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Association of working memory deficit and eye tracking dysfunction in schizophrenia

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(continued on page 3 of cover)

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This study replicates our earlier findings that schizophrenic but not bipolar patients are impaired on oculomotor delayed response tasks, analogous to those used to assess spatial working memory functions of the dorsolateral prefrontal cortex (DLPFC) in monkeys (Park and Holzman, 1992). In addition, we examined the relation between working memory deficits and smooth pursuit eye movement (SPEM) dysfunction, since data from human neuropsychological and animal lesion studies implicate prefrontal pathology in both deficits. Schizophrenic patients showed marked deficits in the oculomotor memory task and the SPEM task relative to the control groups. However, they were not impaired on the oculomotor sensory task in which their responses were guided by external cues rather than by working memory. This result from outpatients replicates our earlier study which was conducted with inpatients. Within the schizophrenic group those patients with good eye tracking performed better than those with impaired pursuit on the oculomotor memory task but there was no correlation between SPEM and performance on the sensory task. These findings support the hypothesis that schizophrenics show a deficit in representational processes and add to the growing evidence for involvement of the dorsolateral prefrontal cortex in schizophrenic pathology.

Key words: Prefrontal cortex; Working memory; Smooth pursuit eye movement; Oculomotor delayed response; (Schizophrenia)

INTRODUCTION

The role of prefrontal cortex in schizophrenic pathology has received support from clinical and neuropsychological observations of the similarity between patients with prefrontal lesions and with schizophrenia, on a variety of tasks (e.g. Kolb and Whishaw, 1983; Fukushima et al., 1988). In recent years, it has become possible to obtain more direct evidence for prefrontal pathology in schizophrenia from brain imaging studies that demonstrate abnormalities of cerebral blood flow in the prefrontal area at rest (Ingvar and Franzen, 1974; Ingvar, 1980) and during the Wisconsin Card Sorting Test (Weinberger et al., 1986).

Further, based on neuroanatomical and neurophysiological observations, Goldman-Rakic (1987, 1991) suggested that at least one fundamental deficit of schizophrenia is a dysfunction of working memory that leads to a breakdown of behaviors guided by internal representations. Working memory is mediated by the dorsolateral prefrontal cortex (DLPFC). Lesions in the DLPFC, in particular, the principal sulcus region of the rhesus monkey, result both in profound deficits in working memory, as assessed by an oculomotor delayed-response task, and in many behaviors that resemble some symptoms of schizophrenia, such as distractibility and perseveration.

Goldman-Rakic's hypothesis was tested by

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developing a human analog of the oculomotor delayed-response paradigm (Park and Holzman, 1992). That study showed hospitalized schizophrenic patients to be significantly impaired in memory-guided but not sensory-guided delayed-response tasks, whether the sense modality was visual or haptic; in contrast, bipolar patients showed no impairments on the same delayed-response tasks. Schizophrenic patients thus showed a deficit in the representational guidance of behavior that is independent of the motor system itself, a deficit that is not restricted to the oculomotor system. The working memory deficit, as assessed by the oculomotor delayed-response task, provided evidence for the existence of prefrontal pathology in schizophrenic patients.

In our previous paper (Park and Holzman, 1992), we suggested the possibility that the prefrontal dysfunction may also be implicated in the smooth pursuit eye movement (SPEM) dysfunction that is present in 50–80% of schizophrenic patients and about 40% of their first degree relatives (Holzman, 1985; Levin, 1984). The hypothesis, implicating prefrontal mechanisms in SPEM dysfunction of schizophrenic patients, was formulated by Levin (1984) who argued that the prefrontal cortex is crucial for inhibiting the saccadic system while the smooth pursuit system is activated, and that the SPEM dysfunction may be understood as an example of weakened frontal control over lower motor systems. Eye tracking deficits correlate with neuropsychological tests of frontal lobe functions but not with non-frontal tasks (Katsanis and Iacono, 1991; Park and Holzman, 1991). Lesions in the dorsolateral prefrontal cortex of the monkey lead to SPEM dysfunction (Lynch, 1987) as well as to working memory deficits (Funahashi, Bruce and Goldman-Rakic 1989, 1990).

In order to test the possibility that the SPEM dysfunction may reflect a prefrontal deficit, a SPEM task was conducted in order to compare the SPEM performance with that of the oculomotor delayed-response tasks. We recruited high-functioning outpatients for the current study in order to see if the working memory deficits are also present in a population of outpatients. We predicted that the performance on the SPEM task will correlate highly with that on the oculomotor memory task but not on the sensory task.

