Modulation of Language Processing in Schizophrenia: Effects of Context and Haloperidol on the Event-Related Potential

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Background: Disturbances in language associations were among the first clinical symptoms reported for individuals described as schizophrenic (Bleuler 1911/1950). Currently, associative language disturbance is a diagnostic feature of schizophrenia (American Psychiatric Association 1994); however, the mechanisms that produce this symptom remain unknown. In the present study, two candidate psychological functions were examined: sensitivity to semantic context and expectancy (attention).

Methods: Visual event-related potentials were recorded during a lexical decision task in which semantic relationship and expectancy (relatedness proportions) were varied. Semantic priming processes were compared between 34 male normal control subjects tested once and 37 male schizophrenic inpatients evaluated during their participation in a double-blind haloperidol maintenance therapy and placebo replacement protocol.

Results: Schizophrenic patients failed to discriminate between associated and unassociated words, as measured by the amplitude of the N400 component (i.e., absence of the N400 priming effect); however, the overall mean amplitude of N400 did not differ between patients and control subjects. In addition, patients and control subjects did not differ significantly in the amplitude of N400 elicited to associated words or to unassociated words. Finally, the effect of expectancy-based processing on the magnitude of the N400 priming effect did not differ between patients and control subjects.

Conclusions: On the basis of these findings, a tentative hypothesis is suggested that schizophrenic patients are characterized by a pattern of indiscriminate or random spread of activation in their semantic network during the processing of single-word semantic contexts. Biol Psychiatry 1999;45:1336–1355 © 1999 Society of Biological Psychiatry

Key Words: Schizophrenia, ERPs, semantic priming, antipsychotic medication

Introduction

Disturbances in language associations were among the first clinical observations reported for individuals described as schizophrenic. Considered by Bleuler to represent both a fundamental and a primary symptom of schizophrenia, the crucial deficiency was believed to involve “a diminution or leveling of the number of affinities” (1911/1950; 350). Kraepelin noted early an apparent connection between associative disturbance and “a failure of attention” in schizophrenia (1989/1919; 20). Currently, associative language disturbances are among the constellation of hallmark symptoms that are diagnostic of schizophrenic disorder (American Psychiatric Association 1987; American Psychiatric Association 1994). The precise mechanisms that produce this symptom remain unknown.

Associative disturbances are most readily observed in the speech of schizophrenic individuals, and an extensive literature now exists that describes the psycholinguistic features and patterns of thought disorder in their language productions (e.g., Andreasen 1979; Cramer 1968; Docherty et al 1996; Holzman et al 1986; Morice and McNicol 1985; Rochester and Martin 1979; Salzinger et al 1964; Solovay et al 1987). A more recent focus has concerned associative disturbances that appear in the receptive language of this patient population. One goal of this recent work has been to increase understanding about the associative or semantic network in schizophrenia. A basic assumption of this line of investigation is the belief that how individuals respond to semantic context reflects fundamental aspects of their semantic network, such as its organization and pathways of access. Parallel to studies of
semantic processing in nonclinical populations, the single-word semantic priming task is commonly used to study the semantic network of schizophrenic individuals (e.g., Barch et al 1996; Henik et al 1995; Kwapił et al 1990; Maher et al 1996; Manschreck et al 1988; Spitzer et al 1994; Vinogradov et al 1992).

 Semantic meaning is constrained by the circumstances or setting that surrounds a linguistic unit (i.e., context) (Givon 1984; Underwood 1983; van Dijk 1977). In particular, semantic context influences word-identification processes (for a review, see Neely 1991). For example, when an initial word (e.g., bread) is followed by a semantically associated second word (e.g., butter), recognition speed and accuracy are increased for that second semantically associated word, as compared with the recognition speed and accuracy of a semantically unassociated second word (e.g., perfume). At the most general level, the first word in the sequence (the prime) is assumed to establish a semantic context for the second word (the target), and this single-word context influences processing in semantic memory. Semantic processing is further constrained by the contents of the semantic network, which are influenced by experiences within the language-speaking community (Anderson 1983; Chomsky 1980; Logan 1988; Underwood 1983). Repeated experiences with a language convey basic information about the frequency or commonality of words and about the semantic relationships that exist among the words in the lexicon of that language. The psychological importance of these linguistic experiences has been established by experiments in which subjects are asked to respond to words that are presented in pairs (semantic priming) and sentences (semantic incongruity). Findings show that electrophysiological signals and behavioral responses vary systematically as a function of semantic association and word frequency. Semantically associated and common words facilitate behavioral response time (Neely 1991); semantically unassociated words produce an enhanced negativity in the event-related potential (ERP) at approximately 400 msec poststimulus (the N400 priming effect) (Bentin et al 1985; Boddy 1986; Holcomb 1988; Kutas and Hillyard 1989; Rugg 1985); and uncommon words elicit a late positive component in the ERP that occurs later and is reduced in amplitude (Polich and Donchin 1988). The cumulative evidence indicates that the amplitude of the N400 component varies as a function of the semantic congruence of words with their surrounding linguistic context, regardless of the syntactic class of the word (Kutas 1997), and that the latency of the late positive peak reflects the amount of time required for stimulus evaluation and categorization, which appears to be independent from response selection and execution processes (Donchin 1981).

 Since the classic experiment on semantic priming by Meyer and Schvaneveldt (1971), investigative efforts have largely been concerned with how the context facilitation effect occurs (Neely 1991). Most accounts of the semantic priming phenomenon include some version of a semantic network in which representations of words in the lexicon are stored as independent units (e.g., Meyer 1970; Rosch et al 1976; Smith et al 1974; although cf. parallel distributed processing (PDP) approaches that are “nodeless,” e.g., McClelland and Rumelhart 1986). Linkages are assumed to interconnect these linguistic representations throughout the semantic network. Also included in most accounts is an automatic or spreading activation mechanism that serves to access the contents of the semantic network (e.g., Collins and Loftus 1975; Neely 1991; Posner and Snyder 1975a; and Posner and Snyder 1975b). A basic principle of the spreading activation hypothesis is that activation of a prime-word representation does not remain localized to the network region immediately surrounding that activated representation. Instead, activation of a prime-word representation is accompanied by automatic spreading of additional activation to representations of words that are semantically associated to that prime word. Dual-mechanism models have also been proposed to explain access processes to the semantic network, which include, in addition to automatic activation, mechanisms that are expectation- or attention-based (e.g., Posner and Snyder 1975a; Posner and Snyder 1975b; cf. the multiple-mechanism model of Neely and Keefe 1989).

 Access to the semantic network likely involves, at minimum, both automatic activation and expectancy-based mechanisms (Neely 1991; Posner et al 1989). Operational criteria for determining whether a process is automatic include activation that occurs without intention (i.e., “strategy independent”), without conscious awareness, and without producing interference with other cognitive activity that might be occurring simultaneously (Posner and Snyder 1975a; Posner and Snyder 1975b; Posner 1986). It is assumed that automatic activation is responsible for facilitating the processing of stimuli that share the same pathway, such as semantically associated words, and that it has no widespread inhibitory effects as a result of that activation (Neely 1991; Posner and Snyder 1975a; Posner and Snyder 1975b). Assumptions vary regarding the capacity of automatic activation, with limitations imposed on activation capacity in some (e.g., Anderson 1983), but not all (e.g., Posner and Snyder 1975a; Posner and Snyder 1975b), theories. In an overview of the historical antecedents of the spreading activation concept, Posner (1986) noted the similarity between current concepts about automatic activation and the concept of the reflex arc, as developed by classical neurophysiologists, such as Sechenov, Sherrington, and Pavlov. In particular, he emphasized the points of concurrence
between the present concept of the pathway and the concept of the reflex, as described by those early investigators—namely, speed, invariance in activation pattern, and separability or functional independence between pathways of different representations within the system.

