The Neuropsychology of Mental Illness

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Chapter

6 Behavioral and electrophysiological approaches to understanding language dysfunction in neuropsychiatric disorders: insights from the study of schizophrenia

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Introduction

Language disturbances are characteristic of several neuropsychiatric disorders including schizophrenia, mania, Alzheimer's disease (and other dementias) and developmental disorders such as the autistic spectrum disorders. Yet it is only over the last 25 years that researchers have begun to study the language system in neuropsychiatric disorders from cognitive, psycholinguistic and neurophysiological perspectives. This chapter aims to review a selection of such studies to illustrate this progress, focusing primarily on schizophrenia. We begin with a summary of how clinical language disturbances in adult psychiatric disorders have traditionally been viewed. We then review selected studies at three basic levels of the language code – words (focusing on conceptual relationships within semantic memory), sentences (focusing on how words are combined to build up linguistic context and propositional meaning), and discourse (focusing on the generation of coherence links across more than one sentence). We then examine the relationship between abnormalities at each of these levels of language with cognitive dysfunction in more general domains, such as attention and working memory.

The functional neuroimaging literature examining the neuroanatomical basis of language abnormalities in neuropsychiatric disorders has generally lagged behind the cognitive behavioral and electrophysiological literatures (but see Kuperberg, 2009, for an overview of potential links between cognitive, electrophysiological and fMRI studies of language in schizophrenia). Although the focus of this chapter is on studies using behavioral and electrophysiological methods, we conclude by discussing how a deeper understanding of the cognitive basis of language abnormalities might inform the design and interpretation of neuroanatomical and neuropharmacological studies, and how such a multifaceted approach might give new information about the underlying neuropathology of schizophrenia and other neuropsychiatric disorders.

Clinical language disturbances in psychosis: thought disorder and beyond

Clinically, the most obvious manifestation of language disturbances in adult psychiatric disorders is the disorganized unintelligible speech produced by patients during psychosis. This has traditionally been termed "thought disorder," reflecting the original perspective of psychopathologists who considered it an underlying disorder of thinking rather than a primary disturbance of language (Bleuler, 1911/1950; Kraepelin, 1971). Today, however, the term "thought disorder" is used purely descriptively without any assumptions about the complex relationship between thought and language (DSM–IV; American Psychiatric Association, 1990). Thought disorder occurs in mania as well as schizophrenia, but its most detailed characterization has been in schizophrenia. Building upon the detailed phenomenological descriptions of Schneider (1930) and others, clinical assessments of thought disorder such as the Thought, Language and Communication (TLC) scale (Andreasen, 1979a, 1979b), emphasize the "form" rather than the content

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of thought/speech, i.e. the way words and sentences are strung together. They include phenomena ranging from tangentiality (the shift in speech from one topic to another without obvious links between them), through neologisms (the use of non-words), as well as poverty of speech. Studies in the late 1970s and early 1980s established that some of these phenomena (including tangentiality, derailment, and incoherent speech) tended to occur more often in patients with positive than negative symptoms (Andreasen, 1979a, 1979b; Harvey *et al.*, 1984; Oltmanns *et al.*, 1985). These phenomena constitute "positive thought disorder." In contrast, phenomena such as "poverty of speech" co-occurred primarily with negative symptoms and were termed "negative thought disorder." Subsequent factor-analytic studies showed that positive thought disorder occurred more frequently with disorganized, non-goal directed behavior as opposed to hallucinations and delusions (Liddle, 1987, 1992; Andreasen *et al.*, 1995). In DSM–IV (1990) positive thought disorder and disorganized behavior are now grouped together as constituting the "disorganization" subsyndrome of schizophrenia.

Original attempts to explain the various phenomena constituting positive thought disorder proposed concepts such as "loosening of association" (Bleuler, 1911/1950), "overinclusive thinking" (a tendency of patients to use concepts beyond their usual boundaries; Cameron, 1939, 1964), and concrete thinking (an inability to think abstractly; Goldstein, 1944). Some of these concepts, particularly Bleuler's "loosening of associations," were intended not only to describe the origins of positive thought disorder (disorganized speech output) itself, but to help explain the underlying cognitive basis of schizophrenia as a whole. In keeping with this idea, although many of the studies reviewed in the current chapter were originally inspired by the disorganized language output produced by some patients, it has become increasingly apparent that language abnormalities in schizophrenia are not confined to patients with positive thought disorder (although they are often more prominent in such patients), or to the language production system. Patients, with and without clinical evidence of thought disorder, can show clear abnormalities in language comprehension. Clinically, these abnormalities are usually subtler than the abnormalities evident in thought-disordered speech, but their study can yield valuable insights into fast, online word-by-word processing mechanisms that may also be impaired during speech production. Moreover, the study of such mechanisms may also give insights into other symptoms of schizophrenia.

These observations, together with the identification of language disturbances in children at risk for schizophrenia (Cannon *et al.*, 2002; Fuller *et al.*, 2002; Ott *et al.*, 2001), as well as in patients in their first episode of psychosis (Fuller *et al.*, 2002; Hoff *et al.* 1999), suggest that a systematic study of the language system may give new insights into the neuropathogenesis of schizophrenia as a whole.

Single words and concepts: semantic memory structure and function

Most studies at the level of single words in neuropsychiatric disorders have examined how words are stored and accessed within semantic memory – an approach inspired by the observation that the speech of some psychotic patients is characterized by strings of word associations (Chaika, 1974). This section reviews studies adopting this perspective: we consider studies that have examined how patients with schizophrenia identify and name concepts, as well as investigations that have used both explicit and implicit measures to explore how such concepts are linked together through perceptual attributes, hierarchical relationships and semantic associations.

Semantic identification and naming

The identification and distinction of objects in the visual world is dependent on a hierarchical ventral visual pathway (Ungerleider & Haxby, 1994) that runs from primary visual cortex (V1) to extrastriate visual areas (V2 and V4) to the inferotemporal cortex, and is a major source of input to the prefrontal cortex. Some of the observed impairments in conceptual classification and identification in schizophrenia, discussed below, may arise because of deficits in visual perception rather than in cognitive semantic function. Although it has often been assumed that the ventral visual pathway is intact in schizophrenia, there has been surprisingly little research to back up this assumption. In one of the few paradigms to explicitly examine basic object identification in schizophrenia, Elvevaag *et al.* (2002b) asked patients to watch pictures of objects (e.g. a pear) morph into other objects (e.g. a lightbulb) and to indicate the frame in the

morphing sequence at which the first object was no longer identifiable. Performances of patients and controls were nearly identical, suggesting that basic object perception was intact.

In humans, basic object identification is linked to the language system through our ability to name objects. Naming involves the activation and retrieval of lexical representations of both meaning and phonological form. Anomia, a word-finding impairment, is characteristic of several types of aphasic syndromes as well as other neurological disorders characterized by a loss of lexico-semantic knowledge such as Alzheimer's disease. Given the hypothesis that schizophrenia is associated with abnormalities in semantic processing, it has been of particular interest to determine how well patients with schizophrenia perform on naming tasks. Early studies suggested that patients with schizophrenia performed worse than controls on simple naming tasks (Faber & Reichstein, 1981), and in some cases as poorly as patients with fluent aphasia (Landre *et al.*, 1992) or Alzheimer's disease (Davidson *et al.*, 1996). Unlike Alzheimer's patients, however, schizophrenia patients improved their performance when given appropriate semantic cues (Laws *et al.*, 1998; Maas & Katz, 1992; McKenna *et al.*, 1994), suggesting that any deficit lay in the access and use of lexical knowledge rather than the loss of this knowledge. A more recent study of object naming by Denke & Goldberg (unpublished data) demonstrated that schizophrenia patients performed as well as healthy controls and significantly better than patients with mild Alzheimer's disease; there was no association between naming deficits and severity of positive thought disorder within the schizophrenia group – a finding that is consistent with previous observations (Aloia *et al.*, 1998; Goldberg *et al.*, 2000).

Explicit knowledge and use of semantic category

Concepts are not represented in isolation of one another, but are thought to be organized hierarchically according to domains and categories of knowledge within semantic memory. It is therefore important to examine whether schizophrenia patients' disordered use of concepts results from their abnormal organization within semantic memory. This issue has been investigated using both semantic production and categorization tasks.

