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Visual object working memory function and clinical symptoms in schizophrenia

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Abstract

Objective: The presence of working memory deficits suggests abnormalities of prefrontal cortex (PFC) in schizophrenia. Although much is known about spatial working memory deficits in schizophrenia, including its potential as a phenotypic marker, it is unclear whether object working memory is similarly affected. Our goal was to examine nonspatial, object working memory function in relation to clinical symptoms. *Methods*: We assessed object working memory and clinical symptoms in 28 schizophrenia patients during acute psychotic episode and 4 months later during partial remission. Delayed-matching-to-sample tasks for familiar object (DMTS-F) and novel shapes (DMTS-N) were used. Symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS). 33 age-matched normal subjects were also tested over the same time period. *Results*: Acutely psychotic patients showed deficits in both DMTS-F and DMTS-N. Four months later, their DMTS-F performance improved significantly but deficits in DMTS-N were still present. During acute psychosis, symptoms correlated with DMTS-F but not with the DMTS-N. Four months later, negative symptoms correlated with both tasks. *Conclusions*: Object working memory as measured by DMTS-N was impaired in schizophrenia patients during both acute and chronic states. When schizophrenia patients were in partial remission, object working memory was associated with negative symptoms.
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Keywords: Schizophrenia; Working memory; Positive and negative symptoms; Frontal cortex; Delayed-matching-to-sample; Visual working memory; Object working memory

1. Introduction

It has been suggested that working memory (Goldman-Rakic, 1991; Park and Holzman, 1992) or 'maintenance of context' (Servan-Schreiber et al., 1996) may underlie a wide range of cognitive deficits observed in schizophrenia patients. Working memory may be understood 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 (1986) model, temporary maintenance of information is achieved by an active control system called the central executive, aided by modality-specific 'slave' systems. Dissociation of verbal and spatial working memories as well as that of spatial and object working memories have been demonstrated in healthy humans (Baddeley, 1986). Thus, cognitive models of working memory posit separable, functional components that can be independently probed.

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Analogous to visual information processing, there is dissociation between pattern-based visual working memory and spatial working memory in humans (Baddeley and Lieberman, 1980; Farah, 1988) and in nonhuman primates (Bachevalier and Mishkin, 1986; Kowalska et al., 1991; Wilson et al., 1993). Both neuroanatomical and psychological data suggest that there are at least two streams of visual information processing in the brain. The dorsal stream, including the posterior parietal cortex and the dorsolateral prefrontal cortex (DLPFC), processes spatial information, whereas the ventral stream, including the temporal cortex and ventral and orbital frontal regions (Ungerleider and Mishkin, 1982; Miller et al., 1993), is involved in processing the featural aspects of visual information. This dissociation has been posited within the prefrontal cortex where spatial working memory appears to be mediated by the DLPFC, especially the principal sulcus region, whereas nonspatial, object working memory seems to be mediated by the ventral and orbital frontal regions (Bachevalier and Mishkin, 1986; Wilson et al., 1993; Oscar-Berman, 1975; Freedman and Oscar-Berman, 1986). These results suggest that working memory may be mediated by domain-specific subsystems and the functional modularity of orbitofrontal/ventral frontal and DLPFC systems. However, it is also possible that the kind of processing demanded by the different working memory tasks rather than the task modality is crucial and that the dorsolateral and ventral prefrontal systems may both contribute to spatial and nonspatial working memory (Petrides, 1998). Petrides (1998) suggests that the orbital and ventral frontal systems actively select, maintain, and compare stimuli in working memory. We have argued previously that maintenance of information over delay may be disproportionately affected in schizophrenia (Park et al., 1995a; Park and O'Driscoll, 1996) in addition to their deficits in executive components. If maintenance is severely impaired, both spatial and object working memory systems should be abnormal.

