Panmodal Processing Imprecision as a Basis for Dysfunction of Transient Memory Storage Systems in Schizophrenia

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Abstract

Schizophrenia is a severe mental disorder associated with cognitive disturbances that may reflect underlying deficits in the functioning of brain transient memory storage systems. This study investigates performance in three distinct tasks that require transient memory storage: (1) tone discrimination, (2) object weight discrimination, and (3) “AX”-type visual continuous performance task. The tests used were chosen to investigate the degree to which a similar pattern of performance deficit could be observed across multiple sensory and cognitive domains in schizophrenia. In each of the paradigms, a similar pattern emerged: subjects with schizophrenia showed severe performance deficits whenever performance depended on functioning of transient memory systems. The deficits were apparent at both short and long interstimulus intervals (ISI), however, and schizophrenia subjects were no more affected by increasing ISI than were controls. Moreover, when short ISI performance was matched across groups by manipulating task difficulty, subsequent decay in performance was equivalent across groups. Thus, although schizophrenia subjects show severe performance deficits in memory-dependent tasks, the deficits do not appear to reflect impaired transient memory per se. Rather, they appear to reflect impaired precision of operation of such systems, irrespective of the duration over which representations must be maintained. The severe deficits in processing precision, despite the relatively preserved maintenance of representation, may be relevant to pathophysiological models of schizophrenia.

Key words: Auditory, visual, somatosensory, cognition, NMDA receptors, schizophrenia.


Deficits in cognitive functioning are a major predictor of chronic disability and poor long-term outcome in schizophrenia (Harvey et al. 1990; Kay and Murrill 1990). Schizophrenia-like cognitive deficits, moreover, are not reproduced by administration of dopaminergic agents to normal controls (Daniel et al. 1991) and improve to only a limited degree following treatment of schizophrenia subjects with either typical or atypical antipsychotics (King 1990; Goldberg et al. 1993). Thus, such deficits are poorly accounted for by the dopamine model of schizophrenia, and their underlying pathophysiology remains obscure. A goal of recent schizophrenia research has been the development of unifying themes that could account for the complex patterns of cognitive dysfunction that are unique to schizophrenia.

A basic process that may be impaired in schizophrenia is the ability to utilize or maintain short-duration memory traces to guide behavior. As opposed to long-term memory systems, which are specialized for permanent memory storage over days, weeks, months, or years, transient memory systems are specialized to retain high-precision representations of events for seconds to minutes, following which traces of the stimulus are lost. Long-term memory and transient memory systems also appear to have distinct anatomical substrates. Whereas long-term memory formation is critically dependent on hippocampal functioning, transient memory storage capabilities are maintained even following complete hippocampal ablation. Instead of being reliant on hippocampal functioning, transient memory storage appears to reflect distributed processing within the cortex, with each cortical region contributing in a modality-specific fashion.

The best-studied example of a transient memory system is the “working memory” system. Working memory is the system that permits individuals to hold information in mind while working on a task or problem (Baddeley 1992). It allows humans to transiently maintain informational representations following cessation of sensory stim-
ulation and to use such representations to plan or decide behaviors (Goldman-Rakic 1994). A fundamental component of working memory is the “central executive,” which allocates among sensory representations depending on the nature of informational analysis that is required for the performance of a specific cognitive task. Operation of the central executive has been associated most closely with functioning of prefrontal and posterior parietal cortices (Goldman-Rakic 1996). In addition to a central executive, several “slave” systems have been identified that retain specialized information over brief time periods. Classic examples of such slave systems include the “phonological loop,” which stores up to seven “items” in short-term memory and the “visuospatial sketch pad,” which stores visual representations (Baddeley 1992).

Several other modality-specific transient memory storage systems have also been described, however. These transient memory systems depend on activation within modality-specific cortical regions; for example, transient memory for faces is associated with activity within the inferotemporal cortex, a brain region that recognizes faces (Li et al. 1993; Lueschow et al. 1994). In contrast, maintenance of transient representations of melodies is associated with activation of the right temporal cortex, a brain region that is specialized for the processing of melodies (Zatorre et al. 1994). Transient memory for tones is critically dependent on structures within the primary auditory cortex (Massopust et al. 1971; Colombo et al. 1996). In general, it appears that each cortical region maintains a transient representation of relevant recent stimuli (Miller et al. 1991; Miller and Desimone 1994).

The fact that schizophrenia subjects perform poorly on tests of working memory and executive functioning has been well-documented (Weinberger et al. 1986; Park and Holzman 1992; Goldman-Rakic 1994; Keefe et al. 1995; Servan-Schreiber et al. 1996; Gold et al. 1997). Recent findings, however, suggest that schizophrenia subjects also perform poorly on tasks requiring modality-specific transient memory storage (Strous et al. 1995; Javitt et al. 1996; Fleming et al. 1997). Thus, deficits in functioning of transient memory systems in schizophrenia may not be limited to the “central executive” type of working memory system. Transient memory systems, in general, require two distinct processes. First, the information must be encoded in a representationally precise fashion that permits its subsequent precise utilization. Second, the representations must be maintained for the duration of the transient memory task. Representations decay over time, leading to progressively less precise performance. These two requirements raise a basic question about impaired transient memory performance in schizophrenia: Are impairments caused by deficits in encoding and subsequent retrieval/utilization of information, or are they caused by impaired maintenance of information between its initial encoding and its subsequent utilization?

