THE NEUROCOGNITIVE CORRELATES OF FORMAL THOUGHT DISORDER IN SCHIZOPHRENIA.

by

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Abstract

Formal thought disorder is among the pathognomonic symptoms of schizophrenia, presenting as irregularities in the structure of speech that result in disorganized or incoherent discourse. Evidence from neuroimaging and behavioural research indicates abnormalities in semantic, linguistic and executive processing all contribute to the expression of this symptom. Additionally, changes in grey matter volume in regions of cortex supporting these functions, particularly the left posterior superior temporal lobe, correlate with the severity of thought disorder. The program of study this thesis represents was broadly focused, with the goal of increasing our understanding of the neurocognitive basis of this symptom.

Thought disorder has the curious quality of displaying severe dysfunction in one language modality, expression, while function in another, reception, is intact. The first study used functional magnetic resonance imaging to investigate the source of this disparity, by assessing brain activation during listening to speech. The second study expanded on the first, incorporating structural magnetic resonance imaging data into a mediation analysis with the functional and symptom data, to test whether increased activation mediates the association between reduced cortical grey matter volume and severity of thought disorder. As evidence increasingly indicates impaired context processing in thought disorder, the third study investigated the impact of symptom severity on the context-dependant automatic and controlled processes contributing to
word recognition. Finally, the fourth study assessed sub clinical thought disorder in a high schizotypy sample, to determine if speech disorder is among the cognitive variables in this population that exhibit continuity with schizophrenia.

The results indicate that increased cortical activation in the left posterior temporal lobe may underlie preserved receptive language function in thought disorder. A proof-of-principle mediation analysis demonstrated that functional and structural brain abnormalities are interdependent and should be considered as such when investigating the neurophysiology of symptom expression. Deficient processing of linguistic context results in failures in both controlled and automatic processes contributing to word recognition. Finally, the speech abnormalities characterizing thought disorder are not associated with normal variation in schizotypy, indicating they may be predictive of transition to psychotic illness in high risk individuals.
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Co-authorship Statement

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Chapter I

An introduction to thought and language in schizophrenia

1.1 Schizophrenia

Schizophrenia is a debilitating brain disease that disrupts many aspects of mental function, including perception, cognition, and emotion, resulting in a dramatic alteration in the sufferer's subjective experience of the world. As with the other major psychiatric illnesses, it has a profound effect on the most fundamental human attributes: language, thought, affect, and sense of self. Approximately 1% of the population worldwide will develop schizophrenia, usually during late adolescence or early adulthood (WHO, 1996). The course of the illness is one of chronic social and cognitive decline, marked by periods of acute psychosis.

Factor analysis has demonstrated that the symptoms of schizophrenia cluster in three distinct profiles or syndromes (Liddle, 1987). The classic psychotic symptoms include auditory hallucinations, or 'hearing voices', and delusions, which are firmly held false beliefs based on distortions of reasoning or misinterpretations of perceptions or experiences. Together, these are the positive symptoms of schizophrenia, so called because they represent an addition to normal experience (Andreasen & Olsen, 1982; Crow, 1980; Liddle, 1987; Wing, Cooper, & Sartorius, 1974). In contrast, affective flattening, alogia (reduced speech) and avolition (loss of motivation) make up the negative symptoms of schizophrenia, representing a deficit of normal function
Disorganization is the third syndrome. While this refers to a general disorganization in thought and behaviour, it is primarily expressed as a symptom called formal thought disorder (more commonly and hereafter simply thought disorder).

Thought disorder manifests as a variety of errors and abnormalities in spoken language which render speech difficult to comprehend (Andreasen, 1979a; Bleuler, 1911/1950; Kraepelin & Defendorf, 1902; Liddle, 1987). Accordingly, assessment of thought disorder is based on speech, although there are also measures of nonverbal disorganized behaviour. For example, thought disordered subjects perform strangely on an object sorting test, classifying unassociated objects as belonging together (Harrow et al., 2003).

Each of these symptoms does not necessarily manifest in every patient, and some, particularly the positive symptoms, may appear in a highly personalized form. As symptom expression is so variable and often individualistic, there is no single definitive symptom profile. Diagnosis of schizophrenia requires consideration of a range of signs and symptoms, in conjunction with impaired social and occupational functioning (APA, 1994). Given this heterogeneity in psychopathology, it is imperative that research into the cognitive basis of schizophrenia addresses discrete symptoms. Evaluating cognition in groups of undifferentiated schizophrenia patients, while possibly providing information
about fundamental disease processes, will almost certainly obscure the specific deficits that underlie symptom expression.

1.2 Thought Disorder

The ‘formal’ that is usually dropped from the term thought disorder refers to a derangement of the form or structure of thought. This fragmentation of mental activity is characterized primarily by its effects on speech, which range from odd word use to a complete loss of meaning. Approximately 80% of individuals with schizophrenia present with thought disorder during some phase of their illness (Marengo & Harrow, 1987). Its severe form, such that speech is incomprehensible, is a rare manifestation of acute psychosis. A much larger proportion of patients show intermittent signs of moderate to mild thought disorder in both the chronic and acute phases, which may increase in frequency with length of illness (Harrow & Marengo, 1986; Marengo & Harrow, 1987). The severity of disorder observed is dependent on multiple external factors including, but not limited to, the topic of discussion, rapport with the conversation partner, and the affective state of the patient.

There are many hallmarks of thought disorder, practically never seen in concert, which primarily seem to reflect disturbances in lexical-semantic processing and discourse planning. The speech of patients with this symptom may be illogical, lacking in substance, or completely incomprehensible. For example, when a patient who participated in one of the studies presented in this thesis was asked to describe a
picture of a tree and small rowboat next to a stream, in which there were no people, he responded:

“Well, I think we got murder here. Tons of murders out here. I think this is where nature kills things that cause problems. Nature kills, that happens. They even have some sort of things, are allergic, ‘cause allergies on these things, they have no choice but to kill them on the other side of the river, put the bad forces out and die. Um, nature, I assume people completely have mastered that times, wipe out all the weak points, bad from the good. But they still won’t get challenges at all. So maybe they sent more on to make sure the tree they see is like clean, make sure there’s no diseases and so on.”

1.2.1 Describing and measuring thought disorder

Thought disorder is noted in the earliest descriptions of the illness. Kraepelin provided the first account of schizophrenia as a disease entity, that he called *dementia praecox* (Kraepelin, 1896/1919). This translates to ‘early dementia,’ a name that reflects the course of the illness: early onset followed by chronic decline. In Kraepelin’s view, thought disorder was the result of a tendency to follow local or oblique associations instead of maintaining a discourse plan. This resulted in a continual shifting of topic away from the original point, a phenomenon he called *derailment*. Bleuler, who renamed the illness schizophrenia, believed disorganization reflected a central disease process (Bleuler, 1911/1950). In his conceptualization, *loosening of associations*, or an
alteration of the normal links between thoughts and ideas, was primary to the illness. Thought disorder was the spoken manifestation of this alteration in thinking.

Other researchers since have provided varying accounts, of which McKenna and Oh have given a thorough accounting (McKenna & Oh, 2005). They note a handful of studies that stand out as having had significant influence over subsequent research or the definition of the symptom. *Overinclusivity* is a term proposed by Cameron that describes an inability to maintain conceptual boundaries, which he believed was the basic disturbance in thought disorder (Cameron, 1944). An emptiness in the speech of some patients was first noted by Wing, who introduced the concept of poverty of speech content (Wing, 1961). Seeking a fresh perspective, Harrow and colleagues focused on description of speech abnormality, which they suggested was a reflection of bizarre-idiosyncratic thinking (Harrow, Lanin-Kettering, Prosen, & Miller, 1983; Marengo, Harrow, Lanin-Kettering, & Wilson, 1986). Several important contributions came from their work, including recognition of stilted speech and the potential influence of impaired social cognition and executive dysfunction on thought disorder (McKenna & Oh, 2005).

While various methods of assessment were developed after thought disorder was initially described, these tended to focus on one particular type of deficit (e.g. abstract and metaphorical thinking; Gorham, 1956), or one theoretical perspective (e.g. the overinclusivity hypothesis; Payne & Friedlander, 1962). Recognizing that thought disorder is highly variable and includes wide-ranging abnormality, Johnson and Holzman
developed the Thought Disorder Index (TDI), a scale encompassing all aspects of thought disorder (Johnston & Holzman, 1979). However, Andreasen's Thought, Language and Communication (TLC) scale, published the same year as the TDI and with the same intentions, has become the standard assessment tool due to ease of use and theoretical neutrality (Andreasen, 1979a). A more recent instrument (used in the studies presented in this thesis), the Thought and Language Index (TLI), is based on both the TDI and TLC, but provides a briefer assessment and was designed to be sensitive to subtle abnormality (Liddle et al., 2002).

1.2.2 The current definition

The modern definition of thought disorder is based on the comprehensive set of terms developed to accompany the TLC (Andreasen, 1979a). A conscious effort was made to provide terms that describe the clinical phenomena without making inference about the underlying psychology. For example, Bleuler's *loosening of associations* was not included, despite wide use, as it describes a hypothetical psychological process and not observable behaviour. Definitions were provided for 18 speech signs associated with thought disorder. As many of these behaviours are observable in healthy people, rating speech as abnormal is subjective and requires reference to social convention and the effectiveness of communication. Summarised definitions of the terms (underlined) and examples where helpful are given below. The speech examples provided here are Andreasen's own, from the original publication (Andreasen, 1979a).
Poverty of speech is a reduction in the amount of spontaneous speech produced. Speech is often exceedingly brief, concrete and unelaborated.

Poverty of content of speech is seen in speech that, although seemingly of normal quantity, conveys very little information. Speech may be vague, repetitive, overly abstract or concrete, or stereotyped.

Pressure of speech is an increase in the amount and speed of talking, such that it exceeds social convention. The patient often speaks very quickly and is difficult to interrupt.

Distractible speech is characterized by frequent change of topic, often interrupting an unfinished sentence, to talk about nearby stimuli (such as an object in the room or the interviewer’s clothing).

Tangentiality refers to the tendency to respond to questions in an oblique, tangential or irrelevant manner. 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. So I don’t know whether I’m Irish or French or Scandinavian or I don’t, I don’t believe I’m Polish but I think I’m, I think I might be German or Welsh. I’m not but that’s all speculation and that that’s one thing that I would like to know and is my ancestors you know where did I originate. But I just never took the time to find out the answer to that question.”
Derailment is related to the concept of loose associations, and describes speech that moves between topics that are only tenuously or idiosyncratically related or are unrelated, gradually getting further away from the original point. Example – Interviewer: “What did you think of the whole Watergate affair?” Patient: “You know I didn’t tune in on that, I felt so bad about it. I said, boy, I’m not going to know what’s going on in this. But it seemed to get so murky, and everybody’s reports were so negative. Huh, I thought, I don’t want any part of this, and I was I don’t care who was in on it, and all I could figure out was Artie had something to do with it. Artie was trying to flush the bathroom toilet of the White House or something. She was trying to do something fairly simple. The tour guests stuck or something. She got blamed because the water overflowed, went down into the basement, down, to the kitchen. They had a, they were going to have to repaint and restore the White House, the enormous living room. And then it was at this reunion they were having. And it’s just such a mess and I just though, well, I’m just going to pretend like I don’t even know what’s going on. So I came downstairs and ‘cause I pretended like I didn’t know what was going, on I slipped on the floor of the kitchen, cracking my toe, when I was teaching some kids how to do double dives.”

Incoherence is when speech becomes incomprehensible due to seemingly random word choice and/or unusual sentence construction.

Example – Interviewer: “What do you think about current political issues like the energy crisis?” Patient: “They’re destroying too many cattle and oil just to make soap. If we
need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should get pop, but the best thing to get is motor oil, and money. May as well go there and trade in some pop caps and, uh, tires, and tractors to car garages, so they can pull cars away from wrecks, is what I believed in.”

Illogicality is seen in statements of non-linear, non sequitur, or faulty inductive reasoning.

Clanging refers to speech that appears to be guided according to the sounds of words rather than their meaning, resulting in rhyming, alliteration, and word repetition.

Neologisms are novel words or private terminology, whose derivation cannot be inferred from the word itself. Example – Patient: “I got so angry I picked up a dish and threw it at the geshinker.”

Word approximations may be real words used in unconventional ways, or new words whose meaning is clear. Examples – “handshoes” to mean gloves, “time vessel” to mean watch.

Circumstantiality is speech that is very indirect, often overly detailed, but which does retain or return to the main topic.

Loss of goal is when a patient fails to complete expression of a thought or idea, usually by drifting away from the topic; often occurs in association with derailment.

Perseveration is the unnecessary or irrelevant repetition of words, phrases or ideas.
Echolalia is repetition of heard speech, often that of the interviewer.

Blocking is when speech is interrupted mid-stream, with the patient reporting that he has forgotten what he wanted to say.

Stilted speech is that which is overly formal or pedantic, due to word choice, excessive politeness and exceedingly precise or formal grammar.

Self-reference is when the patient repeatedly and inappropriately refers the topic of conversation back to himself.

1.2.3 Incidence of thought disorder

Initially, thought disorder was characterized as uniquely schizophrenic, and was believed to represent the expression of a singular dysfunction underlying the illness (Bleuler, 1911/1950). It is now understood as a cluster of speech abnormalities which are observable in other medical populations, in particular bipolar disorder. The profile of thought disorder expressed in bipolar disorder is somewhat different than that seen in schizophrenia, with an increased presence of pressure of speech and distractibility associated with mania, but there is a great deal of overlap (Andreasen, 1979b; Cuesta & Peralta, 1993; Holzman, Shenton, & Solovay, 1986; Solovay, Shenton, & Holzman, 1987). Depression is associated with poverty of speech, but not clearly with any of the other signs of thought disorder (Andreasen, 1979b). Other populations in which disorganized speech abnormalities may be seen include delirium, epilepsy, autism and Asberger’s syndrome (McKenna & Oh, 2005). As with depression and bipolar disorder, these tend
to have some commonalities with, but not complete concordance to, thought disorder as seen in schizophrenia.

Many of the features of thought disorder are also observable in healthy individuals at levels that do not significantly impair communication, and thus are not clinically relevant (Andreasen, 1979b; Johnston & Holzman, 1979; Liddle et al., 2002). The presence of quantifiable abnormality in the speech of healthy people indicates that there may be a continuum of disorganisation in speech in the general population. This has important implications for the nature of thought disorder, as it suggests that disorganization arises from common cognitive processes (Liddle et al., 2002).

There have been attempts to associate sub-clinical speech abnormalities in healthy people with personality variables thought to parallel aspects of schizophrenia, such as creativity and schizotypy. One definition of creativity is that it reflects a divergent or overinclusive thinking style, similar to that postulated to underlie derailment in thought disorder (Dykes & McGhie, 1976; Keefe & Magaro, 1980; Leonhard & Brugger, 1998). Some similarities in thought and speech between highly creative and schizophrenic subjects have been demonstrated, though the relationship appears to be stronger with mania (Andreasen, 1987; Andreasen & Powers, 1975; Jamison, 1989).

Schizotypy is a personality trait observable in healthy people, which is defined as a tendency towards schizophrenic-like perceptual experiences, thought patterns and beliefs (Eckblad & Chapman, 1983; Kwapi, Miller, & Zinser, 1997). Schizotypy in healthy
Subjects is also associated with the divergent style of thinking found in creative and disorganized thought, indicating there may some continuity with schizophrenia (Leonhard & Brugger, 1998; Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001; Schulberg, French, Stone, & Heberle, 1988; Weinstein & Graves, 2001, 2002). A few studies have found evidence of thought disorder in subjects with extremely high schizotypy (Allen & Schulberg, 1989; Coleman, Levy, Lenzenweger, & Holzman, 1996). It isn’t clear if these individuals truly represent a healthy sample, however, as extreme high schizotypy is associated with an increased risk of psychotic illness (Gooding, Tallent, & Matts, 2005; Kwapil et al., 1997; Miller, Lawrie, Byrne, Cosway, & Johnstone, 2002). First-degree relatives of schizophrenia patients also have an elevated risk of illness, increased schizotypal traits and greater speech abnormalities (Johnston & Holzman, 1979; Kendler, McGuire, Gruenberg, & Walsh, 1995; Shenton, Solovay, Holzman, Coleman, & Gale, 1989).

The findings of speech abnormality in schizotypal subjects and family members have significant implications for risk assessment, as these are both groups with an elevated risk of illness. There is currently a trend in schizophrenia research towards improving identification of the prodromal phase of the illness, as it is thought that medical intervention before the onset of frank psychotic symptoms may improve long term prognosis (e.g. Broome et al., 2005; Owens & Johnstone, 2006; Yung & McGorry, 1996; Yung et al., 2003). Present risk assessment tools have a success rate of approximately 25-30% in predicting transition; this is the proportion of those identified
as high-risk who actually become ill (Broome et al., 2005; Yung et al., 2003). As just 1% of the general population will develop schizophrenia, such assessments represent a significant ability to identify high-risk individuals. Although the schizotypy research suggests speech assessment could contribute to successful prediction of illness, language function is not included in current risk assessment interviews. As yet, no studies of thought disorder have been undertaken in a clinically-defined high risk sample, nor is there any empirical description of speech abnormality in healthy people.

1.3 Thought or language?

The reliance on speech to assess thought disorder has resulted in controversy over whether the primary dysfunction underlying disorganization is one of thought or of language. This issue was first raised by Chaika, a linguist who noted that many of the abnormalities present in disorganized speech were qualitatively similar to those seen in aphasia, and even had some correspondence to normal speech errors (Chaika, 1974). She proposed that disorganized speech reflected language processing abnormalities, although she also noted that it did not correspond exactly to any of the known aphasias.

Direct comparison between aphasic and thought disordered patients has demonstrated several parallels between aphasic and disorganized speech, while emphasizing significant differences. A study of blind ratings of schizophrenic and aphasic speech found these were difficult but not impossible to distinguish, with the groups displaying many of the same types of deficits in different proportions (Faber et
Relative to those with aphasia, the schizophrenia subjects demonstrated relatively preserved comprehension and fluency, but increased derailment and tangentiality.