METHODS

Subjects

Eighteen schizophrenic outpatients and 8 bipolar outpatients were recruited from subjects entered into the McLean Hospital Collaborative Schizophrenia Research Project. None of these subjects had participated in our previous in-patient study. These subjects met criteria for a DSM-IIIR diagnosis of schizophrenia or bipolar disorder, as determined from the Standardized Clinical Interview for DSM-IIIR, SCID (Spitzer and Williams, 1985), administered by an experienced interviewer. The schizophrenic and bipolar patients had no evidence of organic brain damage, were under 50 years of age, and were not mentally retarded. 40 normal control subjects (all volunteers) who had no history of mental illness in themselves or in the family, were recruited from the Boston area. There were no statistical differences between the three groups in age, IQ (estimated from the WAIS vocabulary score) and education level, although there were trends towards differences in age and IQ. The two psychiatric groups did not differ significantly in the duration and age at the onset of illness. Table 1 summarizes the demographic information, and Table 2 summarizes the medication information.

Oculomotor delayed response tasks

Procedures

We developed a human analog of the oculomotor delayed response task, utilized by neurophysiological laboratories (see Funahashi et al., 1989, 1990)

TABLE 1

Demographic information of the 3 subject groups

	Schizophrenics *n = 18* *mean (σ)*	*Bipolars* *n = 8* *mean (σ)*	*Normals* *n = 40* *mean (σ)*
Age	34.7 (8.7)	30.8 (11.3)	28.5 (9.7)
IQ—WAIS	104.8 (12.5)	101.7 (15.0)	112.4 (11.3)
Years of education	14.2 (2.1)	13.4 (1.4)	14.9 (2.7)
Illness duration	13.1 (6.1)	9.3 (5.9)	not applicable

in order to assess the working memory function of schizophrenic, bipolar and normal subjects.

Subjects were seated with their heads stabilized by a chin and head rest in front of a stimulus display screen. The fixation point in the center of the screen was a small red dot (0.5 degrees of visual angle). The target was a small black circle (2 degrees of visual angle). The location of the target varied from trial to trial. There were 8 possible target locations, each separated by 45 degrees, on the circumference of an imaginary circle. The distance between the fixation point and any target location was 12 degrees of visual angle. Target locations were presented in a random order.

Subjects were asked to look at the fixation point in the center of the screen. When a subject was ready to begin the experiment, the experimenter clicked a mouse, which initiated a trial. In the *oculomotor memory task*, a target (black circle) then flashed on the screen for 200 ms at one of the eight positions. During this brief period the subject continued to fixate at the center. Immediately after the target disappeared, there was a 10-s delay period, during which the subject performed a distractor task. The distractor task involved reading words that appeared at the center of the screen one after the other and deciding whether the words belonged to the same semantic category or not. This procedure prevented rehearsal and also required the subject to fixate at the center of the screen during the 10-second delay period.

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 prior to its disappearance. If their eyes looked at the correct target position, the screen cleared and the red fixation point 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 were recorded every 20 ms. If the subject did not look at the correct location within a 10-s time limit, 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. This oculomotor memory task assessed the working memory function. The task is a shortened version of that used in Park and Holzman (1992), in that the delay of 10 s was used instead of two delays of 5 s and 30 s, and only one distractor task was used.

A control for the sensorimotor component of the oculomotor delayed response task was an *oculomotor sensory control task*. This oculomotor sensory 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 for 10 seconds and then immediately after the appearance of the reference circles, one of which was the black target, they were required to move their eyes to the black target. This task required no memory since the target never disappeared from screen. Fig. 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. There were 64 trials on the oculomotor memory task and 64 trials on the oculomotor sensory task. All subjects gave full informed consent, and sufficient time was

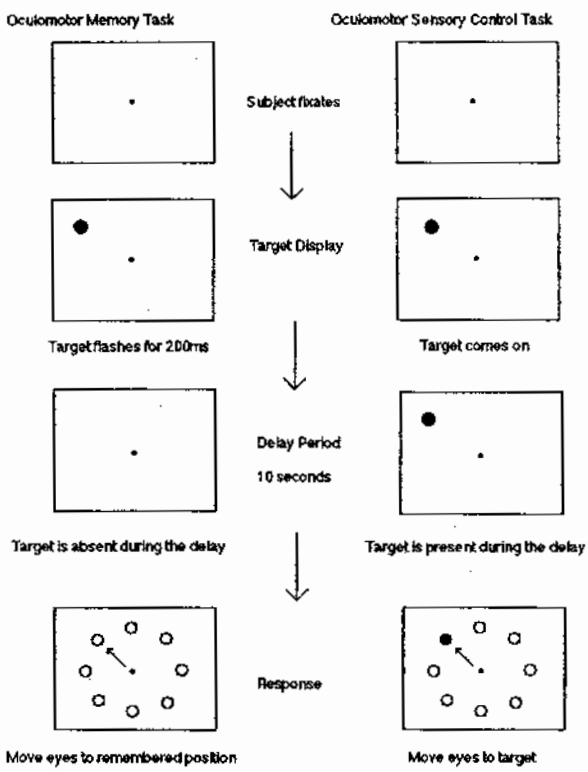

Fig. 1. Schematic diagram of oculomotor delayed response tasks.

taken to be certain that each subject understood the task.

