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Neuropsychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls

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Abstract

Recent reports of spatial working memory deficits in schizophrenia provide evidence for dorsolateral prefrontal cortical (DLPFC) dysfunction. However, the question of how spatial working memory performance relates to other task impairments in schizophrenia considered reflective of frontal dysfunction, such as the Wisconsin Card Sorting Test (WCST) and smooth pursuit eye tracking, has been largely unexplored. Spatial working memory, as measured by a computerized visual–manual delayed response task (DRT), was evaluated in 42 schizophrenia patients and 54 normal controls. Subjects also completed a battery of neuropsychological and oculomotor tasks. Schizophrenia patients performed as accurately as controls on a no-delay, sensory–motor control condition, but showed a significant impairment in spatial accuracy with the addition of an 8-s delay and verbal distraction task. For the patients, working memory impairment was associated with fewer categories on the WCST, impaired eye tracking, fewer words learned on the Rey Auditory Verbal Learning Test, but not with measures of general cognitive and clinical functioning. Results suggest the presence of a sub-group of schizophrenia patients with common pathophysiology that accounts for the co-variance of several tasks implicating prefrontal dysfunction. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The notion that the pathophysiology of schizophrenia involves frontal lobe dysfunction, an idea that dates back to Kraepelin (1971), continues to

represent one of the prevailing neuroanatomical theories of schizophrenia. Support for the frontal lobe theory arises from multiple lines of evidence, including phenomenology (Seidman, 1983; Levin, 1984a), neuropsychological impairment (Goldberg and Weinberger, 1986; Goldsamt et al., 1993), oculomotor functioning (Levin, 1984b), and functional brain imaging (Buchsbaum et al., 1982; Weinberger et al., 1986). In particular, the pioneering series of rCBF activation studies by Weinberger and his colleagues using the Wisconsin Card Sorting Test (WCST) provided compelling evi-

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dence for physiological dysfunction of the prefrontal cortex in schizophrenia.

Recent reports of working memory deficits in schizophrenia provide the latest line of evidence for the frontal dysfunction hypothesis. The concept of 'working memory' has its roots in cognitive psychology (Baddeley, 1986), referring to a memory system responsible for the temporary holding and manipulation of information. Park and Holzman (1992) initially reported that schizophrenia patients were impaired on several delayed response tasks (DRT), the classical working memory paradigm adapted from the animal literature (Hunter, 1913; Goldman-Rakic, 1987). Since then, several replications of spatial working memory impairment in schizophrenia have followed (Park and Holzman, 1993; Spitzer, 1993; Keefe et al., 1995; Carter et al., 1996; McDowell and Clementz, 1996; Fleming et al., 1997).

A considerable body of evidence implicates the involvement of dorsolateral prefrontal cortex (DLPFC) in delayed response tasks. Goldman-Rakic (1987, 1991) has written detailed reviews of the non-human primate literature, establishing the DRT as the paradigmatic task for the activation of delay-specific, directionally sensitive neurons in the principal sulcus region of the DLPFC. Further evidence for DLPFC involvement in delayed response tasks comes from animal lesion studies (Brozoski et al., 1979) and functional imaging techniques in humans (McCarthy et al., 1994; Sweeney et al., 1996; Courtney et al., 1998). Because of the solid empirical support for the spatial DRT as a measure related to prefrontal functioning, DRT impairment in schizophrenia adds strong converging evidence to the long-standing theory of frontal lobe dysfunction.

The question of how spatial working memory relates to performance on other traditional frontal lobe tasks in schizophrenia, however, has received little attention. In schizophrenia research, impairment on one or more executive or frontal tasks is often reported, but patterns of relationships between these measures remain elusive (Goldberg et al., 1988). Goldman-Rakic (1987, 1991, 1994) and others (Kimberg and Farah, 1993; Pennington, 1994) have argued from a theoretical stance that working memory may be the corner-

stone of executive functions, the underlying cognitive process that accounts for seemingly disparate patterns of impairments observed in schizophrenia patients and in individuals with frontal lobe damage. If working memory remains the common denominator of tasks sensitive to frontal dysfunction, one should observe substantial correlations between these measures and spatial DRT performance. Observing covariance would strengthen the case for a single, underlying deficit in schizophrenia patients (or perhaps a sub-group) that is linked to the integrity of the DLPFC. A lack of task associations would suggest that the commonly used 'frontal' tasks are tapping disparate cognitive processes and/or neuroanatomical systems in schizophrenia patients.

A few studies have examined relationships between working memory and other putative frontal tasks in schizophrenia patients. Park and Holzman (1993) reported a correlation of 0.51 between working memory performance on an oculomotor DRT and smooth pursuit eye movements (SPEM) in schizophrenia patients. Although the nature of the pursuit tracking impairment and the neuroanatomical substrates that subservise smooth pursuit remain unresolved, there is evidence of involvement of frontal cortical processes (e.g. frontal eye fields) in normal subjects engaged in smooth pursuit (Gersden et al., 1996; Petit et al., 1997) and in SPEM dysfunction in schizophrenia (Katsanis and Iacono, 1991; Grawe and Levander, 1995). Gold et al. (1997) found a strong correlation ($r=0.74$) between a verbal working memory task and the WCST category achieved score in schizophrenia patients after controlling for Full-scale IQ, but not with the WCST perseveration score. Seidman et al. (1995) reported significant correlations between WCST perseverative responses and patients' performance on an associative working memory task (delayed alternation).

