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Automatic Semantic Priming Abnormalities in Schizophrenia

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Abstract

Abnormal activation of semantic networks characterizes schizophrenia and can be studied using the N400 event-related potential (ERP). N400 is elicited by words that are *not* primed by the preceding context and provides a direct measure of the neural mechanisms underlying semantic priming. Semantic priming refers to facilitated semantic processing gained through pre-exposure to semantic context, which can happen automatically if the interval between the prime and target is very short. We predicted that (1) schizophrenia patients have overly inclusive semantic networks, reflected in a *less negative* than expected N400 to relatively unprimed words, and (2) schizophrenia patients are deficient in their use of semantic context, responding to primed words as if they were unprimed, reflected in a *more negative* than expected N400 to primed words. N400s were acquired from patients with DSM-IV schizophrenia (n=26) and age-matched healthy comparison subjects (n=29) performing a picture-word verification (match vs. non-match) task. Word targets were presented 325ms after a picture prime, which either matched (CAMEL→"camel"), or did not match (In Category: CAMEL→"cow; Out Category: CAMEL→"candle") the prime. N400 data suggest that both patients and controls are sensitive to the difference between primed and unprimed words, but patients are less sensitive than controls. Similarly, N400 data suggest that both groups were sensitive to the subtler difference between classes of unprimed words (In Category versus Out Category picture-word non-matches), but patients are less sensitive, especially those with prominent negative symptoms.

Keywords

Semantic priming; N400; Schizophrenia

Introduction

Abnormal activation of semantic networks may underlie some of the symptoms of schizophrenia (Spitzer, 1997), with over-activity resulting in loose, irrelevant, and bizarre associations (Andreasen, 1979), disorganized thought and speech (Kreher et al., 2008), and delusional thinking (Debruille et al, 2007). The extent of semantic networks and the

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efficiency or speed of the spread within them can be assessed using tasks involving semantic priming. Semantic priming refers to the more efficient processing of a target stimulus when it is preceded by a semantically related stimulus or context. For example, people respond more quickly and accurately to the target word “tomato” when preceded by the prime “lettuce” than when preceded by the more distantly related prime “turnip” or the unrelated prime “wagon”(Neely, 1991). Seeing “lettuce” selectively activates other related concepts (salad vegetables first and then other vegetables) and may inhibit unrelated concepts.

When the prime precedes the target by less than about 300ms, it is thought that there is no time for strategic processes to be enlisted, and any priming that occurs at these short intervals must be invoked automatically. At longer intervals between the prime and target, strategic and higher order cognitive processes can be added, making it difficult to know whether priming effects are due to automatic spreading activation or executive processes.

Scalp-recorded event related potentials (ERPs) provide a direct measure of the neural mechanisms underlying semantic priming. The N400 ERP is a negative-going component occurring at about 400ms following semantic targets that are *not* primed by the preceding context. When targets are primed by the semantic context, they elicit a relatively positive voltage reflecting a minimal or absent N400 (Kutas & Hillyard, 1980). Semantic context can be established by reading sentences (Ford et al., 1996; Ganis et al., 1996; Nigam et al., 1992; Van Petten et al., 1991); making overt yes/no decisions about whether or not a word matches the previous context (Barrett & Rugg, 1990; Friedman et al., 1992; Hamberger et al., 1995; Pratarelli, 1994; Rugg, 1984); or performing a task unrelated to the priming manipulation, such as indicating whether an object is real or not (Holcomb & McPherson, 1994). N400 has been elicited when the target and prime are presented in different forms, such as written word targets primed by pictures (Ford et al., 1996; Mathalon et al., 2002) or in different sensory modalities, such as auditory word targets primed by written words (Kiyonaga et al., 2007). In these cases, priming effects depend on meaning and cannot rely on orthographic or phonologic similarities.

An N400 should be elicited by an unprimed stimulus when it does not fit with the context, regardless of how it is established and regardless of its form or modality. An abnormally negative voltage at the N400 latency following an unprimed stimulus suggests heightened incongruity, perhaps resulting from an overly narrow or constrained semantic network. Conversely, an abnormally positive voltage (or reduced negativity) at this latency following an unprimed stimulus suggests an overly inclusive semantic network that allows integration of an inappropriately wide range of stimuli into the preceding context.

