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Electrophysiological evidence for primary semantic memory functional organization deficits in schizophrenia

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ABSTRACT

N400, an event-related brain potential (ERP) waveform elicited by meaningful stimuli, is normally reduced by stimulus repetition (*N400 repetition priming*), and relatedness between the eliciting stimulus and preceding ones (*relatedness priming*). Schizophrenia patients' N400 relatedness priming deficits suggest impairment in using meaningful prime stimuli to facilitate processing of related concepts in semantic memory. To examine whether this deficiency arises from difficulty activating the prime concept per se, as indexed by reduced N400 repetition priming; or from impaired functional connections among concepts in semantic memory, as reflected by reduced relatedness priming but normal repetition priming; we recorded ERPs from 16 schizophrenia patients and 16 controls who viewed prime words each followed at 300- or 750-ms stimulus-onset asynchrony (SOA) by an unrelated, related or repeated target word, or a nonword, in a lexical-decision task. In both groups, N400s were largest (most negative) for unrelated, intermediate for related, and smallest for repeated targets. Schizophrenia patients exhibited subnormal N400 relatedness priming at the 300-ms SOA, but normal repetition priming at both SOAs, suggesting that their impairment in using prime words to activate related concepts results from abnormal functional connections among concepts within semantic memory, rather than inability to activate the prime concept itself.

1. Introduction

Schizophrenia is associated with abnormalities in the neural processing of relationships between meaningful concepts. According to network models of semantic long-term memory (i.e., our store of knowledge about the world), these concepts are represented as nodes in a neural network with interconnections between related concepts (Collins and Loftus, 1975). When a person encounters a meaningful contextual stimulus such as a word or an object, the corresponding concept node undergoes heightened activation, which then spreads to related concepts, falling off as a function of decreasing relatedness. Activation of related concepts is reflected in facilitated processing of the corresponding stimuli. This *semantic priming* can be measured using the N400 waveform of scalp-recorded event-related brain potentials (ERPs). N400 is a negative voltage deflection, widely distributed over the scalp but maximal at medial centroparietal sites, elicited by any potentially meaningful stimulus (e.g., a word or picture), occurring from approximately 300 to 500 ms and peaking around 400 ms after stimulus onset in healthy young adults. N400 amplitude is reduced (i.e., becomes less negative or even positive) by factors facilitating stimulus processing — such as repetition (Rugg, 1985; Kutas and Federmeier, 2000) or the frequency of a word's usage in its language (Kutas and Federmeier, 2000). Its amplitude is also reduced by semantic relatedness between the eliciting stimulus and preceding contextual stimuli (Kutas and Hillyard, 1980; Holcomb and Neville, 1990). Thus, for example, the target word *MOUSE* elicits a smaller N400 following the related prime word *CAT* than following the unrelated prime *SUN*. Such *N400 relatedness priming effects* (N400 amplitude reductions for related versus unrelated targets) have accordingly been used to index the degree to which activation spreads among related concepts in semantic memory, with reduced amplitude taken to reflect greater activation (all else held constant; Kutas and Federmeier, 2011).

Numerous N400 studies of schizophrenia patients have suggested deficits in making use of meaningful context to facilitate the processing of related concepts. These studies have found larger than normal (more negative) N400 amplitudes to contextually related targets (Niznikiewicz et al., 1997; Strandburg et al., 1997; Kostova et al., 2005; Ditman and Kuperberg, 2007; Kiang et al., 2008; Salisbury, 2008) and/or less than normal N400 relatedness priming effects (Ohta et al., 1999; Kostova et al., 2005; Ditman and Kuperberg, 2007; Kiang

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et al., 2007; Condray et al., 2010) — consistent with deficits in the degree to which meaningful stimuli (e.g., words or sentence contexts) activate related concepts. Moreover, some of these studies have found associations between these N400 abnormalities and disorganized speech (Kostova et al., 2005; Ditman and Kuperberg, 2007) or delusions (Kiang et al., 2007, 2008), in accord with the hypothesis that impaired use of meaningful context to facilitate processing of related items may contribute to these symptoms (Kuperberg et al., 1998; Cohen et al., 1999; McCarley et al., 1999; Kiang et al., 2008).

In contrast, however, some other studies of patients with schizophrenia have reported *smaller* than normal N400 amplitudes to contextually related items, and *increased* N400 relatedness priming effects (Mathalon et al., 2002; Kreher et al., 2008; Salisbury, 2008; Kreher et al., 2009). Importantly, this pattern of results appears specific to short prime-target stimulus-onset asynchronies (SOAs) of ≤350 ms and patients with disorganized speech; and is hence thought to reflect an excess of rapid, automatic spread of activation in the semantic network in disorganized patients in particular (Ditman and Kuperberg, 2007; Salisbury, 2008; Kreher et al., 2009). Thus, this "hyperpriming" is not necessarily mutually exclusive with semantic priming deficits in conditions favoring more controlled or strategic processing (e.g., longer prime-target time intervals) in schizophrenia patients more generally.

Consistent with this dichotomy, N400 studies which have suggested decreased activation of contextually related concepts in schizophrenia have typically employed SOAs of at least 300 ms, including sentence contexts which build up over a more extended period (Strandburg et al., 1997; Ohta et al., 1999; Kostova et al., 2005; Ditman and Kuperberg, 2007; Kiang et al., 2007, 2008; Salisbury, 2008; Condray et al., 2010). This dichotomy parallels that seen in studies of behavioral (reaction time) semantic priming, reviewed, e.g., by Minzenberg et al. (2002) who concluded that "with regard to automatic processes, groups of schizophrenia participants may be composed of individuals with enhanced spreading activation in semantic memory networks," whereas "changes in controlled processing in semantic memory appear more homogeneous," with patients showing "reduced semantic priming effects compared to controls under a number of conditions."

Schizophrenia patients' deficits in activating concepts related to a meaningful prime stimulus could arise from abnormalities at different loci in the information processing stream. For instance, schizophrenia patients might be impaired in extracting orthographic and/or semantic information from the prime stimulus itself. If so, this would prevent normal activation in semantic memory of the prime concept and, in turn, of related concepts. Alternatively, schizophrenia patients could be normal in their ability to make use of a prime stimulus to activate the corresponding concept in semantic memory; this activation, however, might then fail to extend to related concepts in a normal manner, due to abnormal functional organization of concepts within semantic memory. Such an abnormality could stem from aberrant connection strengths and/or generalized noise within neural networks representing associated concepts in semantic memory (Goldberg et al., 1998; Nestor et al., 2001).

