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 investigated the role of behavioral task in determining neural semantic priming effects using ERPs. 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 350msec: 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.**

Index Terms – semantic priming, schizophrenia, N400, thought disorder.

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). Schizophrenia researchers have utilized the semantic priming paradigm to provide evidence for both theories, interpreting their findings with different explanatory mechanisms. 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 (msec) after the onset of primed, versus 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 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 Mizenberg et al., 2002; Pomarol-Clotet et al., 2008). Several researchers have observed that thought-disordered (TD) schizophrenia patients exhibit increased direct (Manschreck et al., 1988; Spitzer et al., 1994; Moritz et al., 2001; Chenery et al., 2004) and indirect (Spitzer, 1993; Weisbrod et al., 1998; Moritz et al., 2001, 2002) semantic priming, relative to non-TD patients and healthy controls. These findings have often been interpreted as evidence for an

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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, Vinogradov, and Shenaut, 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.

Studies utilizing ERPs to index semantic priming 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 at short SOAs in patients. Kreher et al. (2008) reported findings consistent with behavioral studies, demonstrating an increased early (between 300-400msec 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 750msec 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 effects of increased spreading activation in patients: 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. (submitted), reporting an abnormally reduced N400 priming effect in patients to pictures that were directly-related (versus unrelated) to their preceding word primes at an SOA of 325msec when the requirement was 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 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

Participants performed the implicit task in session 1 and the explicit task in session 2. To minimize strategic effects on implicit processing, session 1 always took place at least two weeks before session 2.

2.1. Participants

Eighteen outpatients meeting DSM IV-TR criteria for schizophrenia were recruited from the Lindemann Mental Health Center, Boston, and eighteen healthy volunteers, screened to exclude histories of psychiatric disorders (Spitzer et al., 1992) and current medication affecting the central nervous system, were recruited by advertisement. Of these, seventeen patients and twelve healthy controls completed both lab sessions. All participants were right-handed (Oldfield, 1971; White & 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 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, 1979b) on session 1. There were no changes in medication between session 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 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). Each participant viewed different lists in sessions one and two to ensure that he/she never saw the same target in the same condition more than once.

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 (500msec), followed by a 500msec blank screen. Prime and target words were then each presented for 250msec (ISI 100msec). Following a 900msec ISI (to avoid component overlap), a second word-pair trial appeared. In between every two trials, the 900msec ISI was followed by a 3000msec 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 1250msec (to avoid contamination of the data with vertical eye movement 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 Figure 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 100msec prestimulus baseline) 300-500msec 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 midline 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 omnibus analyses 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 midline and lateral sites (each region contained 3 electrode sites), see Figure 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 x Task x Group interactions were parsed by examining the effect of Priming within each task, in each participant group. The Geisser-Greenhouse correction was applied to repeated measures with more than one degree of freedom (Geisser and Greenhouse, 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

3.2.1. Early ERPs

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 200msec.

3.2.2. 300-500msec: The N400

3.2.2.1. 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 (Table 3), reflecting a widespread direct semantic priming N400 effect across both tasks and groups (although this effect was larger at posterior than anterior regions), Figure 2.

Significant interactions between Priming and Task (Table 3) were observed across all regions, indicating that the modulation of the N400 to directly-related, relative to unrelated, targets was greater in the explicit than the implicit task. Of particular note, a significant interaction between Priming, Task and Group was observed in the posterior midline region (Table 3), indicating that these task effects differed between patients and controls. Follow-up ANOVAs in this region indicated that controls exhibited a large direct N400 priming effect in the explicit task but no direct priming in the implicit task, whereas patients showed significant direct priming N400 effects in both the implicit and explicit tasks (Figure 3, Table 4).

Follow-ups examining the effects of Task on the amplitude of the N400 evoked by directly-related and unrelated targets separately also revealed significant group differences: controls showed no effect of Task on the amplitude of the N400 evoked by directly-related targets, but a significantly more negative N400 to unrelated targets in the explicit than the implicit task. In contrast, patients showed no effect of Task on the N400 evoked by either directly-related or unrelated targets (Table 4).

3.2.2.2. 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 midline and lateral posterior regions, reflecting a significant indirect N400 priming effect across both tasks and both groups (Table 3; Figure 4).

Once again, a significant interaction between Priming, Task and Group was observed in the posterior midline region (Table 3), reflecting a pattern of N400 modulation across tasks that differed between patients and controls (Figure 3). Follow up ANOVAs demonstrated that while patients exhibited a marginal indirect N400 priming effect in the implicit task, they showed no indirect priming at all in the explicit task. Healthy controls showed the opposite pattern, exhibiting a large indirect priming N400 effect in the explicit task, but no indirect priming in the implicit task (Table 4). Additional follow-ups revealed that controls displayed a trend toward more negative N400s to indirectly-related targets, and, as outlined above, significantly more negative N400s to unrelated targets, in the explicit than 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 (Table 4).

