UNIVERSITY OF CALIFORNIA, SAN DIEGO

Event-rated brain potential studies of semantic processing in schizophrenia and schizotypal personality

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by

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The dissertation of Michael Wai Jong Kiang is approved, and it is acceptable in quality and form for publication on microfilm:

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Chair

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To my parents

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ABSTRACT OF THE DISSERTATION

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Existing hypotheses propose that abnormal spread of activation in semantic long-term memory causes disorganized speech in schizophrenia. There is in fact behavioral and event-related brain potential (ERP) evidence that schizophrenia patients are deficient in using meaningful contextual stimuli to pre-activate related concepts and thereby facilitate, or prime, their processing. In contrast, results from other behavioral studies suggest that, following meaningful stimuli, schizophrenia patients activate weakly related concepts in particular to a *greater* than normal degree. In order to account for these

different results, some researchers have proposed that the former abnormality may occur at shorter intervals and the latter at longer intervals following a meaningful stimulus.

The present studies examined in finer detail how relatedness and time course modulate activation of concepts in semantic memory in schizophrenia patients, and in healthy individuals as a function of schizotypal personality, which may be genetically linked to schizophrenia. As a measure of semantic activation, these studies used the amplitude of the N400 ERP component elicited by meaningful stimuli. N400 amplitude is normally reduced by factors thought to pre-activate the eliciting stimulus, such as its relatedness to preceding context.

We found evidence that schizophrenia patients have deficits in using meaningful contextual stimuli to pre-activate related concepts in general, over both a short and a long time course. The apparent discrepancy between these results and those of previous behavioral studies of schizophrenia patients suggesting increased spread of activation to weakly related items may stem from response-related factors affecting behavioral reaction time but not N400 amplitude. In addition, we found that patients' N400 abnormalities were specifically correlated not with disorganized language production, but with positive psychotic symptoms (i.e., delusions and hallucinations). Thus, semantic priming abnormalities may play a causal role in the development of delusions. Analogous to what we observed in schizophrenia patients, N400 data in healthy individuals were consistent with an association between higher schizotypy and decreased use of context to activate relate items and/or to inhibit unrelated items. This finding supports the view that decreased semantic priming may be one of a number of neurophysiological markers common to schizophrenia and schizotypal personality.

Chapter 1

General Introduction

1.1. Schizophrenia and Disorganized Speech

Schizophrenia is a mental disorder with a lifetime prevalence of approximately 1% worldwide (Jablensky & Sartorius, 1988). Its clinical features are often classified into psychotic, "negative," and cognitive symptoms. Psychotic symptoms are: delusions, i.e., fixed false beliefs; hallucinations – sensory perceptions in the absence of real stimuli; and disorganized speech and behaviour, in which sequences of language and action appear logically disconnected or irrelevant to their context. Negative symptoms include apathy, diminished speech, and social withdrawal. Patients with schizophrenia also exhibit deficits in fundamental cognitive functions such as attention and memory. The symptoms of schizophrenia most often manifest in early adulthood and have a chronic fluctuating course thereafter (American Psychiatric Association, 2000). They frequently have a devastating impact on patients' social and occupational function. In fact, schizophrenia is the seventh leading cause of years lived with disability worldwide, and the third leading cause among individuals aged 15 to 44 (Murray & Lopez, 1996). Although epidemiological studies indicate that schizophrenia has both genetic and environmental determinants, these factors, and the mechanisms whereby they lead to symptoms, remain unclear (Sawa & Snyder, 2002).

The pioneering phenomenologist of schizophrenia, Eugen Bleuler, characterized disorganized speech, or "disturbance of associations," as a cardinal sign of the disorder.

He observed that "frequently the patient drops a thought in an entirely matter-of-course way, only to proceed to quite a different one that has no recognizable associative connection with the previous one" (Bleuler, 1911/1950). Furthermore, "often a reply to a question is only a formal retort, but its content has nothing to do with the question posed" (Bleuler, 1911/1950). For instance:

> A female patient, supposed to help in the household work, is asked why she is not working. The answer, "But I don't understand any French," is logically related neither to the question nor to the situation. (Bleuler, 1911/1950)

Disorganized speech can also be seen in the following excerpt from an interview with a schizophrenia patient:

> Interviewer: Name five different animals.
> Patient: The um, cobra, lion, and other structural animals, farm animals, horses, cats and dogs.
> I: Good. Can you name some fruits?
> P: ... Fruit. Fruits are for those who haven't got any fruits. There's all kinds of fruit. Like fruits uh that are served in a restaurant. The fruit that would... And they what?
> I: Name one kind of fruit that you can get in a restaurant.
> P: Fruit. You can get all kinds of fruits, but they're not, they're worthless huh? (Andreasen & Grove, 1979)

Thus, in disorganized speech, sequences of concepts appear illogical or unusual, and responses to questions seem irrelevant.[1] Disorganized speech varies on a continuum of severity, ranging from unusual or vague wording, to tangentiality in which one topic leads to another in a somewhat digressive manner, to "word salad" containing apparently unrelated words or phrases.

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[1] In psychiatry the term "thought disorder" is frequently used synonymously with "disorganized speech," although, as pointed out by Andreasen (1979), this terminology seems to neglect the possibility that disorganized thought is not the only cause of disorganized speech.

1.2. Semantic Activation in Schizophrenia

1.2.1. Network Model of Semantic Memory

Because schizophrenic disorganized speech appears to reflect abnormalities in using semantic context to bring relevant concepts to mind, researchers have hypothesized that this symptom results from disturbances in how concepts activate one another in semantic long-term memory (McCarley et al., 1999; Nestor et al., 1997; Spitzer, 1997). Semantic long-term memory refers to our knowledge about concepts and about the relationships among them. On one general model (Figure 1.1), semantic long-term memory is represented in a neural network in which concepts are nodes, and meaningful relationships between concepts are links among these nodes (J. R. Anderson & Pirolli, 1984; Collins & Loftus, 1975). Related concepts include: objects and their features (e.g., *CAT-FUR; CAT-BLACK*) or actions (*CAT-MEOW*); categories and their exemplars (*ANIMAL-CAT*); and commonly associated concepts (*CAT-MOUSE*). Each link can be assigned a weight between zero and one, representing associative strength (Spitzer, 1997). A pair of concepts may also be "indirectly" related via one or more mediating nodes (e.g., *CAT- CHEESE,* mediated by *MOUSE*). In that case, the associative strength is the product of the weights of the mediating direct links. The total relatedness of two concepts is the sum of associative strengths of the direct and indirect relationships between them. When a concept node is activated – e.g., by its corresponding word or object stimulus – this activation spreads to related nodes, falling off as a function of decreasing relatedness (Figure 1.2). Greater activation of a concept corresponds to greater priming, or facilitation, of its processing. This model accounts for experimental evidence that processing of meaningful stimuli is facilitated when they are preceded by related as compared to unrelated context. For example, in a lexical decision task, in which stimuli are classified as words or nonwords, individuals are faster to recognize words when they are preceded by a related as opposed to an unrelated prime word (Neely, 1977).[2]

1.2.2. Hypothesis: Increased Spread of Activation

According to one hypothesis for how semantic activation is abnormal in schizophrenia, a given meaningful stimulus (the "prime") causes a greater than normal spread of activation from its corresponding concept node through the surrounding network, leading to greater than normal activation of relatively weak associates in particular (dotted line in Figure 1.3; Spitzer, 1997). This mechanism could in turn cause patients to produce sequences of concepts in their speech that are only weakly related, and thus seem disorganized. This hypothesis predicts that the activation difference between weak associates of a prime and completely unrelated concepts will be greater in patients than in controls. Furthermore, because Spitzer's hypothesis proposes that the strongest associates are normally activated, it predicts that the activation difference between strong and weak associates will be reduced in patients compared to controls.

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[2] This nodal model, with its fixed, unitary representations of concepts, is almost certainly a simplification. For example, it does not account for observed effects of verb aspect (*arrested* vs. *was arresting*) or voice (*arrested* vs. *was arrested*) on priming of related nouns (reviewed in McRae, Hare, Elman, & Ferretti, 2005). A more accurate model of real-world linguistic processing may be one which represents each concept as a discrete, contiguous region of a multidimensional space in which each point represents a possible mental state (Elman, 2004). In this model, precisely which point a meaningful stimulus activates in its corresponding region is modulated by the preceding context. However, a nodal model may adequately approximate priming effects of relatively simple experimental stimuli such as single, uninflected words.

1.2.3. Hypothesis: Decreased Context Use

Alternatively or in addition, disorganized speech in schizophrenia may originate from impairment in making use of meaningful context to activate related concepts (dashed line in Figure 1.3). This impairment could occur by a number of possible mechanisms. For instance, it could result from deficits in attending to elements of the context, in integrating these into a coherent internal representation, or in consolidating or retaining this representation in working memory (Fuller, Luck, McMahon, & Gold, 2005; Kuperberg, McGuire, & David, 1998). Another possibility, postulated by Cohen and Servan-Schreiber (1992) to arise from a deficiency of the neurotransmitter dopamine in prefrontal cortex, is that of decreased gain (the ratio of activation to input) in neural networks that represent context. This would lead to a normal distribution of activation, but uniformly decreased magnitudes of activation. Alternatively, the links between concepts in the semantic network – which are established as the individual learns about the world – could be weaker than normal, either because they failed to develop normally, or because they have been degraded by the disease process. Last but not least, there could be an atypical organization of these concepts and links, causing an unusual set of concepts to be activated as a result of a given stimulus (Kuperberg & Caplan, 2003). Each of these possibilities, or some combination thereof, could produce a decrease in the degree to which context activates concepts normatively related to it. If context is also used to inhibit activation of irrelevant stimuli (M. C. Anderson & Spellman, 1995; Cohen & Servan-Schreiber, 1992; Neely, 1977), all but the last possibility might also result in subnormal inhibition of unrelated concepts. It should be noted that decreased context use is not necessarily mutually exclusive with increased spreading activation, as both of these abnormalities could occur in an individual with schizophrenia, perhaps with different time courses.

1.2.4. Behavioral Evidence

Some behavioral experimental data support the existence of increased spread of activation in schizophrenia. In word-association tests, schizophrenia patients produce a greater number of rare (but not unique) responses, compared to normal controls (Merten, 1993). Moreover, some studies have found that, in thought-disordered schizophrenia patients, words prime their indirect associates (*CAT-CHEESE*) but not their direct associates (*CAT-MOUSE*) to a greater than normal degree (Moritz et al., 2001; Moritz, Woodward, Kuppers, Lausen, & Schickel, 2003; Spitzer, Braun, Hermle, & Maier, 1993). Since indirect associates are considered relatively weak associates, these results are consistent with greater than normal spread of activation to weak associates. In these experiments, the participants' task was to pronounce the target words (Moritz et al., 2003), or to perform a lexical decision task on them (Moritz et al., 2001; Spitzer et al., 1993). Importantly, these studies found this evidence for increased spread of activation in schizophrenia only when the stimulus-onset asynchrony (SOA) between prime and target words was 300 ms or less. Therefore, the authors concluded that the results reflected abnormal "automatic" spread of activation through the semantic network during this relatively short time interval following a prime stimulus (Moritz et al., 2003; Spitzer et al., 1993).

In contrast, other behavioral data are consistent with the hypothesis of decreased context use in schizophrenia. For example, Barch et al. (1996) found that semantic priming for related prime-target word pairs was absent in schizophrenia patients at a long

SOA (950 ms), although it was present at shorter SOAs. This reduced semantic priming is consistent with decreased activation of related targets by their primes. In another experiment (Kuperberg et al., 1998), patients and controls viewed a target word (e.g., *GUITAR*), and were asked to press a button if they then heard that word in an auditory sentence. All participants were slower to respond to target words when they were semantically anomalous (*The crowd was waiting eagerly; the young man drank the GUITAR*) than when they were semantically congruent (*The crowd was waiting eagerly; the young man grabbed the GUITAR*). In addition, however, thought-disordered schizophrenia patients were delayed by the anomaly less than were controls or non-thought-disordered schizophrenia patients, suggesting impaired sensitivity to context. Moreover, in a study in which participants read sentences using the subordinate meanings of homographs (e.g., *Because the musicians were great, we really enjoyed the JAM*), schizophrenia patients showed priming of targets related to both the subordinate and dominant meanings (*BAND* and *JELLY* respectively), whereas controls showed priming only of targets related to the subordinate meaning (Titone, Levy, & Holzman, 2000). Titone et al. thus concluded that the patients were deficient in using context to inhibit the homograph's dominant meaning.

Taken together, the results of these behavioral priming studies suggest that, at relatively short intervals (approximately 300 ms or less) after a semantic stimulus, schizophrenia patients may exhibit a broader than normal spread of activation in the semantic network to weakly related concepts (Moritz et al., 2001; Moritz et al., 2003; Spitzer et al., 1993). Over longer periods, however - such as at longer SOAs in a word-pair paradigm, or during establishment of a sentence context - these patients may be impaired in using context to activate related items (Barch et al., 1996) or to inhibit unrelated items (Kuperberg et al., 1998; Titone et al., 2000).

1.2.5. N400 Event-Related Potential Evidence

Another approach to investigating the functional organization of semantic memory has used the technique of event-related brain potentials (ERPs). ERPs record the electroencephalographic response to experimental stimuli. This response, measured as voltage changes at the scalp, indexes neural activity associated with processing these stimuli. In particular, ERPs reflect the synchronous postsynaptic potentials of groups of pyramidal neurons in the cerebral cortex (Kutas & Federmeier, 2000). ERPs track cognitive processing continuously with millisecond-level temporal resolution, and do not require an overt behavioral response (Kutas & Federmeier, 2000; Luck, 2005).

The N400 is a negative ERP deflection peaking approximately 400 ms after presentation of a potentially meaningful stimulus, such as a word or picture. N400 amplitude has been found to be reduced[3] by factors that facilitate stimulus processing – including frequency of linguistic usage (Rugg, 1990; Van Petten & Kutas, 1990); repetition (Rugg, Brovedani, & Doyle, 1992); and semantic relatedness to the preceding context (Holcomb & Neville, 1990, 1991; Kutas, 1985; Kutas & Hillyard, 1980; Stelmack & Miles, 1990).[4] As an example of the effect of semantic relatedness, *MOUSE* elicits a smaller (less negative) N400 amplitude when preceded by the related word *CAT*

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[3] Because the N400 is a negative deflection in the electroencephalogram, we will use the terms “smaller,” “reduced” or “decreased” to refer to a less negative N400 amplitude, and “larger” or “increased” to refer to a more negative amplitude.

[4] However, N400 amplitude in response to words is *increased* by concreteness (West & Holcomb, 2000) and orthographic neighborhood size (Holcomb, Grainger, & O'Rourke, 2002), possibly reflecting the involvement of additional processing networks.

than when preceded by the unrelated word *CUP*. Likewise, MOUSE elicits a smaller N400 when completing a sentence in a congruent manner (*The cat chased the MOUSE*) than in an incongruent manner (*She spread the warm bread with MOUSE*). Within the framework of the semantic network model, N400 amplitude thus appears sensitive to factors that activate a concept and facilitate its processing. Consequently, like behavioral priming, it has been used to assess the relative degree to which concepts in semantic memory activate one another – with reduced amplitude thought to represent greater activation.

The pattern of results of N400 studies in schizophrenia has been mixed (Table 1). A number of prime-target word-pair studies have found reduced *N400 relatedness effects* (i.e., N400 amplitude differences between related and unrelated targets) in patients versus controls, although N400 amplitudes for either related or unrelated targets per se did not significantly differ between patient and control groups (Condray, Siegle, Cohen, van Kammen, & Steinhauer, 2003; Condray, Steinhauer, Cohen, van Kammen, & Kasparek, 1999; Hokama, Hiramatsu, Wang, O'Donnell, & Ogura, 2003). Other experimenters found larger than normal N400 amplitudes to related targets in schizophrenia patients (Strandburg et al., 1997), suggesting decreased activation of related items; or smaller than normal N00 amplitudes to unrelated targets (Grillon, Ameli, & Glazer, 1991), consistent with decreased inhibition of unrelated items. Likewise, some studies employing sentence-final word paradigms have shown reduced *N400 congruity effects* (N400 amplitude differences between congruent and incongruent words; Kostova, Passerieux, Laurent,

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Saint-Georges, & Hardy-Bayle, 2003; Ohta, Uchiyama, Matsushima, & Toru, 1999). These findings generally appear consistent with impaired use of context to activate related items, or to inhibit unrelated items.

On the other hand, in a picture-word matching task, target words referring to an item from the same category as the picture prime elicited a smaller N400 in patients than in controls, consistent with increased activation of related items (Mathalon, Faustman, & Ford, 2002). Since relatedness was not quantified, it is possible that these targets were on average weakly related to the prime, making the results consistent with the hypothesis of broader spread of activation to weakly related items (Spitzer, 1997). The prime-target SOA in this experiment was 325 ms, shorter than that in any of the other experiments described above.

There have also been reports of uniformly larger-than-normal N400 amplitudes in schizophrenia patients, to targets both related and unrelated to context (Kostova et al., 2003; Nestor et al., 1997; Niznikiewicz et al., 1997). These results could be due to processes affecting the N400 in general, rather than differences in the spread of semantic activation. Finally, some studies did not find any significant N400 abnormalities in schizophrenia (Andrews et al., 1993; Koyama et al., 1994; Koyama et al., 1991; Olichney, Iragui, Kutas, Nowacki, & Jeste, 1997), possibly due to sample characteristics or insufficient statistical power.

Taken together, these N400 results appear broadly consistent with behavioral priming results. The results of Mathalon, Faustman and Ford (2002) are consistent with increased activation of weakly related concepts at relatively short SOAs following a prime stimulus, as reflected in smaller than normal N400 amplitudes to targets weakly related to a prime. However, additional N400 studies, using primes and targets with a range of quantified associative strengths, are needed to confirm this hypothesis. In contrast, over longer time courses - as seen with word pairs at long SOA, or with sentence contexts - there seems to be a deficit in using context to activate related items in general, and/or to inhibit unrelated items. These abnormalities would result, respectively, in abnormally large N400 amplitudes to related targets, and abnormally small N400 amplitudes to unrelated targets, thus causing reduced N400 relatedness effects.

1.3. Semantic Activation in Schizotypal Personality

Although patient studies are an essential avenue to understanding semantic processing abnormalities in schizophrenia, such studies are potentially confounded by effects of medications, or of environmental impoverishment caused by chronic mental illness. A complementary line of research which avoids these confounds involves studying individuals from the non-clinical population as a function of schizotypal personality traits, or schizotypy. This approach may help shed light on the pathophysiology of schizophrenia, as there is evidence that schizotypy shares genetic and neurophysiological features with schizophrenia.

Schizotypal traits are defined as: i) ideas of reference – incorrect interpretations of external events as having a particular personal significance; ii) odd beliefs or magical thinking, such as superstitiousness or beliefs in telepathy or the paranormal; iii) unusual perceptual experiences, e.g., sensing another person's presence or hearing a voice murmuring when there is no one else around; iv) odd speech which is vague, circumstantial or over-elaborate; v) suspiciousness or paranoid ideation; vi) constricted affect; vii) odd behavior; viii) lack of close friends; and ix) social anxiety associated with paranoid fears; American Psychiatric Association, 2000). These traits are qualitatively similar to symptoms of schizophrenia but less severe, and tend to be stable over time. Individuals can be classified dichotomously according to whether or not they meet diagnostic criteria for schizotypal personality disorder (SPD), based on whether they have five or more schizotypal traits to a clinically significant degree (American Psychiatric Association, 2000). In addition, however, all persons in the general population are thought to vary on a normal continuum in the degree to which they exhibit these traits (Verdoux & van Os, 2002).

Relatives of schizophrenia patients are more likely to score high in schizotypy (Kendler et al., 1991) and to share a variety of neurophysiological and neuropsychological abnormalities associated with schizophrenia (Siever & Davis, 2004; Tsuang, Stone, & Faraone, 2000). Furthermore, there is evidence that many of these abnormalities increase in prevalence across the general population as a function of schizotypy (Della Casa, Hofer, Weiner, & Feldon, 1999; Ettinger et al., 2005; Kimble et al., 2000; Klein, Andresen, Berg, Kruger, & Rockstroh, 1998; Lubow & De la Casa, 2002). It is likely that these abnormalities are markers of a multifactorial genetic diathesis which, depending on its severity and the variable contribution of precipitating and protective environmental factors, can be expressed as schizophrenia, schizotypal personality disorder, or above-average schizotypy. Further characterization of psychophysiological abnormalities that systematically vary as a function of schizotypy thus may contribute to our understanding of the pathophysiology of schizophrenia.

Evidence suggests that individuals with high schizotypy may exhibit semantic processing abnormalities similar to those seen in schizophrenia. Results from some behavioral studies are consistent with increased activation of weakly related concepts. These studies focused on individuals with odd beliefs, rather than odd speech per se, as they were motivated by theories that over-activation of distant associates gives rise to thoughts that co-incidental events are meaningfully associated. In a word-association study, individuals with higher magical ideation produced a greater number of unusual responses, but a similar number of common and unique responses (Duchene, Graves, & Brugger, 1998). In another study, such individuals gave higher relatedness ratings to indirectly related word triplets (Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001). In the same study, however, these individuals also rated unrelated word pairs and triplets as more highly related, raising the additional possibility of decreased inhibition of unrelated items. In a lexical semantic priming experiment with variable SOAs of 350 ms or longer, magical ideation and perceptual abnormalities were associated with increased priming for words of low normative association (e.g., *horse* and *pig*) within the same category (Kerns & Berenbaum, 2000). In another study, individuals with higher levels of paranormal beliefs showed increased priming for indirectly related words with left though not with right visual field presentation (at SOA=200 ms; Pizzagalli, Lehmann, & Brugger, 2001).

There have been a few N400 ERP studies of the relationship between schizotypy and semantic processing (Table 2). In a word-pair study of persons with SPD, Niznikiewicz et al. (2002) found larger than normal N400 relatedness effects, due to smaller N400 amplitudes to related words. In particular, the experimenters obtained this result when the SOA was 450 ms, but not when it was 1000 ms. They postulated that the apparent contrast between this result and previous reports of *decreased* N400 relatedness effects in schizophrenia stemmed from the use of this comparatively short SOA. Niznikiewicz et al. proposed that their finding reflected over-activation of related words at short SOAs, whereas decreased N400 relatedness effects at longer SOAs in other studies reflects deficient context use. Consistent with deficient context use at longer SOAs, two sentence-processing studies of SPD individuals found increased N400 amplitudes to congruent sentence endings (Niznikiewicz et al., 2004; Niznikiewicz et al., 1999). In the latter study, the authors also reported that this abnormality resulted in significantly smaller than normal N400 congruity effects. In a sentence-processing study of individuals from the general population as opposed to an extreme group, Kimble et al. (2000) also found reduced N400 congruity effects in individuals with above- versus below-average schizotypy (though the differences between groups in N400 amplitudes to either congruent or incongruent endings were not statistically significant).

In summary, behavioral and N400 studies of semantic processing in individuals with high schizotypy have reported mixed results. Some of these results have suggested increased activation of either related items in general (Niznikiewicz et al., 2002) or weakly related items (Duchene et al., 1998; Kerns & Berenbaum, 2000; Mohr et al., 2001; Pizzagalli et al., 2001), whereas others have been consistent with decreased activation of related items (Niznikiewicz et al., 2004; Niznikiewicz et al., 1999), or decreased inhibition of unrelated items (Mohr et al., 2001). Thus, although there is evidence that the way in which concepts activate one another in semantic memory varies with schizotypy, further work is needed to clarify exactly how the type of stimuli, degree of relatedness, and SOA interact to affect this variation.

1.4. Experimental Aims

The overall purpose of the experiments in this dissertation was to improve our understanding of abnormal semantic activation in schizophrenia. To this end, we used the N400 ERP component to examine how activation of concepts in semantic long-term memory in schizophrenia is modulated by: degree of meaningful relatedness to preceding context; time elapsed since this stimulus; and the interaction of these factors. Specifically, we aimed to distinguish conditions in which schizophrenia patients activate weakly related concepts, in particular, more than normally – in accordance with the hypothesis of increased spread of activation; and in which they activate related concepts in general less than normally – in accordance with the hypothesis of deficient context use. In addition, we evaluated these questions with regard to schizotypal traits in the non-clinical population. The rationale for doing so was that, given the phenotypic and genetic links between schizophrenia and schizotypy, semantic processing differences associated with schizotypy may resemble pathophysiological processes in schizophrenia. Thus, characterizing semantic activation differences as a function of schizotypy could help elucidate abnormalities of semantic activation in schizophrenia.

Experiment 1 examined the effects of relatedness on semantic activation in schizophrenia. This experiment focused on a specific type of semantic relationship – the association between categories and their exemplars – for which psychometric relatedness norms are available. We used these norms to design stimuli which – in contrast to those used in previous N400 studies of schizophrenia and schizotypy – further differentiated related concept pairs into strongly and weakly related pairs. This distinction allowed us to test more definitively for increased spread of activation to weakly related concepts. Employing the same stimuli, Experiment 2 examined relatedness effects on semantic activation as a function of schizotypy in a non-clinical sample.

Experiments 3 and 4 assessed whether, in schizophrenia and schizotypy, respectively, differences in relatedness effects on semantic activation are modulated by the time elapsed following a prime stimulus. Based on previous literature, we hypothesized that at relatively short intervals following a prime stimulus, schizophrenia and schizotypy are associated with increased spread of activation to weakly related concepts in particular. In contrast, we hypothesized that, at longer intervals following a prime, schizophrenia and schizotypy are associated with decreased use of context to activate related concepts in general. Experiments 3 and 4 tested these hypotheses using stimuli which, like those of Experiments 1 and 2, differentiated between strongly and weakly related concepts. Specifically, these stimuli included directly (strongly) related, indirectly (weakly) related, and unrelated prime-target word pairs, presented at both short and long SOAs.

Another aim of these studies was to test for associations of abnormal N400 effects with different symptoms of schizophrenia. Specific associations would fit with a causal role for abnormal semantic activation in the development of those particular symptoms. Thus, Experiments 1 and 3 tested for associations of abnormal N400 effects with "positive" (delusions and hallucinations), disorganized, and negative symptoms. Because previous hypotheses about abnormal semantic activation in schizophrenia aimed to explain disorganized speech (McCarley et al., 1999; Spitzer et al., 1993); we expected abnormal N400 effects to be associated with this symptom. In addition Experiment 5 tested schizophrenia patients for an association of abnormal N400 effects with proverb interpretation deficits, another hallmark of the disorder (e.g., Reich, 1981). Such an association would support the hypothesis (Gibbs & Beitel, 1995) that aberrant semantic activation causes these deficits.

Analogously, Experiments 2 and 4 tested for associations between individual differences in N400 effects and specific schizotypal traits. Hypotheses about individual differences in semantic activation were formulated to account for the traits of odd speech and unusual ideation (Pizzagalli et al., 2001); therefore, we expected N400 effects to be associated with these traits. Previous semantic priming studies of schizotypy that assessed odd speech did so using self-rating questionnaires or clinicians' global impressions. In contrast, Experiment 6 applied a novel method of directly and quantitatively measuring this trait. Namely, we quantified the atypicality of individuals' responses on a language production task, the Category Fluency Test (CFT; Spreen & Strauss, 1998). We then examined whether this measure was correlated with N400 effects – consistent with a causal role for semantic priming differences in the production of unusual language.

In sum, this research aimed to use the N400 to further characterize how relatedness and time course affect semantic activation in both schizophrenia and schizotypy. These studies also tested for associations of N400 abnormalities with specific schizophrenic symptoms, and of variation in N400 effects with specific schizotypal traits. Such associations would be consistent with a role for semantic processing differences in the etiology of these symptoms and traits. Thus, taken together, the results of these studies can potentially contribute to deciphering the neurophysiological mechanisms that give rise to symptoms of schizophrenia.

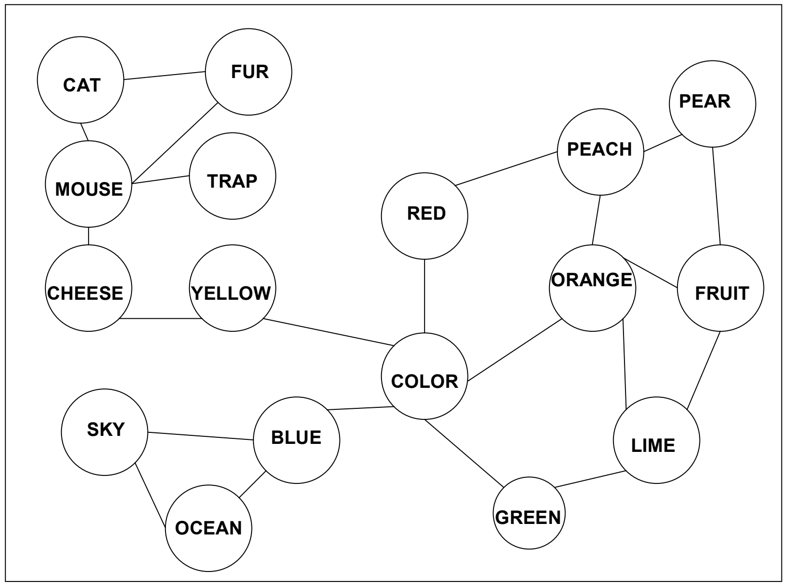

Figure 1.1. Schematic diagram of part of the semantic memory network (after Collins & Loftus, 1975).

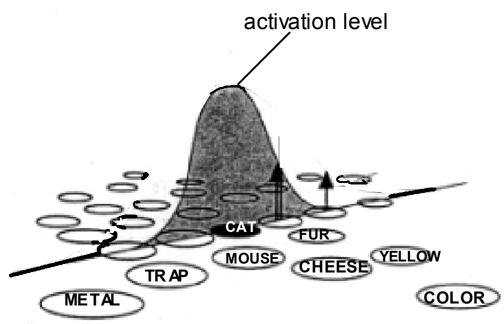

Figure 1.2. Normal activation in the semantic network following a prime stimulus (*CAT*). Activation of a concept is represented by height of the curve above it, and falls off with decreasing relatedness to the prime. After Spitzer (1997).

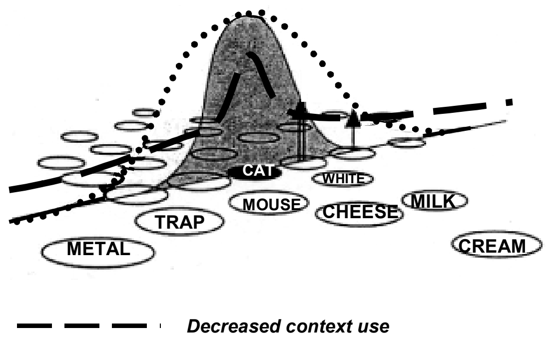

Figure 1.3. Hypothesized abnormalities of semantic activation in schizophrenia, superimposed on the normal activation curve.

Table 1.1. Studies examining N400 amplitudes of schizophrenia patients, grouped by general findings. The included studies were published in English, described methods in detail, and examined N400 amplitude time-locked to a single target. SOAs are given for experiments which employed a prime/target stimulus pair. WP = prime/target word pair; SC = sentence stem with semantically congruent or incongruent final-word target; RSVP = rapid serial visual presentation (one word at a time); LD = lexical decision; CD = congruity decision. Stimuli were visually presented unless otherwise specified. Findings in comparison to control participants are summarized, with regard to group differences in: a) N400 amplitudes to relatedness or congruity conditions, or b) N400 effects between conditions.

Study	**Population Descriptors**	***n* (medicated with antipsychotics / total)**	**Controls Matched on:**	**Stimuli**	**Task**	**SOA (ms)**	**Findings**
No abnormalities							
Koyama et al. (1991)	chronic	13/13	age, sex	WP	LD	1000	No N400 amplitude abnormalities
Andrews et al. (1993)		17/19	age, sex	SC - RSVP	meaningfulness rating		No N400 amplitude or effect abnormalities
Koyama et al. (1994)	chronic	14/28	age, sex	WP	LD	1500	No N400 amplitude abnormalities
Olichney et al. (1997)	elderly	12/18	age, sex, education yrs.	auditory category or antonym definition; visual target word	CD	≅1000	No N400 amplitude or effect abnormalities (trend toward reduced N400 congruity effects)
Increased N400 amplitudes to related or congruent targets							
Strandburg et al. (1997)	outpatients	17/17	age, sex, education yrs.	WP (related pairs formed a phrase)	CD	600	Increased N400 amplitude to related targets

Table 1.1. (continued)

Study	Population Descriptors	*n* (medicated with antipsychotics / total)	Controls Matched on:	Stimuli	Task	SOA (ms)	Findings
Salisbury et al. (2000)	male	?/34	age, sex	sentences ended in target noun congruent with either dominant or subordinate definition of the sentence verb; RSVP	read stimuli aloud		Increased N400 amplitude to both target types; increased amplitude to subordinate targets was correlated with Brief Psychiatric Rating Scale (BPRS) Thinking Disturbance factor
Decreased N400 amplitudes to unrelated or incongruent targets							
Grillon et al. (1991)	chronic male outpatients	14/14	age, education yrs.	WP	relatedness decision	1020	Decreased N400 amplitude to unrelated targets
Adams et al. (1993)	male inpatients	12/12		SC - RSVP	CD		Decreased N400 amplitude to incongruent endings
Increased N400 amplitudes to both related/congruent and unrelated/incongruent targets							
Niznikiewicz et al. (1997)	chronic male	?/13	age	SC – 1) visual - RSVP and 2) auditory; both modalities analyzed in same ANOVA with modality as factor	CD		Increased N400 amplitude to both congruent and incongruent endings
Nestor et al. (1997)		15/15	age, sex	SC - RSVP	CD		Increased N400 amplitude to both congruent and incongruent endings; no N400 congruity effect abnormality

Table 1.1. (continued)

Study	Population Descriptors	*n* (medicated with antipsychotics / total)	Controls Matched on:	Stimuli	Task	SOA (ms)	Findings
Decreased N400 amplitudes to related or congruent targets							
Mathalon et al. (2002)	inpatients and outpatients	18/18	age	Picture prime; target word either matched picture or was member of same category	match decision	325	Decreased N400 amplitude to members of same category
Reduced N400 relatedness or congruity effects							
Condray et al. (1999)		30 taking haloperidol; 21 unmedicated (placebo); 14 patients were members of both groups	age	WP	LD	950	Reduced N400 relatedness effects in both patient groups; no significant N400 amplitude abnormalities
Ohta et al. (1999)	inpatients and outpatients	12/13	age	SC; complete sentence stem shown, followed by final-word target	CD		Reduced N400 congruity effects; no significant N400 amplitude abnormalities

Table 1.1. (continued)

Study	Population Descriptors	*n* (medicated with antipsychotics / total)	Controls Matched on:	Stimuli	Task	SOA (ms)	Findings
Sitnikova et al. (2002)		?/12	sex, parental socio-economic status	sentence with 1st clause ending in homograph used in either dominant or subordinate meaning; 2nd clause began with target word related to homograph's dominant meaning; RSVP	decide whether a subsequent test word was related to sentence		Reduced N400 effects between targets preceded by subordinate homograph and targets preceded by dominant homograph
Hokama et al. (2003)	unmedicated outpatients	0/18	age, sex	WP	LD	1500	Reduced N400 relatedness effects; no significant N400 amplitude abnormalities
Condray et al. (2003)		30 taking haloperidol; 21 unmedicated (placebo); 14 patients were members of both groups	age	WP	LD	350	Reduced N400 relatedness effects in both patient groups; no significant N400 amplitude abnormalities; larger N400 relatedness effects anteriorly in haloperidol vs. unmedicated patients

Table 1.1. (continued)

Study	**Population Descriptors**	***n* (medicated with antipsychotics / total)**	**Controls Matched on:**	**Stimuli**	**Task**	**SOA (ms)**	**Findings**
Kostova et al. (2003)	inpatients and outpatients	13/13	age, vocabulary	1) WP; 2) SC – RSVP of sentence parts, followed by final-word target. Both stimulus types analyzed in same ANOVA with stimulus type as factor	LD	450	No N400 relatedness effects (even though these were present in controls); increased N400 amplitudes to all conditions

Table 1.2. Studies examining the relationship of N400 amplitudes to schizotypal personality, grouped by general findings. The included studies were published in English, described methods in detail, and examined N400 amplitude time-locked to a single target. SOAs are given for experiments which employed a prime/target stimulus pair. SPD = schizotypal personality disorder. WP = prime/target word pair; SC = sentence stem with semantically congruent or incongruent final-word target; RSVP = rapid serial visual presentation (one word at a time); LD = lexical decision; CD = congruity decision. Stimuli were visually presented unless otherwise specified. Findings in comparison to control participants are summarized, with regard to group differences in: a) N400 amplitudes to relatedness or congruity conditions, or b) N400 effects between conditions.