Ample evidence points to the existence of spatial working memory deficits in schizophrenia patients (Park and Holzman, 1992, 1993; Carter et al., 1996; Keefe et al., 1995; Spindler et al., 1997; Gooding and Tallent, 2001). Spatial working memory deficit does not appear to be a simple artifact of neuroleptic medication because almost half of the healthy, first-degree relatives of schizophrenia patients show spatial working memory deficits, in the absence of medication (Park et al., 1995a). In contrast, bipolar patients taking similar neuroleptics show intact spatial working memory (Park and Holzman, 1992, 1993; Gooding and Tallent, 2001). The presence of spatial working memory deficit in the relatives as well as in schizotypal subjects (Park et al., 1995b; Park and McTigue, 1997) suggests that it might be a phenotypic marker for schizophrenia. Indeed, spatial working memory deficit may be a permanent, trait-like feature of schizophrenia since it is present during the acute, psychotic stage of the illness as well as in remission (Park et al., 1999). These findings therefore suggest significant and permanent abnormalities of the functioning of the DLPFC in schizophrenia patients. Neuroanatomical data partly support this view. Abnormally high neuronal density in the DLPFC of schizophrenia patients, implicating a reduction in intraneuronal neuropil, has been reported (Selemon et al., 1995). The next question is whether the working memory deficit extends to nonspatial, visual domains.

One recent study reported both spatial and object working memory impairments in schizophrenic patients (Spindler et al., 1997), suggesting that working memory deficit in schizophrenia extends to nonspatial, visual domains. The next step is to examine whether object working memory deficits are also a permanent feature of schizophrenia. In the present study, we examined nonspatial, object working memory function, in relation to clinical symptoms over a period of 4 months. We recruited acutely ill patients within 2 weeks of admission to a psychiatric hospital and retested the same patients 4 months later when they were in partial remission.

2. Methods

2.1. Subjects

Twenty-eight (10 women) acutely ill schizophrenia patients (mean age = 34.8, S.E. = 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. Subjects were screened for the following criteria: substance abuse, neurological disorders, and history of head

injury. There were two first episode patients. All others were relapse patients. The mean duration of illness was 9.8 years (S.E. = 1.2). Four months later, working memory and clinical symptoms were reassessed. All patients were in partial remission and were clinically stable at the time of retesting. During the acute psychotic episode, the average CPZ equivalent was 302.8 mg (S.E. = 56). Four months later, the CPZ equivalent was 330.3 mg (S.E. = 58). There was not a significant change in the drug dose over the 4 months ($F(1,31) = 0.47$, $p > 0.49$).

Thirty-three (16 women) normal control participants (mean age = 36.3, S.E. = 1.7) were recruited from the same city and were retested 4 months later. Control subjects had no history of substance abuse, head injury, family history of psychiatric illness, or neurological disorders. They were not taking any psychotropic medications.

The two groups did not differ statistically in educational level (normal controls = 12.8 vs. schizophrenia patients = 12.2 years), age (normal controls = 36.3 vs. schizophrenia patients = 34.8 years), and handedness (two left-handers in schizophrenia group vs. three 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 different. An overwhelming majority of the Swiss population belongs to the middle class and almost all Swiss children attend state schools. Informed consent was obtained from all participants.

2.2. Procedure

Clinical interviews and ratings were conducted in the morning and the cognitive experiments in the afternoon at both testing sessions.

2.2.1. Clinical ratings (Positive and Negative Syndrome Scale)

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used. The PANSS consists of 30 items. Each item is rated on a 7-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 three scales to measure negative symptoms (7 items), positive symptoms (7 items), and general psychopathology (16 items). PANSS ratings were completed by a psychiatrist who was blind to the task performance of the subjects.

2.2.2. Object working memory tasks

Subjects fixated in the center and then pressed the spacebar to initiate a trial. A target stimulus was flashed for 200 ms on a computer screen fitted with a touchscreen (TrollTouch™, CA). Then there was a delay period of 10 s, during which subjects performed an intervening task which consisted of observing a series of subtractions that appeared at the center of the screen and deciding whether the calculation was correct or not (Park et al., 1999). The intervening task was included to prevent verbal rehearsal and to force subjects to fixate at the center during the delay. After the delay period (10 s), four pictures were presented on the screen (above, below, to the left, and to the right of the fixation point). Subjects were required to touch the target stimulus that they had seen before the delay period began. The positions of these stimuli were randomly selected so that the target position at the response stage could not be predicted from its original position before the delay. The stimuli were trial unique. See Fig. 1 for procedure.

