Brain Activations in Schizophrenia During a Graded Memory Task Studied With Functional Neuroimaging

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Background: Functional neuroimaging experiments have implicated prefrontal cortex (PFC) in memory processes. Several studies of schizophrenic patients have shown failure of activation in the dorsolateral region of PFC (DLPFC). We used a graded memory challenge to characterize functional neuroanatomical differences between schizophrenic and control subjects. The graded manipulation of task demands enabled us to assess group differences in the context of normal and abnormal psychological task performance.

Methods: Memory-related activity was assessed using positron emission tomography in schizophrenic patients and age-matched controls during performance of a graded memory task. Subjects underwent scanning while learning and recalling word lists of variable length.

Results: We used a model that assessed linear and non-linear effects of memory load. Nonlinear group differences in DLPFC activation were observed. Controls showed a steepening slope of DLPFC increase as task demands increased. By contrast, schizophrenic subjects showed initial DLPFC increases that fell away with increasing memory load. The DLPFC response in schizophrenic subjects was closely related to measured task performance. In addition, schizophrenic subjects failed to show task-related decreases in activity in the left superior temporal and inferior parietal gyrus.

Conclusions: Patients with schizophrenia showed a failure in DLPFC activation only in the face of diminished performance measures, suggesting that a full characterization of task-related changes in DLPFC activation must consider performance levels. However, striking failures of deactivation in superior temporal and inferior parietal regions were independent of task performance, possibly reflecting a core abnormality of the condition.

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FUNCTIONAL neuroimaging has revealed associations between symptoms and altered patterns of neuronal activity in schizophrenia.1-4 There is no unequivocal evidence of a neuronal abnormality that characterizes schizophrenia as a whole. For example, hypofrontality has been found in only a few studies, at least under resting conditions.5,6 A failure of frontal activation under conditions of neuropsychological task activation has been proposed as an alternative functional imaging abnormality in schizophrenia,7,8 although this has not been a consistent finding.5,6,11

One explanation for inconsistency among studies is an uncertainty as to whether hypofrontality in schizophrenia reflects poor task performance or is an intrinsic deficit unrelated to performance. Compared with control subjects, schizophrenic patients typically underperform on cognitive tasks,12 with performance on executive tasks being particularly impaired.13,14 Any associated hypofrontality could therefore reflect an intrinsically abnormal response of the prefrontal cortex (PFC) to cognitive challenge in schizophrenia or a secondary phenomenon that does not represent a specific schizophrenia-related abnormality, but simply reflects the fact that schizophrenic subjects do not perform the task. Attempts to separate neuropsychological task performance from its functional imaging correlates in schizophrenia have produced conflicting findings. Berman et al16 have reported that nonschizophrenic subjects with similar degrees of poor executive test performance as schizophrenic patients do not show task-related hypofrontality. Frith et al17 and Fletcher et al18 did not find evidence of hypofrontality during performance of a verbal fluency task in which patients' performance was balanced, as far as possible, with that of controls.

One approach to characterizing frontal lobe function lies in the use of memory tasks.19,20 Memory deficits in schizophrenia are well documented,21,22 with the degree of impairment often disproportionate to the overall level of intellectual impair-
SUBJECTS AND METHODS

SUBJECTS

Twelve male subjects with DSM-III-R diagnoses of schizophrenia\(^{11}\) and 7 (6 male; 1 female) age-matched controls were studied. Subjects were free of neurologic illness and had normal results of structural magnetic resonance imaging scans. All gave written informed consent, and the study was approved by the hospital ethics committee and the Administration of Radioactive Substances Advisory Committee, London, England.

All subjects had normal premorbid intelligence based on schooling and work records and premorbid IQ as estimated using the National Adult Reading Test (NART).\(^{31}\) Memory status of the schizophrenic patients was determined by their performance on the Rivermead Behavioural Memory Test,\(^{33}\) a clinically oriented, relatively undemanding test that is made up of 12 subtests. Patients were included in the memory-impaired group (n = 6; hereafter referred to as impaired schizophrenic group) if they achieved a screening score in the moderately or severely impaired range (all the patients who finally participated scored in the moderately impaired range). Patients were included in the memory-intact group (n = 6; hereafter referred to as the unimpaired schizophrenic group) if they scored in the normal or poor memory ranges (most of the patients scored in the poor memory range). Strictly speaking, therefore, “memory-impaired” is not accurate but is used for convenience. Basic intellectual and memory test scores for the patients are shown in Table 1. Briefly, the mean NART IQ for the schizophrenic group as a whole was 105 (range, 91-124; SD, 12).

