Schizophrenics Show Spatial Working Memory Deficits

Sohee Park, PhD, Philip S. Holzman, PhD

- The present study demonstrates that schizophrenics are impaired on spatial delayed-response tasks, analogous to those that have been used to assess the working memory function of the dorsolateral prefrontal cortex in rhesus monkeys. Schizophrenic patients and two control groups, normal subjects and bipolar psychiatric patients, were tested on the oculomotor version of the memory task, a haptic version of the same task, and two control tasks: a sensory task that did not require working memory and a digit span test. The schizophrenic patients showed marked deficits relative to the two control groups in both the oculomotor and haptic delayed-response tasks. They were not, however, impaired on the digit span test, which taps verbal working memory as well as voluntary attention, and on the sensory control task, in which their responses were guided by external cues rather than by spatial working memory. These findings provide direct evidence that schizophrenics suffer a loss in representational processing and that this deficit is modality independent. These data on spatial working memory add to the growing evidence for involvement of the dorsolateral prefrontal cortex in schizophrenic disease. (Arch Gen Psychiatry. 1992;49:975-982)

Similarities between schizophrenic symptoms and frontal lobe dysfunctions are compelling and have been recognized by many observers, perhaps beginning with Kraepelin. Although frontal lobe involvement in schizophrenia has often been assumed, this structure has not clearly been implicated as a principal site of dysfunction in psychosis. In recent years, however, evidence of similarities between the deficits of patients with frontal lobe lesions and those exhibited by schizophrenics has continued to mount, and the list of congruences has grown even longer and more compelling. Both groups of patients suffer a loss of integrative function. Apathy, attentional impairment, and flat affect, characteristic of negative-symptom schizophrenics, are also prevalent in patients with frontal lobe lesions and in monkeys with prefrontal lesions.

Neuropsychological testing of schizophrenic patients has yielded symptom profiles similar to those found in patients with frontal and temporal lobe dysfunction, and the pursuit eye movement dysfunctions of schizophrenics have likewise been linked to the frontal eyefields. Schizophrenics, like patients with frontal lobe lesions, are unable to inhibit inappropriate responses in an antisaccade task, which probably implicates the frontal eyefields.

More direct evidence emerges from brain scanning techniques; schizophrenics exhibit a "hypofrontal" pattern of regional cerebral blood flow in a "resting" state, while normal subjects under the same condition typically exhibit "hyperfrontality." In addition, regional cerebral blood flow is not increased in the dorsolateral prefrontal cortex (DLPFC) of schizophrenics as it is in control subjects when both subject populations are engaged in performing the Wisconsin Card Sort Task, impairment on which seems to reflect frontal lesions. Thus, results from clinical observation, neuropsychological testing, and in vivo imaging all indicate an important role for the DLPFC in the psychopathologic and pathophysiologic character of schizophrenia.

The present study was undertaken to specify further the dorsolateral prefrontal contribution to schizophrenic symptoms and to extend the analysis of the underlying pathophysiologic conditions. Specifically, we have adopted for the study of schizophrenic behavior an oculomotor spatial delayed-response paradigm that has recently been used to elucidate the neuropsychological and neuropsychological correlates of cognitive processing in non-human primates. The delayed-response task was first introduced by Hunter, whose primary interest was in studying whether animals (including human children) could guide their behavior on the basis of stored information. The prototype we used is a member of a family of delayed-response and spatial delayed-alternation tasks that have proved to be selective and reliable measures of dorsolateral prefrontal function in nonhuman primates.

The essence of these tasks is that they require the monkey to update its memory on every trial and guide its response by memory of stored information rather than by external stimuli present in the immediate environment. A prototypical delayed-response task involves a simple choice. A monkey sits in front of two identical food wells and observes food being placed in one. Both wells are then hidden from view by an opaque screen. After a delay period (about 1 to 5 seconds for monkeys), the screen is removed and the monkey is allowed to reach for the food. To retrieve the food, the animal must remember where it was hidden before the delay. A variation of this task, called the...
delayed-alternation task, requires the monkey to remember the previous response and pick the other well. To succeed on these tasks, the monkey cannot rely on external cues because the food cannot be seen in the well. Therefore, the monkey must form an internal representation of the location of the food at each trial and update it whenever the situation changes. Lesions of the principal sulcus (Brodmann’s area 46) impair performance on delayed response and delayed alternation in monkeys, . Humans with lesions of the DLPFC show analogous deficits. Moreover, a recent study using the technique of positron emission tomography revealed that normal human subjects performing a delayed-alternation task showed selective activation of the DLPFC in the left hemisphere.