No study has yet reported an association between WCST performance and a spatial delayed response task, which would provide further converging evidence that working memory is a key cognitive component of successful WCST performance. Furthermore, to our knowledge, no study has reported on the relationship between working memory and performance on another aspect of

oculomotor functioning for which there is evidence of prefrontal involvement—the antisaccade task. This task requires subjects to inhibit a prepotent saccade to a suddenly appearing target in the periphery and direct their gaze to the opposite hemifield from the target. Schizophrenia patients have demonstrated antisaccade deficits (Clementz et al., 1994; Tien et al., 1996; Katsanis et al., 1997), as have neurological patients with prefrontal lesions (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991). Functional imaging reports suggest prefrontal involvement in normal subjects (although precisely which prefrontal areas are involved is unclear; O'Driscoll et al., 1995; Sweeney et al., 1996). Therefore, the antisaccade task would be of interest to include in an investigation of the correlates of working memory in schizophrenia.

The aims of the present study were: (1) to replicate the finding that schizophrenia patients are impaired on the working memory components of a spatial delayed response task; and (2) to further characterize the relationships between working memory performance and other clinical and oculomotor tasks purportedly sensitive to frontal lobe functioning. We hypothesized significant correlations between working memory and performance on putative frontal neuropsychological tasks, including the WCST, a verbal fluency task and two measures of figural fluency. Other neuropsychological tasks purportedly sensitive to more posterior regions were used to test the specificity of the frontal deficit hypothesis. In addition, we predicted that working memory would correlate with two oculomotor measures of interest: smooth pursuit eye tracking and antisaccade task performance.

2. Methods

2.1. Participants

Forty-two schizophrenia inpatients were recruited from acute-care psychiatric units of a regional hospital that serves a large metropolitan area. All patients met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia, based on diagnostic interviewing using

the Structured Clinical Interview for DSM-IV (SCID, Modules A–E) (First et al., 1995) and chart reviews. SCID interviewers were advanced graduate students in clinical psychology, with specific training in interviewing and SCID administration. The patients were between the ages of 18 and 65, spoke English fluently, were not currently abusing drugs or alcohol, had not recently undergone ECT treatment, and had no history of neurological disease, systemic disease known to involve CNS functioning (e.g. acquired immune deficiency syndrome, metastatic cancer), clinically significant head injury or mental retardation. All subjects gave written informed consent and were clinically stable at the time of testing. The patients had been ill an average of 12.1 years (s.d. = 9.4), had been hospitalized an average of 11.2 times (s.d. = 11.9), and had an average Global Assessment of Functioning (GAF) score of 26.2 (s.d. = 5.6). At the time of testing, 19 patients were receiving typical neuroleptics, 22 patients were receiving atypical neuroleptics, three were on lithium, 14 were taking anticholinergic agents, eight were receiving antidepressants, seven were on benzodiazepines, and 23 were taking anticonvulsant agents (e.g. sodium valproate, carbamazepine). Five patients were not receiving any neuroleptics, and one patient was not taking any psychiatric medication.

Fifty-four normal control participants were recruited from the community via advertisement posters placed in multiple medical settings (e.g. general medical clinics, dental clinics, dermatology clinics, etc.) at the same hospital from which the patients were recruited. The majority of participants from these medical settings were patients, with the remainder being hospital employees. In addition, posters were placed at similar medical clinics in a university hospital and in several community vocational/technical schools in the region. Control participants were excluded for the same general and medical criteria as the patients. They were free of lifetime diagnoses of major affective, psychotic or substance use disorder, as determined by the same structured interview that the patients received. In addition, individuals with a family history of mental health treatment for any of these

conditions in their first-degree relatives were excluded from participation.

2.2. Measures

2.2.1. Spatial delayed response task

Spatial working memory was assessed using a computerized visual–manual task adapted from Luciana et al. (1992) and used by Zald and Iacono (1999). The task was originally modeled on an oculomotor spatial delayed response task that has been used in non-human primates to investigate DLPFC functioning (Funahashi et al., 1989). Subjects sat in a quiet darkened room with their eyes 27 cm from a color VGA monitor. The head position and distance from the monitor were held constant for each subject by use of a fixed chin–forehead rest and a height-adjustable chair. During each trial, subjects fixated their vision on a small cross presented in the center of the computer monitor. After 2 s, a small target (asterisk character) was presented at one of 16 positions evenly distributed along the circumference of an imaginary circle 4.5 cm from the fixation point. During all task conditions, subjects indicated the location of the target stimulus by touching the computer monitor with a PXL light-pen (FTG Data Systems, Stanton, CA), which recorded the exact pixel location of each response. Subjects were allowed 5 s to respond to a trial before the next trial began. The task was completed in three blocks presented in the following order to all subjects.

