
Spatial Working Memory Deficits and Clinical Symptoms in Schizophrenia: A 4-Month Follow-Up Study

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Background: *Our goal was to examine spatial working memory function in relation to clinical symptoms of schizophrenia over a period of 4 months.*

Methods: *We assessed spatial working memory, spatial detection and clinical symptoms in 34 acutely psychotic schizophrenia patients within the first 2 weeks of hospitalization, and 4 months later. Spatial working memory was assessed by a delayed response task. A spatial control task was included to rule out simple sensorimotor deficits. Positive and negative symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS). Thirty-nine matched normal control subjects were also examined on the same tasks over the same period.*

Results: *Patients showed deficits in working memory, but they performed well on the spatial control task. Both positive and negative symptoms improved at the 4-month follow up. Spatial working memory also improved over time but there was still a significant deficit at the follow-up session.*

Conclusions: *These results indicate that both symptoms and spatial working memory improved 4 months after the initial hospitalization but spatial working memory, hypothesized to be mediated by the dorsolateral prefrontal system, did not normalize. Thus, spatial working memory deficit may be a stable marker for schizophrenia. Biol Psychiatry 1999;46:392–400 © 1999 Society of Biological Psychiatry*

Key Words: Schizophrenia, working memory, positive symptoms, negative symptoms, prefrontal cortex

Introduction

Cognitive deficits of schizophrenia patients span a wide range of information processing, including attention, memory, problem-solving and language. Some of the

recent theories of schizophrenia attempt to explain such seemingly divergent cognitive deficits in terms of a single, major neuropsychological system. It has been suggested that working memory (Goldman-Rakic 1991) or “maintenance of context” (Servan-Schreiber et al 1996) may underlie various cognitive deficits observed in schizophrenia patients. Deficits of “executive” functions such as distractibility, perseveration and failure to inhibit irrelevant responses may reflect an inability to utilize working memory or internal representation to guide context-appropriate behavior. Working memory is thought to be mediated by the prefrontal system (Baddeley 1986; Shallice 1988; Goldman-Rakic 1991).

Working memory may be conceptualized as a “system for the temporary holding and manipulation of information during the performance of a range of cognitive tasks” (Baddeley 1986). In Baddeley’s model, temporary maintenance of information is achieved by an active control system, termed the central executive, which is aided by modality-specific subsystems. Thus, working memory system includes separable, functional components that can be systematically probed.

Recent emergence of interest in the role of working memory in schizophrenia has yielded a substantial body of data from diverse paradigms, methods and techniques. These studies indicate that schizophrenia patients show working memory deficits, transcending differences in specific paradigms or tasks employed (Park and Holzman 1992, 1993; Spitzer 1993; Keefe et al 1995; Carter et al 1996; McDowell and Clementz 1996; Rabinowicz et al 1996; Servan-Schreiber et al 1996; Gold et al 1997; Spindler et al 1997). These deficits are unlikely to be a mere artifact of antipsychotic medication because they are present in unmedicated schizophrenia patients (Carter et al 1996), whereas bipolar patients taking similar neuroleptics show intact spatial working memory (Park and Holzman 1992, 1993). In addition, clinically unaffected relatives of schizophrenia patients (Park et al 1995a) and healthy, psychometric schizotypes, who may carry latent liability for schizophrenia (Park et al 1995b; Park and McTigue 1997) also show working memory deficits.

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Much is known about the role of prefrontal cortex in working memory function and its regulation of higher cognitive functions (Goldman-Rakic 1988, 1991). Neurobiological correlates of spatial working memory have been investigated extensively in the nonhuman primates, with the delayed response paradigm (Jacobsen 1935a, 1935b; Blum 1952; Mishkin 1957; Funahashi et al 1989, 1990, 1993). When an eye movement to a target is delayed, some neurons in principal sulcus (area 46) increase and maintain firing during the delay period. These findings suggest that neurons in the principal sulcus region are involved in the maintenance of spatial information over time and that the integrity of the dorsolateral prefrontal system is necessary for a successful performance on the delayed response task (Goldman-Rakic 1988; Fuster 1995; Funahashi et al 1989, 1990, 1993).