Goldman-Rakic has proposed that the delayed-alternation tasks are a measure of the working memory capacity of the prefrontal cortex and that this capacity is implicated in at least some of the cognitive dysfunction in schizophrenia. The testing of schizophrenic patients on the oculomotor delayed-response paradigm provides a direct test of this hypothesis and, in addition, allows us to infer the cortical areas that might be involved in some of the deficits in schizophrenia. Comparison of performance on the standard delayed-alternation paradigm with that on a sensory-guided task allowed us to control for the sensory motor requirements in the task. Inclusion of a digit span task provided some partial comparison with verbal memory processes. In addition, we compared performance on an oculomotor and a haptic version of the task to evaluate the working memory capacity in more than one sense modality.

In the current study, the oculomotor tasks consisted of an oculomotor memory and an oculomotor sensory task. In both tasks, a target is presented at the beginning of each trial. In the memory task, however, the target is extinguished and a delay (5 or 30 seconds) follows before the response, whereas in the sensory control task the target remains on throughout the delay. Thus, the memory task requires the subjects to move their eyes to the remembered position of a target, whereas the sensory task requires the subject to move their eyes to the target itself. An obvious additional control task is one that includes no delay between stimulus offset and eye movement to the target. This condition, however, is identical to square wave tracking or a test of saccadic accuracy and reaction time. Several previous studies have established that schizophrenic patients do not differ from normal controls on this task, and therefore this control was not included. By comparing performance on the memory task with that on the sensory task, the sensory and motor functions can be separated from working memory functions. Rhesus monkeys with lesions in the principal sulcus are impaired on delayed-response tasks but perform well when no memory is required for successful performance. If schizophrenics are impaired on analogous delayed-response tasks, their performance should be comparable with that of lesioned monkeys, and they could be expected to make more errors as the delay increases, compared with the normal control group. Sensory-guided movements, however, which do not depend on working memory or on an intact prefrontal cortex, would not be impaired.

**METHODS**

**Subjects**

Twelve schizophrenic patients from McLean Hospital (Belmont, Mass) participated in this study. These subjects met the criteria for a DSM-III-R diagnosis for schizophrenia, as determined from a standardized interview (Structured Clinical Interview for DSM-III-R), administered by an experienced interviewer. Twelve bipolar patients served as psychiatric controls. They were recruited from the same hospitals and met the DSM-III-R criteria for bipolar disorder, as determined from data provided from a Structured Clinical Interview for DSM-III-R. The schizophrenic and bipolar patients had no evidence of organic brain disease, were under 50 years of age, and were not mentally retarded. Twelve normal control subjects who had no history of mental illness in themselves or in their first-degree family members were recruited by means of advertisement from McLean and Cambridge. They were paid a modest honorarium for participating.

All patients but one bipolar patient were receiving antipsychotic drugs; many were receiving several medications. Table 1 presents the medication information.

There were no statistically significant differences among the three groups in age, IQ scores, education level, and socioeconomic level, nor did the two psychiatric groups differ significantly in the duration and onset of illness. Table 2 summarizes the demographic information.