In the present study, we used the N400 to seek evidence for each of these two hypotheses. We recorded ERPs in schizophrenia patients and nonpsychiatric control participants (NCPs) while they viewed prime words followed by target words that were either semantically related or unrelated to, or repetitions of, the prime. We expected that, consistent with previous work (Rugg, 1985; Deacon et al., 2004), in NCPs N400 amplitude would be largest (most negative) in response to unrelated targets, smaller (less negative) to related targets, and smallest (most positive) to repeated targets. Furthermore, we hypothesized that if schizophrenia patients have relatively lower-level difficulties in extracting form and/or meaning information from prime stimuli, impairing subsequent activation of the corresponding concepts in semantic memory, then patients would exhibit smaller than normal N400 amplitude reductions for repeated versus unrelated targets (i.e., smaller than normal *N400 repetition priming effects*) — in line with the view that N400 repetition priming indexes ability to make use of the prime stimulus to facilitate subsequent processing of the corresponding concept in semantic memory (Holcomb and Grainger, 2007, 2009; Kutas and Federmeier, 2011). Moreover, we hypothesized that these N400 repetition priming deficits would correlate with concomitant N400 relatedness priming deficits (smaller than normal N400 amplitude reductions for related versus unrelated targets), which would reflect the ensuing subnormal activation of concepts related to the prime concept in semantic memory.

In contrast, if schizophrenia patients are unimpaired in activating concepts in semantic memory corresponding to prime stimuli, but are then deficient in activating related concepts due to a primary abnormality of semantic memory functional organization, then we would expect these patients to exhibit N400 relatedness priming deficits (i.e., smaller than normal N400 amplitude reductions for related versus unrelated targets) in the presence of normal N400 repetition priming.

In addition, we presented prime-target word pairs at two different SOAs, 300 and 750 ms, allowing us to compare the results with those of a previous study in which we found decreased N400 relatedness priming in schizophrenia over these same SOAs (Kiang et al., 2008). Some previous studies have in fact found deficient word N400 repetition priming in schizophrenia patients, but at longer SOAs of 2200 to 3200 ms (Matsuoka et al., 1999; Matsumoto et al., 2001); therefore it was not known whether this abnormality also would be present at the shorter SOAs used in the present study.

2. Methods

2.1. Participants

Participants included 16 outpatients with schizophrenia ($n=11$) or schizoaffective disorder ($n=5$), and 16 NCPs matched for age, sex, and parental socioeconomic status (SES). Patients were recruited in Hamilton, Ontario, Canada from two outpatient clinics that specialize in care of persons with schizophrenia, and are affiliated with the psychiatry department of an academic medical center. NCPs were recruited from the community by advertising online and in local newspapers and on bulletin boards. Participants were assessed for capacity to provide informed consent and, after receiving a detailed description of the study, gave written consent. The protocol was approved by the St. Joseph's Healthcare Hamilton Research Ethics Board. Participants received cash compensation.

Participants were screened diagnostically with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM-IV) diagnoses were established using a best estimate approach based on the MINI and information from medical records and clinician reports. Participants were excluded if they met criteria for a current manic or depressive episode, lifetime substance dependence, or substance abuse in the past six months. NCPs were also excluded if they met criteria for any other Axis I diagnoses, or were taking psychotropic medication. Other exclusion criteria for all participants included: exposure to a language other than English before age five; and current or past self-reported neurological disorder. All participants had normal or corrected-to-normal vision. Handedness was assessed by the Edinburgh Inventory (Oldfield,

Table 1
Demographic and clinical characteristics of the study sample (means ± S.D. given where applicable).

	Schizophrenia patients ($n=16$)	NCPs ($n=16$)
Age, years	41.9 ± 7.6	35.6 ± 11.0
Sex	14 male, 2 female	10 male, 6 female
Handedness	15 right, 1 left	14 right, 2 left
Parental SES	38.4 ± 7.6	43.8 ± 12.2
Years of education[a]	12.9 ± 1.8	15.2 ± 2.3
SANS total	9.1 ± 3.9	
SAPS total	5.1 ± 4.6	
Negative factor	6.7 ± 2.8	
Psychotic factor	3.5 ± 3.0	
Disorganized factor	1.6 ± 1.9	

[a] Patients differed significantly from NCPs, $P=0.003$.

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1971) and parental SES was computed (Blishen et al., 1987). Demographic characteristics of the sample are shown in Table 1.

Eleven patients were prescribed second-generation antipsychotics, two were prescribed first-generation antipsychotics, and three were prescribed a combination of these. Eight patients were prescribed clozapine. Patients' mean daily antipsychotic dose in chlorpromazine equivalents (Bezchlibnyk-Butler and Jeffries, 2007) was 454 mg (S.D. = 229).

2.2. Symptom assessments

Patients were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). From these ratings, we calculated scores for psychotic (hallucinations + delusions), negative (affective flattening + avolition/apathy + anhedonia/asociality), and disorganized symptom factors (positive formal thought disorder + bizarre behavior; Miller et al., 1993). Patients' SAPS/SANS total and factor scores are shown in Table 1.

2.3. Stimuli

Stimuli included 72 related (e.g., *METAL–STEEL*), 72 unrelated (*DONKEY–PURSE*) and 72 repeated (*BREAD–BREAD*) prime-target word pairs. For each related pair, the target was among the words most commonly given as associates to the prime by participants in the University of South Florida word-association norms (Nelson et al., 1999); mean response probability of related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.42 (S.D. = 0.23). For each unrelated pair, prime and target were not associates in the norms. Across these three conditions, targets were matched for mean length and log-transformed frequency (Francis and Kucera, 1982). Across the conditions, primes were also matched for mean length and log-transformed frequency. Stimuli also included 216 word-nonword prime-target pairs (*DRESS–ZORES*), whose targets were pronounceable nonwords. No word occurred more than once among the stimuli.

The 432-trial stimulus list included all prime-target pairs in a fixed randomized order, in six blocks of 72 trials each. The list had two versions, each one administered to half the participants, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300 ms in blocks 1, 2 and 3, and 750 ms in blocks 4, 5, and 6; in version B, the order of SOAs was reversed.

2.4. Task

In an electrically shielded, sound-attenuated chamber, participants were seated 100 cm in front of a video monitor on which stimuli were visually presented, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically. Words were displayed in yellow letters on a black background.

