ORIGINAL ARTICLE

Spatial Working Memory Deficits in the Relatives of Schizophrenic Patients

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Background: Studies in nonhuman primates provide evidence that intact spatial working memory depends on the integrity of specific areas in the prefrontal cortex. Patients with schizophrenia have been shown to be impaired on spatial working memory tasks. Relatives of schizophrenic patients show a range of cognitive deficits in the absence of clinical symptoms (eg, thought disorder, eye tracking dysfunctions). We predicted that a significant proportion of relatives of schizophrenic patients would show deficits in working memory as measured by a delayed response task.

Methods: In experiment 1, we tested 18 schizophrenic patients, 15 first-degree relatives of schizophrenic patients, and 18 normal control subjects on an oculomotor delayed response task. In experiment 2, we assessed the performance of another group of 12 first-degree relatives of schizophrenic patients and 16 different normal control subjects on a visual-manual delayed response task.

Results: Relatives of schizophrenic patients showed significant deficits in working memory on both the oculomotor and visual-manual delayed response tasks.

Conclusions: Some relatives of schizophrenic patients are impaired on tasks that tap spatial working memory and that implicate the prefrontal system. The delayed response paradigm may be useful in elucidating the multidimensionality of the schizophrenic phenotype.

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ONE OF the cognitive deficits of schizophrenia is a dysfunction of working memory that leads to a breakdown of behaviors guided by internal representations.[1,2] Neuroanatomical and neurophysiological observations assign an important role to the prefrontal cortex in working memory deficits.[3-6] In the rhesus monkey, lesions in the dorsolateral prefrontal cortex, in particular, the region of the principal sulcus, lead both to severe deficits in spatial working memory, as assessed by various delayed response tasks (DRTs), and to some symptoms that resemble those of schizophrenia, such as distractibility and perseveration.

In an earlier study,[2] we developed a human analogue of the oculomotor delayed response paradigm to test whether schizophrenic patients show spatial working memory deficits. We reported that schizophrenic inpatients were significantly impaired on a memory-guided DRT, whether the sensory modality was visual or haptic, but showed almost no impairment on a sensory-guided DRT. Bipolar inpatients, in contrast, showed no impairments on the memory-guided DRT. We concluded that (1) schizophrenic inpatients have a deficit in the representational guidance of behavior that is independent of the motor system itself and (2) this impairment is not restricted to the oculomotor system. The working memory deficit, as assessed by the memory-guided DRT, is consistent with evidence that implicates prefrontal dysfunction in schizophrenia. Schizophrenic outpatients in remission were also found to have deficits on the oculomotor DRT.[7]

Some of the healthy relatives of schizophrenic patients show some traits related to schizophrenia. For example, a disorder of smooth-pursuit eye movements is present in nearly half of the first-degree relatives of schizophrenic patients in the absence of clinical symptoms of schizophrenia, whereas the prevalence of this eye tracking dysfunction in the normal population is only about 8%.[8,9] Similarly, a significant elevation of thought disorder in about half of the first-degree relatives has also been reported.[10] The existence of eye tracking dysfunction and thought disorder in a substantial proportion of these relatives cannot be attributed to medication effects, to the effects of the illness itself, or to

generalized deficit. If relatives of schizophrenic patients also show working memory deficits, it would suggest that these deficits are likely to reflect a behavioral trait rather than an effect of illness or its treatment.

A related approach is to study individuals with schizotypal personality characteristics.[11] Both the study of relatives of schizophrenic patients and the study of people with schizotypic traits address the additional issue of latent liability for schizophrenia, an issue that is relevant to genetic transmission.[12,13]

This study examined whether working memory is impaired in a sample of first-degree relatives of schizophrenic patients. We predicted that, as a group, relatives would perform better than the schizophrenic patients but worse than the normal controls on the spatial DRT but that there would be no impairment on a sensory control task.

Two experiments were carried out to test these predictions. In experiment 1, subjects were tested on both the oculomotor memory and sensory DRT. For experiment 2, a replication, we recruited two new groups of subjects (relatives and controls) and tested them on a visual-manual version of the memory and sensory DRT. If first-degree relatives of schizophrenic patients have a working memory deficit, it should be possible to detect it, regardless of the response modality of the DRT.