**Table 1.—Number of Schizophrenic and Bipolar Patients Receiving Medication of Specific Types**

<table>
<thead>
<tr>
<th>Drugs Administered</th>
<th>Schizophrenic (n=12)</th>
<th>Bipolar (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neuroleptics that primarily block D2 dopamine receptors (haloperidol, perphenazine)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Neuroleptics that block both D1 and D2 receptors (fluphenazine, loxapine, succinate, chlorpromazine, clozapine, thioridazine, mesoridazine)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Antianxiety (lorazepam, clonazepam, propranolol, busiprone)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Antidepressant (nortriptyline, desipramine)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Anticholinergic (benztropine)</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2.—Demographic Characteristics of Schizophrenic, Bipolar, and Normal Subject Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenic (n=12)</th>
<th>Bipolar (n=12)</th>
<th>Normal (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.7±4.9</td>
<td>33.6±9.5</td>
<td>34.8±9.1</td>
</tr>
<tr>
<td>IQ (WAIS)</td>
<td>103±14</td>
<td>102±12</td>
<td>107±8</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.5±1.2</td>
<td>13.3±1.8</td>
<td>13.5±1.9</td>
</tr>
<tr>
<td>SES index</td>
<td>41±14</td>
<td>43±10</td>
<td>39±10</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>19.7±3.6</td>
<td>21.1±4.9</td>
<td>...</td>
</tr>
<tr>
<td>Years of illness</td>
<td>11.7±3.4</td>
<td>12.5±8.1</td>
<td>...</td>
</tr>
</tbody>
</table>

*WAIS indicates Wechsler Adult Intelligence Scale; SES, socioeconomic status (Hollingshead-Redlich scale). Values are mean±SD.
Experiment 1: Oculomotor Delayed-Response Tasks

Procedure.—Subjects were seated with their heads stabilized by a chin and head rest in front of a stimulus display monitor. The fixation point in the center of the stimulus display screen was a small red dot (about 0.5° of visual angle). The target, a small black circle (about 2° of visual angle), was displayed on the screen for 200 milliseconds. The location of the target varied randomly from trial to trial over eight possible locations, each separated by 45°. For the subject, the distance between the fixation point and any target location was 12° of visual angle.

For the memory version of the task, subjects were asked to look at the fixation point in the center of the screen (a red dot). The experiment began when the experimenter clicked a mouse, which initiated a trial. A target (a black circle) then flashed on the screen for 200 milliseconds at one of the peripheral locations. This period is short enough to prevent a reflexive saccade in the direction of the target. Immediately after the target disappeared, a delay period of 5 or 30 seconds ensued, during which time the subject was required to perform a distractor task. The distractor task prevented rehearsal and also ensured that the subject continued to look at the center of the screen. Two different distractor tasks were used: a categorization task, which forced the subject to shift semantic categories, and a number subtraction task. (In the category distractor task, as soon as the target was extinguished, a word appeared at the fixation point. This word was a member [eg, apple] or nonmember [eg, pear] of the semantic category such as fruit. After 1 second, the word was replaced by another word from the same category [eg, pear] and so on. At some point, there was a sudden change in the type of word [eg, cat]. When this category change occurred, subjects were required to click a mouse with their left hand. Examples of categories given include fruits, vegetables, animals, insects, flowers, furniture, colors, boys’ names, girls’ names, cities, actors, television shows, states, countries, automobiles, candies, clothing, singers, actors, movies, books, kitchen appliances, and activities. In the number subtraction distractor task, as soon as the target was extinguished, a three-digit number [eg, 729] appeared at the fixation point for 1 second. Subjects were told that the computer is counting backward by twos from this number. After 1 second, this number was replaced by another number smaller by 2. The subtraction occurred every second, but sometimes the computer “calculated incorrectly” and subtracted a number other than 2. When this happened, subjects were told to click a mouse with their left hand to indicate that they had noticed this “mistake.” Distractor tasks were necessary because our pilot studies showed that all subjects, control and patients alike, employed cognitive strategies, such as mnemonic devices, to rehearse and thereby remember the target location. The distractor tasks we used successfully prevented these rehearsal techniques. In addition, we hypothesized that the categorization task may tax frontal functions more than the number task and therefore it may have a greater detrimental effect on working memory.