Analyzing neurobiologically constrained working memory performance in relation to the clinical symptoms of schizophrenia may be particularly useful in understanding the neural correlates of the symptoms. Currently, clinical symptoms are often classified into two broad clusters: negative versus positive symptoms (Andreasen and Olsen 1982) or deficit versus nondeficit symptoms (Carpenter et al 1988). Positive symptoms of schizophrenia are characterized by delusions, hallucination, formal thought disorder, and attentional impairments and they respond well to typical antipsychotic drugs. In contrast, negative symptoms are characterized by affective or motivational abnormalities, emotional/social withdrawal, alogia, and anhedonia. Negative symptoms tend to be treatment-resistant, especially to typical neuroleptics, and related to poor outcome (Pogue-Geile and Harrow 1985).

It has been suggested that negative symptoms may partly be attributed to dysfunctions of the frontal cortex (Andreasen et al 1992). Some recent studies have linked negative symptoms to hypofrontality or impairments on tasks sensitive to frontal lobe function (Katsanis and Iacono 1991; Wolkin et al 1992; Buchanan et al 1993; Stolar et al 1994; Hammer et al 1995). Although, such results have led to the formulation of hypotheses connecting hypofrontality and negative symptoms, the link is not well understood and has not received unequivocal empirical support (Perlick et al 1992; Strauss 1993; Blanchard et al 1994). Longitudinal studies suggest that some cognitive deficits, especially those mediated by frontal lobes persist in spite of improvement in both positive and negative symptoms, whereas other deficits such as attention impairment may be related to positive symptoms and show improvement (Cornblatt et al 1985; Addington et al 1991; Cantor-Graae et al 1995); however, the nature of the link between clinical symptoms and cognitive functions continues to be ill defined. Neurocognitive deficits may be a relatively enduring aspect of the illness, and may account

for continued limiting function after symptoms have been ameliorated through medication (Goldberg et al 1993). Specifically focusing on working memory, one recent study has documented evidence for an association of spatial working memory performance and negative symptoms in unmedicated schizophrenia patients (Carter et al 1996). A similar but much weaker association in psychometric schizotypes has also been reported (Park and McTigue 1997).

In the current study, we examined one component of the working memory system, spatial working memory, in relation to the clinical symptoms of schizophrenia over a 4-month period. We hypothesized that spatial working memory deficit would be present in schizophrenia patients regardless of the illness state. If abnormal spatial working memory function, mediated by the prefrontal system, is a possible trait marker, it should be permanently present regardless of the symptoms. In other words, if spatial working memory deficit is present, independent of the illness state, and also, if it is present in nonpsychotic relatives of schizophrenia patients, it may be a good "marker" for the schizophrenia phenotype. In contrast, the performance on a sensory control task, which does not tap prefrontal function, but is mediated by the occipital and parietal systems, was expected to be unimpaired in schizophrenia patients.

There is partial evidence for the trait-marker hypothesis of working memory deficit. Both inpatients and outpatients show spatial working memory deficits (Park and Holzman 1992, 1993; Spitzer 1993; Keefe et al 1995; Carter et al 1996), as do nonpsychotic, first-degree relatives of schizophrenia patients (Park et al 1995a) and psychometric schizotypes (Park et al 1995b; Park and McTigue 1997). But to our knowledge, no study has examined working memory function and clinical symptoms during an acute psychotic episode and tracked possible changes at a later stage of symptomatic remission within the same group of patients and controls.

We recruited patients with schizophrenia as they were admitted to a psychiatric hospital and tracked their outcome 4 months later. We hypothesized that clinical symptoms would improve significantly by the 4-month retest session, especially the positive symptoms. We also hypothesized that spatial working memory deficits would be present regardless of the time of testing and therefore there would be no consistent relation between clinical symptoms and the spatial working memory performance over time. Clinical symptom ratings and working memory may be significantly correlated at one point in time, but this relationship may not necessarily hold at another time because symptoms may fluctuate but the spatial working memory deficit may be a permanent feature of the disorder.

A spatial sensory control task was included to insure that the patients were able to detect a spatial target and select it in the absence of any working memory requirements. Ability to perform the sensory control task is not dependent on the prefrontal system. Good performance on the sensory task coupled with poor performance on the memory task would indicate the presence of working memory deficit and rule out the possibility of simple sensorimotor deficit. We designed the memory and the sensory control tasks, such that there is only one component that is altered; that of the absence or presence of the target. Every other component is identical, even the required activity during the delay period. Neurobiologically, by manipulating the absence/presence of the target during the delay, we are manipulating the involvement of the dorsolateral prefrontal cortex in performing the task (see Goldman-Rakic 1988).

