Effects of word frequency on semantic memory in schizophrenia: Electrophysiological evidence for a deficit in linguistic access

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A B S T R A C T

Background: Abnormal storage and/or access are among the hypothesized causes of semantic memory deficit in schizophrenia. Neuropsychological and connectionist models have emphasized functional systems that serve the processing of word meaning and frequency: semantic storage disturbance is presumed to result from weak representations of word meaning; defective access is assumed to result from compromises to pathways that activate word frequency knowledge. Candidate biological systems include neuromodulatory pathways that normally function to enhance neural signals (e.g., cholinergic system). Electrophysiological responding may be informative regarding the storage-access distinction for schizophrenia.

Methods: Visual event-related potentials were recorded for 14 schizophrenia outpatients receiving atypical antipsychotics, and 14 healthy controls group-matched to patients on age, gender, and demographics. N400 was elicited using an incidental semantic priming paradigm, in which semantic relatedness and word frequency were varied, and a letter probe task.

Results: Compared to controls, patients showed reduced N400 (µV) discrimination of semantic relatedness. Groups also showed different patterns of N400 to word frequency. Controls' N400 increased in negativity as words decreased in frequency of occurrence, while patients did not show a linear relationship between N400 and word frequency. Groups also differed for N400 to frequently occurring words. Patients exhibited increased negativity to high and very high frequency words, compared to controls. A subgroup of patients receiving antipsychotics with known affinity binding for muscarinic receptors (clozapine and olanzapine) showed significant albeit limited N400 priming, but their N400 to word frequency remained nonsignificant.

Conclusions: Results suggest a deficit in semantic access for schizophrenia, as well as an influence of neuromodulators on the activation of connections among semantic representations. Cumulative findings indicating only limited N400 priming for patients receiving either typical or atypical antipsychotics support the hypothesis that semantic memory deficit represents a trait marker for schizophrenia.

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1. Introduction

Memory impairment is an associated feature of schizophrenia with deficits observed across a broad range of memory systems and processes, including disturbance to semantic memory (reviews: Aleman et al., 1999; Condray, 2005; Kuperberg et al., 2010; Minzenberg et al., 2002). Semantic memory represents a person's cumulative knowledge about the world (e.g., name of the first president of the United States, defining features of tables, etc.) (Tulving, 1972; Schacter et al., 2000), and, in this respect, provides a dynamic record of a person's ongoing learning and experience. Language serves as an important interface between the environment, learning, and memory, and is regarded by some theorists as a key cognitive input system (Fodor, 1983). Language impairment involving deficits in listening and reading may predate the onset of schizophrenia (Cannon et al., 2002; Crow et al., 1995), and is observed in patients across clinical states and medication regimens, and in their healthy family members (reviews: Condray, 2005; DeLisi, 2001; Kremen et al., 1994; Minzenberg et al., 2002). Storage and activation of linguistic representations within semantic memory are therefore an important focus for theories of cognition in schizophrenia.

1.1. Nature of the semantic memory deficit for schizophrenia: storage versus access?

A distinction between semantic storage and access has long been emphasized in cognitive psychology and neuropsychology, and, more recently, in computational neuroscience, and this emphasis could be informative for our efforts to understand semantic memory in schizophrenia. Elizabeth Warrington and her colleagues early...
dissociated word comprehension deficit due to deficient memory access (access/refractory impairment) and deficit caused by a degradation of stored memorial representations (degraded-storage deficit). This contrast evolved from their assessments of patients who presented to neuropsychology clinics with impairment in word comprehension (Warrington, 1975; Warrington and Shallice, 1979; Warrington and Cipolotti, 1996). Their examinations of patient performance profiles suggested that word comprehension deficit differs as a function of the type of neurological disorder. A storage deficit involving cell-based degradation of semantic representations was proposed for degenerative conditions, such as Alzheimer’s dementia, Pick’s disease, and viral infections. In contrast, vascular etiologies were thought to underlie access dysphasias characterized by only sporadic availability of semantic representations. Based on their cumulative data, Warrington et al. emphasized four factors that distinguish the two profiles: semantic relatedness (priming); word frequency; presentation rate; and response consistency (trial-by-trial variability for identical words). A deficit in the access of semantic memory was hypothesized to involve reduced memory accuracy for words presented at rapid rates, no accuracy advantage for high frequency words, an atypical accuracy advantage for semantically unassociated words (atypical or negative priming), and inconsistent accuracy across trials and time points. In contrast, a disorder of semantic storage was proposed to involve a primary disturbance of knowledge about semantic relationships, with no accuracy advantage for either associated or unassociated words (absent priming), but with preserved word frequency effects and response consistency. These contrasting performance profiles as proposed by Warrington and Cipolotti (1996) are summarized in Table 1.

The connectionist model developed by Gotts and Plaut (2002) extended the access/refractory-degraded/store distinction by simulating damage to mechanisms that may account for these deficits; damage to cells that encode and connect semantic memory representations, and damage to slow-acting neuromodulatory pathways that normally function to enhance neural signals otherwise attenuated by refractory processes, including disruptions to the influence of acetylcholine and norepinephrine. By “damaging” neuromodulation and sparing stored connections and, in turn, by damaging stored connections while sparing neuromodulation, their model produced performance that was consistent with the data reported by Warrington and Cipolotti (1996) for the access-refractory and degraded-store profiles, respectively. An important aspect of the Gotts–Plaut model for semantic memory in schizophrenia is its emphasis on the neuromodulatory influence of acetylcholine on transmitter release at pre-synaptic cells and the subsequent activation and sensitivity to excitatory input at post-synaptic cells. Acetylcholine is known to influence learning and memory (reviews: Everitt and Robbins, 1997; Hasselmo, 2006), with muscarinic acetylcholine receptors playing an important role in its effects on cortical function and sensitivity to excitatory input at post-synaptic cells. Acetylcholine receptor class may be important for schizophrenia-related cognitive reductions. Reduced muscarinic receptor density and binding have been observed for schizophrenia patients in brain regions that serve memory and attention, including hippocampal formation, superior temporal gyrus, and dorsolateral prefrontal and anterior cingulate cortices (Crook et al., 2000, 2001; Dean et al., 2002; Deng and Huang, 2005; Raedler et al., 2003b; Zavitsanou et al., 2004). Moreover, a negative association has been observed between postmortem choline acetyltransferase activity and (antemortem) cognitive function in schizophrenia patients (Powchik et al., 1998). Because administration of anticholinergic agents is associated with reduced accuracy of memory and cognitive performance in schizophrenia patients (Strauss et al., 1990; Sweeney et al., 1991), and because antipsychotic medications vary in their anticholinergic load (Minzenberg et al., 2004), it is important to consider semantic memory response within the context of their mechanisms of action. A characteristic of some atypical antipsychotic agents, such as clozapine and olanzapine, is their affinity for muscarinic acetylcholine receptors (Chew et al., 2006; Raedler et al., 2000, 2003a). While these atypical antipsychotics may be generally superior to typical antipsychotics, both for overall cognition as well as for specific domains (attention, learning, verbal fluency, and processing speed) (see meta-analyses by Woodward et al., 2005, 2007), their influence on electrophysiological indices of semantic memory function, such as the N400, has not been determined for schizophrenia. Given the well-established relationship between acetylcholine and memory function, examination of the effect of atypical agents known to have affinities for muscarinic receptors may inform our theories of semantic memory in schizophrenia.