There were two different types of stimuli. In the familiar object matching-to-sample condition (DMTS-F), line drawings of common objects (Snodgrass and Vanderwart, 1980) were used as stimuli. Because humans name or label objects spontaneously, this task ends up tapping verbal working memory. In the novel object matching-to-sample condition, abstract, unfamiliar, nonsense shapes were used as stimuli. These stimuli were selected from a pool of patterns so that they were unlikely to be named or labeled verbally. In a pilot study, 400 random visual patterns were generated by a graphics program on the Macintosh computer and were presented to 30 undergraduate students. They were asked to ‘name’ the patterns within 10 s of presentation of each pattern. Those visual patterns with no incidence of naming were selected as the target stimuli in the object working memory task for novel shapes (DMTS-N). Therefore, DMTS-N is a purer measure of visual object working memory without incidental verbal coding.

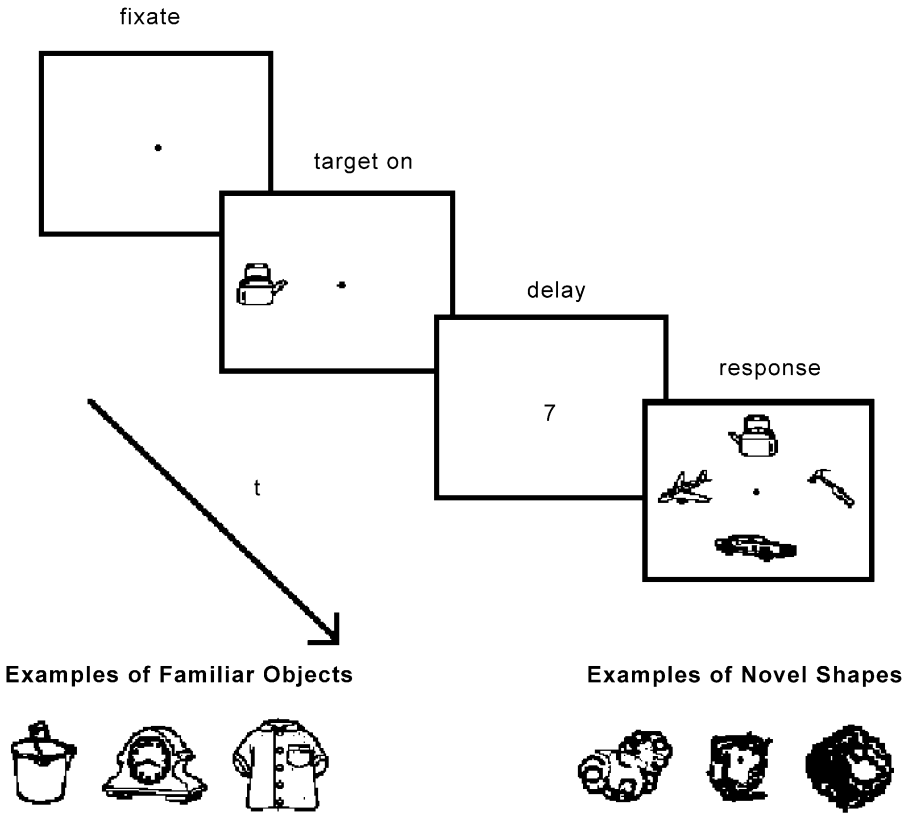

Fig. 1. Delayed-matching-to-sample task.

After eight practice trials, subjects were tested on a block of familiar object working memory trials and a block of novel object working memory trials. There were 32 trials per block. The order of presentation of the blocks was counterbalanced across subjects.