Comparing the performance of thought disordered and aphasic patients on tests of language function have produced similarly ambivalent results: while both groups demonstrate striking impairment in verbal communication, thought disordered subjects show comparatively preserved syntax, naming and comprehension, but reduced spontaneity and relevance (Halpern & McCartin-Clark, 1984; Landre, Taylor, & Kearns, 1992; Lecours & Vanier-Clement, 1976). Another interesting difference is that many thought disordered patients appear unaware of their deficit, while aphasia patients are commonly frustrated by their inability to communicate (Halpern & McCartin-Clark, 1984). A recent study demonstrated that aphasia testing does not differentiate disorganized and non-disorganized schizophrenia patients (Oh, McCarthy, & McKenna, 2002). Across both patient groups in this study, the strongest correlate of performance on the aphasia battery was general intellectual function. This indicates that the cognitive decline commonly seen in schizophrenia contributes to mild language impairment, but does not produce thought disorder. On balance, evidence indicates that while some language deficits exist in schizophrenia, thought disorder is not the result of a discrete, localized dysfunction somewhere within language processing cortex such as commonly underlies aphasia.
1.4 Language processing in thought disorder

1.4.1 Receptive language

In contrast to the at times profound deficit in speech, receptive language functions, including perception and comprehension, are largely preserved in thought disorder. This preservation of function is notable as it occurs despite a reliance on the same neural substrate that supports generative language. There is evidence of mild processing deficits at the acoustic/phonetic level, but these do not seem to interfere with comprehension of spoken language (Holcomb et al., 1995; Kasai et al., 2002; Ngan et al., 2003). In a study in which subjects performed both roles in an instructional conversation, patients had no difficulty in following spoken instructions but were significantly impaired in their ability to give instruction (assessed by whether a control subject could successfully carry out the instructions) (Cohen & Camhi, 1967). The comparisons between aphasia and thought disorder reviewed in Section 1.3 all noted relatively preserved comprehension in schizophrenia as a point of divergence from aphasia (Faber et al., 1983; Halpern & McCartin-Clark, 1984).

There is a mild deficit in comprehension of syntactically complex sentences (discussed in the section following), but this appears to be a function of general cognitive decline or impaired working memory, and is not specifically associated with thought disorder (Bagner, Melinder, & Barch, 2003; Condray, Steinhauer, van Kammen, & Kasparek, 1996; Morice & McNicol, 1985). One receptive function that is significantly impaired in thought disorder is metaphor comprehension (Gregg & Frank, 1967;
Harrison, Spelman, & Mellsop, 1972; Sponheim, Surerus-Johnson, Leskela, & Dieperink, 2003). However, this correlates with executive dysfunction and difficulties with “theory of mind”, and is not associated with language (Brüne & Bodenstein, 2005).

1.4.2 Phonology and syntax

Phonology is preserved in thought disorder; even neologisms follow the rules of pronouncability of the patient’s native language (Chaika, 1974; Lecours & Vanier-Clement, 1976). Although syntactic structure is often said to be normal, both disordered and non-disordered patients have recently been found to produce syntax errors in their speech (Covington et al., 2005; Faber et al., 1983; Halpern & McCartin-Clark, 1984; Oh et al., 2002). Patients were observed to break grammatical rules and omit syntactically important parts of speech more often than healthy subjects, with no difference between the disorganized and non disorganized patients in the frequency of errors.

There is also evidence for reduced syntactic complexity in schizophrenia, as reflected by a higher percentage of simple sentences and fewer deeply embedded clauses in compound sentences in speech (DeLisi, 2001; Fraser, King, & Thomas, 1986; King, Fraser, Thomas, & Kendell, 1990; Morice & Ingram, 1982). Reduced production of complex sentences is associated with a decrease in activation in the right posterior temporal lobe and left superior prefrontal cortex (PFC; Kircher, Oh, Brammer, & McGuire, 2005). These are both regions involved in language: right hemisphere temporal cortex is involved in broad lexico-semantic processing (Mitchell & Crow, 2005), while left PFC contributes to the executive control of language (Binder et al., 1997;
Binder et al., 1995) and syntax processing (Newman, Pancheva, Ozawa, Neville, & Ullman, 2001). Syntactic simplification in speech correlates with reduced comprehension of complex sentences in schizophrenia patients (Morice & McNicol, 1985).

There is no evidence that difficulties with syntax processing are enhanced in or otherwise associated with thought disorder. Syntactic simplification tends to worsen over the course of the illness, as does general cognitive function (King et al., 1990). The link with chronicity and lack of association with thought disorder suggests that syntax processing deficits likely reflect a decline in general cognitive function in schizophrenia (Besche et al., 1997; Oh et al., 2002).

1.4.3 Semantic processing

Normal semantic function is conceptualized according to the network model proposed by Collins and Loftus, in which semantic memory is seen as a network of nodes representing lexical items that are ‘connected’ by associations (Collins & Loftus, 1975). Strong associations equal a close connection between nodes and vice versa; the strength of association may be based on a variety of lexical characteristics such as shared features (bird – bat), category membership (apple – pear), and learned associations (red – stop). Activation within the network proceeds automatically along the basis of the strength of associations and is controlled by two top down processes, facilitation (expectation) and inhibition (Posner & Snyder, 1975; Schneider & Shiffrin, 1977).
A seminal finding in thought disorder research is the increase in semantic priming, or hyperpriming, in disorganized subjects (Manschreck et al., 1988). Semantic priming is the processing advantage conferred during word recognition tasks when the target word is preceded by a semantically associated item, or prime. Thus a word is recognized faster when it follows an associated prime (e.g. recognizing 'coffee' after seeing the word 'tea'), relative to an unrelated or absent prime. Thought disordered subjects have demonstrated both hyperpriming, an enhanced advantage of priming on word recognition, and increased indirect priming relative to non disordered patients and healthy control subjects (Manschreck et al., 1988; Spitzer, Braun, Hermle, & Maier, 1993). Indirect priming is observed when the target and prime are indirectly related via a shared association with a third, unpresented word. For example, the prime 'lion' is indirectly linked to the target 'stripes' by way of the word 'tiger'. These increased priming effects are thought to arise from unregulated automatic spreading activation within the semantic network, due to failures in inhibition (Maher, 1983; Manschreck et al., 1988; Spitzer et al., 1993).

The enhanced priming effect became contentious when several follow up studies were not able to replicate it (Barch et al., 1996; Ober, Vinogradov, & Shenaut, 1997; Vinogradov, Ober, & Shenaut, 1992). More recently, Moritz and colleagues have demonstrated that extremely precise timing is required to elicit priming, and that hyperpriming is reliably observed in thought disordered subjects when an appropriate stimulus onset asynchrony is used (Moritz, Mersmann, Kloss, Jacobsen, Andresen et al.,...
Further investigation has revealed that enhanced priming is closely associated with the presence of thought disorder, and is no longer present in patients after their thought disorder remits (Gouzoulis-Mayfrank et al., 2003). A lateralized priming task demonstrated that thought disordered patients show equally enhanced indirect priming in both hemispheres (Weisbrod, Maier, Harig, Himmelsbach, & Spitzer, 1998). Conversely, healthy subjects and non thought disordered patients showed indirect priming for the right hemisphere only (Chiarello & Richards, 1992; Nakagawa, 1991; Weisbrod, Maier, Harig, Himmelsbach, & Spitzer, 1998). Lateralized indirect priming in healthy subjects is thought to reflect greater inhibition within the left hemisphere semantic fields, biasing for close semantic associations, while the right hemisphere remains open to remote associations (Chiarello & Richards, 1992). Disinhibition in thought disorder would thus result in heightened activation of distant associates, the intrusion of which into speech has been proposed to underly loosening of associations, or derailment (Maher, 1983; Weisbrod et al., 1998).

While priming effects represent abnormal semantic activation, others have proposed that thought disorder results from disorganization in the structure of the semantic network (Allen, Liddle, & Frith, 1993; Goldberg et al., 1998; McKay et al., 1996). This type of impairment in semantic memory would result in faulty access to or connectivity between items, producing disjointed activation that spreads to more distant items in the network. A person with an intact semantic memory will consistently
produce similar responses to the same stimuli presented at different times, such as in naming tasks where simple identification of items is required. Intact semantic memory also predicts close adherence to category boundaries and normal associations in verbal fluency tasks, when subjects are asked to produce as many responses as they can that meet specific criteria (e.g. listing all the different fruits one can think of).

Thought disordered subjects produce a wider variety of words on verbal fluency tasks and are less constrained by category boundaries, indicating abnormal structure of semantic association (Allen et al., 1993; Goldberg et al., 1998; Kerns, Berenbaum, Barch, Banich, & Stolar, 1999). A classification task, in which subjects indicate which two of a set of words are most closely associated, also demonstrates an insensitivity to implied category in thought disorder (Barrera, McKenna, & Barrios, 2005; Tallent, Weinberger, & Goldberg, 2001). Thought disordered subjects also made more errors and gave a greater range of responses relative to non disordered and healthy control subjects on a naming task (Leeson, Laws, & McKenna, 2006). This result indicates both impaired access (resulting in errors) and abnormal activation (resulting in increased variety of responses). As with priming, there is preliminary evidence that semantic memory improves when thought disorder remits (Leeson, McKenna, Murray, Kondel, & Laws, 2005).

There are few neuroimaging studies of semantic function in thought disorder. Semantic processing is supported by bilateral (though left lateralized) temporal, parietal and inferior frontal cortex (Binder et al., 1997; Binder et al., 1995; Demonet et al., 1992;
Vandenbarghhe, Price, Wise, Josephs, & Frackiowack, 1996). A distributed posterior network including left inferior, middle and superior temporal cortex, as well as left angular gyrus, appears to be primarily responsible for lexico-semantic processing, while left PFC supports controlled language processes that in a priming task might include semantic matching (Binder et al., 1997; Kuperberg, Deckersbach, Holt, Goff, & West, 2007). Additionally, inferior PFC is associated with executive processes involved in retrieval of semantic information (Fiez & Peterson, 1998).

A study in chronic, undifferentiated patients found reduced left inferior PFC activation associated with processing semantically related words, while unrelated words produced a normal pattern of slightly attenuated activation (Han et al., 2007). When thought disordered subjects were scanned performing a similar task, a different pattern of altered left inferior frontal and posterior temporal activation was observed (Kuperberg et al., 2007). Relative to the controls, the disordered patients showed increases in activation in left inferior PFC for directly related words, and in left STG for indirectly related words, possibly reflecting disinhibited semantic function.

A similar pattern is seen in neuroimaging studies of verbal fluency. As with semantic priming, the main finding in undifferentiated schizophrenia patients is a reduction in left inferior PFC activation compared to controls (Curtis et al., 1998; Curtis et al., 1999), although one study reports increased right hemisphere involvement (Weiss et al., 2004). In contrast, thought disordered subjects show increased left inferior PFC activation relative to controls when performing a verbal fluency task (Assaf et al.,
When making judgements about semantic relatedness, however, increased inferior PFC activation predicted preserved semantic memory (Simmons, Miller, Feinstein, Goldberg, & Paulus, 2005). Further research will hopefully clarify these inconclusive findings.

The repetition potential (RP) is an evoked response potential (ERP) thought to index single word semantic processing, as it is sensitive to semantic features of words such as concreteness and semantic category (Hinojosa et al., 2001; Martin-Loeches, Hinojosa, Gómez-Jarabo, & Rubia, 2001). When using a simple semantic judgement task with single word stimuli (e.g. respond when the word is a type of animal), thought disordered subjects have a significantly reduced RP relative to non disordered and healthy control subjects (Martin-Loeches, Munoz, Casado, Hinojosa, & Molina, 2004; Matsumoto et al., 2005). The reduced RP effect may indicate a failure to adequately process all features of words including those relevant to the task, such as semantic category.

1.4.4 Pragmatic language

The strong link between semantic dysfunction and thought disorder does not explain the full range of abnormality in disorganized speech. Thought disorder is also characterized by significant disturbance at the pragmatic level of language, or the level of intention. Pragmatic language refers both to the natural, social use of language in communication, as well as the link between a speakers' intended meaning and what is
actually said. Context is important in both senses, as it determines the appropriateness of speech and influences immediate speech production.

Reference failures are a common feature of schizophrenic speech that result in a loss of discourse cohesion (Docherty, Cohen, Nienow, Dinzeo, & Dangelmaier, 2003; Docherty, DeRosa, & Andreasen, 1996; Rochester & Martin, 1979). Appropriate referencing is required to clarify the subject of speech, so that the listener will understand who ‘him’ is, or what location is being referred to in phrases such as ‘I have to go there later’. Several types of reference failures are common in schizophrenia, including incorrect assumption of shared knowledge, indirect references, and the use of vague or ambiguous references (Docherty et al., 1996; Rochester & Martin, 1979). However, reference failures have not been observed to occur more frequently or with greater severity in thought disordered subjects (Rochester & Martin, 1979). Recent evidence suggests they reflect impairment in sustained attention in schizophrenia (Docherty, Strauss, Dinzeo, & St-Hilaire, 2006).

Pauses in speech are also markers of cooperativity in language, by facilitating turn-taking and providing content cues (Thomason & Hopper, 1992). Pauses are context dependent in healthy subjects, occurring at predictable points in speech at which planning is required, such as before an embedded clause (Butterworth, 1975; Holmes, 1988). Thought disordered subjects display altered distribution of pauses in their speech, indicating reduced contextual constraint on speech and possibly altered discourse planning (Maher, Manschreck, & Molino, 1983; Rochester, Thurston, & Rupp, 1977;
Spitzer, Beuckers, Beyer, Maier, & Hermle, 1994). A similar loss of contextual influence appears to be at work in the impaired ability to guess content words (nouns, verbs) missing from blocks of text (de Silva & Hemsley, 1977; Honigfeld, 1963). Increased context improved the ability of healthy subjects to guess missing words, but caused the patients' performance to worsen (de Silva & Hemsley, 1977). Missing words in the speech of schizophrenics are also more difficult to predict from surrounding context, relative to the speech of healthy subjects (Salzinger, Portnov, Pisoni, & Feldman, 1970). Unfortunately, no effort was made to relate the findings to thought disorder in these studies, although they were inspired by observations of disorganized speech.

Chapman and Chapman coined the term 'context insensitivity' after noting a preference in thought disorder for the stronger, or dominant, meaning of an ambiguous word, even when context supports the weaker or subordinate meaning (Chapman & Chapman, 1973; Chapman, Chapman, & Miller, 1964). For example, when asked for the meaning of the word “pen” in the following sentence: “When the farmer bought a herd of cattle, he needed a new pen”, subjects with schizophrenia were more likely to choose the dominant meaning of pen, a writing instrument, rather than the context supported subordinate meaning, a fenced enclosure (Chapman et al., 1964). This was interpreted as an enhancement of the normal biases (dominance, meaning strength) that determine the meaning of words, allowing context-inappropriate associations to impinge upon speech. Context insensitivity has been replicated by several different groups (Benjamin & Watt, 1969; Chapman et al., 1964; Strauss, 1975; Titone, Levy, &
Holzman, 2000), and has been shown to be especially pronounced in thought disordered subjects (Bazin, Perruchet, Hardy-Bayle, & Feline, 2000; Blaney, 1974).

In a recent set of studies, Kuperberg has begun to address context insensitivity from a different perspective. Healthy subjects are progressively slower to recognize target words embedded in sentences containing pragmatic, semantic, and syntactic errors (Tyler, 1992). This implies that normal lexical-semantic processing is differentially influenced by these aspects of sentential context. When listening to violated sentences, thought disordered subjects are largely unaffected by the linguistic violations, compared to both healthy controls and non disordered subjects (Kuperberg, McGuire, & David, 1998, 2000). This result was interpreted as evidence of an impaired use of sentential context when processing speech, and has been shown to resolve with improvement in severity of thought disorder (Kuperberg et al., 2000).

In another study, pragmatic, semantic and morphosyntactic violations had to be integrated in order to decide whether a sentence was acceptable (Kuperberg, Kreher, Goff, & McGuire, 2006). The patient group performed normally upon encountering violations, but had difficulty with semantic and syntactic violations when judging acceptability of the sentences. Kuperberg and colleagues suggest that semantic and syntactic functioning is relatively intact, but integrating these two sources of information, necessary to create sentential context, is impaired.

The N400 is an ERP component indexing the expectedness of a word. The amplitude of this component is thought to reflect the effort required to integrate a
word's meaning into the larger context; a larger N400 indicates an unexpected word that is more difficult to integrate with the preceding context (Brown & Hagoort, 1993; Holcomb, 1993). There is evidence for an enhanced or otherwise abnormal N400 in schizophrenia (Andrews et al., 1993; Nestor et al., 1997; Salisbury, O'Donnell, McCarley, Nestor, & Shenton, 2000; Sitnikova, Salisbury, Kuperberg, & Holcomb, 2002), although a few studies have found normal a N400 response (Grillon, Ameli, & Glazer, 1991; Koyama et al., 1991). The only study that explicitly assessed the N400 in relation to thought disorder found no link (Kiang, Kutas, Light, & Braff, 2007). It remains to be seen whether this index of context processing will be useful in describing disorganization.

In an fMRI study, disordered, non disordered and control subjects were required to generate words in order to complete sentences (Kircher, Bulimore et al., 2001). Compared to the other groups, thought disordered subjects showed reduced right temporal activation when generating words. As right temporal cortex is increasingly activated as context complexity develops (Kircher, Brammer, Andreuc, Williams, & McGuire, 2001; Xu, Kemeny, Park, Frattali, & Braun, 2005), this result supports a deficit of context processing in thought disorder. This and the ERP study by Kiang and colleagues (Kiang, Kutas, Light, & Braff, 2007) are the only neuroimaging investigations of context use in thought disorder to date, further work is needed to clarify these results.

