Impairments in Perceptual Competency and Maintenance on a Visual Delayed Match-to-Sample Test in First-Episode Schizophrenia

Todd Lencz, PhD; Robert M. Bilder, PhD; Elihu Turkel, PsyD; Robert S. Goldman, PhD; Delbert Robinson, MD; John M. Kane, MD; Jeffrey A. Lieberman, MD

**Background:** Deficits in working memory (WM) have been reported in patients with schizophrenia, but WM is a complex construct dependent on several subprocesses, including input representation (perceptual competency) and holding stimuli on-line (maintenance). A visual delayed match-to-sample task (DMST) was developed to isolate perceptual competency from maintenance during delays. It was hypothesized that patients in the first episode of schizophrenia would exhibit dissociable deficits in both WM domains.

**Methods:** Performance on the DMST was assessed in 57 patients in the first episode of schizophrenia or schizoaffective disorder and 22 healthy comparison subjects. In phase 1 of the DMST, a complex visual stimulus (target) was followed immediately by a forced choice between 2 test stimuli, and item difficulty (differences between the test stimuli) was titrated until each subject achieved a consistent accuracy (80%-90%) in this no-delay condition. In phase 2, a delay of 4 or 8 seconds with a mask of randomly illuminated pixels was introduced between target and test stimuli; test stimuli were fixed in difficulty level based on phase 1 titration. Main outcome measures were mean item difficulty attained in the no-delay condition and mean accuracy in matching after delay.

**Results:** Compared with controls, patients attained a lower level of difficulty in the no-delay condition (P=.001) and significantly lower accuracy with delay (P=.002).

**Conclusions:** Deficits in both domains of WM suggest abnormality in the posterior and prefrontal cortices. These deficits can be observed in a task involving complex visual pattern stimuli using only a brief delay and are present even in unmedicated patients in the first episode of illness.

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tients with schizophrenia in several ways, by examining WM for visual pattern information (as opposed to spatial information), explicitly measuring deficits in perceptual competency, and controlling for the effects of individual differences in perceptual competency when examining maintenance processes. Furthermore, we examined patients in the first episode of schizophrenia, including neuroleptic- (and anticholinergic-) naive subjects, to minimize the potential confounds of chronicity, medication, and hospitalization.

METHODS

PARTICIPANTS

Subjects were 79 participants in ongoing studies of first-episode schizophrenia conducted at Hillside Hospital, Glen Oaks, NY; 57 patients were recruited from consecutive admissions to the inpatient service of the Department of Psychiatry if they were admitted for a first episode of psychotic illness and had received less than 12 prior weeks of cumulative lifetime neuroleptic treatment. The patients satisfied Research Diagnostic Criteria28 for schizophrenia (n = 39) or schizoaffective disorder (n = 18) based on structured interviews (Schedule for Affective Disorders and Schizophrenia30) and reviews of history. Patients were excluded for current or past history of serious neurologic or endocrine disorders. After subjects received a complete description of the study, written informed consent was obtained according to a protocol approved by the Institutional Review Board at Long Island Jewish Medical Center, New Hyde Park, NY. Further details about the ascertainment, treatment, and clinical characteristics of a portion of this sample have been published elsewhere.29-32

Patients with schizophrenia were tested as part of a larger neuropsychological battery administered longitudinally. For purposes of the present study, only data for the first point at which each patient was administered the DMST are included. In the current study, data are from 19 patients (33% of the total sample) at neuroleptic-naive baseline and 38 patients tested after 4 weeks to 6 months of treatment. The mean, median, and mode of time to testing are presented in the Table. Of the patients tested while taking antipsychotic medication, 77% received less than 12 prior weeks of cumulative lifetime neuroleptic treatment. The patients satisfied Research Diagnostic Criteria for schizophrenia (n = 39) or schizoaffective disorder (n = 18) based on structured interviews (Schedule for Affective Disorders and Schizophrenia) and reviews of history. Patients were excluded for current or past history of serious neurologic or endocrine disorders. After subjects received a complete description of the study, written informed consent was obtained according to a protocol approved by the Institutional Review Board at Long Island Jewish Medical Center, New Hyde Park, NY. Further details about the ascertainment, treatment, and clinical characteristics of a portion of this sample have been published elsewhere.29-32

