

Slow and steady: sustained effects of lexico-semantic associations can mediate referential impairments in schizophrenia

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Abstract The present study investigated the contribution of lexico-semantic associations to impairments in establishing reference in schizophrenia. We examined event-related potentials as schizophrenia patients and healthy, demographically matched controls read five-sentence scenarios. Sentence 4 introduced a noun that referred back to three possible referents introduced in Sentences 1–3. These referents were contextually appropriate, contextually inappropriate but lexico-semantically associated, and contextually inappropriate and lexico-semantically nonassociated. In order to determine whether participants had correctly linked the anaphor to its referent, the final sentence reintroduced each referent, and participants indicated whether the last two sentences referred to the same entity. Results indicated that between 300 and 400 ms, patients, like healthy controls, used discourse context to link the noun with its preceding referent. However, between 400 and 500 ms, neural activity in patients was modulated only by lexico-semantic associations, rather than by discourse context. Moreover, patients were also more likely than controls to incorrectly link the noun with contextually inappropriate but lexico-semantically associated referents. These results suggest that at least some types of

referential impairments may be driven by sustained activation of contextually inappropriate lexico-semantic associations.

Keywords Schizophrenia · Language · ERPs · Discourse · Referential impairment · Context · Anaphor · Comprehension

Language production and comprehension require going beyond the meaning of the individual words that make up a text or an utterance in order to formulate a global discourse representation, or *situation model* (cf. Zwaan & Radvansky, 1998). Specifically, healthy adults establish causal relationships between events, link multiple references to characters and objects, and represent space and time information by using cues such as context and lexico-semantic associations to integrate relevant information and inhibit irrelevant information. Although building this rich discourse representation occurs quickly and seemingly effortlessly in healthy adults, patients with schizophrenia appear to have difficulty with such processes (for a review, see Ditman & Kuperberg, 2010).

Language disturbances in patients with schizophrenia are well documented. They manifest at their most extreme in patients with thought disorder, in which speech is dominated by semantic associations at the expense of building overall message meaning. Bleuler (1950), however, conceived of semantic associative disturbances as being a fundamental mechanism that can explain not only thought disorder itself but multiple aspects of cognitive dysfunction in schizophrenia. Even patients without clinically obvious thought disorder show evidence of illogical thinking that can lead to poor communication and social dysfunction. One well-

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documented aspect of such poor communication in schizophrenia is a failure to fully establish reference—that is, a failure to link multiple mentions of the same character or object in discourse (see Ditman & Kuperberg, 2010, for a review; see also Docherty, DeRosa, & Andreasen, 1996; Rochester & Martin, 1979). The present study aimed to determine whether and how associative disturbances contribute to such failures to establish referential coherence in schizophrenia.

Most studies of associative disturbances in schizophrenia have examined the relationships between single words using the semantic priming paradigm. The associative semantic priming effect describes the faster response times (RTs) or attenuated electrophysiological response to target words that are preceded by semantically associated (vs. nonassociated) prime words. Under experimental conditions biasing toward automatic processing, most studies find normal priming effects in schizophrenia, suggesting that patients' implicit and automatic use of semantic associations is preserved (Barch et al., 1996; Blum & Freides, 1995; Ober, Vinogradov, & Shenaut, 1995; Vinogradov, Ober, & Shenaut, 1992); indeed, in patients with positive thought disorder, priming can even be increased, suggesting some increase in the automatic spreading activation between semantic associates in such patients (Kreher, Holcomb, Goff, & Kuperberg, 2008; Manschreck et al., 1988; Moritz et al., 2001; Moritz, Woodward, Koppers, Lausen, & Schickel, 2002; Spitzer et al., 1994).

In contrast, under experimental conditions biasing toward strategic, controlled processing, such as the use of longer times between primes and targets or the use of tasks requiring explicit evaluations of the relationships between primes and targets, such as lexical decisions (Barch et al., 1996; Besche et al., 1997; Kiang, Kutas, Light, & Braff, 2008; Passerieux et al., 1997) or explicit semantic judgments (Kreher, Goff, & Kuperberg, 2009), semantic priming effects are abnormally reduced in patients (reviewed by Kuperberg, Ditman, Kreher, & Goldberg, 2009; Minzenberg, Ober, & Vinogradov, 2002; Pomarol-Clotet, Oh, Laws, & McKenna, 2008). These priming deficits are thought to be driven by a failure of patients to engage different types of strategic semantic mechanisms. For example, patients may appropriately activate semantic associates to the prime but, when required to use such information to make a decision about the prime–target relationship, they may fail to select the word that matches the target or to appropriately suppress or inhibit other activated semantic associates. This type of selection and suppression failure might even, under some circumstances, lead to increased activity to semantically associated versus nonassociated targets. Such findings have been detected behaviorally in chronic patients, who can show longer RTs to associated (vs. nonassociated) targets (Maher, Manschreck, Redmond, & Beaudette, 1996), and in a recent

fMRI study, in which we reported increased neural activity to semantically associated relative to nonassociated word pairs in patients (Kuperberg, Deckersbach, Holt, Goff, & West, 2007; see also Han et al., 2007).

During sentence processing, there are once again many situations in which schizophrenia patients are able to effectively use semantic associations between words to derive overall meaning (e.g., Kuperberg, Kreher, Goff, McGuire, & David, 2006; Miller & Phelan, 1980; Sitnikova, Salisbury, Kuperberg, & Holcomb, 2002). In other situations, however, processing breaks down. As in single-word priming paradigms, this is most likely to occur when there is a requirement to select the contextually appropriate meaning and to suppress irrelevant meanings of a word or its associates. For example, patients with schizophrenia, like healthy controls, are able to use a sentence context to activate meanings of homonyms (words with more than one meaning). Unlike controls, however, they appear unable to suppress the contextually inappropriate dominant meanings of these homonyms when the sentence context only moderately biases the subordinate meaning (Titone, Levy, & Holzman, 2000). Such a failure to suppress contextually inappropriate meanings can lead to processing being driven by semantic associates rather than overall sentence context. For example, Sitnikova et al. showed that, when critical words within sentences were associated with the dominant meaning of a preceding homonym but were incongruous with the overall sentence context, patients, unlike controls, failed to detect the incongruity. However, when critical words were both semantically nonassociated with individual preceding words and incongruous with the sentence context, incongruities were normally detected. Finally, we found that patients were insensitive to incongruous verbs within sentences when these verbs were semantically associated with words in the preceding context (Kuperberg, Kreher, et al., 2006; Kuperberg, Sitnikova, Goff, & Holcomb, 2006). Once again, patients showed no problems in detecting incongruities when the violated verb was unrelated to preceding words in the context.