The research on the use of context in thought disorder does not include a clear mechanistic explanation for the processing abnormalities as is provided in the semantic
research (e.g. disinhibition within the semantic network). This may be because linguistic context processing is a complex function that requires the participation of more than one system. Higher level language functions including context processing and discourse planning require the support of executive processes such as working memory and inhibition (Gathercole & Baddeley, 1993; Meyer, Wheeldon, & Krott, 2006). These functions have both been implicated in schizophrenia previously; inhibition in particular is associated with thought disorder.

1.5 Executive function

Although there had been previous speculation about the possible role of impaired cognitive function in thought disorder, McGrath provided the first clear hypothesis that executive dysfunction was the primary deficit (McGrath, 1991). He proposed that the language network relies on executive control to perform four important tasks, all of which are impaired in thought disorder: establishing a ‘set’ or goal-oriented plan for speech, shifting set when appropriate, performing moment-to-moment planning and editing of speech production, and monitoring for and correcting errors.

Prefrontal control of language function is moderated by a subcortical loop including parts of the basal ganglia and thalamus; this is demonstrated by the presentation of subcortical aphasia which can arise following damage to the thalamus, putamen or the internal capsule (Alexander & Crutcher, 1990; Alexander, DeLong, &
Strick, 1986; Alexander, Benson, & Stuss, 1989; Crosson, 1985; Crosson, 1992; Nadeau & Crosson, 1997). This prefrontal-subcortical connection is proposed to have a role in thought disorder, due to the similarity in presentation between thought disorder and subcortical aphasia (Crosson & Hughes, 1987). McGrath expanded on this idea, suggesting that thought disordered subjects were not able to activate this processing loop due to neurotransmitter imbalances accompanying psychosis; when neurochemistry normalizes and symptoms remit, language processing is more successful.

Studies using a dimensional approach to investigate executive function in schizophrenia have demonstrated that executive dysfunction correlates with both disorganization and negative symptoms, but not positive symptoms (Liddle & Morris, 1991; O'Leary et al., 2000). Thought disorder has been found to correlate consistently with a few specific executive functions. The most common of these is reduced executive inhibition, as measured with tasks requiring inhibition of an automatic or prepotent response (Barrera et al., 2005; Kerns & Berenbaum, 2002, 2003; Kravariti, Dixon, Frith, Murray, & McGuire, 2005; Liddle & Morris, 1991; Stirling, Hellewell, Blakey, & Deakin, 2006). This is consistent with the disinhibition hypothesis of thought disorder arising from the semantic research.

Other strong correlations exist with context memory (more on this below) (Kerns & Berenbaum, 2002, 2003), sequencing and planning (Barrera et al., 2005; Nestor et al., 1998; Stirling et al., 2006), and the ability to shift set (Barrera et al., 2005;
Nestor et al., 1998; O'Leary et al., 2000). Interestingly, several of these studies also report significant correlations between thought disorder and semantic memory, as indicated with verbal fluency, associative memory and semantic categorization tasks (Kerns & Berenbaum, 2002; Kravariti et al., 2005; Nestor et al., 1998; Stirling et al., 2006). As was indirectly suggested by the comparisons with aphasia, and more directly by the neurophysiological findings, thought disorder seems to have both linguistic (semantic) and executive components. General cognitive impairment (i.e. reduced IQ) in schizophrenia predicts performance on tests of executive impairment (Weickert et al., 2000), and may be associated with thought disorder (Harvey & Serper, 1990; Rodriguez-Ferrera, McCarthy, & McKenna, 2001). Two of the previous studies have controlled for general cognitive function, and both confirm the associations between aspects of executive function (particularly inhibition) and thought disorder remain significant (Barrera et al., 2005; Stirling et al., 2006).

Another influential theory, not specific to disorganization, is that schizophrenia is primarily a disorder of PFC and one of the essential executive functions subserved there, working memory (Goldman-Rakic, 1994). The concept of context memory, one of the correlates of thought disorder listed above, evolved out of this work (Cohen & Servan-Schreiber, 1992). This definition of context is broad, incorporating all information relevant to current behaviour. Context memory is the internal representation of that information. Using tasks that manipulate the context load in working memory, researchers have demonstrated that performance impairments
associated with increasing context demands are associated with disorganization, but not positive or negative symptoms (Cohen, Barch, Carter, & Servan Schreiber, 1999; Kerns, 2007). Cohen and colleagues suggest that the use of context information is selectively impaired in thought disorder, and that the other components of working memory, storage and rehearsal, are not affected (Perlstein, Carter, Noll, & Cohen, 2001). As yet, no explicit cognitive mechanism applying this theory to the production of disordered speech has been proposed.

One final executive function which may figure in thought disorder is sustained attention, or the ability to maintain focussed attention over time. This is conceptually related to distractibility, an aspect of thought disorder that correlates with reference failures (Andreasen, 1979a; Harvey & Serper, 1990). When measured with a simple continuous performance task (CPT), which has low processing demands but requires constant vigilance, sustained attention has also been associated with reference failures (Docherty et al., 2006), speech errors (Ceccherini-Nelli, Turpin-Crowther, & Crow, 2007), and thought disorder (Subotnik et al., 2006). The loss of focus is thought to contribute to a failure to maintain a discourse plan or goal of speech.

Executive function, including working memory, context processing, and inhibition, is primarily associated with PFC (Diamond & Goldman-Rakic, 1989; George et al., 1994; Miller & Cohen, 2001; Smith & Jonides, 1999). ‘Hypofrontality’ (subdued frontal activation) in schizophrenia is observed in neuroimaging studies during performance of tasks requiring executive participation (Weinberger & Berman, 1996). A
decrease in frontal lobe volume, particularly of the left hemisphere, and reduced left inferior dorsolateral PFC activity while speaking are associated with severity of thought disorder (Liddle et al., 1992; McGuire et al., 1998; Vita et al., 1995). This same region, including but not limited to Broca’s area, is activated during semantic decision and sentence- and discourse-level processing, indicating executive involvement with normal language function (Binder et al., 1997; Kerns, Cohen, Stenger, & Carter, 2004).

Neuroimaging investigations of context memory have demonstrated reduced dorsolateral PFC activity in schizophrenia concurrent with deficits in context processing (Barch et al., 2001; MacDonald & Carter, 2003; Perlstein et al., 2001). The reduction in activation was particular to the conditions under which the patients performed worse than healthy controls, when they performed normally there was no difference in prefrontal activation between the groups. Only one of these studies, however, has demonstrated a correlation between the degree of underactivation of prefrontal cortex and thought disorder (Perlstein et al., 2001).

1.6 Neuroanatomy

Post mortem and imaging studies of brain structure in schizophrenia have demonstrated anatomical abnormality in prefrontal and temporal cortex (e.g. Benes, 1991; Benes, Sorenson, & Bird, 1991; Bilder et al., 1995; R. Brown et al., 1986; Crow, Brown, Bruton, Frith, & Gray, 1992; DeLisi et al., 1997; Falkai et al., 1992; Falkai et al., 1995; Rossi et al., 1992; Shenton et al., 1992). These are generally observed as local
reductions in grey matter volume, independent of the overall reduced brain size in schizophrenia (Brown et al., 1986), which often contribute to a reduction in the normal anatomical asymmetry of the human brain (Petty, 1999). The strongest clinical correlate of this reduced asymmetry in schizophrenia is thought disorder (Luchins & Meltzer, 1983).

The planum temporale has been extensively studied regarding its involvement in language function in schizophrenia. This anatomical area is the dorsal, horizontal surface of the posterior superior temporal gyrus (STG), lying within the lateral sulcus between Heschl's gyrus (primary auditory cortex) and the posterior ascending ramus. It is larger on the left than the right in healthy subjects, a pattern which is thought to reflect the left hemisphere's dominance for language (Geschwind & Levitsky, 1968). The planum temporale largely consists of auditory association cortex; lesion and imaging research indicates involvement in early auditory and phonological processing (Binder et al., 1997; Binder, Frost, Hammeke, Rao, & Cox, 1996; Caplan, Gow, & Makris, 1995; Petersen, Fox, Posner, & Mintun, 1988; Wise et al., 1991).

The normal leftward asymmetry of the planum temporale is reduced or reversed in people with schizophrenia (Shapleske, Rossell, Woodruff, & David, 1999; Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001). Some studies have found decreases in overall volume and grey matter in the left hemisphere (Falkai et al., 1995; Hirayasu et al., 2000; Kwon et al., 1999; Rossi et al., 1994), while others have found a relative increase in volume of the right hemisphere (Barta et al., 1997; Rossi et al., 1992). Patients with
thought disorder show a greater loss of asymmetry in this brain region than do patients without thought disorder (Rossi et al., 1994; Vita et al., 1995).

The posterior STG, which includes Wernicke’s area and overlaps the planum temporale, is thought to be important for lexical-semantic processing (Binder et al., 1997; Luke, Liu, Wai, Wan, & Li, 2002). This region also shows reduced volume in the left hemisphere in schizophrenia (Highley, McDonald, Walker, Esiri, & Crow, 1999; Pearlson et al., 1997). Volume changes in the posterior temporal lobe, including reduction on the left and increases on the right, are correlated with the severity of thought disorder (Menon et al., 1995; Rajarethinam, DeQuardo, Nalepa, & Tandon, 2000; Shenton et al., 1992; Vita et al., 1995).

A relatively consistent and striking finding in morphology studies of the brain in schizophrenia is that of enlarged ventricles (Andreasen et al., 1990; Bogerts, 1993; Brown et al., 1986; Vita et al., 1995). It has been suggested that ventricular enlargement is related to tissue loss in or abnormal development of the temporal lobes. Several studies have looked specifically at the temporal horn of the lateral ventricle; some have observed abnormality in schizophrenia (Bogerts, Meertz, & Schonfeldt-Bausch, 1985; Crow et al., 1989), while others have not (Pearlson, 1997; Sommer, Ramsey, Kahn et al., 2001). Similarly, some studies have found no association between ventricular enlargement and severity of thought disorder (Andreasen, Olsen, Dennert, & Smith, 1982), while others have (Shenton et al., 1991).
Left PFC may participate in language processing by playing an executive role in monitoring and adjusting the discourse plan and performing moment-by-moment editing of speech (Binder et al., 1997; Binder et al., 1995). This area is also thought to support verbal working memory (D'Esposito et al., 1995; Petrides, Alivisatos, & Evans, 1995) and context processing (Cohen & Servan-Schreiber, 1992). Although not a consistent finding, at least one study has found PFC volume inversely correlated with severity of thought disorder (Vita et al., 1995).

Another potentially relevant observation is a reversal of the usual left-greater-than-right pattern of asymmetry in the angular gyrus, another region involved in lexical-semantic processing (Binder et al., 1997; Niznikiewicz et al., 2000). Finally, medial temporal lobe structures including the hippocampus and parahippocampal gyrus have smaller volumes in schizophrenia (Nelson, Saykin, Flashman, & Riordan, 1998; Pearlson et al., 1997; Velakoulis et al., 1999). These structures support memory function and are often activated during performance of language tasks that require memory-encoding processes, such as verbal recall (Binder et al., 1997).

1.7 Brain function and laterality

The altered anatomical asymmetry in schizophrenia is mirrored by a reduction in the normal functional lateralization of the brain, thought to reflect a loss of left hemisphere dominance (Crow, 1997). In approximately 95% of the general population, the left hemisphere is dominant for language. Hemispheric dominance results in (and is
often determined by) lateralized performance on a wide variety of neuropsychological and psychophysiological tests, in which the dominant hemisphere has an advantage. Hand preference is also strongly associated with hemispheric dominance and anatomical asymmetry (Annett, 1975; Foundas, Leonard, & Heilman, 1995; Knecht et al., 2000; Merrell, 1957; Tzourio, Crivello, Mellet, Nkanga-Ngila, & Mazoyer, 1998).

Reduced functional lateralization in schizophrenia has been demonstrated with neuropsychological tests including lexical decision (word recognition) and dichotic listening (sound localization), measures of motor asymmetry (i.e. lateralized strength and dexterity), and handedness (Dragovic & Hammond, 2005; Lohr & Caligiuri, 1995; Nelson, Satz, Green, & Cicchetti, 1993; Robertson & Taylor, 1987; Schweitzer, Becker, & Welsh, 1978; Wexler, Giller, & Southwick, 1991). There is an increased incidence of left and mixed handedness in schizophrenia, an effect that is largest in patients with thought disorder (Manoach, 1994). Speech errors and positive thought disorder are also associated with reduced functional laterality, as measured with tests of neuropsychological function (Ceccherini-Nelli et al., 2007; Silverstein, Marengo, & Fogg, 1991; Taylor, Greenspan, & Abrams, 1979). Atypical lateralization is interpreted as reflecting left hemisphere dysfunction, although some have argued that this may not hold when performance or symptom profile are controlled for (Gruzelier, 1999; Sakuma, Hoff, & DeLisi, 1996).

Functional neuroimaging has also found decreased laterality in language and sensory-motor cortex in schizophrenia, most often interpreted as resulting from left
hemisphere dysfunction (Gur & Chin, 1999; Mattay et al., 1997; Sommer, Ramsey, & Kahn, 2001; Sommer, Ramsey, Mandl, & Kahn, 2003). A few studies have looked at thought disorder in particular. The first of these used positron emission tomography while thought disordered subjects spoke about a set of pictures (McGuire et al., 1998). The severity of thought disorder was inversely correlated with the amount of activity observed in left inferior frontal gyrus (IFG) and posterior STG, and bilateral mid cingulate cortex, suggesting inadequate engagement of brain regions important for semantic processing (STG) and control of speech (IFG, cingulate). Subsequent functional magnetic resonance imaging (fMRI) studies of spontaneous speech have replicated the inverse correlation between thought disorder and left posterior temporal cortical activation (Kircher et al., 2001), and also found increased right temporal activation (Kircher et al., 2002).

The anatomical and functional evidence supports an influential hypothesis proposing that schizophrenia results from abnormalities in the neurodevelopmental organization of the brain, in particular lateralization of language function (Crow, 1990, 1997). Although reduced asymmetry is associated with both schizophrenia and thought disorder, the patterns of deficit are not clearly established. It is also uncertain why the primary neurophysiological correlates of thought disorder lie in language processing regions, when language dysfunction does not provide a complete explanation of thought disorder.
1.8 Objectives

As this review has perhaps underscored, the literature on thought disorder is itself rather disorganized. Despite a large volume of studies, very little has been conclusively demonstrated regarding the cognitive basis of thought disorder. Some major themes emerge however, and these point the way forward. The specificity of thought disorder remains undetermined, with similar speech disturbances observable in other psychiatric and neurological patients, and even the general population. The line between individual variation and psychopathology is not clearly demarcated; where that line is drawn may assist in identifying individuals at high risk of psychotic illness.

Structural and functional neuroimaging, and brain morphological studies, report fairly consistent neurophysiological abnormality in brain regions supporting language and executive function in subjects with thought disorder. Often the pattern of deviation reflects a loss of the normal asymmetry characterizing the human brain, supporting a central role of language in the pathology of schizophrenia. Cognitive research also implicates semantic and executive dysfunction in the expression of thought disorder. These two functions converge in language processing. Linguistic context processing in particular relies heavily on executive functions, and has long been associated with thought disorder.

This thesis presents four studies motivated by separate issues covered in this introduction. The first is the puzzle presented by preservation of receptive language in patients exhibiting severe derangement of speech. Study One uses fMRI to investigate
the neural correlates of thought disorder in subjects listening to comprehensible speech, to look for clues as to the basis of this preservation of function. The second study is a voxel-based morphometry analysis of grey matter in the left posterior temporal lobe. The index of grey matter volume derived was used to test whether the known association between left posterior temporal lobe structural abnormality and thought disorder is mediated by activation during receptive language processing, thereby explaining the preservation of function. Study Three is concerned with the loss of contextual influence over speech in thought disorder. A primed lexical decision task with congruent and incongruent sentence primes allows assessment of the mechanisms by which sentential context influences word choice. One of these (inhibition) has been widely studied in schizophrenia and thought disorder, while the other (facilitation) has never been tested. The final study is an assessment of speech in schizotypy, in order to determine if thought disorder falls along a continuum in the general population as suggested by reports of speech abnormality in healthy subjects.
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Chapter 2

Neural correlates of thought disorder during listening to speech

2.1 Preface

Over the last 15 years, evolving neuroimaging methods have allowed an unprecedented view into the neurophysiological correlates of psychopathology. In schizophrenia, thought disorder has consistently been associated with functional and structural abnormalities in brain regions involved in language processing, most often in the left temporal lobe (e.g. McGuire et al., 1998; Shenton et al., 1992). Without exception, these studies were all investigations of generative language. This is not surprising, as thought disorder is an expressed symptom, observable primarily as abnormality in speech. However, receptive language relies largely on the same brain regions that support generative language, including those found to be compromised in patients with this symptom, but is not affected. We were interested in whether fMRI could shed some light on how one function can be so strikingly impaired while the other remains intact, when both rely largely on the same neural substrate.

2.2 Introduction

Thought disorder is a fundamental symptom of schizophrenia, expressed as disturbance in the organization and coherence of speech. Functional brain imaging studies in thought disordered subjects have found abnormal patterns of activity during the production of speech and performance of language-based tasks. These abnormalities suggest a deviation from the normal pattern of hemispheric lateralization of language functions. Specifically, severity of thought disorder has been observed to correlate negatively with activation in the left posterior superior temporal gyrus (Kircher, Liddle et al., 2001; Kircher et al., 2002; McGuire et al., 1998) and positively with activation in the right superior and middle temporal gyri (Kircher et al., 2002) during continuous speech production. A similar reduction in the normal leftward functional lateralization of language has also been observed in schizophrenia during the performance of other language tasks, such as semantic decision and verbal fluency tasks (Sommer, Ramsey, & Kahn, 2001; Weiss et al., 2004).

Abnormal lateralization in thought disorder is also reflected in the anatomy of the cortex. One of the more consistent morphological findings in schizophrenia is reduced posterior superior temporal lobe asymmetry, and severity of thought disorder is inversely related to the degree of grey matter volume reduction in this area (Rossi et al., 1994; Shenton et al., 1992). Posterior superior temporal lobe is one of the classic language processing regions, incorporating Wernicke's area, and is important for both speech comprehension and production (Binder et al., 2000; Binder et al., 1997;
Buchsbaum, Hickok, & Humphries, 2001; Crinion, Lambon-Ralph, Warburton, Howard, & Wise, 2003; Moore & Price, 1999). The linguistic nature of this symptom coupled with these and other findings have led to the proposal that thought disorder reflects abnormality in language function, marked by a decrease in the normal leftward structural and functional asymmetry of brain regions involved in language processing (Crow, 1997; Kircher et al., 2002).