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 support the hypothesis 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 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.

An impairment in the use of controlled or strategic semantic priming in schizophrenia, has been well documented at longer SOAs (Kuperberg et al., in press). The present study demonstrates that this impairment can lead to abnormally reduced semantic priming in patients even at short SOAs. This is consistent with recent study by Mathalon et al. (submitted) 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[1] 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. 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.

[1] 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).

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.

TABLES AND FIGURES

TABLE 1

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)*	Target: 5 (2)*
Indirectly-related	lion-stripes	Prime: 70.55 (159.01)	Prime: 6 (2)
		Target: 96.37 (478.96)*	Target: 5 (2)*
Unrelated	truck-stripes	Prime: 70 (133)	Prime: 5 (1)
		Target: 96.37 (478.96)*	Target: 5 (2)*

Means are shown with standard deviation in brackets.

*The frequency and word length of the targets across the three conditions are identical because the exactly 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).

TABLE 2

DEMOGRAPHIC AND PSYCHOPATHOLOGICAL DATA OF HEALTHY CONTROLS AND SCHIZOPHRENIA PATIENTS.

Parameter	*Controls*	*Patients*
Gender (M/F)	9/3	11/5
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)

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 pre-morbid IQ (Blair and Spreen, 1989). Patients and controls were matched on gender and race distribution, age, education, parental SES (Hollingshead, 1965) and premorbid IQ (Blair & Spreen, 1989) (all ps > .13).

TABLE 3

MIXED MODEL (PRIMING X TASK X GROUP) ANOVAS AT ALL REGIONS OF ANALYSIS.

Region of Analysis		*Directly-related vs. Unrelated*		*Indirectly-related vs. Unrelated*	
		Effects	F Value	Effects	F Value
Midline	Anterior Frontal	P	14.303***	P	<1
Regional	Midline	P x T	4.246*		
ANOVAs	Frontal Midline	P	23.009***	P	<1
		P x T	11.378**		
	Central Midline	P	22.746***	P	2.540
		P x T	17.594***		
	Central-posterior	P	31.943***	P	8.251**
	Midline	P x T	25.858***		
	Posterior Midline	P	39.336***	P	20.496***
		P x T	28.583***	P x T x G	6.628*
		P x T x G	6.958*		
Lateral	Anterior Lateral	P		P	<1
Regional		P x T			
ANOVAS	Posterior Lateral	P		P	6.775**
		P x T			

†p < .1 *p < .05 **p < .01. ***p < .001.

P = Priming (Directly-related vs. unrelated, Indirectly-related vs. unrelated)

T = Task (Implicit, Explicit)

G = Group (Controls, Patients)

The degrees of freedom for all F-values in this table are [1,26].

TABLE 4

SIMPLE EFFECTS ANOVAS FOLLOWING UP GROUP BY PRIMING BY TASK INTERACTIONS IN THE POSTERIOR REGION

	Controls	*Patients*
A. N400 priming effects: directly-related vs. unrelated		
Implicit task	F < 1	F(1,15) = 10.572**
Explicit task	F(1,11) = 36.837***	F(1,15) = 19.302**
B. N400 priming effects: indirectly-related vs. unrelated		
Implicit task	F < 1	F(1,15) = 4.255†
Explicit task	F(1,11) = 25.504***	F < 1
C. N400 amplitudes: effect of Task		
Directly-related	F < 1	F(1,15) = 2.35
Indirectly-related	F(1,11) = 4.26†	F < 1
Unrelated	F(1,11) = 43.46***	F < 1

†p < .1 *p < .05 **p < .01. ***p < .001.

FIGURE 1

ELECTRODE MONTAGE AND REGIONS USED IN ANALYSIS. MIDLINE REGIONS: A – ANTERIOR FRONTAL, B – FRONTAL, C – CENTRAL, D – CENTRAL-POSTERIOR, E – POSTERIOR. LATERAL REGIONS: F – ANTERIOR, G – POSTERIOR.