EXPERIMENT 1: OCULOMOTOR DRT

Subjects

Fifteen first-degree relatives of schizophrenic patients and 18 outpatients with schizophrenia were recruited from a private psychiatric hospital. The sample of relatives included nine family members of five of the schizophrenic outpatients in this study. Six other relatives were also first-degree relatives of schizophrenic patients (one relative per patient), but these six relatives were not related to the probands in the present study. Results from the schizophrenic outpatients have already been reported[7] and are repeated here only for comparison purposes. Eighteen normal control subjects with no history of schizophrenia, bipolar disorder depression, anxiety disorders, or drug abuse or dependence were also recruited and screened for absence of mental illness (Axis I disorders) in themselves and in their first- and second-degree relatives. All subjects were reimbursed for their participation. The patients met criteria for a *DSM-III-R* diagnosis of schizophrenia, based on a standardized interview (Structured Clinical Interview for *DSM-III-R*[14]) and a review of hospital medical records. None of the relatives of schizophrenic patients had a *DSM-III-R* Axis I diagnosis, as determined from a clinical interview. They were not screened for Axis II conditions. All of the relatives were working full-time. All schizophrenic patients were taking neuroleptic medication. Subjects had no evidence of organic brain damage and were not mentally retarded. The mean (SD) age of the relatives was 35.7 (8.6) years, their mean education was 15.6 (1.9) years, and their mean Wechsler Adult Intelligence Scale (WAIS)–verbal IQ score was 108.0 (1.6). The mean age of the outpatients with schizophrenia was 34.6 (8.7) years, their mean education was 14.2 (2.1) years, and their mean WAIS–verbal IQ score was 105.0 (12.5). The mean age of the normal control subjects was 29.4 (8.6) years, their mean education was 14.7 (2.8) years, and their mean WAIS–verbal IQ score was 112.0 (10.9). There were no statistically significant differences between the three groups in age, WAIS–verbal IQ score, or education level, nor was there any effect of these variables on the principal dependent variables of the DRTs.

Oculomotor DRT

Apparatus. An infrared eye monitoring system (Iscan Inc, Cambridge, Mass), which tracks the difference between the pupil and corneal reflections, was used. An infrared light source was placed in front of the stimulus 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 an Iscan RK-426 pupil/corneal reflection tracking system, which recorded the positions of the center of the pupil and a bright corneal reflection moving over the pupil. The spatial difference between the pupil and the corneal reflection gives the direction and magnitude of the eye movement. This method yields a linear representation of the subject's eye position within ±15° of visual angle. Within the linear range, the accuracy is better than 1°.

The pupil/corneal tracking system was connected to a Macintosh II computer, 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, which calculated the subject's point of regard with respect to the stimulus.

Calibration was performed by asking subjects to fixate on five successive experimenter-defined positions on the stimulus display screen: center, upper left, lower left, upper right, and lower right. We used the autocalibration system, which coordinates the eye position information and calibration position information, to compute the point of regard for subsequent eye movements.

After the calibration, practice trials were performed to ensure that all subjects understood the procedure. Eye movements were monitored on the television screen to ensure that the subject was fixating at the center when each trial began. Further details can be found in previous articles.[2,15]

Procedure. Subjects sat with their heads stabilized by a chin and head rest in front of a stimulus display monitor. A red fixation dot subtending approximately 0.5° of visual angle appeared in the center of the stimulus display screen. The target was a small black circle subtending about 2° of visual angle. The location of the target varied randomly from trial to trial. The distance between the fixation point and any target location was 12° of visual angle.

Subjects were asked to look at the fixation point in the center of the screen. When they were ready to be-

gin, the experimenter clicked a mouse to initiate a trial. In the oculomotor memory DRT, a target (black circle) appeared on the screen for 200 milliseconds in one of the eight possible locations, long enough for it to be seen and identified but too short for an eye movement to be made to it. There were eight possible target locations, equidistant from one another, on the circumference of an imaginary circle. After the presentation of each target, and with the subject continuing to look at the center of the screen, a 10-second delay period followed during which the subject performed a concurrent "category shift" task that forced the subject to shift semantic categories. For example, for the category "animals," animal names (eg, "tiger," "dog") were flashed consecutively, one each second, and occasionally a noncategory word (eg, "car") was flashed, requiring the subject to signal recognition of the noncategory word. A fuller description of the concurrent task is found in Park and Holzman[2] and in Park.[15] This procedure prevented rehearsal and thus circumvented the use of working memory without verbal or other mnemonic mediators and also forced the subjects to fixate in the center of the screen during the delay period. This task does not affect spatial working memory performance.[2,15] 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; this was a memory-guided eye movement, not a reflexive saccade. If subjects looked at the correct target position, the screen cleared and the red fixation dot replaced the reference circles. The next trial could then begin. If the subject did not look at the correct position, the reference circles remained on the screen until the subject looked at the correct position. The eye positions during this period were recorded every 20 milliseconds. If the subject did not look at the correct location within 10 seconds, the reference circles disappeared and the red fixation point reappeared, indicating that a new trial could begin. Subjects rested after every 16 trials. Eye position was recalibrated after each rest period.