Explicit production: semantic fluency

In semantic fluency tasks, participants are required to generate as many exemplars as possible from a given category (e.g. animals) in a defined time period (often one minute), with the assumption that abnormalities in the number and types of items produced will reveal abnormalities in the storage and retrieval of categorical semantic information. Patients with schizophrenia show mild-to-moderate difficulties on this test, producing fewer items per category than control participants. This impairment appears to be at least somewhat specific to producing semantic categorical information; several studies have demonstrated that patients are relatively less impaired on letter fluency tasks in which the requirement is to produce words beginning with a particular letter (Feinstein *et al.*, 1998; Goldberg *et al.*, 1998; Gourovitch *et al.*, 1996). A recent meta-analysis of studies directly comparing category and letter fluency, and controlling for factors like motivation, cooperation, symptomatology and IQ, confirmed a selective deficit on category fluency (Bokat & Goldberg, 2003). Kremen *et al.* (2003) came to a similar conclusion based upon a large well-controlled study that compared the performance of schizophrenia patients, bipolar patients and healthy controls.

The relationship between categorical fluency and thought disorder in schizophrenia is still unclear, however. While Aloia *et al.* (1996) found that the difference score between letter and semantic fluency performance accounted for a significant portion of thought disorder variability, later studies have not replicated this finding (Bokat & Goldberg, 2003).

Several approaches have been developed to examine the pattern of responses produced on semantic categorical fluency tasks. Allen & Frith (1983) and Allen *et al.* (1993) developed a methodology in which semantic fluency tests were repeatedly administered and the number of novel exemplars generated in each session tallied. They demonstrated that, given enough time, patients do eventually produce the same total number of category exemplars as controls. Elvevaag *et al.* (2002a) replicated this finding and went on to demonstrate that patients showed no category-specific deficits. These findings were interpreted as suggesting that there is no overall loss of semantic knowledge in schizophrenia patients: the impairment is in retrieving this knowledge in response to specific task demands.

Others have used multidimensional scaling, pathfinder and clustering techniques to examine

relationships between words within superordinate categories in more depth (Allen & Frith, 1983; Aloia *et al.*, 1996; Paulsen *et al.*, 1996). These studies have suggested that patients are less likely than controls to group superordinate exemplars into related clusters and are more likely to produce bizarre associations. In addition, patients are slower than controls to produce items within a semantic cluster and to produce items that transition from one semantic cluster to the next. Taken together, these findings suggest that either the underlying organization of items stored within semantic memory is abnormal or that the process of retrieval is more disorganized in patients than in controls.

Explicit processing: knowledge of semantic category and semantic attributes

Although potentially useful, semantic fluency tasks are relatively uncontrolled, in that each individual generates different word lists and it is often difficult to derive objective quantitative measures of performance. To probe semantic memory structure in a more controlled fashion, several studies have examined participants' explicit semantic categorization judgments on controlled sets of stimuli.

The most basic type of categorization paradigm is to simply ask participants to decide whether or not an exemplar comes from a specified superordinate semantic category. There is some evidence that schizophrenia patients are slower and less accurate than controls in classifying common prototypes versus marginal exemplars. In two early studies, patients, relative to healthy controls, were slower to make a decision about whether a sparrow is a bird (a prototype) relative to whether a penguin is a bird (a marginal exemplar) (Chen *et al.*, 1994; Clare *et al.*, 1993; Gurd *et al.*, 1997). However, later studies did not replicate this finding (Elvevaag *et al.*, 2002b; McKenna *et al.*, 1994).

A second way of probing semantic knowledge is to ask participants to compare objects according to a particular perceptual semantic attribute, e.g. size. Cohen *et al.* (2005) capitalized on the so-called "distance effects" in size among real-world objects; this pertains to the longer reaction time (RT) to make size similarity judgments about two words or pictures that represent real-world objects of the same size versus different sizes. Despite having slower overall RTs, patients demonstrated a principled distance effect that did not differ from that of healthy controls.

A third method of probing categorical knowledge is to ask participants to classify words or objects using unspecified categories or dimensions. In the "triadic comparisons" test, participants view groups of three words and are asked to select the two words that are most similar. Each word triplet is a permutation derived from an overall word list in which words vary on two continuous dimensions: (1) living and nonliving and (2) "associated with humans" and "not associated with humans." This information is not conveyed to the participants. Participants' responses are analyzed using multidimensional scaling methods to generate graphic maps of the structure of their semantic memories. Tallent *et al.* (2001) used this task with schizophrenia patients and demonstrated less-disorganized maps in patients than healthy controls. Interestingly, the degree of disorganization within these maps predicted severity of thought disorder over time. Moreover, in an unpublished study, Denke & Goldberg showed that these disorganized maps were specific to thought-disordered (TD) patients; they were not found in non-TD patients, patients with Alzheimer's disease or in healthy children.

Impairments in patients' use of categorical knowledge are also evident in declarative memory paradigms. When healthy controls learn a list of words, their recall is better if the list can be organized into semantic categories than if it consists of a sequence of unrelated words. This is thought to reflect the tendency to organize words in semantic memory during encoding (Craik & Lockhart, 1971; Kintsch, 1968). There is now fairly compelling evidence that patients with schizophrenia fail to spontaneously use such semantic categorization strategies during encoding. Several studies have reported that patients often produce largely unorganized word lists at recall (e.g. Iddon *et al.*, 1998; Koh *et al.*, 1973). Interestingly, most of these studies (Iddon *et al.*, 1998; Koh & Kayton, 1974), although not all (Gold *et al.*, 1992), have reported that if material is pre-organized, or if patients are given enough time to organize material during encoding, they do have the capacity to use semantic information to improve recall. Once again these results suggest that there is no overall loss of semantic knowledge in schizophrenia.

There has not been nearly as much study of semantic memory in bipolar disorder as in schizophrenia. However, recent studies suggest some impairments; Deckersbach *et al.* (2004, 2005) reported that bipolar patients can exhibit poorer

organization during encoding than healthy controls, while other studies suggest that, despite using normal semantic clustering strategies during encoding, patients fail to make use of such strategies during recall (Bearden *et al.*, 2006a, 2006b).

Implicit knowledge of semantic and associative relationships

Another way of probing the structure and use of semantic memory is to manipulate semantic relationships between words but conceal the purpose of the study altogether from participants by asking participants to perform an orthogonal task. This yields implicit measures, which not only give information about the nature of categorical relationships between words within semantic memory, but also provide information about associative relationships between words that may not necessarily have semantic features in common. For example, "surgeon" and "scalpel" are associatively related but they are not categorically related and do not share semantic features.

Implicit production: word association tasks and the Latent Semantic Analysis

The classic method of probing implicit associative knowledge has been to use word association tasks in which participants are given a word and then asked to generate the first word (or series of words) that come to mind. Word association studies have a long history in psychiatry. Early experiments carried out by Bleuler, C. G. Jung and Kraepelin demonstrated that schizophrenia patients produced more idiosyncratic associations than normal controls (Jung, 1981). These findings were confirmed by some later studies (reviewed by Spitzer *et al.*, 1992). However, as discussed above with respect to semantic fluency, because word associations differ from individual to individual, it is often difficult to objectively measure the output produced.

Elvevaag *et al.* (2007) have recently addressed this issue by measuring the semantic coherence of words produced on association tasks using a Latent Semantic Analysis (LSA). The LSA derives a measure of coherence not simply on the basis of co-occurrence frequency, but also through examining the similarity of contexts in which words occur in a large text corpus (Landauer *et al.*, 1998). Elvevaag *et al.*'s findings using this measure confirmed that schizophrenia patients' word associations were less semantically cohesive than those of healthy controls. Moreover, the associations produced by TD patients were less cohesive than those produced by non-TD patients.

Implicit processing: semantic priming

An even more objective method of implicitly assessing semantic memory structure and function is through the use of the semantic priming paradigm using an implicit task, such as lexical decision (LD: deciding whether a target word is a real word or a non-word) or word pronunciation (simply naming the target word). The semantic priming effect describes the faster response to target words (e.g. stripes) that are preceded by semantically related words (e.g. tiger), relative to semantically unrelated words (e.g. table) (Meyer & Schvaneveldt, 1971; Neely, 1991). This behavioral priming effect also has a neurophysiological correlate: the attenuation of the N400 event-related potential (ERP) – a negative-going waveform evoked *c.* 400 ms after the onset of a word – to primed versus unprimed targets (Bentin *et al.*, 1985; Rugg, 1985). This attenuation of the N400 amplitude is known as the N400 effect.

There have been numerous studies of semantic priming in schizophrenia over the past two decades and the literature is often contradictory: studies have reported normal priming, increased priming and decreased priming in patients relative to controls. Nonetheless, some consistencies do emerge, particularly when findings are examined in relation to types of experimental conditions (automatic versus controlled) used in each study. Below is a brief review of behavioral and ERP semantic priming studies in schizophrenia (for a more detailed review of the behavioral literature up to 2002, see Minzenberg *et al.*, 2002; for a recent meta-analysis of the behavioral literature, see Pomarol-Clotet *et al.*, 2008, and for a review of the ERP semantic priming literature, see Kuperberg, Kreher & Ditman, in press).

