N400 and Automatic Semantic Processing Abnormalities in Patients With Schizophrenia

Daniel H. Mathalon, PhD, MD; William O. Faustman, PhD; Judith M. Ford, PhD

Background: One factor hypothesized to underlie thinking disturbance in patients with schizophrenia is abnormal or disinhibited automatic spreading activation of semantic networks, which can be assessed using the N400 event-related potential. N400 is a negative-going component elicited at about 400 milliseconds following semantic stimuli that are not primed by the preceding context. Semantic priming refers to facilitated semantic processing gained through preexposure to semantic context, which can happen automatically or strategically. Using N400, inferences can be drawn regarding the extent to which a given context primes a word.

Methods: During a picture-word matching task, N400s to primed (exact match) and unprimed (remotely related) words were recorded from 18 healthy control subjects and 18 patients with schizophrenia performing a picture-word matching task. A short interval (325 milliseconds) between picture and word onset (stimulus-onset asynchrony) was used to optimize the role of automatic spreading semantic activation and to minimize the role of attention, expectancy, preparation, and working memory.

Results: Despite behavioral evidence of normal semantic priming, patients generated an abnormally small N400 (ie, less negative) to unprimed words. The N400 to primed words was neither larger nor smaller in patients than in controls, suggesting normal use of context.

Conclusions: A reduced N400 to unprimed words in patients with schizophrenia suggests that there was inappropriate priming of words by remotely related semantic contexts. This is consistent with an overly broad automatic spread of activation through semantic networks in patients with schizophrenia.

Arch Gen Psychiatry. 2002;59:641-648

From the Department of Psychiatry, VA Connecticut Healthcare System, West Haven, and Yale University School of Medicine, New Haven (Dr Mathalon); the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif (Drs Faustman and Ford); and VA Palo Alto Health Care System, Palo Alto, Calif (Drs Faustman and Ford).
PARTICIPANTS AND METHODS

PARTICIPANTS

Eighteen healthy adults and 18 patients with schizophrenia (with 17 men in each group) participated and gave written informed consent after the procedures were fully described. Demographic data appear in Table 2.

Controls were recruited by newspaper advertisements and word of mouth, screened by telephone using the psychiatric screening questions from the Structured Clinical Interview for DSM-IV,36 and excluded for any significant history of Axis I psychiatric illness. Patients were recruited from community mental health centers and inpatient and outpatient services of the VA Palo Alto Health Care System. All patients met DSM-IV criteria for schizophrenia (6 paranoiac, 1 disorganized, 11 undifferentiated patient subtypes), based on a diagnosis from the Structured Clinical Interview for DSM-IV conducted by a trained research assistant, a psychiatrist (D.H.M.), or a clinical psychologist (W.O.F.) (n=15) or an inpatient medical record review performed by a clinical psychologist (W.O.F.) (n=3). All patients were taking stable doses of medication. Six patients were taking typical antipsychotic medications (haloperidol [n=3], fluphenazine [n=2], or thiothixene [n=1]), and 12 patients were taking atypical antipsychotic medications (clozapine [n=2], olanzapine [n=9], or risperidone [n=1]). Prospective patient and control participants were excluded for a history of significant head injury (loss of consciousness for ≥30 minutes or neurological sequelae) or neurological or other medical illnesses compromising the central nervous system. Although some patients had a history of alcohol (n=1) or drug (n=1) abuse or dependence (n=2), all but 1 (who abused alcohol) were in full remission.