2.2.1.1. No-delay condition. During the first condition, the target remained on screen until the subject indicated its location by touching the monitor with the light-pen. This condition served as a sensory–motor control for the delay condition by providing a measure of the participants' hand–eye coordination and ability to locate an object in space. Sixteen trials were administered (one with each target location). Prior to starting the no-delay condition, subjects were told how to hold and respond with the light-pen, instructed to 'touch the dot as accurately as you can' and given five practice trials.

2.2.1.2. Delay condition. During the second condition the target stimulus was presented for 200 ms.

After target presentation, the screen turned dark for a variable delay (either 0.5 or 8 s). The darkened screen served to disrupt iconic memory and eliminated all visual referents on the screen that could be used to help locate the target. Following the delay, a blank, lightened screen appeared and subjects indicated the location of the last target by touching the screen with the light-pen. Target positions and delay times were intermixed in random order, with all 16 target positions appearing once with each delay time (32 trials total). Subjects were given five practice trials before starting the condition and were instructed to 'touch the screen where you last saw the dot as accurately as you can'. Subjects received additional instructions to make their best guess if they saw the target stimulus but could not remember where it was and to refrain from responding if they failed to see the target stimulus.

2.2.1.3. Verbal distraction condition. The third condition was identical to the delay condition, except that during the delay period, subjects were required to read aloud three- and four-letter words that appeared in the center of the screen. The words were all frequently used in the English language (Kucera and Francis, 1967) and appeared at a rate of one every 2 s. The delay time was 8 s (16 trials total, one in each target position).

Automated software was utilized to record the pixel location of each subject's response as well as the actual location of the target stimulus. The discrepancy between the pixel location of the subject's response and pixel location of each target stimulus was automatically calculated and transformed into millimeters. Following the approach taken by Park and Holzman (1992, 1993), each trial response was scored dichotomously as a 'hit', defined as less than 25 mm total error, or a 'miss', defined as a total error greater than or equal to 25 mm. The cut-point of 25 mm was determined according to the distribution characteristics of the mean total error score across all conditions and corresponded to 80% (cumulative) of all subjects achieving a lower mean total error score. The proportion of hits was calculated for each condition of the task and then logarithmically trans-

formed ($y = \log x + 1$) to reduce skewness in the distribution of scores.

2.2.2. Oculomotor assessment

Oculomotor recordings were obtained in a quiet, darkened room, using both infra-red (IR) and electrooculographical (EOG) recording techniques. Infra-red eye movement recordings were measured with an Eye Trac Model 210 eye movement monitor and infra-red spectacles mounted on eyeglass frames (Applied Science Laboratories, Waltham, MA). Silver–silver chloride electrodes were applied to the outer canthus of each eye for EOG recording of horizontal movement, and at the superior and inferior orbital rims of the left eye to record blinks, with a ground electrode applied to the right shin. Stimuli were presented on a high-resolution Zenith flat-surface color monitor positioned 50 cm from the subject's eyes. The target stimulus consisted of a small yellow circle of light (0.5° of visual arc), which was presented against a darkened computer screen. Head movement was minimized with use of a bite-bar and dental wax impression. An IBM-compatible computer acquired the amplified signals, which were converted to digital form with a 12-bit A/D converter. Recordings were simultaneously displayed on a computer monitor in an adjacent room so that performance could be monitored continuously by the experimenter. All of the reported eye-tracking measures were derived from the IR recordings. Vertical EOG recordings were used to aid in the identification and removal of blinks from the IR record before scoring smooth pursuit performance.

2.2.2.1. Smooth pursuit. In the pursuit tracking task, subjects were required to visually follow a target stimulus moving in a horizontal sinusoidal motion at 0.4 Hz. The target subtended an arc of $\pm 10^\circ$ from center fixation. SPEM performance was quantified using root mean square (RMS) error deviation between the target and eye tracking channels, after adjusting for differences in phase and amplitude of the two waveforms (Iacono and Lykken, 1979). RMS error is a general index of eye tracking accuracy that has established reliability and construct validity as a marker for genetic

risk in schizophrenia (Iacono and Clementz, 1993; Clementz et al., 1996). Additionally, a subjective measure of smooth pursuit eye tracking quality was provided by the qualitative rankings of eye-tracking records by one of the authors (WGI) with more than 25 years of expertise in the eye tracking field. The SPEM records were plotted to obtain hard copies. While blind to subject group membership, the rater ranked the plots from best to worst (i.e. '1' being best performance) according to perceived tracking quality of identifiable segments of smooth pursuit.

