Visual Perceptual and Working Memory Impairments in Schizophrenia

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Background: Impairments in working memory have been proposed to underlie a broad range of cognitive deficits seen in schizophrenia. Visual working memory impairments are frequently reported in schizophrenia. Investigations of visual working memory generally assume intact visual information processing, despite evidence of visual perceptual impairments in schizophrenia. In this study, we evaluated the integrity of the perceptual system for object and spatial visual information and the relevant working memory system, after adjusting for individual perceptual performance differences.

Methods: Thirty patients with schizophrenia and 20 healthy control subjects underwent testing using a task of perceptual discrimination of spatial and object visual stimuli. For testing visual working memory, a delay was introduced to the perceptual discrimination task. A thresholding procedure was used so that each subject adequately perceived the information during the working memory test.

Results: Subjects with schizophrenia exhibited impaired performance relative to controls for object and spatial visual perceptual discrimination. The extent of impairment was greater for the object than for the spatial test. After controlling for perceptual impairments, the subjects with schizophrenia exhibited impaired performance relative to controls for the spatial working memory test but not the object working memory test.

Conclusions: Findings implicate dysfunction of posterior brain areas that mediate visual perceptual processing and the prefrontal areas involved in the active maintenance of information during delay intervals. However, the systems that govern object and spatial visual perception and working memory appear to be affected differentially by schizophrenia.

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Working memory is a multicomponent cognitive system that serves to hold briefly a limited amount of information "online" and to manipulate that information so that it is available for further cognitive processing or to guide response selection. Although working memory can be considered a discrete cognitive function, this elementary capacity is generally thought to be necessary for a wide range of complex cognitive functions such as language comprehension, learning, reasoning, and planning. Patients with schizophrenia typically demonstrate marked deficits on such complex tasks, as well as on more elementary working memory tasks. Thus, it has been proposed that an impairment of working memory may be responsible for much of the observed cognitive disturbance of the illness. In addition, working memory deficits have also been related to symptomatic aspects of the illness, including thought disorder and negative symptoms. Thus, delineation of the nature of working memory dysfunction in schizophrenia may shed important light on the neural substrates of the illness.

Many monkey and human working memory studies have used versions of delayed response and delayed match to sample tasks. In these tasks, the subject is first presented with some type of informative cue or stimulus, followed by a delay during which the cue is removed. The subject then must make a response using a mental representation of the original cue to guide response selection. Correct response selection is dependent on at least 2 potentially independent cognitive processes, ie, the cue must be encoded accurately, and this information must be precisely maintained during the delay interval. Results of single-cell recording studies in nonhuman primates and human functional imaging studies have demonstrated that a widely distributed cortical network mediates the performance of these
SUBJECTS AND METHODS

SUBJECTS

The patient study group, recruited from the Outpatient Research Program of the Maryland Psychiatric Research Center, Baltimore, Md, consisted of 30 clinically stable subjects who met DSM-IV criteria for schizophrenia. This patient population has been shown to be similar to the community mental health clinic population in the area. A best-estimate diagnostic approach was used in which information from the Structured Clinical Interview for DSM-IV Axis I Disorders is supplemented by information from family informants, previous psychiatrists, and medical records. Patients with a DSM-IV diagnosis of current alcohol and other substance use verified with results of blood screens, mental retardation, or a medical-neurologic condition for which the pathologic features or their treatment would likely confound the neuropsychological test results were excluded from the study.

On average, patients were aged 42.9 (±7.2) years, with illness duration of 22.0 (±8.1) years (mean age of onset, 21.0±5.0). Brief Psychiatric Rating Scale total score of 37.0±11.7, and Schedule for the Assessment of Negative Symptoms score of 24.7±13.8. All patients underwent testing while receiving antipsychotics, and 24 patients (80%) were receiving atypical antipsychotics.

A group of 20 healthy controls participated in the study. Controls underwent screening by means of a standardized procedure with detailed medical history, blood screens for drug abuse, complete psychiatric evaluation including Structured Clinical Interview for DSM-IV Axis I Disorders, and physical and neurologic examinations. Controls were excluded if they had (1) past or present DSM-IV Axis I or schizophrenia spectrum Axis II disorder; (2) a family history of psychotic illness in their first- or second-degree relatives ascertainable by means of a standardized demographics checklist; or (3) any other medical illness known to affect brain function.

Patient and control groups were comparable for age (42.9±7.2 and 40.0±11.4 years, respectively; tsub=1.14 [P=.26]), and education (12.8±1.8 and 13.8±1.7 years, respectively; tsub=1.98 [P=.06]). There were more male subjects in the control than the patient group (25/30 [83%] vs 10/20 [50%]; χ²=6.35 [P=.01]).

