COGNITIVE AND PHYSIOLOGICAL CORRELATES OF DISCOURSE COHERENCE DISTURBANCE SYMPTOMS IN SCHIZOPHRENIA

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ABSTRACT

The existing literature on symptoms of thought disorder in schizophrenia does not present a clear picture of the underlying mechanisms involved in these symptoms. This thesis focused on a specific subset of theoretically defined symptoms, namely, discourse coherence disturbance which include symptoms which reflect an inability to maintain a discourse plan. This thesis comprises three studies employing cognitive or physiological measures in the attempt to discover the physiological and cognitive mechanisms underlying symptoms of discourse coherence disturbance in schizophrenia. The first study was a series of case studies investigating cognitive performance in patients with schizophrenia exhibiting symptoms of discourse coherence disturbance. Eight patients with a DSM-IV and ICD-10 diagnosis of schizophrenia exhibiting varying degrees of discourse coherence disturbance were compared to a group of nineteen comparison volunteers. Based on four current theories of discourse coherence disturbance, a range of cognitive areas, including short and long-term memory, semantic priming, contextual naming, working memory, verbal fluency, error-monitoring, and inhibition were explored. Patients with discourse coherence disturbance differed from controls and patients without discourse coherence disturbance on measures of central executive processes of working memory, verbal fluency, and error-monitoring. These results were consistent with McGrath’s (1991) theory that discourse coherence disturbance is due to a disconnection between thought and action reflected in disconnectivity between frontal and temporoparietal regions. The second and third studies were designed to further investigate the predictions of McGrath’s theory. The second study explored the role of the dorsolateral prefrontal cortex in patients with discourse coherence disturbance. Five patients with schizophrenia with varying degrees of discourse coherence disturbance and sixteen healthy comparison volunteers participated in an event-related fMRI study exploring activation in the dorsolateral
prefrontal cortex during a working memory task. This study showed that although patients with discourse coherence disturbance performed poorly on tasks typically associated with activation in the dorsolateral prefrontal cortex, such as working memory tasks, they showed normal activation of the dorsolateral prefrontal cortex while performing these tasks. The third study aimed to explore the interaction between the dorsolateral prefrontal cortex and other brain regions, as well as exploring the nature of the error-monitoring deficit in patients with discourse coherence disturbance. Six patients with discourse coherence disturbance, nine patients without discourse coherence disturbance, and fifteen healthy comparison volunteers participated in an ERP testing session investigating error negativity (ERN) in relation to performance on a reaction time task. The results of this study showed that patients with discourse coherence disturbance are able to detect errors, but are unable to correct them which is consistent with McGrath’s (1991) hypothesised disconnection between thought and action. Further, these patients showed a similar ERN profile to patients with lesions of the dorsolateral prefrontal cortex. These results suggest that impaired interaction between the anterior cingulate and the dorsolateral prefrontal cortex may account for symptoms and cognitive deficits found in patients with discourse coherence disturbance. Given the role of the anterior cingulate in modulating fronto-temporal interactions, it is proposed that there is a disruption to dorsolateral prefrontal networks resulting from impaired communication between the anterior cingulate and dorsolateral prefrontal cortex.
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OVERVIEW

Since the original conception of schizophrenia by Bleuler (1911/1950), formal thought disorder has been described as a central sign\(^1\) in these patients (Cozolino, 1983). Formal thought disorder\(^2\) is a term which has been used to describe a number of observable speech disturbances in patients with schizophrenia including derailment, tangentiality, poverty of speech, perseverations, and idiosyncratic speech (Peralta, Cuesta, & de Leon, 1992).

The focus of this thesis is a subset of thought disorder symptoms, namely, discourse coherence disturbance, including symptoms such as nonsequitur responses, tangentiality, derailment, distractible speech, and loss of goal (Berenbaum & Barch, 1995). The aim of the thesis is to investigate the cognitive and neurological bases of discourse coherence disturbance, relying on theoretical models of these symptoms, in an attempt to overcome some of the problems which have been present in schizophrenia research to date.

This thesis will start by describing the theoretical background of research into thought disorder. In Chapter 2, current theories of thought disorder will be described and reviewed in light of existing literature. Chapters 3-5 will present the findings of the three studies conducted to investigate discourse coherence disturbance in schizophrenia.

\(^1\) Although formal thought disorder is a sign, not a symptom, of schizophrenia, the term "symptom" is commonly used in the literature and will be retained throughout this thesis.

\(^2\) Throughout this thesis, the term "thought disorder" will be used to refer to formal thought disorder symptoms, rather than a disorder of the content of thought, such as delusions.
The first of these studies was a cognitive case study looking at a wide range of cognitive deficits in discourse coherence disturbance. The cognitive areas assessed were based on the theories and cognitive deficits reviewed in Chapter 2. The studies described in Chapters 4 and 5 arose from the findings of the cognitive case study.

Chapter 4 describes a study which used functional Magnetic Resonance Imaging (fMRI) to investigate the role of the dorsolateral prefrontal cortex in patients with discourse coherence disturbance. Chapter 5 describes a study which used Event Related Brain Potentials (ERPs) to determine whether patients with discourse coherence disturbance are aware of their errors, and to explore the relationship between the anterior cingulate and dorsolateral prefrontal cortex in these patients. Finally, in Chapter 6, the results of the three studies are related to the theoretical and cognitive literature discussed in Chapters 1 and 2.
1.1 What is discourse coherence disturbance?

Discourse coherence disturbance symptoms are a subset of those symptoms termed “thought disorder” exhibited by some patients with schizophrenia (Berenbaum & Barch, 1995). Although the term “thought disorder” has been used, these symptoms are manifest in the speech of schizophrenic patients, rather than their thought content. The use of the term “thought disorder” is based on the assumption that these language problems reflect deficient thought processes.

Traditionally, thought disorder symptoms have been treated by researchers either as a homogeneous cluster of symptoms, or been divided into positive and negative symptoms. Positive thought disorder includes symptoms such as incoherence, while negative thought disorder includes poverty of speech, poverty of content etc (Andreasen, 1984a; Andreasen, 1984b; Liddle, 1987). However, the term “thought disorder” covers a range of symptoms and there is considerable variability in the specific thought disorder symptoms exhibited by different patients. Furthermore, thought disorder symptoms fluctuate over time, and the same patient will exhibit heterogeneity of symptoms when assessed at different times (Maher, 1983). There is a growing awareness in the field that the heterogeneity within symptoms of thought disorder necessitates investigation of specific types of thought disorder. Consequently, there have been a number of recent attempts to divide thought disorder symptoms into theoretically meaningful categories (see for example Peralta et al., 1992).

Of particular interest in this thesis, is the categorisation of thought disorder symptoms by Berenbaum and Barch (1995; Barch & Berenbaum, 1997). Berenbaum and Barch used ratings from linguists and non-linguists to develop four categories of
thought disorder symptoms: fluency disturbance; discourse coherence disturbance; content disturbance; and disturbances in social convention. The fluency category consists of symptoms indicating an inability to produce grammatically correct and understandable speech. Symptoms in this category include symptoms such as paraphasia, neologisms, echolalia, and incoherence. Discourse coherence disturbance refers to speech which is difficult for the listener to follow. It includes symptoms such as non-sequitur responses, tangentiality, derailment, distractible speech, and loss of goal. The content category refers to disturbances in the content, rather than the form, of speech, and includes self-reference, perseveration, confabulation, and illogicality. Finally, the social convention category includes symptoms which violate social conventions of speech, such as including too much or too little information. Symptoms included in this category include poverty of content, circumstantiality, and stilted speech.

Berenbaum and Barch’s (1995; Barch & Berenbaum, 1997) division of thought disorder symptoms into disturbances in fluency, disturbances in discourse coherence, disturbances in content, and disturbances in social convention has been particularly useful theoretically, and a number of theories have been posited to explain various symptom clusters. This thesis focuses on symptoms of discourse coherence disturbance, where there is a dysfluency between the speaker and the listener. Patients with discourse coherence disturbance have relatively intact linguistic systems: their grammar, syntax, and phonological encoding are unimpaired, and there is no apparent comprehension deficit (Berenbaum & Barch, 1995; Mazumdar, Chaturvedi, & Gopinath, 1994; Straube & Oades, 1992). However, these patients exhibit a tendency to lose track of what they are saying, become distracted by irrelevant information in the environment, and are unable to adapt their speech to take into account the needs of the listener (Barch & Berenbaum, 1997; Berenbaum & Barch, 1995).
Specific symptoms of discourse coherence disturbance include distractible speech, tangentiality, derailment, non-sequitur responses, and loss of goal. *Distractible speech* occurs when the speaker loses track of what they are saying because they are distracted by external stimuli. They introduce the irrelevant, external information into their speech. For example:

"Then I left San Francisco and moved to ... Where did you get that tie? it looks like it’s left over from the fifties. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba-diving?"


*Tangentiality* involves answering a question off the point, ie, in a tangential or irrelevant manner. For example:

*Interviewer:* "What city are you from?"  *Patient:* "Well, that’s a hard question to answer because my parents ... I was born in Iowa, but I know that I’m white instead of black so apparently I came from the North somewhere and I don’t know where, you know, I really don’t know where my ancestors came from ..." (Andreasen, 1986, p. 476).

*Derailment* occurs when the speaker gradually slips further and further off the point as they are talking. Each point is obliquely related to the previous point, but eventually the discourse has no relevance to the initial question or discourse plan. For example:

*Interviewer:* “Did you enjoy doing that?”  *Patient:* “Um-hm. Oh, hey, well, I, I, oh, I really enjoyed some communities I tried it, and the next day when I’d be going out, you know, um, I took control like, uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago and she was
going to the junior college. And we lived in the Y.W.C.A. so she wanted to put it, um peroxide on my hair, and she did, and I got up and looked at the mirror and tears came to my eyes. Now do you understand, I was fully aware of what was going on but why couldn't I, why, why the tears?... “


Non-sequitur responses involve a logical inference which is not warranted or does not make sense. For example:

“Parents are the people that raise you. Anything that raises you can be a parent.” (Andreasen, 1986, p. 478).

Loss of goal occurs where the speaker gradually wanders off the point of what they are saying and never returns to the original speech plan (Andreasen, 1986). Loss of goal is very similar to derailment in its manifestation, except that it is more severe and the speaker never recovers the point of what they intended to say.

1.2 Cognitive vs linguistic approaches to the study of Formal Thought Disorder

There have been three main classes of theories attempting to explain thought disorder in schizophrenia. Two of these classes emphasise linguistic processes as the basis for thought disorder, and one focuses on the role of cognitive processes in thought disorder. The first class of theories posits that thought disorder symptoms are due to the inability to use the rules of grammar or syntax (Chaika, 1974). There is a small subgroup of patients with thought disorder who exhibit significant language dysfunction resembling aphasia (Faber & Reichstein, 1981; Landre, Taylor, & Kearns, 1992). However, most research indicates that syntactic and grammatical competence is intact in patients with formal thought disorder (Berenbaum & Barch, 1995; Mazumdar et al., 1994; Straube & Oades, 1992).
The second class of theories focuses on deficits in the pragmatic use of language, i.e., they assume that the grammatical aspects of language are preserved but patients with thought disorder are unable to use the social rules of communication to guide their speech. There is some evidence of deficits in schizophrenic speech at the pragmatic level (Thomas, 1995). Deficits in pragmatics seem to underlie thought disorder symptoms such as poverty of speech, pressure of speech, poverty of content, and distractible speech, which largely fall into Berenbaum and Barch’s (1995) social convention category of thought disorder symptoms (Thomas, 1995).

The third category of theories is focused on cognitive deficits which may underlie symptoms of thought disorder. There is considerable evidence that thought disorder is associated with a number of cognitive deficits such as increased distractibility (Caplan, Foy, Asarnow, & Sherman, 1990), impaired verbal memory and executive function (Nestor et al., 1998), and poor sustained attention (Pandurangi, Sax, Pelonero, & Goldberg, 1994).

To a large extent, the development of either linguistic or cognitive explanations of thought disorder has depended on the theoretical assumptions of the particular researcher. The assumptions of a particular field with respect to the relationship between thought and language can be observed in the direction in which their theories develop. For example, linguists tend to focus on linguistic, rather than cognitive processes, and the way in which the linguistic environment of a specific culture affects the thought of individuals within that environment (see for example Whorf, 1956). Research into aphasia has traditionally been conducted by linguists, in contrast to research into thought disorder which tends to be psychological. Traditional linguistic approaches to aphasia (and more recent linguistic analyses of schizophrenic thought disorder, see Chaika, 1974), have viewed the disorder as arising from a disruption to the linguistic system (Schacter, McAndrews, & Moscovitch, 1988). In contrast,
psychological approaches to thought disorder, have focused on the cognitive correlates of disordered speech, reflecting their bias that thought precedes language.

With respect to thought disorder, the use of the term "thought" can be seen to reflect the psychological history of this concept. Schizophrenia has been traditionally investigated by psychiatrists and psychologists, and consequently, the language disruption in schizophrenia, namely, thought disorder has been viewed as reflecting thought disturbances due to impairments in specific cognitive processes. However, the bidirectionality of this relationship cannot be ignored, and it is possible that schizophrenic thought disorder has been investigated by psychologists because it tends to be associated with cognitive deficits. Linguists may have avoided thought disorder because of the apparent lack of linguistic disturbance in these patients. The types of language problems in each of these disorders confirms the fact that the approach taken is dependent on the sort of language problems exhibited. Generally, aphasic patients show language disturbances at the phonological, lexical, and syntactic level (Glosser & Deser, 1990; Ulatowska & Chapman, 1994). Consequently, a linguistic approach is more useful in explaining the mechanisms operating in aphasia because the symptoms seem to reflect specific linguistic impairments rather than general cognitive impairments. By contrast, schizophrenic speech disturbances seem to involve linguistic impairments at conceptual, semantic, or pragmatic levels with relatively intact phonological, lexical, and syntactic processing (Berenbaum & Barch, 1995; Mazumdar et al., 1994; Straube & Oades, 1992). Thus thought disorder seems to involve more general cognitive deficits than aphasia. A similar parallel can be found in patients with Alzheimer's disease who also suffer speech disturbances as the disease develops. Similarly to patients with schizophrenia, patients with Alzheimer's disease exhibit impairments at a macrolinguistic level with relatively intact microlinguistic abilities suggesting impairments in higher order cognitive processes such as attention, memory,
and executive control (Ehrlich, 1994; Glosser & Deser, 1990). Where the impairment is at a macrolinguistic level, an assumption that the thought disturbance precedes the language disturbance appears to be warranted, whereas impairments at a microlinguistic level seem to reflect specific linguistic disturbances (Glosser & Deser, 1990). The lack of general cognitive impairments in patients with aphasia showing impaired speech production is confirmed by their relatively intact performance on non-verbal cognitive tasks (see above; cf Archibald, Wepman, & Jones, 1967; Glosser & Goodglass, 1990; Kertesz, 1988; Kertesz & McCabe, 1975; Vignolo, 1999).

The approach of this thesis is to attempt to understand symptoms of discourse coherence disturbance in terms of disturbances in cognitive and physiological processes. As noted above, a number of converging lines of evidence suggest that symptoms of thought disorder in schizophrenia are best explained in terms of cognitive processes. Thought disorder symptoms are associated with cognitive impairments, and there is little or no language deficit, particularly at a microlinguistic level. This is also the case for symptoms of discourse coherence disturbance, such as tangentiality, derailment, and loss of goal, which have been shown to be primarily associated with cognitive, not linguistic deficits (Caplan et al., 1990; Goldberg et al., 1998; Landre & Taylor, 1995; Speed, Toner, Shugar, & DiGasbarro, 1991). This is reflected in current theoretical models of discourse coherence disturbance which focus on cognitive and physiological processes related to these symptoms.

1.3 Group studies vs case studies

Most studies of thought disorder to date have been relatively large group studies of patients exhibiting any symptoms of thought disorder, or of patients exhibiting either positive or negative symptoms of thought disorder (see for example Goldberg et al., 1998; Rossell & David, 1997; Serper, 1993). Generally, these studies examined only
one or two of the cognitive processes believed to underlie thought disorder symptoms at any one time. As a result of large studies of heterogeneous patients, attempts to replicate specific findings in patients with thought disorder in different patient populations have often led to complicated, inconsistent findings (cf semantic priming; Barch et al., 1996). This combined with inconsistency with respect to the specific thought disorder symptoms focused on has prevented the development of a consistent and unified body of knowledge. Furthermore, at present, it is not clear whether cognitive deficits related to symptoms of thought disorder fluctuate with changing symptomatology, but this is clearly a factor which needs to be considered when investigating these symptoms given the fluctuation in thought disorder symptoms over time (Maher, 1983).

There are a number of problems inherent in large group studies (Shallice, Burgess, & Frith, 1991). First, where only one or two cognitive domains are investigated, poor performance may be due to a generalised deficit, rather than the specific area of cognitive impairment assumed to be causing poor performance. On this point, it is important that where case studies are applied to schizophrenic thought disorder, that the testing be extensive in order to provide an accurate reflection of the cognitive profile of these patients (Shallice, 1988). Secondly, the heterogeneity in thought disorder symptoms means that poor group performance may amalgamate different deficits present in different subsets of patients (Shallice et al., 1991). Although power to detect an effect increases with increasing group size, this only applies if all other things are equal. If increased variability in the patient sample accompanies increased group size, any benefit gained from the larger sample size will be lost (Chassan, 1979).

In contrast to studies of schizophrenia, cognitive neuropsychological studies of disorders such as aphasia typically employ a case study approach. In
fact, so strong is the assumption in cognitive neuropsychology that case studies are an appropriate method for investigating syndromes that in order to present the results of group studies, researchers in the field are expected to establish homogeneity of the group in question or to analyse the results individually for each patient, ie, apply a case study approach (Caramazza, 1986; Shallice, 1988). The justification for this is that although patients may share prominent features, categorising them according to these features and ignoring differences in symptoms profiles fails to take into account differences in other areas which may be important (Goodglass & Wingfield, 1998). Furthermore, researchers have relied on the case study approach in aphasia because the nature of the lesion is not always clear and case studies allow individual cognitive profiles of patients to be constructed. Researchers can use the case-study approach to gain information about the nature of the lesion by comparing their results to other patients with known lesions. This not only provides information about the etiology of the aphasic symptoms, but can also provide information about which cognitive processes are implicated in specific language abilities (Caramazza, 1988). Case studies also allow research to be conducted in fields where theoretical constructs are changing rapidly. By focusing on symptoms in individual patients, the problem of repeating studies with different patients each time a new theoretical framework and new syndromes are proposed is avoided (Ellis, 1987).

Similar problems to these can be raised with respect to patients with schizophrenia and thought disorder symptoms. The symptoms and causes of schizophrenia are heterogeneous, and there have been numerous different attempts to categorise patients with schizophrenia depending on different theoretical frameworks (see for example Andreasen, Arndt, Alliger, Miller, &
As with aphasia, extensive studies of smaller groups of patients with relatively similar symptom profiles may be a more profitable approach, providing information about the etiology of symptoms as well as providing an opportunity to relate processes in patients with schizophrenia to models of normal cognitive functioning. Within the last decade, there has been a greater willingness to employ case studies to the investigation of symptoms of schizophrenia, including thought disorder (Laws, Kondel, & McKenna, 1999; Seidman, 1990; Shallice et al., 1991).

The main criticism of the case study approach is that there is a lack of generalisability where only a small number of patients are studied (Hersen & Barlow, 1976). While case studies may provide a useful tool for investigating symptoms in schizophrenia, their lack of generalisability gives them limited utility. Arguably, the optimal approach to the study of symptoms of thought disorder is to use case studies to identify specific areas of consistent impairment within a small number of patients exhibiting similar symptomatology, then to use this information to conduct larger studies using carefully selected patients to test the generalisability of the results from the case study.

This thesis comprises a series of case studies to investigate theoretical models focusing on cognitive and physiological abnormalities in patients with discourse coherence disturbance. There is also a preliminary attempt to broaden some of these findings to a larger group of patients selected on the basis of specific symptoms of discourse coherence disturbance.

1.4 Summary

This chapter was devoted to a description of discourse coherence disturbance symptoms and a discussion of the possible approaches to investigate these symptoms in...
patients with schizophrenia. The tendency for research into schizophrenia to involve large group studies has obscured areas of cognitive impairment specific to particular symptoms, such as discourse coherence disturbance. In order to overcome this problem, this thesis focuses on a specific set of clearly defined symptoms in a small group of carefully selected patients. The theoretical models guiding this investigation are presented and reviewed in Chapter 2.
CHAPTER 2

FOUR THEORETICAL MODELS OF DISCOURSE COHERENCE DISTURBANCE

2.1 Theories of discourse coherence disturbance

The aim of this thesis is to distinguish between four theories that have attempted to explain the processes underlying discourse coherence disturbance in schizophrenic patients. The first of these theories focuses on executive functions and monitoring deficits (McGrath, 1991; McGrath et al., 1997), the second focuses on impaired perspective (Harrow, Marengo, & Pogue-Geile, 1987), the third focuses on planning (Hoffman, 1986; Hoffman, Stopek, & Andreasen, 1986), and the last theory emphasises semantic memory and working memory (Nestor et al., 1998). The thesis examines these theories at two inter-related levels, namely, the cognitive and physiological level. These areas are intertwined in the theories of discourse coherence disturbance, and in this thesis, evidence from both levels are used to investigate the mechanisms of discourse coherence disturbance in schizophrenia. This chapter outlines the theories to be investigated and reviews these theories in light of existing literature.

All four theories of discourse coherence disturbance predict a disruption to normal speech production processes. In all cases, it is hypothesised that the specified disruptions will be evident as impairments in particular areas of cognitive functioning. The general assumption is that the disruption to speech production results from specific cognitive impairments, but it is also possible that there is another factor operating which affects both cognitive and speech performance. In any event, an association between
symptoms of discourse coherence disturbance and certain cognitive deficits, will provide support for and enable differentiation between the above theories.

2.1.1 Disruption between planning and action.

McGrath (1991; McGrath et al., 1997) suggests that producing normal speech involves sophisticated processes which allow the speaker to translate broad, complex concepts into speech which is a comparatively simplified, linearly organised process. In order to achieve this translation, the speaker must generate and maintain a plan of speech and monitor their speech with reference to this plan. Thus speech involves an ongoing interaction between central executive processes such as planning, monitoring, and editing, and the processes which produce and coordinate motor responses.

McGrath (1991; et al., 1997) proposes that discourse coherence disturbance is due to impaired ability to maintain a speech plan, reflecting an underlying disconnection between thought and action such that central executive ability is disconnected from speech production in thought disordered patients. As a result of the disconnection between thought and action, patients are unable to use their knowledge to edit their speech effectively, leading to a failure to execute the discourse plan they have generated. McGrath (1991) suggests that this disconnection between thought and action reflects disruption at a physiological level to the neural circuit between the prefrontal cortex (involved in planning and editing) and temporoparietal regions (involved in semantic monitoring) via subcortical structures such as the globus pallidus, caudate nucleus, and thalamus (which regulate speech production; Crosson, 1985; Dalton & Hardcastle, 1977; Mega & Cummings, 2001).
At a more specific cognitive level, McGrath hypothesises that patients exhibiting discourse coherence disturbance will show deficits in tasks such as verbal fluency, planning tasks, and working memory tasks which require sophisticated integration of planning, monitoring, and editing to produce the required or optimal action. Because of the disconnection between frontal and temporoparietal regions, patients will perform poorly on these tasks, and will be unable to use information about their own performance to correct their errors (see Table 2.1).

At a physiological level, McGrath’s principal prediction is that patients with discourse coherence disturbance will show disruptions to the circuit between frontal and temporoparietal regions which proceeds via subcortical pathways. This circuit is important in speech monitoring, particularly monitoring semantic aspects of speech (Crosson, 1985; Mega & Cummings, 2001). Connections between the frontal cortex and temporoparietal regions are also implicated in working memory processes, particularly those requiring online manipulation of information (Cohen et al., 1997; Friedman & Goldman-Rakic, 1994; Collette et al., 1999; D’Esposito, Postle, Ballard, & Lease, 1999; Garavan, Ross, Li, & Stein, 2000; Goldman-Rakic, 1996; Mellers, et al., 1995; Petrides, Alivisatos, Meyer, & Evans, 1993; Roberts & Pennington, 1996; Salmon et al., 1996; Van der Linden et al., 1999).

2.1.2 Missing the conversational context

In explaining normal speech, Harrow et al. (1987) focus on the importance of context and the interaction between the speaker and the listener. In order to conform with Grice’s (1975) cooperative principle, Harrow et al. argue that the speaker must continually assess and take account of the context in which they are speaking and modify their speech according to this context.
The context of speech includes the listener’s needs, socially acceptable standards of speech, the speaker’s predictability etc. Harrow et al. used the term “perspective” to describe the ability to recognise and incorporate the appropriate contextual demands.

Harrow et al. (1987) propose that discourse coherence disturbances in schizophrenic thought disorder result from the patient’s inability to comply with Grice’s (1975) cooperative principle. Due to a lack of contextual knowledge and awareness, the speaker is unable to incorporate the conversational context into their discourse plan and to adjust their speech to take account of this context. Harrow et al. hypothesise that the inability to comply with the cooperative principle results from impaired perspective in patients with discourse coherence disturbance (Harrow & Quinlan, 1985; Lanin-Kettering, Harrow, & Prosen, 1987). These patients allow personal material to intermingle with their speech at inappropriate times, and their speech is guided by inappropriate personal themes. That is, patients with discourse coherence disturbance become distracted from the needs of the listener and the demands of the contextual setting in which they are speaking (Harrow et al., 2000). This makes it difficult for the listener to make sense of their speech.

Appropriate use of perspective involves accessing long-term memory to assess whether behaviour is socially and semantically appropriate in a particular situation, and monitoring behaviour to ensure that it conforms to the appropriate standards. Since Harrow et al.’s (1987) theory focuses on coordination between long-term memory and current contextual processing, specific cognitive deficits predicted by this theory are impaired long-delay recall, impaired contextual processing, and impaired monitoring (see Table 2.1). Physiologically, these cognitive processes involve temporal regions, such as the hippocampus, which are involved in forming memory traces and in conscious recollection of
information from memory (Markowitsch, 2000; Moscovitch, 1992; Squire & Knowlton, 2000), left temporoparietal regions involved in contextual processing (Holcomb, 1993; Kutas & Hillyard, 1982; Kutas & Hillyard, 1983), and frontal and cingulate regions which are associated with monitoring (Carter, Braver et al., 1998; Gehring & Knight, 2000; Kiehl, Liddle, & Hopfinger, 2000; Menon, Adleman, White, Glover, & Reiss, 2001).

2.1.3 Inability to form a discourse plan

Hoffman (1986) and others (see for example Barch & Berenbaum, 1997) focus on planning as the principal process in normal speech. They suggest that normal speakers generate an abstract cognitive plan prior to discourse which reflects the gist or intention of what they intend to say. These planning structures are not conscious, but are cognitive precursors to speech (Hoffman et al., 1986). The discourse plan is fundamental to coherent speech: it is sensitive to the goals and beliefs of the speaker, and is used to coordinate the speaker’s fragmented ideas and thoughts into a meaningful and coherent whole (Dalton & Hardcastle, 1977; Levelt, 1989). During discourse, the speaker relies on working memory to store and access the discourse plan and other information necessary to guide their speech (Docherty et al., 1996).

Hoffman proposes that patients exhibiting discourse coherence disturbances are unable to generate or maintain a discourse plan. Due to cognitive impairments such as poor working memory and inability to sustain attention, patients lack the cognitive resources required to generate an appropriate discourse plan. Their speech is disordered because they are attempting to produce speech based only on an abstract intention to speak without a concrete discourse plan which is a necessary prerequisite of coherent speech (Hoffman, 1986). The result of this is that patients rely on phonetic similarities and word play in speech because they are unable to access appropriate strategies to
guide their speech. Speech appears disjointed and incoherent because patients are unable to translate the ideas they wish to communicate into appropriately structured and meaningful speech.

Specific cognitive deficits predicted by Hoffman (1986) include impaired working memory and sustained attention which are hypothesised to be important elements in discourse planning. In order to create and manipulate these planning structures, working memory is required. Therefore, if working memory is impaired, discourse will be similarly impaired. At a higher level, Hoffman predicts a general planning deficit in thought-disordered patients as a result of the underlying impairments in working memory and sustained attention (see Table 2.1).

Physiologically, this theory predicts impairments in regions associated with the planning, sustained attention, and working memory. Planning ability, including discourse planning, appears to be localised to the prefrontal cortex, particularly the dorsolateral or mesial prefrontal regions (Faglioni, 1999; Robbins, 1996; Robbins, 1998; Sirigu et al., 1995; Stuss & Benson, 1984); the right frontal-parietal network seems to be particularly important for sustained attention (Fernandez-Duque & Posner, 2001; Jackson, Marocco, & Posner, 1994; Mennemeier et al., 1994; Posner & Badgaiyan, 1998; Posner & Petersen, 1990; Wilkins, Shallice, & McCarthy, 1987); and working memory processes involve activation of the prefrontal cortex and more posterior regions such as the parietal cortex, premotor areas, and the cingulate gyrus (Cohen et al., 1997; Friedman & Goldman-Rakic, 1994; Goldman-Rakic, 1996; Mellers, et al., 1995; Petrides et al., 1993; Roberts & Pennington, 1996; Salmon et al., 1996; Van der Linden et al., 1999).
2.1.4 Retrieving material from semantic memory

Nestor et al. (1998) focus on the interaction between semantic memory and working memory in speech production. Normally, each representational element of semantic memory is associated with an activation level with a corresponding threshold value. If activation exceeds the threshold value, the element enters into working memory. In addition, models of semantic memory (Neely, 1991) propose that spreading activation to semantically related elements within semantic memory occurs rapidly, automatically, without the person's intention or awareness, and facilitates processing of semantically related information.

According to the activation-based semantic network model of memory, memories are stored in an associative network in which the strength of each concept's representation depends on the frequency of use; and the strength of connections between concepts depends on their frequency and recency of co-occurrence (Ayers & Reder, 1998). When a concept representation is activated, all other associated representations are activated, the extent of this activation depending on the strength of the connection between associated representations. Normally, each representational element of semantic memory is associated with an activation level with a corresponding threshold value. If activation exceeds the threshold value, the element enters into working memory. The automatic spreading activation model of memory is supported by semantic priming data, although other mechanisms are also necessary to fully account for these data (Neely, 1991).

Normal speech relies on an interaction between semantic memory and working memory so that material the speaker wishes to communicate can be readily accessed from semantic memory by working memory. Once the information is in working memory, it is manipulated and coordinated to produce coherent speech. Nestor et al.
(1998; 2001) explain discourse coherence disturbance in terms of dysfunction in working memory and semantic memory systems. They suggest that temporal lobe pathology (Shenton et al., 1992) present in schizophrenia results in a reduction of the threshold values of representational elements within semantic memory. As a result, elements of semantic memory can more readily enter into working memory which becomes overloaded. As well as the reduction in semantic memory threshold parameters, there is a prefrontal, working memory impairment which prevents effective inhibition of irrelevant material once it enters into working memory. Roberts and Pennington (1996) explored the interaction between inhibition and working memory with respect to prefrontal function. They argued that tasks which tap into prefrontal processes require both inhibition of incorrect, prepotent responses, and working memory activation to generate a correct response. Inhibition is dependent upon intact working memory processes: if working memory is strongly generating appropriate responses, inappropriate responses are inhibited by default (Engle, 2001). With respect to Nestor et al.’s theory, prefrontal pathology in patients with discourse coherence disturbance prevents these patients from being able to generate an appropriate response and to inhibit inappropriate responses entering working memory due to overactivation of semantic memory.

Nestor et al.’s (1998) theory specifically predicts deficits in working memory and inhibition, combined with increased spreading activation in semantic memory in patients with discourse coherence disturbance. The increased activation of semantic information is a direct result of lowered threshold parameters of individual elements in semantic memory (see Table 2.1). In terms of physiological processes, Nestor et al. predict abnormal temporal lobe and frontal lobe functioning. Automatic spreading activation of the semantic network seems to rely predominantly on the left temporal lobe (Abernethy & Coney, 1996; Rossell, Bullmore, Williams, & David, 2001), while
working memory processes (see Section 2.1.1) and inhibitory processes are most strongly associated with prefrontal networks (Kawashima et al., 1996; Liddle, Kiehl, & Smith, 2001; Menon, Adleman et al., 2001; Passingham, 1993; Sasaki, Gemba, Nambu, & Matsuzaki, 1993; Stuss & Benson, 1984).

2.1.5 Distinguishing between theories

An obvious problem with testing these theories, is the large overlap between them in terms of predicted cognitive and physiological impairments. However, although these theories have many overlapping components, there are aspects of the models which distinguish them: each theory proposes at least one impairment in a unique cognitive domain that is not shared by others (see Table 2.1). These unique predictions form the four sets of hypotheses to be assessed in light of existing literature, and to be tested in Chapter 3.

Hypothesis 1

McGrath (1991) predicts disconnection between the central executive and motor response manifest at a cognitive level in an inability to utilise errors to correct behaviour, and at a physiological level in a disruption to the prefrontal-temporoparietal neural circuit. If McGrath’s theory is correct, patients with discourse coherence disturbance should show the following cognitive and physiological deficits:

1. impaired ability to maintain a discourse plan
2. a central executive working memory deficit
3. impaired ability to correct errors
4. disruptions to the neural circuit involving the prefrontal cortex and temporoparietal regions proceeding via subcortical regions
Hypothesis 2

Harrow et al. (1987) predict impaired ability to utilise contextual information at a cognitive level, and specific temporoparietal deficits at a physiological level. If Harrow’s theory is correct, patients with discourse coherence disturbance should show the following cognitive and physiological deficits:

1. impaired contextual processing
2. impaired monitoring
3. impaired long-term memory
4. disturbances in temporoparietal activation
5. impaired prefrontal activation

Hypothesis 3

Hoffman et al. (1986) predict impaired sustained attention, as well as a specific prefrontal deficit. If Hoffman’s theory is correct, patients with discourse coherence disturbance should show the following cognitive and physiological deficits:

1. inability to generate a discourse plan
2. central executive working memory deficit
3. impaired sustained attention
4. impairments in prefrontal lobe functioning
Table 2.1 A summary of impaired (×) and preserved (✓) cognitive and physiological processes predicted by each of the four theories of discourse coherence disturbance. (–) denotes an absence of specific prediction for this process.