After the delay period, the fixation point and eight “reference” circles (empty rather than black) appeared on the screen. Subjects were required to move their eyes to the position that the target circle had occupied before its disappearance. If they looked at the correct target position (ie, within a 1.5° radius of the center of the target), the screen cleared and the red fixation point appeared at the center of the screen, indicating that the next trial could begin. If subjects looked at the wrong position, the reference circles remained on the screen until the subjects directed their eyes to the correct position. Eye positions during this period were recorded every 20 milliseconds. If the subject did not make a correct response within a 30-second time limit, the reference circles disappeared and the red fixation point reappeared, indicating a new trial could begin. We were interested in examining only the first eye movement toward a reference circle. Therefore, if the eye looked at a wrong circle first and then eventually moved to the correct position, this response was counted as incorrect.

The sensory control task was identical to the oculomotor memory task except for one aspect: the target remained on the screen at all times. Subjects performed the distractor task, and, immediately after the appearance of the seven additional reference circles, they were required to move their eyes to the black target. Correct performance on this task does not require working memory, since the target never disappeared. Figure 1 shows the schematic plan of the experiment. These tasks were identical in design to those used in monkeys,32 except for the addition of the distractor tasks.

In summary, the procedure included two delay periods (5 and 30 seconds), two different distractor tasks (category and number subtractions), and two different delayed-response tasks (memory and sensory). The order of presentation of these conditions was counterbalanced across subjects, and within the memory and sensory tasks, the order of presentation of delay durations and the distractor tasks was counterbalanced. There were 128 trials on each task, and subjects rested after every 16 trials. All subjects gave full informed consent, and sufficient time was taken to be certain that subjects understood the task.

The Digit Span subscale of the Wechsler Adult Intelligence Scale (digits forward and backward) was also administered to determine if a working memory deficit included verbal working memory.33,34 The Digit Span test also served as a partial assessment of a generalized deficit.

Apparatus.—Eye movements were monitored and recorded by an infrared corneal reflection system. An infrared light source was placed in front of the stimulus video display monitor, facing the subject. The reflected infrared light from the right eye of the subject was recorded by a video camera with an infrared filter. The video camera was connected to a pupil-corneal reflection tracking system (ISCAN RK-424, ISCAN, Inc, Cambridge, Mass) that records the center of the pupil and a bright corneal reflection moving over the pupil. The spatial difference between the pupil center and corneal reflection remains constant if head movement is small (about 1 in2), but it changes with eye movement. This method yields a linear representation of the subject’s eye position within ±15° of visual angle. Within the linear range, accuracy is better than 1°.

The pupil-corneal tracking system was connected to a computer (Macintosh II, Apple Computer, Cupertino, Calif), which recorded and stored the eye position information (x and y coordinates), and to a television monitor, which allowed the experimenter to observe the right eye during the experiment. To take account of small head movements, the pupil-corneal tracker was connected to an ISCAN RK-520 Autocalibration System (ISCAN, Cupertino, Calif).
Inc), which calculated the subject’s point of regard with respect to the stimulus.

Before the experiment began, each subject’s eye movements were calibrated by asking the subject to fixate on five experimenter-defined positions on the stimulus display screen, successively: center, upper left, lower left, upper right, and lower right. We employed the Autocalibration System, which coordinates the eye position information and experimenter-defined calibration position information, to compute the point of regard for subsequent eye movements.

After the calibration, subjects were given practice trials to be sure all subjects understood the procedure. Eye movements were monitored on the eye monitor screen to ensure that the subject was fixating at the center when the trial began. Recalibrations took place after each rest period.

Results.—The percentage of correct responses (referred to herein as “accuracy”) and the latency of the first eye movement toward the target were the principal measures. Data from the oculomotor memory and sensory delayed-response tasks are presented separately below. Each experiment was evaluated by analysis of variance (ANOVA). The analyses revealed no order effects for any variables that were counterbalanced.

Memory-Guided Oculomotor Delayed-Response Task.—Table 3 contains the results for the three subject groups under the two delay periods (5 and 30 seconds) in the oculomotor memory-guided task. Schizophrenics clearly performed more poorly than either the normal controls or the bipolar patients in both delay periods, whether performance was measured by accuracy of eye movements or by reaction time. An ANOVA showed a significant effect of diagnostic group on accuracy (F[2,33]=7.96, P<.002) and on reaction time (F[2,33]=6.04, P<.006).