Automatic semantic priming in schizophrenia

Experimental conditions that bias towards automatic semantic priming are those in which the interval between the presentation of the prime and target (the stimulus onset asynchrony, SOA) is short (usually less than *c.* 400 ms), and in which the proportion

of related words in the stimulus set (the relatedness proportion, RP) is small (usually less than 33%) (Neely, 1977). The mechanism most often invoked to explain the semantic priming effect under these conditions is the spread of activation within semantic memory (Anderson, 1983; Collins & Loftus, 1975), whereby the presentation of the first word (or prime) activates its internal representation, leading to an implicit, automatic spread of activation to nearby and related representations. If a second word, the target, corresponding to one of these partially pre-activated or primed representations is then presented, the individual's response to that target will be facilitated.

One theory proposed to account for the "loosening of associations" seen in thought disorder (TD) is that the spread of activation within semantic memory is abnormally heightened, leading to speech that is difficult to follow because it is dominated by such associations. Evidence for this theory is provided by findings that schizophrenia patients exhibit increased semantic priming under more automatic processing conditions. Manschreck *et al.* (1988) were the first to demonstrate increased semantic priming in TD patients relative to non-TD patients, psychiatric controls and healthy controls (using a LD task). Subsequent studies have confirmed "hyper-priming" in TD patients across a variety of SOAs (Spitzer *et al.*, 1994), during word pronunciation tasks (Moritz *et al.*, 2001a; Moritz *et al.*, 2002) and even when participants viewed triplets, rather than pairs of words (Chenery *et al.*, 2004). Others have reported increased cross-modal (across auditory and visual modalities) semantic priming (Surguladze *et al.*, 2002), as well as increased priming, particularly to high-frequency words (Rossell & David, 2006) in patients with schizophrenia.

Other researchers, however, have failed to show increases in direct priming in schizophrenia under automatic conditions: equal priming in patients and controls has been demonstrated using LD (Barch *et al.*, 1996; Blum & Freides, 1995), double LD (Besche-Richard *et al.*, 2005; Chapin *et al.*, 1989), and word pronunciation (Ober *et al.*, 1995; Vinogradov *et al.*, 1992) tasks. And a few behavioral studies (Henik *et al.*, 1992; Ober *et al.*, 1997; Vinogradov *et al.*, 1992) and two ERP studies (Condray *et al.*, 2003; Mathalon *et al.*, 2002) have reported reduced direct semantic priming using LD tasks in schizophrenia using short SOAs.

All of the studies reviewed above used directly related word pairs (e.g. tiger-stripes). However, since closely associated words are presumably automatically activated by both schizophrenia patients and controls, the use of indirectly related word pairs during semantic priming paradigms may be a more stringent test for a heightened activation (or reduced inhibition) (Spitzer, 1993). In indirect semantic priming paradigms, the prime and target are related only through an unseen mediating word (e.g. "*lion-stripes*" via "*tiger*") (Balota & Lorch, 1986; Chwilla & Kolk, 2002; Kiefer *et al.*, 1998; Kreher *et al.*, 2006; McNamara & Altarriba, 1988; Weisbrod *et al.*, 1999). Unlike direct priming, indirect semantic priming cannot be accounted for by alternative models of automatic semantic priming, and is best explained by spreading activation theory (Kreher *et al.*, 2006; McNamara & Altarriba, 1988; Neely, 1991). The unseen mediating word is thought to be activated by the prime, and this spread of activation activates the target.

Spitzer *et al.* (1993) were the first to report increased indirect priming using a LD task under automatic conditions in TD patients, relative to both healthy individuals and non-TD patients (see also Moritz *et al.*, 2001b). This finding has been replicated both using lateralized presentation (Weisbrod *et al.*, 1998) and using a word pronunciation task (Moritz *et al.*, 2002).

In an ERP study by Mathalon *et al.* (2002), patients showed a smaller amplitude of the N400 than controls to target words that were moderately (but not closely) related to their picture primes. This was interpreted as reflecting increased activation to these targets in schizophrenia patients. Of note, however, these word-pairs were not indirectly related, as they belonged to the same superordinate categories (e.g. camel – fox). In a more recent ERP study, Kreher *et al.* (2008) used a short SOA and an implicit task (semantic monitoring just on filler trials) to demonstrate increased spreading activation in TD schizophrenia patients. In the early part of the N400 time window (300–400 ms after target word onset), TD patients showed increased indirect semantic priming relative to non-TD patients and healthy controls, while the degree of direct semantic priming was increased in only the most severely thought-disordered patients. By 400–500 ms after target word onset, both direct and indirect semantic priming were generally equivalent across the three groups. These findings suggest that under automatic conditions, activation across the semantic network spreads further,

within a shorter period of time, in specific association with positive thought disorder in schizophrenia.

However, experimental task also appears to play a role in whether hyper- or hypoactivation will be observed in schizophrenia patients relative to controls, even under "automatic" conditions. Kreher *et al.* (2009) used an explicit relatedness ratings task with the same group of patients and matched controls, who were presented with the same directly related, indirectly related and unrelated word pairs using the same SOA, and found that schizophrenia patients, as a whole, showed *reduced* direct and indirect N400 priming effects compared with healthy controls. Similarly, Kiang *et al.* (2008) reported reduced N400 effects to both directly and indirectly related targets in schizophrenia patients, compared with controls, using a LD task with a short SOA.

In sum, studies examining semantic priming under automatic conditions have generally revealed normal direct priming in schizophrenia patients as a whole, suggesting that implicit associative activity within the semantic network is normal in such patients. However, there is some evidence that TD patients show increased direct priming, and even more consistent evidence that TD patients show increased indirect priming under these automatic conditions. This suggests that, in patients with severe thought disorder, automatic activation may spread further (and possibly faster) across the semantic network. This may be due to hyperactivity and/or a failure of inhibition. Additionally, requiring a decision to each target word, through relatedness judgments or lexical decision can lead to a reduction in semantic priming in schizophrenia patients even when a short SOA and indirectly related word pairs are used. This is likely to occur because of the engagement of controlled semantic mechanisms which, as discussed below, are impaired in patients.

Controlled semantic priming in schizophrenia

Controlled priming mechanisms involve the generation of predictions or expectations (Becker, 1980), as well as attempts to match the semantic relationship between prime and target (Neely *et al.*, 1989). They have most often been studied under experimental conditions using a long SOA and a high RP.

With the exception of Spitzer *et al.* (1993, 1994) who reported increased semantic priming in patients relative to controls, most studies carried out under such controlled conditions have demonstrated reduced priming in schizophrenia. Using a pronunciation task, Aloia *et al.* (1998) found that TD patients exhibited less priming to both highly associated and moderately associated targets than non-TD patients, and less priming to the highly associated targets than healthy controls. Reduced priming in TD patients at longer SOAs has also been demonstrated using a LD task (Besche *et al.*, 1997; Passerieux *et al.*, 1997) and a variant of the double LD task with a low RP (Besche-Richard *et al.*, 2005). Studies using multiple SOAs have found either reduced (Barch *et al.*, 1996; Chenery *et al.*, 2004) or normal (Henik *et al.*, 1995) priming effects in patients relative to controls at long SOAs.

ERP studies have also reported reduced priming under controlled conditions in patients relative to controls (although see Koyama *et al.*, 1991, 1994). For example, Grillon *et al.* (1991) reported two distinct subgroups of schizophrenic patients: one in which there was a reduced N400 effect, and one in which the N400 effect did not differ from that of controls, and Bobes *et al.* (1996) found that schizophrenia patients showed a smaller N400 effect than controls in a picture priming paradigm. There have also been reports of a reduced N400 effect using LD tasks by Kostova *et al.* (2003, 2005), particularly in TD patients. Others have reported reduced N400 effects both in medicated patients (Condray *et al.*, 1999) and unmedicated patients (Condray *et al.*, 1999; Hokama *et al.*, 2003) at longer SOAs. Using a LD task, Kiang *et al.* (2008) reported reduced N400 effects in schizophrenia patients to both directly and indirectly related words at a long SOA; the reduction in semantic priming was correlated with delusions and hallucinations, but not with thought disorder. Another consistent finding under controlled processing conditions is that the peak latency of the N400 is delayed (Bobes *et al.*, 1996; Condray *et al.*, 1999; Grillon *et al.*, 1991; Hokama *et al.*, 2003; Koyama *et al.*, 1991).