Thus, we departed from the popular practice of administering a battery of neuropsychological tests to schizophrenia patients and examining the patterns of performance. Instead, we chose to focus on one specific hypothesis and one circumscribed, neuroanatomically well-understood function.

Methods and Materials

Thirty-four (13 women) acutely ill schizophrenia patients (mean age = 34.8, SE = 1.7) were recruited and tested within the first 2 weeks of being admitted to a psychiatric ward. Diagnoses were made by a psychiatrist according to DSM-IV criteria (Spitzer and Williams 1987) from structured interviews. Subjects were screened for the following criteria: substance abuse, neurological disorders, or history of head injury. There were 2 first episode patients. All others were relapse patients. The mean duration of illness was 9.8 years (SE = 1.2). Four months later, working memory and clinical symptoms were reassessed. Thirty out of the 34 patients participated at the 4-month follow-up. All patients, in partial remission, were clinically stable at the time of retesting.

Clinical interviews and symptom assessments [Positive and Negative Syndrome Assessment Scale (PANSS)] (Kay et al 1987) were conducted on the same day. The PANSS consists of 30 items. Each item is rated on a Seven-point scale. A score of 1 means the symptom is not present at all, and a score of 7 means that it is present to an extreme degree. The questions are grouped into 3 scales to measure negative symptoms (7 items), positive symptoms (7 items), and general psychopathology (16 items). PANSS ratings were completed by two of the authors who were blind to the task performance of the subjects.

Thirty-nine (13 women) normal control participants were also tested (mean age = 36.3, SE = 1.7). They were retested 4 months later. Control subjects had no history of substance abuse, head injury, psychiatric illness in self or in the family, or neurological disorders. The control subjects were recruited from the community.

The 2 groups did not differ statistically in education level (normal controls = 12.8 versus schizophrenia patients = 12.2

years), age (normal controls = 36.3 versus schizophrenia patients = 34.8 years) and handedness (2 left-handers in the patient group versus 3 left-handers in the control group). We did not explicitly assess the socioeconomic levels of the participants, using indices developed in North America because the socioeconomic structure of Switzerland is rather different. An overwhelming majority of the Swiss population belong to the middle class and almost all Swiss children attend state schools.

Procedure

All subjects gave informed consent to participate in the study. Clinical interviews and ratings were conducted in the morning and the cognitive experiments in the afternoon, at both times of testing.

SPATIAL WORKING MEMORY. Subjects sat with their heads steady on a chin rest in front of a stimulus display monitor which was fitted with a touchscreen (AccuTouch™, Ellinor Technology, Berks, UK). The touchscreen 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 millimeters, as measured on a multipoint sampling basis. Calibration procedure involved touching four reference points on the touchscreen. Subjects were calibrated before the beginning of the experiment.

Subjects were fixated at the center and when they were ready to begin, the experimenter clicked a mouse to initiate a trial. In the spatial working memory task, a target appeared on the screen for 200 ms. Immediately after the target presentation, there was a 10-sec delay period, during which the subject observed a series of numbers at the fixation point. The subject was told that the computer was performing a series of subtractions but occasionally it made a mistake and that the subject must press the spacebar whenever a mistake occurred. 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 remembered position of the target. See Figure 1 for procedure.

In order to control for the sensorimotor component of the working memory task, a 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 working memory since the target was always present. Intact performance on the control task, coupled with poor performance on the memory task would rule out the possibility of a simple sensorimotor deficit.

The order of presentation of the memory and the sensory tasks was counterbalanced across subjects. There were 32 memory and 32 sensory trials. There were also 16 practice trials before the main body of testing began.

Scoring

Accuracy (% correct) was computed. A response was scored as correct only if the subject touched within 1.5 degrees of the center of the target position.