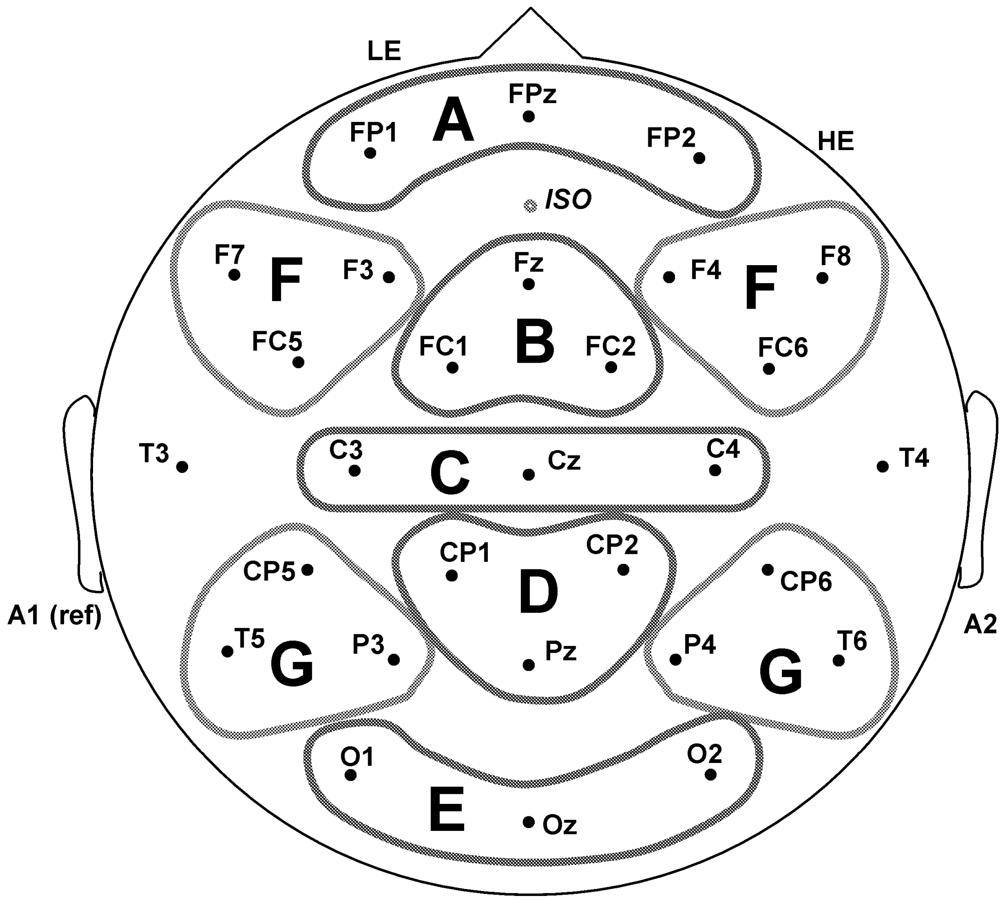


FIGURE 2.
ERPS TO DIRECTLY-RELATED AND UNRELATED TARGET WORDS AT 5 PARIETAL-OCCIPITAL SITES BY GROUP (PATIENT, CONTROL) AND TASK (IMPLICIT, EXPLICIT).