With respect to accuracy, although schizophrenics were significantly less accurate than normal controls (F[1,22]=4.70, P<.05) and bipolar subjects (F[1,22]=28.7, P<.0001), the bipolar patients were significantly more accurate than the normal controls (F[1,22]=4.62, P<.05).

The two delay periods exerted differential effects on performance of all three subject groups, with all subjects showing decreased accuracy in the 30-second rather than in the 5-second delay period (F[1,33]=46.79, P<.0001). The two different distractors, however, did not exert any differential effect on the performance.

Schizophrenics were clearly slower than normal controls in response time (F[1,22]=14.47, P<.002), but they were not slower than the bipolar patients (F[1,22]=1.77, P>.19). Indeed, the bipolar patients were slower than the normal controls (F[1,22]=4.85, P<.04). This pattern of greater accuracy but slower response time by the bipolar patients compared with the normal controls may indicate a speed-accuracy tradeoff, suggesting that the bipolar patients may have been more cautious than the normal controls. The left side of Figs 2 and 3 presents these data graphically.

Sensory-Guided Oculomotor Delayed-Response Tasks.—On the sensory-guided tasks, as shown in Table 3 and the right panel of Fig 2, performance was considerably better than on the memory-guided tasks. All subjects were faster and more accurate on the sensory-guided tasks. Although there was a significant difference among the diagnostic groups with respect to accuracy (F[2,33]=5.93, P<.007), this result is attributable to the greater accuracy of the bipolar patients compared with the schizophrenics (F[1,22]=9.71, P<.006) but not compared with the normal controls. The accuracy of the schizophrenics was not significantly different from that of the normal controls. The finding that bipolar patients were slower than normal controls in the sensory-guided task may explain their superiority to normal controls in accuracy. Here, too, there may have been a speed-accuracy trade-off. However, the schizophrenics did not benefit in a similar way from their slowness. Schizophrenics were significantly slower than the normal controls (F[1,22]=12.6, P<.002), though not significantly slower than bipolar patients. It is not possible, in this study, to determine whether schizophrenics would show an even greater decrement if speed had been required, and therefore whether there actually was a speed-accuracy trade-off for them as well as for the bipolar patients.

The effect of delay periods on accuracy was not significant in the sensory-guided tasks, although there was a significant interaction between illness and delay (F[2,33]=4.91, P<.02), indicating that schizophrenics were less accurate during the longer delay than the other two groups. It is noteworthy that there was a large difference between the memory and sensory tasks in all groups (F[1,33]=116.1, P<.0001), indicating that all groups were more accurate when the target remained on the screen. This large effect is mainly due to the inaccuracy of the schizophrenic patients in the memory task, as implied in the significant interaction between type of task (memory or sensory) and illness (F[2,33]=4.24, P<.05). There were no differential effects of the two distractors on the sensory task. The right side of Figs 2 and 3 presents these data graphically.

In addition, we analyzed difference scores (the difference, for each subject, between the sensory- and memory-guided tasks) to address the issue of covariation between sensory and memory tasks. There was a significant effect of illness on the difference scores (F[2,33]=7.96, P<.0015). Focused comparisons revealed that schizophrenics had greater difference scores than the normal controls (P<.05) and the bipolar patients (P<.05), but there was no difference between the two control groups, indicating a significantly greater deficit on the memory task for the schizophrenics than for the other two groups.

Error Analysis.—Two types of errors were analyzed: perseverative and hemifield. Perseverative errors were defined as those that arose because subjects returned to the position the target had occupied in the previous trial. On trials in which an eye move-
ment was made to a target position next to the current one (ie, a neighbor error), it was not clear if the error was due to perseveration of the response to the previous trial or if it was due to inaccuracy. Therefore, if an error was a neighbor error, it was not recorded as a perseverative error. The total number of perseverative errors was computed for each subject. Schizophrenics made perseverative errors, whereas normal controls and bipolar patients never did (F[2,33]=10.05, P<0.005).

