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What can Event-related Potentials tell us about language, and perhaps even thought, in schizophrenia?

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ABSTRACT

Disturbances of thought and language are fundamental to schizophrenia. Cognitive behavioral and electrophysiological research has implicated problems in two different neurocognitive mechanisms: abnormalities in the structure and function of semantic memory, and abnormalities in combining and integrating words together to build up sentence and discourse context. This review discusses recent electrophysiological evidence suggesting that these two deficits are not completely distinct, but rather that language impairment in schizophrenia results from a dysfunctional interaction between these systems in an effort to build up higher-order meaning. Moreover, although language abnormalities are more pronounced in patients with positive thought disorder, they manifest themselves in all patients when increased demands are placed on the comprehension system. Further investigation of language dysfunction may also provide insights into other aspects of psychotic thought.

1. Introduction

The study of language has a long history in the field of schizophrenia research. From the time of Bleuler, a loosening of the normal associative connections between words and concepts was considered a core component of the schizophrenia syndrome (Bleuler, 1911/1950). Later descriptions featured higher-order language and thought disturbances in schizophrenia, with terms such as verschmelzung (fusion), faseln (muddling), entgleiten (snapping off), entgleisen (derailment) dominating German descriptive psychopathology during the last century (Schneider, 1959). Detailed clinical assessments of thought disorder such as the Thought, Language and Communication (TLC) scale (Andreasen, 1979a), came into widespread use during the 1980s, and describe disturbances at all levels of language: words, sentences and whole discourse.

With the development of cognitive psychological and, more recently, cognitive neuroscientific methods, most focus has been on understanding the neurocognitive basis of "loosening of associations" (Bleuler, 1911/1950) through investigating the structure and function of semantic memory in schizophrenia using semantic priming techniques (Aloia et al., 1998; for reviews see G. Kuperberg et al., 2007; G.R. Kuperberg et al., 2009; Minzenberg et al., 2002; Pomarol-Clotet et al., 2008). In Section 2, we discuss how event-related potentials—an online measure of brain activity—have contributed to our understanding of the neural basis of semantic memory function in schizophrenia.

Although informative, studies examining semantic relationships between individual words are limited in how much they can tell us about the nature of the non-goal-directed and illogical nature of thought processes in schizophrenia. These abnormal thought processes are manifested both by the incoherent language output produced by some patients (positive thought disorder), as well as by delusional thinking, and even by the non-goal-directed thought and behavior characteristic of the negative syndrome. In Sections 3 and 4, we review ERP studies that examine relationships between semantic memory and the build-up of higher-order meaning in sentences and discourse in schizophrenia. In Section 5, we outline some of the relationships between the electrophysiological abnormalities described in earlier sections, and the clinical symptoms and cognitive deficits of schizophrenia. In Section 6, we consider some caveats in the interpretation of ERP findings. Finally, in Section 7, we offer some conclusions.

Throughout this review, our focus will be on the N400 ERP component, although we will also briefly consider other components that are sensitive to aspects of language processing. The N400 is a negative-going waveform that peaks at approximately 400 ms following the onset of a target stimulus. The amplitude of the N400

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is larger (more negative) to words that are preceded by a context that is semantically incongruous, relative to one that is congruous. This context can be a single word, a sentence stem or a whole story. The attenuation of the amplitude of the N400 to congruous relative to incongruous words is termed 'the N400 effect'. The modulation of the N400 is thought to reflect the semantic processing of a word in relation to its preceding context, with a larger N400 amplitude reflecting an increased difficulty in semantic processing (Holcomb, 1993; Kutas and Federmeier, 2000; Kutas and Hillyard, 1980).

2. Words: Semantic priming

Semantic priming has been one of the most frequently studied paradigms exploring the structure and function of semantic memory over the past two decades, both in healthy individuals and in patients with schizophrenia. The behavioral semantic priming effect describes the faster response to targets that are preceded by semantically related, relative to unrelated, prime words (Meyer and Schvaneveldt, 1971; Neely, 1991). There are multiple mechanisms underlying the semantic priming effect that depend on the precise conditions under which the experiment takes place (Neely, 1991). A survey of the behavioral semantic priming literature in schizophrenia can feel overwhelmingly contradictory; patients seem to show every possible pattern of priming: reduced, normal or increased. Fortunately, however, there does seem to be some pattern to these disparate behavioral findings, with evidence that normal and increased semantic priming (the latter, particularly in thought-disordered patients) are primarily evident under automatic experimental conditions, while reduced priming in patients is primarily seen under experimental conditions biasing towards more controlled processing (Kuperberg et al., 2009; Minzenberg et al., 2002; Pomarol-Clotet et al., 2008). Nonetheless, some of the findings are still contradictory and ERP studies have shed some light on this literature.

The ERP semantic priming effect describes the relative reduction of the amplitude of the N400 amplitude to targets that are preceded by semantically related (relative to unrelated) primes (Bentin et al., 1985; Rugg, 1985). Using ERPs to examine semantic priming in schizophrenia has some advantages over reaction times. First, ERPs provide a direct neural index of priming, which may be more sensitive than behavioral measures. Second, ERPs are not confounded by the overall slower RTs typically exhibited by patients, which can sometimes inflate relative differences in RT between related and unrelated targets, leading to spurious behavioral results (Chapman et al., 1994; Spitzer et al., 1993). Third, it is possible to measure ERPs on trials in which participants do not make behavioral decisions (Kreher et al., 2006, 2008; Misra and Holcomb, 2003); they can therefore be used to index semantic processing in the absence of any decision-making neurocognitive operations.

2.1. Automatic semantic priming

One of the most intuitively attractive explanations of a 'loosening of associations' in schizophrenia is that it arises from a faster, and perhaps even further, spread of automatic activation through semantic memory (Manschreck et al., 1988; Spitzer et al., 1994), where semantic memory is conceptualized as a network of interconnected nodes organized by semantic relationship (Anderson, 1983; Collins and Loftus, 1975). Such an automatic spread of activation can only be indexed under automatic experimental conditions: an interval between the onset of the prime and target (stimulus onset asynchrony, SOA) of less than about 400 ms, and a total proportion of related words (the relatedness proportion) within the stimulus set of less than about 33% (Neely, 1991). Under such conditions, the semantic priming effect on a target word is thought to arise from its partial pre-activation due to an automatic spread of activation from its prime.

