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Encoding vs. retention: differential effects of cue manipulation on working memory performance in schizophrenia

Daniel C. Javitt^{a,b}, Esther Rabinowicz^a, Gail Silipo^a, and Elisa Dias^a

a Program in Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute for Psychiatric Research, New York University School of Medicine, 140 Old Orangeburg Road, Orangeburg, NY 10962

b Departments of Psychiatry and Neuroscience, New York University School of Medicine, 140 Old Orangeburg Road, Orangeburg, NY 10962

Abstract

Background—Deficits in working memory performance are among the most widely replicated findings in schizophrenia. Roles of encoding vs. memory retention in working memory retention remain unresolved. The present study evaluated working memory performance in schizophrenia using an AX-type continuous performance test (AX-CPT) paradigm.

Methods—Participants included 48 subjects with schizophrenia and 27 comparison subjects. Behavior was obtained in 3 versions of the task, which differed based upon ease of cue interpretability. In a simple cue version of the task, letters were replaced with red or green circles. In the complex cue version, letter/color conjunctions served as cues.

Results—In the base version of the task, patients showed increased rates of false alarms to invalidly cued targets, similar to prior reports. However, when the cue stimuli were replaced with green or red circles to ease interpretation, patients showed similar false alarm rates to controls. When a feature conjunction cues were used, patients were also disproportionately affected relative to controls. No significant group by interstimulus interval interaction effects were observed in either the simple or complex cue conditions, suggesting normal retention of information even in the presence of overall performance decrements.

Conclusions—These findings suggest first, that cue manipulation disproportionately affects AX-CPT performance in schizophrenia and, second, that substantial behavioral deficits may be observed on working memory tasks even in the absence of disturbances in mnemonic retention.

Keywords

schizophrenia; working memory; AX-CPT; cue; target; dopamine; NMDA

Introduction

Cognitive dysfunction is a significant and enduring feature of schizophrenia and a primary predictor of poor outcome and chronic disability (Goldman, 1998; Harvey et al., 1990; Kay and Murrill, 1990). Dysfunction may be particularly severe in tasks where subjects must form and

Address correspondence to: Daniel C. Javitt, M.D., Ph.D., Director, Program in Cognitive, Neuroscience and Schizophrenia, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd, Orangeburg, NY 10962, tel: (845) 398-6534, fax: (845) 398-6545, email: javitt@nki.rfmh.org

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utilize short-duration memory traces while working on a task or problem, and in performance of tasks that are critically dependent upon prefrontal involvement. (Carter et al., 1998; Gold et al., 1997; Goldman-Rakic, 1991; Goldman-Rakic, 1994; Stone et al., 1998; Weinberger and Berman, 1996; Weinberger et al., 1986). However, schizophrenia subjects also show deficits in tasks involving relatively simple sensory functions, such as matching simple tones (Holcomb et al., 1995; Javitt et al., 1997; Stevens et al., 2000; Strous et al., 1995), weights (Javitt et al., 1999) or visual patterns (Fleming et al., 1997) following brief delay. An unresolved issue, therefore, is the degree to which difficulties in interpreting sensory aspects of stimuli affects performance in working memory tasks. The present study investigates sensory contributions to impaired working memory performance in schizophrenia using modifications of the “AX”-type continuous performance task (AX-CPT), one of the most widely applied paradigms for investigating working memory deficits in schizophrenia.

In the AX-CPT, subjects view a series of letters that are presented sequentially on a monitor, and press whenever a predesignated sequence of letters is presented. In the most common version of the task, the predesignated sequence consists of the letter “A” followed by the letter “X,” with all other sequences to be ignored. Therefore, when subjects see a letter “A” in the cue position they must bias themselves toward response to the subsequent stimulus, whereas if they see any other letter (collectively designated “B”) they must form a bias against response. Commonly, the probability of valid cue, correct probe (“AX”) sequences is relatively high (70%), so that most targets have been validly cued. Thus, in order to perform the task accurately, when subjects see a cue letter other than “A,” they must form a bias against response, and then maintain that bias throughout the cue response period. In schizophrenia, patients show both decreased accuracy in detection of valid cue, correct probe (“AX”) sequences, and increased rates of false alarm to invalid cue, correct probe (“BX”) sequences. In contrast, rates of response to valid cue, invalid probe (“AY”) and invalid cue, invalid probe (“BY”) are not significantly affected (Cohen et al., 1999; Javitt et al., 2000; Perlstein et al., 2003).