Most patients' communication deficits manifest at the level of the whole discourse rather than of individual words or sentences (Andreasen, 1986; Rochester & Martin, 1979). Despite this, very few studies have examined how patients with schizophrenia build up meaning across sentence boundaries, and only one study to date has examined the fast, online neural processes that are engaged as discourse unfolds word by word (Ditman & Kuperberg, 2007). In that study, participants read three-sentence scenarios in which the final sentences varied in their causal relationship with their preceding context. Highly causally related and intermediately causally related scenarios were matched on pure lexico-semantic associations. Neural activity in patients did not differentiate between critical words in these

two types of scenario. These findings suggest that processing was once again driven by association rather than by discourse context, even across sentence boundaries.

The present study examined another mechanism of building coherence in discourse—the establishment of reference. To establish referential coherence, multiple references to the same character or object must be connected together within and across clauses, to come up with a global representation of the described events, actions, and characters, known as a *situation model* (cf. Zwaan & Radvansky, 1998). As indicated above, referential impairments in patients with schizophrenia have been well documented (Docherty et al., 1996; Docherty, Strauss, Dinzeo, & St-Hilaire, 2006; Hoffman, Hogben, Smith, & Calhoun, 1985; Noel-Jorand, Reinert, Giudicelli, & Dassa, 1997; Rochester & Martin, 1979). These impairments include confused references (e.g., a word or phrase that could refer to one of several possible referents), missing-information references (e.g., referring to information that has not been previously mentioned), or vague references (e.g., using a word that lacks specificity) (Docherty et al., 1996, 2006).

Although they are correlated with measures of positive thought disorder, referential failures are not unique to thought-disordered patients, and they appear to be a stable across clinical states in patients with schizophrenia (Docherty, Cohen, Nienow, Dinzeo, & Dangelmaier, 2003; Docherty et al., 1988), suggesting that they may be trait markers of schizophrenia. In addition, they are also more common in first-degree relatives of patients with schizophrenia than in first-degree relatives of healthy controls (Docherty & Gottesman, 2000; Docherty et al., 1998). Understanding the mechanisms contributing to referential disturbances in schizophrenia may therefore provide insight into the neural underpinnings of schizophrenia as a whole.

We aimed to determine whether lexico-semantic associative disturbances contribute to impairments in establishing reference during discourse processing in schizophrenia. Healthy adults quickly use multiple sources of information to modulate the activation of current concepts during comprehension, consistent with theories of discourse comprehension such as the landscape model (Rapp & van den Broek, 2005; van den Broek, Young, Tzeng, & Linderholm, 1999). Of most relevance to the present research, previous studies demonstrated that both lexico-semantic associative and discourse-level global contextual information are used to establish reference in discourse (e.g., Ditman, Holcomb, & Kuperberg, 2007; cf. Rapp & van den Broek, 2005). To investigate the establishment of reference in patients with schizophrenia, we employed a rich five-sentence discourse context that included lexico-semantically associated distractors. In three introductory sentences, we introduced three potential referents. In a fourth sentence, a noun was presented that needed to be linked back to one of

these referents. For example, in the scenario, “A suit is worn to work. A costume is worn during Halloween. A ring is worn on a finger. The night before work, Lisa ironed the outfit,” participants are required to link the noun “outfit” back to one of the three referents (“suit,” “costume,” “ring”). To make the correct link—that is, to link “outfit” back to the word “suit”—we must use the discourse context to override or suppress the lexico-semantic association between “costume” and “outfit.” We predicted that schizophrenia patients would fail to suppress “costume,” leading to a failure to establish the correct reference to “suit.” However, we predicted that, like healthy controls, they would be able to appropriately select “suit” over a nonassociated word, “ring.” In addition, we examined behavioral (accuracy and RT) measures as participants indicated whether the last two sentences referred to the same entity.

To test these hypotheses, we measured event-related potentials (ERPs) in a final sentence that reintroduced one of the three referents. ERPs index neural activity with millisecond temporal resolution. Our focus was on the modulation of the N400, a negative deflection with a centroparietal scalp distribution that peaks approximately 400 ms after word onset, and with larger negative-going amplitudes reflecting the ease of mapping the meaning of a word on to its preceding context and the information stored within semantic memory (e.g., Holcomb, 1993; reviewed by Kutas & Federmeier, 2000). The N400 is sensitive to semantic relationships between words (Bentin, McCarthy, & Wood, 1985; Rugg, 1984), stored knowledge within semantic memory (Federmeier & Kutas, 1999), real-world knowledge (Hagoort, Hald, Bastiaansen, & Petersson, 2004), and sentence- and discourse-level contexts (Kutas & Hillyard, 1984; Van Berkum, Hagoort, & Brown, 1999). Importantly, the N400 is modulated by referential processes across sentence boundaries (Ditman et al., 2007, 2008).

On the basis of our previous study using this paradigm in young, healthy individuals (Ditman et al., 2007), we predicted that healthy controls would produce a smaller-amplitude N400 to the reintroduced correct referent (“suit”) than to the lexico-semantically associated but contextually incongruous referent (“costume”). We predicted that schizophrenia patients would fail to show this difference in ERP modulation and that, relative to controls, they would incorrectly judge scenarios containing these contextually incongruous words to be referentially coherent and would take longer to do so. This would provide evidence that patients’ failure to suppress the semantically associated distractor leads to their failure to establish reference. However, we expected that, like healthy controls, patients would show a smaller N400 to the reintroduced correct referent (“suit”) than to the lexico-semantically nonassociated incorrect referent (“ring”), that they would correctly judge scenarios containing these words to lack referential coher-

ence, and that their RTs would be similar to those for scenarios with correct referents.

Method

Stimulus construction

The creation of the stimuli used in this study has been described in a previous report (Ditman et al., 2007). Five-sentence scenarios were constructed from 252 triplets of words. Each word triplet consisted of a noun describing a category and two exemplars that would serve as referents to that noun (e.g., outfit: “suit,” “costume”). In each scenario, each of the first three sentences presented a potential referent, which was always the subject of the sentence. The fourth sentence introduced the category noun, termed the *anaphor*, always as a sentence-final word that referred back to one of the referents. Two of the potential referents in Sentences 1–3 were exemplars of the categorical anaphor. The context of this fourth sentence biased toward one of the three referents as the correct interpretation of the anaphor. The fifth sentence began with a restatement of one of the three referents introduced in the first three sentences (with the first word always being “The”). This gave rise to three conditions. In the first, the restated referent was the correct referent: It was both contextually appropriate and lexico-semantically associated with the categorical anaphor (e.g., “suit”). In the second, the restated referent was contextually inappropriate but was still associated with the categorical anaphor (e.g., “costume”); in the third, the restated referent was contextually inappropriate and was lexico-semantically nonassociated with the categorical anaphor (e.g., “ring”).