Study	**Population Descriptors**	***n***	**Controls Matched on:**	**Stimuli**	**Task**	**SOA (ms)**	**Findings**
Increased N400 amplitudes to congruent targets							
Niznikiewicz et al. (1999)	SPD, male	17	age, sex, IQ, parental socioeconomic status (SES)	SC – 1) visual – RSVP and 2) auditory; both modalities analyzed in same ANOVA with modality as factor	CD		Increased N400 amplitude to related targets; also, decreased N400 relatedness effects
Niznikiewicz et al. (2004)	SPD, female	17	age, sex, IQ, parental SES	SC – 1) visual – RSVP and 2) auditory; both modalities analyzed in same ANOVA with modality as factor	CD		Increased N400 amplitude to related targets in auditory modality only
Decreased N400 amplitudes to related targets							
Niznikiewicz et al. (2002)	SPD, female	16	age, sex, IQ, parental SES	WP	LD	450/1000	Decreased N400 amplitude to related targets, at 450-ms SOA only
Reduced N400 congruity effects							
Kimble et al. (2000)	7 relatives of schizophrenia patients and 9 non-relatives, who scored higher than median on Scheduled Interview for Schizotypy (SIS)	16	age, sex, education yrs., parental SES, handedness; controls were 8 relatives and 6 non-relatives who scored lower than median on SIS	SC	CD		Reduced N400 congruity effects; no significant N400 amplitude abnormalities

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Chapter 2

Experiment 1 - Electrophysiological insights into conceptual disorganization in schizophrenia

2.1. Abstract

Disorganized speech, or thought disorder, in schizophrenia may reflect abnormal processing of meaningful concepts. To examine whether schizophrenia involves abnormalities in how a meaningful context influences processing of concepts strongly, weakly, or not related to it, we used the N400, an event-related brain potential (ERP) index of semantic relatedness. ERPs were recorded from schizophrenia patients (n=18) and normal controls (n=18) while they viewed category definitions (e.g., *a type of fruit*), each followed by a target word that was either a high-typicality category exemplar (*apple*), low-typicality exemplar (*cherry*), or non-exemplar (*clamp*). Participants' task was to indicate via button-press whether or not the target belonged to the category. In both patients and controls, N400 amplitude was largest (most negative) for non-exemplars, intermediate for low-typicality exemplars, and smallest (least negative) for high-typicality exemplars. Compared to controls, patients showed a trend toward reduced N400 amplitude differences between non-exemplars and low-typicality exemplars. Most importantly, within patients, reduced N400 amplitude differences between high- and low-typicality exemplars were correlated with psychotic symptoms. In schizophrenia patients, an N400 index of semantic processing was associated with psychotic symptoms.

Psychosis may be associated with greater similarity in how concepts strongly and weakly meaningfully related to their context are processed.

2.2. Introduction

"Disturbance of associations" was identified as a core feature of schizophrenia by Bleuler (1911/1950), who observed that in schizophrenic language "associations lose their continuity" and "appear odd, bizarre, distorted" or "senseless." He inferred from this that:

> thinking operates with ideas and concepts which have no, or a completely insufficient, connection with the main idea…The result is that thinking becomes confused, bizarre, incorrect, abrupt.

Disorganized speech in schizophrenia has thus been thought to objectively reflect underlying conceptual disorganization, or "thought disorder."

Bleuler's (1911/1950) notion of abnormalities in "pathways of association and inhibition" presaged more recent theories proposing that schizophrenic disorganization results from abnormalities in how concepts activate one another in semantic memory (McCarley et al., 1999; Nestor et al., 1998; Spitzer, 1997). These theories assume a model of semantic long-term memory in which concepts are nodes in a neural network, and meaningful associations among concepts reflect connectivity among these nodes (Anderson & Pirolli, 1984; Collins & Loftus, 1975; Neely, 1977). When a concept node is activated, as by its corresponding word stimulus, this activation spreads through the network to associated nodes. The degree to which the stimulus concept activates another concept and facilitates its processing is presumably related to the strength of the links between them.

One hypothesis for how abnormal activation in semantic memory may lead to disorganized speech postulates a broader spread of activation to weakly or remotely related items. For instance, Spitzer (1997) proposed that indirect associates - those related through at least one other concept, like *CAT* and *CHEESE* (mediated by *MOUSE*) - activate one another more strongly in schizophrenia, thereby leading to speech containing sequences of apparently unrelated or weakly related concepts.

Some semantic priming data support this hypothesis. Semantic priming refers to the facilitation of response to a target item - e.g., faster reaction time (RT) in a lexical-decision task - when it is preceded by a meaningfully related prime stimulus rather than an unrelated one. Greater priming is thought to reflect greater activation of the target by the prime. Consistent with increased spread of activation to weak associates, an abnormally large priming effect for indirectly related words has been found in thought-disordered schizophrenia patients, although only when the prime-target interval (or stimulus-onset asynchrony (SOA)) is relatively short (≤300 ms) (Moritz et al., 2001; Moritz, Woodward, Kuppers, Lausen, & Schickel, 2003; Spitzer, Braun, Hermle, & Maier, 1993).

A different hypothesis attributes disorganized speech in schizophrenia to impaired ability to use context to activate related items, or to inhibit unrelated items (Cohen & Servan-Schreiber, 1992; McCarley et al., 1999). Importantly, this abnormality is not necessarily mutually exclusive with increased spreading activation, as they could occur in sequence. In fact, whereas RT priming evidence for increased spreading activation has come from word-pair studies employing relatively short SOAs (≤300 ms), most RT priming evidence for impaired context use has come either from word-pair studies employing longer SOAs, or from studies using sentence contexts, which also build up over a longer period. For instance, schizophrenia patients displayed less priming than normal controls for closely related words at a long SOA of 950 ms, but not at shorter (200–700 ms) SOAs (Barch et al., 1996). In a sentence-context study (Kuperberg, McGuire, & David, 1998), both schizophrenia patients and controls were slower to recognize a sentence-final word when it was semantically incongruent with the context than when it was congruent, but patients with high thought-disorder ratings were delayed less than were either controls, or patients with low thought-disorder ratings – consistent with impaired use of context.

Semantic priming effects also have been investigated using the N400 component of scalp-recorded event-related brain potentials (ERPs). The N400 is a negativity occurring from approximately 200 to 500 ms, and peaking at approximately 400 ms, after presentation of any potentially meaningful stimulus such as a word or picture. N400 amplitude is reduced by factors facilitating an item's processing, such as linguistic word frequency or stimulus repetition (reviewed in Kutas and Federmeier, 2000). Of relevance here is that N400 amplitude elicited by a target stimulus is reduced (i.e., made less negative) by increasing semantic relatedness between the target and a preceding prime stimulus (Holcomb & Neville, 1990, 1991; Kutas, 1985; Kutas & Hillyard, 1980; Stelmack & Miles, 1990). In other words, N400 amplitude to a target is smaller (less negative) when it is more related to the prime. N400 amplitude has thus been used to measure the degree to which concepts activate one another in semantic memory, with reduced (less negative) amplitude corresponding to greater activation.

Results of N400 studies in schizophrenia have been mixed. Prime-target word pairs with SOA=450 (Kostova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Bayle, 2003) and 600 ms (Strandburg et al., 1997)) were associated with larger N400 amplitudes to related targets in schizophrenia patients than in normal controls, while amplitudes to unrelated targets did not differ between patients and controls. These results suggest decreased activation of related targets in schizophrenia, consistent with the impaired context use hypothesis. In another word-pair experiment, Condray et al. (2003) reported a reduced N400 priming effect (i.e., reduced difference in N400 amplitude between related and unrelated targets) in patients versus controls, at SOAs of both 350 and 950 ms, although N400 amplitudes did not significantly differ between patients and controls for either related or unrelated targets. In contrast, Spitzer et al. (1997) reported that N400 amplitude for indirectly related words (SOA=200 ms) was smaller in patients compared to controls, consistent with relatively greater activation of weak associates. In a picture-word matching task (SOA=250 ms) (Mathalon, Faustman, & Ford, 2002), target words referring to an item from the same category as the picture elicited a smaller N400 in patients than in controls, consistent with increased activation of related items. Studies with sentence-final word paradigms (Kostova et al., 2003; Ohta, Uchiyama, Matsushima, & Toru, 1999) showed larger N400 amplitudes to congruent words in patients than controls, consistent with impairment in using context to activate semantically congruent items.

Overall, then, the results of these N400 studies, like those of RT priming studies, suggest that schizophrenia patients generally show abnormal semantic priming, although hypothetically for different reasons at different prime-target intervals. Specifically, at relatively short SOAs (approximately ≤ 300 ms), there may be increased or more broadly-spreading activation of related concepts, as reflected in smaller N400 amplitudes for related targets. However, at longer SOAs, including within a sentence context, schizophrenia patients may be impaired in using context to activate related or expected items, as reflected in larger N400s to these items.

One relationship in the semantic network that has been extensively studied in normal participants is the relation between categories and their exemplars. Behavioral norming studies have documented the typicality of different exemplars for a wide range of categories (Battig & Montague, 1969; Hunt & Hodge, 1971; McEvoy & Nelson, 1982; Shapiro & Palermo, 1970). For example, *apple* is a high-typicality exemplar of the category *fruit*, whereas *cherry* is a low-typicality exemplar, meaning that individuals rate *apple* as being a more typical fruit than *cherry*, and, when asked to name fruits, are more likely to say *apple* than *cherry*. Higher typicality is thought to reflect greater semantic relatedness between category and exemplar (Hampton, 1979; McCloskey & Glucksberg, 1978). After a category name, exemplars elicit smaller N400 amplitudes than do non-exemplars (Federmeier & Kutas, ; Heinze, Muente, & Kutas, 1998; Iragui, Kutas, & Salmon, 1996); in addition, high-typicality exemplars elicit smaller N400 amplitudes than do low-typicality exemplars (Federmeier & Kutas, in preparation; Heinze et al., 1998; Stuss, Picton, & Cerri, 1988).

In the present study, we used the N400 to examine whether categories activate their exemplars in the semantic network abnormally in schizophrenia, and whether any such abnormalities are reliably associated with particular symptoms. To that end, we presented schizophrenia patients and normal control participants (NCPs) with category definition phrases followed by target nouns, which were either high-typicality exemplars, low-typicality exemplars, or non-exemplars. Participants were asked to indicate whether or not the target belonged to the category. Thus, where previous N400 studies in schizophrenia used only two types of targets differing in their degree of relatedness to the prime, we aimed to more finely characterize how schizophrenia and its symptoms modulate the effect of relatedness on semantic priming, by distinguishing between targets strongly related (high-typicality exemplars), weakly related (low-typicality exemplars), and unrelated (non-exemplars) to the prime.

We hypothesized that in controls, the N400 would be largest to non-exemplars, intermediate to low-typicality exemplars, and smallest to high-typicality exemplars, consistent with previous findings, and that this general pattern would also hold for patients. In addition, we hypothesized that if schizophrenia is generally accompanied by a broader spread of activation to weaker associates, then categories might activate their less typical exemplars relatively more strongly, as reflected in smaller N400s to low-typicality exemplars in patients versus controls. Consequently, in patients compared to controls, the difference in N400 amplitude between low- and high-typicality exemplars (i.e., the *N400 typicality effect*) would be reduced, and the N400 effect between unrelated non-exemplars and low-typicality exemplars (the *N400 low-typicality category effect*) would be larger. On this account, the difference between unrelated non-exemplars and high-typicality exemplars (the *N400 high-typicality category effect*) would not change.

We also hypothesized that if schizophrenia patients generally make less efficient use of context, then both high- and low-typicality exemplars, as related words, would be less activated, i.e. elicit larger N400s, in patients than in controls. Additionally, non-exemplars might also be relatively less inhibited, or more activated, eliciting smaller (less negative) N400s in patients than in controls. Overall, these abnormalities would lead to smaller high- and low-typicality N400 category effects in the patients. In addition, in patients compared to controls, the N400 typicality effect would either remain unchanged (if activations of both high- and low-typicality exemplars are reduced by a similar magnitude) or decrease (if the activation decrease is larger in magnitude for high-typicality exemplars compared to low-typicality exemplars, in proportion to the difference in their absolute activation levels).

2.3. Methods and Materials

2.3.1. Participants

Participants included 18 schizophrenia patients and 18 NCPs. Patients were all outpatients, recruited through community residential facilities and physician referral. NCPs were recruited through newspaper advertisements, and flyers posted at the University of California, San Diego (UCSD) Medical Center. All participants were assessed on their capacity to provide informed consent, and gave written informed consent via the UCSD Institutional Review Board approved form (#030510). Participants were compensated in cash.

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995), and were screened to rule out any other Axis I diagnosis including substance abuse. NCPs were assessed using the SCID (non-patient version) to rule out any past or present Axis I or II diagnoses including substance abuse, and were also excluded if they were taking any psychotropic medications. Other exclusion criteria for all participants included: exposure to a language other than English at home as a child; and current or past neurological disorder. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971), and parental socioeconomic status (SES) was computed (Hauser and Warren, 1996). Participants completed the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn, 1997) as a measure of receptive vocabulary. Demographic characteristics of the study sample are shown in Table 2.1.

Twelve patients were prescribed second-generation antipsychotic medications (as defined by Lohr and Braff, 2003), 2 were prescribed first-generation antipsychotics, and 2 were prescribed a combination of first- and second-generation antipsychotics. Two patients reported not taking antipsychotics for at least one month before testing.

2.3.2. Assessments

Clinical symptoms in patients were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Based on these ratings, we calculated scores for the Psychotic symptom factor (Hallucinations + Delusions), Negative factor (Affective Flattening + Avolition/Apathy + Anhedonia/Asociality) and Disorganized factor (Positive Formal Thought Disorder + Bizarre Behavior) (Miller et al., 1993). Patients' clinical characteristics are shown in Table 2.2.

2.3.3. Stimuli

Stimuli were based on existing category production norms (Battig and Montague, 1969; Hunt and Hodge, 1971; McEvoy and Nelson, 1982; Shapiro and Palermo, 1970). For each of 120 category phrases, the associated target words included: a) a high-typicality exemplar, b) a low-typicality exemplar and c) an unrelated non-exemplar.

Targets were matched overall for length and word frequency (Francis and Kucera, 1982) across these conditions. The high-typicality exemplar chosen was the exemplar most frequently produced by individuals in the category norms, except where its very high frequency would prevent the conditions from being matched for word frequency. In such cases an exemplar of as high a rank as possible was used. Low-typicality exemplars were chosen from among those ranked 9th or lower by frequency of generation. Examples are shown in Table 2.3.

Using these stimuli, 3 different stimulus lists were generated. In each list, each of the 120 categories appeared once, and 40 categories were paired with each of the 3 target types. Each of the possible target types for each category occurred in one of the 3 lists. Within each list, length and frequency were matched across the 3 target types. Each list also included 40 additional filler categories followed by an unrelated target. Filler stimuli were not analyzed but were included so that each list included an equal number of exemplar and non-exemplar targets (80 each).

2.3.4. Task

Participants were tested in a single session. They were seated comfortably in a chair, 100 cm in front of a video monitor on which stimuli were visually presented, with each letter in a word subtending on average approximately 0.36° of visual angle horizontally, and up to 0.55° vertically. Words were displayed in yellow letters on a black background.

Each participant was presented with one of the 3 lists, with the categories presented in a fixed randomized order. Each of the 3 lists was seen by 6 patients and 6 controls. Each list was divided into four blocks of 40 trials each, separated by breaks during which participants were permitted to rest until ready to continue. Each trial consisted of the following sequence: a) category (e.g. a type of fruit) for 2150 ms, b) blank screen for an interval varied pseudorandomly between 250 and 650 ms (to avoid the superimposition of anticipatory ERP effects which occur when the timing of onset of the target is invariant), c) target (e.g. cherry) for 1000 ms, d) blank screen for 2000 ms, e) the prompt Yes or No? until participants responded with a button-press (see below), f) blank screen for 3000 ms until onset of the next trial. All stimuli were presented centered on the screen horizontally and vertically. A central fixation point remained visible throughout, positioned 0.5° below the bottom-most edge of where the words were presented.

Upon presentation of the prompt, participants were required to press one of two buttons on a keypad, with their right and left thumbs, respectively. One button (labeled "Yes") signaled that the word was a true exemplar of the preceding category, while the other button (labeled "No") signaled that it was a non-exemplar. The assignment of buttons was reversed for half the participants in each group.

2.3.5. Electrophysiological data collection and analysis

The electroencephalogram was recorded from 34 sintered Ag/AgCl electrodes in an electrode cap (EasyCap, Herrsching-Breitbrunn, Germany). Electrode sites corresponded to the International 10/20 system (Fig 2.1). Electrodes placed at the tip of the nose and at Fpz served as reference and ground, respectively. Blinks and eye movements were monitored via electrodes placed on the supraorbital ridge and infraorbital ridge of the left eye, and on the outer canthi of both eyes. Electrode impedances were below 5 kΩ. The EEG was processed through a Neuroscan NuAmps amplifier (Compumedics, El Paso, TX) set at a bandpass of 0.5-100 Hz, continuously digitized at 1 kHz, and stored on hard disk for later analysis.

The EEG was re-referenced off-line to the algebraic mean of the left and right mastoids (TP9/TP10). Continuous data were algorithmically corrected for eyeblink artifact (Semlitsch et al., 1986). ERPs were computed for epochs extending from 100 ms pre-stimulus to 924 ms post-stimulus. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before time-domain averaging; the mean percentage of trials lost to such artifacts was 17% for patients and 6% for controls.

For each trial, N400 latency was defined as the interval between stimulus onset and the largest negative peak between 250 and 650 ms post-stimulus. N400 amplitude was measured as the mean voltage from 350-550 ms post-stimulus (this window chosen because it was centered approximately around the grand mean N400 peak latency). For each participant, N400 effects were derived from the difference waves formed by subtracting the average ERPs between each pair of target types: non-exemplar minus high-typicality exemplar (high-typicality category effect), non-exemplar minus low-typicality exemplar (low-typicality category effect), and low-typicality exemplar minus high-typicality exemplar (typicality effect). Latency of N400 effects was defined as the interval between stimulus onset and the largest negative peak between 250 and 650 ms post-stimulus. Amplitudes of N400 effects were measured as the mean voltage of the appropriate difference wave from 300-500 ms post-stimulus (this window chosen because it was centered approximately around the grand mean N400 effect peak latency).

2.3.6. Statistical analysis

In general, all *p*-values in analyses of variance (ANOVA) with within-subject factors are reported after Greenhouse-Geisser Epsilon correction. Pairwise comparisons of factor-level means were made using the Tukey procedure for simultaneous pairwise comparisons, with a family confidence co-efficient of 0.95. Reported *p*-values for all statistical analyses are two-tailed.

Percentage of correct responses was analyzed in a repeated-measures ANOVA, with Group (schizophrenia vs. control) as a between-subject variable, and Target (high-typicality vs. low-typicality vs. non-exemplar) as a within-subject variable.

N400 latency and N400 amplitude were analyzed in repeated-measures ANOVAs with Group (schizophrenia vs. control) as between-subject variable, and Target (high-typicality vs. low-typicality vs. non-exemplar) and Electrode (34 levels, corresponding to all recording sites) as within-subject variables. To test for between-group differences in N400 effects, each of these effects (high-typicality category effect, low-typicality category effect and typicality effect) was analyzed in an ANOVA with Group (schizophrenia vs. control) as between-subject variable, and Electrode (15 levels, corresponding to a contiguous array of sites where differences in N400 effects were most prominent: Fz, F3, F4, FC1, FC2, FC5, FC6, Cz, C3, C4, T7, T8, CP1, CP2, Pz) as within-subject variable.

To examine the relationship between symptoms and N400 effects in patients, correlation co-efficients were calculated between the high-typicality category effect, low-typicality category effect, and typicality effect at Cz; and SANS and SAPS total and Psychotic, Negative, and Disorganized factor ratings. For correlations involving SAPS total and Psychotic and Disorganized factor ratings, we used Spearman's rank-order co-efficient ρ, since these scores were not normally distributed; otherwise, Pearson's co-efficient *r* was used.

2.4. Results

2.4.1. Behavioral data

Percentages of correct responses for schizophrenia patients and controls for the different conditions are shown in Table 2.4. Overall, the high rate of correct responses indicates that participants were attending to the stimuli. There was a significant Target effect ($F_{2,68}$=32.73, p<0.0001), with correct response rate differing significantly between high- and low-typicality exemplars, and between low-typicality exemplars and non-exemplars, but not between high-typicality exemplars and non-exemplars. There was no Group effect ($F_{1,34}$=1.47, p=0.23), or Group x Target interaction ($F_{2,68}$=0.65, p=0.52), suggesting that patients and controls did not differ in their attention to the stimuli.

2.4.2. Grand average ERPs

Grand average ERPs at all electrodes are shown separately for schizophrenia and control groups in Fig 2.2.

2.4.3. N400 latency

Mean N400 peak latency across the combined patient and control groups for all target types was 452 ms. Mean latency did not vary significantly by Group ($F_{1,34}$=0.19, p=0.67) or Target ($F_{2,68}$=2.01, p=0.22), and there was no Group x Target interaction ($F_{2,68}$=2.01, p=0.14).

Mean peak latency for N400 effects across the combined patient and control groups for all target types was 411 ms. Mean latency was longer for the low-typicality category effect (419 ms) than for the high-typicality category effect (406 ms) or the typicality effect (408 ms) ($F_{2,68}$=4.51, p=0.02). There was no significant Group effect ($F_{1,34}$=0.43, p=0.52) or Group x Target interaction ($F_{2,68}$=2.01, p=0.14).

2.4.4. N400 amplitude

Across patient and control groups, N400 amplitude was largest (most negative) for non-exemplars, intermediate for low-typicality exemplars, and smallest for high-typicality exemplars (main effect of Target: $F_{2,68}$=12.22, p<0.0001) (see Fig. 2.2). N400 effects were broadly distributed over the scalp although largest medially and centrally, consistent with the distribution seen in previous N400 studies of word reading (Federmeier & Kutas, 1999; Kutas & Van Petten, 1994) (Target x Electrode interaction: $F_{50,1100}$=9.86, p<0.0001). There was no Group effect ($F_{1,34}$=0.01, p=0.99) on N400 amplitude, nor any Group x Target interaction ($F_{2,68}$=0.23, p=0.80), indicating that patients and controls did not differ significantly in N400 amplitude to the different target types.

2.4.5. N400 effects

There was a trend for the N400 low-typicality category effect to be reduced in patients compared to controls ($F_{1,34}$=2.79, p=0.10). This difference was decreased slightly when PPVT scores were included as a covariate ($F_{1,33}$=2.32, p=0.14). Patients and controls did not differ significantly in the amplitude of the high-typicality category effect ($F_{1,34}$=0.89, p=0.35) or the typicality effect ($F_{1,34}$=0.24, p=0.63). Amplitudes of these N400 effects for patients and controls at a representative electrode, Cz, are shown in Fig. 2.3. The scalp distribution of the difference in the low-typicality category effect between patients and controls is shown in Fig. 2.4, using the spherical spline interpolation technique (Perrin, Pernier, Bertrand, & Echallier, 1989).

N400 effects were not significantly correlated with PPVT scores, either for patients (high-typicality category effect: ρ=-0.08, p=0.64; low-typicality category effect: ρ=-0.21, p=0.22; typicality effect: ρ=0.16, p=0.35) or for controls (high-typicality category effect: r=0.24, p=0.33; low-typicality category effect: r=0.16, p=0.53; typicality effect: r=0.16, p=0.53).

2.4.6. Relationship between N400 effects and patient characteristics and symptom ratings

Within patients, N400 effects were not significantly correlated with onset of illness (high-typicality category effect: r=-0.17, p=0.50; low-typicality category effect: r=-0.05, p=0.86; typicality effect: r=-0.13, p=0.62) or with its duration (high-typicality category effect: r=0.03, p=0.90; low-typicality category effect: r=0.05, p=0.85; typicality effect: r=-0.02, p=0.95).

Correlation co-efficients between N400 effects and symptom ratings for patients are shown in Table 2.5. Since the N400 has a negative amplitude, positive correlation co-efficients indicate that the N400 effect was smaller with higher symptom ratings. The Psychotic Factor was correlated with reduced N400 typicality effects. In addition, there was a trend for the Psychotic Factor to be correlated with reduced N400 high-typicality category effects, and for the Negative Factor to be correlated with reduced N400 high- and low-typicality category effects.

2.5. Discussion

This study used the N400 component of the ERP as a direct, brain-based method of assessing the functional organization of semantic memory in schizophrenia. Schizophrenia patients and NCPs matched for age, sex and parental SES were presented with prime phrases that were category definitions, each followed by a target noun that was either a high-typicality exemplar, a low-typicality exemplar or an unrelated non-exemplar of the category. As hypothesized, in both patients and controls, the N400 amplitude elicited by targets was largest (most negative) for non-exemplars, intermediate for low-typicality exemplars, and smallest (least negative) for high-typicality exemplars. Contrary to our hypotheses, patients and controls did not differ significantly in the N400 amplitudes elicited by each target type, or in amplitude differences between target types (N400 effects); however, there was a trend toward reduced N400 amplitude differences between non-exemplars and low-typicality exemplars (i.e. the N400 low-typicality category effect) for patients versus controls. Moreover, within the patient group, more severe psychotic symptoms were correlated with reduced N400 amplitude differences between high- and low-typicality exemplars (the N400 typicality effect).

The absence of significant between-group N400 effect differences in the present study contrasts with other studies where such differences were found to be associated with schizophrenia (Condray et al., 2003; Condray, Steinhauer, Cohen, van Kammen, & Kasparek, 1999; Kostova et al., 2005; Kostova et al., 2003; Mathalon et al., 2002; Mitchell et al., 1991; Ohta et al., 1999; Strandburg et al., 1997), or with schizotypal personality (Kiang & Kutas, 2005; Kimble et al., 2000; Niznikiewicz et al., 2002), which is thought to share genetic and neurophysiological substrates with schizophrenia (Siever & Davis, 2004). Our results, however, are not an isolated instance, as there are other published reports in which no such differences were detected between schizophrenia patients and controls (Andrews et al., 1993; Koyama et al., 1994; Olichney, Iragui, Kutas, Nowacki, & Jeste, 1997). As with neurophysiological abnormalities in schizophrenia in general (Johannesen et al., 2005), there is considerable overlap in N400 effects between patients with the disorder and healthy individuals (Grillon, Ameli, & Glazer, 1991), and variation in sample characteristics may thus have contributed to these inconsistent results across studies. For example, in our study, patients' average age was older than in any of the studies cited above except that of Olichney et al. (1997), which also did not find N400 effect differences between patients and controls. Since age is associated in general with smaller N400 effects (Kutas & Iragui, 1998), it might also attenuate differences in these effects between patients and controls. In addition, studies that found N400 effect differences between patients and controls may have examined more severely ill patients than studies that did not find such differences. In support of this hypothesis, some studies that found patient-control differences included a mixture of inpatients and outpatients (Kostova et al., 2005; Kostova et al., 2003; Mathalon et al., 2002; Ohta et al., 1999), whereas studies that found no such differences examined either outpatients only (our study and that of Olichney et al. (1997)), patients with "no acute illness" (Koyama et al., 1994), or patients of unspecified admission status (Andrews et al., 1993). Nevertheless, comparing illness severity among these studies directly is difficult, as they used a variety of symptom rating scales. Further research is necessary to clarify the effects of these and other patient characteristics on the extent of N400 effect abnormalities.

The trend we observed for patients to exhibit reduced low-typicality category effects compared to controls is consistent with the hypothesis that schizophrenia is associated with decreased use of context to activate items related to it, or to inhibit items unrelated to it. According to this hypothesis, either less than normal activation (i.e. larger N400s) for weakly related targets, or less than normal inhibition (i.e. smaller N400s) for unrelated targets, or both, would cause a reduction in the low-typicality category effect. Our results, however, do not fully support this hypothesis, which also predicts less than normal activation for strongly related targets, and hence significantly reduced high-typicality category effects in patients relative to controls.

The lower vocabulary of patients compared to controls raises the question of whether the patients' smaller low-typicality category effects could be explained by unfamiliarity with some of the low-typicality exemplars. Unfamiliar words might be processed as pseudowords, which tend to elicit larger N400 amplitudes than known words (Carreiras, Vergara, & Barber, 2005), thereby decreasing the low-typicality category effect. However, when vocabulary scores were included as a covariate, the difference in the low-typicality category effect between patients and controls only decreased slightly, suggesting that it is not caused primarily by vocabulary differences.

Our results also do not support the hypothesis of broader spread of activation to weakly related concepts in schizophrenia. Were this true, it would have led to smaller N400s to low-typicality exemplars, in turn causing smaller than normal typicality effects and larger than normal low-typicality category effects, which we did not observe. It is important to note, however, that we employed a relatively long SOA between prime and target (2400–2800 ms), giving participants sufficient time to read the longer category definitions. Thus, although we found no ERP evidence for more broadly spreading activation of related concepts in schizophrenia at long SOAs, our study design does not allow us to determine whether this might occur at short SOAs.

Within patients, the observed association between the SAPS-derived Psychotic factor and reduced N400 typicality effects might reflect an association of psychotic symptoms with either decreased context use or a broader spread of activation. If decreased context use leads to proportionally reduced activation for high-typicality exemplars compared to low-typicality exemplars, proportional to their different absolute activation levels (as predicted by Cohen and Servan-Schreiber's (1992) model of decreased gain in a context-representing neural network), this would decrease the activation difference between them, reducing the typicality effect. Broader spread of activation, by reducing the activation difference between high- and low-typicality exemplars, would likewise reduce the typicality effect. However, decreased context use, but not broader spread of activation, predicts a reduction in the high-typicality category effect as well. Therefore, the additional trend we observed toward a correlation of psychotic symptoms with reduced high-typicality category effects suggests that, in our experimental paradigm, decreased context use may be more likely than increased spread of activation to mediate the association between psychotic symptoms and abnormal N400 categorical priming effects.

The finding that N400 effects were correlated with the Psychotic but not the Disorganized factor was somewhat unexpected, since the hypotheses we examined aimed to explain disorganized speech and thought disorder. Moreover, decreased N400 relatedness effects have been reported by Kostova et al. (2005) to correlate with a measure of disorganization, the Thought, Language and Communication Disorders Scale

(Andreasen, 1979). The present study may have been limited in its ability to detect N400 differences associated with disorganized speech because the severity of this symptom in our patient sample was relatively low, or because the SAPS may not have been as sensitive in detecting disorganized speech as more specialized instruments.

Some researchers have proposed that semantic processing abnormalities in schizophrenia could be caused by abnormal organization of concepts within the semantic network (Aloia, Gourovitch, Weinberger, & Goldberg, 1996; Leeson, McKenna, & Laws, 2005; Rossell & David, 2006). This disorganized storage could exist instead of, or along with, deficient access to semantic memory. Our results cannot definitively distinguish between these possibilities, as the N400 is modulated both by factors affecting ease of lexical access (including activation), and by the organization of concepts in semantic memory (see Kutas and Federmeier (2000) for a review of how these different factors influence N400 amplitude). Thus, the trend toward smaller N400 low-typicality category effects in patients could be due either to reduced access to low-typicality exemplars following a category prime; or to degradation of the representations of low-typicality exemplars, or of their links to their categories, within semantic memory. It is possible, however, that future N400 priming studies could be specifically designed to distinguish between abnormalities of semantic memory access and organization. For example, if N400 priming were normal in schizophrenia patients at one SOA but abnormal at another, this might suggest normal organization of the semantic network, with abnormal activation over a specific time window.

Further studies are necessary to confirm whether our observed correlation of psychosis with decreased differences in N400 priming for strongly versus weakly related category members generalizes to other schizophrenia patient samples. If replicated, this finding would suggest that delusions are associated with a smaller than normal difference in processing of typical versus atypical members of a category, at least at a semantic level. In other words, high and low typicality members are treated more similarly by psychotic patients than by normal individuals.

If this finding generalizes to other semantic stimuli, it would suggest that development of delusions may be associated with one type of "conceptual disorganization" – namely, a reduced difference in the degree to which context facilitates processing of other stimuli strongly versus weakly meaningfully related to it. This abnormality could lead to the subjective experience that stimuli weakly related to their context are unusually meaningful. In turn, this could prompt patients to search for an explanation connecting the stimulus and context, even when these are in reality unrelated.

This sequence of events would be consistent with Hemsley's (2005) proposal that "an abnormal view of relationships between events is among the most prominent features of delusional thinking." In common with some previous hypotheses about delusion formation (Kapur, 2003; Maher, 1988; Roberts, 1992), it postulates that delusions reflect an attempt to explain puzzling subjective experiences that stem from pathological neurophysiological processes. Thus, unusual subjective experiences "produced endogenously by various neuropathologies" (Maher, 1988) give rise to a feeling of significance and tension, or "delusional mood." Since "this stage is deeply perplexing and uncomfortable, promoting a powerful drive to understand what is being experienced" (Roberts, 1992), the development of an explanation, even if erroneous, causes relief. Of relevance to our results, the delusional mood has been described as "a fracturing and disintegration of previous meaning patterns" (Roberts, 1992). In particular, psychotic patients commonly report that they have experienced a strong meaningful relationship between stimuli that normal individuals would regard as minimally related, and that their delusional belief explains these experiences. This is seen in the following patient's account, as described by Schneider (1959):

> A dog lay in wait for me as he sat on the steps of a Catholic convent. He got up on his hind legs and looked at me seriously. He then saluted with his front paw as I approached him. Another man was a little way in front of me. I caught up to him hurriedly and asked if the dog had saluted him too. An astonished 'no' told me I had to deal with a revelation addressed to me.

Thus, an alteration in the relative degree to which meaningful stimuli affect processing of concepts strongly versus weakly related to them may be one instance of an aberrant neurophysiological process that predisposes to psychotic symptoms.

This chapter, in full, is a reprint of material as it appears in *Schizophrenia Research, 92*, pp. 225-236. Kiang, Michael; Kutas, Marta; Light, Gregory A.; Braff, David L.; Elsevier, 2007. The dissertation author was the primary investigator and author of this paper.

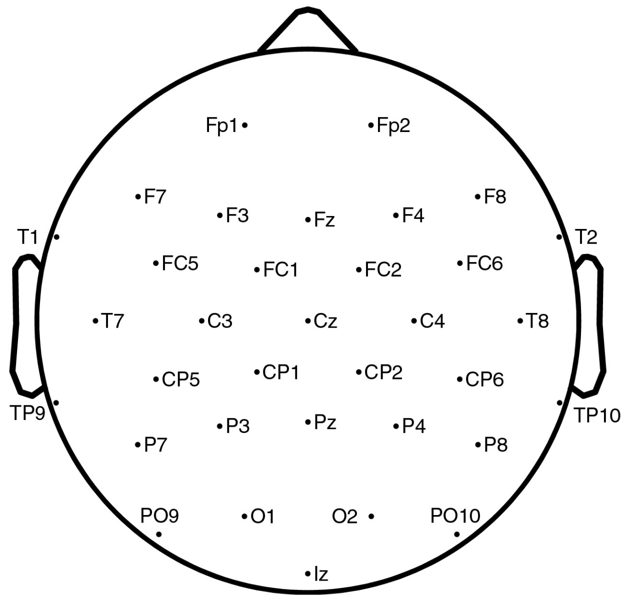

Figure 2.1. Schematic diagram of the electrode array.

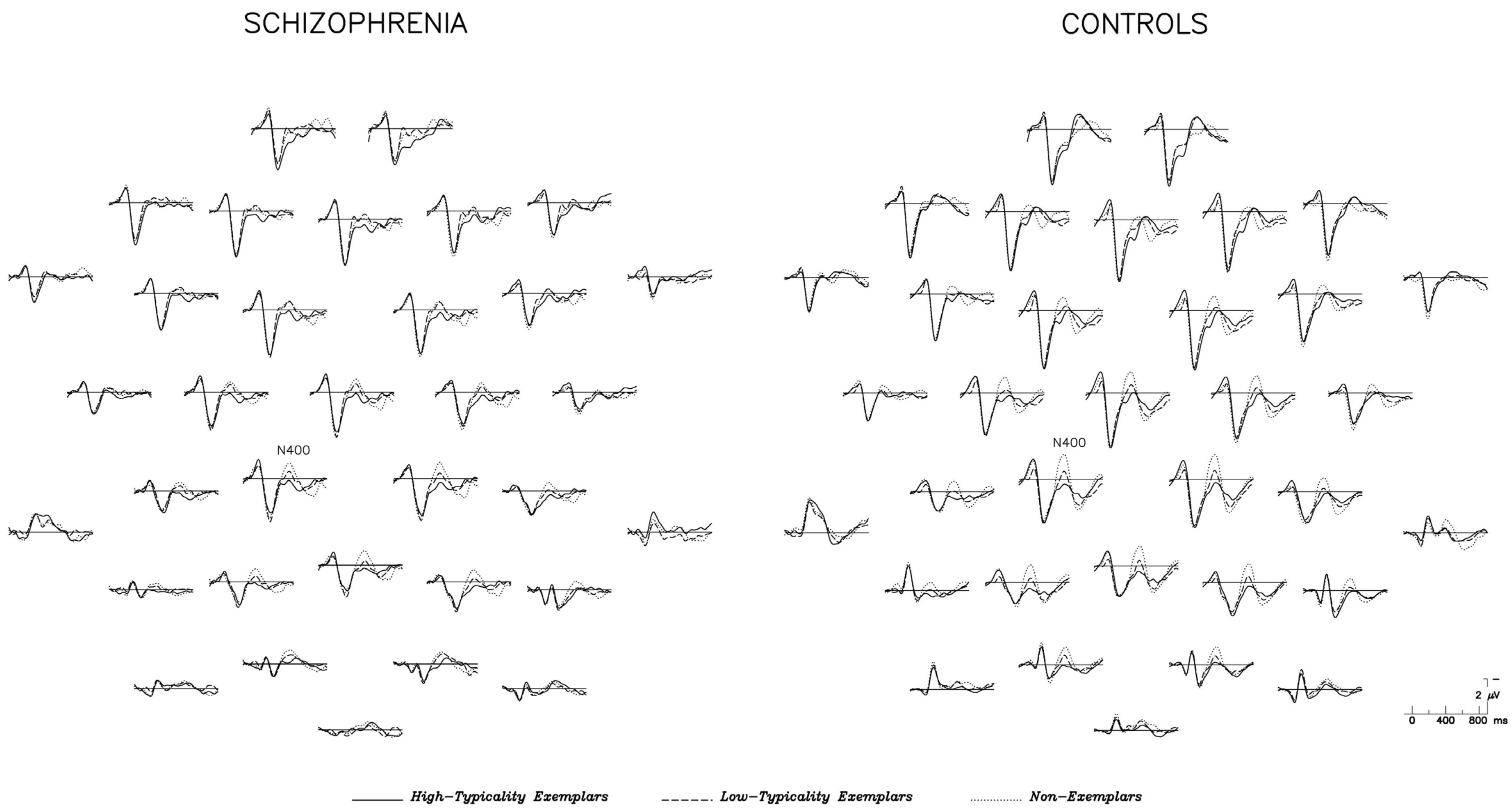

Figure 2.2. Grand average ERPs for the three target types, at all electrode sites, for the schizophrenia and control groups (n=18 per group). As in Figure 2.1, the front of the head is oriented upward.