In sum, behavioral and ERP studies of controlled semantic priming suggest that priming is reduced in patients with schizophrenia relative to controls. This has generally been attributed to impaired controlled mechanisms of accessing information within semantic memory.

Single words and concepts: summary and discussion

The findings reviewed here suggest that semantic memory structure and function in schizophrenia

requires further clarification. There are clearly aspects of semantic memory that are intact: patients perform just as well as healthy controls on simple object perception and some aspects of semantic categorization. Semantic fluency is impaired but, when given enough time, patients produce as many exemplars as controls. Moreover, under automatic experimental conditions patients generally show the same degree of semantic priming as healthy controls, and indeed, patients with thought disorder can show even greater priming effects than controls, suggesting that there may be some automatic hyperactivity within the network in these patients.

This set of findings is important because it sets schizophrenia apart from disorders such as Alzheimer's disease. There does not appear to be an overall loss of knowledge in schizophrenia: the main semantic problem appears to be one of access and/or retrieval, i.e. of using semantic knowledge effectively. This manifests in both explicit and implicit measures. On explicit semantic fluency, word association and categorization tasks, the pattern of responses in patients reveals an abnormality in the organization of semantic memory. Behavioral and ERP studies of implicit semantic memory function examining the semantic priming effect under controlled experimental conditions, suggest that patients fail to employ strategic semantic mechanisms to prime targets, leading to reduced priming.

Sentences, ambiguity and figurative language

As discussed above, thought-disordered speech can be dominated by associations between individual words. Importantly, such associations can result in a failure to build coherence within and across sentences. Consider the following sample of speech produced by a patient with schizophrenia, quoted by Maher (1983): "If you think you are being wise to send me a bill for money I have already paid, I am in nowise going to do so unless I get the whys and wherefores from you to me. But where the fours have been, then fives will be, and other numbers and calculations and accounts to your no-account . . ." In this speech sample, the associations between the individual words are clear; what is unclear is the overall message the patient wishes to convey.

In this section we review studies examining how patients process and make use of contextual information within written and spoken language, at the level of sentences. We focus again on schizophrenia, as most of the work has been carried out in this area. We consider studies that have examined the predictability of the speech produced by schizophrenia patients, as well as studies exploring patients' abilities to predict words within text and to detect and integrate semantic anomalies in sentences. In addition, we review studies exploring the syntactic structure of patients' speech and examining how patients combine syntactic structure with the meaning of individual words during comprehension. Finally, we discuss studies that have explored patients' ability to select the most appropriate meanings of ambiguous words in context, and studies of non-literal language.

Semantic predictability and congruity

The traditional way of measuring language predictability is through the use of the Cloze technique, which requires healthy participants to produce the missing words in text (Taylor, 1953). If they tend to produce the same word, then this indicates that the text was highly predictable. An early schizophrenia study confirmed the clinical impression that patients' speech output was unpredictable (Salzinger *et al.*, 1964). Moreover, when participants were provided with more context, it was harder to predict patients' speech (Salzinger *et al.*, 1970, 1979). Later studies, however, suggested that unpredictable speech was only produced by patients with thought disorder (Hart & Payne, 1973; Manschreck *et al.*, 1979). Impairments in the ability to make predictions about upcoming words in normal speech or text have also been identified in schizophrenia (Blaney, 1974; Honigfeld, 1963). This has been demonstrated using reverse Cloze procedures in which patients are asked to predict upcoming words in speech transcripts of healthy adults. Unlike healthy controls, the performance of acute schizophrenia patients deteriorates when more context is provided (de Silva & Hemsley, 1977).

Another method used to examine how patients use context within sentences is to introduce words that violate semantic contextual constraints. Some studies suggest that chronic schizophrenia patients can accurately judge the appropriateness of semantically anomalous sentences (Miller & Phelan, 1980); however, acutely psychotic patients (Anand *et al.*, 1994) and TD patients (Kuperberg *et al.*, 1998) appear to be relatively impaired. Furthermore, this relative insensitivity to semantic anomalies appears to be

related to the state (i.e. impairment related to symptom exacerbation) rather than the trait (i.e. impairment independent of symptom exacerbation) of thought disorder (Kuperberg *et al.*, 2000).

Measurement of ongoing brain activity using ERPs can also offer insight into the effects of semantic anomalies. Event-related potential studies of sentence processing, like those of single words, have focused on the N400 waveform. In sentences, the N400 is evoked by words that are semantically incongruous or unexpected with their preceding context (Kutas & Hillyard, 1980, 1984) and is thought to reflect the difficulty of semantically integrating words into their preceding context (Holcomb, 1993). Although most studies have reported that the size of the N400 effect is normal in schizophrenia (Andrews *et al.*, 1993; Kuperberg *et al.*, 2006d; Nestor *et al.*, 1997; Niznikiewicz *et al.*, 1997; Ruchsow *et al.*, 2003), there have been some investigations demonstrating that it can be abnormally reduced (Adams *et al.*, 1993; Mitchell *et al.*, 1991; Ohta *et al.*, 1999; Sitnikova *et al.*, 2002). A reduced N400 effect is most evident when the anomalous words fall at the sentence-final position, which is when there are relatively high processing demands (see below for further discussion).

A number of investigators have also identified more negative N400 amplitudes to congruous words (Mitchell *et al.*, 1991; Nestor *et al.*, 1997; Niznikiewicz *et al.*, 1997; Ohta *et al.*, 1999), and incongruous words (Nestor *et al.*, 1997; Niznikiewicz *et al.*, 1997) in patients relative to controls. These data may reflect increased difficulty in semantically integrating words, regardless of whether the context is congruous or incongruous. Other studies, however, have failed to find such differences (Kuperberg *et al.*, 2006d; Ruchsow *et al.*, 2003). Finally, some studies report that the peak of the N400 is delayed, suggesting that integrative semantic processing occurs later in patients than controls (Mitchell *et al.*, 1991; Nestor *et al.*, 1997; Niznikiewicz *et al.*, 1997; Ohta *et al.*, 1999).

Syntax and the semantic-syntactic interface

Syntactic processing has often been considered relatively unimpaired in patients with schizophrenia. The evidence supporting this assumption comes from three early studies using the "click" paradigm in which a short burst of noise (the click) is delivered in the middle of a spoken clause (Fodor & Bever, 1965; Garrett *et al.*, 1966). In these studies, patients and controls perceived the click as occurring at or near a clause boundary, suggesting that patients were using normal syntactic constraints to guide perception (Carpenter, 1976; Grove & Andreasen, 1985; Rochester *et al.*, 1973), and that at least some implicit aspects of syntactic structural processing remained intact. This type of paradigm, however, does not index how well patients can combine syntactic structure with semantic information to assign thematic roles and build up overall meaning.

Thematic roles are the semantic roles that are occupied by each constituent of a sentence around a given action; these are generalizable across a variety of sentence meanings. For example, the Agent of a sentence is the performer of the main action and the Theme is the entity that undergoes the action. While thematic roles are assigned by the syntax, they are considered semantic in nature as they determine "who does what to whom" in a sentence. During normal language production and comprehension, syntax and semantics are combined, word by word, to assign thematic roles (although it is debated whether this combination occurs in a single stage of processing in a parallel constraint-based model (e.g. MacDonald *et al.*, 1994), or at a second stage of processing in a serial model (e.g. Frazier & Rayner, 1982)). In patients with schizophrenia, there is growing evidence for abnormalities in this combination of semantic and syntactic information.

One situation in which there is an increased demand for syntactic structure to be combined with the meaning of individual words is during the production or processing of syntactically complex sentences. In simple "canonical" sentences, the semantic order of constituents of English sentences (e.g. Agent–Action–Theme) corresponds to the syntactic order of constituents (e.g. Subject–Verb–Object). This is not necessarily true of more complex, non-canonical sentences where there is an increased demand on the production and processing systems to use syntactic rules to assign thematic roles. There is fairly compelling evidence that patients with schizophrenia are relatively impaired in processing syntactic complexity during both speech production and language comprehension.

The speech produced by schizophrenia patients is less complex than that of matched controls (Morice & Ingram, 1982; Thomas *et al.*, 1990). Reduced syntactic complexity is associated with negative symptoms and

seems to be relatively unresponsive to treatment (Thomas *et al*., 1990). Although some researchers have postulated that it may represent a premorbid marker of schizophrenia (Thomas *et al*., 1990), a study examining the writing samples of children who later developed schizophrenia, compared with matched controls, did not find differences in syntactic complexity (Done *et al*., 1998).

