Deficits in Auditory and Visual Context-Dependent Processing in Schizophrenia

Defining the Pattern

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Background: Brain mechanisms underlying deficits in precision of transient memory storage in schizophrenia were investigated using a combined behavioral and event-related potential approach. Performance was measured simultaneously in 2 tasks: an AX-type visual continuous performance test (AX-CPT), which required subjects to press a button whenever they saw a letter A followed by a letter X, and a mismatch negativity paradigm. The AX-CPT is designed to assess prefrontal function, whereas mismatch negativity assesses functioning of the auditory sensory memory system.

Methods: Subjects were 17 patients with chronic schizophrenia, 13 with recent-onset schizophrenia, and 20 normal comparison subjects. Potentials were recorded from 36 scalp locations in response to cue stimuli in the CPT and to duration- and pitch-deviant stimuli in the mismatch negativity paradigm. Behavioral measures including responses to incorrect cue-target sequences that should have been ignored (“false alarms”) were analyzed as a function of cue-target interval.

Results: Chronic and recent-onset schizophrenic patients showed significantly decreased mismatch negativity amplitude but normal latency and topography. In the CPT, patients showed significantly higher rates of false alarms following incorrect cues (“BX” errors) and decreased rates of correct detections. Impaired performance correlated with decreased frontocentral event-related potential activation to incorrect cues that was manifest within several hundred milliseconds of cue presentation. All groups performed worse with increasing cue-target intervals. Patients were no more affected by increased cue-target interval than were controls.

Conclusions: Schizophrenic patients are significantly impaired in their ability to form and utilize transient memory traces to guide behavior. These deficits are associated with failures of cortical activation occurring within several hundred milliseconds of stimulus presentation. A similar pattern of deficit is observed across sensory and cognitive systems.

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Cognitive dysfunction is a significant and enduring feature of schizophrenia.1-3 Deficits are particularly pronounced in tasks requiring manipulation and transient maintenance of complex information (“working memory”).4-8 However, patients perform extremely poorly even in tests where simple sensory stimuli, such as tones,9-11 weights,12 or visual patterns13 must be matched following brief delay. The present study uses a combined behavioral and event-related potential (ERP) approach to evaluate mechanisms underlying sensory and cognitive processing dysfunction in schizophrenia.

Event-related potential index electrical activity is related to brain information processing operations. Event-related potentials are characterized by latency (measured in milliseconds), polarity (positive or negative), and scalp topography. Early cortical potentials (50- to 150-millisecond latency) typically reflect stimulus-dependent processing within sensory-specific regions. Subsequent potentials reflect task- or sequence-dependent progression of activation through unimodal and/or heteromodal association regions. As opposed to behavioral measures, which can be obtained only to stimuli that require an overt response, ERP can be obtained whether or not stimuli are attended or task relevant at the time of presentation.

See also pages 1139 and 1149

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SUBJECTS AND METHODS

SUBJECTS

Informed consent was obtained from 17 inpatients with chronic schizophrenia, 13 outpatients with first-episode schizophrenia from the Hillside study \(^{16} \) and referred to in this study as recent-onset patients, and 20 normal comparison subjects. Patients were diagnosed according to DSM-III-R criteria using the Structured Clinical Interview for DSM-III-R \(^{16} \) and/or combination interview, chart review, and discussion with clinical staff. Control subjects were recruited by local advertisement and screened in accordance with Structured Clinical Interview for DSM-III-R—Nonpatient version criteria. Mean ± SD ages of the chronic (37.3 ± 7.1 years) and normal comparison (36.3 ± 9.5 years) groups were similar. Chronic schizophrenic patients all had illness duration of more than 10 years and had been continuously hospitalized for a mean ± SD of 1.9 ± 3.3 years prior to testing. Recent-onset schizophrenic patients were within 3 years of initial presentation, were outpatients at the time of testing, and were significantly younger (27.4 ± 2.7 years) than the other groups (F (1, 80) = 6.9, P < .003). The chronic group consisted of 15 men and 2 women, the recent-onset group had 10 men and 3 women, and the control group consisted of 8 men and 7 women. Mean antipsychotic doses were 398 ± 253 and 638 ± 543 chlorpromazine equivalents per day for recent-onset and chronic groups, respectively. One patient from the recent-onset and 2 from the chronic group were not receiving antipsychotic drugs at the time of testing. Eleven patients with chronic schizophrenia were receiving typical antipsychotic drugs and 4 were receiving atypical drugs (clozapine for 1 patient and sertrindole for 3 patients).