Neuroimaging investigations of language and thought disorder have focused on productive language tasks as this is the domain in which disorder is observed. However, receptive and productive language functions rely largely—though not entirely—on the same brain regions, a key difference being a greater reliance of receptive language on the right hemisphere, particularly at the level of discourse comprehension (Robertson et al., 2000; St George, Kutas, Martinez, & Sereno, 1999). As both functions involve posterior superior temporal lobe processes, the same region in which grey matter density and activation during producing language correlate with severity of thought disorder, it is interesting that thought disorder is not also evident in receptive language. Working memory is also affected in schizophrenia. Increased brain activation has been observed to accompany normal performance on working memory tasks by subjects with schizophrenia; this is thought to reflect compensatory processing (Callicott et al., 2003; Manoach, 2003).

We hypothesized that a similar process may underlie the preservation of receptive language in thought disorder, that is, that compensatory processing allows for
maintenance of this function. If this postulation is correct, severity of thought disorder
should be associated with increased brain activation in receptive language processing
regions. We imaged subjects as they listened to comprehensible speech to test this
hypothesis; specifically, that activity in receptive language processing areas would be
positively correlated with the severity of thought disorder in patients with
schizophrenia.

2.3 Methods

2.3.1 Subjects

Eleven healthy control subjects and 12 patients with schizophrenia were
recruited. Groups were matched for age, IQ as estimated with the Quick Test (Ammons
& Ammons, 1962; Nelson, 1982), and parental socioeconomic status (SES) as
determined with the Hollingshead Index (Hollingshead, 1957). Summary statistics for
these and other sample characteristics are given in Table 1. All subjects were right-
handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), and were
native English speakers with no history of head injury, substance abuse or neurological
disorder. Three patients were receiving typical and 8 atypical antipsychotic medication
and all were stable outpatients with no recent changes to their medication. Patients
with schizophrenia were recruited from the Schizophrenia Day Program at Vancouver
Hospital or through their primary care physician. Diagnosis according to DSM-IV criteria
was confirmed by one of the authors (E.N.). Control subjects were recruited via
advertisements from the University of British Columbia campus. All subjects received 10 dollars per hour remuneration; subjects were screened for MRI compatibility and provided informed written consent before participating. Experimental procedures were approved by the University of British Columbia Clinical Research Ethics Board. A copy of the approval form can be seen in Appendix I.

2.3.2 Procedure

Stimuli were thirty 30-second blocks of speech: 10 English (comprehensible), 10 Mandarin (non-comprehensible), and 10 reversed English (control). The English and Mandarin speech was recorded from a bilingual male speaker fluent in both languages reading trivia about the physical world; the reversed English stimuli were created by reversing the English stimuli using conventional sound editing software. Stimuli were presented pseudorandomly, alternating with 30 seconds of silence and counterbalanced across three 10-minute runs, through insert earphones contained within 30-dB sound attenuating MRI-compatible headphones. As the three conditions were likely to be differentially engaging – comprehensible commanding more attention than either non-comprehensible or reversed speech – a tone detection task was incorporated in an attempt to balance attention. Three or four 1000 Hz tones were embedded in each speech sample at random intervals and subjects were instructed to listen to the auditory stimuli and press a response button when they heard a tone. Although this task may have been distracting during the comprehensible speech, we hoped that it would increase attention during the other two conditions. As this task was simply
intended to maintain attention across the three conditions, it was not included in analysis. We considered including a post-scan memory task to assess whether subjects were listening to the stimuli, but as this would be useful for only one of three conditions we chose not to. The difficulty in assessing memory of non comprehensible speech reinforced our decision to use the tone task to maintain attention. Thought disorder was assessed with the Thought and Language Index (TLI) (Liddle, Ngan, Caissie et al., 2002) and overall symptom severity with the Signs and Symptoms of Psychotic Illness (SSPI) rating scale (Liddle, Ngan, Duffield, Kho, & Warren, 2002).

2.3.3 Neuroimaging

Echo-planar images were collected on a standard clinical GE 1.5 T system fitted with a Horizon Echo-speed upgrade. Conventional spin-echo $T_1$-weighted sagittal localizers were used to view head position and to graphically prescribe the functional image volumes. Functional image volumes sensitive to the blood oxygen-level dependent (BOLD) contrast signal were collected with a gradient echo sequence (TR/TE 3000/40 ms, 90° flip angle, FOV 24 x 24 cm, 64 x 64 matrix, 62.5 kHz bandwidth, 3.75 x 3.75 mm in plane resolution, 5.00 mm slice thickness, 29 slices, 145 mm total brain coverage). The first 4 volumes (12 seconds) collected in each run were discarded to avoid $T_1$ saturation effects.

Functional images were reconstructed offline. Statistical Parametric Mapping software (SPM2, Wellcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/) was used for image reorientation, realignment,
normalization into Talairach stereotaxic anatomical space, and smoothing with a Gaussian kernel (8mm FWHM) to compensate for inter-subject anatomical differences and optimize the signal to noise ratio. Maximum rotation and translation estimates from realignment, were 4 mm and 4 degrees, respectively. The BOLD response for each block of auditory stimuli was modeled as the convolution of a 30 second box-car with a synthetic hemodynamic response function composed of two gamma functions. Beta weights associated with the modelled hemodynamic responses were computed to fit the observed BOLD-signal time course in each voxel using the General Linear Model as implemented in SPM2. Contrasts against baseline were calculated separately for all three conditions in each subject. These contrasts were brought forward to a 2nd level analysis (random effects) to determine the regions of activation for each condition in the two groups.

2.4 Results

All three conditions produced similar patterns of activation relative to baseline in the patient and control groups: posterior superior and middle temporal gyri bilaterally, lateralized to the left. Figure 1 shows the activation observed during listening to English relative to baseline for patients and controls, random effects $p < .05$ corrected for multiple comparisons; cerebral regions, MNI coordinates and voxel-level p-values are given in Table 2. English was associated with greater activation than Mandarin and reversed English for both groups at $p < 0.00001$ uncorrected; cerebral
regions, MNI coordinates and voxel-level p-values for the (English - Mandarin) and (English - reversed English) contrasts are given in Tables 3 and 4, respectively. Neither of the control conditions was associated with increased activity relative to English at this threshold. No significant differences between groups were observed for the baseline or between conditions contrasts.

A whole-brain regression analysis with TLI score entered as a covariate was conducted to identify regions active during listening to English that correlated with thought disorder in patients. This identified a single significant cluster of 54 voxels, spanning the left posterior superior temporal sulcus and middle temporal gyrus (maximum at x y z: -48 -12 -8, cluster-level corrected $p = 0.023$; see Figure 2). No other regions were found to correlate with TLI score, even when the threshold was lowered to $p < 0.05$. The correlation between TLI score and activation (mean beta) in this region while listening to English was $r = .93$. The mean beta value in this region was 2.40 for the patients and 2.02 for the controls, a slight but not significant increase ($p = 0.16$). The regression analysis was repeated for the acoustic control conditions, Mandarin and reversed English, but identified no significant correlations. To test for an association between both overall symptom levels and positive symptom levels with activation during any of the three conditions, SSPI total and SSPI positive scores were separately entered as covariates in regression analyses; no correlations were found.
2.5 Discussion

In this study, while listening to comprehensible English speech, severity of thought disorder in patients with schizophrenia correlated with increased activation in left posterior superior temporal sulcus and middle temporal gyrus. Activation in this region was not associated with thought disorder when listening to either Mandarin or reversed English, or with overall symptomatology. This result contrasts with previous studies of language production, in which thought disorder was associated with decreased activation in this region (Kircher, Liddle et al., 2001; McGuire et al., 1998) or increased activation in the homologous right hemisphere region (Kircher et al., 2002) during continuous speech. A study of speech detection, however, found severity of thought disorder correlated positively with activation in the left temporo-parietal junction (Ngan et al., 2003), while a sentence completion paradigm showed reductions in right temporal and increases in left inferior frontal activation in thought disordered patients (Kircher, Bulimore et al., 2001). This disparity suggests that a reduction in the functional laterality of language may not fully explain this symptom, and that patterns of language-related activation associated with thought disorder are likely task-dependent.

The concept of reduced efficiency in schizophrenia has been introduced in the working memory literature, where in low memory load conditions patients with schizophrenia show greater prefrontal activity than controls and normal performance, whereas at high load conditions patients show a reduction in prefrontal activity with
impaired performance (Cairo, Woodward, & Ngan, 2006; Manoach et al., 1999). This is explained as a shift in the normal inverted-U relationship between memory load and prefrontal activation: in healthy subjects, activity increases commensurate with load until memory capacity is exceeded, at which time both activity and performance drop (Callicott et al., 1999; Goldberg, Berman et al., 1998). In schizophrenia however, the memory system operates at a higher intensity to maintain normal performance at lower load levels and so reaches the capacity threshold earlier; increased activation observed at lower load levels reflects compensatory processing and is a sign of inefficiency in the system.

It is possible that a similar mechanism could explain the apparent preservation of comprehension in patients with thought disorder. Simple speech comprehension is a fundamental element of language, with lower cognitive demands than most productive language functions. An (in)efficiency model would predict that, for this relatively undemanding function, increased activation could compensate for processing deficits resulting in preserved comprehension, while for higher-demand generative language functions such as speech production capacity threshold would be exceeded resulting in reduced activation and impaired performance. Thus, increased left temporal activation in thought disordered subjects during speech comprehension may reflect the compensatory processing necessary to perform normally with an impaired language system. While this group of patients had a slightly higher mean activation than controls in the region correlating with thought disorder, the difference was not significant. This
may reflect the symptomatic heterogeneity of this group. Under the inefficiency model, subjects who are not disordered would not be expected to show greater than normal activation – only those exhibiting the symptom would need to compensate for the underlying functional disturbance.

Our results suggest that thought disorder is associated with abnormal activity when listening to speech; however, these data do not allow direct assessment of between-group differences. The within-groups contrasts of English relative to the control conditions produced roughly similar patterns of activation with both groups showing activation in bilateral temporal cortices. This likely reflects semantic processing, and is consistent with previous findings contrasting speech and non-speech stimuli (Binder et al., 2000; Binder et al., 1997; Demonet et al., 1992). The common focus of activation for all three conditions was the left posterior superior temporal gyrus, a region known to be involved in acoustic and phonological processing (Binder et al., 2000; Demonet et al., 1992; Scott & Johnsrude, 2003). Previous research has found activation in posterior superior temporal gyrus for meaningless speech sounds comparable to that seen in response to comprehensible speech (Binder et al., 2000; Hirano et al., 1997; Wise et al., 1991). While reversed speech stimuli are intended to control for non-phonological acoustic features of speech, there is evidence of partial preservation of phonological information in the acoustic signal. It has been shown, for example, that subjects can phonologically transcribe reversed words with a notable
degree of intra-subject consistency (Binder et al., 2000), and that segment-reversed speech can be comprehensible (Saberi & Perrott, 1999).

If activity observed during the control conditions is primarily due to acoustic or phonological processing, the current correlation between thought disorder and activation when listening to English may reflect abnormal semantic processing. The region of correlation lies almost entirely within the section of left posterior superior temporal lobe implicated in semantic processing, lateral and inferior to the region involved in phonological processing. Both verbal and nonverbal semantic tasks have been found to activate cortex of the left posterior superior temporal sulcus and middle temporal gyrus (Binder et al., 1997; Vandenburghe, Price, Wise, Josephs, & Frackiowack, 1996). Increased semantic priming (Manschreck et al., 1988; Moritz, Woodward, Küppers, Lausen, & Schickel, 2002; Quelen, Grainger, & Raymondet, 2005; Spitzer, Braun, Hermle, & Maier, 1993) suggests that semantic processing is abnormal in thought disorder, and there is evidence that the organization of the semantic network may be disturbed. Unlike healthy subjects, thought disordered subjects fail to use semantic category dimensions to generate words in a verbal fluency task (Aloia, Gourovitch, Weinberger, & Goldberg, 1996; Goldberg, Aloia et al., 1998; Paulsen et al., 1996).

It remains unclear whether temporal lobe functional abnormalities, including semantic processing deficits, are the source of thought disorder or whether they are both secondary to higher level dysfunction. Studies of semantic processing in
schizophrenia have observed reduced inferior frontal activity in addition to overactivation of posterior temporal lobe (Kubicki et al., 2003), and there is evidence of a disconnection between frontal and temporal semantic processing regions (Kim et al., 2005). Recent behavioural studies suggest the strongest predictor of thought disorder is executive dysfunction (Barrera, McKenna, & Barrios, 2005; Kerns & Berenbaum, 2002), but possible interactions between higher-level cognition and language have yet to be explored.
Table 2.1 Sample characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects ((n = 11))</th>
<th>Schizophrenic Subjects ((n = 12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>7:4</td>
<td>7:5</td>
</tr>
<tr>
<td>Age</td>
<td>34.0 ±12.0</td>
<td>35.9 ± 12.6</td>
</tr>
<tr>
<td>IQ (Quick Test)</td>
<td>111.6 ± 14.1</td>
<td>102.7 ± 5.2</td>
</tr>
<tr>
<td>Education (years)</td>
<td>18.4 ± 2.3</td>
<td>15.1 ± 2.4*</td>
</tr>
<tr>
<td>Parental SES</td>
<td>3.0 ± 1.6</td>
<td>3.1 ± 1.7</td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
<td>24.3 ± 6.3</td>
</tr>
<tr>
<td>SSPI (total score)</td>
<td></td>
<td>9.5 ± 5.7</td>
</tr>
<tr>
<td>TLI (total score)</td>
<td></td>
<td>5.0 ± 3.7</td>
</tr>
<tr>
<td>Chlorpromazine equivalent of antipsychotic dose (mg)</td>
<td></td>
<td>412.9 ± 271.4</td>
</tr>
</tbody>
</table>

* \(t(21) = 3.35, p = .003\)
Table 2.2 Localization of activation during listening to English.

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>Region</th>
<th>MNI coordinates</th>
<th># voxels</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>Left:</td>
<td>superior temporal gyrus</td>
<td>-64, -28, 12</td>
<td>54</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inferior frontal gyrus and insula</td>
<td>-36, 12, 4</td>
<td>39</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cerebellum</td>
<td>-20, -76, -44</td>
<td>4</td>
<td>0.005</td>
</tr>
<tr>
<td>Right:</td>
<td>superior temporal gyrus</td>
<td>52, -8, -4</td>
<td>35</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>middle temporal gyrus</td>
<td>48, -28, 0</td>
<td>10</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cerebellum</td>
<td>24, -76, -52</td>
<td>5</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>Left:</td>
<td>superior and middle temporal gyri</td>
<td>-48, -24, 8</td>
<td>142</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>hippocampus</td>
<td>-28, -32, 0</td>
<td>13</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inferior frontal gyrus</td>
<td>-32, 32, 4</td>
<td>3</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Right:</td>
<td>superior and middle temporal gyri</td>
<td>60, -16, 12</td>
<td>200</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>precentral gyrus, inferior frontal gyrus</td>
<td>32, 8, 44</td>
<td>62</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mid cingulate gyrus</td>
<td>12, -28, 40</td>
<td>30</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>caudate nucleus</td>
<td>20, 28, 0</td>
<td>17</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Side</td>
<td>Region</td>
<td>MNI coordinates (x, y, z)</td>
<td># voxels</td>
<td>p</td>
</tr>
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<tr>
<td>Patients</td>
<td>Right:</td>
<td>precentral gyrus</td>
<td>36, -12, 60</td>
<td>9</td>
<td>.003</td>
</tr>
<tr>
<td></td>
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<td>cerebellum</td>
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<td>7</td>
<td>.003</td>
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<tr>
<td></td>
<td></td>
<td>inferior temporal gyrus</td>
<td>40, -52, -8</td>
<td>3</td>
<td>.003</td>
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Table 2.3 Localization of activation for English versus Mandarin.

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>Region</th>
<th>MNI coordinates</th>
<th># voxels</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(x, y, z)</td>
<td></td>
<td></td>
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<tr>
<td>Controls</td>
<td>Left:</td>
<td>postcentral gyrus</td>
<td>-44, -12, 48</td>
<td>62</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>middle temporal gyrus</td>
<td>-60, -56, 0</td>
<td>61</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>superior temporal gyrus</td>
<td>-56, -16, 8</td>
<td>56</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>insula</td>
<td>-28, 16, 4</td>
<td>12</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>supramarginal gyrus</td>
<td>-48, -24, 32</td>
<td>10</td>
<td>.024</td>
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<tr>
<td></td>
<td>Right:</td>
<td>insula, superior temporal</td>
<td>32, -24, 12</td>
<td>219</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>postcentral gyrus</td>
<td>36, -20, 44</td>
<td>126</td>
<td>.000</td>
</tr>
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<td></td>
<td></td>
<td>middle temporal gyrus</td>
<td>44, -40, -4</td>
<td>33</td>
<td>.008</td>
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<td>paracentral lobule</td>
<td>8, -40, 68</td>
<td>19</td>
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<td></td>
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<td>48, 12, 32</td>
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<td>Patients</td>
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<td>middle temporal gyrus</td>
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<td>-32, -32, -8</td>
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<td>-20, -8, 8</td>
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<td>.016</td>
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<td></td>
<td>superior temporal gyrus</td>
<td>-52, 0, 0</td>
<td>4</td>
<td>.030</td>
</tr>
<tr>
<td></td>
<td>Right:</td>
<td>insula, middle temporal gyrus</td>
<td>36, -12, 4</td>
<td>80</td>
<td>.000</td>
</tr>
<tr>
<td>Group</td>
<td>Side</td>
<td>Region</td>
<td>MNI coordinates</td>
<td># voxels</td>
<td>( p )</td>
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<tr>
<td>Patients</td>
<td>Right:</td>
<td>superior temporal gyrus</td>
<td>44, -40, 16</td>
<td>57</td>
<td>.006</td>
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<td></td>
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<td>thalamus</td>
<td>16, -8, 4</td>
<td>16</td>
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<td>middle frontal gyrus</td>
<td>32, 8, 44</td>
<td>10</td>
<td>.016</td>
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<td></td>
<td></td>
<td>postcentral gyrus</td>
<td>48, -12, 32</td>
<td>8</td>
<td>.007</td>
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<td></td>
<td></td>
<td>cerebellum</td>
<td>12, -48, -44</td>
<td>5</td>
<td>.002</td>
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</table>
Table 2.4 Localization of activation for English versus reversed English.