Although patients with schizophrenia reliably show deficits in AX-CPT performance, the basis for these deficits remains an area of active research. In particular, with regard to the disinhibitory deficits, it remains to be determined whether patients solely lack the frontal inhibitory mechanisms needed to maintain the negative response bias produced by the invalid cue, or whether they fail as well to adequately decode the information content of the cue stimuli. In schizophrenia, visual processing deficits have been increasingly documented over recent years (Butler et al., 2005; Schechter et al., 2005), raising the possibility that sensory deficits may contribute to impaired overall performance in this task.

Virtually all studies with AX-CPT have used identical stimulus types (i.e., letters) for cue stimuli. For the present study, ease of decodability of the cue stimuli was manipulated, and effects on task performance were evaluated. Performance on the AX-CPT is critically dependent upon transforming the cue into a representational form that carries information regarding the cue’s implication for future stimulus evaluation and response. This representation form is frequently referred to as context representation (Barch et al., 2001). We use the term decoding to refer to the processes preceding context representation, during which the cue is registered within sensory systems, evaluated relative to external rules or exemplars (e.g. “press if you see an A followed by an X), and appropriately transformed. Because the cue has no intrinsic meaning outside arbitrary meanings provided by the investigator, it may be viewed most accurately as a code that must be decoded relative to external rules or referents.

In addition to the base version of the task, two additional versions were used (Figure 1). In the simple color cue condition, the letter cues were replaced with green or red colored circles that served as valid and invalid cues, respectively. In the complex cue condition, color and letter conjunctions were used. Valid cues consisted of a green letter “A” or a red letter other than

“A”, whereas invalid cues consisted of stimuli with the opposite feature conjunctions. We hypothesized that the simple color cue condition would produce relative normalization of performance in schizophrenia patients vs. controls, whereas the complex cue condition would exacerbate the schizophrenia deficit, consistent with the concept that the inability to correctly decode the information content of presented cue stimuli (i.e. to transform the cue into the appropriate contextual representations) may underlie or contribute to AX-CPT performance deficits in schizophrenia.

Methods

Subjects

This study included 48 individuals with schizophrenia or schizoaffective disorder diagnosed according to DSM IV criteria and 27 non-psychiatric comparison subjects of similar age and sex (Table 1). The study was approved by the New York State Office of Mental Health Institutional Review Board. All subjects provided voluntary informed consent. All patients were receiving antipsychotic medications (typical, atypical or combination) at the time of testing (Table 1). One-quarter of patients were also receiving anticholinergics. Diagnoses were established by a board-certified attending research psychiatrist or a licensed research psychologist using a semi-structured clinical and/or SCID interview (First et al., 1994), chart review, and discussion with mental health professionals familiar with the case. Subjects with a DSM-IV Axis I diagnosis other than schizophrenia or schizoaffective disorder, including psychotic mood disorder, alcoholism or substance dependence during the past six months, were excluded from the study, as were patients with clinically apparent neurological abnormalities. Also excluded were any individuals with significant musical training or ability, as well as any controls who were on any psychiatric medications or who had a history of significant Axis I diagnosis. All subjects were comparably compensated at the completion of testing.

Symptom ratings were performed by master- or PhD-level mental health professionals using the Positive and Negative Symptom Scale (PANSS), and interrater reliability $>.7$. A three-factor model of the PANSS (Kay et al., 1987) was used for correlational analyses.

Comparison subjects consisted of associated personnel of the institutions from which the patient samples were drawn. IQ was assessed for all subjects by the Ammons and Ammons Quick Test (Ammons and Ammons, 1962). Controls, on average, had completed significantly more years of education, ($t=6.81$, $p<.001$) and were of higher IQ ($t=6.35$, $p<.001$) than patients. Nevertheless, between group differences remained significant following covariation for IQ.