In contrast with the automatic activation mechanism, the expectancy- or attention-based mechanism influences semantic processing through a conscious and intentional direction of processing activity (Posner and Snyder 1975a). In expectancy-based theories of semantic priming (e.g., Becker 1979; Neely and Keefe 1989; Posner and Snyder 1975a), the expectancy mechanism is assumed to produce a set of lexical candidates in response to a prime word. The word candidates in this set are semantically related to the prime word and are recognized more quickly than words that lie outside the expectancy-generated set. The expectancy mechanism of Posner and Snyder is capacity limited, and the processing of one stimulus is predicted to produce inhibition for the processing of additional stimuli (Posner 1986; Posner and Snyder 1975a; Posner and Snyder 1975b; Posner et al 1989). Moreover, expectancy-based processes are restricted to accessing from one location in semantic memory at a time. Shifting attention from one memory location to another therefore produces a cost in processing effort and time. Because of this restriction, Posner and Snyder predicted that expectancy- or attention-based processes should be important when the linguistic environment contains a high proportion of associated word pairs; automatic activation should be important when the linguistic environment contains a low number of associated word pairs. This prediction has received support from studies in which the relatedness proportions of the experimental word-pair stimuli have been varied. Findings of such studies indicate that the size of the priming effect increases as the proportion of semantically associated word pairs increases (e.g., .67 associated; .33 unassociated) (Neely 1991). In an ERP study of nonschizophrenic individuals, Holcomb (1988) used the relatedness-proportions strategy to assess the relative contributions of automatic activation versus expectancy-based processing on the amplitude of the N400 component elicited to different levels of semantic context. Results indicated that the magnitude of the N400 priming effect was greater under the condition involving a relatively larger proportion of associated word pairs.

The precise mechanisms that cause associative language disturbances in schizophrenic individuals are unknown. In particular, it is not known whether activation of the semantic network in schizophrenic patients is disrupted independently of disruptions that may be due to expectancy- or attention-based processing. Attention disturbances are well documented for schizophrenic disorder (for reviews, see Asarnow et al 1991; Nuechterlein et al 1991; Spring et al 1991). It is therefore reasonable to hypothesize that associative language disturbances in this patient group may be due to, or may be influenced by, deficits in their attention systems (e.g., Barch et al 1996). The present study was designed to examine the influence of expectancy on selected components of the ERP elicited during the processing of different levels of semantic context in schizophrenic patients. Evaluation of the electrophysiological signals that are coincident with the processing of semantic context can provide information about discrete aspects of language processing that may not be evident in overt behavioral responding. Moreover, ERPs have proven to be highly informative about the temporal course of responding to words within both single-word contexts (e.g., Bentin et al 1985; Boddy 1986; Grillon et al 1991; Holcomb 1988; Kutas and Hillyard 1989; Rugg 1985) and sentential contexts (e.g., Friedman et al 1975; Kutas and Hillyard 1980; Kutas and Hillyard 1984; van Petten 1995).

A second unresolved question concerns the viability of the hyperactivation hypothesis as an account of the disturbances in the associative language processes of schizophrenic patients. The hyperactivation hypothesis was proposed to explain the heightened behavioral priming that has been observed in schizophrenic patients in some (e.g., Henick et al 1995; Kwapił et al 1990; Maher et al 1996; Manschreck et al 1988; Spitzer et al 1994), although not all (e.g., Barch et al 1996; Vinogradov et al 1992), studies. According to this explanation, the heightened response facilitation observed in some patients is due to semantic activation that is either greater in magnitude or more resistant to the rapid decay that characterizes the activation of nonschizophrenic individuals. The following evidence would be necessary to support a hyperactivation account of the N400 component that is elicited during lexical decision in schizophrenic individuals: greater negativity in the overall amplitude of N400 in patients, as compared with control subjects, and greater negativity in the amplitude of N400 elicited to both types of semantic context (associated and unassociated) in patients, as compared with control subjects. Thus, the primary aim of the present study was to determine whether schizophrenic patients and control subjects would differ in the amplitude of the N400 and P300 components of the ERP elicited by different levels of semantic association. A second aim was to determine whether the amplitude of patients’ N400 and P300 to different levels of semantic context would vary under different levels of expectancy, which are assumed to induce predominantly automatic activation versus attention-based processing. Expectancy was varied by presenting word pairs in different relatedness proportions (high versus low proportions of associated word pairs). Pharmacologic status was controlled by testing patients during...
Methods and Materials

Subjects

All study participants (patients and control subjects) were evaluated with the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al. 1989). Psychiatric diagnoses were assigned during case conferences. General exclusion criteria were: American English was not the first language learned, history of major medical or neurological disorders, and reading level < eighth grade (Wide Range Achievement Test [WRAT]). Schizophrenic patients were excluded if they met criteria for current substance use disorder. Table 1 presents the characteristics of the sample. Patients and control subjects did not differ significantly with respect to age (t_{69} = 1.18, p > .20) or reading level (WRAT) (t_{68} = 1.43, p > .15), but the two groups did differ in number of years of formal education (t_{69} = 4.04, p < .0001).

Schizophrenic patients were 37 physically healthy (medical examination) male veterans who were diagnosed with schizophrenia (American Psychiatric Association 1987) or schizoaffective disorder, mainly schizophrenic (Research Diagnostic Criteria: Spitzer et al. 1978), and were voluntarily admitted to the Schizophrenia Research Unit at the Pittsburgh Highland Drive VA Medical Center. One patient was diagnosed with schizoaffective disorder, provisional at the time of his entry into the Schizophrenia Research Unit protocol and participation in the present study. This diagnosis was revised to schizophrenia, paranoid type, at the time of his discharge from the inpatient unit. Of these 37 schizophrenic patients, artifact-free ERP data were recorded for 30 patients during haloperidol maintenance therapy, 21 patients during placebo replacement, and 14 patients during both medicated and drug-free phases. Table 2 presents the schizophrenic disorder diagnoses for the patient group (n = 37), as well as the ratings of their clinical symptoms for the week of study participation. (Clinical ratings reflect missing data for 1 medicated patient and 1 drug-free patient.) For this sample of schizophrenic patients, the mean age at the time of first psychiatric hospitalization was 25.3 years (median = 25; SD = ±5.8; range: 16–37), and the mean number of previous psychiatric hospitalizations was 7.5 (median = 6; SD = ±4.9; range: 0–21).

Table 1. Characteristics of Sample

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<tr>
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<th>Schizophrenic patients (n = 37)</th>
<th>Normal control subjects (n = 34)</th>
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<tr>
<td>Age</td>
<td>38.5 (8.7)</td>
<td>36.1 (7.9)</td>
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<td>Education (years)</td>
<td>13.2 (1.8)</td>
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<td>WRAT reading</td>
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WRAT, Wide Range Achievement Test

Medication Status of Patients

Schizophrenic patients were tested during their participation in a separate, double-blind haloperidol maintenance therapy and placebo replacement protocol. Complete details of that protocol are provided in van Kammen et al (1996). Patients and clinical and research staff were blind to medication status. For the 30 schizophrenic patients tested during haloperidol maintenance therapy, the mean dosage of haloperidol was 8.97 mg daily (median = 8; SD = ±3.9; range: 3–20). Seven patients received adjunct anticholinergic medication (benztpine: mean = 2.71 mg daily; median = 2; SD = ±0.95; range: 2–4), which was discontinued 2 weeks before testing. Of the 21 schizophrenic patients evaluated during placebo replacement, 17 patients were tested at an average of 19 days drug free (median = 17; SD = ±6.1; range: 13–38) and 4 patients entered the protocol drug free. The mean test-retest interval for the 14 patients evaluated during both medicated and drug-free phases was 29 days (median = 26; SD = ±11.9; range: 18–69).

Control subjects were 34 physically healthy (self-report) males who were group matched to patients on age. Control subjects were diagnosed as no lifetime psychiatric disorder, which was based on the results of the SCID (Spitzer et al. 1989). Control subjects were paid $80 for study participation.

Following explanation of procedures and prior to testing, all subjects provided written, informed consent to participate.

ERP Testing

STIMULL. An initial pool of associated word pairs was compiled from traditional published sources (e.g., Battig and Montague 1969; Postman and Keppel 1970; Shapiro and Palmero 1968). Constraints on word-pair selection included the following exclusion criteria: orthographic similarity of prime and target (e.g., affluence-influence); within-list duplications due to polysemous words, such as homographs (e.g., rake-leaves/aban...
dons-leaves) and homophones (e.g., carat-diamond/carrot-rabbit); and words <3 or >12 letters in length. Pairs with the greatest associative strength were assigned to the associated condition \( (n = 188 \text{ pairs}) \). The mean proportion of single-response, free-word associates for associated word pairs was \( .47 \) (SD \( = \pm 0.156 \), which is an index of strength of association that ranges from \( 0.00 \) to \( 1.00 \). Pairs with the lowest associative strength were assigned to the unassociated condition \( (n = 188 \text{ pairs}) \) and then reordered randomly, with the restriction that none of the resulting pairs be semantically related. Frequency of occurrence (times per million) of target words was a nested factor (mean for associated targets \( = 192.1 \), SD \( = \pm 269.4 \); mean for unassociated targets \( = 94.6 \), SD \( = \pm 136.2 \) ) (Kucera and Francis 1967). A set of word-nonword pairs was developed for use as distractors. Nonwords were orthographically legal and pronounceable and were derived from actual words by changing 1–3 letters (e.g., gasbel from gospel).