1.2. Dissociation of structure and process

Recent efforts to clarify semantic memory impairment in schizophrenia as either a deficit of storage or a disturbance of access provide a mixed picture. Based on behavior response accuracy and latency during performance of a semantic priming-lexical decision task, Rossell and David (2006) observed exaggerated word frequency and semantic relatedness (hyperpriming) effects for schizophrenia patients, as well as response consistency across test sessions. As reflected in Table 1, this pattern includes aspects of both storage and access deficits as defined by Warrington and Cipolotti (1996), Laws et al. (2000) used picture naming of line drawings, which portrayed a range of commonly-to-rarely-occurring objects, to evaluate semantic memory in chronic schizophrenia patients. Group performance accuracy was consistent across test sessions and influenced by object familiarity (word frequency), and additional analyses of individual patient’s performance suggested the majority were characterized by these characteristics of a storage deficit. A few investigators have evaluated the storage disorder hypothesis by comparing semantic memory performance between schizophrenia patients and patients with Alzheimer’s disease, which is assumed to involve a primary disturbance of semantic storage. McKay et al. (1996) administered a

Table 1
Patterns of response accuracy produced by hypothesized semantic storage and semantic access disorders as a function of neurological etiology.

<table>
<thead>
<tr>
<th></th>
<th>Storage disorder — degenerative etiology (degradation of semantic representations)</th>
<th>Access disorder — vascular etiology (temporary unavailability of stored semantic representations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation rate</td>
<td>Slow = Fast</td>
<td>Slow &gt; Fast</td>
</tr>
<tr>
<td>Word frequency</td>
<td>High frequency = Low frequency</td>
<td>High frequency = Low frequency</td>
</tr>
<tr>
<td>Semantic relatedness (within-category word-picture matching)</td>
<td>Related = Unrelated (absent priming)</td>
<td>Related = Unrelated (negative priming)</td>
</tr>
<tr>
<td>Response consistency across trials</td>
<td>Consistent</td>
<td>Inconsistent</td>
</tr>
</tbody>
</table>

(Adapted from Warrington and Cipolotti 1996).

a Degenerative conditions including Alzheimer’s dementia, Pick’s disease, and viral infections.

b Acquired dyslexias.

c Storage-disorder patients showed semantic relatedness effect for cross-category pairs only.
battery used in dementia research (Semantic Memory Test: Hodges et al., 1992) to groups of schizophrenia patients that differed in clinical severity and age. Patients’ performance declined with increasing clinical severity and age, and the performance of elderly schizophrenia patients was comparable to that of Alzheimer’s patients. More recently, Doughty and colleagues (2008) selected schizophrenia patients who evidenced cognitive impairment and compared their profile of semantic memory deficits with the profile of Alzheimer’s patients. Performance accuracy of the two groups differed for semantic memory reflected in naming, word-picture matching, and category sorting tasks (Alzheimer’s − Schizophrenia), and a greater proportion of Alzheimer’s patients exhibited a significant word frequency effect compared to patients with schizophrenia (46% versus 14%, respectively). Doughty et al. concluded the profile of deficits observed for schizophrenia patients did not conform to a typical disorder of semantic storage. Thus, the literature to date suggests schizophrenia may be associated with a primary deficit in semantic storage, although a complete dissociation of structure and process may not characterize this cognitive impairment fully.

1.2.1. Measurement

The type and time window of response measure, which likely capture various aspects of the processing stream, may be important factors in tests of the storage-access distinction. To date, the focus of schizophrenia studies addressing the storage-access distinction has involved behavioral data, and it is therefore unknown whether the physiological responding that occurs prior to behavioral response reflects the same admixture of storage and access disturbance described above. For example, although Alzheimer’s disease is generally assumed to involve a primary disturbance of semantic storage (Crutch and Warrington, 2006; Hodges et al., 1992; Salmon et al., 1999; Warrington and Cipolotti, 1996), the cumulative findings show this population is also characterized by disruptions to semantic access (early work reviewed in Nebes, 1989; Rogers and Friedman, 2008). Results from event-related potential (ERP) studies underscore this point. Ford et al. (2001) reported that patients with Alzheimer’s disease, who showed anoma involving reduced naming accuracy, nevertheless produced a typical or normal N400 differentiation of semantic context during a picture-word verification task. A similar finding was reported by Schwartz et al. (2003) who used semantically congruous and incongruent sentence endings to elicit the ERP. In the Schwartz et al. study, Alzheimer’s patients also showed the typical ERP semantic incongruity effect, although they differed from controls with respect to temporal course. Of interest, the scalp distribution of these ERP effects was found to differ between Alzheimer’s patients and controls in both the Ford et al. and Schwartz et al. studies.

1.2.2. Neuromodulatory processes and antipsychotic medication

The effect of neuromodulation on transmitter release may provide an account, in part, for the mixed disorder pattern observed for schizophrenia. As noted above, antipsychotic drugs commonly administered to schizophrenia patients vary in their pharmacodynamic profiles, with the primary action of typical antipsychotics, such as haloperidol, believed to involve antagonism of dopamine (DA) D2 receptors in mesolimbic and mesostriatal regions. In contrast, the action of atypical antipsychotics is thought to include a combination of muscarinic receptor antagonism, 5-hydroxytryptamine (5-HT2A/DA receptor antagonism, and antagonism of extrastriatal D2 receptors in limbic and thalamic regions (Meltzer, 2004). It has been suggested that the increased DA and acetylcholine release in prefrontal cortex observed for atypical antipsychotics may account for their advantageous effects on cognition (Meltzer, 2004). Medication regimens for schizophrenia patients in the studies of the storage-access distinction discussed above involved a variety of pharmacological regimens. The Rossell and David (2006) study included patients receiving typical (28%) and atypical (66%) antipsychotics, as well as patients who were medication free (6%). The Doughty et al. (2008) study also included schizophrenia patients who were receiving typical (5%) and atypical (80%) antipsychotics, as well as patients who were medication free (10%). An additional patient was receiving lithium. The studies reported by Laws et al. and McKay et al. did not include medication information.

1.3. Study hypotheses

The present study examined two aspects of the storage-access distinction, semantic relatedness and word frequency, for a sample of schizophrenia patients and age- and demographically-matched normal controls. All patients were receiving atypical antipsychotic medications at the time of ERP testing. The N400 component was the response measure of theoretical interest. The study design involved an incidental semantic priming paradigm in which semantic relatedness and word frequency were varied, and included a behavioral task (letter probe verification) that was resource demanding, independent of the psycholinguistic factors of interest, and biased toward a shallow level of processing (orthography). It is therefore assumed that the N400 priming effects elicited by this paradigm reflect primarily automatic processing. Our general hypothesis was that patients would exhibit disturbance, indexed by N400, to both storage and access of semantic memory. Firstly, based on the prior behavioral studies of the storage-access distinction in schizophrenia, as well as the extensive literature concerning N400 priming in this patient population, we predicted that patients would show a deficit in semantic memory storage, which would be reflected in a reduced and/or absent N400 semantic priming effect. Secondly, contrary to findings from prior behavioral studies, we predicted patients would show abnormal semantic access reflected in a reduced or absent N400 word frequency effect. Finally, results from neuropsychological studies of schizophrenia patients receiving atypical antipsychotics would lead to the expectation that semantic memory will benefit from atypical agents.

Based on prior work (Condray et al., 1999; 2003), however, we hypothesized that semantic memory, indexed by N400, represents a risk marker for schizophrenia (endophenotype: Braff et al., 2007; Gottesman and Gould, 2003; mediating vulnerability trait: Nuechterlein et al., 1992), and would therefore remain significantly compromised even in patients receiving atypical antipsychotic drugs. Secondary analyses were conducted to address the possibility that neuromodulation due to acetylcholine may influence semantic access (Gotts and Palt, 2002). This possibility was evaluated indirectly by restricting these analyses to a subgroup of patients receiving atypical antipsychotics known for their affinity binding for muscarinic acetylcholine receptors (clozapine and olanzapine).