Each participant was presented with the stimulus list, with short rest breaks between blocks. Each trial consisted of: (a) a row of preparatory fixation crosses for 500 ms; (b) blank screen for 250 ms; (c) prime word for 175 ms; (d) blank screen for 125 ms (in 300-ms SOA trials) or 575 ms (in 750-ms SOA trials); (e) target for 250 ms; (f) blank screen for 1250 ms; (g) the prompt *Yes or No?* until participants responded via button-press; and (h) blank screen for 3000 ms until onset of the next trial. All stimuli were centrally presented.

At the prompt, participants were required to press one of two buttons, positioned under their right and left thumbs respectively. One button (labeled "Yes") signaled that the target was a word, while the other button (labeled "No") signaled that it was a nonword. Assignment of buttons was divided equally among participants, counterbalanced across the two stimulus list versions.

2.5. Electroencephalographic data collection and analysis

During the experimental task, the electroencephalogram (EEG) was recorded using an ActiveTwo system (BioSemi BV, Amsterdam), from 32 sites approximately equally spaced across the scalp, positioned according to a modified International 10–20 System (Fp1-Fp2-AF3-AF4-F7-F3-Fz-F4-F8-FC5-FC1-FC2-FC6-T7-T8-C3-Cz-C4-CP5-CP1-CP2-CP6-P7-P3-Pz-P4-P8-PO3-PO4-O1-Oz-O2). The EEG was referenced to a left parietal Common Mode Sense (CMS) active electrode and a right parietal Driven Right Leg (DRL) passive electrode, which form a feedback loop driving the average potential across the montage as close as possible to the amplifier zero. The EEG was continuously digitized at 512 Hz and low-pass filtered at 128 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. Offline, the EEG was re-referenced to the algebraic mean of the mastoids, and bandpassed at 0.01–100 Hz. Continuous data were algorithmically corrected for eyeblink artifact (Jung et al., 2000). ERPs were computed for epochs from 100 ms pre-stimulus to 900 ms post-stimulus. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before time-domain averaging; mean percentage of trials lost to such artifacts was 14% for patients and 13% for controls.

For each participant, separate ERP averages were obtained for trials with related, unrelated and repeated target words. N400 amplitude was defined as the mean voltage from 300 to 500 ms post-stimulus.

Difference waveforms were obtained by subtracting the ERP average for related targets from the average for unrelated targets (*relatedness priming effect*), and by subtracting the average for repeated targets from the average for unrelated targets (*repetition priming effect*). Peak latencies of the N400 relatedness and repetition priming effects were defined as the interval between target onset and the largest negative peak from 200 to 600 ms post-stimulus. Mean amplitude of N400 relatedness and repetition priming effects were defined as mean voltage from 300 to 500 ms post-stimulus (this window was chosen because it was centered approximately around the peak latency of these effects).

2.6. Statistical analysis

P-values in analyses of variance (ANOVAs) with within-subject factors are reported after Greenhouse–Geisser Epsilon correction. Pairwise comparisons of factor-level means were made with Tukey simultaneous comparisons, with a family confidence coefficient of 0.95. All *P*-values are two-tailed.

Percentage of correct responses was analyzed by repeated-measures ANOVA, with Group (schizophrenia vs. NCP) as between-subject variable, and SOA (300-ms vs. 750-ms) and Target (related vs. unrelated vs. repeated vs. nonword) as within-subject variables.

N400 amplitude was analyzed in an omnibus repeated-measures ANOVA with Group (schizophrenia vs. NCP) as between-subject variable; and SOA (300-ms vs. 750-ms), Target (related vs. unrelated vs. repeated) and Electrode (nine levels, corresponding to a contiguous array of medial posterior sites where differences in N400 effects were most prominent: Cz, P7, P3, Pz, P4, P8, PO3, PO4 and Oz) as within-subject variables.

For N400 relatedness and repetition priming effects, peak latency was analyzed in a repeated-measures ANOVA with Group (schizophrenia vs. NCP) as between-subject variable, and SOA (300-ms vs. 750-ms) and Electrode (nine levels, corresponding to the sites described above) as within-subject variables.

To test for between-group differences in N400 relatedness and repetition priming effects, for each SOA the amplitude of each of these effects was analyzed in a repeated-measures ANOVA with Group (schizophrenia vs. NCP) as between-subject variable, and Electrode (nine levels, corresponding to the sites described above) as within-subject variable.

3. Results

3.1. Behavioral data

The high correct-response rates for schizophrenia patients and NCPs (Table 2) and the absence of a Group effect ($F_{1,30} = 3.01$, $P = 0.09$) on correct-response rates indicate that, overall, participants were attending to the stimuli. There was a Target effect ($F_{3,90} = 15.62$, $p < 0.0001$), with slightly lower accuracy for unrelated targets than for related, repeated or nonword targets. There was no SOA effect ($F_{1,30} = 2.29$, $P = 0.14$). There was, however, a Group × Target interaction ($F_{3,90} = 4.10$, $P = 0.02$) — patients were less accurate in the unrelated condition than in the related, repeated or nonword conditions, whereas NCPs' accuracy did not differ significantly across conditions.

3.2. Grand average ERPs

Grand average ERPs are shown for all electrodes, for schizophrenia and NCP groups, for the 300-ms SOA in Fig. 1 and the 750-ms SOA in Fig. 2. Across the two groups and the nine medial posterior electrodes

Table 2
Percentage of correct lexical-decision responses, by participant group and target condition.

	Patients ($n = 16$)		NCPs ($n = 16$)	
	Mean	S.D.	Mean	S.D.
Short SOA				
Related	97.6	5.7	99.7	1.4
Unrelated	93.7	7.8	97.4	3.6
Repeated	96.7	6.3	98.6	1.5
Nonwords	97.3	4.8	99.2	0.9
Long SOA				
Related	95.7	10.0	98.6	2.0
Unrelated	90.8	11.6	97.7	1.5
Repeated	97.2	6.9	99.1	1.7
Nonwords	97.0	4.4	99.2	1.0

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selected for analysis, mean N400 amplitude was largest (most relatively negative) for unrelated target words (0.24 μV), intermediate for related target words (1.42 μV), and smallest for repeated target words (3.36 μV) which elicited a relative positivity in the N400 time-window (Target main effect: $F_{2,60}=27.70$, $p<0.0001$). There were no Group ($F_{1,30}=0.71$, $P=0.41$), SOA ($F_{1,30}=2.58$, $P=0.12$), Group×SOA ($F_{1,30}=0.01$, $P=0.91$), or Group×Target ($F_{2,60}=1.43$, $P=0.25$) effects.

