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Why all the confusion? Experimental task explains discrepant semantic priming effects in schizophrenia under "automatic" conditions: Evidence from Event-Related Potentials

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ABSTRACT

The schizophrenia research literature contains many differing accounts of semantic memory function in schizophrenia as assessed through the semantic priming paradigm. Most recently, Event-Related Potentials (ERPs) have been used to demonstrate both increased and decreased semantic priming at a neural level in schizophrenia patients, relative to healthy controls. The present study used ERPs to investigate the role of behavioral task in determining neural semantic priming effects in schizophrenia. The same schizophrenia patients and healthy controls completed two experiments in which word stimuli were identical, and the time between the onset of prime and target remained constant at 350 ms: in the first, participants monitored for words within a particular semantic category that appeared only in filler items (implicit task); in the second, participants explicitly rated the relatedness of word-pairs (explicit task). In the explicit task, schizophrenia patients showed reduced direct and indirect semantic priming in comparison with healthy controls. In contrast, in the implicit task, schizophrenia patients showed normal or, in positively thought-disordered patients, increased direct and indirect N400 priming effects compared with healthy controls. These data confirm that, although schizophrenia patients with positive thought disorder may show an abnormally increased automatic spreading activation, the introduction of semantic decision-making can result in abnormally reduced semantic priming in schizophrenia, even when other experimental conditions bias toward automatic processing.

1. Introduction

Language disturbances in schizophrenia have been posited to result from an abnormally heightened automatic spread of activation within semantic memory (Bleuler, 1911/1950; Spitzer et al., 1993), as well as deficits in controlled mechanisms of using context to facilitate word processing (Kuperberg et al., in press-a, b). Schizophrenia researchers have used the semantic priming paradigm to provide evidence for both theories. This study used Event-Related Potentials (ERPs) and a within-subject task manipulation to investigate whether these apparently inconsistent reports might be partially explained by experimental task.

The semantic priming effect describes the faster response to targets preceded by semantically related, relative to unrelated, primes (Meyer and Schvaneveldt, 1971). This behavioral effect has a neurophysiological correlate: the attenuation of a negative-going waveform evoked approximately 400 milliseconds (ms) after the onset of primed, vs. unprimed, targets (Bentin et al., 1985; Rugg, 1985) — the N400 priming effect.

Multiple mechanisms can contribute to behavioral and electrophysiological semantic priming, depending on experimental factors including the time between prime and target onset (the stimulus onset asynchrony; SOA; Neely, 1977), and – the focus of the present study – the experimental task. At short SOAs, tasks that are not dependent on evaluating the semantic

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Table 1
Demographic and psychopathological data of healthy controls and schizophrenia patients.

Parameter	Controls	Patients
Gender (M/F)	3/9	5/11
Race (C/AA)	10/2	14/2
Age (years)	44 (7)	43 (10)
Education (years)	15 (3)	14 (2)
Hollingshead Index	4 (1)	3 (1)
Premorbid IQ	114 (9)	109 (13)
CPZ equivalent	–	364 (283)
Duration of illness (years)	–	17 (12)
PANSS total	–	57 (13)
PANSS hallucination	–	3 (2)
PANSS delusion	–	2 (2)
SANS total	–	34 (14)
TLC total	–	3 (4)

Altogether 18 patients and 18 controls completed the implicit task and 18 patients and 15 controls completed the explicit task. Shown are data for the subset of controls and patients who completed both tasks, as this subset was used in the full mixed model ANOVAs comparing ERP effects. These subsets of patients and controls were matched on gender and race distribution, age, education, parental SES (Hollingshead, 1965) and premorbid IQ (Blair and Spreen, 1989) (all *ps*>.13). The full group of patients and controls who completed both tasks were also matched on all these variables.
Means are shown with standard deviation in brackets.
Abbreviations: M = male; F = female; C = Caucasian; AA = African-American; CPZ = chlorpromazine. Hollingshead Index was used as a measure of parental socio-economic status (Hollingshead, 1965). A-NART was used as a measure of premorbid IQ (Blair and Spreen, 1989).