Items were rotated through conditions, so that on different lists they served as contextually appropriate/associated, contextually inappropriate/associated, and contextually inappropriate/nonassociated referents. This gave rise to four lists in total, each with 126 scenarios: 42 contextually appropriate/associated, 42 contextually inappropriate/associated, and 42 contextually inappropriate/nonassociated. The order of contextually appropriate/associated, contextually inappropriate/associated, and contextually inappropriate/nonassociated referent presentation was counterbalanced across scenarios such that each appeared in the first, second, and third sentences an equal number of times within each list. Each participant viewed one list.

Below is an example scenario from each of the four lists, demonstrating how items were rotated through each condition (although the examples below are shown with the correct referent presented first, the order in which these potential antecedents were presented was also rotated between scenarios). In the example below, the potential

referents appear in bold, the categorical anaphors appear in capital letters, and the restated referents are italicized (but not in the actual study):

1. A **suit** is worn to work. A **costume** is worn during Halloween. A **ring** is worn on a finger. The night before work, Lisa ironed the OUTFIT. The *suit*_{appro/assoc} / *costume*_{inappro/assoc} / *ring*_{inappro/nonassoc} was fancy.
2. A **costume** is worn during Halloween. A **suit** is worn to work. A **bracelet** is worn on a wrist. The night before Halloween, Lisa ironed the OUTFIT. The *costume*_{appro/assoc} / *suit*_{inappro/assoc} / *bracelet*_{inappro/nonassoc} was fancy.
3. A **ring** is worn on a finger. A **bracelet** is worn on a wrist. A **suit** is worn to work. Lisa’s finger sparkled with the JEWELRY. The *ring*_{appro/assoc} / *bracelet*_{inappro/assoc} / *suit*_{inappro/nonassoc} was fancy.
4. A **bracelet** is worn on a wrist. A **ring** is worn on a finger. A **costume** is worn during Halloween. Lisa’s wrist sparkled with the JEWELRY. The *bracelet*_{appro/assoc} / *ring*_{inappro/assoc} / *costume*_{inappro/nonassoc} was fancy.

Participants

Sixteen patients meeting the DSM–IV criteria for schizophrenia, confirmed via the Structured Clinical Interview for DSM–IV–TR Axis I Disorders (First, Spitzer, Miriam, & Williams, 2002b) and chart examination, all but 1 of whom were receiving stable doses of typical and/or atypical antipsychotic medication, were initially recruited from the Lindemann Mental Health Center, Boston. Sixteen demographically matched volunteers on no medication and without histories of psychiatric disorders (First, Spitzer, Miriam, & Williams, 2002a) were recruited through an advertisement. All participants were native, primarily monolingual English speakers who had not learned any other language before age 5 years. All were right-handed (Oldfield, 1971; White & Ashton, 1976) and without histories of head trauma, neurological disorder, substance abuse within the previous 6 months, or histories of substance dependence (as assessed using the DSM–IV). Written informed consent was obtained following the guidelines of the Massachusetts General Hospital and Tufts Medical Center Human Subjects Research Committees. Clinical assessments were carried out using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1987), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989), the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), and the Brief Psychiatric Rating Scale (BPRS; Lukoff, Nuechterlein, & Ventura, 1986) as measures of overall psychopathology.

Demographic and psychopathological data for the patients and controls are summarized in Table 1. The

Table 1 Demographic and psychopathological characteristics of healthy controls and schizophrenia patients

	Controls	Patients
<i>N</i>	16	16
Male/Female	11 M/5 F	10 M/6 F
Age	42.31 (8.11)	40.13 (10.07)
Years of Education	14.63 (2.68)	12.94 (2.14)
Premorbid IQ	112.74 (8.79)	109.79 (11.33)
Parental SES	3.56 (0.96)	2.73 (1.44)
CPZ Equivalent	—	494.44 (440.12)
PANSS	—	64.63 (17.17)
SANS	—	39.33 (16.31)
SAPS	—	38.50 (24.23)

Means are shown with standard deviations in parentheses. SES, social economic status; CPZ, chlorpromazine; PANSS, Positive and Negative Syndrome Scale (Kay et al., 1987); SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1989); SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1987).

patients and controls were matched closely on gender and race, and there was no significant difference between the groups in age, years of education, parental socioeconomic status (SES; as assessed by the Hollingshead Index), or A-NART (Blair & Spreen, 1989) (all $ps > .05$).

Stimulus presentation and task

Each trial began with a 400-ms fixation with an interstimulus interval (ISI) of 100 ms. The first three sentences were presented self-paced. The fourth and fifth sentences were presented word by word at 400 ms per word and with a 100-ms ISI, with the exception of the sentence-final word. This rate of presentation was comparable to that used in a previous ERP discourse comprehension study in patients with schizophrenia (Ditman & Kuperberg, 2007). It is also in keeping with patients' natural speed of reading sentences presented word by word, as indicated in a previous self-paced reading study (Kuperberg, Kreher, et al., 2006). The sentence-final word appeared with a period and was followed by a 750-ms blank screen interval and then a "?". This cued participants to indicate whether the final two sentences were related to one another by pressing a "yes" or a "no" button on a game pad (counterbalanced across participants). This delayed response reduced contamination of the ERP waveform by response-sensitive components such as the P300 (Donchin & Coles, 1988) and triggered the onset of the next trial. Participants completed 6–12 practice trials at the start of the experiment in order to ensure task comprehension. All patients reported being able to comfortably read the words on the computer screen following the practice session.

Electrophysiological recording

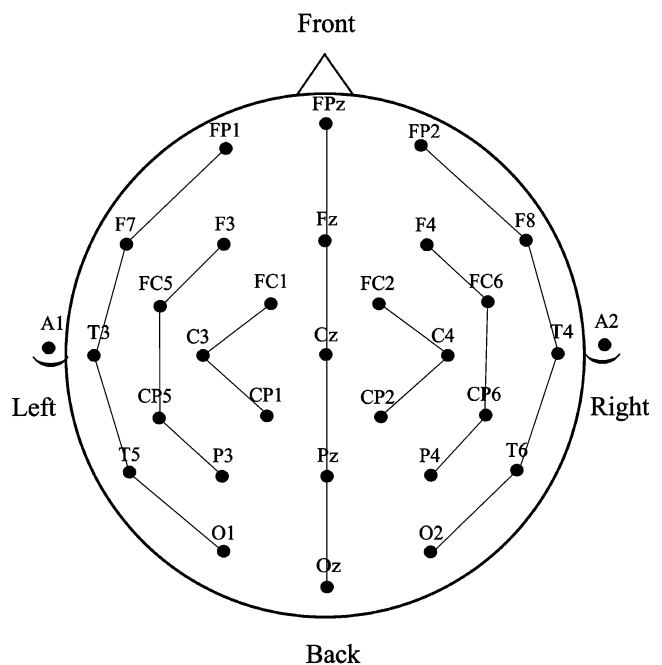
Twenty-nine active tin electrodes were held in place on the scalp by an elastic cap (Electro-Cap International, Inc., Eaton, OH); see Fig. 1. Electrodes were also placed below the left eye and at the outer canthus of the right eye to monitor vertical and horizontal eye movements, and on the left and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

Behavioral data analysis

A 3 (referential condition: contextually appropriate/associated, contextually inappropriate/associated, contextually inappropriate/nonassociated) \times 2 (group: controls, patients) mixed model ANOVA, with Referential Condition as a within-subjects factor and Group as a between-subjects factor, was performed on the accuracy data and on RTs to correctly answered trials. Planned comparisons were conducted to follow up on significant effects.