For this study, we evaluated the performance of subjects with schizophrenia on several tasks that required transient memory storage but differed in terms of informational demands and presumed underlying circuitry. Two tasks were chosen to evaluate the functioning of modality-specific transient memory systems. The specific components evaluated were auditory sensory memory (ASM) and proprioceptive (object weight) memory. These systems subserve the psychophysiological ability to retain brief representations of the sensory properties of tones and weights, respectively. The final task, an “AX” version of the visual continuous performance test (CPT), was chosen to evaluate functioning in a more classic working memory task that is known to be heavily dependent on prefrontal/”central executive” functioning (Cohen et al. 1996). Further, memory retention in the AX-CPT is postulated to depend heavily on prefrontal dopaminergic systems (Cohen et al. 1992).

**Experiment 1—Tone Memory (Auditory Sensory Memory) Performance**

For the initial experiment, we evaluated the performance of schizophrenia subjects in a test of ASM. ASM stores representations of the simple physical properties of a stimulus for periods of seconds to tens of seconds after presentation (Cowan 1984). This system has also been termed echoic, because subjects may experience the memory as an echo of the presented stimulus. A key feature of the ASM system is that it functions in a largely preattentive fashion, so subjects can recall stimuli that were not attended to at the time of presentation (Cowan et al. 1990). Moreover, allocating attention to stimuli at the time of presentation does not improve the precision with which a representation can be created or utilized, nor does it increase the time course over which information can be retained. The nature of an individual’s silent mental activity during the period of transient memory storage also does not affect overall precision of performance (Keller et al. 1995). In contrast, the effects of an intervening sound during the interstimulus interval (ISI) are large, indicating that the memories are labile but not substantially attention-dependent (Deutsch 1970; Massaro 1970; Pechmann and Mohr 1992).

Functioning of the ASM system is assessed most easily with a simple delayed tone-matching task in which two stimuli are presented with a brief intervening delay and subjects are asked to state whether the second stimu-
lus is the same or different from the first. In such a task, subjects typically perform well at short ISIs (e.g., 250 ms), while their performance decays exponentially at longer ISIs. The critical duration over which ASM traces can be retained is on the order of 30 sec. The difficulty of the task can be increased by making stimuli more similar, thereby increasing the precision to which the mnemonic representation must be stored and utilized, or by increasing the ISI, thereby placing greater demands upon memory retention. Stimulus representations are always most precise immediately after they are formed; precision decays thereafter with a characteristic time-course, resulting in a decay in task performance.

Intracortical processes underlying ASM have been localized primarily to modality-specific auditory cortex. The decline of ASM with poststimulus time correlates closely with changes in the electrophysiological state of primary and association areas of the auditory temporal cortex (Lu et al. 1992; Sams et al. 1993). Moreover, functioning of the ASM system is indexed by a specific event-related potential component termed mismatch negativity (MMN) (Cowan et al. 1993; Tiitinen et al. 1994). Although MMN generation is primarily a preattentive process, generation of MMN has been shown to govern performance on attention-dependent tasks, such as those used in this study, that depend upon utilization of the ASM system (Tiitinen et al. 1994). Generators of MMN have been localized to the superior temporal plane in the region of primary auditory cortex using both dipole localization (Hari et al. 1984; Scherg et al. 1989; Cowan et al. 1993; Tiitinen et al. 1994) and intracortical recording (Csépe et al. 1987; Javitt et al. 1994). Finally, lesions of auditory cortex lead to selective disturbances in ASM performance (Massopust et al. 1971; Colombo et al. 1996). Thus, MMN indexes an early stage of auditory information process that contributes to performance of more complex tasks (Cowan 1988; Naatanen 1990).

We have previously reported in smaller studies that schizophrenia subjects show significant deficits in ASM performance (Strous et al. 1995; Javitt et al. 1997), consistent with their demonstrated impairment in MMN generation (Javitt et al. 1995, 1998). This study addresses the degree to which the deficit in tone-matching performance in schizophrenia reflects impairments in the precision with which the ASM functions, as compared with the duration with which auditory sensory information can be retained. To distinguish between these two possibilities, we examined sensory memory in a two-tone discrimination test that we conducted at varying levels of task difficulty and ISI. Tones within each tone pair in the two-tone test could either be identical or could differ in pitch by a fixed percentage of base frequency. In some trial blocks, the differences amounted to 20 percent of the first tone’s pitch (Δf), corresponding to an easy discrimination, whereas in other blocks the differences were only 5 percent, corresponding to a more difficult discrimination. In a pilot study, which utilized a 300-ms delay, schizophrenia subjects in a 20 percent Δf discrimination condition and controls in a 5 percent Δf condition performed similarly (Strous et al. 1995). In this study, a 250-ms delay was used, which represents the earliest time at which the functioning of the long-term phase of ASM can be tested independent of interference effects that occur as a function of stimulus fusion within the short-term phase.