2.2.2.2. Antisaccade. In the antisaccade task, the target began at a central fixation point. Following a 2–3-s pseudorandom interval, the center stimulus was extinguished, and a peripheral target simultaneously appeared at 10° either left or right in an unpredictable fashion. Subjects were instructed not to look at the target but to direct their gaze to the opposite side of the screen. The target then returned to central fixation, signaling the beginning of a new trial. One block of 20 trials (10 leftward and 10 rightward) was presented. Antisaccade trials were scored as correct if the subject directed initial gaze away from the target and counted as an error if the subject looked in the direction of the target (i.e. a reflexive saccade). Trials in which an error was not followed by a corrective saccade were excluded from analysis, following the assumption that the task instructions were not being followed. From the schizophrenia group, there were 11 subjects who failed to make reflexive saccades on at least one trial, and each of these patients had three or fewer of such trials. Only one control subject failed to make a corrective saccade after making an error, and this occurred only on one trial. Two schizophrenia subjects were excluded from antisaccade analyses because they were not able to understand the task (i.e. they made prosaccade errors without correction on nearly every trial).

The order of oculomotor tasks was as follows for all subjects: a brief 0.4-Hz sine-wave practice trial, the 0.4-Hz sine-wave task, three intervening oculomotor tasks that are not reported in the present study, and then a prosaccade task followed by the antisaccade task. The prosaccade task was

similar to the antisaccade task except that subjects were required to make reflexive saccades in the direction of target movement, thus priming the response to be inhibited in the antisaccade task. Because almost none of the subjects made directional errors on the prosaccade task, data from this task were not analyzed.

2.2.3. Neuropsychological assessment

All subjects were administered a battery of neuropsychological tests. Standardized administration procedures outlined in Lezak (1995) were followed for all tests, with the exception of a computerized version of the Wisconsin Card Sorting Test (Rezai, 1988). Scoring for the Wisconsin Card Sorting Test followed the rules provided by Heaton et al. (1993) with the following exception: the first unambiguous error after a category shift was not scored as perseverative, since the subject had not yet received any feedback at that point, indicating that the sorting principle had changed. Other investigators have also scored according to this rule exception (e.g. Seidman et al., 1995).

The following neuropsychological tests purportedly sensitive to frontal lobe functioning were used: the computerized Wisconsin Card Sorting Test (Rezai, 1988), Controlled Oral Word Association Test (COWAT; Benton, 1968), and Design Fluency (Jones-Gotman and Milner, 1977). Measures used from the WCST included the number of categories achieved (reflecting the overall task performance), number of perseverative errors (reflecting the failure to shift cognitive set), non-perseverative errors (reflecting all error types other than the failure to shift cognitive set), and the number of failures to maintain set (reflecting the loss of established cognitive set). The COWAT required subjects to name as many words aloud beginning with a letter (e.g. F, A, S...) in 60 s. The Design Fluency task included two conditions, a 'free' condition that required subjects to draw as many different non-representational figures (i.e. nothing that could be named, such as a house or a circle) as possible within a time limit, and a 'fixed' condition that restricted the number of lines allowed per drawing to four.

Verbal memory was assessed with the Rey

Auditory Verbal Learning Test (RAVLT; Rey, 1964). The total number of words recalled from the acquisition phase of the RAVLT (trials I–V) was used as an overall measure of verbal learning and recent verbal memory. The Rey–Osterrieth Complex Figure Test (ROCFT; Rey, 1941) was used to assess visuospatial organization (copy condition) and recent memory for visuospatial information (immediate recall condition). The overall intellectual functioning was assessed using the Information, Block Design and Digit Span subtests from the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981) and deriving an estimated Full-scale IQ (FSIQ) based on a prorated calculation [Tellegen and Briggs, cited in Sattler (1990)].

The entire study battery was administered within two-to-three separate sessions, with the oculomotor assessment conducted first, then neuropsychological testing, then spatial DRT administration. The typical time period of data collection for a single subject was within one week.

3. Results

Table 1 summarizes the demographic and clinical characteristics of the subject samples. There were no significant differences between groups in age. Normal controls had a significantly higher mean education level than the schizophrenia patients [$t(95)=6.38$; $p<0.0001$]. The estimated

Table 1
Demographic and clinical characteristics of subject groups

Variable	Schizophrenia patients ($n=42$)	Normal controls ($n=54$)
Age (years)		
<i>M</i>	35.7	36.0
s.d.	10.5	13.4
Gender (m/f)	31/11	19/35
Education (years)		
<i>M</i>	12.7	15.0
s.d.	1.8	1.7
Estimated WAIS-R IQ		
<i>M</i>	92.8	109.7
s.d.	13.4	13.4

WAIS-R = Wechsler Adult Intelligence Scale—Revised.

FSIQ also differed significantly between the groups [$t(90)=5.91$; $p<0.0001$]. The lower IQ of the schizophrenia patients is consistent with documented reports in the literature indicating that their mean FSIQ is typically in the 88–90 range (Aylward et al., 1984). Because of the methodological problems inherent in matching subjects on such variables as education level or FSIQ in schizophrenia research (Meehl, 1970), we chose not to match subject groups but rather to investigate the relationship between these variables and cognitive performance.