Evidence for a faster and further spread of activation in schizophrenia comes from observations that, under such automatic conditions, the behavioral semantic priming effect is sometimes greater in patients than controls (Manschreck et al., 1988). Moreover, such increased priming (or 'hyperpriming') is sometimes observed even when the prime is not directly related to the target but rather indirectly associated through an unseen mediator that is associated with both prime and target (e.g. "*lion*-[tiger]-*stripes*") (Spitzer, 1993; Spitzer et al., 1994)—a phenomenon known as indirect semantic priming (Balota and Lorch, 1986; McNamara and Altarriba, 1988). Most behavioral studies have reported that such increased semantic priming in schizophrenia is most closely associated with clinical evidence of positive thought disorder: schizophrenia patients with positive thought disorder can show increased direct behavioral priming (Manschreck et al., 1988; Spitzer et al., 1994) and increased indirect behavioral priming (Moritz et al., 2001, 2002; Spitzer, 1993; Weisbrod et al., 1998), relative to both non-thought-disordered patients and healthy controls. Other investigators, however, have reported normal and sometimes even reduced direct semantic priming in schizophrenia at short SOAs (e.g. Barch et al., 1996; Ober et al., 1997), although some of these latter studies have not accounted for thought disorder.

There are now several electrophysiological studies in healthy individuals suggesting that, under automatic conditions, the amplitude of the N400 is attenuated (i.e. less negative) to targets that are both directly and indirectly related to their preceding prime (each relative to unrelated targets), suggesting that the N400 is sensitive to the effects of automatic processes such as the spread of activation (Chwilla and Kolk, 2002; Kiefer et al., 1998; Kreher et al., 2006; Weisbrod et al., 1999). In schizophrenia, findings are mixed. In a picture–word matching task, with a SOA of 325 ms, Mathalon et al. (2002) reported normal N400 amplitudes to target words that were primed by pictures representing that word, but less negative N400 amplitudes to words that were preceded by moderately related pictures belonging to the same superordinate categories. In this study, positive thought disorder failed to predict N400 amplitude. The smaller N400 to these moderately related targets was interpreted as evidence for hyperactivity of the semantic network in schizophrenia. However, because there were no completely unrelated picture–word pairs, the degree of semantic priming per se was not assessed. Using an implicit task that did not require a behavioral response to trials of interest, and a short SOA of 350 ms, Kreher et al. (2008) demonstrated that, relative to non-thought-disordered patients and healthy controls, positively thought-disordered schizophrenia patients showed an increased early N400 *indirect* semantic priming N400 effect (between 300 and 400 ms after target word onset). By 400–500 ms after target word onset, both direct and indirect semantic priming were generally equivalent across the three groups. This provided neural evidence for a further spread of activation across the semantic network, within a shorter period of time, in specific association with positive thought disorder, see Fig. 1, left.

Nonetheless, the precise task that participants perform appears to play an important role in determining whether hyperactivation or hypoactivation will be observed in patients. This is clearly demonstrated by Kreher et al. (2009) who asked the same group of patients and matched controls to view the same directly related, indirectly related, and unrelated word-pairs under the same SOA, but this time to explicitly link the primes and targets through a relatedness judgment task (rating their semantic relationship). Under these circumstances, the schizophrenia patients showed a reduced direct and indirect N400 priming effect compared with the healthy controls, see Fig. 1, right. Similarly, using a lexical decision task with a 350 ms SOA, Condray et al. (2003) found an abnormally reduced direct semantic priming N400 effect in schizophrenia patients, that was not correlated with thought disorder (Condray et al., 2008). Finally, Kiang et al. (2008), also using a LD task with a short SOA, reported reduced N400 effects to both directly and indirectly related targets in schizophrenia patients compared with controls.

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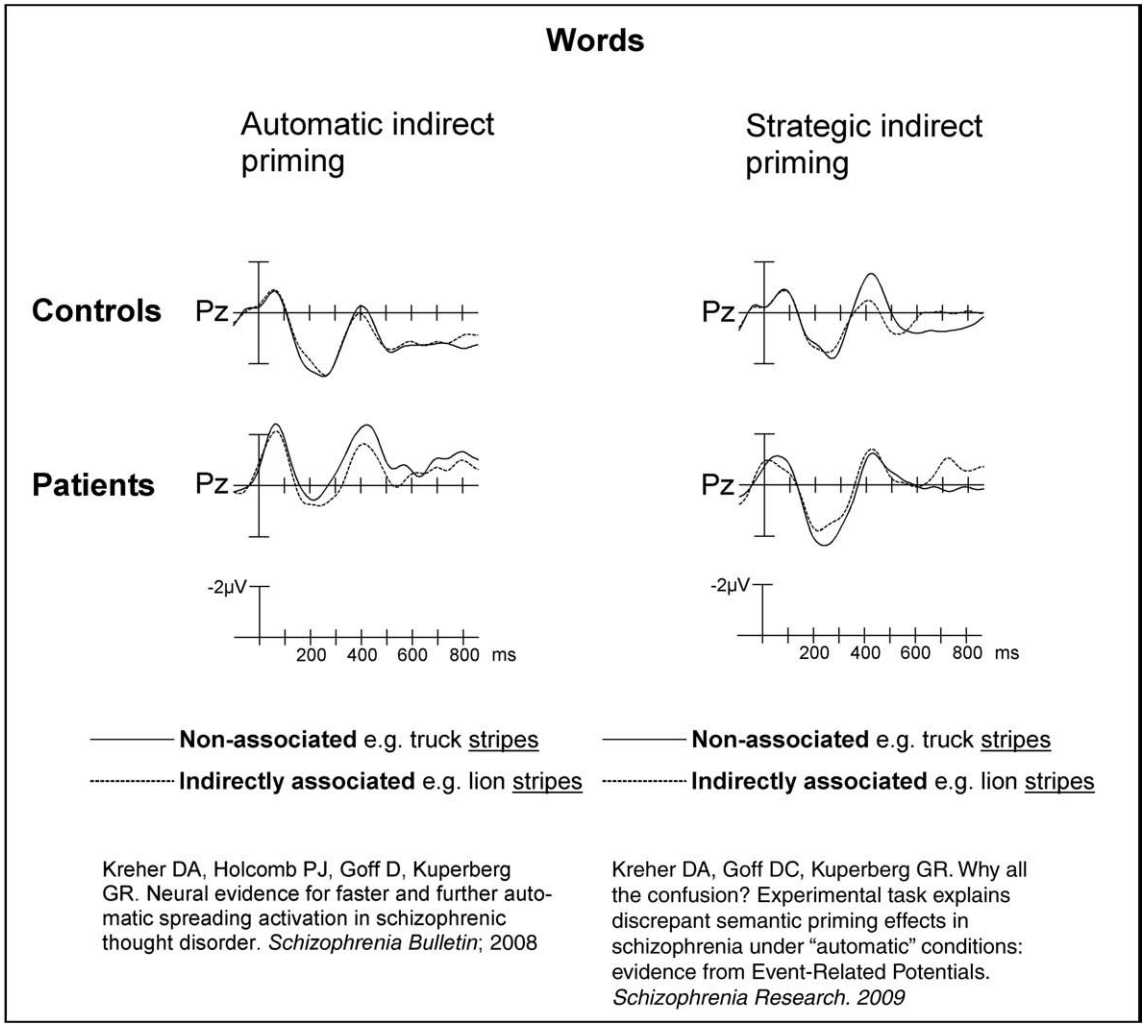

Fig. 1. *Left:* Under automatic experimental conditions, in the absence of any behavioral response requirement to trials of interest, schizophrenia patients with positive thought disorder showed a larger attenuation of the N400 to indirectly related (versus unrelated) target words (underlined in the examples) than healthy controls. *Right:* When participants performed an explicit relatedness judgment task, the same patients, unlike controls, showed no attenuation of the N400 to indirectly related (versus unrelated) target words (underlined in the examples). The plots indicate one central parietal electrode site (Pz) where the N400 effect is maximal.