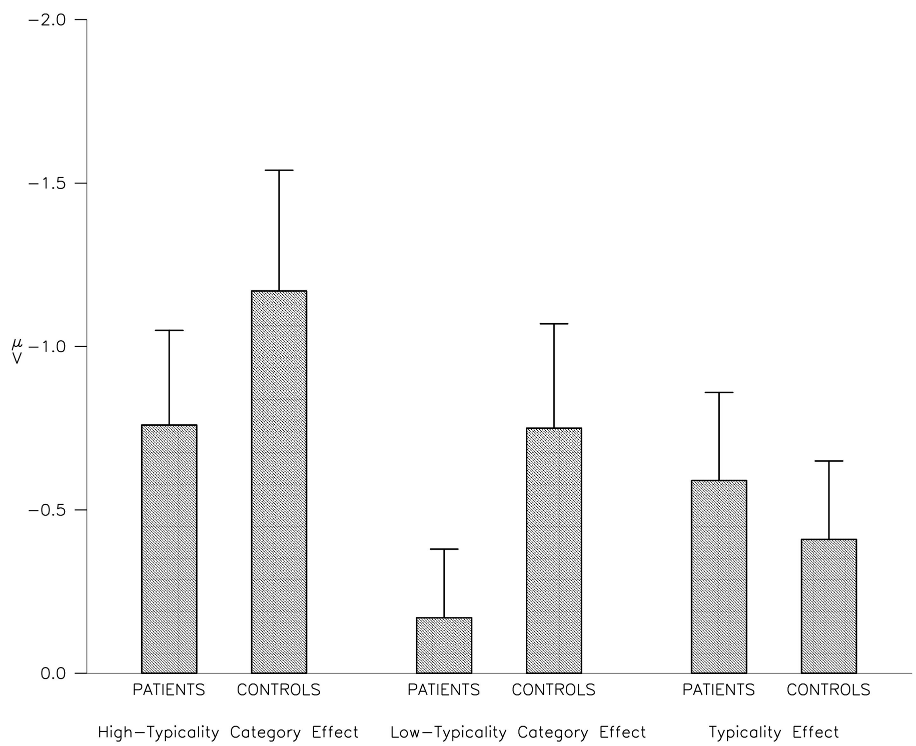

Figure 2.3. Amplitude of N400 effects at Cz. Bars represent mean and standard error.

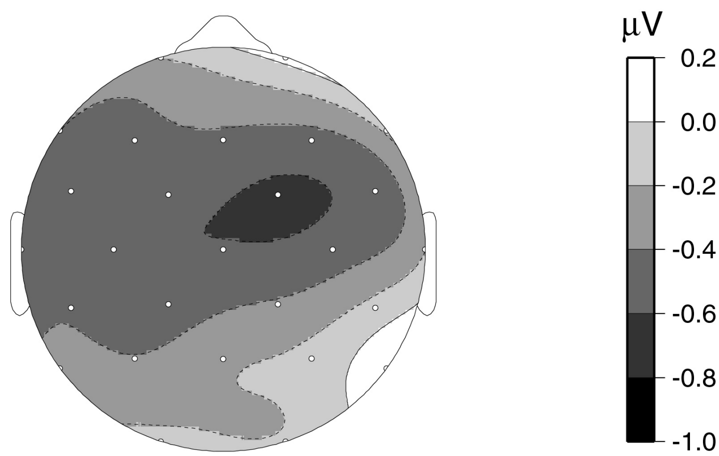

Figure 2.4. Spherical spline interpolation of the scalp distribution of the difference in the low-typicality category effect between the schizophrenia and control groups.

Table 2.1. Demographic characteristics of the study sample (means ± SD given where applicable)

	Schizophrenia Patients	**Healthy Controls**
Age, years	46.3±10.5	43.2±8.4
Sex	13 male, 5 female	12 male, 6 female
Handedness	17 right, 1 left	16 right, 2 left
Parental SES	42.9±19.3	43.3±17.3
Years of Education[a]	12.6±2.2	16.1±2.4
PPVT[b]	173.1±20.9	187.9±8.2

[a]Patients differed significantly from controls, p<.0001
[b]Patients differed significantly from controls, p=.008

Table 2.2. Clinical characteristics of schizophrenia patients (means ± SD given where applicable)

Age of onset, years	23.7±7.3
Duration of illness, years	22.1±10.9
Number of previous hospitalizations	5.9±5.4
SANS Total	8.9±4.2
SAPS Total	3.5±3.4
Negative Factor	8.3±3.7
Psychotic Factor	2.2±2.7
Disorganized Factor	1.7±2.5

Table 2.3. Sample categories and corresponding target stimuli

Category	High-Typicality Exemplars	Low-Typicality Exemplars	Non-Exemplars
A type of fruit	apple	cherry	clamp
A weapon	gun	revolver	musician
A string instrument	guitar	banjo	platform
A farm animal	cow	goat	antenna
A disease	cancer	alcoholism	pottery
Something worn on the feet	shoes	slippers	freight

Table 2.4. Percentage of correct categorization responses, by participant group and target condition

	Schizophrenia Patients (n=18)			Healthy Controls (n=18)		
Target	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
High-Typicality	96.0	6.9	78-100	98.2	3.7	85-100
Low-Typicality	85.4	9.9	55-98	89.0	6.8	70-98
Non-Exemplar	94.3	6.7	78-100	95.0	6.2	80-100

Table 2.5. Correlations of patient symptom ratings with N400 effects (difference wave mean amplitudes from 300-500 ms) at Cz (n=18)

	SANS Total		SAPS Total		SANS/SAPS Factors					
					Negative		Psychotic		Disorganized	
	r	*p*	*ρ*	*p*	*r*	*p*	*ρ*	*p*	*ρ*	*p*
High-typicality category effect	0.43	0.08	0.38	0.12	0.45	0.06	0.42	0.08	0.05	0.85
Low-typicality category effect	0.39	0.11	0.19	0.46	0.42	0.08	-0.26	0.29	-0.10	0.70
Typicality effect	0.14	0.59	0.50	0.04	0.14	0.59	0.64	0.005	0.05	0.86

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Chapter 3

Experiment 2 - Association of schizotypy with semantic processing differences: an event-related brain potential study

3.1. Abstract

Disorganized speech in both schizophrenia and schizotypy has been hypothesized to result from abnormalities in how concepts activate one another in semantic memory. To study whether schizotypy is associated with differences in how categories activate their exemplars, we examined the N400 component of the event-related brain potential (ERP) elicited during a category-verification task. ERPs were recorded in young adults from the general population while they viewed category definitions each followed by a target that was either a high-typicality exemplar, low-typicality exemplar, or non-exemplar; participants' task was to indicate whether or not the target belonged to the category. Schizotypy was assessed via the Schizotypal Personality Questionnaire (SPQ). Overall, N400 amplitude was largest for non-exemplars, smallest for high-typicality exemplars, and intermediate for low-typicality exemplars. SPQ score was associated with decreased N400 amplitude to non-exemplars, and increased amplitude to both types of exemplars. SPQ score was negatively correlated with the N400 amplitude difference between non-exemplars and both low- and high-typicality exemplars, but was not correlated with the amplitude difference between low- and high-typicality exemplars. N400 amplitude differences between non-exemplars and both types of exemplars were correlated with the SPQ Interpersonal factor, but not the Disorganized factor. The results

are consistent with an association of schizotypy with decreased use of context to activate related items and inhibit unrelated items.

3.2. Introduction

Disorganized speech in schizophrenia has been hypothesized to result from abnormalities in how words, and the concepts they represent, activate one another in the brain (McCarley et al., 1999; Nestor et al., 1998; Spitzer, 1997). These hypotheses assume a model of semantic memory in which concepts are represented as nodes in a network, and associations between concepts as links among these nodes (Anderson & Pirolli, 1984; Collins & Loftus, 1975; Neely, 1977). When a concept node is activated, as by its corresponding word stimulus, this activation is thought to spread through the network to associated nodes. The degree to which a concept activates another and facilitates its processing is presumably related to the strength of the links between them in the semantic network.

One class of proposed mechanisms for how abnormal activation in semantic memory may cause disorganized speech in schizophrenia involves either increased or more broadly spreading activation of related items. For instance, Spitzer (1997) postulated that indirect associates - those mediated by at least one other concept, like *CAT* and *CHEESE* (mediated by *MOUSE*) - activate one another more strongly in schizophrenia, and that this accounts for sequences of unrelated or weakly associated concepts in schizophrenic speech.

Some semantic priming data support this hypothesis. Semantic priming refers to the tendency for individuals to respond more quickly to a target item when it is preceded by a related than an unrelated prime item. Greater priming is thought to reflect greater activation of the target by the prime. Consistent with increased spread of activation to indirect associates, an abnormally large priming effect for indirectly related words has been found in thought-disordered schizophrenia patients, though only when the prime-target interval, i.e. stimulus-onset asynchrony (SOA), is relatively short (≤300 ms; Moritz et al., 2001; Moritz, Woodward, Kuppers, Lausen, & Schickel, 2003; Spitzer, Braun, Hermle, & Maier, 1993).

A distinctly different hypothesis attributes disorganized speech in schizophrenia to an impaired ability to use context to activate related items, and to inhibit unrelated items (Cohen & Servan-Schreiber, 1992). This mechanism is not necessarily mutually exclusive with increased spreading activation, as both may occur, albeit with different time courses. In fact, whereas behavioral priming evidence for increased spreading activation has come from studies employing short SOAs, most evidence for impaired context use, whether the context is a word or sentence, has come from experiments with relatively long SOAs. For example, schizophrenia patients exhibited no priming at a long SOA of 950 ms for closely related words that primed at shorter SOAs (Barch et al., 1996). In another study, both schizophrenia patients and controls were slower to recognize a sentence-final word when it was semantically incongruent with the preceding context than when it was congruent; however, thought-disordered patients were delayed less than were controls or non-thought-disordered patients, consistent with impaired use of context (Kuperberg, McGuire, & David, 1998).

Semantic priming effects also have been investigated using the N400 component of scalp-recorded event-related brain potentials (ERPs). The N400 is a negativity peaking approximately 400 ms after presentation of any potentially meaningful stimulus, such as a word or picture. N400 amplitude is sensitive to factors which facilitate an item's processing, such as frequency of usage, repetition, semantic relatedness and congruity; of relevance here is that it varies inversely with the semantic relatedness between the target and its prime (Holcomb & Neville, 1990, 1991; Kutas, 1985; Kutas & Hillyard, 1980; Stelmack & Miles, 1990). In other words, N400 amplitude to a target is reduced (i.e. less negative) when it is more related to the prime. N400 amplitude has thus been used as a measure of the degree to which concepts activate one another in semantic memory, with reduced amplitude corresponding to greater activation.

Results of N400 studies in schizophrenia have been mixed. Prime-target word pairs (SOA=450 (Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Bayle, 2003) and 600 ms (Strandburg et al., 1997)) yielded larger than normal (more negative) N400 amplitude to related targets in schizophrenia patients, suggesting decreased activation, consistent with the impaired context use hypothesis. In another word-pair experiment, Condray et al. (2003) reported a reduced N400 priming effect (i.e. the difference in N400 amplitude between related and unrelated targets) in patients vs. controls, at SOAs of both 350 and 950 ms, although the N400 amplitude for either related or unrelated targets did not significantly differ between patients and controls. On the other hand, Spitzer et al. (1997) reported that N400 amplitude for indirectly related words (SOA=200 ms) was reduced (less negative) in patients compared to controls, consistent with relatively greater activation of weaker associates. In a picture-word matching task (SOA=250 ms; Mathalon, Faustman, & Ford, 2002), target words referring to an item from the same category as the picture elicited a smaller N400 in patients than in controls, consistent with increased activation of related items. Studies with sentence-final word paradigms (Kostova et al., 2003; Ohta, Uchiyama, Matsushima, & Toru, 1999) showed a larger N400 amplitude to congruent words in patients than controls, consistent with impairment in the use of context to activate congruent items.

Overall, then, the results of these N400 studies, like those of behavioral priming studies, suggest that, at relatively short SOAs, there may be increased or broader activation of potentially related concepts, as reflected in smaller N400 amplitudes for targets related to their primes. However, at longer SOAs, including in a sentence context, schizophrenia patients may be impaired in using context to activate related or expected items, as reflected in larger N400s to these items.

A different approach to understanding semantic activation abnormalities in schizophrenia, which avoids potential confounds of medication and chronic illness, is to study semantic processing in the non-clinical population as a function of schizotypal personality traits. All persons are thought to vary on a continuum in the degree to which they exhibit these traits (Verdoux & van Os, 2002). Individuals high in schizotypy have been found to share a genetic diathesis with schizophrenia patients, along with diverse neurophysiological and neuropsychological abnormalities (Tsuang, Stone, & Faraone, 2000). Further characterization of these abnormalities as a function of schizotypy thus may contribute to our understanding of the pathophysiology of schizophrenia.

Persons with high schizotypy have been reported to exhibit semantic priming abnormalities similar to those seen in schizophrenia. These include, at relatively short SOAs, increased behavioral priming for weakly related words (Kerns & Berenbaum, 2000; Pizzagalli, Lehmann, & Brugger, 2001), and an abnormally large reduction in the

N400 to related words (Niznikiewicz et al., 2002), consistent with increased or broader spreading activation. Evidence that higher schizotypy is associated with increased N400 amplitudes to congruent sentence endings (Niznikiewicz et al., 1997), or a decreased difference between the N400 amplitudes to congruent and incongruent endings (Kimble et al., 2000), is consistent with impaired use of context to activate related items over a longer time course. Further research will help more clearly delineate how differences in stimuli, task, and clinical population interact to affect the way in which concepts in the semantic network activate one another in the schizophrenia spectrum.

One relationship in the semantic network that has been extensively studied in normal populations is the relation between categories and their exemplars. Behavioral norming studies have documented the typicality of different exemplars for a wide range of categories (Battig & Montague, 1969; Hunt & Hodge, 1971; McEvoy & Nelson, 1982; Shapiro & Palermo, 1970). For example, *apple* is a high-typicality exemplar of the category *fruit*, whereas *cherry* is a low-typicality exemplar, meaning that individuals rate *apple* as being a more typical fruit than *cherry*, and, when asked to name some fruits, are more likely to say *apple* than *cherry*. Higher typicality is thought to reflect greater semantic relatedness between the category and exemplar (Hampton, 1979; McCloskey & Glucksberg, 1978). After a category name, N400 amplitude is reduced in response to exemplars relative to non-exemplars (Federmeier & Kutas, ; Heinze, Muente, & Kutas, 1998; Iragui, Kutas, & Salmon, 1996); in addition, high-typicality exemplars elicit smaller N400 amplitudes than low-typicality exemplars (Federmeier & Kutas, ; Heinze et al., 1998; Stuss, Picton, & Cerri, 1988).

In the present study, we aimed to use the N400 to examine whether the way categories activate their exemplars in the semantic network varies with schizotypy. We presented individuals from a normal population with category names followed by target nouns, which were either high-typicality exemplars, low-typicality exemplars, or non-exemplars. Participants, subsequently rated on schizotypy, were asked to indicate whether or not the target was an exemplar of the category. We expected that across all participants, consistent with previous findings (Federmeier & Kutas, ; Heinze et al., 1998; Iragui et al., 1996; Stuss et al., 1988), the N400 would be largest to non-exemplars, smallest to high-typicality exemplars, and intermediate to low-typicality exemplars.

In addition, if higher schizotypy is generally accompanied by a broader spread of activation to weaker associates, then categories would activate their less typical exemplars relatively more strongly, as reflected in smaller (i.e. less negative) N400s. Therefore, the difference in N400 amplitude between low- and high-typicality exemplars (which we will refer to as the *N400 typicality effect*) would be reduced, and the N400 effect between unrelated non-exemplars and low-typicality items (the *N400 low-typicality category effect*) would be increased. The difference between unrelated non-exemplars and high-typicality items exemplars (the *N400 high-typicality category effect*) would not change.

Alternatively, if persons with higher schizotypy generally make less, or less efficient, use of context, then both high- and low-typicality exemplars, as related words, would be less activated, i.e. elicit larger N400s, in these individuals than in persons with lower schizotypy. We would also expect non-exemplars to be relatively less inhibited, or more activated, eliciting smaller N400s. Overall, this would lead to a smaller N400 high-typicality category effect and a smaller N400 low-typicality category effect, but no change in the N400 typicality effect (see Table 3.1 for summary of predicted outcomes for these hypotheses).

Clearly, reaction time (RT) data could also be useful in testing some aspects of the hypotheses in question, with broader spread of activation leading to a reduced RT priming effect for high-typicality vs. low-typicality exemplars, and decreased context use reflected in a reduced RT priming effect for both types of exemplars over non-exemplars. In this initial study, however, we chose to use a delayed category-verification response, rendering the behavioral data informative with respect to categorization accuracy but not speed. In the context of examining N400 priming effects, the delayed-response design confers certain advantages: in particular, while the presence of a task helps ensure and verify that participants are attending to the stimuli, freedom from having to make an overt response during reading minimizes movement-related preparatory and executive potentials that could overlap the N400 component and interfere with its interpretation. This is especially important as a baseline for future studies with schizophrenia patients, in whom the motor system may be impacted by various medication regimens.

3.3. Methods

3.3.1. Participants

24 healthy participants [17 female, 18 to 35 years of age, mean age 21.0, SD = 3.5] were recruited from the campus of the University of California, San Diego. Most were undergraduates. Exclusion criteria included: left-handedness, as assessed by the Edinburgh Inventory (Oldfield, 1971); and any self-reported history of: exposure to a

language other than English at home as a child; reading difficulties; visual impairment; current or past neurological or psychiatric disorder; and current use of neurological or psychotropic medications. 14 reported having a left-handed immediate family member. Participants gave written informed consent and were compensated with course credit or cash. The study procedure was approved by the Human Research Protections Program of the University of California, San Diego.

3.3.2. Rating scales

Participants completed the Schizotypal Personality Questionnaire (SPQ), a 72-item validated self-rating instrument for schizotypy, with 9 subscales corresponding to each of the 9 schizotypal traits (Raine, 1991). These subscales have been found to load onto 3 factors: Disorganized (comprising the Odd Behavior and Odd Speech subscales), Cognitive-Perceptual (Ideas of Reference, Odd Beliefs, Unusual Perceptual Experiences and Suspiciousness), and Interpersonal (Social Anxiety, No Close Friends, Constricted Affect and Suspiciousness; Raine et al., 1994). Participants also completed the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1997) as a measure of receptive vocabulary.

3.3.3. Stimuli

Stimuli were based on existing category production norms (Battig and Montague, 1969; Hunt and Hodge, 1971; McEvoy and Nelson, 1982; Shapiro and Palermo, 1970). For each of 120 categories, the associated target words included a) a high-typicality exemplar, b) two low-typicality exemplars (these differed in the degree to which they shared semantic features with the high-typicality exemplar, a distinction made for a separate pilot analysis not directly relevant to this study), and c) an unrelated non-exemplar. Targets were matched overall for length and word frequency (Francis and Kucera, 1982) across these conditions (overall mean length = 6.1 letters; overall mean log frequency = 0.90). The high-typicality exemplar chosen was the exemplar most frequently produced by individuals in the category norms, except where its very high frequency would prevent the conditions from being matched for word frequency. In such cases an exemplar of as high a rank as possible was used. Low-typicality exemplars were chosen from among those ranked 9th or lower by frequency of generation. Examples are shown in Table 3.2.

Using these stimuli, 3 different lists were generated. In each list, each of the 120 categories appeared once, and 40 categories were paired with each of the 3 target types. Each of the possible target types for each category occurred in one of the 3 lists. Because each category had two possible low-typicality targets (see above), each list had 2 versions, such that each of the 40 categories paired with a low-typicality target in that list were paired with a different target in each version, and such that each version contained 20 of each of the 2 kinds of low-typicality target. Within each list, length and frequency were matched across the 3 target types. Each list also included 40 additional filler categories followed by an unrelated target. Filler stimuli were not analyzed but were included so that each list included an equal number of exemplar and non-exemplar targets (80 each).

3.3.4. Task

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

Each participant was presented with one of the 3 lists, with the categories presented in a fixed randomized order. Over the course of the study, an equal number of participants saw each of the 3 lists (and an equal number of participants saw each of the 2 versions of each list). Each list was divided into four blocks of 40 trials each, separated by short rest breaks. Each trial consisted of the following sequence: a) category (e.g. *a type of fruit*) for 2150 ms, b) blank screen for an interval varied pseudorandomly between 250 and 650 ms (to avoid the superimposition of anticipatory ERP effects which occur when the timing of onset of the target is invariant), c) target (e.g. *cherry*) for 1000 ms, d) blank screen for 2000 ms, e) the prompt *Yes or No?* until participants responded with a button-press (see below), f) blank screen for 3000 ms until onset of the next trial. All stimuli were presented centered on the screen horizontally and vertically. A central fixation point remained visible throughout, positioned 0.5° below the bottom-most edge of where the words were presented.

Upon presentation of the prompt, participants were required to press one of two buttons, on joysticks held in the right and left hands respectively. One button (labeled "Yes") signaled that the word was a true exemplar of the preceding category, while the other button (labeled "No") signaled that it was a non-exemplar. The assignment of buttons was reversed for half the participants.

3.3.5. Electrophysiological data collection and analysis

The electroencephalogram was recorded from 26 tin electrodes embedded in an electro-cap, and referenced to the left mastoid. Electrodes were equally spaced across the scalp, with positions and labels as shown in Fig. 3.1. Blinks and eye movements were monitored via electrodes placed on the outer canthus (left electrode serving as reference) and infraorbital ridge of each eye (referenced to the left mastoid). Electrode impedances were kept below 5 kΩ. The EEG was processed through Grass amplifiers set at a bandpass of 0.01–100 Hz, continuously digitized at 250 Hz, and stored on hard disk for later analysis.

The EEG was re-referenced off-line to the algebraic mean of the left and right mastoids. ERPs were computed for epochs extending from 100 ms before stimulus onset to 920 ms after stimulus onset. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line before time-domain averaging; approximately 6% of trials were lost due to such artifacts. If data from a participant contained excessive blinks, they were corrected using a spatial filter algorithm (Dale, 1994); this was applied to only one participant's data.

For each trial, N400 latency was measured as the interval between stimulus onset and the largest negative peak between 250 and 550 ms post-stimulus. N400 amplitude was measured as the mean voltage from 300-500 ms post-stimulus. For each participant, N400 effects were defined as the mean voltage from 300-500 ms post-stimulus for the difference waves between ERPs for each pair of target type: non-exemplar minus high-typicality exemplar (high-typicality category effect), non-exemplar minus low-typicality exemplar *(*low-typicality category effect), and low-typicality exemplar minus high-typicality exemplar (typicality effect).

3.3.6. Statistical analysis

Table 3.3 shows statistics for rating scale scores for the study sample. Mean SPQ score did not differ between men and women, according to a t-test with Welch correction for unequal variance [t=0.41, p=0.69]. The study sample was split by median SPQ score into low- and high-schizotypy groups. Mean SPQ score was 6.0 [SD=3.2] for the low-schizotypy group and 22.2 [SD=6.4] for the high-schizotypy group. These two groups did not differ in vocabulary as measured by the PPVT, according to a t-test with Welch correction for unequal variance [t=1.85, p=0.08]. Mean age was 22.2 [SD=4.6, range=18-35] for the low-schizotypy group and 19.8 [SD=1.2, range=18-22] for the high-schizotypy group; a Mann-Whitney U test (used because the age distribution for the low-schizotypy group was non-normal) showed that this difference approached significance (Z=1.90, p=0.06). 8 of 12 participants in the low-schizotypy group and 9 of 12 in the high-schizotypy group were female; these proportions did not differ significantly (χ^2=0.20, df=1, p=0.65).

Percentage of correct responses was analyzed with repeated-measures analysis of variance (ANOVA), with Schizotypy (low vs. high) as between-subject variable, and Target (high-typicality vs. low-typicality vs. non-exemplar) as within-subject variable. All p-values in this and subsequent ANOVAs with within-subject factors are reported after Greenhouse-Geisser Epsilon correction. In this and subsequent ANOVAs, pairwise comparisons of factor-level means were made using the Tukey procedure for simultaneous pairwise comparisons, with a family confidence co-efficient of 0.95.

Only data from trials with correct responses were included in subsequent ERP analyses.

N400 latency was analyzed in an ANOVA with Schizotypy (low vs. high) as between-subject variable, and Target (high-typicality vs. low-typicality vs. non-exemplar) and Electrode (26 levels, corresponding to all recording sites) as within-subject variables.

N400 amplitude was analyzed in an ANOVA with Schizotypy (low vs. high) as between-subject variable, and Target (high-typicality vs. low-typicality vs. non-exemplar) and Electrode (26 levels, corresponding to all recording sites) as within-subject variables.

To examine the relationship between N400 effects and schizotypy, Pearson product moment correlation co-efficients r were calculated between the high-typicality category effect, low-typicality category effect, and typicality effect, at MiPa, and SPQ total and factor scores.

3.4. Results

3.4.1. Behavioral data

The percentage of correct responses for the low- and high-schizotypy groups for the different conditions are shown in Table 3.4. Overall, the high rate of correct responses indicates that participants were attending to the stimuli. There was a significant effect of Target [$F(2,44)=78.32$, $p<0.0001$], with percentage of correct responses differing significantly between high- and low-typicality exemplars, and between low-typicality exemplars and non-exemplars, but not between high-typicality exemplars and non-exemplars. There was no effect of Schizotypy [$F(1,22)=0.07$, $p=0.80$], nor a Schizotypy x Target interaction [$F(2,44)=1.45$, $p=0.25$].

3.4.2. Grand average ERPs

Grand average ERPs (*n*=12) at all electrodes are shown separately for the low and high-schizotypy groups in Fig. 3.2.

3.4.3. N400 latency

Overall, N400 latency was greater for non-exemplars (mean=418 ms) than for either low-typicality exemplars (mean=396 ms) or high-typicality exemplars (mean=389 ms) [$F(2,44)=4.54$, $p=0.02$]. N400 latency did not differ between schizotypy groups [$F(1,22)=0.02$, $p=0.88$], and there was no Schizotypy x Target interaction [$F(2,44)=1.26$, $p=0.30$].

3.4.4. N400 amplitude

N400 amplitude was largest (most negative) for non-exemplars (mean = -0.82 μV), intermediate for low-typicality exemplars (2.23 μV), and smallest for high-typicality exemplars (4.24 μV) [main effect of Target: $F(2,44)=53.97$, $p<0.0001$]. Although the difference in N400 amplitude between target types was broadly distributed over the scalp, it was largest over medial parietal sites on the right hemisphere, a distribution consistent with that seen in previous N400 studies of word reading (Federmeier & Kutas, 1999; Kutas & Van Petten, 1994) [Target x Electrode interaction: $F(50, 1100)=9.86$, $p<0.0001$].

There was no main effect of Schizotypy [$F(1,22)=0.07$, $p=0.80$] on N400 amplitude. There was however a Schizotypy x Target interaction [$F(2,44)=3.86$, $p=0.03$]. Means for different levels of Schizotypy x Target are illustrated in Fig. 3.3. All factor-level means were significantly different from one another. For both schizotypy groups, N400 amplitude was largest for non-exemplars, intermediate for low-typicality exemplars, and smallest for high-typicality exemplars. In addition, for each of the two exemplar types, N400 amplitude was more negative for the high-schizotypy group than the low-schizotypy group, while for non-exemplars, amplitude was less negative (i.e. smaller N400) for the high-schizotypy group than the low-schizotypy group. There was no Schizotypy x Target x Electrode interaction [$F(50,1100)=0.66$, $p=0.97$], indicating that schizotypy did not affect the distribution of N400 effects.

3.4.5. Correlation of N400 effects with schizotypy

The high-typicality category effect, low-typicality category effect, and typicality effect for low- and high-schizotypy groups at MiPa (Pz in the International 10-20 system) are shown in Fig. 3.4. Scatterplots of the amplitudes of these effects vs. total SPQ score, for all participants, are shown in Fig. 3.5. Correlation co-efficients between these effects and SPQ total and factor scores, across all participants, are shown in Table 3.5. Since the N400 has a negative amplitude, positive correlation co-efficients indicate that the N400 effect was smaller with higher SPQ scores.

Because the high and low-typicality category effects were found to be significantly correlated with the SPQ Interpersonal factor but not with the Cognitive or Disorganized factors, for each of the two category effects we examined *post hoc* whether its correlation with the Interpersonal factor was significantly different from its correlation with each of the other two SPQ factors (Neter et al., 1996). The correlation between the high-typicality category effect and the SPQ Interpersonal score did not differ significantly from the correlation between the high-typicality category effect and either the SPQ Cognitive score ($z^*=1.15$, $p=0.36$) or the SPQ Disorganized score ($z^*=1.25$, $p=0.30$). Likewise, the correlation between the low-typicality category effect and the

Interpersonal score did not differ significantly from the correlation between the low-typicality category effect and either the Cognitive score ($z^*=1.07$, $p=0.58$) or the Disorganized score ($z^*=1.36$, $p=0.25$).

3.5. Discussion

In this experiment, we investigated the relationship between schizotypal personality and semantic processing by using the N400 component of the ERP elicited during a category-verification task. Participants were presented with category primes, each followed after a relatively long interval by a target noun. Across all participants, the N400 amplitude to targets was largest (i.e. most negative) for unrelated non-exemplars, smallest for high-typicality exemplars, and intermediate for low-typicality exemplars. In addition, the amplitudes of the N400 effects between non-exemplars and both exemplar types (i.e. both the high-typicality category effect and the low-typicality category effect) were significantly correlated with SPQ score. As schizotypy increased, both category effects decreased in size, due to decreased N400 amplitudes for non-exemplars, and increased N400 amplitudes for both types of exemplars. In contrast, the N400 typicality effect was not significantly correlated with SPQ score, as N400 amplitude increased with schizotypy equally for both types of exemplars.

These results are consistent with an association of higher schizotypy with impaired context use, leading to less than normal activation (i.e. larger N400s) for both types of exemplars (as related targets), and less than normal inhibition or greater than normal activation (i.e. smaller N400s) for non-exemplars (as unrelated targets). Our results, on the other hand, apparently do not support the hypothesis of increased or broader activation of related concepts with higher schizotypy. This would be expected to cause a smaller N400 to high- or low-typicality exemplars or both, unlike what we observed. It is important to note, however, that we used a relatively long SOA between prime and target (2400 to 2800 ms) in order to ensure participants had enough time to read the longer category definitions. Thus, although we found no ERP evidence for increased or more broadly spreading activation of related concepts as a function of schizotypy at long SOAs, our study design did not allow us to test whether this might be present at short SOAs. Further studies, with different stimuli that allow the inclusion of short SOAs, are necessary to examine this question.

Overall, our results indicate that semantic processing differences, as reflected in N400 effects, vary with schizotypy across the general population. They are consistent with a previous finding of a reduced N400 amplitude difference between congruent and incongruent sentence endings (Kimble et al., 2000), in high- vs. low-schizotypy individuals from a general-population sample. To the extent that these findings parallel N400 evidence for impaired context use in schizophrenia (Condray et al., 2003; Kostova et al., 2003; Ohta et al., 1999; Strandburg et al., 1997) or schizotypal personality disorder (Niznikiewicz et al., 2002; Niznikiewicz et al., 1999), they add to the body of data suggesting that various neuropsychological and neurophysiological findings associated with schizophrenia also increase in prevalence across the general population as a function of schizotypy (Della Casa, Hofer, Weiner, & Feldon, 1999; Ettinger et al., 2005; Kimble et al., 2000; Klein, Andresen, Berg, Kruger, & Rockstroh, 1998; Lubow & De la Casa, 2002).

Our results thus accord well with the model of Cohen and Servan-Schreiber (1992), who hypothesized that schizophrenia is associated with an impaired ability to maintain an internal representation of context. This model is based on the hypothesis that in schizophrenia, there is a deficiency of dopamine in prefrontal regions postulated to be responsible for representing context, and that dopamine maintains the gain in a neural network, potentiating both excitatory and inhibitory responses to afferent inputs. Whatever pattern of activated and inhibited neurons normally represents a particular context, in schizophrenia these are hypothesized to be activated and inhibited, respectively, to a lesser degree. This in turn would lead to decreased activation of related items, and decreased inhibition or increased activation of unrelated items. A diminution in prefrontal dopaminergic activity could result from a neurodevelopmental lesion (Weinberger, 1987) which might lead to either schizophrenia or schizotypy depending on other genetic or environmental factors (Siever & Davis, 2004). Evidence for dopaminergic dysfunction has in fact been found in both schizophrenia and schizotypy (Davis et al., 1985; Siever et al., 1993; Siever & Davis, 2004).

Behavioral studies in the schizophrenia spectrum have provided evidence both for decreased activation of items related to context (Barch et al., 1996), and decreased inhibition of unrelated items (Kuperberg et al., 1998; Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001; Titone, Levy, & Holzman, 2000). However, unlike our results, which are consistent with both these effects, previous N400 studies in these populations have reported evidence for the former (Kostova et al., 2003; Niznikiewicz et al., 1997; Ohta et al., 1999; Strandburg et al., 1997) but not the latter. The reason for this discrepancy is unclear, but a possible explanation may relate to our experimental stimuli and task. In our materials, the target could be viewed as completing either a true or false proposition - it either was or was not a “true” member of the category; moreover, participants’ task was to indicate whether or not this proposition was true. These characteristics were not present in previous studies which used either word-word or sentence-context/final-word paradigms.

This characteristic of our study materials - that the target items carried specific truth values – might suggest a possible alternative explanation for our findings. Perhaps in individuals higher in schizotypy, it is not unrelated items *per se* (as in the impaired context use hypothesis), but false items that are more activated. Schul, Mayo and Burnstein (2004) found that, after experimental manipulations designed to induce mistrust, university students exhibited greater than normal priming for adjectives that were opposites (e.g. *hollow-full*), and less than normal priming for adjectives that were synonyms (e.g. *hollow-empty*), in a grammatical-class identification task. They proposed that mistrust may be associated with increased activation of message-incongruent associations and decreased activation of message-congruent associations, by encouraging a person to focus more on the possibility that a message is invalid. They further speculated that this might occur not only within individuals when mistrust is induced, but also in chronically mistrustful individuals as compared to less mistrustful individuals. Since schizotypy is associated with chronic mistrust, consistent with our results, individuals with higher compared to lower schizotypy, when presented with the category-verification task, might activate words comprising an invalid proposition to a lesser degree, and words comprising a valid proposition to a lesser degree, which would also fit our results.

One unexpected finding was that, of the three SPQ factors, only the Interpersonal factor was significantly correlated with reduction of N400 category effects. Since the hypotheses we examined aimed to explain disorganized speech in schizophrenia, we would have expected the Disorganized factor (which includes the Odd Speech subscale) to correlate most highly with these N400 effects. Nevertheless, it must be noted that, for both the high- and low-typicality category effects, the numerical difference in the correlations between the category effect and the Disorganized factor, and between the category effect and the Interpersonal effect, was not statistically significant. Thus, it cannot be definitively concluded that N400 effect differences were more highly associated with the Interpersonal factor than with the Disorganized factor. Previous ERP studies of schizotypy have not analyzed the N400 in relation to separate schizotypal traits or factors. Likewise, N400 studies that provided evidence for decreased context use in schizophrenia (Kostova et al., 2003; Ohta et al., 1999; Strandburg et al., 1997) did not report correlations with separate symptoms. Unless confirmed by additional studies with greater statistical power, the possibility that N400 category effect reduction is correlated with the Interpersonal factor of schizotypy remains speculative. It is potentially important, because if it were true, it would call into question the inference that N400 differences reflect the semantic processing differences leading to disorganized speech.

If future studies were to confirm the specificity of this correlation there could still be a number of possible explanations. First, as previously mentioned, it may be that in our category-verification task, individuals with higher mistrust or suspiciousness were activating words comprising an invalid proposition to a lesser degree, and words comprising a valid proposition to a lesser degree. This is because the trait of suspiciousness loads on the Interpersonal factor, and other traits loading on this factor – including social anxiety, defined in schizotypal personality as being "associated with paranoid fears rather than negative judgments about self" (American Psychiatric Association, 1994), and lack of close friends - also may be etiologically related to suspiciousness. Second, trait-like semantic processing differences might induce the development of a suspicious personality over time. Finally, it might be that the traits loading on the Interpersonal factor are most specific for the genetic diathesis for schizophrenia. Within a general population, these traits have sometimes been found to be most highly correlated with various neurophysiological and neuropsychological abnormalities also seen in schizophrenia (Kendler et al., 1991; Park & McTigue, 1997; Siever, 1985; Suhr & Spitznagel, 2001). It might be that odd speech in the general population, though qualitatively similar to disorganized speech in schizophrenia, has a variety of etiologies, some unrelated to schizophrenia. This would decrease the correlation between the Disorganized factor and N400 differences that reflect semantic processing differences associated with schizophrenia.