3.1. Spatial delayed response task

Fig. 1 shows the means of the transformed proportions of correct trials for patients and controls under all conditions of the spatial delayed response task. A $4 \times 2 \times 2$ (Delay Condition \times Group \times Gender) repeated-measures MANOVA was carried out, with the no-delay, 0.5-s delay, 8-s delay, and 8-s delay with verbal distraction entered as the repeated measures. Gender was included in the MANOVA because of the difference in gender

proportions between patients and controls. A multivariate approach was used because of its independence from sphericity assumptions (Howell, 1992). The MANOVA resulted in a significant main effect for Delay Condition [Pillai's Trace $F(3,90)=6.56$, $p<0.0001$], indicating a general increase in spatial error with longer delay periods and the addition of verbal distraction across all subjects. There was no significant main effect for Gender and no significant Gender \times Group interaction. The overall difference between groups across all task conditions was not significant [$F(1,92)=2.27$, $p=0.14$], but a significant Group \times Delay Condition interaction emerged [Pillai's Trace $F(3,92)=3.91$, $p<0.001$]. One-way ANOVA follow-up tests indicated the only significant group difference occurred in the 8-s delay condition with verbal distraction, with the schizophrenia patients demonstrating a lower proportion of hits than the normal control group [$F(1,94)=9.06$, $p<0.01$]. We then added estimated FSIQ and years of education as covariates to examine the role of a generalized deficit in the group difference in spatial DRT performance. The Group effect for the 8-s delay condition with

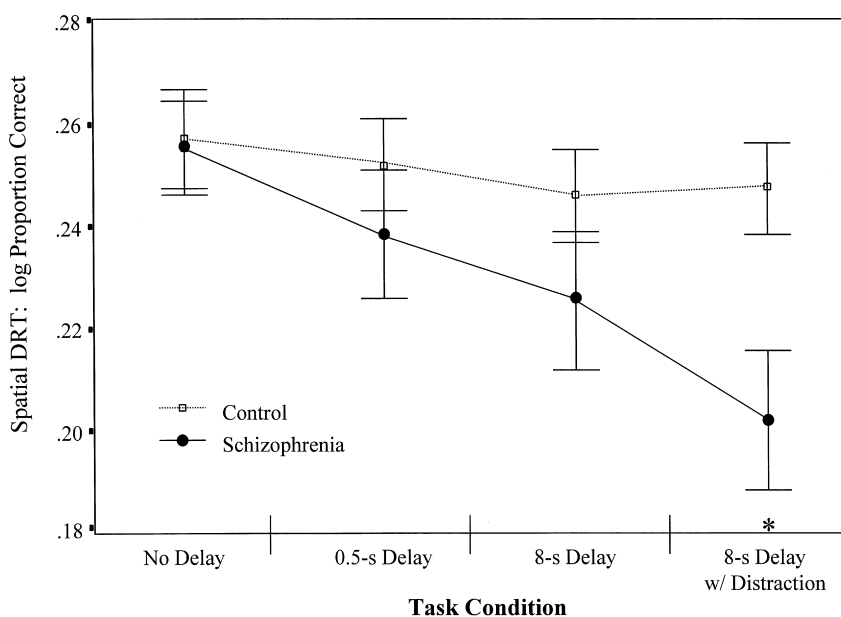


Fig. 1. Effect of delay periods and verbal distraction task on spatial DRT performance. The figure shows the means (\pm SE) of the logarithmically transformed scores (proportion of correct trials) for normal controls and schizophrenia patients across the four conditions of the working memory task. * $p<0.05$ (two-tailed).

verbal distraction remained significant [$F(1,88) = 6.44, p < 0.05$].

In sum, these analyses indicate that while schizophrenia patients and controls were equally proficient in the ability to locate and touch an object in space (i.e. the sensory–motor, no delay control condition), patients showed a significantly greater decrement in performance than controls with the addition of both a delay and the rehearsal-prevention task. Further, the initial differences between schizophrenia patients and controls on estimated FSIQ and level of education are unlikely to account for the group difference in spatial DRT performance.

The issue of whether spatial DRT impairment in schizophrenia is a specific cognitive deficit or reflects a generalized performance deficit was further examined by looking at the relationships between spatial DRT performance and estimated FSIQ, education level and GAF ratings from the SCID. All Pearson product-moment correlations were non-significant; no correlation was greater than 0.10 between performance on any of the spatial DRT conditions and GAF, estimated FSIQ or education level in the schizophrenia group. In the control group, correlations were also low in magnitude and non-significant, with the exception of a correlation between education level and spatial DRT performance (proportion of correct trials) at an 8-s delay ($r = 0.28$, two-tailed $p < 0.05$). These correlations provide further support that spatial DRT deficits in the patient group are not attributable to generalized cognitive or clinical impairment.