Task—Stimuli were presented sequentially on a CRT monitor, in stimulus pairs with letters within a pair separated by either 0.85 or 5 s, and letters between pairs separated by 1 s. Participants were instructed to press a mouse button when they were presented with a sequence consisting of a predesignated valid cue (denoted by the letter “A,” but consisting of different specific stimuli in different versions of the task), followed by a predesignated valid probe (the letter “X”). Participants were further instructed to withhold response if either an invalid cue (denoted by the letter “B,” but consisting of all stimuli other than the predesignated valid cue) or invalid probe (denoted by the letter “Y,” but consisting of all stimuli other than the predesignated target stimulus) stimulus was presented. Thus, incorrect responses consisted either of failures to detect valid cue, valid probe (“AX”) sequences, or false alarms to all other sequence types.

Three separate versions of the AX-CPT task were used (Figure 1). In the base version of the task, letters were used for both cues and targets, with the letter “A” serving as the valid cue and all other letters serving as invalid cues. The letter “X” did not appear in the cue position. In a second version (simple cue), the letters that had been used for cue stimuli were replaced

with solid colored circles of similar size to the letters. Green circles served as valid cues, whereas red circles served as invalid cues. In a third version (complex cue), conjunctions of features were processed. Either a green letter A or red letter other than A were considered valid cues, whereas all other stimuli (i.e., red letter A or green letters other than A) were considered invalid cues.

Each version was presented in a separate block consisting of 240 stimulus pairs, with intermixed long and short ISI trials (50% each). In all task conditions, the letter “X” served as the predesignated correct probe stimulus. All other letters were considered incorrect probe stimuli. The letter “A” was not presented in the probe position. Participants were instructed to press on a mouse button when they detected an AX sequence, and to respond as accurately as possible. In all versions of the task, 70% of the trials were of the AX type, and 10% were of each of the other types (BX, AY, BY).

Statistical analysis—Primary dependent variables consisted of error rate for each of the sequence types. For AX sequences, errors consisted of incorrect omissions (“misses”). For all other sequences, errors consisted of false alarms. Separate repeated measures MANOVA (rmMANOVA) analyses were conducted for each error type and task independently. In each analysis, ISI was coded as a within group group factor, and diagnostic group was coded as a between-group factor. Secondary analyses utilized d' -context scores calculated based upon relative rate of misses and false alarms to BX-trials only, as previously described (Servan-Schreiber et al., 1996). d' -context scores were calculated as the inverse of the cumulative normal distribution function for percent correct detections minus the inverse of the cumulative normal distribution function for percent BX errors. Correlational analyses were conducted using Spearman r_s statistics. All statistics were two-tailed, with present α level of significance of $p < .05$.

Results

Primary analyses

Regular-cue CPT—In the base version of the task (Figure 2A), patients showed significantly lower rate of correct detections of AX sequences at both short and long ISI, leading to a significant main effect of group ($F=11.8$, $df=1,73$, $p<.001$). Both groups showed worse performance in long vs. short delay trials ($F=15.3$, $df=1,73$, $p<.001$). In addition, patients showed greater decay in performance across ISI, as reflected in a significant group X delay interaction ($F=5.71$, $df=1,73$, $p<.02$).

Patients also showed greater rates of false alarms to BX trials ($F=3.85$, $df=1,73$, $p=.05$). As with correct detections, both groups showed worse performance in long vs. short delay trials ($F=119.5$, $df=1,73$, $p<.001$), but the group X delay interaction was non-significant ($F=0.6$, $df=1,73$, $p=.6$). In contrast patients did not show greater numbers of false alarms in either the AY ($F=0.28$, $df=1,73$, $p=.6$) or BY conditions ($F=2.38$, $df=1,73$, $p=.13$), with error rates in both groups being minimal.

In order to compare degree of deficit and pattern of deficit between groups across AX and BX trials, a between-group rmANOVA was performed with within group factors of trial type (AX/BX) and ISI (short/long). There was a highly significant group X trial type interaction ($F=10.6$, $df=1,73$, $p=.002$) indicating significantly greater reduction in AX performance than BX performance at both short and long delays in patients vs. controls. The ISI X trial type interaction was also strongly significant ($F=32.2$, $df=1,73$, $p<.0001$) indicating greater ISI effects on AX, than BX, performance across delays in both groups. The group X ISI interaction was non-significant ($F=1.0$, $df=1,73$, $p=.3$). The group X ISI X trial type interaction was nearly significant ($F=3.38$, $df=1,73$, $df=.07$).