2. Materials and methods

2.1. Sample

All study participants were evaluated with the Structured Clinical Interview for DSM-IV (First et al., 1995–1996), and psychiatric diagnoses (American Psychiatric Association, 2000) were assigned during case conferences. General study inclusion requirements were: American English was the first language learned, no history of major medical or neurological disorders, and vision corrected to 20/20. Schizophrenia patients were excluded if they met DSM-IV criteria for current substance use disorder. Participants were selected from the database of a larger family study based on the presence of sufficient numbers of artifact-free event-related potential (ERP) trials during the semantic priming study (see below), and patients were further selected based on their medication regimen at ERP testing (atypical antipsychotics). Table 2 presents the characteristics of the sample. Patient and control groups (50% female) did not differ with respect to age, education, spelling ability, short-term memory span, parental...
Groups differed for single-word reading (WRAT-3: testing, as follows: mood stabilizers (daily). Some patients were receiving additional medications at clozapine. One patient was also receiving benztropine mesylate (1 mg socio-economic status, handedness, or race (all Table 2 word frequency-semantically associated=45 trials; etc.).

Word frequency-semantically unassociated=45 trials; very high low word frequency-semantically associated=45 trials; very low word frequency-semantically unassociated=45 trials; very high word frequency-semantically associated=45 trials; etc.).

Patients with schizophrenia disorder (n = 14) were recruited from Western Psychiatric Institute and Clinic outpatient programs. 13 were diagnosed with schizophrenia and 1 was diagnosed with schizo-affective disorder. For patients at ERP testing, the mean dosage of risperidone (very low, low, high, and very high) was 311.9 mg daily (median=300; sd=±103.45; range: 150–450), with the number of patients receiving each specific drug as follows: risperidone (n = 4), olanzapine (n = 7), clozapine (n = 1), and quetiapine (n = 1). One patient was receiving both ziprasidone and clozapine. One patient was also receiving benzotropine mesylate (1 mg daily). Some patients were receiving additional medications at testing, as follows: mood stabilizers (n = 4), antidepressants (n = 9), and anti-anxiety medications (n = 2). Normal controls (n = 14) were diagnosed as having no lifetime DSM-IV Axis I or II disorders. Only one normal control reported taking medication within the 24 h before ERP testing (levonorgestrel and ethinyl estradiol). Each study participant was paid $140 for participation. Following explanation of study procedures and before testing, all participants provided written, informed consent to participate using University of Pittsburgh Institutional Review Board approved consent forms.

2.2. Study design

The repeated measures study design involved an incidental semantic priming paradigm, with presentation of word pairs that varied in semantic association and word frequency followed by the behavioral task stimuli (letter probes), which were unrelated to the psycholinguistic features of the word pairs. Prime-target word pairs (n = 360) were created to represent four levels of word frequency (very low, low, high, and very high) and two levels of semantic association (associated and unassociated), which resulted in eight combinations of word frequency and semantic association. Each of the eight word-pair combinations was represented by 45 trials (e.g., very low word frequency-semantically associated=45 trials; very low word frequency-semantically unassociated=45 trials; very high word frequency-semantically associated=45 trials; etc.).

2.3. Stimuli

2.3.1. Word frequency

Word pairs were created to represent a wide range of word frequencies as reflected in word frequency counts. Prime and target words within each pair were matched for word frequency (e.g., low frequency target paired with low frequency prime). Each word was used only once. Prime words were nouns selected to represent the four word frequency intervals used in the Postman (1970) study of discrete or single-word association. These frequency intervals were based on the Thorndike–Lorge (1944) Magazine corpus (L-column) involving 4.5 million words, and represented half-step increases on a logarithmic scale: very low=1–3 occurrences/4.5 million possible occurrences; low=10–33; high=100–333; very high=1000–3333. Researchers commonly report word frequencies based on the Brown Corpus, and descriptive statistics are also provided based on the Francis–Kucera (1982) count of this corpus involving 1 million occurrences. Median frequencies of prime words for each frequency interval based on the Thorndike–Lorge count are: very low=2; low=19.5; high=180; and very high=1591. Target words were also selected from the same word frequency intervals, and the median frequencies for each frequency interval based on the Thorndike–Lorge count are: very low=2; low=16; high=175; and very high=1172.5. Median frequencies of prime words for each frequency interval based on the Francis–Kucera count are: very low=1; low=3; high=32.3; and very high=289.5. The median frequencies of target words for each frequency interval based the Francis–Kucera count are: very low=1.5; low=7; high=31.5; and very high=293. For associated target words, the following exceptions to these frequency intervals were imposed by the nature of word association norms (see Semantic context below): very low frequency (13%=0 occurrences/4.5 million possible occurrences; 15%=7–15 occurrences); low frequency (4%=0–1 occurrences; 22%=6–9 occurrences; 1 word=55 occurrences); very high frequency (>500 occurrences).

Word frequency (4 levels) of word pair stimuli was tested for each of the experimental combinations of prime-target (2 levels) and semantic association (2 levels). ANOVA (word frequency×prime-target×semantic association) showed the word frequency factor (natural log transformation) was highly significant (F1, 111 = 5534.12, p<0.001, linear trend). In contrast, word frequency did not differ between primes and targets (p=n.s.), associated and unassociated word pairs (p=n.s.), or any of the combinations of these factors (no significant interactions involving word frequency, prime-target, and semantic association: all p-values=n.s.).

2.3.2. Semantic context

Semantically associated word pairs (n = 180) were created using published word association norms (Battig and Montague, 1969; Jenkins, 1970; Marshall and Cofer, 1970; Nelson et al., 1998; Postman, 1970) and the considerations detailed above regarding word frequency. An equivalent number of semantically unassociated word pairs (n = 180) were created by randomly ordering additional words selected on the basis of word frequency with the restriction that the resulting pairs were not semantically related. Two strategies were used to verify degree of semantic association for word pairs: (1) strength of association for semantically associated pairs based on tests of discrete or single-word association reported in published sources; (2) independent ratings of the degree of semantic relatedness for each of the 360 word pairs used in the present study.

(1) Strength of association from published sources: Most of the associated word pairs (69%) were characterized by a direct or forward associative relationship, as determined in tests of discrete or single-word association (*"provide the first word that you think of": Jenkins, 1970; Marshall and Cofer, 1970; Nelson et al., 1998; Postman 1970). Mean associative strength
for these discrete association pairs was 0.113 (median/sd = 0.047/0.162; range: 0.001–0.80). The remainder of associated word pairs (31%) included 31 pairs characterized by overlapping associative relationships most of which involved associates to shared semantic categories, such as beaver–skunk within the category of ‘four-footed animal’ (from Battig and Montague 1969). These overlapping pairs showed a mean associative strength of 0.02 (median/sd = 0.002/0.066), computed in the manner described by Nelson et al. (1998). Very low and low frequency words are underrepresented as discrete free-association responses in published word association norms, which necessitated use of lexicon source materials (Thesaurus synonyms and related words) for creating the remaining 24 associated word pairs.

(2) Semantic relatedness ratings: Independent ratings of prime-target word relatedness were recorded for each of the 360 word pairs used in the present study. Ratings were made by a subset of the study sample (n = 17; 53% no-lifetime psychiatric disorder and no family history of schizophrenia). Instructions were:

Mean ratings by all 17 individuals (diagnoses combined) for the 180 semantically unassociated word pairs ranged between ‘moderately related’ and ‘highly related’ (mean/sd = 4.2/0.58; range: 3.3–5.6); mean ratings for the 180 semantically unassociated word pairs ranged between ‘not related at all’ and ‘somewhat related’ (mean/sd = 1.5/0.35; range: 1.2–2.5). Relatedness ratings for associated and unassociated word pairs differed significantly (F1,16 = 251.87, p < 0.001). Mean ratings by normal controls only (n = 9) for the 180 semantically associated word pairs ranged between ‘moderately related’ and ‘related’ (mean/sd = 4.3/0.41; range: 3.5–4.9); mean ratings for the 180 semantically unassociated word pairs ranged between ‘not related at all’ and ‘somewhat related’ (mean/sd = 1.6/0.44; range: 1.2–2.5). Controls’ relatedness ratings for associated and unassociated word pairs also differed significantly (F1,8 = 214.93, p < 0.001).