Because of reports in the literature that the dopamine system likely plays a role in modulating spatial working memory performance (Sawaguchi and Goldman-Rakic, 1991; Luciana et al., 1992; Luciana and Collins, 1997), it is important to assess the possible effects of neuroleptic medications with significant dopaminergic action on spatial DRT performance. This issue was examined in several ways. First, a small group of schizophrenic patients who were not taking neuroleptics ($n = 5$) were compared to the remaining schizophrenia patients taking neuroleptic medication on spatial DRT performance ($n = 37$). There were no significant differences in spatial DRT performance

on any of the task conditions [$t(40)$ range = -0.34 to $-1.32, p$ range = $0.70-0.20$]. In fact, the five patients off neuroleptics had consistently worse spatial DRT scores than the neuroleptic group across task conditions. In addition, schizophrenia patients who were taking haloperidol, a potent and selective D2 antagonist ($n = 10$), were compared to schizophrenia patients taking clozapine, an atypical antipsychotic with a comparatively weaker affinity for D2 receptors ($n = 7$) (Meltzer, 1992). There were significant differences in spatial DRT performance in the opposite of the expected direction, with a worse performance observed in patients taking clozapine [$t(15)$ range = -2.12 to $-2.45, p$ range = $0.02-0.05$]. Although these group differences raise the possibility of a deleterious effect of clozapine on spatial DRT task performance, they argue against the case that dopamine antagonism contributes to the observed schizophrenic spatial DRT impairment in this sample.

Other drug classes were examined for possible effects on spatial DRT performance by comparing all patients on and off medication types. No significant effects were found for anxiolytics, anticholinergics, antidepressants, anticonvulsants, or lithium.

3.2. Relationships between spatial DRT and neuropsychological and oculomotor tasks

Tables 2 and 3 present group means and standard deviations of the neuropsychological and oculomotor measures. For all the variables listed in these tables, ANOVAs were carried out to determine whether the controls subjects performed better than the schizophrenia patients. All the ANOVAs confirmed this to be the case (all Bonferroni-corrected $ps < 0.004$).

Tables 2 and 3 also report Pearson correlation coefficients between spatial delayed response task performance and all other measures, computed separately within groups. In order to minimize the number of computed correlations, only the 8-s delay with verbal distraction condition of the spatial DRT was included, as it was found to be most sensitive to group differences. Schizophrenia patients with a poor spatial DRT performance in the delay condition were more likely to achieve

Table 2

Neuropsychological and oculomotor measures and their correlations with spatial Delayed Response Task (DRT) at 8-s delay with verbal distraction: schizophrenia patients

Measure	<i>M</i>	s.d.	<i>r</i> _{DRT}
Neuropsychological test			
WCST categories	1.6	1.6	0.32*
WCST number PE	37.0	19.9	0.02
WCST number non-PE	32.7	12.9	−0.27
WCST failure to maintain set	2.34	1.95	−0.09
COWAT (number of words)	29.9	10.6	−0.11
Figural fluency (number of figures)			
Free condition	13.3	7.3	−0.08
Fixed condition	11.5	7.3	0.00
WAIS-R subtests (age-scaled scores)			
Information	8.3	2.7	−0.13
Block design	9.2	2.7	0.02
Digit span	7.7	2.4	−0.24
RAVLT trials I–V	35.2	9.4	0.34*
R–O copy	31.1	5.7	0.30
R–O immediate recall	15.0	7.3	0.28
Oculomotor measures			
Log RMS error	2.17	0.28	−0.34*
Qualitative rankings	56.0	—	−0.37*
Antisaccade percentage correct	47.5	23.5	0.13

Spatial DRT performance was measured by the log-transformed proportion of correct trials. WCST=Wisconsin Card Sorting Test; PE=perseverative errors; COWAT=Controlled Oral Word Association Test; WAIS-R=Wechsler Adult Intelligence Scale—Revised; RAVLT=Rey Auditory Verbal Learning Test; R–O=Rey–Osterrieth Complex Figure Test; RMS error=root mean square error.

* $p < 0.05$ (two-tailed).

fewer categories on the WCST and were more deviant on both measures of SPEM. Additionally, they performed more poorly on the total number of words learned during the acquisition phase of the RAVLT. No other correlations attained statistical significance.

Within the controls, a greater spatial DRT error in the delay condition was likewise associated with inferior performance on the WCST, as reflected by fewer categories achieved and a greater number of both perseverative and non-perseverative errors. No other correlations attained significance.

To address the question of how generalized intellectual impairment may contribute to observed associations among tasks, we re-calculated the correlations between spatial DRT performance and the neuropsychological and oculomotor variables while partialling out the effects of estimated full-scale IQ and educational attainment. After doing so, the pattern of significant correlations with DRT spatial error at an 8-s delay with verbal

distraction remained virtually unchanged for the schizophrenia patients (WCST categories, $r = 0.35$, $p < 0.05$; RAVLT total score, $r = 0.35$, $p < 0.05$; SPEM qualitative rankings, $r = -0.36$, $p < 0.05$; RMS error, $r = -0.33$, $p < 0.05$) and within the normal controls (WCST categories, $r = 0.35$, $p < 0.05$; WCST perseverative errors, $r = -0.35$, $p < 0.05$; WCST non-perseverative errors, $r = -0.32$, $p < 0.05$). In addition, the correlation between the R–O copy condition and spatial working memory became significant in the schizophrenia group ($r = 0.35$, $p < 0.05$).