ERP data analysis

Analyses were conducted on the mean amplitudes of ERPs evoked by critical words (using a 100-ms prestimulus baseline), regardless of participants' ratings. We character-

**Fig. 1** Electrode montage

ized the N400 across two 100-ms time windows: 300–400 ms and 400–500 ms. This yielded a fine-grained analysis of the time course of the N400, capturing its upslope and onset as well as its downslope and offset (see De Grauwe, Swain, Holcomb, Ditman, & Kuperberg, 2010; Kreher et al., 2008), as well as captured the differences observed in Figs. 3 and 4 below. Two repeated measures ANOVAs—one at midline sites and one at nonmidline sites—were conducted at each time window in order to yield statistical information about differences in the distribution of effects. Both midline and nonmidline ANOVAs included the within-subjects factor of Referential Condition (contextually appropriate/associated, contextually inappropriate/associated, contextually inappropriate/nonassociated). In addition to this factor, the midline ANOVA included anterior, central, and posterior sites along the midline electrode column (anterior-to-posterior [A–P] distribution: Fz, Cz, Pz) in order to examine the anterior-to-posterior distribution of the effect, and the nonmidline ANOVA included the factors Hemisphere (left, right), A–P Distribution (anterior, central, posterior), and Column (peripheral, lateral, medial), resulting in six regions covering the nonmidline sites: left-peripheral (F7, T3, T5), right-peripheral (F8, T4, T6), left-lateral (FC5, CP5, P3), right-lateral (FC6, CP6, P4), left-medial (FC1, C3, CP1), and right-medial (FC2, C4, CP2) (see Fig. 1). A Greenhouse–Geisser correction was applied to analyses with more than one degree of freedom in the numerator. We report original degrees of freedom with corrected p values. Significant interactions were further examined with simple-effects tests and planned comparisons.

In addition, correlations were conducted between (1) the difference scores between each of the pairwise comparisons in the two time windows and (2) the totals for SAPS and SANS; positive thought disorder, delusions, and hallucinations as assessed by the SAPS; and chlorpromazine equivalents. Alpha was set to $p < .05$.

Results

Behavioral data

Accuracy (See Fig. 2a.) Both patients and controls were fairly accurate in their responses to the probe when it followed contextually appropriate/associated scenarios and contextually inappropriate/nonassociated scenarios, but both were less accurate when the probe followed contextually inappropriate/associated scenarios. A 2 (group: patients, controls) \times 3 (referential condition: contextually appropriate/associated, contextually inappropriate/associated, contextually inappropriate/nonassociated) repeated measures ANOVA was performed on the accuracy data, revealing a main effect of referential condition, $F(2, 60) = 24.91$, $p < .001$, and a marginal Group \times Referential

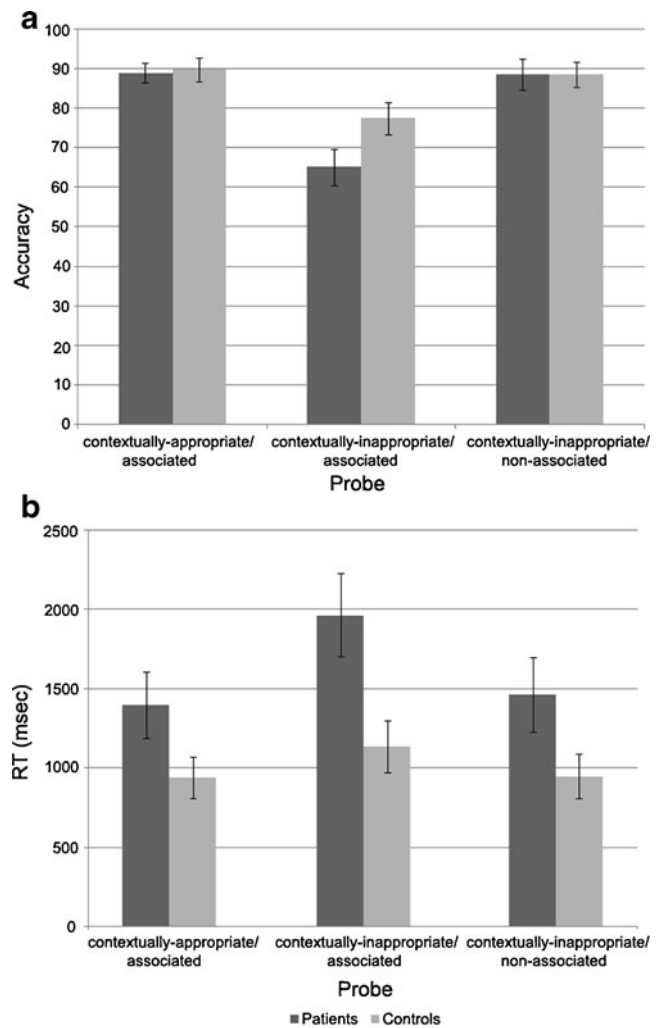


Fig. 2 (a) Accuracy data and (b) response time (RT) data for patients with schizophrenia (dark gray bars) and healthy controls (light gray bars)

Condition interaction, $F(2, 60) = 3.05$, $p < .07$. There was no main effect of group, $F(1, 30) = 1.97$, $p > .10$.

Examination of each group separately indicated that both patients and controls were least accurate in the contextually inappropriate/associated sentences, but this decrement in accuracy was larger in patients than in controls (main effect of referential condition: in controls, $F(2, 30) = 6.99$, $p < .001$; planned comparisons, $p < .05$ for contextually inappropriate/associated relative to other conditions; in patients, $F(2, 30) = 18.53$, $p < .001$; planned comparisons, $p < .001$ for contextually inappropriate/associated relative to other conditions). Follow-ups comparing patients and controls for each condition separately indicated that patients performed less accurately than controls to contextually inappropriate/associated probes, $t(30) = 2.23$, $p < .05$, but there were no between-group differences in responses to contextually appropriate/associated probes, $t(30) = 0.80$, $p > .10$, or contextually inappropriate/nonassociated probes, $t(30) = 0.18$, $p > .10$.