An N400 should not be elicited by a primed stimulus, because it semantically matches the preceding context. Instead, it should be associated with relative positivity at the N400 latency. An abnormally positive voltage is the ERP analogue of hyperpriming, suggesting abnormally facilitated activation of the associated semantic network. An abnormally negative voltage at this latency (i.e., abnormal elicitation of an N400) following a primed stimulus suggests that the stimulus does not fit into the semantic context, as understood by the subject, possibly because of inefficient or deficient use of context, but perhaps also

because of poor working memory for the context if the interval between the prime and the target is long (Carter et al., 1996).

Semantic gradients can be studied with different types of priming paradigms, for example, indirect priming and category priming. With indirect priming, typical prime-target pairs might be: “Birthday”-“Cake” (directly primed), “Birthday”-“Pie” (indirectly primed), and “Birthday”-“Soap” (unprimed). For category priming, typical prime-target pairs might be: “Pear”-“Pear” (exact match, or primed), “Pear”-“Apple” (in-category, unprimed), and “Pear”-“Curtain” (out-of-category, unprimed). Words that are only modestly primed will yield an intermediate N400, more negative than the primed word but less negative than the unprimed word. Expected priming effects on N400 and the implications of the various possible abnormalities are summarized in Table 1.

While some investigators report an N400 *priming effect* as a subtraction of the primed ERP from the unprimed ERP, it should be clear from Table 1 that information can be lost about the processes reflected in the separate N400s that go into the difference waveform. Indeed, difference waveforms can augment leading and trailing aspects of components, and can generate spurious components if the latency to onset is different for the different ERPs going into the difference waveform. Other information can also be obscured by use of difference wave. For example, N400 tends to be largest at Cz but reduced more posteriorly, even though the N400 difference (priming effect) is typically larger at Pz; thus, features of the N400 such as latency to onset or the latency envelope in which the N400 occurs, if similar across conditions, are lost using subtraction waveforms.

N400 has been used to study semantic processing in patients with schizophrenia. Kiang et al. (Kiang et al., 2008) used an indirect priming paradigm to study semantic networks in schizophrenia. As expected, in the healthy controls, N400 amplitude was largest (most negative) following unprimed targets, intermediate after indirectly primed targets, and smallest after directly primed targets. In patients, N400 amplitudes did not distinguish between these target types. N400s to both directly primed (“Birthday”→“Cake”) and indirectly primed (“Birthday”→“Pie”) words were more negative than expected in patients. According to the scheme laid out in Table 1, this suggests that patients had an overly constrained semantic network, such that even “cake” was not well-primed by “birthday”. N400s to unprimed words (“Donkey”→“Purse”) did not differ in patients and controls, suggesting that non-subtle semantic violations such as these are less sensitive to the illness and that semantic abnormalities in schizophrenia might be best assessed using indirect priming. However, Kreher et al. (Kreher et al., 2008) did not find abnormally large N400s to indirectly primed targets (Lion→Stripes) in schizophrenia patients as a group (page 478, right column, last sentence). It is important to point out, however, that the larger the indirect priming effect observed in the thought-disordered patient subgroup, the greater the severity of their thought disorder (Kreher et al., 2008).

In our earlier study of cross-form, within-category priming (Mathalon et al., 2002), schizophrenia-related deficits were apparent over even shorter semantic distances than those used with most indirect priming paradigms. When the word “duck” followed a picture of a SWAN (pictures are designated in UPPER CASE), “duck” was relatively unprimed,

compared to when “swan” followed a picture of a SWAN. The expected priming effect was seen in both patients and controls, with larger N400s to “duck” following a picture of a SWAN. However, N400 to “duck” was relatively less negative (more positive) in patients. We suggested this might reflect excessive priming and insensitivity to subtle incongruities in language, perhaps due to an overly broad or facilitated spread of activation through a loosely structured semantic network. However, because there were no truly unprimed picture-word pairs, the full extent of semantic priming was not assessed. To address this ambiguity, we have added a new category of picture-word pairs in this study. In this way, we can compare N400s elicited when cues directly prime targets (Matches: SWAN→”swan”), when cues indirectly prime targets (In-Category Non-Matches: SWAN→”duck”), and when cues do not prime targets (Out-Category Non-Matches: SWAN→”turnip”).