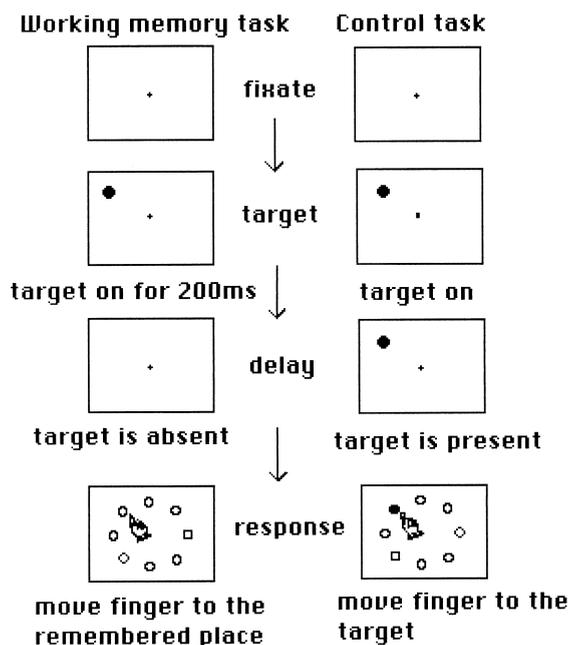


Figure 1. Spatial delayed response tasks.

Statistical Analysis

Repeated measures ANOVAs (Day 1 versus 4 months) were conducted separately for spatial working memory and symptom scores. Specific contrasts were evaluated with *t* tests. Spearman Rank Correlations (RHO) were computed between the PANSS positive and negative symptoms scores and the working memory accuracy for each testing session. Unless specified, two-tailed tests were applied for all the statistical analyses.

Results

Spatial Working Memory

The means and standard errors for the memory and control tasks are summarised in Table 1. A repeated measures ANOVA indicated that there was a main effect of diagnosis [$F(1,68) = 19.5, p < .001$] on working memory. Schizophrenia patients performed less accurately than did the normal controls on Day1 and at the 4-month follow-up. There was a main effect of the time of testing [$F(1,68) = 6.1, p < .017$]. Subjects performed better at the 4-month

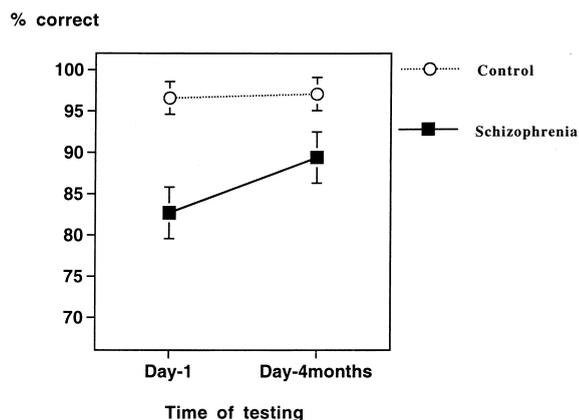


Figure 2. Spatial working memory accuracy.

follow-up than they did on Day 1, but this effect was mainly due to the improvement of schizophrenia patients, as indicated by the significant interaction between the diagnostic group and the time of testing [$F(1,68) = 4.4, p < .041$]. Spatial working memory performance of normal controls did not change over the period of 4 months [$F(1,38) = .5, p > .50$], but schizophrenia patients showed a significant improvement [$F(1,29) = 4.6, p < .041$]; however, in spite of the improvements in working memory at the 4-month follow-up session, schizophrenia patients were still significantly impaired compared with the normal controls. Therefore, spatial working memory deficit appears to be a permanent feature, as indicated by a significant difference between the normal controls and the patients, both on Day 1 [$F(1,72) = 21.7, p < .001$], but also at the 4-month follow-up session [$F(1,68) = 8.5, p < .0047$]. See Figure 2.

For all subjects, the working memory score on Day 1 correlated significantly with the working memory score at the 4-month follow-up ($r = .53, p = .001$). Spearman rank correlations were also examined within the group. For schizophrenia patients, working memory score on Day1 was significantly correlated with working memory score at the 4-month follow-up ($r = .62, p = .007$). The correlation was also significant for the normal controls ($r = .32, p = .046$). Therefore, working memory score may change with time but an individual's rank seems to remain constant.