3.3. N400 priming effects

Semantic relatedness priming effects are shown for midline electrodes, for schizophrenia and NCP groups, for the 300-ms SOA in Fig. 3A and for the 750-ms SOA in Fig. 3B. Repetition priming effects are shown for midline electrodes, for schizophrenia and NCP groups, for the 300-ms SOA in Fig. 4A and for the 750-ms SOA in Fig. 4B.

Across the schizophrenia and NCP groups, and across the nine medial posterior electrodes selected for analysis, mean peak latency for the N400 relatedness priming effect was 399 ms. Peak latency did not vary reliably by Group (schizophrenia: 396 ms, NCPs: 403 ms; $F_{1,30}=0.10$, $P=0.75$). There was a trend for peak latency to be longer at the short SOA than at the long SOA (421 ms vs. 378 ms, $F_{1,30}=3.41$, $P=0.07$). There was also a trend for a Group×SOA interaction ($F_{1,30}=3.44$, $P=0.07$), such that patients exhibited shorter peak latency than NCPs at the short SOA (396 ms vs. 446 ms), whereas NCPs exhibited shorter peak latency than patients at the long SOA (359 ms vs. 396 ms).

Across the two groups, and across the nine electrodes described above, mean peak latency for the N400 repetition priming effect was 421 ms. Peak latency was longer for the short SOA than for the long SOA (438 ms vs. 403 ms; $F_{1,30}=8.83$, $P=0.006$). Peak latency did not vary reliably by Group ($F_{1,30}=1.25$, $P=0.27$). There was no Group×SOA interaction ($F_{1,30}=1.45$, $P=0.24$).

Amplitudes of N400 relatedness and repetition priming effects for patients and NCPs at both SOAs are shown in Fig. 5. For the short SOA, the N400 relatedness priming effect was smaller for patients than for

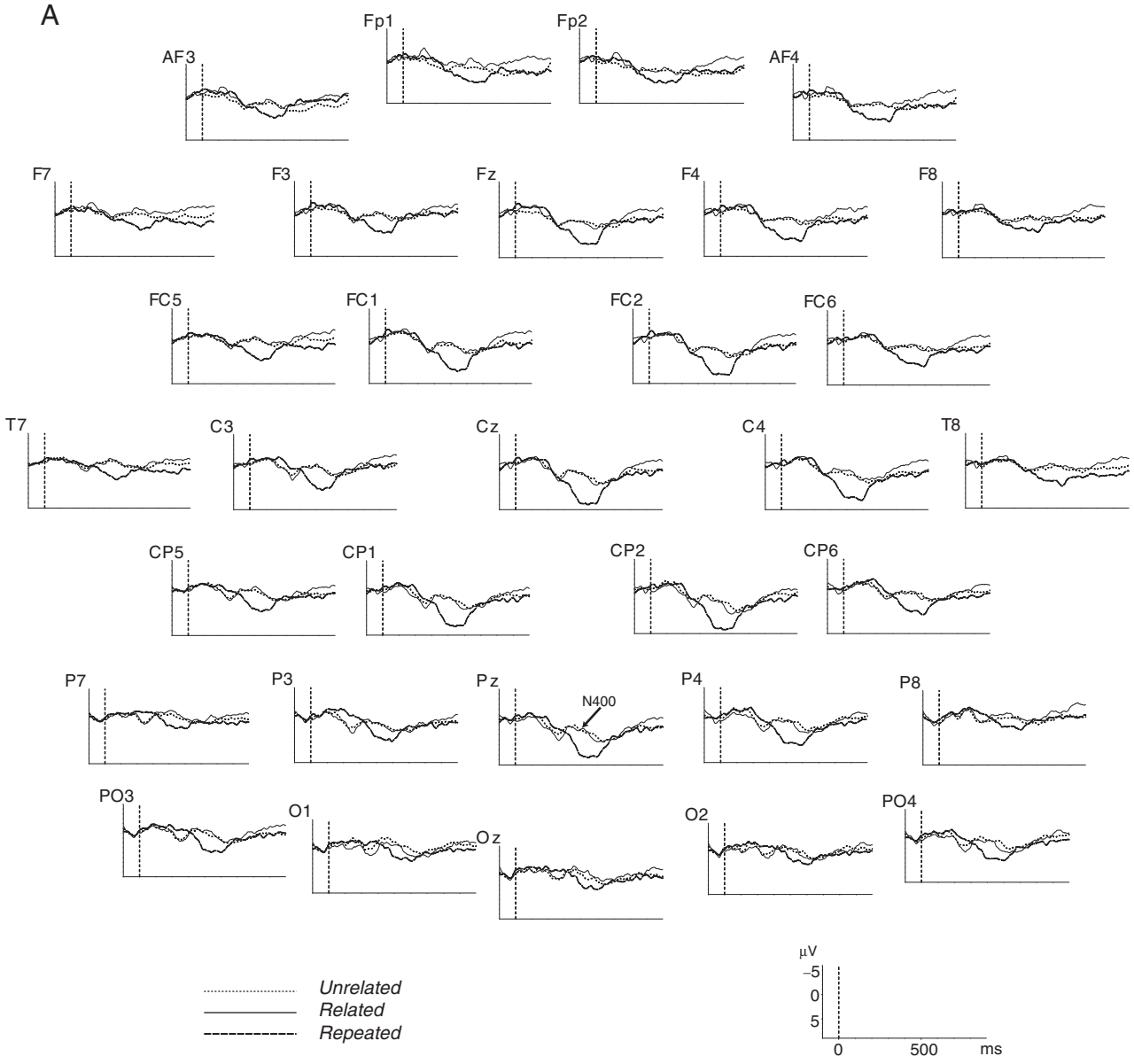

Fig. 1. Grand average ERPs to target words at the 300-ms prime-target SOA, at all electrode sites, for: (A) schizophrenia patients and (B) NCPs. Negative amplitudes are plotted upward.