2.2. Controlled semantic priming

When participants are given more time between the onset of the prime and the target, and when the proportion of related words in the stimulus set is relatively large, reduced semantic priming is generally seen in schizophrenia. Under such experimental conditions, healthy participants are able to employ strategies that facilitate the processing of related target and that slow down the processing of unrelated targets (Neely, 1991): they can, for example, generate predictions of likely targets (expectancy generation) (Becker, 1980), or use the combination of prime and target to bias decision-making (semantic matching) (Neely et al., 1989). Of note, under these experimental conditions, spreading activation may still be occurring (its effects may not have decayed, see Deacon et al., 1999), but in most behavioral tasks, its effects are outweighed and masked by strategic semantic processes (for discussion, see Neely, 1991). The reduction in behavioral semantic priming in schizophrenia patients under controlled conditions suggests that they fail to use such controlled strategies (reviewed by Minzenberg et al., 2002; Pomarol-Clotet et al., 2008).

The ERP controlled semantic priming literature in schizophrenia has generally supported these behavioral findings (although see Koyama et al., 1991, 1994). In a semantic matching task, Grillon et al. (1991) reported two distinct subgroups of schizophrenia patients: one in which there was a reduced N400 effect, and one in which the N400 effect was not different from that of controls. Bobes et al. (1996) used a picture semantic matching task and reported a smaller N400 effect in patients than controls. Using a lexical decision task, Kostova et al. (2003, 2005) demonstrated reduced N400 effects, particularly in thought-disordered patients using a 450 ms SOA but a relatively high relatedness proportion; others too have reported reduced N400 effects both in medicated patients (Condray et al., 1999) and in unmedicated patients (Condray et al., 1999; Hokama et al., 2003) using a lexical decision task. Of note, however, at a long SOA of 950 ms, patients with positive thought disorder showed a larger semantic priming effect than patients without thought disorder (Condray et al., 2008). Finally, using a LD task at a long SOA, Kiang et al. (2008) reported reduced N400 effects in schizophrenia patients to both directly and indirectly related targets.

2.3. Summary

In sum, ERP studies of semantic priming have generally supported behavioral studies. Under automatic conditions, patients are able to access semantic relationships stored within semantic memory and a subset of thought-disordered patients may even show a faster, further neural spread of activation through the semantic network. However, requiring a decision to each target word, through relatedness ratings or lexical decision, can reduce semantic priming in schizophrenia

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patients, even under automatic experimental conditions. Studies examining priming under more controlled experimental conditions confirm that patients are impaired in using semantic strategies to facilitate the processing of primed targets.

3. Sentences

Accessing semantic relationships between individual words is not only something that we are required to do when participating in a semantic priming experiment! While traditional models of sentence comprehension hold that words are combined mainly through the activation of their syntactic frames (reviewed by Osterhout et al., 2008), there is accumulating evidence that building up the meaning of a sentence also requires comprehenders to access semantic relationships between its individual words and to compare such relationships with those that are prestored within semantic memory (Federmeier and Kutas, 1999; Kutas and Federmeier, 2000). In parallel with this 'semantic memory-based' stream of analysis, however, there also proceeds a more complete algorithmic, combinatorial stream of analysis whereby the meanings of individual words are combined and integrated with morphosyntactic and thematic structure to determine 'who does what to whom' within a proposition (Kuperberg, 2007). Under many circumstances, a semantic memory-based analysis may be sufficient, allowing comprehenders to come up with 'good enough' representations of meaning (Ferreira et al., 2002). However, there are circumstances when such 'quick and dirty' representations are not good enough, and can lead to inaccurate interpretations, given the preceding context. In such cases, the product of the semantic memory-based analysis is normally overridden by the more complete combinatorial parse that probably proceeds in parallel. What healthy comprehenders appear to be able to do easily, and seemingly effortlessly, is to know when such a more complete combinatorial parse is necessary and when a semantic memory-based analysis is insufficient. This allows us to come up interpretations quickly, but still accurately: the semantic memory-based analysis is relatively fast, ensuring that we make maximal use of what we have encountered before, but the combinatorial stream proceeds more slowly, ensuring that, if the input is novel, we are still able to interpret it accurately (G.R. Kuperberg, 2007; Sitnikova et al., this issue).

In schizophrenia, one way the combination of 'loosening of associations' and non-goal-directed illogical thinking has been explained is through dual neurocognitive abnormalities: a disturbance within semantic memory and an additional disturbance in the construction and use of linguistic and extralinguistic 'context'. Given the increasing evidence for a continuous interaction between semantic memory-based processes and combinatorial processes during the construction of higher-order meaning in healthy individuals, we will argue that this categorical distinction between semantic memory abnormalities and deficits of higher-order context is somewhat artificial. Rather, we will suggest that at least some of the sentence-level language abnormalities characteristic of schizophrenia may arise from an *imbalance* in semantic memory-based and combinatorial processing streams, with a relative over-reliance on semantic associative activity at the expense of utilizing a combinatory, integrative stream of analysis (see G.R. Kuperberg, in press-b for further discussion).

ERPs provide an ideal way to examine interactions between semantic memory-based and combinatorial processes. As discussed above, the N400 is highly sensitive to the structure of semantic memory and therefore to semantic memory-based processing (Bentin et al., 1985; Rugg, 1985). In addition, it has long been recognized that the N400 is also sensitive to the congruity of sentence context: an increased N400 amplitude is evoked by words that are semantically incongruous or unexpected, relative to words that are congruous with respect to their preceding sentence context (M. Kutas & Hillyard, 1980, 1984). Moreover, even within sentences, the amplitude of the N400 is attenuated by semantic associations between the component individual words (Van Petten, 1993) and by the categorical relationships between expected and encountered words (Federmeier and Kutas, 1999).