Prior to calculating the correlations, all scatterplots of spatial DRT scores and the variables listed in Tables 2 and 3 were visually examined to determine whether correlation values were unduly affected by outlying cases. For the antisaccade/spatial DRT scatterplot, an interesting anomaly emerged. Fig. 2 presents a scatter plot of spatial DRT at an 8-s delay with verbal distraction and antisaccade performance in both subject

Table 3

Neuropsychological and oculomotor measures and their correlations with spatial Delayed Response Task (DRT) at 8-s delay with verbal distraction: control subjects

Measure	<i>M</i>	s.d.	<i>r</i> _{DRT}
Neuropsychological test			
WCST categories	4.6	2.0	0.39**
WCST number PE	17.2	14.9	−0.38**
WCST number non-PE	21.8	9.1	−0.36**
WCST failure to maintain set	1.49	1.34	0.06
COWAT (number of words)	41.6	10.8	0.06
Figural fluency (number of figures)			
Free condition	29.3	14.4	−0.09
Fixed condition	25.4	11.5	−0.11
WAIS-R subtests (age-scaled scores)			
Information	11.1	2.5	0.08
Block design	12.2	2.3	0.03
Digit span	11.2	2.3	0.08
RAVLT trials I–V	52.8	9.9	0.17
R–O copy	34.6	2.6	0.12
R–O immediate recall	23.4	7.6	0.08
Oculomotor measures			
Log RMS error	1.97	0.25	−0.09
Qualitative rankings	39.1	—	0.04
Antisaccade percentage correct	74.5	14.8	−0.26

Spatial DRT performance was measured by the log-transformed proportion of correct trials. WCST = Wisconsin Card Sorting Test; PE = perseverative errors; COWAT = Controlled Oral Word Association Test; WAIS-R = Wechsler Adult Intelligence Scale—Revised; RAVLT = Rey Auditory Verbal Learning Test; R–O = Rey–Osterrieth Complex Figure Test; RMS error = root mean square error. ** $p < 0.01$ (two-tailed).

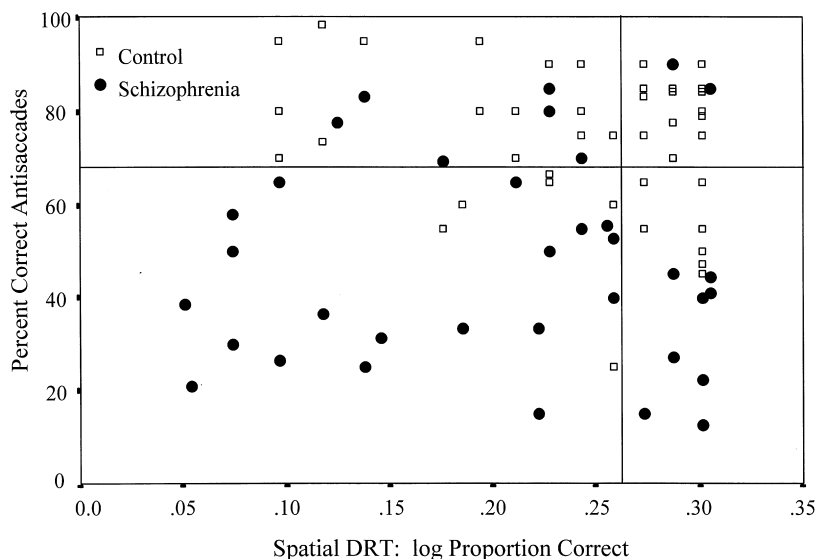


Fig. 2. Relationship between performances on spatial DRT at 8-s delay with verbal distraction and the antisaccade task. Vertical and horizontal lines indicate the median score values for all subjects combined.

groups, divided into quadrants by the medians of each variable (median values were computed for the total sample combined). Inspection of the plot reveals a relative absence of control subjects in the lower left quadrant (i.e. representing a poor performance on both tasks). Although normal controls did exhibit a range of performance on both measures, by and large, only the schizophrenia patients appear to be impaired on both measures (13% of controls who are below the median on either variable are below the median on both variables, versus 50% for schizophrenia patients).

A possible explanation for this pattern is that these particular schizophrenia patients demonstrate a generalized performance impairment. However, the 10 patients who show the greatest impairment on both the antisaccade task and the spatial DRT in Fig. 2 have a non-significant but higher average estimated FSIQ (95.8) and GAF score (29.8) compared to the remaining schizophrenia subjects (mean FSIQ=91.9; mean GAF=25.3). This sub-group also differs from the remainder of the schizophrenia sample in having a worse SPEM [average log RMS error of 2.36 versus 2.09, $t(37)=2.83$, $p<0.01$] and showing a trend toward a poorer performance on the WCST [average of 0.9 categories achieved versus 1.8, $t(37)=1.87$, $p=0.08$]. No other neuropsychological measure differed significantly between these patients and the remainder of the schizophrenia sample. Thus, although antisaccade performance and spatial working memory ability are not associated in a linear manner in this patient sample, the data suggest the presence of a sub-group of schizophrenia subjects with greater impairment on these and several other frontal measures not accounted for by general cognitive or clinical status.

