Spatial Working Memory Deficits and Their Relationship to Negative Symptoms in Unmedicated Schizophrenia Patients

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Introduction

A role for pathology in neural circuits involving the dorsolateral prefrontal cortex (DLPFC) underlying cognitive deficits in schizophrenia has been emphasized in the literature in recent years. In particular, analogies have been drawn between cognitive deficits seen in schizophrenia and working memory deficits observed in behaving nonhuman primates with lesions in the principal sulcal region of the prefrontal cortex (Goldman-Rakic 1987). Activity of neurons in this region during a delay period is associated with accurate performance during oculomotor spatial delayed response tasks. This activity appears dependent upon catecholaminergic, particularly dopaminergic innervation (Brozoski et al 1979; Sawaguchi and Goldman-Rakic 1991). This has led to a model of cognitive deficits in schizophrenia characterized by dysfunction in dopaminergic innervation in dorsolateral prefrontal cortex resulting in impaired working memory function.

Recently, Park and Holzman (1992) reported that medicated schizophrenia patients showed impairment on a human analogue of the oculomotor delayed response task used by Goldman-Rakic in her studies of nonhuman primates, as well as on a haptic version of the task. This finding provided an important empirical link between theory based upon primate neurophysiology and cognitive dysfunction in schizophrenia. Subsequently, this group reported that spatial working memory deficits were correlated with eye tracking dysfunction in a second medicated group of patients (Park and Holzman 1993). Most recently, this group (Park et al 1995) reported impairment on a nonoculomotor version of this task in nonschizophrenic relatives of schizophrenia patients. This suggests that the deficits in working memory performance seen in schizophrenia may not merely be the result of antipsychotic treatment, and that they are generalizable to tasks that do not require an oculomotor response. In the study below we present results using a nonoculomotor spatial delayed response task in medication-withdrawn patients that confirms the presence of spatial working memory pathology in schizophrenia. Our results also provide very preliminary support for an association between spatial working memory deficits and negative symptoms in schizophrenia.

Methods

Subjects

Eighteen outpatients who met the criteria for schizophrenia by the Structured Clinical Interview for DSM-III-R were compared to 15 normal controls who were matched to the patients on years of age [patients: mean 34.1, SD 8.3; controls: mean 34.6, SD 9.0; t (df = 31) = 0.16, p < .90] and gender [patients: 3 women and 15 men; controls: 6 women and 9 men; chi-square (df = 1) = 2.25, p > .13]. As part of their participation in an investigational...
drug study, patients had been withdrawn from oral antipsychotic medications for at least 10 days prior to testing. Prior to withdrawal patients were on a variety of conventional, oral antipsychotics; a subgroup of 4 subjects had been treated with remoxipride. All subjects were free from benzodiazepines and anticholinergic medication for at least 24 hours prior to testing. Patients and control subjects with histories of head trauma, neurological disorders, or substance abuse within the previous 6 months were excluded from the study.

Clinical Ratings

Patients were rated using either the Negative Symptoms Assessment (NSA, Alphs et al 1989, n = 10) or the Schedule for Assessment of Negative Symptoms (SANS, Andreasen 1982, n = 7), and the brief psychiatric rating scale (BPRS, Overall and Gorham 1962). All patients evaluated using the NSA were assessed by a single rater, a masters level psychiatric research nurse (LO-C). All patients evaluated using the SANS were also rated by a single rater (L.K), a psychiatric research fellow. Periodic reliability sessions were conducted by study monitors for the clinical trials in which patients were enrolled to establish and maintain reliability and to prevent rater drift. Negative symptoms consisted of the global negative symptom score on the NSA, or the mean of the global subscales of the SANS. The Global Attention scale of the SANS (Andreasen 1982) was not included, since there are no comparable items on the NSA, and increasing evidence suggests that inattention may be associated with a distinct dimension of symptoms (disorganization) in schizophrenia (Liddle and Morris 1991). Since the SANS is a 5-point and the NSA a 6-point scale, NSA scores were adjusted by collapsing items scored 1 or 2 (none or mild) as 1 prior to conducting the analysis. Ratings were not available for 1 patient. The means and standard deviations for the Negative Symptom rating, the BPRS positive symptoms, and the total BPRS score were 2.65 (SD 0.89), 8.23 (SD 5.07), and 19.76 (SD 11.12), respectively.

Procedures

Subjects were tested in a darkened, quiet room. Stimuli were presented using a Hewlett-Packard 286 PC and color monitor. The task was programmed using MEL software. Subjects received standardized instructions and were practiced on the task prior to the experiment. Subjects performed two blocks of 24 trials, with 12 trials in each block at each of two delay intervals. Each trial began with a central fixation cross presented for 500 msec. A small probe subtending a visual angle of 0.5° then appeared for 150 msec at one of 12 locations along a radius 9° eccentric to fixation. The screen then went completely blank, and after either 0 or 8000 msec an array of 18 letters appeared, one of which marked the location of the probe. The location and identity of the letters varied along the 9° radius randomly. Subjects were required to respond by identifying the letter that marked the location at which the probe appeared. The investigator then confirmed the response with the subject (providing an opportunity to correct their initial response) and keyed it into the computer. This initiated the next trial.