<table>
<thead>
<tr>
<th>Planning</th>
<th>McGrath</th>
<th>Harrow</th>
<th>Hoffman</th>
<th>Nestor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generate</td>
<td>✓</td>
<td>–</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Maintain</td>
<td>×</td>
<td>–</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Central executive</td>
<td>×</td>
<td>–</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Semantic Memory</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>–</td>
<td>×</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Error-monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error detection</td>
<td>✓</td>
<td>×</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Error correction</td>
<td>×</td>
<td>×</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Contextual processing</td>
<td>–</td>
<td>×</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Inhibition</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>–</td>
<td>–</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Physiological predictions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal-temporoparietal connectivity</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Temporoparietal areas</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prefrontal lobe</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>

Hypothesis 4

Nestor et al. (1998) predict facilitated automatic semantic priming at a cognitive level, and a combination of temporal lobe and frontal lobe pathology in patients with discourse coherence disturbance. If Nestor’s theory is correct, patients with discourse coherence disturbance should show the following cognitive and physiological deficits:

1. over-activation of the semantic network

2. central executive working memory deficits
3. impaired inhibition
4. impaired prefrontal lobe function
5. disturbed temporal lobe activation

2.2 The status of existing research into cognitive deficits in discourse coherence disturbance

The cognitive processes that are central to differentiating the above theories of discourse coherence disturbance are planning, working memory, semantic memory, long-term memory, error-monitoring, contextual processing, inhibition, and sustained attention. Hence, this review of the cognitive deficits associated with discourse coherence disturbance is confined to these cognitive areas. Numerous studies have investigated the relationship between cognitive deficits and thought disorder symptoms in patients with schizophrenia. Unfortunately, many of these studies have failed to distinguish between different thought disorder symptoms, while those that have attempted some differentiation have clustered symptoms inconsistently, eg, poverty of content has been defined as both a negative and positive symptom (Andreasen, 1984a; Andreasen, 1984b; Andreasen & Grove, 1986; Liddle, 1987; Marengo, Harrow, & Edell, 1993; Pandurangi et al., 1994). As a result, it is difficult to form a clear picture of how cognitive processes relate to thought disorder and, of particular interest in this thesis, which cognitive processes relate to discourse coherence disturbance. Despite the fact that it is difficult to isolate the specific cognitive deficits associated with discourse coherence disturbance based on existing research, a review of the literature on cognitive deficits in schizophrenic patients with thought disorder provides an indication of the areas of possible impairment which have provided the focus for theories of discourse coherence disturbance reviewed previously.
2.2.1 Planning in discourse coherence disturbance

There are two elements of planning that are relevant to theories of discourse coherence disturbance. First, the inability to generate a discourse plan forms a central part of Hoffman's theory of discourse coherence disturbance (see Section 2.1.3). Secondly, McGrath's theory predicts that due to executive function and monitoring impairments, patients with discourse coherence disturbance are unable to maintain a discourse plan after it has been generated (see Section 2.1.1).

With respect to the generation of a discourse plan, Barch and Berenbaum (1996) found that impaired ability to generate a discourse plan was associated with incompetent references. Incompetent references were defined as "a demonstrative, personal, or comparative reference with either an unrecoverable referent or with two or more possible referents" (Barch & Berenbaum, 1996, p. 83), ie, the speech contained elements which the listener was not able to understand because the speaker failed to provide sufficient information about what was meant. Incompetent references would probably fall into the discourse coherence disturbance category of thought disorder (Berenbaum & Barch, 1995). There was no association between impaired ability to generate a plan and discourse coherence disturbance symptoms such as tangentiality, derailment, or illogicality. In this study, participants were required to select five out of twenty pictures that were relevant to a discourse topic they were given. Failure to select appropriate pictures was assumed to reflect an inability to generate an appropriate discourse plan. Only patients exhibiting incompetent references were impaired on this task, and these patients were not impaired on other cognitive and linguistic tasks employed in Barch and Berenbaum's (1996) study. Thus these results suggest that there is an impaired ability to generate a discourse plan in some patients with schizophrenic thought disorder, but this is specific to those patients exhibiting incompetent references. In a later study, Barch and Berenbaum (1997) found that inability to generate a
discourse plan was associated with negative formal thought disorder symptoms in patients with schizophrenia such as decreased verbosity and syntactic complexity, whereas inability to maintain a discourse plan was associated with symptoms of discourse coherence disturbance. In this study, Barch and Berenbaum (1997) manipulated either the amount of planning generation possible prior to discourse, or the amount of structure to assist maintenance of a plan during discourse. With respect to planning generation, Barch and Berenbaum manipulated the amount of generation that patients could perform prior to hearing a story and answering questions about the story. In the low context condition, patients were simply told that they would hear a story and then be asked questions about the story. In the high context condition, patients were told what the story was about and the sorts of questions they would be asked. The high context condition provided patients with a clear structure which could be used to generate a discourse plan before the questions were asked, whereas the low context condition failed to provide any such structure. When patients were provided with a structure for generating a discourse plan, they were less likely to produce symptoms of negative thought disorder such as poverty of speech and reduced complexity, whereas a lack of structure resulted in increased negative thought disorder. This suggests that the ability to generate a plan is associated with symptoms of negative thought disorder.

With respect to maintaining a discourse plan, Barch and Berenbaum manipulated the level of structure provided to patients during the discourse. Patients were asked either structured or unstructured questions about the story they had heard. It was assumed that structured questions would aid maintenance of the discourse plan by providing a clear and concrete topic for discussion. When patients were asked unstructured questions, they were more likely to produce symptoms of discourse coherence disturbance than when they were asked structured questions. This suggests that discourse coherence
disturbance symptoms result from an inability to maintain a discourse plan once generated.

Barch and Berenbaum's (1997) finding that discourse coherence disturbance is associated with inability to maintain a discourse coherence plan is not consistent with the findings of Hoffman et al. (1986). Hoffman et al. found that patients with schizophrenic thought disorder are less able to generate a discourse plan than bipolar patients with thought disorder or normal controls. The ability to generate a discourse plan was assessed by analysing the hierarchical structure of speech samples produced by patients. Patients with schizophrenic thought disorder generated smaller discourse trees, suggesting that these patients are unable to generate an appropriate discourse plan. Inability to maintain a discourse plan would have resulted in a large but loosely connected discourse tree. The discrepancy between the Hoffman and Barch and Berenbaum studies could be explained by Hoffman et al.'s failure to distinguish between different symptoms of thought disorder. Barch and Berenbaum's (1997) finding of impaired ability to maintain a discourse plan was restricted to patients exhibiting discourse coherence disturbance symptoms. They found impaired ability to generate a discourse plan only in patients with negative formal thought disorder (Barch & Berenbaum, 1996; Barch & Berenbaum, 1997). If Hoffman et al.'s (1986) sample included a greater number of patients exhibiting negative thought disorder than patients exhibiting discourse coherence disturbance, this could account for the different findings in the two sets of studies. Similarly, a large amount of variability in the patients recruited by Hoffman et al. could account for the different results.

Although there has not been extensive investigation of the role of planning in discourse coherence disturbance, the results to date support McGrath's theory that patients with discourse coherence disturbance are unable to maintain a discourse plan. Barch and Berenbaum's (1997) work which was specific to patients with discourse
coherence disturbance showed that these symptoms appear to result from an inability to maintain a discourse plan, and are not associated with an inability to generate a discourse plan. These results are inconsistent with Hoffman’s theory that discourse coherence disturbance symptoms result from an inability to generate a discourse plan.

2.2.2 Working memory in discourse coherence disturbance

All theories, except for Harrow’s, predict impairments to the central executive component of working memory in their explanations of discourse coherence disturbance symptoms.

Working memory is the term that has been coined for processes involved in the short-term retention and manipulation of information (Baddeley, 1984; Baddeley, 1986; Baddeley & Hitch, 1994; Cantor, Engle, & Hamilton, 1991; Gathercole & Baddeley, 1993; Goldman-Rakic, 1991). The model of working memory that is most applicable to theories of discourse coherence disturbance is Baddeley’s model. This model of working memory contains three main elements, namely, the central executive, the phonological loop, and the visuo-spatial sketchpad (Baddeley & Hitch, 1994; Gathercole & Baddeley, 1993). The central executive of working memory coordinates the two subsystems and is also responsible for attentional control, and retrieval of information from other memory systems. The phonological loop and the visuo-spatial sketchpad are involved in short-term maintenance of verbal and visuo-spatial information respectively.

The nature of the central executive has tended to be poorly specified, beyond a general indication that it controls other aspects of working memory. In 1993, Baddeley elaborated his model of central executive by including Shallice’s (1982; 1988; Shallice & Burgess, 1993) Supervisory Attentional System (SAS) which involves the engagement of strategic attentional resources to interrupt habits or routines when novel
behaviour is required. Thus, the SAS is necessary for tasks involving novel behaviour such as planning or decision-making, error-correction, learning complex behaviour, and tasks requiring suppression of a strong prepotent response (Shallice, 1988; Shallice & Burgess, 1991; Shallice & Burgess, 1993). Recently, Baddeley (1996; 2001) has further expanded his initial conceptualisation of the central executive of working memory so that as well as the SAS, it encompasses three further attentional processes: divided attention, ie, dividing attention between two simultaneous tasks; selective attention, ie, selectively attending to a particular stimulus while inhibiting irrelevant material; and switching attention, ie, intentional switching of attention between sources of information or activities.

A serious problem in the central executive literature is difficulty in operationalising the elements of the executive system. Most tasks claiming to assess central executive function involve other abilities such as attention, speed of processing, language ability etc. As a result, the data on central executive function tends to be inconsistent, and it is not always clear that the tasks employed are really assessing central executive processes (Della Sala, Gray, Spinnler, & Trivelli, 1998; Stuss & Benson, 1984). However, bearing this caveat in mind, there is a relatively consistent finding in the literature that poor performance on a range of different measures of central executive performance is associated with some symptoms of schizophrenic thought disorder.

Impairments in patients with thought disorder have been found on tasks assessing the following aspects of central executive function: divided attention, maintenance and manipulation of information, and switching attention. With respect to divided attention, Bressi et al. (1996) found that patients with schizophrenia exhibiting positive symptoms including hallucinations, delusions, and formal thought disorder were impaired when performing a dual task. The dual task required them to physically
track a moving visual stimulus while performing a reaction time task or a digit span task. Patients with positive symptoms performed poorly on this task, suggesting impairments in the central executive ability to divide attention between concurrent tasks. Similarly, Docherty et al. (1996) and Nestor et al. (1998) found impaired performance in patients with thought disorder on the Trails B test. The Trails B test requires participants to connect consecutively numbered and lettered circles, alternating between the two sequences, ie, 1-A-2-B etc. This task can be characterised as a dual task: participants must divide their attention between the two sequences and perform them concurrently. Again, patients with schizophrenic thought disorder produced results indicative of impaired central executive function.

Tasks assessing the inability to maintain and manipulate information are also associated with symptoms of thought disorder. Adler, Goldberg, Malhotra, Pickar, and Breier (1998) found impaired performance on an N-back task after administering ketamine to healthy volunteers. Ketamine is an NMDA antagonist which induces psychotic symptoms, including thought disorder, at subanaesthetic levels. Following the administration of ketamine, healthy volunteers exhibited positive thought disorder symptoms as well as impairments on an N-back task. In the N-back task, participants are presented with numbers one at a time and on receiving a cue, must recall the number that had occurred either immediately prior to the cue (0-back), the number that occurred one before the number immediately prior to the cue (1-back), or the number that occurred two before the number immediately prior to the cue (2-back). Thus, participants must maintain information online and continually update this information. The poor performance of people exhibiting thought disorder symptoms suggests impairments to this central executive function. Similarly, Perlstein, Carter, Noll, and Cohen (2001) found impaired performance on the N-back task in patients with schizophrenia exhibiting symptoms of cognitive disorganisation.
Finally, with respect to switching attention, two studies have found an association between the Wisconsin Card Sorting Test (WCST) and thought disorder (Nestor et al., 1998; Schroder, Tittel, Stockert, & Karr, 1996). The WCST requires participants to sort cards according to one of three dimensions (namely colour, shape, or number) which the subject must deduce from feedback. After 10 correct trials, the dimension for sorting the cards is changed and participants must identify the new sorting rule based on feedback about their performance. Patients with schizophrenic thought disorder tend to show increased perseverations on this task, ie, they are unable to switch to the new rule.

While most studies support an association between impaired central executive performance and symptoms of thought disorder, there is some contradictory evidence. For example, using the WCST, Poole, Ober, Shenaut, and Vinogradov (1999) failed to find an association between central executive performance and disorganisation symptoms, including thought disorder symptoms.

Although these studies employed a variety of tasks assessing different aspects of central executive function, there is a relatively consistent finding that central executive function is impaired in patients with thought disorder. The consistency of this finding across different tasks, suggests that this deficit is not due to other abilities which are engaged in these tasks. To date, no study has specifically related working memory function and discourse coherence disturbance symptoms. However, many of the studies finding an association between thought disorder and executive dysfunction included discourse coherence disturbance symptoms in their definition of thought disorder. The central executive impairment found in groups containing patients with discourse coherence disturbance, may reflect a deficit in those patients, but it may alternatively reflect a deficit in patients exhibiting symptoms other than discourse coherence disturbance who have been included in the group. Consequently, even though patients
with discourse coherence disturbance symptoms were included in these studies, the results are not able to provide any clear evidence about the role of central executive performance in these symptoms.

2.2.3 Semantic memory in discourse coherence disturbance

Abnormal activation of semantic memory forms a central element of Nestor’s model of discourse coherence disturbance (see Section 2.1.4). The increased activation of semantic information is a direct result of lowered threshold parameters of individual elements in semantic memory. As a result, items are more easily activated, and are more likely to enter working memory which then becomes overloaded.

A number of early investigations of semantic priming in schizophrenia, found a facilitation of semantic priming in patients with thought disorder (Manschreck et al., 1988; Moritz et al., 1999; Spitzer et al., 1994; Weisbrod, Maier, Harig, Himmelsbach, & Spitzer, 1998). However, the literature on semantic priming in schizophrenia is inconsistent, and a number of other studies have failed to find any differences between normal controls and schizophrenic patients with thought disorder (Barch et al., 1996; Blum & Freides, 1995; Chapin, Vann, Lycaki, Josef, & Meyendorff, 1989; Henik, Priel, & Umansky, 1992; Ober, Vinogradov, & Shenaut, 1995; Passerieux, Hardy-Bayle, & Widlocher, 1995; Vinogradov, Ober, & Shenaut, 1992). Still further studies have found decreased semantic priming associated with schizophrenic thought disorder (Aloia et al., 1998; Besche et al., 1997; Goldberg, Dodge, Aloia, Egan, & Weinberger, 2000; Henik et al., 1992; Passerieux et al., 1995).

Barch et al. (1996) have criticised the methodology of semantic priming studies in schizophrenia and argue that conflicting results are most likely to be due to methodological differences. Nestor’s model of discourse coherence disturbance suggests that there is overactivation of the semantic network evident in facilitated
priming in these patients (Nestor et al., 1998). Spreading activation within the semantic system is automatic and facilitates processing of semantically related targets (Neely, 1991). Priming tasks which aim to identify overactivation of the semantic network in schizophrenia must tap into the automatic nature of this process (Barch et al., 1996; Neely, 1991). Previous research has revealed that only priming tasks which have a short stimulus onset asynchrony (SOA; less than 250 ms), and which involve word pronunciation with a low proportion of related words (less than 25%) are likely to tap into automatic components of priming. Tasks with a longer SOA, or which involve a lexical decision task, are more likely to assess expectancy processes which are under strategic control and may be either prelexical or postlexical. The prelexical mechanism involves generating associations on the presentation of the prime, while postlexical strategies involve comparing the prime and target after presentation to aid the lexical decision (Besche et al., 1997; Neely, 1991). These processes are both strategic and do not reflect automatic activation of the semantic network.

The studies on semantic priming in thought disorder cited above use a variety of different methodologies and hence are potentially assessing different semantic processes. The studies which have found facilitation of priming in thought disorder have used a lexical decision task with a short SOA (Manschreck et al., 1988; Moritz et al., 1999; Spitzer et al., 1994; Weisbrod et al., 1998) or word pronunciation tasks with a long SOA (Kwapil, Hegley, Chapman, & Chapman, 1990). Such tasks tap into pre-lexical expectancy strategic processes, not automatic activation of the semantic network (Neely, 1991). Thus, facilitation of priming in these patients is probably not due to overactivation of the semantic network but is more likely to involve strategic pre-lexical expectancy processes. Studies using tasks which assess automatic activation of the semantic network, ie, which use word pronunciation at short SOAs, have failed to find facilitation of priming in patients with thought disorder (Barch et al., 1996; Vinogradov
et al., 1992), or have found a reduced priming effect in these patients (Aloia et al., 1998). However, these findings are contradicted by a recent study by Moritz et al. (2001) which found facilitation of semantic priming using a word pronunciation task with a short SOA in patients with schizophrenic thought disorder.

Another important methodological aspect of semantic priming tasks is their ability to assess the extent of activation of the semantic network. Nestor’s theory predicts that the lowered threshold parameters of individual items in semantic memory will lead to activation of larger semantic networks. In order to investigate the extent of semantic activation, semantic priming tasks must include indirect priming (Balota & Lorch, 1986; De Groot, 1983; McNamara & Altarriba, 1988). Indirect priming involves using word pairs that are not directly associated, but are associated via a mediating word, eg, “tiger” is the mediating word between “lion” and “stripes”. A number of studies have found facilitation of indirect priming in patients with thought disorder (Moritz et al., 1999; Spitzer et al., 1993; Weisbrod et al., 1998). This suggests that the extent of semantic activation is wider in patients with thought disorder.

None of the studies investigating semantic processes in schizophrenic thought disorder have focused explicitly on discourse coherence disturbance symptoms. Therefore, it is difficult to draw any conclusions with respect to the validity of Nestor’s proposed role of facilitated semantic activation in patients with discourse coherence disturbance. Furthermore, the lack of consistency in methodology of studies investigating semantic priming makes it difficult to draw any clear conclusions about the role of semantic processes in schizophrenic thought disorder generally. Those studies which have focused on automatic semantic activation tend not to find facilitation of priming in patients with thought disorder. This seems to refute Nestor et al.’s hypothesis that discourse coherence disturbance results from facilitated semantic activation. However, the studies which have assessed the extent of semantic activation
using indirect priming, have found facilitation in patients with thought disorder. This provides some support for Nestor’s model.

2.2.4 Memory and contextual processing in discourse coherence disturbance

Only Harrow et al.’s model of discourse coherence disturbance predicts deficits in long-term memory and contextual processing. In their model, impaired contextual processing is the primary deficit. They explain discourse coherence disturbance in terms of an inability to recognise contextual demands and to adapt discourse to meet these demands (see Section 2.1.2). Impairments in long-term memory are due to an inability to use contextual information to select relevant information from long-term memory.

A number of studies suggest that patients with schizophrenic thought disorder have impairments in their ability to utilise contextual and semantic information. The bulk of evidence comes from tasks assessing patients’ ability to use contextual information to aid recall. Patients with thought disorder fail to show the expected increase in recall with increasing contextual organisation of a text to be remembered. This suggests that they are less able to use context to aid recall than patients without thought disorder or normal controls (Maher, Manschreck, & Rucklos, 1980; Mesure, Passerieux, Besche, Widlocher, & Hardy-Bayle, 1998; Speed et al., 1991). In these studies, patients with thought disorder failed to show the expected increase in recall with increasing contextual organisation of a text to be remembered. Similarly, patients with thought disorder have been found to produce fewer related words on a verbal fluency task (Kerns, Berenbaum, Barch, Banich, & Stolar, 1999). Kerns et al. interpreted this as reflecting a loss of semantic information in these patients. Contextual processing impairments have also been found on a relatively novel task created by Kuperberg, McGuire, and David (1998). In this study, patients with
schizophrenic thought disorder failed to show an effect of context in a task requiring them to respond to a word that they heard embedded in a sentence that was either semantically appropriate or inappropriate. They were also less accurate at judging whether sentences made sense or not. Finally, Goldberg et al. (1998) found an impairment in semantic fluency in patients with schizophrenic thought disorder. This task requires participants to generate words belonging to a particular semantic category. However, patients with positive thought disorder were also impaired on the Peabody Picture Vocabulary Test (PPVT) compared to patients without symptoms of thought disorder. Goldberg et al. explained the poor performance on the PPVT in terms of a specific semantic deficit. The PPVT requires participants to choose which of four pictures best represents a word spoken by the examiner and is commonly used as a measure of verbal IQ (Altepeter, 1989; Altepeter & Johnson, 1989). Poor performance on this task may, therefore, simply indicate poorer general intellectual functioning in the patients with thought disorder, rather than a specific semantic deficit.

Although the above studies show a consistent impairment in contextual processing in patients with schizophrenic thought disorder, at least one study has failed to find a difference between controls and patients in the ability to utilise the level of contextual organisation in a passage to aid recall (Harvey, Earle-Boyer, Wielgus, & Levinson, 1986). Furthermore, the apparent inability to utilise contextual information may actually reflect an inability to maintain contextually relevant information during the discourse, rather than a specific inability to process contextual information. Harrow et al. (2000) assessed the use of context by analysing speech samples generated by patients with thought disorder. They found that these patients initially incorporated contextual material into their speech, but tended to gradually stray from the initial context during the discourse. Characterised in this way, the contextual impairment seems more akin to McGrath's predicted inability to maintain a discourse plan than
Harrow's predicted inability to incorporate contextual information into the discourse plan.

Given Harrow et al.'s (2000) finding, the evidence for a specific contextual processing deficit in patients with thought disorder is not strong. However, a contextual processing deficit does seem to be present in some patients exhibiting thought disorder, although it may be secondary to a working memory deficit which prevents patients from maintaining relevant contextual information over time. Once again, these results are unable to elucidate the role of cognitive deficits in discourse coherence disturbance as the reviewed studies focused on patients with symptoms of positive thought disorder and so included patients exhibiting a range of thought disorder symptoms, including, but not restricted to, discourse coherence disturbance.

2.2.5 Monitoring in discourse coherence disturbance

The ability to utilise information about errors forms an important element of McGrath's model of discourse coherence disturbance, such that these patients are unable to use information about their own behaviour to correct their behaviour (see Section 2.1.1). Error-monitoring is also central to Harrow's model of discourse coherence disturbance. In order to produce contextually appropriate speech, the speaker must monitor their speech to ensure it conforms to the appropriate standard. In discourse coherence disturbance, this monitoring is impaired and the speech is disordered (see Section 2.1.2).

There is evidence of a general monitoring deficit in schizophrenia (Malenka, Angel, Hampton, & Berger, 1982; Malenka, Angel, Thiemann, Weitz, & Berger, 1986), particularly in patients with symptoms of thought disorder (Barch & Berenbaum, 1996; Harvey, 1985; Harvey & Serper, 1990; Wielgus & Harvey, 1988). Malenka et al. (1982) found that on a behavioural task revealing internal error-monitoring and
correction in normal controls subjects, patients with schizophrenia were less likely to
correct their errors than controls subjects, and were more likely to incorrectly adjust
correct responses. A replication of this study confirmed these results and also showed
that patients with schizophrenia are impaired on error-monitoring relative to patients
with depression (Malenka et al., 1986). Wielgus and Harvey (1988) found that patients
with positive thought disorder showed an impaired ability to monitor the level of
organisation in information they were shadowing dichotically. Similarly, Harvey and
Serper (1990) found a source monitoring deficit in patients with schizophrenia
exhibiting symptoms of positive thought disorder. These patients were impaired in their
ability to distinguish between words they had previously said aloud and words they had
previously imagined reading aloud. Using a similar task, Barch and Berenbaum (1996)
found a specific source monitoring deficit in patients with schizophrenia exhibiting the
discourse coherence disturbance symptoms of derailment and non-sequitur responses.

There is evidence of a specific error-monitoring deficit in patients with
schizophrenia generally, and evidence of a general monitoring deficit which is specific
to patients with discourse coherence disturbance. However, none of these studies
specifically address error-monitoring ability in patients with discourse coherence
disturbance. Further studies investigating specific error-monitoring performance of
patients with discourse coherence disturbance are needed to test whether there is an
error-monitoring impairment in patients with discourse coherence disturbance.
Furthermore, studies of error-monitoring in discourse coherence disturbance need to
focus on the specific nature of this deficit. McGrath’s and Harrow’s models make
different predictions about the nature of this deficit. McGrath’s model predicts an
inability to utilise information about errors to correct those errors, ie, error detection is
intact but error correction is impaired. Harrow’s model predicts a more general error-
monitoring deficit such that patients with discourse coherence disturbance are unaware
of the errors they are making. The literature to date does not provide evidence which would allow these theories to be differentiated.

2.2.6 Inhibition in discourse coherence disturbance

Nestor et al. explicitly target inhibitory processes as important elements in discourse coherence disturbance. They argue that patients with discourse coherence disturbance exhibit a prefrontal, working memory impairment which prevents effective inhibition of irrelevant material once it enters into working memory (see Section 2.1.4).

There is evidence that patients with schizophrenia generally, show poor performance on measures of inhibitory function, such as the anti-saccade task (Fukushima et al., 1990; Karoumi, Ventre-Dominey, Vighetto, Dalery, & d’Amato, 1998; Sereno & Holzman, 1995). The anti-saccade task requires participants to inhibit an automatic, prepotent response of looking towards a peripherally presented target (Roberts, Hager, & Heron, 1994; Roberts & Pennington, 1996; Walker, Husain, Hodgson, Harrison, & Kennard, 1998). Patients with schizophrenia produce more errors on this task, indicating a failure to successfully inhibit the prepotent response.

With respect to symptoms of schizophrenic thought disorder, Fukushima et al. (1990) found an association between conceptual disorganisation and increased error-rate on the anti-saccade task. However, most of the behavioural studies examining the role of inhibition in schizophrenic thought disorder have used the Stroop task as a measure of inhibition. Patients with schizophrenia exhibiting symptoms of positive thought disorder, including discourse coherence disturbance, are more likely to perform poorly on the Stroop task (McGrath et al., 1997; Persons & Baron, 1985). In this task, participants are presented with colour words which are printed in the same or a different colour from the colour word. In the interference condition, the participant must name the print colour of the word, ignoring the different colour spelt out by the word.
Patients with schizophrenic thought disorder are slower than control groups at naming colours during this condition. This has been interpreted as a failure to inhibit the prepotent response of reading the word.

There is some dispute over the validity of the Stroop task as a measure of inhibition. While some authors suggest that the Stroop task measures the subject’s ability to inhibit strong responses or distracting information, ie, the colour word (Bestgen & Dupont, 2000; Boucart, Mobarek, Cuervo, & Danion, 1999; McGrath et al., 1997), there is a body of evidence suggesting that performance on the Stroop task depends on a number of factors such as interference from response competition (Bestgen & Dupont, 2000; Burt, 1999; Logan, Zbrodoff, & Williamson, 1984; Vendrell et al., 1995), perceptual confusion (Logan et al., 1984), attention processes (MacLeod, 1991; Vendrell et al., 1995) and executive processes, rather than inhibitory processes. There is some specific evidence that poor performance on the Stroop task by patients with schizophrenia may be due to increased distractibility in these patients (Boucart et al., 1999), or impairments in attention mechanisms (Barch et al., 1999), and not impaired inhibition.

Brain imaging work supports the view that the Stroop task reflects processes other than inhibitory processes. Performance on the Stroop task is associated with anterior cingulate activation (Bench et al., 1993; Bush et al., 1998; Leung et al., 2000; Pardo, Pardo, Janer, & Raichle, 1990). This area is not activated by other inhibitory tasks such as the go/no-go task, which is primarily associated with prefrontal activity (Kawashima et al., 1996; Liddle et al., 2001; Sasaki et al., 1993). The go/no-go task requires participants to inhibit a motor response on the presentation of a cue and is generally thought of as a fairly “pure” measure of inhibition (Band & Van Boxtel, 1999). The regions of activation associated with the Stroop task are consistent with the view that this task involves processes other than inhibition. The anterior cingulate is
generally thought to reflect response conflict processing or error-monitoring (Barch, Braver, Sabb, & Noll, 2000; Barch et al., 2001; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Carter, Botvinick, & Cohen, 1999; Carter et al., 2000; Dehaene, Posner, & Tucker, 1994; Liddle et al., 2001; Posner & DiGirolamo, 1998; Taylor, Kornblum, Minoshima, Oliver, & Koepp, 1994), and parietal areas are implicated in attention (Fernandez-Duque & Posner, 2001; Jackson et al., 1994; Liddle et al., 2001; Mennemeier et al., 1994; Posner & Badgaiyan, 1998; Posner & Petersen, 1990; Wilkins et al., 1987). These results suggest that performance on the Stroop task relies on successful resolution of response competition or attentional processes, rather than inhibitory processes.

Although there is evidence of impaired inhibition in patients with schizophrenia, the evidence with respect to a specific deficit in patients with thought disorder is less clear. Most studies showing an association between symptoms of thought disorder and impaired inhibition have used the Stroop task. However, poor performance on this task could equally be due to increased interference, perceptual impairments, or attention deficits. There have been no investigations focusing on inhibitory processes in discourse coherence disturbance, so it is not possible to draw any conclusions about the role of inhibitory processes in these patients.

2.2.7 Attention in discourse coherence disturbance

Hoffman suggested that discourse coherence disturbance in patients with schizophrenia is related to impairments in sustained attention. The inability to sustain attention means the patients are unable to maintain a discourse plan so that their speech becomes disordered as they lose track of what they intended to say (see Section 2.1.3). Generally, the literature supports an association between thought disorder and poor performance on tasks requiring sustained attention. The most commonly used
measure in these studies is the continuous performance task (CPT). CPT tasks require participants to maintain attention over a period of time. During this period, they must make a behavioural response to a pre-identified stimulus, such as a particular number where stimuli are perceptually graded (degraded stimulus-CPT; CPT-DS; Nuechterlein, Parasuraman, & Jiang, 1983), two consecutive items (CPT A-X; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), or repeated items (identical pairs-CPT; CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988). Impaired sustained attention has been found in patients with schizophrenia exhibiting symptoms of positive thought disorder using both the CPT A-X (Landre & Taylor; 1995; Pandurangi et al., 1994), and the CPT-DS (Nelson, Sax, & Strakowski, 1998; Strauss, Buchanan, & Hale, 1993). However, Nuechterlein, Edell, Norris, and Dawson (1986) failed to find an association between schizophrenic thought disorder and impaired performance on either the CPT-DS or the CPT A-X. Other measures of sustained attention have also found an association between schizophrenic thought disorder and impaired attention. Basso, Nasrallah, Olson, and Burnstein (1998) found that patients with schizophrenia exhibiting disorganised symptoms were impaired on the Attention-Concentration index from the Wechsler Memory Scale-Revised. Similar results were found by Mahurin, Velligan, and Miller (1998) using the attentional capacity test. This task requires participants to count the number of target items presented in a series of aurally presented stimuli. Patients with conceptual disorganisation performed poorly on this task, suggesting sustained attention impairments in this population.

Generally, there is evidence of an association between schizophrenic thought disorder and impaired sustained attention, which may support Hoffman’s theory. However, these studies have clustered thought disorder symptoms together and there have been no studies investigating sustained attention specifically in patients discourse.
coherence disturbance. As a result, these findings are not able to specifically address Hoffman’s model of discourse coherence disturbance.

2.2.8 Summary of cognitive findings to date and a review of the status of the theories

From the results of existing studies examining cognitive deficits in schizophrenia, there is no consistent support for any particular theory of discourse coherence disturbance. Part of the reason for this has been the failure to systematically investigate these cognitive deficits in patients with discourse coherence disturbance. Most of the studies reviewed in this chapter examined cognitive deficits in relation to positive symptoms of formal thought disorder which include some discourse coherence disturbance symptoms but also include other symptoms such as perseverations, neologisms, and incoherence. The only exception to this is in the area of planning, where there is evidence of a specific inability to maintain a discourse plan in patients with discourse coherence disturbance. Furthermore, most of the studies cited used large group studies focusing on a small range of cognitive processes. The failure to account for the heterogeneity of thought disorder symptoms may have produced an artefactual effect resulting from increased variability within the thought disorder sample. Overall, there is some evidence in support of each theory of discourse coherence disturbance, but much of the literature is inconsistent and there has been very little investigation of discourse coherence disturbance, rather than thought disorder symptoms generally.

2.3 The status of existing research into physiological abnormalities in discourse coherence disturbance

The physiological regions that are central to the above theories of discourse coherence disturbance are frontal regions, prefrontal networks, the temporal lobe, and temporoparietal function. This review of the physiological abnormalities associated
with discourse coherence disturbance is confined to these regions. In comparison to studies of cognitive processes, there are relatively few studies investigating physiological dysfunction in patients exhibiting thought disorder, and even fewer focusing on specific thought disorder symptoms. However, a review of the studies that exist will provide some indication of the status of theories of discourse coherence disturbance.

2.3.1 Frontal function in discourse coherence disturbance

All four theories of discourse coherence disturbance predict impairment to either the prefrontal cortex or a network incorporating the prefrontal cortex. Harrow, Hoffman, and Nestor hypothesise a specific impairment to prefrontal function, while McGrath’s model predicts a monitoring deficit in discourse coherence disturbance which is proposed to involve the semantic monitoring network described by Crosson (1985; Crosson & Hughes, 1987). This network incorporates frontal and temporoparietal regions via the globus pallidus and caudate nucleus, as well as the right prefrontal regions.

Similarities between patients with speech disorders and patients with discourse coherence disturbance provide evidence which suggests that the prefrontal cortex is involved in discourse coherence disturbance. Speech disorders resulting from lesions to the right prefrontal cortex, or from lesions to part of the dorsolateral prefrontal network, are similar to those found in discourse coherence disturbance (Alexander, Benson, & Stuss, 1989; Mega & Cummings, 2001; Novoa & Ardila, 1987). Patients with damage to the right dorsolateral prefrontal cortex, or to dorsolateral prefrontal connections with lateral, parietal, and temporal areas, exhibit speech which is characterised by illogicality and an inability to maintain coherent discourse (Alexander et al., 1989; Novoa & Ardila, 1987). These are also included as symptoms of discourse coherence disturbance.
Damage to the right medial frontal cortex leads to an inability to adapt speech to social context, perseveration, confabulations, and disorganised narrative content (Alexander et al., 1989; Novoa & Ardila, 1987). Of these symptoms, inability to adapt to social context is part of discourse coherence disturbance as predicted by Harrow’s model and the other symptoms are also found in schizophrenic thought disorder although are not discourse coherence disturbance symptoms (Berenbaum & Barch, 1995). Although the similarity of symptoms in patients with damage to the dorsolateral prefrontal cortex or dorsolateral prefrontal networks and patients with discourse coherence disturbance does not provide direct evidence of the physiological processes involved in discourse coherence disturbance, the similarity in symptoms may be indicative of a common underlying pathology.

Although relatively few studies have investigated prefrontal function in thought disorder specifically, some studies have found an association between physiological measures of the frontal lobe and symptoms of schizophrenic thought disorder. Liddle et al. (1992) conducted a resting Positron Emission Tomography (PET) study of patients with schizophrenia. Patients with conceptual disorganisation symptoms showed decreased regional Cerebral Blood Flow (rCBF) in the right ventral prefrontal cortex, and increased rCBF in the medial prefrontal cortex. Similarly, a brain morphological study using Magnetic Resonance Imaging (MRI) conducted by Vita et al. (1995) found an association between symptoms of positive thought disorder, including some specific symptoms of discourse coherence disturbance, and reduced prefrontal lobe volume. However, Nestor et al. (1998) failed to find any association between brain morphology in frontal regions and symptoms of schizophrenic thought disorder, and a recent study by Menon, Anagnoson, Mathalon, Glover, and Pfefferbaum (2001) failed to find an association between abnormal frontal activity and symptoms of thought disorder in a
functional Magnetic Resonance Imaging (fMRI) study of patients with schizophrenia while performing an N-back task.