Results from studies of semantic priming in schizophrenia using long prime-target intervals vary, with some studies showing no group differences in N400 (Andrews et al., 1993; Koyama et al., 1991; Mitchell et al., 1991), others showing both abnormally large (Nestor et al., 1997; Niznikiewicz et al., 1997) and small (Bobes et al., 1996; Mitchell et al., 1991) N400s to unprimed stimuli, and some showing abnormally large N400s to primed stimuli (Bobes et al., 1996; Nestor et al., 1997; Niznikiewicz et al., 1997; Salisbury et al., 2000; Strandburg et al., 1997). Variability in the literature may be due to the uncertain admixture of deficits in automatic and executive processes. Two studies allowed the direct comparison of short and long prime-target intervals in patients with schizophrenia: Condray and colleagues (Condray et al., 2003) found larger group differences in *priming effects* at long (850ms) relative to short (250ms) prime-target intervals, perhaps because deficits in both executive and automatic processes contributed to the group difference. Kiang et al (Kiang et al., 2008) found no difference in the group effects with long (750ms) and short (300ms) prime-target intervals. Importantly, N400 to primed words was not significantly less positive in the patients, nor was N400 to unprimed words significantly less negative. Although group effects may not depend on prime-target intervals, short intervals are more “process-pure”, making the effects easier to interpret.

The current study was designed to test several hypotheses regarding the nature of semantic networks in schizophrenia. Hypothesis 1a: Automatically activated semantic networks in schizophrenic patients are overly inclusive, accepting “close but not identical” words as primed (CAMEL→”cow”), resulting in a less negative than expected N400 to unprimed words (“cow” or “candle”) relative to primed words. That is, we expected a Group × Priming interaction. Hypothesis 1b: In addition, schizophrenic patients are less sensitive to subtle semantic distinctions, responding similarly to unprimed words regardless of whether they are in the category of the prime (CAMEL→”cow”) or not (CAMEL→”candle”), generating equivalent and relatively positive N400s. That is, we expected a Group × Category interaction. Hypothesis 2: Schizophrenic patients are deficient in their use of semantic context, responding to primed words as if they were unprimed, generating *more negative* than expected N400s to primed words (CAMEL→”camel”). That is, we expected a main effect of Group for Primed words.

Regarding correlations between ERP and clinical data, we predicted the following. Clinical Hypothesis 1: Schizophrenia patients with thought disorder will have overly inclusive

networks, reflected in a relatively *less negative* N400 to unprimed words. Clinical Hypothesis 2: Schizophrenia patients with unusual thought content will show evidence of deficient use of context, reflected in a relatively *more negative* N400 to primed words.

Prior N400 semantic priming studies have sometimes reported variable hemispheric lateralization of the effects. For example, Kiefer and colleagues (Kiefer et al, 1998) found that while the N400 elicited by unrelated relative to directly related word pairs was evident bilaterally, the N400 priming effect elicited by indirectly related words was mainly evident over the right hemisphere, implicating the right hemisphere semantic system in processing more remote semantic information. In contrast, Frishkoff (2007) found that the N400 priming effect for both strongly and weakly related word pairs, relative to unrelated word pairs, was evident over left parietal sites, whereas the right parietal sites were only sensitive to the N400 priming effect elicited by strongly related versus unrelated words. While the results are somewhat inconsistent across studies, there was sufficient evidence of possible lateralization of the N400 effect to pursue analyses of hemispheric lateralization from off-midline electrode sites in the present study.

Methods

Participants

EEG data were acquired from patients with schizophrenia (n=26) and age-matched healthy comparison subjects (n=29). All gave written informed consent after procedures had been fully described. Demographic and clinical data are summarized in Table 2. Informed consent was obtained from all subjects. This study was approved by the Human Subjects Committees at the Connecticut VA Healthcare System and Yale University.

Patients were recruited from community mental health centers, outpatient services of the Veterans Affairs Healthcare System in West Haven, and outpatient services of Connecticut Mental Health Center in New Haven. Patients met DSM-IV(American Psychiatric Association, 1994) criteria for schizophrenia based on a Structured Clinical Interview for DSM-IV (SCID; (First et al., 1995) conducted by a clinical psychologist, or a SCID conducted by a clinically trained research assistant. Patients with a diagnosis of schizoaffective disorder were not included in this analysis. Patients were excluded if they met DSM-IV criteria for alcohol or drug abuse within 30 days prior to study. In addition, patient and control participants were excluded for significant head injury, neurological disorders, or other medical illnesses compromising the central nervous system. Symptoms were rated using the Positive and Negative Symptom Scale (PANSS)(Kay et al., 1987), a scale used to assess symptom severity in patients with schizophrenia. Positive symptoms refer to psychotic experiences and behaviors that typically involve distortion of normal functions (e.g., hallucinations and delusions), and negative symptoms represent a diminution or loss of normal functions (e.g., blunted affect, diminished motivation, and social withdrawal). In addition, the PANSS also allows for an assessment of formal thought disorder (i.e., disorganized speech).