All subjects were provided a complete description of the proposed study and gave written informed consent before study participation. Patients were required to demonstrate an understanding of study demands, risks, and their rights to withdraw in response to probe questions before signing consent documents. The Institutional Review Board of the University of Maryland School of Medicine, Baltimore, approved the study protocol and consent procedures. Controls were compensated for study participation.

PROCEDURES

The perceptual discrimination and working memory abilities of all subjects were assessed with variants of a basic paradigm validated by Smith et al as measures of object and spatial working memory in a positron emission tomography study with normal controls. It has also been used for previous clinical behavioral studies by Postle et al. The basic paradigm is described first, followed by the specific variants used to assess perceptual discrimination and working memory. In this paradigm, subjects were first asked to focus on a fixation cross in the middle of a blank computer screen. This fixation cross remained on the screen throughout the experiment. Then, a target display composed of 2 abstract figures was presented. Stimuli were gray irregular polygons randomly chosen from 60 shapes adapted from Vanderplas and Garvin. After a delay interval, a single-probe stimulus was presented. Subjects were asked to judge whether the probe matched the target in shape (object) or location (spatial), depending on task instructions. In object trials, each experiment featured an initial presentation of 2 targets irrelevant to each other, and then a probe shape that was similar to (25% of the trials), dissimilar to (25% of the trials), or the same as (50% of the trials) one of the previously presented targets. In the spatial trials, stimuli were presented in randomly determined positions placed on the circumference of an imaginary circle around the fixation cross with a radius of 3.2° of visual angle. In 50% of the trials, the probe was in the same location as one of the targets, in 25% it was near (15°-25° distant) one of the targets, and in 25% it was far (40°-50° distant) from the nearest target. In the spatial trials, probes were never the same shape as any of the targets, half being similar and half being dissimilar. In object trials, probes were never in the same location as any of the targets, half being near and half being far. Subjects indicated their response using 2 keys, one clearly marked yes (match) and another clearly marked no (nonmatch). Accuracy was measured and no limits were set for response time.

Perceptual Discrimination Task Conditions

The goal of this condition was to assess perceptual discrimination abilities, minimizing the role of working memory (Figure 1). To do this, we assessed subjects’ perceptual performance by using 8 different target exposure durations (TED) ranging from 17 to 250 milliseconds. The study blocks were presented in a pseudorandom array so
that a short TED block (17, 167, 334, and 301 milliseconds) followed a long TED block (1002, 1503, 2004, and 2505 milliseconds). A Latin square design was used to ensure that all TEDs were tested in all positions within the session across participants. This target exposure was followed by a 250-millisecond delay interval before the presentation of the probe stimulus. This delay duration was selected to impose a minimal working memory load but to avoid backward masking interference effects that might have occurred at shorter delays. A total of 40 spatial and 40 object trials were tested at each TED. Thus, 640 trials were obtained for the spatial and object conditions, 8 blocks of 40 trials each. Before acquiring study data, subjects performed practice blocks of object and spatial trials using TEDs of 3 seconds to ensure comprehension of task demands.

Visual Working Memory Task

The goal of this condition was to assess the impact of increased retention interval on performance, controlling for individual differences in perceptual discrimination ability (Figure 2). To ensure that subjects could adequately perceive the spatial and object target stimuli before delay testing, an individualized thresholding procedure was developed adapting a 1-up/1-down staircase procedure from psychophysics literature. This is an adaptive thresholding method in which a component of a task (eg, stimulus intensity or stimulus duration) is increased or decreased by a predetermined size or proportion at each step until a predetermined target measure is reached. In our thresholding procedure, the subjects underwent testing using blocks of 20 trials at each step, and the TED of the blocks was decreased or increased 50% until the subject achieved a criterion level of performance of 80% to 90% correct on 2 consecutive blocks. All subjects started the staircase procedure with a TED of 3 seconds, and all trials used a 250-millisecond delay. The lowest TED at which a participant was able to meet an 80% to 90% criterion was considered his or her threshold and was the TED used in the working memory condition. Separate thresholding procedures were done for object and spatial conditions. Thus, subjects typically had different TEDs in their object and spatial working memory tests. The threshold for object and spatial tasks are found on average after 9 blocks of 20 trials (range, 5-22 blocks). The computer program for this paradigm had a minimal stimulus exposure duration of 17 milliseconds. Because of this technical limitation, findings for 2 controls in the object condition and 9 subjects (7 controls and 2 schizophrenic patients) in the spatial condition were above 90% correct with the duration of 17 milliseconds. The working memory of these subjects was tested using the 17-millisecond TED.