SEMANTIC PRIMING APPARATUS AND PROCEDURE. Subjects were tested in a dimly lit, sound-attenuated room. Stimuli were presented on a low persistence phosphor CRT under control of a microcomputer. Stimuli appeared in lowercase letters and were centered in a fixation box (3 cm \( \times \) 6 cm) that was present throughout the experiment. Subjects were seated 18 inches from the screen with their chins in a fixed position so that stimuli subtended an approximate visual angle of 2° horizontally and 1° vertically. Calibration of the illumination of the stimulus field (candelas per meter squared) was accomplished using a Minolta Luminance Meter: background \( = 0.3 \); fixation box alone \( = 1.1 \); mean for fixation box with words \( = 1.2 \).

A set of practice trials \( (n = 19) \) immediately preceded the test trials \( (n = 301) \). Word pairs were presented in blocks that included trials representing each experimental condition (6 blocks/50 trials per block). A 1-minute rest interval occurred between each block. Each word was presented only once, and each target was preceded by its prime. Subjects were instructed to indicate as quickly and accurately as possible whether the second word in each pair was a legal English word or whether it represented a nonword letter string. Each trial began with the presentation of the prime for 100 msec, followed by an interstimulus interval (ISI) of either 250 msec or 850 msec. During the ISI, only the fixation box appeared on the screen. The target followed the ISI and remained on the screen for 1200 msec, during which the subject made a word/nonword discrimination by pressing either the right or left button, respectively, on a computer mouse. Response time and accuracy were recorded automatically. Trials on which response latencies were \( \leq 100 \) msec or \( >1200 \) msec were excluded. Trials were separated by a 2-sec interval, during which only the fixation box appeared on the screen.

Expectancy set, in which the proportions of word-pair conditions were varied, was a between-subjects factor involving two levels. The high-expectancy (attention) condition consisted of 63% associated pairs, 31% unassociated pairs, and 6% word-nonword pairs. The low-expectancy (automatic activation) condition consisted of 31% associated pairs, 63% unassociated pairs, and 6% word-nonword pairs. Subjects were assigned to the expectancy conditions on a quasirandom basis. Comparisons between patients and normal control subjects are based on the following expectancy group compositions: High Expectancy: 13 medicated schizophrenic patients; 12 drug-free schizophrenic patients; 15 normal control subjects. Low Expectancy: 17 medicated schizophrenic patients; 9 drug-free schizophrenic patients; 19 normal control subjects.

ELECTROENCEPHALOGRAM (EEG) RECORDING AND ANALYSIS. The EEG was recorded from midline electrodes (Fz, Cz, Pz, Oz) and referred to linked ears, with forehead as ground. Channels were amplified \( \times 20 \) K with a Grass Model 12 polygraph (bandpass = 0.01–30 Hz). Impedances were \( \leq 5 \) kOhm. The EEG was digitized with an intersampling rate of 8 msec (125 Hz). EEG sampling began 200 msec prior to the onset of each target stimulus and continued for 1000 msec poststimulus, which provided a sampling epoch of 1200 msec per trial. For data analyses, the ERP epoch was examined only up to 800 msec poststimulus, which included the ERP time windows of theoretical interest. This strategy permitted trials that contained blink artifacts between 800 msec and 1000 msec poststimulus to be retained for data analyses. Electrooculogram (EOG) artifacts were assessed from an electrode placed on the infraorbital canthus below the left eye and referred to linked ears. Trials were screened by computer algorithm and rejected when the EOG exceeded 75 \( \mu \)V. Trials in which the EEG at any channel site exceeded this criterion were also rejected. Averaged response curves were computed from artifact-free single trials.

Baseline-peak amplitudes were obtained at all electrode sites for all conditions, with the median of the 200-msec pretarget sample providing the baseline measure. Interactive computer algorithms were used to select peaks within pre-established time windows, and the first and second authors verified the correctness of the selection to prevent misclassification of early multiple peaks. Verification of peak classification was accomplished blind to group membership. Peak identification time windows were set to be comparable to the latency ranges typically observed in visual priming studies (Bentin et al 1985; Boddy 1986; Grillon et al 1991; Holcomb 1988; Kutas and Hillyard 1989). The peaks of interest were N400, which was identified as the most negative peak at Cz between 300 msec and 500 msec, and the late positive component, designated as P300 in this report, which was identified as the most positive peak at Pz between 500 msec and 800 msec. Two area integration measures were also computed using signed deviations from the baseline: N400-I, which was the mean of the amplitudes at Cz over the 270–550 msec range, and P300-I, which was the mean of the amplitudes at Pz over the 490–800 msec range.

STATISTICAL ANALYSES. All analyses were conducted on the ERPs from trials in which a correct behavioral response occurred within 1200 msec. ERPs from trials in which an incorrect behavioral response occurred were excluded from the analyses. The ERP measures of primary interest were N400 and P300. The experimental design was a mixed factorial that included both between- and within-subjects factors. Results were evaluated using analyses of variance (ANOVAs), with diagnosis (two levels) and expectancy (two levels) as the between-subjects factors.
factors and semantic context (two levels) as the within-subjects factor. Pharmacologic status (two levels) was an additional within-subjects factor for a subgroup of patients. To evaluate the effects of diagnosis on the ERP measures of interest, ANOVAs were conducted to compare the ERPs of normal control subjects and schizophrenic patients during each pharmacologic phase. To assess in a more direct manner the effects of pharmacotherapy on the language processing of patients, ANOVAs were additionally conducted using the data from the patients for whom artifact-free ERPs were available during both medicated and drug-free phases. ERPs of these patients from the two pharmacologic phases were compared. The standard significance level of $\alpha = 0.05$ was used for overall ANOVAs. Theoretically meaningful comparisons followed findings of significant results for overall ANOVAs. These analytical comparisons were evaluated at the more stringent significance level of $\alpha = 0.01$ to reduce the risk of Type I errors that may accompany such comparisons (see Keppel 1991). The Greenhouse-Geisser correction was applied to the analyses of electrode site (four levels). If a response variable was not normally distributed, a normalization procedure (square root or log transformation) was conducted prior to the ANOVA (Fleiss 1986). If the distribution for a response measure remained asymmetrical after applying the normalization procedure, the standard significance level of $\alpha = 0.05$ was shifted to the more stringent level of $\alpha = 0.01$ as a correction for potential distortions to the $F$ test (Keppel 1991). The measure of performance accuracy (number of correct word/nonword discriminations) was converted to the proportion correct and then transformed by the arcsine transformation prior to conducting the ANOVA (Fleiss 1986). Although presentation rate was varied using two ISIs (850 msec and 250 msec), data are examined here only for the 850-msec ISI. At the 250-msec ISI, waveforms elicited by the primes and targets overlap in the critical region for identifying the ERP components of interest (i.e., the N400 to the target likely represents a compound component that includes the P300 to its prime), and separate analytic treatment provides the most conservative approach.

**Results**

Presentation of results is organized to emphasize findings for the psychological functions that were addressed by the experimental design—namely, semantic priming and expectancy (attention). As described above, however, all results are based on ANOVAs for the mixed factorial design involving diagnosis and expectancy as the between-subjects factors and semantic context as the within-subjects factor.

**Comparisons of Schizophrenic Patients and Normal Control Subjects**

**ERPs.** Table 3 presents the mean number of artifact-free ERP trials in which correct behavioral responses occurred for each diagnostic group under each expectancy and semantic context condition. The number of artifact-free ERP trials in which correct behavioral responses occurred did not differ between normal control subjects and schizophrenic patients during either the haloperidol maintenance ($F_{1,60} = 1.72, p > .10$) or the drug-free ($F_{1,51} = 3.23, p > .05$) phase. In addition, the diagnostic group × expectancy × semantic context interactions for number of trials were not significant for either pharmacologic phase (both $p$-values $>.20$). Tables 4 and 5 present the mean amplitudes and latencies of the N400 and P300 components elicited to associated and unassociated target words under each expectancy condition for each diagnostic group. Figures 1 and 2 present the grand mean ERP waveforms for each diagnostic group under each expectancy and semantic context condition.

**Effect of Diagnosis**

**N400.** Patients did not differ from control subjects in their overall mean amplitude of N400 during either the haloperidol maintenance therapy phase (N400 peak: $F_{1,60} < 1, p = \text{n.s.}$; N400-I: $F_{1,60} < 1, p = \text{n.s.}$) or the drug-free phase (N400: $F_{1,51} < 1, p = \text{n.s.}$; N400-I: $F_{1,51} = 1.72, p = \text{n.s.}$). Diagnosis did influence N400 peak latency, but this effect was limited to the analyses based on control subjects and patients tested during haloperidol maintenance therapy. Compared with control subjects, the N400 peak occurred later in medicated patients ($F_{1,60} = 7.75, p = .007$).