Few studies have investigated prefrontal circuits in patients with schizophrenic thought disorder. However, those that have looked at regions involved in Crosson’s (1985) circuit tend to find an association between abnormal relationships between these regions and symptoms of thought disorder. Kircher et al. (2001a) and McGuire et al. (1998) found increased activation in the right caudate nucleus which was associated with abnormal activation in other regions which form part of the prefrontal circuitry. In McGuire et al.’s study, increased caudate nucleus activity in patients with thought disorder while producing disordered speech was accompanied by decreased activation in bilateral inferior frontal gyri, left temporal regions, and the anterior cingulate. In Kircher et al.’s study, the increased caudate nucleus activity associated with production of disordered speech was accompanied by increased activation in the cerebellum and right precentral gyrus, and decreased left temporal lobe activation. These findings are consistent with McGrath’s hypothesis of disruptions to the semantic monitoring network identified by Crosson (1985).

The literature to date does not present a clear picture of the role of prefrontal processes in discourse coherence disturbance. Studies focusing on specific prefrontal regions and thought disorder are contradictory. These studies focused on either positive thought disorder or conceptual disorganisation symptoms and differences between studies could be due to sampling differences. The only study that explicitly focused on some symptoms of discourse coherence disturbance found decreased volume of prefrontal regions associated with these symptoms (Vita et al., 1995). The evidence with respect to prefrontal circuitry is more consistent. The two studies investigating this circuitry in patients with thought disorder both found abnormalities in this circuit. However, most of the studies reviewed did not focus on discourse coherence
disturbance and so they are of limited value in evaluating theories of relevance to this
category of thought disorder symptoms.

2.3.2 Temporal lobe function in discourse coherence disturbance

Nestor’s theory of discourse coherence disturbance focuses on abnormal
prefrontal and temporal lobe function in these patients. There is considerable evidence
of abnormal temporal lobe physiology in patients with schizophrenic thought disorder.
Brain morphological studies investigating specific symptoms clusters in schizophrenia
have found reduced volume of the superior temporal gyrus in patients with
schizophrenia exhibiting symptoms of thought disorder (Dieci et al., 1998; Holinger et
al., 1999; Menon et al., 1995; Rajarethinam, DeQuardo, Nalepa, & Tandon, 2000;
Shenton et al., 1992). There is also some evidence of abnormal temporal lobe function
from imaging work. Kircher et al. (2001b) conducted an fMRI study investigating
temporal lobe function in patients with thought disorder while performing a task
requiring them to generate a semantically appropriate word to conclude a sentence.
Once behavioural performance was controlled for, the only region of difference between
patients with thought disorder and control groups was decreased activation of the right
temporal cortex.

There is strong evidence of temporal lobe pathology in patients with symptoms
of thought disorder. This seems to provide support for Nestor’s theory of discourse
coherence disturbance. However, there has been no investigation of temporal lobe
pathology in discourse coherence disturbance and so the role of temporal lobe processes
in this group is not clear.
2.3.3 **Physiological function associated with contextual processing in discourse coherence disturbance**

Harrow et al.'s theory of impaired contextual processing in discourse coherence disturbance, should be reflected in impairments to temporoparietal function in these patients. However, there is very little evidence supporting a specific temporoparietal abnormality in patients with discourse coherence disturbance.

The N400 event-related potential (ERP) component has been used to investigate physiological processes associated with contextual processing in schizophrenia. The N400 component is a negative wave peaking between 300 and 600 ms after presentation of a semantic incongruity, and is largest over temporoparietal and occipital areas (Fischler, Bloom, Childers, Roucos, & Perry, 1983; Holcomb, 1993; Kutas & Hillyard, 1982; Kutas & Hillyard, 1983; Pritchard, Shappell, & Brandt, 1991). The N400 is believed to be related to processing contextual information, and is specific to strategic semantic processes (Bentin, 1987; Bentin, McCarthy, & Wood, 1985; Holcomb, 1987; Kutas & Hillyard, 1983; Osterhout, 1997; Osterhout & Holcomb, 1992). To date, only one study has focused on N400 in patients with schizophrenic thought disorder. This study failed to find any abnormality in the N400 component in these patients (Andrews et al., 1993), even though there is substantial evidence of an abnormality in the N400 component in schizophrenia generally (Adams et al., 1993; Condray, Steinhauer, Cohen, van Kammen, & Kasparek, 1999; Grillon, Ameli, & Glazer, 1991; Koyama et al., 1991; Manschreck et al., 2000; Ohta, Uchiyama, Matsushima, & Toru, 1999; Salisbury, O'Donnell, McCarley, Nestor, & Shenton, 2000; Strandburg et al., 1997; Volz, Mackert, Frick, & Bucker, 1994).

ERP studies do not provide support for Harrow's theory of discourse coherence disturbance. However, there has been very little investigation of temporoparietal processes in thought disorder and so it is difficult to draw any conclusions about
temporoparietal regions in discourse coherence disturbance. The only study investigating the N400 component in thought disorder, did not distinguish between different thought disorder symptoms and is unable to answer Harrow’s specific predictions.

2.3.4 **Summary of physiological findings to date and a review of the status of the theories**

As with most of the cognitive studies, there has been very little physiological investigation specifically targeted at discourse coherence disturbance symptoms. The current body of literature is capable of supporting most of the theories of discourse coherence disturbance described above, since disturbances to all predicted regions have been found either in patients with schizophrenia, or in patients with thought disorder. Physiological evidence can be cited to support the physiological predictions of most of the models, eg, temporal lobe deficits predicted by Nestor, frontal lobe deficits predicted by Hoffman, and frontal network deficits predicted by McGrath. The only theory which does not have any support from the physiological literature is Harrow’s theory.

2.4 **Summary**

This chapter comprised a review of four leading theories of discourse coherence disturbance and a review of the current literature with respect to the predictions made by these theories. This review provided some support for each of the theories of discourse coherence disturbance, but the existing evidence is not sufficient to allow differentiation between the theories. In the remainder of this thesis, I will present the results of three studies which have tested these theories experimentally. Chapter 3 presents a study which investigated the hypotheses of the four theories of discourse coherence disturbance with respect to cognitive deficits. This chapter comprises a series of
cognitive neuropsychological case studies focusing on patients with schizophrenia with and without symptoms of discourse coherence disturbance. Chapters 4 and 5 investigate the physiological predictions of these theories, based on the results of Chapter 3. Chapter 4 comprises the results of an fMRI study looking at the role of the prefrontal cortex in discourse coherence disturbance. Chapter 5 describes an ERP study focusing on error-monitoring in patients with discourse coherence disturbance, as well as prefrontal circuitry in these patients.
CHAPTER 3

STUDY 1

3.1 Introduction

This study explored the cognitive deficits associated with symptoms of discourse coherence disturbance (including tangentiality, loss of goal, derailment, illogicality, and distractible speech; Berenbaum & Barch, 1995; Barch & Berenbaum, 1997) in patients with schizophrenia. The aim of this study was to distinguish between four theories which have attempted to explain the processes underlying discourse coherence disturbance in schizophrenic patients. These theories and the specific predictions made by each are outlined in Chapter 2. The first of these theories focuses on monitoring and attentional deficits (McGrath, 1991; McGrath et al., 1997), the second focuses on impaired perspective (Harrow et al., 1987), the third is based on discourse planning (Hoffman, 1986), and the last theory emphasises semantic memory and working memory (Nestor et al., 1998).

Although these theories of discourse coherence disturbance have many overlapping components, there are aspects of the models which distinguish them: each theory proposes at least one impairment in a unique cognitive domain that is not shared by others. McGrath (1991) predicts disconnection between the central executive and motor response manifest in an inability to utilise errors to correct behaviour. Harrow et al. (1987) predict impaired ability to utilise contextual information and deficits in long-term memory. Nestor et al. (1998) predict facilitated automatic semantic priming. Hoffman et al. (1986) predict impaired sustained attention (see Table 2.1).
The aim of this study was to choose cognitive tasks based primarily on their ability to distinguish between the four theories, but also on their capacity to test the overlapping predictions made by two or more theories.

3.1.1 Central executive function

Nestor, Hoffman, and McGrath propose that the central executive of working memory is impaired in discourse coherence disturbance (see Section 2.1). In this study, central executive function was assessed using phonological verbal fluency, as well as a number of working memory tasks.

Phonological verbal fluency requires a number of different cognitive processes. Troyer, Moscovitch, and Winocur (1997) propose two principal components of verbal fluency: clustering which involves producing a run of words which are semantically or phonemically related; and switching which involves shifting to a new category or strategy for producing words. They provide evidence suggesting that clustering relies on temporal lobe processes such as accessing lexical information from long-term memory while switching requires frontal lobe or central executive processes such as shifting set, strategic search processes, and cognitive flexibility. Specifically, poor switching performance is associated with lesions in the left dorsolateral prefrontal cortex and in superior medial frontal regions (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998).

Impairment in executive function is predicted by McGrath and Hoffman, while Nestor's theory predicts impairment in the relationship between prefrontal and temporal processes. Thus according to McGrath and Hoffman, patients with discourse coherence disturbance should produce fewer switches (this prediction is supported by Robert et al., 1998 who found patients with
schizophrenia exhibiting symptoms of disorganisation produced fewer switches). In contrast, Nestor’s theory would be supported by impaired clustering as well as impaired switching in patients with discourse coherence disturbance.

The working memory tasks chosen for this study were those believed to tap into the central executive of working memory, as well as a task assessing the phonological loop of working memory in order to ensure that apparent central executive impairment was not due to an inability to maintain auditory information over a delay. Central executive working memory was assessed using backward digit span and complex span, and phonological loop was assessed using forward digit span (Lehto, 1996). Forward digit span requires subjects to maintain verbal information over a short period of time, tapping into the phonological loop of working memory (Lezak, 1995). Backward digit span requires subjects to recall numbers in the reverse order, requiring manipulation of information and mental tracking, tapping into central executive working memory processes (Lezak, 1995). Complex span tasks require subjects to recall words while performing mental arithmetic. This involves retrieval of information from long-term memory and mental arithmetic performed concurrently. Both functions involve the central executive of working memory (Baddeley, Lewis, Eldridge, & Thomson, 1984; Hitch, 1980; Lehto, 1996). The complex span task can also be characterised as a dual task requiring divided attention, a process which is incorporated within the central executive of working memory (Baddeley & Hitch, 1994). Arguments have been raised about whether this task assesses the central executive of working memory, or whether performance is dependent on the participants’ ability to perform the operation element of the task, ie, whether poor performance on the memory task is due primarily to inability to perform the arithmetic task. However, there is
no evidence that performance on the operation task predicts performance on the complex span task. Furthermore, the dual-task nature of the test requires central executive processing (Engle, 2001).

3.1.2 Sustained attention

Hoffman’s theory proposes that discourse coherence disturbance is due to planning deficits resulting from impaired central executive function and inability to sustain attention (see Section 2.1.3). Sustained attention was assessed with a degraded stimulus version of the continuous performance task which requires subjects to maintain attention and to respond to pre-specified stimuli over a period of time. This version of the CPT provides a relatively pure measure of sustained attention processes. Other versions, such as the identical pairs version, place a load on working memory by requiring the subject to update information as the task proceeds. The CPT-DS does not load working memory in this way, rather, it loads on the perceptual system by degrading the stimuli (Michie et al., 2000).

3.1.3 Inhibition and monitoring

Nestor et al. hypothesised that there is a disturbance of inhibitory function in patients with discourse coherence disturbance (see Section 2.1.4). Impairments in inhibitory processes were assessed using an anti-saccade task, a task that requires participants to inhibit an automatic, prepotent response towards a peripheral target (Roberts et al., 1994; Roberts & Pennington, 1996; Walker et al., 1998).

Poor error-monitoring is predicted by McGrath and Harrow’s theories. McGrath argued that poor error-monitoring contributes to symptoms of discourse coherence disturbance resulting in patients being able to correct their
speech errors, and Harrow argued for a general monitoring deficit in these patients (see Sections 2.1.1 and 2.1.2). The anti-saccade task was used to assess error-monitoring by calculating the number of self-corrections made by participants.

3.1.4 **Activation of semantic memory**

Nestor et al. suggest that an important element in discourse coherence disturbance is over-activation of semantic memory (see Section 2.1.4). Facilitation of semantic memory was assessed with a semantic priming task which was designed to tap into the automatic aspect of semantic memory (Barch et al., 1996; Besche et al., 1997; Blum & Freides, 1995; Neely, 1991). Different experiment parameters of the semantic priming task are used to investigate the automatic and strategic aspects of activation in semantic memory (see Section 2.2.3). The processes of interest to Nestor et al. are the automatic processes involved in spreading activation (in contrast to the slower conscious processes of expectancy processes, such as matching the prime to the target or generating associations to the prime before the target is presented; Neely, 1991), and the extent of semantic activation. The optimal task to assess automatic semantic processing is a semantic priming task involving word pronunciation (as opposed to a lexical decision task), a short stimulus onset asynchrony, and a low proportion of related words (Barch et al., 1996; Besche et al., 1997; Blum & Freides, 1995; Neely, 1991; Ober et al., 1995). The extent of activation of the semantic network was assessed using an indirect priming task (Balota & Lorch, 1986; De Groot, 1983; McNamara & Altarriba, 1988).

3.1.5 **Contextual information**

Harrow et al. proposed that contextual processing is the principal impairment underlying discourse coherence disturbance (see Section 2.1.2).
This ability was assessed using the contextual naming task developed by Norris (1987). This is a priming task requiring participants to read aloud a word that completes a sentence they have read. The word is either strongly contextually relevant to the sentence, contextually inappropriate to the sentence, or neutral. Norris (1987) found that this task is very sensitive to contextual processing and there is a strong relationship between degree of contextual constraint and facilitation of priming.

3.1.6 Long-term memory

Harrow et al. predicted deficits in long-term memory related to the inability to adapt speech to the conversational context in patients exhibiting discourse coherence disturbance (see Section 2.1.2). An element of the patients' inability to utilise contextual information is impaired ability to access this information from long-term memory. Long-delay memory was assessed using the California Verbal Learning Test, a standard and widely used measure of verbal learning and memory which includes a measure of contextual processing in long-delay memory (Delis et al., 1987; Lezak, 1995).

3.1.7 Summary of theories and predictions

In summary, the cognitive processes focused on in this study are central executive of working memory, sustained attention, inhibition, error-monitoring, semantic priming, long-term memory, and contextual processing.
Hypothesis 1

According to McGrath’s\(^3\) theory, patients with discourse coherence disturbance should exhibit:

1. impaired central executive of working memory, ie, they should perform poorly on the switching aspect of verbal fluency, on the backward digit span task, and the complex span task

2. an inability to utilise errors to correct mistakes, ie, they should show a reduced number of self-corrections on the anti-saccade task

Hypothesis 2

Harrow’s theory predicts the following cognitive deficits in patients with discourse coherence disturbance:

1. impaired use of contextual information, ie, poor performance on the contextual naming task

\(^3\) Although McGrath’s and Hoffman’s theories focus on planning ability, this ability was not investigated in this study. This was partly due to previous research with patients with discourse coherence disturbance which supports McGrath’s hypothesised planning deficit (see Section 2.2.1). In order to confirm this finding, it was initially proposed to apply Deese’s (1978; Hoffman, Stopek, & Andreasen, 1986) hierarchical analysis of speech to speech samples elicited by participants in this study. However, this form of analysis requires relatively long samples of uninterrupted speech from participants (at least 10 statements; Hoffman et al., 1986) and the participants in this study failed to elicit sufficiently long speech samples.
2. poor long-term memory, ie, poor performance on the long-delay indices of the CVLT, particularly those indices focusing on the use of contextual cues in retrieving information from long-delay memory
3. an error-monitoring deficit, ie, fewer self-corrections on the anti-saccade task

**Hypothesis 3**

According to Hoffman’s theory patients with discourse coherence disturbance should show:

1. impaired central executive of working memory, ie, impaired performance on the switching aspect of verbal fluency, as well as poor performance on the backward and complex span tasks
2. an inability to sustain attention, ie, impaired performance on the CPT-DS task

**Hypothesis 4**

Nestor’s theory predicts the following areas of cognitive impairment in patients with discourse coherence disturbance:

1. disturbed relationship between prefrontal and temporal lobe processes, ie, fewer switches and smaller clusters on the verbal fluency task and poor performance on the backward and complex span tasks
2. a disturbance of inhibitory function, ie, increased error-rate on the anti-saccade task
3. over-activation of the semantic network, ie, facilitated semantic priming

These predictions were tested using a series of single case studies in order to overcome the problems inherent in large group studies (see Section 1.3 for a discussion of this). In order to overcome the lack of generalisability in
case studies, four case studies of patients with discourse coherence disturbance, and four case studies of patients without discourse coherence disturbance were conducted, comprising one case study and three successful replications in each population (Hersen & Barlow, 1976).

3.2 Method

3.2.1 Participants

3.2.1.1 Patients Eight male patients were recruited from inpatients and outpatients from a metropolitan psychiatric hospital in Perth, Western Australia. Patients were chosen based on a Research Nurse’s assessment of whether or not they exhibited symptoms of formal thought disorder. Outpatients were provided with transport to the hospital or were paid $10 per session to cover travelling costs. Four patients exhibited symptoms of discourse coherence disturbance at the time of testing, and four patients were free of discourse coherence symptoms. Informed written consent was obtained from all patients. Further details of the patients’ demographic details, case history and clinical profile are provided in Section 3.3.6.

3.2.1.2 Controls Nineteen males were recruited from the general community as a control sample, after giving written consent. These participants were recruited by placing advertisements in the general community. Participants were paid $10 an hour for the reimbursement of travel costs. The age range of the control group was 22 to 40 years of age with a mean age of 33 years. The control group had 12.05 average years of education with a range between 9 and 16 years of education. All control subjects had English as their first language and they were screened for the presence or history of thought disorder and other psychotic symptoms. One control subject was excluded on this basis.
3.2.1.3 Diagnostic Assessment  All participants were administered a
structured or semi-structured diagnostic interview. Control subjects were interviewed
using the Composite International Diagnostic Interview (CIDI), and patients were
interviewed with either the Diagnostic Interview for Psychosis (DIP; Jablensky et al.,
1999; Jablensky et al., 2000) or the Schedules for Clinical Assessment in
Neuropsychiatry (SCAN; WHO, 1997). The DIP is a structured clinical interview
consisting of items selected from the SCAN linked to the Operational Criteria Checklist
(OPCRIT) System database (McGuffin, Farmer, & Harvey, 1991). Based on the DIP
interview (and available case notes for patients), results for all participants were entered
into the OPCRIT System database which was used to generate ICD-10 and DSM-III-R
diagnoses. All patients received an ICD-10 and DSM-III-R diagnosis of schizophrenia.
Patients who were diagnosed using the SCAN had their diagnosis reviewed by a senior
clinician (named in acknowledgements). Current symptoms of discourse coherence
disturbance were assessed using the ratings for tangentiality, loss of goal, derailment,
illogicality, and distractible speech from the Scale for the Assessment of Thought,
Language, and Communication (TLC; Andreasen, 1986). A speech sample of all
participants was elicited using items from SCAN which assess negative symptoms of
schizophrenia (see Appendix 1). These items elicited speech samples lasting
approximately 10 minutes which were then rated by the author using the TLC. Two
other clinicians (named in acknowledgements) rated a selection of these speech
samples. Interrater reliability was measured using intraclass correlations with raters
treated as random effects and the individual rater as the unit of reliability (Shrout &
Fleiss, 1979). Interrater reliability on rating of discourse coherence disturbance items
was significant, $\alpha = 0.67$, $p < 0.05$, and severity of discourse coherence disturbance
rating for each participant was similar\(^4\). The patients’ case notes were used to determine history of symptoms, including thought disorder symptoms.

### 3.2.2 Cognitive tests

#### 3.2.2.1 Control measures
Participants’ pre-morbid and current IQ were assessed using the National Adult Reading Test (NART; Nelson, 1991) and Shipley Institute of Living Scale (Zachary, 1991) respectively.

#### 3.2.2.2 Verbal fluency
Phonological verbal fluency was assessed using the “FAS” test (Lezak, 1995). In this task, participants were given 60 seconds to generate words starting with the given letter. Using an adaptation of the rules generated by Troyer et al. (1997; 1998), and Robert et al. (1998), verbal fluency was scored for the percentage of phonemic switches, percentage of related words, and cluster size (see Appendix 2 for a complete description of the scoring rules).

#### 3.2.2.3 Working Memory
Forward and backward digit span from the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) were administered. Complex working memory span was assessed with a task adapted from Lehto (1996). An arithmetic operation string, consisting of either a subtraction or addition, and a division or multiplication (eg, \(15 + 5/2 = 10\)), was presented on a computer screen for 15 seconds and the participants were required to indicate whether the answer was true or false. Following presentation of each operation, participants were presented with a word they were instructed to remember. The word remained on the screen for

\(^4\) Interrater reliability was significant for each item of discourse coherence disturbance except loss of goal (tangentiality, \(\alpha = 0.78, p < 0.05\); derailment, \(\alpha = 0.84, p < 0.05\); illogicality, \(\alpha = 0.97, p < 0.05\); distractible speech, \(\alpha = 0.94, p < 0.05\); loss of goal, \(\alpha = -0.43, p > 0.05\)).
one second. After the presentation of a number of operations, a row of question marks were presented at which point the participants were asked to recall the “to-be-remembered” words of the preceding operations. There were three trials of two arithmetic operations, followed by three sets of three operations, three sets of four operations and three sets of five operations. The estimate of complex span, the dependent variable, was the number of words the participant was able to recall accurately, averaged over all set sizes (Lehto, 1996).

3.2.2.4 Semantic priming Participants were presented with pairs of words on the computer screen and instructed to read the first prime word silently and then to say the second target word aloud as fast as they could (word pairs are shown in Appendix 3). Reaction time for onset of word pronunciation was automatically recorded by means of a throat-microphone and a voice-activated relay connected to a PC. The prime appeared in uppercase for 100 ms followed by a blank screen for 100 ms. The target word in lowercase was then presented and the subject had two seconds from its onset in which to respond. The target word remained on the screen for two seconds or until the participant responded (Barch et al., 1996). There was a practise block of 12 trials made up of unrelated prime and target pairs followed by the testing session consisting of 192 word pairs. Of these pairs, 25% of primes and targets were directly related (eg, lion-tiger), 25% were indirectly related (eg, lion-stripe), 25% were unrelated control words (eg, lion-window), and 25% were unrelated filler words.

The Edinburgh Associative Thesaurus (http://svr-www.eng.cam.ac.uk/comp.speech/Section1/Lexical/eat.html) was used to determine the relatedness of words. Two words were considered to be directly related if the target word appeared on the thesaurus as a response to the prime word. Two words were considered to be indirectly related if the target word was a response to a word elicited by the prime but not a response to the prime word itself, eg, “prison” and “word” are
indirectly related with "sentence" providing the link between the two words. Two words were unrelated if the target word was not a response to either the prime word or a word elicited by the prime. Three sets of stimuli were used: in each set of stimuli the same prime and target words were used, but the prime words were paired with either directly related, indirectly related, or unrelated control words depending on the stimuli set. In order to generate the desired proportion of related words, ie, to decrease the proportion of related words compared to unrelated words to reduce expectancy effects, filler words were also included. Filler words were unrelated words, ie, neither the target word nor the prime word was a response to the other. The filler words were not included in the data analysis and were not matched with the other word pairs. The order in which the stimuli sets were presented to participants was counterbalanced. The Kucera-Francis frequency of the target words did not differ significantly between the prime conditions within each stimuli set (see Table 3.1).

The dependent measure for the semantic priming task was the median reaction time in each condition. Median reaction time was used to overcome problems associated with the large number of outliers found in reaction time data (Ratcliff, 1993). Comparisons between the unrelated and directly related conditions, and between the unrelated and indirectly related conditions were made by calculating the percentage difference between reaction times in these conditions (calculated as the difference between median reaction times of the two conditions to be compared, divided by the sum of their median reaction time which is based on the method used to calculate percentage difference in the California Verbal Learning Test; Delis et al., 1987). A

5 The formula used to calculate the percentage difference score was, for example in the comparison between related and unrelated words:

\[
\frac{\text{related} - \text{unrelated}}{\text{related} + \text{unrelated}} \times 100
\]
difference score was calculated as the dependent variable in order to control for any overall slowing on this task.

| Table 3.1 Mean Kucera-Francis frequency values for the three sets of target words used in the semantic priming task with standard deviation in parentheses. |
|---------------------------------|---------------------------------|---------------------------------|
| Target words set 1 | Target words set 2 | Target words set 3 |
| 62.88 (94.91) | 70.97 (83.58) | 62.72 (80.30) |

3.2.2.5 Contextual Naming The context naming task was adapted from the task developed by Norris (1987). Participants were presented with incomplete sentences, followed by a word which ended the sentence, on a computer monitor (sentences are presented in Appendix 4). The incomplete sentence ended in a noun, followed by “the”. The word that followed and completed the sentence was either: a highly probable completion (probable condition, eg, The commuter ran to catch the TRAIN); a less probable but acceptable completion (possible condition, eg, The commuter ran to catch the BIRD); or a highly improbable completion (anomalous condition, eg, The commuter ran to catch the TRAP). There was also a neutral condition in which target words followed the sentence “They said it was the”. The probable, possible, and anomalous conditions consisted of 12 sentences each, and there were 24 sentences in the neutral condition (12 of which consisted of words used in the probable condition for other subjects, and 12 consisting of words used in the anomalous or possible conditions for other subjects). There were also 44 filler sentences which were sentences with a probable ending. These sentences were chosen as filler sentences because they increase the strength of an effect of context in normal participants (Norris, 1987). A practise session was administered prior to commencing this task. The practise session consisted of six probable sentences. The stimuli used in this task were taken
from Norris (1987). The sentence appeared for three seconds and then a fixation cross appeared for 100 ms. The final word was then presented for 1.5 seconds and the subject had 2.5 seconds from its onset in which to name the word. The participant’s reaction time was automatically recorded via a throat-microphone.

The dependent measure for the context naming task was the median reaction time of participants’ responses. Percentage differences were calculated for four comparisons of interest as the difference between median reaction times of the two conditions to be compared, divided by the sum of median reaction times: anomalous vs possible condition; neutral vs probable condition; neutral vs possible condition; and neutral vs anomalous condition. Percentage differences were used as the dependent variable to control for any overall slowing.

3.2.2.6 Verbal learning and memory The California Verbal Learning Test (CVLT; Delis et al., 1987) was administered to participants. In this task participants were required to learn a list of 16 words over 5 trials. The list was made up of four semantic categories, each containing four words. Short-delay free recall and cued recall (where participants were asked to recall items in each category) were tested after an interference list was presented. After a 20 minute delay, free and cued recall were assessed again. Finally, recognition memory was assessed.

3.2.2.7 Inhibition and error-monitoring Pro-saccade and anti-saccade eye-movement tasks were utilised to assess inhibition and error monitoring. Stimuli were presented on a monitor, 50 cm from the participant’s eyes. Participants performed 48 trials in each of the two conditions with no feedback during testing. Each of the trials commenced with a central fixation point. After 800 ms, the target (a white ellipse, 11 mm in height and 8 mm in width) was randomly repositioned 15° to the left or right of the initial central location, for 2000 ms. The direction of the target was randomised across trials. The two conditions were modelled on Crawford, Haeger, Kennard, &
Reveley (1995). In the pro-saccade (reflex) condition, participants were instructed to
direct their eyes to the target as quickly as possible and to hold this position until the
target returned to the centre of the screen. In the anti-saccade condition, participants
were instructed to direct their eyes to the opposite direction (a mirror image position)
from the target, until the target returned to the centre of the screen. The inter-trial
interval was varied randomly between 4 and 6 seconds. The pro-saccade condition
always preceded the anti-saccade condition in order to strengthen the prepotent response
of looking towards the target.

Eye-movements were recorded by placing electrodes at the outer canthus of each
eye to record the horizontal electro-oculogram (HEOG) and above and below the left
eye to record the vertical electro-oculogram (VEOG). The ground electrode was placed
on the left mastoid. Both EOG channels were recorded continuously while subjects
carried out the two eye movement tasks (A/D 200Hz, bandpass DC – 30Hz, gain
75,000). The direction of horizontal eye movements was determined by noting the
direction of deflections that occurred within 800 ms after stimulus onset that were at
least 10° in magnitude.

The first 12 trials in each condition were treated as practice items and were
excluded from data analysis. The number of errors in each condition was recorded.
Errors were subdivided into those that were immediately corrected (self-corrected
errors) and those that were never corrected (uncorrected errors). A percentage correct
score was calculated for each participant (% correct responses / total). The percentage
correct score was used as a measure of inhibition of the prepotent response. The
percentage of self-corrected errors (% self-corrected responses / total) and the
percentage of uncorrected errors (% uncorrected errors / total) were also calculated.
Using the error scores, the percentage of total errors which were uncorrected was
 calculated (% uncorrected anti-saccade errors / total anti-saccade errors). This was the
dependent variable for error-monitoring. In all but one instance (Patient 1), no errors were made during the pro-saccade condition. Observation of the patient revealed that he was not performing the task during the pro-saccade condition but he did complete the task satisfactorily during the anti-saccade condition. Because of the generally high performance of subjects during the pro-saccade condition, these were not included in calculating the anti-saccade error rate. Data were acquired and analysed using Neuroscan Inc acquisition software (Scan 4.0).

3.2.2.8 Continuous Performance Test In the degraded stimulus continuous performance task (CPT-DS), single digit numbers were presented on a computer screen and participants were required to press the response key when a "zero" was presented. All stimuli were perceptually degraded, i.e., 60% of the pixels were removed randomly, and they were presented for 50ms at a rate of one per second. 480 digits were presented, 25% of which were targets. The number of hits, the number of false alarms, and the discrimination index \(d_\text{L}\) based on the logistic distribution functions (Snodgrass & Corwin, 1988) were recorded.

3.2.3 Procedure

Participants were tested individually for a total of 3 hours in 3 separate sessions. In all cases, the cognitive assessment and the thought disorder ratings were conducted within a week of each other. During the first session, the diagnostic interview was administered. The first cognitive testing session involved administration of the following tasks: the control measures, verbal fluency, complex span, digit span, semantic priming and contextual naming. During the second cognitive testing session, CVLT, the anti-saccade task, and CPT-DS were administered.
3.3 Results

To examine the profiles of individual patients over the cognitive domains assessed, their scores on individual tasks were converted to Z-scores using the means and standard deviations of the control group.

3.3.1 Control measures

The patients did not differ significantly from the control group on age, education, or estimated pre-morbid IQ. However, current IQ, as estimated by the Shipley Institute of Living Scale (Zachary, 1991), was significantly higher in the control group than the patient group (see Table 3.2).

The two patient groups (ie, patients with discourse coherence disturbance and patients without discourse coherence disturbance) did not differ from each other on any control variable and screening of the data revealed no systematic effect of any control variable, including age, on the results.

3.3.2 Control group

On all tasks except recognition memory, the results of the control group were consistent with those expected from a normal population based on existing literature (see Table 3.3). On recognition memory, the control group results were slightly below the CVLT norms (Delis et al., 1987).
Table 3.2  Age, education, estimated pre-morbid IQ (NART) and estimated current IQ (Shipley) for the control and patient groups including results for patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic group</th>
<th>Control group</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
</tr>
<tr>
<td>Age</td>
<td>32.37</td>
<td>8.94</td>
<td>8</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.75</td>
<td>2.25</td>
<td>8</td>
</tr>
<tr>
<td>NART</td>
<td>101</td>
<td>8.77</td>
<td>8</td>
</tr>
<tr>
<td>Shipley</td>
<td>97.71</td>
<td>8.65</td>
<td>7*</td>
</tr>
<tr>
<td>DCD+ Age</td>
<td>37.25</td>
<td>10.47</td>
<td>4</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.25</td>
<td>2.99</td>
<td>4</td>
</tr>
<tr>
<td>NART</td>
<td>102.25</td>
<td>8.66</td>
<td>4</td>
</tr>
<tr>
<td>Shipley</td>
<td>91.67</td>
<td>7.23</td>
<td>3*</td>
</tr>
<tr>
<td>DCD- Age</td>
<td>27.50</td>
<td>3.70</td>
<td>4</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.25</td>
<td>1.50</td>
<td>4</td>
</tr>
<tr>
<td>NART</td>
<td>99.75</td>
<td>10.01</td>
<td>4</td>
</tr>
<tr>
<td>Shipley</td>
<td>102.25</td>
<td>7.14</td>
<td>4</td>
</tr>
</tbody>
</table>

* One patient was unable to complete the Shipley Institute of Living Skills Scale due to difficulties reading the form.

** p < 0.05.

3.3.3 Medication

The data from patients were inspected for any systematic effect of medication type. An effect of medication was assumed to be present if the z score of patients differed from the control group by one standard deviation or more. The results showed that those patients taking Olanzapine exhibited facilitated semantic priming for related words compared to unrelated words. This result was confounded by the fact that these patients were also the only patients who exhibited perseverations.
3.3.4 Other symptoms

The data were also examined for any systematic effect of symptoms other than thought disorder on performance on cognitive tests. As above, an effect of symptoms other than thought disorder was assumed to be present if the z score of these patients differed from the control group by one standard deviation or more. No relationship was evident between test performance and either auditory hallucinations or delusions, the two most common symptoms other than thought disorder present at testing in this sample.
Table 3.3  Means and standard deviations of the control group on all tasks.