PROCEDURE

Testing was performed in a single session, during which subjects ignored a sequence of auditory stimuli while attending to letters presented sequentially on a computer monitor positioned at an approximate distance of 3 ft (90 cm). Auditory and visual presentation rates were controlled by separate stimulation computers using Neuroscan STIM software (Neuroscan, Herndon, Va). Electroencephalographic activity was recorded continuously, along with separate digital response tags for the auditory and visual stimuli, using Neuroscan SCAN software implemented on a IBM-compatible PC.

Auditory Paradigm

Auditory stimuli consisted of a sequence of 100-millisecond, 1000-Hz standards intermixed with 100-millisecond, 1100-Hz pitch deviants, and 250-millisecond, 1000-Hz duration deviants. Stimuli occurred in fixed order (3 standards, 1 pitch deviant, 3 standards, 1 duration deviant) at a rate of 1.3 to 1.5 stimuli per second, presented through foam insert earphones at nominal intensity of 75-dB sound pressure level. Subjects were instructed to ignore auditory stimuli throughout the task.

Visual Paradigm

Visual stimuli consisted of individual letters presented sequentially on a computer screen for 250 milliseconds each. 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 correct or incorrect cue was followed by a correct or incorrect target (designated “Y,” but consisting of all letters other than A or X). Stimuli were presented in 4 blocks of 256 stimuli (1282-letter sequences) each. Within each block, 30% of cue-target sequences were presented with short interstimulus intervals (ISI) (0.85 second) and 50% with long (5 seconds) ISI, to

presented letters, and press a button whenever a correct cue letter (the letter A) is followed by a correct target letter (the letter X). All other sequences are to be ignored. Cues thus provide stimulus context. \(^{14} \) Patients with schizophrenia are deficient in their ability to withhold responses to incorrectly cued targets (ie, targets following a non-A), but show little impairment in their ability to ignore incorrect targets (ie, letters other than X). \(^{14, 15} \) The deficit in withholding response to incorrectly cued targets has been attributed to failure of prefrontal inhibitory circuits. \(^{16, 17} \) The present study investigates ERP to correct and incorrect cue stimuli, to determine the degree to which impaired cue processing contributes to impaired performance.

Because subjects were performing a difficult visual task in this paradigm, it was also possible to evaluate integrity of memory-dependent auditory processing independent of attentional dysfunction. Integrity of auditory sensory processing is indexed by mismatch negativity (MMN), which is elicited by auditory stimuli that differ in some physical dimension (eg, pitch, intensity, duration) from prior repetitive standards. \(^{18, 19} \) Mismatch negativity generation depends on 2 distinct processes. First, the brain must form a representation of the common physical properties of repetitive stimuli and maintain the representation for a period of seconds to tens of seconds. Second, the brain must compare the physical properties of each newly presented stimulus to the sensory memory trace established by the preceding standards. Mismatch negativity represents the outcome of the comparison process. The ability to generate MMN, like the ability to perform accurately on the AX-CPT, depends on the ability to extract precise information from individual sensory stimuli. Deficits in MMN generation in schizophrenia have been reported in many \(^{20, 21} \) but not all \(^{22, 23} \) prior studies. The present study investigates MMN generation to stimuli presented outside the focus of attention to evaluate preattentive information processing within the sensory memory system.

When recorded on the scalp, MMN overlaps other sensory ERP components such as N1 and P2. Mismatch negativity may be distinguished from purely sensory components through intermixed manipulation of pitch and duration. Pitch deviance can be determined at stimulus...
evaluate the role of context retention in overall performance. Short and long ISI trials were pseudorandomly intermixed. Following each stimulus pair, subjects had 1 second to respond, at which time the next cue was presented. For 70% of the stimulus pairs, a correct cue was followed by a correct target (AX sequence); for 10%, an incorrect cue was followed by a correct target (BX sequence); for 10%, a correct cue was followed by an incorrect target (AY sequence); and, for the final 10%, an incorrect cue was followed by an incorrect target (BY sequence). Correct detections of the AX sequence and correct rejections of all other sequences were recorded separately for short and long ISI trials. Preliminary performance data for control subjects and chronic schizophrenic patients have been published previously.