2.4.2. Procedure

Study participants were tested in one session that lasted approximately two hours, including electrode application, task completion, and electrode removal. Following vision screening and electrode application, a set of practice trials (n = 5) immediately preceded the critical test trials (n = 360). Each trial sequence consisted of a prime word followed by the target word followed by the letter probe task, which was similar to the behavior task used previously by Kutna and Hilliard (1989). Stimuli appeared in lowercase letters (white letters on black screen) and were centered on a computer screen. Subjects were seated 55 cm from the screen (eye-to-screen) with their chins in a fixed position. The height of words was 0.63", and the width of words varied from 1.3" to 5.3". Background illumination of the stimulus field (blank screen) was 0.4 foot candles; when single words appeared on the screen, the luminance varied from 0.3 to 1.3 cd/m2 depending on number and content of letters. Word pairs were presented in blocks that included trials representing each experimental condition (7 blocks of 48 trials per block; 1 block of 24 trials), with block assignment and order of within-block presentation randomized. A 2-minute rest interval occurred between each block. Each word was presented only once, and each target was preceded by its prime. Each letter probe followed its word pair, and subjects were instructed to decide if the letter was present in either of the words in the pair. Subjects were not informed that words would vary in their degree of semantic association or frequency of occurrence in the lexicon. Subjects were instructed to be as accurate as possible, and were allowed up to 3 s to make their response. Each trial began with the presentation of the prime for 200 ms followed by an inter-stimulus interval (ISI) of 800 ms during which only a blank screen appeared. The target, which immediately followed the prime-target ISI, remained on the screen for 200 ms and was followed by a post-target ISI of 1000 ms after which the letter probe was presented; for example: admire (ISI) amuse (ISI) r? The letter probe remained on the screen until the inter-trial interval (ITI) of 1800 ms was triggered by the subject’s response or until 3 s had elapsed, whichever occurred first.

2.4.2.1. Electroencephalogram (EEG) recording and analysis

The visual EEG was recorded from 24 sites (nose-tip electrode served as the reference; forehead electrode served as ground) using Ag/AgCl electrodes inserted in a cap (Physiometrix, Inc.). Electrode placements included midlines (Fz, Cz, Pz and Oz), laterals (F3/4, C3/4, P3/4, O1/2), temporals (T3/4, T5/6), frontal sites (Fp1/2, F7/8), and mastoids (A1/2). Horizontal and vertical electro-oculogram (EOG) was recorded from electrodes placed at the outer canthi of both eyes, and above and below the right eye. Channels were amplified × 10,000 K with a Sensorium EPA-6 amplifier (bandwidth = 0.02–100 Hz). Impedances were <30 kΩ. The EEG was digitized at 250 samples/s (4 ms) using EEGSYS software. EEG sampling began 200 ms prior to the onset of each prime stimulus and continued for 1000 ms post-target stimulus, which provided an analysis epoch of 2400 ms per word-pair trial. Eye movement artifacts were corrected using software developed by Miller et al. (1988) for the Gratton et al. (1983) procedure and adapted in the Pittsburgh laboratory for use with the EEGSYS software. Trials including artifacts >500 μV were immediately rejected before vertical EOG correction; additional trials were rejected before horizontal EOG correction if any remaining artifacts ≥150 μV. In addition, every trial was visually inspected by R.C. and S.R.S., who were blind to identity and group membership, and any trials containing uncorrected artifacts were removed and excluded from further analyses. Averaged waveform responses were computed from artifact-free single trials.

Mean area integration measures were computed using signed deviations from the baseline amplitude (median amplitude for the 200-ms pre-word stimulus sample) at all electrode sites for both
primes and targets under each experimental condition. Successive latency or time windows of interest were set based on prior work regarding visual semantic priming, and the primary focus is the N400 component measured in the time window from 300 to 500 ms post-target word stimulus.

Minima for inclusion in the analyses were ≥ 19 artifact-free event-related potential trials for each of the eight psycholinguistic conditions (2 levels of semantic association and 4 levels of word frequency). The initial analyses were based on the mean integrated N400 amplitude from trials in which a behavioral response for the letter probe task occurred within 3 s. The mixed within-subjects factorial design ANOVA included the between-subjects factor of diagnosis (schizophrenia, no lifetime diagnosis of psychiatric disorder), and the repeated or within-subjects factors of semantic association (associated, unassociated) and word frequency (very low, low, high, and very high). Separate analyses were conducted for each electrode pair (midline, lateral, and temporal), which were selected based on prior studies of linguistic processing (Kutas and Hillyard, 1989; Van Petten and Kutas, 1990; Van Petten et al., 1999), and site was entered as an additional repeated measure. Only significant F ratios are reported. Greenhouse–Geisser correction was applied where appropriate, and corrected degrees of freedom are reported for the associated F-ratios.

The standard significance level of α = 0.05 was used for overall ANOVAs, and theoretically meaningful comparisons followed findings of significant results based on the overall ANOVAs.

As an additional analytic strategy, time windows of significant differences were determined for the contrasts of theoretical interest by using statistical tests at each sampling point along the ERP waveforms recorded at each electrode. To control Type I error for this large number of tests, Guthrie and Buchwald’s (1991) technique was also used, as in our previous publication (Condray et al., 2003). This technique allows segments of waveforms that differ significantly to be identified empirically without a priori specification of those regions, while controlling for Type I error. Monte Carlo simulations were used to estimate the number of consecutive significant differences large enough to be judged not to have occurred by chance with p < 0.05 given the temporal autocorrelation of the data. Contiguous sample-by-sample tests are considered replications. In the present application of this technique, t tests were performed at each point along the difference waveform for the 1 s post-target word epoch. A minimum number of significant consecutive t tests to consider a region-wise difference as significant was derived by simulations that accounted for the temporal autocorrelation for each difference waveform (rxx = 0.97 for both condition-related and difference waveforms across electrodes (std(rxx) < 0.01), and the assumption of five principal component analysis factors associated with the task signal. For each test, 3 runs of 1000 simulations were run to create distributions from which the number of consecutive t tests, significant at p < 0.05 in less than 5% of the cases was extracted, taking the least conservative estimate; nearly identical estimates were produced for all runs. This procedure thus controlled family-wise α at p < 0.05. For each semantic condition, 188 ms (47 samples) of consecutive significant differences at p < 0.1 were required for the waveforms to unassociated and associated target words to be considered statistically significantly different at p < 0.05 using paired t-tests. Similarly, 196 ms (49 samples) of significant consecutive differences at p < 0.1 were required for the waveforms to each word frequency condition between the two groups to be considered statistically significantly different at p < 0.05 using independent samples t-tests.

3. Results

3.1. ERP data

The number of artifact-free ERP trials did not differ (all p-values = n.s.) between patients and controls (mean/sd = 298.4/50.3 and 301.9/42.5, respectively), or between the different levels of semantic association (associated = 149.6/23.2; unassociated = 150.5/22.9) and word frequency (very low = 75.6/12.9; low = 75.1/10.8; high = 74.7/12.5; very high = 74.8/11.2). The two groups also did not differ under the different combinations of semantic association and word frequency (mean/sd): associated pairs — very low = 37.2/6.5, low = 37.9/5.6, high = 37.2/6.3, and very high = 37.3/5.9; unassociated pairs — very low = 38.4/6.6, low = 37.2/5.6, high = 37.5/6.7, and very high = 37.5/5.7.