Simple cue-CPT—When the task was modified so that green or red circles were used instead of letter cues, patients again showed a significant between-group difference in correct detection rate ($F=10.6$, $df=1,72$, $p=.002$) of AX trials (Figure 2B). In this version, as in the base version, there was a significant main effect of time ($F=16.7$, $df=1,72$, $p<.001$), but the group X time interaction was nearly significant ($F=3.70$, $df=1,72$, $p=.06$).

In contrast to impaired correct detection rates, in this condition patients showed no significant difference in rate of false alarms to incorrectly cued targets (BX errors) compared with controls ($F=0.1$, $df=1,72$, $p=.8$). As in the original task, both groups showed worse performance in long vs. short delay trials ($F=13.1$, $df=1,72$, $p=.001$). Also as in the base version, however, patients were again no more susceptible to effects of delay than controls, as reflected in a non-significant group X ISI interaction ($F=0.2$, $df=1,72$, $p=.7$). As in the base version of the task, patients did not differ significantly from controls in rates of either AY ($F=.5$, $df=1,72$, $p=.5$) or BY ($F=.2$, $df=1,72$, $p=.7$) versions of the task.

When performance in this version of the task was compared statistically to performance in the base version of the task, controls showed no significant effect of task for either correct detections ($F=1.74$, $df=1,26$, $p=.2$) or rate of BX errors ($F=0.3$, $df=1,26$, $p=.6$). In contrast, patients showed significantly increased rates of AX errors ($F=9.07$, $df=1,46$, $p=.004$), but significantly reduced rates of BX errors ($F=4.86$, $df=1,46$, $p=.03$) in the simple color cue condition.

When relative pattern of AX and BX error rates were compared across groups, a significant group X trial type interaction was again observed ($F=4.8$, $df=1,72$, $p=.03$), as was a significant ISI X trial type interaction ($F=32.7$, $df=1,72$, $p<.00001$). The group X ISI effect was again non-significant ($F=1.0$, $df=1,72$, $p=.3$). The group X ISI X trial type interaction was nearly significant ($F=2.9$, $df=1,72$, $p=.095$).

Complex cue CPT—When the task was modified so that a more complex cue was used (combined color/letter), patients again showed lower rates of correct detections than controls across delays ($F=14.0$, $df=1,70$, $p<.001$) and greater rates of false alarms to incorrectly cued targets ($F=6.5$, $df=1,70$, $p=.01$) (Figure 2C). In this condition, as in prior versions, there was a significant delay effect across group for AX errors ($F=4.31$, $df=1,70$, $p<.05$), but not for BX errors ($F=2.1$, $df=1,70$, $p=.2$). Further, there were no significant group X delay interactions for either the AX ($F=2.73$, $df=1,70$, $p=.1$) or BX ($F=.1$, $df=1,70$, $p=.8$) conditions.

In this version also, the group X trial type interaction was strongly significant, reflecting greater deficit in AX, than BX, performance ($F=16.0$, $df=1,70$, $p<.0002$). However, neither the ISI X trial type ($F=.04$, $df=1,70$, $p=.8$), the group X ISI ($F=1.0$, $df=1,70$, $p=.3$), nor the group X ISI X trial type ($F=0.4$, $df=1,70$, $p=.5$) interactions were significant.

Across task comparisons—Compared to the base version of the task, control performance on the complex cue version was not significantly different in terms of either AX ($F=.37$, $df=1,25$, $p=.08$) or BX ($F=.7$, $df=1,25$, $p=.4$) errors. In contrast, patients showed significantly higher rates of AX ($F=14.7$, $df=1,45$, $p<.0003$), but not BX ($F=0$, $df=1,45$, $p=.9$), errors in the complex cue than base version of the task.

Compared to the simple cue version of this task, control performance in the complex cue condition was also not significantly different in terms of either AX ($F=.2$, $df=1,25$, $p=.6$) or BX ($F=1.58$, $df=1,25$, $p=.2$) errors. In contrast, patients showed increased rates of both AX ($F=5.5$, $df=1,44$, $p=.02$) and BX errors ($F=5.5$, $df=1,44$, $p=.02$) in the complex vs. simple cue version of the task.