Comparison subjects were recruited by newspaper advertisements and word-of-mouth, screened by telephone using questions from the SCID (First et al., 1995) non-patient screening module, and excluded for any history of Axis I psychiatric illness.

Task

A variant on our earlier picture-word verification task (Ford et al., 2001) was used. The pictures consisted of 102 line drawings, selected for nameability from a set of 120 (Snodgrass & Vanderwart, 1980) 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 comprised a 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.

Each picture was paired with a word that either matched (50%) or did not match (50%) the picture. Of those that did not match, half (25%) were words within the category and half (25%) were outside the category. For example, the picture CAMEL was followed twice by the word “camel” (Primed), once by “cow” (InCat; Unprimed or “Indirectly Primed”) and once by “candle” (OutCat; Unprimed). Note: only words that directly match the picture are considered “primed”; we consider the InCat non-match words to be unprimed (consistent with the convention we previously adopted in Mathalon et al, 2002) although they could be construed as being indirectly primed. Participants pressed buttons with right and left index fingers to indicate if the word matched or did not match the picture. Subjects were told to press with one button to *exact* matches and the other button to non-matches. Subjects were not asked to distinguish between InCat and OutCat unprimed target words. Hand of press was counterbalanced across subjects. Practice was given prior to ERP recording. For InCat and OutCat non-match words, 4% and 2%, respectively, started with the same letter as the picture (e.g., CAMEL→”candle”).

Pictures were presented for 250ms, followed 75ms later by a word. Between picture onset and word onset, 325ms elapsed. No feedback was given to signal performance accuracy. Subjects were told to respond as quickly as possible without sacrificing accuracy. fMRI data were collected from all these subjects with an identical paradigm in a separate session. To accommodate the needs of the MR scanning, occasional null events were inserted between trials, resulting in stimulus onset asynchronies that ranged from 3 to 11s.

EEG acquisition

EEG data were digitized using a 1000Hz sampling rate, low pass filtered at 100Hz, and high pass filtered at 0.05Hz. Data were acquired from F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, and O2. Data were referenced to linked ears. Additional electrodes were placed on the outer canthi of both eyes and above and below the left eye to record eye movements and blinks (vertical and horizontal electrooculogram (EOG); VEOG, HEOG). All impedances were maintained at or below 10kOhm throughout the recording session with most EEG sites around 5kOhm.

EEG processing

First, data were bandpass filtered between 0.1-30Hz. Next, data were epoched and stimulus-locked to picture onset. While in most situations a pre-word baseline might be reasonable for assessing ERP activity associated with word processing, there was only 325 ms between picture and word onset during which time there was considerable ERP activity associated with picture processing. Furthermore, it appeared that there might be differential ERP activity associated with picture processing in the two groups. Thus, individual trials were baseline corrected using the 100ms period preceding picture onset after correcting for eye movements and blinks using EOG data (Gratton et al., 1983). Finally, trials containing artifacts (voltages exceeding $\pm 100\mu\text{V}$) were rejected. Data from F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, and O2 were analyzed to allow for an analysis of 3 levels of the Laterality factor (left, midline, right) and 4 levels of the Anterior-Posterior factor (frontal, central, parietal, occipital). Although patients had fewer remaining trials than the controls ($F(1, 53)=4.59, p=.037$), there were large numbers of trials for each condition for both groups. The mean number of trials and standard deviations (SD) for each condition and each group are: Primed (controls: mean=181, SD=5.4; patients: mean=167, SD=5.8), InCat (controls: mean=88, SD=3.2; patients: mean=75, SD=3.4), OutCat (controls: mean=92, SD=2.9; patients: mean=85, SD=3.0).

For each subject, N400 was identified in the ERP to InCat and OutCat words as the most negative peak between 300 and 500 ms following the word onset at Pz, where N400 was largest. Although primed words should not elicit an N400, we extracted the voltage associated with primed words at the OutCat N400 peak latency. The average amplitudes around the N400 peak (± 30 ms), relative to a pre-picture baseline of 100 ms, were taken as the N400 measures to primed, InCat and OutCat unprimed words.