Response times (See Fig. 2b.) A 2 (group: patients, controls) x 3 (referential condition: contextually appropriate/associated, contextually inappropriate/associated, contextually inappropriate/nonassociated) repeated measures ANOVA was performed on the RT data. This revealed a similar pattern of results, with a main effect of referential condition, $F(2, 60) = 16.50, p < .001$, and a Group x Referential Condition interaction, $F(2, 60) = 3.63, p < .05$. In addition, patients were overall slower in responding [main effect of group: $F(1, 30) = 5.17, p < .05$].

As above, in order to further examine the interaction, we performed simple-effects ANOVAs for patients and controls separately. Both patients and controls were slower to respond to probes following contextually inappropriate/associated scenarios relative to both other conditions, but the relative difference in RTs was larger in patients than in controls [main effect of referential condition: in controls, $F(2, 30) = 4.17, p < .05$; planned comparisons, $p = .05$ for contextually inappropriate/associated vs. contextually appropriate/associated, $p < .01$ for contextually inappropriate/associated vs. contextually inappropriate/nonassociated; in patients, $F(2, 30) = 12.36, p < .001$; planned comparisons, $p < .01$ for contextually inappropriate/associated relative to both other conditions]. In addition, pairwise comparisons comparing groups for each condition separately indicated that patients and controls only differed significantly in RTs to contextually inappropriate/associated probe, $t(30) = 2.67, p < .05$, although there were marginally significant differences between the groups in RTs to contextually appropriate/associated [$t(30) = 1.87, p = .07$] and contextually inappropriate/nonassociated [$t(30) = 1.89, p = .07$] probes.

ERP data

Artifact contamination from eye movements or amplifier blocking led to the rejection of 14.24% of the trials in controls and 15.24% of the trials in patients. A 2 (group: patients, controls) x 3 (referential condition: contextually appropriate/associated, contextually inappropriate/associated, contextually inappropriate/nonassociated) repeated measures ANOVA was performed to ensure that artifact rejection did not differ between the conditions and/or participant groups. There was no main effect of group or referential condition and no interaction between these variables (all $ps > .10$).

Early N400: 300–400 ms As can be seen in Figs. 3, 4, and 5, both patients and controls were sensitive to differences between the referential conditions, although neural activity was modulated differentially by these conditions in patients and controls, as evidenced by Group x Referential Condition x A–P Distribution interactions [midline, $F(4, 120) =$

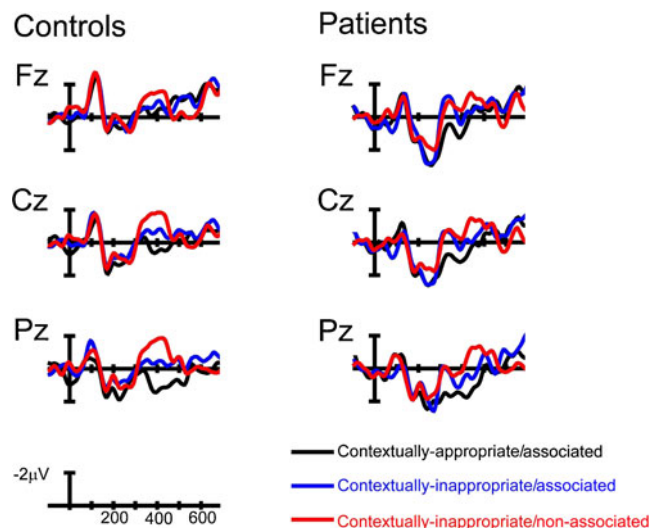


Fig. 3 ERPs in healthy adults and patients with schizophrenia at the midline electrode sites

$3.91, p < .05$; nonmidline, $F(4, 120) = 3.14, p < .05$]. To follow up on these interactions, separate ANOVAs were conducted in controls and patients. In controls, main effects of referential condition [midline, $F(2, 30) = 10.52, p < .001$; nonmidline, $F(2, 30) = 12.70, p < .001$] demonstrated that the reintroduced referents in the contextually appropriate/associated condition evoked the smallest-amplitude N400, followed by a medium-amplitude N400 to contextually inappropriate/associated referents, and the largest-amplitude N400 evoked to contextually inappropriate/nonassociated referents. This effect was seen primarily at centroparietal sites, as demonstrated by Referential Condition x A–P Distribution interactions [midline, $F(4, 60) = 3.97, p < .05$; nonmidline, $F(4, 60) = 3.84, p < .05$], consistent with the scalp distribution of the N400 component.

In contrast, N400 amplitude in patients did not differentiate between the two contextually inappropriate conditions (contextually inappropriate/associated and contextually inappropriate/nonassociated), although both conditions evoked larger-amplitude N400s than did the discourse-appropriate referents (contextually appropriate/associated condition), as evidenced by main effects of referential condition [midline, $F(2, 30) = 4.32, p < .05$; nonmidline, $F(2, 30) = 3.37, p = .05$]. A Referential Condition x Column interaction at nonmidline electrode sites [$F(4, 60) = 3.72, p < .05$] indicated that this effect was maximal at medial and lateral columns. No other interactions with referential condition were statistically significant (all $ps > .10$).

Late N400: 400–500 ms Again, within this later time window, neural activity in both controls and patients differentiated between the referential conditions, but the pattern of neural activity was not the same across both groups, as evidenced by Group x Referential Condition x