Both groups showed significant differences in pattern of AX (ctl: $F=4.5$, $df=1,25$, $p=.04$; pat: $F=11.6$, $df=1,44$, $p=.001$) and BX (ctl: $F=5.0$, $df=1,25$, $p=.035$; pat: $F=9.0$, $df=1,44$, $p=.004$) performance decay over time in the complex vs. simple cue versions of this task as reflected in significant task X ISI interaction, with the delay effect being less prominent in the complex vs. simple cue version for both groups.

Secondary analyses

d'-context—d'-context scores (Figure 3) were calculated based upon BX error rate relative to AX correct detection rate. As with primary analyses, across the 3 task versions there was a highly significant main effect of group ($F=15.9$, $df=1,69$, $p<.001$) and ISI ($F=37.0$, $df=1,69$, $p<.001$), and a significant group X task ($F=5.45$, $df=2,68$, $p=.006$), task X ISI ($F=16.2$, $df=2,68$, $p<.001$) and group X ISI ($F=5.20$, $df=1,69$, $p=.03$) interactions. In contrast, the group X task X ISI ($F=.7$, $df=2,68$, $p=.5$) interaction was not significant. Patient performance was worse than that of controls in all three versions of the task, although the magnitude of the deficit was largest in the complex cue version of the task ($F=20.0$, $df=1,70$, $p<.001$), smallest in the simple cue version of the task ($F=6.1$, $df=1,72$, $p=.02$), and intermediate in the base version ($F=9.9$, $df=1,73$, $p=.002$).

The group X task interaction was due primarily to differential effects of cue manipulation in the two groups. In particular, controls showed equivalent performance in all three versions of the task as shown by a non-significant main effect of task for controls only ($F=0.5$, $df=2,24$, $p=.6$), whereas patients showed a highly significant variation in performance level across the three task versions ($F=9.4$, $df=2,43$, $p<.001$). For patients performance was substantially worse for complex than simple cues ($F=18.3$, $df=1,44$, $p<.001$), whereas performance of controls was similar in the two conditions ($F=.7$, $df=1,25$, $p=.4$).

Task X ISI interactions were due to different temporal profiles across the 3 tasks. In the base version of the task, both groups showed a significant decline in d'-context with increasing ISI as reflected in a main effect of ISI ($F=15.7$, $df=1,73$, $p<.001$). Patients also showed differentially reduced performance at long vs. short ISI as reflected in a group X ISI interaction ($F=5.0$, $df=1,73$, $p=.03$). In the simple cue condition, both groups again showed a significant decline in performance with increasing ISI ($F=40.7$, $df=1,72$, $p<.001$). However, in this condition, the decline in performance was similar across groups, as reflected in a non-significant group X ISI interaction ($F=.6$, $df=1,72$, $p=.4$). In the complex cue condition, both the main effect of ISI ($F=.2$, $df=1,70$, $p=.3$) and the group X ISI interaction ($F=1.2$, $df=1,70$, $p=.6$) were non-significant.

Correlations

In the base version of the task, increased rates of BX errors correlated significantly with severity of PANSS negative symptoms, at both short ($r_s=.43$, $p=.01$) and long ($r_s=.50$, $p=.002$) ISI. No significant correlations were observed with either positive symptoms or general psychopathology score at either short or long ISI.

There were no correlations with CPZ equivalents and any behavioral measures (all $r_s<.2$). Performance was similar in individuals receiving typical vs. atypical antipsychotics on all measures (all $p>.2$). Similarly, no statistical effects were observed for either clozapine or anticholinergic treatment (all $p>.2$).

Discussion

The AX-CPT is one of the best-established tasks for demonstrating executive processing/working memory dysfunction in schizophrenia (Barch et al., 2003; Cohen et al, 1999; Javitt et

al, 2000;Perlstein et al, 2003;Servan-Schreiber et al, 1996). In this task, patients show a characteristic pattern of dysfunction in which they are less accurate both at detecting valid cue-correct probe (AX) sequences, and in withholding response to a correct probe that has been invalidly cued (BX sequence). In contrast, patients show no increased rates of false alarm to valid cue-invalid target (AY) sequences, suggesting a specific deficit in encoding and maintaining the information of the cue, rather than the target, stimulus.