This chapter, in full, is a reprint of material as it appears in *Schizophrenia Research, 77,* pp. 329-342. Kiang, Michael; Kutas, Marta; Elsevier, 2005. The dissertation author was the primary investigator and author of this paper.

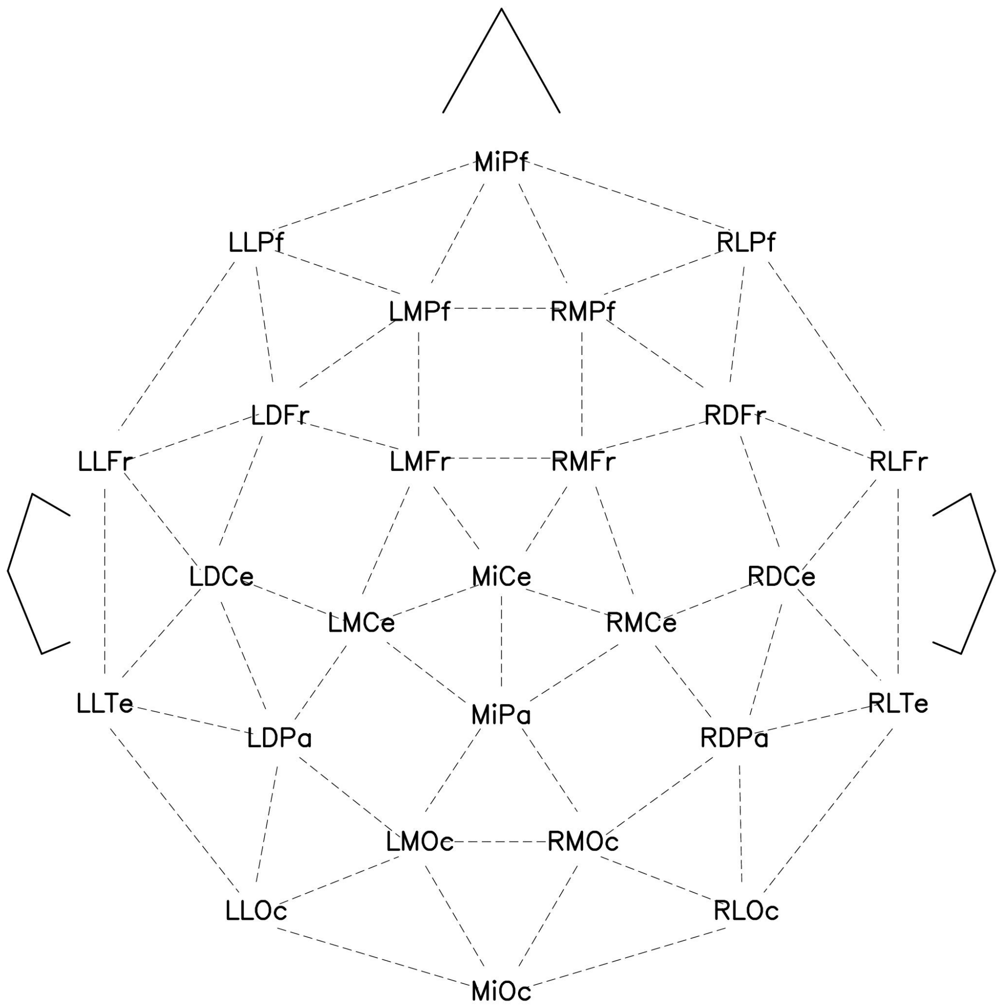

Figure 3.1. Schematic diagram of the electrode array.

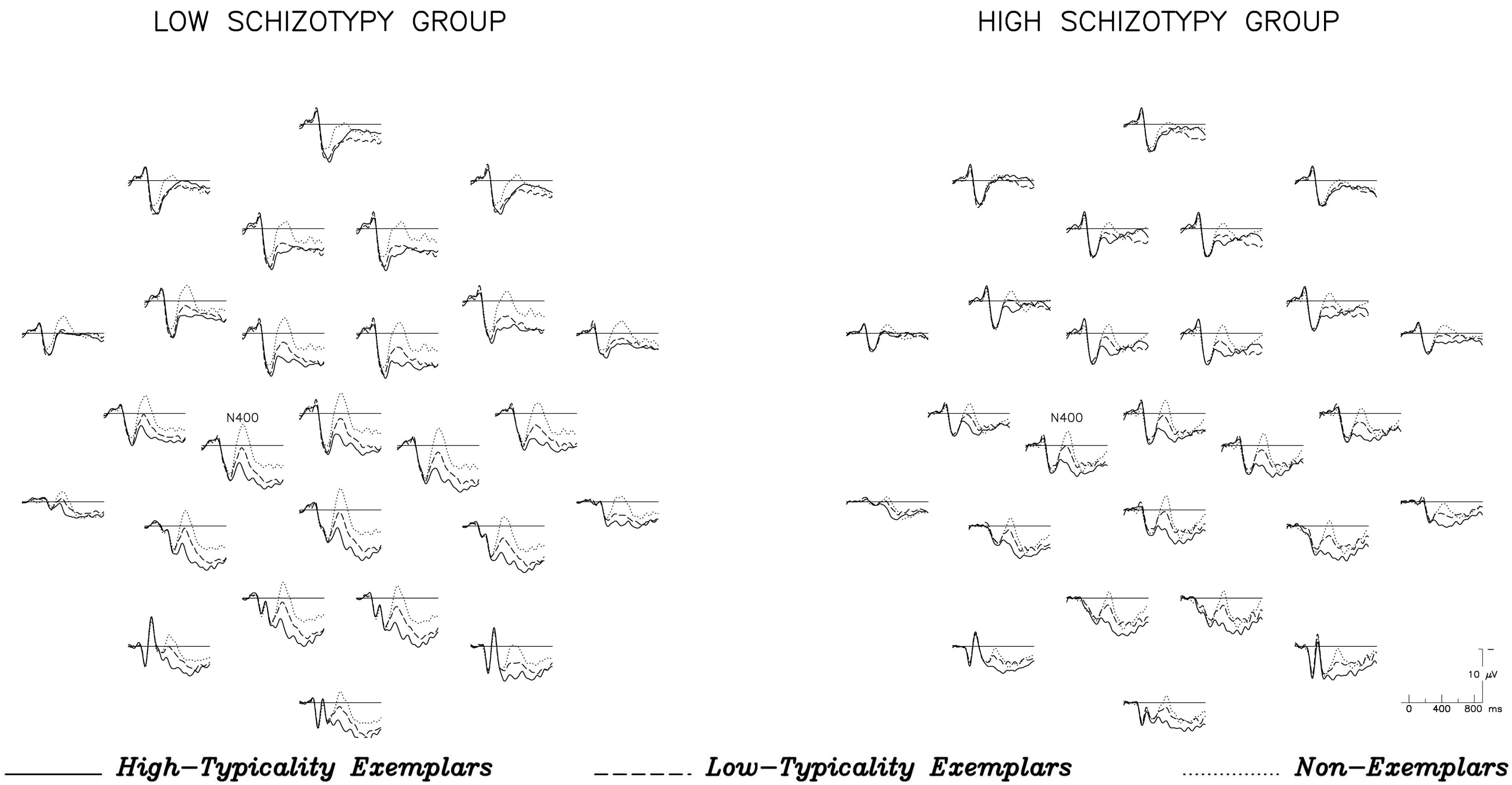

Figure 3.2. Grand average ERPs for the three target types, at all electrode sites, for the low and high-schizotypy groups (n=12 per group).

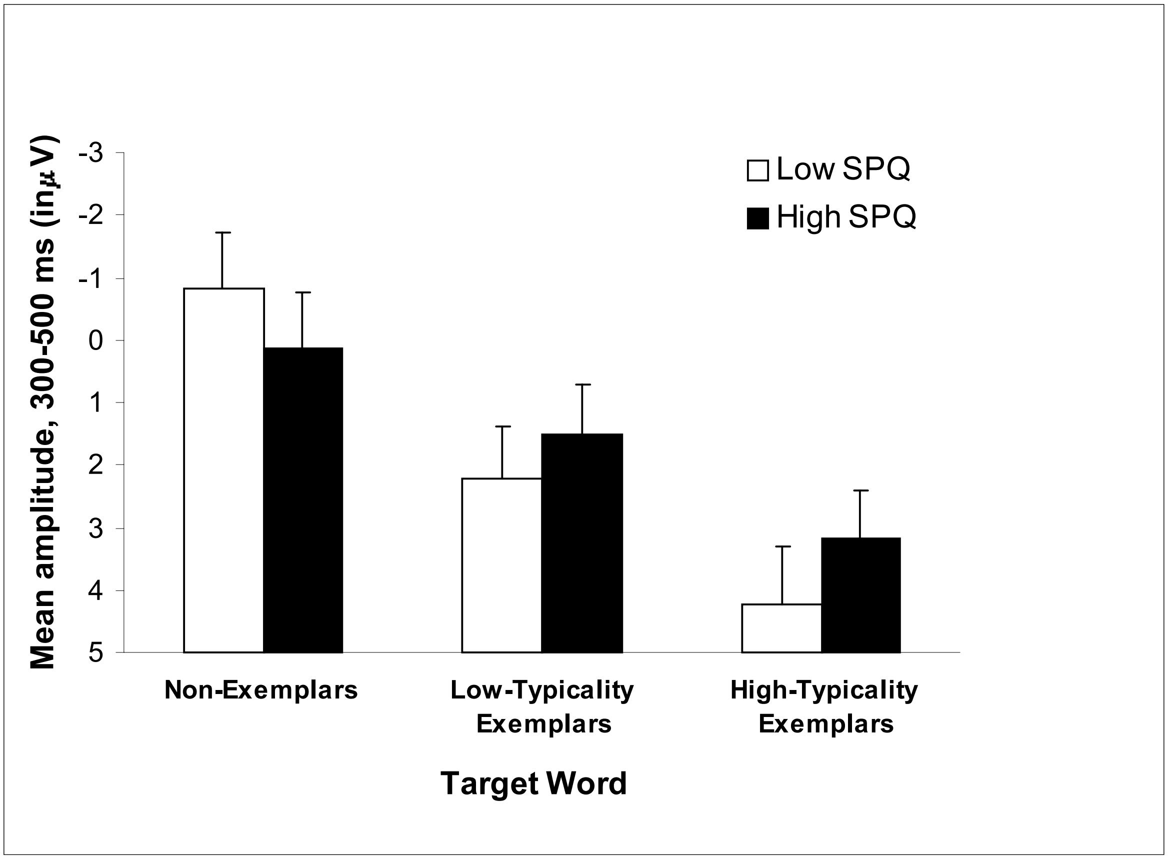

Figure 3.3. Mean N400 amplitude between 300-500 ms, averaged across all electrodes.

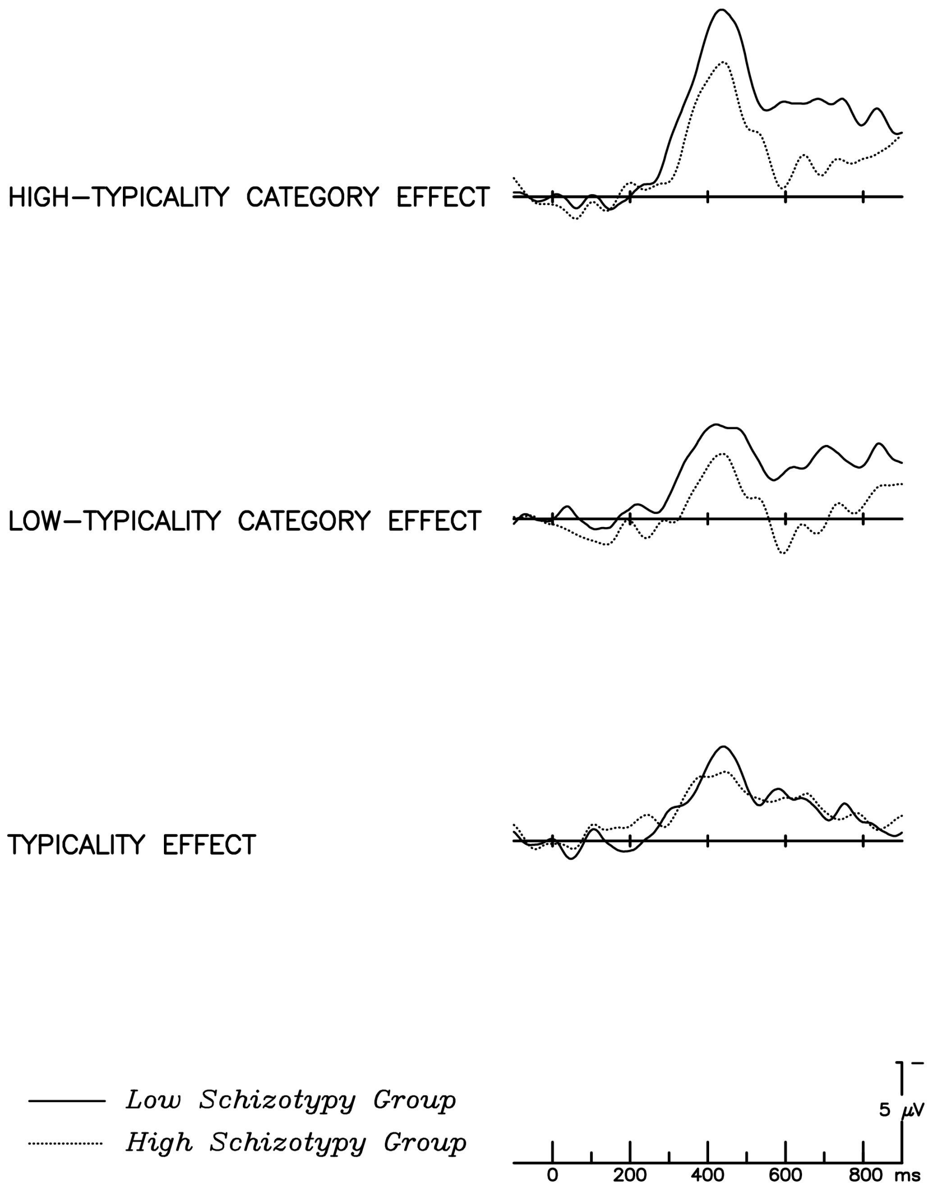

Figure 3.4. ERP difference waves, shown for MiPa.

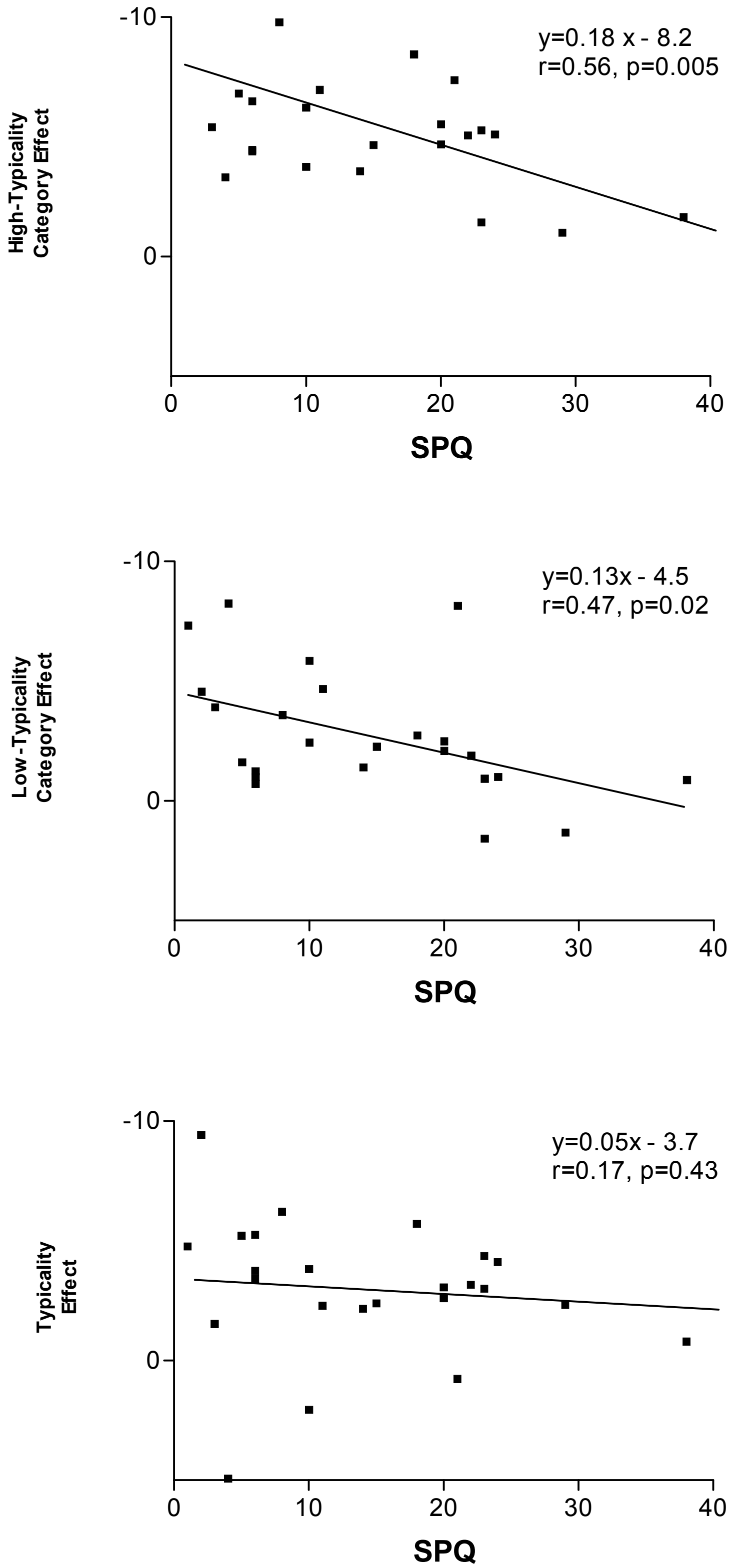

Figure 3.5. Scatterplots of difference wave mean amplitudes (between 300-500 ms at MiPa) vs. total SPQ scores.

Table 3.1. Expected effect of higher schizotypy on N400 amplitudes and N400 effects, according to different hypotheses

Hypothesis	**N400 Amplitudes**			**N400 Effects**		
	High-Typicality Exemplar	**Low-Typicality Exemplar**	**Non-Exemplar**	**Typicality Effect**	**High-Typicality Category Effect**	**Low-Typicality Category Effect**
Greater spread of activation to weak associates	No change	Decreased (i.e. less negative)	No change	Decreased	No change	Increased
Decreased context use	Increased (i.e. more negative)	Increased	No change or decreased	No change	Decreased	Decreased

Table 3.2. Sample categories and corresponding target stimuli

Category	**High-Typicality Exemplars**	**Low-Typicality Exemplars**	**Non-Exemplars**
A type of fruit	apple	prune *or* cherry	clamp
A weapon	gun	revolver *or* stick	musician
A wind instrument	flute	clarinet *or* bagpipes	calendar
A farm animal	cow	goat *or* duck	antenna
A fish	trout	cod *or* eel	parachute
Something worn on the feet	shoes	slippers *or* skis	freight

Table 3.3. Means, standard deviations and ranges of rating scale scores for the study sample (n=24)

Scale	**Mean**	**Median**	**SD**	**Range**	**Maximum possible score**
SPQ (Total)	14.1	12.5	9.7	1-38	74
SPQ Cognitive-Perceptual Factor	5.8	5.0	5.0	0-19	33
SPQ Interpersonal Factor	5.6	4.5	4.9	0-17	33
SPQ Disorganized Factor	4.0	3.5	3.2	0-10	16
PPVT	187.2	190	5.9	170-195	204

Table 3.4. Percentage of correct categorization responses, by schizotypy group and target condition

	Low Schizotypy (n=12)			**High Schizotypy (n=12)**		
Target	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
High-Typicality	95.6	2.2	93-100	94.2	4.8	95-100
Low-Typicality	84.4	4.9	75-90	84.7	5.9	75-93
Non-Exemplar	95.6	4.5	85-100	97.7	2.3	95-100

Table 3.5. Correlations of SPQ scores with difference wave mean amplitudes from 300-500 ms at MiPa (*n*=24)

	High-typicality category effect		**Low-typicality category effect**		**Typicality effect**	
	R	**p**	***R***	**P**	***r***	**p**
SPQ (Total)	0.56	0.005	0.47	0.02	0.17	0.42
SPQ Factors						
Cognitive-Perceptual	0.36	0.08	0.30	0.15	0.11	0.61
Disorganized	0.34	0.11	0.22	0.30	0.16	0.46
Interpersonal	0.63	0.001	0.57	0.004	0.15	0.48

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Chapter 4

Experiment 3 - An event-related brain potential study of direct and indirect semantic priming in schizophrenia

4.1. Abstract

Objective: Following a meaningful prime stimulus, schizophrenia patients have been hypothesized to exhibit impaired neurophysiological activation of related concepts in general, and/or supranormal activation of weakly related concepts in particular, within semantic memory. The former abnormality may occur at relatively longer intervals, and the latter at shorter intervals, after the prime. We tested these hypotheses using the N400 event-related brain potential (ERP) as a probe of activation of concepts in semantic memory.

Method: ERPs were recorded in 16 schizophrenia patients and 16 normal control participants, who viewed prime words each followed by a target which was either a directly (strongly) related, indirectly (weakly) related, or unrelated word, or a nonword, in a lexical-decision task. Equal numbers of each word target type were presented at prime-target SOAs of 300 and 750 ms.

Results: In controls, N400 amplitude was largest (most negative) to unrelated targets, intermediate to indirectly related targets, and smallest to directly related targets. In contrast, in patients, N400 amplitudes did not differ between these target types, reflecting larger amplitudes to both directly and indirectly related targets in patients versus controls; these findings held regardless of SOA. Within patients, at the longer

SOA, larger N400 amplitudes to both directly and indirectly related targets correlated with positive psychotic symptoms.

Conclusions: The results suggest hypoactivation of strongly and weakly related concepts following a meaningful stimulus, regardless of interval, in schizophrenia patients. An N400 index of this hypoactivation correlated with severity of delusions, suggesting a role for abnormal semantic processing in their pathogenesis.

4.2. Introduction

"Disturbance of associations" was identified as a core feature of schizophrenia by Bleuler (1911/1950), who observed that in schizophrenic language "associations lose their continuity" and appear "bizarre" or "senseless." Bleuler's notion of abnormalities in "pathways of association" presaged more recent theories that disorganized speech in schizophrenia results from abnormalities in the activations of conceptual representations in semantic long-term memory (McCarley et al., 1999; Nestor et al., 1998; Spitzer, 1997). These theories assume a model of semantic memory where concepts are nodes in a neural network, and meaningful relationships between concepts are connections between nodes (Collins & Loftus, 1975). On this model, when a concept node is activated, as by its corresponding word stimulus, its subsequent processing is facilitated. This activation then spreads through the network to connected nodes, falling off with decreasing relatedness. The degree to which one concept activates another is thus presumably proportional to their relatedness in the semantic network.

One hypothesis for how disorganized speech in schizophrenia may result from abnormal activation in semantic memory postulates that schizophrenia patients are impaired in using contextual information to activate related items (Cohen & Servan-Schreiber, 1992; McCarley et al., 1999). There is evidence supporting this hypothesis from semantic priming studies, in which the response to a target stimulus - e.g., reaction time (RT) in a lexical-decision or pronunciation task – is facilitated when it is preceded by a meaningfully related rather than an unrelated prime. Greater priming is thought to reflect greater activation of the target by the prime. In contrast to normal control participants (NCPs), schizophrenia patients have exhibited decreased or no semantic priming, consistent with decreased activation of related items by primes (Aloia et al., 1998; Barch et al., 1996; Besche et al., 1997; Passerieux et al., 1997). Although Barch et al. (1996) reported no association between thought disorder (TD) and priming effects within patients, others observed decreased priming effects in TD patients compared to non-TD patients or NCPs (Aloia et al., 1998; Besche et al., 1997; Passerieux et al., 1997). In another study, although all participants were slower to recognize semantically congruent than incongruent sentence-final words, schizophrenia patients with more TD showed smaller congruity effects than patients with less TD or NCPs (Kuperberg, McGuire, & David, 1998) – consistent with impaired use of sentence contexts to activate related items.

Some results have led to the suggestion that, in schizophrenia, activation of related items might become subnormal only after some time following a prime stimulus has elapsed. In fact, Barch et al. (1996) found decreased word-pronunciation RT priming effects when the prime-target stimulus-onset asynchrony (SOA) was 950 ms, but not when it was shorter (200-700 ms). Others, however, have observed decreased RT priming effects in schizophrenia in lexical-decision tasks even with SOAs of 500 ms (Passerieux et al., 1997). Taken together, these results are consistent with the possibility that activation of related items may be subnormal in schizophrenia only approximately 500 ms or more after a prime.

A contrasting, albeit not mutually exclusive, hypothesis for how abnormal activation in semantic memory may cause disorganized speech postulates broader spread of activation to weakly related items in particular, leading to production of minimally related concept sequences (Spitzer, 1997). Consistent with this hypothesis, abnormally large RT priming effects for indirectly related words (those related only through at least one other concept, like *CAT-CHEESE*, mediated by *MOUSE*) have been observed in TD schizophrenia patients (Moritz et al., 2001; Moritz, Woodward, Kuppers, Lausen, & Schickel, 2002; Spitzer, Braun, Hermle, & Maier, 1993). Moritz et al. (2002) suggested that these increased indirect priming effects may occur only when SOAs are approximately 500 ms or less. Indeed, the studies that found these effects used 200-ms prime-target SOAs. (Priming has been proposed to reflect automatically spreading activation at these short SOAs, and consciously-controlled processes, e.g., prediction (Aloia et al., 1998; Barch et al., 1996; Moritz et al., 2002), at longer SOAs. Although this distinction does not appear clear-cut (Barch et al., 1996; Deacon, Uhm, Ritter, Hewitt, & Dynowska, 1999; Hill, Ott, & Weisbrod, 2005), to the extent that it is valid schizophrenia patients could exhibit hyperactivation of weakly related items in the former processes, and/or deficient activation of all related items in the latter.)

Semantic priming effects also have been investigated using the N400 component of electroencephalographic event-related brain potentials (ERPs). The N400 is a negativity approximately 300-500 ms post-stimulus onset, peaking around 400 ms, in response to any potentially meaningful stimulus, such as a word or picture. N400 amplitude is reduced (made less negative) by factors facilitating an item's processing, such as greater linguistic word frequency, or stimulus repetition (2000). N400 amplitude elicited by a target is also reduced by increasing semantic relatedness with a preceding prime (Holcomb & Neville, 1990; Kutas & Hillyard, 1980). Accordingly, N400 amplitude has been used to index the degree to which concepts activate one another in semantic memory, with reduced amplitude associated with greater activation (all else held constant).

Evidence from a number of N400 studies in schizophrenia is also consistent with decreased use of context to activate related items. Prime-target word pairs with SOAs of 450 (Kostova, Passerieux, Laurent, & Hardy-Bayle, 2005; Kostova, Passerieux, Laurent, Saint-Georges, & Hardy-Bayle, 2003) and 600 ms (Strandburg et al., 1997) yielded larger (more negative) N400 amplitudes to related targets in schizophrenia patients than in NCPs, while amplitudes to unrelated targets did not differentiate the two groups. These results suggest decreased activation of related targets due to impaired context use in schizophrenia. In another word-pair experiment, Condray et al. (2003) reported reduced N400 amplitude relatedness effects in patients versus NCPs, at SOAs of 350 and 950 ms (although N400s for either related or unrelated targets did not reliably distinguish the groups). Studies employing sentence stimuli (Kostova et al., 2003; Ohta, Uchiyama, Matsushima, & Toru, 1999) yielded larger N400 amplitudes to sentence-congruent final words in patients than in controls, likewise consistent with impairment in using sentence contexts to facilitate processing of related items.

In contrast, at SOA=250 ms, target words from the same semantic category as a picture prime elicited smaller N400s in schizophrenia patients than in NCPs (Mathalon, Faustman, & Ford, 2002), consistent with *increased* activation of related items. Although relatedness of prime-target pairs in this experiment was not quantified, if they were on average weakly related, then the results could reflect increased spread of activation to weakly related concepts. Taken together, N400 results in schizophrenia patients, like RT priming data, are broadly consistent with decreased use of context to activate related items at longer SOAs, along with increased activation of weakly related items at relatively shorter SOAs.

Whereas these N400 studies compared priming effects only between unrelated and related items in general, we aimed to use the N400 to test for increased spread of activation to weakly related items – specifically, indirectly related word pairs. Thus, we recorded ERPs in schizophrenia patients and NCPs, while they viewed prime-target pairs, in which targets were either words directly related, indirectly related, or unrelated to the prime word, or pronounceable nonwords. Participants' task was to indicate via button-press whether or not the target was a real word. This response was delayed to minimize motor effects on the ERP. An equal number of directly related, indirectly related and unrelated word pairs were presented at each of two SOAs (300 and 750 ms) for each participant.

We predicted that in NCPs, at both SOAs, N400 would be largest (most negative) to unrelated targets, intermediate to indirectly related targets, and smallest to directly related targets, consistent with previous findings (Hill et al., 2005; Kreher, Holcomb, & Kuperberg, 2006; Silva-Pereyra et al., 1999). Furthermore, we hypothesized that if schizophrenia is accompanied by broader spread of activation to weaker associates at short SOAs, then, at the 300-ms SOA, prime words would activate indirectly related targets more strongly in patients than in NCPs, resulting in smaller N400s to these targets in the patients. In addition, if schizophrenia patients make less effective use of context at longer SOAs to activate related items, then, at the 750-ms SOA, both directly and indirectly related targets would be less activated; this would manifest as larger N400s in patients than in controls. We also predicted that since the hypothesized abnormalities in schizophrenia patients are taken to cause their disorganized speech, these abnormalities would correlate with severity of disorganization.

4.3. Method

4.3.1. Participants

Participants included 16 schizophrenia outpatients and 16 NCPs. Patients were recruited through community residential facilities and physician referral. NCPs were recruited through newspaper advertisements and posted flyers. Participants were assessed for capacity to provide informed consent and, after receiving a detailed description of the study, gave written consent. The protocol was approved by the University of California-San Diego Institutional Review Board. Participants received cash compensation.

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID), and were screened to rule out other Axis I diagnoses including substance abuse. NCPs were assessed using the SCID (non-patient version) to rule out past or present Axis I or II diagnoses including substance abuse. Exclusion criteria for all participants included: exposure to a language other than English as a child; and current or past neurological disorder. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971), and parental socioeconomic status (SES) was computed (Hauser & Warren, 1996). Demographic characteristics of the sample are shown in Table 4.1.

Ten patients were prescribed second-generation antipsychotics, 3 were prescribed first-generation antipsychotics, and 3 were prescribed a combination of these; 1 patient in the first group reported not taking antipsychotic for at least 2 weeks before testing.

4.3.2. Assessments

Patients were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). From these ratings, we calculated scores for Psychotic (Hallucinations + Delusions), Negative (Affective Flattening + Avolition/Apathy + Anhedonia/Asociality), and Disorganized symptom factors (Positive Formal Thought Disorder + Bizarre Behavior; Miller, Arndt, & Andreasen, 1993). Patients' clinical characteristics are shown in Table 4.1.

4.3.3. Stimuli

Stimuli included 52 directly related, 52 indirectly related and 52 unrelated prime-target word pairs. For each directly related pair (e.g., *METAL-STEEL*), the target was among the words most commonly given as associates to the prime by participants in the University of South Florida word-association norms (Nelson, McEvoy, & Schreiber, 1999); mean response probability of directly related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.36 (SD=0.23). Indirectly related pairs (*BIRTHDAY-(cake)-PIE)* included 35 pairs from previous studies (Balota & Lorch, 1986; McNamara & Altarriba, 1988; Richards & Chiarello, 1995), and 17 new pairs. For each indirectly related pair, the prime and target were not associates in the norms (i.e., the target was not among words produced by more than one individual in response to the prime), but the mediating word was an associate of the prime (mean response probability 0.38, SD=0.22), and the target was an associate of the mediating word (mean response probability 0.19, SD=0.18). For each unrelated pair (*DONKEY-PURSE*), prime and target were not associates in the norms. Across these three conditions, targets were matched for mean length and log frequency (Francis & Kucera, 1982). Across the conditions, primes were also matched for mean length and log frequency. Stimuli also included 156 word-nonword prime-target pairs (*DRESS-ZORES*), whose targets were pronounceable nonwords. No word occurred more than once among the stimuli.

The 312-trial stimulus list included all prime-target pairs in a fixed randomized order, in four blocks of 78 trials each. The list had two versions, in which the order of prime-target SOAs across blocks was counterbalanced. In version A, SOA was 300 ms in blocks 1 and 3, and 750 ms in blocks 2 and 4; in version B, the order of SOAs was reversed.

4.3.4. Task

Participants were seated 100 cm in front of a video monitor on which stimuli were visually presented, with each letter subtending on average 0.36° of visual angle horizontally, and up to 0.55° vertically. Words were displayed in yellow letters on a black background.

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

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

4.3.5. Electroencephalographic data collection and analysis

The electroencephalogram (EEG) was recorded from 34 sites (FP1-FP2-F7-F3-Fz-F4-F8-T1-FC5-FC1-FC2-FC6-T2-T7-C3-Cz-C4-T8-TP9-CP5-CP1-CP2-CP6-TP10-P7-P3-Pz-P4-P8-PO9-O1-Iz-O2-PO10) referenced to the nose, bandpass filtered at 0.05–100 Hz, and continuously digitized at 1 kHz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges of the left eye, and on the outer canthi of both eyes. Electrode impedances were below 5 kΩ. The EEG was re-referenced off-line to the algebraic mean of the mastoids (TP9/TP10). Continuous data were algorithmically corrected for eyeblink artifact (Semlitsch, Anderer, Schuster, & Presslich, 1986). ERPs were computed for epochs from 100 ms pre-stimulus to 924 ms post-stimulus. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before time-domain averaging; mean percentage of trials lost to such artifacts was 18% for patients and 11% for controls.

For each trial type, N400 latency was defined as the interval between target onset and the largest negative peak from 300-500 ms post-stimulus. N400 amplitude was defined as mean voltage from 300-500 ms post-stimulus.

4.3.6. Statistical analysis

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

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

N400 latency and amplitude were analyzed in ANOVAs with Group (schizophrenia vs. NCP) as between-subject variable, and SOA (300-ms vs. 750-ms), Target (directly related vs. indirectly related vs. unrelated) and Electrode (34 levels, corresponding to all recording sites) as within-subject variables.

To examine the relationship between symptoms and N400 amplitude in patients, correlation coefficients were calculated between N400 amplitude at Pz (midline parietal) for each target type at each SOA, and Psychotic, Negative, and Disorganized factor ratings. For correlations involving Psychotic or Disorganized ratings, we used

Spearman's rank-order coefficient ρ, since these variables were not normally distributed; otherwise, Pearson's *r* was used.

4.4. Results

4.4.1. Behavioral data

The correct-response rates for schizophrenia patients and NCPs (Table 4.2) indicate that, overall, participants were attending to the stimuli. There was a Target effect ($F_{3,60}$=4.53, p=0.005), with lower accuracy for unrelated targets than for directly or indirectly related targets. There was no SOA effect ($F_{1,30}$=2.31, p=0.14); and no Group effect ($F_{1,30}$=2.31, p=0.14) or Group x Target interaction ($F_{3,60}$=0.63, p=0.60), suggesting that patients and controls did not differ significantly in their attention to the stimuli.

4.4.2. Grand average ERPs

Grand average ERPs are shown for midline electrodes, for schizophrenia and NCP groups, for the SOA=300 ms in Fig. 4.1 and SOA=750 ms in Fig. 4.2.

4.4.3. N400 latency

Mean N400 latency across patient and NCP groups for all target types was 396 ms. Mean latency did not vary significantly by Group ($F_{1,30}$=1.97, p=0.17), SOA ($F_{1,30}$=0.23, p=0.64) or Target ($F_{2,60}$=0.67, p=0.52), and there was no Group x SOA ($F_{1,30}$=0.90, p=0.35) or Group x Target interaction ($F_{2,60}$=0.64, p=0.53).

4.4.4. N400 amplitude

N400 amplitudes for schizophrenia patients and NCPs are shown in Table 4.3. Across these two groups, N400 amplitude was largest (most negative) for unrelated targets, intermediate for indirectly related targets, and smallest for directly related targets

(Target main effect: $F_{2,60}$=3.38, p=0.04). N400 effects were broadly distributed over the scalp although largest medially and centro-parietally (Target x Electrode interaction: $F_{66,1980}$=9.86, p=0.02). There were no Group ($F_{1,30}$=2.18, p=0.15), SOA ($F_{1,30}$=1.02, p=0.32), or Group x SOA ($F_{1,30}$=0.70, p=0.41) effects. There was, however, a Group x Target interaction ($F_{2,60}$=3.77, p=0.03) – for controls, N400 amplitudes for the three word target types all differed significantly from one another, whereas for patients there were no differences among them. In addition, N400 amplitudes were larger for patients than for controls for both directly and indirectly related targets, but did not differ between groups for unrelated targets.