ERP RECORDINGS

Electrical recordings were obtained from 36 scalp locations, consisting of standard 10/20 placements, plus additional electrode places in anterior frontal (AF3/4), frontocentral (FC1/FC2 and FC5/FC6), and centrotemporal (C1/ C2 and CP5/CP6) locations, along with vertical and horizontal electro-oculogram electrodes. Activity was amplified relative to a nose reference with a bandpass (2 dB down) of 0.3 to 30 Hz and digitized continuously at a sampling rate of 200 Hz. Digital tags were obtained to all auditory and visual stimuli. For each stimulus type, ERP epochs were constructed that consisted of a 250-millisecond prestimulus and 750-millisecond poststimulus intervals. Epochs in which ERP amplitude exceeded 100 µV at any electrode site were excluded from further averaging. Following rejection of artifact, epochs were averaged off-line for each subject to each stimulus type.

Analyses focused on MMN generation to pitch- and duration-deviant stimuli plus N1/P2 in the auditory modality, and responses to correct vs incorrect cues in the visual modality. Mismatch negativity waveforms were constructed for each subject by subtracting responses to standards from responses elicited by pitch- or duration-deviant stimuli. Waveforms were mathematically rerereferenced to an average-mastoid reference prior to peak detection. Amplitudes were defined as the peak negative or positive amplitude (as appropriate) within the following latency ranges: pitch MMN, 125 to 200 milliseconds; duration MMN, 225 to 300 milliseconds; N1, 50 to 150 milliseconds; and P2, 150 to 250 milliseconds. Response amplitudes to correct and incorrect cues were defined as the peak positivity within the 250- to 700-millisecond latency range. For MMN analyses only if more than 90 sweeps survived artifact rejection, in correct cue condition analyses only if more than 30 sweeps survived, and in the incorrect cue condition only if more than 10 sweeps survived. Visual waveforms were made up of responses only to correctly evaluated stimulus sequences.

RESULTS

MISMATCH NEGATIVITY

As expected, MMN latency to duration-deviant stimuli was approximately 100 milliseconds longer than to pitch-deviant stimuli (Figure 1A). Latency did not differ across groups (Table). Mismatch negativity amplitude at Fz was significantly reduced in the recent-onset and chronic groups, relative to controls, across both pitch- and duration-deviant conditions (F2,36 = 5.3, P = .009). Follow-up pairwise comparisons demonstrated a significant reduction in MMN amplitude for chronic schizophrenic patients vs controls (F1,25 = 9.0, P = .006), and a nearly significant reduction in recent-onset schizophrenic patients vs controls (F1,25 = 3.7, P = .06).

MMN Topography

Further analyses investigated MMN amplitude at specific electrode pairs (C3/C4, P3/P4, T3/T4) reported to be associated with lateralized dysfunction in schizophrenia. In each case, group-by-hemisphere interactions were nonsignificant (all P > .2). Further, amplitude ratios (left/right) computed using these pairs were not significantly different across groups, indicating absence of left- vs right-sided laterality differences across groups in this sample (Figure 1B).

N1/P2

In contrast to the MMN results, N1 (F2,47 = 1.2, P > .3) and P2 (F2,47 = 0.9, P > .4) amplitudes were not significantly different.
different across groups. Patients and controls did not differ in amplitude or latency of either N1 or P2 (Table).

AX-CPT PERFORMANCE

During collection of MMN data, subjects performed the visual AX-CPT, with intermixed trials at short and long ISI. The rate of correct detections of the AX sequence differed significantly across groups (F2,47=7.1, P=.002) (Figure 2). In pairwise comparisons, both chronic (F1,27=15.4, P<.001) and recent-onset (F1,10=3.8, P=.06) groups were impaired relative to the control group. In contrast, the 2 patient groups were statistically indistinguishable (F1,27=0.2, P=.2). All subjects experienced a deterioration in performance with increasing ISI (F1,17=19.9, P<.001). However, the group-by-ISI interaction (F2,47=0.2, P=.8) was nonsignificant, indicating similar sensitivity to increased ISI across subject groups. Statistical power for rejecting a significant group-by-ISI interaction was more than 85%.