Apparatus

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 that records the center of the pupil and a bright corneal reflection moving over the pupil. The spatial difference between the pupil and the corneal reflection remains constant if head movement is small (about 1 cubic inch) but it changes with eye movement. This method yields a linear representation of the subject's eye position within $\pm 15°$ of visual angle. Within the linear range, the accuracy is better than 1 degree.

The pupil/corneal tracking system was connected to a Macintosh II computer, which recorded and stored the eye position information (x, y coordinates), and a TV 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 experimenter-defined positions on the stimulus display screen, successively: center, upper left, lower left, upper right and lower right. We used 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, the 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.

Scoring

Accuracy (% correct) and response times of correct trials (in ms) were the principle dependent variables. A response was scored as correct only if the eye moved within 1.5 degrees of the center of the target position and the eye moved there directly. If the eye moved to a wrong position first and then later moved to the target position, this trial was counted as incorrect.

Smooth pursuit eye movement task

Apparatus

Smooth pursuit eye movements were monitored by infrared light sensors mounted on spectacle frames. Two photodiodes, one for each eye, emitted infrared light, and two infrared sensors measured the amount of reflected light from the eye. The photodiodes and the sensors were mounted on the spectacles such that they were centered on the lower half of each eye. The amount of infrared reflection depends on the eye position. The photodiodes and the sensors were connected to a computer which recorded the changes in the eye position. The target was displayed on an Apple II monochrome monitor, placed about 15 inches from the subject's eyes. The target to be tracked was a white 'X'. The target position was controlled by the computer. Stimulus display and eye movement readings were controlled by hardware and software developed by S. Flanagan of the Beckman Institute, Duarte, CA based on a model constructed by N.J. Yasillo of the University of Chicago.

TABLE 2

Number of patients receiving medication of specific types

Drugs administered	*Schizophrenics n = 18*	*Bipolars n = 8*
Neuroleptics that primarily block D2 receptors (haloperidol, perphenazine)	9	3
Neuroleptics that block both D1 and D2 receptors (fluphenazine, clozapine, thioridazine)	9	2
Lithium	0	4
Anti-anxiety (propranolol)	4	0
Anti-depressant (desipramine, fluoxetine)	5	1
Anti-convulsant (Valproic acid)	3	0

Procedure

Instructions were read to subjects after which they were fitted with the infrared glasses. Their eye position was calibrated as follows. The subject was asked to look at 5 equidistant points on a horizontal line (extreme left, extreme right, center and 2 intermediate points between those three positions) one at a time on the target display monitor. The computer compared the eye position information with the target position and calculated the correlation between the two. After calibration, the eye tracking task began. In the eye tracking task, subjects tracked a sinusoidally moving target, 'X', subtending about 0.4 degrees of visual angle. The target frequency was 0.4 Hz and it subtended 20 degrees of visual angle peak-to-peak, as it moved horizontally across the screen. There were 2 trials of 60 s each. Subjects were given a brief rest before repeating the tracking task. Subjects were tested in a darkened room.

Scoring

The SPEM analog records were plotted to obtain hard copies, and the quality of smooth pursuit was rated as being 'good' or 'impaired' by two highly trained, independent raters (see Solomon et al., 1987). The inter-rater reliability was estimated to be about 0.98 (see Jenkins, 1989). The bipolar patients were tested but they were not included in the analysis because half of them were receiving lithium which disrupts smooth pursuit. (Levy et al., 1984, 1985; Iacono et al., 1982; Abel and Hertle, 1988; Holzman et al., 1991)

RESULTS

Table 3 presents the means for the three subject groups with respect to the delayed response memory and sensory tasks. The schizophrenic patients were less accurate than either the bipolars or the normals in the memory-guided delayed response task, and slower than the other two groups. These differences were tested by analysis of variance.