Subjects then underwent testing at their individual threshold TED with a delay interval of 3000 milliseconds. The TED was kept fixed at the threshold level for each subject, for each condition. A total of 320 trials were administered in the spatial and object conditions in a series of 4 trial blocks each. Task order was balanced across subjects.

STATISTICAL ANALYSES

The data from the perceptual discrimination task were analyzed as follows: to take account of the repeated observations per participant, with missing data at 1 level for 1 participant, percentage of accuracy was predicted with the use of a mixed model for repeated measures using an unstructured covariance matrix. To model immediate response as a function of condition, group, and TED, the initial model fitted included TED × condition, condition × group, group × TED, and group × condition × TED interactions. To allow for nonlinear effects of exposure duration, TED was represented in these models by a set of indicator variables. Backward stepwise selection was used to simplify this model; by eliminating nonsignificant higher-order interactions, this stepwise selection procedure allowed more power (error degrees of freedom) to test the remaining interactions and main effects. All main-effect terms were retained in the final model, as were any interactions for which $P<.10$. The final model was used to estimate least squares means at specified combinations of group, condition, and/or exposure duration, averaged over all levels of the remaining effects with equal weights for the data from each participant in each cell.

The Wilcoxon rank sum test was used to compare threshold TEDs and perceptual performance at threshold TEDs. A repeated-measures analysis of variance (ANOVA) in a group × condition design was used to assess group differences in working memory performance. Post hoc analyses using the Wilcoxon rank sum test were performed for each condition. Since not all the subjects could be thresholded adequately due to technical limitations summarized above, the repeated-measures ANOVA and the post hoc tests were repeated with the subjects whose perceptual thresholds were successfully identified (ie, at the end of thresholding at a range of 80%-90% accuracy). Spearman rank correlations between threshold TED and working memory performance were calculated by group and condition. Mixed-model analysis was performed using a commercially available statistical software package (PROC MIXED, version 8.0; SAS Institute Inc, Cary, NC). Other analyses were performed using a separate package (SPSS 10.0; SPSS Inc, Chicago, Ill). All statistical tests were performed at α = .05 (2-tailed).

tem in humans and other primates. This domain specificity is consistent with the anatomic connectivity of subregions of the prefrontal cortex. Dorsal prefrontal areas are reciprocally connected with inferior/posterior parietal regions thought to subserve spatial processing, and ventral prefrontal areas are reciprocally connected to inferior temporal visual areas that are thought to mediate processing of color, pattern, and facial information (ie, object processing). Thus, working memory performance requires the integrated function of posterior sites involved in the perceptual processing of target stimuli, with prefrontal regions that play a specific role in the maintenance of representations in the absence of perceptual stimuli. Several functional imaging studies, but not all, have suggested a similar domain-specific (spatial vs object) organization of visual working memory function in the human brain (for detailed reviews but also27). Although the claim of domain specificity remains controversial in the literature, the study of spatial vs object working memory potentially provides a means of assessing the functional integrity of broadly distributed, but partially seg-
regarded, cortical networks that involve regions implicated in schizophrenia.

Strong evidence exists that patients with schizophrenia demonstrate impairments on a variety of visual working memory tasks. Impairments have been documented using spatial paradigms (subjects are asked to remember the location of 1 or more irregular shapes, dots, or letters, etc) in patients with chronic illness, medication-naive first-episode patients, nonmedicated patients, first-degree relatives who are not ill, and patients with schizophrenia spectrum personality disorder.2,7-9,25-31 Thus, this appears to be a reliable deficit. Fewer studies have examined working memory for nonspatial visual stimuli (object stimuli, eg, subjects are asked to remember the shape or color of 1 or more objects); available studies suggest impaired performance in this domain as well.8

The cognitive processes that are responsible for the observed impairments, however, have not been clearly established. In studies using auditory tones and weight stimuli, Javitt et al22,23 reported that patients with schizophrenia demonstrate marked impairments in the ability to discriminate between target and probe stimuli separated by minimal delay periods. Further, they found no evidence of additional retention-related impairments when patients and controls were matched for ability to encode and/or discriminate target stimuli using minimal delays. Based on these data, Javitt et al23 have argued that the working memory deficit in schizophrenia may often be attributable to basic perceptual encoding deficits, implicating dysfunction of posterior sensory processing areas. Contrary to this argument, Wexler et al11 and Stevens et al34 have demonstrated auditory tone working memory impairments in schizophrenia, even after they eliminated subjects who demonstrated perceptual tone discrimination impairments. The extensive interest in working memory disturbance in schizophrenia has been driven by the notion that these elementary delayed tasks provide a means of studying the functional integrity of the prefrontal cortex. Thus, determining the origins of the schizophrenia behavioral impairment in working memory tasks is important for understanding cognitive impairments in schizophrenia and delineating the anatomy implicated.