<table>
<thead>
<tr>
<th>Task</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal Fluency:</strong></td>
<td></td>
</tr>
<tr>
<td>Total correct</td>
<td>39.06 (11.71)</td>
</tr>
<tr>
<td>Percent switches</td>
<td>76.14 (10.67)</td>
</tr>
<tr>
<td>Percent related words</td>
<td>41.72 (17.70)</td>
</tr>
<tr>
<td>Mean cluster size</td>
<td>2.33 (0.32)</td>
</tr>
<tr>
<td><strong>Working Memory:</strong></td>
<td></td>
</tr>
<tr>
<td>Complex span</td>
<td>37.94 (4.47)</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>10.28 (2.89)</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>8.11 (2.45)</td>
</tr>
<tr>
<td><strong>California Verbal Learning Test:</strong></td>
<td></td>
</tr>
<tr>
<td>Verbal Learning</td>
<td></td>
</tr>
<tr>
<td>List A total correct</td>
<td>58.17 (12.34)</td>
</tr>
<tr>
<td>List A trial one</td>
<td>8.39 (2.91)</td>
</tr>
<tr>
<td>List A trial five</td>
<td>13.56 (2.36)</td>
</tr>
<tr>
<td>List B total correct</td>
<td>7.06 (2.04)</td>
</tr>
<tr>
<td>Verbal recall</td>
<td></td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>12.22 (3.04)</td>
</tr>
<tr>
<td>Short delay cued recall</td>
<td>13.22 (2.21)</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>12.06 (3.21)</td>
</tr>
<tr>
<td>Long delay cued recall</td>
<td>12.89 (2.32)</td>
</tr>
<tr>
<td>Percent primacy region</td>
<td>30.49 (3.77)</td>
</tr>
<tr>
<td>Percent middle region</td>
<td>42.70 (7.54)</td>
</tr>
<tr>
<td>Percent recency region</td>
<td>26.81 (4.69)</td>
</tr>
<tr>
<td>Perseverations</td>
<td>4.61 (4.74)</td>
</tr>
<tr>
<td>Free recall intrusions</td>
<td>3.28 (2.91)</td>
</tr>
<tr>
<td>Cued recall intrusions</td>
<td>1.00 (1.14)</td>
</tr>
<tr>
<td>Recognition memory</td>
<td></td>
</tr>
<tr>
<td>Total number correct</td>
<td>14.61 (1.58)</td>
</tr>
<tr>
<td>Discriminability</td>
<td>89.02 (22.88)</td>
</tr>
<tr>
<td>False positives</td>
<td>6.22 (23.43)</td>
</tr>
<tr>
<td>Response bias</td>
<td>-0.10 (0.29)</td>
</tr>
<tr>
<td><strong>Anti-saccade task:</strong></td>
<td></td>
</tr>
<tr>
<td>Percent correct</td>
<td>64.09 (21.93)</td>
</tr>
<tr>
<td>Percent self-corrected errors</td>
<td>32.42 (21.14)</td>
</tr>
<tr>
<td>Percent uncorrected errors</td>
<td>3.49 (3.74)</td>
</tr>
<tr>
<td><strong>Continuous Performance Task:</strong></td>
<td></td>
</tr>
<tr>
<td>Percent of hits</td>
<td>94.54 (4.12)</td>
</tr>
<tr>
<td>Hit reaction time</td>
<td>441.91 (43.33)</td>
</tr>
<tr>
<td>Percent of false alarms</td>
<td>4.17 (1.70)</td>
</tr>
<tr>
<td>$\tilde{d}_c$</td>
<td>6.34 (1.07)</td>
</tr>
</tbody>
</table>
Table 3.3 (cont.)

<table>
<thead>
<tr>
<th>Task</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contextual Naming Task:</strong></td>
<td></td>
</tr>
<tr>
<td>Probable ending</td>
<td>527.39 (64.96)</td>
</tr>
<tr>
<td>Possible ending</td>
<td>551.58 (68.11)</td>
</tr>
<tr>
<td>Anomalous ending</td>
<td>587.81 (70.77)</td>
</tr>
<tr>
<td>Neutral (probable)</td>
<td>539.36 (52.69)</td>
</tr>
<tr>
<td>Neutral (possible/anomalous)</td>
<td>535.08 (65.16)</td>
</tr>
<tr>
<td><strong>Semantic Priming:</strong></td>
<td></td>
</tr>
<tr>
<td>Directly related</td>
<td>525.50 (49.12)</td>
</tr>
<tr>
<td>Indirectly related</td>
<td>538.22 (59.21)</td>
</tr>
<tr>
<td>Unrelated control</td>
<td>533.92 (47.88)</td>
</tr>
</tbody>
</table>

3.3.5 Discourse coherence disturbance ratings

Of the eight patients tested, four exhibited symptoms of discourse coherence disturbance during testing and four did not. Within the patients exhibiting symptoms of discourse coherence disturbance, the severity of these symptoms varied with Patient 1 exhibiting the most severe symptoms, and Patient 4 the least severe symptoms. No symptoms of discourse coherence disturbance were present in Patients 5-8, but again, the severity of these symptoms in the patients’ histories varied with Patient 5 showing a strong history of discourse coherence disturbance symptoms, and Patient 8 never having exhibited these symptoms. Table 3.4 presents the ratings of all patients on the TLC items relating to discourse coherence disturbance at the time of testing.

3.3.6 Patients’ performance on cognitive tests

The results for each of the patients on the cognitive assessments are summarised in Table 3.5.

3.3.6.1 Patient 1. Patient 1 was a 43 year old right-handed male inpatient with an estimated premorbid IQ (NART) of 112 and a current predicted IQ of 100 based on the Shipley Institute of Living Skills. He had completed 12 years of education. His age at onset of schizophrenic symptoms was 28 years of age, and he has had 8 psychiatric
hospital admissions. During admissions, his most common symptom was formal thought disorder. Patient 1 exhibited severe discourse coherence disturbance at the time of testing, including distractibility, tangentiality, derailment, and loss of goal (see Table 3.4), as well as other symptoms of formal thought disorder including disturbances in content (perseveration) and in social convention (poverty of content and circumstantiality; Berenbaum & Barch, 1995). Grandiose delusions were also present at the time of testing. Medication included Fluphenazine Decanoate (62.5 mg fortnightly), Olanzapine (10 mg nocte), and Lorazepam (1 mg mane and 2 mg nocte) at the time of testing.

Table 3.4 Ratings of each patient on the TLC items of discourse coherence disturbance (tangentiality, loss of goal, derailment, illogicality, and distractible speech). All items except loss of goal are rated on a 5 item scale with 0 indicating absence of the symptom and 4 indicating extreme manifestation of the symptom. Loss of goal is rated on a 4 item scale with 0 indicating absence of the symptom and 3 indicating severe manifestation of the symptom.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tangentiality</th>
<th>Loss of goal</th>
<th>Derailment</th>
<th>Illogicality</th>
<th>Distractible speech</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Patient 7</td>
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<td>Patient 8</td>
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Table 3.5 Z-scores of all patients on cognitive measures.

<table>
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<tr>
<th>Task</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
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<tr>
<td><strong>Verbal Fluency:</strong></td>
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<td></td>
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<tr>
<td>Total correct</td>
<td>-1.29*</td>
<td>-0.60</td>
<td>-0.60</td>
<td>-0.26</td>
<td>-1.20*</td>
<td>0.93</td>
<td>-0.69</td>
<td>0.51</td>
</tr>
<tr>
<td>Percent switches</td>
<td>0.28</td>
<td>1.06*</td>
<td>0.48</td>
<td>1.46*</td>
<td>-0.39</td>
<td>-0.20</td>
<td>-0.11</td>
<td>-0.05</td>
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<tr>
<td>Percent related words</td>
<td>-0.47</td>
<td>-1.12*</td>
<td>-0.24</td>
<td>-1.41*</td>
<td>0.58</td>
<td>-0.10</td>
<td>0.47</td>
<td>0.28</td>
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<td>Mean cluster size</td>
<td>1.08†</td>
<td>0.01</td>
<td>-1.02*</td>
<td>-1.02*</td>
<td>-0.49</td>
<td>1.67†</td>
<td>-1.02*</td>
<td>-0.71</td>
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<td><strong>Working Memory:</strong></td>
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<td>Complex span</td>
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<td>-2.45*</td>
<td>-4.69*</td>
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<td>-3.12*</td>
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<td>Forward digit span</td>
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<td>-0.44</td>
<td>-0.10</td>
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<td>Backward digit span</td>
<td>-1.27*</td>
<td>-1.68*</td>
<td>-1.68*</td>
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<td>-1.27*</td>
<td>0.36</td>
<td>-0.86</td>
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<td><strong>California Verbal Learning Test:</strong></td>
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<td><strong>Verbal Learning:</strong></td>
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<tr>
<td>List A total correct</td>
<td>-1.15*</td>
<td>-1.47*</td>
<td>-1.71*</td>
<td>-1.96*</td>
<td>-1.55*</td>
<td>-1.31*</td>
<td>-1.63*</td>
<td>-0.09</td>
</tr>
<tr>
<td>List A trial one</td>
<td>-0.13</td>
<td>-0.48</td>
<td>-2.19*</td>
<td>-1.16*</td>
<td>-0.82</td>
<td>-0.82</td>
<td>-0.82</td>
<td>0.21</td>
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<tr>
<td>List A trial five</td>
<td>-2.36*</td>
<td>-1.08*</td>
<td>-1.51*</td>
<td>-1.93*</td>
<td>-1.51*</td>
<td>-1.93*</td>
<td>-1.93*</td>
<td>0.19</td>
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<tr>
<td>Short delay free recall</td>
<td>-1.06*</td>
<td>-0.40</td>
<td>-1.72*</td>
<td>-1.39*</td>
<td>-1.72*</td>
<td>-2.05*</td>
<td>-1.72*</td>
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<tr>
<td>Short delay cued recall</td>
<td>-1.01*</td>
<td>-0.55</td>
<td>-2.81*</td>
<td>-3.27*</td>
<td>-2.36*</td>
<td>-2.81*</td>
<td>-2.81*</td>
<td>-1.01*</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>-0.64</td>
<td>-0.33</td>
<td>-1.89*</td>
<td>-1.26*</td>
<td>-1.89*</td>
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<td>-0.33</td>
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<tr>
<td>Long delay cued recall</td>
<td>-1.24*</td>
<td>-1.24*</td>
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<td>-2.10*</td>
<td>-2.53*</td>
<td>-3.40*</td>
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<tr>
<td>Total number correct</td>
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<td>-0.39</td>
<td>-0.39</td>
<td>-1.02*</td>
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<td>0.25</td>
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<td>Discriminability</td>
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<tr>
<td>False positives</td>
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<td>Response bias</td>
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<td>-1.39*</td>
<td>-0.80</td>
<td>2.43*</td>
<td>0.35</td>
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Table 3.5 (cont.)

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<th>Task</th>
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<th>Patient 3</th>
<th>Patient 4</th>
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<tr>
<td>Percent correct</td>
<td>1.12†</td>
<td>-1.10*</td>
<td>-1.26*</td>
<td>-1.86*</td>
<td>-1.31*</td>
<td>-1.62*</td>
<td>-0.71</td>
<td>0.33</td>
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<td>Percent self-corrected errors</td>
<td>-1.40†</td>
<td>1.17*</td>
<td>0.76</td>
<td>0.99</td>
<td>1.25*</td>
<td>1.44*</td>
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<td>-0.18</td>
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<tr>
<td>Percent uncorrected errors</td>
<td>1.36*</td>
<td>-0.17</td>
<td>3.12*</td>
<td>5.31*</td>
<td>0.64</td>
<td>1.36*</td>
<td>0.60</td>
<td>-0.93</td>
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<td>Percent of total errors</td>
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<td>uncorrected</td>
<td>4.20*</td>
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<td>0.80</td>
<td>1.24*</td>
<td>-0.05</td>
<td>-0.79</td>
<td>0.16</td>
<td>-0.18</td>
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<tr>
<td>Percent of hits</td>
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<td>Hit reaction time</td>
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<td>1.12†</td>
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<td>Percent of false alarms</td>
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<tr>
<td>Anomalous vs possible ending</td>
<td>0.48</td>
<td>-2.44*</td>
<td>-1.09*</td>
<td>0.30</td>
<td>-1.91*</td>
<td>-0.65</td>
<td>-0.34</td>
<td>-0.76</td>
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<tr>
<td>Probable vs neutral ending</td>
<td>-1.76*</td>
<td>-1.36*</td>
<td>-0.77</td>
<td>0.26</td>
<td>-0.88</td>
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<td>-1.43*</td>
<td>0.14</td>
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<td>Possible vs neutral ending</td>
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<td>-1.76†</td>
<td>0.92</td>
<td>1.08*</td>
<td>-0.03</td>
<td>0.96</td>
<td>-0.58</td>
<td>1.08*</td>
</tr>
<tr>
<td>Anomalous vs neutral ending</td>
<td>0.49</td>
<td>0.80</td>
<td>1.26*</td>
<td>0.36</td>
<td>1.34*</td>
<td>0.97</td>
<td>-0.07</td>
<td>1.11*</td>
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<tr>
<td><strong>Semantic Priming:</strong></td>
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<td></td>
</tr>
<tr>
<td>Directly related vs unrelated</td>
<td>1.84†</td>
<td>2.42†</td>
<td>-1.00*</td>
<td>-1.90*</td>
<td>-2.84*</td>
<td>-0.42</td>
<td>-1.87*</td>
<td>1.02†</td>
</tr>
<tr>
<td>Indirectly related vs unrelated</td>
<td>0.19</td>
<td>1.43†</td>
<td>0.18</td>
<td>-0.47</td>
<td>-0.39</td>
<td>0.48</td>
<td>0.43</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* The patient performed at least one standard deviation below the performance of the control group.
† The patient performed at least one standard deviation above the performance of the control group.
NB. Patient 1 failed to complete the CPT adequately and his results on this task are not included.
Patient 1 (see Figure 3.1) differed from the control group on verbal fluency by producing fewer words and having a larger cluster size (see Table 3.5). His performance on two working memory measures, complex span and backward span, was also impaired. Complex span was markedly impaired relative to the control group. He showed poorer learning and recall but not verbal recognition. He had a slightly higher percentage of correct responses than the control group on the anti-saccade task but a smaller percentage of his total responses were self-corrected errors and of the errors he made, a higher percentage were uncorrected compared to the control group. Patient 1’s results on the continuous performance test could not be used because he was observed to be looking away from the computer screen during most of the test. On two comparisons on contextual naming (the comparisons between the neutral condition and probable ending, and the neutral condition and possible ending), he showed a smaller effect of context than the control group. He exhibited facilitated semantic priming for directly related compared to unrelated word pairs.

3.3.6.2 Patient 2. Patient 2 was a 27 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 94 and a current predicted IQ of 104 based on the Shipley Institute of Living Skills. His age at onset of schizophrenic symptoms was 18 years of age and he has had 6 psychiatric hospital admissions. During admission, his principal symptom was disinhibition, but auditory hallucinations and formal thought disorder, including discourse coherence symptoms (derailment, loss of goal, and loose associations) were also common. Patient 2 exhibited severe discourse coherence disturbance at the time of testing, including tangentiality, derailment, illogicality, and loss of goal (see Table 3.4) as well as other symptoms of formal thought disorder including disturbances in social convention (circumstantiality), in fluency (incoherence), and in content (perseveration; Berenbaum & Barch, 1995). Apart from symptoms of thought disorder, patient 2 was relatively symptom free at the time of
testing. His medication included Olanzapine (25 mg nocte), Sodium Valproate (800 mg bd), Sertraline (50 mg mane), and Clonazepam (1 mg nocte).

Patient 2 (see Figure 3.2) did not show the same pattern as patient 1 on verbal fluency, although he made a greater percentage of category switches and produced fewer related words than the control group. However, his performance on working memory tasks was the same as patient 1’s (see Table 3.5) with impaired complex and backward span. Similar to patient 1, patient 2’s performance on learning and recall was impaired but he performed normally on verbal recognition. Patient 2 differed from patient 1 on the anti-saccade task, producing a lower percent of correct responses and a higher percent of self-corrected errors than the control group. On the continuous performance task, he made a larger number of hits and false alarms than the control group. Unlike patient 1, patient 2 displayed a smaller effect of context in the context naming task on two comparisons (anomalous vs possible ending, and neutral condition vs probable ending) and a larger effect of context on one comparison (neutral condition vs possible ending). On the semantic priming task, patient 2 showed facilitated priming for both directly and indirectly related word pairs.

### 3.3.6.3 Patient 3

Patient 3 was a 49 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 107. Patient 3 was unable to complete the Shipley Institute of Living Skills due to difficulty reading the form. He had completed 10 years of education. His age at onset of schizophrenic symptoms was 25 years of age, and he has been admitted to a psychiatric hospital on 9 occasions. During admission, his principal symptoms were delusions and some formal thought disorder, consisting of the discourse coherence symptoms tangentiality and loose associations. He exhibited moderate discourse coherence disturbance at the time of testing, namely, tangentiality, and loss of goal (see Table 3.4) with some other formal thought disorder symptoms, namely, disturbance of social convention (poverty of speech). Otherwise he was
relatively symptom free. His medication included Zuclopenthixol Decanoate (600 mg fortnightly) and Benztropine (1 mg mane).

This patient (see Figure 3.3) differed from both of the preceding patients on the verbal fluency task in that his only difference from the control group was the production of a marginally smaller cluster size. Consistent with patients 1 and 2, patient 3’s working memory results showed impairments on complex and backward span, but he was also slightly impaired on forward span. Patient 3’s learning and recall were particularly poor relative to the control group but his recognition performance was preserved. His performance on the anti-saccade task was characterised by a slightly smaller percentage of correct responses and of the total responses; he displayed a higher percentage of uncorrected errors than the control group. Patient 3 differed from patient 2 on the continuous performance task by displaying a smaller $d_t$, a slower reaction time, and more false alarms than the control group. Patient 3 displayed a marginally smaller effect of context in the contextual naming task on two comparisons (anomalous vs possible ending and neutral condition vs anomalous ending) but did not differ from the control group on semantic priming.

3.3.6.4 Patient 4. Patient 4 was a 30 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 96 and a current predicted IQ of 73 based on the Shipley Institute of Living Skills. He had completed 15 years of education. His age at onset of schizophrenic symptoms was 22 years of age and he has had 6 admissions to psychiatric hospitals. During admission, his principal symptoms were auditory hallucinations and bizarre delusions. He exhibited mild discourse coherence disturbance at the time of testing, with derailment being his only manifest symptom (see Table 3.4). He also exhibited fluency disturbance (neologisms; Berenbaum & Barch, 1995). He had a history of discourse coherence disturbance symptoms including loss of goal, tangentiality, derailment, and illogicality. His medication at the time of testing
included Clozapine (600 mg nocte), Amitryptilene (75 mg nocte), and Propanalol (40 mg AM).

Patient 4 (see Figure 3.4) performed similarly to patient 2 on verbal fluency by producing more switches and fewer related words than the control group. His working memory performance was similar to that of patients 1-3 with impaired complex and backward span (see Table 3.5). As for the other patients, patient 4 was impaired on learning and recall but not on recognition. On the anti-saccade task, of patient 4’s total responses, a smaller percentage were correct responses and a larger percentage were uncorrected errors. Of the total errors made, patient 4 failed to correct a higher percentage than the control group. Unlike the preceding patients, he did not differ from the control group on the continuous performance task. He showed marginally impaired use of context on one contextual naming comparison (neutral condition vs possible ending) and exhibited reduced semantic priming on directly related compared to unrelated word pairs.

3.3.6.5 Patient 5. Patient 5 was a 24 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 86 and a current predicted IQ of 94 based on the Shipley Institute of Living Skills. He had completed 11 years of education. His age at onset of schizophrenic symptoms was 18 years of age, and he had been admitted to a psychiatric hospital on 8 occasions, most recently twelve months prior to testing. During admissions, Patient 5’s primary symptoms were auditory hallucinations which were present at the time of testing. He had a history of discourse coherence disturbance, including distractibility, tangentiality, derailment, illogicality, and loose associations, although he did not exhibit these symptoms at the time of testing (see Table 3.4). He had exhibited discourse coherence disturbance during all of his previous admissions. His medication included Clozapine (150 mg tds), Sertraline (100 mg nocte), Lorazepam (1 mg nocte), and Amitriptyline (10 mg nocte).
Patient 5 (see Figure 3.5) produced fewer total words on the verbal fluency task. On working memory, his performance was similar to the preceding patients with impaired complex and backward span (see Table 3.5). Similar to the other patients, patient 5 displayed impairments in learning and recall but not verbal recognition. His performance on the anti-saccade task was the same as patient 2’s with a smaller percentage of correct responses and a higher percentage of self-corrected errors than the control group. With respect to the continuous performance task, his results were similar to patient 3’s with a smaller $d_1$, a slower reaction time, and more false alarms than the control group. Like many other patients, he showed marginally impaired use of context on two contextual naming comparisons (anomalous vs possible ending and neutral condition vs anomalous ending). Similar to patient 4, patient 5 failed to show a semantic priming effect for directly related words compared to unrelated words.

**3.3.6.6 Patient 6.** Patient 6 was a 32 year old left-handed male outpatient with an estimated premorbid IQ (NART) of 109 and a current predicted IQ of 104 based on the Shipley Institute of Living Skills. He had completed 14 years of education. His age at onset of schizophrenic symptoms was 30 years of age, and he has had 3 admissions to psychiatric hospitals. During admissions, his most common symptoms were auditory hallucinations, paranoid and grandiose delusions, and discourse coherence disturbance consisting of tangentiality and derailment. Although Patient 6 had a history of discourse coherence disturbance symptoms, these symptoms were mild to moderate and not as prominent as his other symptoms. Patient 6 was relatively symptom free at the time of testing and did not exhibit any symptoms of discourse coherence disturbance (see Table 3.4). His medication at the time of testing was Clozapine (375 mg nocte) and Lorazepam (1 mg bd).

Patient 6 (see Figure 3.6) differed from the control group on verbal fluency by producing a larger cluster size, but he did not differ from the control group on working
memory tasks. Patient 6 performed similarly to other patients with impaired learning and recall but intact recognition. Of his total responses on the anti-saccade task, patient 6 showed a smaller percent of correct responses and a higher percent of both self-corrected and uncorrected errors. His results on the continuous performance task were very similar to the control group with only a marginally longer reaction time. With respect to contextual naming, he showed impaired use of context on one comparison (neutral condition vs probable condition), and he did not differ from the control group on semantic priming.

3.3.6.7 Patient 7. Patient 7 was a 29 year old left handed male outpatient with an estimated premorbid IQ (NART) of 101 and a current predicted IQ of 100 based on the Shipley Institute of Living Skills. He had completed 11 years of education. His age at onset of schizophrenic symptoms was 17 years of age, and he has had 5 admissions to psychiatric hospitals, most recently six months prior to testing. During admissions, Patient 7’s principal symptoms were persecutory delusions and auditory hallucinations. He had some history of discourse coherence disturbance, having exhibited loose associations and tangentiality on previous occasions. However, symptoms of discourse coherence disturbance were relatively rare. Patient 7 was relatively symptom free at the time of testing and did not exhibit symptoms of discourse coherence disturbance (see Table 3.4). His medication included Risperidone (2 mg bd fortnightly) and Lorazepam (0.5 mg mane and 1 mg nocte fortnightly).

Patient 7 (see Figure 3.7) produced a marginally smaller cluster size than the control group on the verbal fluency task and, in contrast to all other patients, performed better than the control group on forward span in the working memory tasks. His performance on other working memory tasks was comparable to controls. Similar to other patients, he performed poorly on learning and recall but not recognition. Unlike the preceding patients, patient 7 did not differ from the control group on the anti-
saccade task. Patient 7 performed in a similar manner to patients 3 and 5 on the continuous performance task with a smaller $d_z$, slower reaction time, and more false alarms than the control group. He showed impaired use of context on one contextual naming comparison (neutral condition vs probable ending) and, as for patients 4 and 5, showed impaired semantic priming for directly related compared to unrelated word pairs.

3.3.6.8 Patient 8. Patient 8 was a 25 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 102 and a current predicted IQ of 111 based on the Shipley Institute of Living Skills. He had completed 13 years of education. His age at onset of schizophrenic symptoms was 21 years of age, and he had been admitted to psychiatric hospitals on 4 occasions. During admissions, his most common symptoms were auditory hallucinations and persecutory delusions. Patient 8 was symptom free at the time of testing and had no history of discourse coherence disturbance symptoms (see Table 3.4). His medication at the time of testing included Clozapine (150 mg mane and 300 mg nocte).

This patient’s profile (see Figure 3.8) shows the least difference from the control group of all patient profiles. Patient 8 did not differ from the control group on verbal fluency, working memory, learning, recognition, and anti-saccade measures. On recall, patient 8 showed only a very marginal impairment and his reaction time on the continuous performance test was slightly slower than the control group. Patient 8 showed marginally impaired use of context on two contextual naming comparisons (neutral condition vs possible ending and neutral condition vs anomalous ending) and slightly facilitated semantic priming for directly related compared to unrelated word pairs.
Figure 3.1. Profile plot for Patient 1 showing patient’s z scores plotted against the control group.
NB. CPT-DS is not included because Patient 1 failed to complete this task.
Figure 3.2. Profile plot for Patient 2 showing the z scores plotted against the control group.
Figure 3.3. Profile plot for Patient 3 showing the z scores plotted against the control group.
Figure 3.4. Profile plot for Patient 4 showing the z scores plotted against the control group.
Figure 3.5. Profile plot for Patient 5 showing patient's z scores plotted against the control group.
Figure 3.6. Profile plot for Patient 6 showing patient’s z scores plotted against the control group.
Figure 3.7. Profile plot for Patient 7 showing patient's z scores plotted against the control group.
Figure 3.8. Profile plot for Patient 8 showing patient’s z scores plotted against the control group.
3.3.7 Summary of Patients’ performance

3.3.7.1 Patients versus control differences The results show that relative to a well-matched control group, all patients except Patient 8 had some difficulties with verbal learning and recall (see Figures 3.9-3.11). All patients showed some evidence of impaired performance on the CPT-DS (see Figure 3.12) and impaired use of context on some of the measures (see Figure 3.13). With respect to semantic priming, there was no consistent evidence of either facilitation or impairment (see Fig 3.14).

Figure 3.9. Z scores of all patients on verbal learning tasks.
Figure 3.10. Z scores of all patients on CVLT verbal recall measures.

Figure 3.11. Z scores of all patients on CVLT recognition measures.
Figure 3.12. Z scores of all patients on CPT-DS.

NB. Patient 1 was excluded because he failed to complete this task.

Figure 3.13. Z scores of all patients on the contextual naming task.
3.3.7.2 Discourse coherence disturbance and cognitive performance  The results revealed a consistent pattern of differences between the four patients with current symptoms of discourse coherence disturbance and the four patients without these symptoms in the areas of: verbal fluency; working memory; and the anti-saccade task. On all other measures, there was no systematic effect of the presence of discourse coherence disturbance on cognitive assessments.
3.3.7.3 Verbal Fluency On the verbal fluency task, Patient 1 produced more switches and fewer related words than both the control group and patients without discourse coherence disturbance. This was replicated in Patients 2-4, who showed a similar pattern of performance (see Figure 3.15). Patients with past or present distractible speech generated fewer words in the verbal fluency task (Patients 1 and 5).

![Figure 3.15. Z scores of all patients on the verbal fluency measures.](image)

3.3.7.4 Working Memory On the working memory tasks, Patient 1 had a smaller complex working memory and backward digit span than either the control group or patients without discourse coherence disturbance. This pattern of performance was replicated in Patients 2-4. Patient 5, who had a history of discourse coherence disturbance symptoms, showed a similar pattern of performance to patients 1-4 (see Figure 3.16). Patients 1-4 all exhibited discourse coherence disturbance during testing, and Patient 5 had a long history of severe discourse coherence disturbance. Although
Patients 6 and 7 also displayed discourse coherence disturbance in the past, their symptoms were milder and less frequent. The only patient with no history of discourse coherence disturbance (Patient 8) performed better than any other patient on these tasks.

![Figure 3.16. Z scores of all patients on working memory tasks.](image)

### 3.3.7.5 Anti-saccade
Patient 1 was less likely to correct his errors on the anti-saccade task. This effect was replicated by two other patients with discourse coherence disturbance (Patients 3 and 4). Patient 2 failed to show this effect (see Figure 3.17). The two patients who failed to correct the highest percentage of total errors made, were also the only patients to exhibit the fluency disturbance symptoms of neologisms (Patients 1 and 4).
3.4 Discussion

Patients with discourse coherence disturbance exhibited deficits in working memory tasks tapping into the central executive of working memory, namely, the complex span and backward span tasks. These patients also produced more switches and fewer related words on the verbal fluency task, implying impaired executive function and ability to organise information. Finally, patients with discourse coherence disturbance, with one exception, produced a greater number of uncorrected errors on the anti-saccade task, indicating deficits in their ability to monitor and utilise errors and/or impaired inhibition. However, given the lack of consistency in the results from patients with discourse coherence disturbance and the similar result from one of the patients without discourse coherence disturbance, the anti-saccade results need to be interpreted with caution.

Although the results from this study do not strongly support any particular theory of discourse coherence disturbance, they are most consistent with McGrath’s model. On the other hand, the results do show areas in which patients with discourse
coherence disturbance are not differentially impaired and so enable certain theories of discourse coherence disturbance to be ruled out. Patients with discourse coherence disturbance did not show the pattern of performance predicted by the other theories. Harrow et al.’s (1987) theory predicted impaired use of contextual information and impaired long-delay memory. However, patients with discourse coherence disturbance were not distinguishable from other schizophrenic patients in these areas. All schizophrenic patients tested (including patient 8 who had no history of discourse coherence disturbance symptoms) showed some impairment in their ability to use contextual information. Similarly, most patients exhibited deficits in long-delay verbal memory with no apparent difference between patients with and without discourse coherence disturbance.

Hoffman et al. (1986) predicted impairments in sustained attention and planning ability. The results of this study failed to find a sustained attention deficit specific to discourse coherence disturbance. All patients showed poor performance on the CPT task: the patients with discourse coherence disturbance were not distinguishable from those without. With respect to planning, Hoffman et al. (1986) predicted that patients with discourse coherence disturbance would be unable to either generate or maintain a discourse plan. Although this hypothesis could not be tested in this study, results from previous studies investigating planning in patients with discourse coherence disturbance do not support Hoffman’s predictions (Barch & Berenbaum, 1997; see Section 2.2.1).

Nestor et al.’s (1998) theory centred on predictions about automatic, intralexical semantic priming. According to their theory, patients with discourse coherence disturbance were expected to exhibit facilitated semantic priming and impaired working memory and inhibition. Although the patients with discourse coherence disturbance displayed working memory impairments, there was no explicit evidence of an inhibition deficit. Patients with discourse coherence disturbance did not differ from patients
without discourse coherence disturbance with respect to the number of errors made on the anti-saccade task, suggesting that they were able to successfully inhibit the prepotent response in this task. On this task, patients with discourse coherence disturbance differed from patients without discourse coherence disturbance only in their ability to correct errors they had made. Furthermore, patients with discourse coherence disturbance did not show a systematic facilitation of priming, and, in fact, some of these patients showed reduced semantic priming. This result, however, needs to be interpreted with caution. Recently, Moritz et al. (2001) discussed the importance of presenting the prime for a sufficient amount of time to allow patients with schizophrenia to process it. In their study, they presented the prime for 200 ms and presented the target immediately after this. In this way they combined a longer presentation time with a sufficiently brief SOA of 200 ms which allowed them to tap into the automatic processes of semantic memory. They found that patients with symptoms of loose associations showed facilitation of semantic priming. It is possible that the failure to find facilitated semantic priming in the current study was due to the short presentation period (150 ms) of the prime. However, five of the eight patients showed a semantic priming effect within the normal to above normal range. Therefore, the failure to find a systematic effect of facilitated priming in the patients with discourse coherence disturbance is unlikely to be due to failure to process the prime word. The two patients who showed facilitated semantic priming were also the only patients exhibiting perseverations, a symptom which fits into the category of content disturbance (Berenbaum & Barch, 1995; Barch & Berenbaum, 1997). This may indicate that the effect of facilitated priming that has been found in patients with thought disorder is due to the performance of patients with content disturbance rather than discourse coherence disturbance. However, these two patients were also the only patients being treated by Olanzapine. Effects of medication would have to be controlled before any conclusions
about the association between content disturbances and facilitated priming could be made.

Overall, the performance of the patients with discourse coherence disturbance are best accounted for by McGrath’s (1991) proposed disconnection between central executive processes and co-ordination of motor responses. These patients performed poorly on tasks requiring central executive processes, and the data may suggest that they also performed poorly on tasks where they were required to monitor and correct their behaviour. McGrath suggested that the physiological basis of discourse coherence disturbance is disconnection between the dorsolateral prefrontal cortex and the subcortical areas such as the basal ganglia and thalamic regions which mediate communication between temporoparietal and frontal regions involved in language production, and also communication between temporoparietal and motor regions (Alexander et al., 1989; Alexander, DeLong, & Strick, 1986; Crosson, 1985; McGrath, 1991; McGrath, 1996). The temporoparietal connections with the frontal cortex play an important role in monitoring language during speech production, and the connections which proceed through the subcortical regions to the frontal cortex and motor cortex are important for monitoring the semantic content of speech. The direct connections between temporoparietal and frontal regions are more important for phonological monitoring of language (Crosson, 1985). Disruptions to connections between the frontal and subcortical regions would disrupt the semantic link between prefrontal and temporoparietal regions which would be consistent with the semantic, not phonological impairment in discourse coherence disturbance.

Functional imaging studies investigating verbal fluency and working memory tasks in normal subjects have found that these tasks are associated with activation in prefrontal and parietal cortices (Cardebat et al. 1996; Fletcher, Frith, Grasby, Friston, & Dolan, 1996; McGuire & Frith 1996; Pujol et al., 1996), allowing the possibility that
impaired verbal fluency performance in schizophrenic patients with discourse coherence disturbance results from a disruption to the temporoparietal-prefrontal connection, consistent with McGrath's theory. However, without further physiological investigations, it cannot be concluded that this is the locus of the deficit in these patients.

The area of working memory impairments predicted by McGrath is the central executive of working memory as characterised by Baddeley (Baddeley & Hitch, 1994; Gathercole & Baddeley, 1993). Although the tasks used in this study, namely, the complex span and backward span tasks are believed to tap into the central executive of working memory, these tasks do not provide a “pure” measure of executive processes as these tasks also require subjects to maintain the information in the phonological loop. To an extent this was controlled for by the forward span task (which taps into simple maintenance of information) on which patients with discourse coherence disturbance performed at a level comparable with control subjects, although patients were slightly lower than controls on this measure. Imaging research suggests that manipulation processes involve the dorsolateral prefrontal cortex, while maintenance processes involve the ventrolateral prefrontal cortex (Collette et al., 1999; D'Esposito et al., 1999; Owen, Evans, & Petrides, 1996; Smith, Jonides, & Koeppe, 1996). Thus, based on the current results, the hypothesised disrupted connection in patients with discourse coherence disturbance should be between dorsolateral prefrontal areas and the temporoparietal and subcortical areas which is consistent with McGrath’s theory that the disrupted network in patients with discourse coherence disturbance involves the dorsolateral prefrontal cortex. A specific disruption to the dorsolateral prefrontal circuit is also consistent with the similarity of language disturbance in patients with discourse coherence disturbance and patients with lesions to the dorsolateral prefrontal network.
The anti-saccade task involves two important cognitive functions, namely, error-monitoring and detection, and inhibition of prepotent responses (Roberts et al., 1994; Roberts & Pennington, 1996). As noted above, the response pattern of patients with discourse coherence disturbance is consistent with monitoring problems, not poor inhibition. If these patients were unable to inhibit their prepotent responses, they would have exhibited more errors than patients without discourse coherence disturbance. Patients with discourse coherence disturbance made a similar number of errors as patients without these symptoms, but patients with discourse coherence disturbance failed to correct a greater number of these errors, indicating impaired error-monitoring. This error-monitoring deficit may involve either impaired error-detection, or impaired ability to correct errors. According to McGrath’s theory, patients with discourse coherence disturbance are unable to correct their errors: they are able to detect errors but are unable to use this information effectively to correct errors. This study was unable to distinguish between error-detection processes and error-correction processes. However, further research focusing on physiological processes would enable discrimination between these processes. Such research would focus on the anterior cingulate which seems to be involved in error detection and monitoring (Carter et al., 1999; Dehaene et al., 1994; Holroyd, Dien, & Coles, 1998; Kiehl et al., 2000), and error-related negativity (ERN), an event related potential (ERP) component associated with the detection of errors (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Leuthold & Sommer, 1999; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996). The patients who displayed the greatest percentage of uncorrected errors were also the only patients to exhibit neologisms, within the category of fluency disturbance (Berenbaum & Barch, 1995; Barch &
Neologisms were these patients only symptoms of fluency disturbance, their other symptoms being primarily discourse coherence disturbance symptoms. Unlike other fluency disturbance symptoms such as incoherence, neologisms involve semantic errors, rather than grammatical errors. Thus the impaired semantic monitoring network proposed in McGrath’s theory could explain the failure to detect and correct the use of neologisms in these patients’ speech.