Error rates for incorrect responses (false alarms) to BX sequences were also significantly different across groups (F2,47=4.8, P=.01). In pairwise comparisons, only subjects with chronic illness were significantly distinguishable from controls (F1,37=8.1, P=.007). All groups performed worse at long compared with short ISI (F1,47=18.0, P<.001). However, the group-by-ISI interaction was nonsignificant (F2,47=0.6, P=.5), and power for rejecting a significant between-group difference was more than 85%. Similar statistical results were obtained if a' measures,37 obtained from signal-detection analyses,38 were used in place of BX error rates (main effect of group: F2,47=12.9, P<.001; main effect of ISI: F1,47=21.8, P<.001; group-by-ISI interaction: F2,47=1.3, P=.3). Furthermore, the between-group difference in BX errors at short ISI was significant even when nonparametric statistics were used (Wilcoxon z=3.19, P=.004).

Despite their significantly increased rate of BX errors, patients (recent-onset and chronic) did not show a significant increase in the rate of errors in the AY (F2,47=1.12, P=.3) or BY (F2,47=1.8, P=.2) conditions. When performance measures were entered into a 3-way (stimulus sequence by ISI by group) analysis of variance, a significant group-by-stimulus interaction was observed (F2,47=5.3, P=.008). The interaction remained significant when only AY and BX errors were considered (F2,46=4.8, P=.01), indicating differential sensitivity of schizophrenic patients to the BX vs AY condition. Furthermore, whereas controls showed relatively similar levels of AY and BX errors across ISI (Wilcoxon z=−1.8, P=.07), both recent-onset (Wilcoxon z=2.24, P=.02) and chronic (Wilcoxon z=2.94, P=.003) schizophrenic patients showed significantly greater rates of BX errors than AY errors.

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<th>Event-Related Potential (ERP) Amplitudes in Control Subjects and in Recent-Onset and Chronic Schizophrenia Patient Groups*</th>
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*Values for mismatch negativity (MMN) and N1 amplitude, and amplitudes for the late positivity to correct ("A") and incorrect ("B") cues in the AX-type visual continuous performance test paradigm are given as mean (SD).
ERP TO CORRECT AND INCORRECT CUES

Event-related potentials were obtained separately to the correct (A) and incorrect (B) cues. All groups showed a large amplitude, long-latency (350–500 milliseconds), positive-polarity response to cue stimuli (Figure 3A). The latency of this response was similar across groups (Table). For controls, the long-latency response was significantly larger to the incorrect cues than to the correct cues ($F_{2,16}=4.0$, $P<.04$), whereas no significant difference in amplitude was observed for either chronic ($F_{1,12}=0.02$, $P=.9$) or recent-onset ($F_{2,10}=1.4$, $P=.3$) groups. The difference in degree of augmentation was significant between chronic schizophrenic patients and controls ($F_{1,20}=5.6$, $P=.03$). In contrast, the degree of augmentation for the recent-onset group was intermediate between the other 2 groups and was not significantly different from either the chronic group ($F_{1,28}=3.2$, $P=.09$) or the control group ($F_{1,23}=0.8$, $P=.4$).

In all groups, the differential response to incorrect vs correct cues was frontocentrally located with no evident difference in scalp topography between groups (Figure 3B). Across groups, amplitude of this differential response at Fz correlated significantly with BX error rate ($r=0.98$, $P=.004$) following covariation for between-group effect of ISI. In controls, the long-latency positive response to correct cues was followed by a negative potential peaking at approximately 750 milliseconds. This potential appeared smaller for both patient groups, but could not be analyzed given the constraints of the recording epoch.

Although information processing deficits in schizophrenia are robust, brain mechanisms underlying such dysfunction continue to be the subject of active investigation. One task that has been shown to be sensitive to information processing dysfunction in schizophrenia is the AX-CPT task in which subjects must retain a representation of a cue stimulus while awaiting the presentation of a target. The main findings of the present study are 2-fold. First, this study replicates prior studies indicating that schizophrenic patients are particularly impaired in the use of context, as reflected by a selective deficit in their ability to inhibit responses following presentation of incorrect (“no-go”) cues. Second, it indicates that impaired performance is associated with decreased brain activation directly to the incorrect cue, suggesting that the behavioral deficit is associated with failure of processing precision that is manifest within several hundred milliseconds of cue presentation. The use of ERP measures to analyze brain responses to the cue stimuli is of particular importance since otherwise brain responses to cue stimuli must be inferred indirectly from the behavioral response to the subsequent targets.