Schizophrenia patients did not differ from the control

Table 1. Mean Accuracy (Standard Errors) on the Memory and Sensory Control Tasks for Schizophrenia Patients and Normal Controls

% correct	Day 1		4 Months Later	
	Schizophrenic	Normal	Schizophrenic	Normal
Memory	83.4 (2.95)	96.4 (0.81)	89.3 (2.89)	97.1 (0.68)
Sensory	98.3 (0.49)	98.8 (0.29)	99.6 (0.40)	98.7 (0.51)

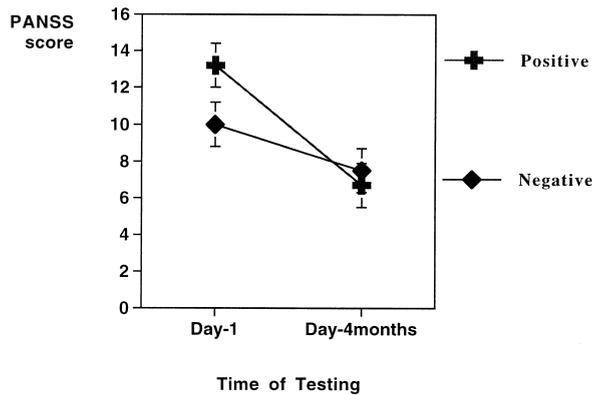


Figure 3. Positive and negative symptom ratings.

subjects on the sensory control task [$F(1,68) = .19, p > .66$]. There was no significant effect of diagnosis or time of testing on the sensory control task. Normal performance on the sensory control task suggests that the spatial working memory deficit observed is not due to a simple sensorimotor deficit. All patients were able to direct spatial attention to a visual target accurately.

Symptoms

Both positive symptoms [$F(1,29) = 60.4, p < .001$] and negative symptoms [$F(1,29) = 7.1, p < .014$] improved significantly by the 4-month follow-up, but it must be noted that all patients were still symptomatic and on medication. Positive and negative symptoms were not correlated significantly with each other on Day 1. At 4 months, there was a trend toward a significant correlation between negative and positive symptoms ($r = .36, p = .077$).

Positive symptoms on Day 1 did not correlate with positive symptoms at the 4-month follow-up. But, negative symptoms on Day 1 correlated significantly with negative symptoms at 4 months ($r = .57, p = .0049$).

We computed an "improvement index" by subtracting the symptoms score at 4 months from that on Day 1. The improvement index for negative symptoms was correlated significantly with that for the positive symptoms ($r = .50, p = .0151$). Thus, although the actual symptoms ratings for positive and negative symptoms do not correlate significantly, the rates of improvement over the period of 4 months are associated. The PANSS rating scores are shown in Figure 3.

Spatial Working Memory in Relation to Clinical Symptoms

NEGATIVE SYMPTOMS. On Day 1, the correlation between negative symptoms and working memory was

significant ($r = -.40, p = .026$), but at 4 months it was not ($r = -.20, p = .33$).

Negative symptom scores on Day 1 correlated significantly with the working memory score 4 months later ($r = -.50, p = .0057$). This finding suggests that the extent of negative symptoms present during the acute psychotic episode may foreshadow the degree of working memory impairment 4 months later. But the working memory score on Day 1 did not predict the negative symptoms 4 months later ($r = -.24, p = .237$). The degree of working memory impairment during the acute psychotic episode does not predict the extent of negative symptomatology 4 months later.

POSITIVE SYMPTOMS. Positive symptoms and working memory performance were not associated. Positive symptoms on Day 1 did not correlate with the working memory score on the same day ($r = -.22, p = .22$). At the 4-month follow-up, positive symptoms and working memory on the same day did not correlate ($r = -.04, p = .83$). Working memory performance on Day 1 did not correlate with positive symptoms 4 months later ($r = -.07, p = .74$) and positive symptoms on Day 1 did not correlate with the working memory score at 4-month follow-up ($r = -.17, p = .34$).