Patient symptoms were assessed by 2 trained raters (a psychiatrist [D.H.M.], a clinical psychologist [W.O.F.], or a clinical neuroscientist [J.M.F.]) administering the 18-item Brief Psychiatric Rating Scale (BPRS)38 conducted on the same day (n=9), within 2 days (n=5), within 1 week (n=2), or within 3 weeks (n=1) of ERP testing. The mean of the 2 ratings was used for analysis. Brief Psychiatric Rating Scale ratings from 1 patient were not available. Three BPRS items, reflecting positive symptom dimensions, were examined: (1) conceptual disorganization (CD), (2) hallucinatory behavior (HB), and (3) unusual thought content (UTC). Because symptom ratings were based on the mean of 2 raters, the intraclass reliability coefficients were adjusted using the Spearman-Brown Prophecy formula.39 Interrater intraclass reliability coefficients were reasonably high (CD, 0.83; HB, 0.92; and UTC, 0.74).

TASK

A picture-word verification task, described in more detail elsewhere,40 was used. The pictures consisted of 102 line drawings, selected for nameability from a set of 12031 based on pilot testing in young adults. Pictures were classified into 10 natural categories (clothing, animal, bird, appliance, tool, vehicle, vegetable, fruit, toy, and musical instrument). The full set of pictures was presented in each block, which was repeated 4 times. Pictures were paired with different words in the different blocks, and the order of the pictures was varied across blocks. There was a 2- to 3-minute rest period between blocks. Two patients were tested with fewer than 4 blocks because of scheduling constraints.

Each picture was presented for 250 milliseconds, followed 75 milliseconds later by a word that either matched (50%) or did not match (50%) the picture. Between picture onset and word onset, 325 milliseconds elapsed. The word remained on the screen until a button was pressed, and the next trial was initiated 1250 milliseconds later. No feedback was given to signal performance accuracy.

All picture-word pairs were from the same category. For example, a picture of a camel was followed twice by the word appropriate semantic networks, such that a primed target is processed faster than normal. Some short SOA studies10,11 have found hyperpriming to be associated with more severe thought disorder in schizophrenic patients, but others have not. For example, one study12 found priming to be more related to medication dose than thought disorder. In another study,13 patients with mild thought disorder showed normal priming, but patients with more severe thought disorder showed the reverse—responding more slowly to primed than unprimed words. At longer SOAs, automatic processes that promote priming and that may contribute to hyperpriming in patients may be offset by controlled processing deficits, resulting in a failure to observe priming effects in patients with schizophrenia.6

Scalp-recorded event-related potentials (ERPs) provide a more direct measure of the neural mechanisms underlying semantic priming than behavioral measures. The N400 ERP is a negative-voltage component occurring at about 400 milliseconds following semantic targets that are not primed by the preceding context, with primed targets eliciting a relatively positive voltage. N400 was first identified in experiments in which subjects read sentences that ended with a word that did not make sense in the context.14 Since then, N400 has been elicited by unprimed words in different tasks: reading sentences silently while trying to make sense of them,15 reading or listening to sentences in preparation for answering questions about them,16,17 making overt yes/no decisions about whether a word matches the previous context,19,20 and performing a task unrelated to the priming manipulation, such as indicating whether an object is real.21 Thus, N400 is elicited by a stimulus that is incongruous with (ie, unprimed by) its semantic context. When the unprimed stimulus is infrequent or a target, it may also elicit a P300, a prolonged positive component usually occurring 300 milliseconds after the stimulus, potentially contaminating the measurement of N400.

N400 protocols have been used to study semantic processing in patients with schizophrenia with varied results. Because ERPs can be recorded without any overt behavioral response, some studies of N400 in patients with schizophrenia have used passive paradigms. Although these studies25-27 have not shown group differences in N400, studies with active task requirements have reported abnormally large28,29 and small25,30 N400s to un-
“camel” (matches), once by “cow” and once by “fox” (nonmatches). Participants held a 7.6- × 12.7- × 1.3-cm response box on their laps and pressed buttons with right and left thumbs to denote if the word matched the picture. Eleven patients and 11 control subjects pressed the right button to matches and the left button to nonmatches; the remaining did the opposite. Practice with different stimuli was given before ERP recording. Data from this study are also presented in a separate report analyzing response-locked ERP data for effects of response accuracy.