Behavioral Response Data

Trials with reaction times (RTs) exceeding 1s were excluded from the analysis of behavioral data. Median RTs were assessed in order to minimize the effect of outliers. Only data from correct trials were included in the analyses.

Statistical Analysis

N400 and Behavioral Data—N400 amplitudes were analyzed using repeated measures analyses of variance (ANOVA) to assess effects of Group (Controls, Patients), Condition (Unprimed-InCat, Unprimed-OutCat, Primed), Anterior-Posterior Site (Frontal, Central, Parietal, Occipital) and Lateral Site (Left, Central, Right) of scalp electrode locations. Median RT data were analyzed similarly, without the scalp distribution factors.

To assess the task priming effects, we opted not to conduct an omnibus test of overall differences between the three task conditions. Instead, we chose to parse the Condition effect into two orthogonal single degree of freedom Helmert contrasts (Category Effect, Priming Effect) to address our two main questions about the Condition effects on N400:

Category Effect: Was N400 more negative for OutCat than InCat unprimed words?

Priming Effect: Was N400 more negative for Unprimed (Mean of InCat and OutCat) words than Primed words?

These specific contrasts and their interactions with Lateral Site, Anterior-Posterior Site, and Group were the focus of the ANOVA analyses.

Clinical Correlations—We predicted that patients would show evidence of overly inclusive semantic networks, indicative of thought disorder and reflected in a relatively *less negative* N400 to unprimed words. We also predicted that patients would show evidence of deficient use of semantic context, indicative of unusual thought content and reflected in a relatively *more negative* N400 to primed words. Accordingly, we predicted a positive correlation between N400 to unprimed words and PANSS-rated Conceptual Disorganization and a negative correlation between N400 to primed words and PANSS-rated Unusual Thought Content.

Exploratory correlations were also calculated to assess the relationship between more subtle semantic distinctions and general positive and negative symptoms. Accordingly, we calculated the correlation between the difference between N400 amplitude to OutCat and InCat words (N400 to OutCat – N400 to InCat) and average PANSS Negative Symptom scores (Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive/Apathetic Social Withdrawal, Difficulty in Abstract Thinking, Lack of Spontaneity and Flow of Conversation, Stereotyped Thinking) and PANSS Positive Symptom scores (Delusions, Unusual Thought Content, Conceptual Disorganization, Hallucinatory Behavior, Excitement, Grandiosity, Suspiciousness/Persecution and Hostility).

All correlations were calculated separately for N400 amplitudes at P3 and P4.

Results

Reaction Time

Median RTs are graphed in Figure 1. RTs were affected by a Priming effect ($F(1,53)=101.17$, $p<.0001$), in which Primed words had faster RTs than Unprimed words, and a Category effect ($F(1,53)=71.04$, $p<.0001$), in which OutCat words had faster RTs than InCat words. There was a Group by Category interaction such that patients tended to be more slowed by the InCat words than the controls ($F(1,53)=4.41$, $p=.04$). There was no Group by Priming interaction ($F(1,53)=1.93$, $p=.17$), indicating that there was no RT evidence of hyperpriming in the patients, which would have been seen as a greater speeding of RTs to primed targets compared to unprimed targets. The Priming effect was 67ms in patients and 51ms in controls.

N400 Amplitude

Grand average ERPs are shown in Figure 2.

N400 was significantly affected by Priming, with Unprimed words eliciting a larger N400 than Primed words [$F(1,53) = 148.16$, $p < .0001$]. The Priming effect interacted with Group ($F(1,53)=12.73$, $p<.001$), with controls having a larger Priming effect than patients,

confirming Hypothesis 1a. We inspected the Group effect for Primed and Unprimed words separately; patients had a larger (i.e., more negative) N400 to Primed words than did controls ($F(1,53)=4.39$, $p=.041$), and controls had a larger (i.e., more negative) N400 to Unprimed words than did patients ($F(1,53)=4.36$, $p=.042$). The larger (i.e., more negative) N400 to Primed words in patients confirmed Hypothesis 2, suggesting that patients were deficient in their use of semantic context. This can be seen in Figure 3 where the means for this interaction are shown.

