Schizophrenic Deficits in the Processing of Context

A Test of a Theoretical Model

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Background: Schizophrenic patients show various deficits in cognitive functions that have been difficult to understand in terms of a common unifying hypothesis. Previously described neural network models of cognitive tasks suggest that several schizophrenic performance deficits may be related to a single function—an impairment in maintaining contextual information over time and in using that information to inhibit inappropriate responses.

Methods: We tested first-episode schizophrenic patients and patients later in the course of their illness on a new variant of the Continuous Performance Test designed specifically to elicit deficits in the processing of contextual information.

Results: Unmedicated schizophrenic patients showed a deterioration of their signal detection performance that followed the pattern predicted by the context hypothesis, i.e., they responded inappropriately when correct responding required the maintenance of context information over time to inhibit the expression of a habitual response. This deficit correlated with positive symptoms. The results also suggested that the deficit may be worse in unmedicated patients who have had a longer course of illness. Medicated patients showed a more diffuse performance deficit.

Conclusions: These results support the view that a single deficit in the processing of context information may underlie various cognitive impairments observed in schizophrenia. They also suggest that such an impairment is associated with positive rather than negative symptoms, and that it may worsen with the course of the illness as in the Kraepelinian view of schizophrenia.

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CHRONIC PATIENTS show deficits in laboratory tasks that probe cognitive functions ranging from attention to language, memory, and problem-solving. There is no clear understanding of what cognitive processes may be disturbed to produce such disparate deficits. In previous work, we addressed this problem by constructing computer simulation models that specify the information-processing mechanisms underlying normal performance in some cognitive tasks.1,2 This suggested that several schizophrenic deficits could be related to a disturbance in a single mechanism with pervasive implications for cognition: the representation and maintenance of context information.3

Context information is information that has to be held actively in mind in such a form that it can be used to mediate an appropriate behavioral response. For example, in the sentence "In order to keep chickens, you need a pen," the phrase "in order to keep chickens" provides context that constrains the word "pen" to its weaker meaning—"fenced enclosure" rather than to its more common meaning—"writing implement." Context information can be the result of processing a sequence of previous stimuli, a specific previous stimulus, or even a set of task instructions. By this definition, context information is relevant to but does not necessarily form part of the content of the actual response. This distinguishes the role of context from that of short-term memory (i.e., storing the identity of recently presented stimuli). We assume that context information is relevant to the performance of almost all cognitive tasks—even simple perceptual tasks—to the extent that subjects must keep in mind at least a set of task instructions that are necessary to identify relevant stimuli and me-

See Subjects and Methods on next page
SUBJECTS AND METHODS

SUBJECTS

Four groups of subjects were studied: unmedicated, first-episode schizophrenic patients (n=11); unmedicated, multiphase schizophrenic patients (n=6); medicated schizophrenic patients (n=21); and psychopharmacologically hospitalized patient controls (n=11). All were inpatients who were moderately to severely ill (mean ± SD) Brief Psychiatric Rating Scale (BPRS) score, 34.5 ± 8.23). The BPRS is a 16-item scale, scaling 1 to 7 for each item. Diagnoses were made by a staff psychiatrist, and confirmed by trained research personnel using the Structured Clinical Interview for DSM-III-R for schizophrenic patients and the Schedule for Affective Disorders and Schizophrenia for mood-disorder patients.

Unmedicated first-episode schizophrenic subjects all were admitted for the first time, without any history of neuroleptic medication. They had a mean duration of prodromal symptoms of 134 weeks (n=6; prodromal data was unavailable for 5 patients). In all cases, the diagnosis of schizophrenia was confirmed 6 months later. Unmedicated multiphase schizophrenic subjects were all newly admitted patients who had a documented history of noncompliance with medication for 1 month or more before admission to the hospital. They were tested before receiving neuroleptic medication. Medicated schizophrenic subjects were recently admitted despite outpatient treatment with standard doses of neuroleptic medication and were tested while continuing to receive the same medication. Two of the medicated schizophrenic patients were first-episode right-handed male subjects who had started to receive medication before admission to the hospital. They were included with the medicated schizophrenic group of 19 multiphase patients because they did not differ in age, education, or any experimental variables (i.e., they fell within 1 SD of the mean of the remainder of the medicated subjects on all measures). Controls were inpatients on the mood disorders unit of Western Psychiatric Institute and Clinic, Pittsburgh, Pa. All were diagnosed as having major depressive disorder, and none experienced psychotic symptoms.