3. Results

3.1. Scoring

Accuracy (%correct) was computed. A response was scored as correct only if the subject touched within 40 pixels of the center of the target object.

3.2. Statistical analyses

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

3.3. Accuracy

The means and standard errors for the familiar and novel object working memory tasks are summarized in Table 1. Repeated measures, multifactorial ANOVA was conducted for the accuracy of familiar and novel object working memory.

There was a main effect of diagnosis ($F(1,59) = 29.1$, $p < 0.0001$). Overall, schizophrenia patients performed less accurately than did the controls. There was also a main effect of the task type ($F(1,59) = 125.9$, $p < 0.0001$). Subjects, regardless of diagnosis, performed better on the DMTS-F than on the DMTS-N. An interaction of task type and diagnosis ($F(1,59)=$

Table 1
Mean (S.E.) visual object working memory accuracy (% correct)

	Day 1		4-month follow-up	
	DMTS-F	DMTS-N	DMTS-F	DMTS-N
Schizophrenia	90.9 (2.2)	74.6 (2.6)	98.2 (0.5)	87.1 (2.0)
Control	99.2 (0.4)	94.6 (0.9)	99.2 (0.3)	96.4 (0.7)

38.6, $p<0.0001$) suggests that schizophrenia patients showed deficits in both familiar and novel object working memory tasks but that they were much more impaired when they had to remember novel shapes.

There was a main effect on the time of testing ($F(1,59)=24.6$, $p<0.0001$). Subjects performed better on the second testing session than on the first but an interaction between the time of testing and diagnosis ($F(1,59)=18.4$, $p<0.0001$) indicates that the improvement at the second testing session reflects the greatly improved performance of the schizophrenia patients and not of the controls whose performance stayed constant. There was a trend towards a three-way interaction between diagnosis, task type, and time of testing ($F(1,59)=2.8$, $p<0.09$).

To further examine the group differences on the two object working memory tasks, contrast analyses were performed for separate testing days. On Day 1, schizophrenia patients performed worse than normal controls on the DMTS-F ($F(1,59)=16.5$, $p<0.0001$). Four months later, the difference between the two groups on this task was greatly reduced to a trend level ($F(1,59)=3.1$, $p<0.09$). However, for the DMTS-N, there was a significant group difference on Day 1 ($F(1,59)=30.4$, $p<0.0001$) and 4 months later ($F(1,59)=20.6$, $p<0.0001$).

There was a concern that the controls were performing at ceiling on the DMTS-F task, and therefore, the assumption of homogeneity of variance may have been violated. In order to address this problem, we performed a nonparametric test (Mann–Whitney U) to compare the two groups. On Day 1, the two groups differed significantly on DMTS-F ($U=168$, $Z=-4.26$, $p<0.0001$). At 4 months, this difference was no longer significant ($U=373$, $Z=-1.29$, $p>0.11$). For the DMTS-N on Day 1, the two groups differed significantly as tested by Mann–Whitney ($U=86$, $Z=-5.5$, $p<0.0001$). At 4 months, this