Of particular interest was the performance of Patient 5 who had a substantial history of discourse coherence disturbance symptoms but was free of these symptoms during testing. Patient 5 can be distinguished from Patients 6 and 7 who had exhibited only mild and infrequent discourse coherence disturbance. Patient 5 performed poorly on complex span and backward span working memory tasks, but did not differ from the patients without discourse coherence disturbance on error-monitoring and the verbal fluency task. One possible explanation for this pattern of results is that there is a stable impairment of the central executive of working memory in schizophrenic patients who develop discourse coherence disturbance. Physiologically, this would be reflected by dysfunction in the dorsolateral prefrontal cortex which has been shown to be involved with central executive working memory processes (Collette et al., 1999; D’Esposito et al., 1999; Owen et al., 1996; Smith et al., 1996). A disconnection between planning and editing ability and the co-ordination of motor response occurs in order for these patients to manifest overt discourse coherence disturbance symptoms. This disconnection would result from an underlying physiological disconnection between prefrontal, subcortical, and temporoparietal regions as predicted by McGrath. This disconnection renders the patients unable to adequately monitor their behaviour which is evidenced by their inability to correct errors on the anti-saccade task, and their poor performance on the verbal fluency task which is a sophisticated task requiring coordination between planning, monitoring, and response.
3.4.1 Future Directions

The results of this study provide a number of directions in which further research could progress. First, as noted above, physiological studies confirming and expanding on these results would provide more support for McGrath’s model of discourse coherence disturbance. Secondly, this study provides a useful model of research into other areas of schizophrenic thought disorder. All patients exhibiting discourse coherence disturbance showed very similar cognitive profiles. This provides support for Berenbaum and Barch’s (1995) categorisation of thought disorder and also confirms that testing small groups of very similar patients provides useful information about schizophrenic symptoms. This is an important finding, given the heterogeneity of schizophrenic symptoms, and the inconsistent findings across many studies. Similar case studies looking at the other categories of thought disorder highlighted by Barch and Berenbaum would be of interest.

There are a number of limitations to this study which could be overcome in subsequent studies. First, planning ability was not assessed in this study. Planning is an important element of McGrath’s and Hoffman’s models and could be used to distinguish between these theories. The incorporation of a task similar to that used by Barch and Berenbaum (1997) would enable the differentiation between predictions of these two theories. Secondly, the measure of error-monitoring derived from the antisaccade task may not be the most suitable for assessing the ability to correct speech errors. This limitation will be partly overcome by assessing the generalisability of this finding in Study 3. Finally, the problem of generalisability which is inherent to case study designs must be considered in interpreting the results of the current study. Further research with a larger group of patients is necessary to confirm the current findings.
3.4.2 Summary

This chapter presented the results of a study which are consistent with the theory that discourse coherence disturbance is due to disconnection between thought and action as hypothesised by McGrath. At a broader level, these results also support the notion that discourse coherence disturbance in schizophrenia is linked to underlying cognitive deficits. Although it is largely accepted that patients with schizophrenia exhibit a number of cognitive deficits, the direction of causation is not clear. Physiological findings which are consistent with and add to the cognitive findings may support the assumption that cognitive deficits precede symptoms. Neurophysiological evidence of disconnection between the prefrontal, subcortical, and temporoparietal cortices, as predicted by McGrath’s (1991) model, would support a general model of schizophrenic thought disorder positing physiological abnormalities underlying cognitive impairments, leading to particular symptoms.

Based on the support from this Chapter for McGrath’s theory, the next two Chapters will focus on further physiological and cognitive processes to test his theory. Chapter 4 presents the results of an fMRI study investigating the role of the prefrontal cortex in discourse coherence disturbance. Chapter 5 focuses on the nature of the error-monitoring deficit in discourse coherence disturbance, as well as providing a preliminary investigation of the role of prefrontal networks in discourse coherence disturbance.
CHAPTER 4

STUDY 2

4.1 Introduction

The aim of Study 2 was to explore the role of the dorsolateral prefrontal cortex in central executive impairments in patients with discourse coherence disturbance. The reason for this focus was twofold. First, as discussed in Chapter 2, prefrontal deficits form a central element in all four theories of discourse coherence disturbance. Furthermore, the predicted deficit differs between McGrath’s theory and the other theories of discourse coherence disturbance: McGrath predicts disruption to the prefrontal network, while the other theories predict a specific prefrontal deficit. Physiological investigation of the prefrontal lobe in patients with and without discourse coherence disturbance will enable differentiation of McGrath’s theory from the other theories. Given the support for McGrath’s theory from Study 1, it is predicted that patients with discourse coherence disturbance will not show a specific prefrontal deficit, rather, there will be a disconnectivity between prefrontal and temporoparietal regions.

The second reason for focusing on prefrontal function in patients with discourse coherence disturbance, arises from the results of Study 1. The strongest finding from Study 1 was a consistent impairment of the central executive function of working memory in patients with discourse coherence disturbance. Considerable work with humans and primates has suggested that the prefrontal cortex is strongly associated with working memory processes (Friedman & Goldman-Rakic, 1994; Goldman-Rakic, 1996; Petrides et al., 1993; Roberts & Pennington, 1996). These studies have consistently found activation of both the prefrontal cortex, and more posterior regions such as the parietal cortex, premotor areas, and the cingulate gyrus across a range of central
executive tasks, including updating tasks (Cohen et al., 1997; Mellers et al., 1995; Salmon et al., 1996; Van der Linden et al., 1999), random generation tasks (de Zubicaray, 1998; Salmon et al., 1996), dual tasks (D’Esposito et al., 1995), and stimulus independent thoughts (McGuire, Paulesu, Frackowiak, & Frith, 1996).

A recent focus of neuro-imaging research has been concerned with fractionation of different aspects of working memory and functional anatomical localisation of these separate processes within the frontal cortex. The studies noted above found activation in prefrontal and posterior regions associated with tasks tapping into central executive function. However, most studies did not separate central executive processes from the maintenance of information which relies on the phonological loop of working memory. As a result, it is difficult to isolate the physiological processes which are specific to the central executive element of the tasks. A number of recent imaging studies have attempted to separate out the brain regions specific to central executive processes. Collette et al. (1999) conducted a PET study comparing maintenance and manipulation processes. The manipulation condition required subjects to re-order letters into alphabetical order and maintain the newly ordered information. This was compared to a maintenance condition in which subjects remembered a set of letters over time. Collette et al. found increased activation of the inferior and superior parietal regions, and bilaterally in the dorsolateral prefrontal cortex near the middle frontal gyrus during the manipulation condition. Also present during this condition was deactivation in the left superior and middle temporal gyrus in the right inferior parietal region and posterior cingulate gyrus. In contrast, the maintenance condition was associated with activation of the cerebellum, left fronto-insular cortex, anterior cingulate, right dorsomedial thalamus, and right premotor cortex. Thus, Collette et al.’s results indicate that there is a network between anterior and posterior regions which is specific to central executive processes. A similar network of regions associated with central executive processes
was found in an fMRI study conducted by Garavan et al. (2000). Using an adaptation of the WCST which varied the amount of switching performed by subjects across conditions, Garavan et al. found that increased switching was associated with increased activation in a range of areas including the dorsolateral prefrontal region near the middle frontal gyrus, premotor, and parietal areas. D'Esposito et al. (1999) conducted an fMRI using a similar behavioural task to that used by Collette et al., ie, participants were required to either remember letters in the order presented or re-order the letters into alphabetical order and remember the new order. D'Esposito et al. found similar results to Collette et al. (1999) with respect to functioning associated with the maintenance and manipulation conditions combined, ie, there was activation of the dorsolateral and ventrolateral prefrontal cortex, the lateral premotor, supplementary motor cortex, the posterior parietal region, and the superior temporal cortex. However, with respect to the manipulation condition, the only way in which this differed from the maintenance condition was increased activation in the dorsolateral prefrontal cortex. There was no area of activation that was specifically associated with the maintenance condition. The role of the dorsolateral prefrontal cortex in central executive processes was confirmed by MacDonald, Cohen, Stenger, and Carter (2000). They conducted an fMRI study in which participants performed the Stroop task. They found the dorsolateral prefrontal cortex was more active during the colour naming than the colour reading condition. They concluded that in this task, the dorsolateral prefrontal cortex is important for the implementation of control and activity in this region associated with central executive processes.

Thus working memory, and central executive processes generally, seem to be associated with activation of prefrontal, premotor, parietal, and superior temporal regions (Clark et al., 2000; Fiez, 2001; Jonides, 2000). More specifically, in terms of frontal regions, central executive function can probably be differentiated from short-
term maintenance of information by increased activation in the dorsolateral prefrontal cortex (Collette et al., 1999; D’Esposito et al., 1999; Garavan et al., 2000). Given the specific association between dorsolateral prefrontal function and central executive processes, impaired dorsolateral prefrontal function would account for the poor performance of patients with discourse coherence disturbance on central executive tasks. However, dorsolateral prefrontal dysfunction need not be a simple impairment confined to this region. An alternative source of the central executive impairment could be disrupted connections between the dorsolateral prefrontal cortex and other regions involved in central executive tasks, such as temporoparietal regions. The findings above suggest that central executive processes do not rely on a single region, but involve activity across a range of brain areas.

Mega and Cummings (2001) described the dorsolateral prefrontal circuit which originates in the dorsolateral prefrontal cortex and extends via the caudate nucleus, substantia nigra, and subthalamic nucleus to the anterior and mediodorsal thalamus before projecting back to the dorsolateral prefrontal cortex. The circuit also has rich connections to the parietal lobe, subcortical regions, supplementary motor area, and the frontal eye fields. Impairments to any part of the dorsolateral prefrontal circuit may result in central executive dysfunction similar to the dysfunction resulting from specific lesions to the dorsolateral prefrontal cortex (Duffy & Campbell, 2001; Mega & Cummings, 2001). This circuit is similar to the circuit described by McGrath, disruption to which can cause speech disturbances similar to discourse coherence disturbance (Alexander et al., 1989; Crosson, 1985; Mega & Cummings, 2001; Novoa & Ardila, 1987). Disruption to this network could account for both the specific speech disturbance found in patients with discourse coherence disturbance, and the central executive impairments present in these patients.
There is evidence of both reduced dorsolateral prefrontal activation, and impaired connectivity, in patients with schizophrenia. Patients with schizophrenia generally show abnormal activations in brain regions associated with executive tasks in healthy volunteers. For example, patients with schizophrenia have been found to show hypofrontality on tasks of executive function, particularly in the dorsolateral prefrontal lobe, as well as reduced activation in the right parietal region (Carter, Perlstein et al., 1998; Menon, Anagnoson et al., 2001). Other studies have found that hypofrontality in patients with schizophrenia while performing central executive tasks is associated with increased activation of the parietal regions (Callicott et al., 1998; Curtis et al., 1998). In contrast, a set of studies have found increased activation in the dorsolateral prefrontal cortex in patients with schizophrenia (Manoach et al., 1999; Manoach et al., 2000).

Few studies have investigated the physiology of central executive in relation to different schizophrenic symptoms. Those that have, found the hypofrontality was related to delusions but not to other symptoms such as conceptual disorganisation (Menon, Anagnoson et al., 2001).

Recent evidence suggests that results of hypofrontality in patients with schizophrenia need to be interpreted with caution. Frith et al. (1995) and Manoach et al. (2000) investigated the role of the frontal cortex in patients with schizophrenia where working memory demands were reduced in the schizophrenic group. In these studies, working memory load or task constraints for patients with schizophrenia were reduced so that they were able to perform equally as well as control subjects. Under these conditions, dorsolateral prefrontal activation was equal for both groups. This is an important finding to note, since there appears to be an “inverted-U” relationship between dorsolateral prefrontal activation and working memory load in normal controls. Callicott et al. (1999) found that in normal controls, dorsolateral prefrontal activation increases with increasing load up to a point. After this point, dorsolateral prefrontal
activation drops off. Callicott et al. posited that this decrease in dorsolateral prefrontal activation could result from overloading the capacity of working memory, ie, the dorsolateral prefrontal cortex no longer works efficiently once working memory capacity is exceeded. Application of this finding to studies of dorsolateral prefrontal cortex in schizophrenia would suggest that if working memory tasks are not modified to take account of the reduced working memory capacity of patients with schizophrenia, any reduction in dorsolateral prefrontal activation may result from overload of working memory and the accompanying inefficiency of dorsolateral prefrontal cortex, rather than impaired dorsolateral prefrontal function.

Recent neuroimaging studies have investigated patterns of activation across the brain in patients with schizophrenia. For example, attenuated prefrontal activation in patients with schizophrenia has been associated with increased activation of the anterior cingulate gyrus (Mellers et al., 1998), the basal ganglia and thalamus (Manoach et al., 2000), or temporal regions (Fletcher et al., 1996; Frith et al., 1995; McGuire & Frith, 1996), or with decreased activation of these regions (Carter, Perlstein et al., 1998; Fletcher et al., 1996). The proposed explanation for these abnormal patterns of activation is a dysfunction of the neural circuitry in patients with schizophrenia (Friston & Frith, 1995; Frith et al., 1995; Manoach et al., 2000). This proposed disconnectivity encompasses a range of circuits including fronto-striatal circuits (Manoach et al., 2000), fronto-temporal circuits (Frith et al., 1995; Friston et al., 1996; McGuire & Frith, 1996; Norman et al., 1997; Peled et al., 2001; Weinberger, Berman, Suddath, & Torrey, 1992), and fronto-thalamic-cerebellar circuits (Andreasen, Paradiso, & O'Leary, 1998). A problem with this line of research is that most studies have not directly tested the interaction between regions. Instead, they rely for support on abnormal patterns of mean activation in specific regions (McGuire & Frith, 1996). Abnormal patterns of mean activation do not necessarily reflect disrupted functional connectivity and a
different approach to functional imaging studies is needed to address this question, ie, methods such as regression analysis or structural equation modelling which allow the hypothesis of disconnectivity to be directly tested (Fletcher, McKenna, Friston, Frith, & Dolan, 1999; Friston, 1994; Friston, 1998; Friston et al., 1997). The few neuroimaging studies that have employed these techniques to explore functional disconnectivity in schizophrenia support a disconnection between frontal, thalamic, and temporal regions (Friston et al., 1996; Mallet, Mazoyer, & Martinot, 1998; Weinberger et al., 1992) with the anterior cingulate as a possible candidate for modulating the interaction between these regions (Fletcher et al., 1999; Spence et al., 2000). To date, no studies have investigated connectivity in patients with discourse coherence disturbance.

The aim of the current study was to explore dorsolateral prefrontal networks and central executive function in patients with discourse coherence disturbance. This aim involved two stages. The first stage was to use an event-related fMRI study to investigate physiological function related to a central executive task in healthy volunteers. The second stage was to use these results to define appropriate regions of interest in dorsolateral prefrontal, temporal, parietal, and cingulate regions to be explored in an event-related fMRI case study of prefrontal network function in patients with and without discourse coherence disturbance. It was expected that the results from these studies would provide information about whether central executive impairments in patients with discourse coherence disturbance are due to impaired function in the dorsolateral prefrontal function, or whether another mechanism, such as impaired connectivity, is necessary to explain the results of Study 1. Specifically, Harrow, Hoffman, and Nestor hypothesise decreased activation of the dorsolateral prefrontal cortex in patients with discourse coherence disturbance. However, if McGrath’s theory holds, there will be no specific dorsolateral prefrontal dysfunction in these patients as
this theory predicts that central executive deficits reflect a disrupted dorsolateral prefrontal network.

4.2 Study 2a: An fMRI study of central executive function in control subjects

4.2.1 Method

4.2.1.1 Participants

Participants were 12 right-handed healthy volunteers, (8 male) with a mean age of 34.25 years (SD = 8.25), recruited by advertisement from the Cambridge, UK area. All participants were screened for psychiatric illness and history of head injury. All participants gave informed consent and were paid £40 to cover any expense or inconvenience resulting from participation in the study. Participants had an average predicted IQ of 104.83 (SD = 8.67) based on scores from the NART (Nelson, 1991).

4.2.1.2 MRI technique

A Bruker Medspec scanner, operating at 3 Tesla, was used to acquire anatomical and gradient-echo echo-planar T2-weighted image volumes with blood oxygenation level dependent (BOLD). 141 images were acquired for each session, four of which were discarded as “dummy scans” to allow for T1 equilibration effects, leaving a total of 137 images per session.\(^6\) Volumes were acquired continuously every 3100 ms. Each volume comprised 21 axial slices (each of 4 mm thickness, interslice gap 1 mm; matrix size 128 x 128). Additional high-resolution anatomical images were acquired for all

\(^6\) For two subjects, technical problems meant that only two sessions could be used. In two other subjects, there were slightly fewer volumes acquired in one of the three session (113 and 123).
subjects using the 3D magnetisation-prepared, rapid acquisition gradient echo (MP-RAGE) sequence.

4.2.1.3 Behavioural Tasks

Pre-scan Test

Prior to scanning, subjects were required to complete a task which was similar to the task they would complete in the scanner. The performance on this task was used to determine the stimuli they would be presented with in the scanner. The task was based on that used by D’Esposito et al. (1999) and was a working memory task in which a set of letters was presented for 2.5 seconds, followed by an instruction cue (FORWARD or ALPHABETISE) for 1.5 seconds. Following this was a 7 second delay during which a fixation cross was presented on the screen, then a probe was displayed for 4 seconds during which the subject was required to respond with a “yes” or a “no” button press (see Figure 4.1). The total stimulus onset asynchrony was 15 seconds. The letters in the initial stimulus were randomly generated consonants, excluding “Y”, and were screened to exclude any common acronyms.

During the pre-scan testing, subjects were required to complete five sessions of this task. Across sessions, the number of letters presented in the initial display varied from two to six. In all sessions, subjects were presented with 20 sets of stimuli, 10 of which involved manipulation of information (manipulation condition), and 10 of which involved maintenance of information (maintenance condition).

In the maintenance condition, the cue was “FORWARD”, which indicated that subjects were required to remember the letters in the order they were presented. The response cue was a letter followed by a number (eg, N-2), and subjects were to give a “yes” response if that letter had been presented in that position in the initial display, and
a "no" response if it had not (eg, a subject would respond "yes" if "N" had been the second letter in the display, and "no" if it had not).

<table>
<thead>
<tr>
<th>Type</th>
<th>Stimulus (2.5 sec)</th>
<th>Instruction (1.5 sec)</th>
<th>Crucial Period (7 sec)</th>
<th>Probe (4 sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low load manipulation</td>
<td>M D B</td>
<td>Alphabetise</td>
<td>+</td>
<td>B-1</td>
</tr>
<tr>
<td>High load manipulation</td>
<td>D F P W R</td>
<td>Alphabetise</td>
<td>+</td>
<td>W-4</td>
</tr>
<tr>
<td>Low load maintenance</td>
<td>B S D</td>
<td>Forward</td>
<td>+</td>
<td>S-3</td>
</tr>
<tr>
<td>High load maintenance</td>
<td>G L H X N</td>
<td>Forward</td>
<td>+</td>
<td>G-1</td>
</tr>
</tbody>
</table>

**EVENT**

Figure 4.1 The experimental design showing the stimuli and time of display for the four conditions.

*Period of event that was modelled. (From start of instruction to half way through crucial period)

In the manipulation condition, the cue was "ALPHABETISE", which indicated that subjects were required to mentally re-arrange the letters into alphabetical order and to remember the letters in the new order. The response cue was the same as for the maintenance condition, ie, a letter followed by a number (eg, N-2), and subjects were to give a "yes" response if that letter had that position alphabetically, and a "no" response if it did not (eg, a subject would respond "yes" if "N" had been the second letter in alphabetical order, and "no" if it had not).
The purpose of the pre-scan testing was to determine the parameters for the high load and low load conditions during scanning. The number of letters to be presented to subjects in the low load condition, was chosen based on the subjects’ ability to perform the manipulation task with an error rate less than 10%, and/or based on self-report indicating that they were able to perform the task comfortably. The number of letters to be presented in the high load condition, was chosen based on the subjects’ ability to perform the manipulation task with an error rate less than 20% where the addition of a further letter increased the error rate to over 30%, and/or based on self-report indicating that the task was “difficult but doable” where the addition of another letter made the task too difficult to be performed properly. In all cases, the load level was determined by performance on the manipulation task, and the number of letters presented was the same for the maintenance and manipulation conditions.

**Scanning Task**

During scanning, subjects performed the same task as they had performed during the pre-scan session. There were four conditions: low load manipulation, high load manipulation, low load maintenance, and high load maintenance. The manipulation and maintenance conditions were the same as those described above, and the load of the conditions was manipulated by varying the number of letters presented in the initial display as described above. Subjects were presented with 80 sets of stimuli, 20 from each condition. The number of letters in this array varied depending on whether the condition was low load or high load. The number of letters presented varied between subjects, based on the results of pre-scan behavioural testing. The testing lasted a total of 20 minutes and was conducted in three sessions, each lasting approximately 7 minutes.

In the response phase where subjects were required to respond with a “yes” or a “no” response based on the position of the cued letter, the hand with which subjects
made the response was counterbalanced between subjects. This meant that half of the subjects responded “yes” with their right hand, and half responded “yes” with their left hand.

### 4.2.1.4 Data Analysis

The data were analysed with statistical parametric mapping (using SPM96 software, Friston et al., 1995) implemented in Matlab (Mathworks Sherborn, MA).

a. **Image pre-processing**

To correct for different acquisition times (relative to the onset of each event), the signal in all slices was shifted relative to the acquisition of the middle slice using a sinc interpolation in time. Each volume was then realigned to the first volume in the session and then realigned across sessions for each subject. Following estimation of movement parameters, this realignment was carried out with resampling of voxels using a sinc interpolation in space. A mean image was then normalised to standard stereotactic space (based on the Montreal Neurological Institute reference brain; Cocosco, Kollokian, Kwan, & Evans, 1997) using a 12 parameter affine transformation and non-linear warping using basis functions (Ashburner & Friston, 1999). The parameters derived from this transformation were used to warp all volumes to the standard brain space. Finally, images were spatially smoothed using a Gaussian kernel (8mm full-width at half-maximum).

b. **Modelling BOLD responses**

The time series in each session was high-pass filtered (average cut-off period = 120 seconds). The event to be modelled was treated as an extended period taken as the time from the presentation of the instruction to halfway through the delay period (that is approximately 3.5 seconds). This was based on the assumption that this was the time...
during which subjects would be continually performing the manipulation task, irrespective of load. It was expected that the high load manipulation task would take the entire delay period, whereas the low load manipulation task would be completed before the end of the delay period after which subjects would simply be required to maintain the reordered stimulus set until the probe cue appeared.

The average haemodynamic responses to each event type were modelled using a canonical, synthetic haemodynamic response function (Friston et al., 1995). This function was used as a covariate in a general linear model in order to generate a parameter estimate for each voxel for each event type. The parameter estimate, derived from the mean least squares fit of the model to the data, reflects the strength of covariance between the collected time series and the canonical response function for a given condition. Responses to different event types were then compared within subjects by setting up pairwise contrasts between the parameter estimates for these events in order to generate a contrast image for each contrast for each subject. These contrast images were taken through to a group analysis in which t values were calculated for each voxel using the average size of effect as the numerator and inter-subject variability as the denominator. Thus, inter-subject variability (represented as a standard error value) was treated as a random effect. The t values were transformed to unit normal Z distribution to create a statistical parametric map for each of the planned contrasts.

For each subject, parameter estimates were obtained for the four conditions and the following comparisons were carried out:

1. Simple main effects of manipulation of information versus maintenance of information (manipulation vs maintenance).

2. Simple main effects of maintenance of information versus manipulation of information (maintenance vs manipulation).
3. Simple main effects of load represented by the number of letters required to be maintained or manipulated by the subject (high load vs low load).

In view of the large numbers of pairwise comparisons that accompany a whole brain functional imaging analysis, and the consequent risk of false positives, I adopted the following policy in setting the statistical threshold: a set of regions was identified on the basis of previous imaging studies and treated as regions of interest in which a threshold of p<0.001 (uncorrected for multiple comparisons) was set. These regions included the dorsolateral and ventrolateral prefrontal cortices, and parietal regions for contrast 1 (manipulation vs maintenance); temporal regions and the anterior cingulate for contrast 2 (maintenance vs manipulation), and dorsolateral prefrontal cortex for contrast 3 (high load vs low load). This approach allowed a specific focus on regions where there were empirical grounds for predicting an effect and reduced the risk of type II error that accompanies the use of a corrected threshold.

4.2.2 Results

4.2.2.1 Behavioural Data

In analysing the behavioural data, the results of one subject were removed because of poor performance. This subject failed to respond on 18 out of 52 trials and had an error rate which varied between 100% and 30% across conditions. Apart from this subject, the greatest variation by a single subject, was error rates of between 35 % and 0%. Removal of the subject with the poorest performance substantially decreased the variance of the group.

The behavioural data showed the predicted pattern of results, with subjects producing more errors and showing a slower reaction time for the manipulation vs the maintenance conditions, and for the high load vs the low load conditions (see Table 4.1).
Table 4.1 Means and standard deviations of the percent of correct responses and reaction times in the easy maintenance, easy manipulation, difficult maintenance, and difficult manipulation conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent Correct</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S. D.)</td>
<td>Mean (ms)</td>
</tr>
<tr>
<td>Low load Maintenance</td>
<td>95.45 (6.50)</td>
<td>1495.3</td>
</tr>
<tr>
<td>High load Maintenance</td>
<td>88.64 (8.09)</td>
<td>1647.47</td>
</tr>
<tr>
<td>Low load Manipulation</td>
<td>93.18 (4.62)</td>
<td>1444.16</td>
</tr>
<tr>
<td>High load Manipulation</td>
<td>84.45 (10.16)</td>
<td>1702.98</td>
</tr>
</tbody>
</table>

A two-way repeated measures ANOVA revealed a significant effect of load on percent correct, $F(1, 10) = 14.18, p < 0.05$. There was no significant effect of task on percent correct, $F(1,10) = 1.92, p > 0.05$. There was no significant interaction between task and load, $F(1,10) = 0.27, p > 0.05$. Post-hoc Bonferroni tests revealed that the effect of load was accounted for by a significantly higher percent of correct responses in the low load ($M = 94.32, SE = 1.31$) than the high load ($M = 86.54, SE = 2.11$) condition. A two-way repeated measures ANOVA revealed a significant effect of load on reaction time, $F(1,10) = 60.76, p < 0.05$. There was no significant effect of task on reaction time, $F(1,10) = 0.01, p > 0.05$. There was no significant interaction between task and load, $F(1,10) = 3.45, p > 0.05$. Post-hoc Bonferroni tests revealed that the effect of load was accounted for by a significantly lower reaction time of correct responses in the low load ($M = 1469.74, SE = 57.10$) than the high load ($M = 1675.23, SE = 68.23$) condition.

4.2.2.2 Imaging Data

The data from two subjects were excluded from image analysis. One of these subjects had poor behavioural data as noted above, the other had poor imaging data which was unable to be corrected with reconstruction.
As discussed in Section 4.2.1.4, all results which are presented and discussed were significant at $p < 0.001$ uncorrected for multiple comparisons. This was justified on the basis of strong a priori hypotheses about predicted regions of activation. Furthermore, results of individual participants are also mentioned to give an indication of the consistency of the effects reported.

![Figure 4.2](image)

**Figure 4.2** Activation produced in the contrast between manipulation and maintenance conditions collapsed across load level for Study 2a.

**Manipulation vs Maintenance**

The contrast between manipulation and maintenance conditions collapsed across load level produced results consistent with previous studies. There was bilateral activation of the dorsolateral prefrontal region near the middle frontal gyrus, and ventrolateral prefrontal regions near the inferior frontal gyrus, with some activation in the left parietal area (see Table 4.2 and Figure 4.2). Analysis of individual subjects revealed bilateral frontal activation in nine of the ten subjects, and left parietal activation in eight subjects.

**Maintenance vs Manipulation**

The contrast between maintenance and manipulation conditions showed bilateral activation of the temporal lobe near the superior temporal gyrus, and activation in the cingulate gyrus (see Table 4.2). Individual analysis showed similar temporal and cingulate activation in eight of the ten subjects.
Figure 4.3 Activation produced in the contrast between high load and low load conditions collapsed across condition level for Study 2a.

**High Load vs Low Load**

The contrast between high and low load was collapsed across task type. The results showed increased activation of the right dorsolateral frontal area near the middle frontal gyrus for the high load condition compared to the low load condition (see Table 4.2 and Figure 4.3). Individual analysis showed right frontal activation in seven subjects.

<table>
<thead>
<tr>
<th>Regions of Interest</th>
<th>X*</th>
<th>Y*</th>
<th>Z*</th>
<th>Volume</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manipulation vs Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Dorsolateral Prefrontal</td>
<td>48</td>
<td>28</td>
<td>32</td>
<td>120</td>
<td>3.86</td>
</tr>
<tr>
<td>Left Dorsolateral Prefrontal</td>
<td>-48</td>
<td>22</td>
<td>32</td>
<td>46</td>
<td>3.49</td>
</tr>
<tr>
<td>Right Ventrolateral Prefrontal</td>
<td>32</td>
<td>28</td>
<td>-4</td>
<td>109</td>
<td>3.89</td>
</tr>
<tr>
<td>Left Ventrolateral Prefrontal</td>
<td>-34</td>
<td>32</td>
<td>-6</td>
<td>62</td>
<td>3.58</td>
</tr>
<tr>
<td>Left Parietal</td>
<td>-38</td>
<td>-44</td>
<td>34</td>
<td>32</td>
<td>3.36</td>
</tr>
<tr>
<td><strong>Maintenance vs Manipulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Temporal</td>
<td>-60</td>
<td>-4</td>
<td>2</td>
<td>355</td>
<td>4.20</td>
</tr>
<tr>
<td>Right Temporal</td>
<td>44</td>
<td>-28</td>
<td>10</td>
<td>19</td>
<td>3.46</td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>-6</td>
<td>-18</td>
<td>40</td>
<td>422</td>
<td>4.24</td>
</tr>
<tr>
<td><strong>High Load vs Low Load</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Dorsolateral Prefrontal</td>
<td>50</td>
<td>30</td>
<td>22</td>
<td>20</td>
<td>3.45</td>
</tr>
<tr>
<td>Left Dorsolateral Prefrontal</td>
<td>50</td>
<td>44</td>
<td>14</td>
<td>44</td>
<td>4.03</td>
</tr>
</tbody>
</table>

*X, Y, and Z are coordinates in a standard stereotactic space in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure.
4.2.3 Discussion

The results of this study are consistent with the results of previous imaging studies investigating working memory. The task involving manipulation of information in working memory was associated with bilateral ventrolateral and dorsolateral prefrontal activation, as well as with left parietal activation. Compared to this condition, simple maintenance of information in working memory was associated with bilateral temporal activation and activation of the cingulate gyrus. Alternatively, this can be viewed as a deactivation of these regions in the manipulation compared with the maintenance condition. These results are consistent with the existing literature (Collette et al., 1999; D'Esposito et al., 1999; Smith et al., 1996).

Increasing the load of the task was associated with activation in the right dorsolateral prefrontal region. This is consistent with Callicott et al.'s (1999) and Manoach et al.'s (1997) findings that the right dorsolateral prefrontal cortex is sensitive to increasing load in working memory tasks so long as working memory capacity is not exceeded. These results also suggest that the pre-scanning testing enabled successful matching of performance, given that seven of the ten subjects showed activation in the dorsolateral prefrontal cortex in this comparison.

The results of this study confirm that this task is suitable for investigating central executive and dorsolateral prefrontal function. Areas of activation and deactivation were similar to those found in previous studies of executive function. Regions in which activation were found in this study, namely, dorsolateral prefrontal regions, ventrolateral prefrontal regions, parietal regions, the temporal lobe, and the cingulate gyrus were used to define regions of interest for Study 2b. In this study, dorsolateral prefrontal and central executive function were investigated in patients with schizophrenia with or without symptoms of discourse coherence disturbance.
4.3 Study 2b: An fMRI study of central executive and dorsolateral prefrontal function in discourse coherence disturbance

4.3.1 Method

4.3.1.1 Participants

Male patients with a diagnosis of schizophrenia (N=5) were selected from outpatients from a metropolitan psychiatric hospital in Perth, Western Australia. A healthy comparison group (N=4) was recruited from the general community, after giving written consent. The healthy comparison and patient groups were similar on age, sex, handedness, and estimated pre-morbid IQ (see Table 4.3). Participants were provided with transport to the hospital or were paid $10 per session to cover travelling costs. Informed written consent was obtained from all participants. All participants had English as their first language and they were screened for the presence and history of thought disorder and other psychotic symptoms.

Table 4.3 Demographic information on the control group (N=4), patients with discourse coherence disturbance (DCD+; N=2), and patients without discourse coherence disturbance (DCD-; N=3) for Study 2b.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>DCD+</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.0 (2.16)</td>
<td>39.5 (14.85)</td>
</tr>
<tr>
<td>NART</td>
<td>108.0 (7.70)</td>
<td>102.5 (12.02)</td>
</tr>
<tr>
<td>Number right-handed</td>
<td>3 out of 4</td>
<td>2 out of 2</td>
</tr>
</tbody>
</table>

4.3.1.2 Diagnostic Assessment

The methods used for clinical assessment were the same as those used in Study 1 (see Section 3.2.1). Briefly, control subjects were interviewed using the Composite International Diagnostic Interview (CIDI), and patients were interviewed with the
Diagnostic Interview for Psychosis (DIP; Jablensky et al., 1999; Jablensky et al., 2000). All patients received an ICD-10 and DSM-III-R diagnosis of schizophrenia. Current symptoms of discourse coherence disturbance were assessed using the ratings for tangentiality, loss of goal, derailment, illogicality, and distractible speech from the Scale for the Assessment of Thought, Language, and Communication (TLC; Andreasen, 1986). In order to assess discourse coherence disturbance, a speech sample of all participants was elicited using items from SCAN which assess negative symptoms of schizophrenia (see Appendix 1). These items elicited speech samples lasting approximately 10 minutes which were then rated by the author and two other clinicians (named in acknowledgements; see Section 3.2.1 for details on interrater reliability).