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>Region</th>
<th>MNI coordinates</th>
<th># voxels</th>
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<td></td>
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<td>(x, y, z)</td>
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<td></td>
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<tr>
<td>Controls</td>
<td>Left:</td>
<td>inferior parietal lobule</td>
<td>-48, -36, 40</td>
<td>28</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mid cingulate</td>
<td>-16, -28, 44</td>
<td>18</td>
<td>.001</td>
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<td></td>
<td></td>
<td>postcentral gyrus</td>
<td>-40, -12, 48</td>
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<td>.012</td>
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<td></td>
<td>Right:</td>
<td>putamen, globus pallidus</td>
<td>28, -4, -8</td>
<td>65</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>superior frontal gyrus</td>
<td>20, 24, 40</td>
<td>24</td>
<td>.000</td>
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<tr>
<td></td>
<td></td>
<td>precentral gyrus</td>
<td>36, 0, 52</td>
<td>23</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>superior temporal gyrus</td>
<td>48, -28, 24</td>
<td>14</td>
<td>.001</td>
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<tr>
<td></td>
<td></td>
<td>inferior frontal gyrus</td>
<td>28, 20, 28</td>
<td>8</td>
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Figure 2.1 Regions of activation observed during listening to English for the control group and patient group, corrected $p < 0.05$. 

![Brain Images](image_url)
Figure 2.2 Region of correlation between TLI score and brain activation in patients with schizophrenia during listening to English, cluster-level corrected $p < 0.05$. 
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Chapter 3

Brain activation mediates the association between planum temporale grey matter volume and thought disorder \(^2\)

3.1 Preface

While abnormalities in both brain structure and function are consistently observed in the temporal lobes of schizophrenia patients with thought disorder (e.g. McGuire et al., 1998; Shenton et al., 1992), no previous attempt had been made to qualify the interrelationships among these three variables. Mediation analysis is a statistical method widely used in the social sciences to investigate a specific type of three-way relationship (Baron & Kenny, 1986), and which had never been applied to neuroimaging data. This method tests whether a relationship between two variables is mediated by a third, that is, whether the mediating variable may be the means by which one variable exerts influence over another. The goal of this study was to determine whether language-related activation mediates the association between thought disorder and left superior temporal lobe grey matter volume.

\(^2\)A version of this chapter has been published. Weinstein, S., Woodward, T.S., Ngan, E.T. (2007). Brain activation mediates the association between structural abnormality and symptom severity in schizophrenia. *NeuroImage, 36,* 188-193.
3.2 Introduction

Brain morphological and neuroimaging studies have reported subtle and wide-ranging irregularity in schizophrenia, frequently associated with specific symptom profiles. Among the few consistent anatomical findings reported in schizophrenia is abnormality of left posterior superior temporal cortex (Barta et al., 1997; Falkai et al., 1995; Menon et al., 1995; Rossi et al., 1992; Shenton et al., 1992), including the planum temporale (Barta et al., 1997; Falkai et al., 1995; Rossi et al., 1992). The planum temporale is the horizontal aspect of the superior posterior temporal lobe, it has a leftward asymmetry (Geschwind & Levitsky, 1968), overlapping with Wernicke’s area, and is classically associated with language function. The planum temporale largely consists of auditory association cortex; lesion and imaging research indicates involvement in early auditory and phonological processing (Binder et al., 1997; Binder, Frost, Hammeke, Rao, & Cox, 1996; Caplan, Gow, & Makris, 1995; Petersen, Fox, Posner, & Mintun, 1988; Wise et al., 1991). In his review of the structural, functional and clinical literature regarding the planum temporale, Shapleske points out that the planum temporale likely engages in language tasks as a functional unit, and is not inherently linguistic (Shapleske, Rossell, Woodruff, & David, 1999).

Reduced grey matter volume in left superior temporal cortex, including planum temporale, is associated with an increased severity of thought disorder in schizophrenia (Menon et al., 1995; Rajarethinam, DeQuardo, Nalepa, & Tandon, 2000; Rossi et al., 1994; Shenton et al., 1992; Vita et al., 1995). The finding is robust, despite
methodological variation in the measurement of cortical abnormality, anatomical
definition of brain regions, and assessment of thought disorder. In a recent fMRI study
we observed a correlation between left posterior temporal activation during listening to
speech and severity of thought disorder in schizophrenic patients (Weinstein, Werker,
Vouloumanos, Woodward, & Ngan, 2006). Other investigators have described
correlations between activation in temporal cortex and thought disorder during the
performance of generative language tasks (Kircher, Bulimore et al., 2001; Kircher, Liddle
et al., 2001; Kircher et al., 2002; McGuire et al., 1998).

Although thought disorder has been linked with both temporal lobe function
and grey matter volume separately, the possibility that these three variables may be
interrelated has not been tested. The planum temporale operates at an earlier linguistic
level than that of posterior superior and middle temporal gyri; therefore, the
relationship between planum temporale structural abnormality and thought disorder
may be arbitrated by the degree of activation in the posterior temporal lobe.
Specifically, our hypothesis is that the association between decreased left planum
temporale grey matter volume and greater severity of thought disorder is mediated by
increased activation in left posterior temporal cortex during language processing.

Mediation implies a very specific type of statistically testable relationship that
extends beyond the concept of a partial correlation. True mediation suggests that an
intermediate variable functions as a mechanism by which an independent variable
exerts its influence on a dependent variable. Although this concept is widely recognized
and tested in the social sciences, we are unaware of any investigation to date that has applied the methodology to neuroimaging data. In this study we used a conventional mediation analysis procedure (Baron & Kenny, 1986) to directly investigate the proposal that temporal lobe functioning is the mechanism by which planum temporale structural abnormality influences severity of formal thought disorder.

3.3 Methods

3.3.1 Subjects

Twelve patients with a DSM-IV diagnosis of schizophrenia were recruited from the Schizophrenia Day Program at Vancouver Hospital or through the primary care physician. Subjects were selected according to psychopathology, to produce a sample with a range of thought disorder (from none detectable to severe). Diagnosis according to DSM-IV criteria was confirmed by one of the authors (EN). All were right-handed (Annett, 1967) native English speakers with no history of head injury, hearing loss, substance abuse or neurological disorder. Sample characteristics are described in Table 1. These subjects were recruited to participate in the fMRI study reported on in Chapter 2 (Weinstein et al., 2006); the current paper presents a novel analysis of data gathered for one condition of the original experiment.

Thought disorder was assessed with the Thought and Language Index (TLI) (Liddle, Ngan, Caissie et al., 2002). Subjects were also assessed with the Signs and Symptoms of Psychotic Illness (SSPI) rating scale, a measure of general symptom
severity (Liddle, Ngan, Duffield, Kho, & Warren, 2002). Three subjects were receiving typical and nine atypical antipsychotic medication and all were stable outpatients with no recent changes to their medication. After complete description of the study to the subjects, written informed consent was obtained. Subjects received 10 dollars per hour remuneration. Experimental procedures were approved by the University of British Columbia Clinical Research Ethics Board. A copy of the approval form can be seen in Appendix I.

3.3.2 Functional neuroimaging

All imaging was performed on a 1.5 Tesla General Electric SiGNA scanner. Subjects listened to 30-second blocks of continuous speech stimuli while in the scanner. There were 10 blocks for each of three conditions, English, Mandarin and reversed English. The speech stimuli were recorded from a bilingual male speaker, fluent in both English and Mandarin, reading trivia-type facts about the physical world. Stimuli were presented pseudorandomly, counterbalanced across three 10-minute runs in a block design and alternating with 30 seconds of silence, through insert earphones contained within 30dB sound attenuating MRI compatible headphones. These functional data are described in greater detail elsewhere (Weinstein et al., 2006); only data from the English condition are reported here. Echo-planar images were collected on a standard clinical GE 1.5 T system fitted with a Horizon Echo-speed upgrade. Conventional spin-echo T1-weighted sagittal localizers were used to view head position and to graphically prescribe the functional image volumes. Functional image volumes sensitive to the
blood oxygen-level dependent (BOLD) contrast signal were collected with a gradient echo sequence (TR/TE 3000/40 ms, 90° flip angle, FOV 24 x 24 cm, 64 x 64 matrix, 62.5 kHz bandwidth, 3.75 x 3.75 mm in plane resolution, 5.00 mm slice thickness, 29 slices, 145 mm total brain coverage). The first 4 volumes (12 seconds) collected in each run were discarded to avoid T₁ saturation effects. Functional images were reconstructed offline. Statistical Parametric Mapping software (SPM2, Wellcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/) was used for image reorientation, realignment, normalization into Talairach stereotaxic anatomical space, and smoothing with a Gaussian kernel (8mm FWHM) to compensate for inter-subject anatomical differences and optimize the signal to noise ratio. Maximum rotation and translation estimates from realignment, were 4 mm and 4 degrees, respectively. The BOLD response for each block of auditory stimuli was modeled as the convolution of a 30 second box-car with a synthetic hemodynamic response function composed of two gamma functions. Beta weights associated with the modelled hemodynamic responses were computed to fit the observed BOLD-signal time course in each voxel using the General Linear Model as implemented in SPM2.

3.3.3 Structural neuroimaging

High resolution T1-weighted anatomical images were acquired with a three-dimensional spoiled gradient recall acquisition sequence (124 sagittal slices, thickness 1.5 mm, TR 11.2, TE 2.1ms Fractional Echo, flip angle 20°, FOV 26 x 26 cm, NEX 1, matrix 256 x 256, 15.6 kHz bandwidth). Structural images were processed following an
optimized voxel based morphometry (VBM) protocol (Ashburner & Friston, 2000; Good et al., 2001). VBM is an automated technique that allows for whole brain voxel-wise estimation of tissue volume or concentration. Images were processed on a Linux workstation using SPM2 (SPM2, Wellcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab 6.0 (MathWorks, Natick, MA). Images were segmented into grey matter, white matter and CSF, normalized to a T1 template, smoothed with a 12 mm FWHM kernel and then modulated to reverse the effect of normalization on the voxel intensities. The prior probability maps and MNI template provided in SPM2 were used for segmentation and normalization, respectively. A mask of the left planum temporale was created in MNI space, using the template the structural images were normalized to, using MRIcro (Rorden & Brett, 2000). The planum temporale was defined as the horizontal aspect of the left posterior temporal lobe. The anterior boundary was defined as the transverse sulcus, which separates the planum temporale from Heschl’s gyrus; the posterior boundary was the onset of the posterior ascending ramus. The lateral border was taken to be the superolateral margin of the superior temporal gyrus. As the planum temporale is of a roughly triangular shape, the medial border was defined, of necessity, as the confluence of the transverse sulcus (heading posteromedially) and the posterior border (heading anteromedially). The mask incorporated 25 sagittal slices, from x = -38 to -62, (z = 0 to 16, y = -5 to -35) with a volume of 3.045 cm$^3$ and is illustrated in Figure 2.
3.3.4 Mediation analysis

A mediation model, illustrated in Figure 1 (figure from Baron & Kenny, 1986), was tested to assess the associations among grey matter volume, brain activation and symptom severity following the multiple regression approach described by Baron and Kenny (Baron & Kenny, 1986). There are four steps to establishing mediation. First, demonstrate that the independent variable is correlated with the dependent variable (Figure 1, path c). Second, show that the independent variable is correlated with the mediator (Figure 1, path a). Third, show that the mediator affects the dependent variable (Figure 1, path b). Fourth, demonstrate that the effect of the independent variable on the dependent variable (Figure 1, path c) is significantly reduced or eliminated when the mediator is controlled for. This analysis is accomplished with three regression equations: the dependent variable is regressed on the independent variable; the mediator is regressed on the independent variable; and the dependent variable is regressed on both the mediator and independent variables. Perfect mediation is defined as the case where the independent variable is found to have no effect in the third equation (i.e. regression coefficient = 0); partial mediation is the case where there is a significant reduction in the effect of the independent variable on the dependent variable in the third equation. The Aroian version of the Sobel test is commonly used to assess the indirect effect of the independent variable on the dependent variable via the mediator (Baron & Kenny, 1986). The Sobel test gives a z score reflecting effect size, and an associated p value. In this study, grey matter volume served as the independent
variable, BOLD response during listening to English as the mediator variable, and thought disorder ratings as the dependent variable.

3.4 Results

TLI scores ranged from 1.50 to 12.75 ($M = 5.01$, $SD = 3.67$). SSPI scores ranged from 0 to 19 ($M = 9.50$, $SD = 5.70$). A whole-brain regression analysis of the fMRI data, with TLI score entered as a covariate, was conducted to identify regions active during listening to English speech in which BOLD correlated with thought disorder (cluster-level corrected $p < .05$). One cluster of 54 voxels was significant at this criterion, spanning the left middle-posterior superior and middle temporal gyri (maximum at -48 -12 -8, $p = .02$). No brain regions were associated with thought disorder while listening to Mandarin or reversed English. The regression analysis was repeated, first with SSPI total score as a covariate and again with SSPI positive symptoms subscale score as a covariate, to determine if either overall or positive symptom severity was associated with activation during any of the three conditions; no significant associations were found. A detailed description of the analysis of these functional data, including comparison with healthy controls, is given elsewhere (Weinstein et al., 2006).

Mean activation (beta) in the left posterior temporal cluster identified in the TLI regression analysis was extracted for each subject and ranged from 0.99 to 4.16 ($M = 2.44$, $SD = 1.02$). Mean grey matter volume (voxel intensity) within the left planum temporale mask was extracted from each subjects' normalized grey matter structural
image. Values ranged from .32 to .62 (M = 0.44, SD = 0.09), and indicate the average proportion of grey matter within each voxel in the mask. The functional cluster and planum temporale mask are shown in Figure 2. As with activation in the functional cluster, grey matter volume within the mask did not correlate significantly with either the SSPI total score, $r = -0.19, p = .55$, or SSPI positive subscale score, $r = -0.19, p = .55$.

Independent samples t-tests conducted to test for sex differences in this mixed sample found no significant differences in mean activation, $t(10) = 0.13, p = .90$, grey matter volume, $t(10) = 1.47, p = .17$, or TLI score, $t(10) = 0.17, p = .87$.

The mediation analysis procedure was followed as described in the methods section above. Grey matter volume within the planum temporale was a significant predictor of severity of thought disorder, $r = -0.56, p = .03$ (Figure 3a), as well as activation in the functional cluster, $r = -0.51, p = .04$ (Figure 3b, path a). As found in the functional analysis, mean activation in the functional cluster was also a significant predictor of severity of thought disorder, $r = 0.89, p < .001$ (Figure 3b, path b). The correlations between TLI score and both functional activation and grey matter volume are illustrated in Figure 4. When thought disorder was regressed on grey matter volume and mean activation simultaneously, the regression coefficient for grey matter volume was reduced to $r = -0.13, p = .45$ (Figure 3b, path c), a significant reduction (from $r = -0.56$) according to the Aroian version of the Sobel test, recommended by Baron and Kenny (Baron & Kenny, 1986), $z = -1.73, p = .04$. Effect size is exactly equivalent to a $z$ score of a standard normal distribution, thus our $z$ score of 1.73 shows that the reduction we
saw is 1.73 standard deviations above the null hypothesis of no reduction. To assess the possibility of reciprocity within the mediation model, i.e. that grey matter volume mediates the association between functional activation and thought disorder, we tested the mediation model with functional activation as the independent variable and grey matter volume as the mediator. The regression coefficient for activation, with TLI score as the dependent variable, dropped slightly from $r = .89$, $p < .001$, to $r = .82$, $p = .001$. The Sobel test found this decrease to be insignificant, $z = 0.65$, $p = 0.51$. In this sample, grey matter is not a significant mediator of the association between functional activation and severity of thought disorder.

3.5 Discussion

The objective of this study was to investigate whether the association between decreased left planum temporale grey matter volume and severity of thought disorder is mediated by increased activation in left posterior temporal cortex during language processing. Until now, the relationships among these three variables had only been investigated with a pair-wise approach. Brain activation during a simple listening task correlated positively with thought disorder in this sample, and we replicated the negative correlation between grey matter volume in the left planum temporale and severity of thought disorder described in earlier reports. We also observed a significant correlation between planum temporale grey matter volume and posterior temporal lobe activation, which has not been previously reported.
The mediation hypothesis was confirmed by a significant reduction in the strength of the association between grey matter volume and severity of thought disorder when functional activation was taken into account. This suggests that the structure-symptom association is partially mediated by the degree of activation in left posterior superior temporal gyrus during language processing. In other words, neural activation acts as a mechanism by which cortical volume changes are expressed in thought disorder. A limitation of the study is the small sample size – low power means that the mediation effect may not hold up with larger samples, as the correlation that reduced to nonsignificance may become significant when power is increased. On the other hand, the correlations that were significant were so despite reduced power, possibly reflecting large effects that would be expected to replicate in larger samples. Further investigation is needed to confirm the present findings.