4.4.5. Correlation of N400 amplitudes with symptom ratings

Within the patient group, at SOA=300 ms, N400 amplitudes to each word target type were not significantly correlated with SAPS/SANS-derived symptom factors (all p>0.10). At SOA=750 ms, however, higher Psychotic scores correlated with larger (more negative) N400s to directly related (ρ=-0.64, p=0.007) and indirectly related targets (ρ=-0.64, p=0.007). Larger N400s to directly and indirectly related targets correlated with both Delusions (directly related: ρ=-0.66, p=0.005; indirectly related: ρ=-0.68, p=0.003) and Hallucinations (directly related: ρ=-0.55, p=0.03; indirectly related: ρ=-0.53, p=0.04) subscale scores. At SOA=750 ms, N400 amplitudes to each target type were not significantly correlated with Disorganized or Negative scores (all p>0.64).

4.5. Discussion

This study used the N400 ERP component as a brain-based method of assessing direct and indirect semantic priming in schizophrenia. Schizophrenia patients and NCPs matched for age, gender and parental SES viewed prime words, followed by target words either directly related, indirectly related, or unrelated to the prime. As hypothesized, in controls, N400 amplitude was largest (most negative) to unrelated targets, intermediate for indirectly related targets, and smallest for directly related targets. By contrast, in patients, there was no significant difference in N400 amplitude elicited by these three target types, suggesting a lack of direct and indirect semantic priming. The absence of reliable priming effects in patients reflected larger N400 amplitudes to both directly and indirectly related targets, compared to controls, at both prime-target SOAs (300- and 750-ms). In addition, within patients, at the 750-ms SOA, higher Psychotic factor scores correlated with larger N400 amplitudes to directly and indirectly related targets.

Overall, our results do not provide evidence for increased spread of activation to weakly related items in schizophrenia. According to this hypothesis, we would expect smaller than normal N400 amplitudes to indirectly related targets, but these were not seen at either SOA. Rather, consistent with a number of previous studies (Condray et al., 2003; Kostova et al., 2005; Kostova et al., 2003; Ohta et al., 1999; Strandburg et al., 1997), the results provide further evidence for decreased activation of related items in schizophrenia. Specifically, patients exhibited larger than normal N400 amplitudes to both directly and indirectly related targets, such that N400s to related items were not statistically distinguishable from those to unrelated items (i.e., no priming effects). Notably, this abnormality occurred across both SOAs, suggesting that decreased activation of related items is in effect by 300 ms after a prime stimulus, and persists thereafter. This finding fits with the view that schizophrenia is associated with impaired use of contextual stimuli even at the shortest time delays, consistent with deficient information consolidation in working memory (Fuller, Luck, McMahon, & Gold, 2005).

Further research is needed to clarify the dissociation between our finding of *decreased* N400 priming effects in schizophrenia, and the *increased* N400 priming effects (25), and RT indirect priming effects (Moritz et al., 2001; Moritz et al., 2002; Spitzer et al., 1993) previously reported, at least at short SOAs. If increased N400 priming is associated with relatively severe TD, then perhaps we did not detect this abnormality because our sample was on average insufficiently high in TD. Nevertheless, we also did not find a correlation across patients between TD (measured by SAPS/SANS Disorganized scores) and increased N400 priming effects, as might have been expected. Further studies are needed to assess the degree to which increased N400 priming effects in schizophrenia are contingent on diagnostic subgroup and on characteristics of the semantic stimuli used. The contrast between our results and those of RT priming studies could also stem from a dissociation between N400 and RT priming effects. Such dissociations have previously been reported (Heinze, Muente, & Kutas, 1998) and may arise if N400 is a more direct measure of semantic activation than RT, which by its nature also incorporates response-related (e.g., decision-making) processes. For example, if patients rely more than controls on checking for a relationship between prime and target in order to decide that the target is indeed a word (a strategy proposed to occur by Balota and Lorch, 1986), and detect some semantic relationship between indirectly related but not unrelated words, this could increase RT differences between indirectly related and unrelated targets more in patients than in NCPs. However, because our study was not designed to measure RT priming, and used a delayed response, we cannot ascertain whether RT and N400 priming effects were dissociated in our sample.

Most patients in our study were taking a second-generation antipsychotic, either alone or in combination with a first-generation agent. Therefore, our data do not allow us to definitively assess whether and how each of these medication classes affects N400 abnormalities in schizophrenia; further research comparing N400 priming in patients on first- versus second-generation antipsychotics and unmedicated patients is needed to do so.

The observed association between decreased N400 semantic priming and psychosis supports the view that abnormally similar neurophysiological processing of stimuli more and less meaningfully-related to their context may play a role in pathogenesis of delusions (Hemsley, 2005; Kiang, Kutas, Light, & Braff, 2007). These results fit with our previous finding that psychosis in schizophrenia correlates with reduced N400 amplitude differences between high- and low-typicality exemplars following category primes (Kiang et al., 2007). A reduced difference in the degree to which a stimulus facilitates processing of items more and less meaningfully-related to it might produce the subjective experience that unrelated stimuli occurring in proximity have some meaningful connection, or conversely that stimuli congruent with their context are unexpected or unusual, perhaps prompting an ultimately delusional explanation.

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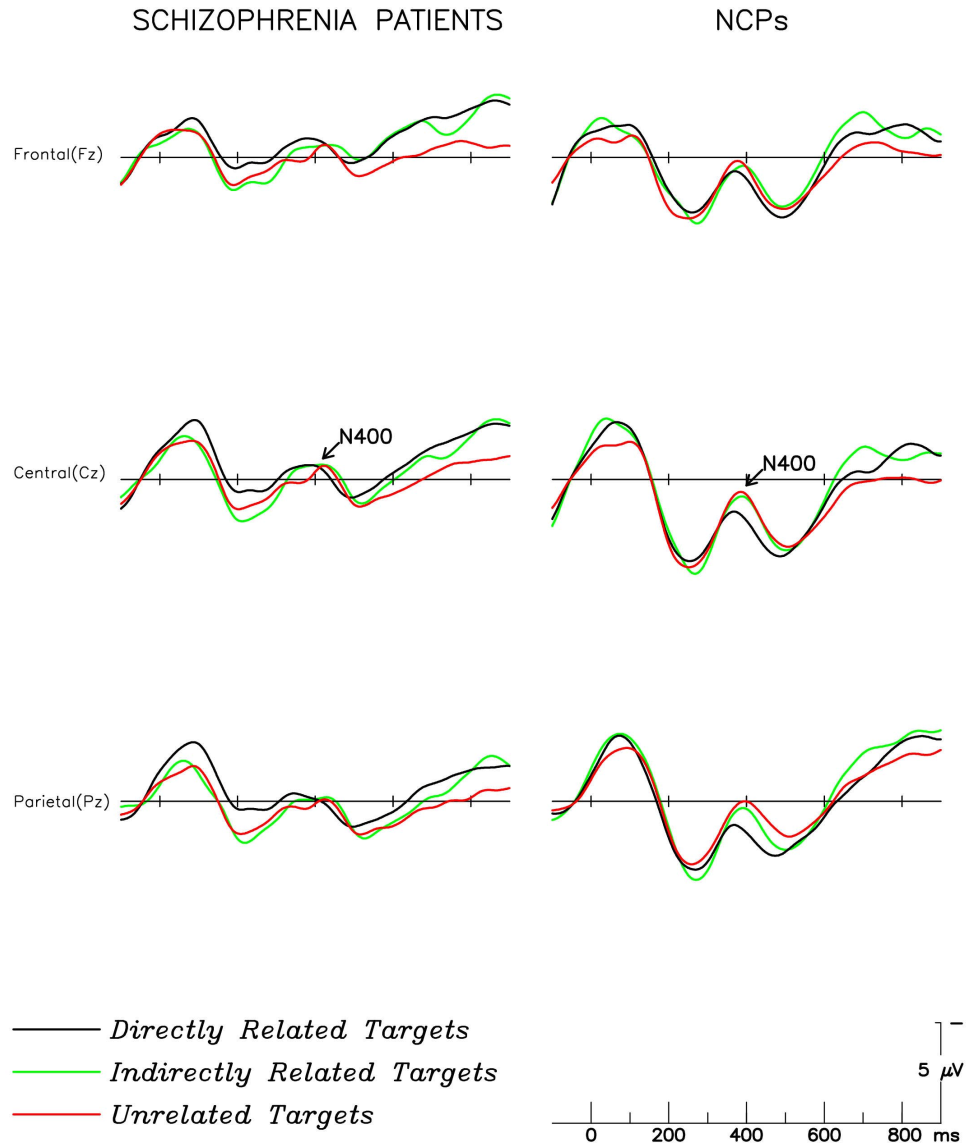

Figure 4.1. Grand average ERPs to target words at the 300-ms prime-target SOA, at midline electrode sites, for schizophrenia patients (*n*=16) and normal control participants (NCPs; *n*=16). Negative amplitudes are plotted upward.

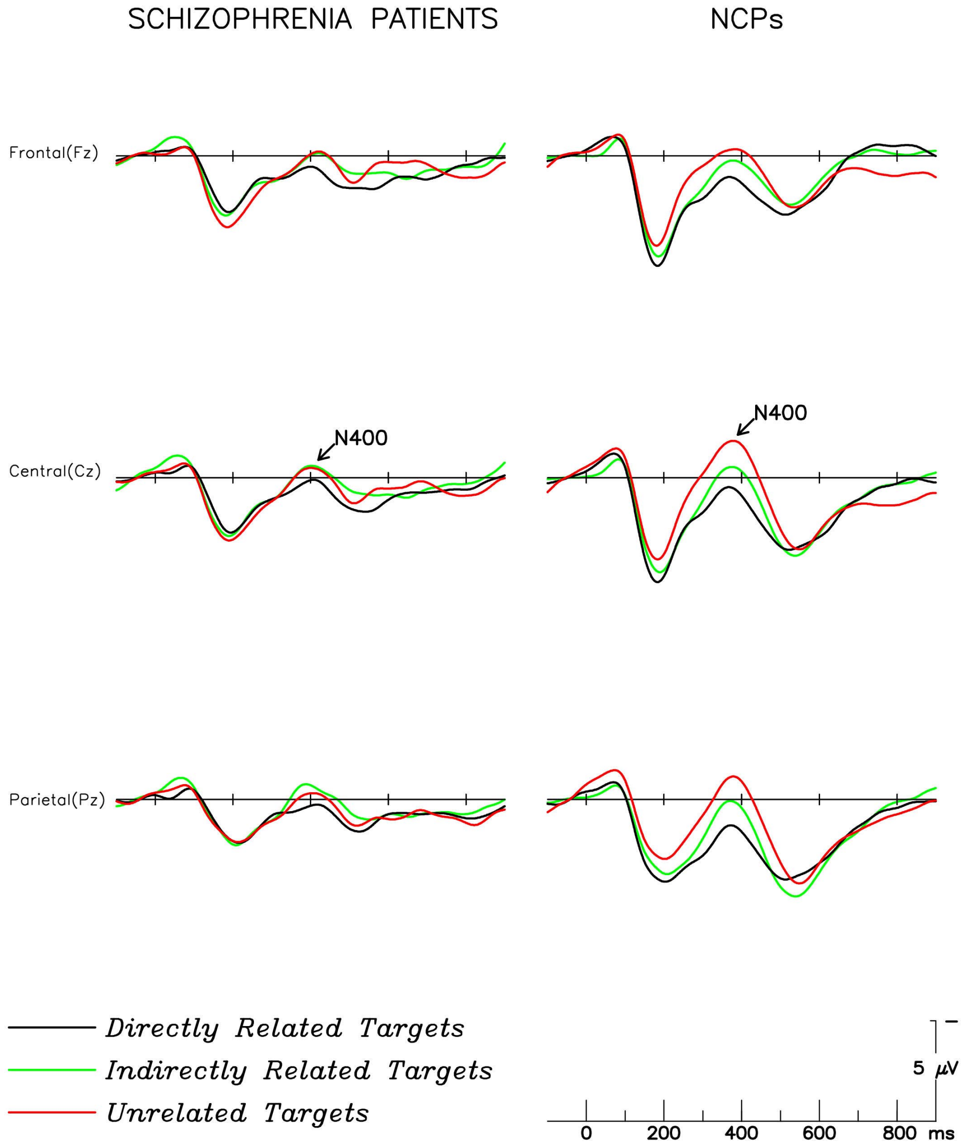

Figure 4.2. Grand average ERPs to target words at the 750-ms prime-target SOA, at midline electrode sites, for schizophrenia patients (*n*=16) and normal control participants (NCPs; *n*=16). Negative amplitudes are plotted upward.

Table 4.1. Demographic and clinical characteristics of the study sample (means ± SD given where applicable)

	Schizophrenia Patients (n=16)	**Healthy Controls (n=16)**
Age, years	45.9±7.7	44.8±13.2
Sex	12 male, 4 female	9 male, 7 female
Handedness	15 right, 1 left	15 right, 1 left
Parental SES	37.5±16.8	38.6±10.6
Years of Education[a]	12.8±2.1	15.3±2.7
Age of onset, years	23.9±8.4	-
Duration of illness, years	22.0±10.9	-
Number of previous hospitalizations	7.3±6.3	-
SANS Total	10.0±4.0	-
SAPS Total	4.9±4.0	-
Negative Factor	8.8±3.4	-
Psychotic Factor	3.3±3.6	-
Disorganized Factor	2.2±3.4	-

[a]Patients differed significantly from controls, p=.007

Table 4.2. Percentage of correct lexical-decision responses, by participant group and target condition

	Schizophrenia Patients (n=16)		**Normal Control Participants (n=16)**	
	Mean	**SD**	**Mean**	**SD**
Short SOA				
Directly Related	94.2	8.5	96.2	7.3
Indirectly Related	93.3	13.5	96.2	8.1
Unrelated	86.6	15.3	91.4	13.6
Nonwords	91.5	13.0	97.8	3.2
Long SOA				
Directly Related	96.2	7.7	97.1	6.9
Indirectly Related	90.6	14.5	98.1	4.2
Unrelated	91.8	10.8	93.5	9.5
Nonwords	87.3	21.5	97.2	4.1

Table 4.3. Mean N400 amplitude (μV), by participant group and target condition

	Schizophrenia Patients (n=16)		**Normal Control Participants (n=16)**	
	Mean	**SD**	**Mean**	**SD**
Short SOA				
Directly Related	-0.28	2.27	0.93	3.20
Indirectly Related	-0.16	1.94	0.70	3.20
Unrelated	-0.06	2.30	0.59	2.62
Long SOA				
Directly Related	0.63	2.53	1.31	2.33
Indirectly Related	0.32	2.13	0.87	2.97
Unrelated	0.45	2.17	0.22	2.45

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Chapter 5

Experiment 4 - An event-related brain potential study of schizotypal personality and associative semantic processing

5.1. Abstract

In order to determine whether schizotypal personality is associated with the degree to which concepts activate each other in semantic memory, event-related brain potentials (ERPs) were recorded during a delayed lexical decision task from healthy volunteers rated for schizotypy. Each target word was either directly, indirectly, or not at all related to a prime word preceding it at a 300- or 750-ms stimulus-onset asynchrony (SOA). Overall, N400 amplitudes were largest for unrelated targets, smallest for directly related targets, and intermediate for indirectly related targets. Higher total Schizotypal Personality Questionnaire (SPQ) scores correlated with smaller N400 indirect priming effects (N400 amplitude differences between unrelated and indirectly related targets) at both SOAs. In addition, schizotypal subscale scores were differentially associated with N400 effects. Higher SPQ Interpersonal scores correlated with larger N400 strength-of-relatedness effects (i.e., N400 amplitude differences between indirectly and directly related targets) at the 300-ms SOA. Higher SPQ Cognitive-Perceptual scores correlated with smaller N400 direct priming effects (N400 amplitude differences between unrelated and directly related targets) at both SOAs, and with smaller N400 indirect priming effects at the 300-ms SOA. This correlation of higher Cognitive-Perceptual scores with smaller N400 priming effects suggests that decreased use of meaningful context to activate

related concepts in general, and/or to inhibit unrelated concepts, may play a role in the development of unusual beliefs.

5.2. Introduction

Schizotypal personality traits include unusual beliefs, ideas of reference (thoughts that external events or situations have special personal significance), odd speech, eccentric appearance or behavior, perceptual abnormalities, suspiciousness, and social isolation (American Psychiatric Association, 2000). Several of these traits appear to reflect the formation of unusual associations between concepts. For instance, odd speech in schizotypy has been characterized as "loose, digressive" (American Psychiatric Association, 2000), or "unusually circumstantial" (Hales & Yudofsky, 2003). Paranormal beliefs, magical thinking, ideas of reference, and suspiciousness also involve the supposition of meaningful associations between objects or occurrences that are normatively regarded as unrelated or co-incidental (Bressan, 2002; Gianotti, Mohr, Pizzagalli, Lehmann, & Brugger, 2001). An association of schizotypy with a propensity for forming uncommon semantic associations is apparent on a number of language-based psychometric tests. Individuals scoring higher in magical or paranormal ideation generate more unusual responses in free word-association tests (Gianotti et al., 2001; E. N. Miller & Chapman, 1983), and give higher relatedness ratings to word pairs that are normatively unassociated (Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001). In addition, individuals higher in schizotypy generate less typical exemplars of fruits in response to the category label (Kiang & Kutas, 2006).

It has been hypothesized that unusual associations in schizotypy reflect some difference in how meaningful concepts activate one another in the brain (Moritz et al., 1999; Niznikiewicz et al., 2002; Pizzagalli, Lehmann, & Brugger, 2001). These hypotheses assume a model of semantic long-term memory in which concepts are represented as nodes in a network, and associations between concepts are links among these nodes (Anderson & Pirolli, 1984; Collins & Loftus, 1975; Neely, 1977). As a concept node is activated – e.g., when the individual encounters its corresponding word or image – activation spreads through the network to associated nodes, falling off as a function of decreasing relatedness. The greater the activation level of a concept, the more facilitated is its processing.

According to one hypothesis, schizotypy involves an increase in the degree to which a given stimulus concept activates its relatively weaker associates in the semantic network, leading to unusual associations in language and reasoning (Mohr et al., 2001; Pizzagalli et al., 2001). Some results from reaction-time (RT) semantic priming paradigms support this hypothesis. RT semantic priming refers to faster responses to a target stimulus when it is preceded by a related prime stimulus as compared to an unrelated prime. Semantic priming is taken to reflect greater activation of the target representation by the related prime than by the unrelated prime. Pizzagalli et al. (2001) examined priming effects for indirectly related word pairs (i.e., not directly related, but mediated by at least one other concept, e.g., *CAT* and *CHEESE*, mediated by *MOUSE*), which are considered relatively weak associates, in paranormal believers compared to non-believers. These indirect priming effects were larger in believers than non-believers (at least for left lateralized targets). In another study, high scorers on the Perceptual

Aberration/Magical Ideation scale exhibited greater priming than control participants for semantically related items that were not named as associates in word-association tests (Kerns & Berenbaum, 2000).

Other results, however, have suggested that, instead of or in addition to being characterized by increased activation of weak associates, schizotypy is characterized by increased activation of strong associates. These studies used electrophysiological data – namely, the N400 component of the scalp-recorded event-related brain potential (ERP), as an index of semantic priming. The N400 is a relative negativity peaking approximately 400 ms after presentation of any potentially meaningful stimulus, such as a word or picture. Its amplitude is reduced (made less negative) by a host of factors facilitating an item's processing (reviewed in (Kutas & Federmeier, 2000) – including greater relatedness to a preceding item (Holcomb & Neville, 1990, 1991; Kutas, 1985; Kutas & Hillyard, 1980; Stelmack & Miles, 1990). With all else held constant, the amplitude of the the N400 can thus serve as a measure of the degree to which concepts activate one another in semantic memory: the greater the activation, the smaller the N400 negativity. Niznikiewicz et al. (2002) found that, at an SOA of 450 ms, women with schizotypal personality disorder (SPD) and control women had similar N400 amplitudes to unrelated word-pair targets, but SPD women had smaller (less negative) N400 amplitudes than control women to related targets. At a longer SOA of 1000 ms, the groups did not differ in N400 amplitudes for any of the stimuli. These results suggested that the interval between prime and target may be critical in determining whether or not reliable group differences obtain: SPD was reliably characterized by greater activation of associated words only at short intervals. In addition, it is important to note that since it is unclear whether the word-pair stimuli in this study were based on word-association norms, it is possible that the pairs, although directly related, may have been only relatively weak associates, making the results consistent with increased activation of weak associates in schizotypy.

According to a different (non-mutually exclusive) hypothesis, schizotypy may be accompanied by decreased use of context to activate related concepts in general, or to inhibit unrelated concepts (Kiang & Kutas, 2005; Niznikiewicz et al., 2002; Niznikiewicz et al., 1999). Consistent with this hypothesis, schizotypy has been found to be associated with larger than normal N400 amplitudes to *congruent* sentence endings (Niznikiewicz et al., 2004; Niznikiewicz et al., 1999), and to exemplars of a category following the category definition (Kiang & Kutas, 2005), suggesting less than normal contextual activation. In another study, SPD was associated with a less than normal difference between N400 amplitudes to congruent and incongruent sentence endings, again consistent with decreased use of sentential context (Kimble et al., 2000).

Not only is decreased use of context not necessarily mutually exclusive with increased or more broadly spreading activation of related items, but it has been proposed that both may occur but at different times: according to one proposal, schizotypy may be characterized by increased or broader activation of related concepts at relatively short SOAs, but by deficient use of context at longer SOAs (Moritz et al., 1999; Niznikiewicz et al., 2002). Taken together, the experimental results are generally consonant with this pattern. The experiments by Pizzagalli, et al. (2001) and Niznikiewicz et al. (2002), whose results suggested increased or broader activation of related concepts with higher schizotypy, employed SOAs of 200 and 450 ms, respectively.[1] In contrast, the results suggesting decreased context use to activate related items or to inhibit unrelated items have come from experiments with longer SOAs, including sentence contexts which build up over several seconds.

In the present study, we sought further evidence on how schizotypal personality, semantic relatedness and time interact to modulate semantic priming effects. To this end, we studied participants from a non-clinical population, who were rated on schizotypy. We examined N400 amplitude of the ERP in these individuals as they read word pairs that were either strongly (directly) related, weakly (indirectly) related or unrelated, and that were presented one word at a time, at both short and long SOAs (300 and 750 ms) for each participant. In constructing the stimuli, we used word-association norms to verify that directly related word pairs were strongly normatively associated, and that indirectly related pairs were not normatively associated (even though the prime and the mediating concept, as well as the mediating concept and the target, were normatively associated).

We hypothesized that, over all participants, consistent with previous N400 studies of indirectly related word pairs (Hill, Ott, & Weisbrod, 2005; Kreher, Holcomb, & Kuperberg, 2006; Silva-Pereyra et al., 1999; Weisbrod et al., 1999), N400 amplitude would be largest (most negative) to unrelated targets, smallest (least negative) to directly related targets, and intermediate to indirectly related targets. Furthermore, we hypothesized that, if schizotypy is associated with *increased activation of weakly related*

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[1] In the study by Kerns and Berenbaum (2000), whose results also suggested broader spread of activation to weak associates, the prime word was presented until the participant named it (up to a maximum of 1500 ms) and then followed by a 350-ms interval until target onset; thus SOAs potentially ranged from 350 to 1850 ms.

concepts such as indirectly related words, as reflected in smaller (less negative) N400 amplitudes to these targets, then schizotypy would be correlated with larger N400 amplitude differences between unrelated and indirectly related targets, i.e., larger N400 *indirect priming effects*. Likewise, if schizotypy is associated with *increased activation of strongly related concepts*, as reflected in smaller N400 amplitudes to directly related targets, then schizotypy would be correlated with larger N400 amplitude differences between unrelated and directly related targets, i.e., larger N400 *direct priming effects*. Moreover, if, as previously hypothesized (Moritz et al., 1999; Niznikiewicz et al., 2002), increased activation of related concepts occurs only at short SOAs, then the correlation between schizotypy and increased indirect and/or direct priming effects would be seen only at the 300–ms SOA and not at the 750–ms SOA.

Alternatively or in addition, we hypothesized that if schizotypy is characterized by *decreased use of context to activate both directly and indirectly related concepts*, then N400 amplitudes to directly and indirectly related targets would increase with schizotypy. In addition, if decreased context use results in decreased inhibition (i.e., increased activation) of unrelated targets, then N400 amplitudes to these targets also might decrease with schizotypy. Schizotypy would thus be correlated with reduced N400 amplitude differences between unrelated targets and both types of related targets, i.e., smaller N400 *direct and indirect priming effects*. Moreover, if decreased context use in schizotypy occurs only at long SOAs, then the correlation of schizotypy with reduced N400 priming effects would be seen only at the 750–ms SOA and not at the 300–ms SOA.

We also hypothesized that specific subsets of schizotypal traits might be differentially related to N400 semantic priming effects. Empirically, individuals' scores on schizotypal traits have been found to load on three semi-independent factors (Raine et al., 1994; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000; Rossi & Daneluzzo, 2002). These factors have been termed *cognitive-perceptual* (comprising ideas of reference, odd beliefs, unusual perceptual experiences, and suspiciousness); *disorganized* (odd behavior and odd speech); and *interpersonal* (social anxiety, lack of close friends, constricted affect, and suspiciousness (Raine et al., 1994). Given the putative role of semantic priming differences in the development of disorganized speech and unusual ideation, we predicted that the disorganized and cognitive-perceptual factors of schizotypy would be those specifically correlated with the N400 priming differences hypothesized above.

5.3. Materials and Methods

5.3.1. Participants

28 healthy participants [15 female, 18 to 23 years of age, mean age 19.7, SD = 1.5] were recruited from the campus of the University of California, San Diego (UCSD). All were undergraduate students. Exclusion criteria included: left-handedness, as assessed by the Edinburgh Inventory (Oldfield, 1971); and any self-reported history of: exposure to a language other than English at home as a child, reading difficulties, visual impairment, current or past neurological or psychiatric disorder, or current use of neurological or psychotropic medications. 13 participants reported having a left-handed first-degree relative. Participants gave written informed consent and were compensated with course credit or cash. The study procedure was approved by the UCSD Human Research Protections Program.

5.3.2. Rating scales

Participants completed the Schizotypal Personality Questionnaire (SPQ; (Raine, 1991), a self-report measure of schizotypy. It consists of 74 dichotomous-choice (Yes or No) questions, comprising 9 subscales corresponding to each of the 9 DSM-IV schizotypal traits (American Psychiatric Association, 2000). These subscales have been found to load onto 3 factors: Cognitive-Perceptual (comprising the Ideas of Reference, Odd Beliefs, Unusual Perceptual Experiences and Suspiciousness subscales), Disorganized (Odd Behavior and Odd Speech), and Interpersonal (Social Anxiety, No Close Friends, Constricted Affect and Suspiciousness; (Raine et al., 1994). The maximum total SPQ score is thus 74; maximum possible factor scores are Disorganized: 16; Cognitive-Perceptual: 33; and Interpersonal: 33.

Participants also completed the Peabody Picture Vocabulary Test (PPVT; (Dunn & Dunn, 1997) as a measure of receptive vocabulary.

5.3.3. Stimuli

The stimuli included 52 directly related, 52 indirectly related and 52 unrelated prime-target word pairs. For each directly related pair, the target was selected from among the words most commonly given as associates to the prime in the word-association norms of Nelson et al. (1999). Mean response probability of directly related targets (i.e., the proportion of individuals who produced that word in response to the prime, in the norms) was 0.36 (SD=0.23). Indirectly related pairs included 35 pairs used in previous studies (Balota & Lorch, 1986; McNamara & Altarriba, 1988; Richards & Chiarello, 1995), and 17 new pairs. For each indirectly related pair, the prime and target were not associates according to the norms (i.e., the target was not among the words produced by more than one individual in response to the prime), but the mediating word was an associate of the prime (mean response probability 0.38, SD=0.22), and the target was an associate of the mediating word (mean response probability 0.19, SD=0.18). Finally, for each unrelated pair, the prime and target were not associates according to the norms. Across these three conditions, targets were matched for mean length, log frequency (Francis & Kucera, 1982), concreteness (Wilson, 1988), and number of orthographic neighbours (Wilson, 1988). Across the conditions, primes were also matched for mean length and log frequency. In addition, the stimuli included 156 word-nonword prime-target pairs, whose targets were pronounceable nonwords from among those used by Deacon et al. (2004). No word occurred more than once among all the stimuli. Examples of prime-target pairs used in the experiment are shown in Table 5.3.

The 312-trial stimulus list included all of the above prime-target pairs in a fixed randomized order. It was divided into four blocks of 78 trials each. In addition, the list had two versions, in which the ordering of prime-target SOAs across blocks was counterbalanced. In version A, prime-target pairs were presented with SOA of 300 ms in blocks 1 and 3, and 750 ms in blocks 2 and 4; in version B, the SOA was 750 ms in blocks 1 and 3, and 300 ms in blocks 2 and 4.

5.3.4. Experimental procedure

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

Each participant was presented with the stimulus list, with short rest breaks between blocks. Half the participants received each version of the list. Each trial consisted of the following sequence: a) a row of preparatory fixation crosses at the center of the screen for 500 ms; b) blank screen for 250 ms; c) prime word for 250 ms; d) blank screen for 50 ms (in 300-ms SOA trials) or 500 ms (in 750-ms SOA trials); e) word or nonword target for 250 ms; f) blank screen for 1250 ms; g) the prompt *Yes or No?* until participants responded with a button-press (see below); and h) blank screen for 3000 ms until onset of the next trial. All stimuli were presented centered on the screen.

Upon presentation of the prompt, participants were required to press one of two buttons, on joysticks held in the right and left hands respectively. One button (labeled "Yes") signaled that the target was a word, while the other button (labeled "No") signaled that it was a nonword. The assignment of buttons was divided equally among participants, counterbalanced across the two versions of the stimulus list.

5.3.5. Electrophysiological data collection and analysis

The electroencephalogram (EEG) was recorded from 26 tin electrodes embedded in an electro-cap, and referenced to the left mastoid. Electrodes were equally spaced across the scalp, with positions and labels as shown in Fig. 5.1. Blinks and eye movements were monitored via electrodes placed on the outer canthus (left electrode serving as reference) and infraorbital ridge of each eye (referenced to the left mastoid). Electrode impedances were kept below 5 kΩ. The EEG was processed through Grass amplifiers set at a bandpass of 0.01–100 Hz, continuously digitized at 250 Hz, and stored on hard disk for later analysis.

The EEG was re-referenced off-line to the algebraic mean of the left and right mastoids. ERPs were computed for epochs extending from 100 ms before stimulus onset to 920 ms after stimulus onset. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line before time-domain averaging; approximately 7% of trials were lost due to such artifacts. If data from a participant contained excessive blinks, they were corrected using a spatial filter algorithm (Dale, 1994); this was applied to 5 participants' data.

For each trial, N400 peak latency was measured as the interval between stimulus onset and the largest negative peak between 250 and 550 ms post-stimulus. N400 amplitude was measured as mean voltage from 300-500 ms post-stimulus. For each participant, N400 effects were defined as the mean voltage from 300-500 ms post-stimulus for the difference waves between ERPs for each pair of target types: unrelated minus directly related (*direct priming effect*), unrelated minus indirectly related (*indirect priming effect*), and indirectly related minus directly related (*strength-of-relatedness effect*).

5.3.6. Statistical analysis

For each SOA condition, N400 peak latency and N400 amplitude were each analyzed in a repeated-measures analysis of variance (ANOVA) over all participants with Target (directly related vs. indirectly related vs. unrelated) and Electrode (26 levels, corresponding to all recording sites) as within-subject variables. *p*-values for ANOVA within-subject factors are reported after Greenhouse-Geisser Epsilon correction. Pairwise comparisons of factor-level means were made using the Tukey procedure for simultaneous pairwise comparisons, with a family confidence coefficient of 0.95.

Based on the observed distribution of N400 effects across the scalp in the grand-average ERPs, a representative site where these effects were prominent (MiPa; Pz in the International 10-20 system) was chosen for computation of statistical significance of Pearson pairwise correlation coefficients *r* between SPQ total/factor scores and N400 measures (N400 mean amplitude for each target condition, and N400 effects).

To assess the topographic generality of correlations between schizotypal factors and N400 effects, *r*-values between SPQ factor scores and N400 effects, for all 26 electrode sites, were plotted on a schematic scalp map (as in Fig. 5.3).

5.4. Results

5.4.1. Rating scales

Table 5.1 shows rating scale scores for the study sample. The distribution of SPQ scores was consistent with previous reports from non-selected community samples (Kiang & Kutas, 2006; Rossi & Daneluzzo, 2002; Wang, Miyazato, Hokama, Hiramatsu, & Kondo, 2004). Independent-samples *t*-tests showed that men and women did not differ on mean SPQ total and factor scores, or PPVT scores (all $p > 0.10$).

5.4.2. Behavioral data

Overall, participants correctly classified 99% of the word targets in the lexical-decision task, indicating that they were attending to the stimuli and task. Across individuals, percentage of correct responses was not significantly correlated with SPQ total or factor scores (all $p > 0.10$).

The lexical-decision task involved a delayed response, and thus was not designed to assess RT priming. Nevertheless, participants' response times (time from response prompt to button press) differed significantly by target condition [$F(2,81)=3.26$, $p<0.05$]. Mean response times were 587 ms for directly related targets, 619 ms for indirectly related targets, and 630 ms for unrelated targets, with response times for directly related and unrelated targets differing significantly from each other. Moreover, higher SPQ total scores were correlated with longer response times for both indirectly related ($r=0.44$, $p=0.02$) and unrelated targets ($r=0.45$, $p=0.02$). Higher SPQ Cognitive-Perceptual scores were correlated with longer response times for directly related ($r=0.40$, $p=0.04$), indirectly related ($r=0.53$, $p=0.003$), and unrelated targets ($r=0.55$, $p=0.002$).

5.4.3. Grand average ERPs

Grand average ERPs ($n=28$) at all electrodes are shown for the 300-ms and 750-ms SOAs in Fig 5.2.

5.4.4. N400 analyses

5.4.4.1. 300-ms SOA

At the 300-ms SOA, mean N400 peak latency was 381 ms for directly related targets, 376 ms for indirectly related targets, and 386 ms for unrelated targets, with no significant difference between these conditions [$F(2,54)=0.91$, $p=0.41$, $\varepsilon=0.91$].

Over all electrodes, N400 amplitude was largest (most negative) for unrelated targets (mean = -0.14 μV), intermediate for indirectly related targets (0.41 μV), and smallest (most positive) for directly related targets (2.36 μV) [$F(2,54)=25.39$, $p<0.0001$, $\varepsilon=0.76$], with all three conditions significantly different from one another. The differences in N400 amplitudes among target types were broadly distributed over the scalp, and largest medially and parieto-occipitally [Target x Electrode interaction: *F*(50, 1350)=4.55, *p*=0.0007, ε=0.10], a distribution consistent with previous N400 studies of word reading (Federmeier & Kutas, 1999; Kutas & Van Petten, 1994).

None of the SPQ total and factor scores were significantly correlated with N400 amplitude at MiPa for any of the target conditions (all $p > 0.10$).

Pairwise correlations between SPQ total/factor scores and N400 effects at MiPa, across all participants, are shown in Table 5.2. Since the N400 has a negative amplitude, *positive* *r*-values indicate that the N400 effect was *smaller* with higher schizotypy scores. Higher SPQ total scores were correlated with smaller indirect priming effects. Higher SPQ Cognitive-Perceptual scores were significantly correlated with smaller direct and indirect priming effects, and higher Interpersonal scores were significantly correlated with larger strength-of-relatedness effects.

The *r*-values between SPQ factor scores and N400 effects for all 26 electrode sites are shown on a schematic scalp map in Fig. 5.3. The correlations of Cognitive-Perceptual scores with smaller direct and indirect priming effects, and of Interpersonal scores with larger strength-of-relatedness effects, were widely distributed across the scalp. The former correlation was largest parieto-occipitally, and the latter was maximal centroparietally.

5.4.4.2. 750-ms SOA

At the 750-ms SOA, over all electrodes, N400 peak latency was shortest for directly related targets (mean=368 ms), intermediate for indirectly related targets (373 ms), and longest for unrelated targets (383 ms) [$F(2,54)=3.34$, $p=0.05$, ε=0.83], with all three conditions significantly different from one another.

Over all electrodes, N400 amplitude was largest (most negative) for unrelated targets (mean = 1.06 μV), intermediate for indirectly related targets (1.72 μV), and smallest for directly related targets (3.29 μV) [$F(2,54)=18.69$, $p<0.0001$, $\varepsilon=0.98$], with all three conditions significantly different from one another. The differences in N400 amplitudes among target types were broadly distributed over the scalp, and largest medially and parieto-occipitally [Target x Electrode interaction: $F(50, 1350)=7.13$, $p<0.0001$, $\varepsilon=0.10$].

Higher SPQ Interpersonal scores were significantly correlated with reduced (more positive) N400 amplitudes at MiPa (midline parietal site) for both unrelated targets ($r=0.47$, $p=0.01$) and directly related targets ($r=0.49$, $p=0.009$). There were no other significant pairwise correlations between SPQ total/factor scores and N400 amplitudes at MiPa for the different target types (all $p > 0.15$).

Pairwise correlations between SPQ total/factor scores and N400 effects at MiPa, across all participants, are shown in Table 5.2. At the 750-ms SOA, like at the 300-ms SOA, higher SPQ total scores were significantly correlated with smaller indirect priming effects, and higher SPQ Cognitive-Perceptual scores were significantly correlated with smaller direct priming effects. Scalp mapping of this latter correlation over all electrode sites showed that it was widely distributed and maximal parieto-occipitally.