All subjects were also tested on an oculomotor sensory control task. This task was identical to the oculomotor memory task except for one aspect: the target remained on the screen at all times. Subjects were required to move their eyes to the target itself after the delay period. This task required no memory since the target was always present. **Figure 1** shows the schematic plan of the experiment.

The order of presentation of the oculomotor memory and the oculomotor sensory conditions was counterbalanced across subjects. Each task consisted of 64 trials, eight for each target location. All subjects gave written informed consent. There were 16 practice trials before the main testing began.

Measures. Accuracy (percent correct) and response times (in milliseconds) of correct trials were recorded. A response was scored as correct only if an eye movement brought the eye directly to within 1.5° of the center of the correct target position. If the eye moved to a wrong position first and then later moved to the correct target position, the trial was counted as incorrect. Response times were measured from the end of the delay period to the initiation of the first eye movement to a target location. All subsequent eye movements to targets were also recorded with their response times.

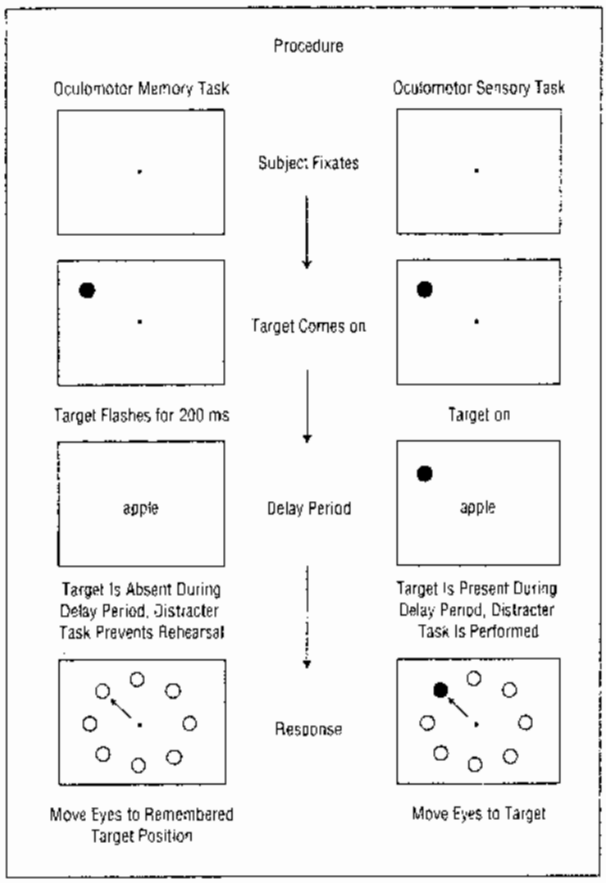

Figure 1. *Oculomotor delayed response memory and sensory tasks.*

Results

Table 1 presents the mean accuracy and response times of the three subject groups for the two DRTs.

Accuracy. In the oculomotor memory task, schizophrenic patients had the lowest percentage of correct scores (mean, 71.4%; SD, 16.0%), normal controls the highest percentage (mean, 95.2%; SD, 4.8%), and relatives fell in between (mean, 86.8%; SD, 7.1%). There were no group differences on the oculomotor sensory task, all groups having scored above 96% correct.

The statistical significance of differences in performance of the groups was compared in a three-way repeated-measures analysis of variance. All subjects, regardless of group, were significantly more accurate on the sensory task than on the memory task, as shown by a main effect of the type of task ($F[1,48]=91.5$; $P<.001$; effect size, 0.81) and a main effect of subject groups ($F[2,48]=16.3$; $P<.001$; effect size, 0.64). The groups differed significantly in accuracy on the memory task ($F[2,48]=21.9$; $P<.001$; effect size, 0.69) but not on the sensory control task ($F[2,48]=0.48$; $P>.60$; effect size, 0.14) (group-by-task interaction: $F[2,48]=22.6$; $P<.001$; effect size, 0.71).

Relatives of schizophrenic patients were less accurate than normal controls on the oculomotor memory task

Table 1. Mean Accuracy and Response Times of Subjects on the Oculomotor Delayed Response Tasks in Experiment 1

	% Correct (SD)		Response Time, ms (SD)	
	Memory Task	Sensory Task	Memory Task	Sensory Task
Schizophrenics	71.4 (16.0)	96.9 (6.4)	1210 (695)	1006 (220)
Relatives	86.8 (7.1)	98.2 (3.6)	767 (239)	781 (269)
Normal controls	95.2 (4.8)	98.2 (2.8)	683 (234)	625 (213)

($F[1,31]=16.5$; $P<.001$; effect size, 0.59), but they did better than the schizophrenic patients ($F[1,31]=11.1$; $P<.003$; effect size, 0.51). When one tests the significance of these differences with nonparametric statistics (Wilcoxon and Kruskal-Wallis tests), the results are identical to those obtained with the parametric analyses of variance.