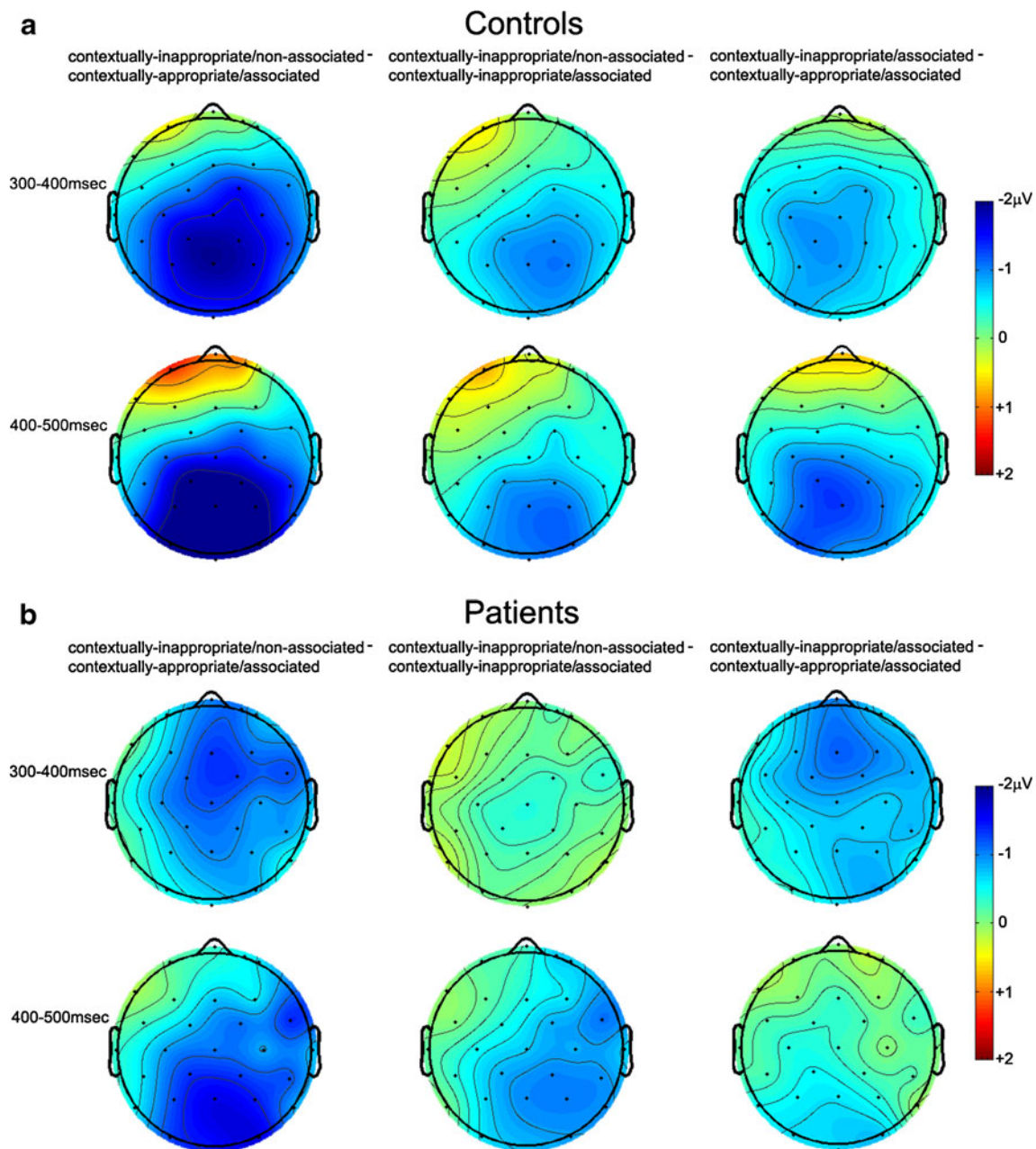


Fig. 4 Voltage maps depicting the distribution of neural activity across the scalp in (a) healthy controls and (b) patients with schizophrenia

A–P Distribution interactions in both midline and nonmidline ANOVAs [midline, $F(4, 120) = 3.76, p < .05$; nonmidline, $F(4, 120) = 3.13, p < .05$]. To follow up on these interactions, separate ANOVAs were conducted to examine control and patient data. As in the 300- to 400-ms time window, neural activity in controls continued to discriminate between the three referential conditions, as evidenced by main effects of referential condition [midline, $F(2, 30) = 7.31, p < .01$; nonmidline, $F(2, 30) = 10.94, p < .001$]. Consistent with the scalp distribution of the N400, this effect was largest at centroparietal sites, as evidenced by Referential Condition \times A–P Distribution interactions

[midline, $F(4, 60) = 14.08, p < .001$; nonmidline, $F(4, 60) = 13.64, p < .001$]. Pairwise t tests at centroparietal electrode sites demonstrated N400 amplitude differences between the three conditions ($ps < .05$).

In patients, unlike in the previous time window, neural activity was modulated by lexico-semantic associations rather than contextual appropriateness. Main effects of referential condition confirmed differences between the three conditions [midline, $F(2, 30) = 3.98, p < .05$; nonmidline, $F(2, 30) = 4.46, p < .05$], which were largest at posterior sites [Referential Condition \times A–P Distribution interactions: midline, $F(4, 60) = 3.46, p < .05$;

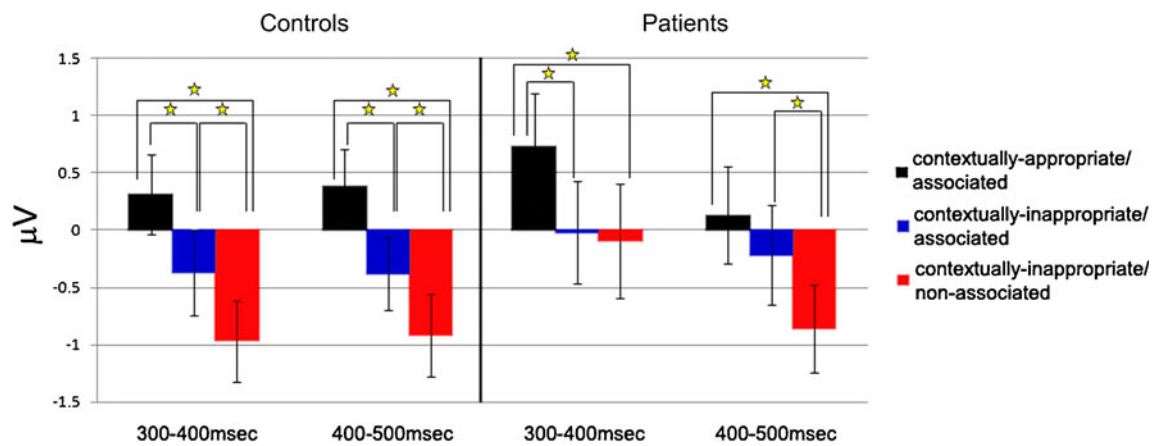


Fig. 5 Mean amplitude (in microvolts) averaged across all electrode sites for controls (*left side*) and patients (*right side*), with error bars depicting the standard errors of the means. Significant differences between conditions are denoted with stars

nonmidline, $F(4, 60) = 5.59, p < .01$]. Pairwise t tests at centroparietal electrode sites demonstrated that both related conditions (contextually appropriate/associated and contextually inappropriate/associated) evoked equal N400 amplitudes that were smaller than those for the nonassociated condition ($ps < .05$).

Correlations with psychopathological variables within the patient group No correlations reached statistical significance (all $ps > .05$).