Both experiments presented herein were designed to evaluate the integrity of perceptual processing of object and spatial information in patients with schizophrenia and the retention of such information during a brief delay. To isolate specific retention impairments, delayed performance was tested using a thresholding procedure adapted from psychophysics that was designed to ensure that the information is perceived adequately during the working memory test. We initially identified the minimum duration that each subject needed to view the targets to recognize them subsequently above a certain criterion performance. We then tested the working memory using every subject's own specific threshold for object or spatial condition. This design provides for a clear examination of the precision of encoding processes and allows for a separate examination of delayed performance, controlling for the impact of encoding differences across groups.

RESULTS

PERCEPTUAL DISCRIMINATION TASK

Observed mean percentage accuracy by TED and processing task (normal controls vs subjects with schizophrenia) are presented in Table 1. The accuracy of normal controls was significantly higher than that of subjects with schizophrenia, with the exception of the object match trial. The difference in performance between the two groups was greater with spatial than object conditions. These findings are consistent with previous reports of working memory impairments in schizophrenia, as demonstrated in the auditory and weight paradigms. The spatial object condition may be more difficult to perform because of the demands placed on the subjects' ability to encode and maintain information in working memory. The data suggest that the working memory impairments in schizophrenia are not limited to tasks that rely on verbal encoding processes.
The performance of both groups improved with increasing TED, as shown in Figure 3. However, the magnitude of this improvement was not identical in both conditions (as seen in the test for condition \times TED interaction). Performance in the spatial condition appears to reach a plateau, with little further improvement with greater TED, more quickly than does performance in the object condition.

**VISUAL WORKING MEMORY**

**Threshold Performance Levels**

On average, patients required considerably longer than controls to attain the performance criterion of 80% to 90% in the thresholding procedure for the spatial (mean threshold TED, 692 ± 1083 vs 109 ± 130 milliseconds; Wilcoxon rank sum test, 385.5 [df = 1; P = .01]) and the object (mean threshold TED, 1937 ± 1808 vs 569 ± 568 milliseconds; Wilcoxon rank sum test, 299 [df = 1; P < .001]) conditions. Despite these large average differences, there was considerable overlap in the distribution of threshold TED between groups. Controls did not differ from patients in accuracy at the threshold TED for the object condition (86.0% ± 3.8% for controls vs 84.5% ± 3.5% for patients; Wilcoxon rank sum test, 696 [df = 1; P = .16]). In the spatial condition, controls performed better than patients at the threshold TED (89.0% ± 5.5% vs 85.0% ± 4.2%; Wilcoxon rank sum test, 636.5 [df = 1; P = .01]). This difference is likely attributable to the fact that a substantial number of controls and some patients achieved accuracy of greater than 90% at the lowest exposure duration used (17 milliseconds).

**Working Memory Performance**

The repeated-measures ANOVA of delayed object and spatial performance yielded main effects of condition (F1,48 = 24.30 [P < .001]) and diagnosis (F1,48 = 10.87 [P = .002]) and an interaction between condition and diagnosis (F1,48 = 4.18 [P = .046]). The nature of this critical interaction is seen in Figure 4. The groups differed significantly in the spatial working memory condition (Wilcoxon rank sum test, 587.5 [df = 1; P < .001]), whereas performance in the object condition did not (Wilcoxon rank sum test, 699 [df = 1; P = .19]). Spatial and object working memory performances were not correlated with each other for controls and patients (r = −0.16 [P = .50] and r = 0.27 [P = .15], respectively). Total scores on the Brief Psychiatric Rating Scale and Schedule for the Assessment of Negative Symptoms were not significantly correlated with object (r = 0.24 [P = .20] and r = 0.08 [P = .68], respectively) or spatial (r = −0.31 [P = .10] for both) working memory performance.