4.3.1.3 Patient information

Patient 1 Patient 1 in this study, was Patient 2 from Study 1 (see Section 3.3.6.2 for details). He was a 27 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 94. His principal symptom was disinhibition, but auditory hallucinations and formal thought disorder, including discourse coherence symptoms (derailment, loss of goal, and loose associations) were also common. Patient 1 exhibited severe discourse coherence disturbance at the time of testing, including tangentiality, derailment, illogicality, and loss of goal (see Table 4.4) as well as other symptoms of formal thought disorder including disturbances in social convention (circumstantiality), in fluency (incoherence), and in content (perseverations; Berenbaum & Barch, 1995). Apart from symptoms of thought disorder, patient 1 was relatively symptom free at the time of testing. His medication included Olanzapine (25 mg nocte), Sodium Valproate (800 mg bd), Sertraline (50 mg mane), and Clonazepam (1 mg nocte).
Patient 2 Patient 2 in this study, was Patient 3 from Study 1 (see Section 3.3.6.3 for details). Patient 2 was a 49 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 107. His principal symptoms were delusions and some formal thought disorder, consisting of the discourse coherence symptoms tangentiality and loose associations. He exhibited moderate discourse coherence disturbance at the time of testing, namely, tangentiality, and loss of goal (see Table 4.4) with some other formal thought disorder symptoms, namely, disturbance of social convention (poverty of speech). Otherwise he was relatively symptom free. His medication included Zuclopenthixol Decanoate (600 mg fortnightly) and Benztropine (1 mg mane).

Patient 3 Patient 3 in this study, was Patient 6 from Study 1 (see Section 3.3.6.6 for details). Patient 3 was a 32 year old left-handed male outpatient with an estimated premorbid IQ (NART) of 109. His most common symptoms were auditory hallucinations, paranoid and grandiose delusions, and discourse coherence disturbance consisting of tangentiality and derailment. Although Patient 3 had a history of discourse coherence disturbance symptoms, these symptoms were mild to moderate and not as prominent as his other symptoms. Patient 3 was relatively symptom free at the time of testing and did not exhibit any symptoms of discourse coherence disturbance (see Table 4.4). His medication at the time of testing was Clozapine (375 mg nocte) and Lorazepam (1 mg bd).

Patient 4 Patient 4 was a 33 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 86. He had completed 10 years of education. The onset of his schizophrenic symptoms was at 21 years of age, and he has been admitted to psychiatric hospitals on 18 occasions. During admissions, his most common symptoms were auditory hallucinations, paranoid delusions, and delusions of reference. Patient 4 had no history of discourse coherence disturbance symptoms. Patient 4 was
relatively symptom free at the time of testing and did not exhibit any symptoms of discourse coherence disturbance (see Table 4.4). His medication at the time of testing was Flupenthixol (60 mg fortnightly) and Benztropine (2 mg mane).

Patient 5 Patient 5 was a 29 year old right-handed male outpatient with an estimated premorbid IQ (NART) of 105. He had completed 11 years of education. His first admission to a psychiatric hospital was at 25 years of age, and that was his only admission. His most common symptoms were auditory hallucinations, paranoid and grandiose delusions, and delusions of reference. Patient 5 had no history of discourse coherence symptoms. Patient 5 was relatively symptom free at the time of testing and did not exhibit any symptoms of discourse coherence disturbance (see Table 4.4). His medication at the time of testing was Clozapine (300 mg nocte).

| Table 4.4 Ratings of each patient on the TLC items of discourse coherence disturbance (tangentiality, loss of goal, derailment, illogicality, and distractible speech). All items except loss of goal are rated on a 5 item scale with 0 indicating absence of the symptom and 4 indicating extreme manifestation of the symptom. Loss of goal is rated on a 4 item scale with 0 indicating absence of the symptom and 3 indicating severe manifestation of the symptom. |
|---|---|---|---|---|
| Tangentiality | Loss of goal | Derailment | Illogicality | Distractible speech |
| Patient 1 | 1 | 2 | 3 | 0 | 1 |
| Patient 2 | 0 | 2 | 2 | 0 | 0 |
| Patient 3 | 0 | 0 | 0 | 0 | 0 |
| Patient 4 | 0 | 0 | 0 | 0 | 0 |
| Patient 5 | 0 | 0 | 0 | 0 | 0 |

4.3.1.4 MRI technique

A Siemens Vision scanner, operating at 1.5 Tesla, was used to acquire anatomical and gradient-echo echo-planar T2-weighted image volumes with blood oxygenation level dependent (BOLD). 108 images were acquired for each session, four of which were discarded as “dummy scans” to allow for T1 equilibration effects,
leaving a total of 104 images per session. Volumes were acquired continuously every 3100 ms. Each volume comprised 25 axial slices (each of 3 mm thickness, interslice gap 1 mm; matrix size 64 x 64). Additional high-resolution anatomical images were acquired for all subjects using the 3D magnetisation-prepared, rapid acquisition gradient echo (MP-RAGE, 170 contiguous sagittal slices, isovoxel 1 mm) sequence.

4.3.1.5 Behavioural Tasks

Pre-scanning task

The on-screen instructions used in the behavioural task in Study 2a were modified following pilot testing which revealed that patients with schizophrenia found the instructions too complex. During the instruction phase, if subjects were to re-order the letters in alphabetical order, the instruction cue was ALPHABET instead of ALPHABETISE. The response cue was also changed so that response cue was a question (eg, Was “N” 2nd?), instead of a letter followed by a number (eg, N-2). Apart from these instruction changes, the pre-scanning behavioural task was identical to that used in Study 2a. The same criteria were used for determining the load for the task during scanning.

Scanning Task

During scanning, subjects performed the same task as they had performed during the pre-scan session. There were four conditions: low load manipulation, high load manipulation, low load maintenance, and high load maintenance. The manipulation and maintenance conditions were the same as those described in Section 4.2.1.3, and the load of the conditions was manipulated by varying the number of letters presented in the initial display as described earlier, in order to match participants’ performance.
Due to lower signal-to-noise ratio expected with a 1.5 T system compared with 3T, an increased number of stimuli were acquired. In particular, subjects were presented with 120 sets of stimuli, 30 from each condition, and thus more volumes per condition were acquired. The number of letters in this array varied depending on whether the condition was low load or high load. The number of letters presented varied between subjects, based on the results of pre-scan behavioural testing. The testing lasted a total of 35 minutes and was conducted in six sessions, each lasting approximately 6 minutes.

Due to the small number of subjects in each group, the hand with which subjects made the responses for “yes” and “no” was not counterbalanced between subjects: all subjects responded with their right hand for “yes” and their left hand for “no”.

4.3.1.6 Data Analysis

The data were analysed with statistical parametric mapping (using SPM96 software, Friston et al., 1995) implemented in Matlab (Mathworks Sherborn, MA).

a. Image pre-processing

Image pre-processing was conducted in the same way as for Study 2a (see Section 4.2.1.4 for details)

b. Modelling BOLD responses

The analysis of data for the control subjects was analysed in a similar way as for Study 2a (see Section 4.2.1.4 for details). However, the t values were calculated for regions of interest, defined as a sphere with a radius of 15 mm around the regions of interest defined as the areas of activation in the contrasts between manipulation and maintenance, and between maintenance and manipulation in Study 2a (see Table 4.2 for these values). A relatively large region of interest (sphere with radius 15 mm) was
chosen to allow for the comparatively poor signal-to-noise ratio from a system operating at 1.5T. In the case of patients, analysis was similar to the analysis of the control data, except that the contrast images were analysed on an individual basis.

4.3.2 Results

4.3.2.1 Behavioural Data

On the basis of pre-scanning test results, three control participants had three letters in the low load condition and five letters in the high load condition, and one control participant had three letters in the low load condition and four letters in the high load condition. Patient 1, Patient 2, Patient 4, and Patient 5 had two and three letters in the low and high load conditions respectively, and Patient 3 had three letters in the low load and four letters in the high load condition.

The behavioural data showed the predicted pattern of results, with subjects producing more errors and showing a slower reaction time for the manipulation vs the maintenance conditions, and for the high load vs the low load conditions (see Table 4.5). These results are similar to those found in Study 2a (see Table 4.2). Although the number of letters in each condition were chosen to ensure that patients were matched to controls outside the scanner, during the scanning session, patients performed worse than controls, particularly during the manipulation condition. However, their performance was still well above chance (see Table 4.5).
Table 4.5 Means and standard deviations of the percent of correct responses and reaction times in the easy maintenance, easy manipulation, difficult maintenance, and difficult manipulation conditions for patients and the control group.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent Correct</th>
<th>Reaction Time</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S. D.)</td>
<td>Mean (ms)</td>
<td>(S. D.)</td>
<td></td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low load Maintenance</td>
<td>94.17 (4.19)</td>
<td>1723.48</td>
<td>(268.84)</td>
<td></td>
</tr>
<tr>
<td>High load Maintenance</td>
<td>89.17 (5.00)</td>
<td>2061.50</td>
<td>(385.97)</td>
<td></td>
</tr>
<tr>
<td>Low load Manipulation</td>
<td>95.83 (4.19)</td>
<td>1690.21</td>
<td>(222.42)</td>
<td></td>
</tr>
<tr>
<td>High load Manipulation</td>
<td>63.33 (22.27)</td>
<td>2105.73</td>
<td>(531.00)</td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low load Maintenance</td>
<td>93.33</td>
<td>2271.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High load Maintenance</td>
<td>90.00</td>
<td>2209.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low load Manipulation</td>
<td>80.00</td>
<td>1932.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High load Manipulation</td>
<td>80.00</td>
<td>2525.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
<td></td>
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Table 4.6 Control group activation effects in the dorsolateral prefrontal cortex for the contrast between manipulation and maintenance conditions collapsed across load level.

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<tr>
<th>Regions of Interest</th>
<th>X*</th>
<th>Y*</th>
<th>Z*</th>
<th>Volume</th>
<th>Z-score</th>
<th>Corrected p-value</th>
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<td><strong>Manipulation vs Maintenance</strong></td>
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<td>&lt; 0.005</td>
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<td>111</td>
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<td>&lt; 0.005</td>
</tr>
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<td>-8</td>
<td>2</td>
<td>2.53</td>
<td>0.006 **</td>
</tr>
<tr>
<td>Left Ventrolateral Prefrontal</td>
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<td>-10</td>
<td>211</td>
<td>4.39</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Left Parietal</td>
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<td>-36</td>
<td>36</td>
<td>121</td>
<td>3.77</td>
<td>&lt; 0.005</td>
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**Maintenance vs Manipulation**

<table>
<thead>
<tr>
<th>Region</th>
<th>X*</th>
<th>Y*</th>
<th>Z*</th>
<th>Volume</th>
<th>Z-score</th>
<th>Corrected p-value</th>
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</thead>
<tbody>
<tr>
<td>Left Temporal</td>
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<td>-4</td>
<td>-4</td>
<td>135</td>
<td>2.56</td>
<td>0.07 **</td>
</tr>
<tr>
<td>Right Temporal</td>
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<td>-26</td>
<td>8</td>
<td>325</td>
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<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
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<td>-30</td>
<td>46</td>
<td>260</td>
<td>3.75</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

*X, Y, and Z are coordinates in a standard stereotactic space in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure.

** These p values are uncorrected for multiple comparisons.

4.3.2.2 Imaging Data

**Control Group**

Region of interest analyses revealed significant activation at a corrected level of significance (p < 0.01) bilaterally in the dorsolateral prefrontal cortex, the left ventrolateral prefrontal cortex, and in the left parietal cortex, for the contrast between manipulation and maintenance conditions collapsed across load level for the control group. In this contrast, the activation in the right ventrolateral prefrontal cortex failed to reach significance (p = 0.006 uncorrected). Region of interest analyses for the contrast between maintenance and manipulation conditions collapsed across load level revealed significant activation at a corrected level of significance (p < 0.01) in the right temporal lobe and cingulate gyrus. In this contrast, the activation in the left temporal lobe failed to reach significance (p = 0.07 uncorrected) (see Figures 4.4 and 4.5, and Table 4.6).
Patients

All patients showed some activity in the dorsolateral prefrontal cortex for the contrast between manipulation and maintenance conditions (see Figures 4.6-4.10 and Table 4.7). With respect to temporal, parietal, and cingulate regions, only two patients showed activation in parietal regions, and one showed relative deactivation in temporal regions (see Figures 4.11-4.15 and Table 4.7). No patient showed evidence of relative deactivation in cingulate regions.

Patient 1  The region of interest analysis revealed significant activation at a corrected level of significance ($p < 0.01$) in the right and left dorsolateral prefrontal regions for the contrast between manipulation and maintenance conditions collapsed across load level for patient 1. There was no evidence of parietal activation in the contrast between manipulation and maintenance. With respect to relative deactivation in temporal and
cingulate regions, the region of interest analysis for maintenance versus manipulation contrast failed to reveal any significant activation in these regions.

**Patient 2** Patient 2 showed significant activation in the right dorsolateral prefrontal region at a corrected level of significance (p < 0.01). Activation in the left dorsolateral prefrontal region failed to reach significance at a corrected level but was significant at an uncorrected level (p = 0.008). A region of interest analysis focusing on the left parietal region in this contrast, approached significance at a corrected level of significance (p = 0.10). In the reverse contrast, exploring relative deactivation in temporal and cingulate regions, activation in the left temporal region approached significance at a corrected level of significance (p = 0.09). There was no evidence of relative deactivation of right temporal or cingulate regions in the region of interest analysis for this contrast.

**Patient 3** The results of Patient 3 approached significance at a corrected level of significance for the right dorsolateral prefrontal cortex (p = 0.066) and for the left dorsolateral prefrontal cortex (p = 0.073). There was no evidence of significant parietal activation for this contrast. In the reverse contrast, exploring areas of relative deactivation, the activation in the left temporal lobe approached significance at a corrected level of significance (p = 0.014) as did the activation in the right temporal region (p = 0.12).

**Patient 4** The results of Patient 4 approached significance at a corrected level of significance for the right dorsolateral prefrontal cortex (p = 0.16) and for the left dorsolateral prefrontal cortex (p = 0.073). However, there was no evidence of left parietal activation in this contrast and the reverse contrast failed to identify temporal and cingulate regions of activation in Patient 4.

**Patient 5** The region of interest analysis revealed significant activation at a corrected level of significance (p < 0.01) in the right and left dorsolateral prefrontal regions and
the left parietal region for the contrast between manipulation and maintenance conditions collapsed across load level for patient 5. The reverse contrast failed to find any areas of significant activation in temporal or cingulate regions.

Figure 4.6 Contrast between manipulation and maintenance conditions collapsed across load for Patient 1 in Study 2b.

Figure 4.7 Contrast between manipulation and maintenance conditions collapsed across load for Patient 2 in Study 2b.

Figure 4.8 Contrast between manipulation and maintenance conditions collapsed across load for Patient 3 in Study 2b.
Figure 4.9  Contrast between manipulation and maintenance conditions collapsed across load for Patient 4 in Study 2b.

Figure 4.10  Contrast between manipulation and maintenance conditions collapsed across load for Patient 5 in Study 2b.

Figure 4.11  Contrast between maintenance and manipulation conditions collapsed across load for Patient 1 in Study 2b.

Figure 4.12  Contrast between maintenance and manipulation conditions collapsed across load for Patient 2 in Study 2b.
Figure 4.13 Contrast between maintenance and manipulation conditions collapsed across load for Patient 3 in Study 2b.

Figure 4.14 Contrast between maintenance and manipulation conditions collapsed across load for Patient 4 in Study 2b.

Figure 4.15 Contrast between maintenance and manipulation conditions collapsed across load for Patient 5 in Study 2b.
Table 4.7 Activation effects for patients in the dorsolateral prefrontal cortex for the contrast between manipulation and maintenance conditions collapsed across load level.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Manipulation vs Maintenance</th>
<th>Maintenance vs Manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X*</td>
<td>Y*</td>
</tr>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>32</td>
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<td>Right Dorsolateral Prefrontal</td>
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<td>10</td>
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<td>Left Parietal</td>
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<tr>
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<td>Cingulate Gyrus†</td>
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* X, Y, and Z are coordinates in a standard stereotactic space in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure.

** These p values are uncorrected for multiple comparisons.

† No activation was found within a 15mm radius.
4.3.3 Discussion

The results of the control group replicate the results of Study 2a. The control group showed significant activation of the dorsolateral prefrontal cortex, the left ventrolateral prefrontal cortex, and the left parietal cortex on the contrast between manipulation and maintenance. There was some evidence of right ventrolateral activation which failed to reach significance at a corrected level. The control group also showed significant activation of the right temporal lobe and cingulate region on the contrast between maintenance and manipulation. In this contrast, there was also some evidence of left temporal activation, although this failed to reach significance at a corrected level. These results are consistent with previous studies of activation during central executive tasks (Collette et al., 1999; D’Esposito et al., 1999; Smith et al., 1996).

All patients, irrespective of symptoms or working memory capacity showed some activation of the dorsolateral prefrontal cortex bilaterally on the contrast between manipulation and maintenance. This activation failed to reach significance in the left dorsolateral prefrontal cortex for one patient with discourse coherence disturbance (Patient 2) and bilaterally in the dorsolateral prefrontal cortex for two patients without discourse coherence disturbance (Patient 3 and Patient 4). These results do not point to a specific dorsolateral prefrontal impairment in patients with discourse coherence disturbance. However, they do support Manoach et al.’s (2000) findings that where patients with schizophrenia are able to perform the task successfully, dorsolateral prefrontal activation is normal. Although the behavioural performance of patients with schizophrenia was slightly worse than that of controls (particularly in the case of low load manipulation), the behavioural data indicates that the patients were still performing at a relatively high level and reports from patients indicated that they were able to perform the task.
With respect to temporal, parietal, and cingulate regions, the patients with discourse coherence disturbance showed disruptions to these areas. Neither patient with discourse coherence disturbance exhibited significant activation in these regions although activity in the parietal region and deactivation in the left temporal region approached significance for one patient with discourse coherence disturbance (Patient 2). The results for patients without discourse coherence disturbance were similar to those of patients with discourse coherence disturbance. Only one patient without discourse coherence disturbance showed significant activation of parietal regions (Patient 5). None of the patients without discourse coherence disturbance showed significant deactivation of temporal or cingulate regions although left temporal deactivation approached significance for one of these patients (Patient 3). These results may reflect disconnectivity between frontal and temporoparietal regions although this finding is not specific to discourse coherence disturbance.

4.4 General Discussion

The results of these studies confirm previous findings that the dorsolateral prefrontal cortex is implicated in tasks of central executive function (Collette et al., 1999; D'Esposito et al., 1999; Smith et al., 1996). They also support the possibility that previous findings of hypofrontality in patients with schizophrenia are due to overloading working memory capacity in these patients (Manoach et al., 2000). In Study 2b, pre-scan behavioural testing was used to ensure that patients were able to perform the task. The behavioural data indicated that although patients' performance fell below that of controls, they were performing the task at a relatively high level, and the imaging data revealed some activation in the dorsolateral prefrontal cortex in all patients. Previous failures to find prefrontal activation in patients with schizophrenia (Callicott et al., 1998; Carter, Perlstein et al., 1998; Curtis et al., 1998; Menon,
Anagnoson et al., 2001) may have reflected overloading of working memory capacity, rather than impaired prefrontal function, in these patients.

The results failed to support the hypothesis that a specific impairment of dorsolateral prefrontal function underlies central executive impairments in patients with discourse coherence disturbance. These patients did not differ selectively from patients without discourse coherence disturbance. All patients showed activation in the dorsolateral prefrontal cortex on a task requiring central executive processes. Of the three patients failing to activate the dorsolateral prefrontal region to a significant level, one had symptoms of discourse coherence disturbance and the others did not. These three patients showed some activation in this region which was significant at an uncorrected level. This reduced activation needs to be interpreted with caution. The images were acquired on a 1.5T machine which has relatively poor signal-to-noise ratio, and this combined with the heterogeneity in the localisation of brain function may have led to a false negative result. Furthermore, even with modifications to the task and prescanning matching for performance, the patients with schizophrenia showed impaired performance on this task compared to the control group. Also, all except one patient had the lowest possible number of letters in the task. Arguably, this task was too difficult for patients and there may have been a floor effect preventing effective matching of patient and control performance. Future research of this effect in patients with schizophrenia should employ a different task which would enable a greater range of performance in the schizophrenia group. The difficulty seemed to result from the complexity of the response, rather than the difficulty of the task itself. Changes to make the response less complicated may improve the patients’ performance on this task. One possibility would be to present a series of letters in the response phase and ask subjects to indicate whether the letters presented matched those to be remembered.
The failure to find impaired dorsolateral prefrontal function in patients with discourse coherence disturbance suggests that the poor performance of these patients on central executive tasks is not due to a specific impairment in this region. The region of interest analyses investigating temporal, parietal, and cingulate regions addressed the issue of disconnectivity between dorsolateral prefrontal and other regions. All patients showed disruption to dorsolateral prefrontal networks as indicated by failure to activate parietal regions or to deactivate temporal and cingulate regions. With the two patients without discourse coherence disturbance who also failed to activate the dorsolateral prefrontal cortex, these results may suggest that an alternative network was implemented to perform the task. The patients with discourse coherence disturbance, and one patient without discourse coherence disturbance, however, produced relatively normal dorsolateral prefrontal activation so the failure to show activity in other regions may be due to disconnectivity between prefrontal and other regions. While these results are able to give an indication that functional connectivity is impaired in patients with discourse coherence disturbance, they must be interpreted with caution. The putative disconnectivity rests on a negative finding, i.e., failure to show activity in temporal, parietal and cingulate regions. Thus it involves accepting a null hypothesis, a result which must be considered with due caution. Secondly, although patients with discourse coherence disturbance showed functional disconnectivity between dorsolateral prefrontal and other regions, this finding was not specific to these patients. Further research examining effective connectivity of patients with and without discourse coherence disturbance in a larger population would overcome these problems. An effective connectivity analysis would allow the disconnectivity theory to be tested without the need to accept a null hypothesis. Further subjects would increase the power of the study to find any activation in both prefrontal and other regions. Alexander et al. (1989) identified a disorder involving speech disturbance resulting from right
dorsolateral lesions which is similar to the discourse coherence disturbance found in patients with schizophrenia. While the results of the current study do not suggest that right dorsolateral prefrontal impairment is the root of discourse coherence disturbance in these patients, given the similarity of symptoms in these groups, the role of the dorsolateral prefrontal cortex in discourse coherence disturbance requires further investigation. A disconnection between the dorsolateral prefrontal cortex and other regions of the brain may account for the similarity between patients with discourse coherence disturbance and patients with right dorsolateral prefrontal lesions.

Further research aimed at exploring effective connectivity between the dorsolateral prefrontal cortex and other brain regions would address the hypothesis that impairments on central executive tasks in patients with discourse coherence disturbance are due to disruptions to the dorsolateral prefrontal network. Such research should use techniques such as structural equation modelling to explore the interaction between regions, including dorsolateral prefrontal, parietal, temporal, and premotor areas which are posited to be involved in both central executive dysfunction and in discourse coherence disturbance.

4.4.1 Summary

The results of this study are not consistent with Harrow’s, Hoffman’s, or Nestor’s theories of discourse coherence disturbance. No specific prefrontal deficit was apparent in patients exhibiting discourse coherence disturbance symptoms. However, the results of Study 1 indicate that there is a central executive function impairment in these patients. Although there was no specific prefrontal deficit in these patients, the patients with discourse coherence disturbance did show reduced activity in temporal, parietal and cingulate areas which is indicative of function disconnectivity. However, this finding was common to patients with and without discourse coherence disturbance.
so the results are not conclusive. In spite of the lack of specificity, the failure to find a specific prefrontal deficit to explain the central executive dysfunction, McGrath's predicted disruption to the prefrontal circuit provides the best explanation of the central executive impairments. Study 3 was designed to further explore the role of prefrontal connections in discourse coherence disturbance, as a preliminary investigation as to whether central executive impairments in these patients reflect an underlying disconnectivity between frontal and temporoparietal regions.
CHAPTER 5

STUDY 3

5.1 Introduction

The results of Study 1 suggest that patients with discourse coherence disturbance have impaired ability to detect and/or correct errors. This is consistent with McGrath’s theory that these patients are unable to monitor and edit their speech effectively due to a disconnection between thought and action. However, behavioural studies have limited ability to separate detection processes from correction processes. McGrath’s theory predicts a specific inability to correct errors but an intact ability to detect errors. Study 1 revealed a general error-monitoring deficit in these patients, but a different approach is required to explore whether the locus of the deficit in patients with discourse coherence disturbance is at the error-detection or error-correction phase. A study investigating error-negativity (ERN), an ERP component associated with error detection, in a group of patients with discourse coherence disturbance was designed to enable these processes to be distinguished. Although, the anti-saccade task showed that patients with discourse coherence disturbance are less likely to correct their errors, the ERN provides a mechanism by which it is possible to ascertain whether these patients are aware of their errors or not, i.e., whether they have a problem with detecting their errors or correcting them. Further to this, the current study enabled the confirmation of an error-monitoring deficit in patients with discourse coherence disturbance. As discussed in Chapter 3, self-correction on an anti-saccade task may not be the most appropriate means of assessing error-monitoring. The assessment of error-monitoring on a different behavioural task will address the issue of the generalisability of the results from Study 1.
The second aim of this study was to explore the role of dorsolateral prefrontal connections in patients with discourse coherence disturbance. The results of Study 1 and McGrath's theory suggest that patients with discourse coherence disturbance have abnormal brain functioning in networks involving dorsolateral prefrontal and temporoparietal regions. Patients with lesions to the right dorsolateral prefrontal cortex display similar speech disturbance to patients with discourse coherence disturbance: they are unable to maintain a coherent discourse and show errors of reasoning (see Section 2.3.1). However, the results of Study 2 failed to support a simple dorsolateral prefrontal deficit since patients with symptoms of discourse coherence disturbance produced normal dorsolateral prefrontal activation on a working memory task. As argued in Section 4.4, this discrepancy between behavioural and physiological results may be explained by impaired connection between the dorsolateral prefrontal cortex and other regions of the brain. The ability of the present study to address this hypothesis will be discussed later.

The current study explored ERN in patients with schizophrenia exhibiting symptoms of discourse coherence disturbance. ERN is a negative component peaking 80-100 ms following an error. It is derived by subtracting the ERP associated with correct trials from that associated with incorrect trials. The resultant subtraction waveform consists of an overall negative peak associated with incorrect responses. ERN is followed by a positive component (Pe) peaking 200-500 ms after the error (see Figure 5.1). ERN is largest at frontal and central sites, while the Pe is focused at central and parietal sites (Falkenstein et al., 2000; Gehring et al., 1993; Leuthold & Sommer, 1999; Scheffers et al., 1996). The results of most studies indicate that ERN is associated with error detection and correction, but more specifically with error detection. Subjects exhibit ERN whenever they make errors, even when these errors are errors of action which cannot be corrected (Scheffers et al., 1996). ERN is largest when
accuracy is emphasised, and decreases when time pressure is increased (Falkenstein et al., 2000; Gehring et al., 1993), suggesting that it is related to conscious error recognition. Furthermore, larger ERN is related to weaker force to execute the incorrect response, it predicts greater probability of immediate correction, and larger ERN precedes slower reaction times on subsequent trials, all of which are behavioural indices of error detection (Scheffers et al., 1996).

Figure 5.1 Comparison of response-locked ERP activity, recorded at the Cz electrode, for correct and incorrect trials on a flanker task (taken from Gehring et al., 1993).

There has been some debate about the cognitive processes related to ERN. A number of researchers argue that ERN does not reflect error detection, but that it is associated with either the detection of response conflict prior to error detection (Carter, Braver et al., 1998; Carter et al., 1999; Carter, 2000), or with an emotional response to error recognition (Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). The argument that ERN reflects processes other than error detection is based on the presence of a small ERN for some correct responses. If ERN reflects error detection processes, it should only be present on incorrect trials, as these are the only trials on which detection of an error is possible. However, there are other explanations for ERN following correct responses. For example, Falkenstein et al. (2000) argue that ERN on correct trials could result from an erroneous belief that the correct response is wrong.
Carter et al.’s view that ERN reflects conflict, such as response competition, rather than error detection per se, argues that ERN tends to occur where there is a conflict between the correct response and the incorrect response, ie, it reflects a comparison process whereby the actual incorrect response is compared to the correct response. This effect is larger on incorrect trials because the difference between correct and incorrect responses is more salient. However, an ERN will sometimes occur on correct trials where the participant is unsure how to respond, although finally selecting the correct response. Bernstein, Scheffers, and Coles' (1995) examined the relationship between ERN and the comparison between the representation of the executed response and the correct response. The magnitude of ERN was measured in relation to the similarity of the correct and actual response by varying the similarity of these responses, ie, where the correct and actual response were similar, the possible responses were made with different fingers of the same hand, while the less similar condition required one of two responses by fingers on different hands. They hypothesised that if ERN involves a comparator process, the magnitude should be greater for incorrect responses within the different (less similar) condition than for incorrect responses within the similar condition. Their results failed to show this effect although when they took into account the strategy used by subjects, there was an effect of similarity. These results seem to provide some support for the theory that ERN reflects a comparison process, rather than error detection. However, the association between ERN and comparison processes may not necessarily be inconsistent with its role in detecting errors. On incorrect trials, ERN will be evoked where there is a conflict between the correct and incorrect responses, ie, where a mismatch between the correct and actual response (ie, an error) is detected. Most importantly, given the primary aim of this study, such a role for ERN would imply that it primarily reflects error detection, not error correction.
Although ERP data are principally useful for temporal, rather than spatial information, techniques such as combining PET or fMRI data with ERP data, or using ERP source localisation techniques such as BESA (Scherg & Berg, 1995) enable researchers to gain spatial information about the generators of ERP components. Such research suggests that ERN generators are largely localised in the anterior cingulate (Carter et al., 1999; Dehaene et al., 1994; Posner & DiGirolamo, 1998), and neuroimaging evidence suggests that error-detection involves an interaction between anterior cingulate and lateral prefrontal cortex activity (Carter, Braver et al., 1998; Kiehl et al., 2000; Menon, Adleman et al., 2001). Using an fMRI study of errors on a CPT-AX task, Carter, Braver et al. (1998) found that error commission was associated with bilateral activation of the dorsolateral prefrontal cortex, anterior cingulate activity, and activation in the left premotor cortex. Anterior cingulate activation was also present on correct trials under conditions eliciting greater response conflict. These results suggest that error-detection may involve interaction between the anterior cingulate and other regions such as the dorsolateral prefrontal cortex, such that the anterior cingulate is involved in detecting response competition, while other regions are involved in other aspects of error-monitoring. Similarly, the results of an fMRI study conducted by Kiehl et al. (2000) showed activation in the anterior cingulate and dorsolateral prefrontal cortex associated with errors on a go/no-go task. Further to these regions of activation, Kiehl et al. found activation in the left medial frontal gyrus associated with error-detection. Menon, Adleman et al. (2001) found a broader range of activation associated with error-processing using an fMRI study of error performance on a go/no-go task. Errors on this task were associated with activation in the anterior cingulate, the medial prefrontal cortex, the inferior frontal cortex, as well as the medial parietal cortex. These regions resemble the network incorporating anterior and posterior areas associated with central executive function (Collette et al., 1999; D'Esposito et al., 1999; Garavan et al., 2000):
error-detection probably requires the involvement of mechanisms able to detect response conflict (anterior cingulate) and working memory processes which maintain information about the correct response (maintenance processes) and compare this information to actual responses (central executive processes).

An ERN study conducted by Gehring and Knight (2000), supports the theory that ERN results from an interaction between the anterior cingulate and prefrontal regions. They found reduced ERN in patients with lesions to the prefrontal cortex, due to a negative peak associated with correct responses in this group, i.e., these patients produced normal negativity on incorrect trials, but on correct trials, they also showed increased negativity. This group was also less likely to correct their responses than the control group. The negativity associated with correct responses did not seem to be due to patients rating their correct responses as errors as these responses were not “corrected” whereas true errors usually were. Gehring and Knight’s (2000) findings are not consistent with any model of error detection which localises the detection in either the prefrontal cortex or the anterior cingulate. Rather, they suggest that error detection relies on an interaction between these areas. Similarly, these data do not support a simple model in which either the prefrontal cortex or the anterior cingulate detects errors and then passes this information on to the other area for correction. Gehring and Knight suggest that a model of error detection consistent with the data is one in which the prefrontal cortex maintains representations of the correct response and then compares this with information from the anterior cingulate about the actual response.

According to Carter and others, the anterior cingulate monitors the response for conflict with the correct response, and is activated when it detects such a conflict (Carter et al., 1998; Carter et al., 1999; Cohen, Botvinick, & Carter, 2000; MacDonald, Cohen, Stenger, & Carter, 2000). According to this theory, ERN is produced on correct trials by patients with prefrontal lesions because, as a result of the lesion, there is no correct
representation with which to compare the actual response. This creates greater
response conflict on correct trials, and consequently, the anterior cingulate is detecting
conflict on correct, as well as incorrect trials. Error correction is impaired in these
patients as a result of poor error detection: patients do not have an accurate
representation of the correct response and so are less likely to recognise their mistakes.

One difficulty with this model of prefrontal-anterior cingulate interaction, is that
although patients with prefrontal lesions showed a greater number of errors and reduced
ERN, they still corrected the majority of their errors and did not attempt to "correct"
correct responses. In Gehring and Knight's (2000) study, the prefrontal lesion group
made the same number of errors as the control group, but corrected approximately 10%
of their errors compared with the control group who corrected approximately 30% of
their errors. This suggests that although the prefrontal regions are important for error
detection, error detection can proceed without these regions, albeit less efficiently.

An alternative model of the interaction between anterior cingulate and prefrontal
processes in error-detection includes other regions such as medial frontal regions and
parietal regions which are activated during error-detection. There is fairly consistent
evidence suggesting that the anterior cingulate is heavily involved in tasks where there
is response conflict (Barch et al., 2001; Carter et al., 1999; Carter, Braver et al., 1998;
MacDonald et al., 2000; Peterson et al., 1999; Taylor et al., 1994), and there is evidence
of a specific role for the dorsolateral prefrontal cortex in central executive processes
(see Section 4.1; Collette et al., 1999; D'Esposito et al., 1999; Garavan et al., 2000).
The other areas which have been associated with error-detection processes, namely,
inferior and medial prefrontal regions, and parietal regions, are implicated in working
memory processes, particularly tasks requiring maintenance of information (Cohen et
al., 1997; Collette et al., 1999; D'Esposito et al., 1995; de Zubizaray, 1998; Mellers et
al., 1995; Salmon et al., 1996; Van der Linden et al., 1999).
The physiological findings associated with error-monitoring could be explained by a model incorporating these different regions and processes. The network of anterior and posterior regions including medial prefrontal regions and parietal regions could be involved in storing the representation of the correct response. Throughout performance on a task, the dorsolateral prefrontal cortex monitors behaviour by comparing the actual response with the correct response which is held in the working memory network. When a conflict between the correct and actual response is detected, anterior cingulate processes are activated to resolve this conflict. In the case of impaired dorsolateral prefrontal function, online monitoring of performance can no longer occur. In such instances, the anterior cingulate may take on the role of monitoring performance. Thus, the anterior cingulate would have two roles: directly compare actual responses with correct responses and detect conflicting information. As a result, anterior cingulate activity would occur after every response, consistent with increased ERN in patients with lesions to the dorsolateral prefrontal cortex.