Accuracy

There was a significant effect of diagnosis on the accuracy of the oculomotor memory task

TABLE 3

Mean scores and standard deviations for three subject groups on the delayed response memory and sensory tasks

	Schizophrenic $n=18$ *mean (s.d.)*	*Bipolar* $n=8$ *mean (s.d.)*	*Normal* $n=40$ *mean (s.d.)*
Delayed response accuracy (%)			
memory	71.4 (15.9)	84.8 (7.1)	88.3 (7.8)
sensory	96.6 (6.4)	97.8 (3.4)	98.1 (2.8)
Delayed response RT (ms)			
memory	1210 (695)	816 (328)	707 (246)
sensory	1006 (220)	888 (282)	667 (227)

($F(2,63)=15.92$, $p<0.0001$). Schizophrenics were significantly less accurate than the bipolars ($F(1,24)=5.1$, $p<0.04$) and the normals ($F(1,56)=29.7$, $p<0.0001$) but there was no difference between the normals and the bipolars ($F(1,46)=1.41$, $p>0.2$). It is clear that only the schizophrenic group was impaired on the oculomotor memory task.

There was, however, no effect of diagnosis on the accuracy of sensory-guided eye movements ($F(2,63)=0.85$, $p>0.43$). Schizophrenics were as accurate as the normals ($F(1,56)=1.57$, $p>0.21$) and the bipolars ($F(1,24)=0.26$, $p>0.6$). Normals and bipolars did not differ from each other in their accuracy ($F(1,46)=0.06$, $p>0.81$).

Response Times

There was an overall effect of diagnosis on the response times of the oculomotor memory task ($F(2,63)=10.2$, $p<0.0002$). Schizophrenics were significantly slower than the normals ($F(1,56)=19.2$, $p<0.0002$) but they were not significantly slower than the bipolars ($F(1,24)=3.2$, $p>0.08$). Bipolars and normals did not differ in their speed of memory-guided eye movements ($F(1,46)=1.3$, $p>0.27$).

In the oculomotor sensory control task, schizophrenics and bipolars did not differ in their speed ($F(1,24)=1.69$, $p>0.20$). But both groups of psychiatric patients were significantly slower than the normals in making eye movements, in the absence of any working memory load. The normal subjects were faster than the schizophrenics ($F(1,56)=31.4$,

$p<0.0001$) and the bipolars ($F(1,46)=6.3$, $p<0.02$). (see Table 3).

Relation between SPEM and oculomotor delayed response tasks

Within schizophrenic population ($n=18$) there was a significant biserial correlation between the quality of SPEM and the accuracy of oculomotor memory task ($r=0.51$, $p<0.05$) but the biserial correlation between SPEM and the accuracy of the oculomotor sensory task was not significant ($r=0.19$)

Medication effects

The possible effect of neuroleptics on working memory deficit must be addressed. Sawaguchi and Goldman-Rakic (1991) have proposed that working memory is mediated by the Dopamine D1 system, and that D1 antagonists but not D2 antagonists impair oculomotor delayed response. Most of our patients were receiving medication (see Table 2) but it is unlikely that the working memory deficit we observed is entirely due to the effects of the neuroleptics for the following reasons. (1) All neuroleptics administered to psychiatric patients, particularly in the U.S.A., act primarily on the D2 system (Tamminga and Gerlach, 1987; Nordstorm et al., 1988). (2) Our previous study (Park and Holzman, 1992) showed that there was no significant difference between those schizophrenics taking haloperidol, which is almost completely a D2 antagonist, and those patients receiving other neuroleptics, which are to some extent mixed, such as fluphenazine. But even the mixed D1–D2 neuroleptics act primarily on the D2 system. In this study, we also divided the schizophrenic patients into those who are receiving mostly D2 antagonists and those who are receiving more mixed neuroleptics. There was no significant difference between these 2 groups in the oculomotor memory task ($F(1,16)=0.35$, $p>0.56$) and the oculomotor sensory task ($F(1,16)=0.11$, $p>0.91$). (3) In our previous paper, the majority of the bipolar controls were also receiving neuroleptics but their accuracy on the memory-guided delayed response task was equal to that of the normals. In this experiment, bipolars performed as accurately as the normal controls even though over half of the bipolar patients were receiving neuroleptics. Therefore, it is probable that the working memory deficit we observe in schizophrenic patients is not simply due to neuroleptic treatment.

DISCUSSION

Schizophrenic outpatients in remission showed a working memory deficit compared with the bipolar outpatients and the normal controls. This result replicates that of our previous study with an inpatient population (Park and Holzman, 1992). We suggest that a working memory deficit is present in schizophrenic patients regardless of illness state, and that this deficit implicates prefrontal dysfunction. In addition, we found a significant correlation between SPEM abnormalities and the working memory function within the schizophrenic population. This finding merits further investigation, since both SPEM and working memory are mediated by the dorsolateral prefrontal cortex, and the SPEM dysfunction has been proposed as a possible genetic indicator for schizophrenia (e.g. Holzman and Matthysse, 1990). Therefore it would be important to investigate the working memory and the SPEM functions in the healthy relatives of schizophrenic patients. Such a study is in progress.

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