A general issue in analysis of information processing dysfunction in schizophrenia is that subjects may show generalized performance deficits due, perhaps, to deficits in motivation or task engagement. An advantage of the AX-CPT paradigm for analyzing mechanisms underlying information processing failure is the presence of intrinsic control conditions. Thus, subjects may respond incorrectly either by pressing after presentation of incorrectly cued targets (BX errors) or after presentation of correctly or incorrectly cued nontargets (AY or BY errors). Control
subjects showed similar rates of BX and AY errors, indicating that, for normal subjects, the context utilization aspects of this paradigm are no more difficult than the target recognition aspects. In contrast, patients showed significantly more BX than AY errors, indicating a selective deficit in the ability to utilize contextual information. The fact that ERP deficits are manifest within several hundred milliseconds of presentation of the incorrect cue indicates that schizophrenic patients are significantly impaired in their ability to extract contextual information (ie, the decision not to respond) from the incorrect cue. The fact that topography was similar across groups indicates that similar brain circuits were engaged. Behaviorally, patients were no more impaired at long, than at short, ISI. Thus, in this study, there is evidence that patients are impaired in their ability to form transient “working memory” representations, but no evidence that impaired performance is due to an inability to maintain such representations once they have been formed.

Patients with recent-onset schizophrenia were less impaired in terms of performance than those with chronic illness, although still significantly impaired compared with controls. Because recent-onset schizophrenic patients were less severely ill than the chronic schizophrenic patients, it cannot be determined from the present study whether the greater deficit observed in the chronic patients reflects greater duration or greater severity of illness. It also cannot be determined whether deficits were present at initial onset of illness, or became manifest within the first several years. Nevertheless, the present study demonstrates deficits in information processing relatively early in the course of schizophrenia.

Performance deficits on the AX-CPT were not limited to false alarms in response to BX sequences. Patients also showed a decrease in overall hit rate. This deficit may reflect impaired ability to recognize correct target stimuli as well as cues. Alternatively, it may reflect decreased ability to extract facilitatory contextual information from the correct cues along with decreased ability to extract inhibitory contextual information for the incorrect cues.

The design of the present study also permits analysis of MMN deficits in schizophrenia when subjects were forced to maintain active visual attention and, thus, to ignore the presented auditory stimuli. Deficits in MMN generation in schizophrenia reflect auditory information processing dysfunction at the level of auditory sensory cortex. Mismatch negativity is considered a pretentive component in that it is generated even when subjects are not paying attention to presented auditory stimuli. However, in the majority of studies on schizophrenia, MMN data have been collected under conditions of “neutral” attention with no formal distraction task, although the task used in that study (simple reaction time) was less cognitively demanding than the one used in the present paradigm. Identification of MMN in the present study was confirmed by the increased latency of duration MMN, relative to pitch MMN, in all groups. Similar reductions were observed for pitch MMN and duration MMN, consistent with the concept of widespread cortical dysfunction in schizophrenia. Alain et al42 also demonstrated pitch-MMN deficits in patients performing a difficult distractor task.

In the present study, duration MMN was distributed more anteriorly than pitch MMN, consistent with prior literature.31 Schizophrenic patients showed a similar topographical shift to controls, indicating normal relative generator geometry despite the overall reduction in amplitude. In one study using a high-density sensor array, decreased MMN amplitudes were reported at left temporal vs right temporal electrode sites.36 In the present study, no such asymmetry was observed even though the recording procedure used was sensitive to the different topography of pitch MMN and duration MMN.

Overall, the present data support the concept that schizophrenic individuals have deficits in extracting relevant information from sensory stimuli across modalities and that such deficits may produce deficits in tasks that require utilization of representations of extracted information. Neurochemical models of cognitive dysfunction in schizophrenia have focused largely on effects of dopaminergic.5,16,42 Alternative models focus on disturbances in glutamatergic functioning,13-16 and, in particular, on disturbances of NMDA receptor-mediated neurotransmission.32-35 The companion article36 investigates the degree to which the NMDA antagonist ketamine induces a pattern of deficit in normal volunteers that resembles the pattern observed in schizophrenia.

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