3.1.1. N400 component

Table 3 presents the mean integrated N400 amplitude (300–500 ms post-target word) elicited at lateral electrodes, collapsed across hemisphere, to associated and unassociated target words under each word frequency condition for each diagnostic group. Results of analyses are reported below and organized according to the psycholinguistic variables of interest. Because the task stimuli were independent of the psycholinguistic factors of interest, results are reported first for N400 elicited during all artifact-free ERP trials regardless of behavior response accuracy, and followed by results for N400 elicited during correct-response trials only. Figs. 1–6 present the grand mean ERP waveforms for each diagnostic group under each semantic association and word frequency condition.

<table>
<thead>
<tr>
<th>Electrode site</th>
<th>Word frequency</th>
<th>Very low</th>
<th>Low</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3/4</td>
<td>−0.583 (0.549)</td>
<td>−0.329 (0.611)</td>
<td>−0.365 (0.674)</td>
<td>−1.623 (0.726)</td>
<td></td>
</tr>
<tr>
<td>C3/4</td>
<td>−1.185 (0.637)</td>
<td>−0.662 (0.539)</td>
<td>−0.258 (0.755)</td>
<td>−1.850 (0.828)</td>
<td></td>
</tr>
<tr>
<td>P3/4</td>
<td>−1.674 (1.272)</td>
<td>−1.096 (1.187)</td>
<td>−1.121 (1.173)</td>
<td>−2.407 (1.395)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Mean integrated N400 amplitude (μV ± sem) at each lateral electrode (collapsed across hemisphere) under each word frequency and semantic relationship condition in schizophrenia patients (n = 14) and normal controls (n = 14).
3.1.1.1. Diagnosis. Schizophrenia patients and normal controls did not differ for overall amplitude of N400 recorded at any of the electrode chains (all \( p \)-values for the main effect of diagnosis = n.s.).

3.1.1.2. Semantic association. Figs. 1 and 2 present the grand mean ERP waveforms for each semantic condition for schizophrenia patients and normal controls, respectively. The overall ANOVA for N400 recorded at midline electrodes showed a significant semantic association \( \times \) electrode \( \times \) diagnosis interaction (\( F_{2, 58} = 5.53, p = 0.005 \)). Analyses of the simple effects of diagnosis indicated the source of this interaction to be the significant effect of semantic association (N400 priming effect) for controls (\( F_{2, 24} = 3.75, p = 0.043 \); quadratic trend: \( F_{1, 13} = 6.31, p = 0.026 \)). In contrast, patients did not show N400 differences between word frequency levels (\( p = 0.49 \)).

A significant difference between patients’ and controls’ N400 response to word frequency was also observed at temporal electrode sites, (\( F_{3, 72} = 3.41, p = 0.025 \), with their N400 response to very high frequency words the likely source of this effect (patients = \(-2.02 \mu V\) and controls = \(+0.147 \mu V\) : \( F_{1, 26} = 4.16, p = 0.052 \)). (See Fig. 7, Supporting Information, which illustrates the results of these analyses to determine the simple effects of diagnosis on N400 to word frequency recorded at lateral and temporal chains.) The effect of diagnosis on the N400 response to word frequency did not reach statistical significance (\( p = 0.066 \)) at midline electrodes.

3.1.1.3. Word frequency. Figs. 3–6 present the grand mean ERP waveforms for each diagnostic group under each word frequency condition. N400 recorded at lateral electrode sites revealed a significant difference between schizophrenia patients and normal controls under the different levels of word frequency (diagnosis \( \times \) word frequency interaction: \( F_{3, 65} = 3.51, p = 0.026 \)). Simple effects analyses indicated the locus of this interaction to be controls’ N400 discrimination between word frequency levels (\( F_{2, 24} = 3.75, p = 0.043 \); quadratic trend: \( F_{1, 13} = 6.31, p = 0.026 \)). In contrast, patients did not show N400 differences between word frequency levels (\( p = 0.49 \)).

The N400 priming effect differed only marginally at the different levels.
of word frequency and only at midline electrodes (semantic association × word frequency × site interaction: $F_{4, 110} = 2.39, p = 0.051$). Moreover, patients and controls did not differ for their N400 priming effect under the different word frequency levels at any of the electrode chains examined (all $p$-values = n.s.).

3.1.2. Time windows of significant differences along ERP difference waveforms

Results of analyses to identify time windows of significant differences for the ERP contrasts of interest showed effects across the 1 s post-target word recording epoch. Because these effects provide an informative picture of the time course for linguistic access of semantic memory in schizophrenia, results are reported and shown graphically for the entire recording epoch following target word onset. The ERP showed both condition- and group-related variation. Results for these analyses are reported below and organized according to the psycholinguistic factors of interest.

3.1.2.1. Semantic association.

Figs. 1 and 2 show the waveforms elicited by associated and unassociated target words for schizophrenia patients and normal controls, respectively. Table 4 presents the time windows of consecutive significant differences along the difference waveforms for semantic condition (unassociated minus associated words) for each group. Patients’ ERP response differed between unassociated and associated words only at Fp1 and within two time windows: 280 to 360 ms and 450 to 570 ms post-target onset. Although their ERP discrimination is of interest because it conformed to the atypical pattern of negative priming (increased negativity to associated words), the length or number of consecutive differences along the difference waveform did not meet the simulations-derived criterion (188 ms/47 samples) for statistical significance. In contrast, controls showed the typical ERP priming pattern involving enhanced negativity to unassociated words, which occurred at multiple time windows and over diverse regions, with onsets beginning within the N400 window and later windows that extended through the end of the epoch. Most of the consecutive differences along the difference waveform that met the simulations-derived criterion (188 ms/47 samples) for statistical significance had an anterior and bilateral scalp distribution.

The group difference waveforms for each word-pair type (associated and unassociated) are provided in Supporting Information in the online version of this paper (Figs. 8 and 9).

3.1.2.2. Word frequency.

Figs. 3–6 show the waveforms for patient and control groups under each word frequency condition. Table 5 presents the time windows of consecutive significant differences along the group difference waveforms for target words under each word frequency and electrode condition. Schizophrenia patients and normal controls differed significantly in their ERP response under all word frequency levels, which included the following general patterns: For very low frequency words (Fig. 3), patients and controls differed within the N400 time window and across multiple windows beginning at 600 ms and later. The length or number of consecutive differences along the group difference waveform that met the

Fig. 2. Grand mean event-related potentials elicited by associated and unassociated target words for normal controls ($n = 14$) using the incidental semantic priming paradigm. Waveforms represent responses for associated (solid line) and unassociated (dashed line) target words. Positivity is downward. The target word was presented at time zero. Regions of significant differences are highlighted by color bars along the x-axes (light pink, $p < 0.1$; dark pink, $p < 0.05$). As shown in the figure, significant differences were widely distributed across the recording epoch and scalp for controls, which conform to the typical priming pattern of greater ERP negativity to unassociated words. The topography map reflects the probability values for the discrimination between semantic conditions for the N400 time window (300–500 ms post-target onset) across the scalp.
simulations-derived criterion (196 ms/49 samples) for statistical significance appeared over bilateral anterior scalp. For low frequency words (Fig. 4), group differences were observed primarily within the N400 time window over posterior scalp, but the length (number) of consecutive differences along the group difference waveform did not reach the criterion (196 ms/49 samples) for statistical significance. For high frequency words (Fig. 5), the length (number) of consecutive differences along the group difference waveform that met the criterion (196 ms/49 samples) for statistical significance began at 500 ms post-target onset and extended through the remaining recording epoch, and these windows were widely distributed over bilateral posterior scalp. Significant consecutive differences along the group difference waveform for very high frequency words (Fig. 6) also began after 500 ms post-target onset, with the locations of these group effects occurring over left posterior scalp. In summary, patients’ increased ERP negativity over bilateral posterior scalp for high frequency words and over left posterior scalp for very high frequency words is of interest with respect to study hypotheses regarding semantic access in schizophrenia.