Subjects and Methods. Subjects consisted of 20 chronic schizophrenia patients and 19 nonpsychiatric controls of similar age (control: 36.8 ± 8.7 yrs; schizophrenia: 38.7 ± 2.0 yrs). Partial data from a subset of these patients have been presented previously (Javitt et al. 1997). All subjects reported that they had normal hearing. Schizophrenia subjects were diagnosed according to DSM–III–R (American Psychiatric Association 1987) criteria. Subjects with DSM–III–R Axis I disorders other than schizophrenia, including alcoholism and substance abuse, were excluded from the study, as were patients with clinically apparent neurological abnormalities or those with significant musical training.

Tone-matching performance was tested at two levels of difficulty: an “easy” condition corresponding to a pitch difference (Δf) of 20 percent between the standard and test tone (e.g., 1,000 vs. 1,200 Hz tone) and a “difficult” condition corresponding to a Δf of 5 percent (e.g., 1,000 vs. 1,050 Hz). These levels were chosen on the basis of a pilot study demonstrating similar performance at short ISI (300 ms) between schizophrenia subjects performing a 20 percent Δf discrimination and controls performing a 5 percent Δf discrimination (Strous et al. 1995). Data were analyzed at four different levels of ISI: 250 ms and 1, 10, and 20 sec. At each ISI and for each difficulty level, 12 stimuli were presented. In half the trials, the reference and test tones were the same, and in the other half, the tones differed by either 5 or 20 percent in pitch. All tones were 100 ms in duration with a rise/fall time of 10 ms. Subjects responded verbally as to whether the second tone was the same or different in pitch as the first.

For statistical analysis, two separate comparisons were made. First, schizophrenia subjects were compared with controls at each level of task difficulty (as determined by Δf level) and ISI in order to determine relative precision of processing. Second, performance of schizophrenia subjects in the easy condition was compared with that of control subjects in the difficult condition in order to determine relative rates of performance decay.
Results. When comparisons were made across groups, task difficulty, and ISI, schizophrenia subjects showed significantly impaired performance under all conditions, as reflected in a highly significant main effect of group \( F = 68.9, df = 1.37, p < 0.0001 \) and highly significant differences in performance at each level of task difficulty and ISI considered independently (all \( p < 0.001 \), table 1). As expected, however, schizophrenia subjects performing the easy discrimination showed a performance level similar to control subjects performing a difficult discrimination, with both groups attaining a level of approximately 85 percent correct responses at 250 ms ISI (figure 1). In order to analyze sensory memory decay over time, therefore, performance of controls in the difficult discrimination condition was compared with that of schizophrenia subjects in the easy condition (figure 1). Analysis of Variance (ANOVA) of these results demonstrated the expected, highly significant effect of ISI \( F = 36.7, df = 3,35, p < 0.0001 \). In contrast, there was no significant main effect for group \( F = 0.33, df = 1.33, p > 0.5 \) and no significant group by ISI interaction \( F = 0.6, df = 3,35, p > 0.5 \). Finally, between-group performance was not significantly different at any subsequent level of ISI considered independently (all \( p \)-values > 0.5) when groups were matched for performance at 250 ms.

Discussion. The main finding of this experiment is that schizophrenia subjects show severe impairments even on an extremely simple form of working memory, that is, the ability to match two tones following an extremely brief (250 ms) delay. As measured by effect size, the degree of impairment is as severe as that observed on much more complex tasks of cognitive functioning (Blanchard and Neale 1994). The fact that performance is impaired even at the shortest testable ISI and does not increase with increasing ISI suggests that performance within the sensory memory system is impaired because the overall precision of the system in schizophrenia subjects is less than it is in controls, rather than because the system is unable to retain stimulus representations over time. This point is further supported by the fact that once correction is made for the decreased precision of performance by decreasing task difficulty for schizophrenia subjects relative to controls, the two groups show essentially identical decay in performance over a 20-sec period, with highly significant decay in performance being observed in both groups. Further, while attention and motivation may contribute to overall performance levels in both schizophrenia and control subjects, the fact that there is no differential decay in performance over time argues against the interpretation that the between-group difference in precision of performance is due to between-group differences in attentional ability or motivation. If that were the case, both groups would be expected to worsen with increasing ISI. In controls, tone-matching performance is significantly related

<table>
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<tr>
<th>ISI</th>
<th>Easy (20% Δf)</th>
<th>Difficult (5% Δf)</th>
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<tr>
<td>250 ms</td>
<td>99.2 ± 0.6</td>
<td>85.0 ± 1.8</td>
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<tr>
<td>1 sec</td>
<td>96.7 ± 1.2</td>
<td>80.3 ± 3.1</td>
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<td>10 sec</td>
<td>92.5 ± 14.2</td>
<td>68.0 ± 3.6</td>
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<td>20 sec</td>
<td>81.6 ± 3.1</td>
<td>73.3 ± 4.2</td>
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Note.—Δf = pitch difference.