**P300.** Diagnosis as a main effect influenced the mean amplitude of the late positive component. During haloperidol maintenance therapy, patients showed a significant reduction in the mean amplitude of P300-I when compared with control subjects ($F_{1,60} = 4.20, p = .05$), although the two groups did not differ in overall mean amplitude of

| Table 3. Number of Artifact-Free ERP Trials for Schizophrenic Patients ($n = 37$) and Normal Control Subjects ($n = 34$) under each Expectancy and Semantic Context Condition. Mean (SD). |
|---------------------------------|---------------------------------|---------------------------------|
|                                | Control Subjects ($n = 15$)     | Schizophrenic Patients ($n = 13$) | Drug-Free Schizophrenic Patients ($n = 12$) |
|                                | (mean)                         | (mean)                          | (mean)                          |
| High expectancy                |                                |                                |                                |
| unassociated                   | 35.9 (9.3)                     | 33.9 (11.1)                     | 31.7 (11.6)                     |
| associated                     | 69.9 (20.3)                    | 68.5 (22.7)                     | 66.3 (24.9)                     |
| Low expectancy                 |                                |                                |                                |
| unassociated                   | 74.0 (13.5)                    | 63.6 (20.5)                     | 59.0 (24.6)                     |
| associated                     | 36.9 (7.3)                     | 32.2 (10.1)                     | 30.3 (11.8)                     |
the P300 peak ($F_{1,60} = 3.06, p = .09$). During the drug-free phase, patients showed significantly reduced mean amplitudes of both the P300 peak ($F_{1,51} = 9.27, p = .004$) and P300-I ($F_{1,51} = 11.30, p = .002$), as compared with control subjects. The two diagnostic groups did not differ in the latency of the P300 peak, as reflected in the analyses based on control subjects and medicated patients ($F_{1,60} < 1, p = n.s.$), and control subjects and drug-free patients ($F_{1,51} < 1, p = n.s.$).

**ERP Priming Effect**

A significant main effect of semantic context was observed in the majority of the analyses. Semantically unassociated words reliably elicited an enhanced negativity in the ERP within the 300–800 msec time window (the ERP priming effect). Figures 3 and 4 present the grand mean ERP waveforms for each expectancy condition, with each semantic context condition (associated and unassociated).
ciated words) superimposed to allow comparisons among the three diagnostic groups.

**N400.** In the analyses based on medicated patients and normal control subjects, a highly significant main effect of semantic context was observed for the N400 peak component ($F_{1,60} = 19.54, p < .0001$), as well as for the averaged area integration measure N400-I ($F_{1,60} = 19.54, p < .0001$). In the analyses based on drug-free patients and normal control subjects, the main effect of semantic context was statistically significant for the N400 peak ($F_{1,51} = 5.98, p = .02$) but was nonsignificant for N400-I ($F_{1,51} = 3.79, p = .06$).

The N400 priming effect was significantly reduced in patients when compared with control subjects. In addition, a weak influence of pharmacotherapy on patients’ N400 priming was observed. In the analyses based on control subjects and patients tested during haloperidol maintenance, the diagnostic group × semantic context interaction was not significant for either the amplitude of the N400 peak ($F_{1,60} = 2.28, p = .14$) or N400-I ($F_{1,60} = 2.34, p = .13$). When examined as an a priori planned comparison, however, the differences in the amplitude of N400 between the two types of word pairs for medicated patients were not statistically significant (i.e., absence of N400 priming effect) ($N400: F_{1,29} = 2.93, p = .10$; N400-I: $F_{1,29} = 3.68, p = .065$). In the analyses based on control subjects and patients tested during the drug-free phase, the diagnostic group × semantic context interactions were highly significant for the amplitude of the N400 peak ($F_{1,51} = 8.14, p = .006$) and N400-I ($F_{1,51} = 11.69, p = .001$). A simple effects analysis of these interactions indicated that differences in the amplitude of N400 between the two types of word pairs for the drug-free patients were not significant (i.e., absence of N400 priming effect) ($N400: F_{1,20} < 1, p = \text{n.s.}$; N400-I: $F_{1,20} < 1, p = \text{n.s.}$). In contrast, differences in

![Figure 2](image_url)  
Figure 2. Grand mean event-related potentials for normal control subjects ($n = 19$), medicated schizophrenic patients ($n = 17$), and drug-free schizophrenic patients ($n = 9$) tested under the low-expectancy condition. Labeling is the same as in Figure 1.

![Figure 4](image_url)  
Figure 4. Data from Figure 2 (low-expectancy condition) are now presented for each semantic context condition (associated and unassociated words), superimposed to allow comparisons among the three diagnostic groups.
the amplitude of N400 between the two types of word pairs for the normal control subjects were highly significant (i.e., absence of N400 priming effect) (N400: $F_{1,33} = 13.88$, $p = .0007$; N400-I: $F_{1,33} = 19.06$, $p = .0001$). In addition, the amplitude of N400 to unassociated words did not differ significantly between drug-free patients and normal control subjects (N400: $F_{1,53} < 1$, $p = n.s.$; N400-I: $F_{1,53} < 1$, $p = n.s.$). And, although the amplitude of N400 to associated words was more negative-going in drug-free patients, as compared with normal control subjects, this difference was not statistically significant (N400: $F_{1,53} = 1.85$, $p > .10$; N400-I: $F_{1,53} = 3.35$, $p = .073$).

**P300.** The priming effect was also observed in the latency range used to identify the late positive component. In the analyses based on medicated patients and normal control subjects, a highly significant main effect of semantic context was observed for the P300 peak ($F_{1,60} = 17.33$, $p = .0001$), as well as for the averaged area integration measure P300-I ($F_{1,60} = 25.96$, $p < .0001$). In the analyses based on drug-free patients and normal control subjects, the main effect of semantic context was statistically significant for the P300-I ($F_{1,51} = 9.98$, $p = .003$) but was nonsignificant for the P300 peak ($F_{1,51} = 2.11$, $p = .15$). Semantic context also influenced P300 latency in the analyses based on drug-free patients and normal control subjects ($F_{1,51} = 4.25$, $p = .04$), with the P300 peak occurring later for unassociated words than for associated words.

Significantly reduced priming was also observed in the amplitude of schizophrenic patients’ late positive component. Patients showed significant reductions in their P300 discrimination of semantic context during both pharmacologic phases. In the analyses based on medicated patients and control subjects, significant diagnosis $\times$ context interactions were observed for the amplitude of both the P300 peak ($F_{1,60} = 5.79$, $p = .02$) and P300-I ($F_{1,60} = 5.28$, $p = .025$). The sources of these interactions included the absence of significant priming in medicated patients (P300: $F_{1,29} = 2.02$, $p = n.s.$; P300-I: $F_{1,29} = 4.18$, $p = n.s.$) and the presence of highly significant priming in control subjects (P300: $F_{1,33} = 24.58$, $p < .0001$; P300-I: $F_{1,33} = 30.33$, $p < .0001$). Analyses were also conducted to determine the simple effects of diagnosis on the amplitude of P300 to the two types of linguistic context. Medicated patients showed significantly reduced P300-I amplitude to associated words, as compared with control subjects ($F_{1,62} = 7.60$, $p < .01$). In contrast, medicated patients and control subjects did not differ in the amplitude of P300-I to unassociated words ($F_{1,62} = 1.42$, $p = n.s.$). A similar pattern was observed for the P300 peak component, although the group difference in peak amplitude to associated words did not reach statistical significance. Figure 5 shows the diagnosis $\times$ semantic context interaction for P300-I that was observed in the analyses based on control subjects and patients tested during the haloperidol maintenance therapy phase.

In the analyses based on drug-free patients and control subjects, significant diagnosis $\times$ context interactions were again observed for both the P300 peak ($F_{1,51} = 23.57$, $p < .0001$) and P300-I ($F_{1,51} = 15.36$, $p = .0003$). The sources of these significant interaction effects included the absence of priming in drug-free patients (P300: $F_{1,20} = 2.84$, $p = n.s.$; P300-I: $F_{1,20} < 1$, $p = n.s.$) and the presence of the highly significant priming in control subjects that is reported above (both $p$-values $< .0001$). Analyses were additionally conducted to evaluate the simple effects of diagnosis for the amplitude of P300 to the two types of linguistic context. Drug-free patients were characterized by a highly significant reduction in P300 amplitude to associated words, as compared with control subjects (P300: $F_{1,53} = 16.99$, $p = .0001$; P300-I: $F_{1,53} = 17.21$, $p = .0001$). In contrast, drug-free patients and control subjects did not differ in the amplitude of P300 to unassociated words (P300: $F_{1,53} = 2.62$, $p = n.s.$; P300-I: $F_{1,53} = 5.29$, $p = n.s.$). It is important to note that these significant two-way interactions observed for P300 in the analyses based on drug-free patients and control subjects must also be viewed within the context of the significant second-order expectancy $\times$ diagnosis $\times$ semantic context interactions that were observed in the same analyses. These three-way interactions are described below.