The NART IQs were measured on 6 of the 7 control subjects (the seventh subject was unavailable for testing).

RESULTS

MEMORY PERFORMANCE

The performance of the 3 groups on the word-list recall task is shown in Figure 1. All 3 groups showed essentially perfect recall with word lists of up to 4 words. Beyond this, performance declined, with the steepest fall in the impaired schizophrenic patients and the shallowest in the controls. Analysis of variance showed significant interactions of group by word list length (controls vs unimpaired patients, P = .007; controls vs impaired patients, P<.001; unimpaired vs impaired patients, P = .009).

FUNCTIONAL NEUROIMAGING RESULTS

The z scores of the activations described below are reported in Table 2 through Table 6. These z scores were derived from Gaussianization of the t statistic with the threshold set at P<.01 (df, 157).

MAIN EFFECTS OF MEMORY LOAD

All 3 groups showed a pattern of activations that encompassed the PFC bilaterally and the posterior parietal cortex (Table 2). Deactivations were seen in temporoparietal regions bilaterally in all 3 groups (Table 3). Deactivations were also seen in the medial frontal cortex for the controls and the unimpaired schizophrenic subjects. These effects were satisfactorily characterized using the first-order model, with no significant gain using the second-order expansion.
FUNCTIONAL NEUROMAGING

All subjects underwent 12 measurements of regional cerebral blood flow during a 2-hour period. A commercially available scanner was used (C 953B-PET; Computerized Tomography Inc, Knoxville, Tenn), with collimating septa retracted. For each regional cerebral blood flow measurement, oxygen 15–labeled water was given as an infusion for 120 seconds. The amount of tracer injected per subject was 4995 MBq (calculated dosimetry at 5 mSv). Images were reconstructed into 63 planes, using a Hanning filter, resulting in a 6.4-mm transaxial and 5.7-mm axial resolution (full width, half maximum).

DATA ANALYSIS

The data were analyzed with statistical parametric mapping (SPM) using SPM software from the Wellcome Department of Cognitive Neurology, London, England, and implemented using Matlab (Mathworks, Sherborn, Mass). After realignment, the scans were transformed into standard stereotactic space and smoothed using a Gaussian filter set at 12-min full width at half maximum. The regional cerebral blood flow equivalent measurements were adjusted to a global mean of 50 mL/dL per minute. We used analysis of covariance to model condition-specific effects with parametric variation in memory load using polynomial regression. Subject-specific effects and global activity were modeled as confounds. Specific effects and interactions were explored with the appropriate contrasts using the paired $t$ statistic, giving a statistic image (SPM(t)) for each contrast. Intersubject variability was treated as a fixed effect. Thus, one must be cautious about the generalizability of the current results. Nevertheless, there is a high intrasubject-intersubject variability in measurements made using positron emission tomography, meaning that the fixed-effects model is more acceptable.

Data analysis focused on the following effects: First, the main effects of memory load were examined for each of the 3 groups separately. Second, the group-by-memory load interaction was assessed to examine the effects of diagnosis (control vs impaired schizophrenia and control vs unimpaired schizophrenia) and the presence of memory impairment (unimpaired vs impaired schizophrenia).

After initial analysis of effects using multilinear regression with a linear model, we explored load-related activity using a second-order polynomial expansion. The use of a nonlinear fit enables a variety of brain responses (and group-related differences in responses) to be modeled. The validity of the second-order term can be assessed by treating linear effects as confounds. In those cases where the expanded model did not produce any significant additional effects, results from the more constrained (linear) model are reported.

In view of the fact that our study explored an auditory-verbal memory paradigm that we have used previously, and because our specific hypotheses and questions concerned only a small number of regions, we used a lower threshold ($P<.01$) in these regions with respect to exploring the data for group differences. This was done mainly to avoid type II statistical error. Such an approach is justified, we believe, with regard to prefrontal function in schizophrenia, because of the large background of functional imaging studies addressing abnormalities in this region. This is particularly important in view of our attempts to show that there was no significant difference between the groups when a linear model was used, but that these differences only emerged with the nonlinear model. Nevertheless, the results we report should be considered preliminary.