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<tr>
<th>ISI</th>
<th>Easy (20% Δf)</th>
<th>Difficult (5% Δf)</th>
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<tr>
<td>250 ms</td>
<td>88.8 ± 2.4</td>
<td>60.0 ± 2.6</td>
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<tr>
<td>1 sec</td>
<td>80.0 ± 2.9</td>
<td>56.7 ± 2.0</td>
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<td>10 sec</td>
<td>63.2 ± 3.9</td>
<td>51.3 ± 2.7</td>
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<td>20 sec</td>
<td>62.9 ± 2.7</td>
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Note.—SEM = standard error of the mean.
to generation of MMN, an event-related potential component that reflects novelty detection within the auditory cortex (Titinen et al. 1994). Deficits in MMN generation in schizophrenia, moreover, correlate with deficits in tone-matching performance (Javitt et al. 1995), indicating that impairments in processing precision may lead to impaired detection of, and response to, stimulus deviance. MMN amplitude is reduced in schizophrenia across a broad range of pitch deviance. When conditions are chosen that permit schizophrenia subjects to perform equivalently to controls (i.e., by adjusting levels of Δf as was done in this study), however, MMN amplitudes are similar in the two groups (Javitt et al. 1998). Thus, the attentive tone-matching deficits observed in this study may reflect, in part, processing imprecision at early stages of cortical stimulus evaluation. We have also recently observed that MMN generation is no more affected by prolongation of ISI in schizophrenia subjects than it is in controls (Javitt et al. 1998), supporting the current suggestion that ASM performance is impaired in schizophrenia due to impaired precision of representation rather than premature decay of sensory information.

Experiment 2—Weight-Discrimination (Proprioception) Performance

In order to test the hypothesis that deficits in transient memory performance are evident across sensory modalities in schizophrenia, we studied an additional transient memory system. We chose the proprioceptive system (Jones 1986) for several reasons. First, like the ASM system, it stores a relatively primitive representation of stimulus feature (object weight). Second, like the ASM system, it maintains this representation over several tenths of seconds, during which time the representation progressively decays. Finally, like the ASM system, proprioceptive representations cannot be encoded verbally. The last reason is crucial because verbally encoded information can be maintained by vocal or subvocal repetition using short-term or "phonological loop" memory that appears to function by different mechanisms than the transient memory components targeted in this investigation (Baddeley 1992).

Proprioceptive functioning has been tested previously in schizophrenia with mixed results. Impaired proprioception was found initially by Rosenbaum and coworkers (1959), who tested subjects at only a single, brief ISI. Similar findings were obtained by Ritzler and Rosenbaum (1974), although the between-group difference was significant only when relatively light (~40 gm) weights were used. Proprioceptive memory was then examined using time intervals of 2, 4, and 8 seconds between stimulus weights. The interaction between diagnosis and time interval was not significant in that study, leading to the conclusion that poor discrimination of light weights was not caused by impaired proprioceptive memory. Ritzler (1977) found proprioceptive deficits in nonparanoid schizophrenia subjects and nonschizophrenia psychotics relative to normal controls, but no discrimination deficit in paranoid schizophrenia subjects. Finally, Leventhal and coworkers (1982) found significant differences between inpatient paranoid and nonparanoid schizophrenia subjects as a group and normal controls in the discrimination of both light and heavy weights, although paranoid schizophrenia subjects were more impaired in discriminating light than heavy weights. In contrast to the findings with inpatients, however, weight discrimination was not significantly impaired in a group of outpatients with either paranoid or nonparanoid forms of schizophrenia. Thus, while the available literature suggests that schizophrenia is associated with deficits in proprioceptive precision that cannot be accounted for by premature decay of sensory representations, it is not clear under what circumstances and in what patient groups deficits may be apparent.

Subjects and Methods. Subjects were 21 medicated chronic schizophrenia inpatients diagnosed according to DSM-III-R criteria, and 22 normal controls. Their mean chronicity of illness was 19 ± 8 years. The patient and control groups were similar in age (control: 38.5 ± 2.4; schizophrenia: 40.1 ± 1.7 year). However, 20 of 21 patients were male, while the control group consisted of 11 males and 11 females.

Proprioceptive memory was tested using plastic canisters filled with varying combinations of sand and Styrofoam such that weight could not be determined by visual inspection. All canisters weighed between 275 and 350 grams. Testing was done in two phases: first, a determination of weight discrimination threshold, and second, a determination of discrimination accuracy over 5- and 30-sec decay periods. Threshold was defined as the weight difference at which subjects could determine with greater than 80 percent accuracy which of two canisters was heavier.