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The healthy comparison group comprised 22 subjects recruited through announcements in local newspapers and within the medical center. These subjects were free of Research Diagnostic Criteria mental disorders as determined by the Schedule for Affective Disorders and Schizophrenia (lifet ime version), interview, physical examination, and results of urinalysis. None of the subjects had histories of substance dependence or current abuse, chronic neurologic or medical illness, or drug treatment known to affect the brain, as determined by interview.

Subject characteristics and comparisons of the patient and reference groups are provided in the Table. The groups did not significantly differ on distribution of sex (χ² = 2.57; P = .11) but did significantly differ in age (t = 2.77; P = .007) and years of education completed (t = 2.97; P = .004; data missing for 1 patient). Consequently, all analyses were conducted both with and without age and education as covariates. However, it should be noted that patients with schizophrenia are expected to attain fewer years of education owing to illness, cognitive difficulties, and downward socioeconomic drift.33 Additionally, as is shown in the Table, the groups did not significantly differ on parental socioeconomic status based on the Hollingshead index (Kolmogorov-Smirnov Z, 1.01; P = .26; data missing for 1 patient).

PROCEDURES

Stimuli

Subjects were instructed that they would see a figure on the screen (target stimulus) and would be asked to then select that figure from a pair of subsequently presented figures (test stimuli). Similar to the task developed by Phillips,34 stimulus figures consisted of 9 × 9 grids containing 81 square cells without a surrounding border. For each stimulus, 40 cells were darkened and the remaining 41 were illuminated (Figure 1A). Darkened cells for each target stimulus were selected randomly on each trial. Each target stimulus was presented centrally for a duration of 500 milliseconds. Test stimuli were smaller 9 × 9 grids presented to the left and right of center until the subject made a response.

On each trial, 1 test stimulus was identical to the target stimulus, whereas the other differed by having some of the previously illuminated cells darkened, and vice versa. The difficulty index is a measure of the similarity of the 2 test stimuli. For each trial, the difficulty index is the percentage of the 81 cells common to both test stimuli; the higher the index, the more difficult the discrimination (Figure 1B and C).

Phase 1: Titration

The purpose of phase 1 was to determine the item difficulty necessary to equate each subject on perceptual competency before a delay component was added to the task. In phase 1, the test stimuli appeared on-screen immediately after presentation of the target stimulus. Item difficulty was dynamically adjusted on each trial to yield a mean accuracy of 80% to 90% across a minimum of 20 trials.

Phase 2: Delay

After obtaining stable performance in the titration phase (80%-90% accuracy across 20 trials), subjects were told that a delay period would be added for phase 2. Subjects who were unable to achieve 80% to 90% accuracy stably at any difficulty level were not tested in phase 2. In phase 2, a delay of either 4 or 8 seconds (randomly distributed) was interposed between target and test stimuli. A total of 20 trials were administered at each delay level. During the delay period, a mask of randomly presented interference characters was presented on-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schizophrenia</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>Sex, % male</td>
<td>58</td>
<td>77</td>
</tr>
<tr>
<td>Age, y</td>
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<td>29.1 (7.2)</td>
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<tr>
<td>Education, y</td>
<td>12.7 (2.5)</td>
<td>14.5 (2.3)</td>
</tr>
<tr>
<td>Parental socioeconomic status†</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Weeks in treatment‡</td>
<td>6.5 (8.4)</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated. Ellipses indicate not applicable.
†Median socioeconomic level according to the Hollingshead index, a noninterval scale (range 1-5).
‡Median and modal number of weeks in treatment at time of testing was 4.0.