Discussion

The present study examined the use of lexico-semantic associations in establishing referential links in discourse context. Schizophrenia patients and healthy adults read scenarios that required them to link a noun back to one of three referents. To determine whether these nouns had been linked to the correct referent—that is, whether referential coherence had been correctly established—each of the three possible referents was restated in the fifth sentence and neural activity was measured. We also measured the RTs and accuracy as participants explicitly judged reference coherence—that is, whether the last two sentences referred to the same entity. Neural activity in both patients and controls showed a centroparietal scalp distribution between 300 and 500 ms, consistent with the timing and distribution of the N400 component. ERP findings in the healthy controls indicated that they were able to use both lexico-semantic associations and global contextual information to establish reference during online processing: The smallest N400 amplitude was evoked to contextually appropriate/associated referents, a medium-sized N400 amplitude was evoked to contextually inappropriate/associated referents, and the largest

N400 amplitude was evoked to contextually inappropriate/nonassociated referents during the entire 300- to 500-ms N400 time window. The behavioral data indicated that these lexico-semantic associations remained partially active, leading to later costs in evaluating referential coherence in scenarios with lexico-semantically associated distractor referents: Accuracy to the contextually incongruous but lexico-semantically associated scenarios was impaired relative to the other two conditions, and participants took relatively longer to make these decisions than they did in the other conditions.

Patients with schizophrenia showed a different pattern of findings. In the early 300- to 400-ms time window, there was no differential effect of lexico-semantic association at all: Both contextually inappropriate referents (contextually inappropriate/associated and contextually inappropriate/nonassociated) evoked larger N400s than did the contextually appropriate referent (contextually appropriate/associated). However, by the later 400- to 500-ms window, patients appeared to be inappropriately dependent on lexico-semantic associations, such that these fully overrode discourse context: There was no difference in the N400 to referents that were lexico-semantically associated with the anaphor, regardless of whether they were contextually appropriate or inappropriate; only the contextually inappropriate/nonassociated referents continued to evoke a larger-amplitude N400. Moreover, lexico-semantic associations continued to inappropriately influence behavioral judgments: Patients were less accurate and slower than healthy controls in judging contextually inappropriate scenarios with lexico-semantically associated distractor referents. This impairment was selective, since the patients and controls performed similarly when responding to the other two conditions.

Taken together, these findings suggest that lexico-semantic associations may be more slowly activated in patients than in healthy adults but, once activated, have a long-lasting influence on discourse comprehension at the

expense of global meaning. These results will be discussed in more detail below.

Our ERP findings in healthy adult controls replicate those of the college-aged healthy adults examined in a previous study (Ditman et al., 2007). Healthy adults quickly used *both* lexico-semantic associative and discourse-level global contextual information to establish reference in discourse. These findings are consistent with theories of discourse comprehension, such as the landscape model (Rapp & van den Broek, 2005; van den Broek et al., 1999), that postulate that the activation of current concepts during comprehension is influenced by multiple sources of information, including associations of the text with concepts in semantic memory and prior and current information from the text. They also converge with other ERP studies in demonstrating that these pieces of information can influence lexical activation in parallel (e.g., Ditman et al., 2007; cf. Rapp & van den Broek, 2005). Behaviorally, decreased accuracy and longer RTs to discourse-incongruous lexico-semantically associated distractor referents suggest that these distractor referents may have remained activated at the point of the probe, leading to increased difficulty with evaluating the referential coherence of scenarios containing these items. This remaining activation may be due to a failure to actively suppress information that is inconsistent with the discourse model by the older adults examined in the present study (cf. Gernsbacher, 1991), or it may be the result of a normally functioning, relatively long decay process for concepts that are not reinforced (cf. Linderholm, Virtue, Tzeng, & van den Broek, 2004).

Patients' failure to show a three-way distinction in electrophysiological modulation across the three conditions in either the early or the late N400 time window indicates that they were unable to use both discourse-level and semantic associative information in parallel to establish referential coherence. During the early N400 time window (300–400 ms), the absence of any modulation to contextually incongruous lexico-semantically associated referents relative to contextually incongruous lexico-semantically nonassociated ones suggests that patients were initially unable to use semantic associations at all to facilitate the establishment of referential coherence. This reduced effect of semantic associations is consistent with the reduced semantic priming effects shown by patients at relatively long SOAs relative to controls: In the present study, the associated referents and the anaphor were in different sentences and the SOA was 500 ms. It is important to note, however, that patients' initial ability to use some discourse context is encouraging and suggests that when such context is highly explicit and reinforces real-world knowledge, patients are able to use such information appropriately.

During the late N400 time window (400–500 ms), the attenuation of the waveform to contextually incongruous/semantically associated relative to contextually incongru-

ous/semantically nonassociated referents indicates that patients were able to use such semantic associations later to establish referential coherence. However, at this later stage of processing, the N400 amplitude was influenced solely by semantic association, at the expense of context: Lexico-semantic associations effectively completely overrode discourse-level context, such that the amplitude of the N400 to contextually inappropriate/associated words was equal to that evoked by contextually appropriate/associated ones. These results are consistent with previous electrophysiological findings at the sentence and discourse levels that have also demonstrated that, when pitted directly against one another, close lexico-semantic associations will override an incongruous context (Ditman & Kuperberg, 2007; Kuperberg, Kreher, et al., 2006; Kuperberg, Sitnikova, et al., 2006; Sitnikova et al., 2002). Importantly, as in these previous studies, the abnormality was quite specific: Patients showed the same differentiation as controls between referents in contextually incongruous and congruous discourse when the referent in incongruous discourse was not incongruous associated. These findings extend the previous findings to show that an overdependence on semantic associations may lead to abnormalities in establishing referential coherence at the discourse level, an impairment that is widely observed in patients with schizophrenia.

These ERP findings argue strongly against a generalized performance deficit in patients, for the following reasons. First, the N400 was differentially modulated by lexico-semantically associated lures in the early and late time windows—a unique pattern of activity that can only be accounted for by the specificity of the manipulation. In the early time window, the N400 was not decreased by lexico-semantically associated lures relative to nonassociated ones. This finding indicates that at this point, patients were able to use the discourse context to activate only the appropriate referent and not semantic associates. However, in the late time window, the N400 *was* modulated by lexico-semantically associated lures relative to nonassociated lures. The finding that the patients did not activate semantic associates initially, and then, once activated, these lures influenced discourse comprehension for a sustained time suggests specific impairments in both the initial activation and the later inhibition, or passive decay, of these associations. Second, N400 amplitude was appropriately modulated by the contextually appropriate/associated and contextually inappropriate/nonassociated conditions in both the early and late N400 time windows. Thus, patients were able to use discourse context to modulate neural activity under these conditions. Had patients been unable to perform the task, we would have expected to observe impaired performance in all conditions. However, this was not the case; the specific manipulation (i.e., the addition of lexico-semantic associations to a discourse-incongruent

context) led to differential neural modulation in response to the contextually inappropriate/associated condition.