Threshold was determined by presenting pairs of canisters that were successively closer in weight, starting with a between-canister weight difference of 25 grams. Subjects held the canisters one at a time in their dominant hand and alternated between canisters as often as necessary to decide which was the heavier. (Alternation was allowed only during the threshold detection component of the task.) At each weight difference level, a block of 12 trials was administered. In each block, the lighter weight was presented first in half of the trials and second in the remaining half. The two conditions were distributed in random order within each block. If subjects had 10 or
more correct responses (83%), canisters of successively smaller weight difference were used, with the degree of weight difference remaining constant within each block (12.5, 6.25, 3.12, and 1.06 gm). Testing continued at successively smaller weight difference levels until a subject was unable to obtain at least 10 correct responses in a block. The smallest weight difference at which a subject responded correctly at least 10 times in a block of 12 trials (83% correct) was considered that subject's weight discrimination threshold. For subjects who did not get 10 correct responses in the first block of 12 trials (conducted at a weight difference level of 25 gm), testing proceeded with blocks of increasing weight difference (37.5 and 50 gm) until they obtained the required level of 10 correct responses.

Following threshold determination, effects of delay were examined. For this study, we tested each subject at his or her individually determined weight discrimination threshold in two final blocks of trials. In the first block, handling of the reference and test weights was separated by 5 sec; in the long ISI block, by 30 sec. Within each block, 12 trials were presented. In half the trials, the first canister was heavier; in the remaining half, the second was heavier. At each time interval, the number of correct responses was recorded. Because of the forced-choice design, the chance performance rate was 50 percent. Between-group differences in weight discrimination threshold were analyzed by one-way between-group ANOVA. Memory decay was determined by repeated measures Multiple Analysis of Variance (MANOVA) with within-group factor of ISI (i.e., delay between presentation of the reference and test weight) and between-group factor of diagnosis (schizophrenia vs. control).

Results. Weight-discrimination thresholds for both groups are shown in figure 2. Schizophrenia subjects required a significantly greater difference between weights to obtain a criterion level of 83 percent correct detections ($F = 6.3, df = 1,41, p < 0.02$). The between-group difference remained strongly significant even following covariation for sex distribution ($F = 8.3, df = 1,41, p < 0.01$). In the control group, there was no significant difference in performance between males and females ($t = 1.0, p > 0.3$). Further, a significant between-group difference was observed even when analyses were restricted to male subjects ($F = 6.1, df = 1,29, p < 0.02$). There was no difference in weight discrimination threshold for subjects with paranoid schizophrenia (23.8 ± 4.1%, $n = 8$) compared with patients diagnosed with chronic undifferentiated schizophrenia (23.8 ± 3.9%, $n = 10$).

When subjects were tested following a 5- or 30-sec delay at their individually determined no-delay threshold levels, both groups showed a progressive decay in performance (main effect of delay $F = 36.0, df = 2,40, p < 0.001$) as shown in figure 2. In contrast, there was no significant main effect of group ($F = 6.2, df = 1,41, p > 0.2$).
or group × time interaction \(F = 1.34, df = 2.40, p > 0.2\). Further, a between-group difference of small-to-moderate effect size could be rejected with a power greater than 0.8. Finally, even when post-hoc t tests were performed, no significant between-group differences in performance accuracy were observed at either 5- \(t = 1.2, p > 0.2\) or 30-sec \(t = 1.4, p > 0.2\) delay. It is interesting, however, that the rate of perseverative errors (number of perseverative errors per block), which were defined as those errors that happened when the subject chose the same incorrect response as in the previous trial, was significantly higher among schizophrenia than control subjects at both 5- (schizophrenia: 2.05 ± 10.2; control: 1.22 ± 0.23, \(t = 2.6, p < 0.02\)) and 30-sec (schizophrenia: 2.47 ± 0.25; control: 1.37 ± 0.27, \(t = 3.1, p < 0.005\)) delays. The rate of non-perseverative errors, in contrast, was virtually identical between groups at both 5- (schizophrenia: 1.52 ± 0.27; control: 1.68 ± 0.32, \(t = 0.8, p > 0.4\)) and 30-sec (schizophrenia: 1.62 ± 0.35; control: 1.95 ± 0.31, \(t = 0.4, p > 0.7\)) delays.

**Discussion.** The results of this study demonstrate that patients with schizophrenia have significantly elevated thresholds for weight discrimination relative to controls. However, when tested at their individually determined weight discrimination threshold, schizophrenia subjects show no difference in their ability to maintain representations over a subsequent 30-sec interval. As with pitch representations, weight representations decayed from a level of approximately 80 percent correct detections to near-chance (50%) levels over a 30-sec time period. The ability to maintain high-precision, short-duration representations thus may be a common feature across multiple sensory modalities.