The distribution of correct scores is shown by individuals in the three subject groups in **Figure 2**.

The 15 relatives were not from 15 different families. Six subjects in the relatives group were siblings of six schizophrenic patients who were not available for this study. The remaining nine relatives came from five families:

From one family, there were a father, mother, and sister of a schizophrenic patient; the patient had a very poor working memory (40.6% correct). The mother's working memory accuracy score was 96.6%, and both the father and the healthy sibling had 84.4% accuracy, which is below the lowest score of the normal group.

From a second family there were two brothers of a schizophrenic patient. The patient and one brother had a very poor working memory (75% and 81.3% accuracy, respectively). The second brother had very few errors on the oculomotor DRT (93.8%).

From a third family there were two relatives, both sisters of a schizophrenic patient. All three members of this family had high numbers of errors on the DRT (84.4% correct for the patient and one sister, 71.9% for the other sister).

There were two families from which one sibling each was tested. In one of these families, the patient had a very poor oculomotor DRT performance (62% correct), but her healthy sister had few errors on the DRT (93.8%). In the second of these two families, the patient had many errors on the DRT (75% correct). His unaffected brother had few errors on the DRT (90.6% correct).

If one selects one random sibling of each schizophrenic patient, the results do not change for these 11 relatives. It therefore appears that the distribution of impaired DRT performance is not unduly weighted by one or two families.

Types of Errors. We grouped the response errors into two kinds, those that are immediately corrected and those that are never corrected during the maximum period allotted for responses (10 seconds). Errors that are immediately corrected are likely to arise from temporary distractions or failures to inhibit irrelevant response tendencies; we labeled these errors E_1. Errors that are never corrected even though subjects make repeated efforts to recall the position of the target are more likely to be caused by a loss of spatial representation of the target during the delay period; we labeled these errors E_n. Park[16] and Park and O'Driscoll[17] reported that these two major types of errors have different distributions in schizophrenic patients, bipolar patients, schizotypic subjects, and normal controls.

The mean (SD) number of E_1 errors for schizophrenic patients in this study was 9.4 (5.8) and the median was 8, while for the normal subjects the mean was 1.8 (1.9) and the median was 1.5, and for the relatives the mean was 2.4 (0.7) and the median was 2.0. The schizophrenic patients made significantly more E_1 errors than did the normal subjects and the relatives ($F[2,48]=21.1$, $P<.001$), but normal subjects and relatives did not differ significantly in the number of E_1 errors. Nonparametric statistical tests (Kruskal-Wallis test) gave identical results. This finding suggests that schizophrenic patients are more susceptible to temporary distractions and to interference by irrelevant response tendencies than are relatives or normal control subjects.

The distribution of E_n errors, however, was quite different. Whereas normal subjects only occasionally made such errors (mean E_n, 1.0; SD, 1.9; median, 1.5), the mean number of E_n errors for the schizophrenic patients was 4.67 (SD, 4.50; median, 2.5), and for the relatives group it was 3.3 (SD, 2.85; median, 4). These differences are statistically significant ($F[2,48]=6.6$, $P<.003$), indicating that the patients and the relatives made significantly more E_n errors than did the normal group. Nonparametric tests of these distributions (Kruskal-Wallis test) gave identical results. The proportion of subjects in each group making more than two E_n errors is instructive: three (17%) of 18 normal subjects (17%) compared with nine (50%) of 18 schizophrenic patients and eight (53%) of 15 relatives. The schizophrenic patients and the relatives did not differ on the number of E_n errors, indicating that they are both prone to loss of memory representation during the delay period.

Response Times. Table 1 shows that the groups differed in response times. The schizophrenic patients were the slowest and the relatives were intermediate between the patients and the normal control subjects. The significance of these differences was tested by a repeated-measures analysis of variance and by a nonparametric test (Kruskal-Wallis test).