Subjects were screened for the following exclusion criteria: alcohol or substance abuse, any substance use within 2 weeks before the study, neurologic illness, or history of head trauma with loss of consciousness. The BPRS was administered within 1 week of admission to the study. Ratings were completed by trained members of the research team who were unaware of the task performance of subjects. The positive symptoms subscale of the BPRS consisted of the sum of 3 items: conceptual disorganization, hallucinatory behavior, and unusual thought content.

No statistically reliable difference was seen between the medicated and unmedicated schizophrenic patients and the patient controls in age, sex, education level, or total BPRS score. However, there were reliably more left-handed medicated patients than unmedicated patients or patient controls by χ² analysis, and more left-handed multiphase schizophrenic patients than first-episode schizophrenic patients or patient controls. These demographic data are given in the Table.

PROCEDURE

All subjects provided informed consent in accordance with the university institutional review board. They were tested within 10 days of their admission to the hospital using a modified version of the A-X CPT. Sequences of letters were presented one at a time in the center of a visual display, and subjects were instructed to respond whenever the letter X ("target") followed the letter A ("cue"). In this task, the cue provided the context within which to evaluate the target. The remaining letters of the alphabet were used as distractors, with the exception of the letter K, which was excluded because it looks like the letter X. Letters were presented on a computer screen, nondegraded, in Helvetica font, in white against a black background, and subtended a visual angle of 3°. Subjects responded by pressing a button with a finger of their dominant hand. Stimuli appeared for 250 milliseconds, and subjects had a total of 1 second from stimulus onset in which to respond. Feedback was provided in the form of a beep for hits (i.e., correct button presses), a buzz for false alarms or misses, and no sound for a correct rejection. This feedback was important to signal to the subjects whether they had responded within the 1-second window (because a failure to respond appropriately to them. However, context information is more important to some tasks than others. In particular, it is expected to play an important role when subjects have to maintain information over time and when they have to inhibit an otherwise habitual response. Conversely, it is expected to be least relevant to tasks that do not involve a delay, or do not require subjects to inhibit their natural tendencies.

We have proposed that a disturbance of context can account not only for a general cognitive impairment but also for the specific pattern of schizophrenic deficits observed across various cognitive tasks. We constructed computer simulation models of 3 tasks that are considered to tap different cognitive processes: the Stroop task (selective attention), the identical pairs version of the Continuous Performance Test (CPT) (vigilance and signal-detection ability), and a lexical disambiguation task (language processing). Models of all 3 tasks used a similar architecture (Figure 1). We showed that, in simulations of all 3 tasks, a single disturbance to the module supporting context produced changes in performance that matched those observed in schizophrenia.

Furthermore, our models specify mechanisms related to 2 cognitive functions thought to be impaired in schizophrenia: working memory* and behavioral inhibition.* Working memory refers to the ability to keep information actively in mind and manipulate it in ways required by a given task. Behavioral inhibition refers to the ability to inhibit a habitual, but inappropriate, response.

Our models show that both the active maintenance of task-relevant information and the inhibition of task-irrelevant information can be carried out by the module responsible for representing and maintaining context. Thus, memory and inhibition reflect the operation of a single underlying mechanism—the context module—
within that time was regarded as a miss). The task was run on an Apple Macintosh computer, using PsyScope software. Testing was done in an isolated room in the patient unit after a brief practice period.