3.1.3. N400 component elicited during correct response trials

Mean integrated N400 amplitude (300–500 ms post-target word) was also examined for trials on which a correct response occurred to the letter probe task. As noted, this task was independent of the psycholinguistic conditions of semantic meaning and word frequency, and, as reflected in the behavior data (Table 6), was difficult for both groups resulting in an overall mean accuracy rate of 53.6%. These analyses are therefore based on fewer artifact-free ERP trials per condition than for the analyses based on all artifact-free ERP trials regardless of accuracy, and results must be viewed accordingly. The number of artifact-free correct-response ERP trials did not differ (all p-values = n.s.) between patients and controls (mean/sd = 162.4/ 29.4 and 169.6/24.7, respectively), or between the two groups under the different levels of semantic association (associated = 87.5/15.1; unassociated = 78.6/12.8) and word frequency (very low = 39.0/7.1; low = 39.9/6.0; high = 42.6/8.0; very high = 44.5/8.0), or between patients and controls under the different combinations of semantic association and word frequency (associated word pairs at each word frequency: very low = 20.9/4.2; low = 21.4/3.4; high = 20.7/3.9; and very high = 24.5/5.2; unassociated pairs at each word frequency: very low = 18.2/3.5; low = 18.5/3.2; high = 21.9/4.8; and very high = 19.9/3.5).

Schizophrenia patients and normal controls did not differ for overall amplitude of N400 elicited during correct-response trials at any of the electrode chains (all p-values for the main effect of diagnosis = n.s.). The principal findings for this set of analyses involved the modulation of the N400 response by the combined effects of semantic association and word frequency. For N400 elicited during correct-response trials, the discrimination of semantic relatedness differed between diagnostic groups at the different levels of word frequency for both lateral (semantic association x word frequency x electrode x diagnosis interaction: F3, 118 = 2.60, p = 0.03) and temporal (semantic association x word frequency x electrode x diagnosis interaction: F3, 66 = 3.08, p = 0.04) chains. The source of the interaction effect at lateral sites is likely patients’ increased N400 negativity over posterior scalp to very high frequency unassociated words (F4, 47 = 2.96, p = 0.03), which was not observed for controls’ N400 response (p = 0.35). The source of the interaction effect at
temporal sites is likely the difference in magnitude of patients’ N400 priming response under the different levels of word frequency and scalp sites \((F_{3, 33} =3.28, p =0.04)\), which was not observed for controls \((p =0.51)\). Although the comparisons of patients’ N400 priming response at each word frequency level failed to reveal any statistically significant effects, the magnitude of their N400 discrimination between semantic conditions appeared greatest for low frequency words at posterior temporal sites (Unassociated minus Associated words = -1.63 µV; \(F_{1,13} =4.44, p =0.055\)). No significant effects were observed for N400 elicited during correct-response trials recorded at midline electrodes (all \(p\)-values = n.s.).

3.1.4. Effect on N400 of atypical antipsychotics with affinity binding for muscarinic receptors

An additional set of analyses was conducted that included only those patients receiving atypical antipsychotic drugs for which the pharmacodynamics indicate appreciable affinity binding for muscarinic receptors (Chew et al., 2006; Chengappa et al., 2000). Nine (56% male) of the 14 schizophrenia patients were receiving medications of this type, including clozapine or olanzapine, and the mean dosage (chlorpromazine equivalents: Woods 2003) was 361.1 mg daily (median = 400; sd = ± 60.1; range: 300–450). Results of the within-group repeated measures ANOVAs based on mean integrated N400 amplitude (300–500 ms post-target) recorded at midline electrodes (all \(p\)-values = n.s.).

3.2. Behavioral data

Table 6 shows accuracy rates, false alarms, and decision reaction times for the letter probe task for each diagnostic group under each semantic association and word frequency condition. Results based on the mixed within-subjects factorial design ANOVAs are reported below for each behavioral measure.

3.2.1. Response accuracy (number correct)

Results revealed significant main effects for semantic association \((F_{2, 13} =5.85, p =0.02)\), with the likely source of this effect patients’ N400 discrimination between unassociated and associated words over anterior scalp (mean N400 priming effect at Fz and Cz = -0.58 and -0.97, respectively) compared to the magnitude of their N400 difference between unassociated and associated words over posterior sites (mean N400 priming effect at Pz and Oz = -0.21 and -0.06, respectively). No other effects were observed for the semantic association factor. Moreover, N400 in this sub-group of patients did not discriminate between the different levels of word frequency at any of the electrode chains. Finally, N400 also did not differ under the various combinations of the semantic association and word frequency factors at any of the electrode chains (\(p\)-values = n.s. for all semantic association × word frequency interactions).

![Fig. 4. Grand mean event-related potentials elicited by low frequency target words for schizophrenia patients (n = 14) and normal controls (n = 14) using the incidental semantic priming paradigm. Waveforms represent responses for patients (solid green line) and controls (dotted black line). Positivity is downward. The target word was presented at time zero. Regions of significant group differences are highlighted by color bars (yellow, \(p < 0.1\); red, \(p < 0.05\)) along the x-axes. The topography map reflects the probability values for the differences between groups for the N400 time window (300–500 ms post-target onset) across the scalp.](image-url)
patients: 52%)

Overall accuracy differed between the two groups (controls: 55%;

- \( p(\text{all}(\text{patients}: \text{F}\text{p}) = 0.002) \). The source of the larger priming effect for controls was their

higher rate of accuracy for associated words (controls: 59% versus

patients: 54%: \( p = 0.023 \)) and word frequency (diagnosis×word frequency interaction: \( F_{1, 26} = 5.84, p = 0.001 \)). The simple effects of diagnosis on semantic association and word frequency were examined to clarify these two interaction effects. Diagnosis influenced accuracy associated with semantic or meaning-related information, with larger semantic priming effects observed for controls (unassociated − associated difference = − 7.4%; \( F_{1, 13} = 83.55, p < 0.001 \)) compared to patients (unassociated − associated difference = − 4.1%; \( F_{1, 13} = 15.14, p = 0.002 \)). The source of the larger priming effect for controls was their higher rate of accuracy for associated words (controls: 59% versus patients: 54%; \( F_{1, 26} = 6.68, p = 0.016 \)). Groups did not differ for unassociated words (controls: 51.6% versus patients: 49.9%; \( p = 0.26 \)). The simple effects of diagnosis on accuracy rates under the different levels of word frequency showed a significant linear trend for word frequency for both groups (controls: \( F_{1,13} = 132.63, p < 0.001 \); patients: \( F_{1,13} = 23.27, p < 0.001 \)), with the likely source of this interaction being the group difference for high frequency words (controls: 57.6% versus patients: 51.9%; \( F_{1, 26} = 11.08, p = 0.003 \)). Moreover, the accuracy difference between the word frequency extremes (very high versus very low) was comparable for controls and patients (9.3% versus 7%, respectively) (\( p = 0.19 \)). Finally, patients and controls did not differ under the joint effects of the semantic association and word frequency factors (diagnosis×semantic association×word frequency interaction: \( p = 0.42 \)).