GROUP BY MEMORY-LOAD INTERACTION

Comparisons of memory-related activations in the control group with those in the unimpaired schizophrenic subjects showed significant bilateral ventrolateral and left-sided dorsolateral PFC differences in activation using the second-order model (Table 4 and Figure 2). The more constrained linear model did not reveal differences in PFC activation, even when a modified significance level of $P<.01$ substituted for $P<.001$ in the analysis. The significant nonlinear differences were seen as reduced activation in schizophrenic subjects in association with increasing memory load. This phenomenon is shown graphically in Figure 3. As load increased, the prefrontal responses in controls differed qualitatively from those in both groups of schizophrenic subjects. Whereas controls responded to increasing word list length with an increasing degree of left PFC activation, both schizophrenic groups showed a tailing off of activation during longer lists.

To summarize, differences in PFC activations between controls and schizophrenic subjects were seen only when a flexible model was fitted to the data. The observed differences can be characterized as a steeper slope of increase in the controls when the tasks became more difficult and performance fell below 100%. In the schizophrenic subjects, the slope of increase of PFC activity became shallower with the longer word lists.

OTHER GROUP DIFFERENCES

Another region, the medial inferior parietal lobe, showed a group-by-task interaction that was adequately characterized using the linear model (Table 5). This region showed a relative failure of activation in the impaired group of schizophrenic subjects compared with the controls and the unimpaired schizophrenic group.

We also examined the data with respect to task-related decreases. In both patient groups, there was a relative failure of decrease in inferior parietal and superior temporal regions bilaterally (Table 6). This interaction was fully characterized by the linear model.

In a final analysis, we explored the group-by-task interactions attempting to remove the effects of medication levels that varied markedly across the patients. The crucial findings were unaffected.

Results of functional imaging studies of auditory-verbal memory in healthy volunteers are strikingly consistent in demonstrating prefrontal and parietal activa-
The findings of activation in these regions in our controls are in accord with these studies, as are the findings of deactivation in medial PFC and superior temporal and inferior parietal cortices. With regard to the question of PFC activation in schizophrenia, our study indicated that there was a non-linear pattern of change that differed across groups. This observation may, in part, explain and reconcile results of previous functional neuroimaging studies of schizophrenia. Whereas frontal activation was normal when performance levels were matched across groups, nevertheless, as task demands increased and performance impoverished, subjects with schizophrenia failed to show an increasing frontal response. This is in accord with studies of schizophrenia using more demanding tasks that have shown a failure of frontal activation, whereas the studies employing less demanding tasks have been associated with apparently unimpaired PFC activation.

Interpretation of the abnormal profile of PFC activity in the schizophrenic groups is, necessarily, speculative. Crucially, it seems that the hypofrontality is manifest only under conditions of cognitive stress, and it does not reflect a simple failure of this region to show activation-related changes. The more demanding tasks may have engaged frontally mediated strategies that the schizophrenic patients did not, or could not, adopt. Thus, the abnormal PFC activation under more demanding conditions may reflect a motivation deficit occurring as the task becomes too difficult for the subjects. Alternatively, there may be a failure to engage or to use the appropriate higher level strategies subserved by PFC.

One obvious interpretation relates to the division between short- and long-term memory. Verbal short-term memory function has been found to be relatively preserved in schizophrenia, whereas the deficit in long-term memory is substantial. Sparing of short-term memory was also evident in our study; both groups of schizophrenic patients had a mean word span length of about 4 words, which is within the normal range. Therefore, it could be argued that the hypofrontality found in our study was a simple function of having to engage the impaired long-term memory system.

Conceptualizing word list recall performance in terms of short- and long-term memory undoubtedly has validity, but it is now widely accepted, from results of...
neuropsychological\textsuperscript{46-52} and functional imaging studies,\textsuperscript{41} that executive and working memory processes, performed at least partly in PFC, also play important roles in retrieval. Another interpretation of our findings therefore could be that the failure of frontal activation in schizophrenic patients reflected failure to engage such processes as task demands increased. This observation is consistent with the finding that when schizophrenic subjects are encouraged to use appropriate cognitive strategies (by sorting study material into categories), their subsequent recall is comparable with that of controls.\textsuperscript{53} However, there was no measurable difference in left PFC activation between the impaired and the unimpaired schizophrenic subjects, although there was a significant difference in performance levels between the groups. It seems likely, therefore, that although performance levels constitute a major effect, they do not account for all of the differences between patients and controls.