5.5. Discussion

In this experiment, we investigated the relationship between schizotypal personality and associative semantic processing by using the N400 component of the ERP elicited during a delayed lexical-decision task. Participants were presented with prime words, each followed by a target letter string that was either a real word or a pseudoword. One third of the target words were directly associatively related to the prime (such as *TOY-DOLL*), one third were only indirectly associatively related (i.e., via a mediating word; *CAT-[MOUSE]-CHEESE*), and one third were unrelated (*FURNACE-SHELL*). Across all participants, N400 amplitudes to target words were largest (most negative) for unrelated words, smallest (least negative) for directly related words, and intermediate for indirectly related words.

In addition, higher SPQ total scores were significantly correlated with smaller N400 indirect priming effects (i.e., N400 amplitude differences between target words unrelated and indirectly related to the prime, at both prime-target SOAs (300 and 750 ms). Higher SPQ Cognitive-Perceptual factor scores were significantly correlated with smaller N400 direct priming effects (N400 amplitude differences between target words unrelated and directly related to the prime), at both SOAs; and with smaller N400 indirect priming effects at the 300-ms SOA. In contrast, higher SPQ Interpersonal factor scores correlated with larger N400 strength-of-relatedness effects (N400 amplitude differences between indirectly and directly related targets) at the 300-ms SOA.

The correlations of higher SPQ total and Cognitive-Perceptual scores with smaller N400 priming effects are consistent with an association of overall and cognitive-perceptual schizotypy with either decreased activation of concepts related to a prime, decreased inhibition of concepts unrelated to it, or both. Our data do not allow us to unequivocally distinguish between these possibilities, because SPQ total and Cognitive-

Perceptual scores were not significantly correlated with raw N400 amplitudes for any of the target conditions.

This finding appears to corroborate previous reports of an association between schizotypy and decreased N400 priming effects (Kiang & Kutas, 2005; Kimble et al., 2000; Niznikiewicz et al., 2004; Niznikiewicz et al., 1999). These previous studies used either relatively long SOAs of 2400 to 2800 ms (Kiang & Kutas, 2005), or sentence contexts (Kimble et al., 2000; Niznikiewicz et al., 2004; Niznikiewicz et al., 1999), which also build up over a relatively long time interval. Taken together, these findings appear most consistent with the hypothesis that cognitive-perceptual schizotypy is associated with less efficient use of context to initiate or maintain activation of related concepts and/or inhibition of unrelated concepts, beginning as early as 300 ms following a contextual stimulus, and continuing thereafter.

A number of the traits that constitute cognitive-perceptual schizotypy – ideas of reference, odd beliefs, and suspiciousness – typically involve the presumption of meaningful associations between objects or actions that would normally be regarded as unrelated or co-incidental (Bressan, 2002; Gianotti et al., 2001). For example, a person may suspect that strangers' glances or hand motions influence the person's own thoughts or feelings; that thinking negatively about others can cause harm to befall them; that statements in a professor's lecture refer specifically to events in the person's own life; or that objects in the person's home have been re-arranged by unknown persons or forces (Eckblad & Chapman, 1983). Accordingly, individual differences in how a meaningful stimulus affects activation of related concepts and/or inhibition of unrelated concepts could plausibly contribute to the development of unusual ideation. If, for instance, following some stimulus, an individual encounters another, unrelated stimulus which has been supranormally activated, this could conceivably lead to the aberrant experience that the two stimuli are meaningfully related. Consequently, the individual might infer a paranormal or self-referential connection between the stimuli in an attempt to explain this subjective experience (Gianotti et al., 2001). Furthermore, common benign stimuli might be viewed as suspicious if they do not bring to mind similar occurrences to a normal degree (D. T. Miller, Turnbull, & McFarland, 1989) by activating the representations of these occurrences in semantic memory.

In addition, the correlation we observed between higher SPQ Interpersonal scores and larger N400 strength-of-relatedness effects at the 300-ms SOA could reflect smaller N400 amplitudes to directly related targets, larger N400 amplitudes to indirectly related targets, or both. We cannot definitively distinguish between these possibilities, because Interpersonal scores were not significantly correlated with raw N400 amplitudes for any of the target conditions, at the 300-ms SOA. However, the observed trend ($p<0.10$) for Interpersonal scores to also correlate with smaller indirect priming effects suggests that, in individuals with higher Interpersonal scores, larger N400 amplitudes to indirectly related targets (reflecting decreased activation) may contribute both to larger strength-of-relatedness effects and to smaller indirect priming effects. Interestingly, this less-broadly spreading activation (i.e., activation more restricted to strong associates) would be opposite to the effects of positive mood on N400 priming in sentence contexts observed by Federmeier et al. (2001), who proposed that such effects might be mediated by changes in dopaminergic activity. In support of the hypothesis that dopaminergic activity modulates semantic activation (Ashby, Isen, & Turken, 1999; Cohen & Servan-Schreiber, 1992), the dopamine precursor L-dopa and the dopamine D1/D2 agonist pergolide have been found to reduce RT indirect priming effects (Angwin et al., 2004; Kischka et al., 1996; Roesch-Ely et al., 2006). Since it has been postulated that schizotypy may be associated with dopaminergic dysregulation (Siever & Davis, 2004), further research is warranted to investigate whether semantic processing differences in schizotypy are indeed mediated by variation in dopaminergic function.

Our data do not support an association of schizotypy with broader spread of activation to weakly related items. If this were the case, we would expect individuals with higher schizotypy to have reduced N400 amplitudes to indirectly related targets, and, as a consequence, larger N400 indirect priming effects. However, contrary to this hypothesis, we found overall schizotypy to be associated with *smaller* N400 indirect priming effects, at both the SOAs we employed. In addition, cognitive-perceptual schizotypy was also associated with smaller indirect priming effects at the 300-ms SOA. Our results thus appear to differ from previously reported associations of higher schizotypy with larger RT indirect priming effects at short SOAs (Pizzagalli et al., 2001). These contrasting results could be due to differences in study methodology or population; unlike our study, Pizzagalli et al. (2001) used left lateralized targets, and measured cognitive-perceptual schizotypy with a questionnaire focusing on paranormal belief. In addition, contrasting results could stem from a dissociation between the dependent measures from which the priming effects were inferred, namely, between electrophysiological (N400) priming effects and RT priming effects. Individuals with higher versus lower schizotypy scores might present with similar N400 indirect priming effects, but larger RT indirect priming effects, as a result of processes specifically affecting RT but not the N400. For example, suppose that individuals check for a relationship between prime and target before responding that the target is a word (as is proposed to occur by Balota and Lorch, (1986) and are able to detect some meaningful relationship between indirectly related words, but not between unrelated words. Then, if individuals higher in schizotypy were to rely more on this strategy, this could lead to a greater RT difference between indirectly related and unrelated targets in these individuals relative to those with lower schizotypy.

Given the hypothesized link between semantic activation differences and disorganized speech in schizotypy (Moritz et al., 1999; Niznikiewicz et al., 2002), the lack of a significant correlation in this study between the SPQ Disorganized factor and N400 effects might seem unexpected. This negative finding, however, is consistent with results of a previous study in which we also did not find any correlation between these variables (Kiang & Kutas, 2005). Taken together, these results suggest that disorganized or unusual speech in the general population, at least as identified by self-report, may arise from processes other than those reflected in the N400 which we presume to reflect differences in how concepts activate one another in semantic memory.

Previously, using a category-exemplar priming paradigm with longer SOAs (2400-2800 ms) than in the present study, we found that SPQ Interpersonal scores correlated with smaller N400 category-exemplar priming effects, due to larger N400 amplitudes to exemplars, and smaller N400 amplitudes to non-exemplars (Kiang & Kutas, 2005). That finding appears somewhat discordant with the correlation in the present study between Interpersonal scores and larger N400 strength-of-relatedness effects; however, this discrepancy could be due to stimulus differences across experiments (e.g., category-exemplar versus word-pair; semantic relatedness; SOA).

Overall, our results suggest that the factors of schizotypy are differentially related to semantic priming – just as they have been found to have dissociable relationships with other neuropsychological and neurophysiological variables. For instance, lower performance in eye-movement (Ettinger et al., 2005; Kendler et al., 1991) and sustained-attention tasks (Chen, Hsiao, & Lin, 1997) correlated with social isolation and anhedonia, but not with unusual ideation or perceptions. In contrast, difficulties on tasks of cognitive control requiring inhibition (e.g., Stroop task; (Kerns, 2006) correlated specifically with disorganized schizotypy. Our findings suggest that further research is needed to clarify how the associations between different schizotypal factors and semantic priming are modulated by the type of semantic stimuli, their degree of relatedness, and their temporal separation.

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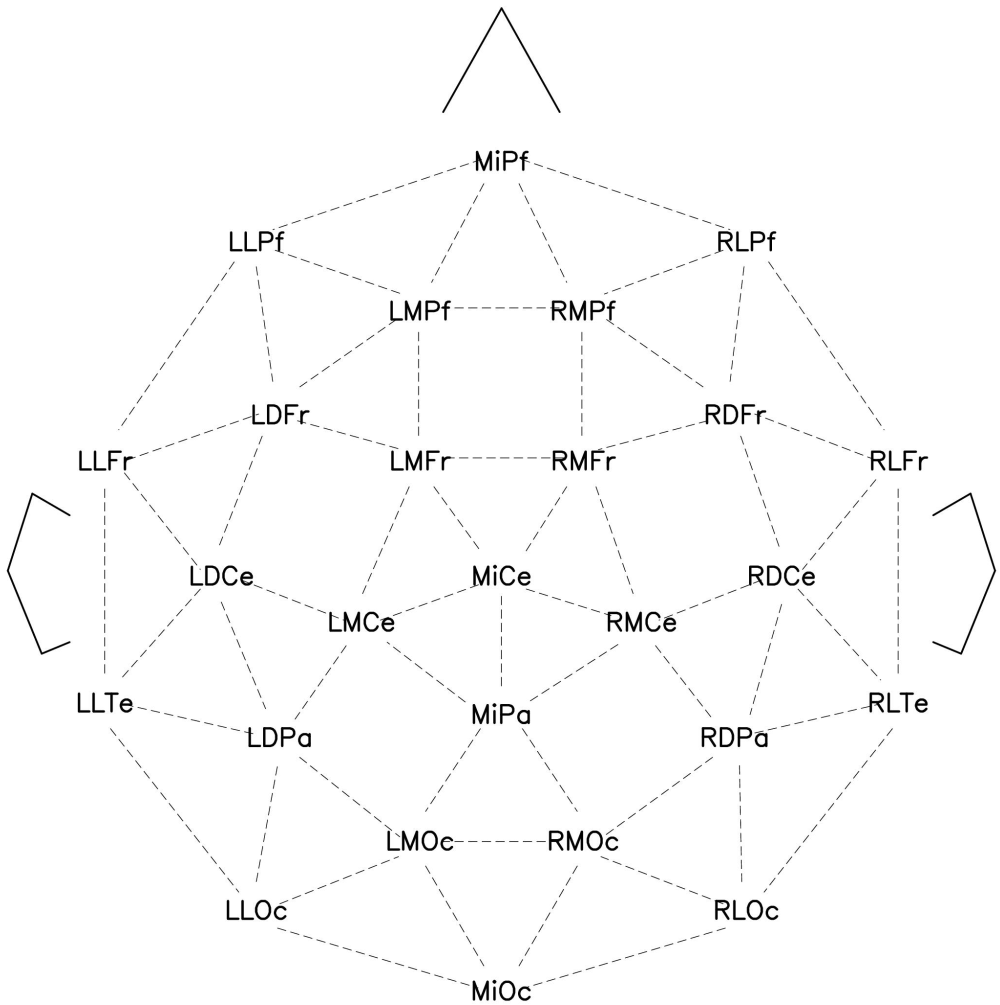

Figure 5.1. Schematic diagram of the electrode array, with nose at the top.

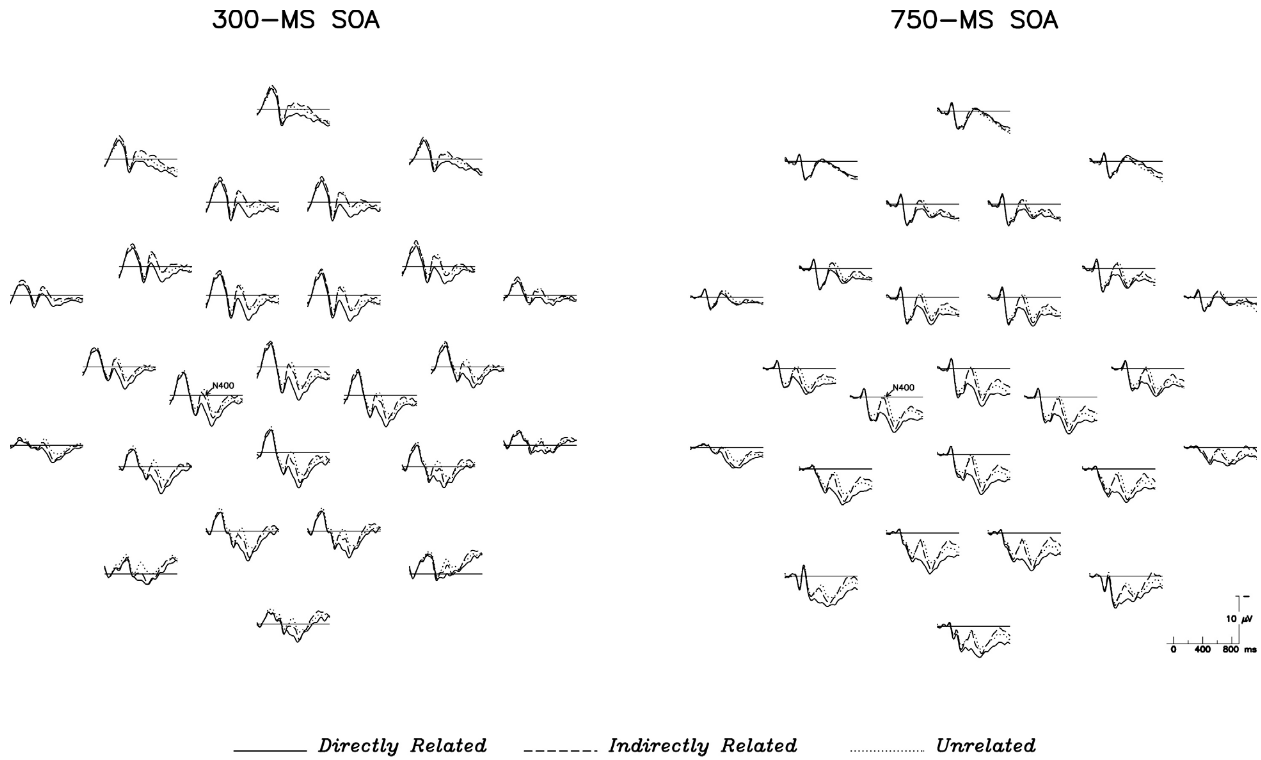

Figure 5.2. Grand average ERPs for all participants (*n*=28), for the three target word types, at all electrode sites. Negative voltage is plotted upward. Electrode sites are arranged as in Figure 5.1.

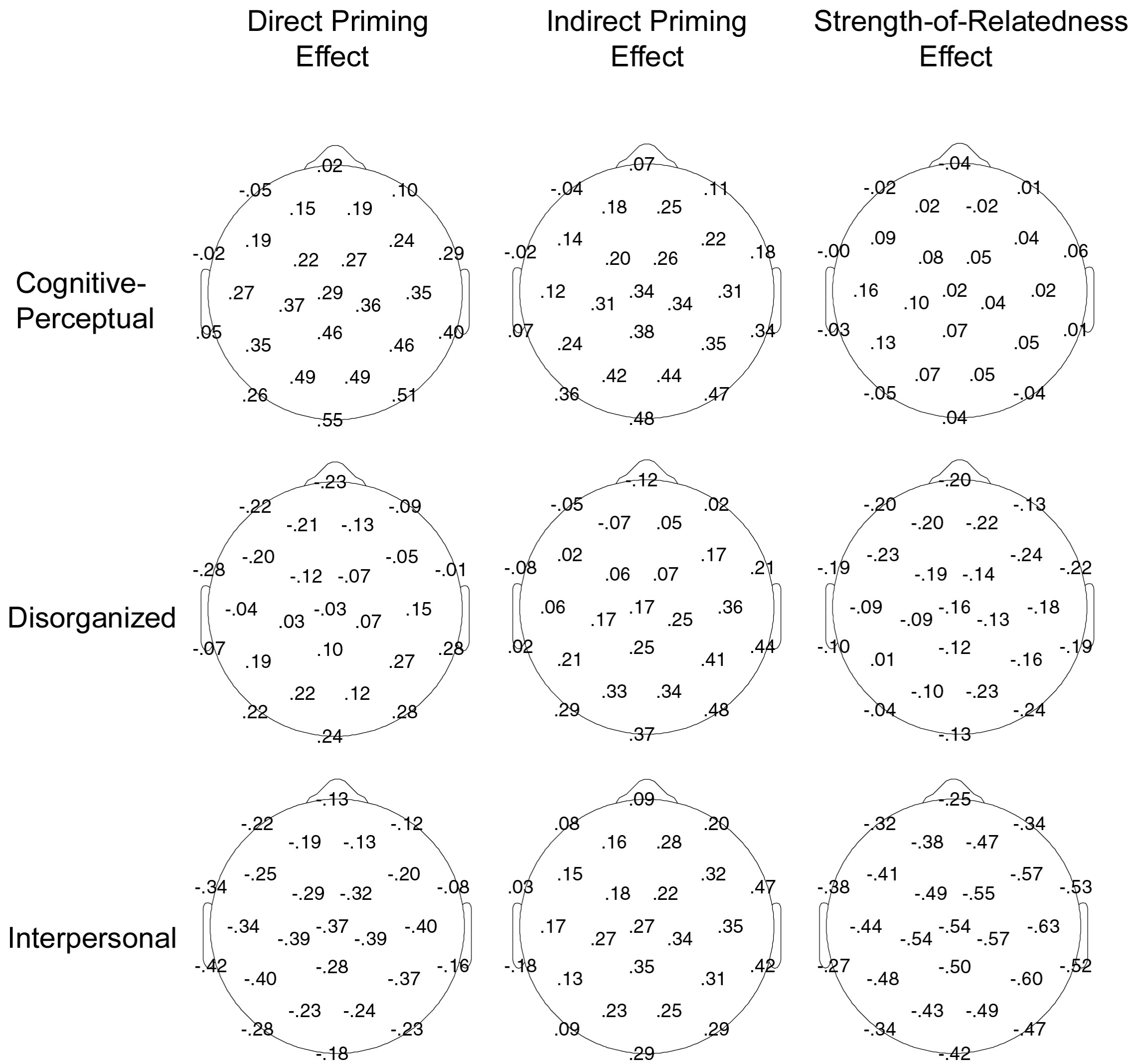

Figure 5.3. Correlation coefficients *r* between SPQ factors and N400 effects, for SOA=300 ms, at all 26 electrode sites, plotted on a schematic head (nose at the top). Since the N400 has a negative amplitude, *positive* *r*-values indicate that the N400 effect was *smaller* with higher schizotypy scores, and *negative* *r*-values indicate that it was *larger* with higher schizotypy scores.

Table 5.1. Means, standard deviations and ranges of rating scale scores for the study sample (*n*=28)

Scale	**Mean**	**SD**	**Range**	**Maximum possible score**
SPQ (Total)	17.4	10.6	1-37	74
SPQ Cognitive-Perceptual Factor	7.8	5.3	0-19	33
SPQ Interpersonal Factor	6.6	5.4	0-21	33
SPQ Disorganized Factor	4.6	4.3	0-12	16
PPVT	186.1	6.3	170-197	204

Table 5.2. Correlation coefficients *r* of SPQ total and factor scores with N400 effects at MiPa (*n*=28 participants)

	Direct priming effect	**Indirect priming effect**	**Strength-of-relatedness effect**
300-ms SOA			
SPQ Total	0.13	0.44*	-0.24
Cognitive-Perceptual	0.46*	0.38*	0.07
Disorganized	0.10	0.25	-0.12
Interpersonal	-0.28	0.35†	-0.50**
750-ms SOA			
SPQ Total	0.22	0.38*	-0.16
Cognitive-Perceptual	0.48*	0.34†	0.15
Disorganized	0.03	0.23	-0.20
Interpersonal	-0.03	0.33†	-0.36†

†$p<0.10$
*$p<0.05$
**$p<0.01$

Table 5.3. Examples of prime-target stimulus pairs used in the experiment.

Directly related word pairs	**Indirectly related word pairs (prime-mediator-target)**	**Unrelated word pairs**	**Word-nonword pairs**
TOAD-FROG	CORK-WINE-GRAPE	GRAIN-SHRUB	JAIL-AGLEM
HEEL-TOE	NAVY-ARMY-TANK	DIALOGUE-CORD	CORNER-DOFUD
UNCLE-AUNT	BLADE-KNIFE-FORK	ILLNESS-TOWER	JOB-GUD
METAL-STEEL	BULL-COW-MILK	BAKER-HUNGRY	CANDLE-LICIN
CAPTAIN-SHIP	SPLASH-WATER-DRINK	WIFE-TEAM	CAVERN-OSPONT
COLOR-BLUE	TOOTH-BRUSH-HAIR	MOUTH-MARKET	FIG-VAD

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Chapter 6

Experiment 5 – Cognitive, neurophysiological and functional correlates of proverb interpretation abnormalities in schizophrenia

6.1. Abstract

A hallmark of schizophrenia is impaired proverb interpretation, which could be due to: (1) aberrant activation of disorganized semantic associations, or (2) working memory (WM) deficits. We assessed 18 schizophrenia patients and 18 normal control participants on proverb interpretation, and evaluated these two hypotheses, respectively, by examining within patients the correlations of proverb interpretation with: (1) disorganized symptoms and N400 event-related brain potential (ERP) priming effects, and (2) auditory WM. Secondarily, we also explored the relationships between proverb interpretation and a spectrum of cognitive functions including auditory sensory-memory encoding (as indexed by the mismatch negativity ERP); executive function; and social/occupational function. As expected, schizophrenia patients produced less accurate and less abstract descriptions of proverbs than did controls. These proverb interpretation difficulties in patients were not significantly correlated with disorganization or other symptom factors or N400 effects, but were significantly correlated ($p<0.05$) with WM impairment, as well as with impairments in sensory-memory encoding, executive function, and social/occupational function. These results offer no support for

disorganized associations in abnormal proverb interpretation in schizophrenia, but implicate WM deficits, perhaps as a part of a syndrome related to generalized frontal cortical dysfunction.

6.2. Introduction

Deficits in understanding proverbs are considered a hallmark of schizophrenia. In general, proverbs used in mental status testing – e.g., *You can't judge a book by its cover* – involve metaphor, in which an expression is used to describe something other than its literal referents (although this is not true of all phrases considered proverbs, such as *Ignorance is bliss*). Compared to normal individuals, schizophrenia patients tend to interpret proverbs less accurately (Brune & Bodenstein, 2005; Harrow, Tucker, & Adler, 1972), less abstractly or more concretely (Braff & Beck, 1974; Gorham, 1956; Reed, 1968; Reich, 1981; Sponheim, Surerus-Johnson, Leskela, & Dieperink, 2003), and more idiosyncratically (Harrow et al., 1972; Shimkunas, Gynther, & Smith, 1967; Sponheim et al., 2003). Although proverb interpretation does not reliably differentiate schizophrenia from other psychiatric illnesses (Andreasen, 1977; Braff & Beck, 1974; Reich, 1981), its frequent impairment in schizophrenia has led to its inclusion in the clinical examination of schizophrenia patients, and in rating scales for the disorder such as the Positive and Negative Syndrome Scale (PANSS) (Kay, Opler, & Lindenmayer, 1989).

The relationship between these proverb interpretation difficulties and the underlying causes of schizophrenia, however, have not been conclusively established. On one view, failure to arrive at the standard interpretation of a proverb is thought to reflect interference from tangential or idiosyncratic associations that also are presumed to cause disorganized speech more generally (Buss & Lang, 1965; Carpenter & Chapman, 1982; Shimkunas et al., 1967). Along similar lines, Gibbs and Beitel (1995) proposed that in schizophrenia patients "the ability to provide figurative interpretations to proverbs is disturbed because (the patients) are more easily distracted by associations between words in proverbs and their own personal experiences." In view of experimental evidence that disorganized speech in schizophrenia patients is associated with a relative overactivation of remote versus strong semantic associations (Kostova, Passerieux, Laurent, & Hardy-Bayle, 2005; Moritz et al., 2001; Moritz, Woodward, Kuppers, Lausen, & Schickel, 2003; Spitzer, Braun, Hermle, & Maier, 1993), advocates of this hypothesis have suggested that this abnormal activation may also lead to tangential and hence inaccurate proverb interpretations.

According to a different hypothesis, first proffered by Goldstein (1944), schizophrenia patients' primary deficit rests in their inability to adopt an "abstract attitude," in which "we detach ourselves from the given impression, and the individual thing represents to us an accidental sample or representative of a category." This hypothesis implies an impairment in establishing a set of correspondences among elements of the proverb and other more abstract concepts.

Studies of schizophrenia patients have identified some neuropsychological and symptomatic correlates of proverb interpretation abnormalities which may help shed light on their underlying causes. In schizophrenia patients, concreteness of proverb responses was found to correlate with lower scores on tests of attention (serial search), memory (figural reproduction) and executive function (planning and set shifting) (Sponheim et al., 2003); while a combined rating of accuracy and abstraction correlated with performance on tests of executive function and theory of mind (Brune & Bodenstein, 2005). In addition, abstraction (Brune & Bodenstein, 2005; Carpenter & Chapman, 1982; Shimkunas, Gynther, & Smith, 1966), accuracy, and lower idiosyncrasy (Carpenter & Chapman, 1982) of proverb responses have been found to correlate with verbal intelligence as measured by vocabulary tests. Taken together, these data suggest that schizophrenia patients may not give the standard, abstract interpretation of a proverb due to fundamental abnormalities impairing a wide range of higher cognitive functions. Moreover, other studies have reported no correlation of accuracy and abstraction with either positive, negative or disorganized symptoms in schizophrenia (Brune & Bodenstein, 2005; Sponheim et al., 2003), although response idiosyncrasy has been found to correlate with disorganization (Sponheim et al., 2003). These results would seem to suggest that while processes underlying disorganized speech may contribute to more idiosyncratic language use in schizophrenia patients, they are unlikely to be the primary cause of their abnormal proverb interpretations.

According to recent advances in cognitive theory, the ability to attain the standard interpretation of a metaphorical proverb can be seen as just one instance of a process of meaning construction called conceptual integration (Coulson & Oakley, 2000; Fauconnier & Turner, 1998). This process involves establishing mappings between elements and their relationships across mental domains, in order to project emergent meaning to a "blended" domain. This theory builds on previous work describing analogical thinking as the selection of one-to-one mappings between aspects of two different situations (Gick & Holyoak, 1983; Hummel & Holyoak, 2003). Conceptual integration is postulated to be essential for a wide range of higher cognitive phenomena, including analogy, metaphor, categorization and hypothetical reasoning. According to conceptual integration theory, a correct understanding of a proverb such as *People in glass houses shouldn't throw stones* requires mapping elements from a concrete source domain to a more abstract target domain. In this case, being in a *glass house* is mapped to the characteristic of having faults or weaknesses, and *throwing stones* to the act of criticizing others. In addition, the relationship between these elements – the fact that the potential reciprocation of stone-throwing would be particularly apt to harm the inhabitant of a glass house – is mapped to the idea that the potential reciprocation of criticism would be particularly apt to harm the individual who has faults or weaknesses. These mappings are reflected in a response such as *Don't go ridiculing people for what they do if you've done it yourself.* In contrast, a schizophrenia patient's response such as *People should watch what they say around other people so they don't hurt their feelings* is a somewhat less complete mapping – although mappings to the target domain are established for *glass house* and *throwing stones*, the relationship between them is absent.

Conceptual integration theory offers a framework for elaborating on hypotheses about the source of proverb interpretation difficulties in schizophrenia. On one view, which we will refer to as the *disorganized-associations hypothesis*, overactivation of unusual associations to concepts, which causes disorganized speech in general, also affects proverb interpretation by preventing correct mappings which involve normatively strong associations (Gibbs & Beitel, 1995). For instance, consider the patient response:

> *If you're the President of a school and you live across from the campus, as they did in Keene, Texas, and Elder Scales was the President of the school, he lived in a glass house, so to speak, because people were always able to see him. You live right across the street from the campus and you*

> *live in a glass house, and people can see what you're doing, they can say: "That's not so."*

Here, *glass house* may have activated an idiosyncratic association (the concept of living in visible proximity to one's associates or subordinates) to an abnormal degree, resulting in the mapping of *glass house* to this concept instead of to its standard counterpart, thus precluding a correct interpretation of the proverb.

Within the conceptual integration model, proverb interpretation difficulties in schizophrenia could also stem from a diminished ability to maintain representations of multiple elements of source and target domains in working memory (WM) while performing the operations necessary to establish aligned mappings between them (we will refer to this view as the *WM-deficiency hypothesis*). In fact, a number of models of relational reasoning in general (Halford, Wilson, & Phillips, 1998; Hummel & Holyoak, 2003; Waltz, Lau, Grewal, & Holyoak, 2000), and of figurative language interpretation in particular, posit an important role for WM in the process (see Glucksberg (2003) for review). Moreover, WM impairments have been extensively described in schizophrenia (see Lee and Park (2005) for a meta-analysis). The WM-deficiency hypothesis is consistent with the view that proverb interpretation deficits in schizophrenia reflect primarily a difficulty in the "abstract attitude," which according to Goldstein (1944) included the ability "to keep in mind simultaneously various aspects," and "to break up a given whole into parts and to isolate them voluntarily," in order to "generalize," "abstract common properties," and "think or perform symbolically."

In the present study, we aimed to test the disorganized-associations and WM-deficiency hypotheses of abnormal proverb interpretation in schizophrenia, by seeking correlational evidence for each of these hypotheses. Importantly, these two hypotheses are not mutually exclusive, especially since disorganization and WM deficits tend to co-occur in schizophrenia patients (Daban et al., 2002; McGrath, Chapple, & Wright, 2001; Melinder & Barch, 2003). Therefore, either or both of the hypotheses could potentially be true, with the latter being the case if WM deficiency contributes to both disorganization and abnormal proverb interpretation.

In order to test these hypotheses, we administered the Delis-Kaplan Executive Function System (D-KEFS) Proverb Test (Delis, Kaplan, & Kramer, 2001) to schizophrenia patients and control participants, and rated responses on both accuracy and abstraction. Patients' symptoms were rated with the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). The N400 event-related brain potential (ERP) (Kutas & Federmeier, 2000) was recorded as an index of activation of atypical associations to conceptual stimuli. Following a visually-presented category definition (prime stimulus), the N400 was recorded in response to target words that were either high-typicality exemplars, low-typicality exemplars, or non-exemplars of the category. Normally, in this paradigm, N400 amplitude is largest to non-exemplars, smallest to high-typicality exemplars, and intermediate to low-typicality exemplars – with smaller N400 amplitudes taken to reflect increased activation of targets that are more related to the prime (Heinze, Muente, & Kutas, 1998; Kiang & Kutas, 2005; Stuss, Picton, & Cerri, 1988). In addition, Letter-Number Span Test (LNS) (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) scores were used as a measure of attention-dependent auditory WM. The LNS was designed as a relatively specific measure of WM, defined as the ability to simultaneously store and manipulate information (Baddeley, 1992; Gold et al., 1997). As a convergent measure, the Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) was also administered. Although this test involves a mixture of complex cognitive operations (Gold et al., 1997; Hartman, Steketee, Silva, Lanning, & Andersson, 2003), performance on it in schizophrenia has been found to reliably correlate with deficits in attention-dependent WM (Gold et al., 1997; Hartman et al., 2003; Kurtz & Wexler, 2006). In addition, the California Verbal Learning Test (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000) was administered as a measure of verbal recall, since there is behavioral and neuroimaging evidence to suggest that deficits in this function and in working memory may result from a common underlying cause (Barch, Csernansky, Conturo, & Snyder, 2002; Bruder, Wexler, Sage, Gil, & Gorman, 2004).

We hypothesized that, if the disorganized-associations hypothesis is true, then lower proverb accuracy and abstraction ratings would correlate with higher scores on the SANS/SAPS-derived Disorganized symptom factor (Miller, Arndt, & Andreasen, 1993). Furthermore, lower proverb interpretation scores would be associated with smaller N400 amplitudes in response to low-typicality exemplars and/or non-exemplars following a category prime – reflecting greater activation of these atypical associations. Lower proverb interpretation scores would thus correlate with smaller N400 typicality effects (i.e., smaller N400 amplitude differences between high- and low-typicality exemplars), and/or smaller high-typicality category effects (i.e., smaller amplitude differences between high-typicality exemplars and non-exemplars. Alternatively or in addition, if the WM-deficiency hypothesis is true, then proverb interpretation ratings would be correlated with LNS, WCST and CVLT-II performance.

As a secondary aim, we sought to characterize whether proverb interpretation deficits in schizophrenia are correlated with a spectrum of lower- to higher-level cognitive operations, from early sensory processing to real-world functioning. Emerging evidence supports the view that deficits in pre-attentional stages of information processing may be a fundamental cause of schizophrenia patients' impairments in more complex cognitive tasks (Kawakubo & Kasai, 2006; Light & Braff, 2005a; Light, Swerdlow, & Braff, in press). In this conception of schizophrenic pathology, pre-attentional processes may determine the extent to which task-relevant information is available for further controlled processing (Braff & Light, 2004). The mismatch negativity (MMN), an ERP component elicited by deviants among unattended auditory stimuli (Naatanen, Gaillard, & Mantysalo, 1978), is considered a measure of pre-attentional sensory processing. It is postulated to reflect discrepancy with a sensory-memory trace (Naatanen, Paavilainen, Alho, Reinikainen, & Sams, 1989), and thus has been used as a measure of accuracy of encoding in sensory (or "echoic") memory (Naatanen, 2003). Its amplitude has been consistently found to be smaller than normal in schizophrenia (reviewed in Michie (2001)), suggesting an abnormality of sensory-memory encoding. The possibility that this abnormality in turn may affect more complex cognitive functions (Javitt, Doneshka, Grochowski, & Ritter, 1995; Javitt, Strous, Grochowski, Ritter, & Cowan, 1997) is raised by the reported correlation of MMN deficits with poor functional status in schizophrenia (Light & Braff, 2005a, 2005b). However, it is unclear whether processes reflected in decreased MMN cause functional impairment, and, if so, what the chain of causally mediating factors might be.

Alternatively, decreased MMN and functional impairment may both be related to some other factor without being directly causally linked (Braff & Light, 2004). As a step toward further clarifying the nature of the relationships between MMN amplitude reductions and functional impairment, we examined the correlations between: (1) MMN, (2) functional status, and (3) proverb interpretation and other neurocognitive functions associated with it. Functional status was measured via a clinician rating and a standardized functional-skills assessment (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001), since a combination of assessment modalities may improve the validity of measurement of actual real-world function (McKibbin, Brekke, Sires, Jeste, & Patterson, 2004). We also cannot infer causation from correlation per se. However, if these variables are intercorrelated, it would be consistent with the possibility that abnormalities in processes involved in proverb interpretation mediate the relationship between sensory-memory encoding deficits and functional impairment, or that some common process underlies all of these deficits. On the other hand, if a particular neurocognitive function is not correlated with MMN and functional measures, this would help rule it out as a mediator between sensory-memory encoding deficits and functional impairment.

6.3. Methods

6.3.1. Participants

Participants included 18 schizophrenia patients and 18 normal control participants. Patients were recruited from community residential facilities and through physician referral. All were outpatients. Controls were selected to match patients on age, sex, and parental socioeconomic status (SES), and were recruited through newspaper advertisements, and flyers posted at the University of California, San Diego (UCSD) Medical Center. All participants were assessed on their capacity to provide informed consent and, after they were given a detailed description of the study, gave written consent via the UCSD Institutional Review Board approved consent form (# 030510). Participants were compensated in cash.

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1995), and were screened to rule out any other Axis I diagnosis including substance abuse. Controls were assessed using the SCID (non-patient edition) to rule out any past or present Axis I or II diagnoses including substance abuse. Exclusion criteria for both patients and controls also included any current or past neurological disorder. Parental SES was computed using the index of Hauser and Warren (1996). Demographic characteristics of the study sample are shown in Table 6.1.

Twelve patients were prescribed second-generation antipsychotic medications, 2 were prescribed first-generation antipsychotics, and 2 were prescribed a combination of first- and second-generation antipsychotics. 2 patients were not taking any antipsychotics.

6.3.2. Symptom ratings

Patients' symptoms were assessed with the SANS (Andreasen, 1984a) and SAPS (Andreasen, 1984a). Based on these ratings, we calculated scores for Psychotic, Negative and Disorganized symptom factors as derived by Miller, Arndt and Andreasen (1993) – the Psychotic factor was the sum of global ratings for delusions and hallucinations; the Negative factor was the sum of global ratings for affective flattening, avolition/apathy and anhedonia/asociality; and the Disorganized factor was the sum of global ratings for positive formal thought disorder and bizarre behavior. Patients' clinical characteristics are shown in Table 6.1.