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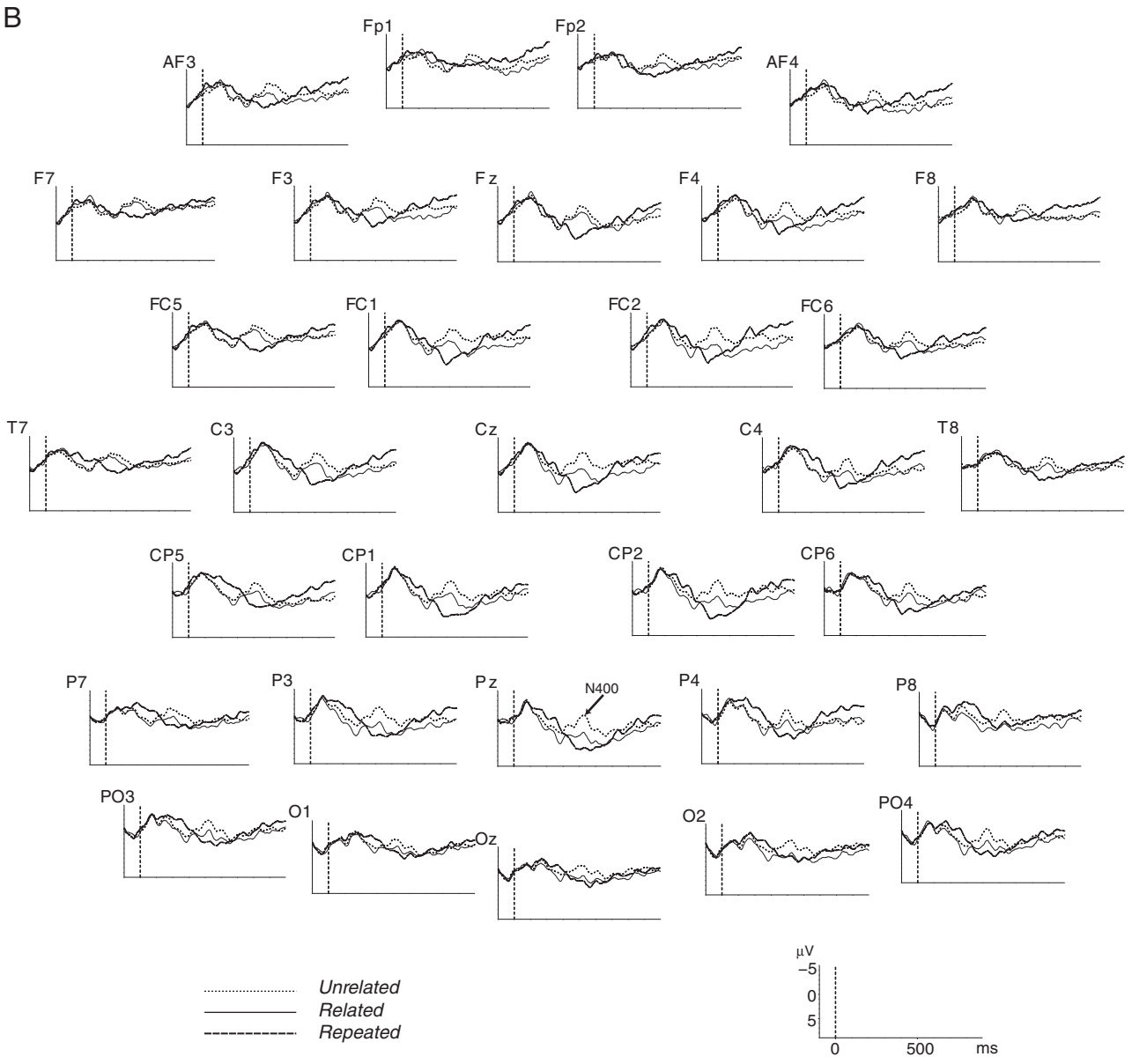

Fig. 1 (*continued*).

NCPs (0.10 μV vs. −1.95 μV, respectively; Group effect: $F_{1,30}=4.35$, $P=0.046$). For the long SOA, the N400 relatedness priming effect did not differ significantly between patients and NCPs (−1.05 μV vs. −1.82 μV, respectively; Group effect: $F_{1,30}=0.39$, $P=0.54$). Additionally, N400 repetition priming effects did not differ significantly between groups at either the short SOA (patients: −2.54 μV, NCPs: −2.85 μV; Group effect: $F_{1,30}=0.06$, $P=0.81$) or the long SOA (patients: −3.21 μV, NCPs: −3.89 μV; Group effect: $F_{1,30}=0.55$, $P=0.47$).

In NCPs, N400 repetition priming effects were significantly correlated with N400 relatedness priming effects at the short SOA ($r=0.51$, $P=0.045$) but not at the long SOA ($r=0.40$, $P=0.13$); N400 repetition and relatedness priming effects were not correlated in schizophrenia patients at either SOA (short SOA: $r=0.40$, $P=0.13$; long SOA: $r=0.28$, $P=0.30$). Among patients, N400 repetition and relatedness priming effects were not correlated with antipsychotic dose in chlorpromazine equivalents, at either SOA (all r values <0.15, all P values >0.60).

3.4. Correlations between N400 relatedness priming effects and symptom ratings

Because schizophrenia patients exhibited N400 relatedness priming deficits at the short SOA, we tested for a relationship between these deficits and symptom severity by examining, across patients, Pearson's correlations r between N400 relatedness priming effects at the short SOA and SAPS/SANS symptom factor scores. However, none of these correlations was statistically significant (all r values <0.30, all P values >0.30).

4. Discussion

We aimed to examine whether schizophrenia patients' previously observed deficits in using meaningful stimuli to facilitate neural processing of related stimuli, as indexed by the N400 ERP, result from (a) difficulty in activating the concept corresponding to the initial stimulus in long-term semantic memory; or (b) deficient functional connections among related concepts within semantic memory. To

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this end, we presented schizophrenia patients and NCPs with prime words, each followed at either a shorter (300 ms) or a longer (750 ms) SOA by a target word that was either semantically related or unrelated to, or was a repetition of, the prime word. As expected, NCPs exhibited N400 amplitudes that were largest (most negative) in response to unrelated targets, smaller (less negative) to related targets (indicating more facilitated processing), and smallest (least negative) to repeated targets. Schizophrenia patients also exhibited this general pattern but, consistent with some previous results in general schizophrenia samples (as opposed to subgroups with elevated disorganization), they exhibited smaller than normal N400 amplitude reductions for related versus unrelated targets – i.e., subnormal N400 semantic relatedness priming effects – at the shorter, 300-ms, SOA. Critically, however, patients exhibited normal N400 amplitude reductions for repeated versus unrelated targets – i.e., normal N400 repetition priming effects – at both SOAs. Thus, patients, like controls, exhibited smaller N400s to target words when these were repetitions of an immediately preceding prime word, than when the target was unrelated to the prime. These normal N400 repetition priming effects at both the 300- and 750-ms SOAs are consistent with unimpaired activation, following a meaningful stimulus, of the corresponding concept within semantic memory (at least over a 750-ms interval). However, the patients' smaller than normal N400 amplitude reductions in response to related versus unrelated targets at the 300-ms SOA suggests that activation failed to extend normally to related concepts within semantic memory, at least during the 300 ms following the prime stimulus.