For the present study, the ease with which the cue stimuli could be decoded, and their information content encoded, was manipulated by substituting both simple and complex cues for the more traditional monochromatic letter stimuli. The primary findings of the present study are that patients were far more susceptible than controls to cue manipulation, and, second, that performance deficits for patients occurred even in the absence of deficits in information maintenance. Additionally, it was observed that delay effects were substantially different for AX and BX trials, suggesting that differential mechanisms may be involved in preparing to respond vs. preparing to override a pre-potent response.

On the simplest level, correct AX-CPT performance requires that the information content of the cue be decoded into a representational form that can then be used to disambiguate a subsequent probe stimulus (Perlstein et al, 2003). Valid cue stimuli must be translated (decoded) into a representation that facilitates response to a subsequent valid probe stimulus, while invalid cues must be translated into a bias against response. Impaired performance can thus reflect either increased difficulty on the part of patients in decoding the information content of the cue into persistent representations, or in maintenance of the representations themselves.

In the base version of the task, patients showed increased rates of BX errors, consistent with prior literature. In contrast, the introduction of a red circle as the invalid cue led to an absolute normalization of BX error rate in patients at both short and long ISI. The normalization was due to an absolute decrease in BX error rate in patients, with no change in BX error rate in controls. These findings suggest that for patients, but not for controls, decoding of the cue may have been rate limiting in terms of BX performance in the base version of the task, leading to impaired ability to establish appropriate context to guide subsequent response. In this condition, interestingly, patient performance in the AX trials worsened in parallel to the improvement in BX performance suggesting that patients nevertheless may be less able than controls to alternate between strong inhibitory and strong facilitatory biases on a trial-by-trial basis (Cohen and Servan-Schreiber, 1992). Nevertheless, patients showed least impairment under this condition, suggesting that simplification of the sensory aspects of the task may significantly ameliorate the patient deficit.

In the complex version of the task, patients were significantly more affected than controls, particularly with regard to AX error rates. Patients showed significantly lower rates of correct detections in this task than in the base version of the task, whereas performance of controls was unaffected. In this version of the task, the valid cue consisted either of green “A”s or red non-“A”s. The difficulty of decoding the information content of the cue was thus significantly increased especially relative to the simple version of the task. Nevertheless, controls showed highly similar performance between the simple and complex cue versions of the task whereas patients showed significantly worse performance in the complex vs. simple version. Thus, patients’ impaired performance on this task may be due primarily to impaired ability to decode the information content of the presented stimuli and to translate such impairments into appropriate instructional representation, whereas other aspects of the task were essentially intact.

Although inability to perform tasks such as the AX-CPT in schizophrenia is commonly referred to as a “working memory” deficit, in both this study and in several prior investigations (Barch

et al, 2003;Cohen et al, 1999;Javitt et al, 2000;Perlstein et al, 2003), it does not appear that the ability to maintain information on line represents the primary pathological event. In the present study, there was no significant group X delay effect for BX errors in any version of the task, suggesting that patients maintained inhibitory context over delay as well as controls across tasks. In the complex version, there was no overall delay effect, suggesting that no decay of the inhibitory trace occurred in either group, yet patient performance was nevertheless significantly impaired.

For AX sequences, increasing ISI in the base version of the task disproportionately increased the error rate for patients, suggesting premature decay of the facilitatory bias imparted by the valid cue stimulus. However, no group X ISI interaction was observed in the other two versions of the task. Moreover, considerable performance decrement was observed even at the shortest ISI, suggesting that establishing the appropriate biases, rather than maintaining them, is the critical event in AX-CPT dysfunction in schizophrenia.

In addition to defining the nature of the between-group differences in task performance on the AX-CPT, the present study may also provide information regarding the nature of the working memory trace maintained during task performance. In both the base and simple cue versions of the task, controls and patients showed a significant delay effect, whereas in the complex cue condition, no such effect was observed for either group. Thus, the strategies used to perform the task may have changed in parallel in the two groups based upon cue-related exigencies.