A more general interpretation would be that the functional imaging differences found between schizophrenic patients and controls merely reflect the state of general cognitive impairment that characterizes most patients with schizophrenia to some degree. General intellectual impairment was certainly evident in our patients (ie, the lower Wechsler Adult Intelligence Scale \textit{current} IQs than NART \textit{premorbid} IQs in almost every case). In these circumstances, it may be impossible to specify whether memory, executive, or other specific cognitive subsystems were dysfunctional and giving rise to functional imaging abnormalities. However, even if such a view is taken, it is not clear that it would affect the validity of the findings. It could be argued that our study merely took advantage of the facts that memory is impaired in schizophrenia, and that memory tasks activate the PFC in functional imaging.

*Groups are described in the “Subjects and Methods” section.
†The numbers in parentheses refer to Brodmann areas.

\textbf{Table 3. Memory-Related Deactivations*}

<table>
<thead>
<tr>
<th>Group Comparison</th>
<th>Region†</th>
<th>Coordinates</th>
<th>( z ) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls vs impaired</td>
<td>Right post–central gyrus (40)</td>
<td>50, −16, 20</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Left post–central gyrus (40)</td>
<td>−50, 0, 16</td>
<td>3.7</td>
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<td></td>
<td>Left superior and middle temporal gyrus (21/22)</td>
<td>−54, −46, 8</td>
<td>3.5</td>
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<tr>
<td></td>
<td>Medial PFC (10)</td>
<td>2, 54, 12</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Left superior temporal gyrus (22)</td>
<td>−50, −50, 12</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Right superior temporal gyrus (22)</td>
<td>46, −48, 16</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Medial PFC (10)</td>
<td>−2, 52, 0</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Anterior cingulate cortex (24)</td>
<td>−4, 30, 0</td>
<td>4.2</td>
</tr>
<tr>
<td>Impaired schizophrenia patients</td>
<td>Right superior temporal gyrus (22)</td>
<td>48, −56, 12</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Left superior temporal gyrus (22)</td>
<td>−48, −56, 12</td>
<td>3.1</td>
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</tbody>
</table>

*PFC indicates prefrontal cortex. Groups are described in the “Subjects” subsection of the “Subjects and Methods” section.
†The numbers in parentheses refer to Brodmann areas.

\textbf{Table 4. Regions Showing Differences in Profiles of Task-Related Brain Activation Identified Using a Second-Order Polynomial Expansion*}

<table>
<thead>
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<th>Group Comparison</th>
<th>Region†</th>
<th>Coordinates</th>
<th>( z ) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls vs impaired</td>
<td>Left middle frontal gyrus (46)</td>
<td>−46, 34, 24</td>
<td>2.8</td>
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<tr>
<td></td>
<td>Left inferior frontal gyrus (47)</td>
<td>−28, 16, −4</td>
<td>2.6</td>
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<tr>
<td></td>
<td>Right middle frontal gyrus (10)</td>
<td>32, 54, 8</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Left middle frontal gyrus (10/46)</td>
<td>−34, 40, 20</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Left inferior frontal gyrus (47)</td>
<td>−30, 10, −4</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Right middle frontal gyrus (10)</td>
<td>34, 44, 12</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*Groups are described in the “Subjects” subsection of the “Subjects and Methods” section.
†The numbers in parentheses refer to Brodmann areas.

\textbf{Table 5. Differential Activations*}

<table>
<thead>
<tr>
<th>Group Comparison</th>
<th>Region†</th>
<th>Coordinates</th>
<th>( z ) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls vs unimpaired schizophrenia patients</td>
<td>Posterior cingulate cortex (30)</td>
<td>22, −38, 16</td>
<td>2.1</td>
</tr>
<tr>
<td>Controls vs impaired schizophrenia patients</td>
<td>Left inferior parietal lobe (40)</td>
<td>−44, −46, 32</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Posterior cingulate cortex (31)</td>
<td>−24, −60, 36</td>
<td>2.2</td>
</tr>
<tr>
<td>Unimpaired vs impaired schizophrenia patients</td>
<td>Left inferior parietal lobe (40)</td>
<td>−10, −58, 24</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Right inferior parietal lobe (40)</td>
<td>−20, −62, 36</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Groups are described in the “Subjects” subsection of the “Subjects and Methods” section.
†The numbers in parentheses refer to Brodmann areas.