Although we found these N400 relatedness priming deficits in the schizophrenia group at the 300-ms prime-target SOA, they were not reliably present at the 750-ms SOA. This dissociation was seemingly inconsistent with previous reports of such deficits in schizophrenia patients at SOAs similar to the latter (Strandburg et al., 1997; Kiang et al., 2008; Condray et al., 2010). A possible explanation for this apparent discrepancy is that, unlike those previous studies, we included repeated word pairs along with related and unrelated pairs. Previously, Rugg (1985) noted, in a study employing related, unrelated, and

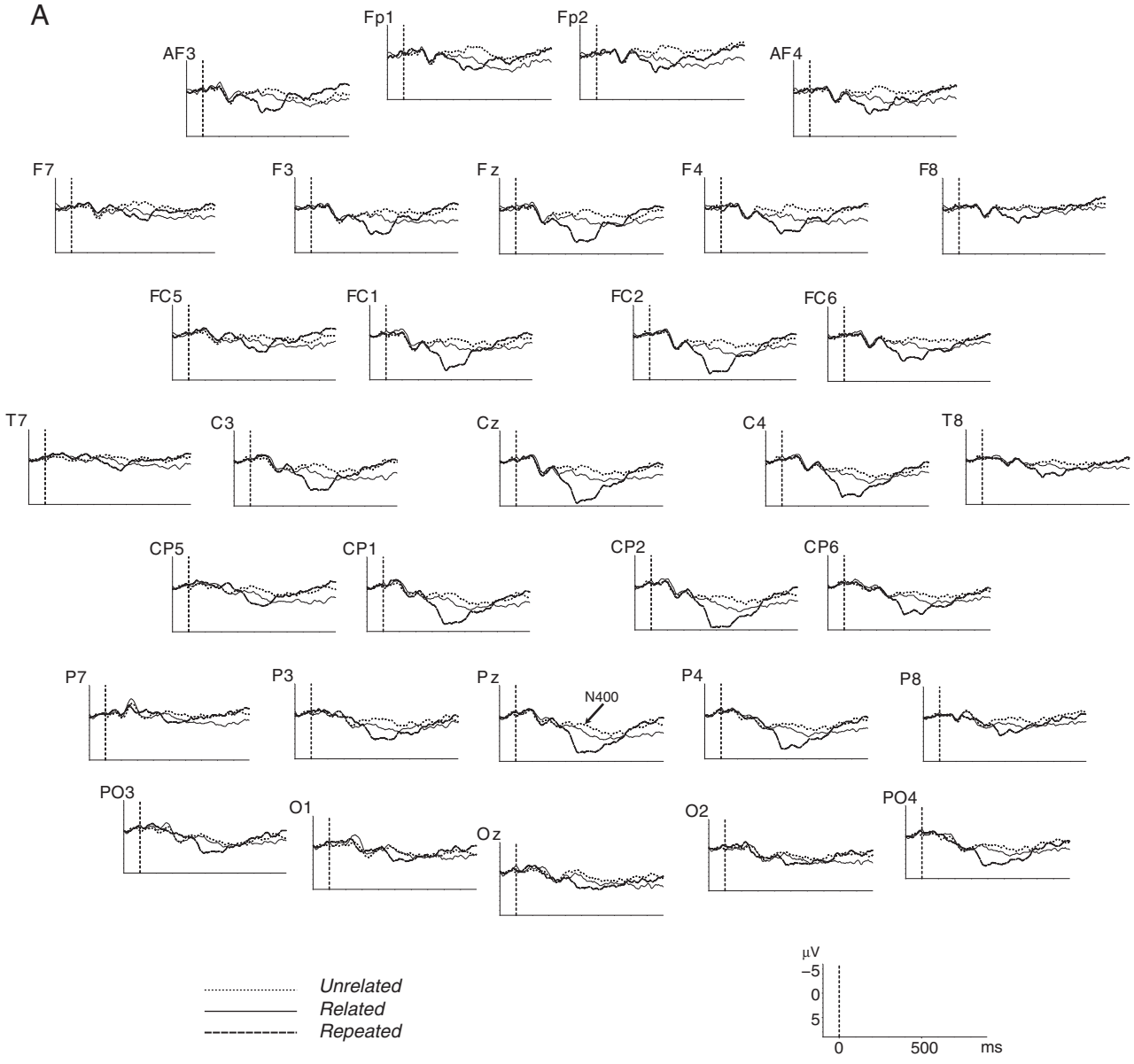

Fig. 2. Grand average ERPs to target words at the 750-ms prime-target SOA, at all electrode sites, for: (A) schizophrenia patients and (B) NCPs. Negative amplitudes are plotted upward.