In all versions of the task, the cue consisted of a visual stimulus that needed to be decoded and translated into an appropriate mnemonic trace. The trace could, theoretically, consist either of a literal representation of the cue, or of its instructional content, or a combination of factors. If a literal representation were maintained, then translation into action would be performed at the time of probe stimulus presentation. Otherwise, translation would be performed at the time of cue presentation and maintained on-line, for example, based upon firing pattern of prefrontal command neurons (Goldman-Rakic, 1995). A possible explanation for the different delay characteristics of the tasks is that the different physical properties of cue stimuli necessitate the use of alternative storage and translational strategies.

In both the base and simple cue version of the task, the physical features of the stimulus are relatively easy to encode either in the form of a visual (iconic) memory trace, or as a verbal representation. For example, in the base version of the task, subjects may rehearse the cue letter subvocally (i.e. repeat to themselves “A,” “B,” etc.) and then, upon presentation of the probe determine whether an appropriate sequence (i.e. “AX”) has been presented. In the simple color version of the task, the color of the cue (“green”/“red”) can also be maintained verbally with relatively ease.

In contrast, in the complex cue condition, vocal maintenance of the cue properties (i.e. “green A or red non-A”) is much more difficult, necessitating use of alternative strategies. Most likely, in this condition the instructional content (A= “go if X”, B=“Nogo even if X”) is decoded at the time of cue presentation and maintained during the subsequent delay interval. One potential explanation for the differential delay properties of the task is that memories for the literal aspect of the cue decay more quickly than those encoding the instructional aspect. Thus, in the complex cue condition, when one is required to utilize an instructional trace, delay effects are substantially less than in other versions. Support for use of subvocalization in maintenance of information comes from an fMRI study in which significant activation of Broca’s area was observed irrespective of response contingencies (Perlstein et al, 2003).

In addition to showing differential absolute performance rates, the present data suggest that the two groups may also have utilized different strategies in the different versions of the task. In the simple cue condition, in which maintaining a literal version of the cue is easiest, both

patients and controls showed prominent decline in d' -context scores over ISI (Figure 3), indicating that the information content of the cue was maintained in labile form. In contrast, in the complex cue condition, neither group showed a significant decay in performance across ISI, suggesting that a non-labile representation was used consistent with the presumed difficulty in maintaining a literal version of the complex cue on line. Relative to these two bracketing conditions, controls showed a decline in performance with ISI in the base version of the task that was intermediate between the decline that they showed in the simple vs. complex cue conditions, suggesting that they may have relied upon both literal and non-literal mnemonic traces. In contrast, patients showed d' -context vs. ISI slopes in the base version of the task that paralleled the slopes observed in the simple cue version. Thus, in the base version, patients may choose to, or may be forced to, rely on more literal representations than controls, leading to ISI-dependent between-group differences. The differential deficit that patients show relative to controls in the complex vs. simple cue condition may reflect a greater deficit in encoding the cue into a conceptual vs. literal mnemonic trace, which, presumably, relies more heavily upon prefrontal mechanisms.

On a neurophysiological level, deficits in AX-CPT performance have been attributed to dysfunction of prefrontal cortex (Barch et al, 2003; Cohen et al, 1999; Javitt et al, 2000; Perlstein et al, 2003; Servan-Schreiber et al, 1996), although underlying mechanisms have yet to be determined. Such attributions have been made based upon both theoretical formulations of prefrontal function (Cohen et al, 1999; Cohen and Servan-Schreiber, 1992), as well as fMRI studies showing reduced prefrontal activation during AX-CPT performance in patients (Barch et al, 2003; Perlstein et al, 2003). In electrophysiological studies, B-cues elicit prefrontal activity that is localized to DLPFC based upon both dipole mapping in humans (Dias et al., 2003), and direct intracortical recordings in primates (Dias et al., 2006). In schizophrenia, increased BX error rates are associated with reduced electrophysiological response to the B-cue. Such reductions occur within the first 300 ms after B-cue presentation, consistent with the concept that the basic deficit in AX-CPT performance in schizophrenia is due to failure to establish appropriate facilitatory vs. inhibitory biases (Javitt et al, 2000).