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darkened cells, changing at a rate of 1 every 100 milliseconds, appeared on a grid similar to that of the target stimulus, accompanied by a distracting tone. The difficulty index for all trials during phase 2 was fixed at the level determined in phase 1. Thus, the key dependent measure from phase 2 was the accuracy, at this constant level of difficulty, for each of the 2 delay intervals.

STATISTICAL ANALYSIS

Performances of patients and control subjects were compared on 3 key dependent measures: (1) percentage of subjects unable to successfully complete phase 1, (2) mean difficulty level attained by subjects successfully completing phase 1, and (3) mean accuracy level attained at each of the 3 delay intervals (no delay, 4 seconds, and 8 seconds). The difference in difficulty level between medicated and unmedicated patients was first compared using a t test, and accuracy was compared using repeated-measures analysis of variance, with 3 within-subjects levels (delay) and 2 between-subjects levels (medicated and unmedicated). In the absence of differences, all patients with schizophrenia were examined together in comparison to control subjects using similar t tests and repeated-measures analysis of variance. Because subjects with schizophrenia and control subjects differed with respect to age and education, the second and third comparisons were also reanalyzed with analyses of covariance, using age and education as covariates. Effect sizes (Cohen d) were computed by dividing the difference in means over the pooled SD.35

RESULTS

Nine patients with schizophrenia (16%) and 1 healthy comparison subject (5%) were unable to attain the criterion (20 consecutive trials in the range of 80% to 90% accuracy) at any difficulty level during the titration phase, although the difference in these percentages was not statistically significant ($\chi^2 = 1.82; P = .18$). These 10 subjects were excluded from subsequent analyses. The remaining subjects (patients, 48; controls, 21) had similar demographic characteristics to the total sample.

There were no differences between unmedicated patients and medicated patients in difficulty level obtained ($t_{46} = 0.78; P = .44$). Compared with controls, patients with schizophrenia achieved a significantly lower difficulty index during the titration phase ($t_{40} = 3.32; P = .001$). The mean (SD) difficulty index attained at the end of phase 1 was 76.9% (12.5%) for the patient group and 84.2% (5.6%) for the comparison group. In other words, test stimuli needed to differ by 19 pixels for patients to attain 80% accuracy in the no-delay condition, whereas healthy subjects met the criterion at a difference of only 13 pixels. Using the Cohen criteria, the effect size for this difference in sensory processing precision was medium to large ($d = 0.67$).35 Results of the 2-group analysis of covariance with age as a covariate also revealed significant group differences ($F_{1,66} = 7.24; P = .009$), as did the analysis of covariance using education ($F_{1,65} = 6.08; P = .02$).

There was no significant difference between medicated and unmedicated patients in their change in accuracy during the delay intervals (group $\times$ delay; $F_{2,90} = 2.21; P = .14$). When patients with schizophrenia were compared with healthy controls, a significant group $\times$ delay interaction ($F_{2,61} = 5.50; P = .006$) revealed that patients with schizophrenia achieved a significantly lower level of accuracy when a 4- or 8-second delay was added between the target and test stimuli. Results did not change when age ($F_{2,66} = 5.50; P = .006$) or education ($F_{2,67} = 5.20; P = .008$) was added as a covariate. There was no significant difference between performance at the 4-second vs the 8-second delay for patients with schizophrenia or control subjects ($F_{1,47} = 0.65; P = .42$ and $F_{1,20} = 0.67; P = .42$, respectively), so these 2 points were collapsed in Figure 2. To compute the effect size of the magnitude of the maintenance deficit, the mean accuracy at either delay interval was compared between patients with schizophrenia and control subjects. For patients with schizophrenia, the mean (SD) accuracy at delay was 60% (9%), and, for control subjects, the mean accuracy was 67% (11%) ($t_{47} = 6.0; P = .004$). The effect size for the maintenance deficit was medium to large ($d = 0.76$).