Complementing these findings in language production, studies of language comprehension have revealed impairments in patients' abilities to comprehend grammatically complex sentences. Condray *et al*. (1996, 2002) compared patients' accuracy on comprehension questions tapping into the assignments of thematic roles (e.g. "Who did what to whom?") and compared more complex, object-relative sentences (e.g. The senator that the reporter attacked admitted the error) to less complex, subject-relative sentences (e.g. The accountant that sued the lawyer read the paper). These sentences were presented at normal (i.e. conversational) and accelerated rates. Initial results (Condray *et al*., 1996) demonstrated that accuracy in both schizophrenia patients and healthy adult controls was negatively impacted by both fast presentation rates and grammatical complexity. These results were replicated and extended by Bagner *et al*. (2003) using a larger sample size. A later study by Condray *et al*. (2002) indicated that, although both patients and controls were more accurate in answering questions about information in the main clause compared to embedded clause, the drop in accuracy between main and embedded clause questions was greater in patients than in controls.

A second situation in which there are increased demands for syntactic structure to be combined with the meaning of individual words is when potentially plausible thematic-semantic relationships contradict the implausible syntactic assignment of thematic roles. For example, in the sentence, "Every morning for breakfast the eggs would eat…", there is a potentially plausible thematic-semantic relationship between "eggs" and "eat" (eggs can be eaten) but the actual interpretation dictated by the syntax is impossible. Kuperberg *et al*. (2006c) recently showed that, when asked to judge the acceptability of such sentences, patients with schizophrenia were less sensitive to these types of anomalies than healthy controls: relative to controls, they showed smaller reaction time differences between these sentences and both non-violated sentences, e.g. "Every morning for breakfast the boys would eat…" and sentences that were only incongruous with real-world knowledge, e.g. "Every morning for breakfast the boys would plant…."

Further evidence that patients show impairments in combining semantic and syntactic information comes from ERP studies. First, as mentioned above, in most of the ERP studies documenting an abnormally reduced N400 effect to semantic anomalies (versus non-violated words) within sentences, the anomalies occurred on the sentence-final word (Adams *et al*., 1993; Mitchell *et al*., 1991; Ohta *et al*., 1999; Sitnikova *et al*., 2002). The demands of integrating semantic with syntactic information are particularly great at the sentence-final position, when there is often an attempt to evaluate and "wrap-up" the meaning of the sentence as a whole (Friedman *et al*., 1975).

Second, there have also been several reports of a reduced Late Positivity (or P600) following the N400 during sentence processing in schizophrenia (Adams *et al*., 1993; Andrews *et al*., 1993; Mitchell *et al*., 1991; Nestor *et al*., 1997). Although the theoretical relevance of the P600 has been debated (see Coulson *et al*., 1998; Kuperberg, 2007; Osterhout & Hagoort, 1999), there is evidence that it reflects the increased demands of integrating semantic and syntactic information under certain circumstances. For example, when there is a potentially plausible semantic-thematic relationship ("eggs"–"eat"), but the actual interpretation dictated by the syntax is impossible ("At breakfast the eggs would eat…") (Kuperberg *et al*., 2003c, 2006a, 2007), it is harder to integrate semantic and syntactic information to come up with this interpretation and a P600 effect is evoked.

A recent study by Kuperberg *et al*. (2006d) demonstrated that, unlike healthy controls, schizophrenia patients failed to evoke a Late Positive effect to these types of anomalies. Yet, in this study the same patients produced a normal N400 effect to violations of real-world knowledge, suggesting that they had no problem in accessing and combining the meanings of individual words based on real-world knowledge alone.

One important question is whether patients' poor performance when required to combine semantic and syntactic information is due to their impaired working memories (Lee & Park, 2005). The relationship between working memory function and syntactic-semantic combinatory processes has been extensively

discussed in normal language processing (Caplan & Waters, 1999; Fedorenko *et al.*, 2006), and there is increasing evidence that the language processing system is influenced by top-down executive function and is therefore more dynamic than has been previously assumed (Kuperberg, 2007). There is some evidence that impairments on some of the measures discussed here are correlated with more general cognitive impairments (this is discussed later in this chapter). However, the precise nature and mechanisms of such links remain to be explored.

Lexical ambiguity

Being able to effectively build up and use context by combining semantic with syntactic information is particularly important for interpreting words that are lexically ambiguous. Context plays a critical role in constraining and selecting the most appropriate meaning of such words. One well-studied source of lexical ambiguity comes from homonyms – words that sound (homophones) and/or look (homographs) the same but have different conceptual representations. For example, in order to interpret the word "pen" in the sentence, "When the farmer bought a herd of cattle, he needed a new pen," one must use the preceding context to inhibit the inappropriate dominant meaning (a writing instrument) and to select the contextually appropriate subordinate meaning (a place where animals live).

In an early study, Chapman *et al.* (1964) asked healthy adults and schizophrenia patients to indicate the meaning (by selecting a response from several choices) of sentences containing homonyms, similar to the sentence above. Patients were more likely than healthy adults to misinterpret homonyms in terms of their dominant meanings, suggesting that they failed to use context to inhibit the prepotent response and to select the most appropriate meaning (see also Benjamin & Watt, 1969). In a more recent study, Bazin *et al.* (2000) examined the use of context to disambiguate homographs. Participants read sentences containing homographs that were preceded by contexts that biased towards the subordinate meaning of the homograph. In addition, they viewed sentence fragments without a biasing context. Resolution of the homograph was measured by whether participants completed sentence fragments according to the dominant or subordinate meaning. When no context was given, both patients and controls showed a similar pattern of results: both groups used the dominant interpretation. Interestingly, when a biasing context preceded the homograph, TD patients relative to healthy controls and non-TD patients, failed to make use of this information and completed the sentences according to the contextually inappropriate dominant meaning of the homograph.

Titone *et al.* (2000) also examined the processing of homonyms using a cross-modal priming paradigm and a LD task. Participants listened to prime stimuli consisting of homonyms embedded in contexts that either moderately or strongly biased towards their subordinate meanings. Targets were related to either the dominant or subordinate meaning of the homonym. Priming of targets related to the dominant meanings of the homonyms indicated an ability to inhibit a prepotent response, as such targets were never contextually appropriate. Priming of targets related to the subordinate meanings of the homonyms indicated an ability to build-up and use context. Healthy adults only showed priming of words related to the subordinate meanings of the homographs, regardless of the strength of the context biasing, suggesting that they were able to inhibit the prepotent response as well as build-up and use context appropriately. Patients also showed priming of words related to the subordinate meaning of the homographs under both contextual biasing conditions. However, with a moderately biasing context, the dominant meaning was also activated, suggesting an inability to inhibit this meaning. When the context strongly biased towards the subordinate meaning of the homograph, patients were able to inhibit the dominant meaning. Thus, in patients, a strong global context was necessary to inhibit local, lexico-semantic associations.

Finally, there have been a few recent studies using ERPs to study how homographs are processed as language is built-up online. Using sentences that did not include any disambiguating context prior to the homonym (e.g. "The toast was sincere"), Salisbury and colleagues demonstrated that patients with schizophrenia were more likely to misinterpret homographs when the correct interpretation of a sentence required the subordinate meaning. This was reflected by larger N400 amplitude to sentence-final words that were consistent with a subordinate interpretation (Salisbury *et al.*, 2000; Salisbury *et al.*, 2002). Taking this a step further, Sitnikova *et al.* (2002) constructed sentences that included a disambiguating context

prior to the homograph. Specifically, the first clause of each sentence biased towards either the dominant meaning (e.g. "Diving was forbidden from the bridge…") or the subordinate meaning (e.g. "The guests played bridge…") of a homograph, followed by a second clause that 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"). As expected, healthy adults produced an N400 effect to contextually inappropriate words (e.g. to "river" when the initial context was "The guests played bridge"). Schizophrenia patients, however, showed an attenuated N400 effect, suggesting that they failed to use context to inhibit the dominant meaning of the homograph ("bridge") that primed "river". Critically, the same patients in the same 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. "cracks" in "…because the river had cracks in it."). Taken together, these findings suggest that patients were able to use some aspects of context (perhaps the lexico-semantic relationships between individual words), but that they had specific difficulty in using global context to inhibit contextually inappropriate, dominant meanings of homographs.

Figurative language

Figurative language is often, by its very nature, ambiguous. Proverbs, metaphors and many idioms have both literal as well as figurative interpretations, posing a particular challenge to the comprehension system to select their most appropriate meaning. Healthy adults very quickly and easily understand the meanings of familiar idioms (e.g. Titone & Connine, 1994). Similarly, most healthy adults are able to interpret metaphor, although there is some debate over whether both the literal and figurative meanings or only the figurative meanings remain active during online processing (e.g. Kintsch, 2000).