The standard procedure for the A-X CPT was modified in 2 ways. First, the frequency of cue-target sequences (A-X) was increased so that these occurred 80% of the time. A randomly chosen noncue letter preceded the target (eg, B-X) in another 10% of trials, and the cue was followed by a distractor (eg, A-Y) in the remaining 10% of trials. Increasing the frequency of cue-target sequences served to engage subjects more actively in the task and to introduce a strong tendency to respond to occurrences of the letter X. This, in turn, forced subjects to rely on the previous letter in the noncue followed by target condition (eg, B-X), as context to inhibit the habitual tendency to respond to X. We predicted that a deficit in this inhibitory function would lead schizophrenic patients to generate a greater number of false alarms to such sequences, which we refer to as "BX errors."

The second modification involved varying the interstimulus interval (ISI) to test subjects' ability to maintain context information over time. We used 2 ISIs: 750 milliseconds and 5 seconds. Each subject was tested in 2 blocks of the task, 1 with the short ISI (750 milliseconds), and 1 with the long ISI (5 seconds). The order was counterbalanced across subjects. A total of 450 stimuli were presented in the short ISI condition and 150 in the long ISI condition, to control for time on task. In each case, the proportion of target and non-target events remained the same (A-X, 80%; B-X, 10%; A-Y, 10%). Subjects had only 1 second to respond, independently of ISI, to prevent differences in speed-accuracy trade-offs between groups from affecting hits and misses differentially across conditions.

We predicted that the performance of control subjects would improve in the 5-second ISI condition, consistent with previous observations that subjects typically perform better in slower-paced tasks. We predicted the reverse for schizophrenic patients: an impairment in the maintenance of context (memory function) would lead to a worsening of performance at the longer delay. More specifically, we predicted an increase in the number of BX errors at the long ISI (evidence that a failure to maintain context [memory] results in an accompanying failure to suppress a strong response tendency [inhibition]).

Finally, we predicted that patients with a recent onset of schizophrenia would have a selective impairment at long delays, but that patients tested at a later stage of illness would fail to withhold responses even at short delays (evidence of a failure to represent as well as maintain context information).

**DATA ANALYSIS**

Hit and false-alarm rates for each subject were used to compute measures of response criterion and sensitivity (d'). C, which is computed as \( -0.5(Z_{hit} + Z_{false\,alarm}) \), is a measure of criterion recommended for tests in which discrimination varies as a function of group. The d' was computed in the standard manner (using all false alarms—BX and AY), and separately using just the BX false alarms. The latter, by directly comparing performance in the AX and BX conditions, provides a measure of the sensitivity of target detection to the nature of the previous stimulus. This was used as a measure of sensitivity to context (hereafter referred to as "d'-context"). For all computations, in cases of a perfect hit rate (1.0) or false-alarm rate (0.0), a small constant correction (0.001) was made to allow estimation of the signal detection indices. This leads to a maximum possible d' value of 6.2 for perfect scores. To verify the assumptions of signal detection theory, the correlations between d' and C were computed within each group, after excluding subjects who made no false alarms (this latter group artificially divides the sample into 2 clusters). After application of the Bonferroni correction for number of significance tests, none of the 6 possible correlations were significant at the .05 level (actual alpha = .01).

We performed a separate repeated-measures analysis of variance (ANOVA) for each of the dependent variables of interest (number of AX false alarms, number of BX false alarms, d', and d'-context). Each ANOVA used group (schizophrenic-medicated, schizophrenic-unmedicated, patient controls) as a between-subject factor, and ISI (short, long) as a within-subject factor. Specific contrasts were evaluated with Student t tests. Unless specifically mentioned, 2-tailed tests were applied. One-tailed t tests were used to evaluate the specific a priori predictions that motivated the study.

under different task conditions. Under conditions of response competition, when a strong response tendency must be overcome for appropriate behavior (eg, accessing the weaker, but contextually appropriate meaning of "pen"), the context module can be seen as playing an inhibitory role. In contrast, when a delay occurs between information relevant to a response and the execution of that response, the context module can be seen as playing a memory role by actively maintaining that information over time and supporting it against the cumulative effects of noise. According to this view, the role of the context module should be most important when there is a need to maintain information over time and a need to use that information to inhibit a habitual response.