A limitation of this study is that controls and schizophrenia subjects were poorly matched for sex. Almost all patients were male while controls were equally distributed male and female. Danziger and Botwinick (1980) reported that men discriminated better than women in a weight discrimination test, while Ross (1987) described males as being superior in weight discrimination performed with the dominant hand while females were superior when the nondominant hand was used. Given that all subjects were tested with their dominant hand and that there were more males in the patient than control group, a sex-related difference in performance would have influenced results against the appearance of a significant between-group difference. However, given the similar performance of male and female controls in our study, it seems unlikely that sex contributed significantly in either direction to the observed pattern of results. An additional limitation of the present study was that all patients were receiving neuroleptics, and no psychiatric control groups were tested. Additional studies will therefore be necessary to investigate the potential effects of medication and the specificity of these findings to schizophrenia.

An interesting finding of this study was that schizophrenia subjects had a significantly greater rate of perseverative errors than controls. To the extent that there was a between-group difference in performance, it was accounted for entirely by this between-group difference in perseveration. Differences in perseverative response rate have also been found in other studies of working memory in schizophrenia (e.g., Park and Holzman 1992). This would indicate that schizophrenia subjects may have a twofold impairment on this task: first, an imprecision in proprioceptive processing causing an elevation in weight discrimination threshold, and second, a relatively higher rate of perseverative responding even when adjustment is made for the elevated weight discrimination threshold.

**Experiment 3—Visual “AX”-Type Continuous Performance Test (AX-CPT) Performance**

The initial experiments in this study investigated transient memory systems that are relatively uninfluenced by attention and thus may be considered “automatic” systems. In contrast, this experiment was designed to target a component of working memory that is specifically dependent on attention and prefrontal processing and that may therefore be considered an “active” or “controlled” system. The goal of this experiment was to evaluate the degree to which similar patterns of deficit could be observed across passive and active transient memory systems. The task that was chosen, an “AX” version of the visual continuous performance test (AX-CPT), has been postulated to depend specifically upon prefrontal processing (Cohen et al. 1996). In this task, letters are presented sequentially and subjects are required to respond to the sequence of a letter “A” followed by a letter “X” and to ignore all other letter sequences. Processing of the target letter (“X”) thus requires retention of information concerning the cue (“A”), which therefore is described as providing context for the subsequent response. Based upon connectionist models, it has been suggested that the prefrontal cortex plays a primary role in the processing and maintenance of contextual representations, which decay over a time course similar to those of other working memory traces (Cohen and Servan-Schreiber 1992). When most of the trials in an AX-CPT consist of an “AX” sequence, a strong bias is set up to respond whenever a target letter (“X”) appears. The main difficulty in the task then becomes to remember *not* to press when a noncue letter
(i.e., a letter other than “A”) is presented prior to a target, that is, to store the negative contextual information. A failure in mnemonic processing of contextual information would thus lead to high rates of false alarms to incorrectly cued targets (termed “BX” errors), especially at long ISI, as has been reported for patients with schizophrenia (Servan-Schreiber et al. 1996). Because of the complexity of the task, it was not possible in this experiment to evaluate performance at multiple levels of task difficulty and determine individual thresholds as was done in the prior experiments. However, it was possible to evaluate performance at discrete levels of ISI and to compare the performance of control and schizophrenia subjects across levels of ISI.

Subjects and Methods. Subjects were 15 chronic schizophrenia inpatients diagnosed according to DSM-III-R criteria and 15 normal controls of similar age (control = 37.4 ± 8.1; schizophrenia = 40.1 ± 11.3). For this task, individual letters were presented sequentially on a computer screen for 250 ms each. Letters were red against a black background, in helvetica font and subtended at an angle of 2°. Subjects were required to press a button whenever the letter A (“cue”) was followed by the letter X (“target”). All other sequences were to be ignored, including sequences in which a letter other than A (designated “B,” but consisting of all letters other than A or X) was followed by the target letter (X) or sequences in which either a cue or noncue was followed by a nontarget (designated “Y,” but consisting of all letters other than A or X). Stimuli were presented in four blocks of 256 stimuli (128 sequences) each. Within each block 50 percent of cue-target sequences were presented with short ISI (0.85 sec) and 50 percent with long ISI (5 sec). Short and long ISI sequences were pseudo-randomly intermixed. Following each stimulus pair, subjects had 1 sec to respond, at which time the next cue was presented. For 70 percent of the stimulus pairs, a correct cue was followed by a correct target (AX sequence); for 10 percent, a noncue was followed by a correct target (BX sequence); for 10 percent, a cue was followed by a nontarget (AY sequence); and, for the final 10 percent, a noncue was followed by a nontarget (BY sequence). Correct detections of the AX sequence were recorded separately for short and long ISI trials. Correct rejections were recorded for all other stimulus pairs. Stimulus sequence differed in the four blocks, but overall ISI and sequence probability remained constant. Data were analyzed using separate repeated measures ANOVA for each stimulus sequence (AX, BX, AX, BY) with within-group factor for each ANOVA of ISI, and between-group factor of diagnosis. Post-hoc comparisons at each ISI level were performed using t tests.