The two regions included in the investigation, planum temporale and the left posterior temporal cluster, are anatomically distinct. The posterior temporal cluster is anterior and inferior to the mask created of the planum temporale; there is only a very narrow region of overlap between the anterior, inferior portion of the mask and the superior, posterior edge of the posterior temporal cluster. The planum temporale is primarily engaged in acoustic and phonetic processing and does not appear to be a dedicated language region, as it responds to sounds such as pure tones (Binder et al., 1996) and signal correlated noise (Wise et al., 2001).
The region of functional correlation, on the other hand, is located on the lateral posterior superior temporal gyrus, an area implicated in phonetic, phonological and lexical-semantic processing (Binder et al., 2000; Binder et al., 1997; Scott, Blank, Rosen, & Wise, 2000; Vandenburghe, Price, Wise, Josephs, & Frackiowack, 1996; Vouloumanos, Kiehl, & Werker, 2001). Investigations into the neuroanatomy of auditory speech perception have found evidence of functional subdivisions within the posterior superior temporal gyrus, accounting for the ability of this region to contribute to all three aspects of speech perception (Boatman, 2004). This functional circuitry appears to be adaptable: recent primate and human neuroimaging studies have found that auditory information can be processed by different temporal lobe pathways depending on task and stimulus demands (Kaas, Hackett, & Tramo, 1999; Rauschecker, Tian, & Hauser, 1995; Romanski, Bates, & Goldman-Rakic, 1999; Wise et al., 2001). Further, the primate literature describes direct cortical projections from an early auditory processing region analogous to the planum temporale to secondary processing regions located within the superior temporal gyrus (Kaas et al., 1999).

There are limits to the flexibility of the auditory speech processing network. Electrocortical mapping studies indicate that left middle-posterior portion of the superior temporal gyrus – the region of correlation with thought disorder in the current study – is essential for acoustic-phonetic processing (Boatman, 2004; Boatman, Hall, Goldstein, Lesser, & Gordon, 1997; Boatman, Lesser, & Gordon, 1995). It may be that, as the anatomical substrate supporting early auditory processing in the planum temporale
becomes compromised, an increase in neural activity is required at a later, perhaps more critical, processing stage to compensate for the deficiency and maintain normal or near-to-normal function. The correlation we observed between severity of thought disorder and functional activation within the left middle-posterior superior temporal gyrus may reflect such compensatory processing.

It is important to note that the task used was a simple listening task, a function which does not appear to be much affected in schizophrenia. The mediation relationship described would likely have a very different dynamic where generative language functions are concerned, as these have a different association with thought disorder than our receptive task. Generally speaking, generative tasks are associated with a reduction in left temporal activation in schizophrenia. In our report on these functional data (Weinstein et al., 2006), we proposed that the positive association between thought disorder and BOLD response reflected compensatory processing. As receptive language is largely spared in thought disorder, perhaps compensation for inefficient early auditory processing is possible by simply ramping up activation at later processing stages. For more complex language functions such as generative tasks, it may be that the inefficiency cannot be overcome with a simple increase in processing power, thus the system becomes overwhelmed and reduced activation is seen.

This is, to the best of our knowledge, the first neuroimaging study to directly assess whether anatomical and behavioural measures are mediated by functional activation. We believe this type of analysis will prove useful not only for investigations
into the physiology of cognitive symptom expression, as in the current report, but also
more generally in clarifying the interplay between brain structure and function that
determines behaviour.
Table 3.1 Sample characteristics.

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<td>Education (years)</td>
<td>15.1 ± 2.4</td>
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<td>Parental SES</td>
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<td>SSPI (total score)</td>
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<td>TLI (total score)</td>
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<td>Chlorpromazine equivalent of antipsychotic dose (mg)</td>
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Figure 3.1 The mediation model.
Figure 3.2 The two brain regions used in the mediation analysis: the mask of the planum temporale is shown in solid purple and the functional cluster is shown in red scale. Brain slice label is given in the x plane of the Talairach system.
Figure 3.3 The correlation between grey matter volume within the left planum temporale and severity of thought disorder before brain activation is included in the mediation model is shown in A; the correlations between grey matter volume within the left planum temporale, severity of thought disorder and brain activation when all three variables are included in the model are shown in B.
Figure 3.4 The correlations between TLI score and both functional activation and grey matter volume prior to mediation analysis. Note that the scale for grey matter volume is inverse.
3.6 References


Chapter 4

Failure of contextual constraint on lexical selection in thought disorder

4.1 Preface

This study was indirectly motivated by the result of the first study presented in this thesis. The positive correlation between brain activity and thought disorder indicated that impaired language processing may not provide a complete explanation, as some compensation for this is possible. In light of increasing evidence associating executive dysfunction with this symptom (Kerns & Berenbaum, 2002), executive control of language appeared to offer a potential explanation for the discrepancy. Executive control interacts with language processing at several levels (e.g. Daneman & Carpenter, 1980; Gunter, Wagner, & Friederici, 2003), indicating that deficits in executive function could produce different patterns of speech abnormality depending on task demands.

The representation and use of context is as an executive process with particular importance in language (Duranti & Goodwin, 1992), and one which is impacted in schizophrenia (Servan-Schreiber, Cohen, & Steingard, 1996). A review of the literature highlighted the absence of information regarding facilitation, a top-down effect of sentential context on lexical selection.

4.2 Introduction

Effective communication is goal-directed and cooperative: there is something to communicate and someone to communicate with. These qualities are often lost in the speech of schizophrenia patients with positive thought disorder, due to features such as derailment (shifting between topics that are only tenuously or idiosyncratically related or unrelated), tangentiality (responding to questions in an oblique or irrelevant manner) unusual word use (including word approximations and neologisms), and illogicality (non sequitur or faulty inductive reasoning) (Andreasen, 1979). Although previous research on the cognitive basis of thought disorder has tended to emphasize semantic impairment (e.g. Goldberg et al., 1998; Manschreck et al., 1988; McKay et al., 1996; Moritz et al., 2001), impaired executive function has also been put forward as a potential explanation (McGrath, 1991).

Recent experimental evidence supports an executive component of thought disorder, demonstrating an association between performance deficits on executive tasks and disorganization (Barrera, McKenna, & Barrios, 2005; Kerns & Berenbaum, 2002, 2003; Perlstein, Carter, Noll, & Cohen, 2001; Stirling, Hellewell, Blakey, & Deakin, 2006). Context memory is an executive component of working memory, responsible for processing information relevant to current behaviour (Cohen & Servan-Schreiber, 1992). Impaired context processing is one of the strongest executive correlates of thought disorder (Cohen, Barch, Carter, & Servan Schreiber, 1999; Kerns & Berenbaum, 2003). It has been suggested that a deficit in processing linguistic context may directly contribute
to producing the speech errors that define the symptom (Kuperberg, McGuire, & David, 1998, 2000).

In the domain of language, context is provided by the words that surround a part of language and determine its interpretation. Thought disorder is associated with an insensitivity to linguistic context, as indicated by a reduced influence of sentential context on lexical (word meaning) selection (Chapman & Chapman, 1973; Chapman, Chapman, & Miller, 1964). A classic example of context insensitivity is the preference for the dominant meaning of a homonym, even when context supports the subordinate meaning (Bazin, Perruchet, Hardy-Bayle, & Feline, 2000; Benjamin & Watt, 1969; Blaney, 1974; Chapman et al., 1964; Strauss, 1975; Titone, Levy, & Holzman, 2000). Other related findings include reduced production of contextually related words during performance of a verbal fluency task (Kerns, Berenbaum, Barch, Banich, & Stolar, 1999), insensitivity to linguistic violations in sentences (Kuperberg et al., 1998, 2000), and an impaired ability to guess words missing from blocks of text (de Silva & Hemsley, 1977; Honigfeld, 1963; Salzinger, Portnov, Pisoni, & Feldman, 1970).

The context insensitivity effect has been interpreted as failure to inhibit irrelevant associations, such as the dominant meaning of a homonym when context supports the subordinate meaning (Maher, Manschreck, & Molino, 1983; Manschreck et al., 1988). While context drives inhibition, these are thought to be distinct (but overlapping) components of executive processing (Goldman-Rakic, 1995; Smith & Jonides, 1998; West, 1996). Additionally, they appear to make dissociable contributions
to thought disorder (Kerns & Berenbaum, 2002, 2003), suggesting there is a deficit associated with context processing separate from that of inhibition.

Sentential context can influence lexical selection by either driving inhibition of irrelevant information or facilitating activation of congruent information (Paul, Kellas, Martin, & Clark, 1992; Simpson, 1984; Tabossi, Colombo, & Job, 1987), mechanisms that can be distinguished based on their time course. Lexical selection is a two stage process: first candidate items within the semantic network are activated or accessed, and then one of the accessed items is selected. Inhibition is a top-down, controlled process that influences lexical selection following access of candidate items (Paul et al., 1992; Simpson, 1984), while facilitation is early and automatic, occurring during the process of lexical access (Hernandez, Fennema-Notestine, Udell, & Bates, 2001; Lucas, 1999; Sereno, Brewer, & O'Donnell, 2003). While inhibition has been widely discussed in relation to schizophrenia and thought disorder (e.g. Beech, Powell, McWilliam, & Claridge, 1989; Frith, 1979; Maher et al., 1983; Manschreck et al., 1988; McCarley et al., 1999; Nestor et al., 1998), the facilitation effect of context on semantic activation has not been investigated in schizophrenia.

Homonyms provide an opportunity to examine the role of contextual information in lexical access and selection, as multiple word meanings are available and must be distinguished in order for correct meaning selection to proceed. Presented in isolation, homonyms are ambiguous and access multiple lexical entries. That is, all meanings of the ambiguous word are activated to varying degrees, with the strength of
activation dependent on lexical characteristics such as word frequency (Frazier & Rayner, 1990; Rayner & Duffy, 1986; Simpson, 1981). Thus, the more common or dominant meaning of a homonym is activated more quickly than the less common or subordinate meaning.

According to the context-sensitive model of lexical selection, sentential context facilitates access to the homonym’s congruent meaning (Paul et al., 1992; Simpson, 1984; Tabossi et al., 1987). A malfunction in facilitation coupled with impaired inhibition could result in many of the speech errors produced in thought disorder, due to a failure to constrain activation within the semantic network. For example, the context insensitivity effect: in the absence of contextual constraint lexical access would proceed on the basis of ease of activation, determined by word frequency. In the absence of inhibition, the lexical item with the strongest activation would then be selected. The dominant meaning would be more likely to be selected and included in speech, even when context supports the subordinate meaning.

To investigate the possible association between facilitation and thought disorder, we used a primed lexical decision task with homonym targets to assess the impact of congruent and incongruent context on lexical selection. Our hypotheses were: 1) control subjects will show a facilitation effect of congruent context for the subordinate meaning of a homonym; 2) subjects with schizophrenia will show a reduced facilitation effect of congruent context that will correlate with the severity of positive thought disorder; 3) both groups will show an inhibition effect for both subordinate and
dominant targets when these are presented in incongruent context; and 4) this inhibition effect will be larger for patients, and correlated with positive formal thought disorder.

4.3 Methods

4.3.1 Subjects

Subjects with schizophrenia (n = 20) were recruited from the UBC Hospital Schizophrenia Day Program or through their primary treating physician; patients currently exhibiting moderate to severe positive thought disorder were selected. Poster advertisements were used to recruit healthy control subjects (n = 20) from the UBC campus. All subjects were right-handed native English speakers with no history of neurological illness; additionally control subjects had no personal or family history of psychotic illness. Subjects provided demographic information and completed the Annett Handedness Scale (Annett, 1970). The National Adult Reading Test (NART) (Nelson, 1982) was used to estimate IQ. Subjects with schizophrenia were assessed with the Signs and Symptoms of Psychotic Illness (SSPI) scale, a measure of overall symptom severity (Liddle, Ngan, Duffield, Kho, & Warren, 2002). Sample characteristics are listed in Table 1. All patients were on stable doses of antipsychotic medication (19 atypical and 1 typical); additionally, 3 patients were on SSRI antidepressants, 3 were on anticonvulsants, and 1 was taking an anticholinergic. None of the control subjects were taking psychiatric medication. All subjects provided written informed consent; this study
was approved by the University of British Columbia Clinical Research Ethics Board. A copy of the approval form can be seen in Appendix II.

4.3.2 Procedure

A cross-model primed lexical decision (LDT) task was used to assess both the facilitating effect of congruent context and the inhibiting effect of incongruent sentential context. Visual target stimuli were 64 heterographic homophone pairs (words with the same pronunciation but different graphical forms, e.g. air/heir) and 128 monosemous words, matched to the homophones on initial phoneme, length (number of letters), frequency, bigram frequency and orthographic neighbourhood. All real words employed as stimuli were nouns. Monosemous trials were included to mask the homonym trials and reduce expectancy effects. Each word appeared once with each of 4 auditory prime types. The first prime type was a single tone (600 ms, 1000 Hz), which alerted the subject that a trial was starting. This provided a ‘baseline’ condition, indexing the unprimed reaction time to the lexical stimuli. The second prime type was a word presented in isolation, without any disambiguating contextual information. This was the ‘context-free’ condition, allowing assessment of the speed of lexical access to primed but context-free words. The third prime type was a sentence providing congruent context; this condition indexed the facilitating effect of congruent sentential context on lexical access. The fourth prime type was a sentence providing incongruent context. This final condition allowed for assessment of the inhibiting effect of incongruent sentential context on lexical access. In both context conditions, the target
word was always in sentence final position. Auditory primes were digitally recorded in a sound booth from a male speaker.

The targets were paired with a different nonword for each of the four presentations. Targets and nonwords were matched for word length (number of letters), size of orthographic neighbourhood and bigram frequency, and all nonwords were orthographically regular and pronounceable. The task had a total of 1024 trials over 12 conditions; these were organized in 4 runs of 256 trials, with each run broken into 4 blocks of 64 trials. Trials were presented in pseudorandom order with the two restrictions: no target appeared more than once in a single run, and conditions never appeared twice in succession. There was a self-paced rest between each block within a run, with longer, experimenter-controlled breaks between runs.

Subjects completed the task on a laptop computer. Subjects initially saw a fixation cross in the center of their field of view, indicating that a trial was beginning and they should look at the center of the screen. Onset of the auditory prime followed after 500ms. Auditory primes were presented over headphones at a standard, comfortable volume level. The visual target and was presented 200ms after offset of the prime. This short stimulus onset asynchrony was chosen to allow assessment of both automatic and controlled processes. Each trial presented both the target and its paired nonword at the same time, one to either side of the fixation cross. Subjects were instructed to pay close attention to the auditory stimulus and to respond to the visual target as quickly as possible, using the keyboard left and right arrow keys to indicate
which of the two visual stimuli is a real word. Target presentation was balanced across
the left and right visual fields to control for hemispheric differences in word recognition.

This variant of the lexical decision task (paired stimulus presentation) was used
to maximize power as facilitation afforded by sentential context is a small effect.

Priming studies comparing reaction time between healthy control subjects and subjects
with schizophrenia have demonstrated effect sizes of approximately $d = 1.3$ (Moritz,
Woodward, Kuppers, Lausen, & Schickel, 2003; Spitzer, Braun, Hermle, & Maier, 1993).

Power analysis gives an item estimate of 60 (the current study has 64 items per analysis
cell) to detect a conservatively estimated effect size of $d = .65$ with alpha $= .05$ and
power $= .80$. The paired stimulus presentation has been used in previous research and
was found to be effective in measuring cognitive effects on word recognition (Leonhard
& Brugger, 1998; Weinstein & Graves, 2002). Inclusion of a nonword with every trial
allows exclusion of the ‘no go’ trials, thereby doubling the number of trials of interest
that can be presented in a given period of time.

Cross-modal priming provides another important advantage by removing the
possibility of phonological priming influencing the results: any priming that occurs must
result from lexical access (Marslen-Wilson, Tyler, Waksler, & Older, 1994). Due to the
short stimulus onset asynchrony employed, a decrease in RT for words presented in
context can be interpreted as reflecting the contribution of an automatic process to
word recognition – facilitation. Additionally, the incongruent context condition allows
assessment of the effects of inhibition on word recognition.
Thought disorder was assessed with the Thought and Language Index (TLI), using speech samples produced in response to a standardized set of images (Liddle, Ngan, Caissie et al., 2002). Subjects were tape recorded while they talked about a set of 8 black and white pictures taken from the Thematic Apperception Test (Morgan & Murray, 1935) one at a time for one minute. Each subject saw the same set of pictures.

4.3.3 Analysis

The TLI speech samples were transcribed by a research assistant and scored by one of the authors (SW), who was blind to group membership. The response data from the LDT were screened for accuracy and all incorrect trials (nonword chosen as the real word) were removed. As the analysis is based on reaction time (RT), the RT data were screened to exclude outliers defined as values falling more than 2 standard deviations from the mean. Mean RTs were calculated within subjects for each condition separately for outlier screening. Data was analyzed with SPSS 14.0 (2005, SPSS Inc., Chicago, http://www.spss.com).

4.4 Results

The TLI is comprised of two subscales, disorganization (peculiar word use, peculiar sentence use, peculiar logic, loosening of associations) and impoverishment (poverty of speech, weakening of goal), with additional scores for perseveration and distractibility. The patient group had moderate to high levels of disorganization (range
0.5 – 14.5, M = 5.11, SD = 4.40), low impoverishment (range 0 – 1.25, M = .28, SD = .42),
low perseveration (range 0 -3.5, M = .60, SD = .94), and no instances of distractibility.

Subjects with schizophrenia made significantly more errors on the LDT (M = 32.40, SD = 60.70) than control subjects (M = 2.10, SD= 3.26; t[38] = 2.23, p = .04). The
number of outliers was not significantly different between subjects with schizophrenia
(M = 17.10, SD = 5.30) and controls (M = 17.50, SD = 1.67; t[38] = .32, p = .76). The mean
RT for each condition, excluding incorrect and outlier trials, is listed for both groups in
Table 2. A word x prime x group (2 x 4 x 2) repeated measures GLM tested the main
effects and interactions for the homonym trials. There was a main effect of group, with
controls performing significantly faster (M = .72, SE = .08) than patients (M = 1.37, SE
= .08) across all conditions (F[1,38] = 34.28, p < .001). The main effect of word type was
significant (F[1,38] = 19.41, p < .001), as RT was significantly faster to the dominant
(M = 1.01, SE = .05) than subordinant (M = 1.08, SE = .06) word type. There was also a main
effect of prime (F[3,38] = 25.50, p < .001). The context free prime produced the fastest
RT (M = .92, SE = .05), followed by congruent context (M = .94, SE = .05), incongruent
context (M = 1.11, SE = .06), with the baseline (tone) prime resulting in the slowest RT
(M = 1.22, SE = .08).