Our models also suggest that memory and inhibition are differentially sensitive to disturbances of the context module. With mild to moderate disturbances, a deficit appears only when a delay occurs between the context and a response. This is because, with partial degradation of the context information, sufficient information may remain at short or no delays to mediate a contextually appropriate response (eg, inhibit a habitual, but irrelevant response). At longer delays, however, representations succumb to the cumulative effects of noise, and a failure to inhibit the inappropriate response may be observed. Thus, the models predict that mild to moderate disturbances in patients with schizophrenia should manifest primarily at long delays, which might be viewed as a "memory" deficit. With sufficiently severe disturbances of the context mechanism, degraded context representations should produce disturbances even at brief delays, which might be viewed as an "inhibition" deficit.

Assuming a Kraepelinian view of schizophrenia, this may relate directly to the course of the illness, with a memory deficit early on, and, as the illness progresses, a
gradual reduction in the delay that can be tolerated. Eventually, late in the illness, a deficit would be observed even without a delay and may be perceived clinically as a "failure of inhibition." In both cases, the same mechanism is impaired, although to a different degree.

To test these predictions, we developed a variant of the CPT, a task that has been used widely in schizophrenia research. This variant forces subjects to maintain context information over a delay and to use that information to inhibit a habitual but inappropriate response.

**RESULTS**

Medicated and unmedicated schizophrenic patients showed generally poorer performance compared with patient controls (Figure 2, top left) (main effect of group, $P < .001$; planned comparisons, $P < .02$ for overall $d'$ in controls vs each group of schizophrenics). The predicted difference in the effect of ISI on performance in the 3 groups was marginally significant in the ANOVA (group×ISI interaction, $P = .06$). Planned comparisons confirmed the hypotheses. Control subjects showed an improvement in overall performance in the long compared with the short ISI condition (planned comparison for $d'$, $P < .01$). The unmedicated schizophrenic patients showed no change in overall performance ($P = .32$). Unexpectedly, however, the medicated patients showed an improvement in performance similar to that of controls at the long ISI ($P < .01$).

The measure of sensitivity to context (d'-context) provided more direct and specific support for our predictions (Figure 2, top right). There was a main effect of group ($P < .01$) and a significant interaction between group and ISI ($P = .02$). The performance of controls on this measure was unaffected by ISI ($P = .45$), nor was the performance of medicated schizophrenic patients ($P = .33$). However, as predicted, unmedicated patients were specifically impaired at the longer ISI ($P = .005$).

Significant predicted differences also were observed in specific types of errors across ISI. The improvement in the overall performance [d'] of controls and medicated schizophrenic patients at the long ISI means that any increases in specific types of errors at the long ISI for unmedicated patients cannot be attributed to a greater overall difficulty of the task in this condition.

Unmedicated schizophrenic patients showed an increase in BX false alarms at the long ISI, but controls and medicated patients showed no such increase (Figure 2, lower left) (group×ISI interaction, $P = .08$; planned contrast for unmedicated patients, $P = .04$, 1-tailed). Finally, for AX false alarms, only a main effect of ISI was seen ($P < .001$) (Figure 2, lower right). Such errors were less common at the long ISI for both groups of schizophrenic patients and for controls ($P < .01$ for each group).

To test our predictions related to the course of illness, we compared the $d'$-context of first-episode with multipisode schizophrenic patients (unmedicated only) and controls. A group×ISI ANOVA with repeated measures disclosed an expected main effect of ISI ($P < .05$, performance across groups was worse at the long ISI), and a main effect of group ($P < .01$, control subjects did better overall). However, only a trend was seen toward a group×ISI interaction ($P = .15$). First-episode patients did not differ from controls at the short ISI, but a trend existed toward a difference at the long ISI ($P < .10$ after Bonferroni correction for 6 comparisons, actual $\alpha = .008$). In contrast, multipisode patients differed from controls at the short and long ISI ($P < .05$ after same Bonferroni correction). Furthermore, a separate ANOVA conducted on only first-episide and multipisode patients disclosed that, while multipisode patients showed overall worse performance, there was no group×ISI interaction ($P = .58$). This indicates that the performance of both types of patients followed the same pattern of degradation with delay.