Table 2
Example of word-pairs, counterbalanced across conditions, derived from the triplet "lion–tiger-stripes".

Priming condition	Example	Frequency	Word length
Directly related	Tiger-stripes	Prime: 92.16 (139.16)	Prime: 5 (2)
		Target: 96.37 (478.96) [a]	Target: 5 (2) [a]
Indirectly related	Lion-stripes	Prime: 70.55 (159.01)	Prime: 6 (2)
		Target: 96.37 (478.96) [a]	Target: 5 (2) [a]
Unrelated	Truck-stripes	Prime: 70 (133)	Prime: 5 (1)
		Target: 96.37 (478.96) [a]	Target: 5 (2) [a]

Means are shown with standard deviation in brackets.
[a] The frequency and word length of the targets across the three conditions are identical because exactly the same words were counterbalanced, across participants, across the three conditions. There were no significant differences in the frequency (Kučera and Francis, 1967) of prime words across the three conditions (all *ps*>.05).

relationship between prime and target, such as word pronunciation (Neely, 1991), or semantic monitoring (Kreher et al., 2006, 2008; Misra and Holcomb, 2003), bias towards more automatic processing. However, if participants are required to make a decision about a target, such as in the commonly-used lexical decision task (Meyer and Schvaneveldt, 1971), or if they are asked to explicitly match prime and target (e.g. Kreher et al., 2006), priming effects are larger and mediated mainly through the strategic use of semantic relationships to facilitate responses to related targets and inhibit responses to unrelated targets (Neely, 1991; Neely and Keefe, 1989).

In schizophrenia, behavioral studies of semantic priming using short SOAs have yielded conflicting results (reviewed by Minzenberg et al., 2002; Pomerol-Clotet et al., 2008). Several researchers have reported that thought-disordered (TD) schizophrenia patients exhibit increased direct (Manschreck et al., 1988; Spitzer et al., 1994; Moritz et al., 2001a, b; Chenery et al., 2004) and indirect (Spitzer et al., 1993; Weisbrod et al., 1998; Moritz et al., 2001a, b, 2002) semantic priming, relative to non-TD patients and healthy controls. These findings have often been interpreted as evidence for an increased spread of activation across semantic memory in association with thought disorder. Other investigators, who have considered schizophrenia patients as a whole, have reported normal (Chapin et al., 1989, 1992; Vinogradov, Ober and Shenaut, 1992; Ober et al., 1995; Blum and Freides, 1995; Barch et al., 1996; Besche-Richard, Passerieux, and Hardy-Bayle, 2005), and sometimes abnormally reduced (Henik, Priel, and Umansky, 1992; Ober, Vinogradov, and Shenaut, 1997) semantic priming.