The word x prime x group interaction was significant (F[3,38] = 4.83, p = .003),
indicating that the groups were differentially affected by the conditions. The interaction
is shown in Figure 1a for controls and Figure 1b for patients. Post-hoc t-tests were
performed on calculated priming effects to determine the conditions underlying the
interaction. The priming effect for the context free trials was calculated as the change in reaction time relative to the baseline trials. Both groups showed a significant decrease in reaction time, an effect which was equivalent for the dominant and subordinate words in both groups (controls \( t[19] = 1.87, p = .08; \) patients \( t[19] = .22, p = .83 \)). The patients reduction in reaction time (\( M = -.43, SE = .11 \)) was significantly larger than that of the controls (\( M = -.17, SE = .01; t[38] = 9.52, p < .001 \)), indicating a larger priming effect of the context free condition for the patients. The context free priming effect was not significantly correlated with positive thought disorder in the patient group (\( r = -.18, p = .22 \)).

Facilitation was calculated as the difference in reaction time between the congruent context and context-free condition. A facilitation effect would have a negative value, reflecting a decrease in RT when the target was presented in congruent context. Inhibition was calculated as the difference in reaction time between the incongruent context and context-free conditions. An inhibition effect would therefore have a positive value, reflecting an increase in RT when the target was presented in incongruent context. Our hypotheses were that the control group would show a facilitation effect for the subordinate word only, and that the inhibition effect would be equivalent between the word types. We hypothesized that the patients would not show a facilitation effect of congruent context for either word type, and that they would have significantly larger inhibition effects for incongruent context relative to the controls for
both word types. We further hypothesized that the calculated facilitation effect would
be correlated with positive thought disorder.

The calculated facilitation and inhibition effects, and associated t-statistics and p
values from single-sample t-tests, are listed in Table 3. Single-sample t-tests tested the
significance of the experimental effects within groups. For both controls and patients,
congruent context actually increased RT to the dominant word, though this effect was
significant for patients only. As hypothesized, the control group showed a significant
facilitation effect of congruent context for the subordinate word, which was not seen in
the patient group. Both groups showed a significant inhibition effect when the
dominant word was paired with incongruent context. Incongruent context with the
subordinate word resulted in a significant inhibition effect for the controls, but only a
trend towards significance for the patients. The calculated facilitation and inhibition
effects for each group are shown in Figure 2.

The subordinate facilitation effect was significantly reduced in the patients
compared to controls ($t[38] = -1.90, p = .03$). Dominant facilitation was not significantly
different between the groups ($t[38] = -.99, p = .17$). Compared to the controls, the
patients showed an enhanced inhibition effect for the dominant word ($t[38] = -4.05, p
< .001$). No difference in inhibition for the subordinate word was seen between the two
groups ($t[38] = -.75, p = .23$). Pearson correlation coefficients were calculated between
the patients' TLI positive subscale score and the experimental effects. The facilitation
effect was significantly correlated with positive thought disorder in the patients for
subordinate words \((r = .53, \ p = .009)\) and is shown in Figure 3. Positive thought disorder was not correlated with any of the other calculated facilitation or inhibition effects: dominant facilitation \((r = .35, \ p = .07)\), dominant inhibition \((r = -.251, \ p = .14)\), subordinate inhibition \((r = .07, \ p = .38)\).

4.5 Discussion

Our hypothesis that a failure in contextual facilitation of lexical selection contributes to positive thought disorder is supported by the results of this study. The control group showed the predicted facilitation effect of congruent context for the subordinate word. Target recognition was significantly faster when it was preceded by disambiguating context, relative to a single word prime that did not disambiguate meaning. This effect was reduced in the patient group, for whom congruent context had no effect on target recognition. Further, the calculated facilitation effect in the patients correlated inversely with positive thought disorder. As thought disorder scores increased, the change in reaction time decreased to zero and then increased – patients with high positive thought disorder were actually slower to recognize subordinate targets presented with congruent context, relative to the context-free condition. It appears that congruent sentential context interferes with lexical access in highly disordered patients.

A similar interference effect of congruent context was seen for the dominant targets. As hypothesized, the control group showed no effect of congruent context on
these trials. This is because the dominant meaning of a homonym is accessed first regardless of context, and thus context confers no processing advantage (Simpson, 1981). In the patient group, however, there was an unexpected effect of congruent context on the RT to the dominant targets: it made them slower, compared to the context-free condition. This increase in RT did not correlate significantly with positive thought disorder.

Incongruent context produced significant inhibition effects for both dominant and subordinate targets in the control group, in other words, subjects took longer to inhibit the incongruent word and make the correct decision. In contrast, incongruent context only resulted in a significant inhibition effect for the dominant targets in the patient group, with a trend towards a significant effect for the subordinate targets. Inhibition was not associated with severity of thought disorder, indicating that problems in inhibition when performing this task were likely a general effect of illness. While disinhibited semantic activation (such as is seen in priming tasks) is thought to contribute to thought disorder (Manschreck et al., 1988; Spitzer et al., 1993), increased inhibition associated with incongruent linguistic context has been previously observed in undifferentiated schizophrenia patients (Titone et al., 2000). In that study, patients showed significantly increased inhibition on a task similar to the current one, but no association with thought disorder was reported.

Direct comparison demonstrated that the inhibition effect for dominant targets was significantly greater in patients than controls, with no difference for subordinate
words. Both groups exhibited greater inhibition for the dominant than subordinate
trials, and patients were significantly more impaired on these trials compared to
controls. This suggests that incongruent context is more difficult to overcome when the
subordinate meaning must be inhibited in order to access the dominant. One
explanation for this unexpected effect is that it reflects the extra processing time
required to perform ‘double inhibition’. When hearing the subordinate meaning in
context, both meanings are activated necessitating inhibition of the dominant meaning
target would then require inhibition of the subordinate word – hence double inhibition.
On the other hand, when the dominant word is presented in context, the subordinate
meaning is not activated and no inhibition is required (Tabossi et al., 1987; Tabossi &
Zardon, 1993), perhaps making the incongruent-subordinate trials easier to process.

Importantly, both patients and controls were significantly faster to recognize
words in the context free condition relative to baseline, and this effect was equivalent
for both dominant and subordinate words. This indicates that basic lexical access and
priming processes, such as word frequency effects, were intact. The effect of the
context-free prime was greater in the patients, which may seem similar to hyperpriming
previously reported in thought disordered subjects (Manschreck et al., 1988; Spitzer et
al., 1993); however, as the target and prime were actually the same word and not
semantic associates, we do not believe this reflects spreading activation within the
semantic network. The hyperpriming effect associated with spreading semantic
activation tends to correlate with positive thought disorder (Manschreck et al., 1988; Moritz et al., 2001; Moritz et al., 2003; Spitzer et al., 1993). In our sample, there was no significant association between single-word priming and positive thought disorder. Rather, this effect is likely an artefact of the much poorer performance of the patient group at baseline: given helpful information, they simply have more room for improvement.

The loss of facilitation and the interference effect we found in this study clearly indicate a deficit in processing linguistic context. In healthy people, sentential context guides normal discourse via facilitation and inhibition, processes which constrain lexical selection by regulating activation within the semantic network (Paul et al., 1992; Simpson, 1984; Tabossi et al., 1987). Facilitation enhances access of context-relevant lexical items (Hernandez et al., 2001; Lucas, 1999; Sereno et al., 2003), while inhibition influences lexical selection following access of candidate items (Paul et al., 1992; Simpson, 1984). As previously discussed, disinhibition within the semantic network has been put forward as the mechanism of enhanced indirect priming in thought disordered patients, by allowing activation of contextually irrelevant but semantically linked words (Manschreck et al., 1988; Spitzer et al., 1993).

Unlike single word semantic priming, which is enhanced in thought disorder, we found that sentence level facilitation of lexical access is reduced in thought disorder. An impaired ability to create sentential context, or represent the overall meaning of a sentence, may be the underlying problem. Evidence suggests that building sentence-
level context is impaired in schizophrenia, particularly in thought disorder.

Schizophrenics’ sensitivity to sentential context is lower for the sentence final word than for mid-sentence targets, when the processing load for creating context would be highest (Adams et al., 1993; Kuperberg, Kreher, Goff, & McGuire, 2006; Mitchell et al., 1991; Ohta, Uchiyama, Matsushima, & Toru, 1999). Disorganized subjects are equally impaired in recognizing words present in normal and violated sentences, suggesting that not only are they insensitive to context-level errors, but also that they have difficulty processing regular sentences (Kuperberg et al., 1998).

More direct support comes from work detailing deficits in semantic-syntactic integration in thought disorder. The syntactic and semantic information contained in a sentence must be integrated in order to create an accurate representation of sentential context (Caplan, 1992). Patients are impaired in their ability to combine this information, reflected in slower performance when judging the acceptability sentences containing errors targeting syntactic-semantic integration (Kuperberg et al., 2006). An impairment in creating or building up context indicates that context may not be available in time to inform lower level processes such as semantic activation, leading to a loss of facilitation when moderate and interference in lexical access when severe.

In the absence of facilitation, lexical access would proceed along the basis of semantic association and word frequency. The former would result in spurious activation within the semantic network, while the latter would bias towards the dominant meaning of ambiguous words. Deficient inhibitory function would result in
failure to block these irrelevant activations, with a final outcome of unconstrained
lexical selection. Such dysregulated activation within the semantic network may
partially explain derailment, tangentiality and other features of positive thought
disorder (Andreasen, 1979).
Table 4.1 Sample characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 20)</th>
<th>Controls (n = 20)</th>
<th>Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Statistic</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>14:6</td>
<td>11:9</td>
<td>$\chi^2 = 0.96$</td>
</tr>
<tr>
<td>Age</td>
<td>36.6 (9.6)</td>
<td>29.4 (11.5)</td>
<td>$t(38) = 2.15$</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>111.3 (7.2)</td>
<td>116.7 (6.1)</td>
<td>$t(38) = 2.55$</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.5 (3.2)</td>
<td>16.4 (4.4)</td>
<td>$t(38) = 2.38$</td>
</tr>
<tr>
<td>Parental SES</td>
<td>3.4 (1.4)</td>
<td>2.6 (1.4)</td>
<td>$t(38) = 1.81$</td>
</tr>
<tr>
<td>Age of onset</td>
<td>26.2 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSPI (total score)</td>
<td>12.1 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalent of antipsychotic dose (mg)</td>
<td>413.3 (345.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.2 Mean reaction times and standard errors for each condition for the control and patient groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Word</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tone</td>
</tr>
<tr>
<td>Controls</td>
<td>Dominant</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td>Subordinate</td>
<td>.89</td>
</tr>
<tr>
<td>Patients</td>
<td>Dominant</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>Subordinate</td>
<td>1.71</td>
</tr>
</tbody>
</table>
Table 4.3 T-tests for the calculated facilitation and inhibition effects within and between groups.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ in RT</td>
<td>t(19)</td>
</tr>
<tr>
<td>Facilitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dominant</td>
<td>.04</td>
<td>1.30</td>
</tr>
<tr>
<td>subordinate</td>
<td>-.05</td>
<td>2.31</td>
</tr>
<tr>
<td>Inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dominant</td>
<td>.17</td>
<td>8.17</td>
</tr>
<tr>
<td>subordinate</td>
<td>.04</td>
<td>3.08</td>
</tr>
</tbody>
</table>

*two-tailed p values
Figure 4.1 Mean reaction times for all conditions for a) the control group and b) the patient group.

a) Control group:

b) Patient group:
Figure 4.2 Change in reaction time, relative to the context-free condition, for a) congruent context (facilitation effect) and b) incongruent context (inhibition effect).

a) Congruent context:

b) Incongruent context:
Figure 4.3 Correlation between patients' calculated facilitation effect for the subordinate words and score on the TLI positive subscale.
4.6 References


Chapter 5

Speech assessment in positive schizotypy: implications for psychosis risk assessment

5.1 Preface

The study presented in this chapter is very different from the previous three, which were concerned with either the neurophysiological or cognitive correlates of schizophrenic thought disorder. It is not an investigation of schizophrenia, nor does it attempt to shed light on the cognitive origin of disorganization. Rather, this study is concerned with the distribution of the speech abnormalities associated with thought disorder. Schizotypy is a personality construct measurable in the normal population that has many cognitive parallels with schizophrenia (e.g. Beech & Claridge, 1987; Lenzenweger, Cornblatt, & Putnick, 1991; Weinstein & Graves, 2001), and which has been used as a model of psychosis in research. As the thought disorder assessment scale developed by Liddle and colleagues was designed to detect even very subtle, subclinical speech abnormality (Liddle et al., 2002), we were interested in determining whether speech abnormalities typical of thought disorder in schizophrenia vary with the degree of positive schizotypy in the healthy population.

5.2 Introduction

Schizotypy is a personality dimension encompassing unusual beliefs and perceptual experiences, anhedonia, and social withdrawal. The spectrum perspective regards schizotypy as continuous with schizophrenia; according to this view schizotypy is a sub clinical expression of schizophrenic psychopathology, reflecting a shared aetiology. Family studies have found that close relatives of people with schizophrenia display higher levels of schizotypal traits, supporting a genetic link (Baron et al., 1985; Fanous, Gardner, Walsh, & Kendler, 2001; Kendler et al., 1993; Silverman et al., 1993), and there is evidence that individuals scoring extremely high on measures of schizotypy have an increased risk of developing psychotic illness (Gooding, Tallent, & Matts, 2005; Kwapiil, Miller, & Zinser, 1997). Additionally, parallels have been described between schizotypy and schizophrenia in several areas of cognitive function, including atypical lateralization (Mohr, Thut, Landis, & Brugger, 2003; Nunn & Peters, 2001; Weinstein & Graves, 2001, 2002), semantic processing (Beech & Claridge, 1987; Gianotti, Mohr, Pizzagalli, Lehmann, & Brugger, 2001; Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001) and sustained attention (Cornblatt & Keilp, 1994; Lenzenweger et al., 1991).

Another similarity is found in the proposed three-factor structure of schizotypy (Bentall, Claridge, & Slade, 1989; Gruzelier, 1996; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000; Venables & Bailes, 1994; Venables & Rector, 2000), which closely resembles that of schizophrenia (Liddle, 1987). The positive dimension includes odd perceptual experiences and paranormal beliefs, attenuated versions of the positive,
reality distortion symptoms of schizophrenia. Likewise, the negative dimension includes anhedonia, corresponding to the negative, psychomotor poverty symptoms of schizophrenia. The third dimension of schizotypy is variably defined as social impairment (Venables & Rector, 2000), disorganization (Reynolds et al., 2000), or a combination of these (Bentall et al., 1989). It is unclear whether this third dimension is analogous to disorganization in schizophrenia, which comprises the third factor of the illness. In schizophrenia, disorganization is primarily expressed as Formal Thought Disorder, observable as abnormality in the organization and structure of speech. Thought Disorder also has positive and negative aspects: positive thought disorder includes derailment and tangentiality, while negative thought disorder is associated with poverty of speech and loss of goal (Andreasen, 1979). No association has been found between disorganization in schizotypy and Formal Thought Disorder (Ulhaas, Silverstein, Phillips, & Lovell, 2004).

The language abnormalities associated with thought disorder in patients with schizophrenia are detectable in the speech of healthy people, albeit at a much lower frequency and severity than is observed in patients with this symptom (Liddle et al., 2002). It is currently unknown whether sub-clinical speech abnormality varies systematically with positive schizotypy in healthy adults; this study was undertaken to determine whether such an association exists. If so, this may be a point of divergence between schizotypy and schizophrenia, as Formal Thought Disorder in schizophrenia appears to be distinct from the reality distortion symptoms of the illness (Liddle, 1987).
If not, the presence of speech abnormality in highly schizotypal individuals may be an early indicator of cognitive dysfunction, denoting an increased risk of psychotic illness.

5.3 Methods

5.3.1 Subjects

Participants were 107 students recruited from the University of British Columbia campus. All were native English speakers with no personal or first degree family history of psychiatric illness. Subjects gave written informed consent before participating and received either a $10 honorarium or credit in an Introduction to Psychology course. All experimental procedures were approved by the University of British Columbia Behavioural Research Ethics Board. A copy of the approval form can be seen in Appendix III.

5.3.2 Procedure

The National Adult Reading Test (NART) (Nelson, 1982) was used to estimate IQ. Parental socioeconomic status was determined with the Hollingshead Index (Hollingshead, 1957). A single schizotypy questionnaire was created by randomly mixing the items of two separate scales, Perceptual Aberration (PA), measuring unusual perceptual experiences (Chapman, Chapman, & Raulin, 1978), and Magical Ideation (MI), measuring paranormal belief (Eckblad & Chapman, 1983). The MI and PA are highly correlated and are often used together as an index of positive schizotypy. Speech samples were collected and scored according to the guidelines for the Thought and
Language Index (TLI), an instrument for the assessment of thought disorder (Liddle et al., 2002). The TLI has two nearly orthogonal component subscales reflecting the positive and negative aspects of thought disorder, and was designed to be sensitive to minor aberrations present in the speech of healthy individuals as well as florid thought disorder such as that seen in patients with schizophrenia.

Participants provided demographic information and completed the schizotypy questionnaire. Questionnaires were scored immediately while participants waited, and subjects found to have scored in the top (n = 23) and bottom (n = 27) quartiles of the questionnaire (cutoff scores determined a priori from the scale norms provided by T.R. Kwapisil, personal communication) also completed the TLI. The TLI speech samples were recorded on cassette tape and transcribed verbatim. Samples were scored by one of the authors (SW), who was blind to identity and group membership.