Single unit recordings in monkeys performing the oculomotor delayed-response task have revealed that a large fraction of cells in each hemisphere codes the location of targets in the contralateral visual field, and reversible lesions confined to one hemisphere produce deficits in memory for contralateral targets. In view of this evidence for contralateral coding of working memory in primate prefrontal cortex, it was of interest to examine the possibility of laterality differences in the schizophrenic patients. Accordingly, we analyzed whether any given subject made more errors to targets in the right or the left visual field, ie, hemifield errors.

The eye movements that landed in the opposite hemifield from that of the target were computed for each subject. Schizophrenics made more hemifield errors than the other groups (F[2,33]=5.38, P<.01), but there were no indications of a difference between the two hemifields.

**Digit Span Test.**—Table 3 displays the mean number of digits, forward and backward, correctly repeated by each diagnostic group. On the Digit Span test, there were no significant differences among the three groups on the forward and backward versions of this task. The absence of group differences on the backward Digit Span indicates that simple verbal working memory is not significantly impaired in schizophrenics. The Digit Span task concerns linguistic representations rather than spatial, and it is also less complex than the spatial delayed-response tasks. Therefore, further research is needed to test the integrity of verbal working memory in schizophrenic patients.

**Experiment 2: Haptic Delayed-Response Task**

A haptic delayed-response task was conducted with the same 36 subjects to test whether the deficit found in schizophrenics in the oculomotor delayed-response experiment is a general spatial deficit, and one not restricted to the visual modality. It is likely that injections of bicuculline, a γ-aminobutyric acid antagonist, into the principal sulcus of rhesus monkeys produced deficits on somatosensory, auditory, and visual tasks with spatially directed responses, indicating that spatial working memory is modality independent. The haptic delayed-response experiment was almost identical to the oculomotor delayed-response experiment in design and procedure. In the haptic domain, however, perception is necessarily more sequential than in the visual domain. A target cannot be “flashed” in the periphery of the sensorium in the haptic modality, since perception is limited to the areas that are in contact with the tactile receptors, in this case, the hand. Therefore, the sensory control task was modified to fit this condition.

**Procedure.—**The design of the haptic memory task was identical to that of the oculomotor memory task. There were two delay conditions (5 and 30 seconds) and two types of distractor tasks (category and number tasks). The presentation order of the delays and the distractor types was counterbalanced.

Subjects were asked to close their eyes and to place the index finger of their right hand on a plastic thumbtack, which was the “fixation” point in the center of a circular stimulus display board. An opaque screen between the subject and the stimuli prevented the subject from seeing the stimuli, even if the eyes were open. Subjects were then asked to explore the stimulus board with their hand and find a soft target, approximately 1.5 cm in diameter (a Dr Scholl’s circular corn pad), that was placed in the periphery of the stimulus display board, 15 cm from the center of the fixation point. The position of the target on the circumference varied randomly from trial to trial. Possible target locations were separated by 45°.

The sensory control task was the following: when the target was found, subjects were asked to return to the fixation point and then immediately to place their index finger back on the target. This control condition established that the subject had adequate motor skills to be able to perform the task. All subjects were able to perform the sensory control task.

After subjects placed their index finger on the target, they were required to return to the fixation point immediately and to keep their finger there until the end of the ensuing delay. During the delay period, subjects were asked to perform the distractor task to prevent rehearsal, still keeping their eyes closed. These distractor tasks were essentially the same as those described in the oculomotor experiment but were delivered auditorily. After the delay, subjects were asked to move their index finger back to the original target. There were 128 trials. Figure 4 displays a diagram of the apparatus.
After the completion of the haptic memory task, the opaque screen was removed and subjects were asked to move their index finger to each target position from the center fixation point, under visual guidance. This procedure checked whether each subject could point to the correct spot accurately, and this task served as a second sensory control, which all subjects performed without error.

Results.—As in the oculomotor task, accuracy and type of error were recorded. Table 31 and Fig 5 contain the results for the three subject groups under the two delay periods. As with the oculomotor tasks, schizophrenics performed more poorly than the normal controls and the bipolar patients in both delay periods (F[2,33]=64.6, P<.0001). Although schizophrenics were significantly less accurate than normal controls (F[1,22]=72.2, P<.0001) and bipolar patients (F[1,22]=89.1, P<.0001), there was no difference between the normal controls and the bipolar patients.