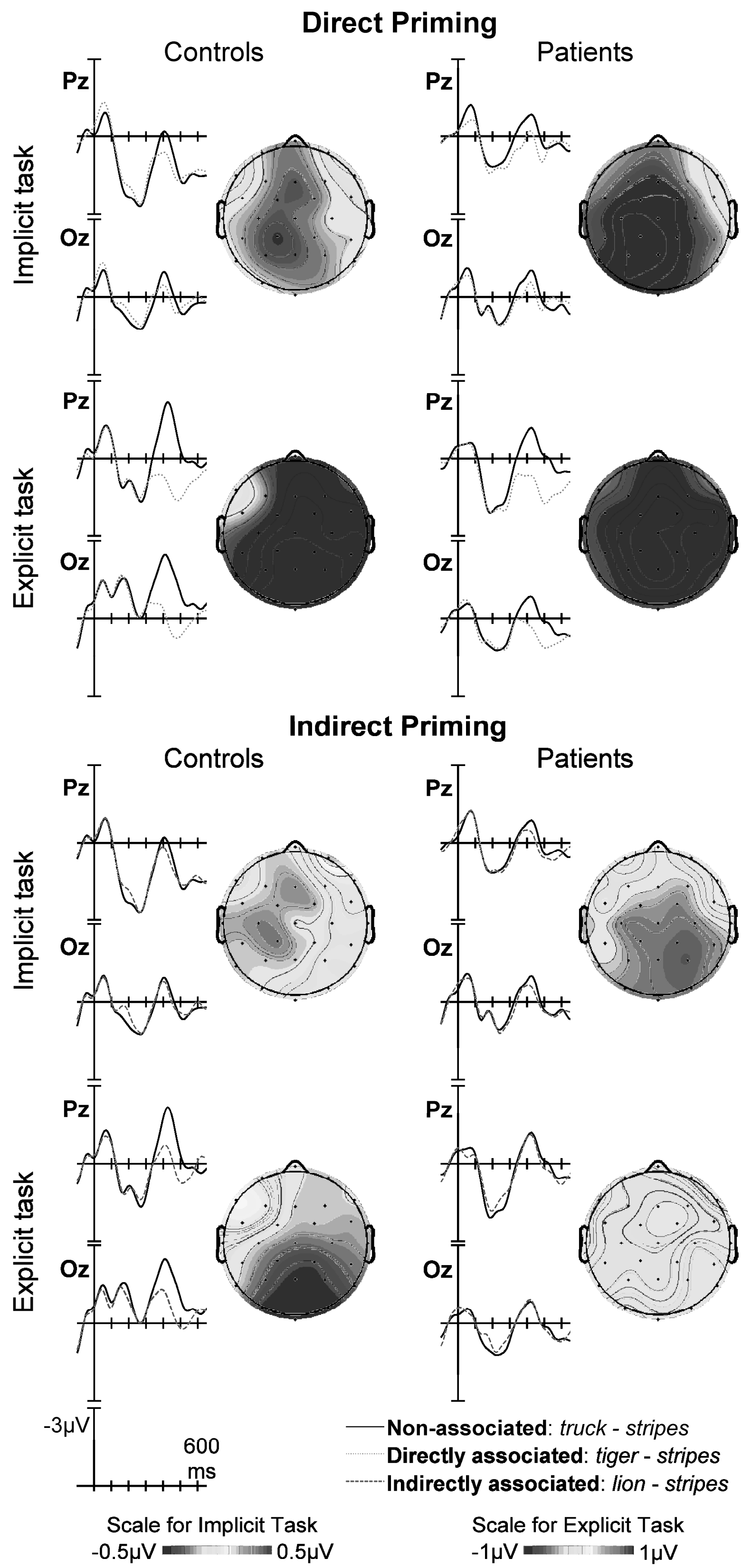
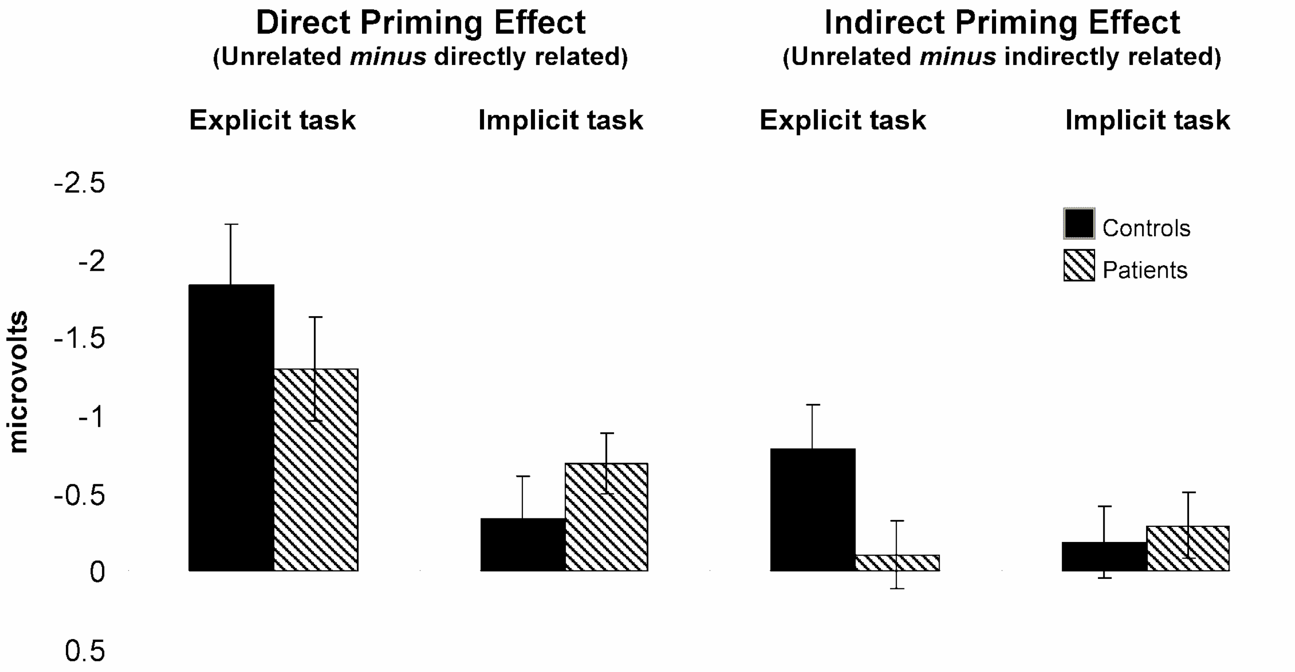


FIGURE 3.

BAR GRAPH DEPICTING N400 DIFFERENCE SCORES (UNRELATED-DIRECTLY-RELATED; UNRELATED-INDIRECTLY-RELATED) BY GROUP (PATIENT, CONTROL) AND TASK (IMPLICIT, EXPLICIT).



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