The normal subjects were fastest, relatives next, and schizophrenic patients slowest on both the sensory and memory components of the procedure, as reflected in the significant main effect of subject groups ($F[2,48]=11.6$, $P<.001$), but there was no main effect of task type ($F[1,48]=1.9$, $P>.17$), and there was no significant interaction between subject groups and task type ($F[2,48]=1.1$, $P>.34$). Further analyses of simple effects showed that schizophrenic patients were slower than both the normal controls ($F[1,31]=8.6$, $P<.007$) and the relatives ($F[1,31]=6.0$, $P<.03$) on the oculomotor memory task. On the sensory task as well, schizophrenic patients were slower than both the normal controls ($F[1,31]=22.9$, $P<.001$) and the relatives ($F[1,31]=5.7$, $P<.03$). The relatives and the normal controls did not differ significantly in response times. The nonparametric tests gave identical results, except for the difference between normal controls and relatives on the sensory task,

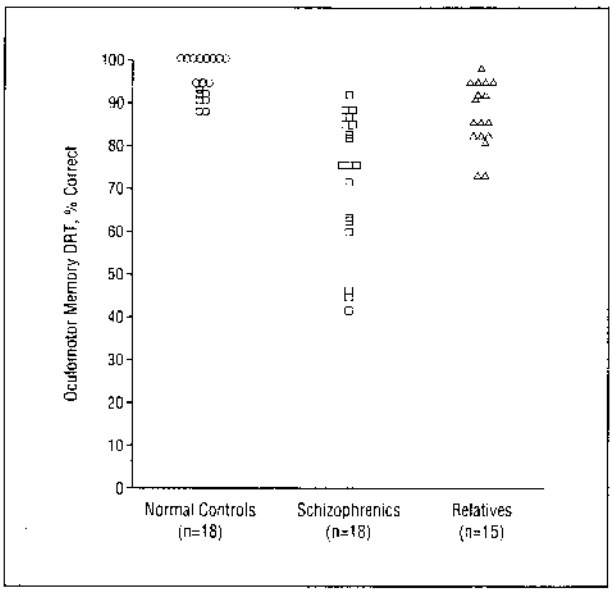

Figure 2. *Scatterplot of accuracy scores of normal controls, schizophrenic patients, and relatives of schizophrenic patients performing the oculomotor memory delayed response task (DRT) in experiment 1.*

where the relatives showed a nonsignificant but borderline tendency to be slower in response time.

Comment

Our data indicate that some first-degree relatives of schizophrenic patients show spatial working memory deficits, as assessed by an oculomotor DRT. We previously reported that schizophrenic inpatients and outpatients show working memory deficits,[2,7] but in those studies it was not possible to rule out the possible effects of medication even though clinical state was shown not to be a decisive factor. In the present experiment, we observed the delayed response deficits in nonpsychotic relatives of schizophrenic patients. It therefore appears that such abnormalities can occur in the absence of any neuroleptic exposure and in the absence of psychotic symptoms. Schizophrenic patients made many E_i errors, but the normal controls and relatives seldom made this type of error. This type of error may reflect temporary inefficiency, perhaps secondary to state factors. In contrast, both the schizophrenic patients and their relatives made significantly more E_n errors, indicating that both the schizophrenic patients and the relatives are susceptible to loss of spatial representation during the delay period. Because the sample size was small, we conducted a second delayed response experiment using a different sensory modality in new groups of relatives and controls.

EXPERIMENT 2: VISUAL-MANUAL DRT

Results from experiment 1 showed that the first-degree relatives of schizophrenic patients, like schizophrenic patients themselves, are impaired on the oculomotor DRT. In experiment 2, subjects were required to respond with their hands rather than with their eyes. In this version of the DRT, targets were presented visually and the responses were made by hand movements, a procedure that requires a crossmodal transfer of spatial representation. For this experiment we recruited another group of first-degree relatives of schizophrenic patients and another normal control group.

Subjects

We recruited 12 first-degree relatives of schizophrenic patients (seven women), with only one relative per family. None of these subjects had participated in experiment 1. Sixteen normal control subjects (seven women) were recruited from Zürich, Switzerland. The control subjects, none of whom participated in experiment 1, were nurses, clerical workers, or students. They were selected if there was no Axis I *DSM-III-R* psychiatric disorder in any first- or second-degree relative, as determined by a brief psychiatric interview. They had no evidence of organic brain damage and were not mentally retarded. The mean age of the normal control subjects was 36.7 (11.3) years, and their mean education was 14.0 (3.3) years. The mean age of the relatives was 43.4 (14.1) years, and their mean education was 15.4 (3.0) years. There was no significant difference between the two groups in age ($F[1,26]=1.86$, $P>.18$) or education level ($F[1,26]=1.19$, $P>.28$).

Visual-Manual DRT

Procedure and Apparatus. All procedures were identical to those described in experiment 1, except for the modality of response; subjects responded by touching a position on a computer screen rather than by an eye movement.