Subjects in all three groups showed less accuracy in the 30-second than in the 5-second delay period (F[1,33]=44.9, P<.0001). The effect of lengthening the delay period, however, was much greater for the schizophrenic group than for the other two groups, as indicated by a significant interaction of subject groups and delay (F[2,33]=11.2, P<.0003).

Error Types.—The number of perseverative errors showed a main effect of subject groups (F[2,33]=9.33, P<.0007). Schizophrenics made almost all the perseverative errors. Normal controls made no perseverative errors at all, and there was only one perseverative error made by a bipolar patient. Accuracy was the same for both hemifields.

In summary, the results from the haptic delayed-response experiment indicate that schizophrenics as a group are impaired on delayed-response tasks and that the impairment is not restricted to the visuospatial modality. The accuracy scores from the memory-guided tasks in the visual and haptic domains were significantly correlated (r[34]=47, P<.01). The difference between the schizophrenic group and the two control groups was highly significant in both modalities.

COMMENT

The experiments described yielded three unequivocal results: (1) schizophrenic patients showed a significant impairment in memory-guided delayed responses, whether the sense modality was visual or haptic; (2) bipolar patients, on the other hand, showed no impairments on delayed-response tasks and that the impairment is not restricted to the visuospatial modality. The accuracy scores from the memory-guided tasks in the visual and haptic domains were significantly correlated (r[34]=47, P<.01). The difference between the schizophrenic group and the two control groups was highly significant in both modalities.

Do Schizophrenics Have a General Spatial Working Memory Deficit?

The question of modality-specific impairment was addressed by testing spatial working memory in two domains, oculomotor and haptic. Schizophrenics were significantly impaired in both modalities. Moreover, accuracy in the oculomotor task was highly correlated with accuracy in the haptic task for all subjects. This pattern of results implies that the deficit is spatial in nature and that it is not restricted to one sense modality. The issue of whether the working memory deficit is even more general was addressed by administering a simple verbal working memory task. The results of the backward Digit Span task indicate that verbal working memory is not impaired in schizophrenics, at least when the task demands are relatively low. Future studies are necessary to determine whether the verbal working memory is intact even when task load is increased.

Do Schizophrenics Show a Deficit in Representational Memory?

Performance on the visuospatial and the haptic spatial tasks indicates that spatial working memory is significantly impaired in schizophrenics. Schizophrenics were much more vulnerable to longer delay periods and they were more susceptible to perseverative errors than either the bipolar patients or the normal subjects. This deficit is probably not a simple motor problem. The accuracy performance of schizophrenics did not differ from that of the normal controls in the sensory condition. In the haptic delayed-response task, all subjects were accurate when no memory was required, that is, all subjects were able to move their fingers to the target position with or without vision. Both the oculomotor and haptic sensory and memory tasks were identical except for one component: in the memory task, subjects must form an internal representation of the target position and later use it to guide their response, whereas in the sensory task, the target is present at the time of the response and therefore the working memory component is not required. The addition of the working memory component severely affected the schizophrenics but did not significantly affect the performance of the control groups. We conclude that the deficits observed in the oculomotor and haptic delayed-response tasks are likely to be due to working memory problems rather than to a simple motor problem of the eye or the hand.

schizophrenic illness. First, do schizophrenic patients show a deficit in the representational guidance of behavior that is independent of the motor system itself? Second, if schizophrenics show such impairment, is it restricted to the oculomotor modality, or is a more general spatial working memory deficit indicated?