Furthermore, without the efficiency of the central executive dorsolateral prefrontal processes, fewer errors are detected.

The results of a study conducted by MacDonald et al. (2000) support Gehring and Knight’s (2000) hypothesised model of anterior cingulate and dorsolateral prefrontal cortex interaction in error detection. Using a modified Stroop task, they found that activity within the dorsolateral prefrontal cortex was associated with maintaining an instruction and controlling behaviour, whereas the anterior cingulate was selectively active for incongruent as opposed to congruent colour-naming trials. Applied to error detection, this finding supports an interaction whereby the anterior cingulate detects response conflict and this conflict is resolved according to task instructions by the dorsolateral prefrontal cortex. MacDonald et al. focused only on dorsolateral prefrontal and anterior cingulate function in this study. Consequently, it is
unable to address the role of other regions, such as inferior prefrontal and parietal regions, in error-detection.

McGrath’s model predicts that patients with discourse coherence disturbance are aware that they are making errors, but are unable to utilise this information to enable them to correct their errors. This impairment results from a disconnection between the prefrontal cortex and other brain regions. A number of studies of functional connectivity in schizophrenia posit the anterior cingulate as a possible modulator of this disconnection (Fletcher et al., 1999; Spence et al., 2000). Similarly, there is evidence of abnormal anterior cingulate activation in patients with schizophrenic thought disorder (Liddle et al., 1992; McGuire et al., 1998). The impaired ability to correct errors in patients with discourse coherence disturbance, may result from a disruption to the prefrontal network which is modulated by an abnormal interaction between the anterior cingulate and dorsolateral prefrontal cortex. Such a disconnection would explain the results found in Study 1, i.e., impaired error-monitoring in patients with discourse coherence disturbance. This disconnection would also explain the similarity in symptoms of patients with dorsolateral prefrontal lesions and patients with discourse coherence disturbance. Finally, disruption to the dorsolateral prefrontal network would explain the impaired central executive function found in patients with discourse coherence disturbance.

Based on the model of error-monitoring suggested above, disrupted communication between the prefrontal cortex and the anterior cingulate in discourse coherence disturbance should produce similar results to those found by Gehring and Knight (2000) in patients with lateral prefrontal lesions. In order to effectively monitor performance, the dorsolateral prefrontal cortex must communicate with regions involved in maintaining a representation of the correct response, and with the anterior cingulate. Disconnection between the dorsolateral prefrontal cortex and other brain
regions would prevent the dorsolateral prefrontal cortex from being involved in error-monitoring. Consequently, monitoring would have to proceed via the anterior cingulate and the network encompassing inferior prefrontal regions and parietal regions, i.e., disconnection between dorsolateral prefrontal cortex and other regions will produce the same result, in terms of error-monitoring, as a specific lesion to this region. If McGrath’s theory is correct, therefore, patients with discourse coherence disturbance should resemble patients with lesions to the dorsolateral prefrontal cortex with respect to error-monitoring performance. Patients with discourse coherence disturbance should still generate a negative component on incorrect trials, but due to the role of the anterior cingulate in monitoring performance, a negative component will also be generated on correct trials. Thus, ERN should be reduced in patients with discourse coherence disturbance due to increased negativity on correct trials.

There has been no research to date investigating ERN in schizophrenic patients with discourse coherence disturbance. However, there is evidence of impaired error-monitoring in patients with schizophrenia. Malenka et al. (1982) found that on a behavioural task revealing internal error-monitoring and correction in normal controls subjects, patients with schizophrenia were less likely to correct their errors than controls subjects, and were more likely to incorrectly adjust correct responses. A replication of this study confirmed these results and also showed that patients with schizophrenia are impaired on error-monitoring relative to patients with depression (Malenka et al., 1986). The results of Study 1 indicate that patients with discourse coherence disturbance are less likely to correct errors than normal control subjects or schizophrenic patients without discourse coherence disturbance.

Kopp and Rist (1999) conducted an ERN study with patients with schizophrenia and found a reduced ERN component associated with incorrect trials for patients with paranoid schizophrenia compared to patients with other types of schizophrenia and a
normal control group. However, there was no indication as to whether the diminution of the ERN effect was due to reduced negativity on incorrect trials or increased negativity on correct trials. Ford (1999) describes an unpublished study in which ERN was investigated in patients with schizophrenia. The results showed a similar effect to that described above in patients with prefrontal lesions, i.e., there was a diminished ERN in the schizophrenic group as a result of negativity on correct trials. To date, no studies have investigated ERN in association with different schizophrenic symptoms.

The purpose of the present study was twofold. First, it aimed to use the ERN component to determine whether patients exhibiting discourse coherence disturbance are aware of their errors. Based on the support for McGrath’s theory from Studies 1 and 2, it is hypothesised that patients with discourse coherence disturbance will produce an ERN when they make errors, even if they fail to correct these errors. Such a pattern of results would reflect an impairment in correction processes, but not in detection processes.

The second aim was to investigate the role of the dorsolateral prefrontal cortex in discourse coherence disturbance. Any impairments in this region, including a disconnection between this region and other areas of the brain, especially the anterior cingulate, should lead to an abnormal ERN similar to that found in patients with lesions in the dorsolateral prefrontal cortex. On this basis, it is hypothesised that patients with discourse coherence disturbance will show reduced ERN resulting from negativity associated with correct trials, i.e., these patients will show a normal pattern of negativity on incorrect trials but the negativity produced on correct trials will lead to a reduction in overall ERN when correct trials are subtracted from incorrect trials.
5.2 **Method**

5.2.1 **Participants**

Male patients with a diagnosis of schizophrenia (N=15) were selected from inpatients and outpatients from a metropolitan psychiatric hospital in Perth, Western Australia. Six patients exhibited symptoms of discourse coherence disturbance at the time of testing, and nine patients were free of discourse coherence disturbance symptoms (see Table 5.1). All patients were prescribed antipsychotic medication. Seven of the patients without discourse coherence disturbance were prescribed atypical antipsychotics and two typical antipsychotics. Five of the patients with discourse coherence disturbance were prescribed atypical antipsychotics and one typical antipsychotics.

**Table 5.1** Demographic information and discourse coherence disturbance ratings on the control group (N=15), patients with discourse coherence disturbance (DCD+; N=6), and patients without discourse coherence disturbance (DCD-; N=9) for Study 3.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Controls</th>
<th>DCD+</th>
<th>DCD-</th>
<th>Controls</th>
<th>DCD+</th>
<th>DCD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.0 (11.86)</td>
<td>41.8 (9.47)</td>
<td>35.9 (8.33)</td>
<td>20-54</td>
<td>28-54</td>
<td>24-50</td>
</tr>
<tr>
<td>NART</td>
<td>103.7 (11.31)</td>
<td>97.8 (11.20)</td>
<td>100.0 (12.24)</td>
<td>75-116</td>
<td>84-111</td>
<td>85-118</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>-</td>
<td>24.5 (7.58)</td>
<td>22.4 (6.81)</td>
<td>-</td>
<td>17-37</td>
<td>14-33</td>
</tr>
<tr>
<td>Duration of Illness (years)</td>
<td>-</td>
<td>17.3 (7.12)</td>
<td>13.22 (6.22)</td>
<td>-</td>
<td>9-28</td>
<td>4-24</td>
</tr>
<tr>
<td>Medication (Cpz equiv.)</td>
<td>-</td>
<td>991.7 (359.75)</td>
<td>783.3 (342.78)</td>
<td>-</td>
<td>650-1600</td>
<td>450-1600</td>
</tr>
<tr>
<td>TLC Ratings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tangentiality</td>
<td>0</td>
<td>1.17 (0.98)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loss of Goal</td>
<td>0</td>
<td>2.17 (0.75)</td>
<td>0</td>
<td>0</td>
<td>1-3</td>
<td>0</td>
</tr>
<tr>
<td>Derailment</td>
<td>0</td>
<td>2.50 (0.55)</td>
<td>0</td>
<td>0</td>
<td>2-3</td>
<td>0</td>
</tr>
<tr>
<td>Illogicality</td>
<td>0</td>
<td>0.50 (0.55)</td>
<td>0</td>
<td>0</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>Distractibility</td>
<td>0</td>
<td>0.17 (0.41)</td>
<td>0</td>
<td>0</td>
<td>0-1</td>
<td>0</td>
</tr>
</tbody>
</table>
A healthy comparison group (N=15) was recruited from the general community, after giving written consent. The healthy comparison and patient groups did not differ significantly on age, sex, and estimated pre-morbid IQ (see Table 5.1), and the patient groups did not differ significantly on duration of illness. Outpatients and control participants were provided with transport to the hospital or were paid $10 per session to cover travelling costs. Informed written consent was obtained from all participants. All participants had English as their first language and they were screened for the presence and history of thought disorder and other psychotic symptoms.

5.2.2 Diagnostic Assessment

The methods used for clinical assessment were the same as those used in Study 1 and Study 2b (see Section 3.2.1). Briefly, control subjects were interviewed using the Composite International Diagnostic Interview (CIDI), and patients were interviewed with the Diagnostic Interview for Psychosis (DIP; Jablensky et al., 1999; Jablensky et al., 2000). All patients received an ICD-10 and DSM-III-R diagnosis of schizophrenia. Current symptoms of discourse coherence disturbance were assessed using the ratings for tangentiality, loss of goal, derailment, illogicality, and distractible speech from the Scale for the Assessment of Thought, Language, and Communication (TLC; Andreasen, 1986). In order to assess discourse coherence disturbance, a speech sample of all participants was elicited using items from SCAN which assess negative symptoms of schizophrenia (see Appendix 1). These items elicited speech samples lasting approximately 10 minutes which were then rated by the author and two other clinicians (named in acknowledgements; see Section 3.2.1 for details on interrater reliability).
5.2.3 Behavioural measure

Participants performed the Eriksen flanker task (Eriksen & Eriksen, 1974). This task has been used extensively in studies of ERN. This task elicits an error-rate of approximately 10% in control populations, and errors on this task reliably produce ERN in control populations (Gehring et al., 1993; Kopp & Rist, 1999). Participants were given the following instructions: “Respond to the letters as soon as you can. Don’t worry too much if you don’t get it right, everyone makes a few mistakes. Just make sure you respond as quickly as possible”. Stimuli were presented on a monitor, 50 cm from participants’ eyes. Each stimulus consisted of a linear array of five white letters on a black background. Letters were 10 mm high and a 2 mm high cross was presented below the central letter. During the task, subjects were presented with 672 letter arrays, in 14 blocks of 48 arrays. Each block lasted for approximately 2.5 minutes, and there was a short break between each block. The 48 letter arrays consisted of four arrays (two compatible and two incompatible) with a probability of 0.25 for each array. The order of presentation was randomised. The four arrays were: HHHHH (compatible), SSHSS (incompatible), SSSSS (compatible), and HHSHH (incompatible). Each stimulus array was presented for 100ms and the stimulus onset asynchrony (SOA) was randomly varied between 2000ms and 3000ms. Subjects were instructed to respond with their right hand if H was the central letter and with their left hand if S was the central letter. Responses involved squeezing one of two dynamometers. The force applied to the dynamometer was transformed into a voltage by a transducer which was sampled at 500 Hz.

5.2.4 Physiological recording

The continuous electroencephalogram (EEG) was recorded from 5 tin electrodes located at Fz, Cz, and Pz (according to the 10/20 international system), and C3’ and C4’
(placed 4cm to the left and right of Cz respectively). All electrodes were referenced to linked mastoids, and the subject ground was located at the midline between Fz and Cz. A vertical electro-oculogram (VEOG) was monitored by a bipolar set above and below the eye. The EEG was digitised at 500Hz with a bandpass of 0.15 to 30 Hz using a 32-channel Synamps and Scan 4.0 software (NeuroScan Labs). Impedance for all EEG electrodes was below 10 kOhm. Artifact rejection included: manual removal of blocks of data in the continuous recording contaminated by gross artifact; automatic rejection of epochs contaminated by other artifacts (± 100 µV); and eyeblink artifact correction procedures based on methods outlined by Semlitsch et al. (1986).

Right and left forearm flexor electromyogram (EMG) activity was recorded using tin electrodes at the standard locations, ie, one electrode placed one-third of the distance from the medial humeral epicondyle to the styloid process of the radius, and the other placed two inches from this electrode towards the styloid process of the radius (Lippold, 1967). The EMG signals (electrode impedance < 20 kOhm) were digitised at 500Hz with a bandpass of 10 to 100 Hz.

5.2.5 Procedure

All participants completed the ERP task which lasted approximately one to one and a half hours. This was followed by the diagnostic interview lasting approximately one hour. All participants completed all aspects of the study on the same day.

5.2.6 EMG Analysis

Participants' overt responses were evaluated using the integrated EMG activity for the left and right forearms. A computer algorithm determined the onset latency of the EMG associated with responses of both the left and right hand. First, both EMG channels were scanned and the maximum absolute value of EMG signal within 500 ms of a response was found in each channel. The threshold value of the EMG signal was
calculated as 25% of the average of all the values within 500 ms of a response that exceeded 75% of the maximum EMG signal. Next, periods of EMG activity were located. EMG activity began when the EMG signal was equal to or greater than the threshold level and ended when its value dropped below the threshold level for a period of 75 ms or longer. The local maximum absolute value of EMG signal was found for each EMG activity period. This involved identifying the first peak or trough in each burst and finding the local maxima within this peak. The onset of EMG signal was defined as the point where the EMG signal was for the first time equal to or greater than 25% of the maximum value of the peak. Any EMG activity that followed the stimulus code within 200 ms or less, was ignored.

5.2.7 Data Analysis

EEG epochs were averaged beginning 200 ms before the response on each trial and extending until 500 ms after the response. EEG epochs for each subject were averaged to obtain event-related potential waveforms that were time-locked to the EMG response on each trial. This was done separately for correct trials and error trials, and for compatible and incompatible trials (incompatible-correct, incompatible-error, compatible-correct, and compatible-error). To reduce residual noise, the averaged ERPs were filtered with a digital low-pass filter (40 Hz; 12 dB/octave). The negative peak was measured by taking the average value between 75 and 125 ms following EMG response, relative to a baseline of the preceding positive peak which was measured as a mean amplitude over 0 to 50 ms. The negative peak was estimated using this procedure in ERPs to compatible and incompatible stimuli resulting in correct responses and errors. The ERN was then measured by subtracting the estimate of the negative peak associated with correct responses from the negative peak associated with errors, for both compatible and incompatible trials.
5.3 Results

5.3.1 Behavioural Task

The results of two patients without discourse coherence disturbance and one control were excluded because of the level of noise in the EMG and EEG channels for these subjects made the data uninterpretable. The means and standard deviations for total number of errors, number of uncorrected errors, and percentage of total errors uncorrected for each group on the Eriksen flanker task are presented in Table 5.2. The percentage of errors produced by the control group was 9.97%, similar to that found in other studies (Gehring et al., 1993; Kopp & Rist, 1999). A one-way ANOVA failed to find a significant difference between groups for total number of errors, $F(2, 24) = 1.91$, $p > 0.05$, or for total number of uncorrected errors, $F(2, 24) = 1.45$, $p > 0.05$. However, a one-way ANOVA revealed a significant difference between groups for percentage of total errors which were uncorrected, $F(2,24) = 7.39$, $p < 0.05$. Post-hoc Scheffe tests revealed that this effect was accounted for by a greater percentage of uncorrected errors in the patients with discourse coherence disturbance ($M = 42.75$, $SD = 28.04$) than in the control group ($M = 9.78$, $SD = 9.04$). The difference between the patients with discourse coherence disturbance ($M = 42.75$, $SD = 28.04$) and between patients without discourse coherence disturbance ($M = 19.29$, $SD = 20.08$) approached significance ($p = 0.08$). The difference between controls and patients without discourse coherence disturbance was not significant.
Table 5.2 Means and standard deviations of total number of errors, number of uncorrected errors, and percentage of total errors uncorrected for controls, patients with discourse coherence disturbance (DCD+), and patients without discourse coherence disturbance (DCD-).

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Mean (SD) DCD+</th>
<th>DCD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total errors (Percentage errors)</td>
<td>67.00 (48.81)</td>
<td>38.17 (26.40)</td>
<td>44.29 (21.88)</td>
</tr>
<tr>
<td></td>
<td>(9.97)</td>
<td>(5.68)</td>
<td>(6.59)</td>
</tr>
<tr>
<td>Number of uncorrected errors</td>
<td>5.29 (4.34)</td>
<td>16.33 (22.67)</td>
<td>7.57 (8.66)</td>
</tr>
<tr>
<td>% of total errors uncorrected</td>
<td>9.78 (9.04)</td>
<td>42.75 (28.04)</td>
<td>19.29 (20.09)</td>
</tr>
</tbody>
</table>

5.3.2 Error-related Negativity

Response-locked ERPs for correct and error trials for the compatible and incompatible conditions for the three groups are presented in Figures 5.2 and 5.3 at Cz. The mean amplitude over 0 – 50 ms has been used as a baseline for overlaying the ERP plots. Error negativity is evident around 100 ms, particularly in the incompatible condition. Consistent with previous literature, this effect is not as evident in the compatible condition. The average peak amplitude for the difference between the negative peak (average value over 75 and 125 ms) and the positive baseline (average value over 0 and 50 ms) for the compatible and incompatible conditions can be found in Table 5.3.
Controls

DCD+

DCD-

Figure 5.2 Response-locked ERPs for correct responses and errors in the compatible condition for the control group, patients with discourse coherence disturbance (DCD+), and patients without discourse coherence disturbance (DCD-). Note: negativity is up.
Figure 5.3 Response-locked ERPs for correct responses and errors in the incompatible condition for the control group, patients with discourse coherence disturbance (DCD+), and patients without discourse coherence disturbance (DCD-). Note: negativity is up.
Table 5.3 Average mean amplitudes over 75 – 125 ms (relative to mean amplitude over 0 – 50 ms in ERPs associated with correct (cor) and incorrect (err) responses in the compatible (comp) and incompatible (incomp) conditions for patients with discourse coherence disturbance (DCD+), patients without discourse coherence disturbance (DCD-), and the control group.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Comp Cor</th>
<th>Comp Err</th>
<th>Incomp Cor</th>
<th>Incomp Err</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Peak</td>
<td>Peak</td>
<td>Peak</td>
<td>Peak</td>
</tr>
<tr>
<td>Fz</td>
<td>-2.49 (2.34)</td>
<td>-2.35 (4.07)</td>
<td>-2.28 (2.31)</td>
<td>-2.06 (3.59)</td>
<td></td>
</tr>
<tr>
<td>Cz</td>
<td>-1.58 (2.61)</td>
<td>-1.82 (4.37)</td>
<td>-1.68 (2.13)</td>
<td>-2.71 (4.26)</td>
<td></td>
</tr>
<tr>
<td>Pz</td>
<td>-0.82 (3.06)</td>
<td>-0.38 (3.98)</td>
<td>-0.99 (2.45)</td>
<td>-1.18 (3.50)</td>
<td></td>
</tr>
<tr>
<td>C3'</td>
<td>-1.48 (2.35)</td>
<td>-1.38 (4.74)</td>
<td>-1.52 (1.88)</td>
<td>-2.28 (3.66)</td>
<td></td>
</tr>
<tr>
<td>C4'</td>
<td>-1.32 (2.64)</td>
<td>-1.38 (4.47)</td>
<td>-1.31 (2.10)</td>
<td>-2.00 (3.97)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DCD+</th>
<th>Peak</th>
<th>Peak</th>
<th>Peak</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fz</td>
<td>-2.42 (1.49)</td>
<td>-1.62 (3.62)</td>
<td>-2.76 (1.41)</td>
<td>-3.67 (3.42)</td>
<td></td>
</tr>
<tr>
<td>Cz</td>
<td>-3.10 (1.67)</td>
<td>-0.79 (2.99)</td>
<td>-2.93 (1.35)</td>
<td>-3.87 (3.70)</td>
<td></td>
</tr>
<tr>
<td>Pz</td>
<td>-2.86 (1.89)</td>
<td>0.03 (1.50)</td>
<td>-1.89 (1.61)</td>
<td>-3.49 (3.07)</td>
<td></td>
</tr>
<tr>
<td>C3'</td>
<td>-2.69 (1.46)</td>
<td>-0.34 (2.81)</td>
<td>-2.52 (1.16)</td>
<td>-3.30 (3.07)</td>
<td></td>
</tr>
<tr>
<td>C4'</td>
<td>-2.74 (1.89)</td>
<td>-1.30 (3.24)</td>
<td>-2.48 (1.82)</td>
<td>-3.63 (3.77)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DCD-</th>
<th>Peak</th>
<th>Peak</th>
<th>Peak</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fz</td>
<td>-3.03 (2.42)</td>
<td>-6.68 (6.41)</td>
<td>-2.78 (2.45)</td>
<td>-6.86 (4.63)</td>
<td></td>
</tr>
<tr>
<td>Cz</td>
<td>-3.20 (2.52)</td>
<td>-5.73 (4.56)</td>
<td>-3.10 (2.15)</td>
<td>-7.73 (5.82)</td>
<td></td>
</tr>
<tr>
<td>Pz</td>
<td>-2.34 (2.35)</td>
<td>-3.89 (3.26)</td>
<td>-2.05 (1.74)</td>
<td>-4.72 (4.69)</td>
<td></td>
</tr>
<tr>
<td>C3'</td>
<td>-2.58 (2.22)</td>
<td>-4.63 (3.67)</td>
<td>-2.49 (1.83)</td>
<td>-6.58 (5.15)</td>
<td></td>
</tr>
<tr>
<td>C4'</td>
<td>-2.83 (2.68)</td>
<td>-4.05 (3.43)</td>
<td>-2.65 (2.31)</td>
<td>-5.82 (4.27)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.4 presents the ERN values for the compatible and incompatible conditions for the three groups. These values were computed by subtracting the estimate of the negative peak for correct responses from the negative peak for errors.
Table 5.4 Error negativity (ERN) values for the compatible and incompatible conditions for controls, patients with DCD (DCD+), and patients without DCD (DCD-)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>DCD+</th>
<th>DCD-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compatible condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>0.14 (4.40)</td>
<td>0.80 (4.38)</td>
<td>-3.65 (5.53)</td>
</tr>
<tr>
<td>Cz</td>
<td>-0.24 (4.55)</td>
<td>2.31 (4.01)</td>
<td>-2.54 (3.78)</td>
</tr>
<tr>
<td>Pz</td>
<td>0.44 (3.18)</td>
<td>2.89 (2.55)</td>
<td>-1.54 (3.14)</td>
</tr>
<tr>
<td>C3'</td>
<td>0.10 (5.04)</td>
<td>2.35 (3.99)</td>
<td>-2.05 (2.92)</td>
</tr>
<tr>
<td>C4'</td>
<td>-0.06 (4.63)</td>
<td>1.35 (4.29)</td>
<td>-1.22 (2.58)</td>
</tr>
<tr>
<td><strong>Incompatible condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>0.22 (2.52)</td>
<td>-0.91 (2.87)</td>
<td>-4.08 (4.20)</td>
</tr>
<tr>
<td>Cz</td>
<td>-1.03 (3.43)</td>
<td>-0.93 (3.26)</td>
<td>-4.63 (5.26)</td>
</tr>
<tr>
<td>Pz</td>
<td>-0.19 (2.81)</td>
<td>-1.61 (2.20)</td>
<td>-2.67 (3.95)</td>
</tr>
<tr>
<td>C3'</td>
<td>-0.76 (2.92)</td>
<td>-0.78 (2.83)</td>
<td>-4.09 (4.75)</td>
</tr>
<tr>
<td>C4'</td>
<td>-0.68 (3.20)</td>
<td>-1.16 (3.25)</td>
<td>-3.17 (3.70)</td>
</tr>
</tbody>
</table>

A repeated measures ANOVA on ERN amplitude with electrode site as the within groups factor (Fz, Cz, Pz, C3', C4') and patient group as the between groups factor (controls, patients with discourse coherence disturbance, patients without discourse coherence disturbance) found a significant group by site interaction, \( F(8, 96) = 2.72, p < 0.05 \) for the incompatible condition. However, there was no significant effect of site, \( F(4, 96) = 1.88, p = 0.12 \), or of group, \( F(2, 24) = 2.35, p = 0.12 \). Multiple comparisons (uncorrected) of group differences at each electrode site revealed a trend for patients without discourse coherence disturbance to produce a larger ERN than either controls or patients with discourse coherence disturbance, particularly at Fz, Cz and C3 (see Table 5.5 and Figure 5.5).

For the compatible condition, there was no significant effect of group for ERN in the compatible condition, \( F(2, 24) = 1.80, p = 0.19 \), and no significant group by site interaction for the compatible condition, \( F(8, 96) = 1.74, p = 0.10 \). However, there was a significant effect of site in the compatible condition, \( F(4, 96) = 3.73, p < 0.05 \). While...
multiple comparisons of group difference at each site are not appropriate given that, overall, there was no site by group interaction, these comparisons reveal a similar pattern to that seen for incompatible trials. However, this pattern is evident only for the group contrast between patients with and without discourse coherence disturbance, ie, there is a larger ERN in patients without discourse coherence disturbance than in patients with discourse coherence disturbance.

Table 5.5 \( t \) (with uncorrected \( p \)-values in parentheses) values for comparisons between groups for ERN in the compatible and incompatible condition.

<table>
<thead>
<tr>
<th></th>
<th>Controls vs DCD+</th>
<th>Controls vs DCD-</th>
<th>DCD+ vs DCD-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compatible condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>0.31 (0.76)</td>
<td>1.71 (0.10)</td>
<td>1.59 (0.14)</td>
</tr>
<tr>
<td>Cz</td>
<td>1.18 (0.25)</td>
<td>1.15 (0.26)</td>
<td>2.24 (0.05)</td>
</tr>
<tr>
<td>Pz</td>
<td>1.66 (0.11)</td>
<td>1.35 (0.19)</td>
<td>2.76 (0.02)</td>
</tr>
<tr>
<td>C3'</td>
<td>0.97 (0.35)</td>
<td>1.03 (0.31)</td>
<td>2.29 (0.04)</td>
</tr>
<tr>
<td>C4'</td>
<td>0.64 (0.53)</td>
<td>0.61 (0.55)</td>
<td>1.34 (0.21)</td>
</tr>
<tr>
<td><strong>Incompatible condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fz</td>
<td>0.88 (0.39)</td>
<td>2.95 (0.008)</td>
<td>1.56 (0.15)</td>
</tr>
<tr>
<td>Cz</td>
<td>0.06 (0.95)</td>
<td>1.90 (0.07)</td>
<td>1.49 (0.16)</td>
</tr>
<tr>
<td>Pz</td>
<td>1.10 (0.29)</td>
<td>1.67 (0.11)</td>
<td>0.58 (0.57)</td>
</tr>
<tr>
<td>C3'</td>
<td>0.01 (0.99)</td>
<td>2.00 (0.06)</td>
<td>1.49 (0.16)</td>
</tr>
<tr>
<td>C4'</td>
<td>0.30 (0.77)</td>
<td>1.59 (0.13)</td>
<td>1.03 (0.32)</td>
</tr>
</tbody>
</table>
Figure 5.4 ERN mean amplitude with standard error bars showing +/-1 standard errors at Cz in the compatible condition for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).

Figure 5.5 ERN mean amplitude with standard error bars showing +/-1 standard errors at Cz in the incompatible condition for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).

A repeated measures ANOVA with electrode site as the within groups factor (Fz, Cz, Pz, C3', C4') and patient group as the between groups factor (controls, patients with discourse coherence disturbance, patients without discourse coherence...
disturbance) failed to reveal a significant main effect of group in average amplitude of the negative peak for correct responses in either the compatible, \( F(2, 24) = 1.00, p = 0.38 \) or incompatible conditions, \( F(2, 24) = 0.97, p = 0.39 \). However, for the compatible condition, there was a significant main effect of site, \( F(4, 96) = 2.54, p < 0.05 \) and a significant group by site interaction, \( F(8, 96) = 2.12, p < 0.05 \). For the incompatible condition, there was a significant main effect of site, \( F(4, 96) = 5.03, p < 0.05 \) but no significant interaction between group and site, \( F(8, 96) = 1.79, p = 0.19 \). Post-hoc tests failed to reveal any significant difference between groups at the individual sites in the compatible condition. However, there was a trend for patients with schizophrenia both with and without discourse coherence disturbance to show a larger minimum amplitude in both compatible and incompatible conditions (see Table 5.6 and Figures 5.6 and 5.7).

A repeated measures ANOVA with electrode site as the within groups factor (Fz, Cz, Pz, C3', C4') and patient group as the between groups factor (controls, patients with discourse coherence disturbance, patients without discourse coherence disturbance) revealed a significant main effect of site, \( F(4, 96) = 7.40, p < 0.05 \), but no significant main effect of group, \( F(2, 24) = 2.42, p = 0.11 \) and no significant interaction between group and site, \( F(8, 96) = 0.87, p = 0.54 \) for error responses in the compatible condition. Similarly, for the incompatible condition, there was a main effect of site, \( F(4, 96) = 6.90, p < 0.05 \), but no significant main effect of group, \( F(2, 24) = 2.78, p = 0.08 \) and no significant interaction between group and site, \( F(8, 96) = 1.62, p = 0.13 \).
Table 5.6  t values (with uncorrected p-values in parentheses) for comparisons between groups for negative peak correct and error responses in the compatible condition and incompatible condition.

<table>
<thead>
<tr>
<th></th>
<th>Correct responses</th>
<th>Error responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls vs DCD+</td>
<td>Controls vs DCD-</td>
</tr>
<tr>
<td><strong>Compatible condition</strong></td>
<td>0.07 (0.95)</td>
<td>0.49 (0.63)</td>
</tr>
<tr>
<td>Fz</td>
<td>1.31 (0.21)</td>
<td>1.36 (0.19)</td>
</tr>
<tr>
<td>Cz</td>
<td>1.50 (0.15)</td>
<td>1.15 (0.26)</td>
</tr>
<tr>
<td>Pz</td>
<td>1.16 (0.26)</td>
<td>1.03 (0.31)</td>
</tr>
<tr>
<td>C3'</td>
<td>1.19 (0.25)</td>
<td>1.23 (0.23)</td>
</tr>
<tr>
<td>C4'</td>
<td>0.47 (0.64)</td>
<td>0.46 (0.65)</td>
</tr>
<tr>
<td></td>
<td>1.33 (0.20)</td>
<td>1.44 (0.17)</td>
</tr>
<tr>
<td><strong>Incompatible condition</strong></td>
<td>0.82 (0.42)</td>
<td>1.02 (0.32)</td>
</tr>
<tr>
<td>Fz</td>
<td>1.19 (0.25)</td>
<td>1.12 (0.28)</td>
</tr>
<tr>
<td>Cz</td>
<td>1.18 (0.25)</td>
<td>1.33 (0.20)</td>
</tr>
<tr>
<td>Pz</td>
<td>0.38 (0.71)</td>
<td>1.90 (0.07)</td>
</tr>
<tr>
<td>C3'</td>
<td>0.52 (0.61)</td>
<td>1.91 (0.07)</td>
</tr>
<tr>
<td>C4'</td>
<td>0.24 (0.81)</td>
<td>2.01 (0.06)</td>
</tr>
<tr>
<td><strong>Compatible condition</strong></td>
<td>0.49 (0.63)</td>
<td>1.59 (0.13)</td>
</tr>
<tr>
<td>Fz</td>
<td>0.003 (0.99)</td>
<td>1.38 (0.18)</td>
</tr>
<tr>
<td>Cz</td>
<td>0.93 (0.36)</td>
<td>2.63 (0.02)</td>
</tr>
<tr>
<td>Pz</td>
<td>0.58 (0.57)</td>
<td>2.26 (0.04)</td>
</tr>
<tr>
<td>C3'</td>
<td>1.40 (0.18)</td>
<td>1.96 (0.06)</td>
</tr>
<tr>
<td>C4'</td>
<td>0.58 (0.57)</td>
<td>2.22 (0.04)</td>
</tr>
<tr>
<td><strong>Incompatible condition</strong></td>
<td>0.86 (0.40)</td>
<td>2.03 (0.06)</td>
</tr>
</tbody>
</table>
Figure 5.6 Negative peak mean amplitude with standard error bars showing +/-1 standard errors at Cz for correct responses in the compatible condition for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).

Figure 5.7 Negative peak mean amplitude with standard error bars showing +/-1 standard errors at Cz for correct responses in the incompatible condition for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).
Figure 5.8 Negative peak mean amplitude with standard error bars showing +/-1 standard errors at Cz for error responses in the incompatible condition for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).

Figure 5.9 Negative peak mean amplitude with standard error bars showing +/-1 standard errors at Cz for error responses in the compatible condition for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).
Response-locked ERPs for uncorrected errors collapsed across conditions are presented in Figure 5.10 (NB, the large negativity occurring around 200 ms is not an error negativity as it occurs too late). Table 5.7 presents the average peak amplitude and latency for negative peaks for uncorrected errors collapsed across conditions.

A repeated measures ANOVA with electrode site as the within groups factor (Fz, Cz, Pz, C3', C4') and patient group as the between groups factor (controls, patients with discourse coherence disturbance, patients without discourse coherence disturbance) failed to find any difference between groups in terms of the negative peak associated with uncorrected errors at any site, $F(2, 19) = 0.79, p = 0.47$ or any significant group by site interaction, $F(8, 76) = 1.27, p = 0.27$, although there was a significant main effect of site, $F(4, 76) = 2.65, p = 0.04$ (see Figure 5.11).
Figure 5.10  Response-locked negativity for uncorrected errors in the incompatible condition for the control group, patients with discourse coherence disturbance (DCD+), and patients without discourse coherence disturbance (DCD-). Note: negativity is up.
Table 5.7 Average negative peak amplitude for uncorrected errors collapsed across compatible and incompatible conditions of the flanker task for patients with discourse coherence disturbance (DCD+), patients without discourse coherence disturbance (DCD-), and the control group.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Uncorrected Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fz</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-4.10 (4.16)</td>
</tr>
<tr>
<td></td>
<td>Cz</td>
<td>-3.53 (5.71)</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>-1.48 (5.75)</td>
</tr>
<tr>
<td></td>
<td>C3'</td>
<td>-3.26 (4.34)</td>
</tr>
<tr>
<td></td>
<td>C4'</td>
<td>-2.99 (5.38)</td>
</tr>
<tr>
<td></td>
<td>PCP+</td>
<td>Fz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-8.99 (16.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3.09 (3.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2.26 (4.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2.08 (2.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C4'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3.15 (4.08)</td>
</tr>
<tr>
<td></td>
<td>PCP-</td>
<td>Fz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.70 (3.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.59 (4.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.56 (4.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.83 (3.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C4'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.02 (4.20)</td>
</tr>
</tbody>
</table>

Figure 5.11 Negative peak mean amplitude with standard error bars showing +/-1 standard errors at Cz for uncorrected errors collapsed across compatible and incompatible conditions for the control group, patients with discourse coherence disturbance (DCD+) and patients without discourse coherence disturbance (DCD-).
5.4 Discussion

The aim of this study was twofold: to investigate whether patients with discourse coherence disturbance are able to detect errors; and to explore the role of the dorsolateral prefrontal cortex in patients with discourse coherence disturbance.