**Effect of Expectancy**

**N400.** Expectancy influenced the N400 priming effect. Individuals who received the high-expectancy (atten-
tion) condition exhibited greater N400 discrimination between semantic contexts, as compared with individuals who received the low-expectancy (automatic activation) condition. Specifically, significant expectancy × context interactions were observed for the N400 peak in the analyses based on medicated patients and control subjects ($F_{1,60} = 9.68, p = .003$), as well as in the analyses based on drug-free patients and control subjects ($F_{1,51} = 19.69, p < .0001$). This pattern was observed in the N400-I measure only in the analyses based on drug-free patients and control subjects ($F_{1,51} = 11.61, p = .001$). The effect of expectancy on the magnitude of the N400 priming effect did not differ between the two diagnostic groups during either pharmacologic phase (i.e., all $p$-values > .20 for the expectancy × diagnosis × context interactions).

**P300.** In contrast to the findings for the N400 component, there was some evidence that individuals who received the low-expectancy (automatic activation) condition showed greater P300 discrimination between semantic contexts, as compared with the individuals who received the high-expectancy (attention) condition. This effect, however, was observed only for the P300 peak in the analyses based on medicated patients and control subjects ($F_{1,60} = 5.59, p = .02$).

The effect of expectancy on the P300 discrimination of semantic context (priming effect) was different in the two diagnostic groups. Moreover, this effect appeared to be influenced by pharmacotherapy in patients. In the analyses based on medicated patients and control subjects, the expectancy × diagnosis × semantic context interactions were not statistically significant (P300: $F_{1,60} = 1.05; p = \text{n.s.}$; P300-I: $F_{1,60} < 1, p = \text{n.s.}$). In the analyses based on drug-free patients and control subjects, however, significant expectancy × diagnosis × semantic context interactions were observed for both the P300 peak ($F_{1,51} = 7.95, p = .007$) and P300-I ($F_{1,51} = 7.46, p = .009$) measures. Thus, the combination of diagnosis and semantic context (i.e., the two-way diagnosis × context interactions) produced a different pattern of results under each of the two levels of the expectancy factor.

For a more detailed understanding of the expectancy × diagnosis × context interactions that were observed in the analyses based on drug-free patients and control subjects, a set of simple effects was tested for each of the two expectancy conditions. First, under the high-expectancy (attention) condition, the diagnosis × context interaction was not statistically significant for either the P300 peak ($F_{1,25} = 2.13, p = \text{n.s.}$) or P300-I ($F_{1,25} < 1, p = \text{n.s.}$). Under the low-expectancy (automatic activation) condition, however, the diagnosis × semantic context interaction was highly significant for both the P300 peak ($F_{1,26} = 28.66, p < .0001$) and P300-I ($F_{1,26} = 35.36, p < .0001$). The sources of these two-way interactions were the typical priming effect (enhanced negativity to unassociated words) in control subjects (P300: $F_{1,18} = 19.61, p < .001$; P300-I: $F_{1,18} = 24.53, p < .0001$) and an atypical or reversed priming effect (enhanced negativity to associated words) in the drug-free patients (P300: $F_{1,8} = 14.44, p < .01$; P300-I: $F_{1,8} = 20.51, p < .01$). Analyses were also conducted to determine the simple effects of diagnosis on the amplitude of P300 to the two types of semantic context. As compared with control subjects, drug-free patients were characterized by a significant reduction in P300 amplitude to associated words (P300: $F_{1,26} = 16.19, p < .001$; P300-I: $F_{1,26} = 13.63, p = .001$). In contrast, drug-free patients and control subjects did not differ in the amplitude of P300 to unassociated words (P300: $F_{1,26} < 1, p = \text{n.s.}$; P300-I: $F_{1,26} = 1.11, p = \text{n.s.}$). Thus, the source of these three-way interactions was an atypical or reversed priming effect (enhanced negativity to associated words) in the drug-free patients who received the low-expectancy (automatic activation) condition. Figure 6 shows this expectancy × diagnosis × context interaction for P300-I that was observed in the analyses based on control subjects and drug-free patients.

Expectancy influenced the latency of the P300 peak component. The diagnosis × expectancy interaction was significant in the analyses based on medicated patients and control subjects ($F_{1,60} = 6.66, p = .012$), as well as in the analyses based on drug-free patients and control

![Figure 6. Mean (+SEM) integrated amplitude of P300 at Pz to associated and unassociated target words as a function of expectancy condition and diagnosis. Drug-free schizophrenic patients ($n = 21$) and normal control subjects ($n = 34$).](image-url)
subjects ($F_{1.51} = 8.68, p = .005$). Although a simple effects analysis of this interaction indicated that the differences between the two diagnostic groups were non-significant, the general pattern involved an earlier P300 peak in the control subjects who received the high-expectancy (attention) condition, as compared with the control subjects who received the low-expectancy (automatic activation) condition. This pattern was reversed in patients. Finally, a significant expectancy $\times$ semantic context interaction was observed in the analyses based on medicated patients and control subjects ($F_{1.60} = 4.16, p = .05$). Again, analyses of the simple effects showed nonsignificant results, although the general pattern involved a later P300 peak to unassociated words under the high-expectancy (attention) condition, as compared with the P300 latency to associated words.

### Difference Waveforms

Difference waveforms were created by a point-by-point subtraction of the ERPs to semantically associated words from the ERPs to semantically unassociated words. These difference waveforms are presented in Figures 7 and 8. In Figure 7, for each expectancy condition, the ERP difference waveforms for each diagnostic group are superimposed. In Figure 8, for each diagnostic group, the ERP difference waveforms for each expectancy group are superimposed. Analyses were conducted on the resulting difference waveform measures for N400 (peak amplitude and latency). Results were generally in line with findings from the conventional analyses presented above. In the analyses based on medicated patients and control subjects, amplitude of the N400 difference peak was not significantly influenced by diagnostic group ($F_{1.60} = 1.82, p = \text{n.s.}$) or expectancy ($F_{1.60} = 1.40, p = \text{n.s.}$). The diagnostic group $\times$ expectancy interaction was also non-significant ($F_{1.60} < 1, p = \text{n.s.}$). In the analyses based on drug-free patients and control subjects, however, the N400 difference peak was more negative-going in control subjects when compared with patients (mean $\mu V$: $-2.95; 0.80$, respectively: $F_{1.51} = 12.98, p < .001$). The N400 difference peak was also more negative-going under the high-expectancy condition when compared with the low-expectancy condition (mean $\mu V$: $-2.84; 0.69$, respectively: $F_{1.51} = 11.48, p < .002$). The diagnosis $\times$ expectancy interaction was not significant ($F_{1.51} = 3.89, p > .05$). Finally, latency of the N400 difference peak was not significantly influenced (all $p$-values $>.20$) by diagnostic group membership (means: medicated patients: 426.9 msec; drug-free patients: 426.4 msec; control subjects: 410.5 msec), expectancy set, or the interaction of diagnosis and expectancy set.

### Scalp Distribution of the N400 Effect

The scalp distribution of the N400 effect was examined in normal control subjects and schizophrenic patients during each pharmacologic phase. Analyses were conducted following normalization of amplitudes (McCarthy and Wood 1985). The Greenhouse-Geisser correction was applied when appropriate. The N400 peak

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**Figure 7.** Difference waveforms (unassociated–associated) are presented for each expectancy condition, superimposed as before to allow comparisons among the diagnostic groups. Note that the amplitude for the N400 difference shows the typical maximum effect at Pz.