These findings provide tentative support for our prediction of poorer performance at the long delay compared with the short delay (ie, memory deficit) at all stages of illness, combined with an additional deficit specific to later stages of the illness that affects short delays (ie, inhibition deficit). Age did not confound findings re-
related to first vs multiepisode status, because no effect of age group (above or below the median of 31 years) was seen on performance at either ISI.

We also evaluated our d'-context measure in relation to clinical symptoms using BPRS scores. Because none of the controls performed below d'-context of 2.5, and many of the unmedicated schizophrenic patients did (Figure 3), we divided the patients into 2 groups, those who performed in the same range as controls (d'-context ≥ 2.5) and those who did not (d'-context < 2.5). This division of unmedicated schizophrenic patients into high and low sensitivity to context disclosed a strong association with clinical symptoms. The point-biserial correlation between high and low sensitivity to context and BPRS was 0.66 (P < .01) (Figure 4). Most of this association was accounted for by positive symptoms (r = 0.60, P < .01) rather than negative symptoms (r = 0.23, P = .38) or other symptoms. No such correlation existed between sensitivity to context and BPRS at the short ISI (r = 0.30, P = .28). Furthermore, medicated schizophrenic patients—who had a similar degree of clinical impairment (Table)—also did not show such an association (point biserial correlation with BPRS total, r = 0.12, P = .62, for the long ISI).

**COMMENT**

This study was motivated by a set of computer simulation models of the biological mechanisms underlying cognitive deficits associated with schizophrenia. It was designed to test 2 specific predictions made in a previous report: the performance of schizophrenic patients on a CPT task should be sensitive to the delay between the presentation of contextual information (the cue) and an ambiguous stimulus (the target), and schizophrenic patients should show a specific inability to use contextual information to inhibit the habitual response to an ambiguous stimulus. Both predictions were confirmed. Our results suggest that the deficit is modified by neuroleptic medications and the course of illness, and is associated with specific clinical symptoms of schizophrenia.

**PROCESSING OF CONTEXT: SPECIFIC VS GENERALIZED DEFICIT?**

Impaired CPT performance typically has been attributed to a nonspecific "diffuse loss of attention" rather than to a deficit in a circumscribed cognitive mechanism. A general attention deficit is unlikely to be an explanation for our present findings, because unmedicated schizophrenic patients responded to potential targets (X not preceded by A), but not to nontargets (Y), more often than did patient controls and medicated schizophrenic patients. This shows that they were engaged in the task and attentive to the nature of the stimuli.

Deficits in the processing of context have pervasive effects on cognition and may account for performance deficits in a wide array of cognitive tasks. Even "sensory-processing" tasks may be affected by the inability to maintain expectations about the experimental stimuli and to maintain a preparatory response set (ie, context). One
then may ask whether the hypothesis of a deficit in the processing of context is so encompassing as to become vacuous. To the contrary, this hypothesis explains and refines the more general concept of a "diffuse loss of attention" associated with schizophrenia since Emil Kraepelin. Although a context deficit produces a general impairment of all cognitive processing, it is not akin to "neglect" of external stimuli. Rather, it induces specific types of errors that can be predicted from a knowledge of a subject's habitual response tendencies and the requirement to maintain information across delays. Furthermore, a deficit in the processing of context does not produce a "generalized deficit" in the sense of Chapman and Chapman, in which differences in the severity of the impairment are due only to a difference in difficulty or other psychometric properties of the task. We designed this version of the CPT precisely to reveal a specific deficit (inability to use context at long delays to inhibit habitual responses) within a more general deficit (impaired signal detection performance). In this task, the long and short delay conditions had the same overall level of difficulty and similar psychometric properties (data not shown). Nevertheless, schizophrenic patients showed a specific impairment in the long delay condition, which puts the highest demands on the processing of context, compared with the short delay condition, which challenged subjects' ability to keep up with a more rapid pace.

Finally, "memory for context" is not equivalent to short-term memory. We view it as a component of the more general construct of working memory. Previous studies have indicated that schizophrenic patients do not show deficits on short-term memory tasks such as digit span, even when they show deficits in working memory. Although some tasks have been purported to elicit deficits of short-term memory in schizophrenics, these involve supraspan conditions (i.e., remembering more than 7 digits) or distractions. Such tasks require the use of encoding strategies that rely on the representation and maintenance of context information rather than simply short-term memory to manage supraspan items or to prevent the influence of intervening distracting items.