Subjects sat with their heads steady on a chin and head rest in front of a stimulus display monitor. The stimulus display monitor was fitted with a touch screen (AccuTouch, Ellinor Technology, Berkshire, England). The touch screen consisted of a glass plate covered with a tight-fitting plastic cover sheet. Conductive coatings were applied to the glass plate and the plastic sheet so that light finger pressure caused internal electrical contact at the point of touch. This voltage was then digitized. Position accuracy was better than ±4.6 mm (13 pixels), as measured on a multipoint sampling basis. Calibration procedure involved touching four reference points on the touch screen. Calibration was performed before each subject began the experiment.

Subjects stared fixedly at the center of the screen, and when they were ready to begin, the experimenter clicked a mouse to initiate a trial. In the visual-manual memory task, a target appeared on the screen for 200 milliseconds. Immediately after the target presentation, there was a 10-second delay period, during which the subject performed the category shift task (the distracter task). After the delay period, the fixation point and eight "reference" circles (empty rather than black) appeared on the screen. Subjects were required to touch the screen at the remembered position of the target. If they touched the correct target position, the screen cleared and the next trial could begin. If the subject did not touch the correct position, the reference circles remained on the screen until the subject chose the correct position, or until 10 seconds had elapsed, whichever was sooner.

To control for the sensorimotor component of the visual-manual memory task, a sensory control task was conducted. The sensory control task was identical to the memory task except for one aspect: the target remained on the screen at all times. Subjects were required to touch the target itself after the delay period. This task required no memory since the target was always present.

The order of presentation of the memory and sensory conditions was counterbalanced across subjects. There were 64 trials on the memory task and 64 on the sensory task, eight at each location in both tasks. All subjects gave written informed consent. There were 16 practice trials before the main body of testing began, to ensure that the subjects understood the task.

Measures. Accuracy (percent correct) and response times (in milliseconds) of correct trials were recorded. A response was scored as correct only if the subject touched within 1.5° of the center of the target position and if the finger moved there directly. If the finger moved to a wrong position first and then later moved to the correct target position, this response was counted as incorrect.

Results

Accuracy. **Table 2** presents the mean accuracy scores of the two subject groups. Relatives of schizophrenic patients were less accurate than the normal controls on the visual-manual memory DRT (86.5% vs 95.4%) but not the sensory DRT (98.2% vs 99.4%). The differences between the two groups were tested by a repeated-measures analysis of variance. There was a main effect of subject group ($F[1,26]=10.04$; $P<.004$; effect size, 0.53), a main effect of the task type ($F[1,26]=48.3$; $P<.001$; effect size, 0.80), and a subject-by-task interaction ($F[1,26]=12.8$; $P<.002$; effect size, 0.57), indicating that the relatives of schizophrenic patients were significantly less accurate than the normal controls in making the memory-guided hand movements ($F[1,26]=12.86$; $P<.002$; effect size, 0.70), but the two groups did not differ on the sensory-control task ($F[1,26]=1.23$, $P>.27$). The nonparametric tests (Kruskal-Wallis test) gave identical results. **Figure 3** shows the distribution of accuracy scores on the memory-guided DRT for the two subject groups.

Types of Errors. We examined the distributions of the two types of errors, E_1 and E_n errors. The relatives made more E_1 errors than did the normal controls. The mean (SD) number of E_1 errors for the normal control subjects was 1.94 (1.44); for the relatives the mean number of E_1 errors was 6.24 (4.44). This difference is statistically significant ($F[1,26]=14.9$, $P<.001$); a nonparametric test gives a similar significance value. In experiment 2, then, the relatives made more E_1 errors than did the relatives in experiment 1.

The mean number of E_n errors for the normal group was 0.44 (0.73); the mean number of E_n errors for the relatives of schizophrenic patients was 1.42 (1.38). This group difference was statistically significant whether tested by a parametric analysis of variance ($F[1,26]=5.92$, $P=.02$) or a nonparametric Kruskal-Wallis test. Five (31%) of 16 normal controls compared with 15 (94%) of 16 relatives of schizophrenic patients made more than two E_1 errors. No normal control made more than two E_n errors, compared with four (25%) of 16 relatives of schizophrenic patients.

These results are consistent with those obtained in experiment 1. Some relatives of schizophrenic patients perform poorly on tasks that require spatial working memory regardless of the modality of the response.

