16</td>
<td>180</td>
</tr>
<tr>
<td>Insula</td>
<td>Left</td>
<td>28 11 20</td>
<td>52</td>
</tr>
<tr>
<td>Right</td>
<td>50 18 4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>35 18 8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus: Brodmann’s area 21</td>
<td>Left</td>
<td>–64 57 3</td>
<td>140</td>
</tr>
<tr>
<td>Inferior parietal lobule: Brodmann’s area 40</td>
<td>Right</td>
<td>13 33 2</td>
<td>208</td>
</tr>
<tr>
<td>Parahippocampal gyrus: Brodmann’s area 27</td>
<td>Right</td>
<td>11 4 8</td>
<td>60</td>
</tr>
<tr>
<td>Head of caudate nucleus</td>
<td>Left</td>
<td>–7 1 8</td>
<td>8</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>10 2 17 668</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>11 74 4</td>
<td>1604</td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus (extending into cerebellum)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia patients with acute psychosis versus schizophrenia patients in remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate gyrus: Brodmann’s area 24</td>
<td>Left &gt; right</td>
<td>–27 7 32</td>
<td>1440</td>
</tr>
<tr>
<td>Middle frontal gyrus: Brodmann’s area 9</td>
<td>Left</td>
<td>–36 36 33</td>
<td>200</td>
</tr>
<tr>
<td>Inferior frontal gyrus: Brodmann’s area 44</td>
<td>Right</td>
<td>40 11 19</td>
<td>540</td>
</tr>
<tr>
<td>Insula</td>
<td>Right</td>
<td>44 15 4</td>
<td>28</td>
</tr>
<tr>
<td>Left</td>
<td>35 13 4</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Anterior insula</td>
<td>Right</td>
<td>27 25 8</td>
<td>8</td>
</tr>
<tr>
<td>Superior temporal gyrus: Brodmann’s area 42</td>
<td>Left</td>
<td>–27 16 16</td>
<td>8</td>
</tr>
<tr>
<td>Inferior parietal lobule: Brodmann’s area 40</td>
<td>Left</td>
<td>–60 31 22</td>
<td>244</td>
</tr>
<tr>
<td>Putamen</td>
<td>Right</td>
<td>–49 37 48</td>
<td>28</td>
</tr>
</tbody>
</table>

a Significant differences were found for both the left and the right hemisphere, but the difference in the left hemisphere was more pronounced.
is associated with an acoustic noise that can make it difficult for subjects and investigators to hear overt verbal responses (59), and overt articulation can be associated with head movement (60). We therefore employed a “clustered” acquisition sequence that incorporated brief periods of silence (61, 62), which allowed subjects to speak and hear their responses in the absence of noise and reduced the risk of articulation-related movement artefacts (45). Online measurement of behavioral responses indicated that all three groups were able to adequately perform the letter verbal fluency paradigm, with no significant between-group differences in the proportion of errors produced. We also covaried for task performance when comparing activation between groups.

The schizophrenia group as a whole showed impaired activation, relative to the comparison group, in the inferior frontal and anterior cingulate gyri bilaterally and in the right but not the left middle frontal gyrus. These findings are broadly consistent with those reported in the literature, and the absence of differences in the left middle frontal gyrus is compatible with data from previous studies of verbal fluency that used a paced presentation of stimuli in which task performance was equivalent in the patient and comparison groups (24, 33, 36, 42, 43). We predicted that abnormalities of prefrontal activation would be more evident in patients who were actively psychotic than in patients who were in remission. However, the group in remission showed a more marked attenuation of prefrontal activation, relative to the comparison subjects, than did the acute psychosis group, and direct comparison of the patient groups revealed that there was significantly greater activation in the inferior frontal and dorsolateral prefrontal, insular, and anterior cingulate cortices bilaterally in the actively psychotic patients. Thus, although the patients in remission engaged these regions less than did the healthy volunteers, in the actively psychotic patients, less activation, relative to that in the comparison subjects, was evident in the anterior cingulate cortex, but not in lateral prefrontal areas. These observations may seem counterintuitive in the light of evidence that prefrontal function in schizophrenia is more impaired in patients with positive psychotic symptoms than those in remission (44, 63, 64). However, compromised prefrontal function in schizophrenia may also be manifested as increased activation during cognitive processing. For example, Sommer et al. (36) found a correlation between the severity of auditory hallucinations in schizophrenia and right prefrontal activation during verbal fluency. Moreover, Callicott et al. (31) reported greater prefrontal activation in patients with schizophrenia than in comparison subjects during a verbal working memory task, and we have found that healthy volunteers with positive psychotic symptoms induced by ketamine show greater engagement of prefrontal areas during verbal fluency than when performing the task while taking placebo (65). These observations are consistent with the notion that in patients with impaired prefrontal capacity, additional activation may be needed to maintain normal task performance (31).