6.3.3. N400 ERP effects

ERPs were recorded from all participants in the paradigm described in detail in Kiang, Kutas, Light and Braff (Kiang, Kutas, Light, & Braff, 2007). In brief, ERPs were recorded while participants viewed category definitions (e.g., *A fruit*), followed by target words that were either high-typicality exemplars (*apple*), low-typicality exemplars (*cherry*), or non-exemplars (*clamp*). The N400 ERP component elicited by target words was analyzed; detailed results are presented in Kiang, Kutas. Light and Braff (Kiang et al., 2007). Of relevance here, for each participant, we computed the N400 high-typicality category effect (i.e., N400 amplitude difference between non-exemplars and high-typicality exemplars), low-typicality category effect (amplitude difference between non-exemplars and low-typicality exemplars), and typicality effect (amplitude difference between low- and high-typicality exemplars), at a representative electrode site (midline central; Cz according to the International 10-20 electrode placement system).

6.3.4. Neuropsychological tests

The tests described in this section were administered to both patients and controls.

The Free Inquiry section of the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) was administered. The test proverbs are shown in Table 6.2. Accuracy and abstraction of each response were rated according to the test manual by two independent raters, one of whom was blind to participant group. Accuracy and abstraction are rated independently of each other. Accuracy (rated 0, 1 or 2) reflects the degree to which the response includes key elements of either the literal or figurative meaning of the proverb. Abstraction (rated 0 or 2) is defined as generalization to concepts other than those referred to in the proverb (regardless of accuracy). For each participant, overall accuracy and abstraction scores from each rater were computed, by averaging the corresponding ratings across all proverbs.

In the LNS test of auditory WM (Gold et al., 1997), the examiner verbally presents strings of alternating numbers and letters (e.g., *W7T4*), and participants respond by saying the numbers from smallest to largest followed by the letters in alphabetical order (*47TW*). The test involves 3 trials at each string length, beginning with 2-item strings and proceeding up to 8-item strings. The test is terminated if a participant fails all 3 trials at any one string length. The overall score consists of the number of trials answered correctly (out of a maximum of 21).

Participants also received a 64-card short form of the WCST (Haaland, Vranes, Goodwin, & Garry, 1987; Heaton et al., 1993), which was scored on the number of perseverative responses, and the number of categories achieved.

Participants completed the California Verbal Learning Test (CVLT-II) (Delis et al., 2000) as a measure of verbal recall. This involves 5 trials in which the same list of 16 words (which can be grouped into 4 semantic clusters) is presented; recall is assessed after each trial. The *immediate free recall* score is the sum of the number of words recalled after each of these 5 trials. Recall of this list is then also assessed after administration of an intervening, different list (*short-delay free recall*), and after a 20-minute delay (*long-delay free recall*), with the scores being the number of words recalled.

Participants also completed the Peabody Picture Vocabulary Test (PPVT) (Dunn & Dunn, 1997) as a measure of receptive vocabulary. (Delis et al., 2000)

6.3.5. MMN

The MMN ERP component was elicited and recorded according to the procedure described in additional detail in Light and Braff (2005a). Participants were presented binaurally with 1-kHz 85-dB tones with stimulus-onset asynchrony of 500 ms while they watched a silent cartoon video; standard tones (P=0.90) are 50 ms in duration, and deviant tones (P=0.10) are 100 ms in duration. For each participant, recording was terminated after at least 225 artifact-free deviant trials were collected. A difference ERP was formed by subtracting the average ERP to standard stimuli from the average ERP to deviant stimuli. MMN amplitude was measured as the mean amplitude from 135 to 205 ms of the difference ERP, at the midline frontal site Fz, with the tip of the nose as reference.

6.3.6. Assessments of functional status

The Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000) was used to assess patients' current overall psychological, social and occupational functional status via a single anchored measure. The GAF Scale is divided into 10 ranges of functioning. Each 10-point range contains a description with 2 components: (1) symptom severity and (2) functioning. A clinical rater selects a score within a particular decile if either the symptom severity or the level of functioning falls within that range.

Patients' everyday functioning was also assessed through the UCSD Performance-Based Skills Assessment (UPSA) (Patterson et al., 2001). In contrast to the GAF, the UPSA directly measures functional skills, using standardized tasks that are commonly encountered in everyday situations and considered necessary for independent community living. Participants role-play these tasks, which encompass 5 domains:

general organization and planning, finance, communication, transportation, and household chores. The examiner assigns points for correct performance of different components of each task. Subscale scores range from 0 to 20 points, and total scores range from 0 to 100 points.

6.3.7. Data analysis

To determine whether patients and controls differed on continuous dependent measures, independent-samples *t*-tests were performed, with the following exceptions. If the measure was not normally distributed for at least one group, the Mann-Whitney test was used. If the measure was normally distributed for both groups but variances were unequal, Welch's *t*-test was used. Normality was assessed by the Shapiro-Wilk test. To determine whether patients and controls differed on sex distribution (a categorical dependent variable), a χ^2 test was used.

To assess inter-rater reliability for the Proverb Test, Cohen's kappa was calculated for each proverb for the two independent raters.

Within patients, pairwise correlations were calculated among assessment scores. When both variables were normally distributed, Pearson's correlation co-efficient r was calculated; if at least one of the variables was not normally distributed; Spearman's rank-order co-efficient ρ was calculated.

6.4. Results

6.4.1. D-KEFS Proverb Test

Cohen's kappa between the two independent raters for accuracy ratings ranged from 0.63 to 0.91 for the eight proverbs, with a mean value of 0.83. Kappa for abstraction ratings ranged from 0.68 to 1, with a mean value of 0.86. These values confirmed high inter-rater reliability for both accuracy and abstraction ratings. The mean of the two raters' scores was used in subsequent analyses.

Mean accuracy and abstraction scores for the two groups are shown in Table 6.3. Patients scored lower than controls on both measures. When analyzed with years of education as a covariate, abstraction remained lower in patients than in controls [$F(1,33)$=4.83, p=0.035], although accuracy no longer differed significantly between the two groups [$F(1,33)$=2.73, p=0.11].

6.4.2. Other cognitive measures and functional measures

Mean scores on other cognitive measures and functional measures for the two groups are also shown in Table 6.3. Grand-average MMN ERPs for the two groups are shown in Fig. 6.1. Compared to controls, patients scored lower on the PPVT, LNS, and CVLT-II, and had smaller MMN amplitudes.

6.4.3. Correlations between D-KEFS Proverb Test scores and other measures

For the patient group, D-KEFS Proverb Test accuracy and Abstraction scores were not significantly correlated with any of the three symptom factors, as shown in Table 6.4. In addition, neither accuracy (ρ=-0.16, p=0.53) nor abstraction (ρ=-0.04, p=0.86) was correlated with the Positive Formal Thought Disorder subscale of the SAPS. Correlations of D-KEFS Proverb Test scores with cognitive and functional measures are shown in Table 6.5 for patients, and in Table 6.6 for controls. Patients' accuracy and abstraction scores were significantly correlated with more perseverative responses on the

WCST, lower PPVT scores, smaller MMN amplitudes and lower UPSA scores. In addition, accuracy was correlated with lower LNS and CVLT-II scores; and abstraction was correlated with fewer categories achieved on the WCST.

6.5. Discussion

As expected based on previous literature, we found that schizophrenia patients exhibited proverb interpretation deficits compared to matched controls, as indexed by lower accuracy and abstraction scores on the D-KEFS Proverb Test. In the patient group, both accuracy and abstraction were significantly correlated with a greater number of perseverative responses on the WCST, lower PPVT scores, smaller MMN amplitudes, and lower UPSA scores. In addition, accuracy was correlated with lower LNS and CVLT-II scores, and abstraction was correlated with fewer categories achieved on the WCST. However, neither accuracy nor abstraction ratings were significantly correlated with patients' Disorganized, Psychotic or Negative symptom factors, or with their N400 category or typicality priming effects.

In contrast to the predictions of the disorganized-associations hypothesis, we did not find a correlation between greater proverb interpretation deficits and either more severe disorganized symptoms or reduced N400 priming effects. According to this hypothesis, overactivation of remote semantic associations, which is presumed to cause disorganized speech, also causes proverb interpretation deficits. More generally, the lack of any significant correlation between proverb interpretation scores and disorganized, psychotic or negative symptoms fits with the findings of Sponheim et al. (2003), and with the view that a variety of cognitive deficits in schizophrenia are relatively independent of positive and negative symptoms (Keefe et al., 2006).

However, our results do provide support for the WM-deficiency hypothesis of proverb interpretation deficits in schizophrenia. The ability to produce a correct response to a proverb – one that includes the standard abstract interpretation of all the main elements – was correlated with LNS scores, consistent with a role for auditory WM in proverb interpretation. The correlations of proverb interpretation accuracy with working memory and executive function are in keeping with the conceptual integration model, which implies that proverb comprehension requires the ability to maintain and manipulate information from multiple domains in WM while aligning mappings between them (see Coulson and Van Petten (2002)). This account is buttressed by the report that other higher mental processes such as categorization and general language comprehension (Fauconnier & Turner, 2002), which depend on conceptual integration processes, are also impaired in schizophrenia in proportion to WM deficits (Bagner, Melinder, & Barch, 2003; Condray, Steinhauer, van Kammen, & Kasparek, 1996; Glahn, Cannon, Gur, Ragland, & Gur, 2000; Silver, Feldman, Bilker, & Gur, 2003).

Although LNS scores were significantly correlated with ratings of proverb accuracy, they were not significantly correlated with abstraction. This suggests that adequate WM capacity may be necessary but not sufficient for proverb interpretation, implicating other capacities in either selecting the correct abstract target domain or performing appropriate mappings between it and the source domain. These other capacities may be related in some way to vocabulary, as vocabulary was strongly correlated with both accuracy and abstraction, and has also been reported elsewhere to be associated with proverb interpretation ability in schizophrenia patients (Brune & Bodenstein, 2005; Carpenter & Chapman, 1982; Shimkunas et al., 1966; Sponheim et al., 2003). It is unlikely that low vocabulary per se prevented patients from understanding individual words in the tested proverbs, since all of these words were likely within the functional vocabulary of the patients. It is possible, however, that vocabulary indexes general world knowledge – including knowledge about the types of abstract domains that people commonly use proverbs to describe – and that the disease process impairs development, maintenance, and/or quick access to this type of knowledge.

Lower proverb accuracy and abstraction ratings were both associated with reduced MMN amplitudes and with poorer skills of daily functioning (as measured by the UPSA), but not with a clinician-rated measure of global functional status (the GAF). In addition, MMN amplitudes were associated with GAF scores but not with UPSA scores. Thus, some of these variables shared significant variance but others did not, as represented diagrammatically in Fig. 6.2. Proverb interpretation may have been significantly associated with UPSA scores but not GAF scores because the GAF is a less direct indicator of deficits in functional skills than is the UPSA (see McKibbin et al. (2004) for a review of the different characteristics and biases of different types of functional measures). Our data are also consistent with the possibility that MMN reflects processes which affect GAF through one set of mediating mechanisms, and affect UPSA through another, although the present study was not designed to test such causal hypotheses.

The correlation of proverb interpretation deficits with both decreased MMN amplitudes and impaired functional skills raises the possibility that some process or processes necessary for proverb interpretation also may mediate the previously reported association between reduced MMN and poorer everyday functioning in schizophrenia patients (Light & Braff, 2005a). One candidate for such a process might be deficits in auditory verbal memory, which have been found to be associated with reduced MMN amplitudes in schizophrenia (Kawakubo et al., 2006). Thus, it may be that auditory sensory-memory encoding deficits contribute to a reduced capacity for short-term storage of verbal information, which could in turn interfere not only with proverb interpretation, but also with everyday tasks, like those tested in the UPSA, that involve the use of linguistic information. This conjecture is also supported by the correlations observed in our patient sample between reduced MMN amplitudes and the ability to recall verbal information as tested by the CVLT-II. Further work is necessary to confirm whether the relationship between decreased MMN amplitude, deficits in higher cognitive functions such as proverb interpretation, and functional impairment is causal, and, if so, to clarify the mediating mechanisms.

Alternatively, difficulties with proverb interpretation might be correlated with both decreased MMN and impaired functional skills not because these deficits are causally linked, but because they are all independently related to some other process. Our overall results, in combination with previous findings, are consistent with these deficits forming part of a syndrome of abnormalities in schizophrenia related to generalized frontal cortical dysfunction. First, we found that proverb interpretation difficulties in schizophrenia patients were correlated both with WM deficits, and with a commonly-used measure of executive function (the WCST). Multiple lines of evidence suggest that WM deficits in schizophrenia are mediated by prefrontal cortical dysfunction (Barch et al., 2002; Goldman-Rakic & Selemon, 1997). These deficits have in turn been proposed to underpin impairments in more complex cognitive tasks, such as executive function and abstract reasoning, that are also associated with frontal lobe pathology (Gold et al., 1997; Goldman-Rakic & Selemon, 1997; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2004). Second, there is evidence that decreased MMN amplitude in schizophrenia, which we found to be correlated with proverb interpretation difficulties, reflects a specific deficiency in a prefrontal cortical neural generator (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002; Naatanen, 2003; Sato et al., 2003). Third, additional support for a frontal-lobe mechanism for proverb interpretation deficits comes from their increased prevalence in dementia of the frontal type in particular (Moretti, Torre, Antonello, Cazzato, & Bava, 2002), and from the association of frontal lobe disease with deficits in figurative language comprehension and in analogical reasoning (Cacciari et al., 2006; Morrison et al., 2004). Taken together, these results are consistent with the view that proverb interpretation deficits in schizophrenia are one manifestation of generalized frontal cortical pathology.

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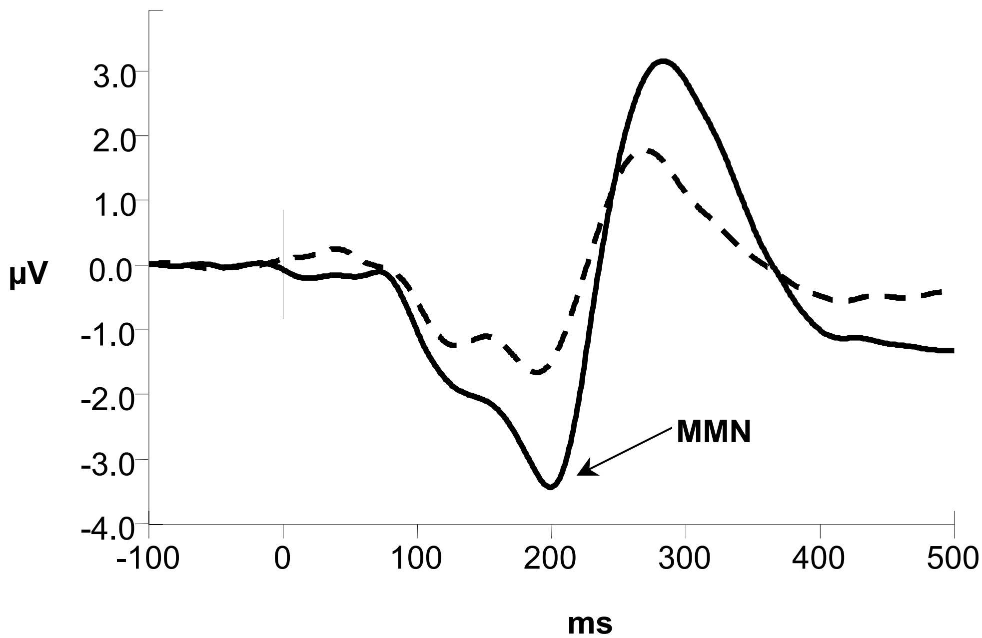

Figure 6.1. Grand-average difference waves formed by subtracting average ERPs to standard tones from average ERPs to deviant tones, for schizophrenia patients (*n*=18; dashed line) and healthy controls (*n*=18; solid line), at electrode site Fz. ERPs are time-locked to tone onset.

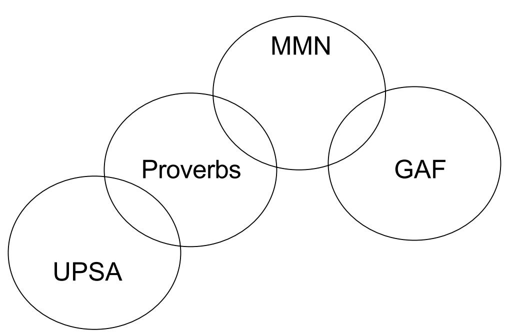

Figure 6.2. Venn diagram representing shared variance between variables as the area of overlap between circles (Cohen & Cohen, 1983).

Table 6.1. Demographic characteristics of the study sample, and clinical characteristics of the patient group (means ± SD given where applicable)

	Schizophrenia Patients	**Healthy Controls**	***p***
Age, years	46.3±10.5	43.2±8.4	0.34.
Sex	13 male, 5 female	12 male, 6 female	0.72
Parental SES	42.9±19.3	43.3±17.3	0.96
Years of Education[b]	12.6±2.2	16.1±2.4	<0.0001
Age of onset, years	23.7±7.3	–	–
Duration of illness, years	22.1±10.9	–	–
Number of previous hospitalizations	5.9±5.4	–	–
SANS Total (sum of subscale global ratings)	8.9±4.2	–	–
SAPS Total (sum of subscale global ratings)	3.5±3.4	–	–
Negative Factor	8.3±3.7	–	–
Psychotic Factor	2.2±2.7	–	–
Disorganized Factor	1.7±2.5	–	–

Table 6.2. Proverbs comprising the D-KEFS Proverbs Test (Delis et al., 2001)

1. *You can't judge a book by its cover.*
2. *Don't count your chickens before they are hatched.*
3. *Rome wasn't built in a day.*
4. *Too many cooks spoil the soup.*
5. *People who live in glass houses shouldn't throw stones.*
6. *An old ox plows a straight row.*
7. *A small leak will sink a large ship.*
8. *No bread is without a crust.*

Table 6.3. Mean scores (± SD) on experimental measures for schizophrenia patients, and healthy controls (where applicable)

	Schizophrenia Patients	**Healthy Controls**	***p***
D-KEFS Proverb Test (Free Inquiry)			
Accuracy	9.7±2.6	12.6±2.0	0.0007
Abstraction	10.4±6.1	15.3±1.4	0.003
PPVT	173.1±20.9	187.9±8.2	0.01
N400 mean amplitudes, µV			
High-typicality exemplars	0.37±1.75	0.35±1.62	0.97
Low-typicality exemplars	-0.13±1.25	-0.04±1.53	0.85
Non-exemplars	-0.55±1.16	-0.75±1.33	0.63
LNS	8.8±3.6	10.8±2.8	0.03
WCST			
Perseverative responses	17.1±13.3	12.5±13.4	0.08
Categories achieved	2.6±1.5	3.1±1.5	0.38
CVLT-II			
Immediate free recall	42.4±15.3	53.8±10.3	0.01
Short-delay free recall	7.8±3.0	11.8±13.3	0.0003
Long-delay free recall	8.6±3.7	12.2±3.1	0.003
MMN, µV	-1.5±1.0	-2.5±0.8	0.002
GAF	46.7±11.7	-	-
UPSA	80.7±14.1	-	-

Table 6.4. Spearman correlations of patient SANS/SAPS factor scores with D-KEFS Proverbs Test accuracy and abstraction ratings (*n*=18)

	Accuracy		**Abstraction**	
	ρ	***p***	***ρ***	***p***
Negative	-0.19	0.46	-0.34	0.17
Psychotic	0.03	0.90	0.15	0.55
Disorganized	0.17	0.50	0.05	0.83

Table 6.5. Pairwise correlations of D-KEFS Proverb Test scores and cognitive and functional measures, for schizophrenia patients. Correlations shown are Pearson's r or Spearman's rank-order ρ (when in italics).

	D-KEFS Proverb Test: Abstraction	PPVT	N400 effects, µV			LNS	WCST		CVLT-II			MMN, µV	GAF	UPSA
			High-typicality category	Low-typicality category	Typicality		Perseverative responses	Categories achieved	Immediate free recall	Short-delay free recall	Long-delay free recall			
D-KEFS Proverb Test														
Accuracy	*0.68*	***0.54***[a]	**0.22**	**0.11**	**0.36**	***0.66***[c]	***-0.48***[a]	*0.38*	***0.51***[a]	***0.54***[a]	***0.66***[c]	***-0.46***[a]	*0.35*	***0.65***[c]
Abstraction	–	***0.66***[c]	**0.16**	**-0.09**	**0.34**	*0.31*	***-0.48***[a]	***0.47***[a]	*0.29*	*0.27*	*0.37*	***-0.54***[a]	*0.36*	***0.49***[a]
PPVT		–	**-0.15**	**-0.28**	**0.17**	***0.47***[a]	***-0.62***[c]	***0.69***[c]	*-0.02*	*0.25*	*0.36*	*-0.39*	*0.35*	*0.42*
N400 effects, µV														
High-typicality category			–	**0.53a**	**0.72**[d]	**-0.28**	**0.41**	**-0.43**	**0.21**	**0.04**	**0.25**	**-0.28**	**0.10**	**0.23**
Low-typicality category				–	**-0.21**	**0.07**	**0.22**	**-0.42**	**0.24**	**0.06**	**0.18**	**-0.19**	**0.33**	**-0.09**
Typicality					–	**-0.15**	**0.15**	**-0.09**	**0.04**	**0.00**	**0.14**	**-0.17**	**-0.15**	**0.34**
LNS						–	***-0.70***[c]	***0.53***[a]	*0.41*	***0.64***[c]	***0.66***[c]	*-0.29*	*0.37*	***0.60***[b]
WCST														
Perseverative responses							–	***-0.89***[d]	*-0.28*	***-0.53***[a]	***-0.54***[a]	*0.30*	*-0.43*	***-0.69***[c]
Categories achieved								–	0.04	0.26	0.27	-0.05	0.19	***0.53***[a]
CVLT-II														
Immediate free recall									–	**0.87**[d]	**0.76**[d]	-0.45	0.29	*0.31*
Short-delay free recall										–	**0.86**[d]	**-0.56**[a]	0.43	*0.38*
Long-delay free recall											–	**-0.68**[c]	**0.46**[a]	***0.60***[b]
MMN, µV												–	**-0.57**[a]	-0.43
GAF													–	0.44
UPSA														–

[a] $p<.05$
[b] $p<.01$
[c] $p<.005$
[d] $p<.001$

Table 6.6. Pairwise correlations of D-KEFS Proverb Test scores and cognitive and functional measures, for healthy controls. Correlations shown are Pearson's *r* or Spearman's rank-order ρ (when in italics).

	D-KEFS Proverb Test: Abstraction	PPVT	N400 effects, µV			LNS	WCST		CVLT-II			MMN, µV
			High-typicality category	Low-typicality category	Typicality		Perseverative responses	Categories achieved	Immediate free recall	Short-delay free recall	Long-delay free recall	
D-KEFS Proverb Test												
Accuracy	*0.35*	***0.54*[a]**	*0.46*	***0.48*[a]**	*0.01*	*0.13*	*-0.05*	*-0.08*	*-0.14*	*-0.05*	*0.06*	*-0.16*
Abstraction	–	*0.26*	*0.05*	*0.19*	*-0.14*	*0.02*	*-0.37*	*0.16*	*0.40*	*0.43*	*0.36*	*0.11*
PPVT		–	0.19	0.18	0.03	0.25	*-0.34*	0.21	0.32	0.29	*0.20*	0.37
N400 effects, µV												
High-typicality category			–	**0.82[d]**	0.38	-0.30	*-0.17*	-0.36	-0.20	-0.10	-0.08	-0.21
Low-typicality category				–	-0.22	-0.27	*-0.19*	*-0.27*	-0.10	-0.05	0.01	-0.18
Typicality					–	-0.07	*-0.10*	*-0.06*	-0.18	-0.08	-0.15	-0.06
LNS						–	*-0.22*	**0.48[a]**	**0.55[a]**	***0.48*[a]**	***0.52*[a]**	0.30
WCST												
Perseverative responses							–	***-0.71*[c]**	*-0.47*	***-0.60*[b]**	***-0.48*[a]**	*-0.12*
Categories achieved								–	0.28	0.20	*0.21*	0.21
CVLT-II												
Immediate free recall									–	**0.89[d]**	***0.84*[d]**	0.22
Short-delay free recall										–	***0.78*[d]**	0.23
Long-delay free recall											–	*0.32*
MMN, µV												–

[a] $p<.05$
[b] $p<.01$
[c] $p<.005$
[d] $p<.001$

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Chapter 7

Experiment 6 – Abnormal typicality of responses on a category fluency task in schizotypy

7.1. Abstract

Existing hypotheses about semantic processing in schizophrenia and schizotypy suggest that both conditions are associated with a less than normal difference in the degree to which some concept activates the mental representation of other concepts that are strongly versus weakly related to it in meaning. To seek further evidence for this, we examined response typicality on the Category Fluency Test (CFT) as a function of schizotypy. Individuals from a non-clinical population verbally generated as many exemplars as they could in one minute for each of four categories (fruits, four-footed animals, articles of clothing, vehicles). Participants subsequently completed the Schizotypal Personality Questionnaire (SPQ). SPQ score was not significantly correlated with the total number of responses generated for any of the categories. Individuals with higher (as opposed to lower) SPQ scores, however, generated more atypical members of the fruit category both in their initial responses and overall (as indexed by the average ratio of each response's ordinal position to its position in population typicality norms). These results support the hypothesis that semantic memory organization in non-clinical individuals with higher schizotypy is functionally altered.

7.2. Introduction

Schizotypal personality traits qualitatively resemble the defining symptoms of schizophrenia but are quantitatively less severe. Thus, the schizophrenic symptoms of delusions, hallucinations, frank disorganization, and negative symptoms have counterparts in the schizotypal traits of ideas of reference, unusual perceptual experiences, odd speech and behavior, and social isolation, respectively. The degree to which individuals in the general population exhibit schizotypal traits varies on a continuum (Kendler et al., 1991), and is thought to reflect the total loading on multiple genetic and environmental factors that also can contribute to schizophrenia (Jang, Woodward, Lang, Honer, & Livesley, 2005; Siever & Davis, 2004). In support of this view, schizotypy in non-clinical samples has been found to be associated with a higher prevalence of various psychophysiological markers that characterize schizophrenia patients (Della Casa, Hofer, Weiner, & Feldon, 1999; Ettinger et al., 2005; Kiang & Kutas, 2005; Kimble et al., 2000; Klein, Andresen, Berg, Kruger, & Rockstroh, 1998; Lubow & De la Casa, 2002).

Odd speech in schizotypy includes “distinctive or peculiar” language that “may have meaning only to” the speaker, “and may often need interpretation” (Sadock & Sadock, 2003). In research settings it can be quantified by a clinician’s interview-based rating, or by the individual’s self-rating on a questionnaire such as the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991).

The propensity toward unusual language production in schizotypy is also measurable by appropriate psychological and neuropsychological tests. In free word-association tests, for example, individuals are presented with a word and asked to generate the first word that comes to mind. In a non-clinical population, high scorers on the Perceptual Aberration-Magical Ideation scale generated more unusual responses and fewer common responses, compared to controls, on free association (Miller & Chapman, 1983). Scores on the Eysenck Psychoticism Scale were also found to be correlated with the proportion of unusual word-association responses, at least in men (Ward, McConaghy, & Cates, 1991), or with the proportion of unique responses (Merten, 1993). These results parallel the common finding that schizophrenia patients produce a greater proportion of unusual or unique responses compared to controls on word-association tests (Janowsky, Huey, Storms, & Judd, 1977; Johnson & Shean, 1993; Shakow, 1980).

These results from word-association tests appear consistent with the view that schizophrenia, and perhaps by extension schizotypy, may be associated with abnormalities in how concepts activate one another in semantic memory. Such hypotheses assume a model of semantic memory in which concepts are represented as nodes in a network, and associations between concepts (e.g., between an object and its features) as links among these nodes (Anderson & Pirolli, 1984; Collins & Loftus, 1975; Neely, 1977). Whenever a concept node is activated, as by its corresponding word stimulus, this activation is thought to spread through the network to associated nodes. The degree to which one concept activates another and facilitates its processing – e.g. making it more likely to be generated as a word associate - is presumed to be related to the strength of the links between them.

According to one hypothesis, unusual associations in schizophrenia result from an abnormally broad spread of activation in the semantic network, such that activation of the mental representation of an item (i.e. word or picture) not only leads to a normal degree of activation for the representation of items strongly related to it, but also to a greater than normal degree of activation for that of items weakly related to it (Spitzer, 1997). As a consequence, more items would become activated in semantic memory, and the difference in resulting activation between strongly and weakly related items would be less than normal. This, in turn, could increase the likelihood that weakly related items would be produced in a word-association test. According to an alternative hypothesis that also could account for the production of unusual associations in schizophrenia, there is decreased gain control in prefrontal neural networks presumed to be involved in maintaining representations of context in working memory (Cohen & Servan-Schreiber, 1992). In this model, decreased gain proportionally reduces the degree of activation or inhibition of all the neurons typically comprising such representations. If we view a given item as a contextual stimulus represented in working memory by a particular pattern of neural activation, then decreased gain in this representation might in turn lead to decreased activation of semantically related items as well as to decreased inhibition (i.e. increased activation) of semantically unrelated items, and hence to production of a greater number of unusual responses in a word-association test.

There is in fact support for both the above hypotheses from behavioral priming and N400 event-related brain potential (ERP) data in schizophrenia (reviewed in Minzenberg, Ober and Vinogradov (2002)). The evidence implicates a broader spread of activation at shorter time intervals (<250 ms) after a stimulus, and poor use of context at longer intervals. There are also data pointing to similar abnormalities in association with schizotypy (Kiang & Kutas, 2005; Kimble et al., 2000; Moritz et al., 1999; Niznikiewicz et al., 2004; Niznikiewicz et al., 2002; Niznikiewicz et al., 1999).

The Category Fluency Test (CFT; Spreen & Strauss, 1998) is another neuropsychological test, with some similarities to the word-association test, that also offers a window into the functional organization of semantic memory (Aloia, Gourovitch, Weinberger, & Goldberg, 1996; Paulsen et al., 1996; Rossell, Rabe-Hesketh, Shapleske, & David, 1999; Sumiyoshi et al., 2001; Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998) and thus might likewise be a sensitive measure of unusual language production in schizophrenia and schizotypy. In this test, individuals are given the name of a semantic category (e.g. fruits, animals, tools), and asked to produce as many exemplars of it as possible within a given time period. The total number of responses generated, or fluency, on the CFT has been found to be lower in schizophrenia patients than in controls (Allen & Frith, 1983; Allen, Liddle, & Frith, 1993; Aloia et al., 1996; Giovannetti, Goldstein, Schullery, Barr, & Bilder, 2003; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001). To our knowledge, however, prior work has not examined whether the *typicality* of CFT responses also varies as a function of schizophrenia or schizotypy.

The typicality of a category exemplar is defined as its relative frequency of production by individuals asked to name members of the category of which it is a member (McCloskey & Glucksberg, 1978; Stuss, Picton, & Cerri, 1988). Population norms for the typicality of exemplars for various categories have been collected in this way (Hunt & Hodge, 1971; McEvoy & Nelson, 1982; Shapiro & Palermo, 1970; Yoon et al., 2004). For example, according to these norms *apple* is a more typical fruit than *mango* (at least in the United States). This measure of typicality is also correlated with individuals' ratings of how typical the exemplar is of the category (Mervis, Catlin, &

Rosch, 1976), and with the featural overlap between the exemplar and either the set of other category exemplars or the category concept itself (Hampton & Gardiner, 1983; Rosch & Mervis, 1975). Within the network model of semantic memory, higher typicality is thought to reflect greater total strength of the links between the category and the exemplar (McCloskey & Glucksberg, 1978).

The primary aim of the present study was to examine the typicality of CFT responses as a function of schizotypy in a non-clinical sample. We hypothesized that individuals with higher schizotypy would produce more atypical responses. This would be consistent with the view that individuals with higher vs. lower schizotypy, when presented with a semantic stimulus (i.e., the category), experience a less than normal difference in the degree of activation enjoyed by strongly versus weakly related items (i.e., high- and low-typicality exemplars, respectively). This in turn would reduce the likelihood that they would produce high-typicality exemplars while increasing the likelihood that they would produce low-typicality exemplars. This outcome would be consistent with either the hypothesis of Cohen and Servan-Schreiber (1992) or that of Spitzer (1997), and would provide additional evidence that schizotypy in the general population modulates how concepts activate one another in semantic memory in a manner similar to that seen in schizophrenia.

A related, secondary aim of the study was to examine the correlation between CFT response typicality and N400 ERP semantic priming effects, in a subset of the participants for whom the latter data were available. ERPs were recorded while participants viewed target words that were either high-typicality exemplars, low-typicality exemplars, or non-exemplars of a preceding category definition (prime stimulus). Normally, in this paradigm, N400 amplitude is largest to non-exemplars, smallest to high-typicality exemplars, and intermediate to low-typicality exemplars – with smaller N400 amplitudes taken to reflect increased activation of targets that are more related to the prime {Heinze, 1998 #28;Kiang, 2005 #113;Stuss, 1988 #30}. Here, we sought convergent evidence that lower typicality of CFT responses results from a less than average activation difference between high- and low-typicality exemplars following a category prime. Thus, we hypothesized that lower typicality of CFT responses would be correlated with smaller *N400 typicality effects* (i.e., smaller N400 amplitude differences between high- and low-typicality exemplars).

Another secondary aim of the study was to examine the correlation between schizotypy and total number of responses on the CFT. If decreased category fluency in schizophrenia reflects deficits that also vary on a continuum of severity across the general population in proportion to the degree of genetic susceptibility to schizophrenia, then in a non-clinical sample we might also expect individuals with higher schizotypy to exhibit lower fluency – that is, to generate fewer category members – than those with lower schizotypy.

We administered the CFT for four categories – fruits, four-footed animals, articles of clothing and vehicles. We chose these categories so that both living things and human artifacts would be represented. These two classes of categories have been postulated to have different characteristics, based on studies of neurological patients with class-specific deficits (McRae & Cree, 2002). We also chose these categories because they were among those included in the recent typicality norms for young Americans by Yoon et al. (2004), and thus could serve as norms for our participant sample. As a measure of the typicality of the first response generated by an individual for a given category, we used the "response probability" of that exemplar in the Yoon et al. (2004) norms. In that study, subjects' responses were viewed as drawn from an underlying multinomial distribution in which each exemplar has a particular frequency, and the response probability was an estimate of this frequency, based on a rank-order logit model. Additionally, we calculated a typicality index for the entire set of responses given for each participant in each category, by averaging, over all responses, the ordinal position of each response with its position in the response probability ranking from the population norms. Participants subsequently completed the SPQ. For each category, we hypothesized that higher SPQ score would be correlated with lower typicality of the first response and of the entire response set, and with a lower total number of responses.

7.3. Methods

7.3.1. Participants

Sixty native English speakers [34 female, 18 to 35 years of age, mean age 20.9, SD = 3.5] were recruited from the University of California (San Diego) campus. Most were undergraduates. Participants gave written informed consent and were compensated with course credit or cash. The study procedure was approved by the Human Research Protections Program of the University of California (San Diego).

7.3.2. Assessments

For the CFT, each of the 60 participants was asked to verbally generate as many names of fruits as possible in one minute. Thirty-four of these participants [16 female, 18 to 34 years of age, mean age 20.8, SD=3.6] were also asked to verbally generate as many names of four-footed animals, articles of clothing, and vehicles as they could in one minute each.

Participants subsequently completed the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1997) for an estimate of vocabulary, followed by the SPQ for an estimate of schizotypy. The SPQ is a self-report scale with 74 dichotomous-choice (Yes or No) questions. The maximum possible total score is thus 74; maximum possible scores for its three factors (Disorganized, Cognitive-Perceptual, and Interpersonal) (Raine et al., 1994) are Disorganized: 16; Cognitive-Perceptual: 33; and Interpersonal: 33.

7.3.3. Analysis of CFT responses

The total number of responses produced by each participant for each category was recorded.

For each category, as a measure of the typicality of each participant's first response, its "response probability" was obtained from the category production norms for young Americans compiled by Yoon et al. (2004). In that study, responses were viewed as drawn from a multinomial distribution in which each response has an innate frequency, and the response probability was an estimate of this frequency. For example, response probabilities for fruit ranged from 41.8% for *apple* to 0.1% for *coconut.* Higher response probabilities thus correspond to higher typicality.

In addition, as a measure of overall typicality of the participant's response set for a particular category, a typicality index t was calculated:

$$t = \frac{\sum_{i=1}^{n} [f_i / i]}{n}$$

where n = the total number of responses, i = the ordinal position of each response, and f = its position in the ranking of exemplars by response probability in the Yoon et al. (2004) norms (e.g., for fruit, f ranged from 1 for *apple*, to 30 for each of 13 different exemplars - such as *coconut* and *prune* - with a response probability of 0.1). If a given response did not occur in the norms, it was assigned a rank one greater than the total number of items occurring for that category in the norms. In other words, t represents the mean, over all responses, of the ratio of each response's rank in the norms to the position in which it was produced by the individual, with lower values of t corresponding to higher typicality. If an individual's responses exactly matched the response probability rankings, beginning with the first-ranked exemplar, t would have the minimum possible value of 1 - for example, for fruit, this could occur if the individual produced the response set *"apple, orange, banana, pear, grape, strawberry,"* which, in that order, are the first six exemplars in the norms ranked by response probability. If, on the other hand, the *individual* produced these same six exemplars but in reverse order, t would equal 1.86. The typicality index would be even lower if the individual said *"peach, kiwi, mango, pineapple, watermelon, plum,"* which are the seventh through twelfth exemplars in the norms (t = 3.45).