Patients with schizophrenia have particular difficulties in understanding figurative language. Indeed, proverb interpretation is commonly used clinically to assess language and thought disturbances in schizophrenia (it constitutes one item on the PANSS; Kay *et al.*, 1987). Misinterpretations usually take the form of an over-reliance on the literal meaning, sometimes triggering semantic associations. For example, when asked to interpret the proverb, "Gold goes in at any gate except heaven's," one patient responded, "There's jewelry, there's platinum. They use it on your teeth for filling. There's gold in churches. There's gold in the mosque areas; like Lincoln's tomb" (example taken from Harrow & Quinlan, 1985). Consistent with these clinical observations, several studies have indicated that schizophrenia patients often choose concrete interpretations when asked to interpret figurative language (Chapman, 1960; Brune & Bodenstein, 2005; Kiang *et al.*, 2007).

There have been several investigations using behavioral and/or ERP measures to test the hypothesis that patients are specifically impaired in inhibiting the literal meaning of idioms and metaphors during comprehension. Titone *et al.* (2002) conducted a priming experiment in which the priming context constituted idioms with both literal and figurative meanings (ambiguous idioms, e.g. "kick the bucket") or idioms with only figurative meanings (non-ambiguous idioms, e.g. "be on cloud nine"). In healthy controls, the figurative meanings of both types of idioms primed semantically related target words (e.g. "death" for the first example, and "elated" for the second example); in addition, the literal meaning of the ambiguous idioms primed semantically related target words (Titone & Connine, 1994). In patients with schizophrenia, however, only non-ambiguous idioms (without literal meanings) were effective in priming targets that were semantically related to their idiomatic meanings; ambiguous idioms only primed targets that were related to their literal meanings, suggesting that a failure to inhibit the literal meanings of these idioms prevented patients' access to their figurative meanings. Consistent findings were reported by Strandburg *et al.* (1997) who measured ERPs as participants judged the meaningfulness of word-pairs that were idiomatic ("pot luck"), literal ("vicious dog"), or that made no sense ("square wind"). Note that in this experiment all idiomatic expressions were unambiguous, i.e. no plausible literal interpretation was possible. Relative to healthy controls, patients took longer to respond and showed more errors and larger N400 amplitudes to the second word of the idiomatic, relative to the literal, word-pairs, suggesting that they had particular difficulty in accessing the figurative meaning of the idioms.

In contrast to these two studies, Iakimova *et al.* (2005) did not find specific impairments in processing metaphors in schizophrenia. Healthy adults

and schizophrenia patients made meaningfulness judgments while reading metaphorical, literal and incongruous sentences. All participants showed a similar pattern of results: incongruous sentences elicited the most negative N400 amplitudes, followed by a medium-sized N400 to literal sentence endings, and the smallest amplitude N400 to metaphorical endings. However, in schizophrenia patients, there was an overall delay in the latency of both the N400 and Late Positivity components. In addition, the negativity of the N400 was greater and the amplitude of the Late Positivity was reduced. Thus, the authors concluded that patients are impaired in integrating the semantic context of sentences (both figurative and literal), rather than showing a specific deficit in metaphor processing.

One reason for these discrepancies may be differences in the symptom profiles of patients participating in these studies: some researchers have implicated delusions as being specifically related to metaphor interpretation (Rhodes & Jakes, 2004), whereas others have associated poor metaphor comprehension with negative symptoms (Langdon & Coltheart, 2004).

Sentences, ambiguity and figurative language: summary and conclusion

There is now fairly compelling evidence that patients with schizophrenia show impairments in building up sentence context, which leads to unpredictable speech and also to problems in predicting words within speech and text. Although patients appear to be able to use semantic relationships between individual words within sentences to generate some representation of meaning (leading to normal N400 effects under many circumstance), both behavioral and electrophysiological abnormalities are observed when the demands of combining the meaning of individual words with syntactic structure are high. This occurs at the final word of sentences when comprehenders usually wrap-up sentence meaning, in producing and processing syntactically complex sentences, and in comprehending sentences in which semantic relationships between individual words contradict overall meaning.

Many of these abnormalities are evident in patients without prominent positive thought disorder, although they may be more marked in thought-disordered patients. Impairments in building up context may lead to speech that is dominated by semantic associative relationships between individual words at the expense of whole meaning. It may also lead to specific problems in resolving lexical ambiguity where context plays a particularly important role in determining whether the dominant meaning of a homonym is inhibited and the subordinate meaning is appropriately selected. Finally, there is some evidence that it may lead to specific impairments with inhibiting contextually inappropriate literal interpretations of figurative expressions (Titone *et al.*, 2002), although others have failed to find such specific deficits (Iakimova *et al.*, 2005).

Discourse

Language comprehension and production go beyond accessing the meaning of individual words and combining this with syntactic structure to build up meaning of sentences. When healthy adults produce and comprehend language, they are able to integrate ideas across multiple sentences to generate or construct a coherent discourse model. This connected discourse has two main properties: cohesion and coherence (Halliday & Hasan, 1976; Sanford & Garrod, 1994). Coherence can be established through linguistic cohesive devices that specifically link information within and across sentences (e.g. "the man," "he," "the show-off" must each be linked to a single referent). In addition we must establish logical and psychological consistency between events (e.g. through the generation of causal inferences).

Clinically, patients with schizophrenia show prominent abnormalities at the level of discourse (Andreasen *et al.*, 1995; for reviews, see Covington *et al.*, 2005; McKenna & Oh, 2005; Pavy, 1968). Indeed, tangentiality and derailment – shifts in speech from one topic to another without obvious links between them – are amongst the most common phenomena described in thought-disordered speech (Andreasen, 1979a, 1979b; Earle-Boyer *et al.*, 1986; Mazumdar *et al.*, 1995). Below we review evidence that patients with schizophrenia show abnormalities in establishing coherence during language production and processing (also see Mitchell & Crow, 2005, for a discussion of the potential role of the right hemisphere in discourse impairments, and see Ditman & Kuperberg (in press) for a framework for exploring the breakdown of links across clause boundaries in schizophrenia).

Referential coherence

In a seminal study, Rochester & Martin (1979) examined the use of cohesion markers in the speech

produced by patients with schizophrenia. Irrespective of thought disorder, schizophrenia patients failed to use cohesion markers to the same degree as healthy controls and had a tendency to point to (rather than verbally identify) referents. However, more specific impairments in the use of cohesion markers did distinguish between patients with and without thought disorder. Non-TD schizophrenia patients used fewer indirect references than healthy controls, whereas TD patients used more obscure referents and were more likely to refer to information that had not been presented.

Findings of cohesion impairments in schizophrenia have been replicated and described in more detail by other researchers (Docherty *et al*., 1996a; Hoffman *et al*., 1985; Noel-Jorand *et al*., 1997). For example, Docherty and colleagues have developed a comprehensive measure that captures a range of referential communication failures including vague, confused and missing references. Interestingly, there is evidence that some types of referential impairments are trait markers of schizophrenia. Specifically, this evidence suggests that (1) some types of referential impairment are stable over time (Docherty *et al*., 2003), and (2) first-degree family members of schizophrenia patients have more referential disturbances than first-degree family members of controls (Docherty *et al*., 1998; Docherty & Gottesman, 2000). On the other hand, in some patients, these impairments can improve with medication (Abu-Akel, 1997).

Although there has been little work to determine whether patients with schizophrenia are specifically impaired in referential processes (linking anaphors to their antecedents) during online language comprehension, one recent ERP study provides some neural evidence that, with a sufficiently strong context, patients are able to use both semantic and contextual information to disambiguate anaphors during online comprehension, similar to healthy controls (Ditman & Kuperberg, 2008). When later asked to explicitly resolve the anaphors, however, patients were more likely than controls to erroneously resolve anaphors with contextually inappropriate, but semantically related, words. Thus, strong contextual constraints led to discourse-appropriate neural responses but later decisions were more likely guided by semantic associations. One possible explanation for this pattern of findings is that patients failed to use control mechanisms to suppress such associations, leading to their prolonged, inappropriate influence at later stages of processing.

Finally, there is some intriguing evidence for correlations between referential communication measures and performance on neuropsychological tasks indexing more general cognitive functions, such as working memory and other executive functions (discussed later in the chapter). This hypothesis could be further tested in the future using psycholinguistic paradigms that have been developed in healthy individuals to specifically tap into these working memory processes (Anderson & Holcomb, 2005; Swaab *et al*., 2004; van Berkum *et al*., 1999).