ELECTROPHYSIOLOGICAL RECORDING PROCEDURES

Electroencephalogram data recorded from 9 central sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4) are reported herein. Vertical electro-oculogram (EOG) data were recorded from electrodes placed above and below the right eye and horizontal EOG data were recorded from electrodes placed at the outer canthus of each eye. Electroencephalogram and EOG data were acquired every 5 milliseconds, and were bandpass filtered between 0.1 and 30 Hz. Single trials exceeding ±100 µV were rejected (for controls, mean number of rejected trials was 14.2, representing 2.9% of their trials; for patients, mean number of rejected trials was 14.7, representing 3.6% of their trials). Remaining trials were corrected for the effects of eye blinks and eye movements based on correlations of the vertical and horizontal EOGs with the electroencephalogram recorded at each electrode site. Event-related potential averages were high pass filtered to minimize activity below 1 Hz, removing the influence of the late positive component from the N400.

For each subject, N400 was identified in the ERP to unprimed words as the most negative peak between 300 and 500 milliseconds following the word onset at Pz, where N400 was largest. The latency of this peak was then applied to primed and unprimed waveforms at all 9 leads, and the average amplitudes at this latency (±30 milliseconds), relative to a pre-picture baseline of 100 milliseconds, were taken as the N400 measures. While in most situations a pre-word baseline might be reasonable for assessing ERP activity associated with word processing, there was only 325 milliseconds between picture and word onset during which there was considerable ERP activity associated with picture processing. Thus, a pre-picture baseline minimized the influence of any differential activity associated with picture processing in the 2 groups.

BEHAVIORAL RESPONSE DATA

Trials with RTs exceeding 5 seconds were excluded from the analysis of behavioral data. Median RTs were assessed to minimize the effect of outliers. Errors of commission were tallied; there were no errors of omission because word trials did not terminate until a response was made. Only correct trials contributed to N400 measurements.

STATISTICAL ANALYSIS

N400 amplitudes were analyzed using repeated-measures analyses of variance to assess effects of group (controls or patients), priming (primed or unprimed), and anterior-posterior (frontal, central, or parietal) and lateral (left, central, or right) sites of scalp electrode locations. Reaction times were analyzed in a 2-way group by priming repeated-measures analysis of variance. Greenhouse-Geisser corrections were used for repeated measures factors with 3 or more levels. Post hoc analyses used Newman-Keuls tests for between-group comparisons and paired t tests for within-group comparisons.

To examine whether positive symptoms of schizophrenia were related to priming abnormalities, N400 amplitudes at Pz to primed and unprimed words and the RT difference between unprimed and primed words were correlated with the BPRS items CD, HB, and UTC using Pearson product-moment correlations.

<table>
<thead>
<tr>
<th>Possible N400 Findings</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N400 absent</td>
<td>Normal semantic priming</td>
</tr>
<tr>
<td>Abnormally small (positive) N400</td>
<td>Abnormally facilitated activation of appropriate semantic network (hyperpriming)</td>
</tr>
<tr>
<td>Abnormally large (negative) N400</td>
<td>Deficient use of context or poor memory of context</td>
</tr>
</tbody>
</table>

Table 1. N400 Amplitudes During Semantic Priming: Possible Findings and Interpretations

Inappropriately wide range of stimuli into the preceding context. Expected normal priming effects on N400 and the implications of the various possible abnormalities are summarized in Table 1.
Patients With Schizophrenia

Schizophrenic Patients (n = 18)

Accordingly, subtler semantic discriminations were elicited by patients with schizophrenia relative to controls. Specifically, word stimuli and the pictures priming them were always drawn from the same semantic category, resulting in partial priming of the “unprimed” words at the superordinate category level (eg, the word “duck” following a picture of a swan) relative to strong priming of the words semantically matched to the preceding picture (eg, the word “swan” following a picture of a swan).