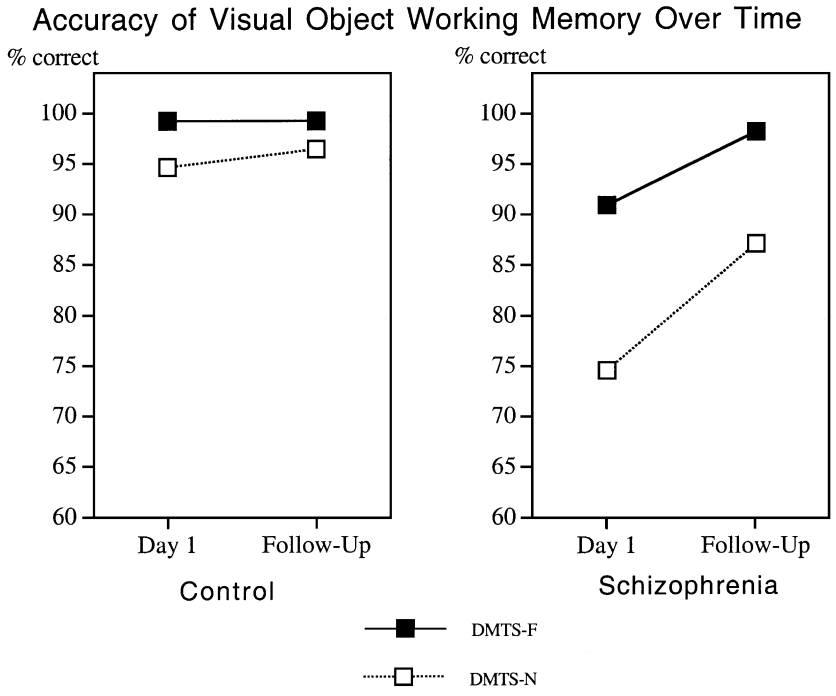

Fig. 2. Accuracy of visual object working memory over time.

difference was still significant. ($U=207$, $Z=-3.76$, $p<0.0002$). For the summary of object working memory function scores, see Fig. 2.

3.4. Symptoms

On Day 1, the mean negative symptoms score was 12.0 (S.E. = 1.3). At 4 months, it was reduced to 7.1 (S.E. = 1.3). The mean positive symptoms score on Day 1 was 15.5 (S.E. = 1.2) and at 4 months was 6.9 (S.E. = 1.3). A repeated-measures ANOVA was performed to examine the symptoms over time. Both positive symptoms ($F(1,27)=38.4$, $p<0.0001$) and negative symptoms ($F(1,27)=13.7$, $p<0.001$) improved significantly at the 4 months follow-up. Correlations were computed between the positive and negative symptom scores and the two object working memory scores for each testing session.

On Day 1, accuracy of familiar object working memory was significantly correlated with both positive ($r=-0.38$, $p<0.05$) and negative symptoms ($r=-0.37$, $p<0.05$). Those who performed better on DMTS-F tended to have lower PANSS scores but the accuracy of DMTS-N was not associated with the positive ($r=-0.23$, $p>0.22$) or with the negative symptoms ($r=-0.18$, $p>0.35$). Thus, during acute psychosis, only the DMTS-F was associated with symptoms.

Four months later, the pattern of association between symptoms and object working memory was different. Negative symptoms correlated significantly with the familiar object working memory ($r=-0.49$, $p<0.02$) and with the novel object working memory ($r=-0.60$, $p<0.005$), but the positive symptoms did not correlate significantly with the familiar object DMTS ($r=-0.04$, $p>0.90$) or with the novel shape DMTS ($r=-0.28$, $p>0.20$). These results suggest that during partial remission, object working memory performance was associated only with the negative symptoms.

We also examined the correlation between the working memory performance on Day 1 and the symptoms score 4 months later to see if we could predict future clinical symptoms from the cognitive performance on Day 1. Working memory for familiar objects on Day 1 did not predict the negative symptoms ($r=-0.31$, $p>0.11$) or the positive symptoms ($r=-0.21$, $p>0.15$) 4 months later. However, novel object working memory score on Day 1 was associated with the negative symptoms 4 months later ($r=-0.40$, $p<0.05$), while there was no significant correlation for the positive symptom 4 months later ($r=-0.27$, $p>0.15$).

4. Discussion

We examined visual object working memory in schizophrenia patients and healthy controls over a period of 4 months. The patients were acutely ill at the first testing session but were in partial remission 4 months later. At 4 months, working memory for familiar object and novel shapes both improved but deficits were still very much significant for the novel shapes. Thus, visual object working memory as assessed by DMTS-N may be a stable feature of schizophrenia.

There was a significant difference between the two object working memory tasks. It can be argued that the familiar object DMTS is ‘easier’ than the novel shape DMTS. But why is it easier? All subjects verbally named the familiar objects automatically, and therefore, familiar object DMTS may end up becoming essentially a verbal working memory task for humans, with access to both visual and verbal representations. Availability of verbal labels may significantly improve the performance. With the novel shapes, verbal labeling was prevented, and therefore, the novel shape DMTS was a purer test of visual object working memory.