Other types of discourse coherence

One way of examining how patients construct links between sentences and concepts is to ask them to describe or recall what they see, read, or hear, and then transcribe the speech produced and examine its discourse structure in detail. Hoffman and colleagues took this approach and constructed "discourse trees" that depicted relationships between propositions within discourse. Normal discourse exhibits a systematic hierarchical structure in which propositions branch out from a central proposition. The transcripts of psychotic speech showed a more disorganized tree structure than that of controls and manic patients (Hoffman, 1986; Hoffman *et al*., 1982).

Another approach was taken in a study by Allen (1984) in which patients were asked to describe pictures and speech transcripts that were decomposed into "ideas" (individual sentences, semantic propositions, phrases and words), and then rated them according to whether they were appropriate to the picture or inferential. Thought-disordered patients produced significantly fewer inferences than controls, but exhibited a trend towards an increase in the number of ideas classified as inappropriate.

In a more recent study, Leroy *et al*. (2005) asked healthy adults and linguistically skilled patients with schizophrenia to read a story aloud and then, immediately after, to recall its contents. In healthy adults, the discourse macrostructure (the structure related to the global discourse topic) normally functions to constrain its microstructure (its more detailed structure) (Kintsch & van Dijk, 1978), so that irrelevant information is inhibited and generalizations are made. Although patients generated similar discourse plans with the same overall numbers of micro- and

macro-propositions as controls, they had an increased tendency to connect micro-propositions. This was interpreted as reflecting an impairment in inhibiting irrelevant information.

Another way of probing the coherence links constructed during discourse comprehension is by examining the overall content of what is extracted and recalled. In a classic study, Bransford & Franks (1971) established that healthy adults combine propositions to extract an overall "gist." They presented healthy adults with groups of sentences, e.g. "The ants were in the kitchen. The ants ate the jelly. The jelly was sweet." On a later memory test, healthy participants misremembered (as measured by confidence ratings), encoding larger sentences, e.g. "The ant in the kitchen ate the sweet jelly." In other words, they integrated the individual propositions to create a global representation of the discourse. Knight & Sims-Knight (1979) examined whether patients with schizophrenia extracted the gist of a discourse message in a similar way. Results suggested that patients with a history of poor (or lower level) functioning (compared with controls and patients with good premorbid histories) were not able to extract the gist. However, a subsequent study using the gist paradigm by Grove & Anderson (1985) failed to find group differences between healthy adults, patients with mania and schizophrenia patients.

Healthy individuals are not only able to combine individual propositions to construct an overall gist; they can also extract messages during everyday conversations, even when normal communication norms are violated (i.e. Grice's maxim; Grice, 1975). In normal conversation, these norms may be violated under certain circumstances, requiring the comprehender to infer the intentions of the speaker to fully understand the conversation. For example, the response "Is the Pope Catholic?" to the question "Did Mike get drunk last night?" violates the maxim of relevance but indirectly communicates the speaker's opinion about Mike's drinking habits. Importantly, an inability to draw this inference would lead to a communication breakdown. Tényi *et al.* (2002) examined the ability of paranoid schizophrenia patients and healthy adult controls to comprehend conversational vignettes in which the maxim of relevance was flouted. Patients made more errors than controls in interpreting the true meaning intended by the characters in the vignettes, suggesting an inability to infer communicators' intentions.

Finally, one can examine whether schizophrenia patients can construct coherence links between individual sentences by determining whether they are able to benefit from such links when later asked to recall such sentences. Healthy adults' ability to recall individual sentences is improved when the encoded material is organized into a coherent discourse, relative to when it is presented as random disconnected sentences. Schizophrenia patients fail to show this improvement in recall (Harvey *et al.*, 1986). These findings could not be attributed to poorer general memory performance. In another study, TD patients (a mixed group of mania and schizophrenia patients) showed superior recall than controls to sentences that were presented in random order during encoding (Speed *et al.*, 1991). Schizophrenia patients have also been found to perform worse than controls when asked to organize pictures depicting various aspects of a story into a coherent discourse (Brune & Bodenstein, 2005).

Despite the evidence reviewed above that patients' speech is less coherent than that of controls, and that they are impaired in their use of coherence links to improve recall of individual sentences, there has been very little work examining whether patients can establish coherence links between sentences during online processing. Ditman & Kuperberg (2007) have some preliminary evidence supporting this hypothesis; they measured ERPs as patients and healthy controls read three-sentence discourse scenarios. While healthy controls showed a robust N400 effect to critical words within congruous sentences that were completely unrelated and intermediately related with their preceding two-sentence discourse context, patients failed to show such N400 effects. This is interesting as the N400 effect in schizophrenia is often normal to semantic anomalies within single sentences (as described above), and it therefore suggests that patients were unable to construct coherence links between sentences and build up global discourse context.

Discourse: summary and conclusion

There is now fairly robust evidence that the speech of patients with schizophrenia lacks coherence in comparison with that produced by healthy controls. Patients' speech lacks normal referential links and has an abnormal discourse structure. In addition, patients fail to benefit from coherent links between sentences

to improve recall, although it remains controversial whether they are able to extract the gist of messages.

There has been very little investigation of how coherence links are established as discourse is built up during online processing in schizophrenia.

Relationship between language abnormalities and other cognitive dysfunction

Each level of language processing can be influenced by cognitive systems and processes that are used in domains other than language, such as attention, working memory and executive function. Given that schizophrenia is a disorder that affects multiple domains of cognitive function, understanding these relationships will prove essential to understanding language dysfunction in this disorder. Thus far, the approach taken to understand such links has been to correlate clinical and psychological measures of language disturbances with patients' performance in various neuropsychological tasks. Below, we review a selection of such studies.

Thought disorder

There have now been several studies reporting correlations between positive thought disorder in schizophrenia and various neuropsychological measures, including distractibility (Docherty & Gordinier, 1999; Harvey & Serper, 1990), selective attention as measured by the Stroop task (Barch *et al.*, 1999), sustained attention as measured by the Continuous Performance Test (Nuecheterlein *et al.*, 1986; Pandurangi *et al.*, 1994; Strauss *et al.*, 1993), measures of executive dysfunction (Nestor *et al.*, 1998) and lower-level information processing deficits such as prepulse inhibition (Dawson *et al.*, 2000; Perry & Braff, 1994). In a recent meta-analysis, Kerns & Berenbaum (2002) reported a strong association between thought disorders and impaired executive functioning.

Single words and concepts

As discussed earlier in the chapter there is some evidence that, under automatic experimental conditions, a faster and/or wider spread of activation across words within the semantic network may underlie positive thought disorder in schizophrenia. One mechanism for this less "focused" activity may be reduced executive control. In line with this hypothesis, there have been some recent reports of significant correlations between measures of executive functioning and semantic priming. In healthy participants, Keifer *et al.* (2005) found that decreased working memory capacity was associated with increased semantic priming, and indirect semantic priming in particular. Poole *et al.* (1999) administered measures of executive dysfunction, response inhibition, motor coordination and intelligence to patients with schizophrenia, and found that only decreased response inhibition was correlated with increased automatic priming (using a short SOA and low RP). Neither motor dyscoordination nor general intelligence was associated with any measures of semantic priming. Interestingly, decreased executive functioning was associated with diminished controlled semantic priming, suggesting that different aspects of executive function may interact with automatic and controlled mechanisms of priming.

Sentences

Earlier in the chapter we discussed evidence that patients with schizophrenia are impaired in comprehending syntactically complex sentences, possibly because of difficulties in combining semantic with syntactic information to assign thematic roles. Condray *et al.* (1996) demonstrated that, in both patient and control groups, working memory capacity, as measured using a reading span task, predicted comprehension accuracy. The authors concluded that observed language comprehension deficits may be related to working memory impairments (see Bagner *et al.*, 2003, for similar findings; and see Kiang *et al.*, 2007, for similar findings with proverb comprehension).

Discourse

The most careful documentation of associations between various measures of clinical and referential language disturbances and performance on various neuropsychological tasks comes from studies by Docherty and colleagues. This group has focused on their detailed measure of referential coherence during language output (discussed above) and has demonstrated associations between referential communication disturbances and poor performance on tasks of immediate auditory memory (Docherty & Gordinier,

1999), auditory distractibility (Docherty & Gordinier, 1999; Hotchkiss & Harvey, 1990), working memory and attention (Docherty *et al*., 1996b). In more recent studies, they have confirmed associations between referential impairments and performance on tasks indexing sustained attention, immediate auditory memory, and conceptual sequencing (Docherty, 2005). Moreover, referential communication failures appear to be better predictors of performance on sustained attention and sequencing tasks than global "thought disorder," as measured using the Thought Language and Communication Scale or structural discourse abnormalities (Docherty, 2005; Docherty *et al*., 1996b).