5.4 Results

Statistical analysis was performed with SPSS version 14 (SPSS Inc., Chicago IL). Sample demographics are described in Table 1. A one-way ANOVA was used to test for group differences in age, parental socio-economic status, years of education and estimated IQ. No significant differences were found for age, $F(1,48) = .318, p = .58$, parental socio-economic status, $F(1,48) = .103, p = .75$, or education, $F(1,48) = .374, p = .54$. Estimated IQ was significantly higher in the low schizotypy group, $F(1,48) = 5.86, p = .02$. Mean scores for the two schizotypy scales and the TLI subscales, as well as the p-
values for the differences between groups, are given in Table 2. Another one-way ANOVA was performed to test for group differences on the MI, PA and TLI subscales. Unsurprisingly, the groups were highly significantly different on both the MI, $F(1,48) = 412.33$, $p < .000$, and the PA, $F(1,48) = 81.49$, $p < .000$. No significant differences were found between groups on either TLI subscale: disorganization, $F(1,48) = 1.37$, $p = .254$, impoverishment $F(1,48) = 1.59$, $p = .213$.

5.5 Discussion

There was no evidence of thought disorder in either the high or low schizotypy group, with both groups scoring far below the mean observed for the chronic patients described in the validation of the TLI (Liddle et al., 2002). Additionally, the scores for both groups were accumulated exclusively from speech events scored at .25, denoting phenomena of possible abnormality: these subjects were not exhibiting any clinically significant speech abnormality, but rather events of questionable normality. The TLI is composed of two nearly orthogonal subscales, disorganization and impoverishment, reflecting positive and negative thought disorder respectively. There were no significant differences between the groups on either scale. These data suggest that, while schizotypal traits are normally distributed in the general population (Eckblad & Chapman, 1983), the speech abnormalities typical of thought disorder are not.

Dissociation between schizotypy and thought disorder indicates the latter may be a variable with utility for predicting illness. As it is not systematically associated with
'normal' degrees of schizotypy, the presence of thought disorder may predict who, within a highly schizotypal or high-risk group, is at highest risk of psychotic illness. That is, thought disorder observed in those at high-risk may indicate a greater risk of illness than the risk criteria alone. A recent longitudinal study provides some preliminary evidence of this; thought disorder in a small high-risk sample was found to be among the variables differentiating between those who subsequently converted to psychotic illness and those who did not (Haroun, Dunn, Haroun, & Cadenhead, 2006).

Previous findings of thought disorder in high risk subjects identified via schizotypy screening – thus scoring much higher than in the current sample – support this conclusion. A group selected for psychosis-proneness on the PA (scoring 2 standard deviations above the mean or higher) showed signs of positive thought disorder, with a few (6 of 30) subjects scoring in the range exhibited by acutely psychotic patients (Coleman, Levy, Lenzenweger, & Holzman, 1996). A study looking at proverb interpretation found a higher degree of idiosyncratic/bizarre interpretation of unfamiliar proverbs, which is characteristic of positive thought disorder, in another psychosis-prone sample (defined as above, also using the PA) (Allen & Schuldberg, 1989).

As there is evidence of speech abnormality in high risk populations, which does not seem to reflect normal individual variability, we believe the outcome of this study may have implications for risk assessment. Where there is ambiguity as to whether a person’s behaviour and beliefs represent a high level of schizotypy or a low level of
schizophrenic pathology, the presence or absence of thought disorder may be a relevant factor in making that distinction. In other words, signs of positive thought disorder in a high risk population might have added predictive value in identifying those individuals who are at highest risk of conversion. A careful assessment of speech in individuals at high risk of psychotic illness is required to determine if speech disorder, subtle or otherwise, is useful for distinguishing between those who are likely to transition to illness and those who are not.
<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Initial Sample (n=107)</th>
<th>High Schizotypy (n=23)</th>
<th>Low Schizotypy (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handedness (R:L)</td>
<td>94:10</td>
<td>19:4</td>
<td>25:2</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>36:71</td>
<td>13:10</td>
<td>8:19</td>
</tr>
<tr>
<td>Age</td>
<td>25.5 (9.4)</td>
<td>25.7 (5.6)</td>
<td>24.6 (8.3)</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>101.6 (9.7)</td>
<td>99.8 (12.6)</td>
<td>106.9 (7.7)</td>
</tr>
<tr>
<td>Parental SES</td>
<td>2.87 (1.1)</td>
<td>2.80 (1.3)</td>
<td>2.91 (.99)</td>
</tr>
<tr>
<td>Years of Education</td>
<td>16.2 (2.8)</td>
<td>16.6 (3.4)</td>
<td>16.0 (2.7)</td>
</tr>
</tbody>
</table>
Table 5.2 Mean scores on the schizotypy scales and Thought Disorder Index, with associated p values.

<table>
<thead>
<tr>
<th>Experimental Variable</th>
<th>Low Schizotypy Group</th>
<th>High Schizotypy Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magical Ideation</td>
<td>2.67 (1.64)</td>
<td>17.39 (3.33)</td>
<td>&lt; .000</td>
</tr>
<tr>
<td>Perceptual Aberration</td>
<td>3.11 (2.95)</td>
<td>14.78 (5.92)</td>
<td>&lt; .000</td>
</tr>
<tr>
<td>TLI positive subscale</td>
<td>.73 (.66)</td>
<td>1.02 (1.09)</td>
<td>.25</td>
</tr>
<tr>
<td>TLI negative subscale</td>
<td>.04 (.15)</td>
<td>.17 (.54)</td>
<td>.21</td>
</tr>
</tbody>
</table>
5.6 References


Chapter 6

General discussion

6.1 Summary of results and implications

This thesis represents a diverse set of studies, motivated by a common interest in the natural history of thought disorder. The first study used fMRI to examine the neural correlates of thought disorder while subjects listened to comprehensible speech. Receptive language, including perception and comprehension, is largely preserved in thought disorder, despite profound impairment in generative language (Grove & Andreasen, 1985). These two language functions share a reliance on left posterior superior temporal cortex, a region with reduced grey matter volume in thought disordered subjects (Rossi et al., 1994; Shenton et al., 1992; Vita et al., 1995). The results demonstrate that receptive language in thought disordered subjects is associated with functional abnormalities opposite those generally observed in association with generative language.

It seems that while local decreases in activation and reduced functional lateralization of language correlate with thought disorder (Kircher et al., 2002; McGuire et al., 1998), they do not provide a complete picture of the underlying neurophysiology. The results of this study emphasize that patterns of language related cortical activation associated with thought disorder are task dependent, and should be interpreted in the framework of the experimental paradigm employed. A compensatory mechanism was
proposed, in which increased activation in the posterior middle temporal gyrus (MTG), a region functionally downstream from the site of reduced grey abnormality in the posterior superior temporal gyrus, allows for preserved receptive language in thought disorder.

The second study borrowed a common data analysis technique from the social sciences (Baron & Kenny, 1986) to answer a question raised by the first: is the increase in activation directly related to the anatomical correlates of thought disorder? Despite the small sample size, this study replicated the well established finding of a negative correlation between left posterior superior temporal grey matter volume and severity of thought disorder (Shenton et al., 1992). The reduction in grey matter volume was also significantly correlated with increased MTG activation, such that as grey matter volume decreased, activation increased. The mediation analysis demonstrated that increased activation during receptive language processing, as seen in the first study, mediates the association between anatomical abnormality and thought disorder.

The success of the mediation analysis provides support for the compensation hypothesis proposed in the first study, by illustrating that activation in one region can be directly associated with, and thus potentially be compensating for, deficiencies in another. More generally, the second study also demonstrated the potential of this technique to contribute to investigations into the pathophysiology of mental illness. Anatomical abnormalities have been described in several brain regions in schizophrenia, most notably in posterior superior temporal regions involved in language function, and
medial temporal lobe structures fundamental to memory processing (McCarley et al., 1999). There is nothing controversial about the idea that failures in core processing regions may have downstream functional consequences, but this is challenging to study in vivo. Chapters Two and Three demonstrate that such a process is statistically testable, and occurs in subjects with thought disorder.

Research into the cognitive basis of thought disorder has recently shifted from a focus on semantic processing to include higher level cognitive functions. The third study investigated an aspect of executive control of language. This study was partially inspired by the results of first two studies, which implied that the neural correlates of thought disorder were more complex than earlier research suggested. Recent evidence supports the involvement of executive dysfunction in thought disorder, an aspect of which is aberrant context processing (Kerns & Berenbaum, 2003; Kuperberg, McGuire, & David, 1998). While one mechanism of context, inhibition, has been discussed in relation to schizophrenia (e.g. Beech, Powell, McWilliam, & Claridge, 1989; Frith, 1979; Nestor et al., 2001) and thought disorder (e.g. Maher, Manschreck, & Molino, 1983; Spitzer, Braun, Hermle, & Maier, 1993), the other mechanism of context associated with language, facilitation, has not been addressed. The results of study three demonstrate a striking failure of context driven facilitation in subjects with thought disorder.

As discussed in detail in Chapter Four, facilitation is an early, automatic effect of context that biases lexical access (Paul, Kellas, Martin, & Clark, 1992; Tabossi, Colombo,
A loss of facilitation means that context appropriate words are not selectively enhanced prior to lexical selection. This deficiency, coupled with disinhibition within the semantic network (Manschreck et al., 1988; Spitzer et al., 1993), may explain the tendency for semantic and phonological features of words to have undue influence on the speech of patients with positive thought disorder. Automatic spreading activation within the semantic network is governed by the strength of intrinsic associations. The absence of contextual influence over pre-selection activation would thus result in activation of items which share close semantic and phonological ties with the most recently selected words, regardless of relevance. The subsequent failure to inhibit these inappropriate activations would result in speech overly influenced by local semantic and phonological features of words.

Patients with marked negative symptoms, on the other hand, including poverty of speech, have demonstrated executive impairment with relative preservation of semantic function (Kravariti, Dixon, Frith, Murray, & McGuire, 2005; Williams, 1996). It may be that positive thought disorder results from combined semantic and executive impairment, while impairment restricted to the latter would produce poverty of speech. There is convincing evidence that both semantic and executive processes are impaired in thought disorder (Kerns & Berenbaum, 2002, 2003; Manschreck et al., 1988; McGrath, 1991; McKay et al., 1996; Spitzer et al., 1993; Stirling, Hellewell, Blakey, & Deakin, 2006).

The competence versus performance distinction in psycholinguistic research provides a useful framework in which to conceptualize the cognitive deficits in thought
disorder. Jackendoff's influential conceptual-semantic theory of language proposes that the neural computation supporting language takes place simultaneously at three levels, the phonological, syntactic, and semantic/conceptual, which interact during processing (Jackendoff, 2002). In this conception of language, dysfunction of competence implies deficiency within one or more of the psycholinguistic levels of processing or in their interaction. Impaired performance, on the other hand, implies that the output of the language system is impaired due to the influence of external factors such as memory and executive function.

A semantic/executive co-deficit would translate as failures in both competence and performance in thought disorder. While phonology, and perhaps to a lesser degree syntax, seem to function normally (DeLisi, 2001; Rodriguez-Ferrera, McCarthy, & McKenna, 2001), dysregulation of the semantic/conceptual level in thought disorder represents a failure of linguistic competence. In contrast, impaired use of context and other executive functions would be categorized as performance deficits. Together, these failures in competence and performance provide an explanation for how local features of speech may exert undue influence over speech production, thereby accounting for the most common features of thought disorder: derailment, tangentiality and loss of goal (Andreasen, 1979). In other words, they explain the tendency of semantic and phonological associations to direct speech, which may be the most uniquely schizophrenic characteristic of disorganized language (Covington et al., 2005)
The fourth study is somewhat tangential to the first three. Many of the speech abnormalities associated with thought disorder are observable in healthy people in attenuated forms (Liddle et al., 2002). This study investigated whether the frequency or severity of such subclinical speech abnormality is associated with schizotypy, a personality construct with cognitive parallels to schizophrenia (e.g. Beech & Claridge, 1987; Cornblatt & Keilp, 1994; Nunn & Peters, 2001; Weinstein & Graves, 2001, 2002). The results demonstrate that speech abnormality does not covary with positive schizotypy. As high positive schizotypy is a risk factor for psychosis, speech abnormality in this population may indicate an even greater risk of illness. In the following section, a study is described that is directly addressing this possibility.

6.2 Current and future questions

Three lines of inquiry are currently being pursued that were directly motivated by experiments presented in this thesis. The first is an adaptation of the lexical decision paradigm presented in Chapter Four. Patients with thought disorder are undergoing fMRI scanning while they perform a version of the task that includes only homonym trials with either congruent or incongruent context. This modification will allow us to focus on the neural correlates of inhibition and facilitation in these subjects, to help untangle the executive and language components of thought disorder.

The dorsolateral prefrontal cortex (DLPFC) supports general context processing (Diamond & Goldman-Rakic, 1989; Miller & Cohen, 2001). Investigations of context
processing in schizophrenia have consistently found altered DLPFC activation; although somewhat task-dependent, this abnormality is usually seen as reduced activation (Barch et al., 2001; Holmes et al., 2005; MacDonald & Carter, 2003; MacDonald et al., 2005). In a study of context effects on language processing in healthy subjects, Kerns and colleagues found that activation in DLPFC predicted context-appropriate responding (Kerns, Cohen, MacDonald et al., 2004). Additionally, anterior cingulate cortex (ACC), a region implicated in conflict detection, showed greater activation for incongruent responses in the same subjects (Kerns, Cohen, MacDonald et al., 2004). It appears that DLPFC is involved in the representation and/or application of linguistic context, while ACC appears to be sensitive to context incongruence during responding. We anticipate that thought disordered subjects will show reduced activation in DLPFC during congruent context processing, which will be most pronounced for subordinate targets, reflecting the greater difficulty of processing context in that condition. We also predict decreased activation in ACC on trials with incongruent targets.

The second study, although also motivated by the results presented in Chapter Four, takes a different approach. While we were able to demonstrate weakened use of linguistic context in that study, our task did not address the possible mechanisms of context failure. There appear to be two stages at which contextual processing could break down: generation of an adequate representation of context (Kuperberg, Kreher, Goff, & McGuire, 2006), and maintenance of context (Cohen, Barch, Carter, & Servan Schreiber, 1999; Servan-Schreiber, Cohen, & Steingard, 1996).
Although there is a strong argument for a breakdown in context maintenance in thought disorder, this explanation assumes that the initial representation of context is both intact and accurate. A study is underway that seeks to determine whether that assumption is correct. A task was designed to assess the initial creation of linguistic context, by eliciting a verbal response to three apparently unrelated words. Responses indicate whether the subject is able to integrate the stimulus words into a single idea, thereby creating context where none is explicitly provided. Preliminary results presented at the 2007 International Congress on Schizophrenia Research indicate the initial creation of context may be impaired in thought disordered subjects (Weinstein, Ngan, & McGuire, 2007).

The third study underway was motivated by the results presented in Chapter Five. Speech samples are being collected from subjects meeting criteria for an at-risk mental state (Yung et al., 2005); to date approximately four dozen subjects have participated. These subjects are at high risk of transition to psychotic illness, with approximately 25% expected to become ill within a year of the initial assessment. This study will address the possibility raised in Chapter Five, that sub clinical speech errors may have predictive value when attempting to identify those at highest risk of imminent psychotic illness - when they may most benefit from medical intervention.

The success of the mediation analysis presented in Chapter Three demonstrates the usefulness of this technique in investigating the interrelationships present among neurophysiological and neurocognitive correlates of behavioural, including
psychopathology. Many studies have demonstrated correlations between symptom severity and both brain physiology and brain function in schizophrenia. For example, auditory verbal hallucinations are associated with reduced grey matter volume in anterior superior temporal cortex (Barta, Pearlson, Powers, Richards, & Tune, 1990) and middle and inferior temporal regions (Onitsuka et al., 2004), and also with increased activation in Broca's area (McGuire, Shah, & Murray, 1993) and reduced activation in middle and superior temporal cortex and other brain regions (McGuire et al., 1995; Shergill, Bullmore, Simmons, Murray, & McGuire, 2000). The mediation technique may be able to clarify how these various structural and functional abnormalities interact in the production of auditory hallucinations.

Mediation may also be relevant to the executive-semantic hypothesis of positive thought disorder proposed in Chapter Four. Structural abnormalities in the left posterior temporal lobe, an area important for semantic processing (Geschwind, 1970; Hickok & Poeppel, 2000; Vandenbarghe, Price, Wise, Josephs, & Frackiowack, 1996), could increase the processing load in regions downstream. One such region, the prefrontal cortex, supports executive control of language as well as semantic function (Demb et al., 1995; Gabrieli, Poldrack, & Desmond, 1998; Kerns, Cohen, Stenger, & Carter, 2004; Poldrack et al., 1999). The mediation technique could help determine whether the reductions in prefrontal cortical activation that have been observed in connection with language processing in thought disordered subjects (Curtis et al., 1998; Kuperberg, Deckersbach, Holt, Goff, & West, 2007; McGuire et al., 1998; Yurgelun-Todd...
et al., 1996) are directly related to the temporal lobe structural abnormalities seen in patients with this symptom.

6.3 Conclusion

Thought disorder is both fascinating and frustrating in its complexity. It is the most compelling of the core psychotic symptoms, perhaps because it engages the listener directly in its expression. Ultimately, thought disorder represents an impairment of one of the most fundamental characteristics of being human, our capacity for communication. This loss deepens the isolation of those with psychotic illness, interfering with medical treatment and social functioning. An explanation that can account for the various manifestations of thought disorder would provide a foundation for the development of treatments targeting this symptom.

This thesis provides evidence that local changes in language related activation, and by inference language dysfunction, cannot wholly explain thought disorder. The observed deficit in context processing in combination with semantic dysfunction may have considerable power to explain some of the most prominent features of this symptom. Thought disorder is not associated with normal levels of positive schizotypy; the close alignment with psychosis suggests speech assessment may improve prediction of transition to illness in those at high risk.

While previous research has tended to emphasize a single deficit solution, the results presented here suggest this approach is overly simplistic. It seems more likely
that thought disorder is the consequence of a co-occurrence of dysfunction in separate cognitive systems. It may be that these are independent in the sense of reflecting distinct disease processes, or that they share a pathophysiological origin. Either way, it may be that thought disorder reflects the interaction of malfunctioning systems, rather than one specific functional deficiency.
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