Hypotheses were tested regarding the nature of semantic networks in patients with schizophrenia: (1) Automatically activated semantic networks in schizophrenic patients are overly inclusive, accepting related but not identical unprimed words as primed, resulting in a smaller than normal N400 to unprimed words. (2) Schizophrenic patients are deficient in their use of semantic context, responding to primed words as if they were unprimed, generating larger than normal N400s to primed words. (3) Alternatively, schizophrenic patients are overly efficient in their use of context, resulting in hyperpriming and smaller than normal N400s to primed words. The relationship of priming abnormalities to positive symptoms of schizophrenia was also explored.

### RESULTS

#### REACTION TIME

Median RTs are graphed in **Figure 1**. A 2-way group by priming analysis of variance revealed a main effect for group (F\(1,34\)\(=\)5.59, P = .02), in which schizophrenic patients had longer RTs than did controls, and a main effect for priming (F\(1,34\)\(=\)51.93, P<.001), in which RTs to unprimed words were longer than to primed words, but no interaction (F\(1,34\)\(=\)1.43, P = .24). Although patients responded more slowly, they showed an equivalent behavioral priming effect to controls.

#### N400 AMPLITUDE AND LATENCY

Mean N400 amplitudes are illustrated in Figure 1, and grand average ERPs are shown in **Figure 2**. A 4-way group by priming by lateral site by anterior-posterior site analysis of variance revealed a main effect of priming (F\(1,34\)\(=\)4.60, Greenhouse-Geisser P<.001), in which unprimed words elicited a larger (ie, more negative) N400 than primed words. In addition, there was a priming by group interaction (F\(1,34\)\(=\)4.00, P = .05). The interaction was parsed in 2 ways: by assessing priming effects within each group separately and by assessing group effects within primed and unprimed words.
unprimed words separately. The effects of priming were significant for controls (t₁₇=6.49, P<.001) and patients (t₁₇=3.16, P=.006). The effects of group were significant for unprimed (F₁,34=6.25, P=.02, Newman-Keuls P<.05) but not for primed (F₁,34=0.32, P=.57, Newman-Keuls P>.05) words, with patients showing a smaller N400 than controls to unprimed words but no tendency to show inappropriately large or small N400s to primed words. N400 latency at Pz was not affected by group (F₁,34=0.32, P=.58).

CLINICAL CORRELATIONS

None of the BPRS positive symptoms examined was correlated significantly with N400 amplitude to primed (CD: r=0.12, P=.64; HB: r=−0.38, P=.14; and UTC: r=−0.20, P=.44) or unprimed (CD: r=0.24, P=.36; HB: r=0.29, P=.26; and UTC: r=−0.10, P=.80) words. The RT priming effect (RT for unprimed words – RT for primed words) was not significantly related to CD (r=−0.01, P=.96) or UTC (r=0.05, P=.86), but did show a significant negative correlation with HB (r=−0.56, P=.02), indicating that patients with more severe hallucinations showed a smaller RT priming effect.

In this report, we present neurophysiological evidence of abnormally broad automatic spread of semantic activation in patients with schizophrenia, but normal automatic use of semantic context. N400 is a neurophysiological index of semantic priming; in healthy subjects, unprimed words elicit a large N400 and primed words elicit no N400. As such, inferences can be drawn regarding the extent to which a given context primes a word. In our paradigm, when the word “duck” followed a picture of a swan, it was relatively unprimed, and when the word “swan” followed a picture of a swan, it was completely primed. In both groups, unprimed words elicited larger N400s than primed words—the neurophysiological signature of priming. However, patients with schizophrenia generated smaller N400s to un-
primed words than did controls, suggesting that these words were abnormally primed by the relatively incongruous picture context. This abnormally small N400 to unprimed words suggests insensitivity to subtle incongruities in language, perhaps due to an overly broad or facilitated spread of activation through a loosely structured semantic network. The N400 to primed words was normal in patients; it was neither abnormally large nor abnormally small. That is, when presented with the pictorially congruous context, patients used it effectively, priming neither too little nor too much (ie, hyperprime). However, because the unprimed picture-word pairs were moderately related (swan-duck), belonging to the same superordinate category, abnormally small N400s to these pairs could be construed as evidence of hyperpriming. That is, schizophrenic patients showed more priming than did controls when pictures primed words at the superordinate categorical level. Hyperpriming over this span of semantic space occurred in the patients despite the absence of hyperpriming when the picture prime exactly matched the subsequent word.