Like the ERP semantic priming literature, ERP findings at the sentence level in schizophrenia are mixed. Many studies have demonstrated a normal N400 effect in schizophrenia (Andrews et al., 1993; Kuperberg et al., 2006b; Nestor et al., 1997; Niznikiewicz et al., 1997; Ruchsow et al., 2003). Others, however, report that it can be abnormally reduced (Adams et al., 1993; Mitchell et al., 1991; Ohta et al., 1999). Indeed, Sitnikova et al. (2002) described both a normal N400 effect and a reduced N400 effect in the same patients, at different points within the same sentences. Others have demonstrated a normal N400 effect but a reduced late positivity or P600 effect in patients relative to controls (Andrews et al., 1993; Ruchsow et al., 2003; Kuperberg et al., 2006b). Below we discuss four factors that may explain some of the variability in these findings. We will suggest that during sentence processing in both healthy individuals and schizophrenia patients, the modulation of ERPs is often driven by semantic memory-based processes, but that, in healthy individuals, they are also driven by combinatory processes that integrate syntactic, thematic and lexico-semantic information together (for discussion of the normal language processing system, see Osterhout et al., 2008 and Kuperberg, 2007). In patients, semantic memory-based processing usually appears to be intact during sentence comprehension. However, unlike healthy individuals, patients show reduced ERP effects in situations where combinatory and integrative demands are particularly high.

3.1. The position of a critical word in a sentence

Integration demands are usually maximal on the final word within a clause or a sentence. This is because, over and above the incremental word-by-word build-up of meaning, there are additional 'wrap-up' requirements to integrate all semantic and syntactic information together and evaluate the entire propositional meaning as a whole (Friedman et al., 1975). Interestingly, in many of the studies reporting a reduced N400 effect in schizophrenia patients relative to controls, the semantic anomaly fell on the final word of the sentence (Adams et al., 1993; Mitchell et al., 1991; Ohta et al., 1999). One reason for this may be because patients are particularly impaired in their ability to combine multiple sources of information together. Future studies should test the hypothesis that, in patients, the N400 effect to incongruous, relative to congruous, words is smaller when such incongruities occur at the sentence-final position than when they occur earlier in a sentence.

3.2. Semantic ambiguity

A second situation in which it becomes particularly important to combine lexico-semantic with syntactic information is when the resulting representation of context must be used to constrain the interpretation of a word that is stored with more than one meaning: a homonym. There have been a few ERP studies examining how homonyms are processed as language is built up online in schizophrenia. For example, Salisbury et al. (2000, 2002) showed that in sentences such as "The toast was sincere", a larger N400 amplitude was observed to "sincere" in patients relative to controls, suggesting that patients interpreted "sincere" as anomalous, having failed to correctly integrate its meaning with the subordinate meaning of its preceding contextual homonym, "toast".

Sitnikova et al. (2002) took this a step further by demonstrating that a failure of context to override the dominant meaning of a homonym was evident, even when the entire preceding context was consistent with its subordinate meaning. In this study, sentences were constructed in which the first clause biased towards either the dominant meaning (e.g., "Diving was forbidden from the bridge…") or

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the subordinate meaning (e.g., "The guests played bridge…") of a homonym ("bridge"), and the second clause contained a critical word that was always semantically associated with the dominant meaning of the homonym (e.g., "…because the river had rocks in it"). Healthy adults produced an N400 effect to the contextually-inappropriate words (e.g. to "river" when the initial context was "the guests played bridge"), suggesting that they had combined the meanings of individual words to come up with a propositional interpretation of the preceding clause. Schizophrenia patients, however, showed an attenuated N400 effect suggesting that they were inappropriately influenced by the dominant meaning of the homonym, "bridge," that semantically primed "river" see Fig. 2, right. Critically, the same patients in this study showed a normal N400 effect to unambiguously contextually incongruous words that, in half the sentences, were introduced towards the end of the second clause (e.g. to the words, "cracks" in "…because the river had cracks in it."), see Fig. 2, left. Similarly, Titone et al. (2000) provided behavioral evidence that, unlike healthy adults, patients failed to inhibit the dominant meaning of a homonym in sentence contexts that were moderately biased toward the subordinate meaning. Interestingly however, the use of a stronger context resulted in the suppression of the inappropriate dominant meaning of the homonym in patients as well as healthy adults, providing encouraging evidence that at least some language comprehension impairments may be mitigated by increasing sentential constraint.

3.3. Combining word meaning with syntactic and thematic structure: the late positivity/P600

Direct evidence that patients show difficulty in combining the meaning of words with syntactic or thematic structure to determine 'who does what to whom' in a sentence, comes from examining another later ERP waveform of opposite polarity to the N400 and that peaks later than the N400 at around 600 ms after stimulus onset—a late positive component or P600 (Hagoort et al., 1993; Osterhout and Holcomb, 1992). The P600 was originally taken to index syntactic integration and/or reanalysis (Hagoort et al., 1993; Osterhout and Holcomb, 1992), although there has been debate as to whether the processes it reflects are common to those indexed by the P300 family of components (see Coulson et al., 1998; Osterhout and Hagoort,