4.1. Reduced cognitive capacity?

When the patients were acutely psychotic, they performed worse than controls on both DMTS-F and DMTS-N, but when they were in partial remission at 4 months, they showed almost intact working memory for the familiar objects. All subjects, regardless of diagnosis, remembered the familiar objects better than the novel shapes but this difference is even greater for the schizophrenia patients. It is possible that acute psychosis impairs cognitive ability in general, and therefore, the patients show deficits even on the ‘easier’ task. Hence, the object working memory deficit observed on Day 1 may be partly due to an overall reduction in *all* cognitive and perceptual

functions, stemming from the acutely psychotic state. When the symptoms are significantly reduced at 4 months, schizophrenia patients perform almost as well as the controls on the familiar object working memory task. A global improvement in cognitive functioning may be enough to normalize the performance on the 'easier' familiar object DMTS but not enough to normalize the novel shape DMTS. The next question is whether the observed deficit for the novel shape DMTS at 4 months is also a manifestation of generalized cognitive deficit rather than that of working memory deficit. While this is a possibility, it seems unlikely. First, familiar object working memory was almost intact at 4 months. Moreover, these patients were not impaired in all aspects of neurocognitive functioning. The same group of subjects also participated in an attentional inhibition study over the same time period. We found that attentional inhibition was impaired only during the acute episode and that it was restored when the patients were in partial remission (Park et al., 2002). Thus, some of the core cognitive functions were intact in these patients at 4 months.

4.2. Symptoms and object working memory

We found that the performance of schizophrenics on the DMTS-N was impaired at both testing sessions, suggesting that this deficit is present regardless of positive symptoms. This finding is similar to our earlier reports of stability of spatial working memory deficit in schizophrenia patients (Park et al., 1999). Our data suggest that object working memory may be impaired even when the patients are in partial remission. The correlation between the clinical symptoms and the DMTS-N was inconsistent over time. When the patients were acutely ill, the symptoms and the DMTS-N were not associated, but at 4 months, negative symptoms correlated significantly with DMTS-N. During acute psychosis, a range of perceptual and cognitive functions are impaired, especially those functions that allow us to inhibit irrelevant stimuli. Latent inhibition, negative priming, as well as other attentional functions are disrupted during acute psychosis but can be restored with antipsychotic medication (Baruch et al., 1988; Gray et al., 1991; Swerdlow et al., 1998). These attentional abnormalities may affect subcomponents of the working memory task and, hence, mask the potential relation between the symptoms and the working memory performance. For example, an inability to ignore distractor stimuli may increase errors on the object working memory task. At the response stage, schizophrenia patients may not be able to inhibit the three incorrect stimuli and, therefore, choose the distractor instead of the correct target, even if they had maintained the correct representation over the delay period. At the 4-month follow-up, the patients still were symptomatic but their PANSS scores were substantially reduced. At this stage, only the negative symptoms correlated with the DMTS-N.

To conclude, we found that visual object working memory, as assessed by the novel DMTS, is impaired in schizophrenia patients. Previously, we reported that spatial working memory, mediated by the DLPFC, is impaired in a majority of schizophrenia patients and about half of their relatives. Object working memory for novel shapes is similarly affected in schizophrenia and persists during partial remission. We also found a significant correlation between the negative symptoms and the visual object working memory during partial remission. The nature of negative symptoms revolves around poor social and emotional functioning. There is substantial evidence to support the role of orbitofrontal and ventral frontal cortex in regulation of social and affective behaviors (see Bechara et al., 1997; Girgis, 1971). The visual object working memory task was designed to tap these systems. Although the connection is still tenuous, it may be fruitful to investigate changes in the object working memory function in relation to reduction in negative symptoms. Such investigations may be helpful in assessing the efficacy of new antipsychotic drugs targeting negative symptoms.

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