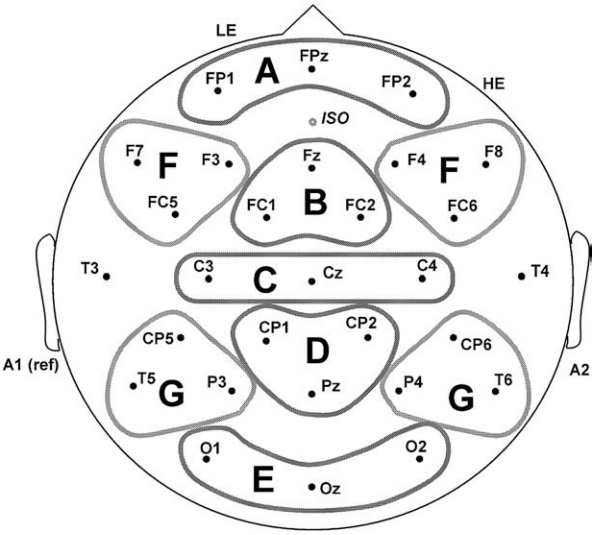
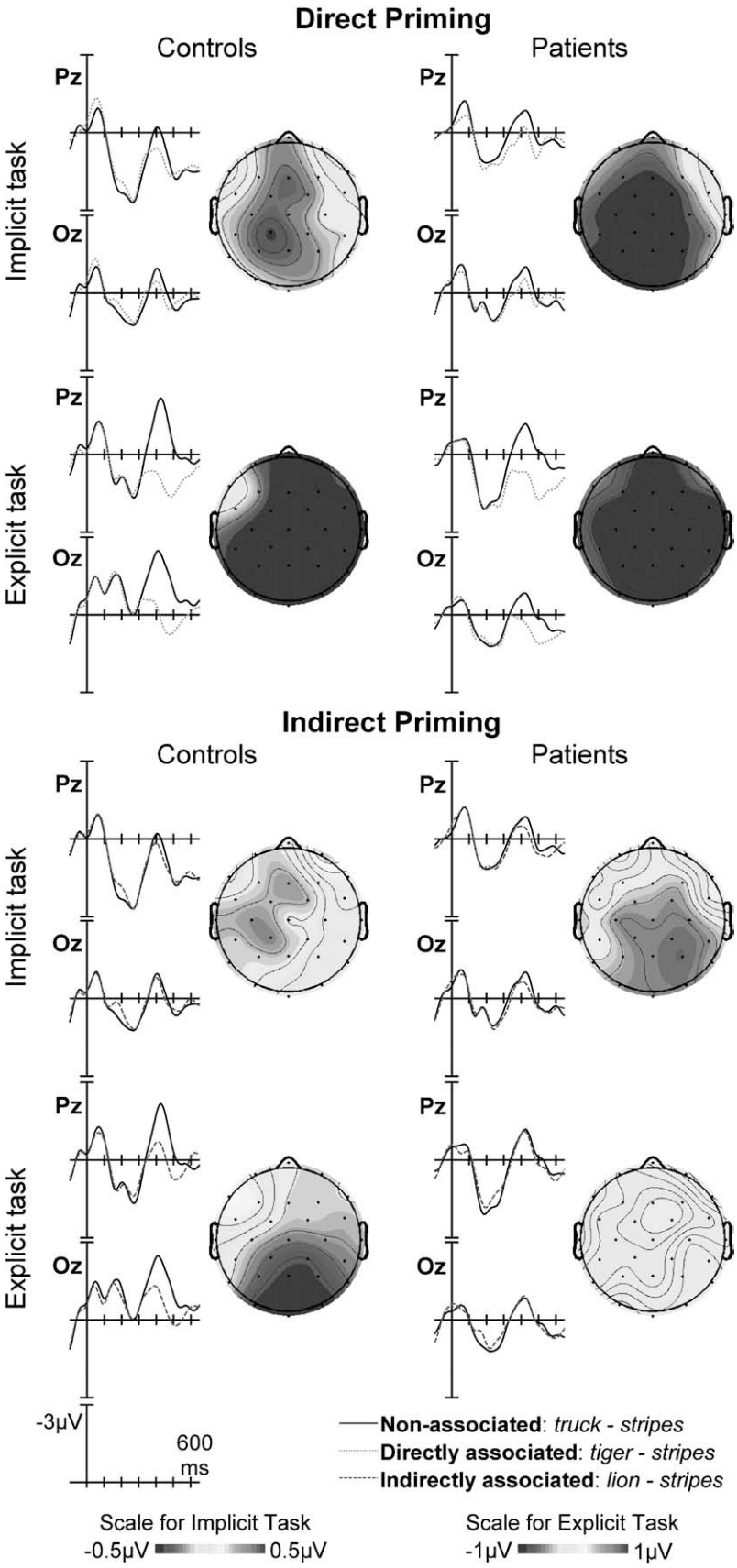


Fig. 1. Electrode montage and regions used in analysis. Mid regions: A — anterior frontal, B — frontal, C — central, D — central–posterior, E — posterior. Lateral regions: F — anterior, G — posterior.