Interestingly, a study by the same group demonstrated a more specific association between the frequency of one specific type of referential failure (missing information references) and performance on a source-monitoring task (Nienow & Docherty, 2005). The authors hypothesized that missing information references might arise from the speaker being unable to distinguish what they had just thought and what they had vocalized aloud. This finding is interesting as source memory deficits have been hypothesized to underlie other symptoms of schizophrenia such as hallucinations (Ditman & Kuperberg, 2005), and also because such deficits have been previously related to global measures of thought disorder (Harvey, 1985; Harvey & Serper, 1990) and theoretically linked to mechanisms of thought disorder (Frith, 1992).

Language abnormalities and other cognitive dysfunction: summary and conclusions

In sum, there is fairly compelling evidence that clinical and cognitive measures of language dysfunction in schizophrenia can be linked with dysfunction in domains other than language. At the word level, reduced inhibitory control has been associated with increased semantic priming under conditions which bias toward more automatic processing, both in healthy controls and patients with schizophrenia. In addition, reduced executive functioning has been related to decreased controlled semantic priming in schizophrenia patients. At the sentence level, working-memory measures predict comprehension accuracy, while at the level of discourse, measures of sustained attention and sequencing predict referential impairments.

Given these associations and our understanding of schizophrenia as a disorder that affects multiple domains of cognitive function, it becomes particularly important to understand how the mechanisms of language dysfunction in schizophrenia interact with these systems. The normal language processing system does not act in isolation, but is closely linked with working memory and executive mechanisms. There is increasing evidence that variation in working-memory function may account for individual variability in language function amongst healthy individuals, and researchers have developed a number of theories describing the nature of interactions between the language system and cognitive functions in other domains (Caplan & Waters, 1999; Just & Carpenter, 1992). More recently, neuroimaging studies have demonstrated overlaps in the neural circuitry subserving working memory, semantic memory and language function (Barde & Thompson-Schill, 2002; Thompson-Schill, 2003). The challenge now is to understand the nature of such links more precisely so as to determine how they are disturbed in disorders such as schizophrenia. This can be investigated through studies examining relationships between measures of verbal working memory and attention that are believed to specifically interact with the language system, and patients' performance on selected psycholinguistic tasks.

Implications and future directions

Clinical implications

Clinical abnormalities of language and communication in schizophrenia can be very disabling, impacting on all aspects of daily living. In schizophrenia, positive thought disorder is a strong predictor of maladaptive social and vocational functioning (Harrow & Quinlan, 1985; Hoffmann & Kupper, 1997; Norman *et al*., 1999). Yet there have been few attempts to alleviate it via cognitive methods. As reviewed above, the majority of evidence suggests that there is no overall loss of items stored in semantic memory; rather patients seem impaired in accessing and using items appropriately. Encouragingly, the use of strategies such as semantic cuing can improve performance in some semantic tasks, providing some hope that such deficits may be remediable. Cognitive remediation programs in schizophrenia have thus far focused on improving executive, memory and attention functions in schizophrenia, and are in their infancy.

It is also not clear how far they generalize to improving communication or quality of life. Understanding the cognitive basis of language and communication abnormalities in schizophrenia will allow the development of more specific strategies for remediation.

Implications for understanding brain dysfunction in schizophrenia

Another major implication of understanding the cognitive basis of language abnormalities in neuropsychiatric disorders is that, in combination with neuroanatomical and neurochemical measures, it may give new insights into the neurobiology of such disorders as a whole. Functional neuroimaging studies in healthy individuals have established that language and semantic processing are dependent on activity within a widespread network, distributed particularly across prefrontal, inferior parietal and temporal cortices. Many of the same regions are modulated by semantic relationships between individual words in priming paradigms (Kuperberg *et al.*, 2008a; Rossell *et al.*, 2003), sentences (Kuperberg *et al.*, 2003b, 2008b) and whole discourse (Kuperberg *et al.*, 2006b).

In schizophrenia, neuroimaging studies indicate that many of these regions are abnormally modulated during semantic processing (Kubicki *et al.*, 2003; Ragland *et al.*, 2004, 2005; Weiss *et al.*, 2003). In a recent study, Kuperberg *et al.* demonstrated that patients, relative to controls, showed inappropriate increases in activity within temporal and prefrontal cortices to semantically associated (relative to unrelated) word pairs (Kuperberg *et al.*, 2007). At the level of sentences, when integration demands are high, patients, relative to controls, show reduced activity within the superior dorsolateral prefrontal and parietal cortices when integration demands were particularly high (Kuperberg *et al.*, 2008b).

In schizophrenia, there is also evidence of subtle but significant cortical gray matter thinning in many of the same temporal and prefrontal regions that show functional abnormalities (Kuperberg *et al.*, 2003a). Finally, there is some preliminary evidence that semantic abnormalities in schizophrenia may arise from abnormalities within the dopaminergic systems and/or the glutamatergic systems. Increasing dopaminergic and glutamatergic activity can lead to reduced semantic priming under controlled conditions. Kischka *et al.* (1996) demonstrated a decrease in indirect semantic priming (as assessed by reaction time on a speeded lexical decision task) in healthy participants when they were administered 100 mg of L-dopa. This reduced controlled priming may be due to D1/D2 activity; Roesch-Ely reported that pergolide (a D1/D2 agonist), but not bromocriptine (a selective D2 agonist), reduced controlled semantic priming within the right hemisphere in healthy individuals (Roesch-Ely *et al.* 2006). Reduced controlled priming has also been reported in healthy individuals in association with the acute administration of ketamine (an NMDA receptor antagonist leading to increased glutamatergic activity) (Morgan *et al.*, 2006). This is particularly interesting as the administration of ketamine in healthy individuals can lead to clinical language disturbances that are similar to thought disorder (Adler *et al.*, 1998, 1999).

It remains unclear how such cognitive, functional neuroanatomical, structural neuroanatomical and neurochemical findings are related. But it is possible that widespread temporal-prefrontal cortical thinning may reflect widespread abnormalities in cortical synaptic function. This could potentially lead to an inappropriate increase in cortical activity through specific disruption of inhibitory circuitry, and in schizophrenia lead to overdependence on semantic associative links at the expense of building up context through normal modulatory activity. For example, Cohen & Servan-Schreiber (1992, 1993) have proposed that dopamine modulates the signal-to-noise ratio in cortical information processing and have suggested that increased noise in the activity of the dopamine system leads to abnormal "gating" of information into prefrontal cortex, thereby leading to impairments in both the maintenance and updating of contextual information (Braver *et al.*, 1999).

Such relationships are currently speculative. However, with the development of theoretically grounded cognitive models of language processing in neuropsychiatric disorders, it may be possible to draw more specific links with synaptic and molecular models of brain dysfunction.

Conclusions

In this review, we have shown how paradigms at the level of words, sentences and discourse can be used to study neuropsychiatric disorders, and we have reviewed evidence suggesting that schizophrenia patients

show deficits at all these levels of the language code. We are not yet at the point where we can account for all these abnormalities by postulating a single neurocognitive deficit. However, we can provide a broad theoretical framework to help understand the relationships between these levels of dysfunction and to help pave the way towards future theoretically motivated studies.

Abnormalities in semantic memory function and in building up linguistic context in schizophrenia have often been viewed as being distinct deficits. We suggest that they may be functionally related, reflecting two sides of the same coin. For example, in schizophrenia, patients' relative dependence on semantic relationships between individual words may contribute to their impairments in combining meaning with syntactic structure (see Kuperberg, 2007 for a more theoretical discussion). Under most circumstances, patients' relatively unimpaired ability to use semantic relationships between words within sentences would lead to an accurate representation of sentence meaning. However, impairments in combining syntactic with semantic information to build up context could lead to particular problems in selecting the most appropriate meaning of ambiguous words (e.g. homonyms) and expressions (e.g. metaphor or ambiguous idioms). It could also lead to significant problems at the level of discourse, where the build-up of an overall representation of meaning of each sentence is critical to the generation of coherent links between sentences.

Such impairments might account for the clinical observation that the meaning of sentences tends to be driven by semantic relationships between individual words, whilst the meaning of discourse tends to be driven by the meaning of individual sentences, i.e. that local context tends to inappropriately override the build-up of global context in schizophrenia. The real challenge to researchers of language dysfunction in neuropsychiatric disorders is to define the nature of these global-local contextual interactions more precisely in relation to psycholinguistic models of normal language processing, and to understand the mechanisms by which they are impacted upon by working memory, attentional, and executive dysfunction. Tackling these questions seems well worth our while as it has major implications for how we attempt to treat such language and communication disorders, as well as for linking between cognitive, neuroanatomical and neurochemical abnormalities to understand the pathogenesis of such disorders as a whole.

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