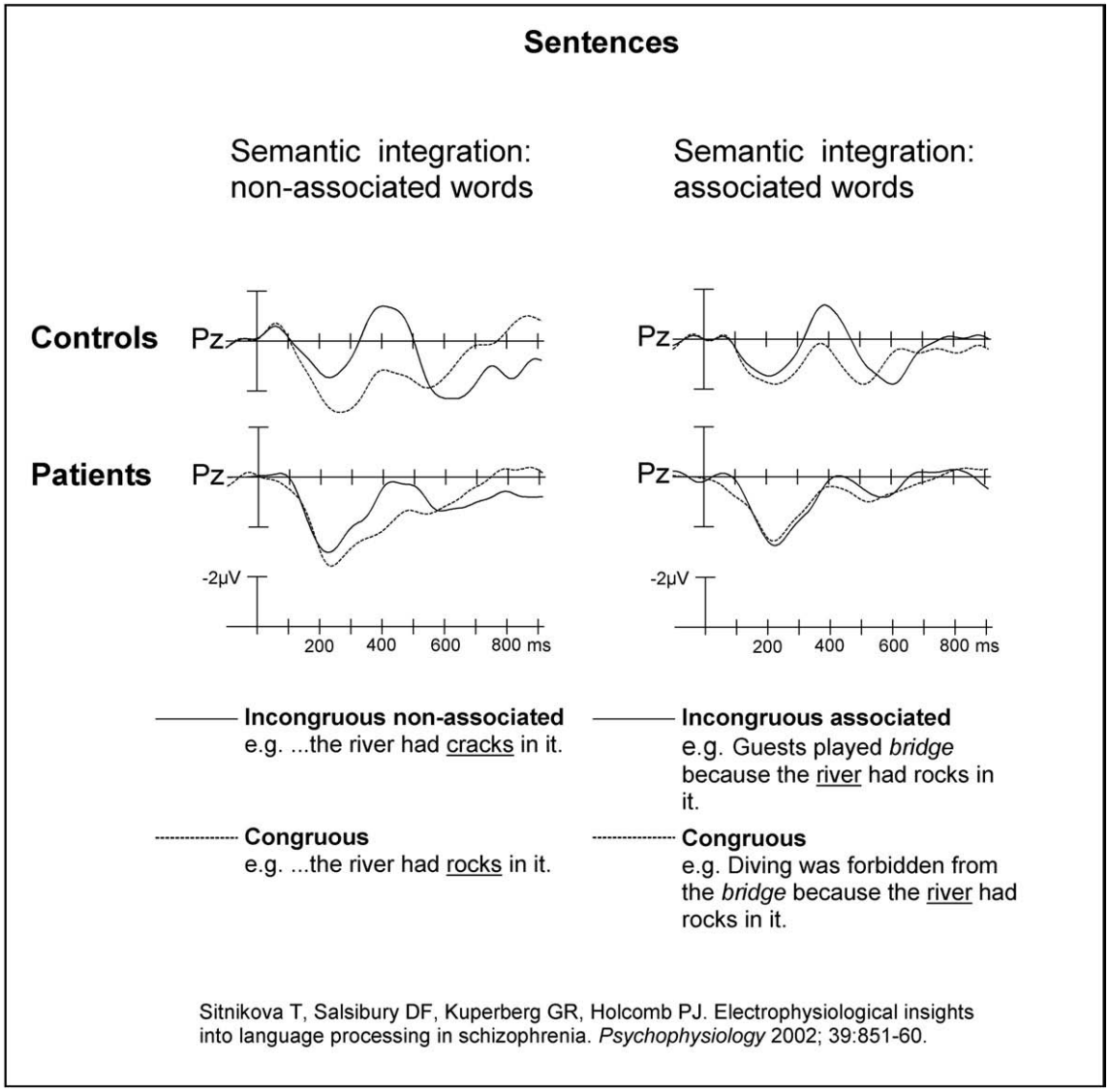

Fig. 2. *Left:* Schizophrenia patients, like healthy controls, showed an increase in the N400 amplitude to critical words (underlined in the examples) that were incongruous and non-associated (versus congruous) with their preceding sentence context. *Right:* Schizophrenia patients, unlike healthy controls, failed to show an increase in the N400 amplitude to critical words (underlined in the examples) that were incongruous (versus congruous) with their preceding sentence context, when these words were semantically associated with the dominant meaning of a preceding homonym. The plots indicate one central parietal electrode site (Pz) where the N400 effect is maximal.

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1999). There is now evidence that the P600 is also sensitive to certain semantic factors and can be evoked by certain types of verb argument violations (reviewed by G.R. Kuperberg, 2007, and see Sitnikova et al., this issue). Most generally, it is thought to reflect a continued or second-pass attempt to make sense of a sentence, that can be triggered by syntactic, semantic verb-argument violations or other types of structural violations or ambiguities (G.R. Kuperberg, 2007).

In schizophrenia, syntactic violations evoke an abnormally reduced P600 effect, suggesting that patients fail to incur such later processing costs when demands for integrating individual word meaning with syntactic structure are increased (Kuperberg et al., 2006b; Ruchsow et al., 2003). In addition, Kuperberg et al. (2006b) demonstrated that, unlike healthy controls, schizophrenia patients failed to produce any ERP effects at all when the semantic relationship between a verb and its argument was violated, but the verb and argument were semantically associated, e.g. "Every morning at breakfast the eggs would eat…". In healthy individuals, the semantic relationship between "eggs" and "eat" leads to an attenuation of the N400 effect (termed a temporary semantic illusion), but there is a later cost in semantic–thematic integration, reflected by the P600 effect, as readers determine that it is the eggs that are doing the eating, rather than the eggs that are being eaten (reviewed by Kuperberg, 2007). The absence of any P600 effect in patients suggests that the processing of these sentences was dominated purely by the semantic associations between "breakfast", "eggs" and "eat", at the expense of combining word meaning with syntactic structure. This interpretation was supported by patients' erroneous final interpretations of these sentences (Kuperberg et al., 2006b) as well as by the pattern of findings in a behavioral self-paced reading study using similar stimuli (Kuperberg et al., 2006a).

3.4. Summary

Taken together, these findings suggest that, during sentence processing, patients are able to build up some context by matching incoming content words and their associations with information stored within semantic memory (semantic memory-based processing). However, unlike controls, they fail to override this semantic memory-based analysis during online sentence processing when demands for a deeper combinatorial and integrative analysis are increased. The balance between semantic memory-based and combinatorial, integrative processing appears to be disturbed in schizophrenia.

4. Discourse

Language comprehension and production go well beyond computing the meaning of individual sentences. They require the integration of ideas across multiple clauses through the establishment of coherence. For example, to causally link the statements "Annalise was going to a birthday party. She went to the store in the morning.", one must deduce that Annalise went to the store in order to buy a present for the party. In addition, multiple references must be linked to the same entity to establish referential cohesion. First mentions of the entity are referred to as antecedents and subsequent mentions are termed anaphors. For example, in the above example, one must link "She" (the anaphor) with "Annalise" (the antecedent).

In schizophrenia, failures to establish logical coherence (clinically referred to as tangentiality and derailment) (Andreasen, 1979b; Earle-Boyer et al., 1986; Mazumdar et al., 1995) as well as referential coherence (Docherty et al., 1996; Rochester and Martin, 1979), during communication are amongst the most common clinical phenomena described. Despite these observations, there has been surprisingly little ERP work examining how schizophrenia patients build up meaning over more than one sentence (for an overview, see Ditman and Kuperberg, in press). One reason for this is that the use of ERP components to study discourse-level processes even in healthy individuals is relatively recent. van Berkum et al. (1999b) were amongst the first to demonstrate that critical words within sentences that were internally congruous, but incongruous with their entire discourse contexts, evoked an N400 effect, illustrating that this waveform is sensitive to discourse-level integrative processes. Just as within sentences, however, semantic memory-based processes are also thought to play an important role during the normal build up of discourse coherence. For example, in an important study, Federmeier and Kutas (1999) showed that the amplitude of the N400 varied according to the degree of semantic feature overlap between unexpected and expected words within two-sentence discourse scenarios. Similarly, Ditman et al. (2007) showed that discourse context and lexico-semantic relationships also interact as comprehenders establish referential coherence across more than one sentence.