N400 was affected by Category ($F(1,53) = 17.78$, $p < .0001$), with OutCat words eliciting a larger N400 than InCat words. However, there was a Group $\times$ Category $\times$ Lateral Site interaction ($F(1,53)=10.65$, $p<.002$). The means are plotted in Figure 4. We tested the Group $\times$ Category interaction separately for the midline, and right and left hemispheres. The Group $\times$ Category interaction was significant on the right ($F(1,53)=5.16$, $p=.027$), but not on the left ($p=.482$) or along the midline ($p=.15$). That is, we confirmed Hypothesis 1b that there would be a Group $\times$ Category interaction, but only for the right hemisphere electrode sites. On the right, controls exhibited a significant Category effect ($F(1,28)=16.845$, $p<.0001$) not seen in the patients ($F(1,25)=1.784$, $p=.19$). Importantly, there was a main effect of Category on the left ($F(1,53) = 17.433$, $p < .0001$) and along the midline ($F(1,53) = 17.447$, $p < .0001$) indicating that in both groups OutCat words elicited a larger (i.e., more negative) N400 than InCat words.

N400 Latency

N400 latency at Pz tended to be increased among patients (392ms) compared to controls (369ms) (Group: $F(1,53)=3.675$, $p=.06$).

Clinical Correlations

N400 amplitudes to unprimed words were not correlated with Conceptual Disorganization (InCat at P3: $r = 0.003$, n.s.; InCat at P4: $r = 0.072$, n.s.; OutCat at P3: $r = -0.103$, n.s.; OutCat at P4: $r = 0.012$, n.s.). N400 amplitudes to primed words were not correlated with Unusual Thought Content (P3: $r = -0.015$, n.s.; P4: $r = 0.066$, n.s.).

Patients with the most severe negative symptoms had the smallest N400 difference between OutCat and InCat (N400 to OutCat – N400 to InCat) words at both P3 ($r = .537$, $p=0.006$) and P4 ($r = .466$, $p=0.019$). It is possible that these correlations are mediated by an unmeasured third variable, such as intelligence; however, this N400 difference was not related to years of education (P3: $r = -0.01$, n.s. and P4: $r = -0.041$, n.s.) in this group of patients. The PANSS Positive Symptom scores were not correlated with OutCat-InCat N400 difference scores at either P3 ($r = -.068$, n.s.) or P4 ($r = .053$, n.s.).

Discussion

In both patients and controls, unprimed words elicited larger N400s than primed words, the canonical *priming effect*. However, the priming effect was stronger in the controls than in the patients. As explained above and denoted in Table 1, these priming effects can best be understood when N400s to primed and unprimed words are inspected separately.

Regarding N400s to unprimed words, patients with schizophrenia generated smaller (i.e., less negative) N400s to unprimed words than controls, suggesting that unprimed words were more primed than they should have been. That is, when they saw “duck” after seeing the picture SWAN, the semantic incongruity was less strongly evident to them. This might result from diminished sensitivity to incongruities in language perhaps due to an overly broad or facilitated spread of activation through a loosely structured semantic network.

Within the set of unprimed words, we presented subjects unprimed words along a semantic gradient of relatedness; words were in the same category as the picture (InCat: SWAN→”duck”) or not (OutCat: SWAN→”turnip”). As expected, OutCat words elicited larger N400s than words that were in the same semantic category (InCat). While this sensitivity to subtle semantic distinctions was evident over all brain regions in controls, it was only significant over the left hemisphere and midline in patients. That is, in patients, recordings over the right hemisphere failed to reveal an N400 difference between OutCat and InCat words ($p=.19$). Regardless of whether right hemispheric linguistic structures were not adequate for the job, or not invoked to get the job done, ERPs over the right hemisphere did not distinguish between InCat and OutCat words in the patients. However, it would be incorrect to conclude that patients failed to distinguish OutCat from InCat unprimed words, since this distinction was significantly evident and similar to healthy controls for the N400s recorded at midline and left hemisphere sites. Interestingly, the right-sided deficit in the N400 Category effect in patients is consistent with dysfunction in the right hemisphere semantic system that Kiefer et al (1998) identified as being most sensitive to remotely or indirectly related semantic information.