Studies utilizing ERPs to index semantic priming at short SOAs have largely conformed to this pattern, with reports of both normal (Mathalon et al., 2002) and abnormally reduced (Condray et al., 2003; Kiang et al., 2008) priming of directly-related words in schizophrenia patients. Kreher et al. (2008) reported findings consistent with behavioral studies, demonstrating an increased early (between 300 and 400 ms after target word onset) *indirect* N400 priming effect in TD patients, relative to non-TD patients and healthy controls. In contrast, Kiang et al. (2008) reported an abnormally reduced indirect N400 priming effect in patients, regardless of whether a 300 or 750 ms SOA was used.

While Kreher et al. used an entirely implicit task of semantic processing, Kiang et al. required a lexical decision to each target. It is possible that this requirement obscured any neural effects of increased spreading activation in patients[1]:

[1] Increased behavioral semantic priming in severely thought-disordered patients has been reported using lexical decision tasks (Spitzer et al., 1993; Weisbrod et al., 1998; Moritz et al., 2001a, b, 2002). However, these studies have largely used in-patient samples, which may represent an extreme form of aberrant cognitive processes. In addition, ERP measures may be a more direct measure of the automaticity of neural spreading activation and thus may be even more susceptible to task requirements than behavior (Kreher et al., 2006).


Direct Priming
Controls
Patients
Implicit task
Explicit task
Pz
Oz
Indirect Priming
-3μV
600
ms
Non-associated: truck - stripes
Directly associated: tiger - stripes
Indirectly associated: lion - stripes
Scale for Implicit Task
-0.5μV
0.5μV
Scale for Explicit Task
-1μV
1μV

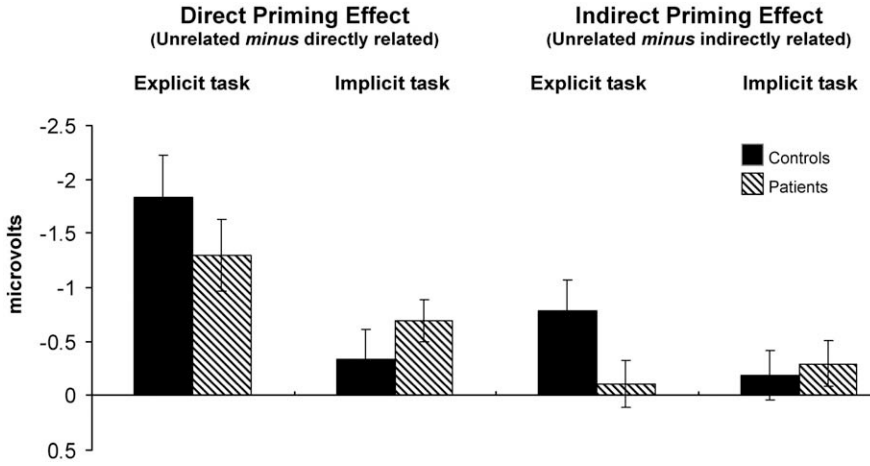


Fig. 3. Bar graph depicting N400 difference scores (unrelated–directly related; unrelated–indirectly related) by group (patient, control) and task (implicit, explicit). Negative is plotted upward for ease of comparison with ERP plots.

unlike healthy controls, schizophrenia patients may be impaired in mobilizing semantic matching strategies, resulting in N400 hypo-priming relative to controls, even at short SOAs. Some support for this notion comes from a recent study by Mathalon et al. (in press), reporting an abnormally reduced N400 priming effect to pictures that were directly related (vs. unrelated) to their preceding word primes at an SOA of 325 ms when patients were required to decide whether prime and target were related.