3.2.2. False alarms (incorrect ‘Yes’ responses)

Significant main effects were observed for semantic association (\( F_{1, 26} = 92.75, p < 0.001 \)) and word frequency (\( F_{3, 71} = 17.41, p < 0.001 \)), which showed increased rates of false alarms for unassociated words (semantic priming effect) and for very low and low frequency words. Moreover, the interaction of semantic association and word frequency (\( F_{3, 66} = 79.49, p < 0.001 \)) involved significant semantic priming only for very low (\( F_{1, 26} = 195.59, p < 0.001 \)) and high (\( F_{1, 26} = 92.51, p < 0.001 \)) frequency words. In contrast, negative priming (increased rate of false alarms for associated pairs) was observed for low frequency words (\( F_{1, 26} = 18.49, p < 0.001 \), and absent priming (no difference between the rate of false alarms for associated and unassociated pairs) for very high frequency words (\( p = 0.18 \)). The overall number of false alarms did not differ between groups (controls: 20.5%; patients: 21.6%; \( p = 0.53 \)). However, patients and controls differed for the number of false alarms under the different levels of semantic association (diagnosis×semantic association interaction: \( F_{1, 26} = 9.85, p = 0.004 \)) and word frequency (diagnosis×word frequency interaction: \( F_{3, 71} = 4.68, p = 0.006 \)). Analyses of the simple effects of diagnosis on semantic association showed significant priming effects for both controls (unassociated − associated difference = 7.1%; \( F_{1,13} = 200.54, p < 0.001 \)) and patients (unassociated − associated difference = 3.6%; \( F_{1,13} = 13.22, p = 0.003 \)). Analyses of the effects of diagnosis on the false alarm rate for each word-pair type confirmed the source of this interaction to be the larger priming effect for controls; false alarm rates of patients and
controls did not differ for either associated \((p = 0.14)\) or unassociated \((p = 0.70)\) words. Examination of the simple effects of diagnosis on word frequency indicated that only normal controls showed a significant effect for the word frequency factor \((\text{patients: } p = 0.15; \text{controls: } F_{2, 25} = 27.64, p < 0.001, \text{cubic trend: } F_{1, 13} = 11.57, p = 0.005)\). Finally, the false alarm rates of patients and controls did not differ under the joint effects of the semantic association and word frequency factors \((\text{diagnosis} \times \text{semantic association} \times \text{word frequency interaction: } p = 0.83)\).

### 3.2.3. Decision reaction times

No significant main effects of semantic association or word frequency were observed for decision reaction times \((\text{harmonic means})\). Mean reaction times differed between associated and unassociated words under the different levels of word frequency \((\text{semantic association} \times \text{word frequency interaction: } F_{3, 74} = 20.34, p < 0.001)\), with the likely source of this interaction the negative priming effect \((\text{Unassociated}_{\text{RT}} - \text{Associated}_{\text{RT}} = -75.1 \text{ ms})\) for very low frequency words \((F_{1, 26} = 26.89, p < 0.001)\). Typical reaction time priming effects \((\text{Unassociated}_{\text{RT}} - \text{Associated}_{\text{RT}})\) were observed for all other word frequency levels \((\text{low} = 44.4 \text{ ms}; \text{high} = 35.7 \text{ ms}; \text{very high} = 51.3 \text{ ms}; \text{all } p\text{-values} < 0.02)\). Overall mean reaction time did not differ between patients and controls \((p = 0.09; \text{controls: } 1026.9 \text{ ms versus patients: } 1189.9 \text{ ms})\), nor did the two groups differ for the magnitude of the semantic priming effect \((p = 0.70; \text{patients: } 17.29 \text{ ms and controls: } 10.85 \text{ ms})\). However, response times differed between groups under the different levels of word frequency \((\text{diagnosis} \times \text{word frequency interaction: } F_{2, 62} = 3.25, p = 0.037)\), with controls showing a significant word frequency effect \((F_{2, 29} = 11.97, p < 0.001; \text{linear trend: } F_{1, 13} = 19.21, p = 0.001)\) but patients’ response times not discriminating among word frequency levels \((p = 0.68)\). No other interactions involving the diagnosis factor reached statistical significance.

### 4. Discussion

#### 4.1. Overview

The N400 component was elicited using an incidental semantic priming paradigm, in which semantic relatedness and word frequency were varied, and a letter probe recognition task that was resource demanding, independent of the psycholinguistic factors of interest, and biased toward an orthographic or shallow level of processing. Due to the task-induced bias for orthographic processing, the N400 priming effects elicited by this paradigm are assumed to reflect primarily automatic activation. N400 was compared between schizophrenia patients receiving atypical antipsychotic medications and normal controls who were group-matched to patients on age, gender, and demographic characteristics. Compared to normal controls, schizophrenia patients showed significantly reduced N400 discrimination of semantic relatedness and word frequency. Patients showed very limited N400 differentiation of semantically associated and unassociated word pairs, and the priming that was observed involved the atypical pattern of increased N400 to associated target words \((\text{negative priming})\), and was restricted to left anterior scalp. In contrast, controls showed the typical pattern of enhanced ERP negativity to unassociated target words, which occurred at multiple time windows over diverse scalp regions. Moreover, the two diagnostic
groups showed markedly different patterns of N400 response to word frequency information. Controls exhibited significant discrimination of word frequency, with their N400 amplitude increasing in negativity as target words decreased in frequency of occurrence in the lexicon. In contrast, patients did not show a linear relationship between N400 and word frequency. The groups also differed in their response to frequently occurring target words. Patients exhibited increased negativity to high and very high frequency target words, compared to controls. Additional group differences were observed across the recording epoch and scalp for the ERPs elicited under each word frequency level. Compared to patients, controls showed greater negativity within the N400 time window over fronto-central scalp sites for the extremes of the word frequency range (very low and very high). In contrast, patients showed increased negativity, compared to controls, beginning within the N400 time window and over bilateral posterior scalp for low and high frequency target words, and over left posterior scalp for very high frequency target words. Thus, group differences in ERP response varied temporally and spatially under the different levels of word frequency.

The role of acetylcholine in learning and memory is well established (reviewed in the Introduction), and it has been suggested that the increased dopamine and acetylcholine release in prefrontal cortex that is produced by atypical agents may account for their advantageous effects on cognition (Meltzer, 2004). N400 was therefore additionally examined for a subgroup of patients who were receiving atypical antipsychotic drugs with known affinity binding for muscarinic acetylcholine receptors (clozapine and olanzapine). N400 priming was observed at vertex for this subgroup of patients. However, their N400 did not discriminate the different levels of word frequency. The limited N400 priming response observed in this subgroup receiving clozapine and olanzapine is consistent with the earlier finding for schizophrenia patients who were receiving the typical antipsychotic drug haloperidol (Condray et al., 2003). These combined results therefore suggest that haloperidol, clozapine, and olanzapine may produce similar effects on the N400 semantic priming response in schizophrenia patients. The absence of even a limited advantage for patients’ N400 response to word frequency information during treatment with clozapine or olanzapine is of clinical and theoretical interest.

4.2. Storage versus access deficit in schizophrenia

A question raised at the beginning of this report is whether the storage-access distinction can inform our understanding about semantic memory deficit in schizophrenia. The preponderance of data from previous studies in which the storage-access distinction was examined for this disorder has been interpreted as support for a
storage deficit (reviewed in Introduction). That prior work was based on behavior response measures, and the present N400 study provides information regarding activation occurring earlier in the processing stream. The pattern of N400 responding observed in the present study (see summary in Table 7) is consistent with disturbance to both semantic storage and access as defined by Warrington, Shallice, and colleagues (Table 1). Patients' failure to manifest N400 differentiation of word frequency is strongly suggestive of a disturbance to semantic access; patients' reduced N400 semantic priming is also consistent with a storage disorder. The significant albeit limited N400 semantic priming observed in the subgroup receiving atypical antipsychotics with affinity binding for muscarinic receptors is potentially important.