5.4.1 Error negativity

A serious problem with this study is the failure to find an ERN in the control group. This study replicated similar studies which have found a reliable ERN in control populations (Falkenstein et al., 2000; Gehring et al., 1993). The reason for the lack of such a result in this study is difficult to explain, especially since error negativity was present in the schizophrenia groups, particularly in the patients without discourse coherence disturbance, and the control group responded incorrectly on approximately 10% of trials which is consistent with previous findings (Gehring et al., 1993; Kopp & Rist, 1999). There is no reasonable explanation for the lack of ERN in the control group. This groups produced roughly the same number of errors as healthy controls in the past, and they were no more variable than patients without discourse coherence disturbance who produced an ERN. Due to the lack of error negativity in the control group, the discussion of the results will be focused on the comparison between patients with and without discourse coherence disturbance. Both groups of patients showed error negativity in association with incorrect responses in the compatible and incompatible conditions. Furthermore, the comparison between these groups is in many respects a more appropriate comparison since any difference between groups will be specific to those with discourse coherence disturbance symptoms and not reflective of the diagnosis of schizophrenia.
5.4.2 Error detection

With respect to error monitoring, the behavioural results from this study are similar to those found in Study 1, namely, patients with discourse coherence disturbance were less likely to correct errors than control subjects. Patients without discourse coherence disturbance fell between controls and patients with discourse coherence disturbance and were not significantly different from either group. These results support the conclusion from Study 1 that patients with discourse coherence disturbance have a deficit in their ability to monitor errors.

The ERP results are inconclusive with respect to whether this behavioural deficit is due to impaired error correction or error detection. For most comparisons, there was no significant difference in ERN amplitude between patients with and without discourse coherence disturbance. While there was a trend for patients with discourse coherence disturbance to show a reduced ERN amplitude within the compatible condition which may reflect impaired error detection, the general failure to show a reduced amplitude suggests that error detection is intact in patients with discourse coherence disturbance. Such a finding must be interpreted with caution because of the low power resulting from small sample sizes and consequent problems associated with accepting a null hypothesis. The only conclusion that can be safely made is that there is no strong evidence for a failure to detect errors and that a failure to correct errors may underlie the behavioural impairment in patients with discourse coherence disturbance. On uncorrected errors, patients with discourse coherence disturbance revealed a negative peak that did not differ significantly from that found in patients without discourse coherence disturbance. Again, these results are difficult to interpret given the low power. However, these results appear to support McGrath’s theory that patients with discourse coherence disturbance are aware of their errors but are unable to use this information to modify their behaviour. It is important to note that this result must be
interpreted with extreme caution. Due to the very small number of uncorrected errors in each group, there is considerable variability, particularly in the control group and in patients without discourse coherence disturbance. The lack of difference between groups may have been due to the large variance, and further studies with larger samples and more trials (and a consequent increase in uncorrected errors) would be needed to confirm the ability of patients with discourse coherence disturbance to detect errors.

5.4.3 Dorsolateral prefrontal function

With respect to dorsolateral prefrontal function, the results of patients with discourse coherence disturbance are not consistent with those of patients with dorsolateral prefrontal lesions. Patients with discourse coherence disturbance did not differ from patients without discourse coherence disturbance on correct trials within either the compatible or incompatible condition, but showed decreased negativity on incorrect trials compared to patients without discourse coherence disturbance. This difference was significant (when uncorrected for multiple comparisons) in the compatible condition at Cz, Pz, and C3'. These results do not show the same pattern as that found in patients with dorsolateral prefrontal lesions (Gehring & Knight, 2000). In patients with dorsolateral prefrontal lesions, the reduced ERN appears to be due to increased negativity associated with correct responses, whereas patients with discourse coherence disturbance seem to show reduced negativity on incorrect responses.

These results are consistent with those of Study 2 in their failure to find impairments to the dorsolateral prefrontal cortex. However, the behavioural results and the decreased negativity in association with incorrect responses do suggest an impaired ability to correct errors. A possible explanation for these data may be an impairment to the network involved in error correction, rather than a specific dorsolateral prefrontal
deficit. This is consistent with the results of Study 2 showing disrupted activity in temporal, parietal and cingulate regions, even where dorsolateral prefrontal function was preserved. Given the impairment to ERN (compared to patients without discourse coherence disturbance) and the apparent disconnectivity found in Study 2, a possible explanation is a disconnection between the dorsolateral prefrontal cortex and other brain regions, predominantly, in this case, the anterior cingulate gyrus. As discussed earlier, ERN appears to result from interaction between the dorsolateral prefrontal cortex and the anterior cingulate. According to the model outlined in Section 5.1, impaired connection between these regions would prevent the production of a normal ERN, even though some error-detection can still occur. This interpretation of the results is consistent with McGrath’s predicted inability to correct errors. Due to the disconnection between dorsolateral prefrontal cortex and other regions, error-detection must proceed via the anterior cingulate. The loss of the dorsolateral prefrontal cortex in this process, and the rich connections between the dorsolateral prefrontal cortex and other regions such as the motor cortex and parietal regions, results in impaired ability to correct errors, even where error-detection is intact.

The results of this study combined with Study 2, are also consistent with Fletcher et al.’s (1999) finding that the anterior cingulate modifies the interaction between frontal and temporal areas in patients with schizophrenia. Impaired communication between the anterior cingulate and the dorsolateral prefrontal cortex could be responsible for disruption of fronto-temporoparietal networks in patients with discourse coherence disturbance which could underlie the central executive impairment and symptoms of speech disorder in patients with discourse coherence disturbance.

Overall, the meaning of these results are unclear, but they are consistent with a disconnectivity between prefrontal and cingulate regions. The results are not consistent with a dorsolateral prefrontal deficit. While, dorsolateral prefrontal dysfunction is
clearly implicated in abnormalities in error-monitoring, the results of this study are not consistent with a dorsolateral prefrontal deficit in patients with discourse coherence disturbance. However, some sort of disconnectivity incorporating the dorsolateral prefrontal region and anterior cingulate is a strong candidate for explaining the symptoms and cognitive deficits in these patients.

5.4.4 Limitations

A major concern with this study was the small number of subjects and the consequent low power. As a result, it is difficult to draw any firm conclusions with respect to error negativity in patients with discourse coherence disturbance. A particular concern was the failure to find a clear ERN in the control group. Due to this, the results of patients with discourse coherence disturbance have been discussed in relation to those of patients without discourse coherence disturbance. However, given the very small number of subjects in each group, and the large variability in each group, the results need to be interpreted with caution. Further research with larger samples is warranted to clarify the issues. On all ERP peak measures, the patients without discourse coherence disturbance showed more variability than either patients with discourse coherence disturbance or the control group. The patients with discourse coherence disturbance showed very little variability, consistent with a common underlying pathology. A productive direction for further research would be to compare patients with discourse coherence disturbance with a more homogeneous group of patients with schizophrenia without discourse coherence disturbance. Such research should focus on other symptoms of schizophrenia in an attempt to determine the specific nature of the error monitoring deficit.

With respect to patients with discourse coherence disturbance, the results of the current study suggest that further investigation into the role of the anterior cingulate in modulating the interaction between dorsolateral prefrontal and temporoparietal regions
is warranted. Neuroimaging work with structural equation modelling of the interaction between these regions would provide a further test of McGrath's theory that there is a disconnection between prefrontal and temporoparietal regions in patients with discourse coherence disturbance.
CHAPTER 6

GENERAL DISCUSSION AND CONCLUSIONS

The results of the three studies comprising this thesis provide the basis for an explanation of discourse coherence disturbance symptoms in schizophrenia. Based on these data, this chapter presents a number of concluding arguments. The first conclusion is that the pattern of cognitive impairments in patients with discourse coherence disturbance is consistent with McGrath’s (1991; et al., 1997) model of these symptoms. That is, discourse coherence disturbance symptoms result from a disconnection between thought and action resulting in an impaired ability to monitor performance and execute a discourse plan. The second conclusion is that symptoms of discourse coherence disturbance, and executive dysfunction in these patients, do not result from a specific prefrontal deficit. Instead, these symptoms and cognitive impairments seem to be due to disconnection between prefrontal areas and other brain regions.

6.1 Cognitive processes in patients with discourse coherence disturbance

In Chapter 2, four models of discourse coherence disturbance were described. These models focused on cognitive correlates of discourse coherence disturbance symptoms in patients with schizophrenia. The first of these theories focused on monitoring and attentional deficits (McGrath, 1991; McGrath et al., 1997), the second focused on impaired perspective (Harrow et al., 1987), the third was based on discourse planning (Hoffman, 1986), and the last theory emphasised semantic memory and working memory (Nestor et al., 1998). Specifically, McGrath’s theory predicted cognitive impairments in terms of an inability to maintain a discourse plan, deficits in central executive function, and inability to correct errors. Harrow’s theory predicted error-monitoring deficits and impaired contextual processing. Hoffman’s theory
predicted impaired ability to generate a discourse plan, impaired central executive function, and poor sustained attention. Finally, Nestor’s theory predicted facilitation of semantic activation, central executive impairment, and an inhibitory deficit.

As reviewed in Chapter 2, the existing studies of cognitive processes in patients with schizophrenic thought disorder provide insufficient support for any of these theories. There has been very little systematic investigation of cognitive domains in patients with discourse coherence disturbance: most studies reviewed focused on thought disorder as a whole, without distinguishing between different thought disorder symptoms. The aim of Study 1 was to conduct a series of detailed case studies, addressing the cognitive predictions included in each of the above theories of discourse coherence disturbance.

The results of Study 1 were consistent McGrath’s theory of discourse coherence disturbance and were inconsistent with the alternative models of discourse coherence disturbance. Patients with discourse coherence disturbance performed poorly on tasks assessing the central executive of working memory, they showed impairments on aspects of verbal fluency performance assessing frontal processes, and they were less likely to correct their errors on the anti-saccade task. Evidence from existing literature provides support for McGrath’s hypothesised deficit in the ability to maintain a discourse plan in patients with discourse coherence disturbance (Barch & Berenbaum, 1996; Barch & Berenbaum, 1997). The results of Study 1 failed to support any of the alternative theories of discourse coherence disturbance. There was no apparent deficit in contextual processing in the patients with discourse coherence disturbance. Such an impairment is central to Harrow’s theory of discourse coherence disturbance. Hoffman’s theory was not supported by the results of this study: patients with discourse coherence disturbance did not show impaired sustained attention, the aspect that distinguishes Hoffman’s theory from other theories. Furthermore, previous studies
investigating planning in discourse coherence disturbance have failed to find an impaired ability to generate a plan in patients exhibiting these symptoms (Barch & Berenbaum, 1996; Barch & Berenbaum, 1997). Finally, the results of Study 1 failed to find facilitated semantic activation in patients with discourse coherence disturbance, or an inhibitory deficit in these patients. These results are not consistent with Nestor's theory.

Overall, the results of Study 1 were most consistent with McGrath's proposed disconnection between thought and action. Patients with discourse coherence disturbance showed deficits in central executive function, and in their ability to utilise information about their performance to correct behaviour. McGrath's theory suggests that symptoms of discourse coherence disturbance occur because these patients are unable to maintain a speech plan, due to an underlying disconnection between thought and action such that central executive ability is disconnected from speech production in these patients.

6.2 Error-monitoring in patients with discourse coherence disturbance

The results of Study 1 suggested that there is an error-monitoring impairment in patients with discourse coherence disturbance. However, Study 1 did not address the specific nature of this deficit. Study 3 aimed to differentiate between error-detection and error-correction processes in patients with discourse coherence disturbance. Study 3 supported the findings of Study 1 with respect to error-monitoring. On the flanker task, patients with discourse coherence disturbance showed a similar pattern of error-correction to the patients tested in Study 1. On this task, patients with discourse coherence disturbance did not differ significantly from other groups in the number of errors made, but they were less likely to correct their errors. However, Study 3 was unable to provide further information on the nature of the error-monitoring deficit in
patients with discourse coherence disturbance because the data were noisy and there was a very small number of uncorrected errors in each group. Further trials would be required to determine whether ERN data confirm McGrath’s prediction that patients with discourse coherence disturbance are able to detect their errors, but are unable to use this information to correct their behaviour.

6.3 Prefrontal function in patients with discourse coherence disturbance

The strongest finding in terms of cognitive deficits from Study 1, was impaired central executive function in patients with discourse coherence disturbance. Central executive processes are associated with prefrontal function, in particular with activation of the dorsolateral prefrontal cortex and the dorsolateral prefrontal circuit generally (Collette et al., 1999; D’Esposito et al., 1999; Garavan et al., 2000). The dorsolateral prefrontal circuit encompasses subcortical and posterior regions, such as the caudate nucleus and thalamus, and has rich connections to the parietal lobe, subcortical regions, supplementary motor area, and the frontal eye fields (Mega & Cummings, 2001). Damage to this circuit may result in central executive dysfunction (Duffy & Campbell, 2001; Mega & Cummings, 2001). Furthermore, damage to prefrontal regions, especially dorsolateral prefrontal circuitry, will result in symptoms similar to those displayed by patients with discourse coherence disturbance (Alexander et al., 1989; Mega & Cummings, 2001; Novoa & Ardila, 1987). Consequently, there is good reason to suppose that either the dorsolateral prefrontal cortex, or dorsolateral prefrontal networks play a role in discourse coherence disturbance.

In Chapter 2, the physiological predictions of the four theories of discourse coherence disturbance were reviewed. Each theory predicted prefrontal dysfunction in some form: Harrow, Hoffman, and Nestor predicted a specific prefrontal deficit, and McGrath predicted disruptions to Crosson’s (1985) prefrontal network. This network
encompasses the dorsolateral prefrontal cortex and the subcortical areas such as the
basal ganglia and thalamic regions which mediate communication between
temporoparietal and frontal regions involved in language production, and also
communication between temporoparietal and motor regions (Alexander et al., 1989;
Alexander et al., 1986; Crosson, 1985; McGrath, 1991; McGrath et al., 1996). The aim
of Study 2 was to investigate the role of the prefrontal cortex in discourse coherence
disturbance using an fMRI study.

The results of Study 2 provided further support for McGrath’s theory over the
other theories as there was no evidence of a specific dorsolateral prefrontal deficit in
patients with discourse coherence disturbance, but there was evidence of disruption to
the temporoparietal network with patients failing to activate these regions appropriately.
Using functional connectivity analysis, Study 2 showed impaired connectivity in
temporoparietal regions in all patients. However, this deficit was not specific to patients
with discourse coherence disturbance but was found in all patients with schizophrenia.
Furthermore, there was no specific impairment in prefrontal regions, suggesting that
impaired performance on tasks which are traditionally seen as loading onto prefrontal
function in Study 1 do not reflect a simple prefrontal deficit. Disruption to the
dorsolateral prefrontal network would lead to central executive impairments similar to
those found in patients with discourse coherence disturbance (Duffy & Campbell, 2001;
Mega & Cummings, 2001). Given the lack of a specific impairment of dorsolateral
prefrontal regions in patients with discourse coherence disturbance, as well as the
disruption to temporoparietal and cingulate regions, disconnectivity is a strong
candidate as an explanation for central executive impairments in these patients.
6.4 Discourse coherence disturbance and the dorsolateral prefrontal circuit

The results of Study 1 revealed impairments in patients with discourse coherence disturbance consistent with impaired dorsolateral prefrontal function. Investigation of dorsolateral prefrontal function in patients with discourse coherence disturbance suggested that this may be due to fronto-temporoparietal disconnectivity, rather than to any specific impairment in frontal regions (see Study 2). However, patients without discourse coherence disturbance showed a similar fronto-temporoparietal disconnectivity. Study 3 comprised a further investigation of dorsolateral prefrontal connections in discourse coherence disturbance. In this study, ERP activity associated with errors was measured in patients with and without discourse coherence disturbance compared to a control group. There is evidence suggesting that normal ERN relies on communication between the dorsolateral prefrontal cortex and other regions, especially the anterior cingulate, and patients with lesions to prefrontal regions show decreased ERN as a result of increased negativity on correct trials (Gehring & Knight, 2000). The results of Study 3 failed to show a reduced ERN amplitude in patients with discourse coherence disturbance. Consequently, this study was unable to provide any further information about the nature of the error-monitoring deficit in patients with discourse coherence disturbance. The failure to find any significant results in Study 3 seems to be due to the lack of power and poor signal-to-noise of the ERP data. Further studies with larger samples and an increased number of trials in the ERP paradigm are required to investigate the nature of the prefrontal deficit within the context of an ERN study. However, the results of Study 3 are not consistent with the presence of a simple prefrontal deficit in patients with discourse coherence disturbance. Patients with prefrontal lesions show a reduced ERN and corresponding increased negativity on correct trials. This pattern was not found in patients with discourse coherence disturbance. Although this result must be interpreted with caution...
due to the difficulties involved in accepting the null hypothesis, they are consistent with the failure to find a simple prefrontal impairment in these patients in Study 2.

As discussed in Chapter 2, patients with discourse coherence disturbance closely resemble patients with speech disorder symptoms resulting from damage to the dorsolateral prefrontal cortex, particularly the right dorsolateral prefrontal cortex (Alexander et al., 1989; Mega & Cummings, 2001; Novoa & Ardila, 1987). Patients with damage to the dorsolateral prefrontal cortex show impaired abstract thinking and conceptualisation, emotional disinhibition, free association, inability to maintain a coherent discourse, and impaired inferential reasoning. The speech disturbances found in these patients (loose associations and inability to maintain a discourse plan) are similar to those exhibited by patients with discourse coherence disturbance (Berenbaum & Barch, 1995). Cognitive impairments, especially central executive dysfunction, in patients with discourse coherence disturbance, are consistent with a dorsolateral prefrontal deficit in these patients. However, there is also evidence of cognitive impairments, specifically error-monitoring deficits, in patients with discourse coherence disturbance which are consistent with impairments to a network incorporating the frontal and temporoparietal regions via connections in the thalamus, globus pallidus, and caudate nucleus.

Any model of the disconnectivity in discourse coherence disturbance, must be able to account for the presence of central executive impairments, and the specific nature of the error-monitoring deficit, as well as the symptoms of discourse coherence disturbance. McGrath (1991) suggested that the disconnectivity in discourse coherence disturbance exists within the neural circuit between the prefrontal cortex and temporoparietal regions via subcortical structures such as the globus pallidus, caudate nucleus, and thalamus. This network is important in semantic monitoring of speech (Crosson, 1985; Dalton & Hardcastle, 1977) and patients with discourse coherence
disturbance show speech which is disrupted at the semantic rather than phonological, grammatical, or lexical level. Disruption to this circuit would explain the speech disturbance in discourse coherence disturbance and the central executive dysfunction. However, it does not incorporate the anterior cingulate which is implicated in error-monitoring which are impaired in patients with discourse coherence disturbance.

Gehring and Knight (2000) suggested a model of error-monitoring whereby the dorsolateral prefrontal cortex maintains a representation of the correct response and compares this to information about the actual response which is held in the anterior cingulate. However, this model is unable to account for the fact that patients with lesions to the dorsolateral prefrontal cortex continue to correct the majority of their incorrect responses. Furthermore, it does not incorporate findings that medial frontal and parietal regions are involved in error-monitoring (Carter, Braver et al., 1998; Kiehl et al., 2000; Menon, Adleman et al., 2001). In Chapter 5, I proposed an alternative model of error-monitoring which provides a possible explanation of error-correction impairment in patients with discourse coherence disturbance. According to this model, the dorsolateral prefrontal cortex plays an ongoing role in monitoring performance by comparing the actual response to the representation of the correct response held in the inferior frontal regions. When a mismatch is detected, information is sent from the dorsolateral prefrontal cortex to the anterior cingulate which resolves the conflict between the correct and actual response by alerting parietal and motor areas, possibly via the dorsolateral prefrontal cortex, of the need for corrective action. In patients with discourse coherence disturbance, communication between the dorsolateral prefrontal cortex and other regions is disrupted. As a result, error-monitoring cannot proceed in the same way, and the anterior cingulate takes over the role of error-detection. This system is less efficient than the dorsolateral prefrontal system, and patients will detect
fewer errors. Electrophysiological measures will show reduced negativity on incorrect trials, as a result of the impoverished efficiency of this method of detecting errors. There was a trend in this direction in the data from Study 3, i.e., there was a trend in the direction of reduced negativity on incorrect trials. A model of discourse coherence disturbance incorporating the anterior cingulate and dorsolateral prefrontal circuit is able to account for symptoms and cognitive impairments in these patients. Furthermore, there is some evidence that disconnectivity in schizophrenia may be modulated by the anterior cingulate (Fletcher et al., 1999). Consequently, impaired communication between the anterior cingulate and the dorsolateral prefrontal cortex could be the basis of the disruption of fronto-temporoparietal networks in patients with discourse coherence. This extends McGrath's model of disconnectivity between frontal and temporoparietal regions via the subcortical regions, by including a role for the anterior cingulate to modulate the disconnectivity.

The predictions of this model of disconnectivity in discourse coherence disturbance could be tested using imaging studies. According to the model, the dorsolateral prefrontal network should be disrupted in patients with discourse coherence disturbance. In association with error-monitoring tasks, there should be increased communication between the anterior cingulate and other regions, as the anterior cingulate takes over the role of the dorsolateral prefrontal cortex. Furthermore, there should be impaired communication between the anterior cingulate and the dorsolateral prefrontal cortex which forms the basis of the frontal-temporoparietal disconnectivity.

6.5 The case study approach to specific symptoms in patients with thought disorder

This thesis focused on a subset of symptoms in schizophrenic thought disorder which were defined by Berenbaum and Barch (1995; Barch & Berenbaum, 1997) as
discourse coherence disturbance. The results of the studies comprising this thesis support this as a sensible categorisation. These symptoms tended to cluster together in patients (see Study 1), and in all three studies, the patients with discourse coherence disturbance showed less variability than other groups in physiological and cognitive processes. Reducing the variability by focusing on specific symptoms of thought disorder may have allowed the detection of effects which would have been lost if the focus had been thought disorder symptoms generally, or even positive thought disorder symptoms.

An important point to note is that this thesis focused on a set of symptoms that was defined theoretically rather than using techniques such as factor analysis. The meaningful results produced by the studies comprising this thesis support the use of theoretical divisions of symptoms as a viable basis for understanding symptoms in schizophrenia. This supports further investigation of symptoms, rather than syndromes in schizophrenia research. Further research with patients matched closely for symptoms would provide an indication of whether research based on symptoms, irrespective of diagnosis, would be a more profitable direction for research into psychosis.

The use of case studies, particularly in Study 1, allowed in-depth investigation of cognitive deficits: the results of Study 1 provided a clear picture of the processes involved in patients with discourse coherence disturbance which was confirmed in a slightly larger sample of patients in Study 3. The studies reviewed in Chapter 2 failed to provide any consistent and clear picture of the cognitive processes involved in thought disorder in schizophrenia. This is in part due to the failure to base research on particular symptoms, and partly due to the fact that these studies focused on a small range of cognitive areas in a large population. Given the heterogeneity of symptoms in schizophrenia between patients, and within patients over time, large group studies of a cluster of symptoms can fail to provide a clear explanation of the phenomena of interest.
The results of this study confirm that a case study approach is a viable and informative approach in its application to schizophrenic symptoms.

6.6 Limitations of this set of studies

A number of limitations in the studies comprising this thesis must be acknowledged, and any future research in the area should be designed to overcome these problems. First, in Study 1, there was no assessment of planning ability. Planning ability is central to McGrath's and Hoffman's models of discourse coherence disturbance, and different predictions with respect to planning are made by each model. The need to measure planning was somewhat obviated by Barch and Berenbaum's (1996; 1997) findings that the inability to maintain a plan is specific to patients with discourse coherence disturbance, consistent with McGrath's theory. However, including a measure of planning in Study 1 would have provided information about planning processes in these patients in the context of other cognitive domains. The second area of concern in Study 1 was the measure chosen for assessing error-monitoring. The task chosen to measure monitoring behaviour was the error-correction behaviour on the anti-saccade task. Although this provides an indication of monitoring behaviour on this task, it may be specific to this task and not reflect a general monitoring impairment. This was partially overcome by using a similar error-correction measure with a different task in Study 3. In the flanker task, patients with discourse coherence disturbance showed a similar pattern of error-correction performance as the patients in Study 1. This provides some evidence of a general monitoring deficit. However, further studies focusing on error-detection processes in speech would indicate whether an error-detection impairment is associated with disordered speech in patients with discourse coherence disturbance.
With respect to Study 2, the major area of concern was the behavioural task used to measure central executive function. Although this task is reliably associated with activation in regions thought to be involved in central executive function (see Study 2a; Collette et al., 1999; D’Esposito et al., 1999), behavioural and self-report evidence suggests that this task was very difficult for patients with schizophrenia. Four of the five patients in Study 2b performed at floor level on this task. The finding that all patients showed activation in the prefrontal cortex suggests that they were able to perform the task to some extent. However, in future studies of patients with schizophrenia, this task should be modified to enable a wider range of performance in these patients. The second limitation of Study 2 was the limited analysis of the results. Although the analysis conducted was able to test the hypothesis that there is a specific dorsolateral prefrontal deficit in patients with discourse coherence disturbance and used functional connectivity analysis to investigate fronto-temporoparietal connectivity, it did not address the issue of effective disconnectivity in these patients. Further studies using structural equation modelling to investigate effective disconnectivity in patients with discourse coherence disturbance are warranted.

With respect to Study 3, the greatest problem was the poor signal-to-noise ratio in the data. There was a lot of variability in the ERP data, particularly in the patients without discourse coherence disturbance and the control group. This could be overcome by testing more subjects and having more trials so that a greater number of errors are elicited.

Finally, with respect to all three studies, there is a problem of limited generalisability due to the small samples tested. The approach of this thesis was to test relatively small numbers of patients with similar symptoms in order to account for the variability of symptoms in patients with schizophrenia. However, based on the results of these studies, further studies testing larger numbers of carefully selected patients are
warranted. The results of such studies would provide information about the
generalisability of the findings presented in this thesis.

6.7 Summary

The findings of this thesis suggest that discourse coherence disturbance
symptoms in schizophrenia have a similar origin to speech disorder symptoms in
patients with dorsolateral prefrontal lesions. However, on the basis of these results, it is
hypothesised that the symptoms of patients with discourse coherence disturbance are
due to disruption to a network encompassing dorsolateral prefrontal and temporoparietal
regions, rather than to a specific deficit in dorsolateral prefrontal function. Lack of
effective communication between the anterior cingulate and the dorsolateral prefrontal
cortex underlies the disruption to this network by preventing the necessary modulation
of frontal-temporoparietal interaction. The result of this disconnection is a cognitive
and linguistic profile whereby patients with discourse coherence disturbance exhibit
some of the cognitive deficits found in patients with dorsolateral prefrontal
impairments, but do not resemble these patients on physiological measures. Patients
with discourse coherence disturbance exhibit symptoms, such as impaired semantic
monitoring, consistent with disrupted cingulate-dorsolateral and frontal-temporoparietal
networks.

Further research exploring the connectivity between brain regions including the
anterior cingulate, the dorsolateral prefrontal cortex, and temporoparietal regions in
patients with discourse coherence disturbance would enable this hypothesis to be tested.
The results of this thesis provide a useful theoretical framework for investigating
disturbed effective connectivity between brain regions in discourse coherence
disturbance. It is predicted that the network between the dorsolateral prefrontal cortex
and temporoparietal regions via the basal ganglia and thalamic regions is disrupted. The
cause of this disruption is impaired communication between the anterior cingulate and the dorsolateral prefrontal cortex, this communication is important in modulating the network between dorsolateral prefrontal cortex and temporoparietal areas. These predictions provide a causal model which can act as the framework for exploring effective connectivity of these regions in patients with discourse coherence disturbance.
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Appendix 1. Questions used to elicit speech sample for thought disorder rating taken from SCAN.

What do you really enjoy about life?
Do other people seem to enjoy things more than you do?
What upsets you?
What makes you sad?
What irritates you or makes you angry?

What do you find interesting?
What do you spend a lot of time thinking about?
What would you like to know more about?
Have you read the newspapers, or listened to the news on TV or radio recently?
Can you tell me about a big news story you have heard about recently?

Who do you spend time with?
Do you usually do things alone or with other people?
Some people like to be with others: some people prefer to be alone. how would you describe yourself?
Why do you prefer to be alone?
Do you get lonely sometimes?
Do you want to spend more time with people?
Do you seek people out?
Do you usually wait for others to ask you to do something with them?
When you get together with people, who decides what to do?
When you spend time with others, do you initiate it, or do they?

Do you have trouble interacting with other people?
Do other people make fun of you or tease you?
How confident do you feel dealing with other people?
Appendix 2. Scoring rules for clustering and switching.

Four scores were calculated for verbal fluency:

*Total number of correct words generated (total correct).* This was calculated as the sum of all words produced excluding errors and repetitions.

*Percent of switches.* This was calculated as the total number of transitions between clusters, including single words for the three trials. Errors and repetitions were included. This total was used to calculate the percent of the total correct which were switches.

*Percent of related words.* This was calculated as the total number of words which were related phonemically. Errors and repetitions were included. This total was used to calculate the percent of the total number of correct words which were related.

*Mean cluster size.* This was calculated as the mean number of words per cluster. Errors and repetitions were included.

**Clustering**

Clusters consisted of successively produced words that shared any of the following characteristics:

1. *First letters:* at least two successive words beginning with the same two letters such as “fill, finish”.

2. *Rhymes:* words that rhyme such as “song, strong”

3. *First and last sounds:* words differing by only a vowel sound regardless of the actual spelling such as “fit, fight, fate”

4. *Homophones:* at least two successive words with the same sound but different spellings such as “bear, bare” as indicated by the participant.
Appendix 3. Word pairs for semantic priming task.

Set 1

<table>
<thead>
<tr>
<th>Unrelated prime</th>
<th>Indirectly related prime</th>
<th>Directly related prime</th>
<th>Target</th>
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<tbody>
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<td>insect</td>
<td>cube</td>
<td>sugar</td>
<td>spice</td>
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<td>wasp</td>
<td>ceiling</td>
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Unrelated filler word pairs.

- election/yellow
- debate/grass
- strawberry/fat
- plum/word
- apricot/heavier
- tale/peg
- fish/bare
- full/type
- cough/bone
- marsh/life
- destiny/sit
- fuel/raincoat
- question/meat
- cement/stew
- response/site
- remain/drawers
- few/rider
- boat/bank
- maths/forest
- bronze/western

- major/cage
- deceit/walking
- salt/feet
- charter/ruby
- butter/vote
- green/argue
- short/fields
- sentence/pudding
- lighter/peach
- tent/story
- thread/chips
- touch/empty
- back/cold
- home/swamp
- stand/future
- umbrella/petrol
- steak/answer
- beef/concrete
- building/reply
- chest/stay
Appendix 4. Sentences used in the context naming task (each word is followed by an indication of which condition it was, ie, probable ending (pr), possible ending (po), or anomalous ending (an)).

| The commuter ran to catch the | train (pr) | bird (po) | trap (an) |
| They climbed into the house through the | routine (an) | window (pr) | hole (po) |
| The couple adopted the | cupboard (an) | routine (po) | child (pr) |
| The doctor visited the | hospital (pr) | matches (an) | cupboard (po) |
| The accountant balanced the | matches (po) | books (pr) | smell (an) |
| The interpreter learned the | smell (po) | hole (an) | language (pr) |
| The bartender served the | drink (pr) | cannon (an) | ace (po) |
| The cowboy fired the | cannon (po) | gun (pr) | whale (an) |
| The ship was in the | glove (an) | trap (po) | harbour (pr) |
| The baker smelled the | bread (pr) | ace (an) | glove (po) |
| The boy was bitten by the | whale (po) | dog (pr) | factory (an) |
| The man made tea in the | bird (an) | factory (po) | pot (pr) |
| The dentist filled the | tooth (pr) | truck (po) | rain (an) |
| The carpenter drove in the | rain (po) | start (an) | nail (pr) |
| The gardener dug with the | auction (an) | spade (pr) | plate (po) |
| The criminal was sent to the | jail (pr) | plate (an) | auction (po) |
| The patient swallowed the | truck (an) | lie (po) | pill (pr) |
| The country was ruled by the | bottom (an) | king (pr) | comedian (po) |
| The film was at the | cinema (pr) | bottom (po) | dwarf (an) |
| The meal was prepared by the | dwarf (po) | costume (an) | cook (pr) |
| Water dripped from the | costume (po) | tap (pr) | lie (an) |
The wine was served from the bottle (pr) reward (an) start (po)
The doctor gave the reward (po) prescription (pr) winter (an)
The soldiers flew in the comedian (an) winter (po) plane (pr)
The landlord raised the rent (pr) blinds (po) desert (an)
The train pulled into the desert (po) meal (an) station (pr)
The jewel thieves planned the robbery (pr) horse (an) meal (po)
The teacher punished the horse (po) pupil (pr) barbecue (an)
The politician attended the barbecue (po) hedge (an) meeting (pr)
The barber trimmed the field (an) hair (pr) hedge (po)
The painter fell off the ladder (pr) scales (po) hem (an)
The cold girl turned up the scales (an) hem (po) heating (pr)
The girl skated across the blinds (an) ice (pr) field (po)
The woman dialled the number (pr) baker (po) film (an)
The waiter handed them the film (po) garage (an) menu (pr)
They worshipped in the baker (an) church (pr) garage (po)

**Filler sentences**

The farmer picked an apple from the tree
The skier was buried in the snow
The train went over the bridge
It is the brightest star in the sky
The house was built at the end of the street
The man poured beer into the glass
The flood waters broke over the dam
Filler sentences (cont.)

The plane was buffeted by the wind
Behind the wheel was the driver
The hay was in the barn
The housewife waxed the floor
The politician appealed to the people
The preacher spread the word
The cat drank from the bowl
The pianist played at the concert
We stayed until the end
The car came down the hill
The tennis player found the ball
The awards were presented after the dinner
The librarian read all of the book
The couple made up after the fight
The man paid the bill
The bomb destroyed everything in the area
The house was destroyed by the fire
The team won the game
The city stored water in the tank
The climber reached the top
The whale was injured by the harpoon
The body was stolen from the grave
The comb was on the table
The game warden fined the poacher
Filler sentences (cont.)

The general revised the plans
The skier lived in the house
The doctor gave the injection
The fisherman exceeded the limit
She ordered the dress from the shop
The tree was uprooted in the storm
The lamp provided the light
Music blared from the speaker
The witness confirmed the story
The antiseptic killed the germs
The radiation caused the sickness
The singers clapped their hands to the beat
The man put his leg in the trousers