Table 2. Mean Accuracy and Response Times of Subjects on the Visual-Manual Delayed Response Task in Experiment 2

	% Correct (SD)		Response Time, ms (SD)	
	Memory Task	Sensory Task	Memory Task	Sensory Task
Relatives	86.5 (9.1)	98.2 (4.2)	1317 (247)	1311 (251)
Normal controls	95.4 (3.4)	99.4 (1.3)	1120 (156)	1076 (66)

Response Times. Table 2 shows that the relatives were slower than the normal controls on both the memory and sensory tasks. A repeated-measures analysis of variance reveals that there was a main effect of subject group on the response times ($F[1,26]=13.3$, $P<.001$) but no main effect of the task ($F[1,26]=0.52$, $P>.47$) and no interaction between subject group and the task ($F[1,26]=0.25$, $P>.62$). One-way analysis of variance revealed that the two subject groups differed on the memory task ($F[1,26]=6.67$, $P<.02$) and on the sensory task ($F[1,26]=13.05$, $P<.002$). The relatives were significantly slower than the normal controls on both tasks (1317 and 1311 milliseconds vs 1120 and 1076 milliseconds on the memory and sensory tasks, respectively). This result differs from that found in experiment 1, in which there was no global oculomotor response time difference between the normal controls and the relatives, although there was a trend in the same direction.

Oculomotor and Visual-Manual Spatial Working Memory Performance in the Relatives. We compared the accuracy of the relatives from experiment 1 and experiment 2. There were no differences between the two groups of relatives on the working memory task ($F[1,26]=0.12$, $P>.73$) on the sensory control task ($F[1,26]=0.01$, $P>.91$). As far as accuracy of delayed response is concerned, it does not seem to matter whether the actual test is conducted with the oculomotor paradigm or with the visual-manual paradigm. Similarly, dorsolateral prefrontal lesions in experimental primates induce working memory deficits whether the tasks used to measure these difficulties require oculomotor[5] or manual[18] responses.

We did not directly compare the response times because of the different inherent speed requirements for making an eye movement and a hand movement. Instead, we computed a relative change in the response times

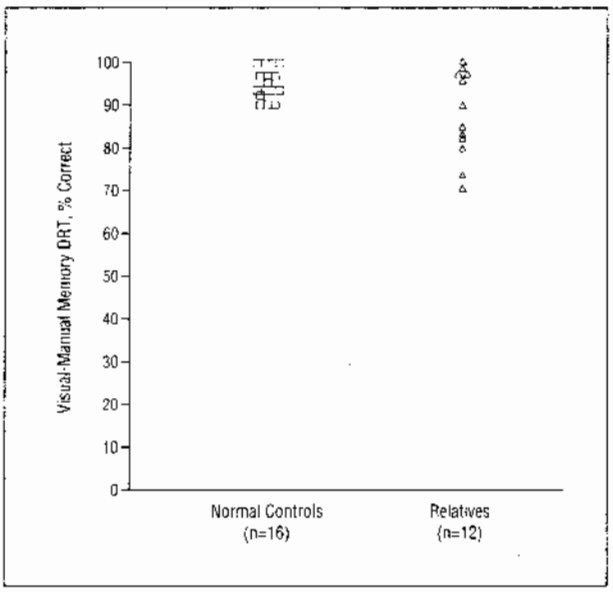

Figure 3. *Scatterplot of accuracy scores of normal controls and relatives of schizophrenic patients performing the visual-manual memory delayed response task (DRT) in experiment 2.*

in the memory-guided task compared with the sensory control task for each subject, as follows:

$$\%\ \text{Increase in RT} = [(RT_{\text{Memory Task}} - RT_{\text{Sensory Task}}) / (RT_{\text{Sensory Task}})] \times 100,$$

where RT indicates response time.

On the oculomotor task, relatives had a 6.40% increase in response time, and on the visual-manual task, they had a 2.04% increase in response time. The magnitude of the change in response time was not statistically significant ($F[1,26]=0.21$, $P>.65$).

COMMENT

In this study we examined spatial working memory in first-degree relatives of schizophrenic patients. On the oculomotor working memory task, we observed that a significant number of these relatives had impaired performance. Similarly, on the visual-manual working memory task, the relatives were less accurate than the normal controls.

We classified the types of errors into E_1 and E_n errors. We believe that different psychological processes underlie these two types of errors. In the case of E_1 errors, temporary distractions may be the main source of error. In the case of E_n errors, however, the spatial memory representation is not recoverable, which denotes a failure to maintain the spatial representation in working memory.