To our knowledge, this is the first neurophysiological study of semantic priming in patients with schizophrenia to use a short SOA, allowing only automatic spreading activation of semantic networks. Longer SOAs allow both automatic and controlled semantic processing, but in unknown proportions, possibly contributing to inconsistencies in the literature on the effects of schizophrenia on N400 semantic priming. In addition, perhaps because of the short SOA, this is the first report, to our knowledge, showing no slowing of N400 in patients with schizophrenia. This equivalence of N400 latency in the 2 groups reinforces the notion that the paradigm used in this study tapped into semantic processes that were unaffected by attention, strategy, and motivation.

Bobes et al30 reported abnormally small N400s to unprimed pairs but abnormally large N400s to primed pairs.
in patients with schizophrenia, using picture-picture pairs presented with long SOAs. Comparison of the Bobes et al study with ours is complicated by their use of a long SOA and by our exclusive use of within-category picture-word pairs. If the effects of priming cannot be sustained over relatively long intervals in schizophrenic patients because of working memory deficits, the long SOA might be responsible for their reduced sensitivity to both incongruity and congruity in the Bobes et al study. While within-category pairs enabled us to assess subtle abnormalities in semantic activations in the range in which semantic slippage underlying thinking disturbance in patients with schizophrenia may be most evident, the absence of categorically unrelated pairs (e.g., swan-truck) makes comparison with other studies difficult. Moreover, this feature distinguishes our study from others’ that have found RT hyperpriming in patients at short SOAs.

Reaction time and ERP measurement modalities can bring important and somewhat independent information to bear on the question of whether schizophrenia is associated with an abnormally broad spread of activation through semantic networks. While the N400 data from the present study indicate abnormal spread of semantic activation in the patients, the RT data indicate normal RT priming, a finding that is both consistent and inconsistent with other studies using short SOAs. Compared with RT, N400 is a relatively direct measure of neural processes associated with priming, unaffected by response selection and execution. Moreover, the N400 index of priming does not depend on taking a difference score between 2 conditions to draw conclusions about semantic congruity effects, a limitation of behavioral RT measures of priming. Nevertheless, assuming some correspondence between behavioral and neurophysiological measurements, we would have expected a smaller RT priming effect in patients than controls based on N400 data. The dissociation of N400 and RT effects observed herein suggests that neurophysiological indices have relatively greater sensitivity to semantic processing abnormalities in patients with schizophrenia.

Consistent with many, but not all, prior ERP priming studies, the present study did not yield any significant relationships between severity of thought disorder and N400 measures of priming. In our case, one possible reason for this may be that the BPRS does not provide as precise an assessment of thought disorder as other more extensive measurements. Another reason is that underlying semantic processing abnormalities may reflect traitlike aspects of schizophrenia, whereas patient symptoms can fluctuate over the illness course in a state-like fashion and respond differentially to antipsychotic medication. Thus, clinical state fluctuations and medication effects would attenuate the cross-sectional relationships between semantic priming abnormalities and symptoms. Many patients who no longer appear to have thought disorder may still have the neurobiological circuitry allowing loose and bizarre associations, as reflected by neurophysiological priming abnormalities.

Reaction time indices of priming also failed to show significant correlations with formal thought disorder, consistent with some, but not all, prior reports. However, this study did show a significant tendency for patients with more severe hallucinations to exhibit relatively smaller RT priming effects, suggesting that the automatism of semantic inexactitude in patients with schizophrenia may underlie other misperceptions of reality, including auditory hallucinations.