Medication

Past studies suggest that anti-psychotic medication probably does not cause working memory deficits in schizophrenia patients (Park and Holzman 1992, 1993; Park et al 1995a,b; Carter et al 1996). In the current study, schizophrenia patients showed improvements in spatial working memory at the 4-month follow-up session. All the patients who participated at both testing sessions were taking antipsychotic medications. Two patients during the acute state were unmedicated on Day 1 but neither were tested at 4 months. About half were taking atypical neuroleptics. Recent studies suggest that atypical neuroleptics may be more effective in improving cognitive deficits. We compared the working memory performance of subjects taking atypical versus typical antipsychotic medication. There were 14 subjects in the atypical group and 12 subjects in the traditional neuroleptic group. Four subjects were excluded because their medications were changed. There was no difference between the patients who were taking atypical antipsychotic drugs and those taking the traditional neuroleptics; however, our sample size is too small to rule out the possible beneficial effects of atypical antipsychotic drugs. To test the drug effects directly, a large scale longitudinal study must be conducted in the future.

Discussion

Stability of working memory deficit

Spatial working memory deficit was present in schizophrenia patients during an acute psychotic episode and also at a stabilized, chronic state 4 months later. Although the working memory deficit showed a significant improvement over the course of 4 months, schizophrenia patients remained significantly impaired compared with the normal controls. This pattern of results suggests that residual spatial working memory deficit is present in schizophrenia patients, regardless of their clinical status. In past studies of spatial working memory, both inpatients (Park and Holzman 1992) and outpatients (Park and Holzman 1993; Carter et al 1996; Keefe et al 1995) with schizophrenia showed deficits in spatial working memory, whether medicated (Park and Holzman 1992, 1993; Keefe et al 1995) or unmedicated (Carter et al 1996). These results suggest that spatial working memory, mediated by the dorsolateral prefrontal system, may be a stable, trait-like feature of schizophrenia. Our current results obtained from a within-subjects design confirm the presence of spatial working memory over time in schizophrenia patients. It must be noted however, that these patients were still symptomatic at 4 months. One important question remains as to whether complete recovery (e.g., PANSS score of zero) would be accompanied by intact working memory. Our past studies however, with healthy individuals who may carry liability for schizophrenia (i.e., psychometric schizotypes and first degree relatives), suggest that absence of symptoms does not eliminate working memory deficits.

Spatial working memory, as assessed by the delayed response task, is mediated by a neural circuitry that includes the dorsolateral prefrontal cortex and the dorsal visual information processing streams (Goldman-Rakic 1988). Schizophrenia patients show persistent deficits in the spatial delayed response task over time, suggesting that the deficit may be permanent. Our current findings are consistent with the presence of hypothesized abnormalities in the dorsolateral prefrontal neural circuitry mediating spatial working memory.

The role of prefrontal cortex in schizophrenia has been extensively studied, starting with Kraepelin (1904). Neuroimaging data indicate that schizophrenia patients may have hypofrontal metabolism (Weinberger et al 1986; Ingvar 1987) or inefficient functioning of the dorsolateral prefrontal system (Manoach et al in press). Structural studies also point to abnormalities of the prefrontal cortex in schizophrenia; the arrangement and density of cells in the prefrontal cortex may be anomalous (Lewis and Anderson 1995; Selemon et al 1995). Altered dopamine D1 receptor function as well as abnormalities of the

glutamates and serotonin systems may also play important roles in the observed spatial working memory deficit.

Working Memory and Clinical Symptoms

Carter et al (1996) reported that negative symptoms correlated significantly with spatial working memory deficit in unmediated outpatients with schizophrenia. We have partially replicated their findings. First, positive symptoms were not correlated with the spatial working memory deficit. Second, on Day 1, we found a significant association of spatial working memory performance and negative symptoms. These results support an association between working memory deficit, negative symptoms and prefrontal dysfunction, at least when patients were hospitalized during an acutely psychotic episode. In our study, however, the relation between spatial working memory and the negative symptoms was inconsistent over time. Although, during the acute state (Day 1), spatial working memory deficit and the negative symptoms were significantly correlated, 4 months later, this was no longer the case. When schizophrenia patients had been under stable medication and were partially remitted, with moderate levels of positive and negative symptoms, there was no significant association between their symptoms and the spatial working memory function.

One explanation hinges on the range of symptom scores being restricted as the patients improve. This is not the case since the standard errors of the symptoms score were almost identical for the negative symptoms (SE on Day 1 = 1.2, SE at 4 months = 1.2) and for the positive symptoms (SE on Day 1 = 1.1, SE at 4 months = 1.2). Thus, although the mean symptoms scores were significantly reduced by the 4-month follow-up, the variance of the symptoms within this group of patients did not alter. A similar pattern is seen in the working memory scores of schizophrenia patients; the standard error for Day 1 was 2.95 and that for the 4-month follow-up was 2.89. Again, the mean working memory score improved over a period of 4 months, but the range of performance within the schizophrenic group did not change.