**Figure 8.** Difference waveforms (same data as Figure 7) are presented for each diagnostic group, superimposed by expectancy condition.
amplitude and the N400 priming effect (enhanced negativity to unassociated words) were maximal at different electrode sites in the two diagnostic groups; however, this pattern was statistically significant only in the analyses based on normal control subjects and medicated patients. Specifically, in the analyses based on normal control subjects and patients tested during haloperidol maintenance, the diagnosis × semantic context × electrode site interaction was significant for the amplitude of the N400 peak ($F_{3,180} = 6.88, p = .001$). This effect was also seen in the amplitude of the N400 peak identified from the difference waveform, with a significant diagnostic group × electrode site interaction ($F_{3,180} = 5.14, p = .006$) observed in the analyses based on medicated patients and normal control subjects. Comparisons were conducted to identify the sources of the three-way interaction for the N400 peak identified from the conventional waveforms. In medicated patients, a significant main effect of electrode site interaction was observed for N400 peak amplitude ($F_{3,84} = 6.43, p = .004$), with the maximum negativity occurring at the frontal electrode site (mean $\mu$V: Fz: 0.08; Cz: 0.25; Pz: 1.88; Oz: 0.40). Pairwise comparisons showed that patients’ N400 amplitude differed between frontal and parietal electrode sites ($p < .001$) and between vertex and parietal electrode sites ($p < .0001$), but did not differ between frontal and vertex electrode sites or between frontal and occipital electrode sites. Although the differences in the amplitude of N400 to the different types of words (associated and unassociated) appeared maximal at the frontal electrode site in medicated patients, the semantic context × electrode site interaction failed to reach statistical significance ($F_{3,84} = 3.35, p > .01$). In normal control subjects, although the amplitude of the N400 peak appeared most negative at the vertex electrode site (mean $\mu$V: Fz: 1.23; Cz: −0.45; Pz: 0.95; Oz: 0.34), the main effect of electrode site was not statistically significant ($F_{3,96} = 3.95, p > .01$). The semantic context × electrode site interaction, however, did reach significance in controls ($F_{3,96} = 5.32, p = .01$), with the N400 priming effect (enhanced negativity to unassociated words) appearing maximal at the parietal electrode site (mean $\mu$V unassociated–mean $\mu$V associated words: Fz: −0.82; Cz: −1.67; Pz: −2.31; Oz: −1.85).

Behavioral Performance Data

Accuracy. In general, subjects showed a high rate of accuracy in responding in the lexical decision task. During haloperidol maintenance therapy, however, schizophrenic patients were significantly less accurate in their word/non-word discrimination when compared with control subjects (overall accuracy: 79.9% and 88.9%, respectively) ($F_{1,60} = 7.63, p = .008$). In contrast, the response accuracy of patients tested during the drug-free phase (82%) did not differ significantly from that of control subjects ($F_{1,51} = 2.97, p = .09$). Response accuracy was influenced by semantic context, with greater accuracy occurring for associated words. This effect was observed in the analyses based on medicated patients and control subjects (associated words: 85.7%; unassociated words: 82.9%) ($F_{1,60} = 11.00, p = .002$), as well as in the analyses based on drug-free patients and control subjects (associated words: 87%; unassociated words: 83.9%) ($F_{1,51} = 14.44, p = .0004$). Finally, in both of the overall analyses, accuracy rate did not differ under any of the different combinations of diagnosis and semantic context, or diagnosis and expectancy and semantic context (i.e., no significant diagnosis × context, or diagnosis × expectancy × context interactions).

REACTION TIMES. Table 6 presents the response times recorded during the lexical decision task for each diagnostic group under each expectancy and semantic context condition. Similar patterns of effects were observed in both of the overall ANOVAs. In the analyses based on medicated patients and control subjects, a significant main effect of diagnostic group was observed ($F_{1,60} = 14.37, p = .0004$), with slower overall response times occurring in patients. A highly significant main effect of semantic context was also observed ($F_{1,51} = 14.44, p = .0004$), with faster response times occurring to associated words than unassociated words (i.e., the behavioral semantic priming effect). In addition, the diagnostic group × semantic context interaction was significant ($F_{1,50} = 5.03, p = .03$). The source of this interaction was a behavioral priming effect that was smaller in magnitude in medicated patients, as compared with the behavioral priming effect observed in control

| Table 6. Response Times (msec) in the Lexical Decision Task for Schizophrenic Patients ($n = 37$) and Normal Control Subjects ($n = 34$) under each Expectancy and Semantic Context Condition. Mean (SD). |
|----------------------------------|-----------------|-----------------|-----------------|
|                                 | Normal control subjects ($n = 15$) | Medicated schizophrenic patients ($n = 13$) | Drug-free schizophrenic patients ($n = 12$) |
| High expectancy                 |                 |                 |                 |
| unassociated                    | 664.2 (86.6)    | 747.3 (98.3)    | 722.8 (132.9)   |
| associated                      | 601.3 (77.1)    | 706.1 (98.9)    | 689.7 (123.8)   |
| Low expectancy                  |                 |                 |                 |
| unassociated                    | 651.3 (115.9)   | 746.1 (121.3)   | 669.3 (107.7)   |
| associated                      | 606.6 (99.0)    | 719.2 (122.2)   | 662.9 (110.7)   |
subjects. Despite its reduced magnitude, however, the behavioral priming effect in medicated patients was statistically significant. Specifically, analyses of the simple effects of semantic context for each diagnostic group showed that the priming effect was statistically significant in both medicated patients ($F_{1,29} = 38.62, p < .0001$) and control subjects ($F_{1,33} = 59.72, p < .0001$). In the analyses based on drug-free patients and control subjects, the main effect of semantic context was also highly significant ($F_{1,51} = 49.89, p < .0001$), with faster response times occurring to associated words. Although drug-free patients exhibited slower overall response times, as compared with control subjects, the main effect of diagnosis was not significant ($F_{1,51} = 3.54, p = .066$). The diagnosis $\times$ context interaction was significant ($F_{1,51} = 10.72, p = .002$), and the source of this interaction was a smaller behavioral priming effect in drug-free patients, as compared with the size of the priming effect observed in control subjects. Analyses of the simple effects of semantic context for each diagnostic group showed that the priming effect was significant in drug-free patients ($F_{1,26} = 7.97, p = .011$) and, as reported above, significant in control subjects ($p < .0001$).

Finally, the expectancy $\times$ semantic context interaction was significant in the analyses based on drug-free patients and control subjects ($F_{1,51} = 4.67, p = .04$). This interaction was due to a larger behavioral priming effect in the individuals who received the high-expectancy (attention) condition (mean unassociated response time–mean associated response time: 48 msec) ($F_{1,26} = 45.13, p < .0001$), as compared with the magnitude of the priming effect observed in the individuals who received the low-expectancy (automatic activation) condition (mean unassociated response time–mean associated response time: 25.5 msec) ($F_{1,27} = 16.86, p = .0003$). The longest response time occurred to unassociated words under the high-expectancy (attention) condition.

Comparisons of Schizophrenic Patients Across Medicated and Drug-Free Phases

To provide a more direct test of the effects of pharmacotherapy on the ERP measures of interest in schizophrenic patients, additional analyses were conducted using the data from a subgroup of patients ($n = 14$) for whom artifact-free ERP recordings (correct response trials) were obtained during both medicated and drug-free phases. The ERPs of these patients were compared using ANOVAs, with expectancy (high or low) as the between-subjects factor and pharmacologic phase (haloperidol maintenance or placebo replacement) and semantic context (associated or unassociated) as the within-subjects factors. These comparisons are based on the following expectancy group compositions: high expectancy–7 patients; low expectancy–7 patients.

Effect of Pharmacotherapy

Haloperidol maintenance therapy, as a main effect, did not significantly influence the overall mean amplitude of patients’ N400 (N400 peak: $F_{1,12} = 3.90, p = .07$; N400-I: $F_{1,12} = 4.39, p = .06$) or P300 (P300 peak: $F_{1,12} = 2.71, p = .13$; P300-I: $F_{1,12} = 2.59, p = .13$). The latencies of these ERP measures were also not affected significantly by treatment with antipsychotic medication (N400: $F_{1,12} < 1, p = n.s.$; P300: $F_{1,12} < 1, p = n.s.$).

ERP Priming Effect

Schizophrenic patients did not discriminate between semantically associated and unassociated contexts. The main effects of semantic context were not statistically significant for either N400 (N400 peak: $F_{1,12} < 1, p = n.s.$; N400-I: $F_{1,12} < 1, p = n.s.$) or P300 (P300 peak: $F_{1,12} < 1, p = n.s.$). In addition, patients’ responses to semantic context did not differ between the two pharmacologic phases. Specifically, none of the pharmacologic phase $\times$ semantic context interactions was statistically significant (N400 peak: $F_{1,12} = 1.19, p = n.s.$; N400-I: $F_{1,12} = 1.13, p = n.s.$; P300 peak: $F_{1,12} = 1.87, p = n.s.$; P300-I $F_{1,12} < 1, p = n.s.$).