In experiment 1, we found that schizophrenic patients made significantly more E_1 errors than did normal subjects or the first-degree relatives. Such evidence of temporary inefficiency is not unexpected in this group. What is noteworthy and thus far not reported, however, is the appearance of large numbers of E_n errors not only among the patients but also among a large proportion of their relatives. This result, found in both experiment 1 and experiment 2, suggests that in some of these otherwise clinically normal relatives, there is a detectable dysfunction in efforts to hold a spatial representation "on line." The patients, as noted above, showed a significant tendency toward temporary inefficiency in experiment 1. This same tendency in the relatives was noted in experiment 2 but not in experiment 1. The normal controls, however, showed no increase in these E_1 errors in experiment 2. It is quite possible that the recruitment of a second response system (hand movement to the target), which introduced a second modality into the response process, complicated the performance for the relatives compared with the simple eye movement response in experiment 1. This hypothesis will be tested in further studies.

One may properly wonder whether the relatives who showed the working memory dysfunction have schizophrenia spectrum disorders. Although systematic examination of the relatives for Axis II disorders, particularly schizotypal personality disorder, was not undertaken, we offer a tentative answer, pending such examination, which is now under way in our laboratory. It is possible that some of the relatives have schizotypal characteristics. For at least two reasons, however, it would be implausible to assume that impaired working memory is a function of schizotypy in this population of relatives. First, the prevalence of schizotypal personality disorder in the first-degree family members of a schizophrenic patient ranges from about 7% to 14%.[19] From these estimates, we would expect at the most two relatives in each of the experiments to have schizotypal personality disorder. In the present experiments, however, six (40%) of 15 relatives in experiment 1 and six (50%) of 12 relatives in experiment 2 had significant working memory impairments (Figures 2 and 3), with "impairment" defined as scores greater than 2 SDs from those of their specific normal population comparison group. It is noteworthy, moreover, that this study examined the working memory of an unselected sample of relatives, who were essentially volunteers. Schizotypal traits, such as interpersonal aversiveness, suspiciousness, social anxiety, guardedness, and lack of motivation, are among those personal qualities that would make it less likely for such people to volunteer for a study such as the present one. The present cohort of relatives thus probably contains even fewer cases than indicated by the cited prevalence of schizotypal personality disorders, although some schizotypal traits may exist in a subgroup of relatives. Since about 40% to 50% of the relatives in experiments 1 and 2 had working memory dysfunction, far greater than the reported prevalence of schizotypal personality disorder in the biological relatives of patients with schizophrenia,[19] we would here opt for a conservative interpretation, maintaining that the majority of the relatives with working memory dysfunction in the present study do not have schizophrenia spectrum disorders.

Second, in a previous study, otherwise normal college students who scored high on an inventory tapping experiences of perceptual aberrations, one of the manifestations of schizotypy,[20,21] made significantly more working memory errors as a group than did those who were selected for having very few or no schizotypal signs. However, only about 25% of these schizotypal students had working memory impairment, and several students with no schizotypal signs also had working memory impairment.

The working memory system may be said to operate like a "mystic writing pad,"[22] providing temporary and limited access to long-term or associative memory; it needs to be wiped clean or updated to be ready to accept new stimuli for temporary storage to guide action. In Baddeley's model,[23,24] the working memory system is supported by modality-specific "slave" or auxiliary systems that allow for focused rehearsals of information in the buffer, such as repeating the telephone number just found in the telephone book or visualizing a spatial array. By employing a distracter task, our experimental paradigm removed the possibility of rehearsals and therefore of the use of these auxiliary aids to working memory and allowed us to detect significant impairments. It is quite possible that the relatives with impaired accuracy on the DRT, who otherwise seem to function adequately, rely on these "subslave" auxiliary systems to mask spatial working memory impairments.

It is noteworthy that a subset of the first-degree relatives of schizophrenic patients show deficits in working memory. These relatives are clinically unaffected and do not manifest any *DSM-III-R* Axis I conditions. Some may, however, have or have had Axis II conditions, and a further study of this possibility is under way. This pool of subjects has generally been neglected for psychobiological investigation. Psychopathologists, and particularly geneticists, have typically focused their attention on the sickest patients and on families with the highest concentrations of morbidity. We have argued that a thorough study of relatives, including those who appear to be well, can offer a richer yield in the search for insights into the disease process, one that penetrates beyond the obvious phenotypic symptoms.[25] In this search, psychology, the neurosciences, and related disciplines have much to contribute in exploring the hidden nature of the phenotype. One of these has been the study of eye tracking dysfunctions in schizophrenia.[6] The present study strongly suggests that spatial working memory dysfunction as measured by the DRT is another behavioral marker that can take its place alongside smooth-pursuit abnormalities as an aid not only in illuminating the pathophysiologic characteristics of schizophrenia but also in characterizing the multidimensional qualities of the schizophrenic phenotype to trace the transmission of schizophrenia-related genes.

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