Results. Performance for schizophrenia and control subjects is shown in figure 3. As expected, schizophrenia subjects had a significantly lower rate of correct detection of correct cue/target sequences (AX sequence) than did controls across both the long and short ISI (main effect of group $F = 7.3$, $df = 1.28$, $p < 0.02$). Schizophrenia subjects also showed significantly lower rates of correct rejections of target letters preceded by an incorrect cue (BX sequence) than controls across ISI (main effect of group $F = 5.6$, $df = 1.28$, $p < 0.03$). Both groups also showed the expected main effect of ISI such that performance decreased as ISI increased. This result was reflected in a significant main effect of ISI for both groups in correct detections of AX sequences ($F = 9.7$, $df = 1.28$, $p < 0.005$) and correct rejections of BX sequences ($F = 13.5$, $df = 1.37$, $p < 0.001$). However, the group X ISI interaction was not significant for either correct detection of AX sequences or correct rejections of BX sequences ($F < 0.1$, $df = 1.28$, $p > 0.5$ for both). Finally, when the decay in performance over time was computed by subtracting accuracy rates at long ISI from those at short ISI, the two groups showed nearly identical rates of performance decrement (figure 4). Thus, while performance...
accuracy was lower overall, no differential effect of time was observed. Groups did not differ in correct rejection rate for sequences in which the target stimulus was incorrect (AY and BY sequences).

Discussion. As with the previous experiments, this experiment demonstrates impaired functioning of schizophrenia subjects in a task that requires transient, trial-specific memory storage. In the prior experiments, the information to be retained consisted of relatively unprocessed sensory information. In contrast, in this paradigm the information to be retained may have consisted of either a representation of the cue letter itself or, more likely, a representation of the context ("go"/"no-go") for interpreting a subsequent target that is provided by a valid or invalid cue. The decision not to respond could theoretically be maintained verbally or by some other strategy (e.g., by removing one's finger from the response button until a correct cue was presented). The ISI-dependent decline in performance that was evident in both groups argues against such strategies having been used, however, and reinforces the concept that a nonverbal representation of stimulus context was retained and utilized by subjects in both groups in order to perform the discrimination. The fact that schizophrenia subjects did not respond any more frequently to nontarget stimuli (AY or BY sequences) than did controls argues against the concept that schizophrenia subjects are unable to recognize letters appropriately or are less motivated to perform the test accurately than controls. If it is assumed, based on the lack of incorrect responses to nontarget stimuli, that schizophrenia subjects are able to recognize letters as well as controls, then it can be concluded that the deficit for schizophrenia subjects is due to a greater degree of difficulty in decoding the information inherent in the cue, that is, translating the noncue presentation to a "no-go" contextual representation. As opposed to the prior experiments in which there was decreased precision in the degree to which simple stimulus representations could be stored (i.e., pitch, weight), in this experiment schizophrenia subjects appear to be impaired in the precision with which they can form or utilize go/no-go decisions based on a presented stimulus. This capability is thought to depend primarily on prefrontal cortex. The results of this study are thus similar to those obtained by Servan-Schreiber and coworkers who reported increased BX errors in medicated schizophrenia subjects compared with controls, but no increased sensitivity to ISI prolongation (Servan-Schreiber et al. 1996).

General Discussion

This investigation evaluates data from three separate studies of transient memory storage in schizophrenia using paradigms that alternately target sensory or cognitive brain regions. A common finding across the studies is that schizophrenia subjects perform poorly in tests that require transient memory storage. However, the performance deficit is not due to the memory component of the task per se; rather, it reflects imprecision in the overall level of processing, such that schizophrenia subjects utilize both sensory and cognitive information less precisely than controls. Larger sensory differences or more robust cognitive information must therefore be provided to schizophrenia subjects to permit them to perform with the same degree of accuracy at the same level as nonpsychiatric controls. If such information is provided, the duration over which it is maintained appears to be similar, at least in the paradigms assessed in this investigation.

The results of these experiments suggest that similar abnormalities should be observed in other tests of working memory. In support of this prediction, two studies of spatial recall have found relatively greater deficits in performance when a delay is imposed between stimulus presentation and response (i.e., when a memory trace must be formed and utilized) than when an immediate response is permitted (Park and Holzman 1992; Keefe et al. 1995). In one of the studies (Keefe et al. 1995), performance was tested at two levels of ISI (30 and 60 sec), and no differential decay in performance was observed between schizophrenia and control subjects. The concept that schizophrenia subjects process information less precisely than controls is consistent with the results of studies of visual perceptual organization. It has been demonstrated that schizophrenia subjects are less able than controls to recognize the gestalt features of a visual scene (for example, shape outlines made up of incomplete dot patterns) and to take advantage of gestalt features in visual processing (Place and Gilmore 1980; Knight et al. 1985; Rabinowicz et al. 1996). It has recently been demonstrated, however,
that when the stimulus features are made more salient, schizophrenia subjects are able to use stimulus features equivalently to controls (Silverstein et al. 1996), indicating decreased precision of processing but otherwise normal perceptual organization.