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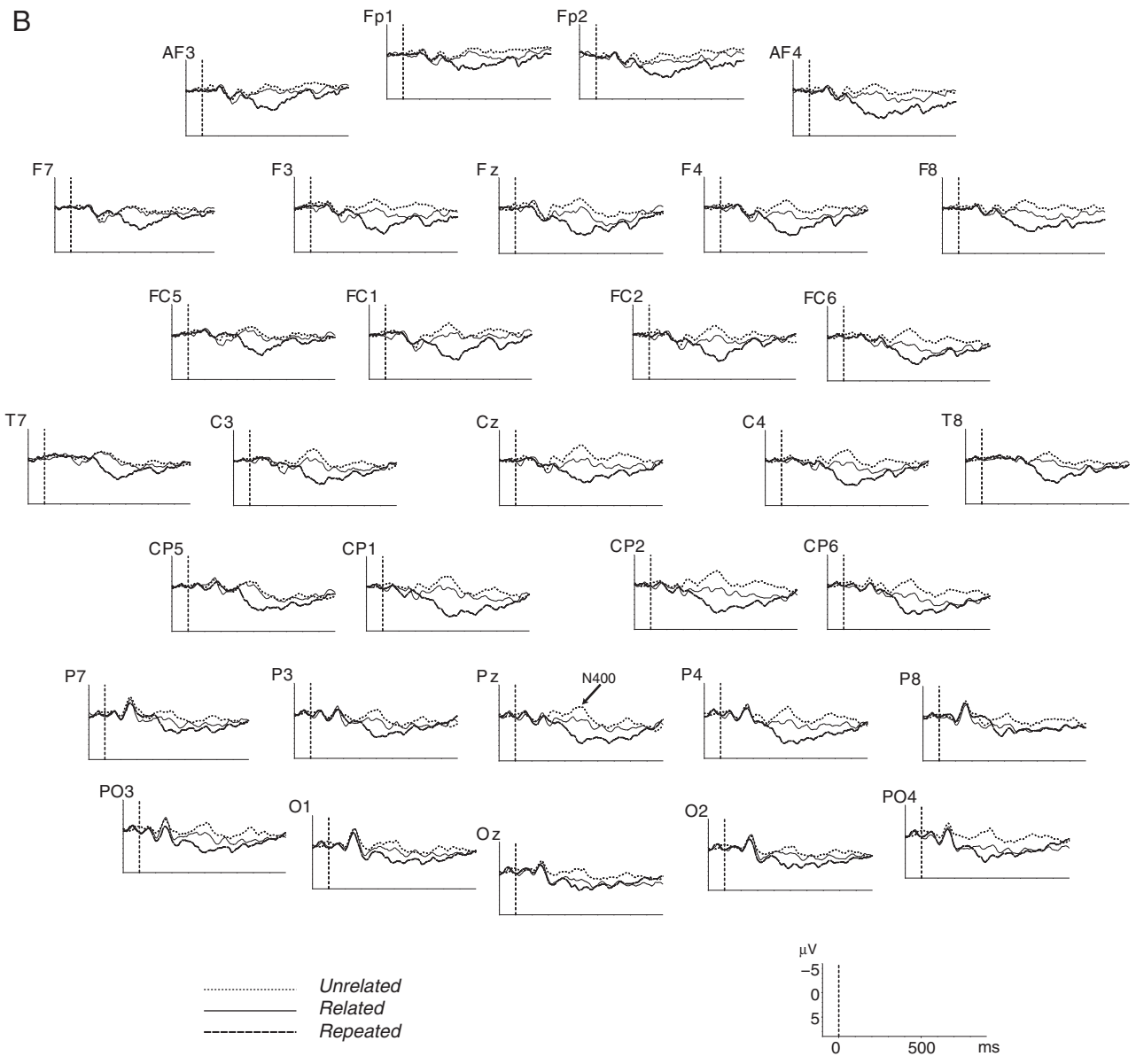

Fig. 2 (*continued*).

repeated words (and SOAs of several seconds), that N400 relatedness priming effects appeared smaller than in another study which had not included repeated pairs. The addition of repeated word pairs, with their relative salience, may decrease N400 relatedness priming effects at relatively long SOAs, by diverting individuals' processing resources toward recognition of word repetitions, and away from detecting relationships between pairs of words. If such a phenomenon attenuated N400 relatedness priming in NCPs in the present study, this may have reduced the difference in this effect between patients and NCPs.

Our results did not provide evidence that, following a meaningful prime stimulus, schizophrenia patients experience impaired activation of the corresponding concept within semantic memory. Patients exhibited normal N400 repetition priming effects — i.e., N400 amplitude was less negative to targets that were repetitions of their prime, as compared to targets that were unrelated to their prime, consistent with normally facilitated semantic processing of the corresponding concept (Holcomb and Grainger, 2007; Kutas and Federmeier, 2011). In contrast, unlike controls, patients did not exhibit N400 relatedness priming effects at the 300-ms SOA, suggesting that the prime stimulus did not facilitate activation of related concepts, compared to unrelated ones, in semantic memory over this time interval. This deficit could result from various, not necessarily mutually exclusive, functional abnormalities of semantic-memory neural networks — including slowed activation of related concepts; failure of inhibition leading to overactivation of unrelated concepts (McCarley et al., 1999); aberrant connection weights, e.g., a relative predominance of weak or idiosyncratic connections (Goldberg et al., 1998; McCarley et al., 1999; Vinogradov et al., 2003); and/or failure to develop functional neural connections between normatively related concepts (Sumiyoshi et al., 2009).

In this study, schizophrenia patients' N400 relatedness priming deficits were not significantly correlated with any SAPS/SANS symptom factor ratings. This contrasted with previous studies in which N400 relatedness priming deficits correlated with more severe disorganized or psychotic symptoms (Kostova et al., 2005; Ditman and Kuperberg, 2007; Kiang et al., 2007, 2008). This apparent discrepancy

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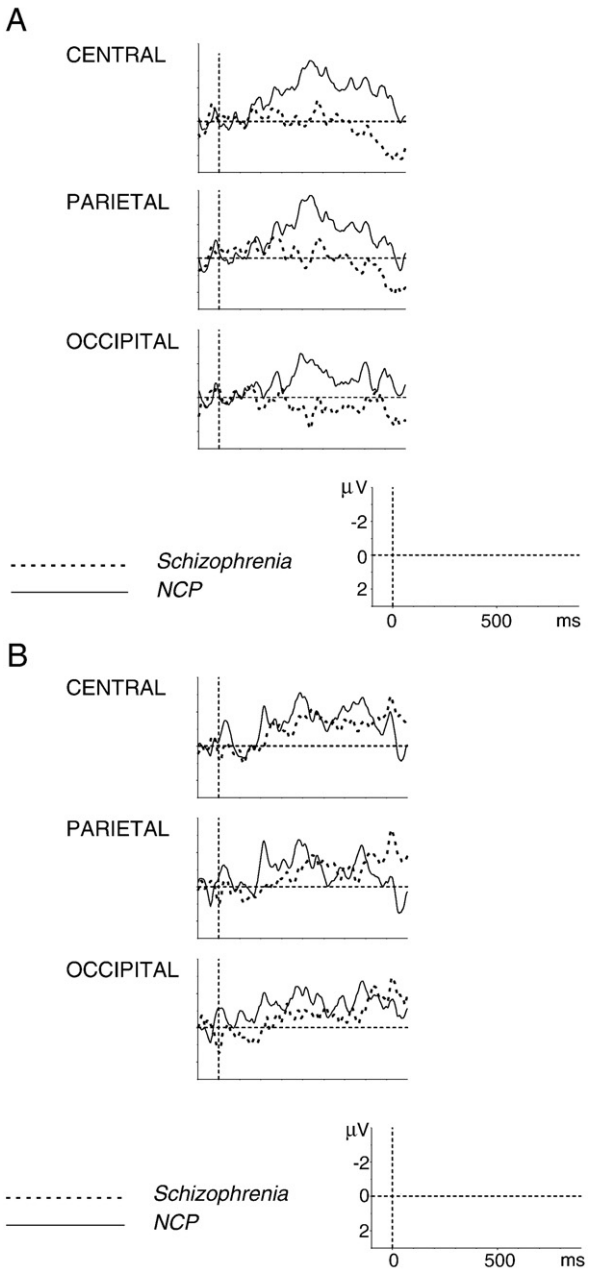

Fig. 3. Grand average relatedness priming effects (formed by subtracting ERPs for related targets from ERPs for unrelated targets), at midline electrode sites, for schizophrenia patients and NCPs, for: (A) the 300-ms SOA and (B) the 750-ms SOA. Negative amplitudes are plotted upward.