The present study examined direct and indirect ERP semantic priming during both an implicit semantic monitoring task, and an explicit semantic matching task, at a short SOA, within the same schizophrenia patients and healthy controls. If requiring a decision to each target word does introduce strategic processes, then patients, relative to controls, should show reduced N400 priming during the explicit, but not the implicit, task. If the absence of such a decision allows for the detection of any effects of automatic spreading activation, then thought disorder should be positively associated with the magnitude of priming in the implicit, but not the explicit, task.

2. Materials and methods

To minimize strategic effects on implicit processing, participants performed the implicit task in session 1 and the explicit task in session 2 with at least two weeks between sessions.

2.1. Participants

Outpatients meeting DSM IV-TR criteria for schizophrenia (First et al., 2002b) were recruited from the Lindemann Mental Health Center, Boston, and healthy volunteers, screened to exclude histories of psychiatric disorders (First et al., 2002a) and current medication affecting the central nervous system, were recruited by advertisement. In total, 18 patients and 18 controls completed the implicit task; 15 controls and 18 patients completed the explicit task. Of these, a subset of 12 controls and 17 patients completed both tasks. All participants were right-handed (Oldfield, 1971; White and Ashton, 1976) native English speakers, had normal/corrected-to-normal vision, no history of traumatic head injury, and no substance abuse within 6 months, or any history of substance dependence. Written informed consent was obtained from all participants according to the Massachusetts General Hospital and Tufts Human Subjects Research guidelines. All but one unmedicated patient were receiving stable doses of antipsychotic medication (Table 1). Patients' symptomatology was rated using the Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) within four weeks of ERP testing. Thought disorder was assessed by the first author using the scale for the assessment of Thought Language and Communication (TLC; Andreasen, 1979a, b) on session 1. There were no changes in medication between sessions 1 and 2. A language disorganization/positive thought disorder score was calculated by summing the following TLC items: circumstantiality, tangentiality, loss of goal, derailment, illogicality and incoherence (Kreher et al., 2008; Kuperberg et al., 1998, 2006). Patients and controls were well-matched on demographic characteristics (Table 1).

2.2. Design and procedures

Two-hundred-and-one triplets were developed in which target words (e.g. stripes) were paired with directly-related primes (e.g. tiger), indirectly-related primes (e.g. lion), or

Fig. 2. (Top) ERPs to directly-related and unrelated target words at 2 parietal–occipital sites by group (patient, control) and task (implicit, explicit). Linearly interpolated voltage maps showing the scalp distribution of differences in ERPs elicited by target words produced using EEGLAB v4.512 for MatLab software: scalp distributions of comparisons between unrelated and directly related in controls and patients in the N400 time window. (Bottom) ERPs to indirectly-related and unrelated target words at 2 parietal–occipital sites by group (patient, control) and task (implicit, explicit). Linearly interpolated voltage maps showing the scalp distribution of differences in ERPs elicited by target words produced using EEGLAB v4.512 for MatLab software: scalp distributions of comparisons between unrelated and indirectly related in controls and patients in the N400 time window.

unrelated primes (e.g. truck, see Table 2). Targets were counterbalanced across three lists in a Latin Square design (67 pairs per condition) such that, across all participants, exactly the same target was seen in each of the three conditions (see Kreher et al., 2006). Participant viewed different lists in sessions one and two to ensure that they never saw the same target in the same condition more than once, thus avoiding any systematic repetition priming effects.

2.2.1. Session 1: implicit semantic monitoring

Participants pressed a button only when they detected a word describing a type of food. Such food words were introduced as occasional filler probes; no food word appeared in the prime–target pairs of interest.

Trials began with a central fixation (500 ms), followed by a 500 ms blank screen. Prime and target words were then each presented for 250 ms (ISI 100 ms). Following a 900 ms ISI (to avoid component overlap), a second word-pair trial appeared. In between every two trials, the 900 ms ISI was followed by a 3000 ms non-verbal cue indicating participants could blink.