On a neural level, mnemonic representations may reflect sustained alterations in response patterns within distributed nodal networks, with each node encoding a specific element of a task. For example, in monkeys performing a spatial delayed response task, neural ensembles have been demonstrated that encode the spatial location of the target stimulus (Funahashi et al. 1993). The precision with which a given node can encode and maintain a particular task element (e.g., spatial location) will determine the precision with which a given task can be performed.

It is impossible to determine neurophysiological mechanisms of cognitive dysfunction in schizophrenia from behavioral data alone. However, the pattern of working memory dysfunction observed in this study permits the development of two general principles. First, the fact that similar deficits were observed in three separate sensory/cognitive domains suggests that the underlying dysfunction should be widespread across cortical regions. This hypothesis is consistent with results of some neuropsychological test batteries that have demonstrated generalized (Blanchard and Neale 1994) or multifocal (Sullivan et al. 1995) patterns of cognitive test batteries in schizophrenia, with imaging studies showing generalized gray matter volume reduction (Zipursky et al. 1992) and with post-mortem studies showing similar degrees of neuropil reduction in prefrontal and occipital cortical regions (Selemon et al. 1995).

A second principle that is supported by these findings is that dysfunction or dysregulation of functioning within a specific transmitter system, the glutamate/N-methyl-d-aspartate (NMDA) receptor system, may contribute to cognitive dysfunction in schizophrenia. NMDA receptors are one of several types of receptor for the neurotransmitter glutamate, which is the major excitatory neurotransmitter in cortex. Phencyclidine (PCP or “angel dust”) and other NMDA antagonists (e.g., ketamine) induce a psychotic state that closely resembles schizophrenia (Luby et al. 1962; Krystal et al. 1994; Lahti et al. 1995), leading to the hypothesis that disturbances in NMDA receptor-neurotransmission may contribute to the pathophysiology of schizophrenia (Javitt and Zukin 1991; Olney and Farber 1995; Coyle 1996; Hirsch et al. 1997; Heresco-Levy and Javitt 1998). We have previously demonstrated that infusion of NMDA antagonists into auditory cortex induces a schizophrenia-like deficit in MMN generation, indicating that deficits in NMDA receptor-mediated neurotransmission may contribute to the disturbances of ASM and MMN generation seen in schizophrenia (Javitt et al. 1996). Similarly, it has been demonstrated that PCP administration to normal volunteers induces a disturbance in proprioception similar to that observed in schizophrenia. Administration of LSD or sodium amytal, in contrast, did not induce weight discrimination deficits (Rosenbaum et al. 1959). Finally, ketamine infusion in normal volunteers has been reported to induce deficits in visual CPT performance similar to those observed in schizophrenia (Krystal et al. 1994). Thus, while mechanisms underlying NMDA dysfunction in schizophrenia remain to be determined, dysfunction or dysregulation of these receptors might lead to symptom production and cognitive dysfunction similar to that observed in schizophrenia.

NMDA receptors are unique among neurotransmitter receptors in that they function in a manner that is both voltage- and neurotransmitter-dependent. This dual dependence permits them to play a crucial role in cognitive functioning, learning and memory formation, and developmental plasticity (Cotman et al. 1988). Because of their voltage-dependent activation, NMDA receptors are regulated by gamma-aminobutyric acid (GABA)-ergic feedback circuits in cortex, as demonstrated by the fact that infusion of GABA antagonists into cortex leads to uncontrolled NMDA receptor-mediated excitations that can be reversed by the administration of NMDA antagonists (Schroeder et al. 1990; Javitt et al. 1996). Although it is unclear whether NMDA receptors themselves are functionally abnormal in schizophrenia (Akbarian et al. 1996), several studies have demonstrated disturbances of GABAergic innervation, including decreased GABA synthesis (Akbarian et al. 1995) despite increased GABA receptor density (Benes et al. 1992). Disturbances in the strength or precision of GABA/NMDA feedback leading to failure of appropriate NMDA receptor recruitment during task performance could lead to the imprecision of cortical processing observed in the present study. In summary, this study demonstrates widespread deficits in the precision of cortical processing in schizophrenia. These deficits are most easily interpretable in the context of disturbances in the interplay between widely distributed neurotransmitter/neuroreceptor systems.

References


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Acknowledgments

This study was supported by National Institute of Mental Health (NIMH) grants R29MH49334 and K02MH01439 and grants from the National Alliance for Research in Schizophrenia and Depression (NARSAD) and the McDonnell-Pew Foundation to Daniel C. Javitt.

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The Stanley Foundation Research Programs, created in 1989, is the largest nongovernment funder of research on the causes and treatment of schizophrenia and bipolar disorder, with an awards program that exceeds $20 million per year.

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