Effect of Expectancy

Expectancy influenced the amplitude of patients’ N400 and P300 components elicited to semantic context. Significant expectancy $\times$ semantic context interactions were observed for the N400 peak ($F_{1,12} = 9.65, p = .009$) and P300-I ($F_{1,12} = 9.55, p = .009$). Analyses of the simple effects to determine the source of the interaction for the N400 peak showed nonsignificant results. The general pattern, however, indicated greater N400 discrimination between semantic contexts in the patients who were tested under the high-expectancy (attention) condition, as compared with the patients who were tested under the low-expectancy (automatic activation) condition. In addition, the amplitude of N400 was more positive-going to associated words in the patients who received the high-expectancy (attention) condition, as compared with the patients who received the low-expectancy (automatic activation) condition. In contrast, N400 amplitude to unassociated words was similar under both expectancy conditions. Analyses of the simple effects to determine the source of the interaction effect for the amplitude of P300-I also showed nonsignificant results. The general pattern...
included markedly reduced discrimination of semantic context in the patients tested under the low-expectancy (automatic activation) condition. In contrast, patients tested under the high-expectancy (attention) condition showed relatively greater P300-I discrimination between semantic contexts. Finally, the expectancy × pharmacologic phase × semantic context interactions were not statistically significant (P300 peak: \( F_{1,12} = 6.98, p > .01; \) P300-I: \( F_{1,12} = 4.38, p = .058 \)).

**Discussion**

The present study was designed to examine the influence of expectancy on selected components of the ERP elicited during the processing of semantic context in schizophrenic patients. The principal question concerned whether activation of the semantic network in schizophrenic patients is disrupted independently of disruptions that may be due to expectancy- or attention-based processing. The primary aim was to determine whether schizophrenic patients and normal control subjects would differ in the amplitude of N400 and P300 elicited by different levels of semantic association. A second aim was to determine whether the amplitude of patients’ N400 and P300 to different levels of semantic context would vary under different levels of expectancy, which are assumed to induce predominantly automatic activation versus attention-based processing. Expectancy was varied by presenting word pairs in different relatedness proportions; a high proportion of associated word pairs was presented in the high-expectancy (attention) condition, and a low proportion of associated word pairs was presented in the low-expectancy (automatic activation) condition. Pharmacologic status was controlled by testing patients during their participation in a separate, double-blind haloperidol maintenance therapy and placebo replacement protocol.

Variations in the amplitude of N400 and P300 were observed as a function of semantic association, expectancy condition, psychiatric diagnosis, and pharmacologic status in the patient group. Semantically unassociated target words reliably elicited an enhanced negativity in the ERP within the 300–800 msec time window (the ERP priming effect). Regarding the primary aim of the study, results showed that semantic activation differed significantly between schizophrenic patients and control subjects. Control subjects consistently exhibited highly significant discrimination between levels of semantic context, which was reflected in the amplitude of both N400 and P300 components. Schizophrenic patients showed abnormalities in their semantic activation during both pharmacologic phases. During haloperidol maintenance therapy, the N400 priming effect in patients did not differ significantly from the N400 priming effect in control subjects. It is notewor-

th, however, that the differences in the amplitude of N400 between associated and unassociated words for medicated patients failed to reach statistical significance (i.e., absence of the N400 priming effect). During the drug-free phase, the N400 priming effect in patients was significantly reduced when compared with the N400 priming effect in control subjects, with patients again failing to exhibit the N400 priming effect. Patients also differed from control subjects in the amplitude of their P300 to different levels of semantic context. This effect occurred during both pharmacologic phases, and the source of this difference was a significantly reduced P300 amplitude to associated words in patients, as compared with control subjects. In contrast, patients and control subjects did not differ with respect to the amplitude of P300 to unassociated words. The absence of a significant priming effect in patients was also observed in results from the analyses based on the subgroup of patients who were successfully tested during both pharmacologic phases. Regarding the second aim of this study, results also showed that expectancy significantly influenced the semantic priming effect. Individuals who received the high-expectancy (attention) condition exhibited greater N400 discrimination between the levels of semantic context (larger N400 priming effect), as compared with the individuals who received the low-expectancy (automatic activation) condition. This relatedness proportion effect did not differ in the two diagnostic groups, regardless of patients’ pharmacologic status. In contrast, the effect of expectancy on the P300 discrimination between levels of semantic context did differ in the two diagnostic groups, and this effect appeared to be influenced by pharmacotherapy in patients. Specifically, an atypical or reversed priming effect (an enhanced negativity to associated words relative to unassociated words) was observed in the P300 amplitude of the drug-free patients who received the low-expectancy (automatic activation) condition. Finally, a difference in the scalp distribution of the N400 peak and the N400 priming effect was observed in medicated patients and control subjects. In patients, the N400 peak was most negative-going at the frontal electrode. In control subjects, the N400 priming effect was maximal at the parietal electrode.

Selected aspects of the findings from the present study are in general agreement with results from recent work. Using a semantic categorization task, Grillon et al (1991) found a reduction in the N400 peak based on the difference waveform, as well as a later N400 peak in medicated schizophrenic patients when compared with normal control subjects. In contrast to the present findings, Nestor et al (1997) and Niznikiewicz et al (1997) reported an increased negativity in N400 elicited to both congruent and incongruent terminal sentence words in medicated
schizophrenic patients when compared with control subjects. It is important to note, however, that sentence processing likely relies on additional cognitive mechanisms, such as working memory processes (Condray et al 1996; Just and Carpenter 1972; van Petten 1995), which makes a direct comparison between the N400 components elicited during semantic priming and sentence processing problematic. Finally, the limited effect of haloperidol maintenance therapy that was observed in the present study appears generally consistent with findings from prior work (Duncan et al 1987; Ford et al 1994). Using visual oddball tasks, Ford et al (1994) found that P300 amplitude remained stable in schizophrenic patients across medicated and drug-free phases, and Duncan et al (1987) observed that P300 amplitude increased only in medicated patients who showed clinical improvement. It should be emphasized that significant differences likely exist in the type of cognitive processes examined in the present study and in those latter two studies—namely, the presence versus absence of relatively complex semantic characteristics in the eliciting stimuli. The differences in stimulus characteristics may therefore account for the different findings with respect to diagnostic group membership. Specifically, the amplitude of the visual P300 to the oddball stimuli (plus and minus signs) did not differ between patients and control subjects in the Ford et al (1994) study. In contrast, patients and control subjects in the present study did differ in their P300 elicited to the experimental language conditions.

**HYPERACTIVATION HYPOTHESIS VERSUS RANDOM ACTIVATION HYPOTHESIS.** On the basis of findings from the present study, a tentative hypothesis is proposed that schizophrenic patients are characterized by a pattern of random or indiscriminate spread of activation in their semantic network during lexical decisions about single-word contexts. The present ERP findings do not suggest support for hyper- or overactivation of the semantic network in schizophrenic patients during lexical decision. Several investigators have proposed the hyperactivation hypothesis to explain the heightened behavioral priming observed in schizophrenic patients in some studies (e.g., Henik et al 1995; Kwapil et al 1990; Maher et al 1996; Manschreck et al 1988; Spitzer et al 1994). According to the hyperactivation account, the heightened or greater response facilitation that some subgroups of schizophrenic patients exhibit is likely due to semantic activation that is either larger in magnitude or more resistant to the rapid decay that characterizes the activation of nonschizophrenic individuals. The following evidence would be required, at minimum, to suggest a hyperactivation account of N400 elicited during the lexical decision task in the present study: (a) greater overall negativity in the amplitude of N400 in patients, as compared with control subjects, and (b) greater negativity in the amplitude of N400 elicited to both types of semantic contexts in patients, as compared with control subjects. Based on these minimum criteria, several of the present findings produce a serious challenge to the hyperactivation hypothesis as a viable account of schizophrenic patients’ semantic activation during lexical decision. First, patients and control subjects did not differ in the negativity of their overall N400 amplitude. Second, patients showed an equivalent negativity in the amplitude of N400 elicited to associated and unassociated words (i.e., absence of N400 priming effect). Moreover, patients and control subjects did not differ in the amplitude of N400 to unassociated words. Finally, although patients’ N400 to associated words showed a tendency toward greater negativity, as compared with that of control subjects, this difference did not reach statistical significance. Some version of the hyperactivation hypothesis may ultimately prove correct for some aspects of semantic processing in schizophrenia (e.g., attention-based or postlexical processing; see discussions in Barch et al 1996; Vinogradov et al 1992); however, there are serious obstacles to its viability as an explanation of the semantic activation that is reflected in the amplitude of patients’ N400 elicited during lexical decision.