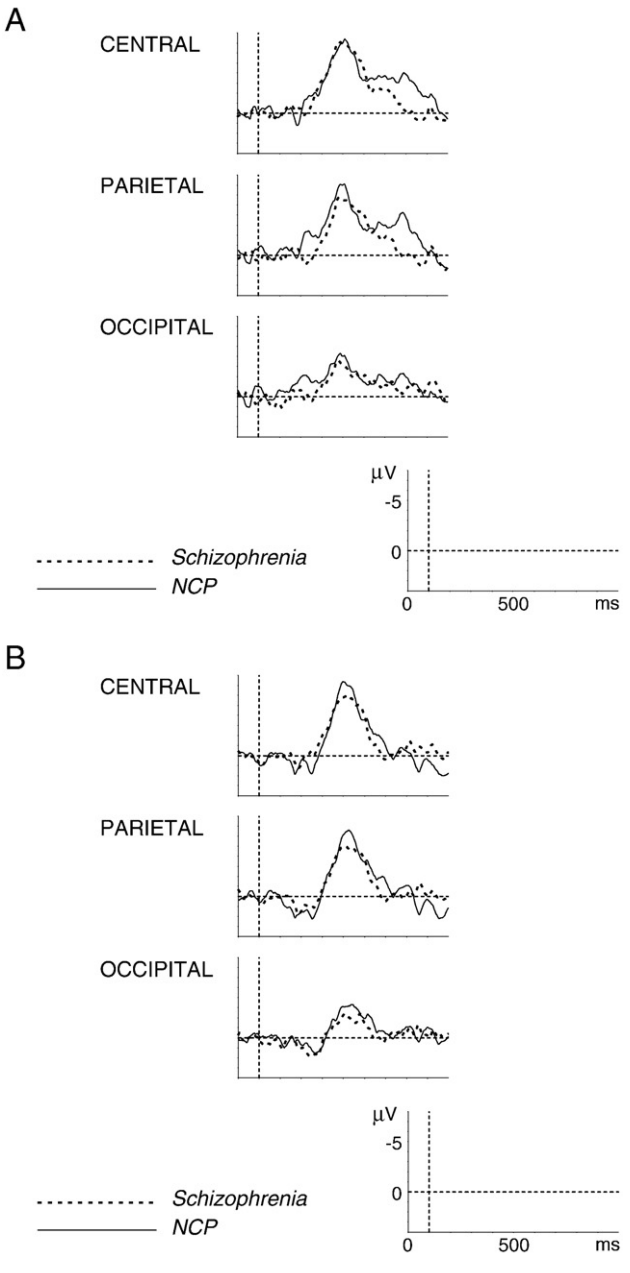

Fig. 4. Grand average repetition priming effects (formed by subtracting ERPs for repeated targets from ERPs for unrelated targets), at midline electrode sites, for schizophrenia patients and NCPs, for: (A) the 300-ms SOA and (B) the 750-ms SOA. Negative amplitudes are plotted upward.

may have been due to insufficient statistical power in the current study to detect such correlations. Alternatively, with regard to disorganized symptoms, this discrepancy may also have resulted from their relatively low level in our sample. With regard to psychotic symptoms, the contrasting results may be due to differences across studies in the underlying causes of these symptoms. Across schizophrenia patients, psychotic symptoms have been hypothesized to develop via a number of heterogeneous etiologic pathways, each associated with a different profile of neuropsychological deficits (Kirkpatrick et al., 2001; Sprong et al., 2008). If this is the case, then perhaps only some of these patient subgroups, and not others, exhibit N400 semantic priming deficits. Thus, different distributions of these subgroups across studies could result in associations of N400 semantic priming deficits with psychotic symptoms in some studies but not others. Accordingly, further research could investigate whether these N400 deficits, in conjunction with other neurophysiological and genetic tests, are a useful biological marker for helping to differentiate these subgroups.

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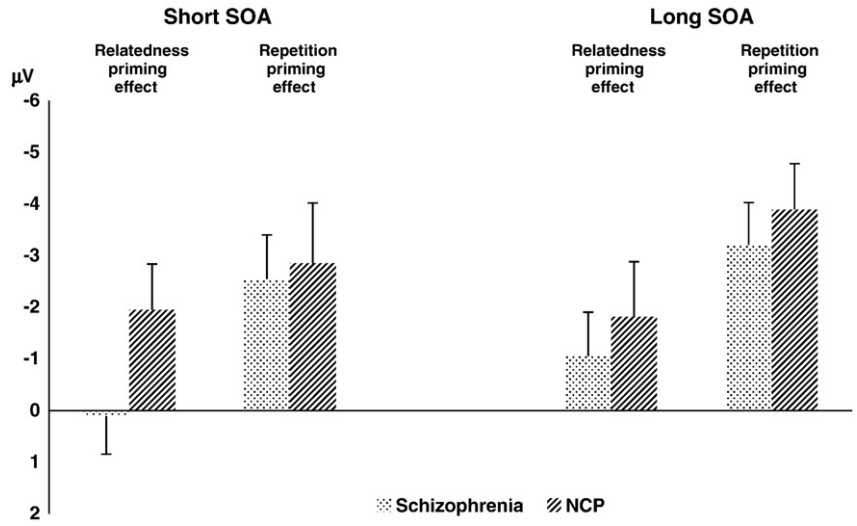

Fig. 5. Amplitudes of N400 relatedness and repetition priming effects (averaged across nine medial posterior sites: Cz, P7, P3, Pz, P4, P8, PO3, PO4 and Oz) for patients and NCPs. Error bars indicate standard deviations.

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