The most serious of the criticisms of the Warrington et al. storage-access hypothesis has been the lack of a fully developed theory of semantic access (Rapp and Caramazza, 1993), and the connectionist model proposed by Gotts and Plaut (2002), in which semantic access is instantiated in neuromodulatory terms, is significantly advanced this construct. It may therefore be instructive to consider the limited but significant N400 priming effect observed for the subgroup of patients receiving clozapine or olanzapine from the perspective of that model. Gotts and Plaut used a neural refractory mechanism, synaptic depression, to operationalize Warrington and colleagues' functional "refractoriness" hypothesis, in which the ability to use the semantic system is reduced for an abnormally prolonged period of time following activation. The heart of the Gotts–Plaut hypothesis regarding access/refractory impairment involves the idea that semantic access in the neurologically intact brain is determined by central neuromodulatory systems that normally operate to enhance neural signals that are otherwise attenuated by neural refractory processes, such as synaptic depression. Synaptic depression normally occurs when pre-synaptic neurons fire repeatedly resulting in a temporary attenuation in the activation and sensitivity to excitatory input of post-synaptic cells. The degree of synaptic depression in the healthy brain appears to be a function of the influence of slow-acting, long-lasting neuromodulatory processes. Neuromodulators, such as acetylcholine, are known to influence the probability of neurotransmitter release at both excitatory and inhibitory synapses in cortex and neocortex, and, subsequently, to influence the degree of synaptic depression. Thus, acetylcholine may increase the level of activation of post-synaptic neurons as a result of its influence on the probability of transmitter release pre-synaptically. Gotts and Plaut argued that if neuromodulatory systems are compromised, the network will be shifted disproportionately toward synaptic depression. Viewing the N400 responding of patients in the present study within the framework of this set of assumptions suggests the following account: Because neuromodulators such as acetylcholine are known to suppress neurotransmitter release, and because synaptic depression depends on the probability of neurotransmitter release, the presence of acetylcholine is expected to reduce the degree of synaptic depression. Atypical antipsychotic drugs are known to increase acetylcholine in cortex. The significant albeit limited N400 priming observed for the subgroup of patients receiving the atypical agents clozapine or olanzapine may therefore reflect a pharmacologically-induced reduction of synaptic depression within the semantic network.

As a final consideration, schizophrenia patients' semantic priming response was also reduced across behavioral response measures compared to controls. Moreover, patients' responding indicated a reduced (number correct and false alarms) and absent (reaction times) behavior discrimination of word frequency. In contrast, previous studies based on behavioral measures have shown word frequency effects that were greater in magnitude for patients than those observed for controls (Rossell and David, 2006; Titone and Levy, 2004). It is possible that differences in type of experimental task (word identification versus letter-probe recognition) and semantic memory paradigm may account for these inconsistencies across studies. Despite these differences, however, a striking consistency appears between the N400 data from the present study and the accuracy data reported by Titone and Levy. Those researchers showed the source of patients' word identification errors to be high frequency words from high density neighborhoods. That latter finding is generally consistent with our present results showing an increased N400 negativity to very high frequency words for patients compared to controls.

### 4.3. Limitations of present study

Several study limitations must be recognized. Firstly, although the clinical groups of interest were well matched with respect to age, gender, and relevant demographic characteristics, findings from the present study must be qualified on the basis of the modest sample size. Secondly, the present findings based on semantic relatedness and word frequency provide strong electrophysiological support for the presence of a deficit in semantic access for schizophrenia, as well as for disturbance of semantic storage. However, examination of the remaining two criteria originally proposed by Warrington and

### Table 6

Behavioral responding to orthographic probes during incidental semantic priming under each word frequency and semantic relationship condition in schizophrenia patients ($n = 14$) and normal controls ($n = 14$).

<table>
<thead>
<tr>
<th>Schizophrenia patients</th>
<th>Very low</th>
<th>Low</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated words</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct (%)</td>
<td>0.52 (0.05)</td>
<td>0.54 (0.07)</td>
<td>0.51 (0.07)</td>
<td>0.59 (0.11)</td>
</tr>
<tr>
<td>False alarms (%)</td>
<td>0.16 (0.05)</td>
<td>0.25 (0.09)</td>
<td>0.18 (0.07)</td>
<td>0.20 (0.08)</td>
</tr>
<tr>
<td>Reaction times (ms)</td>
<td>1212.5 (231.3)</td>
<td>1175.1 (219.7)</td>
<td>1163.0 (232.6)</td>
<td>1174.5 (189.2)</td>
</tr>
</tbody>
</table>

| Unassociated words     |         |     |      |          |
| Number correct (%)     | 0.46 (0.06) | 0.49 (0.07) | 0.53 (0.06) | 0.52 (0.06) |
| False alarms (%)       | 0.29 (0.07) | 0.19 (0.06) | 0.25 (0.07) | 0.20 (0.07) |
| Reaction times (ms)    | 1150.9 (242.5) | 1227.2 (240.9) | 1194.9 (231.7) | 1212.2 (239.9) |

| Normal controls        |         |     |      |          |
| Word frequency         |         |     |      |          |
| Associated words       |         |     |      |          |
| Number correct (%)     | 0.57 (0.06) | 0.56 (0.05) | 0.56 (0.04) | 0.67 (0.04) |
| False alarms (%)       | 0.13 (0.04) | 0.25 (0.04) | 0.14 (0.02) | 0.16 (0.03) |
| Reaction times (ms)    | 1058.6 (293.3) | 1034.3 (207.9) | 995.7 (253.8) | 957.6 (238.0) |

| Unassociated words     |         |     |      |          |
| Number correct (%)     | 0.46 (0.04) | 0.48 (0.05) | 0.59 (0.07) | 0.54 (0.04) |
| False alarms (%)       | 0.31 (0.05) | 0.22 (0.03) | 0.24 (0.04) | 0.19 (0.04) |
| Reaction times (ms)    | 1010.1 (274.0) | 1070.9 (281.1) | 1035.3 (274.8) | 1013.4 (250.8) |

Mean (SD).

### Table 7

Summary of findings based on the N400 component and behavior response elicited during incidental semantic priming for schizophrenia patients ($n = 14$).

<table>
<thead>
<tr>
<th>N400 (µV)</th>
<th>Absent or reduced</th>
<th>Normal</th>
<th>Exaggerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic priming effect</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word frequency effect</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavioral data</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic priming effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False alarm</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Word frequency effect</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Accuracy</td>
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<td>False alarm</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

X = response compared to normal controls ($n = 14$).
colleagues for the storage-access distinction (presentation rate and response consistency) were not accomplished for this same set of study participants. N400 data on the same individuals are therefore desirable for all four categories of criteria. In particular, the hypothesis that a deficit in access is fundamental to semantic disorder in schizophrenia requires examination of patients’ response variability, which is considered the hallmark of aphasic behavior (Goodglass, 1993; Kolk, 2007). Finally, although important information was supplied regarding the effect of atypical antipsychotic drugs on N400 response to semantic challenge in schizophrenia, it is important to emphasize that patients were also receiving additional medications (mood stabilizers, antidepressants, and anxiolytics). Statements regarding the effects of atypical antipsychotic medications on N400 priming therefore must be tempered by recognition that an atypical agents only contrast was not included.

4.4. N400 semantic priming response as an endophenotype for schizophrenia

The present study provides support for the hypothesis that the N400 response to semantic memory challenge is a candidate risk marker for schizophrenia. Earlier conceptualizations of heritable risk markers included the idea of deficits in diagnosed patients that are modulated by fluctuations in internal state (e.g., symptom exacerbations and remissions; pharmacological agents), but that never fully resolve to normal responding (mediating vulnerability traits: Nuechterlein et al., 1992). The endophenotype construct was more recently developed to reflect characteristics that are close to genetic variation and linked to heritable risk (Braff et al., 2007; Gottesman and Gould, 2003). The criterion for endophenotype status that is relevant for the present data is the requirement that the characteristic is associated with illness, and is stable or trait-related. The cumulative findings from our Pittsburgh laboratory for the N400 priming response measured in schizophrenia patients show consistency across samples and hospitalization status (inpatient and outpatient), behavior tasks (lexical decision, orthography recognition), and type of antipsychotic medication (typical and atypical agents).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.jpysoc.2009.10.010.

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