As predicted, abnormalities of prefrontal activation became more marked with increased task demand in patients with positive symptoms. However, comparison of the acute psychosis group and the group in remission revealed that rather than leading to a further reduction of activation, increasing demand in the symptomatic patients was associated with greater engagement of the right prefrontal and anterior cingulate cortex. The findings cannot be easily attributed to thought disorder or other disorganization symptoms, as neither group had significant measures on these symptoms. Although we cannot exclude the possibility that we may have detected subtle degrees of formal thought disorder if we had used detailed instruments for this purpose, we think this outcome is unlikely. None of the patients had any previous history of formal thought disorder, and patients with formal thought disorder usually have a record of

FIGURE 3. Effects on Prefrontal Cortical Activation of the Interaction Between Increased Task Demand During a Verbal Fluency Task and Psychotic State in Schizophrenia Patients With Acute Psychosis and Schizophrenia Patients in Remission, Relative to Healthy Comparison Subjectsa

\[8\text{ In the acute psychosis group, but not the group in remission, increased task demand was associated with activation in the right prefrontal cortex, left anterior cingulate gyrus, precuneus, angular gyrus, and a left temporo-parietal region (areas colored yellow). Conversely, a region in the right inferior temporal cortex (colored in purple) showed activation with increased task difficulty in the group in remission, but less activation with increased task difficulty in the acute psychosis group. The interaction in the right middle frontal gyrus (Brodmann’s area 9; Talairach and Tournoux coordinates in millimeters: x=41, y=15, z=31; cluster size=68 voxels) between task demand and psychotic state is shown in the plot of change in blood-oxygen-level-dependent (BOLD) response for the easy and difficult task conditions for each group.}\]
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this symptom across the course of illness. Instead, these observations suggest that the effect of increasing the demands of verbal fluency in schizophrenia depends on the level of positive psychotic symptoms at the time of scanning. If actively psychotic patients need to engage the prefrontal cortex to a greater extent than those in remission to attain a given level of performance, this greater extent of activation may be particularly evident when the task becomes more demanding. In our study, patients were able to maintain adequate task performance, even when the demands were increased. However, had performance substantially deteriorated, the effects of task demand on activation may have been quite different. Thus, data from other studies indicate that attenuated engagement of the prefrontal cortex in schizophrenia is evident only when the task load has been increased to the extent that patients can no longer perform the task (28, 30). Alternatively, we cannot exclude the possibility that the remitted patients differed from the psychotic group on neuropsychological performance, as formal measurements were not performed, and that this difference may have been related to their hypofrontality.

A further speculative explanation involves an influence of dopaminergic neurotransmission on cerebral blood flow and the blood-oxygen-level-dependent response that is measured in fMRI. Acute psychosis in schizophrenia, but not schizophrenia in remission, is associated with increased phasic dopamine release, a “hyperdopaminergic” state (66–69). The severity of central dopaminergic dysfunction appears to be correlated with abnormal prefrontal activation during the Wisconsin Card Sorting Test in schizophrenia (70–74). Experimental administration of dopaminergic agents modulates prefrontal activation during cognitive tasks (75, 76), and their effects on activation during verbal fluency differ between patients with schizophrenia and comparison subjects (42). Differential activation in prefrontal regions in patients with active psychotic symptoms, relative to patients in remission, may thus be related to a state-related perturbation of central dopaminergic activity, which might also underlie their positive symptoms. This possibility could be further investigated by directly comparing the effects of dopaminergic agents on prefrontal activation in actively psychotic patients and patients in remission.

One limitation of the present study was that all the subjects with schizophrenia were taking antipsychotic medication. Treatment with antipsychotic medications has been associated with increased metabolism in the basal ganglia (77–82). Their effect on activity in the prefrontal cortex is less clear, although Honey et al. (83) reported that patients treated with risperidone showed greater activation during a verbal working memory task than when they were treated with typical antipsychotics. However, a differential effect of atypical versus typical antipsychotic drugs is unlikely to account for the differences between the patient groups in our study, as the proportions of patients who received atypical and typical antipsychotics in each group were comparable.

Overall our data suggest that while schizophrenia is associated with impaired prefrontal function, how this impairment is manifest in functional imaging studies of cognitive tasks can vary with the severity of psychotic symptoms at the time of scanning and the level of task difficulty. When patients can carry out a task as well as comparison subjects, the presence of active psychosis and increasing task demand may necessitate engagement of prefrontal areas in order to maintain behavioral performance. On the other hand, if the task is such that patients can no longer carry it out, the engagement of the prefrontal cortex may be attenuated.

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Supported by a Wellcome Trust Travelling Fellowship.

The authors thank the study participants and the radiographers at the South London and Maudsley Trust MRI Unit for their assistance.

References


48. Andreasen NC: Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, University of Iowa, 1984

49. Andreasen NC: Scale for the Assessment of Negative Symptoms (SANS). Iowa City, University of Iowa, 1983


PREFRONTAL FUNCTION IN SCHIZOPHRENIA


59. Lurito JT, Kareken DA, Raine ALS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M: Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci USA 2000; 97:8104–8109

60. Weinberger DR: Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987; 44:660–669

61. Weinberger DR, Berman DF, Illowsky BP: Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia, III: a new cohort and evidence for a monoaminergic mechanism. Arch Gen Psychiatry 1988; 45:609–615


70. Weinberger DR, Berman DF, Illowsky BP: Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia, III: a new cohort and evidence for a monoaminergic mechanism. Arch Gen Psychiatry 1988; 45:609–615