7.3.4. N400 ERP effects

In 24 participants (all of whom were administered only the fruit category in the CFT), ERPs were recorded in the paradigm described in detail in Kiang and Kutas (2005). In brief, ERPs were recorded from these participants while they viewed category definitions (e.g., *A string instrument*), followed by target words that were either high-typicality exemplars (*guitar*), low-typicality exemplars (*banjo*), or non-exemplars (*platform*). The N400 ERP component elicited by target words was analyzed; detailed results are presented in Kiang and Kutas (2005). Of relevance here, for each participant, we computed the N400 high-typicality category effect (i.e., N400 amplitude difference between non-exemplars and high-typicality exemplars), low-typicality category effect (amplitude difference between non-exemplars and low-typicality exemplars), and typicality effect (amplitude difference between low- and high-typicality exemplars), at a representative (midline parietal) electrode site.

7.3.5. Statistical analyses

To examine correlations between pairs of variables, Pearson product moment correlation co-efficients r were computed with two-tailed significance levels, if both variables passed the Kolmogorov-Smirnov test for normality (α=0.05). For all four categories, response probability of the first response was not normally distributed, because these responses were more likely to be exemplars with higher response probability; therefore, for correlations involving this variable, Spearman's ρ was computed, with two-tailed significance levels.

7.4. Results

7.4.1. Overall assessment scores

Table 7.1 shows descriptive statistics for assessment scores for the study sample. In the CFT, no participants gave any inappropriate responses (i.e., items that could not be considered a member of the category). Overall, the distribution of the first responses produced by participants for each category appeared consistent with the response probabilities from the Yoon et al. (2004) norms, suggesting that the presumed underlying response distribution was similar between their study population and ours. For example, the most common first response for fruit was *apple*, produced by 30 of 60 participants, a proportion similar to its response probability of 41.8% in the norms. Likewise, 14 of 60 first responses (23%) for fruit were exemplars whose response probability in the norms was 4% or less, consistent with the fact that the summed response probability of these exemplars in the norms was 24%.

There appeared to be substantial variability between individuals in overall typicality of responses. For example, for fruit, one participant (with a total SPQ score of 6) produced the relatively high-typicality response set [*apple, orange, banana, pear, peach, plum, pineapple, mango, strawberry, cantaloupe, melon, grapefruit, grapes, tangerine*], while another (SPQ = 23) produced the low-typicality response set [*cherimoya, banana, apple, orange, tangerine, grape, passionfruit, kiwi, jackfruit, lime, lemon, cherry, strawberry, persimmon, cantaloupe, Persian melon, plum, nectarine, peach, avocado*].

There was no significant correlation between total SPQ score and vocabulary as measured by the PPVT [r=0.19, p=0.15].

7.4.2. Correlations between CFT measures and SPQ scores

None of the correlations between SPQ scores (either total or factor scores) and the number of responses on the CFT for different categories approached significance (p> 0.20 for all correlations).

Correlations between SPQ scores and response probabilities of first responses, and between SPQ scores and the typicality index t for the overall response set, are shown in Tables 7.2 and 7.3, respectively. For fruit, total SPQ score and all three factor scores were significantly correlated with lower response probability of the first response, and total SPQ score and the Disorganized and Interpersonal factor scores were significantly correlated with higher *t* values – suggesting that higher schizotypy was associated with lower response typicality of both the first response and the overall response set**.** In contrast, neither the response probability of the first response nor *t* was correlated with SPQ total or factor scores for any of the other three categories assessed.

One possible explanation for this contrast between the pattern of results for fruit and for the other categories might have been that the subset of participants who completed the CFT for the other categories somehow differed from the overall sample, such that they exhibited no significant correlation between SPQ scores and typicality even for the fruit category. This possibility was ruled out, however, by the finding that even for just these 34 participants, *t* for fruit was significantly correlated with total SPQ score (r=0.42, p=0.01) and with the Disorganized (r=0.39, p=0.02), Interpersonal (r=0.39, p=0.02), and Cognitive-Perceptual (r=0.39, p=0.02) scores, and response probability of first response was significantly correlated with total SPQ score (ρ=-0.38, p=0.03), and with the Cognitive-Perceptual (ρ=-0.48, p=0.004) score.

In order to test the post hoc hypothesis that the contrasting pattern of results seen for fruit compared to the other categories might be associated with lower individual variability in response typicality for fruit, we compared the variances of the typicality index *t* for all pairs of categories, using Levene's test for equality of variance. Variance was indeed smaller for fruit than for either four-footed animals [F=13.96, df=(1,92), p=0.0003], articles of clothing [F=6.71, df=(1,92), p=0.01], or vehicles [F=35.11, *df*=(1,92), *p*<0.0001], while it did not differ significantly among the latter three categories.

7.4.3. Correlations between CFT results and N400 effects

Table 7.4 shows correlations between measures of CFT response typicality and N400 effects. CFT results were for the fruit category only, as this was the only category administered to the 24 participants in whom N400 data were recorded. None of these correlations were statistically significant.

7.5. Discussion

In this study, we assessed the hypothesis that schizotypy, like schizophrenia, may be characterized by abnormal activation of items in semantic memory, by examining the total number and typicality of the items generated in a one-minute category fluency task. We calculated the number of responses and the typicality of the initial response as well as that of the entire set of an individual's responses for four categories – fruits, four-footed animals, articles of clothing and vehicles. In contrast to what is generally observed with schizophrenia, we found no correlation between schizotypy and the total number of responses generated for any of the four categories assessed. However, individuals from our non-clinical population who scored high on schizotypy were in fact more likely to generate more atypical exemplars of the fruit category; i.e., schizotypy was reliably associated with decreased response typicality of both the first response and the overall response set for the fruit category, though not for any of the other categories.

This association between higher schizotypy and lower response typicality for the fruit category fits a model in which schizotypy and schizophrenia share abnormalities in how concepts in semantic memory activate one another. In particular, the results suggest that schizotypy is associated with less of a difference in the degree to which a meaningful stimulus (such as a category name) activates concepts (such as category members) that are strongly and weakly meaningfully-related to it. This is consistent with both the hypothesis of Spitzer (1997) – in which activation spreads more broadly to weakly related items – and that of Cohen and Servan-Schreiber (1992) – in which the gain function that determines the activation of related items is decreased.

One question raised by our results is why an association between schizotypy and typicality was obtained only for fruit and not for the other categories. Although dissociations between semantic processing of living things and human artifacts have been reported in other neuropsychiatric disorders (McRae & Cree, 2002), this distinction cannot explain our findings, given that we observed a similar lack of association between schizotypy and typicality for four-footed animals as for articles of clothing and vehicles. There are, however, reasons to believe that the category of fruits does differ from that of the other categories examined. In particular, data from category norming studies suggest that there is less inter-individual variability not only in the set of responses generated, but also in the order in which they are generated, for the fruit category relative to most other categories. First, people as a whole offer fewer different exemplar names in response to the fruit category than for four-footed animals (Battig & Montague, 1969; Yoon et al., 2004), articles of clothing (Battig & Montague, 1969; Hunt & Hodge, 1971; Yoon et al., 2004), or vehicles (Battig & Montague, 1969; Ruts et al., 2004; Yoon et al., 2004). Second, in a study conducted in Dutch (Ruts et al., 2004), fruit ranked first out of 13 categories, including vehicles and various classes of animals, on the negative correlation between exemplar generation frequency and mean rank position of generation, suggesting that different participants tended to generate the same exemplar fruits in similar ordinal positions. Third, Yoon et al. (2004) measured the similarity in response probabilities for category exemplars among four subpopulations – younger and older adults, in China and the United States – and found that fruit was among only 13 out of 105 categories with "roughly equivalent category responses across all four culture-by-age groups". By contrast, this was not the case for the category of four-footed animals, articles of clothing, or vehicles. Finally, we too found that the variance in the typicality index was significantly lower for the fruit category than for any of the other three categories, whose variances were similar to each other. Lower variability in response probability for the fruit category, compared to other categories, probably reflects relatively homogeneous experience with members of the category despite distinctly different cultural (e.g., regional, ethnic, gender, age) backgrounds. Given that our participants also differed to some extent in subcultural background both from one another and from the population sampled by Yoon et al. (2004), a lower baseline variability in response probability for the fruit category could have rendered variation due to schizotypy more detectable by increasing the signal-to-noise ratio between these factors.

By showing that individuals scoring higher on the SPQ produce more atypical responses on a category production task, our results further support the convergent validity of the SPQ as a metric for the propensity to produce unusual speech. Our results also suggest that response typicality particularly for the fruit category on the CFT may be useful as a sensitive, quantitative, objective, and rapidly administered measure of unusual speech.

Contrary to one of our secondary hypotheses, however, lower response typicality for the fruit category was not correlated with smaller N400 typicality effects (i.e., N400 amplitude differences between high- and low-typicality exemplars). We had predicted that a propensity to produce less typical exemplars in response to a category cue – presumably reflecting smaller activation differences in semantic memory between high- and low-typicality exemplars – would be indexed by smaller differences between N400 amplitudes elicited by these two types of exemplars. The absence of such an association may reflect the fact that N400 typicality effects were averaged over stimuli representing many different categories, rather than the fruit category alone, which, as discussed above, may be particularly sensitive for detecting individual differences in typicality effects.

In addition, contrary to what was hypothesized on the basis of the literature on schizophrenia per se, schizotypy was not correlated with the number of CFT responses. This contrasts with the decreased category fluency (i.e., fewer items generated) typically observed in schizophrenia patients, which has been hypothesized to reflect an inability to generate semantically-related response clusters due to degradation of normal links in the semantic network (Aloia et al., 1996; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001), or an inability to switch clusters due to compromised executive function mechanisms (Giovannetti et al., 2003). Siever and Davis (2004) have proposed that the capacity to activate other frontal regions in compensation for certain prefrontal deficits determines whether individuals with a genetic susceptibility to schizophrenia are in fact spared the disease. The normal category fluency that we observed even in individuals with higher schizotypy scores might reflect such compensatory mechanisms. Alternatively, decreased category fluency in schizophrenia but not schizotypy could mean that in schizophrenia this decrease reflects secondary effects of psychotropic medication, acute psychosis, or social deterioration rather than primary deficits in semantic memory and/or executive functions.

Future studies can confirm whether schizophrenia, like schizotypy, is associated with decreased typicality of category fluency responses. If so, this would be evidence for at least somewhat distinct processes leading to decreased typicality of responses and decreased number of responses, with the former reflecting an underlying abnormality common to schizotypy and schizophrenia, and the latter being specifically associated with the development of schizophrenia.

In summary, we found that higher schizotypy was associated with decreased typicality of responses for the fruit category on a category fluency task, both for initial responses and for the overall response set. The results support the view that schizotypy, like schizophrenia, is associated with less of a difference in the degree to which a meaningful stimulus activates concepts in semantic memory that are strongly and weakly related to it.

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Table 7.1. Means, standard deviations and ranges of assessment scores for the study sample (*n*=60, except *n*=34 for CFT data for four-footed animals, articles of clothing, and vehicles)

	Mean	SD	Range
SPQ Total	16.6	12.7	1-60
Cognitive-Perceptual Factor	5.8	4.8	0-19
Disorganized Factor	4.7	3.9	0-14
Interpersonal Factor	6.3	4.8	0-17
PPVT	188.2	5.8	170-196
CFT **Number of responses produced**			
Fruit	15.6	3.7	6-22
Four-footed animals	16.1	4.5	8-29
Articles of clothing	19.4	3.4	12-27
Vehicles	14.5	3.6	8-23
Response probability (%) of first response			
Fruit	24.9	17.5	0-41.8
Four-footed animals	21.6	18.5	0.3-47.2
Articles of clothing	9.2	10.8	0-32.2
Vehicles	33.1	27.9	0.1-57.5
Typicality index *t*			
Fruit	2.1	0.6	1.3-3.9
Four-footed animals	3.0	1.1	1.5-6.1
Articles of clothing	3.0	1.2	1.4-8.1
Vehicles	4.3	1.4	1.9-7.0

Table 7.2. Correlations of SPQ scores with response probability of the first CFT response (by category), with two-tailed test of significance

	Fruit		**Four-footed animals**		**Articles of clothing**		**Vehicles**	
	ρ	***P***	ρ	***P***	ρ	***P***	ρ	***P***
SPQ Total	-0.36	0.006*	0.02	0.92	-0.20	0.26	0.27	0.13
Cognitive-Perceptual Factor	-0.28	0.03*	0.02	0.90	-0.23	0.19	0.22	0.20
Disorganized Factor	-0.37	0.004*	0.07	0.71	-0.22	0.22	0.13	0.48
Interpersonal Factor	-0.30	0.02*	0.02	0.90	-0.23	0.19	0.22	0.20

* $p < 0.05$

Table 7.3. Correlations of SPQ scores with typicality index *t* of CFT responses (by category), with two-tailed test of significance

	Fruit		**Four-footed animals**		**Articles of clothing**		**Vehicles**	
	r	***P***	***r***	***P***	***r***	***P***	***r***	***P***
SPQ Total	0.35	0.006*	0.12	0.48	0.07	0.72	-0.03	0.87
Cognitive-Perceptual Factor	0.24	0.07	0.13	0.47	0.07	0.68	-0.08	0.64
Disorganized Factor	0.37	0.004*	0.11	0.55	0.04	0.83	0.12	0.51
Interpersonal Factor	0.33	0.01*	0.12	0.50	0.07	0.70	-0.10	0.58

* $p < 0.05$

Table 7.4. Correlations of CFT response typicality measures (for fruit category) with N400 effects, with two-tailed test of significance (n=24)

	Response probability of first response		**Typicality index *t***	
	r	***P***	***r***	***P***
High-typicality category effect	0.07	0.76	0.02	0.94
Low-typicality category effect	-0.01	0.96	-0.03	0.91
Typicality effect	0.17	0.44	0.04	0.84

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Chapter 8

General Conclusions

8.1. Disordered Semantic Activation in Schizophrenia

A primary objective of these experiments was to further characterize disordered semantic activation in schizophrenia. Building on previous work, we examined in finer detail how relatedness and time course modulate activation of concepts in semantic long-term memory in schizophrenia patients. As a measure of activation, we used the amplitude of the N400 ERP component elicited by semantic stimuli. This amplitude is reduced (made less negative) by factors presumed to have activated the stimulus concept in semantic memory (Kutas & Federmeier, 2000; Kutas & Hillyard, 1984). We aimed to identify conditions in which, following a meaningful prime stimulus, schizophrenia patients activate weakly related concepts, in particular, more than normally – in accordance with increased spread of activation in the semantic network. We also aimed to identify conditions in which they activate related concepts in general less than normally – in accordance with deficient context use. Both of these abnormalities have been proposed as possible causes of disorganized speech (McCarley et al., 1999; Spitzer, 1997).

Experiment 3 compared the effect of relatedness on semantic activation in schizophrenia patients and healthy controls, by visually presenting to these participants prime words followed by target words which were either directly (strongly) related, indirectly (weakly) related, or unrelated to the prime. Furthermore, in order to evaluate the effect of time course on activation, these stimuli were presented at either short (300 ms) or long (750 ms) prime-target SOAs. In controls, as expected, N400 amplitudes were largest (most negative) to unrelated targets, intermediate to indirectly related targets, and smallest to directly related targets. In contrast, in patients, N400 amplitudes did not differ between these three target types, reflecting larger amplitudes to both directly and indirectly related targets in patients compared to controls. In other words, schizophrenia patients lacked normal N400 semantic priming effects for both strongly and weakly related concepts. Moreover, these results were manifest at both SOAs. These results suggested that schizophrenia patients are deficient in using meaningful context to activate related concepts, in general, over both a short and a long time course.

In Experiment 1, schizophrenia patients and controls viewed category definition prime phrases, followed at a relatively long interval (2400 to 2800 ms) by target words that were either high- or low-typicality exemplars or non-exemplars of the category. These three types of targets were thus strongly related, weakly related, and unrelated to their primes, respectively. We observed a trend (p=0.10) toward decreased N400 amplitude differences between low-typicality exemplars and non-exemplars. Although this result was not statistically significant, it pointed to the possibility of decreased activation of weakly related concepts relative to unrelated ones – which would again be consistent with deficient use of context to activate related items.

In contrast, results from these experiments did not support the hypothesis of increased spread of activation to weakly related concepts following a meaningful stimulus in schizophrenia. Experiments 1 and 3 did not find evidence in schizophrenia patients for supranormal activation of targets weakly related to primes – in the form of smaller than normal N400 amplitudes – at a range of SOAs (300 to 2800 ms). It is possible that we did not detect such an abnormality because it is present in only a subgroup of patients – for example, those with high levels of disorganized speech, as postulated by Moritz et al. (2003). In that case, however, we might have expected severity of disorganization across patients to correlate with smaller N400 amplitudes to weakly related targets. Yet we found no such correlation. Nevertheless, it is possible that we might have found a correlation using different, more sensitive measures of disorganized speech. Alternatively, the discrepancy between our findings and previous results suggesting increased spread of activation to weakly-related concepts (Mathalon, Faustman, & Ford, 2002; Moritz et al., 2001; Moritz et al., 2003; Spitzer, Braun, Hermle, & Maier, 1993) may be due to differences in sample characteristics. In addition, most of these previous studies (Moritz et al., 2001; Moritz et al., 2003; Spitzer et al., 1993) measured RT rather than N400 priming; thus (as discussed in detail in Chapter 4), discrepancies with these studies might stem from between-group differences between patients and controls in response-related factors affecting RT but not N400 amplitude.

As a secondary objective, we also examined the relationship between N400 priming abnormalities and symptoms of schizophrenia. Associations with specific symptoms would be consistent with a causal role for abnormal semantic activation in the development of those symptoms. Because previous hypotheses about abnormal semantic activation in schizophrenia aimed to explain disorganized speech (McCarley et al., 1999; Spitzer, 1997), we expected N400 priming abnormalities to be associated with this symptom. Instead, N400 priming differences were not significantly correlated with disorganization ratings in either Experiment 1 or Experiment 3. Moreover, Experiment 5, which examined the relationship between N400 priming effects and another manifestation of unusual language production in schizophrenia, namely, abnormal proverb interpretation, did not find any significant correlations. Together, these findings suggest that abnormal semantic activation may in fact not be a principal cause of unusual language production in schizophrenia. Instead, disorganized speech may result from other cognitive mechanisms, such as deficits in working memory or in inferences about others' mental states, both of which have been found to correlate specifically with disorganization (Daban et al., 2002; Greig, Bryson, & Bell, 2004; Langdon, Coltheart, Ward, & Catts, 2002).

In contrast, we found that N400 priming differences were associated with positive psychotic symptoms (i.e., delusions and hallucinations). In Experiment 1, reduced N400 typicality effects (smaller N400 amplitude differences between high- and low-typicality exemplars) correlated specifically with positive symptoms. In Experiment 3, larger N400 amplitudes to both strongly and weakly related targets also correlated specifically with these symptoms. As discussed in Chapters 2 and 4, these results suggest that a reduced difference in the degree to which meaningful stimuli activate strongly versus weakly related concepts may contribute to the pathogenesis of delusions. Delusions typically presume meaningful connections between objects or events that would not normally be regarded as related. For instance, a delusional patient may believe that a stranger's hand movements affect the patient's own thoughts, or that a television announcer's statements refer to events in the patient's life. A reduced difference in the degree to which context facilitates processing of stimuli that are more versus less related to it might cause a patient to experience a sequence of normatively weakly related or unrelated stimuli as being unusually related. Alternatively or in addition, perhaps a failure to pre-activate representations of stimuli that are related to context leads to the experience that they are unusual (cf. Miller, Turnbull, & McFarland, 1989). Such abnormalities of semantic activation may underlie shifts in subjective relatedness described by schizophrenia patients, in retrospective accounts of the onset of psychotic episodes. For instance, one patient stated, "When I'm in this state of confusion. I can't relate past experience to what is happening now. I can't keep things in mind long enough" (Chapman, 1966). Another recalled, "Completely unrelated events became inextricably connected in my mind" (Bowers & Freedman, 1966). In seeking to understand such anomalous experiences (Maher, 1988; Roberts, 1992), the patient might ultimately arrive at a delusional explanation.

8.2. Semantic Activation Differences and Schizotypal Personality

Experiments 2 and 4 used the N400 to examine the effects of relatedness and time course on semantic activation as a function of schizotypal personality in the non-clinical population. These experiments studied healthy individuals rated on schizotypy, and used the same stimuli as Experiments 1 and 3, respectively. Thus, in Experiment 2, participants viewed category definition prime phrases, followed at long SOAs (2400 to 2800 ms) by target words that were either strongly related to the category (high-typicality exemplars), weakly related (low-typicality exemplars), or unrelated (non-exemplars). In Experiment 4, participants viewed prime words followed by target words either directly (strongly) related, indirectly (weakly) related, or unrelated to the prime, at SOAs of 300 and 750 ms.

In Experiment 2, higher schizotypy correlated with reduced N400 category effects – i.e., reduced N400 amplitude differences between unrelated targets (category non-exemplars) and both types of related targets (high- and low-typicality exemplars). This reduction reflected smaller N400 amplitudes to non-exemplars, and larger amplitudes to both types of exemplars. In addition, in Experiment 4, higher schizotypy correlated with smaller N400 indirect priming effects (i.e., N400 amplitude differences between unrelated and indirectly related targets), at both SOAs. Together, these results are consistent with an association between schizotypy and decreased use of context to activate related items in general, and/or to inhibit unrelated items, over a range of SOAs (300 to 2800 ms). Decreased use of context to activate related items would fit with previous reports of smaller N400 sentence congruity effects in schizotypy due to larger N400 amplitudes to congruent endings (Kimble et al., 2000; Niznikiewicz et al., 2004; Niznikiewicz et al., 1999). Decreased activation of related items also resembles what we observed in schizophrenia patients in Experiment 3. Thus, it may be one of a number of neurophysiological markers associated with both schizophrenia and schizotypy (Della Casa, Hofer, Weiner, & Feldon, 1999; Ettinger et al., 2005; Kimble et al., 2000; Klein, Andresen, Berg, Kruger, & Rockstroh, 1998; Lubow & De la Casa, 2002), whose characterization in non-clinical populations as a function of schizotypy may help shed light on mechanisms of schizophrenia. This overlap between neurophysiological correlates of schizophrenia and schizotypy supports the view that common genetic factors underlie these conditions (Tsuang, Stone, & Faraone, 2000). Finally, also analogous to our studies of schizophrenia patients, we did not find evidence in Experiments 2 and 4 for an association between schizotypy and broader spread of activation to weakly related concepts, across the range of SOAs employed.

By assessing participants not only on overall schizotypy, but also on its separable factors, we found that these are differentially associated with variation in semantic priming. Population studies have shown that schizotypal traits load on three semi-independent factors, referred to as cognitive-perceptual, disorganized, and interpersonal schizotypy (Raine et al., 1994; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000; Rossi & Daneluzzo, 2002). These factors seem qualitatively similar to the positive psychotic, disorganized, and negative symptom factors of schizophrenia, respectively. The schizotypal traits of ideas of reference, odd beliefs, unusual perceptual experiences and suspiciousness load on the cognitive-perceptual factor; odd behavior and odd speech load on the disorganized factor; and social anxiety, lack of close friends, constricted affect and suspiciousness load on the interpersonal factor (Raine et al., 1994). In Experiment 2, smaller N400 category effects were correlated specifically with higher interpersonal schizotypy. In Experiment 4, smaller N400 direct and indirect priming effects correlated with higher cognitive-perceptual schizotypy, whereas *larger* N400 strength-of-relatedness effects correlated with higher interpersonal schizotypy. Taken together, these results are somewhat confusing, and further research is necessary to clarify how different schizotypal factors modulate semantic priming. These data seem consistent with an association of cognitive-perceptual and interpersonal schizotypy with smaller activation differences between unrelated and related items in general – perhaps analogous to what we observed in relation to positive symptoms in schizophrenia. In addition, interpersonal schizotypy in particular might also be associated with *increased* activation of *strongly* related items and/or *decreased* activation of *weakly* related items – i.e., activation that is more focused on the strongest associates. Interestingly, such a relationship might have contributed to the findings of Niznikiewicz et al. (2004), in which women with SPD produced smaller than normal N400 amplitudes to related word-pair targets (at SOA=450 ms) – suggestive of increased activation of these words that were presumably strongly related to their context. More focused activation of strong associates has not typically been seen in N400 studies of schizophrenia; thus, this particular characteristic may be related to processes associated with schizotypy but not with schizophrenia.

In the non-clinical population, we found that disorganized schizotypy, as measured by the SPQ (Experiments 2 and 4) and by CFT response atypicality (Experiment 6), was not associated with N400 priming differences. Instead, these priming differences were associated with cognitive-perceptual and interpersonal schizotypy. These results seem analogous to our finding that N400 priming abnormalities in schizophrenia were not significantly correlated with disorganized speech. These data raise the possibility that, in the general population as in schizophrenia, semantic activation differences may be an important determinant of unusual beliefs, but not of disorganized speech.

8.3. Context Processing in Schizophrenia

Our results were broadly consistent with the view that schizophrenia patients are impaired in using meaningful context to pre-activate related concepts in semantic long-term memory. Semantic priming is thus one of numerous paradigms in which schizophrenia patients appear to have difficulty using context normally. Context can be defined as "the parts of a written or spoken statement that precede or follow a specific word or passage, usually influencing its meaning or effect" (*Random House Dictionary of the English Language)*. Thus, for example, following sentences biasing the subordinate meaning of a homonym, both schizophrenia patients and control participants primed target words related to this subordinate meaning, but only the patients also primed targets related to the dominant meaning, suggesting that the patients were not using context normally to inhibit this meaning (Titone, Levy, & Holzman, 2000). The second, more general dictionary definition of context is "the set of circumstances or facts that surround a particular event, situation, etc." Along the lines of this definition, schizophrenia patients performed worse than normal when they viewed three sequential pictures of a comic strip, and then had to choose the most appropriate completion of the story from among a set of additional pictures (Sarfati, Hardy-Bayle, Besche, & Widlocher, 1997).

Some researchers have proposed that a more general impairment in using context, across a variety of cognitive domains, is a core feature of schizophrenia (Cohen & Servan-Schreiber, 1992; Hemsley, 2005). Cohen et al. (1999) define context as "information that must be actively held in mind in such a form that it can be used to mediate task appropriate behavior," such as "specific prior stimuli, the result of processing a sequence of prior stimuli, or more abstract information such as task instructions." Abnormalities in schizophrenia patients which have been taken to support a more general definition of impaired context use include: more errors on the AX-Continuous Peformance Test (AX-CPT) in which participants must respond to a target letter sequence (Cohen et al., 1999); and less slowing by incongruent flanking letters on a letter target recognition task (Jones, Hemsley, & Gray, 1991). A generalized deficit in using context arguably extends to pre-attentional processing as well, as reflected in schizophrenia patients' smaller than normal auditory mismatch negativities (MMN) (Michie, 2001). As discussed in Chapter 6, the MMN is elicited by infrequent stimuli embedded among frequent ones, when the individual is not actively attending to any of them. The MMN is thought to index discrepancy with a sensory memory trace of previous stimuli (Javitt, Doneshka, Grochowski, & Ritter, 1995; Naatanen, Paavilainen, Alho, Reinikainen, & Sams, 1989). This trace can be viewed as one instance of context, and smaller MMN in schizophrenia patients could thus reflect impairment in representing or using this context.

Chapter 1 enumerated a number of (non-mutually-exclusive) pathologies that could interfere with the normal use of context to modulate semantic activation. Our findings point to some of these mechanisms more than to others. The lack of N400 priming effects in schizophrenia patients in Experiment 3 could reflect impairment in attending to the contextual stimuli, or in integrating their elements into a holistic representation. This result is also compatible with reduced gain in neural networks that represent context, as proposed by Cohen and Servan-Schreiber (1992) to occur in prefrontal cortex as a result of dopaminergic deficiency. In contrast, the data do not provide evidence for a deficit in maintaining contextual representations over time, because the observed N400 abnormalities were similar across a shorter and a longer SOA. Nevertheless, it is possible that a greater range of SOAs might have revealed a decrement over time in N400 effects in patients relative to controls, consistent with deficits in maintaining contextual representations. Furthermore, the data are compatible with normal representation of context, accompanied by abnormal structure of the semantic network itself, which would affect the degree to which context modulates activation of different concepts. This abnormal structure of semantic long-term memory could take the form of either: (a) aberrant organization, in which the relative associative strengths of different concept pairs are abnormal;[1] or (b) uniformly and proportionately weaker than normal links between normally organized concepts.[2] Further research is required to determine which of these potential abnormalities are present in schizophrenia.

It is important to note that this model of semantic long-term memory as a network of concept nodes is likely a simplification. In this model, each concept corresponds to a fixed set of neurons, whose activation in turn modulates that of other concepts depending on their relatedness. However, there is probably not a simple one-to-one correspondence between concepts and neural representations. Thus, Elman (2004) has proposed that each instance of activation of a given concept represents a somewhat different mental state, or pattern of neural activation, depending on the preceding context. Thus, the neural representation of *cat* would be different when the context is about wild animals than when it is about a domestic setting. Moreover, the representations of related concepts that are subsequently activated as a result would also differ. Along similar lines, a number of experiments have shown that a given verb concept primes related nouns to different degrees depending on its aspect (*arrested* vs. *was arresting*) or voice (*arrested* vs. *was arrested*; reviewed in McRae et al., 2005). According to Elman (2004), a particular

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[1] For example, although *MOUSE* is normally a stronger associate of *CAT* than *FUR* is, in a specific individual with schizophrenia, the opposite might be the case.

[2] These abnormalities could reflect either disrupted development, or degradation of a previously normal network. Longitudinal studies of schizophrenia patients, and of at-risk individuals before illness onset, are necessary to distinguish these possibilities.

concept is defined by the fact that all its instantiations are similar enough to occupy a discrete, contiguous region of a multidimensional space, in which each point represents a mental state. A nodal network model may adequately approximate priming effects of relatively simple experimental stimuli such as those used in the present studies, where the prime words or categories were uninflected and occurred in isolation from any additional context. In contrast, a more complex model of semantic long-term memory may be necessary to describe priming effects in more naturalistic processing. Finally, a nodal network schema of semantic long-term memory may be misleading if it is taken to imply that conceptual representations are localized to a brain region or module. Instead, there is evidence that these representations are distributed across different brain areas involved in processing conceptual features (Damasio, 1989; Martin, 2007; Simmons & Barsalou, 2003), including sensory and motor regions. On this view, a given concept may be represented as the collective activation of those neurons that process all the features of the concept. For example, the representation of *hammer* would include the neurons activated by visual and tactile features of hammers, as well as by the planning of movements involving a hammer.

If schizophrenia patients are impaired in using contextual information in semantic processing as well as in a variety of other cognitive domains, do these deficits share a common upstream locus of pathology? One possibility is that they are all caused by reduced gain in prefrontal neural networks responsible for representing context. This abnormality could then affect performance on context-dependent tasks in a variety of cognitive domains. In fact, schizophrenia patients’ deficits on the AX-CPT, and on both letter and visuospatial working memory tasks, are all associated with decreased activity in dorsolateral prefrontal cortex (DLPFC) as measured by fMRI (Cannon et al., 2005; MacDonald et al., 2005; Perlstein, Carter, Noll, & Cohen, 2001). It is unclear, however, whether schizophrenia patients' semantic priming deficits are also associated with decreased activity in this region. Currently, there are few data that bear on this question. In a semantic priming paradigm, Kuperberg et al. (2007) did not detect any abnormalities of fMRI activation in DLPFC in schizophrenia patients. In a different semantic task, in which participants viewed pairs of words simultaneously and decided whether or not both represented features of the same object, schizophrenia patients showed *increased* activation of the right DLPFC (Assaf et al., 2006). If confirmed, a lack of association between semantic priming deficits and decreased DLPFC activity in schizophrenia would suggest that these semantic priming deficits are not caused by decreased gain in neural networks in DLPFC. Rather, semantic priming deficits might be caused by deficient representation of semantic context in other brain regions, or by abnormal structure of semantic long-term memory. Also consistent with a dissociation between semantic priming deficits and deficient context maintenance in DLPFC, Experiment 5 found that, in schizophrenia patients, N400 effects were not significantly correlated with deficits in MMN, executive function or working memory, all of which have been linked to DLPFC dysfunction (Alho, Woods, Algazi, Knight, & Naatanen, 1994; Cannon et al., 2005; Osaka et al., 2007; Perlstein et al., 2001; Smith, Taylor, Brammer, & Rubia, 2004).

8.4. Schizophrenia and Neural Synchrony

Recent advances in neurophysiology suggest that information processing in the brain requires the synchronous oscillatory firing of neuronal assemblies (Varela, Lachaux, Rodriguez, & Martinerie, 2001). On this view, the composition of these assemblies is fluid, and depends on the particular cognitive task at hand (Schnitzler & Gross, 2005). The size of these assemblies ranges from groups of neurons within a local brain region to larger-scale networks across regions. The former would subserve more fine-grained and specific processing, whereas the latter would mediate information flow between regions. Neural synchrony may "control the strength of a signal, and hence the downstream circuits that it reaches, rather than the nature of the information that it conveys" (Salinas & Sejnowski, 2001). Computational modeling demonstrates that synchrony of inputs to a neural network can increase its gain (Salinas & Sejnowski, 2001; Schnitzler & Gross, 2005). Synchrony may also optimize "relations between…'top-down' and 'bottom-up' communication, both within and between brain areas…This optimization might have particular importance during motivated anticipation of, and attention to, meaningful events and associations" (Makeig, Debener, Onton, & Delorme, 2004). Examples of processes requiring large-scale, interregional synchronization could include: transferring and filtering information from one level of processing to a higher one, integrating information from different sensory modalities, and "top-down" modulation of selective attention. Of relevance to the present studies, the use of meaningful context to activate related concepts could plausibly involve synchronization between prefrontal areas that represent context and other regions that store semantic long-term memory. Positron emission tomography (PET) and intracranial ERP studies of semantic processing suggest that these regions may lie in the inferior and medial temporal lobes (Nobre, Allison, & McCarthy, 1994; Nobre & McCarthy, 1995; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Whatnough, Chertkow, Murtha, & Hanratty, 2002). In addition, semantic activation could also depend on more local synchrony within the semantic network itself.

There is emerging experimental evidence to support the view that neural synchrony is essential to cognitive processing. One method of measuring synchrony involves examining EEG power at specific combinations of frequency and post-stimulus latency, at particular electrode sites. Thus, mean change in power compared to baseline can be represented as color on a two-dimensional event-related spectral perturbation (ERSP) plot, with frequency and latency on the x and y axes respectively (Makeig et al., 2004). Power at a given frequency reflects synchronous oscillatory firing of groups of neurons at that frequency. Higher-frequency oscillations correspond to more local activity, whereas lower-frequency oscillations are generated by larger-scale assemblies (Varela et al., 2001). Increased power may or may not be manifest in the ERP, depending on whether it is phase-locked to the stimulus across trials, since the ERP represents the average response over multiple trials. In other words, increased power of random phase across trials would cancel out in the ERP, whereas phase-synchronous increase in power across trials would result in maximal amplitude change in the ERP. Conversely, ERP peaks may reflect phase synchronization without change in power. Large-scale synchrony can also be examined by measuring phase correlation *between* electrodes at a particular frequency and latency following a stimulus. Using these methods, increased power and phase correlation among parietal and occipital electrodes in the gamma band (30-80 Hz) have been observed during face and object recognition (Gruber, Muller, & Keil, 2002; Varela et al., 2001). In the domain of semantic processing, sentence congruency judgments were associated with increased theta (4-7 Hz) power; in addition, they were associated with increased gamma power frontally following world-knowledge violations, and pre-frontally over the right hemisphere following congruent words (Hagoort, Hald, Bastiaansen, & Petersson, 2004; Hald, Bastiaansen, & Hagoort, 2006).

Reductions in event-related synchrony have been observed in schizophrenia, and may contribute to apparently disparate cognitive symptoms of the disorder. Deficient activity of cortical GABAergic interneurons in schizophrenia has been proposed to cause decreased synchrony, via decreased inhibition of background or irrelevant neural activity (Ford, Krystal, & Mathalon, 2007; Lewis, Hashimoto, & Volk, 2005). Consistent with decreased synchrony, schizophrenia patients showed reduced steady-state EEG entrainment to oscillatory auditory stimuli in the gamma band (40 Hz) specifically (Kwon et al., 1999; Light et al., 2006). In another study, schizophrenia patients did not demonstrate the normal increase in occipital gamma power in response to visual Gestalt stimuli (Spencer et al., 2003). Furthermore, in a task designed to assess executive function by requiring either a congruent or incongruent motor response to the direction of an arrow (depending on the color of a preceding cue), schizophrenia patients exhibited a less than normal increase in prefrontal gamma power in response to the more difficult (incongruent) condition (Cho, Konecky, & Carter, 2006). Failure to achieve normal synchrony might thus be the underlying mechanism for a variety of cognitive deficits in schizophrenia (Ford et al., 2007). Deficient synchrony could account for schizophrenia patients' impairment in using context to modulate neurophysiological and behavioral responses, perhaps by reducing gain in context-representing networks, or interfering with communication between these and other brain regions. The consequences could include semantic activation abnormalities such as those found in the present work, as well as deficits in other context-contingent responses, both preattentional and attention-dependent. Decreased synchrony could also underlie reduced cross-modal sensory integration, which is suggested, for example, by schizophrenia patients' better than normal performance on a task in which healthy individuals experience cross-modal interference (the McGurk effect; de Gelder, Vroomen, Annen, Masthof, & Hodiamont, 2003; Williams, Ramachandran, Light, & Braff, 2007). Finally, deficient synchrony might produce schizophrenia patients' impairment in top-down modulation of selective visual attention (Fuller et al., 2006). Further research is needed to elucidate the antecedents of abnormal neural synchrony in schizophrenia, and to confirm its causal role in semantic processing deficits and other cognitive abnormalities.

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