4. Discussion

Consistent with other reports, this investigation demonstrated impairment in schizophrenia patients on the working memory component of a spatial delayed response task. This study contributes further to the spatial working memory literature by including a sensory–motor control condition, multiple delay periods, as well as an 8-s

delay with and without an intervening distraction task. Although the schizophrenia patients tended to demonstrate a worse performance than controls during the 0.5-s and 8-s delay periods without verbal distraction, the only significant group difference appeared with the addition of the verbal task during the delay period. This finding suggests that vulnerability to distracting stimuli in schizophrenia patients may be an important mechanism in the impairment in on-line maintenance of spatial information. This hypothesis is consonant with the findings of Seidman et al. (1995) in which spatial DRT performance was related to auditory and visual vigilance in schizophrenia patients. However, another consideration is that the delay conditions without the intervening verbal task allow subjects to ‘rehearse’ the visual location of each target by fixing their eyes on precisely that spot on the monitor. Since some subjects may have utilized this rehearsal strategy and others not, the addition of the intervening word-reading task would serve to eliminate task variance due to the use of rehearsal strategies, increase standardization and result in a more reliable and valid test of working memory.

Correlations between spatial DRT performance and other tasks in this study were relatively low in magnitude, although this is not surprising given the reliabilities and complex nature of most of the tasks. Spatial working memory was found to be associated with the category score of the WCST in the schizophrenia group, but not with the perseverative number of errors. This finding is intriguing, as the lack of association with WCST perseveration is somewhat unexpected based upon theories of how working memory influences types of WCST error. Goldman-Rakic (1987) reasons that the failure of working (or ‘representational’) memory to maintain the current sorting principle during WCST performance leads to perseveration of the previously correct sorting principle. Kimberg and Farah (1993), modeling the weakening of associations between elements in working memory, found both the WCST category score and perseverative errors to be affected in their model. However, the present findings are consistent with those of Gold et al. (1997), who found that performance in schizophrenia patients on an

auditory working memory task (letter-number span) predicted the WCST category score, but not WCST perseverative errors. Based upon existing empirical evidence, it appears that working memory impairment in schizophrenia patients is more predictive of general failure on the WCST than a specific class of errors such as perseveration or failure to maintain set. Within control subjects, as well, spatial working memory appears to be associated with overall WCST performance, as the category score and both perseverative and non-perseverative errors were significantly correlated with spatial DRT performance.

We hypothesized that in the schizophrenia group, spatial working memory performance would show stronger associations with tasks purportedly sensitive to frontal lobe functioning, compared to control tasks sensitive to other cortical areas or to generalized functioning. Among the frontal tasks, spatial DRT performance was correlated with performance on the WCST and with quality of smooth pursuit eye movement; however, spatial DRT performance was not associated with any of the fluency tasks. These findings argue against a unitary account of working memory as the cognitive common denominator among traditional 'frontal' tasks in schizophrenia. Spatial DRT performance was also associated with verbal learning and memory (RAVLT). Thus, whereas spatial DRT performance is relatively independent of general cognitive status in the patient group, success on the spatial DRT for schizophrenia patients appears multi-factorially determined and to be related to frontal functions as well as those reflective of more posterior (i.e. mesial-temporal) structures. However, although the RAVLT was initially added to serve as a control for more posterior cortical (i.e. mesio-temporal) functioning, this correlation is noteworthy in light of a growing literature on the influence of frontal functions on tests of declarative memory (Wheeler et al., 1995).

The observed correlations between SPEM and spatial working memory are consistent with Park and Holzman's finding (Park and Holzman, 1993). Performance on the antisaccade task was not significantly correlated with spatial DRT performance; however, there is a suggestion of a sub-group of schizophrenia patients who performed

poorly on both tasks, as well as on the WCST and smooth pursuit tracking. This finding is tentative yet intriguing, as such a sub-group of patients with associated deficits in spatial DRT, WCST, SPEM, antisaccade performance is consistent with a multi-trait genetic model of schizophrenia, as outlined by Iacono and Grove (1993). In this model, the authors posit that the pleiotropic action of a single major gene can account for a number of characteristic abnormalities observed in some, but not all, schizophrenia patients and their relatives, including eye-tracking dysfunction and deficits on frontally sensitive neuropsychological tests. Further research with a larger sample is necessary for replication of this identified 'prefrontal' sub-group. The question of a genetic link among these prefrontal measures can be addressed in schizophrenia family studies in which correlations are examined between one relative's score on a given variable and the scores of other relatives on different variables (Grove et al., 1991).

In sum, the present results support the theory of a specific working memory impairment in schizophrenia. Impairment in working memory appears to be related to impairments in WCST performance, SPEM, and possibly to antisaccade performance in a subgroup of schizophrenia patients. These associations between spatial working memory and other putative indices of prefrontal functioning provide further converging evidence for a common pathophysiological process in some schizophrenia patients that is linked to prefrontal cortical dysfunction.

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