In order to determine whether schizophrenia patients are able to establish causal coherence during online neural processing, Ditman and Kuperberg (2007) asked patients and healthy controls to read three-sentence scenarios in which the final sentences were highly related to their preceding contexts, e.g. "John and Jack had an argument. Jack hit John. The next day John had bruises." These were compared with scenarios where the final sentences were intermediately related to their contexts, e.g. "John and Jack had an argument. Jack got very angry. The next day John had bruises.": here, participants needed to generate a bridging inference (Jack hit John) to establish coherence. These two types of scenarios were matched in terms of their semantic relationships between their individual component words. Whereas healthy controls attenuated the amplitude of the N400 to the highly related relative to intermediately related critical words ("bruises"), patients failed to show such an N400 effect. Patients also failed to show an N400 effect to completely unrelated, relative to the highly related, scenarios, e.g. "John and Jack had an argument. Jack got very angry. The next day John ate breakfast.", suggesting that they were unable to use lexico-semantic relationships across sentence boundaries, see Fig. 3, right. Interestingly, patients showed the same pattern of behavioral findings across conditions as controls, suggesting that, at a later stage of processing, they were able to compensate for their impairments during immediate online neural processing (Ditman and Kuperberg, 2007).

Encouragingly, in a recent study, Ditman & Kuperberg (2008) showed that schizophrenia patients were able to establish referential links across sentences, at least under highly constrained conditions when participants were given explicit information about the real world. Patients and controls were presented with 5-sentence scenarios, beginning with such real-world information, such as *"Champagne is served at a New Year's party. Beer is served at a ballpark. Cake is served at a birthday party."*, and ending with statements like *"At the New Year's party, Bill took a sip of the alcohol. The champagne/beer/cake was good."* ERPs were examined to the critical word in the final sentence, which was contextually-appropriate and lexico-semantically related *("champagne")*, contextually-inappropriate but lexico-semantically related *("beer")*, or contextually-inappropriate and unrelated *("cake")* to the anaphor in the preceding sentence *("alcohol")*. Results demonstrated that unrelated words ("cake") evoked a larger N400 amplitude relative to words that were contextually-appropriate and related ("champagne") in both patients and controls, see Fig. 3, left. However, although neural modulation in controls also differed between the two lexico-semantically related conditions ("champagne" and "beer"), patients only did so early in the N400 time window. This suggests that when the context is highly constrained and real-world information is explicitly provided, patients are able to integrate meaning across sentences initially. However, later comprehension is influenced by lexico-semantic associations.

5. Relationship between ERP abnormalities, specific symptoms and cognitive deficits of schizophrenia

We began this review by referring to the loosening of associations that characterizes the symptom of positive thought disorder in

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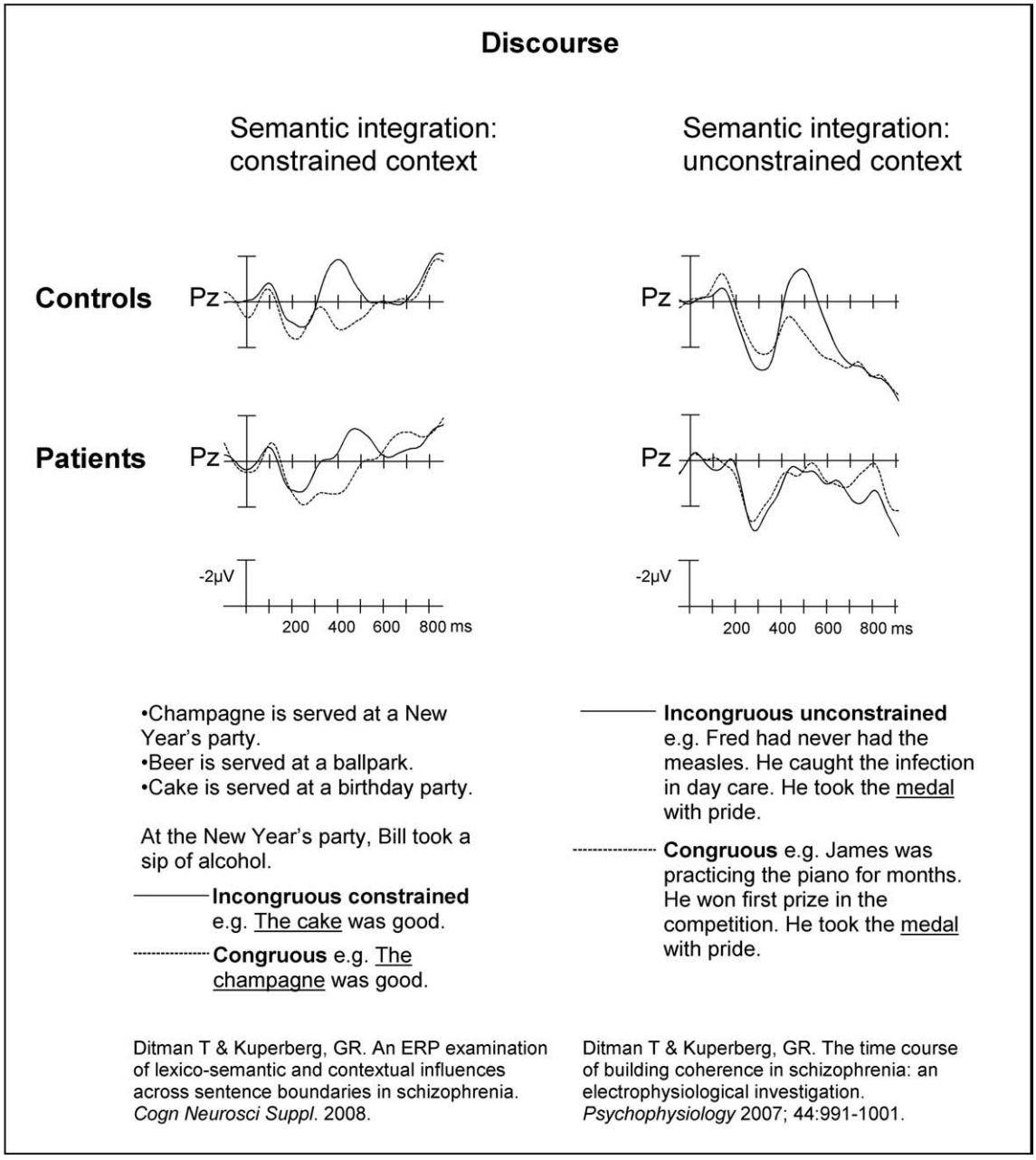