\textbf{Table 6. Differential Deactivations*}

<table>
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<tr>
<th>Group Comparison</th>
<th>Region†</th>
<th>Coordinates</th>
<th>( z ) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls vs unimpaired schizophrenia patients</td>
<td>Right post–central gyrus and superior temporal gyrus</td>
<td>48, −6, 16</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Left post–central gyrus and superior temporal gyrus</td>
<td>−52, 0, 16</td>
<td>2.4</td>
</tr>
<tr>
<td>Controls vs impaired schizophrenia patients</td>
<td>Right post–central gyrus and superior temporal gyrus</td>
<td>44, −16, 8</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Left post–central gyrus and superior temporal gyrus</td>
<td>−40, −22, 12</td>
<td>2.3</td>
</tr>
<tr>
<td>Unimpaired vs impaired schizophrenia patients</td>
<td>Left post–central gyrus and superior temporal gyrus</td>
<td>−6, 54, 12</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Medial frontal gyrus</td>
<td>−40, −24, 12</td>
<td>3.0</td>
</tr>
</tbody>
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*Groups are described in the “Subjects” subsection of the “Subjects and Methods” section of the text.

The numbers in parentheses refer to Brodmann areas.
bing studies, to provide a further examination of the question of whether the PFC is dysfunctional in schizophrenia. Whether the cognitive dysfunction that produces the hypofrontality is specific or general might legitimately be regarded as immaterial.

A noteworthy observation in our study was that a region showing impaired activation, the posterior parietal region (Brodmann area 40), was specific to the impaired schizophrenic group. Posterior parietal activations are a common finding in functional imaging studies of memory retrieval. It is striking that the unimpaired schizophrenic group showed high activity in this region, despite performance that was significantly inferior to that seen in controls. Whereas the roles of this area of cortex have yet to be fully explored, the ubiquity with which it appears to be active in functional imaging studies of memory is striking. The significant reduction of its activation in the impaired schizophrenic group may reflect an impairment in long-term memory retrieval processes in schizophrenia.

An important finding in our study is the replication of previous findings of a relative failure of superior temporal and inferior parietal deactivation in both groups of schizophrenic subjects. The fact that the linear model fully characterized this effect implies that the lateral superior temporal and inferior parietal activity, although related to changing task load, is unaffected by performance levels (in controls or schizophrenic subjects). Results of a number of previous positron emission tomography studies of healthy volunteers have presented evidence of a relative decrease in activity of this region during tasks that engage frontal lobes. The finding of a relative failure of this deactivation in schizophrenic subjects has been found in 2 previous studies and has been discussed in terms of a functional disconnection between temporal and prefrontal regions. In 1 study, a dopaminergic challenge, which augmented anterior cingulate cortex activity, was associated with a relative normalization of the superior temporal response. This was interpreted in terms of cingulate modulation of prefrontotemporal connectivity. There may be an abnormality of frontotemporal integration in the schizophrenic subjects, with this phenomenon being reflected in poorer cognitive abilities. The functional significance of the inverse relationship between frontal and temporal regions in normal brain function is unclear. The superior temporal region may be concerned with semantic elaboration of verbal material. In the context of the memory task, this may be inappropriate and, in the normal situation, it is inhibited, an inhibition that does not occur in the schizophrenic subjects. This suggestion is clearly speculative, and exploring the nature of abnormal frontotemporal relationships in schizophrenia will require specifically designed experiments.

There was no evidence of medial temporal lobe activation in our study. This is not unusual in positron emission tomography studies of memory function and there is no consensus as to why this should be so. Recent data suggest that, in a memory task, the hippocampal region is differentially sensitive to novelty of material. If this is
so, then our study, in which each scan contained frequently repeated words, would not be expected to show strong change in this region. Whereas the small numbers of subjects, and the fact that they were receiving antipsychotics, mean that our findings must be treated as preliminary, we have shown that, in schizophrenic patients, there is an abnormal profile of task-related activation in prefrontal regions. This profile was intimately related to task demands and performance. In controls, increasing memory demands lead to increasing left PFC activity, whereas schizophrenic subjects, under the same conditions, showed a falling away of PFC activity. Unimpaired PFC activation across the shorter subspan lists suggests that task-related hypofrontality in schizophrenia may reflect a failure to engage critical cognitive processes necessary to optimize performance in the face of increasing task demands. We conclude that PFC activity in schizophrenia cannot be evaluated independently of task demands and associated performance measures, since it is only observed in the situation where task demands are high and performance is impaired.

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REFERENCES

23. Gur RC, Jaggi JL, Shtasel J, Ragland JD, Gur RC. Cerebral blood flow in schizo-


44. Berman KF, Zec RF, Weinberger DR. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. Arch Gen Psychiatry. 1986;43:126.