2.2.2. Session 2: explicit semantic matching

Participants pressed a button following the presentation of each word-pair to indicate whether the prime and target were unrelated, somewhat related, or highly related. Stimulus presentation was identical to that of the first session, with the exception that, following the target in each word-pair, the screen was blank for 1250 ms (to avoid vertical eye movement artifact as participants prepared to enter their responses).

2.3. ERP recording and analysis

Twenty-nine active tin electrodes were held in place on the scalp by an elastic cap (Electro-Cap International, Inc., Eaton, OH), see Fig. 1 for montage. Electrodes were placed below the left eye and at the outer canthus of the right eye to monitor eye movements, and also over the left mastoid (reference) and right mastoid (recorded actively to monitor for differential mastoid activity). The EEG signal was amplified by an Isolated Bioelectric Amplifier System Model HandW-32/BA (SA Instrumentation Co., San Diego, CA) with a bandpass of 0.01 to 40 Hz and was continuously sampled at 200 Hz by an analogue-to-digital converter. The stimuli and behavioral responses were monitored by a digitizing computer.

Averaged ERPs, time-locked to target words, were formed off-line from trials free of ocular and muscular artifact and were quantified by calculating the mean amplitude (relative to a 100 ms prestimulus baseline) 300–500 ms post-target onset. As we were interested, a priori, in examining differences between groups in N400 priming effects, we proceeded straight to ANOVAs that examined direct priming effects (directly-related vs. unrelated targets) and indirect priming effects (indirectly-related vs. unrelated targets) (see Kreher et al., 2008). For each contrast, two omnibus mixed-design analyses of variance (ANOVAs) – one covering mid regions and another covering lateral regions across the scalp – were conducted in order to examine the relative modulation of the N400 mean amplitude within this time window to primed and unprimed target words. Each of these initial omnibus analyses included only participants who took part in both tasks (12 controls and 17 patients) and had within-subject factors of Priming (2 levels: directly related vs. unrelated; indirectly related vs. unrelated) and Task (2 levels: implicit vs. explicit) and a between-subject factor of Group (2 levels: patients vs. controls). In order to examine how the modulation of the waveforms varied across the scalp surface, the scalp was subdivided into regions along the anterior–posterior distribution of the scalp surface, at both mid and lateral sites (each region contained 3 electrode sites), see Fig. 1, and each ANOVA also included these within-subject scalp topography factors — Region and, for the lateral ANOVA, Hemisphere. Significant interactions involving the Priming and Region factors were first parsed by assessing the ERPs at each Region. After that, significant Priming × Task × Group interactions were parsed in each participant group in two ways: first, by examining the effect of Priming within each task,[2] and second, by examining the effects of Task on the amplitude of the N400 evoked by related, indirectly-related and unrelated targets separately. The Geisser–Greenhouse correction was applied to repeated measures with more than one degree of freedom (Greenhouse and Geisser, 1959) and a significance level of alpha = .05 was used as, in all cases, a priori hypotheses were tested.

3. Results

3.1. Behavioral accuracy

3.1.1. Implicit task

One patient with a 40% error rate was excluded from all ERP analyses. Both groups correctly identified food words more than 90% of the time; controls were significantly more accurate than patients in identifying food words appearing in the prime position ($t(26) = 2.299$, $p < .05$) but not the target position ($p > .1$).

3.1.2. Explicit task

Both patients and controls were significantly more accurate in their ratings of unrelated word-pairs than directly-related and indirectly-related word-pairs (all Fs > 7.7, all ps < .05). Additionally, both groups were significantly less accurate in classifying indirectly-related word-pairs than directly-related word-pairs ($F(1,26) = 41.44$, $p < .001$). The absence of Group by Priming interactions indicated that there were no significant differences in relatedness ratings accuracy between patients and controls (all ps > .3).

3.2. ERPs

10% of trials across all participants and conditions were excluded due to EEG artifact.