COMMENT

This study examined 2 subcomponents of the WM process. Patients in the first episode of schizophrenia exhibited deficits in both perceptual competency and online maintenance during a delay of 4 to 8 seconds. Notably, WM maintenance deficits in schizophrenia were found even when initial processing was matched to controls us-
ing an adaptive titration procedure, and the effect sizes of the 2 deficits were similar and in the medium to large range.35 Both types of deficits were found among patients in the first episode of illness and do not appear to be secondary to medication effects or other illness consequences. These deficits also do not appear to be secondary to differences in age or education.

Few studies of WM in schizophrenia have attempted to separate initial encoding from maintenance during a delay. Results of the present study stand in contrast to the studies of Javitt et al.,39-22 in which patients with schizophrenia did not show maintenance deficits when initial stimulus difficulty was matched to that of controls. It should be noted that in most of those studies, difficulty titration was performed on a group basis (ie, patients were compared with controls, with each group at a fixed level of difficulty) rather than an individual basis. Thus, individual differences in perceptual competency may have contributed noise to the subsequent measurement of maintenance, obscuring group differences.19(p322) Contrary to both those findings and the present study, Goldberg et al20 failed to observe any perceptual competency deficit in patients with schizophrenia on a subthreshold span task.

The results of the present study are more consistent with studies revealing the presence of both perceptual competency and WM maintenance deficits in schizophrenia.4,5 For example, Wexler et al4 identified perceptual competency deficits, at least in a subsample of their patients with schizophrenia, that were not sufficient to account for observed deficits in verbal WM. Similarly, Tek et al43 reported maintenance deficits on a spatial WM task even when perceptual competence was matched using titration of stimulus presentation times (although maintenance of nonspatial information was not significantly impaired after titration of perceptual competency). Results of the present study extend these findings by utilizing complex visual pattern stimuli that are not easily verbalized, employing a titration technique that is both quantifiable and continuous in order to match subjects for perceptual competency at the individual level, directly titrating the perceptual discrimination that must be made between target stimuli, and identifying both perceptual competency and maintenance deficits in first-episode patients, including neuroleptic-naïve subjects.

The results of the present study suggest that patients with schizophrenia have abnormalities in visual processing and stimulus matching, even in the absence of delay. The precise nature of this deficit is not yet known, but there are several candidate mechanisms. It is possible that patients with schizophrenia have abnormalities in early, preattentive visual processing centers in the occipital cortex, where evidence for neuropathologic and neurophysiologic abnormalities has been reported.36-38 This interpretation is consistent with findings of impaired mismatch negativity in sensory cortex,9 as well as findings from functional neuroimaging studies implicating posterior sensory cortex in the initial processing of to-be-remembered stimuli.39-40 However, the results of Bruder et al41 and a review by Knight42 suggest that these visual processing deficits are attentional or conceptual, rather than purely sensory, in nature. Current evidence is insufficient to determine which hypothesis may account for the perceptual competency deficits reported in the present study, but the complex nature of the stimuli suggests the likely involvement of both preattentive and attentive processes, which may be subserved by thalamocortical circuits and primary sensory areas as well as corticocortical circuits in secondary and tertiary sensory areas of the posterior cortex.

The present study also reports WM deficits even after initial encoding processes have been controlled using a titration procedure (Figure 2). Although numerous studies have reported WM deficits in schizophrenia, the present study differs in several notable ways. In addition to the use of the difficulty titration procedure, the delay period during which maintenance was required (4-8 seconds) was shorter than that used in many prior studies, particularly those examining visual WM. In this context, the lack of performance decline when the delay was increased from 4 to 8 seconds must be discussed. Although similar findings were reported by Wexler et al,4,44 it is possible that other cognitive processes, including executive function and attention, as well as the presence of the distractor, may have affected maintenance processes during the delay period and that these processes may have had their primary impact on performance within the first 4 seconds. It is also possible that even the 8-second delay was insufficiently long, relative to the 4-second delay, to detect further maintenance deficits. A recent functional magnetic resonance imaging study showed significant decrements from 15 seconds to 24 seconds, with different patterns of frontal and other cortical activations for the initial maintenance period compared with the later period.45 Nevertheless, the deficits in maintenance at the 4- and 8-second delays are not likely to be due to perceptual competency, which was controlled.