**Do Schizophrenics Show a Deficit in Representational Memory?**

Performance on the visuospatial and the haptic spatial tasks indicates that spatial working memory is significantly impaired in schizophrenics. Schizophrenics were much more vulnerable to longer delay periods and they were more susceptible to perseverative errors than either the bipolar patients or the normal subjects. This deficit is probably not a simple motor problem. The accuracy performance of schizophrenics did not differ from that of the normal controls in the sensory condition. In the haptic delayed-response task, all subjects were accurate when no memory was required, that is, all subjects were able to move their fingers to the target position with or without vision. Both the oculomotor and haptic sensory and memory tasks were identical except for one component: in the memory task, subjects must form an internal representation of the target position and later use it to guide their response, whereas in the sensory task, the target is present at the time of the response and therefore the working memory component is not required. The addition of the working memory component severely affected the schizophrenics but did not significantly affect the performance of the control groups. We conclude that the deficits observed in the oculomotor and haptic delayed-response tasks are likely to be due to working memory problems rather than to a simple motor problem of the eye or the hand.
Indeed, lesions in the frontal eyefields have now been shown to produce a deficit in predictive continuation of smooth-pursuit tracking in monkeys analogous to the eye tracking deficits observed in patients. 34 Therefore, further testing of schizophrenic patients and their families on both the spatial working memory task and the smooth-pursuit eye tracking procedures would be of interest. If healthy family members also display the spatial working memory deficit, we can then utilize the delayed-response task, a cognitive measure, in an attempt to enrich and broaden the phenotype of schizophrenia as an aid to subsequent genetic studies.

A preliminary statement can be offered concerning prefrontal dysfunction in schizophrenia. The tasks employed in these studies have been previously shown to reveal impairment in animals with prefrontal damage. 24,25 A series of studies on human and nonhuman primates showed that impairments of the DLPFC result in noteworthy deficits in delayed-response performance. 16,23,24,25 Sawaguchi and Goldman-Rakic have also demonstrated that local blockade of dopamine D2 receptors in the DLPFC (by the use of the D2 antagonist SCH 23390) impaired performance on the oculomotor delayed-response task which is a finding similar to ours in almost all respects (with the exception of our inclusion of distractor tasks to prevent rehearsal). The monkeys' performance became abnormal on the oculomotor memory task but not on the sensory control task. A serotonin antagonist and a D3 antagonist (raclopride) did not produce the same performance abnormalities, suggesting that activation of D2 receptors is critical for memory processes mediated by the prefrontal cortex.

Finally, we address the possible effect of neuroleptic medication. It is possible that neuroleptics, especially those that block D2 receptors, may have affected schizophrenics' performance on working memory tasks. We believe that neuroleptic medication is unlikely to be the cause of the impaired performance of schizophrenics in this study. First, eight of the 12 bipolar patients were also taking neuroleptics, but these bipolar patients performed slightly better than the normal controls. Therefore, neuroleptics did not impair their performance. Second, most neuroleptics currently in use have little effect on the D1 system. 23 Some compounds, such as haloperidol and perphenazine, are almost exclusively D2 antagonists, 24,25 whereas others, such as fluphenazine and clozapine, also act weakly on the D1 system. In this study, half the schizophrenic and bipolar patients were taking D2-selective neuroleptics but the others were not. We examined the difference between all the patients taking D2-selective drugs (six schizophrenics and four bipolar patients) and those taking nonspecific neuroleptics (six schizophrenics and four bipolar patients). There were no significant differences between these two groups in either the oculomotor memory (P > .08) or the sensory task (P > .06). We also examined each diagnostic group separately. Schizophrenics taking D2-specific neuroleptics did not differ from schizophrenics taking nonspecific drugs in either the memory (P > .9) or the sensory (P > .7) task. Similarly, the bipolar patients taking D2 antagonists did not differ from the bipolar subjects taking nonspecific neuroleptics in either the memory (P > .6) or the sensory (P > .3) task. Therefore, even without any D2 antagonist, schizophrenics are impaired on the spatial working memory tasks.

Inasmuch as schizophrenics in our study performed in a manner strikingly similar to that of surgically and chemically lesioned monkeys, 39 and similar also to that of humans with lesions of the prefrontal cortex, we conclude that prefrontal dysfunction is involved in schizophrenic illness, possibly implicating the D2 receptor system. It is worth noting that the projections from the prefrontal cortex to many other areas—thalamus, caudate nucleus, superior colliculus, and parietal cortex, for example—caution that involvement of the prefrontal cortex implies involvement also of an entire network of cortical and subcortical structures. 44

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References