Fig. 3. *Left:* When real-world knowledge was explicitly provided in the context, schizophrenia patients, like healthy controls, showed an attenuation of the N400 amplitude to critical words (underlined in the examples) that were congruous (versus incongruous) with their entire discourse context. *Right:* When the context was unconstrained, schizophrenia patients, unlike healthy controls, failed to attenuate the N400 to critical words (underlined in the examples) that were congruous (versus incongruous) with their entire discourse context. The plots indicate one central parietal electrode site (Pz) where the N400 effect is maximal.

schizophrenia. Indeed, most of the studies we have discussed have looked to the disorganized speech produced by some patients as providing some face validity with the electrophysiological language abnormalities described. The question therefore arises whether these language-related electrophysiological abnormalities are specific to the symptom of thought disorder, or whether they characterize the schizophrenia syndrome as a whole. The answer appears to be somewhere in between these two accounts. As discussed in Section 2, increases in automatic semantic associative activity appear to be most marked in positively thought-disordered patients (Spitzer et al., 1994). Similarly, at the sentence and discourse levels, some of the electrophysiological abnormalities described seem to be more marked in patients with the most severe thought disorder. For example, Kuperberg et al. (2006b) reported that, in addition to the absent P600 effect that was seen in the patient group as a whole, patients with the most severe thought disorder showed the smallest N400 effects to semantically anomalous critical words within sentences. In addition, Ditman and Kuperberg (2007) demonstrated that patients' failure to differentiate between highly related, intermediately related and unrelated discourse scenarios during the N400 time window was specifically correlated with positive thought disorder. These findings suggest that some of the abnormalities described here may be more extreme in positively thought-disordered patients, and that positive thought disorder may manifest clinically when there is a complete breakdown in the effective use of linguistic context (see Kuperberg et al., 1998, 2000 for consistent behavioral findings). However, it is also important to note that, in most of the sentence and discourse-level ERP studies described in this review, abnormalities were not limited to the positively thought-disordered patients. This suggests that the ERP findings discussed might also give insights into the

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mechanisms of thinking that characterize other symptoms of schizophrenia, such as delusions or negative symptoms.

There is indeed some preliminary evidence for links between language-related electrophysiological abnormalities and symptoms other than positive thought disorder. For example, Debruille et al. (2007) reported that patients with severe delusions showed smaller N400 effects to target words that they correctly labeled as discrepant with their preceding categorical context, than patients with less severe delusions, arguing that this failure to neurally integrate novel information might play a causal role in the persistence of delusional belief. Kiang et al. (2007) reported that patients with more severe delusions and hallucinations showed reduced N400 effects to targets that were high, relative to low, typicality exemplars of a preceding description of a category. They speculated that such semantic abnormalities might contribute to the experience of some patients that environmental stimuli, which are only weakly related to their context, are unusually meaningful, leading to delusional beliefs. Finally, Condray et al. reported a positive correlation between the N400 effect at a short SOA and measures of paranoia in unmedicated patients (Condray et al., 2008). The challenge for future studies will be to determine whether different symptoms can be linked specifically with distinct abnormalities in the integration of different types of meaningful information. For example, as discussed earlier, thought disorder may arise from an over-reliance on semantic memory-based associative information. However, delusions—beliefs that are incongruent with real-world knowledge despite all evidence to the contrary—may be more specifically associated with impairments in the integration of knowledge about the real world, particularly when such information is emotionally salient.

Another example of how ERPs have begun to be used to explore thought processes in schizophrenia, other than 'loosening of (language) associations', comes from studies that have explored the neural correlates of processing non-literal language. Thus far, the two ERP studies that have addressed this question have yielded contradictory findings. On the one hand, Iakimova et al. (2005) failed to demonstrate any electrophysiological differences between patients and healthy controls during the online processing of metaphorical sentences (relative to literal plausible and incongruous sentences). In contrast, an earlier study by Strandburg et al. (1997) examining ERPs to word-pairs with idiomatic (pot luck), literal (vicious dog), and nonsensical (square wind) meanings reported selectively larger N400 amplitudes to the second word of the idiomatic, relative to the literal, word-pairs, suggesting specific difficulties in accessing the figurative meaning of the idioms (for consistent behavioural findings, see Titone et al., 2002). It is possible that the discrepancy between these studies arises from different symptom profiles within the patient groups. For example, clinically, deficits in abstract thinking have traditionally been associated with negative symptoms (for example, they are part of the negative subscale of the PANSS, Kay et al., 1987), and behavioral studies also suggest that deficits in metaphor comprehension are associated with negative symptoms (Langdon and Coltheart, 2004).

In addition to exploring relationships between language-related ERPs and different clinical phenomena within the schizophrenia syndrome, future studies should also explore relationships between these neurophysiological abnormalities and cognitive deficits outside the linguistic domain such as working memory dysfunction. Individual variation in working memory in healthy populations is known to explain some behavioral variability in language function at both the sentence (Caplan and Waters, 1999; Just and Carpenter, 1992) and discourse levels (Singer and Ritchot, 1996). Such individual variation in working memory capacity can also influence the precise patterns of electrophysiological modulation during sentence processing (Nakano et al., in press; Van Petten et al., 1997). Indeed, the normal balance between semantic memory-based and combinatorial processing mechanisms may, in part, be modulated by working memory and executive control processes (Kolk and Chwilla, 2007; Kuperberg, 2007). This raises the interesting possibility that the abnormal balance between the semantic memory-based and combinatory processing streams discussed in this review as leading to language dysfunction in schizophrenia might be mediated by abnormalities of executive and working memory dysfunction.

Evidence that an impairment in working memory can directly influence language dysfunction in schizophrenia might also come from examining an ERP component that is thought to more directly reflect the engagement of working memory processes during language comprehension—the left anterior negativity (LAN) (King and Kutas, 1995). One situation in which a LAN (or a non-lateralized anterior negativity) is observed is when comprehenders attempt to link an anaphor with its preceding referent; thus, a larger LAN is seen to nouns preceded by definite (versus indefinite) articles (Anderson and Holcomb, 2005) as well as to anaphors without (versus with) unique referents (van Berkum et al., 1999a). The increased LAN has been interpreted as reflecting the working memory cost associated with attempts to locate the correct referent of that anaphor.

As discussed above, when the context is highly constrained and explicitly provided, schizophrenia patients do appear to be able to link an anaphor with its referent and establish coherence at least during the earliest stages of processing (Ditman and Kuperberg, 2008). Nonetheless, given the robust evidence that schizophrenia patients, even those without thought disorder, fail to construct cohesive reference links during language production (Docherty et al., 1996; Rochester and Martin, 1979), patients might not fare so well when the referent is ambiguous (e.g. "Jack and Bill went to the store. He bought some apples…"). Future studies will determine whether schizophrenia patients show a selective decrease in the LAN in such situations.