Table 1. Percentage of Correct Responses (out of a Total of 24 Trials) for Each of the Two Groups (Schizophrenia Patients and Normal Controls) for the Two Delay Periods (0 and 8 s)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Accuracy no delay</th>
<th>% Accuracy 8-s delay</th>
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</thead>
<tbody>
<tr>
<td>Schizophrenia patients</td>
<td>92.4 (SD 7.6)</td>
<td>76.2 (SD 17.3)</td>
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<tr>
<td>(n = 18)</td>
<td></td>
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<tr>
<td>Normal controls</td>
<td>98.1 (SD 3.5)</td>
<td>90.0 (SD 9.8)</td>
</tr>
<tr>
<td>(n = 15)</td>
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The significant group by delay interaction indicates that schizophrenia patients show a greater degradation of performance during the delay, and hence an impairment of spatial working memory performance, compared to controls.

Analysis

The number of correct responses under delay and nondelay conditions were cast into an analysis of variance (ANOVA) with group as the between-subjects factor and delay as the within-subjects factor. Within the patient group the relationship between negative symptoms and working memory deficits was evaluated by computing the Pearson Product–Moment Correlation Coefficient. To establish the specificity of this relationship, correlations were also performed between the total BPRS score and the positive symptoms subscale of the BPRS (Kane et al 1988).

Results

The accuracy of schizophrenia patients and normal controls is shown in Table 1. ANOVA on total correct responses revealed a main effect of group [F(1,31) = 8.7, p < .01], a main effect of delay [F(1,31) = 36.9, p < .001], and a significant group by delay interaction [F(1,31) = 4.2, p < .05]. Patients showed a greater increase in errors during the delay period, indicating a spatial working memory deficit. The Pearson Product–Moment Correlation Coefficient between negative symptoms and delay errors (the difference between a subject's accuracy under the delay and under the no-delay condition) was .50, p < .05. Correlations between delay errors and the BPRS total score, and the BPRS positive symptom factor were R = .36, p < .16 and R = .46, p < .08, respectively.

Discussion

Although schizophrenia patients made more errors overall, the significant interaction with delay confirms the presence of spatial working memory impairment in medication-withdrawn patients with this illness. This result is consistent with the presence of hypothesized abnormalities in neural circuits mediating spatial working memory performance, which have been confirmed in recent positron emission tomography (PET) studies of normal humans (Jonides et al 1993) to include the DLPC. It is noteworthy that, as in the study of Park et al (1995), this abnormality was evident in a task that does not require an overt oculomotor response. This indicates that this deficit extends beyond neural systems related to the control of memory-guided saccades, and is amenable to investigation without the need for eye movement measurement.

Unlike previous studies of spatial working memory perfor-
formance in schizophrenia (Park and Holzman 1992, 1993), the patients in the current study had been withdrawn from medication for a minimum of 10 days prior to testing. Our decision to use a 10-day washout represented a compromise between what might be pharmacologically ideal, and the need to ensure that patients would not relapse during this period. It might be argued this washout would produce a relative, rather than absolute, unmedicated state, since in rats (Clow et al 1980) the behavioral effects of neuroleptics may persist for up to a month after discontinuation from chronic use; however, these results, together with the recent observation that the never-medicated relatives of schizophrenia patients also show deficits of spatial working memory (Park et al 1995), suggest strongly that this deficit is not the result of medication, but reflects pathology associated with the illness itself.

We found that the degree of spatial working memory impairment correlated significantly with the patient's level of negative symptoms. This result provides support for an association between negative symptoms, working memory dysfunction, and prefrontal cortical dysfunction. The caveat to the above conclusion is that BPRS positive symptoms and total BPRS scores also tended to correlate, albeit less strongly, with delay errors, and in fact symptom scores tended to be correlated with one another in this mildly ill ambulatory group of patients. The specificity of this relationship is, therefore, not established by the current data. Further studies of patients with a wider range of symptoms are required to establish both the reliability and the specificity of this relationship in schizophrenia.

Working memory performance reflects the function of a complex cognitive system (Baddeley 1976). It would be valuable to conduct experiments using cognitive dissection (Holzman 1994) to more precisely isolate the nature of the cognitive deficit underlying the impaired performance during spatial delay tasks. Park et al (1995) suggested that because patients (and their relatives) were impaired on never-corrected trials, this abnormality is isolated to the "maintaining" operation, within a spatial buffer system, rather than nonspecific factors such as increased distractibility. Our result is to some degree consistent with this interpretation, since patients had the opportunity to correct their initial responses; however, it remains possible that impairments in other factors contributing to spatial working memory performance, such as spatial attention and encoding or updating processes, may also be impaired in schizophrenia. In support of this latter possibility, inspection of Table 1 reveals that patients made more errors at the 0-sec delay than did controls, suggesting the presence of an encoding or attentional deficit. A post hoc comparison indicated that this difference was statistically significant [t(31) = 2.7, p < .01]. Future studies of spatial working memory pathology in schizophrenia should begin to isolate components of working memory to determine the precise nature of this aspect of the cognitive dysfunction seen in schizophrenia.

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References