In a similar study of indirect priming, Kiang and colleagues (Kiang et al., 2008) were not able to demonstrate sensitivity in patients to the semantic difference between related, indirectly related, and unrelated words. The Kiang et al. study differed from ours in several ways. They had slightly fewer subjects than we did, so their analysis may have been underpowered. We were asking subjects to make semantic distinctions, but Kiang et al were not. Thus, our task may have oriented patients to semantic distinctions that they would not have noticed otherwise. Also, in the Kiang et al study, the prime-target interval varied randomly from trial-to-trial; the temporal uncertainty may have distracted patients from interest in the relatedness of prime-target pairs. In addition, while we assume we were using a shorter semantic distance for our InCat primed pairs (SWAN→”duck”) than Kiang et al had with their indirectly primed pairs (“birthday”→ “pie”) it is not necessarily the case that the difference between our directly primed (SWAN→”swan”) and indirectly (un)primed (SWAN→”duck”) conditions is smaller than the difference between the direct, associative primes (“birthday”→”cake”) and indirect primes (“birthday”→”pie”) used by Kiang et al. This might contribute to the different N400 indirect priming effects obtained in their study compared to ours.

Regarding ERPs to primed words, patients and controls also differed in the ERP to primed words (SWAN→”swan”) at the latency of N400. Patients had greater negativity at this latency than controls, suggesting a deficient use of the semantic context established by the picture prime. That is, even when immediately preceded by a picture of a SWAN, the word “swan” was less primed that would be expected. Bobes et al (Bobes et al., 1996) also noted

abnormally large (i.e., more negative) N400s to primed pictures in schizophrenia, using picture-picture pairs presented with a long prime-target interval. Possibly, the interval was so long the patients could not remember the prime. This is unlikely to be the case in our study, as there was only 350ms between prime onset and target onset. Importantly, we did not see a similar effect in our earlier study, which differed from this one in two ways; we added OutCat unprimed words, and we added a variable inter-trial interval in order to optimize the task for the fMRI environment. Although both might have affected priming by adding to the overall cognitive load of the experiment, RTs were actually faster in this study than in our earlier one. This deficient use of semantic context may be an instance of a general failure to process and maintain context previously noted by us (Ford et al., 2004) and others (Barch et al., 2001; Carter et al., 2001; Henik et al., 2002; Servan-Schreiber et al., 1996).

The groups did not differ significantly in N400 latency, although there was a tendency ($p=.06$) for patients to have later N400s. Generally, other studies using short prime-target intervals have also found no group difference in N400 latency (e.g., Kiang et al., 2008). Kreher and colleagues did find thought disordered patients to have later N400s than non-thought disordered patients, but thought disordered patients did not have later N400s than controls (Kreher et al., 2008).

RT and N400 offer independent information on the question of whether schizophrenia is associated with an abnormally broad spread of activation through semantic networks. The N400 data from the present study revealed a Group $\times$ Priming interaction, suggesting relatively abnormal spread of semantic activation in the patients. The RT data, however, indicate normal RT priming, as the Group $\times$ Priming interaction was not significant. This is both consistent (e.g., Barch et al., 1999) and inconsistent (e.g., Aloia et al., 1998) with RT data reported in other studies using short SOAs.

In addition, while N400 and RT were affected by a Group $\times$ Category interaction, the effects were in opposite directions. On the one hand, N400 data suggested patients were less sensitive to the difference between InCat and OutCat unprimed words than controls (at least at right hemisphere electrode sites). On the other hand, RT data suggested patients were more slowed by InCat than OutCat words compared to controls. Compared to RT, N400 is a more direct measure of neural processes, unaffected by response selection and execution. Moreover, the N400 index of priming does not depend on taking a difference score between two conditions to draw conclusions about semantic congruity effects, a limitation of behavioral RT measures of priming.

Consistent with many (Bobes et al., 1996; Mitchell et al., 1991; Nestor et al., 1997; Niznikiewicz et al., 1997; Salisbury et al., 2000; Strandburg et al., 1997), but not all (e.g., Kreher et al., 2008; Spitzer et al., 1993) 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 PANSS does not provide as precise an assessment of thought disorder as other more extensive measurements (e.g., Holzman et al., 1986). Another reason is that underlying semantic processing abnormalities may reflect trait-like 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 thought disordered may still have the neurobiological circuitry allowing loose and bizarre associations, as reflected by neurophysiological priming abnormalities.

In summary, our N400 data suggest people with schizophrenia appear to have both overly broad spread of semantic activation and deficient use of semantic context. That is, both patients and controls are sensitive to the difference between primed and unprimed words, but patients are less sensitive than controls. Similarly, N400 data suggest that both groups are sensitive to the more subtle difference between classes of unprimed words, but patients are less sensitive. While the N400s to primed and unprimed words were not correlated with symptoms of the illness, these deficits in subtle linguistic processing may contribute to some of the difficulties schizophrenia patients have integrating themselves into social groups and the larger community, difficulties that reflect negative symptoms of the illness. Indeed, patients with the worst negative symptoms showed the least sensitivity to subtle distinctions between different types of unprimed words.