On a neurochemical level, it was proposed that deficits in AX-CPT performance may relate to reduced dopaminergic activity (Braver et al., 1999; Cohen and Servan-Schreiber, 1993). More recent theories of schizophrenia have posited dysfunction of *N*-methyl-D-aspartate (NMDA) type glutamate receptors, based upon psychotomimetic effects of phencyclidine, ketamine and other NMDA antagonists (Javitt and Zukin, 1991). Previously, a reversible pattern of deficit has been observed following administration of the NMDA antagonist ketamine to normal volunteers (Umbricht et al., 2000). As in the present study, ketamine administration was found to reduce correct detection of AX sequences and increase BX error rates, while not affecting error rates for either AY or BY sequences. The pattern of AX-CPT dysfunction observed in this study is thus consistent with the pattern predicted from NMDA models of the disorder. Finally, similar deficits in AX-CPT performance have been observed following administration of the 5-HT_{2A} receptor agonist psilocybin to normal volunteers (Umbricht et al., 2003), suggesting that convergent dysfunction of multiple transmitter systems may conspire to disrupt prefrontal function in schizophrenia.

In the present study, significant correlation was found between BX errors at both short- and long-delay and severity of PANSS-rated negative symptoms. This finding is consistent with prior studies showing correlations between BX errors and both disorganization and poverty symptoms of the PANSS (Barch et al, 2003). In that study, elevated BX error rates were observed as well in acute psychotic patients at index, but not following treatment. Such findings are consistent with neurochemical findings that both ketamine and psilocybin can induce similar AX-CPT deficits, but that only in the case of ketamine are such deficits associated with disorganization and poverty symptoms (Umbricht et al, 2000; Umbricht et al, 2003). Thus,

dysfunction of NMDA transmission may serve as a unifying explanation for the presence of both negative symptoms and cognitive dysfunction, including impaired ability to form and/or maintain contextual representations in schizophrenia.

A limitation of the proposed study is that reaction times were not monitored in the different versions of the task. Thus, patients could have employed different accuracy/speed trade-offs that might have provided further information regarding nature of between-group differences. Further, in this version of the AX-CPT, subjects pressed only to valid cue, correct probe trials. Nevertheless, the task is similar to that used in previous patient (Javitt et al, 2000), ERP (Dias et al., 2003), and neurochemical manipulation (Umbricht et al, 2000;Umbricht et al, 2003) studies, permitting direct comparison of present and past results

In summary, deficits in AX-CPT performance in schizophrenia have been well established. In this study, difficulty of the AX-CPT was manipulated by altering the decodability of the cue stimuli. Patients were significantly more affected by these manipulations than controls, suggesting that deficits in this task may occur primarily during the sensory decoding stage, and may reflect primarily inability to establish appropriate response biases rather than impaired ability to maintain such representations across delay. The pattern of dysfunction in this study is thus consistent with predictions of NMDA dysfunction models of schizophrenia.

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<u>VERSION</u>	<u>CUE</u>	
	<u>Valid</u>	<u>Invalid</u>
Regular	A	{B,C,D,...}
Simple color
Complex color	{B,C,D,...}	{B,C,D,...}

Figure 1.
Schematic illustration of cue stimuli used for the base, simple color and complex color versions of the task.

Figure 2.

Performance of schizophrenia patients and controls on the base, simple color and complex color versions of the task for short (0.85 sec) and long (5.0 sec) ISI trials. For AX trials, rate for errors of omission (misses) is shown. For other trial types, rate for errors of commission (false alarms) is shown.

Figure 3. d' -context values for the 3 task versions. d' -context reflects hit rate to AX trials relative to false alarm rate for BX trials calculated for each ISI in each version of the task separately.

Table 1

Mean (sd) demographic information for patients (n=48) and controls (n=27)

Measure	Patients	Controls
Age (yrs)	36.3 (9.1)	36.4 (2.2)
Gender	29M/19F	15M/12F
IQ	99.0 (10.3)	117.3 (12.4)*
Education (yrs)	12.8 (2.3)	16.3 (2.2)*
Antipsychotic dose	881.6 (543.0)	NA

*
p<.001