The behavioral findings give further insights into the observed referential impairment. Like the controls, patients' behavioral performance was worse in the presence of a lexico-semantically associated distractor referent, which continued to exert an influence on participants' actual judgments about these referential relationships. However, this relative deficit was particularly marked in patients. Patients and controls did not differ in accuracy or RTs to probes following contextually congruous scenarios or scenarios with contextually incongruous and lexico-semantically nonassociated critical words; rather, patients only performed less accurately and responded more slowly when contextually incongruous words were lexico-semantically associated with the anaphor. This finding suggests that patients were able to use the global context to appropriately evaluate scenarios that were contextually congruous or incongruous without lexico-semantic associations, but they were specifically impaired at evaluating the coherence of the scenarios when they contained lexico-semantically associated lures. Whether this prolonged activation was the result of an inability to actively suppress globally incongruous information (cf. Gernsbacher, 1991) or of a potentially longer, more passive decay process for information that is not reinforced (cf. Linderholm et al., 2004) is unclear. However, the results unequivocally demonstrate that these contextually incongruous lexico-semantic associations remain activated to a greater extent, and thus more severely impair comprehension and (specifically) the ability to establish referential coherence, in patients with schizophrenia than in healthy adults.

Slow and steady: mechanisms of semantic associative abnormalities in schizophrenia

The combination of online neural and behavioral measures in this study sheds some light on the interaction between the automatic activation of lexico-semantic associates and the controlled semantic selection and suppression mechanisms in schizophrenia. There is now fairly consistent evidence that patients are able to use context to appropriately activate lexico-semantically associative information. Most problems occur when there are increased demands to select the most appropriate lexical item and to suppress or deactivate contextually inappropriate distractors. Here, we used the precise temporal resolution of ERPs to demonstrate again that patients are able to use lexico-semantic associations during language processing (albeit with slight delay), but that they later fail to suppress or deactivate these associations, which becomes manifest a few milliseconds later in the ERP response and at the end of the discourse in the behavioral response. This provides evidence for

the inappropriately sustained effect of lexico-semantic associations.

This inappropriately sustained effect of lexico-semantic associations in schizophrenia may be most likely to manifest during sentence and discourse processing when there are increased demands to integrate or combine different types of representations to construct an overall meaning: Within sentences, there are demands to integrate and combine semantic and syntactic information in order to determine “who does what to whom” (Kuperberg, Sitnikova, et al., 2006), and across sentences, coherence must be built through the establishment of referential and other types of discourse relationships (Ditman & Kuperberg, 2010). Patients' impairments in combination and integration may leave associative semantic memory-based activity relatively unchecked; thus, as previously argued, abnormalities in integrative and associative activity may actually reflect two sides of the same coin (see Kuperberg, 2007, for a theoretical framework in healthy individuals, and Kuperberg, 2010, for a discussion of how this may play out in schizophrenia). An open question is whether such an imbalance between integrative/combinatorial and associative activity during the buildup of meaning can be explained by more general working memory and executive function mechanisms (including selection and suppression) that are also known to be impaired in schizophrenia (Barch & Smith 2008; Kerns, Nuechterlein, Braver, & Barch, 2008; Lee & Park, 2005).

Relationship with thought and communication failures in schizophrenia

Nonetheless, this raises the question of how thought disorder (disorganized speech) actually arises. In previous work, we argued that thought disorder reflects the extreme of an imbalance between integrative and associative activity (Kuperberg, 2010), suggesting that an additional, bottom-up, automatic associative abnormality (see, e.g., Kreher et al., 2008; Spitzer et al., 1994) shifts the system into further imbalance, leading to the intrusion of semantic associates to speech output. The present study does not provide direct evidence for this hypothesis: We saw no correlation between neural patterns of activity and clinical measures of thought disorder within the patient group. However, the relatively small number of participants in the present experimental study may have limited our ability to detect a correlation.¹

¹ Previous studies that have found an association between positive thought disorder and referential communication disturbances were based on at least twice as many participants as the present study. In addition, positive thought disorder and referential communication impairments are more likely to correlate in severely ill patients (Docherty et al., 2003), and we employed a relatively stable outpatient sample in the present study.

Open questions

As with all studies in patients with chronic schizophrenia, it is important to consider the possible confound of medication effects. We did not observe any correlation of medication dosage with neural or behavioral measures in schizophrenia patients in the present study. However, it will be important for future studies to examine these types of processes in patients in their first episode of illness, as well as to investigate whether these impairments are present in first-degree relatives of schizophrenia patients, in whom referential disturbances have been previously reported (Docherty & Gottesman, 2000; Docherty et al., 1998).

It is also unclear from the present study what is the neuroanatomical basis of the abnormally sustained effect of lexico-semantic associations we observed in the schizophrenia patients. ERPs have excellent temporal but poor spatial resolution, and we can therefore deduce little about the sources underlying the patterns of ERP activity observed at the surface of the scalp. Previous intracranial electrode studies (e.g., Nobre & McCarthy, 1995), fMRI studies using N400 paradigms (e.g., Kuperberg et al., 2003), and studies using source localization algorithms in conjunction with magnetoencephalography (MEG) and fMRI (e.g., Dale et al., 2000) have indicated that the N400 component has multiple neuroanatomical sources, with lexico-semantic activity likely localized within the left posterior lateral temporal cortex but influenced by both bottom-up, automatic activity from the inferior temporal cortex and top-down activity from prefrontal cortices (reviewed by Lau, Poeppel, & Phillips, 2008). Integrative activity during language processing is thought to be mediated primarily within the left inferior prefrontal cortex and more superior dorsolateral prefrontal cortices (cf. Hagoort, 2005; e.g., Kuperberg, Sitnikova, & Lakshmanan, 2008). In previous work, we hypothesized that an imbalance between integrative and lexico-semantic associative activity is linked to an imbalance in activity across temporal and prefrontal cortices, and some evidence for this idea comes from a study of language processing at the sentence level in schizophrenia (Kuperberg, West, Lakshmanan, & Goff, 2008). Future studies using fMRI in conjunction with ERPs and MEG will determine whether a similar imbalance of activity is seen when, as in the present paradigm, semantic associations are pitted against referential coherence during the buildup of meaning across a whole discourse.

Conclusions

In sum, the present study used a novel psycholinguistic paradigm to investigate the influences of discourse context and semantic associations in establishing discourse coherence in patients with schizophrenia. We found that when a strong

context was provided, patients were able to initially use this to modulate neural activation. However, ultimately, when this context was pitted against conflicting semantic associations, patients were unable to maintain the influence of context, and activation was instead modulated by these lexico-semantic associations, leading to referential failure. These findings are the first to link associative disturbances to failures of reference in schizophrenia. More generally, they clearly show that associative abnormalities in schizophrenia are not specific to clinical thought disorder, but may, as Bleuler (1950) hypothesized, reflect a fundamental mechanism that contributes to other types of thought and communication deficits in schizophrenia.

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