[2] To maximize power, these within-group/within-task follow-ups included all participants who completed the task of interest. Within-group analyses using the subsample of participants who completed both tasks revealed the same pattern of findings except for the indirect N400 priming effect in patients during the implicit task that approached, rather than reached, significance ($F(1,15) = 4.3$, $p = .06$).

3.2.1. 300–500 ms: the N400[3]

3.2.1.1. Direct priming. In comparing ERPs to directly-related and unrelated targets, omnibus ANOVAs revealed significant main effects of Priming (all $Fs > 29.4$, all $ps < .001$), and interactions between Priming and Region (all $Fs > 9.7$, all $ps < .01$). Follow-up ANOVAs revealed main effects of Priming in all regions (all $Fs > 12.4$, all $ps < .01$), reflecting a widespread direct semantic priming N400 effect across both tasks and groups (although this effect was larger at posterior than anterior regions).

A significant interaction between Priming, Task and Group was observed in the posterior mid region ($F(1,26) = 7.0$, $p < .05$), reflecting a differing pattern of N400 modulation across tasks between patients and controls. Follow-ups examining priming in this region indicated that controls exhibited a large direct N400 priming effect in the explicit task ($F(1,14) = 37.1$, $p < .001$) but no direct priming in the implicit task ($F < 1$), whereas patients showed significant direct priming N400 effects in both the implicit and explicit tasks ($Fs > 6.3$, $ps < .05$; Fig. 2). Follow-ups examining the effects of Task in this region indicated that controls showed no effect of Task on the N400 evoked by directly-related targets ($F < 1$), but a significantly more negative N400 to unrelated targets in the explicit than the implicit task ($F(1,11) = 43.5$, $p < .001$). In contrast, patients showed no effect of Task on N400 amplitudes to directly-related or unrelated targets ($Fs < 2.4$, $ps > .1$; Fig. 3).

3.2.1.2. Indirect priming. In comparing ERPs to indirectly-related and unrelated targets, the omnibus ANOVAs revealed significant interactions between Priming and Region (all $Fs > 8.3$, all $ps < .01$). Follow-ups showed main effects of Priming in mid and lateral posterior regions, reflecting a significant indirect N400 priming effect across both tasks and both groups (all $Fs > 6.8$, all $ps < .01$; Fig. 2).

Once again, a significant interaction between Priming, Task and Group was observed in the posterior mid region ($F(1,26) = 6.6$, $p < .05$). Follow-ups demonstrated that while patients exhibited a significant indirect N400 priming effect in the implicit task ($F(1,16) = 4.5$, $p < .05$), they showed no indirect priming in the explicit task ($F < 1$). Healthy controls showed the opposite pattern, exhibiting a large indirect priming N400 effect in the explicit task ($F(1,14) = 25.1$, $p < .001$), but no indirect priming in the implicit task ($F < 1$; Fig. 2). Additional follow-ups revealed that controls displayed a trend toward more negative N400 s to indirectly-related targets ($F(1,11) = 4.3$, $p = .06$), and, as outlined above, significantly more negative N400s to unrelated targets, in the explicit than in the implicit task. In contrast, schizophrenia patients once again showed no effect of Task on the amplitude of either the indirectly-related or the unrelated targets ($Fs < 1$; Fig. 3).

[3] There were no significant main effects of Group (all $Fs < 1$), Priming (all $Fs < 1.21$, all $ps > .3$) or Group by Priming interactions (all $Fs < 1$) on the amplitude of ERPs during the first 200 ms. Thus, any effects of Group or Priming on later ERP components cannot be attributed to baseline differences.