INHIBITION AND MEMORY FUNCTIONS IN SCHIZOPHRENIC DEFICITS

Various studies have attributed cognitive deficits in schizophrenia to deficits in working memory, or in inhibition, functions that have been thought to involve distinct subsystems of the prefrontal cortex (PFC). Our models have shown how active maintenance and inhibition can be ascribed to a single processing mechanism, operating under different task conditions. Roberts et al provided empirical support for this view by showing that increasing memory load produces failures of inhibition in an antisaccade task. This suggests that both functions rely on a single resource-limited mechanism. Our present findings are consistent with this view and show that a failure of this mechanism can manifest as what seems to be a memory deficit or an inhibition deficit, depending on the nature of the task.

SENSITIVITY TO CONTEXT AND DEVELOPMENTAL COURSE OF THE ILLNESS

Our models suggest that when the initial representation of context is only moderately disturbed, performance at short delays is unaffected, yet the cumulative effects of noise over time produce a deficit at longer delays. In this study, this was the pattern found in the unmedicated first-episode schizophrenic patients at the short ISI (near-normal performance) compared with the long ISI (impaired performance).

However, further deterioration of the initial representation of context—as might be expected from a progression of the illness—results in a deficit even at short delays. This is the pattern of deficit that was shown by multiepisode schizophrenic patients.

In traditional terms, first-episode schizophrenic pa-
patients showed a memory disturbance (deficits only after a delay). In comparison, multiepisode patients showed an inhibition disturbance (i.e., a failure to override inappropriate responses without a significant delay). Only a longitudinal study could show a progression of deficits from a memory impairment to a memory and inhibition impairment.

SENSITIVITY TO CONTEXT AND CLINICAL SYMPTOMS

One of our more surprising results concerned the correlation between sensitivity to context and clinical symptoms. Several investigators, including ourselves, have hypothesized a relation between cognitive dysfunction and negative symptoms of schizophrenia. However, sensitivity to context correlated with positive symptoms of the illness but not with negative symptoms. The hypothetical link between negative symptoms, hypofrontality, and impaired performance on working memory tasks in schizophrenic patients has not received strong support from empirical studies.

An association between positive symptoms and attentional disturbance also has often been proposed, and several studies have documented such a relation. A common interpretation is that positive symptoms distract subjects during the laboratory task. Indeed, a disturbance in the processing of context would be expected to lead to distractibility (the traditional "failure to maintain set"). This is supported in our study by the correlation between positive symptoms and poor performance on the d-context measure in unmedicated patients.

SENSITIVITY TO CONTEXT AND NEUROLEPTIC MEDICATIONS

The performance of medicated patients (as measured by d-context) was inferior to that of patient controls (P < 0.05 with Bonferroni correction), but was not influenced by ISI. In contrast, unmedicated patients (first and multiepisode patients) showed an impairment in d-context at the long ISI compared with the short ISI. It is as though the neuroleptics, while inducing a general degradation in performance, protected the medicated patients from the degrading effects of noise at the long ISI. Earle-Boyer et al. reported a similar finding. The different patterns of performance shown by the medicated and unmedicated patients exemplifies the difference in effects produced by a "generalized deficit" in the sense of Chapman and Chapman (overall worsening of performance with medication) on the one hand, and a "specific deficit" on the other hand (differential impairment in the long vs short delay conditions due to an impairment in the processing of context).

LIMITATION OF THE STUDY

Based on our models and a large body of indirect evidence, we have previously argued that PFC houses the mechanism responsible for processing context, and that schizophrenic deficits on the CPT are related to a disturbance of dopamine function in PFC. The present study does not directly address this relation. Recent functional imaging studies have shown the role of PFC in a version of the CPT that relies on mechanisms similar to the ones described in this article. However, whether CPT deficits are related to a disturbance of dopamine in PFC remains a question for future research.

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