The present study also extends prior findings of visual WM deficits in schizophrenia by virtue of the stimuli involved. Most studies of visual WM in schizophrenia examined maintenance of information concerning spatial location.3,16,17,46-48 It is widely accepted that spatial (“where”) information and nonspatial (“what”) information are processed along dorsal and ventral cortical pathways, respectively, after initial processing in the stri-
ate cortex, and it has been suggested that these distinctions are paralleled in distinct prefrontal areas subserving WM. Whereas other studies have reported WM impairments for nonspatial stimuli in schizophrenia, none used a delayed matching-to-sample paradigm. One prior study comparing spatial and nonspatial tasks reported maintenance deficits in the former but not the latter. By comparison, the visual patterns to be remembered in the present study were more complex and may have required both spatial and nonspatial ("object") processing mechanisms.

Thus, another difference between the present study and prior reports lies in the complexity of the stimuli used. The partially illuminated matrix stimuli were designed to be sufficiently complex so as to be novel and difficult to verbalize (unlike, for example, certain face or letter stimuli). Although this complexity may have increased the role of nonsensory factors, such as attention and executive function, in both the initial encoding and maintenance of the stimuli, it may also have been responsible for our ability to detect deficits in maintenance when initial perceptual competency (including some of these nonsensory factors) was controlled. It is possible that some previous studies failed to find maintenance deficits due to insufficient taxing of the WM system. An alternate explanation, favoring the role of attention and executive functioning, cannot be ruled out but is reduced in likelihood by the use of the titration procedure. If true, this would still support the contention that nonsensory system abnormalities (ie, prefrontal and frontoparietal regions) are likely involved in the maintenance deficit.

The idea that the maintenance deficits observed in the present study are linked to functional abnormalities of the prefrontal cortex and its connections to posterior secondary and tertiary sensory cortices is supported by a substantial literature. Prefrontal cortex has repeatedly been observed to be critical for WM performance in animal and human lesion studies, single-unit recordings in nonhuman primates, and functional neuroimaging studies in humans. Controversy remains about the participation of different prefrontal subregions in maintaining information from different stimulus modalities and processing demands. For example, results of primate lesion and single-unit recording studies suggest that tasks reliant on more dorsal prefrontal regions are those that have spatial stimulus properties and/or require monitoring of stimulus information only, whereas tasks that show more ventral dependency are nonspatial and/or require monitoring of the previous response. On the other hand, one recent review of the human neuroimaging literature suggests that continuous updating of stimulus representations imposes greater demands on executive processes linked to the dorsolateral prefrontal cortex, irrespective of stimulus type. Furthermore, to the extent that attention or other executive functions, such as encoding strategy, impinged on results, it is possible that more dorsal prefrontal cortex units may be recruited. Preliminary functional magnetic resonance imaging findings using the DMST in healthy subjects suggests that both dorsal and ventral frontal regions may participate in the maintenance process for this task (J. A. Spicer, BA, K. H. Knuth, PhD, D. Guilfoyle, PhD, et al, unpublished data, 2001). It is hoped that this paradigm may be useful in further investigations focused on separating the contributions of perceptual from maintenance processes in the overall WM deficit of persons with schizophrenia.

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Corresponding author and reprint: Todd Lencz, PhD, The RAP Program, 444 Lakeville Rd, Suite 303, Lake Success, NY 11042 (e-mail: lencz@lij.edu).

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