3.3. Effects of clinical variables

Spearman rank correlations within the patient group explored relationships between direct and indirect N400 priming effects (calculated by subtracting mean amplitudes of primed from unprimed target words) and clinical measures at the CP2 electrode site (Kreher et al., 2008). Language disorganization on the TLC correlated with both direct (Spearman's $r = .53$, $p < .05$) and indirect (Spearman's $r = .57$, $p < .05$) priming effects in the implicit, but not the explicit, task ($ps > .1$). This association was specific: there were no significant correlations between N400 priming effects in the implicit task and negative symptoms, hallucinations, delusions, overall psychopathology excluding conceptual disorganization, chlorpromazine equivalents, or length of illness (all $ps > .1$).

4. Discussion

The use of the semantic priming paradigm in schizophrenia patients has produced differing findings, alternately suggesting that concepts in semantic memory are hyper-activated, hypo-activated, or not differentially activated in patients relative to healthy controls. Our results suggest that these alternate accounts of semantic memory function in schizophrenia may not be inconsistent with one another, and that the different results reported may be explained, in part, by experimental task. At a short SOA, and using a task requiring no behavioral response on trials of interest, schizophrenia patients, relative to healthy controls, showed normal (and, in TD patients, increased) direct and indirect neural priming at posterior sites. Using the same SOA and stimuli, when these same patients were explicitly instructed to semantically match prime and target, they exhibited reduced direct and indirect priming at these sites compared with controls. These findings demonstrate that semantic decision-making significantly reduces neural semantic priming in schizophrenia patients, even when other experimental conditions bias toward automatic processing.

In controls, the increase in the N400 semantic priming effect during explicit, relative to implicit, processing is consistent with our previous findings in younger individuals (Kreher et al., 2006): the N400 evoked by unrelated (and, to some extent, indirectly-related) targets was more negative in the explicit than in the implicit task, reflecting a more extensive strategic search for a semantic relationship. In contrast, schizophrenia patients showed no such increase in N400 amplitude to unrelated targets across tasks, suggesting that they failed to employ a strategic search through semantic memory. During the explicit task, this resulted in reduced or absent N400 priming effects, relative to healthy controls.

A reduced N400 effect due to an impairment in the use of controlled or strategic semantic priming in schizophrenia has been well documented at longer SOAs (reviewed by Kuperberg et al., in press-a, b). The present study demonstrates that this impairment can lead to abnormally reduced semantic priming in patients even at short SOAs. This is consistent with the recent study by Mathalon et al. (in press) who also demonstrated reduced N400 priming in schizophrenia at a short SOA using a semantic matching task. We also suggest that a failure to mobilize semantic search strategies may help

explain the abnormally reduced N400 priming in schizophrenia at short SOAs using a lexical decision task (e.g. Kiang et al., 2008). In healthy individuals, there is a substantial body of literature indicating that strategic searches for semantic relationships between prime and target can bias such lexical decisions (see Neely, 1991 for discussion).

During the implicit task, patients, but not controls[4] exhibited direct and indirect priming effects at posterior sites. Thought disorder was significantly correlated with the magnitude of direct and indirect priming effects within the patient group. No such correlation was observed in the explicit task. These observations suggest that when the experimental task does not entail a strategic semantic search on each target, and when the SOA is short, abnormal increases in automatic spreading activation in TD patients can be detected.

In sum, these findings may serve to illuminate some sources of discrepancies within the schizophrenia semantic priming literature, and provide further evidence that the mechanisms of increased spreading activation and reduced strategic use of context in schizophrenia patients are not mutually exclusive, and may, in fact, occur in the same patients under different circumstances.

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Contributors

Authors Kreher and Kuperberg designed the study, performed statistical analyses, and wrote the manuscript. Author Goff is Director of the MGH Schizophrenia Program and Medical Director of the Freedom Trail Clinic where all patients were recruited. He contributed to diagnostic assessment, training of raters and interpretation of data. All authors have approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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[4] In contrast to a previous study in young healthy adults (Kreher et al., 2006), the control group in the present study did not show a significant indirect ERP priming effect during the implicit task. We attribute this discrepancy to the effect of age, which is known to reduce the amplitude of the N400 in healthy adults (e.g. Kutas and Iragui, 1998).

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