Any theoretical account of semantic activation in schizophrenia must accommodate what is known about activation of the pathways in the semantic network in nonschizophrenic individuals. A primary characteristic of activation during semantic priming is its sensitivity to both word frequency and word relatedness information. One of the most striking and important points about the present data is that the amplitude of patients’ N400 did not reflect such sensitivity to word frequency and word relatedness information. To re-emphasize: The amplitude of patients’ N400 to associated and unassociated words did not differ significantly; patients’ N400 amplitude to unassociated words did not differ from that of control subjects; and although patients’ N400 amplitude to associated words was more negative-going, as compared with that of control subjects, this difference was not significant. Thus, the most parsimonious explanation is that patients engaged in a more extensive activation of the semantic network in response to associated words, as compared with control subjects. In contrast, patients did not exhibit an equivalent extension in their semantic activation in response to unassociated words. On the basis of the present ERP evidence, a tentative hypothesis is proposed that schizophrenic patients are characterized by a pattern of random or indiscriminate spread of activation in their semantic network in response to linguistic context.

What the present ERP data do not provide is a clear
understanding of whether the pattern of semantic activation observed in schizophrenic patients was due to a) abnormalities in their representations of words stored within the semantic network (i.e., a “node” problem) (cf. PDP approaches, e.g., McClelland and Rumelhart 1986); b) abnormalities in their pathways that enable access to the representations of words stored within the semantic network (i.e., a “linkage” problem); or c) some combination of both problems. The following comments regarding these general possibilities are obviously speculative but are raised for consideration. First, it may be necessary for patients to activate more extensively in response to associated words because a shift has occurred in their frequency-based activation threshold for recognition of associated words. Schizophrenic individuals may have never developed, or may have somehow lost, their frequency counting mechanism (e.g., alteration in a mechanism like the logogen proposed by Morton 1969). As a result, patients’ recognition threshold may be set so that a higher level of activation is required for recognition of associated words. In effect, this may make the activation thresholds for associated and unassociated words equivalent in schizophrenic individuals. Hence, more extensive activation is necessary for schizophrenic patients to achieve a recognition hit for associated words. Whether such potential compromises to frequency-based recognition thresholds in schizophrenia would more likely involve a “node” problem or a “linkage” problem is uncertain. In the present study design, word frequency was a nested factor, so that associated words had a higher word frequency than did unassociated words. A study that disentangled the effects of word frequency versus word relatedness on the amplitude of N400 in schizophrenic patients would likely provide increased clarity on this issue (e.g., Becker 1979). Of additional relevance to this issue are the results obtained for the behavioral response times of schizophrenic patients in the present study, which showed that sensitivity to word frequency and relatedness was clearly preserved in patients’ behavioral responding. This latter finding is consistent with the findings from prior studies of behavioral priming in schizophrenic patients (e.g., Chapin et al 1992; Henik et al 1995; Manschreck et al 1988; Spitzer et al 1994). Thus, the present ERP data indicate that the difficulties that occurred during patients’ semantic activation may be quite different from the difficulties that occurred during their response execution, as indicated by the reaction time data. As a second possibility, patients’ activation of the semantic network may be nondiscriminating with respect to context because the linkages that connect word representations throughout the network are compromised. To understand how these pathways may be compromised functionally will likely require integrated examinations of psychological and neurobiological mechanisms. Although the originating source of the N400 component is unknown, ERPs that are recorded from the scalp are believed to reflect mainly the summed postsynaptic potentials in activated pyramidal cells in the neocortex (for a discussion, see Kutas and Federmeier 1998; Martin 1991). Examinations of possible abnormalities in the mechanisms that affect structure (e.g., excessive synaptic pruning in cortical and subcortical areas; see Keshavan et al 1994), as well as neurochemical modulation, may therefore be advantageous. For example, an atypical or reversed priming effect was observed in the amplitude of P300 in the patients tested under the automatic activation condition; however, this effect was observed only during the drug-free phase. This latter aspect raises obvious questions about the influence of dysregulations in neurochemical modulation on the P300 elicited under the automatic activation condition. It is possible that the amplitude of P300 in drug-free patients, who were tested in the automatic activation condition, was modulated by a complex sequence involving hyperdopaminergic activity in the temporal lobe, which resulted in underactivity in the prefrontal cortex dopamine system, with a potential additional role played by the glutamate and gamma-aminobutyric acid systems. Such a sequence could be the result of a temporal lobe lesion (e.g., Lipska et al 1995; Lipska et al 1995; McCarley et al 1991; Shenton et al 1992; Weinberger and Lipska 1995). Studies that combine psychophysiological techniques (e.g., ERPs, functional magnetic resonance imaging, and positron emission tomography) would be helpful in achieving a better understanding of this latter finding.

AUTOMATIC ACTIVATION AND EXPECTANCY-BASED PROCESSES. In the present study, no a priori assumptions were made regarding the functional significance of the N400 component, beyond its status as an electrophysiological signal of known sensitivity to variations in the meaning of linguistic context. Some comments are in order, however, about the implications of the present findings from the perspective of what is currently understood about the psychological processes tapped by this ERP component. In general, it has not been established unequivocally whether the N400 elicited during lexical decision reflects automatic activation during semantic priming (e.g., lexical access or recognition) (Kutas and Hillyard 1989) or whether it taps higher-order processes that are strategically directed (e.g., lexical integration) (Brown and Hagoort 1993; for a discussion, see Holcomb 1993). To assist in disentangling these possibilities, investigators have used a variety of experimental procedures, including the relatedness proportions strategy (Holcomb 1988), as well as the masked prime word (Brown and Hagoort 1993) and degraded target word (Holcomb 1993)
methods. In a study of the effects of different relatedness proportions on the amplitude of N400 in non schizophrenic individuals, Holcomb (1988) observed that the magnitude of the N400 priming effect was relatively greater under the condition involving a greater proportion of associated word pairs. This finding is similar to the result observed in the present study. As originally described by Posner and Snyder (1975a), attention-based processes are assumed to be important when the linguistic environment includes a relatively high proportion of associated words; automatic activation is assumed to be important when the linguistic environment includes a relatively low proportion of associated words. Thus, one implication of these findings is that it is possible for expectancy-based processes to influence the N400 component elicited to different levels of semantic context. Findings from the masked prime word (Brown and Hagoort 1993) and degraded target word (Holcomb 1993) priming studies are more difficult to interpret. The N400 priming effect was absent under the prime masking condition and equivalent in magnitude under the intact target and degraded target conditions. Both versions of the lexical decision task were assumed to tap an automatic lexical access process. The fact that different results were obtained in these two studies of the same putative process (lexical access) therefore prevents a straightforward interpretation with respect to N400 as an index of that process. It is noteworthy that both prime masking and target degradation tasks produced a reaction time-ERP dissociation, with the N400 data showing different effects than the effects observed in the reaction time data. Finally, an important complication in these considerations is logical. Empirical efforts have been expended largely to define the functional significance of the N400 component elicited during semantic priming tasks in a disjunctive (either/or) manner. That is, the N400 component tends to be viewed as reflecting either an automatically activated lexical access process or a higher-order, strategy-driven lexical integration process. It is possible that it will be more accurate to regard the N400 component in a conjunctive (and) fashion. The N400 component may reflect both processes, depending on the nature of the eliciting stimulus conditions and task demands. Such a perspective about automatic versus strategy-driven processes was suggested in Posner’s comment that “it is not my intention to argue that no aspect of the activation pattern can be varied by context or intentions. Rather the idea is that automatic activation of complex codes may go on without the subject’s intention or even despite intentions that it not take place” (1986: 90). Task manipulations designed to evaluate the obligatory nature of automatic activation even in the presence of interference from simultaneously occurring activity may be informative regarding the issue of the psychological processes indexed by the N400 component (e.g., Posner et al 1989).

In summary, findings from the present study indicate that schizophrenic patients were characterized by a failure to discriminate between associated and unassociated semantic contexts, as measured by the N400 component of the ERP. Patients’ failure to discriminate between semantic contexts was not accompanied by an increased negativity in overall amplitude of the N400 component, as compared with control subjects. Moreover, patients and control subjects did not differ with respect to the amplitude of N400 to associated or unassociated words. A weak effect of pharmacotherapy was observed on patients’ N400 to different levels of semantic context, when compared with control subjects; however, the N400 priming effect was absent in patients during both pharmacologic phases. Finally, N400 was modulated by the expectancy variable, with a relative increase in the magnitude of the N400 priming effect occurring under the condition assumed to induce expectancy- or attention-based processing; however, the effect of expectancy-based processing on the magnitude of the N400 priming effect did not differ between patients and control subjects. On the basis of these findings, a tentative hypothesis is suggested that schizophrenic patients are characterized by a pattern of indiscriminate or random spread of activation in their semantic network during decision tasks involving single-word semantic contexts.

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