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Figure 1.

Median RT (+ standard error of the mean) to primed, in-category unprimed, and out-of-category unprimed target words are shown for normal control subjects and patients with schizophrenia.

Figure 2.

ERPs associated with primed, in-category unprimed (InCat), and out-of-category unprimed (OutCat) target words are shown for normal control subjects (a) and patients with schizophrenia (b). Picture onset is shown with a vertical dotted line at -325 ms, word onset by a vertical dotted line at 0 ms, and an additional dotted line at 400 ms shows the approximate location of the N400 component.

Figure 3.

N400 amplitudes (+ standard error of the mean) to primed and unprimed (mean of in-category and out-of-category) target words are shown for normal control subjects and patients with schizophrenia.

Figure 4.

N400 amplitudes (+ standard error of the mean) to primed, in-category unprimed, and out-of-category unprimed target words are shown for normal control subjects and patients with schizophrenia recorded from electrodes over the left (F3, C3, P3, O1) and right hemispheres (F4, C4, P4, O2), and midline (Fz, Cz, Pz, Oz).

Table 1

Results of N400 Studies of Automatic Priming in Schizophrenia.

N400 Study Result	Interpretation	Current Paper	Mathalon et al. 2002 [*]	Kiang et al. 2008 ^{**}	Kreher et al. 2007 ^{**}	Condray et al. 2003 ^{****}
<i>Type of Priming</i>		<i>Category Priming</i>	<i>Category Priming</i>	<i>Indirect Priming</i>	<i>Indirect Priming</i>	<i>Simple Priming</i>
Patient vs. Control Difference in N400 to Primed Words						
Smaller (i.e., less negative) than controls	Hyperpriming	No	No	No		No
Same as controls	Normal semantic priming	No	Yes	No		Yes
Larger (i.e., more negative) than controls	Deficient use of context	Yes	No	Yes		No
Patient vs. Control Difference in N400 to Unprimed Words						
Smaller (i.e., less negative) than controls	Abnormally broad spread of semantic activation	Yes	Yes	No	No	No
Same as controls	Normal semantic priming	No	No	Yes	No	Yes
Larger (i.e., more negative) than controls	Overly constrained semantic network	No	No	No	Yes ^{***}	No
Patient vs. Control Difference in N400 to Indirectly Primed or In-Category Words						
Smaller (i.e., less negative) than controls	Abnormally broad spread of semantic activation	Yes	Yes ^{*****}	No	No	
Same as controls	Normal semantic priming	No	No	No	Yes	
Larger (i.e., more negative) than controls	Overly constrained semantic network	No	No	Yes	No	
Not reported, or not collected						

* All patients were medicated.

** All but one patient was medicated.

*** Thought disordered patients had more negative N400 than healthy controls.

**** This summary is for medicated patients only (page 1137).

***** Indirectly primed words were the same as Unprimed words in this paper.

Table 2

Sample Demographics.

Variable	Normal Control Subjects (n=29)		Schizophrenia Patients (n=26)		Independent Group t-test p-value
	Mean	SD	Mean	SD	
Age (years)	37.29	12.62	35.19	13.52	p = .83
Education (years)	16.24	2.15	12.54	1.48	p<.001
Parental Socioeconomic Status ^a	32.10	16.28	40.8	16.5	p<.06
Average PANSS [*] Symptom Scores					
Positive Symptoms			2.19	0.68	
Negative Symptoms			2.04	0.70	
Disorganization Symptoms			1.81	0.62	
Age at Illness Onset ^{***}			21.04	6.78	
Duration Illness ^{**}			18.07	15.15	
Number of Controls					
Number of Patients					
Handedness ^o					
Right	27		26		
Left	2		0		
Gender					
Men	23		21		
Women	6		5		
Diagnosis					
Undifferentiated Schizophrenia			4		
Paranoid Schizophrenia			19		
Residual Schizophrenia			3		
Antipsychotic Medication type					
Atypical			22		
Typical			1		
Atypical +Typical			3		

* Missing data for 1 patient. PANSS = Positive and Negative Symptom Scale.

** Missing data for 2 patients.

^a Determined using the scale of Hollingshead and Redlich (1958). Smaller numbers reflect a higher socio-economic status.

^d Determined using the scale of Crovitz and Zener, (1962).