Although the thresholding strategy ensured that the perceptual demands of the working memory task was met by both groups in both conditions, a criticism might arise from the fact that the control group exhibited significantly better threshold performance in the spatial condition before entering working memory testing. We addressed this by repeating the working memory data analysis after excluding 11 subjects (9 controls and 2 pa-
Adjusted Mean Perceptual Performance in Schizophrenic and Control Groups by Object vs Spatial Condition∗

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall (N = 50)</th>
<th>Control Group (n = 20)</th>
<th>Schizophrenic Group (n = 30)</th>
<th>t₀₆</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>84.8 (1.1)</td>
<td>86.1 (1.3)</td>
<td>76.2 (1.1)</td>
<td>6.85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Spatial</td>
<td>80.7 (1.3)</td>
<td>87.0 (1.5)</td>
<td>80.7 (1.3)</td>
<td>4.80</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Object</td>
<td>87.5 (1.0)</td>
<td>88.2 (1.3)</td>
<td>71.7 (1.2)</td>
<td>7.89</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>t₀₆</td>
<td>9.06</td>
<td>5.02</td>
<td>9.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

∗Adjusted means and SEs are calculated by averaging across the remaining effects in the model: immediate performance = condition + group + TED + (condition × TED) + (group × condition). TED indicates target exposure duration.

In this study, we documented an impairment in visual perceptual performance for patients with schizophrenia relative to normal control subjects. Perceptual impairment for patients with schizophrenia was greater for the object than for the spatial perceptual task. We also documented a domain-specific spatial working memory deficit in patients with schizophrenia. The spatial working memory impairment was observed even after between-group differences in perceptual processing were controlled for, suggesting a genuine deficit in the retention of spatial material.

We observed deficits in the perceptual discrimination of object form and spatial location in patients with schizophrenia. These data are consistent with a growing body of work documenting deficits in a number of fairly elementary sensory and perceptual tasks among patients with the illness. Several recent studies have highlighted deficits in the discrimination of motion, trajectory, or location cues, suggesting a relatively specific deficit in the dorsal visual-processing stream. The present data suggest that the impairment extends to the ventral system as well: patients demonstrated more pronounced deficits in the object condition than in the spatial condition. Consistent with earlier studies of visual perception in schizophrenia, patients needed longer stimulus exposures to achieve perceptual performance comparable with that of normal controls. However, since the impairment was evident even after extended encoding times, a slowing of visual processing cannot plausibly account for the extent of perceptual impairment observed. Instead, it appears that patients have deficits in the precise encoding of visual stimuli, with maximal impairments when fine-feature processing is needed. Given the role of attention in the modulation of sensory processing, it is not possible to parse the source of the pa...
tient behavioral deficit further as reflecting a fundamental perceptual or attentional defect. In this type of task, effective behavioral performance requires the integrated function of attention in the service of perception.

We also have replicated previous studies reporting spatial working memory impairments among patients with schizophrenia. In addition, we found evidence of impairment in the retention of spatial information, even after controlling for perceptual deficits, and somewhat unexpectedly, that this impairment does not extend to the retention of object stimuli. Indeed, O’Donnell and colleagues have previously reported that patients demonstrated far greater impairment with delayed spatial than with object tasks. Our findings are also consistent with the work of Javitt et al. in highlighting the extent to which sensory/perceptual encoding impairment in schizophrenia contributes to working memory impairment. However, there also appears to be additional impairment in the retention of spatial information. A specific spatial (but not object) working memory impairment in schizophrenia lends support to the hypotheses that object and spatial visual working memory are dissociable, likely mediated by partially segregated brain areas, and can be affected differentially by pathologic processes. Although it is tempting to argue that brain areas, and can be affected differentially by pathologic processes, object and spatial visual working memory impairments, patients with schizophrenia exhibited spatial but not object visual working memory impairments. These dual deficits in perceptual encoding and retention suggest that the working memory impairment in schizophrenia is multifactorial and point toward dysfunction in posterior, perceptual processing areas and possibly prefrontal regions that play a critical role in maintenance of representations during delays. Future studies using functional imaging techniques may provide further information on the integrity of these brain areas and/or circuitry in schizophrenia.

We have shown visual perceptual processing impairments in schizophrenia. This impairment was greater for visual information about features of the objects than for their spatial location. After controlling for perceptual impairments, patients with schizophrenia exhibited spatial but not object visual working memory impairments. These dual deficits in perceptual encoding and retention suggest that the working memory impairment in schizophrenia is multifactorial and point toward dysfunction in posterior, perceptual processing areas and possibly prefrontal regions that play a critical role in maintenance of representations during delays. Future studies using functional imaging techniques may provide further information on the integrity of these brain areas and/or circuitry in schizophrenia.

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