6. Caveats in the interpretation of ERP studies

ERPs can reveal important information about the mechanism of online language comprehension in schizophrenia. Like all techniques, however, they have their limits in what information they can yield, and there are important caveats in their interpretation. Two of these caveats are briefly discussed here.

The first concerns the interpretation of the amplitude of a particular ERP component evoked by a particular condition with respect to baseline (often a prestimulus baseline) but without reference to the response evoked by another condition. There are several studies that have taken this approach to compare ERPs across schizophrenia and healthy populations; thus, rather than comparing the N400 effect (the *relative* modulation of the N400 to incongruous relative to congruous items) across patients and controls, they have directly compared the absolute amplitude of the N400 elicited by congruous or incongruous words between patients and controls. For example, Mathalon et al. (2002) reported that, under automatic experimental conditions, the N400 to words preceded by semantically unrelated pictures was smaller (less negative) in patients than controls. This was interpreted as reflecting easier automatic semantic processing of unrelated words in patients than controls. Under experimental conditions that biased towards more controlled processing (longer SOAs), Bobes et al. (1996) reported that the N400 to words preceded by semantically related pictures was greater (more negative) in patients than controls. This was interpreted as suggesting that the effort required to integrate words into a semantically related context was greater in patients than controls. Other semantic priming studies, however, have failed to find significant effects in such direct group comparisons (Condray et al., 1999, 2003).

At the sentence level, a more negative N400 amplitude to congruous words (Mitchell et al., 1991; Nestor et al., 1997; Niznikiewicz et al., 1997; Ohta et al., 1999) and, in some studies also to incongruous words (Nestor et al., 1997; Niznikiewicz et al., 1997) in patients relative to controls, has been interpreted as reflecting increased difficulty in semantically integrating words, sometimes regardless of whether the context is congruous or incongruous. Again, however, other studies have failed to find differences in the absolute amplitude of the N400 to

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either condition alone between patients and controls (e.g. Ruchsow et al., 2003; Kuperberg et al., 2006b).

Although this approach of comparing the amplitude of an ERP evoked in one condition between patients and controls can be informative, it is not without its drawbacks. This is because of the problems of overlapping ERP components on the scalp surface. The more classical way of considering ERP "effects" (the modulation of an ERP component evoked by one condition relative to another condition), rather than the amplitude of a component to one condition regardless of another condition, has important theoretical underpinnings: it makes the assumption of pure insertion in an attempt to isolate the cognitive process of interest (Coles and Rugg, 1995; Donders, 1868/1969). This theoretical assumption is particularly important when interpreting the relative modulation of the N400 ERP component in patients relative to controls, as the N400 can often overlap in time with other ERP components that may be sensitive to different neurocognitive processes and that may also differ between patients and controls. Consider, for argument's sake, a situation in which the N400 is followed by a late positivity that may not be sensitive to semantic association. This late positivity may overlap in time with the N400 and act to 'decrease' the amplitude of the N400 detected at the scalp surface such that it is rendered less negative (more positive) in healthy individuals. In schizophrenia, as discussed earlier, the late positivity may be less positive than in healthy controls. Therefore, if one were to compare the N400 across patients and controls, its absolute amplitude would appear to be more negative (less positive) in patients than controls in both congruous and incongruous conditions. It would not necessarily be justified to conclude that patients have more difficulty in *semantic* associative processing than controls. By thinking about differences in N400 effects between patients and controls, reflected by Group by Condition interactions, the assumption is that non-semantic effects (with the exception of noise) subtract out.

A second important consideration in the interpretation of ERP data is their poor spatial resolution. It is often tempting to think of differences in distribution (such as laterality) between patients and controls as reflecting true differences in underlying neural sources, given that ERPs are a direct index of neural activity. However, even with a large number of electrodes, it is difficult to estimate the source of underlying neural activity. This is due, in part, to a "blurring" effect of the scalp and skull (Nunez, 1990), but, even more problematic is that the attempt to estimate underlying neural generators on the basis of the distribution of scalp-recorded ERPs—the inverse problem—is mathematically ill-posed: there is no unique solution (Hamalainen et al., 1993; Nunez, 1990). This is particularly problematic when there are multiple underlying sources as is likely for the N400 component. One way around this is to examine ERP data in combination with complementary techniques with better spatial resolution, such as fMRI. There has certainly been some progress in qualitatively comparing these two techniques using similar paradigms (e.g. see Kuperberg, 2008, for an overview of some of our own work in schizophrenia), as well as in combining them more quantitatively (Dale and Halgren, 2001). However, it is important to realize that these two techniques index neural activity at very different time scales; because the fMRI signal integrates neural activity over seconds, it reflects activity that is not necessarily reflected by ERPs, and this can lead to differences in the patterns of modulation seen using the two techniques. For example, while ERP studies of controlled semantic priming tend to reveal smaller N400 effects in patients than in controls, a recent fMRI study demonstrated a reversed hemodynamic priming effect in patients, with more activity to semantically associated than to non-associated words within temporal and inferior frontal cortices, possibly reflecting a prolongation of neural activity to semantic associations that was not detected with ERPs (G. Kuperberg et al., 2007).

7. Conclusion

During normal language processing we constantly compute semantic relationships between individual words and compare this information with the relationships that are stored within semantic memory. This semantic memory-based stream of analysis is likely to proceed partially in parallel with algorithmic, combinatorial, integrative streams of processing in which lexico-semantic information is integrated combinatorially with syntactic and thematic structure to come up with propositional representations of meaning (Kuperberg, 2007). We have suggested that, in schizophrenia, the balance in operation of these streams is altered such that, at least at the speeds at which normal language comprehension proceeds, patients are overly dependent on the semantic memory-based stream at the expense of combinatorial mechanisms that build up propositions within clauses and coherence between clauses. This means that, although, for the most part, schizophrenia patients understand language normally, they encounter problems when there are increased demands on integrating all incoming information, such that the end of clauses or sentences, upon encountering ambiguity, and when the initial outputs of these streams contradict one another. Moreover, we have suggested that a reliance on a semantic memory-based mechanism of comprehension is inadequate for integrating material over more than one sentence, possibly because of the longer time lags between words at sentence boundaries.

As discussed by Sitnikova et al. (this issue), this model also has implications for understanding deficits in real-world comprehension and goal-directed action outside the language system in schizophrenia. More generally, we propose that exploring higher-order language and semantic dysfunction in schizophrenia within a framework of normal language and semantic processing, will not only give insights into positive thought disorder, but may also, as Bleuler hoped, provide a window into the neurocognitive mechanisms of all aspects of psychotic thought and real-world behavior.

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