Another possibility is that the symptoms and working memory deficit are indirectly associated. Spatial working memory tasks require maintenance of representation (e.g., efficient functioning of the dorsolateral prefrontal cortex), moving attention to spatial locations (e.g., efficient functioning of the parietal system) as well as control of response selection and inhibition of irrelevant stimuli (e.g., dorsolateral and orbitofrontal systems). We have previously argued elsewhere (Park et al 1995a; Park and O'Driscoll 1996; Park in press) that the performance of the schizophrenia patients on spatial working memory tasks is characterized by a failure to maintain information during

the delay period, more than by a failure to inhibit distracting stimuli. Carter et al (1996) suggest that there may be additional deficits in efficient encoding of spatial location. We characterize the spatial working memory deficit in schizophrenia as consisting of a fundamental core failure to maintain representation via the circuitry mediated by the dorsolateral prefrontal system, plus a contingent deficit in either efficient encoding of the spatial location or temporary disinhibition during the response stage. It is possible that clinical symptoms may be associated with the contingent deficits more than with the hypothesized core deficit of representational failure. This possibility should be tested in future studies.

One very interesting finding is that the negative symptoms (but not positive symptoms) during the acute state correlated significantly with the degree of spatial working memory deficit at the 4-month follow-up session. Those with more severe negative symptoms during the acute phase tended to have greater deficits in spatial working memory and this working memory deficit persisted over the period of 4 months. Future research can determine whether more severe negative symptoms indicate also a greater degree of pathology and therefore, enduring deficits in prefrontal function.

Absence of stable associations between the clinical symptoms and the spatial working memory performance over time is consistent with our hypothesis that spatial working memory deficit may be a permanent feature of the pathophysiology of schizophrenia. In support of this view, about half of the nonpsychotic, first degree relatives of schizophrenia (Park et al 1995a) and a subgroup of psychometrically ascertained schizotypes (Park et al 1995b; Park and McTigue 1997) have also been found to show spatial working memory deficits, in the absence of clinical symptoms. But although symptoms and cognitive functions may be associated, the nature of the link remains unspecific. It is interesting to note that spatial working memory was weakly associated with a psychometric scale tapping social withdrawal (i.e., negative symptomatology) in one study of schizotypal individuals (Park and McTigue 1997), and with the perceptual aberration scale (i.e., positive symptomatology) in another study (Park et al 1995b).

In schizophrenia patients, we may observe associations at one given time because the manifestations of clinical symptoms and cognitive deficits may be mediated by overlapping neural systems. But it is an awkward process to compare cognitive performance, measured by functionally specific and modular tasks with clinical symptoms ratings, because the categorical boundaries of clinical symptoms are naturally fuzzy (Smith and Medin 1981). We are dealing with fundamentally different levels of descriptive psychopathology. The division of negative

from positive symptoms is a useful distinction, but it is unlikely that these two clinical categories will map neatly onto two distinct neural systems. The cluster of behaviors tapped by just one item in the BPRS or the PANSS may be mediated by multiple and diffuse cortical and subcortical neural circuits. The same may be true for complex cognitive tasks, but it is still possible to create simple paradigms to tap specific neural systems. Moreover, by including appropriate control tasks, it is possible to rule out generalized deficits and to narrow down the possible neural systems involved in mediating one particular component of a cognitive task. Although current psychiatric symptom rating scales are valid and reliable, one ought to strive for cognitively and neurobiologically constrained rating systems in the future.

Finally, the heterogeneity of schizophrenia must be considered. Future studies should adequately address the individual differences within the schizophrenia category. Although most schizophrenia patients show spatial working memory deficits, some patients do perform within the normal range. Whether those schizophrenia patients with intact spatial working memory may have a better long term outcome is unknown, but remains an important empirical question. In conclusion, we suggest that the spatial working memory function, mediated by the dorsolateral prefrontal cortex, is impaired in a substantial proportion of schizophrenia patients and that this deficit may be an essential feature of the phenotype of the schizophrenia spectrum.

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